ESC European Society of Cardiology

European Heart Journal (2025) **00**, 1–102
https://doi.org/10.1093/eurheartj/ehaf194

ESC GUIDELINES

2025 ESC/EACTS Guidelines for the management of valvular heart disease

Developed by the task force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Authors/Task Force Members: Fabien Praz *†, (ESC Chairperson) (Switzerland), Michael A. Borger *†, (EACTS Chairperson) (Germany), Jonas Lanz ‡, (ESC Task Force Co-ordinator) (Switzerland), Mateo Marin-Cuartas ‡, (EACTS Task Force Co-ordinator) (Germany), Ana Abreu (Portugal), Marianna Adamo (Italy), Nina Ajmone Marsan (Netherlands), Fabio Barili (Italy), Nikolaos Bonaros (Austria), Bernard Cosyns (Belgium), Ruggero De Paulis (Italy), Habib Gamra (Tunisia), Marjan Jahangiri (United Kingdom), Anders Jeppsson (Sweden), Robert J.M. Klautz (Netherlands), Benoit Mores (Belgium), Esther Pérez-David (Spain), Janine Pöss (Germany), Bernard D. Prendergast (United Kingdom), Bianca Rocca (Italy), Xavier Rossello (Spain), Mikio Suzuki (Serbia), Holger Thiele (Germany), Christophe Michel Tribouilloy (France), Wojtek Wojakowski (Poland), and ESC/EACTS Scientific Document Group

* Corresponding authors: Fabien Praz, Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, Tel: +41 31 632 83 50, Email: fabien.praz@insel.ch and Michael A. Borger, University Clinic of Cardiac Surgery, Leipzig Heart Center, Leipzig, Germany, Tel: +49 341 865 1422, Email: michael.borger@helios-gesundheit.de

† The two Chairpersons contributed equally to the document and are joint corresponding authors.

‡ The two Task Force Co-ordinators contributed equally to the document.

Author/Task Force Member affiliations are listed in author information.

ESC Clinical Practice Guidelines (CPG) Committee: listed in the Appendix.

ESC subspecialty communities having participated in the development of this document:

Associations: Association for Acute CardioVascular Care (ACVC), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), and Heart Failure Association (HFA)

Working Groups: Cardiovascular Pharmacotherapy

Patient Forum

Table 1 **Classes of recommendations**

Classes of recommendations	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2 **Levels of evidence**

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

involved with the medical care of patients with this pathology and to include patient representatives and methodologists. The selection procedure included an open call for authors and aimed to include members from across the whole of the ESC region and from relevant ESC Subspecialty Communities. Consideration was given to diversity and inclusion.

Guidelines Task Forces perform a critical review and evaluation of the published literature on diagnostic and therapeutic approaches including assessment of the risk–benefit ratio. Recommendations are based on major randomized trials and relevant systematic reviews and meta-analyses, when available. Systematic literature searches are conducted in cases of controversy or uncertainty to ensure that all key studies were considered. For recommendations related to diagnosis and prognosis, additional types of evidence are included, such as diagnostic accuracy studies and studies focused on the development and validation of prognostic models. The strength of each recommendation and the level of evidence supporting it are weighed and scored according to pre-defined criteria as outlined in *Tables 1 and 2*. Patient-Reported Outcome Measures (PROMs) and Patient-Reported Experience Measures (PREMs) are also evaluated when available as the basis for recommendations and/or discussion in these guidelines.

Evidence tables summarizing key information from relevant studies are generated to facilitate the formulation of recommendations, to

enhance comprehension of recommendations after publication, and to reinforce transparency in the guidelines development process. The tables are published in their own section of the guidelines and reference specific recommendation tables.

After an iterative process of deliberations, a first Task Force vote on all recommendations is conducted prior to the initiation of rounds of review. A second Task Force vote on all recommendations is conducted after the final round of review and revision. For each vote, the Task Force follows ESC voting procedures and all recommendations require at least 75% agreement among voting members to be approved. Voting restrictions may be applied based on declarations of interests.

The writing and reviewing panels provide declaration-of-interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest are reviewed according to the ESC declaration-of-interest rules, which can be found on the ESC website (http://www.escardio.org/doi) and are compiled in a report published in a supplementary document with the guidelines. Funding for the development of these ESC/EACTS Guidelines was derived entirely from the ESC and the EACTS with no involvement of the healthcare industry.

The ESC CPG Committee supervises and co-ordinates the preparation of new guidelines and approves their publication. In addition to review by the ESC CPG Committee, these ESC/EACTS Guidelines underwent multiple rounds of double-blind peer review on a dedicated online review platform. The review was conducted by topic experts, including members from ESC National Cardiac Societies, EACTS Network of National Cardiac Surgery Societies and from relevant ESC Subspecialty Communities. The Guideline Task Force considered all review comments and was required to respond to all those classified as major. After appropriate revisions, the Task Force, the ESC CPG Committee members and the EACTS Council members approved the final document for publication in the *European Heart Journal* and in the *European Journal of Cardio-Thoracic Surgery*.

Unless otherwise stated, the guideline content refers to sex, understood as the biological condition of being male or female, defined by genes, hormones, and sexual organs. Off-label use of medication may be presented in this guideline if a sufficient level of evidence shows that it can be considered medically appropriate for a given condition. However, decisions on off-label use must be made by the responsible health professional giving special consideration to ethical rules concerning healthcare, the specific situation of the patient, patient consent, and country-specific health regulations.

2. Introduction

New evidence has accumulated since the publication of the *2021 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) Guidelines for the management of valvular heart disease*, leading to the need for new recommendations (*Table 3* New recommendations) and revision of existing recommendations (*Table 4* Revised recommendations) concerning the following topics:

- The importance of shared and patient-centred decision-making by multidisciplinary expert Heart Teams working within a regional network has been reinforced. Patients with complex conditions or requiring complex procedures should be referred to high-volume centres, where corresponding expertise is concentrated to ensure high-quality treatment.
- Advanced imaging modalities—such as three-dimensional (3D) echocardiography, cardiac computed tomography (CCT), and cardiac magnetic resonance (CMR) imaging—have gained importance and become a central aspect in the screening and evaluation of patients with valvular heart disease (VHD).
- Emphasis is put on the importance of correctly assessing the cause(s) and mechanism(s) of all valve diseases. In particular, the distinction between atrial and ventricular secondary mitral regurgitation (SMR) has clear implications in terms of prognosis and management.
- New evidence has been published regarding the benefits of intervention for the treatment of severe aortic stenosis (AS) irrespective of symptoms, left ventricular ejection fraction (LVEF), and flow reserve.
- The criteria used for decision-making concerning the optimal modality of AS treatment [transcatheter aortic valve (AV) implantation (TAVI) or surgical AV replacement (SAVR)] based on a Heart Team approach have been refined, including the combination of key aspects such as age, procedural risk, and anatomical suitability, incorporating estimated life expectancy and lifetime management considerations.
- Further randomized evidence confirming the mid-term safety and efficacy of TAVI in low-risk patients has been published.
- The indications for TAVI in patients with bicuspid AV (BAV) stenosis or severe aortic regurgitation (AR) at high surgical risk, based on anatomical suitability and a comprehensive Heart Team evaluation, are discussed.
- Several advancements have been made regarding the treatment of patients with primary mitral regurgitation (PMR): refinement of the criteria for intervention in asymptomatic patients; demonstration of the value of minimally invasive mitral valve (MV) surgery to reduce the length of hospital stay and accelerate recovery; and large-scale data confirming the role of transcatheter edge-to-edge repair (TEER) in high-risk patients.
- Longer-term follow-up data and two new randomized controlled trials (RCTs) concerning the management of patients with ventricular SMR have been published.
- The evidence for the treatment of tricuspid valve (TV) disease is growing—including new randomized data supporting concomitant TV repair during left-sided valve surgery, and transcatheter options (repair and replacement) that reduce tricuspid regurgitation (TR), promote reverse right ventricular (RV) remodelling, and improve quality of life compared with medical treatment.
- Efforts have been made to provide improved guidance regarding the diagnostic steps and management of patients with multiple and mixed VHD.
- Definitions of structural valve deterioration (SVD) have been updated and unified.
- The recommendations concerning the use of direct oral anticoagulants (DOACs) in patients with VHD have been updated, and the importance of education and (self-)monitoring is emphasized.
- Sex-specific considerations in patients with VHD have been extended and regrouped into a new dedicated section (see *Section 17*).

Because of demographic changes, patients with VHD frequently present with concomitant cardiovascular diseases, increasing the complexity of treatment strategies. These Guidelines focus on acquired

VHD and do not deal in detail with overlapping cardiovascular diseases such as infective endocarditis,[5] chronic coronary syndrome,[6] and atrial fibrillation (AF),[7] as well as all scenarios of aortic or congenital disease,[8,9] because these topics are covered in separate Guidelines.

The *2025 ESC/EACTS Guidelines for the management of valvular heart disease* aim to be concise, focused on relevant issues for clinicians and patients, and to provide clear and simple practical recommendations, assisting healthcare providers in their daily clinical decision-making. A compilation of the evidence considered for new recommendations, or those with an updated class of recommendation or level of evidence, can be consulted online (see Supplementary data online, *Evidence Tables*). The Task Force for these Guidelines acknowledges that multiple factors influence and ultimately determine the most appropriate treatment of individual patients within a given community. These factors include the availability of equipment and technology, and the expertise and volumes, in complex procedures, such as valve repair or transcatheter interventions. Moreover, given the lack of evidence on some topics related to VHD, several recommendations are the result of expert consensus opinion. Therefore, deviations from these Guidelines may be appropriate in certain clinical circumstances, and decision-making should always be based on a collaborative, multidisciplinary Heart Team approach centred on individual characteristics, needs, and prognosis, as well as the preferences of the informed patient.

2.1. What is new

Table 3 New recommendations

Recommendations	Class[a]	Level[b]
Diagnosis of coronary artery disease—*Section 6.1*		
Omission of invasive coronary angiography should be considered in TAVI candidates, if procedural planning CT angiography is of sufficient quality to rule out significant CAD.	IIa	B
PCI should be considered in patients with a primary indication to undergo TAVI and ≥90% coronary artery stenosis in segments with a reference diameter ≥2.5 mm.	IIa	B
Indications for intervention in severe aortic regurgitation—*Section 7.4*		
TAVI may be considered for the treatment of severe AR in symptomatic patients ineligible for surgery according to the Heart Team, if the anatomy is suitable.	IIb	B
Indications for intervention in symptomatic and asymptomatic severe aortic stenosis, and recommended mode of intervention—*Section 8.5*		
Intervention should be considered in asymptomatic patients (confirmed by a normal exercise test, if feasible) with severe, high-gradient AS and LVEF ≥50%, as an alternative to close active surveillance, if the procedural risk is low.	IIa	A
TAVI may be considered for the treatment of severe BAV stenosis in patients at increased surgical risk, if the anatomy is suitable.	IIb	B
Indications for intervention in severe primary mitral regurgitation—*Section 9.1*		
Surgical MV repair is recommended in low-risk asymptomatic patients with severe PMR without LV dysfunction (LVESD <40 mm, LVESDi <20 mm/m^2, and LVEF >60%) when a durable result is likely, if at least three of the following criteria are fulfilled: • AF • SPAP at rest >50 mmHg • LA dilatation (LAVI ≥60 mL/m^2 or LA diameter ≥55 mm) • Concomitant secondary TR ≥ moderate.	I	B
Minimally invasive MV surgery may be considered at experienced centres to reduce the length of stay and accelerate recovery.	IIb	B
Indications for intervention in secondary mitral regurgitation—*Section 9.2*		
MV surgery, surgical AF ablation, if indicated, and LAAO should be considered in symptomatic patients with severe atrial SMR under optimal medical therapy.	IIa	B
TEER may be considered in symptomatic patients with severe atrial SMR not eligible for surgery after optimization of medical therapy including rhythm control, when appropriate.	IIb	B
MV surgery may be considered in patients with moderate SMR undergoing CABG.	IIb	B
Indications for mitral valve surgery and transcatheter intervention in clinically severe rheumatic and degenerative mitral stenosis—*Section 10.3*		
TMVI may be considered in symptomatic patients with extensive MAC and severe MV dysfunction at experienced Heart Valve Centres with expertise in complex MV surgery and transcatheter interventions.	IIb	C

Continued

Indications for intervention in tricuspid regurgitation—*Section 11.4*		
Careful evaluation of TR aetiology, stage of the disease (i.e. degree of TR severity, RV and LV dysfunction, and PH), patient operative risk, and likelihood of recovery by a multidisciplinary Heart Team is recommended in patients with severe TR prior to intervention.	I	C
Surgery of concomitant severe mitral regurgitation—*Section 13.3*		
MV surgery is recommended in patients with severe MR undergoing surgery for another valve.	I	C
Indications for intervention in patients with mixed moderate aortic stenosis and moderate aortic regurgitation—*Section 13.3*		
Intervention is recommended in symptomatic patients with mixed moderate AV stenosis and moderate regurgitation, and a mean gradient ≥40 mmHg or V_{max} ≥4.0 m/s.	I	B
Intervention is recommended in asymptomatic patients with mixed moderate AV stenosis and moderate regurgitation, with V_{max} ≥4.0 m/s and LVEF <50% not attributable to other cardiac disease.	I	C
Prosthetic valve selection—*Section 14.1*		
An MHV should be considered in patients with an estimated long life expectancy, if there are no contraindications for long-term OAC.	IIa	B
Management of antithrombotic therapy in patients with a mechanical heart valve—*Section 14.3*		
It is recommended that INR targets are based on the type and position of MHV, patient's risk factors, and comorbidities.	I	A
Patient education is recommended to improve the quality of OAC.	I	A
Management of antithrombotic therapy in patients with mechanical heart valves undergoing elective non-cardiac surgery or invasive procedures—*Section 14.3*		
Continuing VKA treatment is recommended in patients with an MHV for minor or minimally invasive interventions associated with no or minimal bleeding.	I	A
Interruption (3–4 days before surgery), and resumption of VKA without bridging, may be considered to reduce bleeding in patients with new-generation aortic MHV and no other thromboembolic risk factors undergoing major non-cardiac surgery or invasive procedures.	IIb	B
Management of antithrombotic therapy in patients with a biological heart valve or valve repair—*Section 14.3*		
Surgical biological heart valve without indication for oral anticoagulation		
Lifelong low-dose ASA (75–100 mg/day) may be considered 3 months after surgical implantation of an aortic or mitral BHV in patients without clear indication for OAC.	IIb	C
Transcatheter aortic valve implantation without indication for oral anticoagulation		
DAPT is not recommended to prevent thrombosis after TAVI, unless there is a clear indication.	III	B
Surgical repair without indication for oral anticoagulation		
Low-dose ASA (75–100 mg/day) may be considered after surgical MV or TV repair in preference to OAC in patients without clear indication for OAC and at high bleeding risk.	IIb	B
Surgical biological heart valve with indication for oral anticoagulation		
OAC continuation is recommended in patients with a clear indication for OAC undergoing surgical BHV implantation.	I	B
DOAC continuation may be considered after surgical BHV implantation in patients with an indication for DOAC.	IIb	B
Surgical repair with indication for oral anticoagulation and/or antiplatelet therapy		
Continuation of OAC or antiplatelet therapy should be considered after surgical valve repair in patients with a clear indication for an antithrombotic therapy.	IIa	B
Management of mechanical heart valve failure—*Section 14.4*		
Reoperation is recommended in symptomatic patients with significant valve dysfunction not attributable to valve thrombosis.	I	C
Management of valve thrombosis—*Section 14.4*		
TOE and/or 4D-CT are recommended in patients with suspected valve thrombosis to confirm the diagnosis.	I	C

4D, four-dimensional; AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; ASA, acetylsalicylic acid; AV, aortic valve; BAV, bicuspid aortic valve; BHV, biological heart valve; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CT, computed tomography; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; INR, international normalized ratio; LA, left atrium/left atrial; LAAO, left atrial appendage occlusion; LAVI, left atrial volume index; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to body surface area; MAC, mitral annular calcification; MHV, mechanical heart valve; MR, mitral regurgitation; MV, mitral valve; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; PH, pulmonary hypertension; PMR, primary mitral regurgitation; RV, right ventricle/right ventricular; SMR, secondary mitral regurgitation; SPAP, systolic pulmonary artery pressure; TAVI, transcatheter aortic valve implantation; TEER, transcatheter edge-to-edge repair; TMVI, transcatheter mitral valve implantation; TOE, transoesophageal echocardiography; TR, tricuspid regurgitation; TV, tricuspid valve; VKA, vitamin K antagonist; V_{max}, peak transvalvular velocity.
[a]Class of recommendation.
[b]Level of evidence.

Table 4 Revised recommendations

Recommendations in 2021 version	Class[a]	Level[b]	Recommendations in 2025 version	Class[a]	Level[b]
Management of coronary artery disease in patients with valvular heart disease—*Section 6.1*					
CCTA should be considered as an alternative to coronary angiography before valve surgery in patients with severe VHD and low probability of CAD.	IIa	C	CCTA is recommended before valve intervention in patients with moderate or lower (≤50%) pre-test likelihood of obstructive CAD.	I	B
Coronary angiography is recommended before valve surgery in patients with severe VHD and any of the following: • History of cardiovascular disease • Suspected myocardial ischaemia • LV systolic dysfunction • In men >40 years of age and post-menopausal women • One or more cardiovascular risk factors.	I	C	Invasive coronary angiography is recommended before valve intervention in patients with high and very high (>50%) pre-test likelihood of obstructive CAD.	I	C
Coronary angiography is recommended in the evaluation of severe SMR.	I	C	Invasive coronary angiography is recommended in the evaluation of CAD in patients with severe ventricular SMR.	I	C
PCI should be considered in patients with a primary indication to undergo TAVI and coronary artery diameter stenosis >70% in proximal segments.	IIa	C	PCI may be considered in patients with a primary indication to undergo transcatheter valve interventions and coronary artery stenosis ≥70% in proximal segments of main vessels.	IIb	B
PCI should be considered in patients with a primary indication to undergo transcatheter MV intervention and coronary artery diameter stenosis >70% in proximal segments.	IIa	C			
Management of atrial fibrillation in patients with native valvular heart disease—*Section 6.2*					
LAAO should be considered to reduce the thromboembolic risk in patients with AF and a CHA_2DS_2-VASc score ≥2 undergoing valve surgery.	IIa	B	Surgical closure of the LA appendage is recommended as an adjunct to OAC in patients with AF undergoing valve surgery to prevent cardioembolic stroke and systemic thromboembolism.	I	B
Concomitant AF ablation should be considered in patients undergoing valve surgery, balancing the benefits of freedom from atrial arrhythmias and the risk factors for recurrence (LA dilatation, years in AF, age, renal dysfunction, and other cardiovascular risk factors).	IIa	A	Concomitant surgical ablation is recommended in patients undergoing MV surgery with AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, according to an experienced team of electrophysiologists and arrhythmia surgeons.	I	A
			Concomitant surgical ablation should be considered in patients undergoing non-MV surgery with AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, according to an experienced team of electrophysiologists and arrhythmia surgeons.	IIa	B
The use of DOACs is not recommended in patients with AF and moderate-to-severe MS.	III	C	The use of DOACs is not recommended in patients with AF and rheumatic MS with an MVA ≤2.0 cm^2.	III	B
Indications for surgery in severe aortic regurgitation—*Section 7.4*					
AV repair may be considered in selected patients at experienced centres when durable results are expected.	IIb	C	AV repair should be considered in selected patients with severe AR at experienced centres, when durable results are expected.	IIa	B
Surgery may be considered in asymptomatic patients with LVESD >20 mm/m^2 BSA (especially in patients with small body size) or resting LVEF ≤55%, if surgery is at low risk.	IIb	C	AV surgery may be considered in asymptomatic patients with severe AR and LVESDi >22 mm/m^2 or LVESVi >45 mL/m^2 [especially in patients with small body size (BSA <1.68 m^2)], or resting LVEF ≤55%, if surgical risk is low.	IIb	B
Indications for intervention in symptomatic severe aortic stenosis—*Section 8.4.1*					
Intervention is recommended in symptomatic patients with severe low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) AS with reduced LVEF (<50%), and evidence of flow (contractile) reserve.	I	B	Intervention is recommended in symptomatic patients with low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) AS with reduced LVEF (<50%) after careful confirmation that AS is severe.	I	B

Continued

Intervention should be considered in symptomatic patients with low-flow, low-gradient (<40 mmHg) AS with normal LVEF after careful confirmation that the AS is severe.	IIa	C	Intervention should be considered in symptomatic patients with low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) AS with normal LVEF (≥50%) after careful confirmation that AS is severe.	IIa	B
Indications for intervention in asymptomatic severe aortic stenosis—*Section 8.5*					
Intervention should be considered in asymptomatic patients with severe AS and LV dysfunction (LVEF <55%) without another cause.	IIa	B	Intervention should be considered in asymptomatic patients with severe AS and LVEF ≥50%, if the procedural risk is low and one of the following parameters is present: • Very severe AS (mean gradient ≥60 mmHg or V_{max} >5.0 m/s). • Severe valve calcification (ideally assessed by CCT) and V_{max} progression ≥0.3 m/s/year. • Markedly elevated BNP/NT-proBNP levels (more than three times age- and sex-corrected normal range, confirmed on repeated measurement without other explanation). • LVEF <55% without another cause.	IIa	B
Intervention should be considered in asymptomatic patients with LVEF >55% and a normal exercise test if the procedural risk is low and one of the following parameters is present: • Very severe AS (mean gradient ≥60 mmHg or V_{max} >5 m/s). • Severe valve calcification (ideally assessed by CCT) and V_{max} progression ≥0.3 m/s/year. • Markedly elevated BNP levels (more than three times age- and sex-corrected normal range) confirmed by repeated measurements and without other explanation.	IIa	B			
Mode of intervention in symptomatic severe aortic stenosis—*Section 8.5*					
The choice between surgical and transcatheter intervention must be based upon careful evaluation of clinical, anatomical, and procedural factors by the Heart Team, weighing the risks and benefits of each approach for an individual patient. The Heart Team recommendation should be discussed with the patient who can then make an informed treatment choice.	I	C	It is recommended that the mode of intervention is based on Heart Team assessment of individual clinical, anatomical, and procedural characteristics, incorporating lifetime management considerations and estimated life expectancy.	I	C
TAVI is recommended in older patients (≥75 years), or in those who are high risk (STS-PROM/EuroSCORE II >8%) or unsuitable for surgery.	I	A	TAVI is recommended in patients ≥70 years of age with tricuspid AV stenosis, if the anatomy is suitable.	I	A
SAVR is recommended in younger patients who are low risk for surgery (<75 years and STS-PROM/EuroSCORE II <4%), or in patients who are operable and unsuitable for transfemoral TAVI.	I	B	SAVR is recommended in patients <70 years of age, if the surgical risk is low.	I	B
SAVR or TAVI are recommended for remaining patients according to individual clinical, anatomical, and procedural characteristics.	I	B	SAVR or TAVI are recommended for all remaining candidates for an aortic BHV according to Heart Team assessment.[1–4]	I	B
Non-transfemoral TAVI may be considered in patients who are inoperable and unsuitable for transfemoral TAVI.	IIb	C	Non-transfemoral TAVI should be considered in patients who are unsuitable for surgery and transfemoral access.	IIa	B
Indications for intervention in severe primary mitral regurgitation—*Section 9.1.4*					
Surgery should be considered in asymptomatic patients with preserved LV function (LVESD <40 mm and LVEF >60%) and AF secondary to MR or PH (SPAP at rest >50 mmHg).	IIa	B	MV surgery should be considered in asymptomatic patients with severe PMR without LV dysfunction (LVESD <40 mm, LVESDi <20 mm/m^2, and LVEF >60%) in the presence of PH (SPAP at rest >50 mmHg), or AF secondary to MR.	IIa	B
Surgical MV repair should be considered in low-risk asymptomatic patients with LVEF >60%, LVESD <40 mm, and significant LA dilatation (volume index ≥60 mL/m^2 or diameter ≥55 mm) when performed in a Heart Valve Centre and a durable repair is likely.	IIa	B	Surgical MV repair should be considered in low-risk asymptomatic patients with severe PMR without LV dysfunction (LVESD <40 mm, LVESDi <20 mm/m^2, and LVEF >60%) in the presence of significant LA dilatation (LAVI ≥60 mL/m^2 or LA diameter ≥55 mm), when performed in a Heart Valve Centre and a durable repair is likely.	IIa	B

Continued

TEER may be considered in symptomatic patients who fulfil the echocardiographic criteria of eligibility, are judged inoperable or at high surgical risk by the Heart Team, and for whom the procedure is not considered futile.	IIb	B	TEER should be considered in symptomatic patients with severe PMR who are anatomically suitable and at high surgical risk according to the Heart Team.	IIa	B
Severe ventricular secondary mitral regurgitation and concomitant coronary artery disease—*Section 9.2*					
In symptomatic patients who are judged not appropriate for surgery by the Heart Team on the basis of their individual characteristics, PCI (and/or TAVI) possibly followed by TEER (in case of persisting severe SMR) should be considered.	IIa	C	PCI followed by TEER after re-evaluation of MR may be considered in symptomatic patients with chronic severe ventricular SMR and non-complex CAD.	IIb	C
Indications for intervention in severe ventricular secondary mitral regurgitation without concomitant coronary artery disease—*Section 9.2*					
TEER should be considered in selected symptomatic patients not eligible for surgery and fulfilling criteria suggesting an increased chance of responding to the treatment.	IIa	B	TEER is recommended to reduce HF hospitalizations and improve quality of life in haemodynamically stable, symptomatic patients with impaired LVEF (<50%) and persistent severe ventricular SMR, despite optimized GDMT and CRT (if indicated), fulfilling specific clinical and echocardiographic criteria.	I	A
In high-risk symptomatic patients not eligible for surgery and not fulfilling the criteria suggesting an increased chance of responding to TEER, the Heart Team may consider in selected cases a TEER procedure or other transcatheter valve therapy if applicable, after careful evaluation for ventricular assist device or heart transplant.	IIb	C	TEER may be considered for symptom improvement in selected symptomatic patients with severe ventricular SMR not fulfilling the specific clinical and echocardiographic criteria, after careful evaluation of LVAD or HTx.	IIb	B
Valve surgery may be considered in symptomatic patients judged appropriate for surgery by the Heart Team.	IIb	C	MV surgery may be considered in symptomatic patients with severe ventricular SMR without advanced HF who are not suitable for TEER.	IIb	C
Indications for intervention in tricuspid regurgitation in patients with left-sided valvular heart disease requiring surgery—*Section 11.4*					
Surgery is recommended in patients with severe primary TR undergoing left- sided valve surgery.	I	C	Concomitant TV surgery is recommended in patients with severe primary or secondary TR.	I	B
Surgery is recommended in patients with severe secondary TR undergoing left-sided valve surgery.	I	B			
Surgery should be considered in patients with moderate primary TR undergoing left-sided valve surgery.	IIa	C	Concomitant TV repair should be considered in patients with moderate primary or secondary TR, to avoid progression of TR and RV remodelling.	IIa	B
Surgery should be considered in patients with mild or moderate secondary TR with a dilated annulus (≥40 mm or >21 mm/m^2 by 2D echocardiography) undergoing left-sided valve surgery.	IIa	B	Concomitant TV repair may be considered in selected patients with mild secondary TR and tricuspid annulus dilatation (≥40 mm or >21 mm/m^2) to avoid progression of TR and RV remodelling.	IIb	B
Indications for intervention in patients with severe tricuspid regurgitation without left-sided valvular heart disease requiring surgery—*Section 11.4*					
Transcatheter treatment of symptomatic secondary severe TR may be considered in inoperable patients at a Heart Valve Centre with expertise in the treatment of TV disease.	IIb	C	Transcatheter TV treatment should be considered to improve quality of life and RV remodelling in high-risk patients, with symptomatic severe TR despite optimal medical therapy, in the absence of severe RV dysfunction or pre-capillary PH.	IIa	A
Prosthetic valve selection—*Section 14.1*					
A mechanical prosthesis may be considered in patients already on long-term anticoagulation due to the high risk for thromboembolism.	IIb	C	An MHV may be considered in patients with a clear indication for long-term OAC.	IIb	C
Management of antithrombotic therapy in patients with a mechanical heart valve—*Section 14.3*					
OAC using a VKA is recommended lifelong for all patients with an MHV prosthesis.	I	B	Lifelong OAC with a VKA is recommended for all patients with MHVs to prevent thromboembolic complications.	I	A

Continued

For patients with a VKA, INR self-management is recommended provided appropriate training and quality control are performed.	I	B	INR self-monitoring and self-management are recommended over standard monitoring in selected, trained patients to improve efficacy.	I	A
In patients with MHVs, it is recommended to (re)initiate the VKA on the first post-operative day.	I	C	Following cardiac surgery with MHV implantation, it is recommended to start UFH or LMWH bridging and VKA within 24 h, or as soon as considered safe.	I	B
In patients who have undergone valve surgery with an indication for post-operative therapeutic bridging, it is recommended to start either UFH or LMWH 12–24 h after surgery.	I	C			
The addition of low-dose ASA (75–100 mg/day) to VKA may be considered in selected patients with MHVs in case of concomitant atherosclerotic disease and low risk of bleeding.	IIb	C	The addition of low-dose ASA (75–100 mg/day) to VKA should be considered in selected patients with MHVs in case of concomitant symptomatic atherosclerotic disease, considering the individual bleeding risk profile.	IIa	B
The addition of low-dose ASA (75–100 mg/day) to VKA should be considered after thromboembolism despite an adequate INR.	IIa	C	Either an increase in INR target or the addition of low-dose ASA (75–100 mg/day) should be considered in patients with MHVs who develop a major thromboembolic complication despite documented adequate INR.	IIa	C
DOACs are not recommended in patients with an MHV prosthesis.	III	B	DOACs and/or DAPT are not recommended to prevent thrombosis in patients with an MHV.	III	A
Management of antithrombotic therapy in patients with mechanical heart valves undergoing elective non-cardiac surgery or invasive procedures—*Section 14.3*					
It is recommended that VKAs are timely discontinued prior to elective surgery to aim for an INR <1.5.	I	C	It is recommended to discontinue VKA at least 4 days before major elective non-cardiac surgery, aiming for an INR <1.5, and to resume VKA treatment within 24 h after surgery, or as soon as considered safe.	I	B
In patients with MHVs, it is recommended to (re)initiate the VKA on the first post-operative day.	I	C			
Therapeutic doses of either UFH or subcutaneous LMWH are recommended for bridging.	I	B	VKA interruption and resumption with bridging should be considered in patients with an MHV and thromboembolic risk factors undergoing major non-cardiac surgery.	IIa	B
Bridging of OAC, when interruption is needed, is recommended in patients with any of the following indications: • MHV • AF with significant MS • AF with CHA_2DS_2-VASc score ≥3 for women or 2 for men • Acute thrombotic event within the previous 4 weeks • High acute thromboembolic risk.	I	C			
Management of antithrombotic therapy in patients with a biological heart valve or valve repair—*Section 14.3*					
Lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC.	I	A	Low-dose ASA (75–100 mg/day) is recommended for 12 months after TAVI in patients without indication for OAC.	I	A
			Long-term (after the first 12 months) low-dose ASA (75–100 mg/day) should be considered after TAVI in patients without clear indication for OAC.	IIa	C
OAC is recommended lifelong for TAVI patients who have other indications for OAC.	I	B	OAC is recommended for TAVI patients who have other indications for OAC.	I	B
OAC with VKA should be considered during the first 3 months after mitral and tricuspid repair.	IIa	C	OAC, with either VKAs or DOACs, should be considered during the first 3 months after surgical MV or TV repair.	IIa	B
Routine use of OAC is not recommended after TAVI in patients without baseline indication.	III	B	Routine use of OAC is not recommended after TAVI in patients without baseline indication.	III	A
Management of haemolysis and paravalvular leak—*Section 14.4*					
Decision on transcatheter or surgical closure of clinically significant PVLs should be considered based on patient risk status, leak morphology, and local expertise.	IIa	C	It is recommended that the decision between transcatheter or surgical closure of clinically significant PVLs is based on Heart Team evaluation, including patient risk, leak morphology, and local expertise.	I	C

Continued

Transcatheter closure should be considered for suitable PVLs with clinically significant regurgitation and/or haemolysis in patients at high or prohibitive surgical risk.	IIa	B	Transcatheter closure should be considered for suitable PVLs with clinically significant regurgitation and/or haemolysis.	IIa	B
Management of biological heart valve failure—*Section 14.4*					
Reoperation is recommended in symptomatic patients with a significant increase in transprosthetic gradient (after exclusion of valve thrombosis) or severe regurgitation.	I	C	Reintervention is recommended in symptomatic patients with significant valve dysfunction not attributable to valve thrombosis.	I	C
Transcatheter, transfemoral valve-in-valve implantation in the aortic position should be considered by the Heart Team depending on anatomical considerations, features of the prosthesis, and in patients who are at high operative risk or inoperable.	IIa	B	Transcatheter transfemoral valve-in-valve implantation in the aortic position should be considered in patients with significant valve dysfunction who are at intermediate or high surgical risk, and have suitable anatomical and prosthesis features, as assessed by the Heart Team.	IIa	B
Transcatheter valve-in-valve implantation in the mitral and tricuspid position may be considered in selected patients at high risk for surgical reintervention.	IIb	B	Transcatheter transvenous mitral or tricuspid valve-in-valve implantation should be considered in patients with significant valve dysfunction at intermediate or high surgical risk, if the anatomy is suitable.	IIa	B
Management of mechanical heart valve thrombosis—*Section 14.4*					
Urgent or emergency valve replacement is recommended for obstructive thrombosis in critically ill patients without serious comorbidity.	I	B	Heart Team evaluation is recommended in patients with acute HF (NYHA class III or IV) due to obstructive MHV thrombosis to determine appropriate management (repeat valve replacement or low-dose slow infusion fibrinolysis).	I	B
Fibrinolysis (using recombinant tissue plasminogen activator 10 mg bolus + 90 mg in 90 min with UFH or streptokinase 1 500 000 U in 60 min without UFH) should be considered when surgery is not available or is very high risk, or for thrombosis of right-sided prostheses.	IIa	B			
Management of biological heart valve thrombosis—*Section 14.4*					
Anticoagulation using a VKA and/or UFH is recommended in BHV thrombosis before considering reintervention.	I	C	OAC using VKA is recommended in BHV thrombosis before considering reintervention.	I	B

2D, two-dimensional; AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; ASA, acetylsalicylic acid; AV, aortic valve; BHV, biological heart valve; BNP, brain natriuretic peptide; BSA, body surface area; CAD, coronary artery disease; CCT, cardiac computed tomography; CCTA, coronary computed tomography angiography; CHA_2DS_2-VASc, congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, sex category (female); CRT, cardiac resynchronization therapy; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GDMT, guideline-directed medical therapy; h, hour; HF, heart failure; HTx, heart transplantation; INR, international normalized ratio; LA, left atrium/left atrial; LAAO, left atrial appendage occlusion; LAVI, left atrial volume index; LMWH, low-molecular-weight heparin; LV, left ventricle/left ventricular; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to BSA; LVESVi, left ventricular end-systolic volume indexed to BSA; MHV, mechanical heart valve; min, minute; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; MVA, mitral valve area; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; PH, pulmonary hypertension; PMR, primary mitral regurgitation; PVL, paravalvular leak; RV, right ventricle/right ventricular; SAPT, single antiplatelet therapy; SAVR, surgical aortic valve replacement; SMR, secondary mitral regurgitation; SPAP, systolic pulmonary artery pressure; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality; SVi, stroke volume index; TAVI, transcatheter aortic valve implantation; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation; TV, tricuspid valve; UFH, unfractionated heparin; VHD, valvular heart disease; VKA, vitamin K antagonist; V_{max}, peak transvalvular velocity.
[a]Class of recommendation.
[b]Level of evidence.

3. The Heart Team and Heart Valve Centre

3.1. The Heart Valve Network

Despite increasing attention within the medical community, VHD continues to be underdiagnosed and undertreated in the general population, and public awareness remains low.[10–13] Beside screening using auscultation and imaging when appropriate, the co-ordinated implementation of Heart Teams, Heart Valve Centres, and Heart Valve Networks at a local level represents an essential step to timely diagnose and treat patients with VHD.

An integrated regional Heart Valve Network, incorporating outpatient Heart Valve Clinics (for initial diagnosis and ongoing surveillance) and specialist Heart Valve Centres (for advanced imaging and surgical or transcatheter intervention), allows optimal patient care through timely access to specialist assessment, accurate diagnosis, improved decision-making, and matching of patients to healthcare providers with appropriate expertise, experience, and resources (*Figure 1*).[12] In addition, dedicated Heart Valve Clinics ensure consistent application of clinical guidelines, efficient use of resources, and overall high-quality patient care, which in turn may improve outcomes.[14,15] Medical goals include careful clinical and echocardiographic evaluation, monitoring at appropriate time intervals (so-called 'watchful waiting'), application

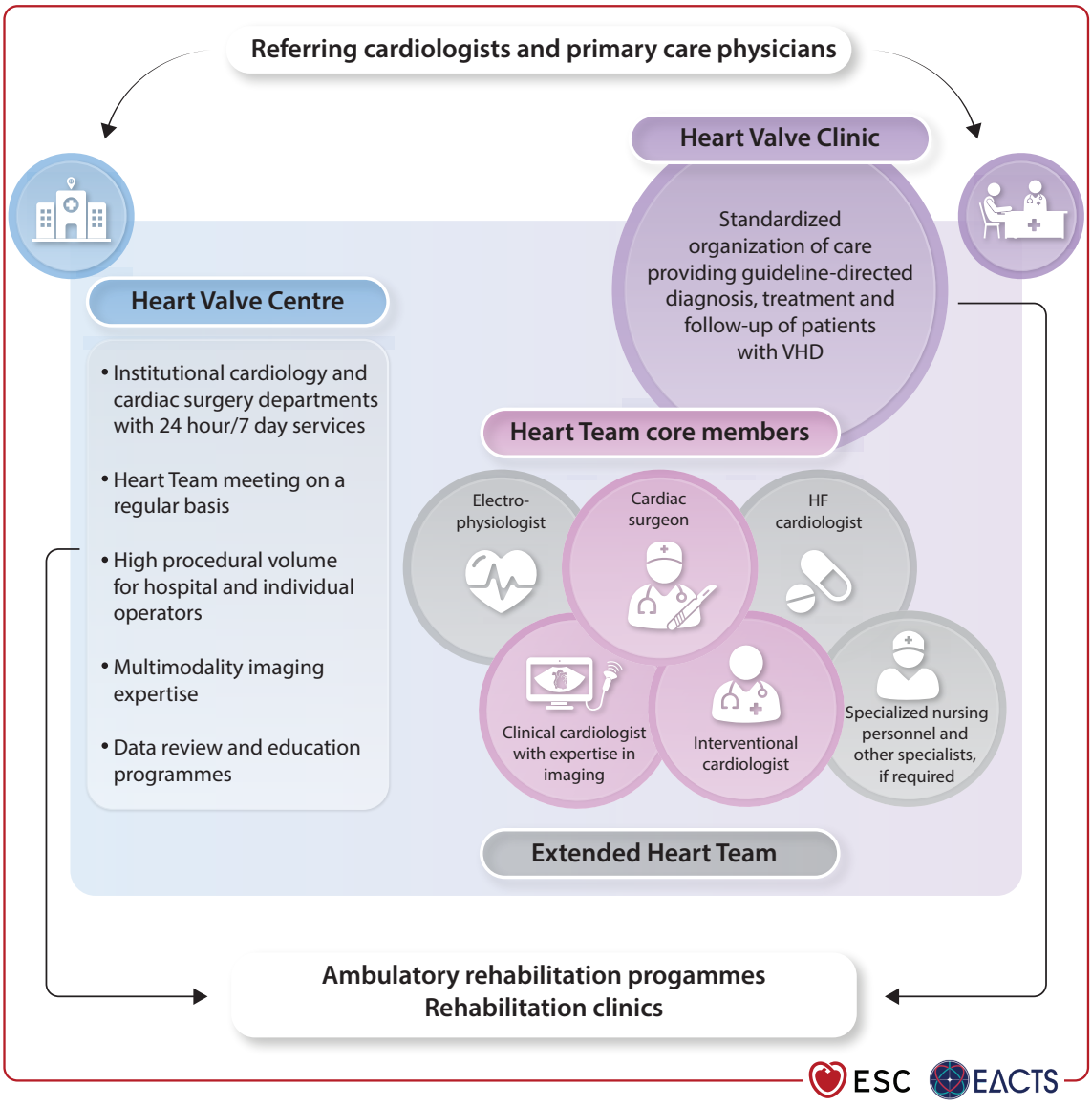

Figure 1 The Heart Valve Network. HF, heart failure; VHD, valvular heart disease.

of guideline-directed medical therapy (GDMT), timely referral, and post-procedural follow-up.[15,16] Broader aims include patient education, the training of physicians and nurse specialists, swift and efficient access to specialist care, and recruitment into clinical trials.

Heart Valve Centres should ensure that their facilities match institutional and local statutory requirements (*Table 5*), report procedural volumes and outcomes, and monitor treatment quality. They hold responsibility for the training and education of surgeons, interventional and imaging cardiologists, dedicated nurses, and allied professionals.[17,18] Expertise in the surgical management of coronary artery disease (CAD), vascular diseases, and complications must be available. New techniques should be taught by trained mentors using simulator models, when feasible, to minimize learning-curve effects. More broadly, Heart Valve Centres co-ordinate the management of patients with VHD across the entire Heart Valve Network, supporting services at community level, encouraging early referral, and promoting education and communication with other medical departments, referring cardiologists, primary care physicians, and rehabilitation clinics.

3.1.1. Composition of the Heart Team

The Heart Team is now an established feature of VHD programmes that has been formally endorsed by previous ESC/EACTS Guidelines[19,20] and corresponding organizations worldwide.[17]

The value of the Heart Team approach has become increasingly apparent as options for the treatment of VHD have extended to include high-risk and inoperable patients (most of whom now undergo transcatheter interventions), and low-risk and asymptomatic patients (who derive prognostic benefit from increasingly safe procedures). Despite significant accumulation of data concerning the management of VHD over the last two decades, many patients in daily practice have clinical characteristics that do not match those of participants included in clinical trials. The Heart Team approach is therefore particularly helpful when there is uncertainty or a lack of strong evidence.

The Heart Team meeting facilitates balanced presentation of all appropriate options for medical, interventional, and surgical treatment, using tools and techniques for shared decision-making.

The patient's preference plays a central role in this process, although the Heart Team recommendation should be based upon key objective medical considerations (particularly the relative risks and benefits of any procedure).

Meetings should take place on a regular basis with standardized minimum datasets (to ensure that all relevant information is available) and appropriate administrative support (often provided by specialist nurses with expertise in the care of patients with VHD). In-person meetings of the full Heart Team may not be feasible for every patient, and local standardized protocols may be implemented to facilitate swift decision-making for specific cohorts (e.g. elderly TAVI candidates or young patients with BAV disease). Equally, the need for Heart Team evaluation should not paralyse clinical decision-making, and *ad hoc* discussions remain appropriate in urgent situations.

Core members of the Heart Team include the cardiologist treating the patient (who is best placed to present their case and act as their advocate), specialists in advanced cardiovascular imaging and peri-procedural guiding,[21,22] surgeons, and interventional cardiologists with training and expertise in surgical and transcatheter valve procedures. Specialized nursing personnel play an essential role to improve patient information and education, as well as co-ordinate work-up and management steps in high-volume centres (*Figure 1*; *Table 5*). Cardiologists with expertise in heart failure (HF) and electrophysiology, as well as geriatricians, cardiovascular anaesthetists, and intensivists involved in peri-procedural care, should also be available to facilitate the discussion of particularly complex clinical scenarios when needed (extended Heart Team) (*Figure 1*; *Table 5*).

Table 5 Requirements for a Heart Valve Centre

Requirements
Centre performing heart valve procedures with on-site interventional cardiology and cardiac surgery departments providing 24-h/7-day services. **Heart Team core members:** Cardiologist with imaging expertise, interventional cardiologist, cardiac surgeon. **Additional specialists, if required (Extended Heart Team):** Specialized nursing personnel, HF specialist, electrophysiologist, cardiovascular anaesthetist, geriatrician, and other specialists (e.g. intensive care, vascular surgery, infectious diseases, neurology, radiology). The Heart Team must meet on a regular basis and work according to locally defined standard operating procedures and clinical governance arrangements. A hybrid cardiac catheterization laboratory is desirable. High volume for hospital and individual operators.
Multimodality imaging (including advanced echocardiography, CCT, CMR, and nuclear techniques) and expertise in peri-procedural imaging guidance of surgical and transcatheter procedures.
Heart Valve Clinic for outpatient assessment and follow-up.
Data review: continuous monitoring, evaluation, and reporting of procedural volumes and quality indicators, including clinical outcomes, as well as PROMs complemented by local/external audits. Education programmes targeting primary care and referring physicians, operators, and diagnostic and interventional imaging specialists.

CCT, cardiac computed tomography; CMR, cardiac magnetic resonance; HF, heart failure; PROM, patient-reported outcome measure.

3.1.2. Procedural volume and clinical outcomes

The correlation between high institutional (and individual operator) volume and best procedural outcomes is intuitive, yet complex. Nevertheless, there is evidence of such a relationship for many cardiovascular procedures including SAVR,[23,24] surgical MV repair,[25,26] mitral and tricuspid TEER,[27–30] and TAVI (particularly in centres with an associated high-volume SAVR programme).[31–33] Studies have shown that an annualized operator volume of approximately 25 surgical mitral valve procedures,[26] 50 TAVIs (~100 per centre),[33] a cumulative experience of ~50 M-TEER procedures per operator/centre,[27] and a site volume of more than 20 T-TEERs/year[30] are associated with improved technical and clinical outcomes. Higher institutional surgical volume is associated with lower complication rates,[34–36] improved management,[37] and better infrastructural support.[38,39]

National procedural activity varies widely between high-, middle-, and low-income countries,[40] and it is therefore difficult to provide recommendations concerning the precise number of institutional or operator procedures that is required for high-quality care, excellent facilities, and processes. Instead, a network approach that highlights the importance of centres performing a high volume of procedures (e.g. based upon quartiles in individual countries or regions) seems more suitable, with complex procedures concentrated in the centres with the highest volumes (*Table 6*).

Table 6 Complex procedures ideally performed in the most experienced Heart Valve Centres

Transcatheter interventions	Surgical interventions
• Transfemoral TAVI in patients with high-risk features: – Low coronary ostia – Difficult femoral anatomy – Bicuspid valve – Severe calcification protruding into the LVOT – Severe LV and/or RV impairment – Pure AV regurgitation – Multiple valve disease – Complex coronary artery disease – Severe extracardiac disease (e.g. renal failure, PH) • Non-transfemoral TAVI • Valve-in-valve (including TAV-in-TAV) • All leaflet modification procedures (BASILICA, LAMPOON etc.) • PVL closure procedures • Complex M-TEER[a] • Redo M-TEER procedures • Tricuspid or mitral valve-in-ring or valve-in-valve, valve-in-MAC • TMVI • All tricuspid procedures	• High-risk procedures (especially in patients with LV and/or RV impairment) • Redo procedures • Minimally invasive and robotic valve surgery • Complex MV repair – Barlow disease – Anterior or bileaflet prolapse – High risk of SAM – Severe MAC • AV repair • Ross procedure • Valve surgery combined with complex surgery of the aorta • Endocarditis surgery

AV, aortic valve; BASILICA, Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction; LAMPOON, Laceration of the Anterior Mitral leaflet to Prevent Outflow ObstructioN; LV, left ventricular/left ventricle; LVOT, left ventricular outflow tract; MAC, mitral annular calcification; M-TEER, mitral transcatheter edge-to-edge repair; MV, mitral valve; PH, pulmonary hypertension; PVL: paravalvular leak; RV, right ventricular/right ventricle; SAM, systolic anterior movement; TAV, transcatheter aortic valve; TAVI, transcatheter aortic valve implantation; TMVI, transcatheter mitral valve implantation.
[a]See Supplementary Table S2.

Internal quality assessment (see dedicated document concerning TAVI from the ESC[41]), systematic recording, and public availability of the volume and outcome data of the performed procedures are essential. Participation in national or international registries should be encouraged. These considerations are of particular importance regarding asymptomatic low-risk patients (where low mortality and procedural safety are paramount), those with multiple comorbidities (where the need for multidisciplinary collaboration is essential), and new techniques with a steep learning curve (where better results may be obtained at experienced centres).

There is a pressing need to ensure higher dispersion and adoption of interventions for VHD, especially (but not exclusively) in middle- and lower-income countries where rheumatic heart disease (RHD) remains the principal cause of VHD.[42,43] Key strategies include awareness programmes, increased public and medical education, simplified and improved diagnostic tools, and measures to reduce costs and facilitate access to evidence-based treatment options.[44]

4. Imaging of patients with valvular heart disease

Multimodality imaging is now the standard approach in VHD management to determine the pathophysiology, assess severity, plan interventions, and identify complications (*Figure 2*). The use of imaging for the assessment of each specific valve lesion is described in the corresponding sections. The role of imaging is transversal from diagnosis to follow-up and should encompass an integrative assessment.

4.1. Initial valve assessment

Comprehensive transthoracic echocardiography (TTE) is the first-line examination to confirm valve dysfunction, and determine the aetiology, mechanism, and severity of VHD, as well as cardiac chamber anatomy and damage.[45,46] It should be performed by properly trained imagers.[47–49] Quantitative imaging analysis (as opposed to visual) should be the goal in all patients with relevant VHD, complemented by qualitative and semi-quantitative evaluation. The severity of VHD should be assessed using an integrative approach of all criteria checked for consistency. When TTE is of poor quality or inconclusive, transoesophageal echocardiography (TOE) and/or additional diagnostic imaging modalities should be applied (e.g. calcium scoring and anatomy of the valve using CCT). In specific clinical scenarios [e.g. thrombosis, prosthetic valve dysfunction, endocarditis, mitral stenosis (MS), assessment of MV or TV anatomy], TOE has a central diagnostic role.[50,51]

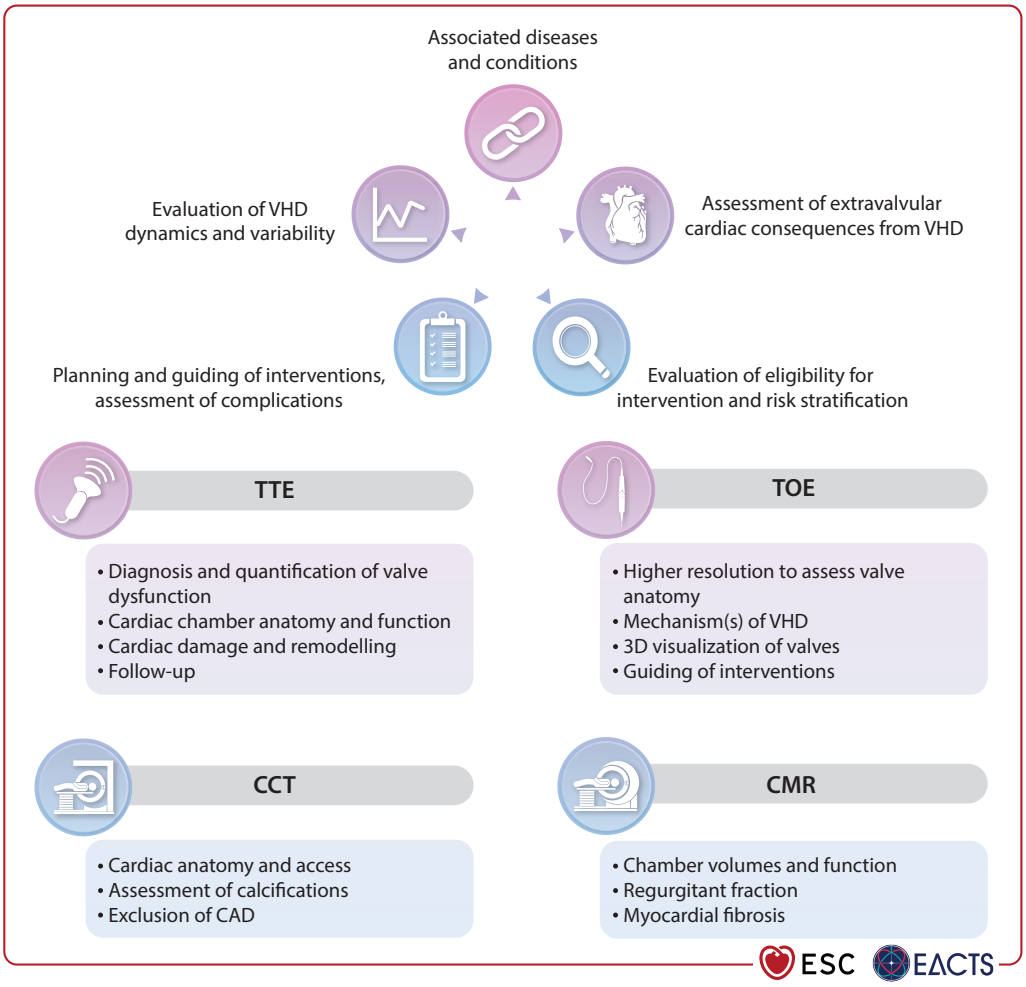

Figure 2 Integrative imaging assessment of patients with valvular heart disease. 3D, three-dimensional; CAD, coronary artery disease; CCT, cardiac computed tomography; CMR: cardiac magnetic resonance; TOE; transoesophageal echocardiography; TTE, transthoracic echocardiography; VHD, valvular heart disease.

Moreover, in patients with regurgitant lesions, particularly AR, CMR has gained key value in clinical practice.

4.2. Associated diseases and conditions

Imaging plays a crucial role in identifying associated diseases and conditions. The presence of concomitant left ventricular (LV) systolic or diastolic dysfunction, RV systolic dysfunction, red flags indicating cardiomyopathies (e.g. amyloidosis, hypertrophic cardiomyopathy), and aortopathy should prompt further examinations to ensure optimal risk stratification and VHD management. In addition to TTE, advanced imaging modalities, like CCT, may be required to assess the aorta, single-photon emission computed tomography (CT) for detection of ischaemia/necrosis, positron emission tomography (PET) for inflammation, nuclear scintigraphy for cardiac amyloidosis, or CMR for tissue characterization.

4.3. Evaluation of valvular heart disease dynamics and variability

Serial imaging studies to detect changes over time, or variability due to haemodynamic conditions or initiation/up-titration of medical therapy, are of utmost importance to guide decisions. The dynamic pattern of VHD may convey additional prognostic information. Exercise echocardiography helps to identify the cause of dyspnoea, unveil symptoms in apparently asymptomatic patients, identifies dynamic changes of VHD severity, and can contribute to refinement of the indication for an intervention, especially for AS and mitral regurgitation (MR).[52]

4.4. Assessment of extravalvular cardiac consequences from valvular heart disease

Several studies investigating different valve lesions have established the relevance of extravalvular cardiac damage in terms of prognosis,[53–55] recovery after intervention,[56] and quality of life.[57] The presence of LV hypertrophy, left atrium (LA) dilatation, LV or RV dysfunction and/or remodelling, myocardial fibrosis, and pulmonary hypertension (PH) provide important prognostic information, and may influence the timing and type of treatment. Although not necessarily chronological in their order of appearance, the understanding of cardiac damage, particularly damage involving the LV, is essential to guide appropriate medical therapy before and after any intervention. Transthoracic echocardiography (TTE) including global longitudinal strain (GLS) and CMR can be particularly useful in that regard.[58–60]

4.5. Evaluation of eligibility, planning, and guiding of interventions

Transoesophageal echocardiography (TOE) (preferentially 3D) is the preferred tool for the assessment of suitability for aortic, mitral, and TV repair.[45,49,61–63] Risk stratification for an intervention should integrate all the points mentioned above.

Transoesophageal echocardiography (TOE), including standard 3D views, is also the modality of choice to guide atrioventricular transcatheter interventions and should be performed by specially trained interventional echocardiographers.[61,64] Cardiac computed tomography (CCT) is frequently used to evaluate the relationship of the valve with adjacent structures [e.g. coronary arteries and left ventricular outflow tract (LVOT)], the extension of calcification [e.g. in mitral annular calcification (MAC)], and for sizing of the prosthesis. CT angiography is frequently employed to evaluate the anatomy of surgical, arterial, or venous access routes and detect cardiac or extracardiac complications (e.g. bleeding or embolic events). Coronary CT angiography (CCTA) is increasingly utilized to assess the presence of CAD.

5. Clinical evaluation of patients with valvular heart disease

5.1. Clinical examination

Patients with VHD can be either asymptomatic or present with a wide spectrum of symptoms, including acute or chronic HF. An initial meticulous history and a comprehensive physical examination of the patient with auscultation, documentation of clinical signs of HF such as dyspnoea, impaired physical capacity and fatigue, peripheral oedema, and pleural effusion, as well as a systematic frailty assessment, are crucial.[65] In addition, comorbidities and coexisting cardiac conditions should be documented (*Figure 3*). Particular attention should be given to recent changes in symptoms or physical findings indicating a potential worsening of the valve lesion or ventricular function.

5.2. Assessment of comorbidities and risk stratification

Risk stratification of patients with VHD has been mainly developed based on surgical populations. The European System for Cardiac Operative Risk Evaluation II (EuroSCORE II)[66,67] (https://www.euroscore.org) and the Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) score[68] (http://riskcalc.sts.org/stswebriskcalc/calculate) are the most commonly used scoring systems to estimate surgical risk. Both risk scores have been calibrated to predict post-operative outcomes.[69–71] The STS-PROM score is dynamic to account for changes in patient risk profiles, the type of procedure (aortic, mitral, and tricuspid), and outcomes over time. The outdated (logistic) EuroSCORE I model systematically overestimated surgical mortality.[70,72]

In patients considered for TAVI, surgical risk scores have lower accuracy and tend to overestimate the risk of events.[73–75] Discrepancies between observed and predicted peri-procedural mortality after TAVI using surgical risk scores point towards a need for TAVI-specific scores. Models predicting short- and medium-term survival specifically designed for TAVI are rarely used in daily clinical practice due to limitations of their predictive performance.[76–79] Specific scores have also been developed for patients undergoing mitral TEER (M-TEER),[80–82] but the high heterogeneity of the population with MR limits their external validity and therefore routine clinical use so far.[83] Recently, a dedicated clinical score has been calibrated and validated to stratify the risk associated with first-time and repeat isolated TV surgery (TRI-SCORE; https://www.tri-score.com/), and its use should be encouraged for patients with TV disease,[84,85] as an alternative to the more complex Society of Thoracic Surgeons (STS) score for isolated TV surgery (https://isolatedtvsurgcalc.research.sts.org/).

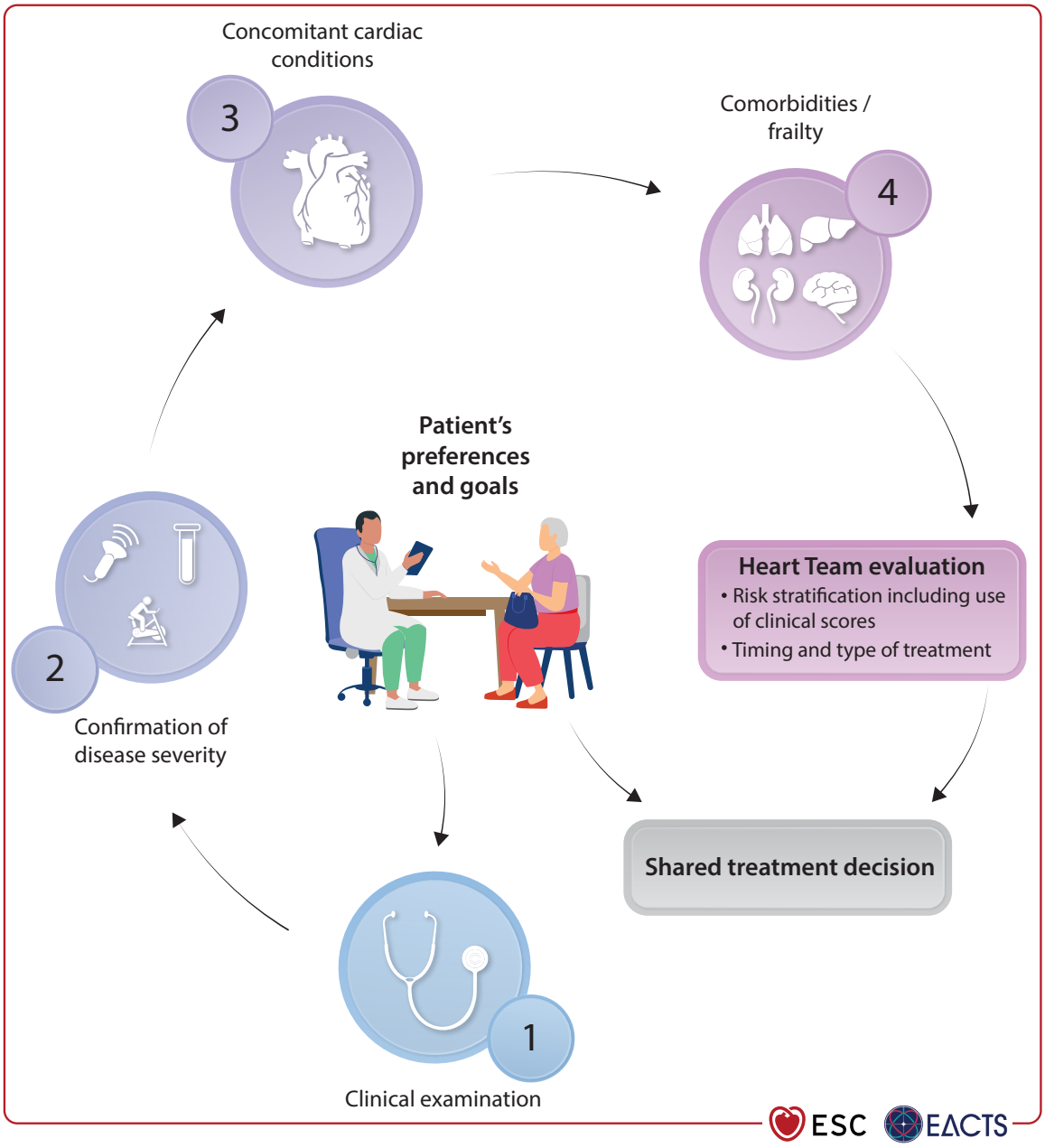

Figure 3 Central illustration. Patient-centred evaluation for treatment of valvular heart disease.

Other cardiac conditions and comorbidities—such as CAD, concomitant multiple valve and aortic disease, and RV dysfunction, as well as chronic kidney disease (CKD)—are not always appropriately captured in risk models, even if they are known to impact outcomes.[86] Similarly, specific unfavourable characteristics like porcelain aorta, mobile aortic atheroma, and previous mediastinal radiation therapy increase the surgical risk, and therefore may favour transcatheter treatment options. Frailty, including nutritional state, represents another important determinant of outcomes after valve interventions,[87–89a] which can be evaluated using appropriate tools as summarized in a recent consensus statement.[90] Several methods have been proposed, from the simple Fried Frailty Index to more complex scores[91] such as the Hospital Frailty Risk Score, which has been validated in a large cohort of TAVI and M-TEER patients.[92]

The use of PROMs that engage patients in the co-evaluation of their health and wellbeing is encouraged. Several scoring systems have been proposed and validated for reproducibility and association with clinical outcomes, like the Quality of Recovery 15-item PROM or the Kansas City Cardiomyopathy Questionnaire (KCCQ).[93–95]

5.3. Biomarkers

Biomarker levels indicating either cardiac wall stress [e.g. brain natriuretic peptide (BNP)] or myocardial damage (e.g. troponin), in asymptomatic and symptomatic patients, may help to monitor VHD progress and determine the most appropriate timing of intervention. In patients with VHD, the natriuretic peptide ratio [the ratio of measured BNP or N-terminal pro-B-type natriuretic protein

(NT-proBNP) to upper limit of normal for age, sex, and assay] has been shown to be a powerful, independent, and incremental predictor of mortality.[96–98] In patients undergoing AV replacement, the accumulation of several elevated biomarkers of cardiovascular stress was associated with higher all-cause and cardiovascular mortality, and a higher rate of repeat hospitalization.[99,100]

5.4. Exercise testing

Because of the slow progression of valve lesions, patients may gradually limit their activity levels over several years and deny having actual symptoms that can be unmasked by exercise testing.[12] This is particularly important in cases of AS, because once symptoms occur there is a sharp increase in the risk of sudden cardiac death, unless a valve intervention is performed.[101–104] Exercise testing may provide additional information about the haemodynamic severity of VHD and help determine the risk and optimal timing of intervention by objectively evaluating functional capacity.[101,103] Cardiopulmonary exercise testing has a prognostic role and can assist decision-making in patients with VHD of intermediate severity, particularly those with asymptomatic AR.[101,105,106]

Exercise echocardiography is used for the assessment of LV global and segmental function, pulmonary artery pressure, and aortic and mitral pressure gradients.[101,107] It also documents exercise-induced increase of MR and TR severity, especially in patients with secondary disease.[108,109] Prognostic impact has been shown mainly for AS and MR.[110,111] Misconceptions regarding its risk and tolerability contribute to the overall underuse of exercise testing in patients with VHD,[12] despite data confirming its safety in most asymptomatic patients.[112,113]

5.5. Invasive investigations

5.5.1. Coronary angiography

Coronary artery assessment is recommended to evaluate the need for revascularization when valve surgery or an intervention is planned. The information regarding the existence of concomitant CAD should be available at the time of Heart Team discussion. CCTA is recommended as an alternative to coronary angiography to rule out CAD in patients who are at low or moderate risk of obstructive CAD.

Coronary blood flow and fractional flow reserve (FFR) are altered in the setting of concomitant VHD, and functional haemodynamic assessment of CAD in these patients is not well established.[114–118]

5.5.2. Cardiac catheterization

Right heart catheterization (RHC) should be performed in patients with equivocal echocardiographic findings, particularly those with MV disease, as well as in all candidates for the treatment of severe TR. In exceptional cases with unclear AS severity, it can be combined with measurements of the transaortic gradients allowing estimation of the aortic valve area (AVA). Right heart catheterization contributes to assess the repercussions of any left-sided VHD or LV impairment on the pulmonary circulation and right side of the heart. It provides information regarding volume state, cardiac output, and vascular resistance, differentiating between pre- and post-capillary PH, and should be ideally performed in euvolaemia.

Measurements of the pulmonary capillary wedge pressure v-wave can inform about MR severity, but are neither sensitive nor specific, and may also be increased if the compliance of the LA is reduced or in case of diastolic LV dysfunction, as in patients with MS or chronic HF.[119]

Similarly, the height of the right atrium (RA) v-wave, and the pressure curve mimicking the RV pattern ('ventricularization' of the RA pressure), are signs of relevant TR, which are frequently accompanied by increased RV end-diastolic pressure in case of associated RV dysfunction. In patients with severe TR, pulmonary vascular resistance (PVR) should be calculated to unmask pulmonary vascular disease, which may not be captured by echocardiography due to RV systolic dysfunction or underestimation of pulmonary pressures because of TR.

5.6. Patient-centred care and shared decision-making

Given that treatment of VHD typically involves several modalities and specialities, and may result in a complex and sometimes time-consuming decision-making process, patient education and information, using online material and face-to-face conversations, are essential at each step. A clearly defined point of contact for all questions relating to the disease or type of treatments should be communicated to the patient and their relatives.[120] The symptomatic and prognostic benefits, as well as the advantages and disadvantages of any treatment option, should be presented in an open and evidence-based manner. This includes mortality and risks of reintervention and complications (also over the long term), as well as recovery time and the need for cardiac, and if necessary psychological, rehabilitation until return to physical activity and work. Other issues to be discussed before the procedure include the need for oral anticoagulation (OAC) and its monitoring, as well as the noise generated by mechanical heart valves (MHVs). Information regarding centre experience and volume for a specific procedure should be provided. Misconceptions (e.g. subjective overestimation of the risk of surgery) should be addressed and potential interactions with individual lifestyle factors—including social activities, family and professional life, and hobbies—should be discussed in detail.

The Heart Team recommendation regarding the treatment and its modality must be based on evidence and anatomical considerations, balancing the risks and benefits of available treatment options.[16] The patient and patient's relatives need to be well informed about the rationale leading to the Heart Team recommendation, and given ample time to share personal preferences.[121] At the end of the process, a shared decision is made between the treating team and the informed patient and relatives (*Figure 3*).

6. Management of conditions associated with valvular heart disease

6.1. Diagnosis and management of coronary artery disease

The presence of CAD plays an important role in decision-making regarding the timing and modality of treatment, and should be assessed before Heart Team discussion. In patients with a low or moderate pre-test likelihood of obstructive CAD (≤50%), CCTA is recommended to rule out relevant CAD with high sensitivity.[122–124]

Several studies have investigated the value of CCT angiography for CAD screening in elderly TAVI candidates. While sensitivity for the detection of obstructive CAD is high (95%–97%), specificity (68%–73%) is

modest, mainly explained by the high prevalence of coronary artery calcification and AF in patients with severe AS, which limit imaging resolution and interpretability.[125,126] If CCT angiography obtained during standard pre-TAVI evaluation is of sufficient quality to exclude relevant CAD, omission of invasive coronary angiography should be considered.[125–129]

The value of invasive functional haemodynamic assessment of CAD in patients with severe AS may be limited, because AS impacts coronary haemodynamics. Therefore, caution is warranted in the interpretation of functional measurements in the presence of severe AS until more data are available.[115,116]

Recommendations for the management of chronic CAD associated with VHD are provided below (*Recommendation Table 1*), as well as in dedicated guideline documents.[6] The indications for coronary artery bypass grafting (CABG) in patients undergoing surgery for the treatment of VHD are mainly based on observational data, which do not provide detailed information on the degree of stenosis and the complexity of CAD.[130] It has been demonstrated that subendocardial blood flow in the myocardium improves early after SAVR, most likely due to improved cardiac output and reduction of LV wall stress.[131] The presence of CAD is associated with peri-operative and late adverse events in patients with AS undergoing SAVR[132] that likely outweigh the increased risk of peri-procedural adverse events of combined SAVR and CABG compared with isolated SAVR. Indeed, in a large observational study, patients with CAD demonstrated better long-term survival after combined SAVR and CABG compared with SAVR alone, despite longer cross-clamp times.[133] In patients with a primary indication for valve surgery, CABG is recommended in patients with coronary artery stenosis of ≥70% and should be considered in those with stenosis of ≥50%–70%, given the opportunity of concomitant full revascularization.

The impact of CAD in patients undergoing TAVI remains under investigation. The randomized Nordic Aortic Valve Intervention (NOTION)-3 trial compared a strategy of routine percutaneous coronary intervention (PCI) versus conservative management in 455 patients with severe symptomatic AS undergoing TAVI, who also had stable CAD and at least one stenosis of ≥90% based on visual angiographic assessment or FFR of ≤0.80 in a segment with ≥2.5 mm reference diameter.[134] Percutaneous coronary intervention was associated with lower risk of a composite endpoint event including all-cause death, myocardial infarction or urgent revascularization at a median follow-up of 2 years. Exploratory analyses suggest that the increased risk in the conservative treatment arm was driven by differences in the risk of myocardial infarction and urgent revascularization in patients with a diameter stenosis of ≥90%, rather than those with positive FFR and stenosis of <90%. The risk of bleeding was higher in the PCI than in the conservative treatment group. Another multicentre RCT, the PercutAneous Coronary inTervention prIor to transcatheter aortic VAlve implantaTION (ACTIVATION) trial, was discontinued due to slow recruitment.[135] In this underpowered and thus inconclusive trial, a routine PCI strategy of ≥70% stenoses in main epicardial vessels (or ≥50% if protected left main or vein graft) did not meet non-inferiority compared with conservative CAD treatment with respect to the composite of all-cause death and rehospitalization; moreover, PCI was associated with higher bleeding rates. Observational data show that TAVI can be performed safely in patients with untreated CAD with low short- and long-term rates of acute coronary syndrome and unplanned coronary revascularization.[135–139] In two recent meta-analyses of mostly observational data, PCI was not associated with a mortality benefit in patients with chronic CAD undergoing TAVI.[140,141]

Optimal timing of PCI in patients undergoing TAVI remains yet to be determined. In NOTION-3, PCI was performed before TAVI in the majority of the patients (concomitantly or shortly after in only 26% of the patients). Decision-making concerning the timing of PCI should take into account the type of valve used for TAVI and the complexity of the coronary lesions.[142,143] Valves with a high frame—particularly in the context of a narrow aortic root, commissural misalignment, or valve-in-valve procedures—can pose challenges for coronary access following TAVI.[144,145] The presence of significant CAD should therefore be considered for optimal transcatheter valve selection and reinforces the importance of optimized implantation technique and commissural alignment.[143,146] Several RCTs comparing the value and timing of PCI with medical therapy are ongoing (NCT04634240, NCT04310046, and NCT05078619).

Based on the available data, PCI should be considered in patients with a primary indication to undergo TAVI and high-grade (≥90%) coronary artery stenosis in large vessels of ≥2.5 mm. In patients with stenosis of ≥70%, PCI may be considered based on symptom status.[142,143] In patients with ischaemic ventricular SMR, surgical revascularization of CAD has been associated with MR reduction[147] and favourable clinical outcomes in observational studies.[148,149] According to very limited data, improvement of SMR may occur in a minority of patients (about one-third) after PCI, which may therefore be considered prior to MV intervention.[150]

For patients with VHD presenting with acute coronary syndrome, treatment decisions should be made according to the most recent ESC Guidelines.[151] In patients presenting with non-ST-segment elevation acute coronary syndrome, it may be particularly challenging to determine the leading cause of elevated troponin levels, which are also frequently observed in decompensated VHD. Therefore, the treatment strategy should be determined by the Heart Team, taking into account symptoms, as well as coronary, valve, and access anatomy.[136,138,139]

Recommendation Table 1 — Recommendations for the management of chronic coronary syndrome in patients with valvular heart disease (see also Supplementary data online, *Evidence Table 1*)

Recommendations	Class[a]	Level[b]
Diagnosis of coronary artery disease		
CCTA is recommended before valve intervention in patients with moderate or lower (≤50%) pre-test likelihood of obstructive CAD.[122–124]	I	B
Invasive coronary angiography is recommended before valve intervention in patients with high and very high (>50%) pre-test likelihood of obstructive CAD.	I	C
Invasive coronary angiography is recommended in the evaluation of CAD in patients with severe ventricular SMR.	I	C
Omission of invasive coronary angiography should be considered in TAVI candidates, if procedural planning CT angiography is of sufficient quality to rule out significant CAD.[125–129]	IIa	B

Continued

Indications for myocardial revascularization		
CABG is recommended in patients with a primary indication for valve surgery and coronary artery stenosis ≥70%.[c]	I	C
CABG should be considered in patients with a primary indication for valve surgery and coronary artery stenosis ≥50%–70%.	IIa	C
PCI should be considered in patients with a primary indication to undergo TAVI and ≥90% coronary artery stenosis in segments with a reference diameter ≥2.5 mm.[134]	IIa	B
PCI may be considered in patients with a primary indication to undergo transcatheter valve interventions and coronary artery stenosis ≥70% in proximal segments of main vessels.[135–137]	IIb	B

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CT, computed tomography; PCI, percutaneous coronary intervention; SMR, secondary mitral regurgitation; TAVI, transcatheter aortic valve implantation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Stenosis ≥50% can be considered for left main stenosis.

6.2. Atrial fibrillation

The interplay between AF and VHD is complex, and has an essential role in the prognosis and evolution of VHD during the patient's lifetime. Valvular heart disease is independently associated with AF and almost one-third of patients with AF have a history of VHD.[152] Conversely, AF is the main trigger of the development of atrial secondary MR and TR. In a recent cohort study, 8% of individuals with AF developed moderate or severe TR within 3 years of follow-up compared with only 2% in those in sinus rhythm.[153] While disturbed annular dynamics have been postulated,[150,154] the exact pathophysiology leading to secondary atrioventricular VHD in some, but not all patients with AF remains largely unclear.

Detailed recommendations on the anticoagulation management of patients with VHD and AF are provided below (*Recommendation Table 2*) and in *Section 14*, as well as in specific Guidelines.[7] Patients with a combination of VHD and AF have a high incidence of thromboembolic or bleeding complications.[155] DOACs have replaced vitamin K antagonists (VKAs) in most clinical scenarios and are recommended for patients with VHD presenting with AF, except for patients with a MHV or mitral stenosis with a valve area ≤2.0 cm^2. The use of apixaban,[156] dabigatran,[157] edoxaban,[158] and rivaroxaban[159] is supported by subgroup analyses of large RCTs. Recommendations regarding the antithrombotic treatment of patients with MHVs and biological heart valves (BHVs) are described in *Section 14* of these Guidelines.

In the Left Atrial Appendage Occlusion Study (LAAOS) III trial, surgical left atrial appendage occlusion (LAAO) in patients with AF and a CHA_2DS_2-VASc [congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, sex category (female)] score of ≥2 points undergoing cardiac surgery was associated with a 33% reduction of the risk of stroke or systemic embolism at a mean follow-up of 3.8 years.[160] These findings were confirmed by a large meta-analysis including four RCTs.[161] A subanalysis of LAAOS III showed that the benefit of LAAO remains consistent irrespective of the use of VKAs or DOACs, as well as in the absence of OAC (although representing only 10% of the included population).[162] In an RCT including patients with severe AS and AF undergoing TAVI, concomitant transcatheter LAAO was non-inferior to medical therapy with respect to a composite primary endpoint including all-cause mortality, stroke, and major bleeding at 2 years. Of note, rates of major or life-threatening bleeding were similar in the two groups and arterial or venous thromboembolisms more frequent in the TAVI/LAAO arm, leaving uncertainty regarding the usefulness of combining both procedures.[163]

Recommendation Table 2 — Recommendations for the management of atrial fibrillation in patients with native valvular heart disease (see also Supplementary data online, *Evidence Tables 2 and 3*)

Recommendations	Class[a]	Level[b]
Anticoagulation		
DOACs are recommended for stroke prevention in preference to VKAs in patients with AF and AS, AR, or MR who are eligible for OAC.[156–159,164]	I	A
The use of DOACs is not recommended in patients with AF and rheumatic MS with an MVA ≤2.0 cm^2.[165]	III	B
Surgical interventions		
Concomitant surgical ablation is recommended in patients undergoing MV surgery with AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, according to an experienced team of electrophysiologists and arrhythmia surgeons.[166–173]	I	A
Surgical closure of the LA appendage is recommended as an adjunct to OAC in patients with AF undergoing valve surgery to prevent cardioembolic stroke and systemic thromboembolism.[160–162]	I	B
Concomitant surgical ablation should be considered in patients undergoing non-MV surgery with AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, according to an experienced team of electrophysiologists and arrhythmia surgeons.[167,169,174,175]	IIa	B

AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; DOAC, direct oral anticoagulant; LA, left atrium/left atrial; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; MVA, mitral valve area; OAC, oral anticoagulation; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.

6.3. Cancer and radiation therapy

Valvular heart disease is commonly associated with cancer and represents a well-known long-term side effect of intensive radiation therapy[176] for treatment of Hodgkin or non-Hodgkin lymphoma, breast cancer, and other thoracic malignancies.[177] Clinically significant VHD most commonly appears decades after radiotherapy. The incidence of radiation-induced VHD is increasing owing to longer survival of patients with cancer. Risk factors are summarized in Supplementary data online, *Table S1*. Patients at risk should be screened for VHD using TTE 10 years after radiation exposure and followed up every 5 years thereafter.[178]

Radiotherapy may lead to aortic and/or valvular calcification, CAD of proximal segments, restrictive cardiomyopathy, pericardial adhesions and calcifications with constriction, restrictive lung disease, chest wall scarring, and impaired wound healing, especially in patients who underwent radiation by means of older techniques (>20 years ago). The above factors complicate any surgical approach and increase the operative risk, which is underestimated by traditional risk scores.[179–181] TAVI is proposed as an alternative for patients presenting with radiation-induced AS in the *2022 ESC Guidelines on cardio-oncology*[182] based on favourable, but limited, observational data,[183,184] because this category of patients has been excluded from RCTs.[183,184] Furthermore, M-TEER in patients presenting with radiation-induced MV disease with MR is often limited by thickened leaflets with restricted movement and subsequent risk of iatrogenic stenosis.

In patients with active or stable cancer and severe AS, both TAVI and SAVR can be considered based on life expectancy, age, prognosis, and disability following cancer treatment, with a trend towards more TAVI utilization.[185] TAVI procedural complication rates appear similar compared with those of control subjects without cancer.[186] To avoid futility, treatment decisions discussed by the Heart Team should involve the treating oncologists.[5,182]

6.4. Prophylaxis of rheumatic fever

Rheumatic heart disease remains the most common cause of death from VHD worldwide.[187] Prevention should preferentially target the first occurrence of acute rheumatic fever. Correct diagnosis and early antibiotic treatment of group A *Streptococcus* throat or skin infection is key for primary prevention. Large-scale screening combined with prophylaxis in children or adolescents with latent RHD appears to be an effective strategy to reduce the risk of disease progression and RHD prevalence.[188–190] In patients with established RHD, secondary long-term prophylaxis with benzathine benzyl penicillin 1.2 million international units (IU) every 3–4 weeks over 10 years is recommended to prevent recurrent episodes, especially in children and adolescents. Long-term prophylaxis into adulthood should be considered in high-risk patients according to the severity of VHD and exposure to group A *Streptococcus*.[191,192]

6.5. Cardiogenic shock and acute heart failure

Acute presentation or decompensation of VHD can result in cardiogenic shock due to rapid haemodynamic deterioration and altered cardiac function. Alternatively, pre-existing VHD can be a bystander of an acute cardiovascular condition further exacerbating circulatory impairment until the occurrence of cardiogenic shock. In this setting, assessment of the severity of VHD, as well as its contribution to acute HF, may be difficult. Evidence concerning acute VHD management in this context is scarce and only exists for the MV and AV.[193,194]

Hospital admission for acute decompensated AS is a frequent problem seen in up to 25% of AS hospitalizations.[195,196] However, only a minority of these patients (1.6%–3.2%) present with cardiogenic shock.[197,198] While intensive care treatment remains the cornerstone of haemodynamic stabilization and support, an intervention should be considered early, because it represents the only way to reverse progressive organ dysfunction due to low cardiac output. Balloon aortic valvuloplasty has been used in this context in the past, but has been largely replaced by TAVI in recent years, due to the high risk of severe AR and mortality in the acute setting.[199–201] Several large observational studies have established the feasibility of TAVI in patients with cardiogenic shock with similar device success, even if LVEF is low, although 30-day mortality remains higher (13%–19%) compared with routine TAVI.[194,197,198] Surgery represents the preferred treatment in patients with acute AR, while TAVI has only been described in individual cases or patients with a failed surgical valve (valve-in-valve). Fast pacing over a temporary pacemaker lead shortens the diastole and may temporarily improve haemodynamics until the intervention.[5,8]

Except for papillary muscle rupture, acute PMR rarely leads to cardiogenic shock and may be best treated by surgical valve repair or replacement. In contrast, increasing evidence supports the use of M-TEER in patients with acute ventricular SMR, particularly following acute myocardial infarction, due to lower mortality compared with surgery or medical treatment in propensity-matched analyses.[194,202,203] This strategy might also be helpful to facilitate weaning from mechanical circulatory support.

6.6. Palliative care

In some patients with advanced VHD not qualifying for surgical or transcatheter therapies, medical HF treatment remains the only, and sometimes best, available option. These patients usually present late, have extensive cardiac damage, develop terminal HF during the natural evolution of VHD, and are ineligible for mechanical circulatory support or heart transplantation (HTx). Early implementation of expert multidisciplinary palliative and end-of-life care, with the support of HF specialists,[204–206] reduces the number of hospitalizations and improves quality of life and symptom burden, in particular dyspnoea, pain, and anxiety.[207] Continuous co-ordination between all involved subspecialties, and transparent communication with the patient and their relatives, are key to ensure high quality of care.

7. Aortic regurgitation

7.1. Prevalence and aetiology

Chronic AR is mainly due to intrinsic abnormalities of the AV cusps and/or secondary to progressive dilatation of the aortic root and/or ascending aorta. In high-income countries, degenerative changes are the leading cause of AR, while RHD is more frequent in middle- and low-income countries.[12] Acute presentations are usually related to infective endocarditis or extension of aortic dissection into the aortic root. Chronic pure severe AR is more frequent in men and is associated with BAV and concomitant dilatation of the aorta in more than one-half of cases.[208]

7.2. Evaluation

During stepwise AR evaluation, the following aspects should be addressed: the severity of AR, its mechanism, and aetiology; the haemodynamic impact on LV function and pulmonary pressure; and evaluation of the ascending aorta. While echocardiography is the first-line modality, CMR and CCT are more accurate for the measurement of specific parameters (*Figure 4*). The results of the evaluation need to take into consideration the haemodynamic condition of the patient, particularly the blood pressure (BP), since high pressures can lead to overestimation of the regurgitant volume (RVol).

Assessment of AR severity with TTE follows an integrative approach considering qualitative, semi-quantitative, and quantitative parameters, but remains challenging.[45] Consequences of AR on LV size and function must be carefully assessed. Cut-offs for intervention are mostly based on two-dimensional (2D) echocardiographic measurements. However, 3D echocardiography and CMR allow more accurate

evaluation of LV volumes and LVEF than 2D echocardiography, and are useful in borderline cases (*Figure 4*).[45,209] Strain imaging can be helpful in identifying subclinical LV dysfunction[209–211] and can therefore influence the optimal timing of intervention. Reduced longitudinal strain and contractile reserve at stress echocardiography,[212] elevated biomarkers (BNP),[213,214] and the presence of myocardial fibrosis detected by CMR need to be integrated in the decision-making process, even if not entirely validated yet.[209]

Given its close relationship with AV function, accurate measurements of the aortic diameter are required at all levels: the annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta.[8,215,216] The largest diameter is used to indicate the specific aortic phenotype: root phenotype, ascending phenotypes, and extended or mixed forms (see Supplementary data online, *Figure S1*).[8] The mechanism of AR and aortic diameters determine suitability for AV sparing or repair.[217,218]

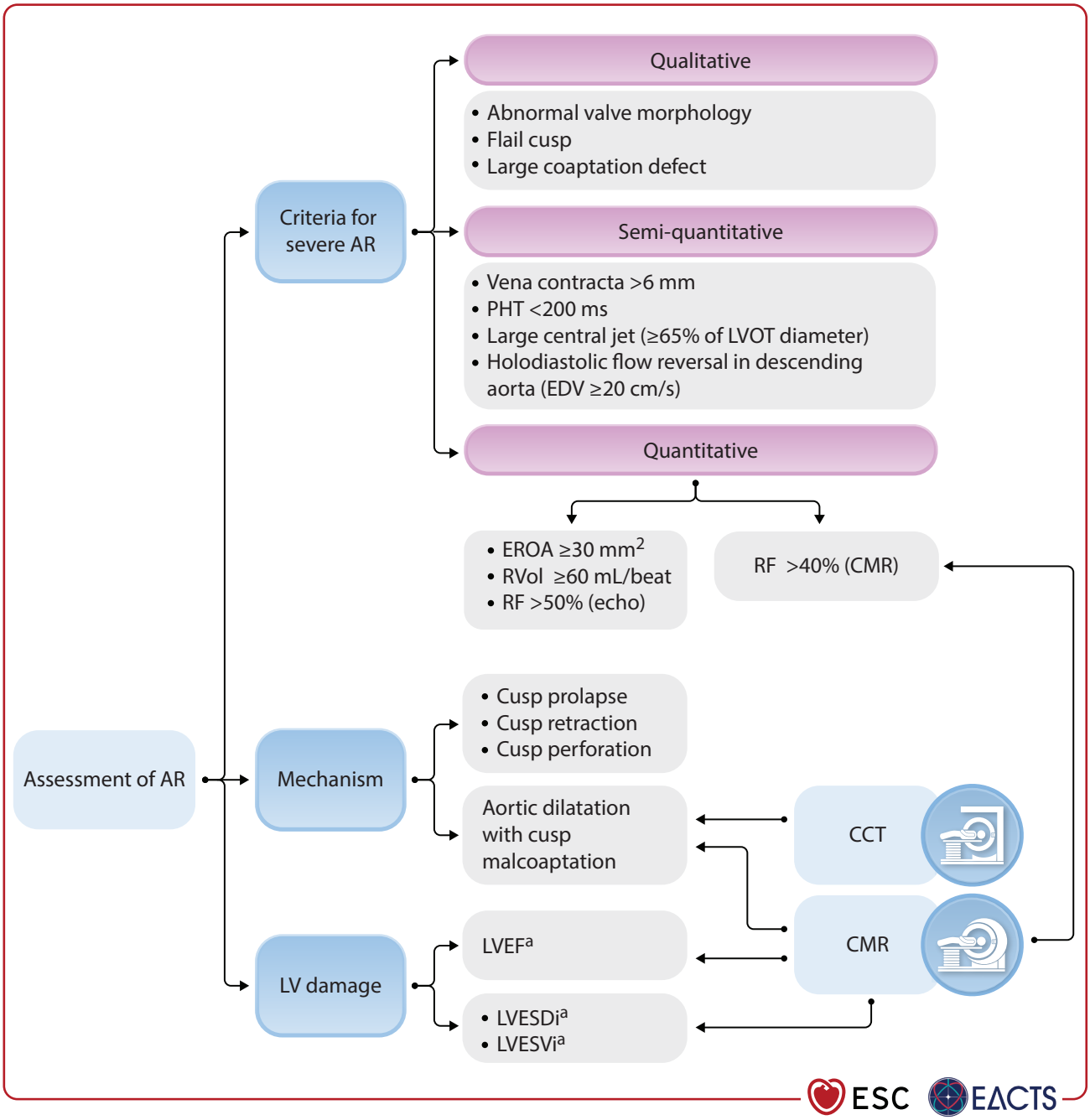

Figure 4 Imaging assessment of patients with aortic regurgitation. AR, aortic regurgitation; CCT, cardiac computed tomography; CMR, cardiac magnetic resonance; EDV, end-diastolic velocity; EROA, effective regurgitant orifice area; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; LVESDi, left ventricular end-systolic diameter indexed to body surface area; LVESVi, left ventricular end-systolic volume indexed to body surface area; LVOT, left ventricular outflow tract; PHT, pressure half-time; RF, regurgitant fraction; RVol; regurgitant volume. [a]See *Recommendation Table 3* for specific cut-offs.

The morphology of the AV represents a critical aspect in the diagnosis and treatment of AR. Pure AR in the context of BAV uncommonly manifests with normal aortic diameters, being more often associated with a dilated ascending aorta and/or root. It is important to define the valve phenotype to determine the repair probability and long-term result of AV repair or AV-sparing procedures. The degree of symmetry is an important predictor of BAV reparability with better long-term results in more symmetric phenotypes.[219–221]

7.3. Medical therapy

Medical therapy, especially angiotensin-converting enzyme-inhibitors (ACE-Is) or dihydropyridine calcium channel blockers, may provide symptomatic improvement in individuals with chronic severe AR for whom surgery is not feasible or contraindicated. The value of ACE-Is or dihydropyridines in delaying surgery in the presence of moderate or severe AR in asymptomatic patients has not been established, and their use is not recommended for this indication. The use of beta-blockers increases the length of the diastole and therefore the RVol, and should be used with caution if indicated for another reason. However, beta-blockers can be used along with ACE-Is or angiotensin receptor blockers (ARBs) after surgery, if indicated (systolic HF or heart rate control).[222,223]

7.4. Indications for intervention

Acute severe AR usually requires immediate surgery depending on the aetiology, such as infective endocarditis or spontaneous, traumatic, or iatrogenic aortic dissection.[5,8] Surgery for the treatment of chronic severe AR is indicated depending on symptoms and/or the effects of the RVol on LV size and function (see *Recommendation Table 3* and *Figure 5*). The presence of associated aortic dilatation dictates surgery, irrespective of AR severity. When the patient is symptomatic and AR severe, surgery is recommended unless the anticipated surgical risk is prohibitive.[224–228] Concomitant surgical treatment of severe AR is also recommended, irrespective of symptoms, in patients requiring CABG, ascending aorta surgery, or any other cardiac surgical procedures.[229,230]

For the asymptomatic patient with severe AR, indications for surgery are based on the degree of functional impairment of the LV [LVEF ≤50%, left ventricular end-systolic diameter (LVESD) >50 mm, or left ventricular end-systolic diameter indexed to body surface area (BSA) (LVESDi) >25 mm/m^2, especially in those with small BSA (BSA <1.68 m^2) and elderly patients with low ventricular compliance].[226,228,231–234] If surgery is deemed low risk, there is observational evidence from echocardiographic studies that early intervention might be beneficial for long-term prognosis when LVEF is ≤55%, LVESDi is >22 mm/m^2, and/or left ventricular end-systolic volume indexed to BSA (LVESVi) is >45 mL/m^2.[235–239] A volumetric cut-off value of LVESVi ≥43 mL/m^2 using CMR was recently proposed to guide the management of asymptomatic patients[240,241] and appears to have better predictive value than LV diameter.[242] Surgery may also be discussed in selected low-risk asymptomatic patients with significant LV dilatation (left ventricular end-diastolic diameter >65 mm) and progressive increase of LV diameters and/or decrease of LVEF during follow-up. Exercise testing should be performed, when feasible, in patients with severe AR who do not report symptoms and do not meet criteria for surgery.[212]

AV replacement is still the standard surgical approach in most AR cases (see *Section 14.1* regarding prosthesis type considerations). However, owing to a better understanding of the pathophysiology of the aortic root (see Supplementary data online, *Figure S1*) paralleled with favourable long-term results, valve-sparing aortic root replacement (VSARR) and AV repair are increasingly performed in centres with appropriate expertise (*Figure 5*).[243–255] In patients with root enlargement and good tissue quality (i.e. pliable AV cusps with normal motion), a valve-sparing procedure has been demonstrated to be superior to the use of a composite valve graft (Bentall procedure) in terms of long-term mortality and overall morbidity (thromboembolism and endocarditis, with similar need for reoperation),[250–253,255–257] and should be therefore favoured by experienced centres, in particular in patients with an estimated long life expectancy.[258] Valve preservation or valve repair should also be considered for patients with BAV based on age, anatomical presentation, and centre experience (*Figure 5*).[220,245,246,259]

When performed by experienced surgeons in well-selected young individuals, pulmonary autograft implantation (Ross operation) may also be a good alternative to prosthetic valve replacement.[260–263]

TAVI may be considered at experienced centres for selected patients with AR who are ineligible for surgery. The use of non-dedicated transcatheter valves for this indication is off-label and associated with an increased risk of valve malpositioning and residual AR, with consecutively higher rates of second valve implantation (about 10%) or surgical conversion, as compared with TAVI in AS.[264–268] Dedicated devices appear to minimize the risk of valve migration and residual AR in selected patients, but are associated with a high new permanent pacemaker implantation rate (24%).[267–269]

Aortic dilatation is closely linked to AR. Dedicated ESC Guidelines give guidance regarding the evaluation and management of aortic root and ascending aortic dilatation.[8] The aortic phenotype (see Supplementary data online, *Figure S1*), degree and rate of progression of aortic dilatation, and the underlying aetiology all affect timing of surgery, with the main indication being maximum aortic diameter.[270–272] Dilation of the aortic root, which typically occurs in Marfan syndrome and other patients with connective tissue disease, has a worse prognosis compared with isolated dilatation of the ascending aorta and requires closer surveillance.[270–272] Surgery is recommended in all patients with a maximal aortic root or ascending aneurysm diameter of ≥55 mm. In the presence of additional risk factors, a threshold of 50 mm may be considered for selected low-risk patients treated at experienced centres.[8] If the patient has an established indication for AV surgery (due to AR or AS), concomitant surgery of the aortic root or the ascending aorta should be considered at a diameter of ≥45 mm. This threshold has been more clearly demonstrated in patients with BAV and should also be based on the patient's height[273] or specific intraoperative findings, such as the shape and thickness of the aortic wall.

7.5. Follow-up

A multimodality imaging approach[45,274] and biomarkers like BNP[213,214] might help identify patients at increased risk of LV damage early and guide the appropriate timing of intervention. Yearly follow-up is recommended in asymptomatic patients with severe AR. Closer follow-up (3–6 months) is recommended for those approaching thresholds for surgery, or showing a progressive dilatation of the LV or decrease of LVEF. Cardiac magnetic resonance can be especially useful in such a setting. Patients with moderate AR should be followed on a yearly basis, with echocardiography performed every 2 years.

When a dilated ascending aorta is initially diagnosed by TTE, a multislice electrocardiographic-triggered CCT/CMR scan is recommended

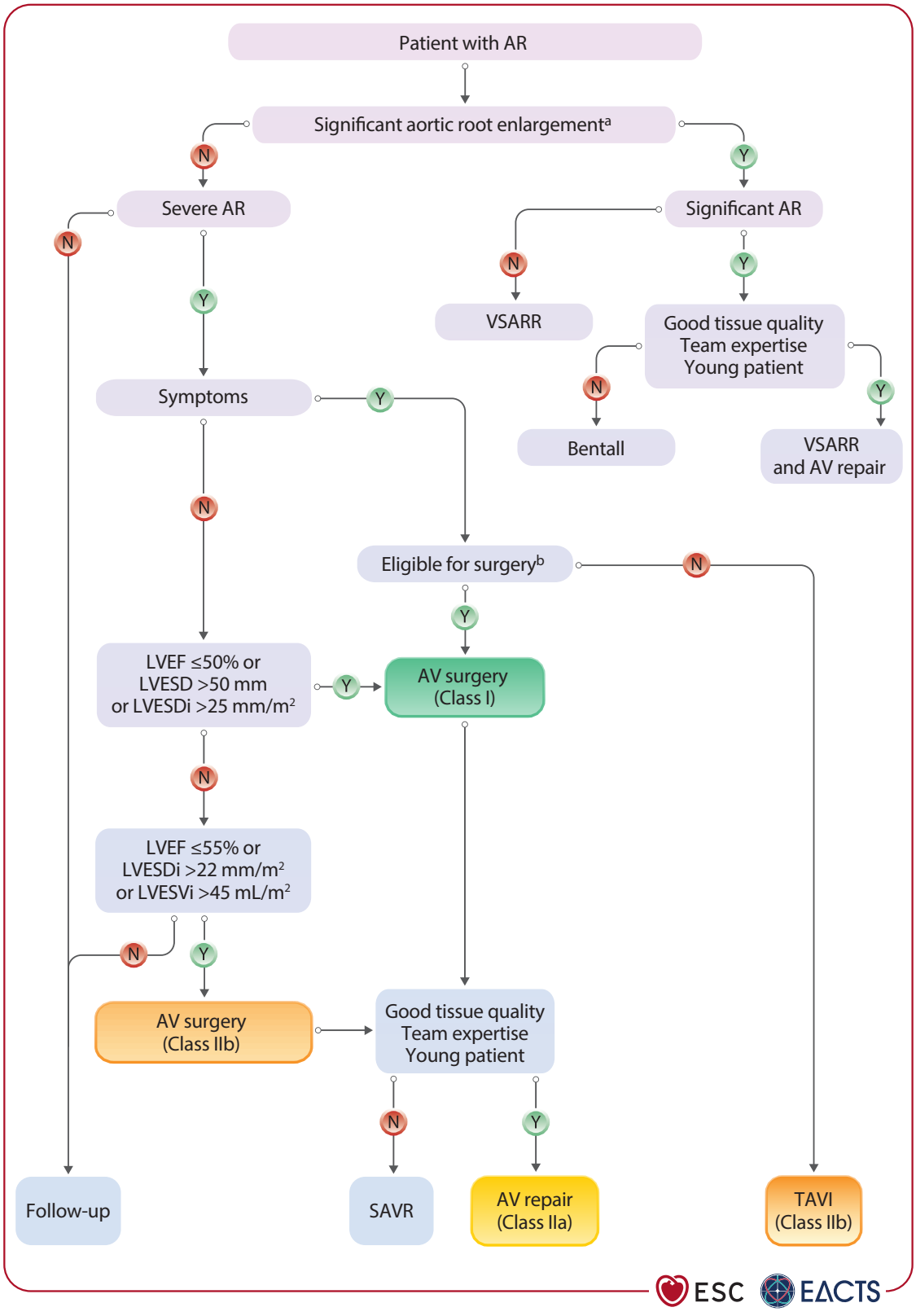

Figure 5 Management of patients with aortic regurgitation. AR, aortic regurgitation; AV, aortic valve; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to body surface area; LVESVi, left ventricular end-systolic volume indexed to body surface area; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve replacement; VSARR, valve-sparing aortic root replacement. [a]Indications for surgery on the root/ascending aorta are described in the *2024 ESC Guidelines for the management of peripheral arterial* and *aortic diseases*.[8] [b]Concomitant replacement of the aortic root or ascending aorta should be considered if the maximal diameter is ≥45 mm and the predicted surgical risk is low.

to confirm maximal diameter, rule out isolated single sinus dilatation, and provide a baseline reference. When the baseline aortic diameter is >45 mm, a second TTE examination is recommended at 6 months to confirm the stability of the finding, followed by serial examinations on a yearly basis thereafter.[275] Any increase of >3 mm should be validated by CT angiography/CMR and compared with baseline data.[275] After repair of the ascending aorta, patients with Marfan syndrome and other connective tissue diseases remain at risk for dissection of untreated portions of the aorta, and require lifelong regular multidisciplinary follow-up at an expert centre.[8]

7.6. Special patient populations

Patients with concomitant VHD and those with AS combined with AR are discussed in *Section 13.3.3*. In patients with moderate AR and indication for CABG or MV surgery, the decision to treat the AV should be discussed by the Heart Team based on the aetiology of AR and other clinical factors, like the estimated life expectancy and the operative risk, as data show that progression of moderate AR may be very slow.[276]

The presence of aortic dilation and AR in asymptomatic patients poses the problem of limiting the level of physical activity, but consistent data are lacking. Current recommendations for participation in competitive sport are restrictive, especially regarding isometric exercise in patients with connective tissue disease,[277] while a more liberal approach is likely to be appropriate in other patients.

Given the familial risk of thoracic aortic aneurysms, screening with appropriate imaging studies and testing for genetic abnormalities in first-degree relatives is indicated in patients with connective tissue disease.[278] Since aortic dilation is present in ~10% of first-degree relatives of patients with a BAV, it is also considered appropriate to encourage echocardiographic screening in this specific population.[275,279]

Recommendation Table 3 — Recommendations on indications for intervention in severe aortic regurgitation (see also Supplementary data online, *Evidence Tables 4–8*)

Recommendations	Class[a]	Level[b]
Severe aortic regurgitation		
AV surgery is recommended in symptomatic patients with severe AR regardless of LV function.[224–228]	I	B
AV surgery is recommended in asymptomatic patients with severe AR and LVESD >50 mm or LVESDi >25 mm/m^2 [especially in patients with small body size (BSA <1.68 m^2)] or resting LVEF ≤50%.[226,228,231,233,234]	I	B
AV surgery is recommended in symptomatic and asymptomatic patients with severe AR undergoing CABG or surgery of the ascending aorta.	I	C
AV repair should be considered in selected patients with severe AR at experienced centres, when durable results are expected.[220,245,246,259]	IIa	B
AV surgery may be considered in asymptomatic patients with severe AR and LVESDi >22 mm/m^2,[226,228,231–234] or LVESVi[c] >45 mL/m^2 [especially in patients with small body size (BSA <1.68 m^2)],[235–241] or resting LVEF ≤55%, if the surgical risk is low.	IIb	B
TAVI may be considered for the treatment of severe AR in symptomatic patients ineligible for surgery according to the Heart Team, if the anatomy is suitable.[264,265,268,269]	IIb	B
Concomitant surgery of the ascending aorta		
Valve-sparing aortic root replacement is recommended in young patients with aortic root dilatation at experienced centres, when durable results are expected.[247,250–253,255]	I	B
When AV surgery is indicated and the predicted surgical risk is low, replacement of the aortic root or ascending aorta should be considered if the maximal diameter is ≥45 mm.[d]	IIa	C

AR, aortic regurgitation; AV, aortic valve; BSA, body surface area; CABG, coronary artery bypass grafting; CMR, cardiac magnetic resonance; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to BSA; LVESVi, left ventricular end-systolic volume indexed to BSA; TAVI, transcatheter aortic valve implantation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Using echocardiography or CMR.
[d]Considering age, BSA, the aetiology of the valvular disease, the presence of a bicuspid AV, and the intraoperative shape and thickness of the ascending aorta.

8. Aortic stenosis

8.1. Prevalence and aetiology

Even if AS is the most common primary valve lesion referred for intervention in Europe and North America,[12] underdiagnosis and undertreatment remain relevant concerns.[10] Degenerative pathogenesis with cusps calcification is most common in developed countries and prevalence is rising rapidly because of the ageing population.[11,12,187] BAVs, or more rarely unicuspid AVs, are prone to earlier degeneration, constitute the dominant valve morphology in younger patients requiring AV replacement, and are frequently associated with dilatation of the aortic root or ascending aorta.[280,281] In low- and middle-income countries, rheumatic aetiology remains frequent and AS usually presents combined with rheumatic MV disease.[282]

8.2. Evaluation

8.2.1. Echocardiography and cardiac computed tomography

Aortic stenosis is a disease slowly evolving from mild to severe valve obstruction as a consequence of increasing valve fibrosis and calcification, although progression accelerates as haemodynamic severity increases.[283]

Echocardiography is key to confirm the diagnosis and allows comprehensive assessment of the anatomy and severity of stenosis. Evaluation of the haemodynamic consequences on cardiac function and geometry, and the detection of aortic pathology or concomitant valve disease, provide important prognostic information that may influence management.[284] Staging of extravalvular damage has been proposed,[53] but it may be difficult to attribute other cardiac abnormalities to AS itself, because comorbidities are frequent in patients with AS and the observed damage may not occur in the expected chronological sequence. However, the detection of concomitant cardiac conditions [e.g. HF with preserved EF (HFpEF), amyloidosis, or hypertrophic

cardiomyopathy] may help to optimize medical treatment before and after valve intervention.[285,286]

Current European recommendations for the echocardiographic grading of AS rely on measurement of the mean pressure gradient (most robust parameter), peak transvalvular velocity (V_{max}), and effective AVA. Although AVA is theoretically the ideal parameter for assessing severity, there are numerous technical limitations associated with its calculation.[284,287]

Aortic stenosis may be further categorized according to flow state based on stroke volume index (SVi) when there is discordance between echocardiographic parameters (*Figure 6*). A threshold of 35 mL/m^2 is conventionally accepted to discern low from normal flow, although sex-specific thresholds have been proposed.[292]

Concordant criteria:

- High-gradient AS [mean gradient ≥40 mmHg, V_{max} ≥4.0 m/s, AVA ≤1 cm^2 (or ≤0.6 cm^2/m^2)] is considered severe irrespective of LV function and flow conditions.

Discordant criteria:

- Low-flow, low-gradient AS with reduced LVEF (mean gradient <40 mmHg, AVA ≤1 cm^2, SVi ≤35 mL/m^2, LVEF <50%).
- Low-flow, low-gradient AS with preserved LVEF (mean gradient <40 mmHg, AVA ≤1 cm^2, SVi ≤35 mL/m^2, LVEF ≥50%).
- Normal-flow, low-gradient AS with preserved EF (mean gradient <40 mmHg, AVA ≤1 cm^2, SVi >35 mL/m^2, LVEF ≥50%).
- Discordant high-gradient AS (mean gradient ≥40 mmHg, AVA >1 cm^2).

Patients with discordant normal-flow, low-gradient AS usually have moderate stenosis.[293–295] Discordant high-gradient AS is considered severe if not caused by a reversible high-flow status.[296–298]

In patients with low-flow, low-gradient AS with reduced LVEF, dobutamine stress echocardiography (DSE) can help to discriminate between pseudo-severe and true severe AS in the presence of flow reserve (increase in stroke volume of ≥20%).[289,299]

Cardiac computed tomography calcium AV scoring is readily available and provides important adjunctive information in patients with low-flow, low-gradient AS because it correlates with haemodynamic severity, progression, and clinical outcomes.[300,301] Values of >2000 Agatston units (AU) in men and >1200 AU in women indicate severe AS with high sensitivity and specificity (~85%).[302,303] While higher thresholds (men >3000 AU, women >1600 AU) are very specific, severe AS becomes unlikely in patients with calcium AV scoring of <1600 AU in men and <800 AU in women.[284,302,303] Cautious interpretation is required in patients who can develop severe AS without pronounced AV calcification such as in BAV, concomitant amyloidosis, and predominantly fibrotic stenosis associated with post-rheumatic, radiation-induced and inflammatory disease.[304–308]

In low-flow, low gradient AS with reduced LVEF, CCT AV calcium scoring and DSE provide complementary information. If findings are equivocal, an integrated assessment considering all available clinical, morphological, and haemodynamic factors is required.

8.2.2. Additional diagnostic and prognostic parameters

The ratio of the LVOT to the AV Doppler jet velocity time integral (VTI, dimensionless index or velocity ratio) does not require calculation of LVOT area and may assist evaluation when other parameters are equivocal (<0.25 suggests that severe AS is highly likely).[309]

Assessment of GLS can be useful for risk stratification[310] and evaluation of extravalvular cardiac damage.[311,312] It provides additional information regarding LV function and a threshold of −15% may contribute to identifying patients with severe asymptomatic AS at increased risk of clinical deterioration or premature mortality.[59]

Estimated valvuloarterial impedance has been shown to be prognostic of adverse clinical outcomes before and after valve replacement.[313–315]

Transoesophageal echocardiography (TOE) allows morphological evaluation of the valve, planimetry of AVA and assessment of potential subvalvular obstruction (unless there is acoustic shadowing caused by calcification), and evaluation of concomitant valve disease, and can be of value for peri-procedural imaging in challenging clinical or anatomical scenarios.[316]

Natriuretic peptides can be used to arbitrate the sources of symptoms in patients with multiple potential causes and help to identify those with high-risk asymptomatic AS who may benefit from early intervention.[97,317]

Exercise testing can unmask symptoms and haemodynamic intolerance (fall in BP >20 mm Hg) and is recommended for risk stratification in asymptomatic patients with severe AS.[102,318] Exercise echocardiography may provide additional prognostic information by assessing the increase in mean pressure gradient and change in LV function.[319] Cardiopulmonary exercise testing, eventually complemented by echocardiography, can help to uncover cardiac dysfunction in asymptomatic patients, discriminate cardiac from pulmonary limitation or deconditioning in patients with non-specific symptoms, and inform risk stratification.[105,106,320,321]

Cardiac magnetic resonance is used to identify altered global LV geometry due to remodelling, as well as to quantify myocardial scarring and diffuse fibrosis, which are associated with the occurrence of adverse events.[322–324]

Transthyretin cardiac amyloidosis may coexist with AS in elderly patients and the two conditions may causally interrelate.[325] When transthyretin cardiac amyloidosis is suspected, the presence of monoclonal protein in serum and urine should be excluded using immunofixation and quantitative determination of free light chains, and diagnosis ascertained by means of diphosphonate scintigraphy.[326] Despite the limited long-term prognosis associated with cardiac transthyretin amyloidosis, patients with concomitant severe AS usually benefit from valve intervention.[327]

LV catheterization is not recommended unless there are symptoms and signs of severe AS, and non-invasive investigations are inconclusive.

8.2.3. Procedural planning

Cardiac computed tomography is key to determining suitability for TAVI and planning the procedure. It is the preferred imaging tool to assess AV anatomy including annulus size, dimensions of the aortic root and ascending aorta, the extent and distribution of valve and LVOT calcification, the distance of coronary ostia from the annular plane, optimal fluoroscopic projections for transcatheter valve deployment, and the feasibility of vascular access.[49,328,329]

Transoesophageal echocardiography (TOE), which is more operator-dependent and does not allow assessment of coronary and peripheral vascular anatomy, or CMR may be considered when CCT is difficult to interpret or relatively contraindicated (e.g. in patients with renal failure).[330,331]

8.3. Medical therapy

No medical therapies have been shown to influence the natural history of AS to date. Neither statins, which demonstrated favourable effects in pre-clinical studies,[332–334] nor substances

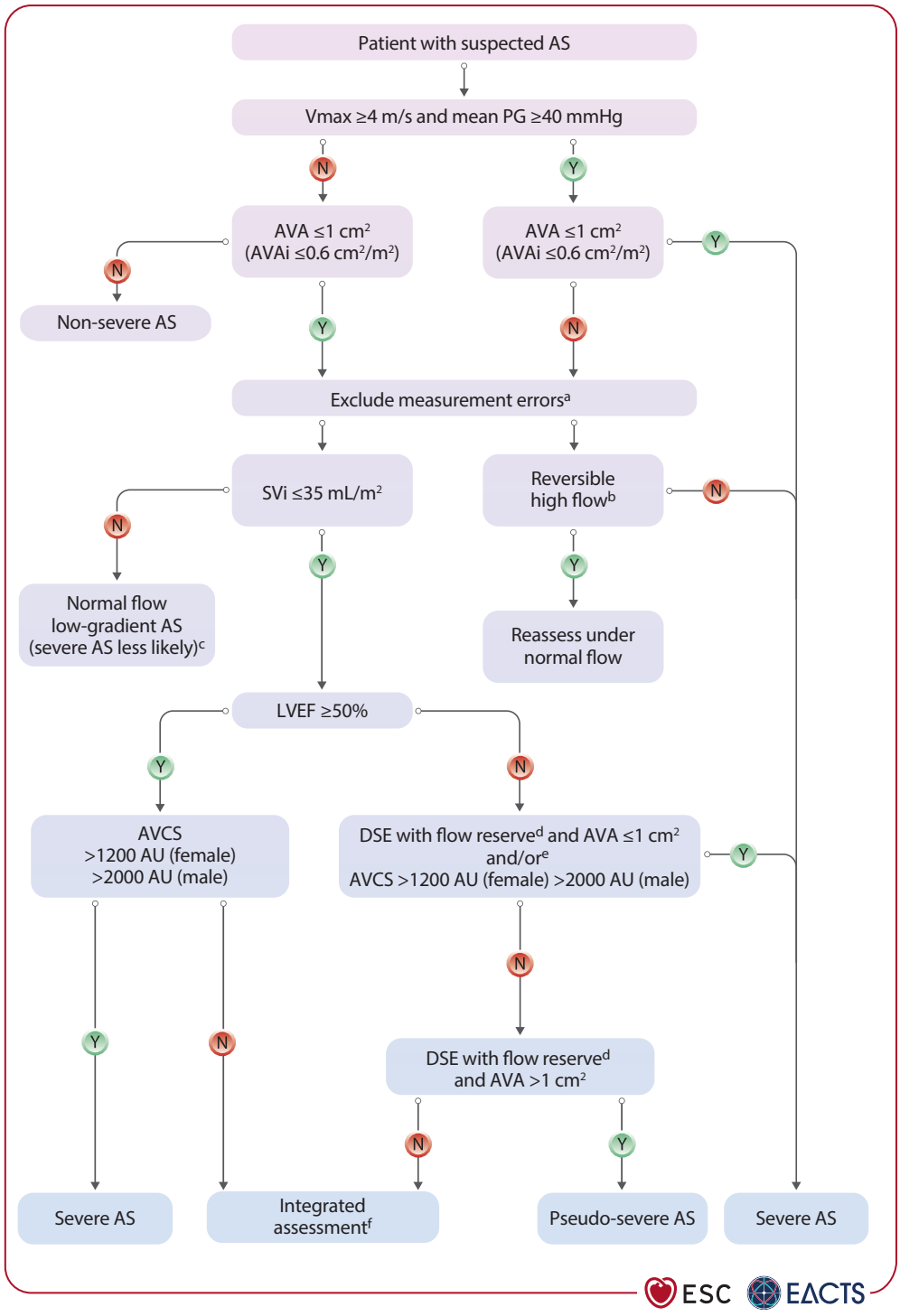

Figure 6 Integrative imaging assessment of patients with aortic stenosis. AS, aortic stenosis; AU, Agatston units; AV, aortic valve; AVA, aortic valve area; AVAi; aortic valve area indexed for body surface area; AVCS, aortic valve calcium score; CCT, cardiac computed tomography; CT, computed tomography; DSE, dobutamine stress echocardiography; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MRI, magnetic resonance imaging; mean PG, mean pressure gradient; SVi, stroke volume indexed for BSA; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; V_{max}, peak transvalvular velocity. [a]In particular, verify LVOT diameter and multiwindow Doppler interrogation. [b]High flow may be reversible (anaemia, hyperthyroidism, or arteriovenous fistulae). Upper limit of normal flow using pulsed Doppler: cardiac index 4.3 L/min/m^2, SVi 58 mL/m^2.[288] [c]Available evidence refers to patients with preserved LVEF. Check for bradycardia or uncontrolled hypertension, which may lead to prolonged ejection time and reduced flow rate. Depending on symptoms, integrated assessment complemented by CCT AV calcium scoring may be pursued. [d]Flow reserve: ≥20% increase in stroke volume in response to low-dose dobutamine or if change in stroke volume of 10%–20%, calculate projected AVA.[289,290] [e]If one test is not conclusive, complement diagnostics with the other test. [f]Based on clinical judgement (typical symptoms without other explanation), morphological valve changes, LV hypertrophy (in absence of coexistent hypertension), and consistent findings using different modes of assessment [TTE and TOE, invasive assessment, AV planimetry by CT or MRI (cut-off 1.2 cm^2)][291].

targeting calcification pathways alter disease progression.[335,336] Coexistent hypertension should be treated to avoid additional afterload, preferably using renin-angiotensin system blockers, although careful titration is required to avoid symptomatic hypotension.[337]

In patients with symptomatic severe AS and HF, initiation of medical therapy or temporary improvement in symptoms should not delay intervention. Medication frequently requires re-adjustment following valve intervention and preventive therapies should be implemented according to current Guidelines.[338] In patients with persisting HF and/or reduced LVEF, medical therapy should be introduced before and up-titrated after valve intervention according to the current HF Guidelines.[339,340]

8.4. Indication for intervention

8.4.1. Symptomatic severe aortic stenosis

Symptomatic severe AS has an unfavourable prognosis if left untreated, and early intervention is strongly recommended in all patients with an estimated life expectancy exceeding 1 year[10] (*Figure 7*).

Intervention is recommended in all eligible symptomatic patients with high-gradient severe AS. However, management of patients with low-gradient AS is more challenging:

- Low-flow, low-gradient AS with reduced LVEF: reduced LV function usually improves after intervention if it is predominantly caused by excessive afterload.[341–343] However, improvement is unlikely if the primary cause is fibrosis due to myocardial infarction or cardiomyopathy. Intervention is recommended when severe AS is confirmed by CCT (calcium scoring) or stress echocardiography,[341] while patients with pseudo-severe AS should receive GDMT.[339,344] Although the absence of flow reserve is associated with increased surgical and long-term mortality, both modes of intervention improved LVEF and clinical outcomes in observational studies.[341,342,345–347]
- Low-flow, low-gradient AS with preserved LVEF: outcomes are improved with intervention (either TAVI or SAVR) compared with medical treatment alone in patients with low-flow, low-gradient AS and preserved LVEF.[348,349] Intervention should therefore be considered in patients with symptoms after careful confirmation that AS is severe.
- Normal-flow, low-gradient AS with preserved LVEF: prognosis of these patients is similar to that of moderate AS. Unless multimodality diagnostic evaluation clearly suggests severe AS, regular clinical and echocardiographic surveillance is recommended.[293,294,350]

8.4.2. Asymptomatic severe aortic stenosis

Up to 40% of patients with severe AS do not report symptoms at the time of diagnosis.[351,352] In roughly one-third of these, exercise testing can uncover symptoms or reduced exercise capacity attributable to AS,[102,103,318] and such patients should be treated as symptomatic. However, exercise testing is not always feasible because of frailty or impaired mobility.[353] Intervention is recommended in asymptomatic patients with severe AS and an LVEF of <50% without another cause.[14,102,318,319,354–360] For patients with severe high-gradient AS and no adverse prognostic features, close active clinical surveillance, so-called 'watchful waiting', has previously been the default management strategy. However, four RCTs comparing early AV intervention with clinical surveillance suggest that early intervention should be considered as an alternative in patients at low procedural risk.[360–363] This approach is reinforced if additional adverse prognostic features (very high V_{max},[14,353,364] elevated natriuretic peptides,[97,317,365,366] severe valve calcification,[303,364] rapid V_{max} progression,[353,364] or LVEF of <55%[14,354,356–359]) are present. Restricted local resources (that may impede close surveillance) or long waiting lists (that preclude prompt treatment when symptoms develop) are further arguments favouring an early intervention.

The Evaluation of TAVR Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis (EARLY TAVR) trial[360] randomized 901 patients to early TAVI or clinical surveillance and demonstrated a reduction of 50% in the primary composite endpoint of all-cause mortality, stroke, or unplanned hospitalization for cardiovascular causes associated with pre-emptive intervention.[360] The result was driven by 26.2% of the patients in the clinical surveillance group who converted to TAVI within 6 months of randomization due to the development of symptoms or adverse prognostic factors. There was no significant difference in strokes and all-cause mortality over 5-year follow-up.

In the Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients with Severe AS (EVoLVeD) RCT, which included 224 asymptomatic patients with severe AS and myocardial fibrosis (late gadolinium enhancement on CMR), early valve intervention (with SAVR or TAVI) failed to reduce the incidence of all-cause death or unplanned AS-related hospitalization compared with clinical surveillance.[361] However, the study was underpowered and the median time to intervention was prolonged to 5 months in the experimental arm.

Two previous smaller trials compared early SAVR with clinical surveillance. In the Randomized Comparison of Early Surgery vs Conventional Treatment in Very Severe Aortic Stenosis (RECOVERY) trial (145 patients), there was a reduction in all-cause mortality following early SAVR over a mean follow-up of 6.2 years.[362] In the Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis (AVATAR) trial (157 patients), a reduction in the composite primary endpoint was noted after a mean follow-up of 2.5 years with a significant reduction in HF hospitalizations and mortality at long-term follow-up.[363,367] Limitations of these surgical studies included their small sample sizes, enrolment of selected young populations at low surgical risk (mean ages 64 and 67 years, respectively), and inclusion of patients with mostly very severe AS.

A meta-analysis of the four RCTs showed that early intervention is associated with a significant reduction in unplanned cardiovascular or HF hospitalization and stroke, but not all-cause or cardiovascular mortality. Limitations of this analysis include the heterogeneity of the pooled trials and lack of granularity with respect to specific events owing to the study-level analysis.[368]

Additional RCTs (NCT04204915 and NCT03972644) will further inform and refine the management of patients with severe asymptomatic AS.

8.4.3. Moderate aortic stenosis

Surgical intervention for moderate AS should only be performed in patients undergoing CABG,[369] surgery of the ascending aorta or other valve disease (see *Section 13*). There is evidence of an association between moderate AS and adverse outcomes in patients with and without HF with reduced EF (HFrEF),[370–372] but it is unknown whether this is causal or related to comorbidities. In an early terminated trial randomizing 178 patients with moderate AS and HFrEF to TAVI or clinical surveillance, no differences with respect to hard clinical endpoints were

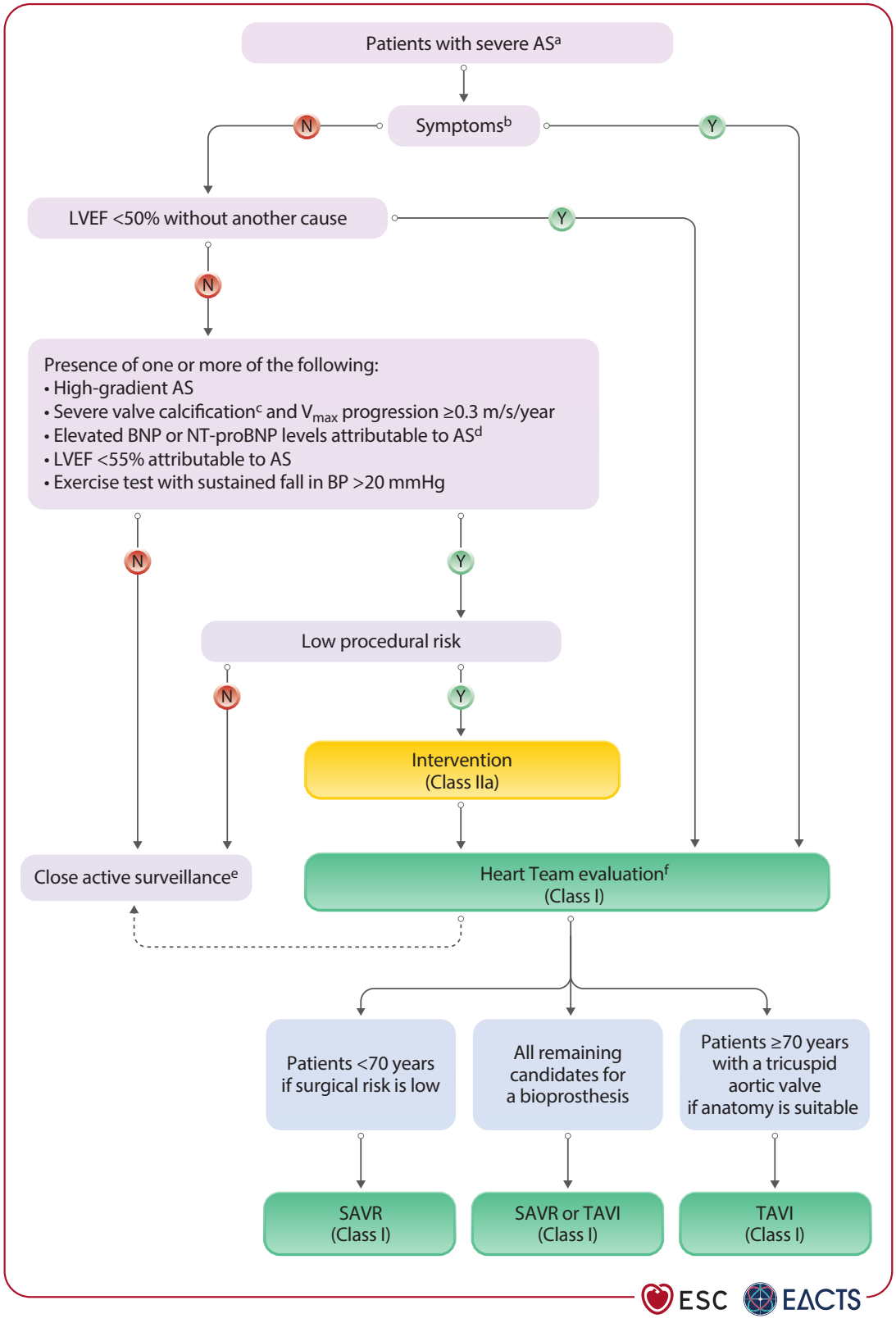

Figure 7 Management of patients with severe aortic stenosis. AS, aortic stenosis; AVCS, aortic valve calcium score; BNP, brain natriuretic peptide; BP, blood pressure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; V_{max}, peak transvalvular velocity. [a]Integrative imaging assessment of AS (*Figure 6*). [b]Confirmed by a normal exercise test, if feasible. [c]AVCS >2000 in men, >1200 in women. [d]More than three times age- and sex-corrected normal range. [e]Educate patient and reassess at least every 6 months (or promptly if symptoms occur). [f]Heart Team assessment based upon individual patient factors (*Figure 9*; *Recommendation Table 4*). Dashed arrow only applies to asymptomatic patients.

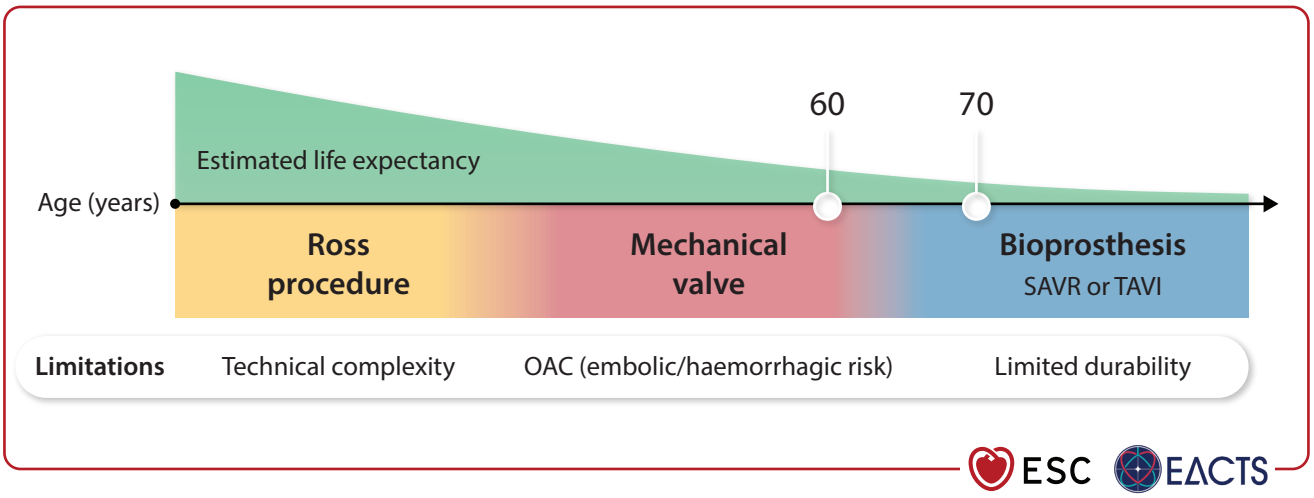

Figure 8 Aortic valve treatment options. OAC, oral anticoagulation; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

found, while patients undergoing TAVI had improved quality of life (change in KCCQ of 12.8 ± 21.9 points vs 3.2 ± 22.8 points; $P = 0.018$).[373] Ongoing trials are expected to provide new insights (NCT04889872 and NCT05149755).

8.5. Treatment options

The mode of AV intervention depends on the estimated life expectancy, expected prosthesis durability, patient preference, and specific trade-offs associated with different treatment options (*Figure 8*). Most patients with AS undergoing valve intervention in Europe and North America receive a BHV (by either SAVR or TAVI).[374] BHVs do not require long-term anticoagulation but have limited durability that varies between devices and is inversely associated with age.[375] MHVs are durable but require long-term anticoagulation, with associated thromboembolic and bleeding risks.[260,376] In general, an MHV should be preferred in patients aged <60 years and a BHV in patients aged >65 years in aortic position (see *Section 14.1*).

The Ross procedure (replacement of the AV with the patient's pulmonary autograft combined with homograft pulmonary valve replacement) is associated with excellent long-term survival when performed in selected patients at centres with high expertise.[260,263,377,378] Although a valuable surgical option in young patients with prolonged life expectancy in whom anticoagulation is undesirable or contraindicated, it is associated with procedural complexity and the need for reintervention in ~15% of patients within 15 years (*Figure 8*).[263,377]

Balloon aortic valvuloplasty may be rarely considered as a bridge to TAVI or SAVR in carefully selected patients with decompensated AS, and in those with severe AS who require urgent high-risk non-cardiac surgery (NCS) (see *Section 15.2.1*). The procedure carries significant risks of acute complications.[379]

A substantial increase in the number of patients undergoing AV intervention has been observed over the past decade as a consequence of the introduction of TAVI, improved diagnostic techniques, and evolving indications for intervention.[374,380–383] Nevertheless, there is still wide variation in worldwide access to TAVI as a result of high device costs in comparison with surgical prostheses and variation in healthcare resources and reimbursement systems between countries.[384–386] In addition, registries suggest that late referral and undertreatment remain frequent.[12,387]

8.5.1. The mode of intervention in candidates for a bioprosthesis

The two modes of BHV replacement, TAVI and SAVR, have been compared in RCTs across the spectrum of surgical risk in predominantly elderly patients with tricuspid AS.

In patients unsuitable for surgery, TAVI was superior to medical therapy with a number-needed-to-treat of five to prevent one death at 1-year follow-up.[388] Subsequently, RCTs showed non-inferiority of TAVI compared with SAVR in patients at high,[389–391] intermediate,[3,392,393] and low surgical risk,[1,394,395] with comparable longer-term outcomes demonstrated during follow-up periods ranging from 4 to 10 years.[2,4,396–398] Of note, the majority of patients included in RCTs were male, while patients with low-flow low-gradient AS or adverse anatomical characteristics (including BAVs or complex CAD) were excluded per protocol.

Meta-analyses of RCTs show a risk reduction in all-cause death and disabling stroke with TAVI in low-risk patients at 1 year, but no differences to SAVR at longer-term follow-up or in patients at intermediate or high surgical risk.[399,400] The early benefit of TAVI in low-risk patients has since been corroborated in the investigator-initiated Randomized, Multicenter, Event-Driven Trial of TAVI vs SAVR in Patients with Symptomatic Severe Aortic-Valve Stenosis (DEDICATE), which met its non-inferiority target with a composite of death and stroke rate at 1 year of 5.4% in the TAVI group vs 10.0% in the SAVR group [hazard ratio (HR), 0.53; 95% confidence interval (CI), 0.35–0.79] and all-cause death rates of 2.6% and 6.2% (HR 0.43; 95% CI, 0.24–0.73), respectively.[395]

Rates of vascular complications and paravalvular leak (PVL) are consistently higher after TAVI despite refined transcatheter heart valve (THV) designs, whereas severe bleeding, acute kidney injury, and new-onset AF are more frequent after SAVR.[2,4,399,401] Even though PVL has been associated with adverse clinical outcomes,[402,403] it does not seem to impact the comparison of clinical outcomes between TAVI and SAVR in RCTs.[2,4,395]

New pacemaker implantations are more frequent after TAVI, particularly when using self-expanding valves.[3,394,404] Conflicting data exist regarding the long-term impact of new pacemaker implantation or new-onset left bundle branch block following AV intervention.[405–407] Patients undergoing TAVI have quicker recoveries, shorter hospital

stays, and more rapid improvements in quality of life compared with those who undergo SAVR.[1,2,408,409]

Available data do not suggest systematic differences in durability between the two treatment modalities. Randomized controlled trials and observational studies have reported comparable rates of BHV failure related to SVD with transcatheter and surgical valves up to 10 years.[2,398,410] However, potential selection and survival bias, the use of variable definitions of SVD, limited follow-up durations, differential attrition rates,[2,4,396,400] competing risk of death, and the use of multiple valve types in the surgical arms of RCTs may limit direct comparison.[411]

Although conclusive evidence is still lacking, concomitant non-complex CAD can be addressed either by CABG or PCI, while complex CAD favours CABG (see *Section 6.1*). In the only RCT comparing these two strategies, the transcatheter valve and vessels (TCW) trial, randomization of patients with severe AS and concomitant CAD to FFR-guided PCI plus TAVI resulted in fewer deaths and major bleeding events compared with combined SAVR plus CABG at 12 months.[412] However, inferences from trial results are limited due to early termination, modest sample sizes, event rates deviating from those observed in registries and other RCTs, and a low prevalence of complex CAD.

8.5.1.1. Age and life expectancy

The relationship between estimated life expectancy and prosthetic heart valve durability determines the likelihood of a future reintervention. Although life expectancy may be a theoretically better guide than age alone for treatment decisions, it is difficult to estimate for an individual patient owing to large geographical (https://ghdx.healthdata.org/record/ihme-data/gbd-2019-life-tables-1950-2019) and interindividual variability.[413] In combination with cardiac and extracardiac comorbidities, as well as anatomical factors, age contributes to risk estimation and represents a pragmatic surrogate for life expectancy. In addition, age thresholds characterize the populations enrolled in RCTs better than life expectancy. It is notable that younger patients with AS seem to have lower life expectancy than the general population despite valve replacement, whereas life expectancy almost normalizes after treatment in older cohorts.[414,415] While several trials compared TAVI with SAVR in study populations aged 70–85 years accross the surgical risk spectrum, the representation of patients aged <70 years in RCTs is low and therefore evidence limited.[1,394,395,416]

8.5.1.2. Anatomical features

The advantages of TAVI demonstrated in RCTs are largely confined to patients treated via the transfemoral approach.[401] While SAVR remains the preferred treatment option when iliofemoral artery disease precludes transfemoral TAVI, TAVI via a non-transfemoral access (transaxillary, transcarotid, transcaval, transinnominate, or transapical) constitutes an alternative supported by observational data in patients unsuitable for surgery.[417–423]

Other anatomical factors that favour SAVR or led to exclusion of patients from RCTs comparing TAVI with SAVR are (*Figure 9*):

- Aortic annular dimensions that lie outside sizing recommendations for currently available transcatheter devices.
- Excessive or bulky calcifications of the annulus or LVOT, which increase the risk of PVL and annular rupture.[424,425]
- Increased risk of coronary obstruction with TAVI (cusp height greater than coronary height in combination with shallow sinuses of Valsalva, or high calcium burden of corresponding cusp).[329]

In contrast, anatomical findings such as porcelain aorta, severe chest deformation, or intact grafts post-CABG favour TAVI. Right anterior thoracotomy or upper hemisternotomy are minimally invasive access alternatives to sternotomy for performing SAVR, which are being used with increasing frequency.[426,427]

In BAV patients, severe AS usually occurs earlier compared with tricuspid AV and is frequently associated with aortopathy.[219,281,428] Prevalence of BAV anatomy sharply increases in younger AS patients.[429] BAV anatomy adds complexity to TAVI because of asymmetric AV calcification and elliptical annular shape, as well as the lack of standardization of valve sizing.

Patients with BAV have been excluded from almost all landmark RCTs comparing TAVI with SAVR to date.[429,430] In the NOTION 2 trial, the composite of all-cause death, stroke, or valve- or HF-related rehospitalization was numerically more frequent (seven vs two events) at 1 year in the underpowered subgroup of 100 patients with BAV (HR, 3.8; 95% CI, 0.8–18.5; $P = 0.07$).[416] Whereas some observational studies report favourable outcomes with TAVI in selected BAV patients,[430–432] others suggest higher stroke, annular rupture, and PVL rates as compared with TAVI in tricuspid AS.[433] Heavy cusp calcification, particularly in conjunction with a calcified raphe, is associated with increased risk of aortic root injury, PVL, and mortality after TAVI.[434] Data on TAVI in two-sinus BAV (Sievers type 0) are scarce.[219,435]

For the above-mentioned reasons, SAVR remains the primary mode of treatment for stenotic BAV, particularly if patients are young or have coexistent aortopathy or unfavourable valve morphology. TAVI may be considered in patients at increased surgical risk, if anatomy is suitable.

Patients with small annuli in relation to their body stature are at increased risk of prosthesis–patient mismatch (PPM) after valve replacement. Annular enlargement allows for implantation of larger BHVs with SAVR. Given its technical complexity it should be performed in experienced centres, and the benefit must be balanced against a possibly higher risk of operative mortality.[436] Prostheses with supra-annular design reduce PPM risk with TAVI, although randomized long-term data evaluating the impact on clinical outcomes or valve durability are pending.[394,437,438]

8.5.1.3. Lifetime management

Decision-making concerning the mode of intervention and type of prosthesis needs to integrate expected valve durability, and the potential risks of future reinterventions (*Figure 9*). Surgical THV explantation followed by SAVR is a rare (<1% of all TAVI procedures) but technically challenging procedure.[439–441] Although its incidence among patients undergoing TAVI is stable, absolute numbers are increasing due to the total increase in TAVI procedures performed and the perioperative risk remains high (early mortality rates as high as 12%–17%).[440–445] The majority of surgical THV explantations are performed in patients at high surgical risk with urgent or emergent, non-SVD-related indication for reintervention (frequently endocarditis) within 2 years after TAVI.[440,442–444]

Implanting a transcatheter aortic valve inside a surgical (TAV-in-SAV) or prior transcatheter valve (TAV-in-TAV) is associated with lower peri-procedural risk compared with redo SAVR.[446–451] However, valve-in-valve implantation (particularly TAV-in-SAV) increases the risk of severe PPM,[448] which has been linked to adverse outcomes in observational studies.[452–455] In addition, valve-in-valve implantation immobilizes the leaflets of the failed prosthesis in an open position, creating a covered tube (or neo-skirt) that may cause direct coronary obstruction in patients with shallow sinuses of Valsalva or indirect

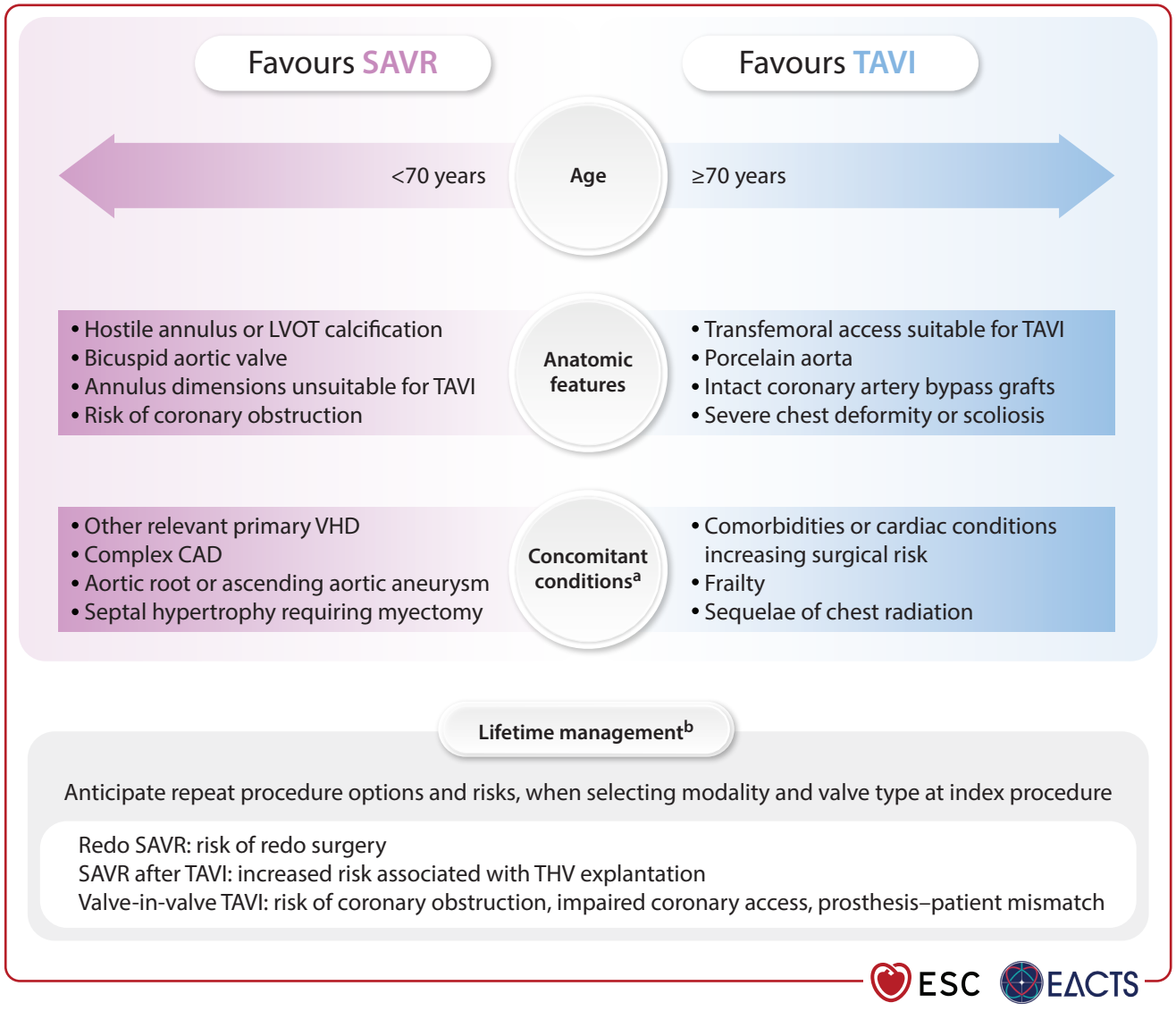

Figure 9 Factors to be considered when selecting the mode of intervention for aortic stenosis. CAD, coronary artery disease; LV, left ventricular; LVOT, left ventricular outflow tract; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; THV, transcatheter heart valve; VHD, valvular heart disease. [a]LV thrombus and infective endocarditis are relative contraindications to TAVI and are therefore not listed. [b]Particularly relevant for patients in whom the anticipated life expectancy is thought to exceed valve durability.

coronary flow obstruction as a result of sinus sequestration if the ascending aorta is narrow and the neo-skirt reaches the sinotubular junction.[456,457]

The risk of coronary obstruction varies considerably depending on the index valve type, and is particularly increased if a stentless SAV or stented SAV with externally mounted leaflets is in place.[457] The risk of sinus sequestration at the time of TAV-in-TAV implantation is particularly increased in supra-annular valves with a high neo-skirt.[458,459] Even if coronary flow is preserved, coronary access may be difficult or impossible in a relevant proportion of patients after valve-in-valve implantation, especially after TAV-in-TAV.[460–462]

In patients who require a reintervention due to dysfunction of a surgical or transcatheter bioprosthesis, but are at increased risk of severe PPM or coronary obstruction, redo SAVR may be preferable despite the increased surgical risk. Fracture of surgical valves and leaflet modification techniques have been proposed for patients at high surgical risk and, if contemplated, should be performed in carefully selected patients at experienced centres (*Table 6*).[463,464]

The need for a meticulous CT-based anatomical analysis is paramount in patients with an estimated life expectancy exceeding the assumed valve durability to anticipate future risks at the time of the index valve intervention. Based on individual assessment, the following measures should be considered with respect to lifetime management:

- Use of surgical and transcatheter valves with proven long-term durability to reduce the likelihood of reintervention.[2,4,375,410,411,465–467]
- SAVR with aortic root enlargement or implantation of a supra-annular transcatheter valve in patients with a small annulus at risk of severe PPM based on the predicted effective orifice area (EOA).[436,438,468,469]
- No implantation of stentless prostheses or prostheses with externally mounted leaflets in patients at risk of coronary obstruction during future TAV-in-SAV implantation.[457]

- Anticipation of the feasibility and risks of a possible future TAV-in-TAV procedure considering related technical aspects at the index TAVI (device choice, neo-skirt height, commissural alignment, and implantation depth).[456,470]

Considering life-time management aspects and the scarcity of randomized data in patients younger than 70 years, SAVR remains the preferred treatment in patients <70 years of age if surgical risk is low. TAVI is recommended as the primary treatment modality in elderly patients ≥70 years of age with a tricuspid AV, if anatomy is suitable and transfemoral access is feasible, to reduce the risk of early adverse outcomes and accelerate recovery.

For all other candidates for a bioprosthesis, the most appropriate mode of intervention should be carefully selected by the Heart Team, taking into account procedural risk based on anatomical characteristics and comorbidities, expected outcomes, lifetime management considerations, and patient preference (*Figure 9*; *Recommendation Table 4*). Recommendations for concomitant valve replacement at the time of CABG or ascending aortic surgery are listed in *Recommendation Table 5*.

Recommendation Table 4 — Recommendations on indications for intervention in symptomatic and asymptomatic severe aortic stenosis, and recommended mode of intervention (see also Supplementary data online, *Evidence Tables 9–13*)

Recommendations	Class[a]	Level[b]
Symptomatic patients with severe aortic stenosis		
Intervention is recommended in symptomatic patients with severe, high-gradient AS [mean gradient ≥40 mmHg, V_{max} ≥4.0 m/s, AVA ≤1.0 cm^2 (or ≤0.6 cm^2/m^2 BSA)].[388,471–474]	I	B
Intervention is recommended in symptomatic patients with low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) AS with reduced LVEF (<50%) after careful confirmation that AS is severe.[342,345,346,348,475]	I	B
Intervention should be considered in symptomatic patients with low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) AS with normal LVEF (≥50%) after careful confirmation that AS is severe.[c] [293,348,349,476–481]	IIa	B
Asymptomatic patients with severe aortic stenosis		
Intervention is recommended in asymptomatic patients with severe AS and LVEF <50% without another cause.[14,354–359]	I	B
Intervention should be considered in asymptomatic patients (confirmed by a normal exercise test, if feasible) with severe, high-gradient AS and LVEF ≥50% as an alternative to close active surveillance, if the procedural risk is low.[360–363,367,368]	IIa	A
Intervention should be considered in asymptomatic patients with severe AS and LVEF ≥50% if the procedural risk is low and one of the following parameters is present: • Very severe AS (mean gradient ≥60 mmHg or V_{max} >5.0 m/s).[14,362,363,482–484] • Severe valve calcification (ideally assessed by CCT) and V_{max} progression ≥0.3 m/s/year.[303,353,364] • Markedly elevated BNP/NT-proBNP levels (more than three times age- and sex-corrected normal range, confirmed on repeated measurement without other explanation).[97,365] • LVEF <55% without another cause.[14,354,356–359]	IIa	B
Intervention should be considered in asymptomatic patients with severe AS and a sustained fall in BP (>20 mmHg) during exercise testing.	IIa	C
Mode of intervention		
It is recommended that AV interventions are performed in Heart Valve Centres that report their local expertise and outcome data, have on-site interventional cardiology and cardiac surgical programmes, and a structured collaborative Heart Team.	I	C
It is recommended that the mode of intervention is based on Heart Team assessment of individual clinical, anatomical, and procedural characteristics, incorporating lifetime management considerations and estimated life expectancy.	I	C
TAVI is recommended in patients ≥70 years of age with tricuspid AV stenosis, if the anatomy is suitable.[d] [1–4,389–397,465,485,486]	I	A
SAVR is recommended in patients <70 years of age, if the surgical risk is low.[e] [413,429,487]	I	B
SAVR or TAVI are recommended for all remaining candidates for an aortic BHV according to Heart Team assessment.[2,4,396,397,429,488–490]	I	B
Non-transfemoral TAVI should be considered in patients who are unsuitable for surgery and transfemoral access.[417–423,491–498]	IIa	B
TAVI may be considered for the treatment of severe BAV stenosis in patients at increased surgical risk, if the anatomy is suitable.[430–432,434,499–502]	IIb	B
Balloon aortic valvotomy may be considered as a bridge to SAVR or TAVI in haemodynamically unstable patients, and (if feasible) in those with severe AS who require urgent high-risk NCS.	IIb	C

AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; BAV, bicuspid aortic valve; BHV, biological heart valve; BNP, brain natriuretic peptide; BP, blood pressure; BSA, body surface area; CCT, cardiac computed tomography; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; NCS, non-cardiac surgery; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality; SVi, stroke volume index; TAVI, transcatheter aortic valve implantation; V_{max}, peak transvalvular velocity.

[a]Class of recommendation.

[b]Level of evidence.

[c]Explanations (such as measurement errors, uncontrolled blood pressure, and conditions lowering the stroke volume) other than severe AS for a small AVA but low gradient despite preserved LVEF are frequent and must be carefully excluded.

[d]Suitability regarding transfemoral access, annulus dimensions, device landing zone calcification pattern, and coronary obstruction risk (*Figure 9*).

[e]Surgical risk based on STS-PROM (http://riskcalc.sts.org/stswebriskcalc/#/calculate) and EuroSCORE II (http://www.euroscore.org/calc.html) <4% and Heart Team assessment.

Recommendation Table 5 — Recommendations on indications for concomitant aortic valve replacement at the time of coronary artery bypass grafting or ascending aorta surgery

Recommendations	Class[a]	Level[b]
SAVR is recommended in symptomatic and asymptomatic patients with severe AS undergoing CABG or surgical intervention on the ascending aorta.	I	C
SAVR should be considered in symptomatic and asymptomatic patients with moderate AS[c] undergoing CABG or surgical intervention on the ascending aorta.	IIa	C

AS, aortic stenosis; AVA, aortic valve area; CABG, coronary artery bypass grafting; SAVR, surgical aortic valve replacement.
[a]Class of recommendation.
[b]Level of evidence.
[c]Defined as an AVA of 1.0–1.5 cm^2 (or mean aortic gradient of 25–40 mmHg) in normal-flow conditions. Clinical assessment is essential to determine whether SAVR is appropriate for an individual patient.

8.6. Follow-up

The rate of progression of AS varies widely and asymptomatic patients, their family, and medical caregivers need careful education, with particular emphasis on the importance of regular follow-up (ideally at a Heart Valve Centre)[14] and prompt reporting of symptoms. Asymptomatic patients with severe AS should be followed up at least every 6 months to allow detection of early symptoms (using exercise testing if complaints are inconclusive) and any change in echocardiographic parameters (particularly LVEF). Serial measurements of natriuretic peptides can provide additional useful information regarding the timing of treatment.

Younger patients with mild AS and no significant leaflet calcification may be followed up every 2–3 years. With increasing stenosis severity, progression accelerates and follow-up intervals should be gradually reduced.[283,503] Several studies suggest that the prognosis of moderate degenerative AS is worse than previously considered,[504,505] particularly if there is significant valve calcification, and these patients should be re-evaluated at least annually.

Cardiac rehabilitation is frequently performed after AV intervention, especially after surgery and in elderly patients, and is associated with improved activities of daily living and 6-minute walking distance.[506] After valve intervention, an early echocardiographic examination within the first weeks after valve replacement is recommended to document baseline prosthetic valve function. Cardiological evaluations and echocardiographic examinations are recommended annually in patients with a bioprosthesis, and whenever changes in clinical symptoms or signs suggestive of valve dysfunction are noted.

9. Mitral regurgitation

Chronic MR is one of the most common acquired valve pathologies,[12,187] while acute MR is observed in the context of infective endocarditis, chordal rupture, or as a complication of myocardial infarction (papillary muscle rupture). MR either relates to anatomical changes of the MV apparatus (primary), or to LV or LA dilatation and dysfunction (secondary).[193] Since natural history, prognosis, and management differ according to aetiologies, populations should be clearly distinguished in clinical practice and research.[12,507]

9.1. Primary mitral regurgitation

9.1.1. Prevalence and aetiology

Primary mitral regurgitation relates to an anatomical lesion of one or more of the three main components (not including the annulus) of the MV apparatus (valve leaflets, chordae tendineae, and papillary muscles). PMR is observed in 55% of patients with MR who require treatment.[507] While degenerative disease related to fibroelastic deficiency or myxomatous alterations (in its most severe form, Barlow's disease) are the most common aetiologies in higher-income countries, RHD is most frequently found in the rest of the world. MV endocarditis is a separate entity of PMR caused by acute or chronic infectious conditions and is discussed in the corresponding Guidelines.[5] In a small subgroup of patients, PMR is associated with a higher incidence of ventricular arrhythmias, and sudden cardiac death has been reported in individual cases, especially in patients with Barlow's disease.[508] The arrhythmogenic burden is independent from MR severity and has been associated with mitral annular disjunction. Atrial displacement of the posterior MV leaflet hinge point is assumed to cause excessive mobility of the valvular apparatus and increases tension on the papillary muscles and the posterobasal myocardium, causing local fibrosis, which may lead to ventricular arrhythmias and sudden cardiac death.[509]

9.1.2. Evaluation

9.1.2.1. Echocardiography and right heart catheterization

Echocardiography is the diagnostic method of choice for the quantification of MR, determination of its aetiology, and identification of cardiac consequences (*Figure 10*). TTE is used for initial evaluation that includes: (i) assessment of valve morphology (presence and location of prolapse or flail, calcifications, and/or mitral annular disjunction); (ii) integrative severity grading; and (iii) quantification of LV and LA dimensions and function, as well as assessment of concomitant RV dysfunction.[46] Quantitative parameters such as the effective regurgitant orifice area (EROA) have prognostic implications.[510,511] Volumetric methods provide additional information on MR severity [RVol and regurgitant fraction (RF)].[512] Accurate colour flow settings must be used to avoid overestimation of MR severity.

Transoesophageal echocardiography (TOE) represents the method of choice to assess valve anatomy, leaflet quality, motion, and coaptation, as well as to confirm MR severity.[513] Three-dimensional TOE provides an excellent morphological and functional view of the different valve segments, and should be used systematically when planning and performing surgical or transcatheter repair.[514]

Exercise echocardiography evaluates dynamic changes in regurgitant jet and pulmonary pressures during peak exercise, and might be helpful in patients with discordant symptoms and regurgitation severity at rest.[515,516]

In asymptomatic patients with severe PMR, increased LV or LA dimensions, as well as elevated pulmonary pressures (>50 mmHg at rest), moderate or more secondary TR, and AF are important markers of worse prognosis, and should be considered for intervention timing (*Figure 11*; *Section 9.1.4*).[517,518]

Right heart catheterization remains important in patients with PMR for confirmation of pulmonary artery pressures in case of discrepancy between echocardiographic MR severity and clinical symptoms, as well as in the presence of concomitant lung disease.[519]

9.1.2.2. Biomarkers

Cardiac biomarkers are recognized indicators of disease severity with prognostic implications, but may also be non-specific. NT-proBNP levels are directly related to the New York Heart Association (NYHA) functional class in PMR.[520]

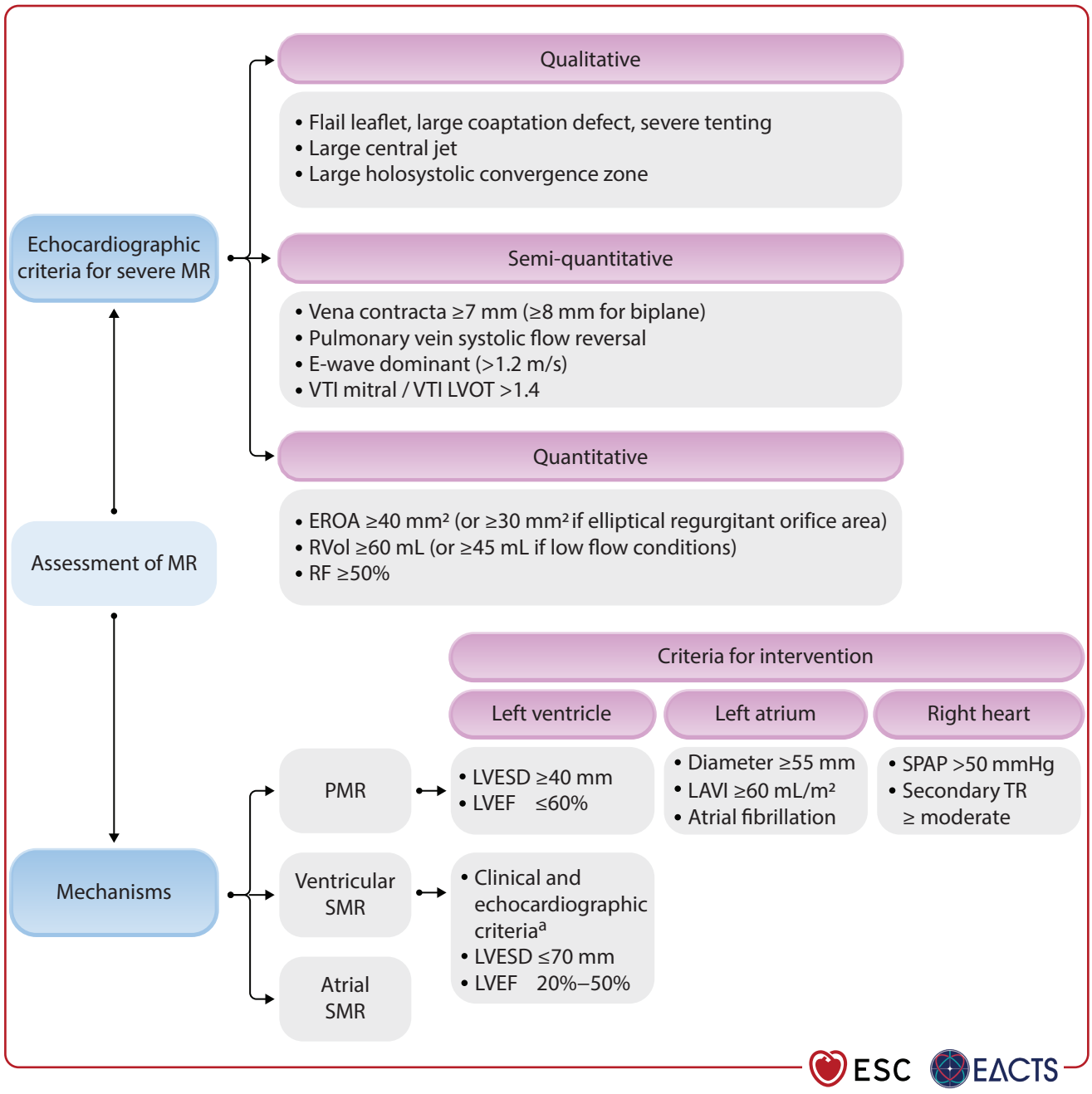

Figure 10 Echocardiographic assessment of patients with mitral regurgitation. EROA, effective regurgitant orifice area; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVOT, left ventricular outflow tract; MR, mitral regurgitation; PMR, primary mitral regurgitation; RF, regurgitant fraction; RVol, regurgitant volume; SMR, secondary mitral regurgitation; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation; VTI, velocity time integral. [a]See *Table 7* for criteria predicting outcome improvement.

In a multicentre registry including more than 1300 patients with PMR, increased BNP level was an independent predictor of long-term mortality under medical treatment. However, pre-operative BNP activation did not impact long-term mortality after surgical treatment.[96]

9.1.2.3. Cardiac magnetic resonance and computed tomography

Cardiac magnetic resonance imaging is an alternative to precisely quantify RVol and RF in cases of inconclusive or discordant measurements, and the gold standard to determine cardiac dimensions and chamber volumes.[521,522] The combination of planimetered volumetric methods and phase contrast measurement of the MV inflow are used for this purpose.[523] In patients with Barlow's disease and mitral annular disjunction, CMR-detected myocardial fibrosis[524] has been associated with ventricular arrhythmias and sudden cardiac death.[525]

Cardiac computed tomography provides high-resolution anatomical details of the entire MV apparatus[523,526] and increasingly plays a role in MV intervention planning, particularly in the assessment of arterial access for extracorporeal circulation and the presence of MV calcification in minimally invasive surgery,[527] as well as the feasibility of transcatheter MV implantation (TMVI) based on annulus size and risk of LVOT obstruction.[528]

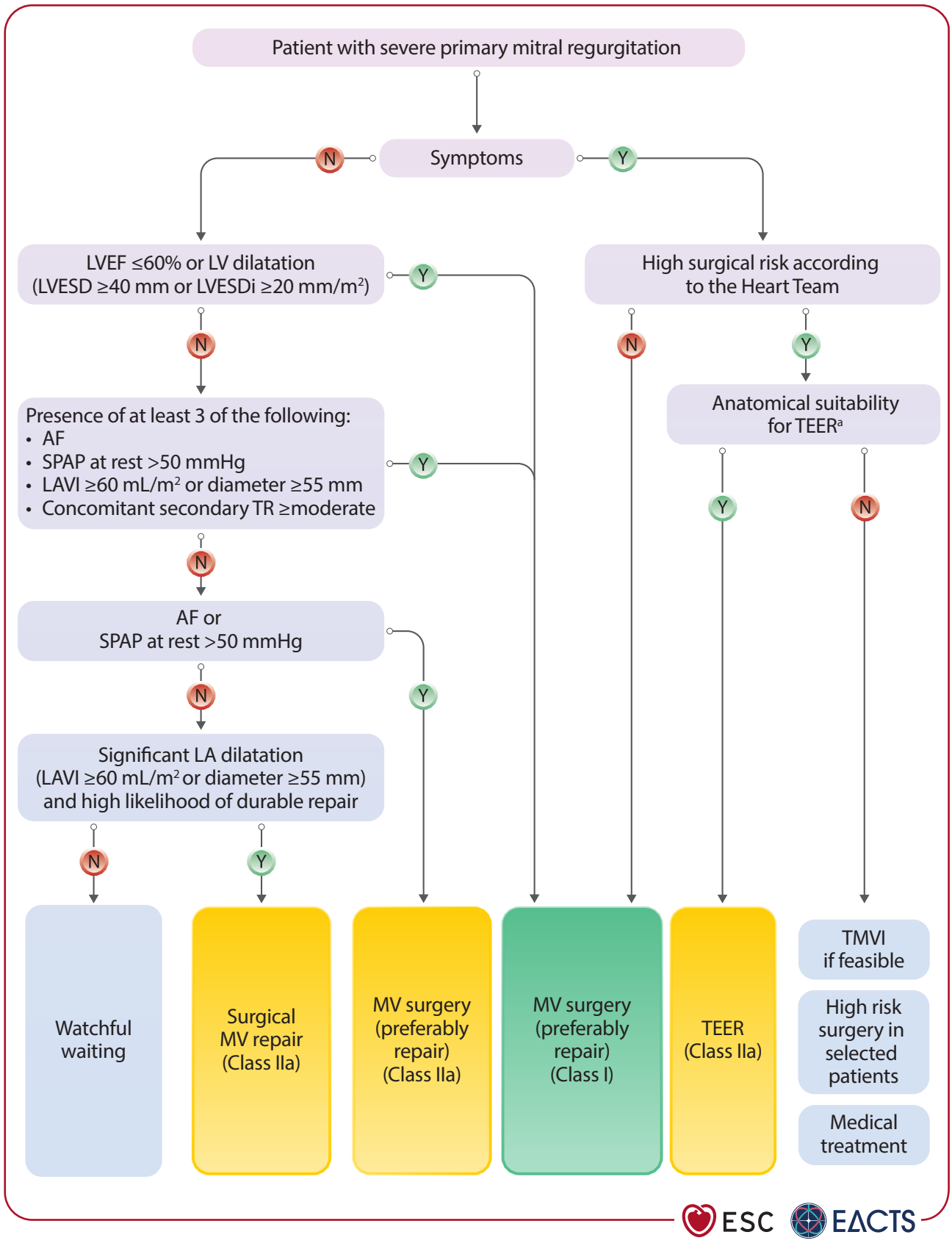

Figure 11 Management of patients with severe primary mitral regurgitation. AF, atrial fibrillation; LA, left atrial; LAVI, left atrial volume index; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to BSA; MV, mitral valve; SPAP, systolic pulmonary artery pressure; TEER, transcatheter edge-to-edge repair; TMVI, transcatheter mitral valve implantation; TR, tricuspid regurgitation. [a]See Supplementary data online, *Table S2*.

Due its high sensitivity for detection of calcifications, CCT is instrumental for procedural planning (surgical and transcatheter) in patients with MAC.[529]

9.1.2.4. Genetic evaluation

There is increasing evidence that specific mitral pathologies may be associated with genetic conditions. A meta-analysis of six genome-wide association studies identified 14 potential genetic loci associated with primary MR. By comprising epigenetic, transcriptional, and proteomic data, the following genes could be identified as potential genetic sources of the pathology: *LMCD1*, *SPTBN1*, *LTBP2*, *TGFB2*, *NMB*, and *ALPK3*.[530] However, genetic testing is not recommended in routine practice.

9.1.3. Medical therapy

Medical therapy has a limited role in patients with PMR. Afterload reduction with sodium nitroprusside has been used as a bridge to an intervention in patients with acute severe PMR without signs of hypotension. Inotropic agents and diuretics are usually indicated to reduce filling pressures and control pulmonary congestion, while the implantation of an intra-aortic balloon pump helps to further reduce afterload in exceptional cases of acute PMR.

In chronic PMR without signs of LV dysfunction or criteria for an intervention, there is no evidence supporting prophylactic afterload reduction. Patients with PMR and impaired LV function should receive GDMT according to HF Guidelines.[340]

9.1.4. Indications for intervention

Urgent surgery or transcatheter treatment is indicated in patients with acute severe PMR because it is poorly haemodynamically tolerated. In patients with papillary muscle rupture and endocarditis, surgical valve replacement is generally required, while acute degenerative chordal rupture can be treated with surgical MV repair or TEER in high-risk patients.

Indications for surgery in patients with chronic asymptomatic and symptomatic PMR are summarized in *Recommendation Table 6* and *Figure 11*. In cases of severe PMR, restoring the anatomy by surgical MV repair, including annuloplasty, is the treatment of choice in operable patients when an optimal and durable result is expected. According to contemporary data, the procedure can be performed with a low mortality risk (1.2%) in appropriately selected patients.[531] Compared with replacement, MV repair has been associated with lower peri-operative mortality along with significantly better long-term survival and functional outcomes.[532,533] Repair of more complex pathologies such as valves with annular or leaflet calcifications, as well as in cases of RHD, is challenging and should be attempted in experienced Heart Valve Centres.[534–536] When MV repair is not feasible, valve replacement with preservation of the subvalvular apparatus should be performed.[537]

High-risk and elderly patients with chronic PMR, though uncommon, may benefit from a less-invasive M-TEER procedure.[538] Peri-interventional and mid-term results with regard to residual MR and mean transmitral gradient are closely related to patient outcomes.[538] The use of latest-generation devices along with a growing team experience have improved results, and allow for the successful treatment of more complex anatomical conditions (Supplementary data online, *Table S2*).[539,540] The decision regarding the mode of intervention or conservative treatment should be made by the Heart Team, considering clinical and anatomical characteristics, as well as procedural risks and patient preference. The longer-term efficacy of TEER compared with surgery is still under investigation in high- (NCT03271762) and intermediate-risk PMR patients (NCT04198870), as well as in all-risk-category patients >60 years of age (NCT05051033).[541] TMVI is very effective in abolishing MR in selected high-risk patients, particularly those with complex MV anatomy for TEER (Supplementary data online, *Table S2*).[542,543] The major drawbacks of current TMVI systems include limited availability, high screening failure rate, as well as the risk of LVOT obstruction and valve thrombosis. Limited data exist for PMR patients and regarding mid-term prosthesis durability.

In patients with asymptomatic PMR with signs of LV dysfunction (i.e. LVEF ≤60%, LVESD ≥40 mm, or LVESDi ≥20 mm/m^2) the benefit of early surgery is well established.[544–546] Furthermore, there is increasing evidence that the presence of LA dilatation [LA volume index (LAVI) ≥60 mL/m^2 or LA diameter ≥55 mm], AF, systolic pulmonary artery pressure (SPAP) at rest of >50 mmHg, and concomitant moderate or severe secondary TR are associated with worse long-term prognosis irrespective of LV function after corrective surgery, and should therefore prompt referral in low-risk patients, particularly if a high probability of MV repair is expected.[517,518,547] A recent study showed that women have a higher risk of long-term mortality after MV repair than men, even at lower degrees of ventricular dilatation and dysfunction, suggesting the potential usefulness of sex-specific indexed thresholds.[548] Ventricular arrhythmias in patients with MV prolapse have been linked to impaired prognosis and possibly sudden cardiac death, especially in the presence of mitral annular disjunction.[549–551] Ring annuloplasty stabilizes the posterior annulus, reduces traction on the subvalvular apparatus,[552] and may lower the risk of arrhythmias.[553] Minimally invasive surgery via right mini-thoracotomy is used with increasing frequency in experienced centres.[554–556] A recent RCT demonstrated similar safety and efficacy compared with conventional sternotomy. Mini-thoracotomy was associated with shorter hospital stay and improved physical activity within the first 6 weeks after surgery, a difference that disappeared at 12 weeks.[557] The use of minimally invasive MV surgery may therefore be considered to reduce hospital stay and accelerate recovery in experienced centres. However, in a national registry, these benefits were less clear.[558]

Recommendation Table 6 — Recommendations on indications for intervention in severe primary mitral regurgitation (see also Supplementary data online, *Evidence Tables 14–16*)

Recommendations	Class[a]	Level[b]
MV repair is the recommended surgical technique to treat patients with severe PMR when the result is expected to be durable.[26,532,533,559,560]	I	B
MV surgery is recommended in symptomatic patients with severe PMR considered operable by the Heart Team.[26,532,533,561]	I	B
MV surgery is recommended in asymptomatic patients with severe PMR and LV dysfunction (LVESD ≥40 mm or LVESDi ≥20 mm/m^2 or LVEF ≤60%).[522,544,545]	I	B

Continued

Surgical MV repair is recommended in low-risk asymptomatic patients with severe PMR without LV dysfunction (LVESD <40 mm, LVESDi <20 mm/m^2, and LVEF >60%) when a durable result is likely, if at least three of the following criteria are fulfilled:[517,547,562–564] • AF • SPAP at rest >50 mmHg • LA dilatation (LAVI ≥60 mL/m^2 or LA diameter ≥55 mm) • Concomitant secondary TR ≥ moderate.	I	B
MV surgery should be considered in asymptomatic patients with severe PMR without LV dysfunction (LVESD <40 mm, LVESDi <20 mm/m^2, and LVEF >60%) in the presence of PH (SPAP at rest >50 mmHg), or AF secondary to MR.[517,518,562,565]	IIa	B
Surgical MV repair should be considered in low-risk asymptomatic patients with severe PMR without LV dysfunction (LVESD <40 mm, LVESDi <20 mm/m^2, and LVEF >60%) in the presence of significant LA dilatation (LAVI ≥60 mL/m^2 or LA diameter ≥55 mm), when performed in a Heart Valve Centre and a durable repair is likely.[517,565]	IIa	B
TEER should be considered in symptomatic patients with severe PMR who are anatomically suitable and at high surgical risk according to the Heart Team.[538,540,566]	IIa	B
Minimally invasive MV surgery may be considered at experienced centres to reduce the length of stay and accelerate recovery.[557,567]	IIb	B

AF, atrial fibrillation; LA, left atrium/left atrial; LAVI, left atrial volume index; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to body surface area; MR, mitral regurgitation; MV, mitral valve; PH, pulmonary hypertension; PMR, primary mitral regurgitation; SPAP, systolic pulmonary artery pressure; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation.
[a]Class of recommendation.
[b]Level of evidence.

9.1.5. Follow-up

Asymptomatic patients with severe MR not fulfilling the criteria for an intervention, and with documented preserved exercise capacity, should undergo clinical and echocardiographic follow-up twice per year (watchful waiting strategy), ideally in the setting of a Heart Valve Clinic.[568] Follow-up may also include serial measurements of BNP levels, electrocardiogram (ECG) and/or Holter monitoring, and (in selected cases) exercise echocardiography and CMR to confirm MR severity, and cardiac chamber function and dimensions.[46] Asymptomatic patients with moderate MR and preserved LV function can be followed on a yearly basis with echocardiographic assessment every 1 or 2 years.

The frequency of follow-up after an intervention depends on the type of procedure performed. Very good long-term durability of MV repair in PMR due to valve prolapse with a low recurrence rate has been reported at experienced centres with freedom from moderate or severe MR of 87.5% at 20 years.[533,559] Serial clinical and echocardiographic follow-up in patients without pre-operative LV dysfunction or rhythm abnormalities every 2–3 years thereafter is sufficient. Patients with atrial or ventricular arrhythmias possibly related to MV disease should be further evaluated using continuous ECG monitoring. Patients with recurrent MR after surgical ring annuloplasty frequently undergo repeat surgery (usually MV replacement), while transcatheter alternatives are reserved for selected high-risk patients because of the risk of increased gradients (M-TEER), PVL, and LVOT obstruction (mitral valve-in-ring procedures).[569,570] In patients undergoing MV replacement, closer follow-up on a yearly basis is required due to the risk of prosthetic valve dysfunction or SVD (see *Section 14.4*). Following TEER, reported rates of residual MR and increased transmitral gradients are higher than after surgical repair, suggesting that yearly follow-up is appropriate.[571] Although rare, the need for surgical treatment after failed TEER is associated with increased peri-operative mortality and low valve repair rates,[541,572] while transcatheter solutions to detach TEER implants and replace the valve have been described in few cases.[573,574]

9.2. Secondary mitral regurgitation

9.2.1. Prevalence and aetiology

Secondary mitral regurgitation is present when the MV structure appears grossly normal but the MV is nonetheless incompetent, due to alterations in LV and LA geometry, dyssynchrony, and imbalances between MV closing and tethering forces.[575] The prevalence of severe SMR in patients with chronic HF is ~10% and higher in patients with reduced vs preserved LVEF (25% vs 4%).[576] Secondary mitral regurgitation can be classified as atrial or ventricular with different pathophysiological and morphological characteristics, as well as contrasting prognostic and therapeutic implications.[577] Ventricular SMR is more common and associated with worse long-term prognosis.[513,578–580] Dilated or ischaemic cardiomyopathy are the most frequent causes of severe ventricular SMR. Acute HF exacerbation may occur in patients with chronic HF due to a renewed ischaemic event, arrhythmia, infection, or volume overload. Atrial SMR is due to pure mitral annular dilation and is observed in patients with long-standing AF and/or HFpEF.[581] Factors predisposing to atrial SMR include age ≥65 years, female sex, LA dilatation, and diastolic dysfunction.[582] From a morphological point of view, ventricular SMR is characterized by leaflet tethering and restricted motion combined with annular dilation, while annulus enlargement and flattening leading to planar coaptation are predominantly observed in atrial SMR. The prevalence of atrial SMR has been underestimated in the past and was occasionally misclassified as PMR due to pseudo-prolapse with leaflet tethering in advanced stages.

9.2.2. Evaluation

Echocardiographic criteria to define significant SMR according to aetiology are reported in *Figure 10*. Importantly, SMR assessment should be performed after optimization of medical therapy and in a euvolaemic and normotensive state. When quantifying EROA and RVol in SMR, lower thresholds may apply to define severe regurgitation because of the potential elliptical regurgitant orifice and/or the low-flow state. An EROA of ≥30 mm^2 and/or an RVol of ≥45 mL has been identified as having a significant impact on outcomes,[45] with prognosis improved after treatment.[583,584] Cardiac magnetic resonance is used to confirm SMR severity and assess cardiac chamber function and dimensions. The extent of myocardial fibrosis, as assessed with CMR, has been associated with poor prognosis.[585] Owing to the dynamic nature of SMR, exercise echocardiography may help to identify patients with severe SMR when values at rest are inconclusive.[45]

9.2.3. Definition of atrial secondary mitral regurgitation

Characteristics distinguishing between atrial and ventricular SMR are displayed in *Figure 12*.

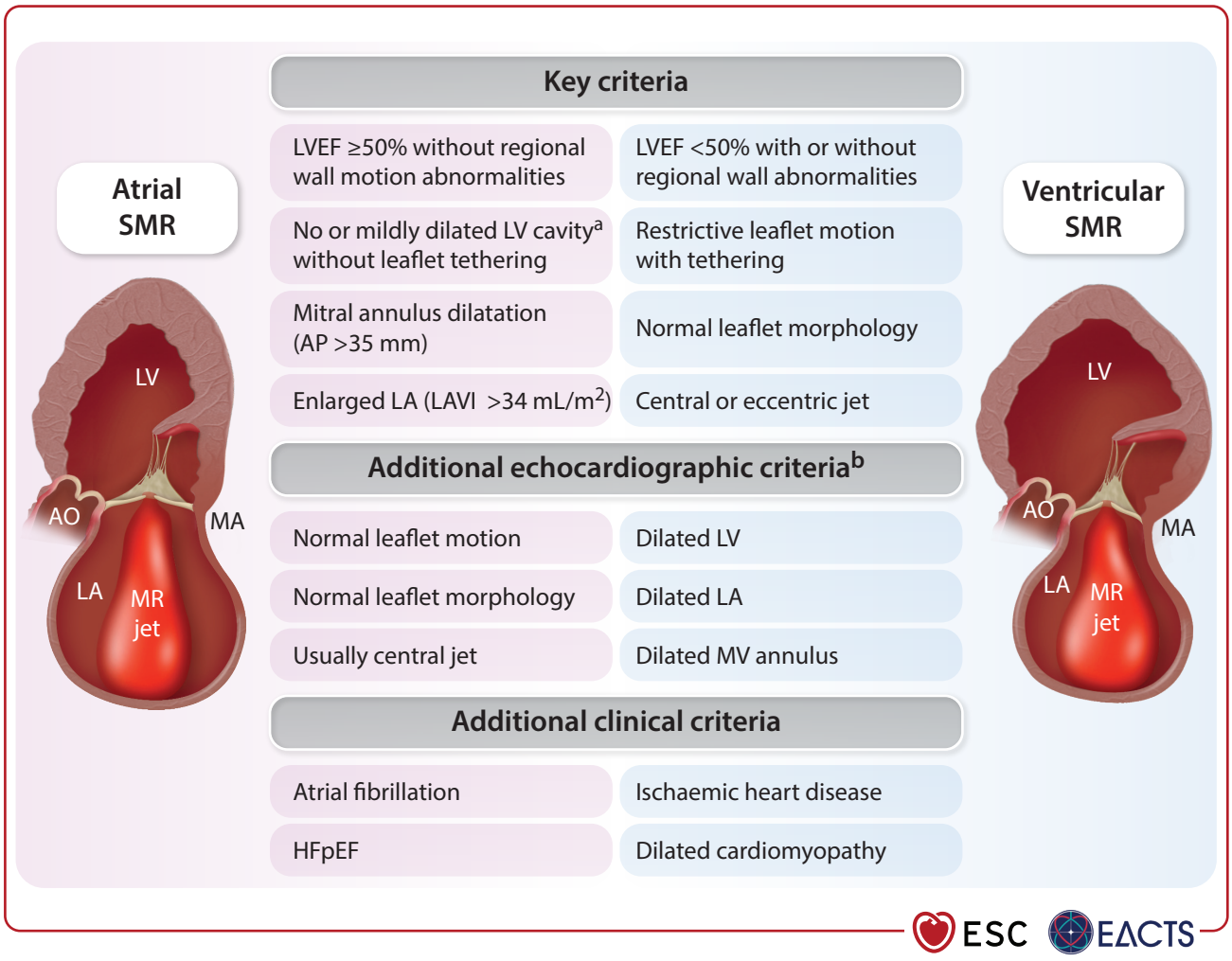

Figure 12 Most frequently used criteria for the diagnosis of atrial secondary mitral regurgitation. AO, aorta; AP, anteroposterior; HFpEF, heart failure with preserved ejection fraction; LA, left atrium/left atrial; LAVI, left atrial volume index; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; MA, mitral annulus; MR, mitral regurgitation; MV, mitral valve; SMR, secondary mitral regurgitation. [a]LV end-diastolic dimension of <56 mm in females and <63 mm in males; indexed LV end-diastolic volume <71 mL/m^2 (in women) or <79 mL/m^2 (in men). [b]Additional echocardiographic criteria for atrial SMR may no longer be fulfilled in advanced stages.

Atrial SMR is most frequently defined by the presence of the following key criteria:[513,578–580,586–590]

- preserved LVEF (≥50%) without regional wall motion abnormalities or leaflet tethering; AND
- no or mildly dilated LV cavity [LV end-diastolic dimension of <56 mm in women and <63 mm in men; indexed LV end-diastolic volume of <71 mL/m^2 (in women) or <79 mL/m^2 (in men)]; AND
- mitral annulus (MA) dilatation [anteroposterior (AP) diameter of >35 mm]; AND
- enlarged LA (LAVI >34 mL/m^2).

Echocardiography frequently reveals normal leaflet motion with planar coaptation, and normal leaflet morphology with a central MR jet in atrial SMR. However, at advanced stages, an overlap between atrial and ventricular SMR criteria can be observed in the case of late LV damage due to continuous volume overload.[591,592] Clinical criteria (i.e. history of AF and/or diagnosis of HFpEF) are also useful and should be taken into consideration.

9.2.4. Management of ventricular secondary mitral regurgitation

9.2.4.1. Medical and device therapy

In patients with ventricular SMR, GDMT for the treatment of HF is recommended prior to any MV intervention.[339,340] The combination of ACE-Is/ARBs or angiotensin receptor/neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium–glucose co-transporter 2 inhibitors (SGLT2is) at the maximum tolerated doses is recommended according to the HF Guidelines.[340] Initiation and up-titration of neurohormonal drugs need to be tailored according to the patient profile, mainly based on BP, heart rate, potassium levels, and renal function.[593] Notably, GDMT up-titration must be rapid (within 6 weeks) and take place in the context of close follow-up visits, especially in the case of a recent hospitalization for acute HF.[594] About 40% of patients with ventricular SMR experience improvement of SMR severity after 1–3 months of optimized GDMT.[595,596] Cardiac resynchronization therapy (CRT) should also be considered as part of HF management before an MV intervention according to HF guideline criteria (LVEF ≤35% and wide QRS).[597,598] Although no dedicated RCTs

exist, SMR reduction by at least one grade has been described in 40%–60% of patients and is associated with reverse LV remodelling and improved clinical outcomes.[597,599,600]

9.2.4.2. Indications for intervention

The management of patients with ventricular SMR should be discussed by a multidisciplinary Heart Team including HF specialists. The indication for intervention is based on the persistence of symptoms (i.e. NYHA class II–V) despite adequate GDMT and CRT, if indicated (*Figure 13*). GDMT is the only option for very frail patients or those with limited life expectancy.

In the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial, M-TEER was shown to be safe and reduced recurrent HF hospitalization and all-cause mortality at 2 and 5 years of follow-up, compared with optimized GDMT in patients with ventricular SMR without relevant CAD.[583,584] In a second study (Percutaneous Repair with the MitraClip Device for

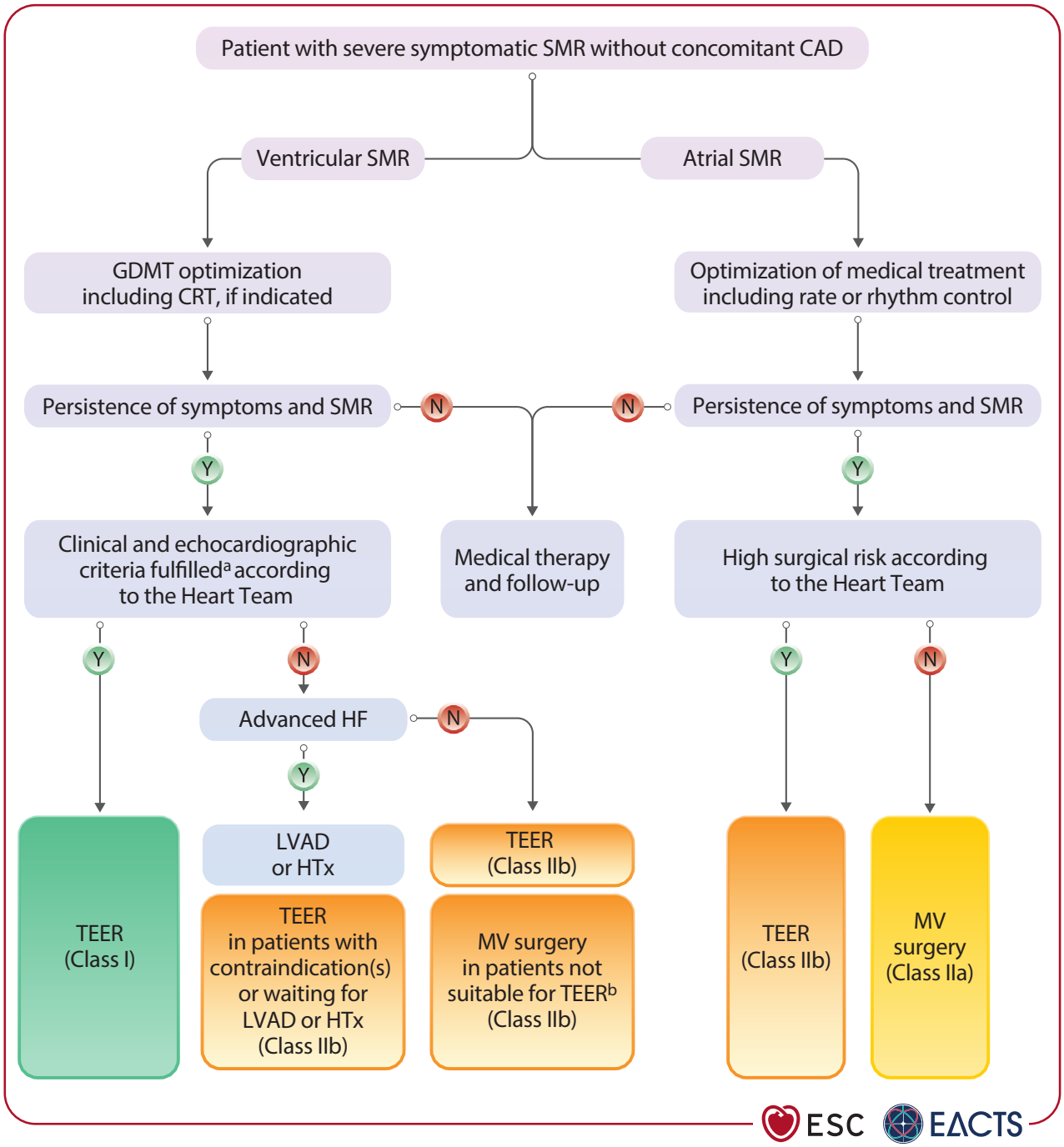

Figure 13 Treatment of severe secondary mitral regurgitation without concomitant coronary artery disease. CAD, coronary artery disease; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HTx, heart transplantation; LVAD, left ventricular assist device; MV, mitral valve; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair. [a]See *Table 7*. [b]See Supplementary data online, *Table S2*.

Severe Functional/Secondary Mitral Regurgitation, MITRA-FR), no differences were demonstrated for the combined primary endpoint of all-cause mortality or HF hospitalization at 1 and 2 years.[601,602] These diverging results might be explained by effect sizes of the trials, differences in trial design, patient selection and follow-up, echocardiographic assessment of SMR severity, use of GDMT, and technical factors.[603–605] A third RCT, the Randomized Investigation of the MitraClip Device in Heart Failure: 2nd Trial in Patients with Clinically Significant Functional Mitral Regurgitation (RESHAPE-HF-2) trial showed a 36% reduction in the rates of HF hospitalization or cardiovascular death at 2 years in the intervention arm driven by reduction of first or recurrent HF hospitalization. When considered in isolation, cardiovascular mortality was not significantly reduced during the observation period. In addition, there was a significant improvement in quality of life as measured by the KCCQ overall score (mean difference between study groups, 10.9 points; 95% CI, 6.8–15.0; P <0.001).[606] A recent study-level meta-analysis of these three trials showed a significant reduction of HF rehospitalization at 24 months (HR, 0.63, 95% CI, 0.50–0.80) and the composite of death and all-cause hospitalizations (HR, 0.72, 95% CI, 0.51–0.999).[607] However, there was no statistically significant difference in death from any cause or cardiovascular death at 24 months. Transcatheter edge-to-edge repair is therefore recommended to reduce HF hospitalizations, and improve quality of life, in symptomatic patients with persisting severe SMR despite optimized GDMT fulfilling specific clinical and echocardiographic criteria (*Table 7*). Although less challenging than in PMR, anatomical suitability for TEER needs to be assessed upfront (Supplementary data online, *Table S2*). There is also increasing observational evidence supporting the use of TEER for the improvement of symptoms, functional capacity, and quality of life in patients with ventricular SMR not fulfilling the clinical and echocardiographic criteria for outcome improvement.[608–612] This particularly applies to patients not tolerating GDMT in whom TEER may help up-titration, as well as those with recent myocardial infarction and persistent severe ventricular SMR.[203,613]

Transcatheter implantation of an indirect annuloplasty device into the coronary sinus has been proposed as an alternative that preserves valve integrity. Despite rather modest SMR reduction (22.4% decrease in mitral RVol) and no significant effect on quality of life in a small sham-controlled RCT, symptomatic improvement and reverse remodelling were observed in registries at 1 year.[614,615] Heart transplantation or left ventricular assist device (LVAD) implantation should be considered in selected patients with severe ventricular SMR and advanced HF.

In patients with ventricular SMR without relevant CAD, indications for isolated MV surgery are restrictive owing to procedural risks and the absence of proven mortality benefit.[616] The Multicenter, Randomized, Controlled Study to Assess Mitral Valve Reconstruction for Advanced Insufficiency of Functional or Ischemic Origin (MATTERHORN) trial, which included a mixed population mainly composed of patients with ventricular SMR (84%), demonstrated that TEER is non-inferior to surgical repair or replacement with regard to a composite endpoint of death, HF hospitalization, MV reintervention, implantation of an assist device, or stroke within 1 year after the procedure, and showed a better safety profile.[617] In patients with severe ischaemic ventricular SMR and concomitant CAD requiring coronary revascularization, MV surgery at the time of CABG is recommended, unless the patient is at high surgical risk and/or the coronary anatomy is suitable for PCI. Although isolated undersized mitral annuloplasty is the most commonly performed MV repair procedure, recurrent MR rates were high with this technique in an RCT[618] and reverse LV remodelling is limited, especially in patients with an increased tenting area (>1.35 cm^2/m^2 BSA),[619] in whom MV replacement is usually required.[620] The addition of subvalvular modification in patients with LV dilatation and pronounced MV leaflet tenting may improve results for MV repair,[621] but durability and impact on HF symptoms with this technique require further investigation.

The treatment of moderate ischaemic SMR in patients undergoing CABG remains controversial. Meta-analyses, including four RCTs comparing CABG with concomitant MV surgery vs CABG alone, have shown lower rates of recurrent MR but no benefit in terms of mortality and clinical outcomes.[622–624] Therefore, clinical decision-making should weigh peri-operative risks of more complex surgery against the long-term risk of MR progression.

9.2.4.3. Follow-up

Patients with ventricular SMR need to be followed up carefully after intervention by an HF specialist, because they remain at increased risk of events despite intervention. The 5-year cumulative incidence of all-cause death or HF hospitalization was 73.6% in the device arm of the COAPT study.[584] Clinical, laboratory, and echocardiographic evaluation every 3 or 6 months, according to the HF stage, is recommended. Durability of the procedural result, as well as congestion status and the need for further GDMT optimization facilitated by SMR reduction,[613] need to be assessed. Patients and families should be trained in monitoring vital signs, body weight, and HF symptoms to avoid late hospital admissions and facilitate management of possible decompensation. Also, patients must be educated on the importance of not discontinuing medical therapies after intervention since the two treatments (devices and drugs) are complementary.

Patients with ventricular SMR, who are asymptomatic and/or have moderate or dynamic MR, should undergo clinical and echocardiographic follow-up at least twice per year.

Table 7 Clinical and echocardiographic criteria predicting outcome improvement in patients with severe ventricular secondary mitral regurgitation undergoing mitral transcatheter edge-to-edge repair

Anatomy deemed suitable for M-TEER
NYHA class ≥II
LVEF 20%–50%
LVESD ≤70 mm
At least one HF hospitalization within the previous year or increased natriuretic peptide levels (BNP ≥300 pg/mL or NT-proBNP ≥1000 pg/mL)
SPAP ≤70 mmHg
No severe RV dysfunction
No Stage D or advanced HF
No CAD requiring revascularization
No severe AV and/or TV disease
No hypertrophic, restrictive, or infiltrative cardiomyopathies

AV, aortic valve; BNP, brain natriuretic peptide; CAD, coronary artery disease; HF, heart failure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; M-TEER, mitral transcatheter edge-to-edge repair; NT-proBNP, N-terminal pro-B-type natriuretic protein; NYHA, New York Heart Association; RV, right ventricle/right ventricular; SPAP, systolic pulmonary artery pressure; TV, tricuspid valve.

9.2.5. Management of atrial secondary mitral regurgitation

9.2.5.1. Medical therapy and rhythm management

In patients with atrial SMR, underlying causes need to be recognized and treated. Associated HFpEF and AF should be managed according to the relevant Guidelines.[7,340] The use of SGLT2is should be encouraged in patients with HFpEF due to their proven efficacy in reducing cardiovascular death and HF hospitalization.[625] Limited data show that rhythm control may contribute to reduce atrial SMR severity and reverse LA dilatation.[626]

9.2.5.2. Indications for intervention

Registry data demonstrate that patients with atrial SMR are typically elderly with associated AF. Mitral valve surgery has been recently associated with lower rates of HF hospitalizations and mortality compared with GDMT in a matched population, despite a higher risk profile in the surgical arm at baseline.[627] Data from several observational studies also suggest that surgical annuloplasty is effective and durable in patients with atrial SMR, because it counteracts the main mechanism of MR progression.[628–630] Its combination with surgical AF ablation (Maze procedure) and concomitant LAAO may have further advantages,[630,631] while the frequently associated relevant TR can also be addressed during the same procedure.[627] Transcatheter edge-to-edge repair may also be considered because observational studies have demonstrated high safety and procedural success,[588–590,632,633] as well as compared with surgery in a small subgroup ($n = 34$) of the MATTERHORN RCT.[634] However, the risk of increased gradient due to planar leaflet coaptation, large regurgitant jet, and limited MV area (MVA) needs to be taken into consideration.[592,635] Further studies are warranted to investigate the treatment modalities of patients with atrial SMR.

9.2.5.3. Follow-up

Patients with atrial SMR undergoing surgical or transcatheter intervention should be followed up on a yearly basis, including clinical and echocardiographic evaluation. In cases of HFpEF, as an underlying cause of atrial SMR, consultation with an HF specialist is necessary.

Asymptomatic patients with severe atrial SMR not fulfilling the criteria for an intervention should undergo clinical and echocardiographic follow-up at least once per year.

Recommendation Table 7 — Recommendations on indications for intervention in secondary mitral regurgitation (see also Supplementary data online, *Evidence Tables 17–20*)

Recommendations	Class[a]	Level[b]
Severe atrial secondary mitral regurgitation		
MV surgery, surgical AF ablation, if indicated, and LAAO should be considered in symptomatic patients with severe atrial SMR under optimal medical therapy.[627–630,636,637]	IIa	B
TEER may be considered in symptomatic patients with severe atrial SMR not eligible for surgery after optimization of medical therapy including rhythm control, when appropriate.[588,590,638,639]	IIb	B
Ventricular secondary mitral regurgitation and concomitant coronary artery disease		
MV surgery is recommended in patients with severe ventricular SMR undergoing CABG.[640]	I	B
MV surgery may be considered in patients with moderate SMR undergoing CABG.[622–624,641,642]	IIb	B
PCI followed by TEER after re-evaluation of MR may be considered in symptomatic patients with chronic severe ventricular SMR and non-complex CAD.[150]	IIb	C
Severe ventricular secondary mitral regurgitation without concomitant coronary artery disease		
TEER is recommended to reduce HF hospitalizations and improve quality of life in haemodynamically stable, symptomatic patients with impaired LVEF (<50%) and persistent severe ventricular SMR, despite optimized GDMT and CRT (if indicated), fulfilling specific clinical and echocardiographic criteria.[c] [583,584,606,608,643]	I	A
TEER may be considered for symptom improvement in selected symptomatic patients with severe ventricular SMR not fulfilling the specific clinical and echocardiographic criteria,[c] after careful evaluation of LVAD or HTx.[203,608–610]	IIb	B
MV surgery may be considered in symptomatic patients with severe ventricular SMR without advanced HF who are not suitable for TEER.[617]	IIb	C

AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HTx, heart transplantation; LAAO, left atrial appendage occlusion; LVAD, left ventricular assist device; LVEF, left ventricular ejection faction; MR, mitral regurgitation; MV, mitral valve; PCI, percutaneous coronary intervention; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair.
[a]Class of recommendation.
[b]Level of evidence.
[c]See *Table 7*.

10. Mitral stenosis

10.1. Prevalence and aetiology

The aetiology of MS is most frequently rheumatic or degenerative, while rare forms can be drug-induced, inflammatory, or carcinoid-related. Rheumatic fever is the most common cause of MS and death due to VHD worldwide. Its prevalence has decreased in high- and middle-income countries, but remains a major healthcare problem in low-income countries, where it predominantly affects young patients.[12,187,644] Degenerative MS related to MAC is a distinct age-dependent pathology requiring different treatment strategies.[645–647] Both aetiologies are more frequent in females.[648]

10.2. Rheumatic mitral stenosis

10.2.1. Evaluation

Echocardiography is the preferred method for screening in endemic regions and the assessment of the severity, extent of anatomical lesions, and haemodynamic consequences of MS. Involvement of other valves, particularly secondary TR, should be identified. Mitral valve area using

2D planimetry is the most commonly used measurement to assess stenosis severity, but 3D TTE and TOE have additional diagnostic value.[649] An MVA of ≤1.5 cm^2 in conjunction with clinical factors (symptoms, high risk of thromboembolism, or haemodynamic decompensation) is indicative of clinically severe MS. Mean transvalvular gradient and pulmonary pressures reflect its consequences and have prognostic value.[649,650] Leaflet thickening and fibrosis, along with commissural fusion and shortening of the subvalvular apparatus, are the most important pathomechanisms of stenosis associated with RHD. The presence and extent of leaflet and subvalvular calcifications influence treatment decisions. Scoring systems have been developed to assess the suitability of patients for percutaneous mitral commissurotomy (PMC) (see Supplementary data online, *Table S3*).[651–653]

Exercise testing is indicated in asymptomatic patients or patients with symptoms that are equivocal or discordant with the severity of stenosis. Exercise echocardiography provides additional information on exercise capacity and related changes in mitral gradient and pulmonary artery pressure, and is preferred over DSE, especially when there are contraindications to dobutamine.[654] Transoesophageal echocardiography should be systematically performed in PMC candidates to exclude LA thrombus or after an embolic episode, and may play an essential role for procedural guidance.[52,655]

10.2.2. Medical therapy

Diuretics, beta-blockers, digoxin, non-dihydropyridine calcium channel blockers, and ivabradine can improve symptoms by controlling volume overload and heart rate. Anticoagulation with a VKA with a target international normalized ratio (INR) between 2 and 3 is indicated in patients with AF, and DOACs should be avoided in patients with an MVA of ≤2.0 cm^2 according to current evidence.[165,656,657] Interventions to restore sinus rhythm (cardioversion or catheter pulmonary vein isolation) are unlikely to be successful in patients with untreated severe MS. If AF is of recent onset and the LA moderately enlarged, cardioversion can be attempted soon after successful intervention or in patients with moderate MS combined with amiodarone treatment.[658,659] In patients in sinus rhythm, OAC is indicated after systemic embolism or if a thrombus is present in the LA, and should also be considered when TOE shows dense spontaneous echocardiographic contrast or an enlarged LA (M-mode diameter >50 mm or LA volume >60 mL/m^2).[660] Prophylaxis of infective endocarditis is indicated as appropriate.[5]

10.2.3. Indications for intervention

The type (PMC or surgery) and timing of treatment should be decided based on clinical characteristics, the anatomy of the valve and subvalvular apparatus, and local expertise.[661–663] The management of clinically severe rheumatic MS is summarized in *Figure 14* and *Recommendation Table 8*.

In general, indication for intervention should be limited to patients with clinically severe rheumatic MS (MVA <1.5 cm^2) in whom PMC is expected to have a significant impact on clinical outcome. In higher-income countries, where the incidence of rheumatic fever and the number of PMCs performed is low, this treatment should be restricted to expert operators in specialized centres to improve safety and procedural success rate.[661,664] Efforts should be made to increase the availability of PMC in lower-income countries, where access to treatment is limited for economic reasons.[665,666] Percutaneous mitral commissurotomy may be also considered in symptomatic patients with an MVA of >1.5 cm^2, if symptoms cannot be explained by another cause and if the anatomy is favourable (see *Table 8*). Percutaneous mitral commissurotomy should be considered as a first-line treatment for patients with anatomically suitable rheumatic MS and mild-to-moderate calcification without severe subvalvular impairment. Selected patients with unfavourable anatomical and clinical characteristics can still benefit from PMC, particularly if they are at increased surgical risk. When symptomatic restenosis occurs after surgical commissurotomy or PMC, reintervention in most cases requires surgical valve replacement, but redo PMC can be proposed in selected candidates with favourable characteristics, if the predominant mechanism is commissural refusion. Long-term follow-up has shown favourable results following PMC despite a growing number of elderly patients with suboptimal clinical and anatomical characteristics.[663–665]

For patients in whom PMC is contraindicated (*Table 8*), surgical MV repair or, more frequently, replacement are good alternatives. Although repair is much more challenging than for PMR, it can be attempted at experienced centres.[663]

For patients with multiple VHD including MS, a comprehensive evaluation by the Heart Team and an individualized approach is necessary. Surgery is preferable to PMC in patients with severe MS and severe AV disease, unless the surgical risk is high. In selected cases with severe MS and moderate AV disease, PMC can be performed to postpone surgical treatment of both valves.

In high-risk cases with concomitant severe TR, PMC may be considered in selected patients with sinus rhythm, moderate atrial enlargement, and secondary TR due to post-capillary PH. In non-high-risk cases, surgery on both valves is preferred.[651,652,662,667] Treatment of patients with low-gradient severe MS (MVA <1.5 cm^2, mean gradient <10 mmHg) is challenging, because these patients are often older and have unfavourable anatomy.[668,669]

10.2.4. Follow-up

Asymptomatic patients with clinically severe MS who have not undergone intervention should be followed up yearly by TTE, and at longer intervals (2–3 years) in cases of moderate stenosis. After PMC, the post-procedural MVA and mean mitral gradient are important parameters that influence long-term clinical outcomes. Follow-up of patients after successful PMC is necessary because asymptomatic restenosis may occur. Progressive rheumatic involvement of other valves should be periodically assessed, irrespective of the therapy modality. Finally, education and the engagement of the family is key in patients with rheumatic MS, since it usually affects young individuals and women of childbearing age.

10.3. Degenerative mitral stenosis with mitral annular calcification

Patients presenting with MAC are elderly and have significant comorbidities, including disease of other valves. Mitral annular calcification is also an indicator of cardiovascular disease severity and is associated with an increased risk of AF, stroke, and death.[670,671] The incidence of MAC varies substantially, depending on the age of the studied population and the imaging modality used. It can be a consequence of many different pathological processes and, depending on the underlying disease, can be accompanied by stenosis, regurgitation, or both. However, most patients with MAC do not have significant valvular dysfunction.[647,672]

Generally, MS occurs due to calcific extension into the MV leaflets or subvalvular apparatus, and in some patients it is associated with combined MR.[673] Treatment options (including transcatheter and surgical approaches) are high-risk procedures and evidence from RCTs is lacking.

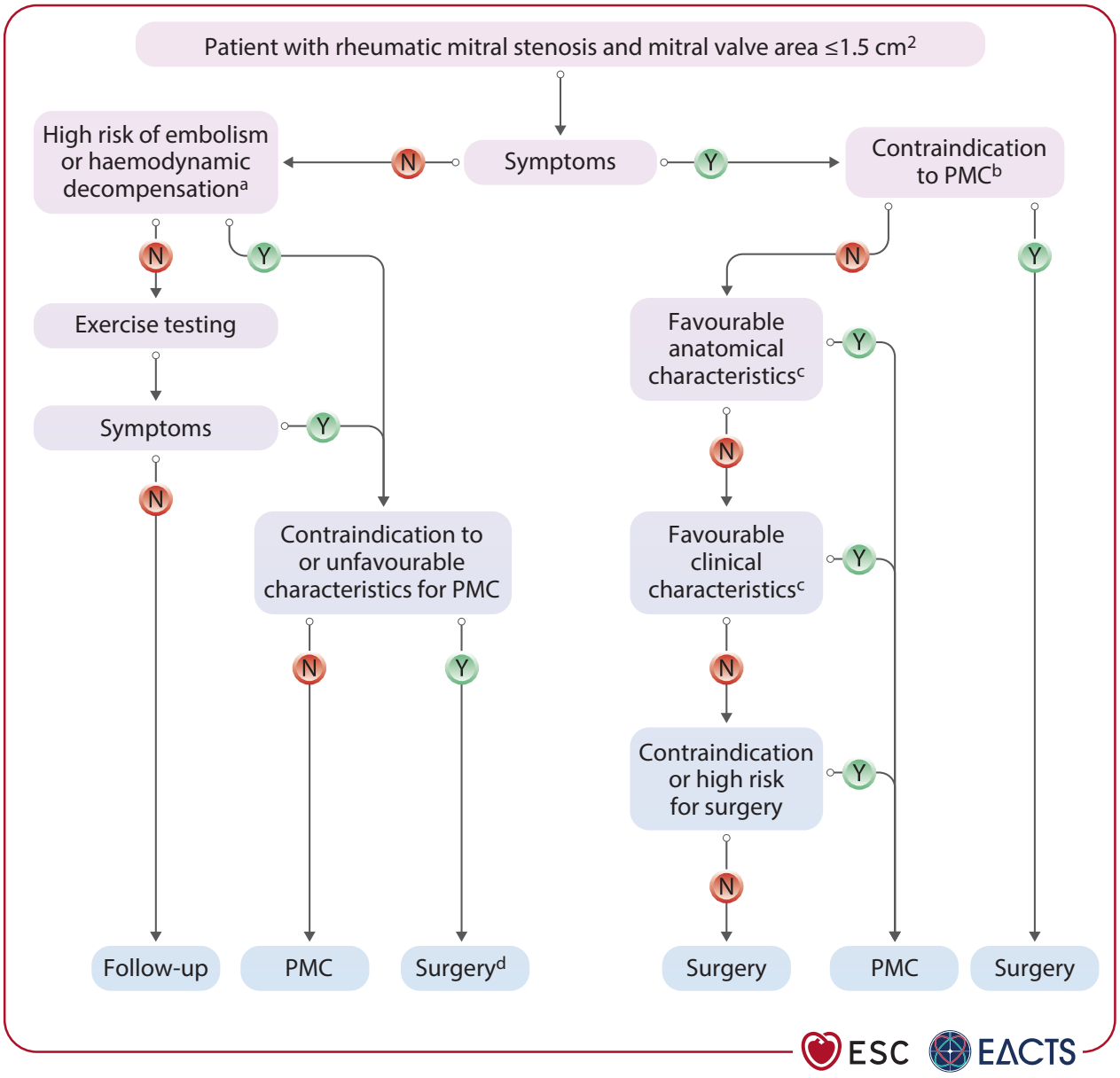

Figure 14 Management of clinically severe rheumatic mitral stenosis (mitral valve area ≤1.5 cm^2). AF, atrial fibrillation; LA, left atrium; MS, mitral stenosis; MV, mitral valve; MVA, mitral valve area; NCS, non-cardiac surgery; NYHA, New York Heart Association; PH, pulmonary hypertension; PMC, percutaneous mitral commissurotomy; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation. [a]High thromboembolic risk: history of systemic embolism, dense spontaneous contrast in the LA, new-onset AF. High-risk of haemodynamic decompensation: SPAP >50 mmHg at rest, need for major NCS, desire for pregnancy or pregnant. [b]See *Table 8*. [c]Favourable = absence of unfavourable characteristics for PMC defined by unfavourable anatomical characteristics [echocardiographic score >8, Cormier score 3 (calcification of MV of any extent as assessed by fluoroscopy), severe TR] or unfavourable clinical characteristics (old age, history of commissurotomy, NYHA class IV, permanent AF, severe PH) (for the definition of scores see Supplementary data online, *Table S3*). [d]If operative risk is low.

10.3.1. Evaluation

Echocardiography is used for initial evaluation, but is frequently limited by acoustic shadowing due to severe calcification. Evaluation of MVA by planimetry is less reliable than in rheumatic MS, and TOE should therefore be used liberally. Degenerative MS can coexist with varying degrees of MR. Mean transmitral gradient has been shown to be associated with increased mortality irrespective of MR severity.[674] Electrocardiogram-gated CCT is necessary to assess the degree and locations of calcifications, especially if an intervention is planned.[647,674–676] Calcifications are usually more prominent at the posterior aspect of the annulus.

10.3.2. Indications for intervention

Intervention is recommended in symptomatic patients who are not responsive to medical therapy, weighing the potential benefits of the procedure against its associated risks. In elderly patients with degenerative MS and MAC, surgery is technically challenging and high risk. However,

surgical MV repair or replacement with extensive decalcification and patch reconstruction of the annulus can be performed in selected patients at experienced centres (e.g. young patients post-chest radiation), where mortality rates of <5% have been reported.[677–679]

Degenerative MS is not amenable to PMC because commissural fusion is absent. In symptomatic high-risk patients with suitable anatomy, transcatheter implantation of a TAVI prosthesis in the mitral position is feasible but associated with frequent complications, including LVOT obstruction, valve embolization, stroke, and haemolysis due to PVL. Open surgical valve replacement via the LA with a TAVI device is an alternative that allows complete anterior leaflet removal;[680] however, mortality remains high. The use of dedicated TMVI devices is therefore encouraged because it appears to be safer.[542,681] Heart Team evaluation should guide the choice of treatment avoiding futility, because mortality remains high, even after successful treatment (10%–30% within 1 year).

Recommendation Table 8 — Recommendations on indications for percutaneous mitral commissurotomy, mitral valve surgery, and transcatheter intervention in clinically severe rheumatic and degenerative mitral stenosis (see also Supplementary data online, *Evidence Table 21*)

Recommendations	Class[a]	Level[b]
PMC is recommended in symptomatic patients in the absence of unfavourable characteristics for PMC.[c] [651–653,662,665]	I	B
PMC is recommended in any symptomatic patients with a contraindication or at high risk for surgery.	I	C
MV surgery is recommended in symptomatic patients who are not suitable for PMC.	I	C
PMC should be considered as initial treatment in symptomatic patients with suboptimal anatomy but no unfavourable clinical characteristics for PMC.[c]	IIa	C
PMC should be considered in asymptomatic patients without unfavourable clinical and anatomical characteristics for PMC, and: • High thromboembolic risk (history of systemic embolism, dense spontaneous contrast in the LA, new-onset or paroxysmal AF), and/or • High risk of haemodynamic decompensation (SPAP >50 mmHg at rest, need for major NCS, pregnant or desire for pregnancy).	IIa	C
TMVI may be considered in symptomatic patients with extensive MAC and severe MV dysfunction at experienced Heart Valve Centres with expertise in complex MV surgery and transcatheter interventions.[542,680,681]	IIb	C

AF, atrial fibrillation; LA, left atrium/left atrial; MAC, mitral annular calcification; MV, mitral valve; NCS, non-cardiac surgery; NYHA, New York Heart Association; PH, pulmonary hypertension; PMC, percutaneous mitral commissurotomy; SPAP, systolic pulmonary artery pressure; TMVI, transcatheter mitral valve implantation; TR, tricuspid regurgitation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Unfavourable characteristics for PMC can be defined by the presence of several of the following characteristics: clinical characteristics (old age, history of commissurotomy, NYHA class IV, permanent AF, severe PH); anatomical characteristics [echocardiographic score >8, Cormier score group 3 (calcification of MV of any extent as assessed by fluoroscopy), severe TR] (for the definition of scores see Supplementary data online, *Table S3*).

Table 8 Contraindications for percutaneous mitral commissurotomy in rheumatic mitral stenosis

Contraindications
MVA >1.5 cm^2 [a]
LA thrombus[b]
More than mild MR
Severe or bi-commissural calcification
Absence of commissural fusion
Severe concomitant AV disease, or severe combined tricuspid stenosis and regurgitation requiring surgery
Concomitant CAD requiring bypass surgery

AV, aortic valve; CAD, coronary artery disease; LA, left atrium/left atrial; MR, mitral regurgitation; MVA, mitral valve area; OAC, oral anticoagulation; PMC, percutaneous mitral commissurotomy; TOE, transoesophageal echocardiography.
[a]PMC may be considered in patients with MVA of >1.5 cm^2 with symptoms that cannot be explained by another cause and if the anatomy is favourable.
[b]When the thrombus is located in the LA appendage, PMC may be considered in patients with contraindications to surgery or those without urgent need for intervention, in whom OAC can be safely given for 1–3 months, provided repeat TOE confirms resolution of thrombus.

11. Tricuspid regurgitation

11.1. Prevalence and aetiology

TR is a common echocardiographic finding in the general population, with higher prevalence in women and older patients. Trivial or mild TR is mostly a benign condition. Significant TR (≥ moderate) has a reported age- and sex-adjusted prevalence of 0.55% (4% in people aged ≥75 years).[682] Severe TR is associated with increased risk of death and HF, independent of comorbidities, ventricular function, and pulmonary pressures.[683–686]

Only 8%–10% of patients with TR present with clear anatomical abnormalities of the TV apparatus (primary TR), which can be due to infective endocarditis, RHD, carcinoid syndrome, congenital abnormalities (e.g. Ebstein's anomaly), chest radiation, or myxomatous disease, as well as trauma or iatrogenic valve damage (e.g. after endomyocardial biopsy).[682] Cardiac implantable electronic device (CIED)-related TR represents a separate entity requiring a specific diagnostic approach and management.[687] In patients with a CIED, diagnostic efforts should be made to clarify if the lead is the cause of TR (CIED-related TR) or incidental (CIED-associated TR).[688]

In patients with secondary TR, TV leaflets are structurally normal and regurgitation is caused by annular dilatation and/or leaflet tethering due to RA dilatation, and/or RV dilation and dysfunction. Based on the main morphological and haemodynamic characteristics, two phenotypes of secondary TR have been proposed:[689] (i) atrial secondary TR, mainly due to AF and characterized by the absence of significant leaflet tethering, but with marked RA and annular dilatation along with preserved RV size/function, pulmonary pressure, and LV function; and (ii) ventricular secondary TR, due to annular dilatation and leaflet tethering as a consequence of left-sided ventricular or valvular disease (post-capillary PH), pre-capillary PH, or primary RV cardiomyopathy/ischaemia (also after left-sided valve surgery).[690] At an advanced disease stage, these two phenotypes may no longer be distinguishable, and therefore early characterization is key to determine outcome.[691,692] Evidence of an impact on patient management is currently lacking; therefore, current recommendations for intervention consider mainly primary vs secondary TR.

11.2. Evaluation

Echocardiography is recommended to assess patients with TR[45] and should include evaluation of severity and aetiology (including characterization of left-sided heart disease and, if applicable, CIED lead location and interaction with the valve apparatus), the impact of TR on the right-sided chambers (RV and RA size and function), and assessment of central venous (inferior vena cava) and pulmonary pressures. Transthoracic echocardiography provides sufficient diagnostic information in most patients. Transoesophageal echocardiography is necessary for when visualization of the TV apparatus. In candidates for an intervention, advanced techniques, such as strain analysis and 3D echocardiography, should also be applied when available.

Assessment of TR severity should be ideally performed in euvolaemic status, with optimized pulmonary and systemic pressures, and based on an integrative approach considering multiple qualitative and quantitative parameters (*Figure 15*).[45,693] A grading scheme extending beyond severe, including 'massive' and 'torrential' grades, has been proposed to refine TR reduction assessment after transcatheter interventions and has been used in several studies.[694,695] Although this five-grade scale may be associated with a proportional increase in symptoms and event risk,[694,695] an intervention should be considered without delay, as soon as TR is severe, with the aim of reducing TR to moderate or less.[696,697]

Echocardiographic assessment of the RV is challenging due to its complex geometry, imaging constraints, and the high dependency on loading conditions. When accurate measurements of RV size and function, as well as RV volume, are necessary for decision-making, CMR should be used because of its high accuracy and reproducibility.[698,699] In *Figure 15*, upper limits of normal for different RV size parameters are provided to guide definition of RV dilatation and remodelling. In the setting of severe TR, RV function is often overestimated and therefore the most conservative/cautious thresholds are suggested for the currently used echocardiographic parameters to identify RV dysfunction at the earliest stage possible. Cut-off values for severe RV dysfunction are also provided to indicate high-risk or possibly futile interventions. Although robust validation is lacking, all these reference values are chosen based on large multicentre reports of normative data and outcomes.[60,697,700–704]

Echocardiography often underestimates pulmonary pressures in cases of severe TR.[705] Right heart catheterization is therefore recommended in all candidates for an intervention to assess the haemodynamic consequences of TR on the RA and venous circulation (e.g. ventricularization of the RA pressure curves), measure end-diastolic RV pressure, and document volume overload. The assessment of pulmonary pressures and vascular resistance are key to exclude masked severe pre-capillary PH.[706]

RV–pulmonary artery coupling refers to the ability of the RV systolic performance to match a given pulmonary afterload maintaining adequate cardiac output, and can be measured invasively or approximated using echocardiography [i.e. tricuspid annular plane systolic excursion (TAPSE)/SPAP].[707,708] RV–pulmonary artery uncoupling (low TAPSE/SPAP) occurs when sustained increases in afterload cannot be matched by RV contractile reserve and has been associated with poor prognosis in different HF conditions, including severe TR. Although not yet prospectively validated, this index may improve risk stratification.

Electrocardiogram-gated CCT with dedicated protocols ensuring sufficient contrast enhancement of the right heart cavities provides detailed characterization of the RA, RV, and vena cava anatomy, the location of the right coronary artery, and is crucial to assess suitability and device sizing for several transcatheter interventions.[689,697]

Before any intervention is considered, careful evaluation of TR aetiology, disease stage (TR severity, RV and LV dysfunction, and PH), patient operative risk, and likelihood of recovery by a dedicated collaborative Heart Team is recommended (*Figure 16*). Dedicated clinical risk scores for TR patients have been described recently. The TRI-SCORE[709] and the STS isolated TV risk calculator[710] take into consideration clinical and echocardiographic signs of RV dysfunction, and secondary organ (particularly hepatic and renal) impairment. They both allow improved estimates of peri-procedural risk in patients with severe TR undergoing surgery and possibly help to avoid futile interventions.[84,711] The importance of risk stratification was demonstrated in a recent registry analysis ($n = 2413$) comparing any interventions with conservative management. Early TV intervention (transcatheter valve repair or surgery) was associated with improved mid-term survival in patients with a low or intermediate TRI-SCORE (up to 5 points), while patients with a high TRI-SCORE (≥6) did not derive any benefit compared with conservative management.[696] Moreover, isolated TV surgery (repair or replacement) improved survival at 10 years in patients with a low TRI-SCORE (≤3). The same benefit was observed in patients with an intermediate TRI-SCORE (4–5) after successful TV repair only.[689,697,709] Patients with moderate or severe TR should be regularly followed up clinically and by echocardiography at least every 6 months.

11.3. Medical therapy

Patients with relevant TR should be first treated according to the assumed aetiology, including optimal HF treatment, pulmonary vasodilators for PH, and rhythm control for AF.[339,693]

In the case of HF symptoms, diuretics should be initiated in a stepwise approach,[339] beginning with loop diuretics eventually combined with aldosterone antagonists, thiazide diuretics, and/or SGLT2is.[712] However, according to current knowledge, medical therapy has very limited effect on the evolution of TR severity and none of these measures should delay evaluation of an intervention at an expert centre.[713]

11.4. Indications for intervention

11.4.1. Surgery

Patients are often referred too late for surgery when significant RV and other organ failure have occurred. Isolated TV surgery has therefore been considered to be generally high risk, with in-hospital mortality rates of 8%–10% in several reports,[714,715] but contemporary cohorts have demonstrated improved outcomes when patients are referred earlier and more effective techniques are used.[716] Valve repair using an annuloplasty ring is preferred over replacement, whenever technically feasible, especially in low-risk patients with suitable anatomy.[709] However, TV replacement may be necessary in cases of advanced disease with marked annular dilatation and leaflet tethering.[688,717] For CIED-related TR, preparation of any entrapped tricuspid leaflet and possibly lead extraction with implantation of an epicardial system has been associated with improved TV function.[688,717]

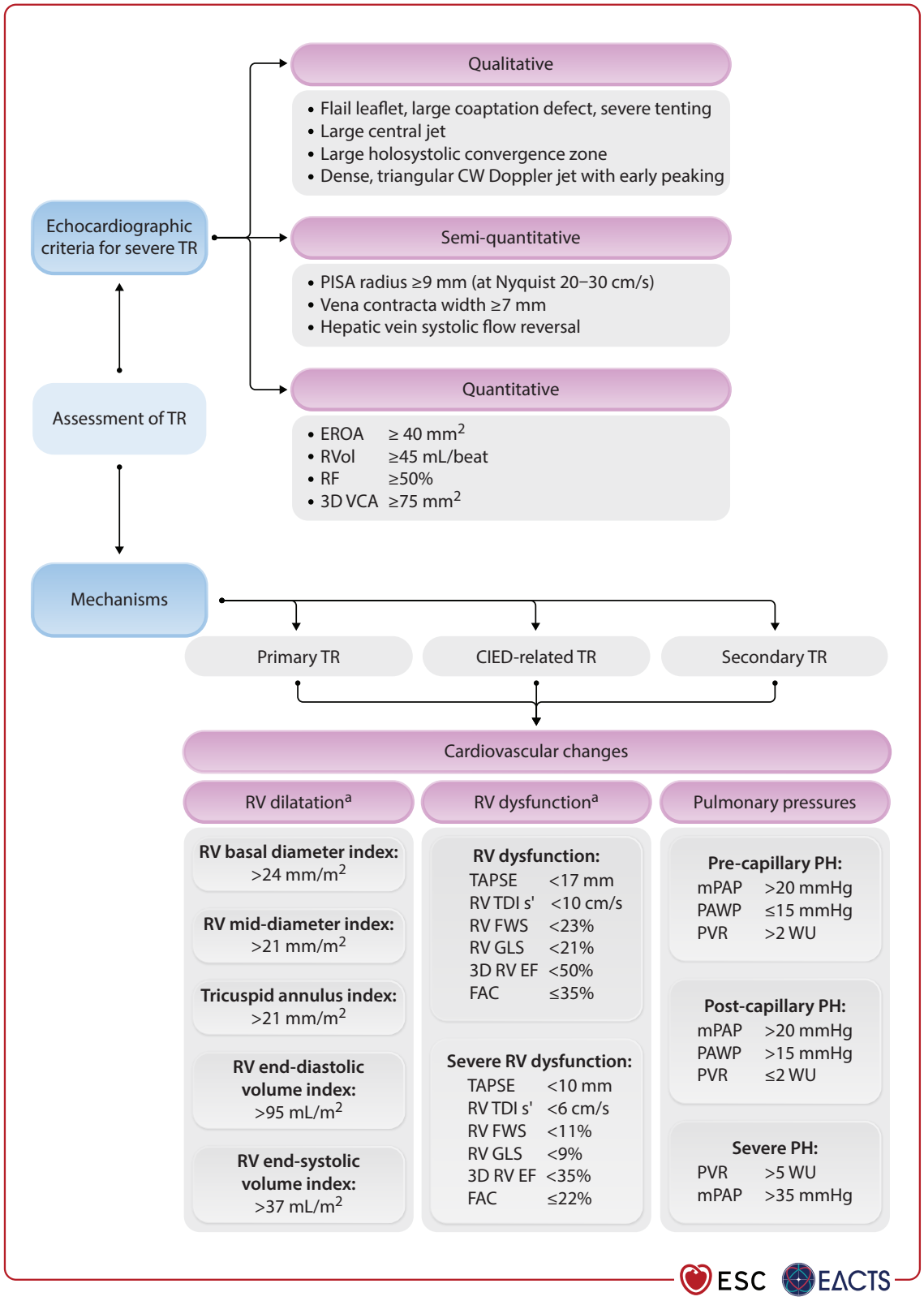

Figure 15 Echocardiographic and invasive assessment of tricuspid regurgitation. 3D, three-dimensional; CIED, cardiac implantable electronic device; CW, continuous-wave; EROA, effective regurgitant orifice area; FAC, fractional area change; FWS, free wall strain; GLS, global longitudinal strain; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PISA, proximal isovelocity surface area; PVR, pulmonary vascular resistance; RF, regurgitant fraction; RV, right ventricle/ventricular; RVEF, right ventricular ejection fraction; RVol, regurgitant volume; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging; TR, tricuspid regurgitation; VCA, vena contracta area; WU, wood unit.
[a]RV apical focused view.

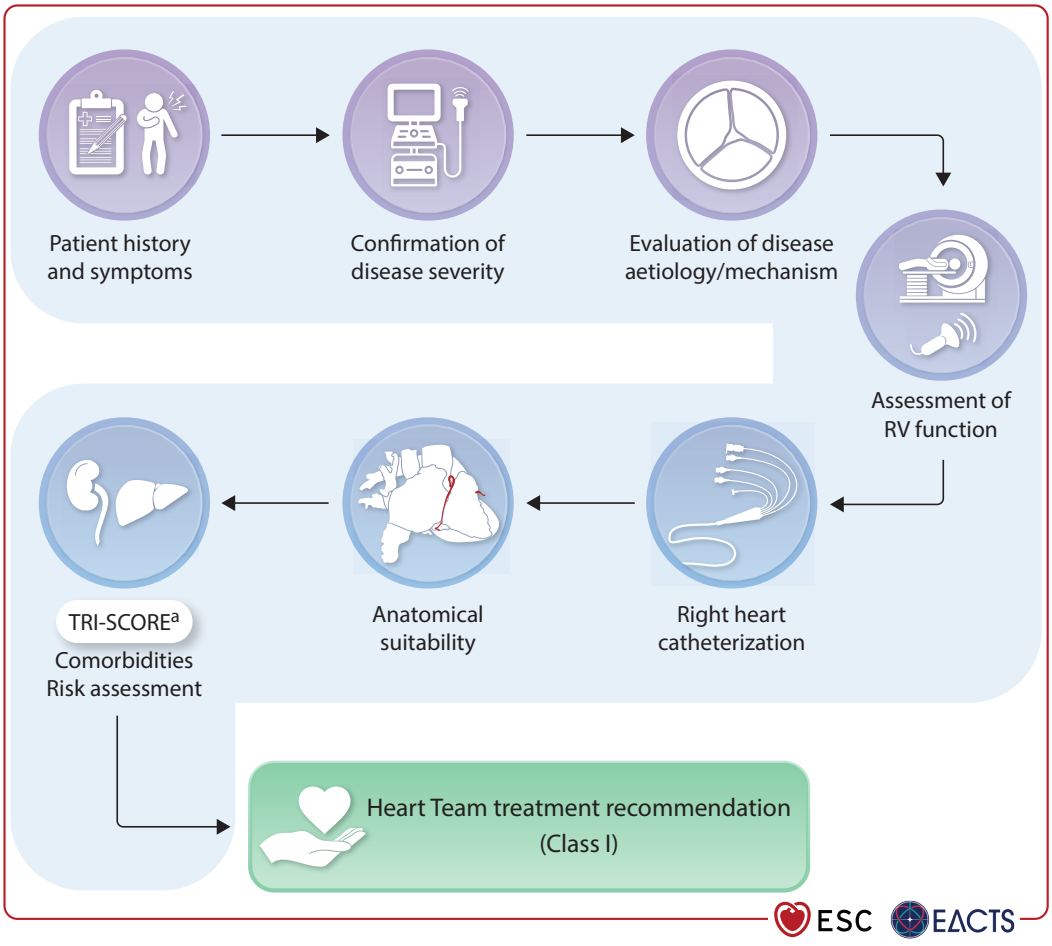

Figure 16 Stepwise evaluation of patients with tricuspid regurgitation. RV, right ventricle/right ventricular. [a]See Supplementary data online, *Table S4*.

11.4.1.1. Patients without indication for left-sided valve surgery

In patients with severe TR but without the need for left-sided valve surgery, surgical intervention is recommended in operable symptomatic patients with primary TR (*Figure 17*; *Recommendation Table 9*).[718] Furthermore, it should be considered in symptomatic patients with secondary TR, or in asymptomatic patients with primary or secondary TR and signs of RV dilatation or RV function deterioration.[719] However, patients with severe LV/RV dysfunction or PH do not qualify due to high operative risk.[84,686,720]

11.4.1.2. Patients with indication for left-sided valve surgery

Severe primary or secondary TR is unlikely to improve after isolated surgical treatment of left-sided valve disease, and reoperation for TR treatment is associated with high peri-operative mortality.[721] Therefore, TV surgery is recommended at the time of the index procedure.

Mild TR with associated significant annular dilatation or moderate TR, if left uncorrected at the time of left-sided valve surgery, will progress in approximately one-quarter of patients and is associated with worse outcome.[690,722] In patients with moderate TR, TV repair annuloplasty during MV surgery should be considered, because large retrospective studies[723,724] and two recent RCTs have shown beneficial effects on TR progression and RV remodelling over time.[725,726] However, no effects on mortality, HF events, or reoperation were observed in the repair group.[725,727] Concomitant TV repair has also been associated with a higher risk of conduction disturbances requiring pacemaker implantation (up to 14%),[725,728] with potential negative impacts on longer-term outcomes.[729,730] In patients with mild TR and annular dilatation (≥40 mm or >21 mm/m^2) undergoing left-sided valve surgery, previous observational studies have demonstrated a benefit of concomitant TV repair in terms of TR progression[723,724] and RV function,[731] and a trend towards improved long-term survival.[724] However, a subanalysis of a recent RCT did not identify any difference in the progression of TR or other outcomes in this category of patients

during a 2-year follow-up period.[725] In turn, the need of pacemaker implantation after surgery led to a subsequent increase in HF hospitalizations, endocarditis, and mortality.[729] Annuloplasty may therefore be considered after careful evaluation of the risk factors for progressive annular dilatation and TR (AF, RA size, pulmonary pressures, etc.), balancing against the risk of possible pacemaker implantation (Supplementary data online, *Table S5*).[732]

11.4.2. Transcatheter techniques

Several transcatheter approaches for the treatment of TR have been developed, including TEER, direct annuloplasty, and orthotopic and heterotopic TV replacement. Data from large multicentre registries, single-arm clinical trials, and two recent RCTs in patients with severe TR at intermediate and high risk for surgery have shown the safety of transcatheter repair, as well as the ability to reduce TR to moderate or less in

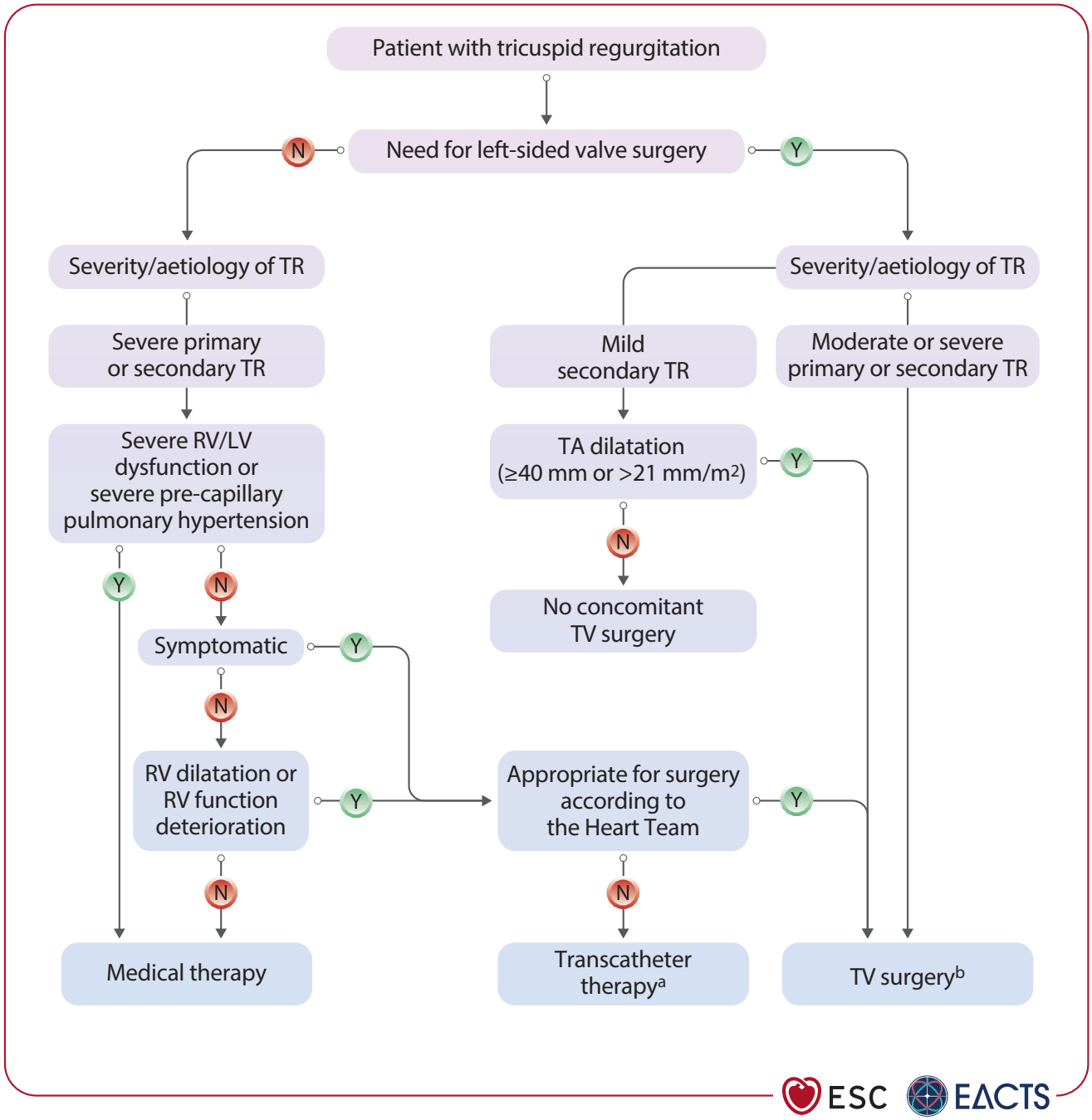

Figure 17 Management of patients with tricuspid regurgitation. LV, left ventricle/left ventricular; RV, right ventricle/right ventricular; TA, tricuspid annulus; TR, tricuspid regurgitation; TV, tricuspid valve. [a]The Heart Team with expertise in the treatment of TV disease evaluates anatomical eligibility for transcatheter therapy including jet location, coaptation gap, leaflet tethering, and potential interference with pacing lead. [b]Repair whenever possible, particularly in cases of moderate TR or mild TR with significant TA dilatation.

more than 80% of cases when anatomical suitability was confirmed.[713,733–735] The Clinical Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System (TRILUMINATE) Pivotal Trial showed also a lower incidence of the composite endpoint of death from any cause or TV surgery, HF hospitalization, and improvement in quality of life as measured with the KCCQ score after tricuspid TEER compared with medical treatment that was exclusively driven by improved quality of life [11.7 points (95% CI, 6.8–16.6); P <0.001].[713] At 2 years, a lower incidence of HF hospitalizations has been observed in the intervention group, despite a high rate of crossovers (59%).[736]

Another investigator-initiated RCT (the Tri.Fr trial) demonstrated the benefit of tricuspid TEER in combination with GDMT over medical therapy alone, for a composite score driven by improved PROMs.[737] Another recent RCT (the Edwards EVOQUE Transcatheter Tricuspid Valve Replacement: Pivotal Clinical Investigation of Safety and Clinical Efficacy using a Novel Device (TRISCEND) II trial), comparing transcatheter TV replacement with optimized medical therapy in patients with symptomatic severe TR, showed similar results with a win ratio favouring TV replacement mainly explained by symptom and quality-of-life improvement. In these studies, reverse RV remodelling was also observed. However, the safety profile of transcatheter TV replacement was less favourable, including higher risk for major bleeding (15%) and post-procedural pacemaker implantation in about one-quarter of the pacemaker-naïve patients after 12 months of follow-up.[738] Based on these data, transcatheter treatment should be considered to improve quality of life and RV remodelling in high-risk patients with symptomatic severe TR, despite optimal medical therapy, but without severe RV dysfunction or pre-capillary PH.

Transvenous CIED lead repositioning or extraction can be considered in selected patients to improve TR or avoid lead jailing before any tricuspid interventions, although the efficacy of this procedure is uncertain and the risk of damaging the TV not negligible.[688,717,739]

Recurrent TR after previous tricuspid annuloplasty usually requires cardiac reoperation for surgical TV replacement. Transcatheter valve-in-ring implantation is an off-label procedure to treat residual TR in high-risk patients. Challenges are the non-circular shape and the open form of the surgical annuloplasty ring.[740] However, transcatheter tricuspid valve-in-valve procedures have been performed with satisfactory results.[741]

Transcatheter TV procedures should be performed at an experienced Heart Valve Centre with expertise in the treatment of TV disease (*Table 6*). Careful evaluation of clinical and anatomical suitability is key for appropriate patient and device selection to achieve optimal TR reduction and symptomatic response to the therapy.

Recommendation Table 9 — Recommendations on indications for intervention in tricuspid regurgitation (see also Supplementary data online, *Evidence Tables 22 and 23*)

Recommendations	Class[a]	Level[b]
Careful evaluation of TR aetiology, stage of the disease (i.e. degree of TR severity, RV and LV dysfunction, and PH), patient operative risk, and likelihood of recovery by a multidisciplinary Heart Team is recommended in patients with severe TR prior to intervention.[691,742]	I	C
Patients with tricuspid regurgitation and left-sided valvular heart disease requiring surgery		
Concomitant TV surgery[c] is recommended in patients with severe primary or secondary TR.[725,731,743,744]	I	B
Concomitant TV repair should be considered in patients with moderate primary or secondary TR, to avoid progression of TR and RV remodelling.[723,724,726,731]	IIa	B
Concomitant TV repair may be considered in selected patients with mild secondary TR and tricuspid annulus dilatation (≥40 mm or >21 mm/m^2), to avoid progression of TR and RV remodelling.[723–726,731,743]	IIb	B
Patients with severe tricuspid regurgitation without left-sided valvular heart disease requiring surgery		
TV surgery[c] is recommended in symptomatic patients with severe primary TR without severe RV dysfunction or severe PH.	I	C
TV surgery[c] should be considered in asymptomatic patients with severe primary TR who have RV dilatation/RV function deterioration, but without severe LV/RV dysfunction or severe PH.	IIa	C
TV surgery[c] should be considered in patients with severe secondary TR who are symptomatic or have RV dilatation/RV function deterioration, but without severe LV/RV dysfunction or PH.[685,720,745–747]	IIa	B
Transcatheter TV treatment should be considered to improve quality of life and RV remodelling in high-risk patients with symptomatic severe TR despite optimal medical therapy in the absence of severe RV dysfunction or pre-capillary PH.[713,733,735,738,748–751]	IIa	A

LV, left ventricle/left ventricular; PH, pulmonary hypertension; RV, right ventricle/right ventricular; TR, tricuspid regurgitation; TV, tricuspid valve.
[a]Class of recommendation.
[b]Level of evidence.
[c]Valve repair whenever possible.

12. Tricuspid stenosis

12.1. Prevalence and aetiology

Tricuspid stenosis (TS) is a relatively rare disease that is most commonly associated with congenital conditions or enzymatic disorders, such as Whipple's or Fabry's disease. It can also be acquired as an isolated manifestation of RHD or occur in combination with aortic and/or MV involvement. Moreover, TS can be the consequence of carcinoid disease due to serotonin-mediated proliferation, causing apposition of fibroblasts and extracellular matrix on the valve leaflets and the subvalvular apparatus. Rare causes include medications (e.g. fenfluramine or methysergide) or inflow obstruction due to CIED-associated thrombus formation or endocarditis with large vegetations.

12.2. Evaluation

Valve evaluation and diagnosis of TS is based on echocardiography, and consists of the anatomical assessment of the leaflet tissue and the subvalvular apparatus. Leaflet thickening with or without calcifications and

commissural fusions are pathognomonic findings of rheumatic involvement. A mean diastolic transvalvular gradient of >5 mmHg at a normal heart rate indicates severe TS.[649]

12.3. Medical therapy

Medical therapy is a bridge to surgical or transcatheter intervention. Intensive sodium restriction and concomitant diuretic therapy can lead to symptom improvement and diminish hepatic congestion.

12.4. Indications for intervention

Although valve repair is preferred in younger patients,[752] valve replacement is frequently required (see *Recommendation Table 10*). Biological heart valves have demonstrated adequate mid- and long-term results, and are preferred over MHVs because of high thrombogenicity in the low-pressure system.[753] In the case of BHV degeneration, transcatheter valve-in-valve procedures are good alternatives to re-replacement.[754] Transcatheter TV implantation is an emerging field, although limited experience is available for the treatment of TS.[749,755] In patients with carcinoid disease, a stable oncological situation is a prerequisite for any valve intervention to maximize survival and valve durability.[756]

Although data are very limited, TV balloon valvuloplasty can be an option in selected patients with TS (and no relevant TR), as well as in those with concomitant mitral and tricuspid rheumatic pathology.[757] However, in contrast to rheumatic MS, tricuspid rheumatic disease more frequently presents as combined stenosis and regurgitation, which limits the applicability of balloon valvuloplasty.

Recommendation Table 10 — Recommendations on indications for intervention in tricuspid stenosis

Recommendations	Class[a]	Level[b]
Surgery[c] is recommended in symptomatic patients with severe TS.[d]	I	C
Surgery[c] is recommended in patients with severe TS undergoing left-sided valve intervention.[e]	I	C

MV, mitral valve; PMC, percutaneous mitral commissurotomy; TS, tricuspid stenosis; TV, tricuspid valve.
[a]Class of recommendation.
[b]Level of evidence.
[c]Usually TV replacement.
[d]Percutaneous balloon valvuloplasty can be attempted as a first approach if TS is isolated.
[e]Percutaneous balloon valvuloplasty can be attempted if PMC can be performed on the MV.

13. Multiple and mixed valvular heart disease

13.1. Prevalence and undertreatment

Patients frequently present with disease of more than one native heart valve [multiple VHD (MVHD)], or coexisting stenosis and regurgitation of the same valve (mixed VHD).[758] While the main cause of MVHD or mixed VHD has shifted to degeneration in high-income countries, the leading aetiology in low- and middle-income countries remains RHD.[758,759] Regurgitation of atrioventricular valves secondary to cardiomyopathy or long-standing primary valve disease, and late effects of radiation therapy, are further causes of MVHD.[758,760] Challenges in diagnostic evaluation coupled with limited data to guide clinical decisions contribute to late referral and undertreatment of patients with MVHD.[758]

13.2. Evaluation and diagnostic pitfalls

In view of the complex haemodynamic interplay of multiple and mixed valve lesions, assessment by a Heart Team at a Heart Valve Centre and use of an integrative multimodality approach is key to gain diagnostic certainty, detect cardiac damage, and evaluate therapeutic options.[761,762] In the light of paucity of data on diagnostic and prognostic parameters in patients with MVHD, assessment largely focuses on pathophysiological considerations and evidence derived from isolated valve lesions.

Echocardiography is the main tool to diagnose MVHD, assess mechanism, severity, and associated cardiac damage, and monitor disease progression.[761] Haemodynamic interdependence between multiple valve defects alters the loading and flow conditions, thereby limiting the diagnostic validity of measures established to grade single valve defects (*Table 9*). In the presence of MVHD, low-flow states are frequent. The continuity equation becomes erroneous if transvalvular flows are unequal, and pressure half-time (PHT)-derived methods are inaccurate if the ventricular compliance or filling is altered.[761] In this context, TOE can provide important detailed anatomical and mechanistic flow-independent information.[46,761]

If symptoms or echocardiographic findings are equivocal, multimodality diagnostics should be considered on an individual basis to assess the cumulative repercussions of MVHD.

Measures obtained during cardiopulmonary exercise testing reflect the effect of MVHD on functional capacity.[52,105,654,761,779] Levels of natriuretic peptides such as NT-proBNP correlate with functional and echocardiographic parameters, and provide incremental prognostic value in patients with mixed aortic disease and MVHD.[98,780] AV calcium scoring confirms the diagnosis of true severe AS under low-flow conditions, as described in *Section 8.2*.[777] Cardiac magnetic resonance imaging enables the independent assessment of valvular regurgitation using volumetric methods or direct flow quantification.[45,46,522,762,781] Importantly, invasive cardiac output-derived measures based on thermodilution or the Fick equation using estimated oxygen uptake are inaccurate in low-flow conditions or severe TR, commonly present in MVHD.[782]

13.3. Indications for intervention

Given the heterogeneity of clinical scenarios and the lack of evidence on optimal treatment pathways, it is recommended that patients with MVHD are evaluated for intervention by a collaborative Heart Team at a Heart Valve Centre with experience in multimodality imaging and treatment of complex VHD.[16,764]

Patients presenting with a lesion fulfilling criteria for an intervention based on recommendations for single VHD should be treated accordingly. In the remaining patients, assessment of symptoms and functional status, as well as cardiac damage (which may be masked by the consequences of concomitant lesions and occur before symptoms manifest), is required. The risk–benefit ratio of intervention needs to take into account diagnostic (un)certainty, the mechanisms and severity of MVHD, and patient-specific factors, as well as procedural options and risks to determine the mode, timing, and sequence of valve treatment.

13.3.1. Multiple valvular heart disease

Multiple VHD with primary (as opposed to secondary) valvular disease usually requires surgical treatment of all relevant valvular lesions. Simultaneous treatment of concomitant severe valve defects is recommended and treatment of concomitant moderate AS, or moderate TR, should be considered (*Recommendation Table 11*).

Table 9 Echocardiographic pitfalls, robust measures, and complementary multimodality imaging parameters in multiple or mixed valvular heart disease

		Valve lesion to be assessed			
		AS	**AR**	**MS**	**MR**
Concomitant valve lesion	**AS**	—	PHT unreliable LV volume increase less pronounced *(hypertrophy, disproportionate diastolic LV pressure overload[763])*	PHT unreliable *(LV compliance ↓ [764])* Low gradient due to low flow possible *(low-flow state[669])*	Regurgitant volume ↑ MR colour-flow jet area ↑ *(increased afterload and transmitral systolic pressure gradient[46])*
	AR	Simplified Bernoulli equation overestimates gradient if LVOT velocity ↑ [765]	—	PHT unreliable *(gradient ↓, altered LV compliance[766])* MVA by continuity equation using aortic forward flow unreliable[46]	Doppler volumetric method using net aortic forward flow invalid Mitral-to-aortic VTI ratio unreliable *(increased transaortic flow[46])*
	MS	Low-flow low-gradient possible *(low-flow state[761])*	LV volume increase less pronounced *(reduced preload[761])*	—	Mitral-to-aortic VTI ratio unreliable *(increased mitral VTI due to stenosis[767])* Calcifications may shadow jet area
	MR	Low-flow low-gradient *(MR-induced low-flow state[768])* AS confused with MR jet	PHT unreliable *(altered LV compliance[763])* Doppler volumetric method using net mitral forward flow invalid *(increased flow[46])*	PHT unreliable *(altered LA and LV compliance[769,770])* Continuity equation unreliable *(increased transmitral flow[761])*	—
	TR	Low-flow low-gradient possible *(TR induced low-flow state[771])*	—	Low gradient possible *(low-flow state[668])* PHT may be less reliable *(impaired LV filling due to ventricular interdependence[772,773])*	Regurgitant volume↓ in SMR possible *(decreased preload[774])*
Robust echocardiography measurements		AVA (continuity equation), DVI[761] *In mixed AR and AS: V_{max} and mean gradient reflect combined burden[765]*	EROA (PISA), vena contracta[46,761]	Planimetry and 3D MVA (TOE)[529,775] *In mixed MR & MS: mean gradient reflects combined burden[674,776]*	EROA (PISA), vena contracta[46,761]
Alternative imaging modalities		CT: AV calcium scoring[777]	CMR: regurgitant volume and fraction[45,46]	—	CMR: regurgitant volume and fraction[45,46]

Measures reported refer to assessment of the valve lesions listed in the columns. Adapted from [761].
3D, three-dimensional; AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; CMR, cardiac magnetic resonance; CT, computed tomography; DVI, Doppler velocity index; EROA, effective regurgitant orifice area; LA, left atrium/left atrial; LV, left ventricle/left ventricular; LVOT, left ventricular outflow tract; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; PHT, pressure half-time; PISA, proximal isovelocity surface area; SMR, secondary mitral regurgitation; TOE, transoesophageal echocardiography; TR, tricuspid regurgitation; VHD, valvular heart disease; V_{max}, peak transvalvular velocity; VTI, velocity time integral; ↑, increase; ↓, decrease; —, none.

Transcatheter treatment options are established for severe AS (TAVI), rheumatic MS (PMC), and primary MR and TR (TEER or transcatheter replacement) in patients with MVHD at high surgical risk, if anatomy is suitable.[401,783] In the context of a transcatheter strategy, a staged approach—typically beginning with the downstream lesion (aortic, followed by mitral and tricuspid)—is generally preferred to avoid potential haemodynamic deterioration.[784,785]

MVHD with severe secondary regurgitation of both atrioventricular valves is usually the consequence of either HFrEF with ventricular SMR and secondary TR, or atrial dilatation leading to both atrial MR and TR

(often TR > MR). While surgery aims to address all relevant valve lesions in a single procedure, a stepwise transcatheter strategy offers the possibility of reassessing the upstream valve(s) under altered loading conditions, usually 3 months after the initial intervention. In very selected cases simultaneous transcatheter valve treatment may be considered.[788,789] However, evidence is limited and primarily derived from modestly sized observational studies.[786–789]

13.3.2. Mixed aortic valve disease

The severity of mixed AV disease is often underestimated and patients with balanced moderate AR and AS show adverse event rates comparable to patients with severe isolated AS.[790,791]

Transvalvular gradients measured by Doppler reflect the overall haemodynamic burden of both regurgitation and stenosis, and are strongly associated with adverse outcomes.[765,791–793] Therefore, the presence of high transvalvular gradients justifies valve intervention in patients with moderate mixed AV disease, even if regurgitation is graded as moderate and the calculated or planimetric AVA is >1 cm^2 (*Recommendation Table 12*). Patients presenting with mixed AV disease, but with gradients below thresholds for intervention, should undergo careful multimodality diagnostics including assessment of cardiac damage to inform individual treatment strategies. Global longitudinal strain and natriuretic peptides have shown incremental prognostic value beyond symptom status and single lesion severity in patients with preserved LVEF.[762,794–796]

13.3.3. Mixed mitral valve disease

Mixed MV disease is usually present in patients with rheumatic valve disease or MAC. If MVA is ≤1.5 cm^2, recommendations for isolated MS apply. However, patients with an MVA of >1.5 cm^2 and moderate MR may be evaluated for valve replacement based on symptoms, anatomical characteristics, transmitral gradient, and signs of cardiac damage such as LA dilatation, AF, or PH.[529,674,776,797]

Recommendation Table 11 — Recommendations on indications for surgery of concomitant left-sided valvular heart disease[a]

Recommendations	Class[b]	Level[c]
Concomitant aortic stenosis		
SAVR is recommended in patients with severe AS undergoing surgery for another valve.	I	C
SAVR should be considered in patients with moderate AS[d] undergoing surgery for another valve.	IIa	C
Concomitant aortic regurgitation		
AV surgery is recommended in patients with severe AR undergoing surgery for another valve.	I	C
Concomitant mitral regurgitation		
MV surgery is recommended in patients with severe MR undergoing surgery for another valve.	I	C

AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; MR, mitral regurgitation; MV, mitral valve; SAVR, surgical aortic valve replacement; TV, tricuspid valve.
[a]Recommendations for surgery of concomitant TV disease are listed in *Section 11* and *Section 12*.
[b]Class of recommendation.
[c]Level of evidence.
[d]Defined as an AVA of 1.0–1.5 cm^2 (or mean aortic gradient of 25–40 mmHg) in normal-flow conditions. Clinical assessment is essential to determine whether SAVR is appropriate for an individual patient.

Recommendation Table 12 — Recommendations on indications for intervention in patients with mixed moderate aortic stenosis and moderate aortic regurgitation (see also Supplementary data online, *Evidence Table 24*)

Recommendations	Class[a]	Level[b]
Intervention is recommended in symptomatic patients with mixed moderate AV stenosis[c] and moderate regurgitation, and a mean gradient ≥40 mmHg or V_{max} ≥4.0 m/s.[790–793]	I	B
Intervention is recommended in asymptomatic patients with mixed moderate AV stenosis[c] and moderate regurgitation with V_{max} ≥4.0 m/s, and LVEF <50% not attributable to other cardiac disease.[791]	I	C

AV, aortic valve; AVA, aortic valve area; LVEF, left ventricular ejection fraction; V_{max}, peak transvalvular velocity.
[a]Class of recommendation.
[b]Level of evidence.
[c]AVA >1 cm^2.

13.4. Follow-up

Due to the cumulative haemodynamic impact of MVHD or mixed VHD, progression of its severity and the development of cardiac damage may be faster than in single VHD.[761] Therefore, follow-up intervals should be adjusted according to individual patient characteristics.

14. Management of patients with prosthetic valves or valve repair

14.1. Choice of prosthetic valve

When choosing between an MHV and a BHV prosthesis for an individual patient, age, life expectancy, lifestyle, bleeding and thromboembolic risks, possibility of pregnancy, and patient preference should be considered. Life expectancy is estimated according to age, sex, comorbidities, ethnicity, and geographical area.[798] An MHV is preferred in younger patients with longer life expectancy and in those with a pre-existing indication for long-term OAC (*Recommendation Table 13*). Generally, a BHV is implanted in patients with shorter life expectancy, increased bleeding risk due to frailty or comorbidities, in women contemplating pregnancy, and in patients in whom stable INRs with adequate times in therapeutic range are unlikely.[799] Importantly, the performance of different BHV prostheses can vary considerably.[800] The impact of the aetiology of the native valve disease, if any, on the choice between an MHV and a BHV remains unexplored.

Several large observational studies, smaller RCTs, and meta-analyses have compared long-term mortality with BHV and MHV prostheses in patients aged 50–70 years.[376,801–805] Some of the studies showed lower mortality with an MHV in AV patients <60 years and MV patients <65 years old,[801,804] while others failed to show any differences.[376,802,803] Most of these studies were limited by their observational nature and missing information on the type of prostheses implanted. RCTs with sufficient statistical power comparing biological and mechanical prostheses are warranted.

Replacement of the AV using an autograft (Ross procedure) is an alternative to an MHV in young patients that should be performed at experienced centres by operators with dedicated expertise (see also *Section 8*).[806] General recommendations are summarized in *Recommendation Table 13*.

Recommendation Table 13 — Recommendations for prosthetic valve selection

Recommendations	Class[a]	Level[b]
Mechanical heart valve		
An MHV is recommended according to the desire of the informed patient and if there is no contraindication to long-term anticoagulation.	I	C
An MHV should be considered in patients with an estimated long life expectancy,[c] if there are no contraindications for long-term OAC.[801,807–811]	IIa	B
An MHV should be considered in patients aged <60 years for prostheses in the aortic position and aged <65 years for prostheses in the mitral position.[801,807–811]	IIa	C
An MHV should be considered in patients with a pre-existing MHV in another position.	IIa	C
An MHV may be considered in patients with a clear indication for long-term OAC.	IIb	C
Biological heart valve		
A BHV is recommended according to the desire of the informed patient.	I	C
A BHV is recommended when an adequate quality of anticoagulation with VKA is unlikely, in patients at high bleeding risk, or with estimated short life expectancy.[c]	I	C
A BHV should be considered in patients aged >65 years for prostheses in the aortic position or aged >70 years for prostheses in the mitral position.	IIa	C
A BHV should be considered in women contemplating pregnancy.	IIa	C

BHV, biological heart valve; MHV, mechanical heart valve; OAC, oral anticoagulation; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Life expectancy should be estimated according to age, sex, comorbidities, ethnicity, and geographical area.

14.2. Follow-up of patients with prosthetic valves

All patients with prosthetic valves require lifelong clinical and echocardiographic follow-up to detect deterioration of prosthetic function, associated cardiac damage, or progressive disease of another valve. Serial TTE measurements of transprosthetic gradients, calculation of the effective valve area, and evaluation of leaflet motion and morphology should be performed in patients receiving a BHV within 3 months after valve implantation, again at 1 year, and annually thereafter, or sooner if new cardiovascular symptoms occur.[812] TOE is recommended in all cases of suspected prosthetic valve dysfunction or endocarditis. In the latter case, CCT and PET-CT are also recommended, if the diagnosis is unclear, and to identify primary or secondary infection foci.[5]

Cinefluoroscopy for MHVs and CCT provide useful additional information, if valve thrombus or pannus is suspected.[812] Imaging should be repeated in the case of thrombolytic and antithrombotic treatment of MVH thrombosis, even if gradients are normalized.[813]

14.3. Antithrombotic therapy in patients with treated valvular heart disease

14.3.1. Mechanical heart valves

14.3.1.1. Post-operative anticoagulation and therapeutic targets

Mechanical heart valves require lifelong treatment with a VKA guided by the INR. Bridging with either therapeutic unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) and VKA should be initiated within 24 h after MHV implantation, or as soon as considered safe. Heparin can be stopped when the INR is documented for 2 consecutive days within the therapeutic range (*Figure 18*).[814] Two meta-analyses and a prospective study have suggested slightly lower bleeding rates using UFH bridging compared with LMWH after MHV replacement or cardiac surgery.[814–816] However, RCTs comparing the timing and dosage of each bridging strategy are lacking.

For all patients with an MHV, lifelong VKA is recommended to avoid major thrombotic complications, since cardioembolic or valve thrombosis rates without anticoagulation are substantial (12% per year and 22% per year for first-generation aortic and mitral MHVs, respectively).[817] The INR target and range should be chosen considering the type, position, and number of valves, the patient's thrombotic risk, and comorbidities (see *Table 10* and *Recommendation Table 14*). In patients with an MHV developing a major thromboembolic complication despite adequate INR and time in therapeutic range (TTR, usually defined as >60%),[820] either increased VKA intensity (e.g. INR target and range increased by 0.5 units) or the addition of low-dose acetylsalicylic acid (ASA) (75–100 mg/day) should be considered.[818] Direct oral anticoagulants or dual antiplatelet therapy (DAPT) are contraindicated to prevent thromboembolism in patients with an MHV.[821–824]

Given the complexity of lifelong VKA therapy due to high intra- and interpatient variability, the need for monitoring, drug and food interactions,[825,826] the narrow therapeutic window, influence of comorbidities, and non-modifiable characteristics (e.g. ageing, genetics, and ethnicity), RCTs have shown that patient's education, as well as disease and treatment awareness, significantly improves anticoagulation quality and adherence.[827–830] International normalized ratio self-monitoring and/or self-management increase efficacy, but not safety, as compared with a standard approach; INR self-monitoring can be used by motivated patients after adequate training.[827–830]

The indication for VKA and DAPT combination in MHV patients presenting with acute coronary syndrome is described in the corresponding ESC Guidelines.[151,831] In patients with an MHV and an indication for single antiplatelet therapy (SAPT) due to symptomatic major atherosclerotic diseases and low bleeding risk, low-dose ASA in combination with a VKA should be considered, because this strategy has been shown to significantly lower the incidence of major adverse cardiovascular events.[818] However, the combination of antiplatelet agents (single or dual) and VKA increases the risk of bleeding,[825] and therefore their use should be carefully weighted. In a large meta-analysis that included MHV patients, the combination of VKA with either ASA or clopidogrel increased clinically relevant bleeding compared with VKA alone (clopidogrel odds ratio, 3.55; 95% CI, 2.78–4.54; ASA odds ratio, 1.50; 95% CI, 1.29–1.74), which may be aggravated because of potential pharmacokinetic drug interactions on the cytochrome P (CYP)450s 2C19 and 3A4.[825]

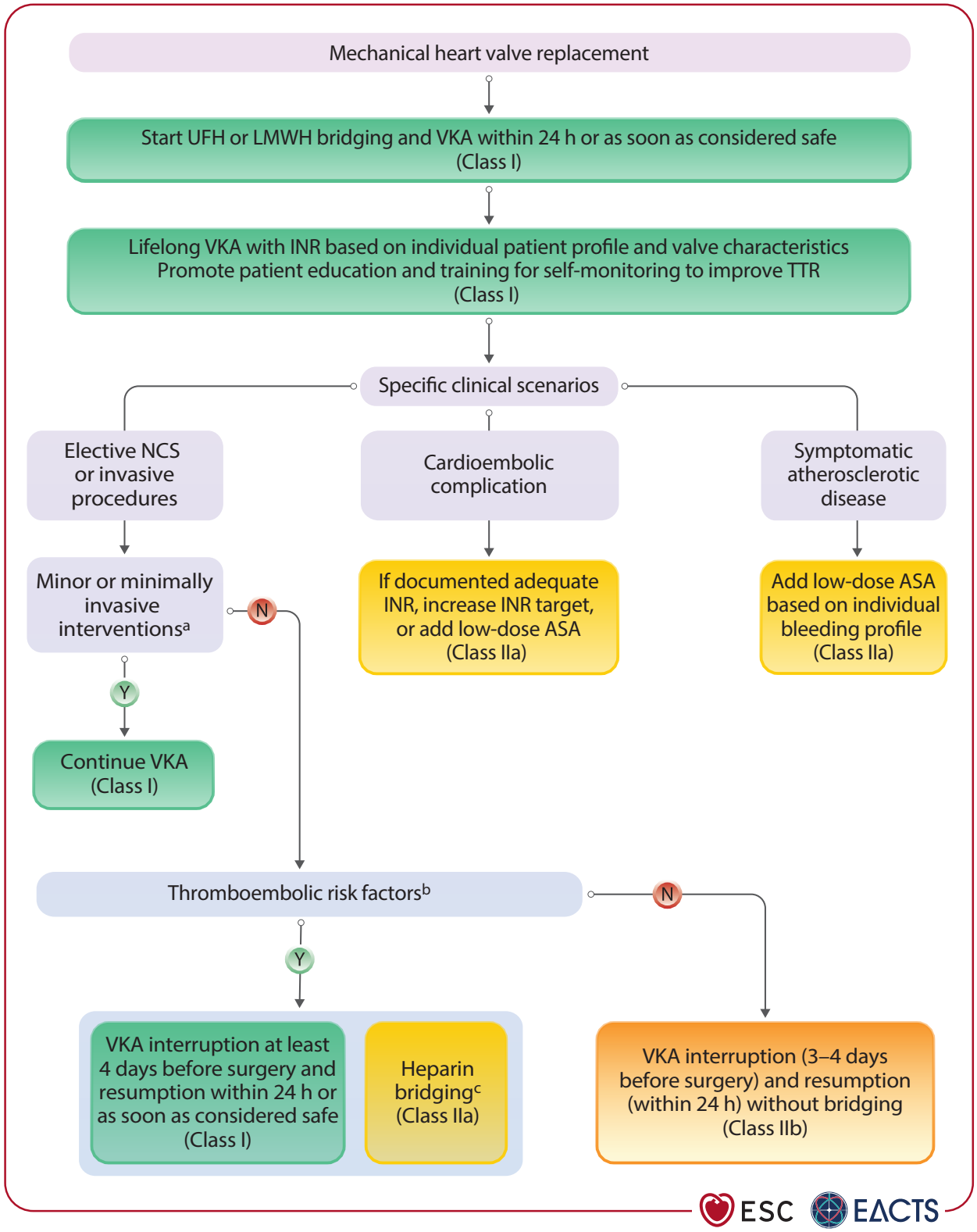

Figure 18 Antithrombotic therapy following mechanical heart valve implantation. AF, atrial fibrillation; ASA, acetylsalicylic acid; INR, international normalized ratio; LMWH, low-molecular-weight heparin; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; MHV, mechanical heart valve; MS, mitral stenosis; N, no; NCS, non-cardiac surgery; TTR, time in therapeutic range; UFH: unfractionated heparin; VKA, vitamin K antagonist; Y, yes. [a]Skin; minor eye surgery including cataract; dental cleaning, treatment of caries, and dental extractions; pacemaker or device implantation; and diagnostic cardiac catheterization. [b]MHV in mitral or tricuspid position, older MHV generations in any position, inherited or acquired hypercoagulable state, LV dysfunction (LVEF <35%), AF with significant MS, recent (<12 months) major thrombotic event (i.e. cardioembolic stroke, deep vein thrombosis, pulmonary embolism). [c]Bridging needs to be started as soon as INR reaches a sub-therapeutic value and on the first postoperative day or as soon as considered safe.

Recommendation Table 14 — Recommendations for the management of antithrombotic therapy in patients with a mechanical heart valve

Recommendations	Class[a]	Level[b]
Following cardiac surgery with MHV implantation, it is recommended to start UFH or LMWH bridging and VKA within 24 h, or as soon as considered safe.[815,816,832–834]	I	B
Lifelong OAC with a VKA is recommended for all patients with MHVs to prevent thromboembolic complications.[821–823,835–838]	I	A
INR self-monitoring and self-management are recommended over standard monitoring in selected, trained patients to improve efficacy.[827,828]	I	A
It is recommended that INR targets are based on the type and position of the MHV, patient risk factors, and comorbidities.[c] [818,819,835–838]	I	A
Patient education is recommended to improve the quality of OAC.[827–830]	I	A
The addition of low-dose ASA (75–100 mg/day) to VKA should be considered in selected patients with MHVs in case of concomitant symptomatic atherosclerotic disease considering the individual bleeding risk profile.[818]	IIa	B
Either an increase in INR target or the addition of low-dose ASA (75–100 mg/day) should be considered in patients with MHVs who develop a major thromboembolic complication despite documented adequate INR.[818]	IIa	C
DOACs and/or DAPT are not recommended to prevent thrombosis in patients with an MHV.[821–824]	III	A

ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; h, hour; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MHV, mechanical heart valve; OAC, oral anticoagulation; UFH, unfractionated heparin; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]See *Table 10* for details.

Table 10 International normalized ratio targets and therapeutic ranges for patients with a mechanical heart valve

MHV type and position	Additional pro-thrombotic factors[a]	INR target and (range)
First-line treatment with VKA only		
Ball-in cage, tilting disc valve in any position, all MHV in mitral/tricuspid position	No	3 (2.5–3.5)
	Yes	3.5 (3–4)[b]
Bileaflet, current-generation single-tilting aortic MHV	No	2.5 (2–3)[c]
	Yes	3 (2.5–3.5)

AF, atrial fibrillation; ASA, acetylsalicylic acid; INR, international normalized ratio; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; MHV, mechanical heart valve; MS, mitral stenosis; VKA, vitamin K antagonist.
[a]Inherited or acquired hypercoagulable state, LV dysfunction (LVEF <35%), AF with significant MS, recent (<12 months) major thrombotic event (i.e. cardioembolic stroke, deep vein thrombosis, pulmonary embolism).
[b]In patients at very high thrombotic risk, low-dose ASA may be added instead.[818]
[c]In patients at high bleeding risk, INR target could be maintained at a lower interval: 2 (1.5–2.5).[819]

14.3.1.2. Prevention and management of bleeding

Since patients with MHVs receive lifelong VKA, strategies to prevent bleeding need to be implemented. Proton pump inhibitors reduce the risk of upper gastrointestinal bleeding by approximately 40% in patients taking VKAs[825,839,840] and should therefore be prescribed to patients with MHVs, particularly in those with additional bleeding risk factors (e.g. elderly, antiplatelet agent co-administration, chronic use of non-steroidal anti-inflammatory drugs, high INR, or alcohol abuse). Randomized controlled trials and a meta-analysis did not demonstrate a benefit of oral vitamin K1 supplementation in addition to temporary VKA cessation in non-bleeding patients with a supratherapeutic INR (4.5–10.0), with a trend toward reduced safety, which may be relevant for MHV patients.[841,842] For non-bleeding patients with an INR of >10.0, oral vitamin K1 (2.0–3.0 mg) should be administered, avoiding overcorrection.[841,843]

In cases of uncontrolled life-threatening or other major bleeding,[844] VKA use must be interrupted and reversal with non-activated four-factor prothrombin complex concentrates is preferred over fresh frozen plasma, because of higher safety and effectiveness.[845–848] A reduced starting dose (12.5 rather than 25 IU/kg) in patients with more thrombogenic MHVs may be considered.[849] In addition, vitamin K1 should be administered to reverse the effect of VKA. Intravenous route corrects INR ~4 h faster than oral administration,[850] with no differences at 24 h and an unknown clinical impact. VKA should be restarted as soon as major bleeding is controlled.

14.3.1.3. Management of anticoagulation therapy before and after non-cardiac invasive procedures

In patients with an MHV, VKA treatment should not be interrupted for: minor or minimally invasive procedures on the skin or eyes (including cataract with topical anaesthesia); dental cleaning, treatment of caries, and dental extractions; pacemaker implantation; cardiac catheterization; and endoscopic procedures (*Recommendation Table 15*; *Table 11*).[851–856] Topical antifibrinolytic or haemostatic agents may improve local haemostasis.[853]

In patients with an MHV and high thromboembolic risk (*Recommendation Table 16*; *Table 11*) undergoing non-cardiac, elective major invasive procedures with high risk of bleeding (see Supplementary data online, *Table S6*), VKA treatment must be interrupted at least 4 days before the procedure, bridging with LMWH should be started as soon as the INR reaches a subtherapeutic value, and the INR should be <1.5 on the day of surgery.[816,857,858] Measuring anti-Xa activity at peak and trough may be appropriate to manage LMWH dosing in selected patients, such as those with severe obesity or underweight.[859] In cases of urgent, major invasive procedures, four-factor prothrombin complex concentrate should be administrated to timely correct the INR for the intervention, if needed. For the management of antithrombotic drugs in patients undergoing major cardiac surgery, please refer to recent EACTS Guidelines.[860]

Recommendation Table 15 — Recommendations for the management of antithrombotic therapy in patients with a mechanical heart valve undergoing elective non-cardiac surgery or invasive procedures

Recommendations	Class[a]	Level[b]
Continuing VKA treatment is recommended in patients with an MHV for minor or minimally invasive interventions[c] associated with no or minimal bleeding.[851–856]	I	A
It is recommended to discontinue VKA at least 4 days before major non-cardiac elective surgery, aiming for an INR <1.5, and to resume VKA treatment within 24 h after surgery, or as soon as considered safe.[816,857,858]	I	B
VKA interruption and resumption with bridging[d] should be considered in patients with an MHV and thromboembolic risk factors[e] undergoing major NCS.[816,857,858]	IIa	B
Interruption (3–4 days before surgery) and resumption of VKA without bridging may be considered to reduce bleeding in patients with new-generation aortic MHVs and no other thromboembolic risk factors[e] undergoing major NCS or invasive procedures.[816,857,858,861–864]	IIb	B

AF, atrial fibrillation; h, hour; INR, international normalized ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; MHV, mechanical heart valve; MS, mitral stenosis; NCS, non-cardiac surgery; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Skin; minor eye surgery including cataract; dental cleaning, treatment of caries, and dental extractions; pacemaker or device implantation; diagnostic cardiac catheterization; gastroscopic, colonoscopic, bronchoscopic, or genitourinary diagnostic or therapeutic procedures considered at low bleeding risk.
[d]Bridging needs to be started as soon as INR reaches a subtherapeutic value and on the first post-operative day or as soon as considered safe.
[e]MHV in mitral or tricuspid position, older MHV generations in any position, inherited or acquired hypercoagulable state, LV dysfunction (LVEF <35%), AF with significant MS, recent (<12 months) major thrombotic event (i.e. cardioembolic stroke, deep vein thrombosis, pulmonary embolism).

Table 11 Peri-operative management of antithrombotic treatment in patients with a mechanical heart valve undergoing non-cardiac surgery based on type of procedure and underlying risk

		Minimally invasive procedures[a]		Major NCS or invasive procedures[a]	
		Pre-procedure	Post-procedure	Pre-procedure	Post-procedure
Low thromboembolic risk					
New-generation aortic MHV and no additional risk factors[b]	**OAC**	No interruption of VKA	Continue VKA	Interrupt VKA at least 3–4 days prior to procedure with target INR <1.5 on the day of surgery	Resume VKA as soon as feasible, within 24 h
	Bridging	—	—	No bridging may be considered	No bridging may be considered, unless unable to administer OAC
	Supporting measures	—	Topical antifibrinolytic or haemostatic agents may be considered to improve local haemostasis	—	Mechanical and pharmacological VTE prophylaxis, if indicated
Moderate-to-high thromboembolic risk					
MHV in mitral or tricuspid position or other thromboembolic risk factors[b]	**OAC**	No interruption of VKA	Continue VKA	Interrupt VKA at least 4 days prior to procedure with target INR <1.5 the day of the procedure	Resume VKA within 24 h
	Bridging	—	—	Bridging with LMWH or UFH if CKD stage IV or V, starting at INR below the therapeutic range	Bridging with UFH or LMWH post-operatively within 24 h
	Supporting measures	—	Topical antifibrinolytic or haemostatic agents may be considered to improve local haemostasis	—	Appropriate mechanical and pharmacological VTE prophylaxis

AF, atrial fibrillation; CKD, chronic kidney disease; h, hour; INR, international normalized ratio; LMWH, low-molecular-weight heparin; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; MHV, mechanical heart valve; MS, mitral stenosis; NCS, non-cardiac surgery; OAC, oral anticoagulation; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.
[a]See Supplementary Table S6.
[b]Inherited or acquired hypercoagulable state, LV dysfunction (LVEF <35%), AF with significant MS, recent (<12 months) major thrombotic event (i.e. cardioembolic stroke, deep vein thrombosis, pulmonary embolism).

For patients with an MHV and low cardioembolic risk (e.g. a new-generation MHV in the aortic position without additional risk factors) undergoing elective major NCS or invasive procedures, VKA interruption (3–4 days before surgery)[816,857,858,861–864] and resumption[861–863] within 24 h may be performed without bridging to reduce post-surgical bleeding without increasing the risk of thrombosis (see *Figure 18*).

14.3.2. Biological heart valves

The management of antithrombotic treatment after BHV implantation or valve repair is summarized in *Recommendation Table 16* and *Figure 19*.

14.3.2.1. Patients with a surgical biological heart valve and no indication for oral anticoagulation

The optimal antithrombotic strategy early after surgical implantation of an aortic BHV remains controversial due to the lack of high-quality evidence. Multiple observational studies support the short-term use of VKAs to reduce the risk of thromboembolism,[865,866] while data on DOACs are missing. A small RCT and a meta-analysis found that VKA treatment for 3 months significantly increased major bleeding compared with low-dose ASA, without reducing mortality or thromboembolic events, but statistical power was low.[867,868] Therefore, both strategies (OAC or ASA) are reasonable within 3 months of surgical aortic BHV implantation. In the absence of randomized evidence, patients undergoing mitral or tricuspid BHV implantation should receive OAC for at least 3 months due to the increased risk of AF and thromboembolisms.

14.3.2.2. Patients with a transcatheter heart valve and no indication for oral anticoagulation

Based on evidence from RCTs, lifelong low-dose ASA is the recommended antithrombotic treatment after TAVI in patients without OAC indication. In the Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPular TAVI) trial (cohort A), the incidence of bleeding and the composite of bleeding or thromboembolic events were both reduced with ASA compared with DAPT at 1 year.[869] One RCT [Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivAroxaban-based antithrombotic strategy to an antipLatelet-based strategy after transcatheter aortIc vaLve rEplacement (TAVR) to Optimize clinical outcomes, GALILEO], which investigated a systematic

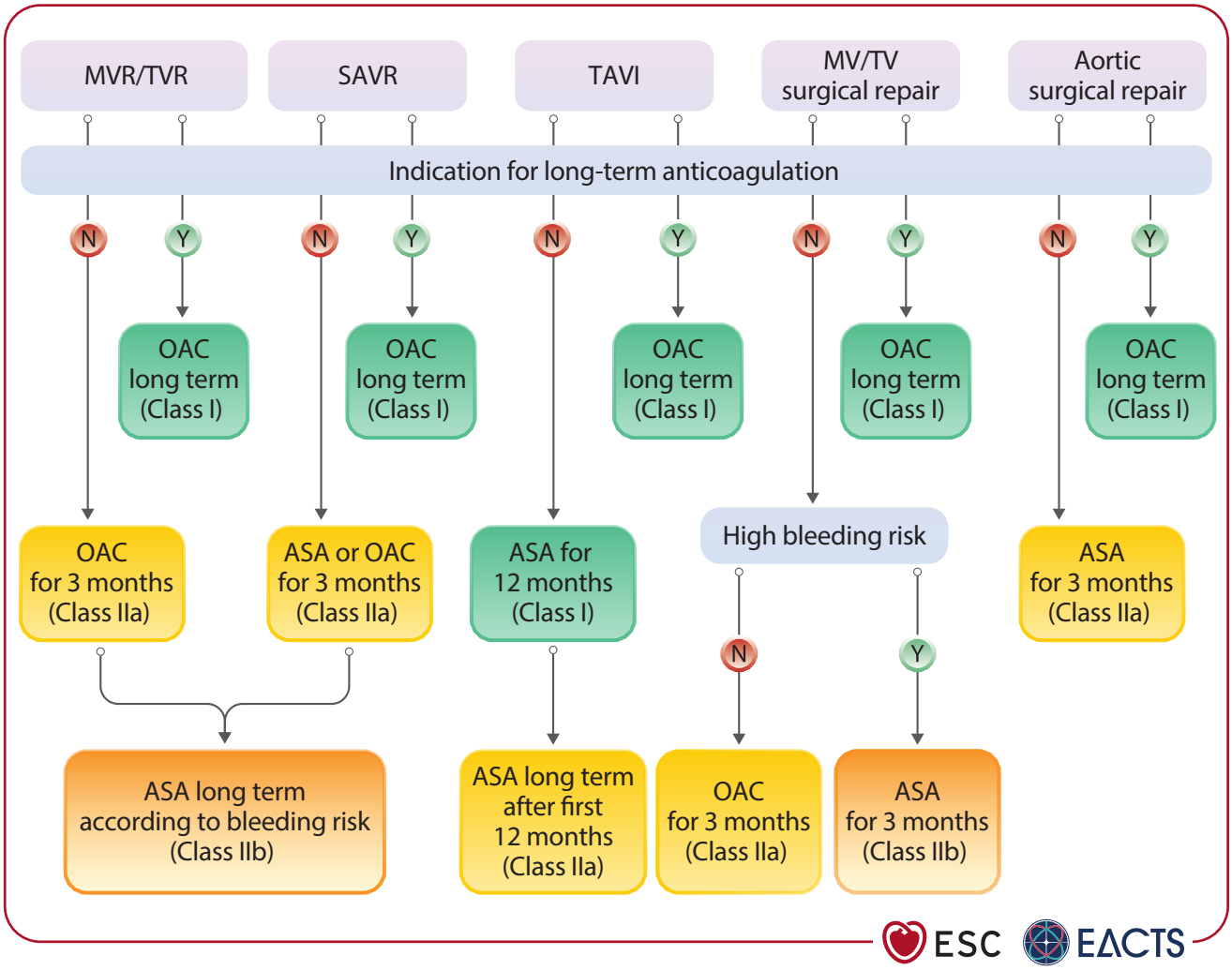

Figure 19 Antithrombotic therapy following biological heart valve implantation or surgical valve repair. ASA, acetylsalicylic acid; MV, mitral valve; MVR, mitral valve replacement; OAC, oral anticoagulation; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; TV, tricuspid valve; TVR, tricuspid valve replacement.

antithrombotic strategy of rivaroxaban (10 mg/day) in combination with low-dose ASA compared with DAPT with clopidogrel for the first 3 months, was halted prematurely due to an increased risk of death or thromboembolic complications, and an increased risk of bleeding in the rivaroxaban/ASA group.[870] The systematic use of DOACs after TAVI in patients without indication for OAC is therefore not recommended. Data on antithrombotic management after implantation of transcatheter mitral BHVs or tricuspid BHVs are limited. Vitamin K antagonist treatment for ≥3 months is commonly prescribed, while DOACs may represent an alternative allowing for earlier discharge and a lower risk of short-term bleeding complications (median follow-up, 4.7 months).[871]

For patients without baseline OAC undergoing mitral or tricuspid transcatheter valve implantation, OAC (either with DOAC or VKA) is initiated and usually pursued for at least 6 months or indefinitely (in particular after valve implantation in the tricuspid position), while patients undergoing TEER usually receive single long-term antiplatelet therapy with ASA.

14.3.2.3. Patients with a surgical biological heart valve and an indication for oral anticoagulation

Lifelong OAC is recommended for patients with surgical BHVs with other indications for OAC. The evidence supports the use of DOACs in preference to VKAs in patients with AF, even during the early post-operative period.[872–877] A previously existing therapy with a DOAC may be continued after BHV implantation and should be re-started, as soon as considered surgically safe, usually within 2–3 days of surgery.[860]

14.3.2.4. Patients with a transcatheter biological heart valve and an indication for oral anticoagulation

In the POPular TAVI trial (cohort B), the incidence of bleeding over a period of 1 month or 1 year was lower with OAC than with OAC plus clopidogrel.[878] Oral anticoagulation alone was non-inferior to OAC plus clopidogrel with respect to ischaemic events, but the non-inferiority margin was large. In Edoxaban vs Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation (ENVISAGE-TAVI-AF),[879] edoxaban was non-inferior to VKA regarding the composite primary endpoint (death from any cause, myocardial infarction, ischaemic stroke, systemic thromboembolic event, valve thrombosis, or major bleeding), but the incidence of major bleeding was higher with edoxaban than with VKA. The Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS) trial[880] showed that apixaban was not superior to VKA after TAVI when there was a pre-existing indication for OAC, and there was a signal of higher non-cardiovascular mortality with apixaban. Therefore, no definitive recommendation can be made concerning the use of VKAs vs DOACs in patients who have undergone TAVI with a pre-existing indication for OAC.

Antithrombotic therapy after transcatheter MV or TV implantation remains empirical because data are limited. A high proportion of patients are already under OAC because of AF (almost 50% of the population with MR and 80%–90% of the candidates for TR treatment). Common practice is to continue the pre-existing anticoagulation regimen. Vitamin K antagonists and DOACs have been used in this setting with or without combination with ASA.[871] However, the high bleeding risk of this usually elderly population needs to be taken into consideration.

Recommendation Table 16 — Recommendations for the management of antithrombotic therapy in patients with a biological heart valve or valve repair

Recommendations	Class[a]	Level[b]
Surgical biological heart valve without indication for oral anticoagulation		
Low-dose ASA (75–100 mg/day) or OAC using a VKA should be considered for the first 3 months after surgical implantation of an aortic BHV in patients without clear indication for OAC.[865,866]	IIa	B
A VKA should be considered for the first 3 months after surgical implantation of a mitral or tricuspid BHV in patients without clear indication for OAC.[867,868]	IIa	B
Lifelong low-dose ASA (75–100 mg/day) may be considered 3 months after surgical implantation of an aortic or mitral BHV in patients without clear indication for OAC.	IIb	C
Transcatheter aortic valve implantation without indication for oral anticoagulation		
Low-dose ASA (75–100 mg/day) is recommended for 12 months after TAVI in patients without indication for OAC.[869,880–883]	I	A
Long-term (after the first 12 months) low-dose ASA (75–100 mg/day) should be considered after TAVI in patients without clear indication for OAC.	IIa	C
DAPT is not recommended to prevent thrombosis after TAVI, unless there is a clear indication.[881]	III	B
Routine use of OAC is not recommended after TAVI in patients without baseline indication.[869,880]	III	A
Surgical repair without indication for oral anticoagulation		
OAC, with either VKAs or DOACs, should be considered during the first 3 months after surgical MV or TV repair.[884–888]	IIa	B
Low-dose ASA (75–100 mg/day) should be considered for the first 3 months after surgical AV repair in patients without indication for OAC.	IIa	C
Low-dose ASA (75–100 mg/day) may be considered after surgical MV or TV repair in preference to OAC in patients without clear indication for OAC and at high bleeding risk.[884–888]	IIb	B
Surgical biological heart valve with indication for oral anticoagulation		
OAC continuation is recommended in patients with a clear indication for OAC undergoing surgical BHV implantation.[877,889,890]	I	B
DOACs should be considered over VKAs after 3 months following surgical implantation of a BHV in patients with AF.[872–874,876,891]	IIa	B
DOAC continuation may be considered after surgical BHV implantation in patients with an indication for DOAC.[877,889,890]	IIb	B

Continued

Transcatheter biological heart valve with indication for oral anticoagulation		
OAC is recommended for TAVI patients who have other indications for OAC.[879,892–894]	I	B
Surgical repair with indication for oral anticoagulation and/or antiplatelet therapy		
Continuation of OAC or antiplatelet therapy should be considered after surgical valve repair in patients with a clear indication for an antithrombotic therapy.[890]	IIa	B

AF, atrial fibrillation; ASA, acetylsalicylic acid; AV, aortic valve; BHV, biological heart valve; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; MV, mitral valve; OAC, oral anticoagulation; TAVI, transcatheter aortic valve implantation; TV, tricuspid valve; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.

14.4. Management of prosthetic valve dysfunction and complications

Prosthetic valve dysfunction can occur due to intrinsic permanent changes to the prosthetic valve (defined as SVD) or non-structural valve dysfunction resulting from any abnormality not intrinsic to the prosthetic valve itself. Valve thrombosis and endocarditis are considered separate entities due to their specific presentation and management, but may both result in SVD.

14.4.1. Structural valve deterioration

Structural valve deterioration has been defined by several consensus documents[812,895,896] and includes wear and tear, leaflet disruption, leaflet fibrosis or calcification, and stent or strut fracture or deformation. BHV (transcatheter or surgical) SVD is more frequent than MHV SVD. The incidence of SVD may be underestimated by the simple analysis of patients with valve-related deaths or those undergoing reintervention. To ensure timely diagnosis, serial measurement should be performed and compared with the TTE performed at discharge, or within 1–3 months after valve implantation.

The criteria for haemodynamic deterioration associated with aortic and mitral SVD can be found in *Table 12*.[895,896] The diagnosis of moderate or severe haemodynamic deterioration should prompt referral to an experienced Heart Valve Centre for evaluation and treatment, and to exclude all causes of non-structural valve dysfunction, particularly PVL or PPM, as well as thrombosis and endocarditis. This step requires the use of advanced imaging techniques (TOE, CCT, and/or PET-CT) to document SVD-related morphological changes and elucidate its mechanism. Structural valve deterioration associated with corresponding clinical criteria (e.g. new onset or worsening of symptoms, LV or RV dilation/dysfunction, or PH) indicates BHV failure with potential need for reintervention. Decisions about the treatment modality (redo surgery or transcatheter valve-in-valve implantation) should be made within the interdisciplinary Heart Team, depending on re-operation risk and anatomical considerations,[445,897] including the risk of coronary obstruction,[144,442,446,461] as well as prosthesis type and size.[898–900] When considering a valve-in-valve procedure for a degenerated aortic BHV, the possibility of creating a PPM in small valves should be anticipated and may impact intervention or valve selection.[448]

Given the larger sizes of BHVs in mitral or tricuspid positions, transfemoral/transseptal valve-in-valve implantation represents an attractive alternative to redo open surgery.[570,900–903] In the case of mitral valve-in-valve implantation the risk of LVOT obstruction, although

Table 12 Criteria for the diagnosis of moderate or severe aortic and mitral haemodynamic valve deterioration

	Moderate	Severe
Aortic BHV SVD or non-structural valve dysfunction (except PVL or PPM),[a] thrombosis, or endocarditis	Increase in mean transvalvular gradient ≥10 mmHg resulting in mean gradient ≥20 mmHg	Increase in mean transvalvular gradient ≥20 mmHg resulting in mean gradient ≥30 mmHg
	AND	**AND**
	Decrease in EOA ≥0.3 cm^2 or ≥25%, and/or decrease in DVI ≥0.1 or ≥20%, compared with echocardiographic assessment performed 1–3 months post-procedure	Decrease in EOA ≥0.6 cm^2 or ≥50%, and/or decrease in DVI ≥0.2 or ≥40%, compared with echocardiographic assessment performed 1–3 months post-procedure
	OR	***OR***
	New occurrence or increase of ≥1 grade of intraprosthetic AR resulting in ≥ moderate AR	New occurrence or increase of ≥2 grades of intraprosthetic AR resulting in ≥ moderate-to-severe AR
Mitral BHV SVD or non-structural valve dysfunction (except PVL or PPM),[b] thrombosis, or endocarditis	Increase in DVI ≥0.4 or ≥20%, resulting in DVI ≥2.2, or decrease in EOA ≥0.5 cm^2 or ≥25%, resulting in EOA <1.5 cm^2, usually associated with increase of transmitral gradient ≥5 mmHg	Increase in DVI ≥0.8 or ≥40%, resulting in DVI ≥2.7, or decrease in EOA ≥1.0 cm^2 or ≥50%, resulting in EOA <1 cm^2, usually associated with increase of transmitral gradient ≥10 mmHg
	OR	***OR***
	New occurrence or increase of ≥1 grade of intraprosthetic MR resulting in ≥moderate MR	New occurrence or increase of ≥2 grades of intraprosthetic MR resulting in ≥moderate-to-severe MR

Adapted from [895,896].
AR, aortic regurgitation; AV, aortic valve; BHV, biological heart valve; DVI, Doppler velocity index; EOA, effective orifice area; MR, mitral regurgitation; PPM, prosthesis–patient mismatch; PVL, paravalvular leak; SVD, structural valve deterioration.
[a]Obstruction by pannus; dilatation of the aortic root after stentless BHV; or AV-sparing operations.
[b]Leaflet entrapment by pannus, chordae, or suture.

infrequent, should be carefully ruled out, especially in patients with small and hypertrophic ventricles.[904]

14.4.2. Non-structural valve dysfunction

14.4.2.1. Prosthesis–patient mismatch

Prosthesis–patient mismatch should be prevented whenever possible after either transcatheter or surgical valve-replacement procedures (see *Section 8.5.1.2*). When occurring in the aortic position, severe PPM is associated with decreased quality of life, increased rate of rehospitalization and reintervention, and possible reduction in long-term survival, although findings are not consistent throughout all studies.[454,905–909] Moderate PPM is more common, but seems to have a limited impact on outcomes. The projected indexed EOA may be predicted prior to valve implantation to avoid severe PPM,[908] although this concept has been challenged.[910] Less is known about the prevalence and consequences of PPM in the mitral and tricuspid positions, and established definitions are lacking.

Prosthesis–patient mismatch is an infrequent indication for reintervention. However, reoperation should be considered in symptomatic patients with severe PPM, particularly if the patient is low risk.[394,437,438]

14.4.2.2. Paravalvular leak and haemolysis

The diagnosis of PVL requires systematic TOE, because TTE may be inconclusive. Haemolytic anaemia can often be detected in patients with prosthetic valves and is best assessed by measuring lactate dehydrogenase and haptoglobin serum levels, but rarely leads to symptoms. Intervention is needed if a PVL causes haemolysis requiring blood transfusions or symptoms, or if secondary to valve endocarditis. Transcatheter PVL closure is a valid alternative to surgery in the case of significant regurgitation or haemolysis, if feasible depending on the size and location of the leak, but requires specific expertise and planning. Care must be taken not to interfere with mechanical leaflet motion in MHV patients. Reported results for transcatheter PVL closure are inconsistent, with several patients returning with recurrent PVL and/or haemolysis.[911] When surgery or transcatheter intervention are contraindicated, medical therapy aims to counteract the effect of haemolysis (iron supplementation and erythropoietin) or reduce it (beta-blockers).[912]

14.4.3. Endocarditis

Antibiotic prophylaxis is recommended in all patients with a prosthetic valve (including transcatheter valve prostheses) and after valve repair using prosthetic material or with previous episode(s) of infective endocarditis, and should also be considered after transcatheter MV or TV repair.[5] It is recommended in such patients when undergoing dental extractions, oral surgery, or other procedures requiring manipulation of the gingival or peri-apical region of the teeth. Particular attention to dental and cutaneous hygiene, and strict aseptic measures during any invasive procedure, are also advised in this population. Additional details on endocarditis prophylaxis are mentioned in the *2023 ESC Guidelines for the management of endocarditis*.[5]

14.4.4. Valve thrombosis

Valve thrombosis occurs mainly in MHVs,[913,914] but can also be observed in BHVs.[915,916] The spectrum of BHV thrombosis ranges from incidental CCT findings, such as hypo-attenuated leaflet thickening (HALT) with or without reduced leaflet motion but normal gradients, to clinically apparent presentations with elevated gradients, symptoms of valve obstruction, or thromboembolic events.[917–919]

14.4.4.1. Hypo-attenuated leaflet thickening

Hypo-attenuated leaflet thickening is detected by CCT in 10%–30% of aortic BHVs depending on antithrombotic management, the definition of HALT, the timepoint of assessment, and the type of valve.[917,919–921] The significance and clinical implications of these findings with respect to thromboembolic risk and valve durability remain uncertain. Accordingly, routine use of CCT to detect HALT is not indicated.[918–920] In patients with relevant increases in gradients, in whom HALT and restricted leaflet motion is confirmed by CCT, elective use of DOACs or VKAs should be considered to resolve leaflet thrombosis.[918,921,922]

14.4.4.2. Clinically significant valve thrombosis

Obstructive valve thrombosis should be suspected in any patient with any type of prosthetic valve who presents with new-onset dyspnoea or HF symptoms, an embolic event, or an unexpected increase in transvalvular gradients. If TTE findings are uncertain, the diagnosis should be confirmed by TOE and/or CCT to distinguish between thrombus, pannus, and degeneration.[923–925] Cinefluoroscopy can detect impaired MHV leaflet motion and reduced opening angles.

Adequate anticoagulation must be promptly restored in all patients with MHV thrombosis and subtherapeutic INR. Although surgery remains the first-line option in critically ill patients, emergency valve replacement is associated with increased risk, whereas bleeding and systemic embolism are increased with fibrinolysis.[926–928] Slow, low-dose infusion appears to lower complication rates, while preserving thrombolytic success rates.[928–931a] It is recommended that the decision between surgery and fibrinolysis is taken within the Heart Team, and individualized by weighing clinical factors and local expertise (*Figure 20*).

Management of non-obstructive thrombosis or obstructive thrombosis of an MHV without pronounced HF symptoms depends mainly on the occurrence of a thromboembolic event and the size of the thrombus. Surgery should be considered for a large (>10 mm) non-obstructive prosthetic valve thrombus that is complicated by embolism or persists despite optimal OAC.[913,932,933]

Anticoagulation using a VKA is the first-line treatment for clinically relevant BHV thrombosis, unless urgent reintervention or fibrinolysis is required due to progressive acute HF or haemodynamic instability.[934–938] Because clinically relevant BHV thrombosis is associated with recurrence and may contribute to prosthetic degeneration, indefinite anticoagulation may be considered after a confirmed episode, but this strategy must be balanced against the risk of bleeding.[936,939]

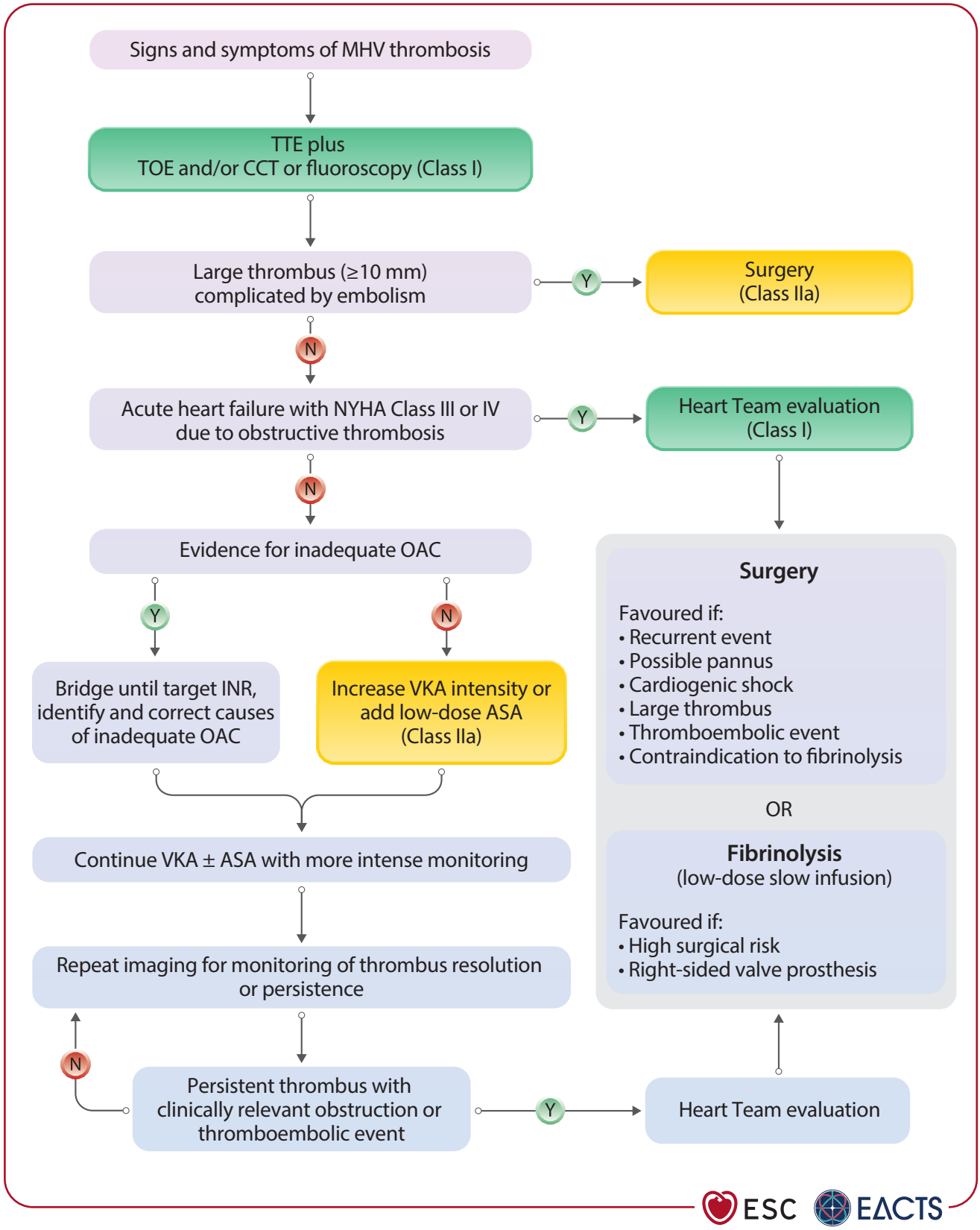

Figure 20 Management of left-sided obstructive and non-obstructive mechanical heart valve thrombosis. ASA, acetylsalicylic acid; CCT, cardiac computed tomography; INR, international normalized ratio; MHV, mechanical heart valve; NYHA, New York Heart Association; OAC, oral anticoagulation; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; VKA, vitamin K antagonist.

Recommendation Table 17 — Recommendations for the management of prosthetic valve dysfunction (see also Supplementary data online, *Evidence Table 25*)

Recommendations	Class[a]	Level[b]
Haemolysis and paravalvular leak		
It is recommended that the decision between transcatheter or surgical closure of clinically significant PVLs is based on Heart Team evaluation, including patient risk, leak morphology, and local expertise.	I	C
Reoperation is recommended if a PVL is related to endocarditis, or causes haemolysis requiring repeated blood transfusion or leading to HF symptoms.	I	C
Transcatheter closure should be considered for suitable PVLs with clinically significant regurgitation and/or haemolysis.[940]	IIa	B
Mechanical heart valve failure		
Reoperation is recommended in symptomatic patients with significant valve dysfunction not attributable to valve thrombosis.	I	C
Biological heart valve failure		
Reintervention is recommended in symptomatic patients with significant valve dysfunction not attributable to valve thrombosis.	I	C
Transcatheter, transfemoral valve-in-valve implantation in the aortic position should be considered in patients with significant valve dysfunction who are at intermediate or high surgical risk, and have suitable anatomical and prosthesis features, as assessed by the Heart Team.[447,448,450,451,941]	IIa	B
Transcatheter transvenous mitral or tricuspid valve-in-valve implantation should be considered in patients with significant valve dysfunction at intermediate or high surgical risk, if the anatomy is suitable.[569,570,681,942–944]	IIa	B
Reoperation should be considered in asymptomatic patients with significant prosthetic dysfunction, if surgical risk is low.	IIa	C
Valve thrombosis		
TOE and/or 4D-CT are recommended in patients with suspected valve thrombosis to confirm the diagnosis.[914,918,923,925,945–948]	I	C
Mechanical heart valve thrombosis		
Heart Team evaluation is recommended in patients with acute HF (NYHA class III or IV) due to obstructive MHV thrombosis to determine appropriate management (repeat valve replacement or low-dose slow infusion fibrinolysis).[923,926–929,931,949–954]	I	B
Surgery should be considered for large (>10 mm) prosthetic thrombus complicated by embolism.[913,932,933]	IIa	C
Biological heart valve thrombosis		
OAC using VKA is recommended in BHV thrombosis before considering reintervention.[867,934–937,955,956]	I	B
OAC should be considered in patients with leaflet thickening and reduced leaflet motion leading to elevated gradients at least until resolution.[918,920–922]	IIa	B

4D, four-dimensional; BHV, biological heart valve; CT, computed tomography; HF, heart failure; MHV, mechanical heart valve; NYHA, New York Heart Association; OAC, oral anticoagulation; PVL, paravalvular leak; TOE, transoesophageal echocardiography; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.

15. Management during non-cardiac surgery

In patients with significant VHD who undergo NCS, the risk of perioperative cardiovascular complications is increased and related to both the timing of the procedure (i.e. urgent vs non-urgent) and type of surgery (low, intermediate, or high risk), as well as patient-specific factors (type and severity of VHD, LV function, etc.).[194,957–959] Detailed recommendations related to NCS are available in the *2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery*.[960]

15.1. Pre-operative evaluation

Echocardiography should be performed in all patients with VHD requiring NCS. Patient- and surgery-specific factors, along with risk calculators, can be used to guide the treatment strategy. Determination of functional capacity is a pivotal step for pre-operative risk assessment, measured either by the ability to perform activities in daily life or by exercise testing. Screening for frailty using validated tools is advisable.[90] Decisions on pre- and perioperative management, surveillance, and continuation of chronic cardiovascular medical treatment should be taken after multidisciplinary discussion involving cardiologists, surgeons, and cardiac anaesthesiologists, as well as the team who will be in charge of the NCS. Patients receiving OAC treatment should be managed as described in *Section 14*.

15.2. Specific valve lesions

15.2.1. Aortic stenosis

In patients with severe symptomatic AS, the treatment depends on the urgency and risk of NCS. If life-saving time-sensitive NCS is needed, it should be performed under careful haemodynamic monitoring avoiding rapid changes of volume status, with prompt treatment of arrhythmia regardless of AS severity. In cases of urgent high-risk NCS, TAVI or balloon aortic valvuloplasty should be considered in patients with critical AS prior to surgery, considering the risk of developing severe acute AR after

balloon aortic valvuloplasty.[194,961] Urgent low- and intermediate-risk NCS can be performed relatively safely in patients with severe AS.[962]

Patients in whom NCS can be deferred (i.e. non-urgent NCS) should undergo pre-operative Heart Team evaluation to determine whether SAVR or TAVI is preferable. TAVI may be preferred to SAVR if faster recovery plays a role, particularly in elderly patients in whom complex or high-risk NCS is planned.[963] The treatment of asymptomatic patients with severe AS should be individualized (*Figure 21*).[964]

15.2.2. Mitral stenosis

Heart rate and fluid balance should be controlled to prevent pulmonary oedema during NCS and arterial vasodilators should be avoided. Non-cardiac surgery is safe in patients with an MVA of >1.5 cm^2, and in asymptomatic patients with MVA ≤1.5 cm^2 and SPAP of <50 mmHg. Symptomatic patients or those with SPAP of >50 mmHg should undergo PMC or other appropriate valve intervention before high-risk NCS, if possible.[965,966] Asymptomatic patients with MVA ≤1.5 cm^2 can undergo low-to-moderate-risk NCS under careful monitoring, especially if PMC is unsuitable. Multidisciplinary management is advised for patients with significant MS who are ineligible for valve intervention.

15.2.3. Aortic and mitral regurgitation

Non-cardiac surgery can usually be performed safely in asymptomatic patients with severe MR or AR and preserved LV function. If NCS is urgent, patients should undergo surgery under strict haemodynamic monitoring, regardless of symptom status. In cases of elective (non-urgent) NCS in patients with severe ventricular SMR, medical therapy should be optimized. If symptoms persist and NCS is intermediate or high risk, TEER should be considered after Heart Team discussion based on clinical

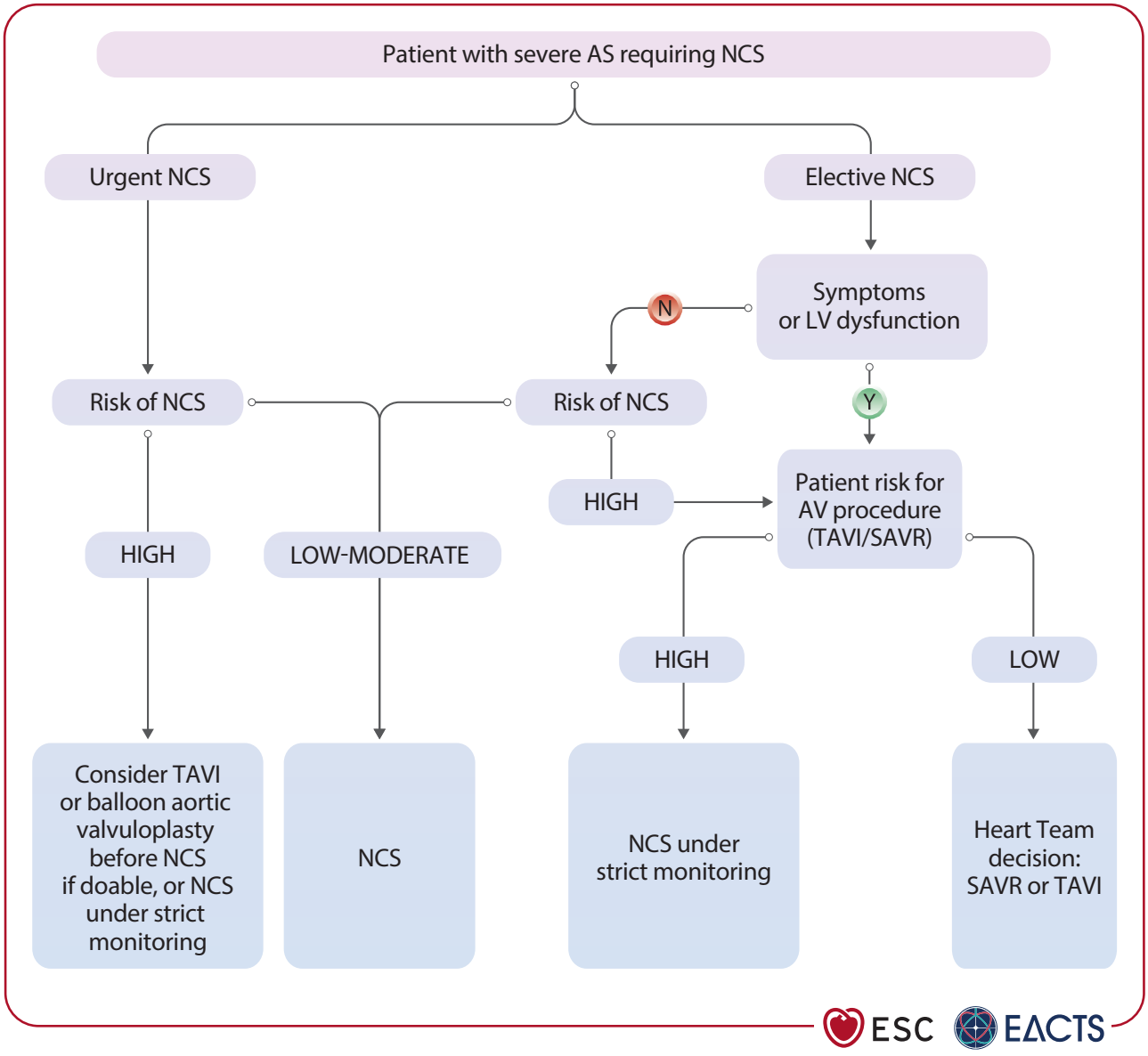

Figure 21 Management of non-cardiac surgery in patients with severe aortic stenosis. AS, aortic stenosis; AV, aortic valve; LV, left ventricular; NCS, non-cardiac surgery; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

and anatomical selection criteria.[194,584] Valve treatment should be performed for patients with AR meeting the criteria for valve intervention before any elective intermediate- or high-risk NCS.[966,967]

15.3. Peri-operative monitoring

Heart rate control (particularly in MS) and careful fluid management (particularly in AS and MR with reduced LVEF) are needed throughout the procedure. The involvement of specialized cardiovascular anaesthesiologists should be considered in complex situations because TOE monitoring may be considered. Pulmonary artery catheterization is not routinely used.

16. Management of valvular heart disease during pregnancy

Specific ESC Guidelines on this topic are available (the *2025 ESC Guidelines on cardiovascular disease during pregnancy*) and should be consulted for further details.[968] Pregnancies in patients with VHD should be considered high risk and managed under the close supervision of a cardiologist and a multidisciplinary Pregnancy Heart Team. The importance of midwives and other specialized nursing personnel is increasingly recognized for high-quality direct patient interactions. Shared decision-making is especially important when addressing the cardiovascular risk of pregnancy and the benefit–risk ratios of therapeutic options and modes of delivery (*Figure 22*).

16.1. Management before pregnancy

Ideally, women should undergo a thorough physical examination by their general practitioner for VHD screening prior to pregnancy. A specialized evaluation including TTE should be performed by a cardiologist in the case of clinical suspicion.[968,969]

If VHD is diagnosed, pre-pregnancy counselling is imperative. Unplanned pregnancies in patients with VHD should be discouraged. Contraception methods should be recommended after discussion with the patient in the presence of a significant maternal and/or foetal risk. In patients contemplating pregnancy, the maternal risk should be assessed using the modified WHO classification and other scores such as the CARPREG or DEVI risk score (see Supplementary data online, *Table S7*).[970]

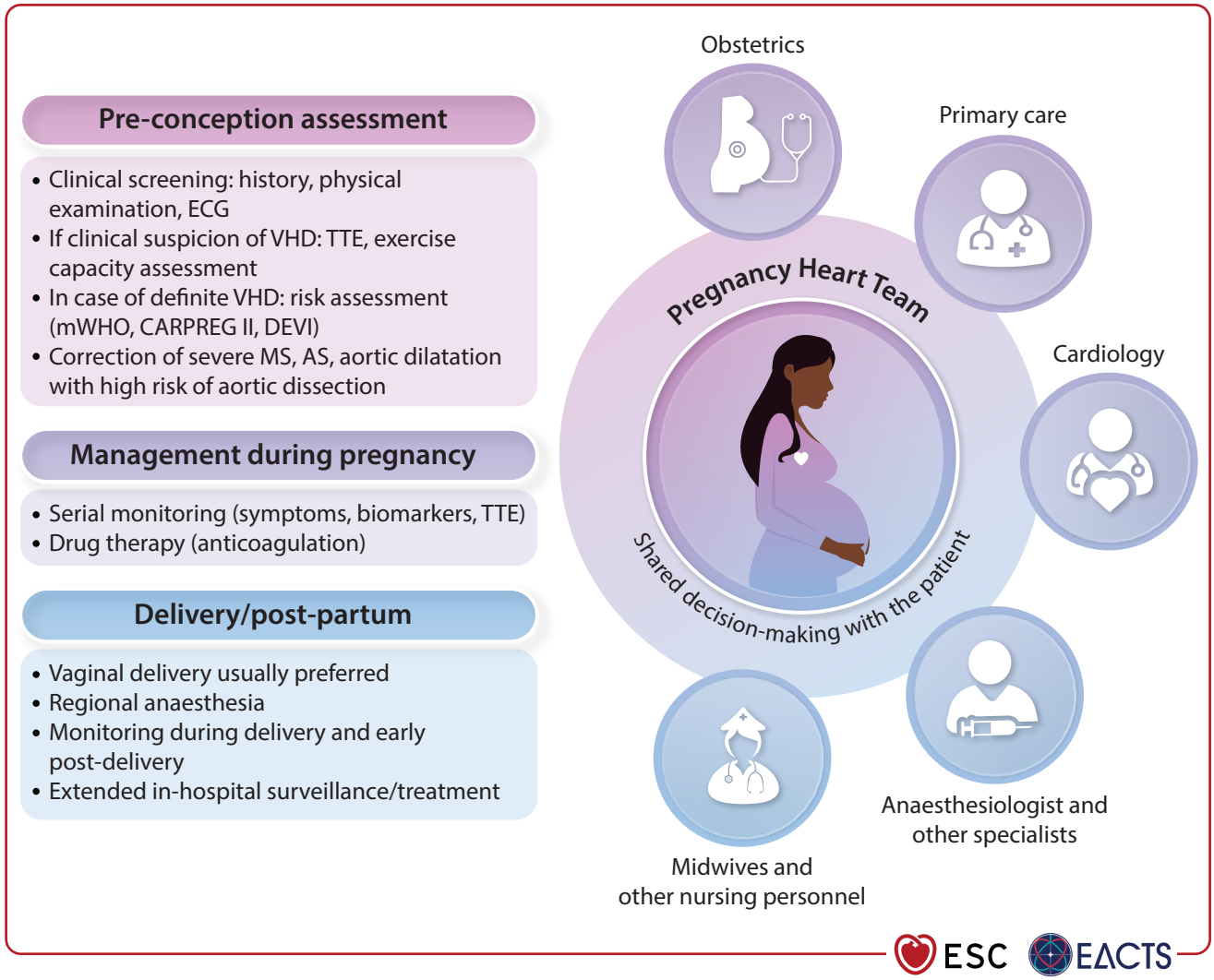

Figure 22 The Pregnancy Heart Team model of care. AS, aortic stenosis; ECG, electrocardiogram; MS, mitral stenosis; TTE, transthoracic echocardiography; VHD, valvular heart disease.

Before recommending pregnancy, the following conditions need to be corrected:

- MS with MVA <1.5 cm^2, even when asymptomatic.[971]
- Severe AS with symptoms, or abnormal exercise test, or LV systolic dysfunction.[972]
- Heritable aortic disorders and high risk of aortic dissection: prophylactic aortic repair is recommended prior to pregnancy in women with Marfan syndrome and an aortic diameter of >45 mm, and may be considered in women with an aortic diameter between 40 and 45 mm when risk factors for dissection exist.[973] Aneurysmal dilation in women with BAV should be corrected when the aortic diameter is ≥50 mm.[974] Close follow-up in dedicated units and beta-blocker therapy during pregnancy and post-partum are recommended unless contraindicated, although strong evidence is only available for Marfan syndrome.

Valvular regurgitant lesions are generally well tolerated during pregnancy. Prophylactic intervention is therefore not recommended in the absence of class I or IIa indications.

The first therapeutic option for MS in a woman considering pregnancy should be PMC. When implantation of a prosthetic valve is necessary, BHVs are recommended, although early SVD remains a serious concern.[975] Mechanical heart valves must be avoided due to the high risk of maternal and foetal complications linked to the potential teratogenic effects of VKAs, as well as the increased risk of bleeding.[976] The Ross procedure may be considered for the treatment of AV disease at centres with expertise.

16.2. Management during pregnancy

16.2.1. Patients with native valve disease

Pregnancy can worsen the clinical course of left-sided stenotic valvular lesions because increased cardiac output causes an increment of transvalvular gradient of ~50%, mainly between the first and second trimesters. Regurgitant lesions are less likely to cause complications, except in high-risk cases (LV systolic dysfunction, PH, and cardiac events before pregnancy).[977]

Mild MS is generally well tolerated.[978] Heart failure occurs in one-third of pregnant women with an MVA of <1.5 cm^2 and in one-half of those with an MVA of <1.0 cm^2, most often during the second trimester.[971] Percutaneous mitral commissurotomy should be considered if symptoms or SPAP of >50 mmHg persist despite optimal medical therapy (diuretics and beta-1-selective beta-blockers), preferably after the 20th week of pregnancy.

Regarding AS, pregnancy is generally well tolerated if prior exercise tolerance was normal, even in severe AS, while HF has been reported to occur in up to 25% of symptomatic patients.[972] In symptomatic patients despite medical therapy (i.e. diuretics), TAVI seems to be the preferred option in very selected patients, although evidence is lacking. Percutaneous balloon valvuloplasty may be an alternative option. Procedures should be performed in an experienced valve centre.[972,979,980]

Surgery under cardiopulmonary bypass is associated with a high rate of foetal loss and should be restricted to conditions that threaten the mother's life if transcatheter intervention is not possible or has failed.

Vaginal delivery is the first choice for the majority of patients. Caesarean section is preferred if there is an obstetric indication, and in the case of severe MS or AS, ascending aortic diameter of >45 mm, severe PH, or if delivery starts while the patient is being treated with OAC.

16.2.2. Patients with prosthetic valves

Pregnant patients with MHVs should be followed in a centre with corresponding expertise. In a cohort of 212 women with MHVs, valve thrombosis occurred in 10 (4.7%) pregnancies and haemorrhagic events occurred in 49 (23.1%).[976] Therapeutic OAC during pregnancy is essential to avoid thrombosis. The higher efficacy of VKAs compared with LMWH to prevent thrombosis must be balanced against increased foetal risks.[981]

In patients requiring ≤5 mg/day of warfarin, OAC with warfarin throughout pregnancy, changing to UFH before delivery, is advocated, in order to reduce the risk of thrombosis. In patients requiring higher doses, switching to dose-adjusted LMWH at least twice per day with strict anti-Xa monitoring during the first trimester is recommended to avoid the teratogenic effect of VKAs (for corresponding flowcharts see the *2025 ESC Guidelines for the management of cardiovascular diseases during pregnancy*[968]).

Lifetime management of women with a BHV considering pregnancy is central and transcatheter valve-in-valve implantation may be considered as a bridge to MHV implantation.[982]

17. Sex-specific considerations in patients with valvular heart disease

Although men and women are equally likely to experience VHD, sex-specific prevalence exists according to valve type and disease pathophysiology.[644,648,983] Women more frequently suffer from MV disease such as prolapse, RHD or TR, while men more often present with AS or AR, especially associated with BAV.[984] Men also suffer from endocarditis of any valve more frequently.[985]

Female sex is associated with higher mortality in the presence of various VHDs,[986] including early post-treatment,[987] and is included as a risk factor in surgical risk prediction tools such as the STS and EuroSCORE calculators. However, risk scores are often derived from populations including a majority of men.[988] In addition, risk prediction scores are susceptible to referral bias that results in a well-established higher risk of undertreatment or delayed treatment of VHD in women.[983,984,986]

17.1. Aortic valve disease

Female patients with severe AS present more often with shortness of breath, whereas males more frequently have angina, presumably due to the higher incidence of CAD.[989] The pathophysiology of AS seems to differ according to sex, with women having less calcium and more fibrosis.[990] Concentric ventricular hypertrophy and remodelling are also more frequently observed in women than in men, resulting in higher LVEF but smaller LV cavity and stroke volume.[991] Consequently, paradoxical low-flow, low-gradient constellations are frequent and may both contribute to the underdiagnosis of severe AS in women and delay an intervention.[992] The use of sex-specific thresholds to define flow limitation (<40 mL/m^2 for men and <32 mL/m^2 for women) has therefore been suggested,[292] and the use of CCT to quantify the calcium score should be performed in women with discordant echocardiographic parameters.[777]

Women are less likely to be referred to a cardiologist and undergo investigations. Surgical aortic valve replacement is performed less frequently in women, especially if echocardiographic parameters are discordant.[993] In patients presenting with severe

AS and Class I indications for SAVR, a significantly higher proportion of men than women are referred for evaluation by a cardiac surgeon.[994,995]

Male patients derive a clearer benefit from SAVR compared with women, who have higher in-hospital and long-term mortality and morbidity,[987,996] possibly explained by more severe concentric hypertrophy[991] and a smaller aortic annulus predisposing to PPM.[997] Conversely, in a randomized trial (RHEIA) that compared TAVI with SAVR in 443 women with a mean age of 73 years, TAVI was superior in reducing the primary endpoint composed of death, stroke, or rehospitalization at 1 year, predominantly driven by a reduction in rehospitalization for valve- or procedure-related symptoms or worsening HF.[998] Several observational studies suggest that elderly women have lower mortality after TAVI,[999] even if the rates of major vascular complications and bleeding tend to be higher.[997]

Indexed cut-offs to indicate treatment of AR are validated, but only partially account for sex differences. Newer studies using echocardiographic volumes[1000] and CMR[1001] suggest that women may experience higher event rates at lower cut-offs compared with men, but this requires further investigation.

17.2. Mitral valve disease

Patients with RHD are often young women and have a high prevalence of major cardiovascular complications with far-reaching impacts on reproductive health and access to care.[282] Although women experience favourable outcomes compared with men when treated by percutaneous balloon valvuloplasty, access to these procedures is still limited in low-income countries.[662]

Fibroelastic disease with MV prolapse is also more frequent in women, and may be accompanied by morphological abnormalities of the MA associated with fibrosis of the papillary muscles or the inferobasal LV that may act as the substrate for sudden cardiac death, even in the absence of severe MR.[1002] Recent evidence has supported considering lower women-specific cut-offs for intervention with regard to LVESD (36 mm; indexed LVESD, 1.8 cm/m^2), while the LVEF cut-off was similar to men (58%), albeit with higher mortality.[548]

Ventricular SMR associated with low LVEF is more frequent in men with HF,[1003] while atrial SMR due to chronic AF and/or HFpEF affects more women (58% vs 42% male).[579]

Female sex is a risk factor for the development of MAC and was reported to account for 68% of the patients included in a large-scale transcatheter MV replacement in MAC registry.[1004] Furthermore, women present with a faster disease progression.[1005]

17.3. Tricuspid valve disease

Tricuspid regurgitation is more prevalent in women,[208] and female sex is associated with accelerated disease progression.[1006–1008] Hypotheses to explain these observations include the overall higher prevalence of HFpEF and AF in women.[1009] Women are usually diagnosed at an older age and the cause of TR is most frequently a consequence of left valvular disease or annular dilatation attributable to RA dilatation.[1010] No differences have been detected to date in terms of adverse events after surgery[1011] or transcatheter TV interventions.[1012,1013]

18. Key messages

Heart Team and Heart Valve Centre

- An integrated regional Heart Valve Network incorporating outpatient Heart Valve Clinics and specialist Heart Valve Centres allows optimal patient care.
- Heart Valve Centres should fulfil institutional and local statutory requirements, and strive for high procedural volume and excellent clinical outcomes.
- Heart Team recommendations should be based upon these guideline recommendations, relevant updated evidence, key medical considerations, and patient preferences.
- Core members of the Heart Team include the primary clinical cardiologist, cardiologists with subspecialty expertise in VHD, specialists in advanced cardiovascular imaging and peri-procedural imaging guidance, and surgeons and interventional cardiologists with training and expertise in valve interventions.
- A network approach that distinguishes between higher- and lower-volume centres is appropriate, with more complex procedures focused in the most experienced (i.e. upper quartile) centres. Information on the network organization should be communicated to patients, as well as referring cardiologists and general practitioners.

Aortic regurgitation

- Assessment of AR severity with TTE remains challenging and current cut-offs for intervention are mostly based on 2D measurements, although 3D echocardiography and CMR allow more accurate evaluation of LV volumes and LVEF.
- Mechanisms of AR may be closely related to the aortic diameters that should be measured accurately at all levels of the aortic root (annulus, sinuses, and sinotubular junction).
- Indication for operation is based on symptoms, LV volumes, LVEF, and aortic diameters. Although valve replacement remains the standard treatment, AV repair (or AV sparing when associated with root aneurysm) is being increasingly used to avoid prosthesis-related complications, especially in experienced centres.
- Current transcatheter options for AR are limited and applicable only in patients who are ineligible for surgery.

Aortic stenosis

- Diagnosis of severe AS requires integrative evaluation of pressure gradients (the most robust measurements), AVA, flow conditions, the extent of valve calcification, and LV function.
- Selection of the most appropriate mode of intervention should take into account clinical characteristics (age and estimated life expectancy, concomitant conditions), access and valve anatomy (particularly the feasibility of transfemoral TAVI and calcification patterns), and surgical risk, as well as repeat procedure options and risks (lifetime management).

Mitral regurgitation

- The echocardiographic diagnostic workup of patients with MR includes multiparametric assessment of MR severity, evaluation of

MV anatomy (often with 3D TOE), identification of the mechanism (PMR, ventricular SMR, or atrial SMR), and evaluation of cardiac damage.
- Surgical MV repair is the preferred method of treatment in severe PMR. Transcatheter edge-to-edge repair is recommended in patients who are inoperable or high risk according to the Heart Team.
- Surgical MV repair is the procedure of choice for asymptomatic patients with primary MR and signs of cardiac damage, including moderate or more TR.
- In patients with ventricular SMR, GDMT (including CRT if indicated) is the initial and essential treatment step. In symptomatic patients without CAD needing revascularization, M-TEER is recommended. In patients with concomitant complex CAD and those not suitable for TEER, mitral surgery may be considered.
- In patients with atrial SMR, MV surgery, AF ablation if indicated, and LAAO should be considered after optimization of medical therapy. Transcatheter edge-to-edge repair may be considered in patients at high surgical risk.

Mitral stenosis

- Most patients with severe rheumatic MS and favourable valve anatomy should undergo PMC, which is the standard of care. Surgery is recommended for symptomatic patients with contraindications or unfavourable anatomical and clinical characteristics for PMC.
- Decision-making in patients with unfavourable anatomy should take into account local PMC experience.
- In selected patients with clinically severe degenerative MS and MAC, transcatheter intervention or surgery may improve symptoms.

Tricuspid regurgitation

- Concomitant TV repair is the preferred method for patients with left-sided valve pathology and associated moderate or severe TR.
- The use of risk scores for the assessment of RV and secondary organ dysfunction should be strongly encouraged in patients with isolated severe TV disease.
- In isolated severe TR without severe RV dysfunction, surgery should be performed at an early stage in patients at low operative risk.
- In isolated severe TR patients at increased surgical risk, tricuspid TEER or transcatheter replacement should be considered to improve quality of life and RV remodelling, in the absence of severe RV dysfunction or pre-capillary PH.

Tricuspid stenosis

- TS is a very rare manifestation of acquired VHD in high-income countries.
- TS is mainly associated with rheumatic valve disease, carcinoid syndrome, or enzymatic disorders such as Fabry's or Whipple's disease.
- Treatment of symptomatic TS mainly involves surgical TV replacement.

Multiple and mixed valvular heart disease

- Transvalvular gradients and velocities reflect the combined burden of regurgitation and stenosis in mixed aortic and mitral disease.
- Treatment decisions should be based on the assessment of symptom and functional status, cardiac damage, anatomical suitability, and the risk–benefit ratio of intervention and lifetime management considerations.
- Patients with mixed moderate AS and AR have similar detrimental outcomes compared with those with severe isolated AS.
- In transcatheter procedures, which allow a sequential approach, downstream lesions should be treated first to prevent potential haemodynamic deterioration and allow improvement of upstream lesions due to changing loading conditions and reverse remodelling.

Antithrombotic treatment in patients with a mechanical heart valve

- International normalized ratio therapeutic range should be balanced to the type and anatomical site of MHV, as well to the thrombotic risk profile of the individual patient.
- Patient training, self-monitoring, and education can increase INR stability and TTR.
- Minor or minimally invasive NCS procedures do not require VKA interruption in patients with an MHV.
- In patients with an MHV undergoing elective major NCS, bridging may be omitted if the thromboembolic risk is low.

Non-cardiac surgery

- The risk of peri-operative cardiovascular complications related to surgery and to patient-specific factors should be evaluated and communicated to the patient and surgical team.
- In patients with symptomatic severe AS requiring urgent high-risk NCS, BAV or TAVI should be considered prior to surgery. In patients planned for elective NCS, AV intervention is recommended prior to NCS.

Pregnancy

- In women with VHD, decisions regarding management before and during pregnancy should be taken after discussion by the multidisciplinary Pregnancy Heart Team. Unplanned pregnancies should be discouraged.
- The following conditions should be corrected prior to considering pregnancy:
  - clinically severe MS (MVA <1.5 cm^2), even when asymptomatic
  - severe symptomatic AS, or asymptomatic patients with impaired LV function or a pathological exercise test
  - heritable aortic disorders and high risk of aortic dissection.
- Vaginal delivery is the first choice for the majority of patients. Indications for Caesarean section include pre-term labour in patients on OAC, severe MS or AS, aggressive aortic pathology, acute intractable HF, and severe PH.
- Women with MHVs should be managed in expert centres.

19. Gaps in evidence

General aspects

- Patient-reported outcome measures are infrequently reported in VHD studies. Patient-reported outcome measure-oriented studies are required to improve quality of life and patient satisfaction.
- Methods to address underdiagnosis and undertreatment of VHD need to be identified and implemented.

Heart Team and Heart Valve Centre

- Structured research is required to investigate the relationship between procedural volume and clinical outcomes, in order to define minimum annual thresholds for individual operators and institutions undertaking surgical and transcatheter valve interventions.
- There is a pressing need to ensure higher dispersion and adoption of interventions for VHD, especially in middle- and low-income countries.

Conditions associated with valvular heart disease

- CAD:
  - The prognostic value of functional assessment of stable, moderate coronary stenosis in VHD patients remains to be determined.
  - The optimal strategy (invasive vs non-invasive) for CAD assessment in specific VHD populations remains to be elucidated.
  - The optimal timing of PCI in patients with CAD undergoing TAVI is yet to be determined.
  - The benefit of complete coronary revascularization with CABG in patients with combined VHD and CAD requires further research.
- AF:
  - It is unclear which patients with chronic persistent AF and concomitant VHD are deemed to be suitable for rhythm control therapy.
  - The protective effect against stroke of OAC with VKA or DOACs in patients after surgical or transcatheter LAAO remains to be determined.
- Cardiogenic shock and acute HF:
  - The optimal treatment strategy in VHD patients presenting with cardiogenic shock and acute HF is unknown.

Aortic regurgitation

- Impact of early LV remodelling on prognosis in asymptomatic AR patients is unknown.
- Prognostic value of CMR-derived indices in asymptomatic patients needs to be determined.
- More data are required on long-term results of surgical AV repair for AR.
- More evidence is required on transcatheter treatment options for AR, in particular using dedicated devices.

Aortic stenosis

- Better understanding of the pathophysiology of AS is needed to propose innovative medical therapy.
- Further research is required on:
  - Refined prognostic markers to guide timing of intervention in asymptomatic patients.
  - The role of revascularization in patients with severe AS and asymptomatic concomitant CAD.
  - Further data on the long-term durability of transcatheter valves in comparison with surgical BHVs in younger patients.
  - The role of TAVI in patients with BAV AS and patients <70 years of age.
  - Results of intervention (valve or coronary) after TAVI or SAVR.
  - Determining the optimal lifetime management strategy for AS patients.

Mitral regurgitation

- The association between primary MR and ventricular arrhythmias requires more investigation, including the impact of intervention on ventricular arrhythmias.
- More data are required on the role of TEER in patients with advanced HF.
- Long-term results of TEER need to be further assessed, including the clinical relevance of transmitral gradients after treatment of both primary and secondary MR.
- Results of ongoing trials comparing MV surgery with TEER in non-high risk primary MR patients are awaited.
- Data on the mid- and long-term clinical impacts of transcatheter MV replacement are required.
- More data on the clinical impacts of surgical and transcatheter treatment of atrial SMR are required.

Mitral stenosis

- The potential role of TMVI using dedicated devices in high-risk patients is to be determined, particularly those with severe MAC.

Tricuspid regurgitation

- The long-term risks and benefits of concomitant TV surgery in patients with less than moderate TR and annular dilatation undergoing left-sided valve surgery need to be determined.
- Further investigations are required on the outcomes of TV intervention in asymptomatic patients with severe TR and RV dysfunction or significant dilation.
- The importance of addressing concomitant AF in patients with TR needs to be investigated.
- More data are required on the indications, timing, and long-term outcomes of TV repair and replacement for TV disease.
- Better understanding is required of the respective role of surgery vs transcatheter TV therapy for TR treatment.

Tricuspid stenosis

- The role of transcatheter TV replacement remains unexplored in patients with TS. The most efficient way to achieve ventricular pacing in patients after TV replacement needs to be investigated.

Multiple and mixed valvular heart disease

- Further evaluation of the impact on outcomes and indication for intervention, as well as timing and modalities of intervention, is required.

Prosthetic valves

- Further development of current prosthetic valve devices is required to address their main complications (e.g. improved tissue processing to reduce degeneration of bioprostheses or new mechanical valve designs to reduce risk of thrombosis).
- Antithrombotic drugs in MHV patients:
  - Whether UFH or LMWH should be preferred as bridging therapy after MHV implantation, as well as their timing and dosage, remains to be established.
  - For patients with MHV undergoing major NCS, the optimal postoperative management and bridging of VKA needs further investigation.
  - The role of pharmacogenomics for VKORC1, CYP2C9, and CYP4F2 in patients with highly variable INR, and low TTR or major vascular complications despite good adherence, should be further investigated.
  - More data on the risks and benefits of slow thrombolysis for valve thrombosis are required.

Pregnancy

- More data are required on optimal management of anticoagulation in pregnant women with MHVs. Prospective studies comparing different antithrombotic regimens are lacking.

Non-cardiac surgery

- Clinical utility of scales for peri-operative risk evaluation needs to be determined.

Sex-specific considerations

- The development of sex-adjusted surgical risk prediction tools is required.
- Additional data are needed to validate sex-specific cut-offs indicating interventions.
- Further research is needed to investigate sex-related differences in the prognosis and treatment of specific valve diseases, especially TR.

20. 'What to do' and 'What not to do' messages from the Guidelines

Class I and Class III recommendations from throughout the guideline document are summarized in *Table 13*.

Table 13 'What to do' and 'what not to do'

Recommendations	Class[a]	Level[b]
Recommendations for the management of coronary artery disease in patients with valvular heart disease		
CCTA is recommended before valve intervention in patients with moderate or lower (≤50%) pre-test likelihood of obstructive CAD.	I	B
Invasive coronary angiography is recommended before valve intervention in patients with high and very high (>50%) pre-test likelihood of obstructive CAD.	I	C
Invasive coronary angiography is recommended in the evaluation of CAD in patients with severe ventricular SMR.	I	C
CABG is recommended in patients with a primary indication for valve surgery and coronary artery diameter stenosis ≥70%.	I	C
Recommendations for the management of atrial fibrillation in patients with native valvular heart disease		
DOACs are recommended for stroke prevention in preference to VKAs in patients with AF and AS, AR, or MR who are eligible for OAC.	I	A
Concomitant surgical ablation is recommended in patients undergoing MV surgery with AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, according to an experienced team of electrophysiologists and arrhythmia surgeons.	I	A
Surgical closure of the LA appendage is recommended as an adjunct to OAC in patients with AF undergoing valve surgery to prevent cardioembolic stroke and systemic thromboembolism.	I	B
The use of DOACs is not recommended in patients with AF and rheumatic MS with an MVA ≤2.0 cm^2.	III	B
Recommendations on indications for surgery in severe aortic regurgitation		
AV surgery is recommended in symptomatic patients with severe AR regardless of LV function.	I	B
AV surgery is recommended in asymptomatic patients with severe AR and LVESD >50 mm or LVESDi >25 mm/m^2 [especially in patients with small body size (BSA <1.68 m^2)] or resting LVEF ≤50%.	I	B
Valve-sparing aortic root replacement is recommended in young patients with aortic root dilatation at experienced centres when durable results are expected.	I	B
AV surgery is recommended in symptomatic and asymptomatic patients with severe AR undergoing CABG or surgery of the ascending aorta.	I	C
Recommendations for intervention and mode of intervention in severe aortic stenosis		
Symptomatic patients with severe aortic stenosis		
Intervention is recommended in symptomatic patients with severe, high-gradient AS [mean gradient ≥40 mmHg, V_{max} ≥4.0 m/s, and AVA ≤1.0 cm^2 (or ≤0.6 cm^2/m^2 BSA)].	I	B
Intervention is recommended in symptomatic patients with low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) AS with reduced LVEF (<50%) after careful confirmation that AS is severe.	I	B
Asymptomatic patients with severe aortic stenosis		
Intervention is recommended in asymptomatic patients with severe AS and LVEF <50% without another cause.	I	B
Mode of intervention in patients with symptomatic severe aortic stenosis		
It is recommended that AV interventions are performed in Heart Valve Centres that report their local expertise and outcome data, have on-site interventional cardiology and cardiac surgical programmes, and a structured collaborative Heart Team.	I	C
It is recommended that the mode of intervention is based on Heart Team assessment of individual clinical, anatomical, and procedural characteristics, incorporating lifetime management considerations and estimated life expectancy.	I	C

Continued

TAVI is recommended in patients ≥70 years of age with tricuspid AV stenosis, if the anatomy is suitable.	I	A
SAVR is recommended in patients <70 years of age, if the surgical risk is low.	I	B
SAVR or TAVI are recommended for all remaining candidates for an aortic BHV according to Heart Team assessment.	I	B
Concomitant aortic valve surgery at the time of coronary artery bypass grafting or ascending aorta surgery		
SAVR is recommended in symptomatic and asymptomatic patients with severe AS undergoing CABG or surgical intervention on the ascending aorta.	I	C
Recommendations for intervention in severe mitral regurgitation		
Primary mitral regurgitation		
MV repair is the recommended surgical technique to treat patients with severe PMR when the result is expected to be durable.	I	B
MV surgery is recommended in symptomatic patients with severe PMR considered operable by the Heart Team.	I	B
MV surgery is recommended in asymptomatic patients with severe PMR with LV dysfunction (LVESD ≥40 mm or LVESDi ≥20 mm/m^2 or LVEF ≤60%).	I	B
Surgical MV repair is recommended in low-risk asymptomatic patients with severe PMR without LV dysfunction (LVESD <40 mm, LVESDi <20 mm/m^2, and LVEF >60%) when a durable result is likely, if at least three of the following criteria are fulfilled: • AF • SPAP at rest >50 mmHg • LA dilatation (LAVI ≥60 mL/m^2 or LA diameter ≥55 mm) • concomitant TR ≥ moderate.	I	B
Ventricular secondary mitral regurgitation and concomitant coronary artery disease		
MV surgery is recommended in patients with severe ventricular SMR undergoing CABG.	I	B
Ventricular secondary mitral regurgitation without concomitant coronary artery disease		
TEER is recommended to reduce HF hospitalizations and improve quality of life in haemodynamically stable, symptomatic patients with impaired LVEF (<50%) and persistent severe ventricular SMR, despite optimized GDMT and CRT (if indicated), fulfilling specific clinical and echocardiographic criteria.	I	A
Recommendations for mitral stenosis		
Indications for mitral valve surgery and transcatheter intervention in clinically severe rheumatic and degenerative mitral stenosis		
PMC is recommended in symptomatic patients in the absence of unfavourable characteristics for PMC.	I	B
PMC is recommended in any symptomatic patients with a contraindication or a high risk for surgery.	I	C
MV surgery is recommended in symptomatic patients who are not suitable for PMC.	I	C
Recommendations for tricuspid regurgitation		
Indications for intervention in tricuspid regurgitation		
Careful evaluation of TR aetiology, stage of the disease (i.e. degree of TR severity, RV and LV dysfunction, and PH), patient operative risk, and likelihood of recovery by a multidisciplinary Heart Team is recommended in patients with severe TR prior to intervention.	I	C
Patients with left-sided valvular heart disease requiring tricuspid valve surgery		
Concomitant TV surgery is recommended in patients with severe primary or secondary TR.	I	B
Patients with severe tricuspid regurgitation (without left-sided valvular heart disease requiring surgery)		
TV surgery is recommended in symptomatic patients with severe primary TR without severe RV dysfunction or severe PH.	I	C
Recommendations on tricuspid stenosis		
Surgery is recommended in symptomatic patients with severe TS.	I	C
Surgery is recommended in patients with severe TS undergoing left-sided valve intervention.	I	C
Recommendations for surgery of concomitant left-sided valvular heart disease		
Concomitant aortic stenosis		
SAVR is recommended in patients with severe AS undergoing surgery for another valve.	I	C
Concomitant aortic regurgitation		
AV surgery is recommended in patients with severe AR undergoing surgery for another valve.	I	C
Concomitant mitral regurgitation		
MV surgery is recommended in patients with severe MR undergoing surgery for another valve.	I	C

Continued

Recommendations on indications for intervention in patients with mixed moderate aortic stenosis and moderate aortic regurgitation		
Intervention is recommended in symptomatic patients with mixed moderate AV stenosis and moderate regurgitation, and a mean gradient ≥40 mmHg or V_{max} ≥4.0 m/s.	I	B
Intervention is recommended in asymptomatic patients with mixed moderate AV stenosis and moderate regurgitation with V_{max} ≥4.0 m/s, and LVEF <50% not attributable to other cardiac disease.	I	C
Recommendations for prosthetic valve selection		
Mechanical heart valves		
An MHV is recommended according to the desire of the informed patient and if there is no contraindication to long-term anticoagulation.	I	C
Biological heart valves		
A BHV is recommended according to the desire of the informed patient.	I	C
A BHV is recommended when an adequate quality of anticoagulation with VKA is unlikely, in patients at high bleeding risk, or with estimated short life expectancy.	I	C
Recommendations for the management of antithrombotic therapy in patients with a mechanical heart valve replacement		
Lifelong OAC with a VKA is recommended for all patients with MHVs to prevent thromboembolic complications.	I	A
INR self-monitoring and self-management are recommended over standard monitoring in selected, trained patients to improve efficacy.	I	A
It is recommended that INR targets are based on the type and position of the MHV, and the patient's risk factors and comorbidities.	I	A
Patient education is recommended to improve the quality of OAC.	I	A
Following cardiac surgery with MHV implantation, it is recommended to start UFH or LMWH bridging and VKA within 24 h, or as soon as considered safe.	I	B
DOACs and/or DAPT are not recommended to prevent thrombosis in patients with an MHV.	III	A
Recommendations for the management of antithrombotic therapy in patients with mechanical heart valves undergoing elective non-cardiac surgery or invasive procedures		
Continuing VKA treatment is recommended in patients with an MHV for minor or minimally invasive interventions associated with no or minimal bleeding.	I	A
It is recommended to discontinue VKA at least 4 days before major elective NCS, aiming for an INR <1.5, and to resume VKA treatment within 24 h after surgery, or as soon as considered safe.	I	B
Recommendations for the management of antithrombotic therapy in patients with a biological heart valve or valve repair		
Transcatheter aortic valve implantation without indication for oral anticoagulation		
Low-dose ASA (75–100 mg/day) is recommended for 12 months after TAVI in patients without indication for OAC.	I	A
DAPT is not recommended to prevent thrombosis after TAVI, unless there is a clear indication.	III	A
Routine use of OAC is not recommended after TAVI in patients without baseline indication.	III	A
Surgical biological heart valve with indication for oral anticoagulation		
OAC continuation is recommended in patients with a clear indication for OAC undergoing surgical BHV implantation.	I	B
Transcatheter biological heart valve with indication for oral anticoagulation		
OAC is recommended for TAVI patients who have other indications for OAC.	I	B
Recommendations on management of prosthetic valve dysfunction		
Haemolysis and paravalvular leak		
It is recommended that the decision between transcatheter or surgical closure of clinically significant PVLs is based on Heart Team evaluation, including patient risk, leak morphology, and local expertise.	I	C
Reoperation is recommended if a PVL is related to endocarditis, or causes haemolysis requiring repeated blood transfusion or leading to HF symptoms.	I	C
Mechanical heart valve failure		
Reoperation is recommended in symptomatic patients with significant valve dysfunction not attributable to valve thrombosis.	I	C
Biological heart valve failure		
Reintervention is recommended in symptomatic patients with significant valve dysfunction not attributable to valve thrombosis.	I	C
Valve thrombosis		
TOE and/or 4D-CT are recommended in patients with suspected valve thrombosis to confirm the diagnosis.	I	C

Continued

Mechanical heart valve thrombosis		
Heart Team evaluation is recommended in patients with acute HF (NYHA class III or IV) due to obstructive MHV thrombosis to determine appropriate management (repeat valve replacement or low-dose slow infusion fibrinolysis).	I	B
Biological heart valve thrombosis		
OAC using VKA is recommended in BHV thrombosis before considering reintervention.	I	B

4D, four-dimensional; AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; ASA, acetylsalicylic acid; AV, aortic valve; AVA, aortic valve area; BHV, biological heart valve; BSA, body surface area; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCTA, coronary CT angiography; CRT, cardiac resynchronization therapy; CT, computed tomography; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulation; GDMT, guideline-directed medical therapy; h, hour; HF, heart failure; INR, international normalized ratio; LA, left atrium/left atrial; LAVI, left atrial volume index; LMWH, low-molecular-weight heparin; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to BSA; MHV, mechanical heart valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; MVA, mitral valve area; NCS, non-cardiac surgery; NYHA, New York Heart Association; OAC, oral anticoagulation; PH, pulmonary hypertension; PMC, percutaneous mitral commissurotomy; PMR, primary mitral regurgitation; PVL, paravalvular leak; RV, right ventricle/right ventricular; SAVR, surgical aortic valve replacement; SMR, secondary mitral regurgitation; SPAP, systolic pulmonary artery pressure; SVi, stroke volume index; TAVI, transcatheter aortic valve implantation; TEER, transcatheter edge-to-edge repair; TOE, transoesophageal echocardiography; TR, tricuspid regurgitation; TS, tricuspid stenosis; TV, tricuspid valve; UFH, unfractionated heparin; VKA, vitamin K antagonist; V_{max}, peak transvalvular velocity.
[a]Class of recommendation.
[b]Level of evidence.

21. Evidence tables

Evidence tables are available at *European Heart Journal* online.

22. Data availability statement

No new data were generated or analysed in support of this research.

23. Author information

Jonas Lanz, Department of Cardiology, Bern University Hospital, Bern, Switzerland; **Mateo Marin-Cuartas**, University Department of Cardiac Surgery, Leipzig Heart Center, Leipzig, Germany; **Ana Abreu**, Faculdade de Medicina da Universidade de Lisboa (FMUL), ISAMB, IMPSP, CCUL, CAML, Lisboa, Portugal; Serviço Cardiologia, Unidade de Reabilitação Cardiovascular, ULS Santa Maria/FMUL, Lisboa, Portugal; **Marianna Adamo**, Institute of Cardiology, ASST Spedali Civili, Brescia, Italy; Department of medical and surgical specialties, radiological sciences, and public health, University of Brescia, Italy; **Nina Ajmone Marsan**, Department of Cardiology, Leiden University Medical Center, Leiden, Netherlands; **Fabio Barili**, Department of Biomedical and Clinical Sciences, Università Degli Studi Di Milano, Milan, Italy; University Cardiac Surgery Unit, IRCCS Ospedale Galeazzi - Sant'Ambrogio, Milan, Italy; Department of Epidemiology, Harvard T.H. Chan School of Public Health Boston, MA, United States of America; **Nikolaos Bonaros**, Department of Cardiac Surgery, Medical University of Innsbruck, Innsbruck, Austria; University Hospital Innsbruck, Innsbruck, Austria; **Bernard Cosyns**, Cardiology department, Universitair Ziekenhuis Brussel, Brussels, Belgium; **Ruggero De Paulis**, Department of cardiac surgery, European Hospital, Rome, Italy; Unicamillus University, Rome, Italy; **Habib Gamra**, Cardiology University of Monastir, Monastir, Tunisia; **Marjan Jahangiri**, Cardiac Surgery, St George's Hospital, London, United Kingdom; **Anders Jeppsson**, Cardiothoracic surgery, Sahlgrenska University Hospital, Gothenburg, Sweden; Molecular and clinical medicine, Institute of medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; **Robert J.M. Klautz**, Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, Netherlands; Department of Cardiothoracic Surgery, Amsterdam University Medical Center, Amsterdam, Netherlands; **Benoit Mores**, (Belgium), ESC Patient Forum, Sophia Antipolis, France; **Esther Pérez-David**, Cardiology Department, Hospital Universitario La Paz, IdiPaz (Hospital la Paz Research Institute), Facultad de Medicina Universidad Europea de Madrid, Madrid, Spain; **Janine Pöss**, Department of internal medicine/cardiology, Heart Centre Leipzig at University of Leipzig, Leipzig, Germany; **Bernard D. Prendergast**, Heart Vascular & Thoracic Institute, Cleveland Clinic London, London, United Kingdom; Department of Cardiology, St Thomas' Hospital, London, United Kingdom; **Bianca Rocca**, Department of Medicine and Surgery, LUM University Casamassima (Ba), Italy; **Xavier Rossello**, Cardiology Department, Hospital Universitari Son Espases, Palma de Mallorca, Spain; Health Research Institute of the Balearic Islands (IdISBa), Universitat de les Illes Balears (UIB), Palma de Mallorca, Spain; **Mikio Suzuki**, (Serbia), ESC Patient Forum, Sophia Antipolis, France; **Holger Thiele**, Department of Internal Medicine/Cardiology, Heart Centre Leipzig at Leipzig University, Leipzig, Germany; Leipzig Heart Science, Leipzig, Germany; **Christophe Michel Tribouilloy**, Cardiology department, Amiens University Hospital, Amiens, France; and **Wojtek Wojakowski**, Division of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland.

24. Appendix

ESC/EACTS Scientific Document Group

Includes Document Reviewers, ESC National Cardiac Societies and EACTS Network of National Cardiac Surgery Societies

Document Reviewers: Alec Vahanian (ESC Review Co-ordinator) (France), Carlos-A. Mestres (EACTS Review Co-ordinator) (South Africa), Leila Abid (Tunisia), Suleman Aktaa (United Kingdom), Elena Arbelo (Spain), Folkert W. Asselbergs (Netherlands), Emanuele Barbato (Italy), Giuseppe Boriani (Italy), Margarita Brida (Croatia), Sergio Buccheri (Sweden), Robert Byrne (Republic of Ireland), Ovidiu Chioncel (Romania), Lenard Conradi (Germany), Michele De Bonis (Italy), Victoria Delgado (Spain), Enoch F. Akowuah (United Kingdom), Anna Franzone (Italy), Kristina Hermann Haugaa (Norway), Bettina Heidecker (Germany), Borja Ibanez (Spain), Bernard Iung (France), Stefan James (Sweden), Lars Køber (Denmark), Konstantinos C. Koskinas (Switzerland), Ulf

Landmesser (Germany), Gregory Y.H. Lip (United Kingdom), John William McEvoy (Ireland), Gil Meltzer (Israel), David Messika-Zeitoun (Canada), Borislava Mihaylova (United Kingdom), Richard Mindham (United Kingdom), Inge Moelgaard (Denmark), Jens Cosedis Nielsen (Denmark), Gareth Owens (United Kingdom), Agnes A. Pasquet (Belgium), Thomas Pilgrim (Switzerland), Eva Prescott (Denmark), Eduard Quintana (Spain), Volker Rudolph (Germany), Rafael Sadaba (Spain), Anna Sannino (Germany), Felix C. Tanner (Switzerland), Marina Urena (France), Ilonca Vaartjes (Netherlands), Christiaan Vrints (Belgium), Alexander Wahba (Norway), Thomas Walther (Germany), Adam Witkowski (Poland), and Katja Zeppenfeld (Netherlands)

Contributor either withdrew or was engaged in only a part of the review process: Davide Capodanno

ESC National Cardiac Societies actively involved in the review process of the 2025 ESC/EACTS Guidelines for the management for valvular heart disease:

Albania: Albanian Society of Cardiology, Naltin Shuka; **Algeria:** Algerian Society of Cardiology, Brahim Kichou; **Armenia:** Armenian Cardiologists Association, Aram L. Chilingaryan; **Austria:** Austrian Society of Cardiology, Philipp Emanuel Bartko; **Azerbaijan:** Azerbaijan Society of Cardiology, Fuad Samadov; **Belgium:** Belgian Society of Cardiology, Caroline M. Van de Heyning; **Bosnia and Herzegovina:** Association of Cardiologists of Bosnia and Herzegovina, Zumreta Kusljugic; **Bulgaria:** Bulgarian Society of Cardiology, Elena Kinova; **Croatia:** Croatian Cardiac Society, Josko Bulum; **Cyprus:** Cyprus Society of Cardiology, Christos Eftychiou; **Czechia:** Czech Society of Cardiology, Hana Linkova; **Denmark:** Danish Society of Cardiology, Emil Fosbøl; **Egypt:** Egyptian Society of Cardiology, Hesham Bahaa; **Estonia:** Estonian Society of Cardiology, Jaagup Truusalu; **Finland:** Finnish Cardiac Society, Jarkko Piuhola; **France:** French Society of Cardiology, Erwan Donal; **Georgia:** Georgian Society of Cardiology, Shalva Petriashvili; **Germany:** German Cardiac Society, Tanja Katharina Rudolph; **Greece:** Hellenic Society of Cardiology, Maria Drakopoulou; **Hungary:** Hungarian Society of Cardiology, Attila Kertész; **Iceland:** Icelandic Society of Cardiology, Hjalti Guðmundsson; **Ireland:** Irish Cardiac Society, Ben Cole; **Israel:** Israel Heart Society, Shemy Carasso; **Italy:** Italian Federation of Cardiology, Alessandro Navazio; **Kazakhstan:** Association of Cardiologists of Kazakhstan, Madina Sugralimova; **Kosovo (Republic of):** Kosovo Society of Cardiology, Gani Bajraktari; **Kyrgyzstan:** Kyrgyz Society of Cardiology, Alina Kerimkulova; **Libya:** Libyan Cardiac Society, Elham Omran Elgdhafi; **Lithuania:** Lithuanian Society of Cardiology, Sigita Glaveckaite; **Luxembourg:** Luxembourg Society of Cardiology, Frederic Lebrun; **Malta:** Maltese Cardiac Society, Daniela Cassar Demarco; **Moldova (Republic of):** Moldavian Society of Cardiology, Dorin Mihail Lisii; **Netherlands:** Netherlands Society of Cardiology, Sebastian Streukens; **North Macedonia:** National Society of Cardiology of North Macedonia, Emilija Antova; **Norway:** Norwegian Society of Cardiology, Håvard Dalen; **Poland:** Polish Cardiac Society, Tomasz Kukulski; **Portugal:** Portuguese Society of Cardiology, Cristina Gavina; **Romania**: Romanian Society of Cardiology, Bogdan A. Popescu; **San Marino:** San Marino Society of Cardiology, Roberto Bini; **Serbia:** Cardiology Society of Serbia, Igor Ivanov; **Slovakia:** Slovak Society of Cardiology, Martin Hudec; **Slovenia:** Slovenian Society of Cardiology, Matjaž Bunc; **Spain:** Spanish Society of Cardiology, Thomas Javier Bermejo; **Sweden:** Swedish Society of Cardiology, Carl Johan Cronstedt Meurling; **Switzerland:** Swiss Society of Cardiology, Raban Jeger; **Tunisia:** Tunisian Society of Cardiology and Cardio-Vascular Surgery, Leila Abid; **Türkiye:** Turkish Society of Cardiology, Muzaffer M. Degertekin; **Ukraine:** Ukrainian Association of Cardiology, Elena G. Nesukay; **United Kingdom of Great Britain and Northern Ireland:** British Cardiovascular Society, Madalina Garbi; **Uzbekistan:** Association of Cardiologists of Uzbekistan, Guzal Mullabayeva.

EACTS Network of National Cardiac Surgery Societies actively involved in the review process of the 2025 ESC/EACTS Guidelines for the management for valvular heart disease:

Austria: Austrian Society of Cardiac and Thoracic Vascular Surgery, Martin Grabenwoeger; **Belgium:** Belgian Association for Cardio-Thoracic Surgery, Frederic Vanden Eynden; **Czechia:** The Czech Society for Cardiovascular Surgery, Jan Vojacek; **France:** The French Society for Thoracic and Cardiovascular Surgery; André Vincentelli; **Germany:** German Society for Thoracic and Cardiovascular Surgery, Volkmar Falk; **Greece:** Hellenic Society of Thoracic and Cardiovascular Surgeons, Panagiotis Dedeilias; **Italy:** Italian Society for Cardiac Surgery, Alessandro Parolari; **Netherlands:** Netherlands Association for Cardio-thoracic surgery, Jerry Braun; **North Macedonia:** North Macedonian Society of Cardiac Surgery, Aleksandar Nikolic; **Norway:** Norwegian Association for Cardiothoracic Surgery, Vegard S. Ellensen; **Portugal:** Sociedade Portuguesa de Cirurgia Cardíaca Torácica e Vascular, Miguel Sousa-Uva; **Serbia:** Serbian Society for Cardiovascular Surgery, Slobodan Micovic; **Spain:** Sociedad Española de Cirugía Cardiovascular y Endovascular, Juan J. Legarra; **Switzerland:** Swiss Society for Thoracic and Cardiovascular Surgery, Enrico Ferrari; **United Kingdom:** The Society for Cardiothoracic Surgery in Great Britain and Ireland, Narain Moorjani

ESC Clinical Practice Guidelines (CPG) Committee: Ulf Landmesser (Chairperson) (Germany), Stefan James (Co-Chairperson) (Sweden), Marianna Adamo (Italy), Suleman Aktaa (United Kingdom), Folkert W. Asselbergs (Netherlands), Colin Baigent (United Kingdom), Michael A. Borger (Germany), Giuseppe Boriani (Italy), Margarita Brida (Croatia), Robert A. Byrne (Ireland), Estelle Gandjbakhch (France), Bettina Heidecker (Germany), Anja Hennemuth (Germany), Borja Ibanez (Spain), Peter Jüni (United Kingdom), Gregory Y.H. Lip (United Kingdom), John William McEvoy (Ireland), Borislava Mihaylova (United Kingdom), Inge Moelgaard (Denmark), Lis Neubeck (United Kingdom), Eva Prescott (Denmark), Bianca Rocca (Italy), Xavier Rossello (Spain), Anna Sannino (Germany), Felix C. Tanner (Switzerland), Wojtek Wojakowski (Poland), and Katja Zeppenfeld (Netherlands)

EACTS Council: Volkmar Falk (President) (Germany), Patrick Myers (Secretary General) (Switzerland), Joseph Bavaria (United States of America), Korkut Bostanci (Türkiye), Filip Casselman (Belgium), Mario Gaudino (United States of America), Jurgen Hoerer (Germany), Nabil Hussein (United Kingdom), Virginia Litle (United States of America), Franca Melfi (Italy), Rafael Sadaba (Spain), Florian Schoenhoff (Switzerland), Matthias Siepe (Switzerland), and Tanya Warburton (United Kingdom)

25. References

1. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, *et al.* Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;**380**:1695–705. https://doi.org/10.1056/NEJMoa1814052
2. Mack MJ, Leon MB, Thourani VH, Pibarot P, Hahn RT, Genereux P, *et al.* Transcatheter aortic-valve replacement in low-risk patients at five years. *N Engl J Med* 2023;**389**:1949–960. https://doi.org/10.1056/NEJMoa2307447
3. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, *et al.* Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017;**376**:1321–31. https://doi.org/10.1056/NEJMoa1700456

4. Forrest JK, Deeb GM, Yakubov SJ, Gada H, Mumtaz MA, Ramlawi B, *et al.* 4-Year outcomes of patients with aortic stenosis in the Evolut low risk trial. *J Am Coll Cardiol* 2023;**82**:2163–65. https://doi.org/10.1016/j.jacc.2023.09.813
5. Delgado V, Ajmone Marsan N, de Waha S, Bonaros N, Brida M, Burri H, *et al.* 2023 ESC Guidelines for the management of endocarditis. *Eur Heart J* 2023;**44**:3948–4042. https://doi.org/10.1093/eurheartj/ehad193
6. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, *et al.* 2024 ESC Guidelines for the management of chronic coronary syndromes: developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2024;**45**:3415–537. https://doi.org/10.1093/eurheartj/ehae177
7. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns H, *et al.* 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2024;**45**:3314–414. https://doi.org/10.1093/eurheartj/ehae176
8. Mazzolai L, Teixido-Tura G, Lanzi S, Boc V, Bossone E, Brodmann M, *et al.* 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases. *Eur Heart J* 2024;**45**:3538–700. https://doi.org/10.1093/eurheartj/ehae179
9. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller G-P, *et al.* 2020 ESC Guidelines for the management of adult congenital heart disease: the Task Force for the management of adult congenital heart disease of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Adult Congenital Heart Disease (ISACHD). *Eur Heart J* 2020;**42**:563–645. https://doi.org/10.1093/eurheartj/ehaa554
10. Généreux P, Sharma RP, Cubeddu RJ, Aaron L, Abdelfattah OM, Koulogiannis KP, *et al.* The mortality burden of untreated aortic stenosis. *J Am Coll Cardiol* 2023;**82**:2101–9. https://doi.org/10.1016/j.jacc.2023.09.796
11. d'Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J, *et al.* Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. *Eur Heart J* 2016;**37**:3515–22. https://doi.org/10.1093/eurheartj/ehw229
12. Iung B, Delgado V, Rosenhek R, Price S, Prendergast B, Wendler O, *et al.* Contemporary presentation and management of valvular heart disease: the EURObservational research programme valvular heart disease II survey. *Circulation* 2019;**140**:1156–69. https://doi.org/10.1161/CIRCULATIONAHA.119.041080
13. Gaede L, Di Bartolomeo R, van der Kley F, Elsässer A, Iung B, Möllmann H. Aortic valve stenosis: what do people know? A heart valve disease awareness survey of over 8,800 people aged 60 or over. *EuroIntervention* 2016;**12**:883–9. https://doi.org/10.4244/eijy16m06_02
14. Lancellotti P, Magne J, Dulgheru R, Clavel MA, Donal E, Vannan MA, *et al.* Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. *JAMA Cardiol* 2018;**3**:1060–8. https://doi.org/10.1001/jamacardio.2018.3152
15. Lancellotti P, Rosenhek R, Pibarot P, Iung B, Otto CM, Tornos P, *et al.* ESC Working Group on Valvular Heart Disease Position Paper—heart valve clinics: organization, structure, and experiences. *Eur Heart J* 2013;**34**:1597–606. https://doi.org/10.1093/eurheartj/ehs443
16. Chambers JB, Prendergast B, Iung B, Rosenhek R, Zamorano JL, Pierard LA, *et al.* Standards defining a 'Heart Valve Centre': ESC Working Group on Valvular Heart Disease and European Association for Cardiothoracic Surgery Viewpoint. *Eur Heart J* 2017;**38**:2177–83. https://doi.org/10.1093/eurheartj/ehx370
17. Nishimura RA, O'Gara PT, Bavaria JE, Brindis RG, Carroll JD, Kavinsky CJ, *et al.* 2019 AATS/ACC/ASE/SCAI/STS Expert Consensus Systems of Care document: a proposal to optimize care for patients with valvular heart disease: a joint report of the American Association for Thoracic Surgery, American College of Cardiology, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2019;**73**:2609–35. https://doi.org/10.1016/j.jacc.2018.10.007
18. Dreyfus G, Windecker S. How to shape the future of cardiology and cardiac surgery? *Eur Heart J* 2020;**41**:3693–701. https://doi.org/10.1093/eurheartj/ehaa707
19. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, *et al.* 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2022;**43**:561–632. https://doi.org/10.1093/eurheartj/ehab395
20. Leonardi S, Capodanno D, Sousa-Uva M, Vrints C, Rex S, Guarracino F, *et al.* Composition, structure, and function of heart teams: a joint position paper of the ACVC, EAPCI, EACTS, and EACTA focused on the management of patients with complex coronary artery disease requiring myocardial revascularization. *Eur Heart J Acute Cardiovasc Care* 2021;**10**:83–93. https://doi.org/10.1093/ehjacc/zuaa013
21. Agricola E, Ancona F, Brochet E, Donal E, Dweck M, Faletra F, *et al.* The structural heart disease interventional imager rationale, skills and training: a position paper of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2021;**22**:471–9. https://doi.org/10.1093/ehjci/jeab005
22. Hahn RT, Mahmood F, Kodali S, Lang R, Monaghan M, Gillam LD, *et al.* Core competencies in echocardiography for imaging structural heart disease interventions: an expert consensus statement. *JACC Cardiovasc Imaging* 2019;**12**:2560–70. https://doi.org/10.1016/j.jcmg.2019.10.008
23. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003;**349**:2117–27. https://doi.org/10.1056/NEJMsa035205
24. Khera R, Pandey A, Koshy T, Ayers C, Nallamothu BK, Das SR, *et al.* Role of hospital volumes in identifying low-performing and high-performing aortic and mitral valve surgical centers in the United States. *JAMA Cardiol* 2017;**2**:1322–31. https://doi.org/10.1001/jamacardio.2017.4003
25. Gammie JS, O'Brien SM, Griffith BP, Ferguson TB, Peterson ED. Influence of hospital procedural volume on care process and mortality for patients undergoing elective surgery for mitral regurgitation. *Circulation* 2007;**115**:881–7. https://doi.org/10.1161/CIRCULATIONAHA.106.634436
26. Chikwe J, Toyoda N, Anyanwu AC, Itagaki S, Egorova NN, Boateng P, *et al.* Relation of mitral valve surgery volume to repair rate, durability, and survival. *J Am Coll Cardiol* 2017;**69**:2397–406. https://doi.org/10.1016/j.jacc.2017.02.026
27. Chhatriwalla AK, Vemulapalli S, Szerlip M, Kodali S, Hahn RT, Saxon JT, *et al.* Operator experience and outcomes of transcatheter mitral valve repair in the United States. *J Am Coll Cardiol* 2019;**74**:2955–65. https://doi.org/10.1016/j.jacc.2019.09.014
28. Bonow RO, O'Gara PT, Adams DH, Badhwar V, Bavaria JE, Elmariah S, *et al.* 2019 AATS/ACC/SCAI/STS Expert Consensus Systems of Care document: operator and institutional recommendations and requirements for transcatheter mitral valve intervention: a joint report of the American Association for Thoracic Surgery, the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, and The Society of Thoracic Surgeons. *J Am Coll Cardiol* 2020;**76**:96–117. https://doi.org/10.1016/j.jacc.2019.12.002
29. Grayburn PA, Mack MJ, Manandhar P, Kosinski AS, Sannino A, Smith RL 2nd, *et al.* Comparison of transcatheter edge-to-edge mitral valve repair for primary mitral regurgitation outcomes to hospital volumes of surgical mitral valve repair. *Circ Cardiovasc Interv* 2024;**17**:e013581. https://doi.org/10.1161/circinterventions.123.013581
30. Wild MG, Stolz L, Rosch S, Rudolph F, Goebel B, Köll B, *et al.* Transcatheter valve repair for tricuspid regurgitation: 1-year results from a large European real-world registry. *J Am Coll Cardiol* 2025;**85**:220–31. https://doi.org/10.1016/j.jacc.2024.10.068
31. Carroll JD, Vemulapalli S, Dai D, Matsouaka R, Blackstone E, Edwards F, *et al.* Procedural experience for transcatheter aortic valve replacement and relation to outcomes: the STS/ACC TVT registry. *J Am Coll Cardiol* 2017;**70**:29–41. https://doi.org/10.1016/j.jacc.2017.04.056
32. Mao J, Redberg RF, Carroll JD, Marinac-Dabic D, Laschinger J, Thourani V, *et al.* Association between hospital surgical aortic valve replacement volume and transcatheter aortic valve replacement outcomes. *JAMA Cardiol* 2018;**3**:1070–8. https://doi.org/10.1001/jamacardio.2018.3562
33. Vemulapalli S, Carroll JD, Mack MJ, Li Z, Dai D, Kosinski AS, *et al.* Procedural volume and outcomes for transcatheter aortic-valve replacement. *N Engl J Med* 2019;**380**:2541–50. https://doi.org/10.1056/NEJMsa1901109
34. Edwards FH, Ferraris VA, Kurlansky PA, Lobdell KW, He X, O'Brien SM, *et al.* Failure to rescue rates after coronary artery bypass grafting: an analysis from the Society of Thoracic Surgeons adult cardiac surgery database. *Ann Thorac Surg* 2016;**102**:458–64. https://doi.org/10.1016/j.athoracsur.2016.04.051
35. Wallen T, Habertheuer A, Bavaria JE, Hughes GC, Badhwar V, Jacobs JP, *et al.* Elective aortic root replacement in North America: analysis of STS adult cardiac surgery database. *Ann Thorac Surg* 2019;**107**:1307–12. https://doi.org/10.1016/j.athoracsur.2018.12.039
36. Geirsson A, Ahlsson A, Franco-Cereceda A, Fuglsang S, Gunn J, Hansson EC, *et al.* Hospital volumes and later year of operation correlates with better outcomes in acute Type A aortic dissection. *Eur J Cardiothorac Surg* 2018;**53**:276–81. https://doi.org/10.1093/ejcts/ezx231
37. Gonzalez AA, Dimick JB, Birkmeyer JD, Ghaferi AA. Understanding the volume-outcome effect in cardiovascular surgery: the role of failure to rescue. *JAMA Surg* 2014;**149**:119–23. https://doi.org/10.1001/jamasurg.2013.3649
38. Wakeam E, Asafu-Adjei D, Ashley SW, Cooper Z, Weissman JS. The association of intensivists with failure-to-rescue rates in outlier hospitals: results of a national survey of intensive care unit organizational characteristics. *J Crit Care* 2014;**29**:930–5. https://doi.org/10.1016/j.jcrc.2014.06.010
39. Ward ST, Dimick JB, Zhang W, Campbell DA, Ghaferi AA. Association between hospital staffing models and failure to rescue. *Ann Surg* 2019;**270**:91–4. https://doi.org/10.1097/sla.0000000000002744
40. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, *et al.* European Society of Cardiology: cardiovascular disease statistics 2019. *Eur Heart J* 2020;**41**:12–85. https://doi.org/10.1093/eurheartj/ehz859
41. Ali N, Aktaa S, Younsi T, Beska B, Batra G, Blackman DJ, *et al.* European Society of Cardiology quality indicators for the care and outcomes of adults undergoing transcatheter aortic valve implantation. *Eur Heart J Qual Care Clin Outcomes* 2024;**10**:723–36. https://doi.org/10.1093/ehjqcco/qcae006
42. Messika-Zeitoun D, Baumgartner H, Burwash IG, Vahanian A, Bax J, Pibarot P, *et al.* Unmet needs in valvular heart disease. *Eur Heart J* 2023;**44**:1862–73. https://doi.org/10.1093/eurheartj/ehad121

43. van Dijk WB, Schuit E, van der Graaf R, Groenwold RHH, Laurijssen S, Casadei B, *et al.* Applicability of European Society of Cardiology guidelines according to gross national income. *Eur Heart J* 2022;**44**:598–607. https://doi.org/10.1093/eurheartj/ehac606
44. Sengupta PP, Kluin J, Lee SP, Oh JK, Smits A. The future of valvular heart disease assessment and therapy. *Lancet* 2024;**403**:1590–602. https://doi.org/10.1016/s0140-6736(23)02754-x
45. Lancellotti P, Pibarot P, Chambers J, La Canna G, Pepi M, Dulgheru R, *et al.* Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular heart disease position paper. *Eur Heart J Cardiovasc Imaging* 2022;**23**:e171–232. https://doi.org/10.1093/ehjci/jeab253
46. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, *et al.* Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;**30**:303–71. https://doi.org/10.1016/j.echo.2017.01.007
47. Popescu BA, Andrade MJ, Badano LP, Fox KF, Flachskampf FA, Lancellotti P, *et al.* European Association of Echocardiography recommendations for training, competence, and quality improvement in echocardiography. *Eur J Echocardiogr* 2009;**10**:893–905. https://doi.org/10.1093/ejechocard/jep151
48. Chambers JB, Garbi M, Nieman K, Myerson S, Pierard LA, Habib G, *et al.* Appropriateness criteria for the use of cardiovascular imaging in heart valve disease in adults: a European Association of Cardiovascular Imaging report of literature review and current practice. *Eur Heart J Cardiovasc Imaging* 2017;**18**:489–98. https://doi.org/10.1093/ehjci/jew309
49. Agricola E, Ancona F, Bartel T, Brochet E, Dweck M, Faletra F, *et al.* Multimodality imaging for patient selection, procedural guidance, and follow-up of transcatheter interventions for structural heart disease: a consensus document of the EACVI Task Force on Interventional Cardiovascular Imaging: part 1: access routes, transcatheter aortic valve implantation, and transcatheter mitral valve interventions. *Eur Heart J Cardiovasc Imaging* 2023;**24**:e209–68. https://doi.org/10.1093/ehjci/jead096
50. Zoghbi WA, Jone PN, Chamsi-Pasha MA, Chen T, Collins KA, Desai MY, *et al.* Guidelines for the evaluation of prosthetic valve function with cardiovascular imaging: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance and the Society of Cardiovascular Computed Tomography. *J Am Soc Echocardiogr* 2024;**37**:2–63. https://doi.org/10.1016/j.echo.2023.10.004
51. Faletra FF, Agricola E, Flachskampf FA, Hahn R, Pepi M, Ajmone Marsan N, *et al.* Three-dimensional transoesophageal echocardiography: how to use and when to use—a clinical consensus statement from the European Association of Cardiovascular Imaging of the European Society of Cardiology. *Eur Heart J Cardiovasc Imaging* 2023;**24**:e119–97. https://doi.org/10.1093/ehjci/jead090
52. Picano E, Pibarot P, Lancellotti P, Monin JL, Bonow RO. The emerging role of exercise testing and stress echocardiography in valvular heart disease. *J Am Coll Cardiol* 2009;**54**:2251–60. https://doi.org/10.1016/j.jacc.2009.07.046
53. Genereux P, Pibarot P, Redfors B, Mack MJ, Makkar RR, Jaber WA, *et al.* Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J* 2017;**38**:3351–8. https://doi.org/10.1093/eurheartj/ehx381
54. Stolz L, Doldi PM, Orban M, Karam N, Puscas T, Wild MG, *et al.* Staging heart failure patients with secondary mitral regurgitation undergoing transcatheter edge-to-edge repair. *JACC Cardiovasc Interv* 2023;**16**:140–51. https://doi.org/10.1016/j.jcin.2022.10.032
55. Dietz MF, Prihadi EA, van der Bijl P, Ajmone Marsan N, Delgado V, Bax JJ. Prognostic implications of staging right heart failure in patients with significant secondary tricuspid regurgitation. *JACC Heart Fail* 2020;**8**:627–36. https://doi.org/10.1016/j.jchf.2020.02.008
56. Généreux P, Pibarot P, Redfors B, Bax JJ, Zhao Y, Makkar RR, *et al.* Evolution and prognostic impact of cardiac damage after aortic valve replacement. *J Am Coll Cardiol* 2022;**80**:783–800. https://doi.org/10.1016/j.jacc.2022.05.006
57. Genereux P, Cohen DJ, Pibarot P, Redfors B, Bax JJ, Zhao Y, *et al.* Cardiac damage and quality of life after aortic valve replacement in the PARTNER trials. *J Am Coll Cardiol* 2023;**81**:743–52. https://doi.org/10.1016/j.jacc.2022.11.059
58. Kwak S, Everett RJ, Treibel TA, Yang S, Hwang D, Ko T, *et al.* Markers of myocardial damage predict mortality in patients with aortic stenosis. *J Am Coll Cardiol* 2021;**78**:545–58. https://doi.org/10.1016/j.jacc.2021.05.047
59. Magne J, Cosyns B, Popescu BA, Carstensen HG, Dahl J, Desai MY, *et al.* Distribution and prognostic significance of left ventricular global longitudinal strain in asymptomatic significant aortic stenosis: an individual participant data meta-analysis. *JACC Cardiovasc Imaging* 2019;**12**:84–92. https://doi.org/10.1016/j.jcmg.2018.11.005
60. Prihadi EA, van der Bijl P, Dietz M, Abou R, Vollema EM, Marsan NA, *et al.* Prognostic implications of right ventricular free wall longitudinal strain in patients with significant functional tricuspid regurgitation. *Circ Cardiovasc Imaging* 2019;**12**:e008666. https://doi.org/10.1161/CIRCIMAGING.118.008666
61. Little SH, Rigolin VH, Garcia-Sayan E, Hahn RT, Hung J, Mackensen GB, *et al.* Recommendations for special competency in echocardiographic guidance of structural heart disease interventions: from the American Society of Echocardiography. *J Am Soc Echocardiogr* 2023;**36**:350–65. https://doi.org/10.1016/j.echo.2023.01.014
62. Hahn RT, Saric M, Faletra FF, Garg R, Gillam LD, Horton K, *et al.* Recommended standards for the performance of transesophageal echocardiographic screening for structural heart intervention: from the American Society of Echocardiography. *J Am Soc Echocardiogr* 2022;**35**:1–76. https://doi.org/10.1016/j.echo.2021.07.006
63. Nicoara A, Skubas N, Ad N, Finley A, Hahn RT, Mahmood F, *et al.* Guidelines for the use of transesophageal echocardiography to assist with surgical decision-making in the operating room: a surgery-based approach: from the American Society of Echocardiography in collaboration with the Society of Cardiovascular Anesthesiologists and the Society of Thoracic Surgeons. *J Am Soc Echocardiogr* 2020;**33**:692–734. https://doi.org/10.1016/j.echo.2020.03.002
64. Popescu BA, Stefanidis A, Fox KF, Cosyns B, Delgado V, Di Salvo GD, *et al.* Training, competence, and quality improvement in echocardiography: the European Association of Cardiovascular Imaging Recommendations: update 2020. *Eur Heart J Cardiovasc Imaging* 2020;**21**:1305–19. https://doi.org/10.1093/ehjci/jeaa266
65. Iung B, Delgado V, Lazure P, Murray S, Sirnes PA, Rosenhek R, *et al.* Educational needs and application of guidelines in the management of patients with mitral regurgitation. A European mixed-methods study. *Eur Heart J* 2018;**39**:1295–303. https://doi.org/10.1093/eurheartj/ehx763
66. Nashef SAM, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, *et al.* EuroSCORE II. *Eur J Cardiothorac Surg* 2012;**41**:734–44; discussion 744–735. https://doi.org/10.1093/ejcts/ezs043
67. Ad N, Holmes SD, Patel J, Pritchard G, Shuman DJ, Halpin L. Comparison of EuroSCORE II, original EuroSCORE, and the Society of Thoracic Surgeons Risk Score in Cardiac Surgery Patients. *Ann Thorac Surg* 2016;**102**:573–9. https://doi.org/10.1016/j.athoracsur.2016.01.105
68. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, *et al.* The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2—isolated valve surgery. *Ann Thorac Surg* 2009;**88**:S23–42. https://doi.org/10.1016/j.athoracsur.2009.05.056
69. Duchnowski P, Hryniewiecki T, Kuśmierczyk M, Szymanski P. Performance of the EuroSCORE II and the Society of Thoracic Surgeons score in patients undergoing aortic valve replacement for aortic stenosis. *J Thorac Dis* 2019;**11**:2076–81. https://doi.org/10.21037/jtd.2019.04.48
70. Provenchere S, Chevalier A, Ghodbane W, Bouleti C, Montravers P, Longrois D, *et al.* Is the EuroSCORE II reliable to estimate operative mortality among octogenarians? *PLoS One* 2017;**12**:e0187056. https://doi.org/10.1371/journal.pone.0187056
71. Taleb Bendiab T, Brusset A, Estagnasié P, Squara P, Nguyen LS. Performance of EuroSCORE II and Society of Thoracic Surgeons risk scores in elderly patients undergoing aortic valve replacement surgery. *Arch Cardiovasc Dis* 2021;**114**:474–81. https://doi.org/10.1016/j.acvd.2020.12.004
72. Roques F, Michel P, Goldstone AR, Nashef SAM. The logistic EuroSCORE. *Eur Heart J* 2003;**24**:882–3. https://doi.org/10.1016/S0195-668X(02)00799-6
73. Al-Azizi K, Shih E, DiMaio JM, Squiers JJ, Moubarak G, Kluis A, *et al.* Assessment of TVT and STS risk score performances in patients undergoing transcatheter aortic valve replacement. *JSCAI* 2023;**2**:100600. https://doi.org/10.1016/j.jscai.2023.100600
74. Compagnone M, Moretti C, Marcelli C, Taglieri N, Ghetti G, Corsini A, *et al.* Surgical risk scores applied to transcatheter aortic valve implantation: friends or foes? Short-term and long-term outcomes from a single-center registry. *J Invasive Cardiol* 2019;**31**:E282–88.
75. Tarantini G, Lefèvre T, Terkelsen CJ, Frerker C, Ohlmann P, Mojoli M, *et al.* One-year outcomes of a European transcatheter aortic valve implantation cohort according to surgical risk. *Circ Cardiovasc Interv* 2019;**12**:e006724. https://doi.org/10.1161/CIRCINTERVENTIONS.118.006724
76. Arnold SV, Reynolds MR, Lei Y, Magnuson EA, Kirtane AJ, Kodali SK, *et al.* Predictors of poor outcomes after transcatheter aortic valve replacement: results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. *Circulation* 2014;**129**:2682–90. https://doi.org/10.1161/circulationaha.113.007477
77. Edwards FH, Cohen DJ, O'Brien SM, Peterson ED, Mack MJ, Shahian DM, *et al.* Development and validation of a risk prediction model for in-hospital mortality after transcatheter aortic valve replacement. *JAMA Cardiol* 2016;**1**:46–52. https://doi.org/10.1001/jamacardio.2015.0326
78. Iung B, Laouénan C, Himbert D, Eltchaninoff H, Chevreul K, Donzeau-Gouge P, *et al.* Predictive factors of early mortality after transcatheter aortic valve implantation: individual risk assessment using a simple score. *Heart* 2014;**100**:1016–23. https://doi.org/10.1136/heartjnl-2013-305314
79. Arnold SV, Afilalo J, Spertus JA, Tang Y, Baron SJ, Jones PG, *et al.* Prediction of poor outcome after transcatheter aortic valve replacement. *J Am Coll Cardiol* 2016;**68**:1868–77. https://doi.org/10.1016/j.jacc.2016.07.762
80. Raposeiras-Roubin S, Adamo M, Freixa X, Arzamendi D, Benito-González T, Montefusco A, *et al.* A score to assess mortality after percutaneous mitral valve repair. *J Am Coll Cardiol* 2022;**79**:562–73. https://doi.org/10.1016/j.jacc.2021.11.041
81. Shah N, Madhavan MV, Gray WA, Brener SJ, Ahmad Y, Lindenfeld J, *et al.* Prediction of death or HF hospitalization in patients with severe FMR: the COAPT risk score. *JACC Cardiovasc Interv* 2022;**15**:1893–905. https://doi.org/10.1016/j.jcin.2022.08.005
82. Hausleiter J, Lachmann M, Stolz L, Bedogni F, Rubbio AP, Estévez-Loureiro R, *et al.* Artificial intelligence-derived risk score for mortality in secondary mitral regurgitation

treated by transcatheter edge-to-edge repair: the EuroSMR risk score. *Eur Heart J* 2024;**45**:922–36. https://doi.org/10.1093/eurheartj/ehad871
83. Adamo M, Rubbio AP, Zaccone G, Pighi M, Massussi M, Tomasoni D, *et al.* Prediction of mortality and heart failure hospitalisations in patients undergoing M-TEER: external validation of the COAPT risk score. *EuroIntervention* 2023;**18**:1408–17. https://doi.org/10.4244/EIJ-D-22-00992
84. Dreyfus J, Audureau E, Bohbot Y, Coisne A, Lavie-Badie Y, Bouchery M, *et al.* TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. *Eur Heart J* 2022;**43**:654–62. https://doi.org/10.1093/eurheartj/ehab679
85. Dreyfus J, Bohbot Y, Coisne A, Lavie-Badie Y, Flagiello M, Bazire B, *et al.* Predictive value of the TRI-SCORE for in-hospital mortality after redo isolated tricuspid valve surgery. *Heart* 2023;**109**:951–8. https://doi.org/10.1136/heartjnl-2022-322167
86. Lantelme P, Aubry M, Peng JC, Riche B, Souteyrand G, Jaafar P, *et al.* Comorbidities may offset expected improved survival after transcatheter aortic valve replacement. *Eur Heart J Open* 2022;**2**:oeac029. https://doi.org/10.1093/ehjopen/oeac029
87. Piankova P, Afilalo J. Prevalence and prognostic implications of frailty in transcatheter aortic valve replacement. *Cardiol Clin* 2020;**38**:75–87. https://doi.org/10.1016/j.ccl.2019.09.011
88. Kim DH, Afilalo J, Shi SM, Popma JJ, Khabbaz KR, Laham RJ, *et al.* Evaluation of changes in functional status in the year after aortic valve replacement. *JAMA Intern Med* 2019;**179**:383–91. https://doi.org/10.1001/jamainternmed.2018.6738
89. Scotti A, Coisne A, Granada JF, Driggin E, Madhavan MV, Zhou Z, *et al.* Impact of malnutrition in patients with heart failure and secondary mitral regurgitation: the COAPT Trial. *J Am Coll Cardiol* 2023;**82**:128–38. https://doi.org/10.1016/j.jacc.2023.04.047
89a. Pagnesi M, Adamo M, Stolz L, Pancaldi E, Kresoja KP, von Stein J, *et al.* Malnutrition and outcomes in patients with tricuspid regurgitation undergoing transcatheter tricuspid valve repair. *Eur J Heart Fail* 2025. https://doi.org/10.1002/ejhf.3623. Epub ahead of print. PMID: 39980251.
90. Sündermann SH, Bäck C, Bischoff-Ferrari HA, Dehbi HM, Szekely A, Völler H, *et al.* Preinterventional frailty assessment in patients scheduled for cardiac surgery or transcatheter aortic valve implantation: a consensus statement of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Preventive Cardiology (EAPC) of the European Society of Cardiology (ESC). *Eur J Cardiothorac Surg* 2023;**64**:ezad181. https://doi.org/10.1093/ejcts/ezad181
91. Richter D, Guasti L, Walker D, Lambrinou E, Lionis C, Abreu A, *et al.* Frailty in cardiology: definition, assessment and clinical implications for general cardiology. A consensus document of the Council for Cardiology Practice (CCP), Association for Acute Cardio Vascular Care (ACVC), Association of Cardiovascular Nursing and Allied Professions (ACNAP), European Association of Preventive Cardiology (EAPC), European Heart Rhythm Association (EHRA), Council on Valvular Heart Diseases (VHD), Council on Hypertension (CHT), Council of Cardio-Oncology (CCO), Working Group (WG) Aorta and Peripheral Vascular Diseases, WG e-Cardiology, WG Thrombosis, of the European Society of Cardiology, European Primary Care Cardiology Society (EPCCS). *Eur J Prev Cardiol* 2022;**29**:216–27. https://doi.org/10.1093/eurjpc/zwaa167
92. Kundi H, Popma JJ, Reynolds MR, Strom JB, Pinto DS, Valsdottir LR, *et al.* Frailty and related outcomes in patients undergoing transcatheter valve therapies in a nationwide cohort. *Eur Heart J* 2019;**40**:2231–9. https://doi.org/10.1093/eurheartj/ehz187
93. Brusco NK, Atkinson V, Woods J, Myles PS, Hodge A, Jones C, *et al.* Implementing PROMS for elective surgery patients: feasibility, response rate, degree of recovery and patient acceptability. *J Patient Rep Outcomes* 2022;**6**:73. https://doi.org/10.1186/s41687-022-00483-6
94. Arnold SV, Spertus JA, Lei Y, Allen KB, Chhatriwalla AK, Leon MB, *et al.* Use of the Kansas City Cardiomyopathy Questionnaire for monitoring health status in patients with aortic stenosis. *Circ Heart Fail* 2013;**6**:61–7. https://doi.org/10.1161/circheartfailure.112.970053
95. Arnold SV, Spertus JA, Gosch K, Dunlay SM, Olds DM, Jones PG, *et al.* Validation of the Kansas City Cardiomyopathy Questionnaire in patients with tricuspid regurgitation. *JAMA Cardiol* 2025;**10**:117–25 https://doi.org/10.1001/jamacardio.2024.4266
96. Clavel MA, Tribouilloy C, Vanoverschelde JL, Pizarro R, Suri RM, Szymanski C, *et al.* Association of B-type natriuretic peptide with survival in patients with degenerative mitral regurgitation. *J Am Coll Cardiol* 2016;**68**:1297–307. https://doi.org/10.1016/j.jacc.2016.06.047
97. Clavel MA, Malouf J, Michelena HI, Suri RM, Jaffe AS, Mahoney DW, *et al.* B-type natriuretic peptide clinical activation in aortic stenosis: impact on long-term survival. *J Am Coll Cardiol* 2014;**63**:2016–25. https://doi.org/10.1016/j.jacc.2014.02.581
98. Zhang B, Xu H, Zhang H, Liu Q, Ye Y, Hao J, *et al.* Prognostic value of N-terminal pro–B-type natriuretic peptide in elderly patients with valvular heart disease. *J Am Coll Cardiol* 2020;**75**:1659–72. https://doi.org/10.1016/j.jacc.2020.02.031
99. Lindman BR, Breyley JG, Schilling JD, Vatterott AM, Zajarias A, Maniar HS, *et al.* Prognostic utility of novel biomarkers of cardiovascular stress in patients with aortic stenosis undergoing valve replacement. *Heart* 2015;**101**:1382–8. https://doi.org/10.1136/heartjnl-2015-307742
100. Lindman BR, Clavel MA, Abu-Alhayja'a R, Cote N, Dagenais F, Novak E, *et al.* Multimarker approach to identify patients with higher mortality and rehospitalization rate after surgical aortic valve replacement for aortic stenosis. *JACC Cardiovasc Interv* 2018;**11**:2172–81. https://doi.org/10.1016/j.jcin.2018.07.039
101. Henri C, Piérard LA, Lancellotti P, Mongeon F-P, Pibarot P, Basmadjian AJ. Exercise testing and stress imaging in valvular heart disease. *Can J Cardiol* 2014;**30**:1012–26. https://doi.org/10.1016/j.cjca.2014.03.013
102. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. *Eur Heart J* 2005;**26**:1309–13. https://doi.org/10.1093/eurheartj/ehi250
103. Redfors B, Pibarot P, Gillam LD, Burkhoff D, Bax JJ, Lindman BR, *et al.* Stress testing in asymptomatic aortic stenosis. *Circulation* 2017;**135**:1956–76. https://doi.org/10.1161/CIRCULATIONAHA.116.025457
104. Lund O, Nielsen TT, Emmertsen K, Fløe C, Rasmussen B, Jensen FT, *et al.* Mortality and worsening of prognostic profile during waiting time for valve replacement in aortic stenosis. *Thorac Cardiovasc Surg* 1996;**44**:289–95. https://doi.org/10.1055/s-2007-1012039
105. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Eur Heart J* 2018;**39**:1144–61. https://doi.org/10.1093/eurheartj/ehw180
106. Hoedemakers S, Pugliese NR, Stassen J, Vanoppen A, Claessens J, Gojevic T, *et al.* mPAP/CO slope and oxygen uptake add prognostic value in aortic stenosis. *Circulation* 2024;**149**:1172–82. https://doi.org/10.1161/CIRCULATIONAHA.123.067130
107. Lancellotti P, Dulgheru R, Go YY, Sugimoto T, Marchetta S, Oury C, *et al.* Stress echocardiography in patients with native valvular heart disease. *Heart* 2018;**104**:807–13. https://doi.org/10.1136/heartjnl-2017-311682
108. Gentry JL III, Phelan D, Desai MY, Griffin BP. The role of stress echocardiography in valvular heart disease: a current appraisal. *Cardiology* 2017;**137**:137–50. https://doi.org/10.1159/000460274
109. Lancellotti P, Magne J. Stress echocardiography in regurgitant valve disease. *Circ Cardiovasc Imaging* 2013;**6**:840–9. https://doi.org/10.1161/CIRCIMAGING.113.000474
110. Lancellotti P, Magne J, Donal E, O'Connor K, Dulgheru R, Rosca M, *et al.* Determinants and prognostic significance of exercise pulmonary hypertension in asymptomatic severe aortic stenosis. *Circulation* 2012;**126**:851–9. https://doi.org/10.1161/CIRCULATIONAHA.111.088427
111. Coisne A, Aghezzaf S, Galli E, Mouton S, Richardson M, Dubois D, *et al.* Prognostic values of exercise echocardiography and cardiopulmonary exercise testing in patients with primary mitral regurgitation. *Eur Heart J Cardiovasc Imaging* 2022;**23**:1552–61. https://doi.org/10.1093/ehjci/jeab231
112. Saeed S, Rajani R, Seifert R, Parkin D, Chambers JB. Exercise testing in patients with asymptomatic moderate or severe aortic stenosis. *Heart* 2018;**104**:1836–42. https://doi.org/10.1136/heartjnl-2018-312939
113. Saeed S, Chambers JB. Exercise testing in aortic stenosis: safety, tolerability, clinical benefits and prognostic value. *J Clin Med* 2022;**11**:4983. https://doi.org/10.3390/jcm11174983
114. Scarsini R, Pesarini G, Zivelonghi C, Piccoli A, Ferrero V, Lunardi M, *et al.* Physiologic evaluation of coronary lesions using instantaneous wave-free ratio (iFR) in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *EuroIntervention* 2018;**13**:1512–9. https://doi.org/10.4244/EIJ-D-17-00542
115. Pesarini G, Scarsini R, Zivelonghi C, Piccoli A, Gambaro A, Gottin L, *et al.* Functional assessment of coronary artery disease in patients undergoing transcatheter aortic valve implantation: influence of pressure overload on the evaluation of lesions severity. *Circ Cardiovasc Interv* 2016;**9**:e004088. https://doi.org/10.1161/circinterventions.116.004088
116. Ahmad Y, Götberg M, Cook C, Howard JP, Malik I, Mikhail G, *et al.* Coronary hemodynamics in patients with severe aortic stenosis and coronary artery disease undergoing transcatheter aortic valve replacement: implications for clinical indices of coronary stenosis severity. *JACC Cardiovasc Interv* 2018;**11**:2019–31. https://doi.org/10.1016/j.jcin.2018.07.019
117. Ardehali A, Segal J, Cheitlin MD. Coronary blood flow reserve in acute aortic regurgitation. *J Am Coll Cardiol* 1995;**25**:1387–92. https://doi.org/10.1016/0735-1097(95)00018-Y
118. Akasaka T, Yoshida K, Hozumi T, Takagi T, Kaji S, Kawamoto T, *et al.* Restricted coronary flow reserve in patients with mitral regurgitation improves after mitral reconstructive surgery. *J Am Coll Cardiol* 1998;**32**:1923–30. https://doi.org/10.1016/S0735-1097(98)00490-2
119. D'Alto M, Dimopoulos K, Coghlan JG, Kovacs G, Rosenkranz S, Naeije R. Right heart catheterization for the diagnosis of pulmonary hypertension: controversies and practical issues. *Heart Fail Clin* 2018;**14**:467–77. https://doi.org/10.1016/j.hfc.2018.03.011
120. Lindman BR, Arnold SV, Bagur R, Clarke L, Coylewright M, Evans F, *et al.* Priorities for patient-centered research in valvular heart disease: a report from the National Heart, Lung, and Blood Institute Working Group. *J Am Heart Assoc* 2020;**9**:e015975. https://doi.org/10.1161/JAHA.119.015975
121. Dharmarajan K, Foster J, Coylewright M, Green P, Vavalle JP, Faheem O, *et al.* The medically managed patient with severe symptomatic aortic stenosis in the TAVR era: patient characteristics, reasons for medical management, and quality of shared decision making at heart valve treatment centers. *PLoS One* 2017;**12**:e0175926. https://doi.org/10.1371/journal.pone.0175926

122. Ren X, Liu K, Zhang H, Meng Y, Li H, Sun X, *et al.* Coronary evaluation before heart valvular surgery by using coronary computed tomographic angiography versus invasive coronary angiography. *J Am Heart Assoc* 2021;**10**:e019531. https://doi.org/10.1161/jaha.120.019531
123. Opolski MP, Staruch AD, Jakubczyk M, Min James K, Gransar H, Staruch M, *et al.* CT angiography for the detection of coronary artery stenoses in patients referred for cardiac valve surgery. *JACC Cardiovasc Imaging* 2016;**9**:1059–70. https://doi.org/10.1016/j.jcmg.2015.09.028
124. Meijboom Willem B, Mollet Nico R, Van Mieghem Carlos AG, Kluin J, Weustink Annick C, Pugliese F, *et al.* Pre-operative computed tomography coronary angiography to detect significant coronary artery disease in patients referred for cardiac valve surgery. *J Am Coll Cardiol* 2006;**48**:1658–65. https://doi.org/10.1016/j.jacc.2006.06.054
125. Gatti M, Gallone G, Poggi V, Bruno F, Serafini A, Depaoli A, *et al.* Diagnostic accuracy of coronary computed tomography angiography for the evaluation of obstructive coronary artery disease in patients referred for transcatheter aortic valve implantation: a systematic review and meta-analysis. *Eur Radiol* 2022;**32**:5189–200. https://doi.org/10.1007/s00330-022-08603-y
126. Diller GP, Gerwing M, Boroni Grazioli S, De-Torres-Alba F, Radke RM, Vormbrock J, *et al.* Utility of coronary computed tomography angiography in patients undergoing transcatheter aortic valve implantation: a meta-analysis and meta-regression based on published data from 7458 patients. *J Clin Med* 2024;**13**:631. https://doi.org/10.3390/jcm13020631
127. Kondoleon NP, Layoun H, Spilias N, Sipko J, Kanaan C, Harb S, *et al.* Effectiveness of pre-TAVR CTA as a screening tool for significant CAD before TAVR. *JACC Cardiovasc Interv* 2023;**16**:1990–2000. https://doi.org/10.1016/j.jcin.2023.05.030
128. Malebranche D, Hoffner MKM, Huber AT, Cicovic A, Spano G, Bernhard B, *et al.* Diagnostic performance of quantitative coronary artery disease assessment using computed tomography in patients with aortic stenosis undergoing transcatheter aortic-valve implantation. *BMC Cardiovasc Disord* 2022;**22**:178. https://doi.org/10.1186/s12872-022-02623-8
129. Chieffo A, Giustino G, Spagnolo P, Panoulas VF, Montorfano M, Latib A, *et al.* Routine screening of coronary artery disease with computed tomographic coronary angiography in place of invasive coronary angiography in patients undergoing transcatheter aortic valve replacement. *Circ Cardiovasc Interv* 2015;**8**:e002025. https://doi.org/10.1161/circinterventions.114.002025
130. Patel KP, Michail M, Treibel TA, Rathod K, Jones DA, Ozkor M, *et al.* Coronary revascularization in patients undergoing aortic valve replacement for severe aortic stenosis. *JACC Cardiovasc Interv* 2021;**14**:2083–96. https://doi.org/10.1016/j.jcin.2021.07.058
131. Miyagawa S, Masai T, Fukuda H, Yamauchi T, Iwakura K, Itoh H, *et al.* Coronary microcirculatory dysfunction in aortic stenosis: myocardial contrast echocardiography study. *Ann Thorac Surg* 2009;**87**:715–9. https://doi.org/10.1016/j.athoracsur.2008.11.078
132. Beach JM, Mihaljevic T, Svensson LG, Rajeswaran J, Marwick T, Griffin B, *et al.* Coronary artery disease and outcomes of aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol* 2013;**61**:837–48. https://doi.org/10.1016/j.jacc.2012.10.049
133. Thalji NM, Suri RM, Daly RC, Greason KL, Dearani JA, Stulak JM, *et al.* The prognostic impact of concomitant coronary artery bypass grafting during aortic valve surgery: implications for revascularization in the transcatheter era. *J Thorac Cardiovasc Surg* 2015;**149**:451–60. https://doi.org/10.1016/j.jtcvs.2014.08.073
134. Lønborg J, Jabbari R, Sabbah M, Veien KT, Niemelä M, Freeman P, *et al.* PCI in patients undergoing transcatheter aortic-valve implantation. *N Engl J Med* 2024;**391**:2189–200. https://doi.org/10.1056/NEJMoa2401513
135. Patterson T, Clayton T, Dodd M, Khawaja Z, Morice MC, Wilson K, *et al.* ACTIVATION (PercutAneous Coronary inTervention prIor to transcatheter aortic VAlve implantaTION): a randomized clinical trial. *JACC Cardiovasc Interv* 2021;**14**:1965–74. https://doi.org/10.1016/j.jcin.2021.06.041
136. Okuno T, Demirel C, Tomii D, Heg D, Häner J, Siontis GCM, *et al.* Long-term risk of unplanned percutaneous coronary intervention after transcatheter aortic valve replacement. *EuroIntervention* 2022;**18**:797–803. https://doi.org/10.4244/eij-d-22-00342
137. Persits I, Layoun H, Kondoleon NP, Spilias N, Badwan O, Sipko J, *et al.* Impact of untreated chronic obstructive coronary artery disease on outcomes after transcatheter aortic valve replacement. *Eur Heart J* 2024;**45**:1890–900. https://doi.org/10.1093/eurheartj/ehae019
138. Ogami T, Kliner DE, Toma C, Sanon S, Smith AJC, Serna-Gallegos D, *et al.* Acute coronary syndrome after transcatheter aortic valve implantation (results from over 40,000 patients). *Am J Cardiol* 2023;**193**:126–32. https://doi.org/10.1016/j.amjcard.2023.02.003
139. Mentias A, Desai MY, Saad M, Horwitz PA, Rossen JD, Panaich S, *et al.* Incidence and outcomes of acute coronary syndrome after transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2020;**13**:938–50. https://doi.org/10.1016/j.jcin.2019.11.027
140. Yassen M, Moustafa A, Venkataramany B, Schodowski E, Royfman R, Eltahawy E. Clinical outcomes of transcatheter aortic valve replacement with and without percutaneous coronary intervention—an updated meta-analysis and systematic review. *Curr Probl Cardiol* 2023;**48**:101980. https://doi.org/10.1016/j.cpcardiol.2023.101980
141. Altibi AM, Ghanem F, Hammad F, Patel J, Song HK, Golwala H, *et al.* Clinical outcomes of revascularization with percutaneous coronary intervention prior to transcatheter aortic valve replacement: a comprehensive meta-analysis. *Curr Probl Cardiol* 2022;**47**:101339. https://doi.org/10.1016/j.cpcardiol.2022.101339
142. Tomii D, Pilgrim T, Borger MA, De Backer O, Lanz J, Reineke D, *et al.* Aortic stenosis and coronary artery disease: decision-making between surgical and transcatheter management. *Circulation* 2024;**150**:2046–69. https://doi.org/10.1161/circulationaha.124.070502
143. Tarantini G, Tang G, Nai Fovino L, Blackman D, Van Mieghem NM, Kim WK, *et al.* Management of coronary artery disease in patients undergoing transcatheter aortic valve implantation. A clinical consensus statement from the European Association of Percutaneous Cardiovascular Interventions in collaboration with the ESC Working Group on Cardiovascular Surgery. *EuroIntervention* 2023;**19**:37–52. https://doi.org/10.4244/eij-d-22-00958
144. Barbanti M, Costa G, Picci A, Criscione E, Reddavid C, Valvo R, *et al.* Coronary cannulation after transcatheter aortic valve replacement: the RE-ACCESS study. *JACC Cardiovasc Interv* 2020;**13**:2542–55. https://doi.org/10.1016/j.jcin.2020.07.006
145. Costa G, Sammartino S, Strazzieri O, Motta S, Frittitta V, Dipietro E, *et al.* Coronary cannulation following TAVR using self-expanding devices with commissural alignment: the RE-ACCESS 2 study. *JACC Cardiovasc Interv* 2024;**17**:727–37. https://doi.org/10.1016/j.jcin.2023.12.015
146. Tang GHL, Amat-Santos IJ, Backer OD, Avvedimento M, Redondo A, Barbanti M, *et al.* Rationale, definitions, techniques, and outcomes of commissural alignment in TAVR. *JACC Cardiovasc Interv* 2022;**15**:1497–518. https://doi.org/10.1016/j.jcin.2022.06.001
147. Campwala SZ, Bansal RC, Wang N, Razzouk A, Pai RG. Factors affecting regression of mitral regurgitation following isolated coronary artery bypass surgery. *Eur J Cardiothorac Surg* 2005;**28**:783–7. https://doi.org/10.1016/j.ejcts.2005.10.010
148. Castleberry AW, Williams JB, Daneshmand MA, Honeycutt E, Shaw LK, Samad Z, *et al.* Surgical revascularization is associated with maximal survival in patients with ischemic mitral regurgitation: a 20-year experience. *Circulation* 2014;**129**:2547–56. https://doi.org/10.1161/CIRCULATIONAHA.113.005223
149. Samad Z, Shaw LK, Phelan M, Ersboll M, Risum N, Al-Khalidi HR, *et al.* Management and outcomes in patients with moderate or severe functional mitral regurgitation and severe left ventricular dysfunction. *Eur Heart J* 2015;**36**:2733–41. https://doi.org/10.1093/eurheartj/ehv343
150. Yousefzai R, Bajaj N, Krishnaswamy A, Goel SS, Agarwal S, Aksoy O, *et al.* Outcomes of patients with ischemic mitral regurgitation undergoing percutaneous coronary intervention. *Am J Cardiol* 2014;**114**:1011–7. https://doi.org/10.1016/j.amjcard.2014.07.012
151. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, *et al.* 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;**44**:3720–826. https://doi.org/10.1093/eurheartj/ehad191
152. Thomas KL, Jackson LR 2nd, Shrader P, Ansell J, Fonarow GC, Gersh B, *et al.* Prevalence, characteristics, and outcomes of valvular heart disease in patients with atrial fibrillation: insights from the ORBIT-AF (outcomes registry for better informed treatment for atrial fibrillation). *J Am Heart Assoc* 2017;**6**:e006475. https://doi.org/10.1161/jaha.117.006475
153. Naser JA, Castrichini M, Ibrahim HH, Scott CG, Lin G, Lee E, *et al.* Secondary tricuspid regurgitation: incidence, types, and outcomes in atrial fibrillation vs. sinus rhythm. *Eur Heart J* 2024;**45**:2878–90. https://doi.org/10.1093/eurheartj/ehae346
154. Naser JA, Pislaru C, Roslan A, Ciobanu AO, Jouni H, Nkomo VT, *et al.* Unfavorable tricuspid annulus dynamics: a novel concept to explain development of tricuspid regurgitation in atrial fibrillation. *J Am Soc Echocardiogr* 2022;**35**:664–6. https://doi.org/10.1016/j.echo.2022.02.009
155. Vinereanu D, Wang A, Mulder H, Lopes RD, Jansky P, Lewis BS, *et al.* Outcomes in anticoagulated patients with atrial fibrillation and with mitral or aortic valve disease. *Heart* 2018;**104**:1292–9. https://doi.org/10.1136/heartjnl-2017-312272
156. Avezum A, Lopes RD, Schulte PJ, Lanas F, Gersh BJ, Hanna M, *et al.* Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Circulation* 2015;**132**:624–32. https://doi.org/10.1161/CIRCULATIONAHA.114.014807
157. Ezekowitz MD, Nagarakanti R, Noack H, Brueckmann M, Litherland C, Jacobs M, *et al.* Comparison of dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY trial (randomized evaluation of long-term anticoagulant therapy). *Circulation* 2016;**134**:589–98. https://doi.org/10.1161/CIRCULATIONAHA.115.020950
158. De Caterina R, Renda G, Carnicelli AP, Nordio F, Trevisan M, Mercuri MF, *et al.* Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. *J Am Coll Cardiol* 2017;**69**:1372–82. https://doi.org/10.1016/j.jacc.2016.12.031
159. Breithardt G, Baumgartner H, Berkowitz SD, Hellkamp AS, Piccini JP, Stevens SR, *et al.* Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. *Eur Heart J* 2014;**35**:3377–85. https://doi.org/10.1093/eurheartj/ehu305
160. Whitlock RP, Belley-Cote EP, Paparella D, Healey JS, Brady K, Sharma M, *et al.* Left atrial appendage occlusion during cardiac surgery to prevent stroke. *N Engl J Med* 2021;**384**:2081–91. https://doi.org/10.1056/NEJMoa2101897

161. Martín Gutiérrez E, Castaño M, Gualis J, Martinez-Comendador JM, Maiorano P, Castillo L, *et al.* Beneficial effect of left atrial appendage closure during cardiac surgery: a meta-analysis of 280 585 patients. *Eur J Cardiothorac Surg* 2020;**57**:252–62. https://doi.org/10.1093/ejcts/ezz289
162. Connolly SJ, Healey JS, Belley-Cote EP, Balasubramanian K, Paparella D, Brady K, *et al.* Oral anticoagulation use and left atrial appendage occlusion in LAAOS III. *Circulation* 2023;**148**:1298–304. https://doi.org/10.1161/CIRCULATIONAHA.122.060315
163. Kapadia SR, Krishnaswamy A, Whisenant B, Potluri S, Iyer V, Aragon J, *et al.* Concomitant left atrial appendage occlusion and transcatheter aortic valve replacement among patients with atrial fibrillation. *Circulation* 2024;**149**:734–43. https://doi.org/10.1161/circulationaha.123.067312
164. Dawwas GK, Dietrich E, Cuker A, Barnes GD, Leonard CE, Lewis JD. Effectiveness and safety of direct oral anticoagulants versus warfarin in patients with valvular atrial fibrillation: a population-based cohort study. *Ann Intern Med* 2021;**174**:910–9. https://doi.org/10.7326/m20-6194
165. Connolly SJ, Karthikeyan G, Ntsekhe M, Haileamlak A, El Sayed A, El Ghamrawy A, *et al.* Rivaroxaban in rheumatic heart disease-associated atrial fibrillation. *N Engl J Med* 2022;**387**:978–88. https://doi.org/10.1056/NEJMoa2209051
166. Rankin JS, Grau-Sepulveda MV, Ad N, Damiano RJ Jr, Gillinov AM, Brennan JM, *et al.* Associations between surgical ablation and operative mortality after mitral valve procedures. *Ann Thorac Surg* 2018;**105**:1790–6. https://doi.org/10.1016/j.athoracsur.2017.12.035
167. Badhwar V, Rankin JS, Ad N, Grau-Sepulveda M, Damiano RJ, Gillinov AM, *et al.* Surgical ablation of atrial fibrillation in the United States: trends and propensity matched outcomes. *Ann Thorac Surg* 2017;**104**:493–500. https://doi.org/10.1016/j.athoracsur.2017.05.016
168. Gillinov AM, Gelijns AC, Parides MK, DeRose JJ Jr, Moskowitz AJ, Voisine P, *et al.* Surgical ablation of atrial fibrillation during mitral-valve surgery. *N Engl J Med* 2015;**372**:1399–409. https://doi.org/10.1056/NEJMoa1500528
169. Huffman MD, Karmali KN, Berendsen MA, Andrei AC, Kruse J, McCarthy PM, *et al.* Concomitant atrial fibrillation surgery for people undergoing cardiac surgery. *Cochrane Database Syst Rev* 2016;**2016**:CD011814. https://doi.org/10.1002/14651858.CD011814.pub2
170. Wang H, Han J, Wang Z, Yin Z, Liu Z, Jin Y, *et al.* A prospective randomized trial of the cut-and-sew Maze procedure in patients undergoing surgery for rheumatic mitral valve disease. *J Thorac Cardiovasc Surg* 2018;**155**:608–17. https://doi.org/10.1016/j.jtcvs.2017.07.084
171. Lawrance CP, Henn MC, Miller JR, Sinn LA, Schuessler RB, Maniar HS, *et al.* A minimally invasive Cox maze IV procedure is as effective as sternotomy while decreasing major morbidity and hospital stay. *J Thorac Cardiovasc Surg* 2014;**148**:955–61; discussion 962–952. https://doi.org/10.1016/j.jtcvs.2014.05.064
172. Cheng DC, Ad N, Martin J, Berglin EE, Chang BC, Doukas G, *et al.* Surgical ablation for atrial fibrillation in cardiac surgery: a meta-analysis and systematic review. *Innovations (Phila)* 2010;**5**:84–96. https://doi.org/10.1097/IMI.0b013e3181d9199b
173. McClure GR, Belley-Cote EP, Jaffer IH, Dvirnik N, An KR, Fortin G, *et al.* Surgical ablation of atrial fibrillation: a systematic review and meta-analysis of randomized controlled trials. *Europace* 2018;**20**:1442–50. https://doi.org/10.1093/europace/eux336
174. Yoo JS, Kim JB, Ro SK, Jung Y, Jung SH, Choo SJ, *et al.* Impact of concomitant surgical atrial fibrillation ablation in patients undergoing aortic valve replacement. *Circ J* 2014;**78**:1364–71. https://doi.org/10.1253/circj.cj-13-1533
175. Malaisrie SC, Lee R, Kruse J, Lapin B, Wang EC, Bonow RO, *et al.* Atrial fibrillation ablation in patients undergoing aortic valve replacement. *J Heart Valve Dis* 2012;**21**:350–7.
176. Gujral DM, Lloyd G, Bhattacharyya S. Radiation-induced valvular heart disease. *Heart* 2016;**102**:269–76. https://doi.org/10.1136/heartjnl-2015-308765
177. Lee C, Hahn RT. Valvular heart disease associated with radiation therapy: a contemporary review. *Struct Heart* 2023;**7**:100104. https://doi.org/10.1016/j.shj.2022.100104
178. Lancellotti P, Nkomo VT, Badano LP, Bergler-Klein J, Bogaert J, Davin L, *et al.* Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr* 2013;**26**:1013–32. https://doi.org/10.1016/j.echo.2013.07.005
179. Wu W, Masri A, Popovic ZB, Smedira NG, Lytle BW, Marwick TH, *et al.* Long-term survival of patients with radiation heart disease undergoing cardiac surgery: a cohort study. *Circulation* 2013;**127**:1476–85. https://doi.org/10.1161/CIRCULATIONAHA.113.001435
180. Donnellan E, Masri A, Johnston DR, Pettersson GB, Rodriguez LL, Popovic ZB, *et al.* Long-term outcomes of patients with mediastinal radiation-associated severe aortic stenosis and subsequent surgical aortic valve replacement: a matched cohort study. *J Am Heart Assoc* 2017;**6**:e005396. https://doi.org/10.1161/JAHA.116.005396
181. Donnellan E, Alashi A, Johnston DR, Gillinov AM, Pettersson GB, Svensson LG, *et al.* Outcomes of patients with mediastinal radiation-associated mitral valve disease undergoing cardiac surgery. *Circulation* 2019;**140**:1288–90. https://doi.org/10.1161/CIRCULATIONAHA.119.040546
182. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, *et al.* 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J* 2022;**43**:4229–361. https://doi.org/10.1093/eurheartj/ehac244
183. Yazdchi F, Hirji SA, Nohria A, Percy E, Harloff M, Malarczyk A, *et al.* Transcatheter compared with surgical aortic valve replacement in patients with previous chest-directed radiation therapy. *JACC CardioOncol* 2021;**3**:397–407. https://doi.org/10.1016/j.jaccao.2021.07.005
184. Zafar MR, Mustafa SF, Miller TW, Alkhawlani T, Sharma UC. Outcomes after transcatheter aortic valve replacement in cancer survivors with prior chest radiation therapy: a systematic review and meta-analysis. *Cardiooncology* 2020;**6**:8. https://doi.org/10.1186/s40959-020-00062-y
185. Ullah W, Thalambedu N, Zahid S, Muhammadzai Hamza Zahid U, Sandhyavenu H, Kumar A, *et al.* Trends and outcomes of TAVI and SAVR in cancer and noncancer patients. *JACC Adv* 2023;**2**:100167. https://doi.org/10.1016/j.jacadv.2022.100167
186. Lind A, Totzeck M, Mahabadi AA, Janosi RA, El Gabry M, Ruhparwar A, *et al.* Impact of cancer in patients undergoing transcatheter aortic valve replacement: a single-center study. *JACC CardioOncol* 2020;**2**:735–43. https://doi.org/10.1016/j.jaccao.2020.11.008
187. Yadgir S, Johnson CO, Aboyans V, Adebayo OM, Adedoyin RA, Afarideh M, *et al.* Global, regional, and national burden of calcific aortic valve and degenerative mitral valve diseases, 1990–2017. *Circulation* 2020;**141**:1670–80. https://doi.org/10.1161/CIRCULATIONAHA.119.043391
188. Rwebembera J, Marangou J, Mwita JC, Mocumbi AO, Mota C, Okello E, *et al.* 2023 World Heart Federation guidelines for the echocardiographic diagnosis of rheumatic heart disease. *Nat Rev Cardiol* 2023;**21**:250–63. https://doi.org/10.1038/s41569-023-00940-9
189. Karki P, Uranw S, Bastola S, Mahato R, Shrestha NR, Sherpa K, *et al.* Effectiveness of systematic echocardiographic screening for rheumatic heart disease in Nepalese schoolchildren: a cluster randomized clinical trial. *JAMA Cardiol* 2021;**6**:420–26. https://doi.org/10.1001/jamacardio.2020.7050
190. Beaton A, Okello E, Rwebembera J, Grobler A, Engelman D, Alepere J, *et al.* Secondary antibiotic prophylaxis for latent rheumatic heart disease. *N Engl J Med* 2022;**386**:230–40. https://doi.org/10.1056/NEJMoa2102074
191. Kumar RK, Antunes MJ, Beaton A, Mirabel M, Nkomo VT, Okello E, *et al.* Contemporary diagnosis and management of rheumatic heart disease: implications for closing the gap: a scientific statement from the American Heart Association. *Circulation* 2020;**142**:e337–57. https://doi.org/10.1161/cir.0000000000000921
192. World Health Organization. *WHO Guideline on the Prevention and Diagnosis of Rheumatic Fever and Rheumatic Heart Disease*. https://www.who.int/publications/i/item/9789240100077 (28 March 2025, date last accessed).
193. Chioncel O, Adamo M, Nikolaou M, Parissis J, Mebazaa A, Yilmaz MB, *et al.* Acute heart failure and valvular heart disease: a scientific statement of the Heart Failure Association, the Association for Acute CardioVascular Care and the European Association of Percutaneous Cardiovascular Interventions of the European Society of Cardiology. *Eur J Heart Fail* 2023;**25**:1025–48. https://doi.org/10.1002/ejhf.2918
194. Lüsebrink E, Lanz H, Kellnar A, Karam N, Kapadia S, Makkar R, *et al.* (December 11, 2024) Management of acute decompensated valvular heart disease. *Eur J Heart Fail*, https://doi.org/10.1002/ejhf.3549
195. Kolte D, Khera S, Vemulapalli S, Dai D, Heo S, Goldsweig AM, *et al.* Outcomes following urgent/emergent transcatheter aortic valve replacement: insights from the STS/ACC TVT registry. *JACC Cardiovasc Interv* 2018;**11**:1175–85. https://doi.org/10.1016/j.jcin.2018.03.002
196. Elbadawi A, Elgendy IY, Mentias A, Saad M, Mohamed AH, Choudhry MW, *et al.* Outcomes of urgent versus nonurgent transcatheter aortic valve replacement. *Catheter Cardiovasc Interv* 2020;**96**:189–95. https://doi.org/10.1002/ccd.28563
197. Masha L, Vemulapalli S, Manandhar P, Balan P, Shah P, Kosinski AS, *et al.* Demographics, procedural characteristics, and clinical outcomes when cardiogenic shock precedes TAVR in the United States. *JACC Cardiovasc Interv* 2020;**13**:1314–25. https://doi.org/10.1016/j.jcin.2020.02.033
198. Goel K, Shah P, Jones BM, Korngold E, Bhardwaj A, Kar B, *et al.* Outcomes of transcatheter aortic valve replacement in patients with cardiogenic shock. *Eur Heart J* 2023;**44**:3181–95. https://doi.org/10.1093/eurheartj/ehad387
199. Buchwald AB, Meyer T, Scholz K, Schorn B, Unterberg C. Efficacy of balloon valvuloplasty in patients with critical aortic stenosis and cardiogenic shock—the role of shock duration. *Clin Cardiol* 2001;**24**:214–8. https://doi.org/10.1002/clc.4960240308
200. Moreno PR, Jang IK, Newell JB, Block PC, Palacios IF. The role of percutaneous aortic balloon valvuloplasty in patients with cardiogenic shock and critical aortic stenosis. *J Am Coll Cardiol* 1994;**23**:1071–5. https://doi.org/10.1016/0735-1097(94)90592-4
201. Llah ST, Sharif S, Ullah S, Sheikh SA, Shah MA, Shafi OM, *et al.* TAVR vs balloon aortic valvotomy for severe aortic stenosis and cardiogenic shock: an insight from the national inpatient sample database. *Cardiovasc Revasc Med* 2023;**55**:1–7. https://doi.org/10.1016/j.carrev.2023.05.006
202. Tang GHL, Estevez-Loureiro R, Yu Y, Prillinger JB, Zaid S, Psotka MA. Survival following edge-to-edge transcatheter mitral valve repair in patients with cardiogenic shock: a nationwide analysis. *J Am Heart Assoc* 2021;**10**:e019882. https://doi.org/10.1161/jaha.120.019882

203. Haberman D, Estevez-Loureiro R, Benito-Gonzalez T, Denti P, Arzamendi D, Adamo M, *et al.* Conservative, surgical, and percutaneous treatment for mitral regurgitation shortly after acute myocardial infarction. *Eur Heart J* 2021;**43**:641–50. https://doi.org/10.1093/eurheartj/ehab496
204. Hill L, Prager Geller T, Baruah R, Beattie JM, Boyne J, de Stoutz N, *et al.* Integration of a palliative approach into heart failure care: a European Society of Cardiology Heart Failure Association position paper. *Eur J Heart Fail* 2020;**22**:2327–39. https://doi.org/10.1002/ejhf.1994
205. Kyriakou M, Middleton N, Ktisti S, Philippou K, Lambrinou E. Supportive care interventions to promote health-related quality of life in patients living with heart failure: a systematic review and meta-analysis. *Heart Lung Circ* 2020;**29**:1633–47. https://doi.org/10.1016/j.hlc.2020.04.019
206. Fendler TJ, Swetz KM, Allen LA. Team-based palliative and end-of-life care for heart failure. *Heart Fail Clin* 2015;**11**:479–98. https://doi.org/10.1016/j.hfc.2015.03.010
207. Brännström M, Boman K. Effects of person-centred and integrated chronic heart failure and palliative home care. PREFER: a randomized controlled study. *Eur J Heart Fail* 2014;**16**:1142–51. https://doi.org/10.1002/ejhf.151
208. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, *et al.* Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol* 1999;**83**:897–902. https://doi.org/10.1016/s0002-9149(98)01064-9
209. Lee JKT, Franzone A, Lanz J, Siontis GCM, Stortecky S, Gräni C, *et al.* Early detection of subclinical myocardial damage in chronic aortic regurgitation and strategies for timely treatment of asymptomatic patients. *Circulation* 2018;**137**:184–96. https://doi.org/10.1161/circulationaha.117.029858
210. Alashi A, Khullar T, Mentias A, Gillinov AM, Roselli EE, Svensson LG, *et al.* Long-term outcomes after aortic valve surgery in patients with asymptomatic chronic aortic regurgitation and preserved LVEF: impact of baseline and follow-up global longitudinal strain. *JACC Cardiovasc Imaging* 2020;**13**:12–21. https://doi.org/10.1016/j.jcmg.2018.12.021
211. deCampos D, Teixeira R, Saleiro C, Botelho A, Gonçalve L. Global longitudinal strain in chronic asymptomatic aortic regurgitation: systematic review. *Echo Res Pract* 2020;**7**:39–48. https://doi.org/10.1530/erp-20-0024
212. Lee SY, Park SJ, Kim EK, Chang SA, Lee SC, Ahn JH, *et al.* Predictive value of exercise stress echocardiography in asymptomatic patients with severe aortic regurgitation and preserved left ventricular systolic function without LV dilatation. *Int J Cardiovasc Imaging* 2019;**35**:1241–7. https://doi.org/10.1007/s10554-019-01565-1
213. Pizarro R, Bazzino OO, Oberti PF, Falconi ML, Arias AM, Krauss JG, *et al.* Prospective validation of the prognostic usefulness of B-type natriuretic peptide in asymptomatic patients with chronic severe aortic regurgitation. *J Am Coll Cardiol* 2011;**58**:1705–14. https://doi.org/10.1016/j.jacc.2011.07.016
214. Kočková R, Línková H, Hlubocká Z, Mědílek K, Tuna M, Vojáček J, *et al.* Multiparametric strategy to predict early disease decompensation in asymptomatic severe aortic regurgitation. *Circ Cardiovasc Imaging* 2022;**15**:e014901. https://doi.org/10.1161/circimaging.122.014901
215. Goldstein SA, Evangelista A, Abbara S, Arai A, Asch FM, Badano LP, *et al.* Multimodality imaging of diseases of the thoracic aorta in adults: from the American Society of Echocardiography and the European Association of Cardiovascular Imaging: endorsed by the Society of Cardiovascular Computed Tomography and Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2015;**28**:119–82. https://doi.org/10.1016/j.echo.2014.11.015
216. Czerny M, Grabenwöger M, Berger T, Aboyans V, Della Corte A, Chen EP, *et al.* EACTS/STS Guidelines for diagnosing and treating acute and chronic syndromes of the aortic organ. *Eur J Cardiothorac Surg* 2024;**65**:ezad426. https://doi.org/10.1093/ejcts/ezad426
217. le Polain de Waroux JB, Pouleur AC, Goffinet C, Vancraeynest D, Van Dyck M, Robert A, *et al.* Functional anatomy of aortic regurgitation: accuracy, prediction of surgical repairability, and outcome implications of transesophageal echocardiography. *Circulation* 2007;**116**:I264–9. https://doi.org/10.1161/CIRCULATIONAHA.106.680074
218. Lansac E, Di Centa I, Raoux F, Al Attar N, Acar C, Joudinaud T, *et al.* A lesional classification to standardize surgical management of aortic insufficiency towards valve repair. *Eur J Cardiothorac Surg* 2008;**33**:872–8; discussion 878–880. https://doi.org/10.1016/j.ejcts.2007.12.033
219. Michelena HI, Della Corte A, Evangelista A, Maleszewski JJ, Edwards WD, Roman MJ, *et al.* International consensus statement on nomenclature and classification of the congenital bicuspid aortic valve and its aortopathy, for clinical, surgical, interventional and research purposes. *Eur J Cardiothorac Surg* 2021;**60**:448–76. https://doi.org/10.1093/ejcts/ezab038
220. Ehrlich T, de Kerchove L, Vojacek J, Boodhwani M, El-Hamamsy I, De Paulis R, *et al.* State-of-the art bicuspid aortic valve repair in 2020. *Prog Cardiovasc Dis* 2020;**63**:457–64. https://doi.org/10.1016/j.pcad.2020.04.010
221. Evangelista Masip A, Galian-Gay L, Guala A, Lopez-Sainz A, Teixido-Turà G, Ruiz Muñoz A, *et al.* Unraveling bicuspid aortic valve enigmas by multimodality imaging: clinical implications. *J Clin Med* 2022;**11**:456. https://doi.org/10.3390/jcm11020456
222. Elder DHJ, Wei L, Szwejkowski BR, Libianto R, Nadir A, Pauriah M, *et al.* The impact of renin-angiotensin-aldosterone system blockade on heart failure outcomes and mortality in patients identified to have aortic regurgitation: a large population cohort study. *J Am Coll Cardiol* 2011;**58**:2084–91. https://doi.org/10.1016/j.jacc.2011.07.043
223. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, *et al.* Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:1169–86. https://doi.org/10.1002/ejhf.1531
224. Chaliki HP, Mohty D, Avierinos JF, Scott CG, Schaff HV, Tajik AJ, *et al.* Outcomes after aortic valve replacement in patients with severe aortic regurgitation and markedly reduced left ventricular function. *Circulation* 2002;**106**:2687–93. https://doi.org/10.1161/01.cir.0000038498.59829.38
225. Kaneko T, Ejiofor JI, Neely RC, McGurk S, Ivkovic V, Stevenson LW, *et al.* Aortic regurgitation with markedly reduced left ventricular function is not a contraindication for aortic valve replacement. *Ann Thorac Surg* 2016;**102**:41–7. https://doi.org/10.1016/j.athoracsur.2015.12.068
226. Tornos P, Sambola A, Permanyer-Miralda G, Evangelista A, Gomez Z, Soler-Soler J. Long-term outcome of surgically treated aortic regurgitation: influence of guideline adherence toward early surgery. *J Am Coll Cardiol* 2006;**47**:1012–7. https://doi.org/10.1016/j.jacc.2005.10.049
227. Klodas E, Enriquez-Sarano M, Tajik AJ, Mullany CJ, Bailey KR, Seward JB. Optimizing timing of surgical correction in patients with severe aortic regurgitation: role of symptoms. *J Am Coll Cardiol* 1997;**30**:746–52. https://doi.org/10.1016/s0735-1097(97)00205-2
228. Dujardin KS, Enriquez-Sarano M, Schaff HV, Bailey KR, Seward JB, Tajik AJ. Mortality and morbidity of aortic regurgitation in clinical practice. A long-term follow-up study. *Circulation* 1999;**99**:1851–7. https://doi.org/10.1161/01.cir.99.14.1851
229. Fiedler AG, Bhambhani V, Laikhter E, Picard MH, Wasfy MM, Tolis G, *et al.* Aortic valve replacement associated with survival in severe regurgitation and low ejection fraction. *Heart* 2018;**104**:835–40. https://doi.org/10.1136/heartjnl-2017-312024
230. Tribouilloy CM, Enriquez-Sarano M, Schaff HV, Orszulak TA, Fett SL, Bailey KR, *et al.* Excess mortality due to coronary artery disease after valve surgery. Secular trends in valvular regurgitation and effect of internal mammary artery bypass. *Circulation* 1998;**98**:II108–15.
231. Forman R, Firth BG, Barnard MS. Prognostic significance of preoperative left ventricular ejection fraction and valve lesion in patients with aortic valve replacement. *Am J Cardiol* 1980;**45**:1120–5. https://doi.org/10.1016/0002-9149(80)90468-3
232. Bonow RO, Lakatos E, Maron BJ, Epstein SE. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. *Circulation* 1991;**84**:1625–35. https://doi.org/10.1161/01.cir.84.4.1625
233. Bhudia SK, McCarthy PM, Kumpati GS, Helou J, Hoercher KJ, Rajeswaran J, *et al.* Improved outcomes after aortic valve surgery for chronic aortic regurgitation with severe left ventricular dysfunction. *J Am Coll Cardiol* 2007;**49**:1465–71. https://doi.org/10.1016/j.jacc.2007.01.026
234. Sambola A, Tornos P, Ferreira-Gonzalez I, Evangelista A. Prognostic value of preoperative indexed end-systolic left ventricle diameter in the outcome after surgery in patients with chronic aortic regurgitation. *Am Heart J* 2008;**155**:1114–20. https://doi.org/10.1016/j.ahj.2007.12.025
235. Yang LT, Michelena HI, Scott CG, Enriquez-Sarano M, Pislaru SV, Schaff HV, *et al.* Outcomes in chronic hemodynamically significant aortic regurgitation and limitations of current guidelines. *J Am Coll Cardiol* 2019;**73**:1741–52. https://doi.org/10.1016/j.jacc.2019.01.024
236. Mentias A, Feng K, Alashi A, Rodriguez LL, Gillinov AM, Johnston DR, *et al.* Long-term outcomes in patients with aortic regurgitation and preserved left ventricular ejection fraction. *J Am Coll Cardiol* 2016;**68**:2144–53. https://doi.org/10.1016/j.jacc.2016.08.045
237. de Meester C, Gerber BL, Vancraeynest D, Pouleur AC, Noirhomme P, Pasquet A, *et al.* Do guideline-based indications result in an outcome penalty for patients with severe aortic regurgitation? *JACC Cardiovasc Imaging* 2019;**12**:2126–38. https://doi.org/10.1016/j.jcmg.2018.11.022
238. Yang LT, Anand V, Zambito EI, Pellikka PA, Scott CG, Thapa P, *et al.* Association of echocardiographic left ventricular end-systolic volume and volume-derived ejection fraction with outcome in asymptomatic chronic aortic regurgitation. *JAMA Cardiol* 2021;**6**:189–98. https://doi.org/10.1001/jamacardio.2020.5268
239. Yang LT, Lee CC, Su CH, Amano M, Nabeshima Y, Kitano T, *et al.* Analysis of left ventricular indexes and mortality among Asian adults with hemodynamically significant chronic aortic regurgitation. *JAMA Netw Open* 2023;**6**:e234632. https://doi.org/10.1001/jamanetworkopen.2023.4632
240. Hashimoto G, Enriquez-Sarano M, Stanberry LI, Oh F, Wang M, Acosta K, *et al.* Association of left ventricular remodeling assessment by cardiac magnetic resonance with outcomes in patients with chronic aortic regurgitation. *JAMA Cardiol* 2022;**7**:924–33. https://doi.org/10.1001/jamacardio.2022.2108
241. Malahfji M, Crudo V, Kaolawanich Y, Nguyen DT, Telmesani A, Saeed M, *et al.* Influence of cardiac remodeling on clinical outcomes in patients with aortic regurgitation. *J Am Coll Cardiol* 2023;**81**:1885–98. https://doi.org/10.1016/j.jacc.2023.03.001
242. Vermes E, Iacuzio L, Levy F, Bohbot Y, Renard C, Gerber B, *et al.* Role of cardiovascular magnetic resonance in native valvular regurgitation: a comprehensive review of

protocols, grading of severity, and prediction of valve surgery. *Front Cardiovasc Med* 2022;**9**:881141. https://doi.org/10.3389/fcvm.2022.881141
243. Flynn CD, Tian DH, Wilson-Smith A, David T, Matalanis G, Misfeld M, *et al.* Systematic review and meta-analysis of surgical outcomes in Marfan patients undergoing aortic root surgery by composite-valve graft or valve sparing root replacement. *Ann Cardiothorac Surg* 2017;**6**:570–81. https://doi.org/10.21037/acs.2017.11.06
244. Chauvette V, Kluin J, de Kerchove L, El Khoury G, Schäfers HJ, Lansac E, *et al.* Outcomes of valve-sparing surgery in heritable aortic disorders: results from the AVIATOR registry. *Eur J Cardiothorac Surg* 2022;**62**:ezac366. https://doi.org/10.1093/ejcts/ezac366
245. Wilson-Smith AR, Wilson-Smith CJ, Strode Smith J, Ng D, Muston BT, Eranki A, *et al.* The outcomes of three decades of the David and Yacoub procedures in bicuspid aortic valve patients—a systematic review and meta-analysis. *Ann Cardiothorac Surg* 2023;**12**:286–94. https://doi.org/10.21037/acs-2023-avs2-19
246. Zuo Y, Tan R, Qin C. Outcomes of valve-sparing aortic root replacement in patients with bicuspid aortic valve and tricuspid aortic valve: a systematic review and meta-analysis. *J Cardiothorac Surg* 2023;**18**:206. https://doi.org/10.1186/s13019-023-02329-8
247. Mastrobuoni S, Govers PJ, Veen KM, Jahanyar J, van Saane S, Segreto A, *et al.* Valve-sparing aortic root replacement using the reimplantation (David) technique: a systematic review and meta-analysis on survival and clinical outcome. *Ann Cardiothorac Surg* 2023;**12**:149–58. https://doi.org/10.21037/acs-2023-avs1-0038
248. Aicher D, Fries R, Rodionycheva S, Schmidt K, Langer F, Schafers HJ. Aortic valve repair leads to a low incidence of valve-related complications. *Eur J Cardiothorac Surg* 2010;**37**:127–32. https://doi.org/10.1016/j.ejcts.2009.06.021
249. de Meester C, Pasquet A, Gerber BL, Vancraeynest D, Noirhomme P, El Khoury G, *et al.* Valve repair improves the outcome of surgery for chronic severe aortic regurgitation: a propensity score analysis. *J Thorac Cardiovasc Surg* 2014;**148**:1913–20. https://doi.org/10.1016/j.jtcvs.2014.02.010
250. Klotz S, Stock S, Sievers HH, Diwoky M, Petersen M, Stierle U, *et al.* Survival and reoperation pattern after 20 years of experience with aortic valve-sparing root replacement in patients with tricuspid and bicuspid valves. *J Thorac Cardiovasc Surg* 2018;**155**:1403–11.e1401. https://doi.org/10.1016/j.jtcvs.2017.12.039
251. Elbatarny M, Tam DY, Edelman JJ, Rocha RV, Chu MWA, Peterson MD, *et al.* Valve-sparing root replacement versus composite valve grafting in aortic root dilation: a meta-analysis. *Ann Thorac Surg* 2020;**110**:296–306. https://doi.org/10.1016/j.athoracsur.2019.11.054
252. Leontyev S, Schamberger L, Davierwala PM, Von Aspern K, Etz C, Lehmann S, *et al.* Early and late results after David vs Bentall procedure: a propensity matched analysis. *Ann Thorac Surg* 2019;**110**:120–6. https://doi.org/10.1016/j.athoracsur.2019.10.020
253. Mastrobuoni S, de Kerchove L, Navarra E, Watremez C, Vancraeynest D, Rubay J, *et al.* Long-term experience with valve-sparing reimplantation technique for the treatment of aortic aneurysm and aortic regurgitation. *J Thorac Cardiovasc Surg* 2019;**158**:14–23. https://doi.org/10.1016/j.jtcvs.2018.10.155
254. Lansac E, Di Centa I, Sleilaty G, Lejeune S, Khelil N, Berrebi A, *et al.* Long-term results of external aortic ring annuloplasty for aortic valve repair. *Eur J Cardiothorac Surg* 2016;**50**:350–60. https://doi.org/10.1093/ejcts/ezw070
255. Lee H, Cho YH, Sung K, Kim WS, Park KH, Jeong DS, *et al.* Clinical outcomes of root reimplantation and Bentall procedure: propensity score matching analysis. *Ann Thorac Surg* 2018;**106**:539–47. https://doi.org/10.1016/j.athoracsur.2018.02.057
256. Norton EL, Patel PM, Levine D, Wei JW, Binongo JN, Leshnower BG, *et al.* Bentall versus valve-sparing aortic root replacement for root pathology with moderate-to-severe aortic insufficiency: a propensity-matched analysis. *Eur J Cardiothorac Surg* 2023;**64**:ezad231. https://doi.org/10.1093/ejcts/ezad231
257. Arabkhani B, Klautz RJM, de Heer F, De Kerchove L, El Khoury G, Lansac E, *et al.* A multicentre, propensity score matched analysis comparing a valve-sparing approach to valve replacement in aortic root aneurysm: insight from the AVIATOR database. *Eur J Cardiothorac Surg* 2023;**63**:ezac514. https://doi.org/10.1093/ejcts/ezac514
258. Levine D, Patel P, Zhao Y, Chung M, Singh S, Childress P, *et al.* Valve-sparing aortic root replacement versus composite valve graft with bioprosthesis in patients under age 50. *J Thorac Cardiovasc Surg* 2023;**168**:992–1002.e1. https://doi.org/10.1016/j.jtcvs.2023.07.016
259. Schneider U, Hofmann C, Schöpe J, Niewald AK, Giebels C, Karliova I, *et al.* Long-term results of differentiated anatomic reconstruction of bicuspid aortic valves. *JAMA Cardiol* 2020;**5**:1366–73. https://doi.org/10.1001/jamacardio.2020.3749
260. Mazine A, Rocha RV, El-Hamamsy I, Ouzounian M, Yanagawa B, Bhatt DL, *et al.* Ross procedure vs mechanical aortic valve replacement in adults: a systematic review and meta-analysis. *JAMA Cardiol* 2018;**3**:978–87. https://doi.org/10.1001/jamacardio.2018.2946
261. Takkenberg JJM, Klieverik LMA, Schoof PH, van Suylen RJ, van Herwerden LA, Zondervan PE, *et al.* The Ross procedure: a systematic review and meta-analysis. *Circulation* 2009;**119**:222–8. https://doi.org/10.1161/CIRCULATIONAHA.107.726349
262. Yokoyama Y, Kuno T, Toyoda N, Fujisaki T, Takagi H, Itagaki S, *et al.* Ross procedure versus mechanical versus bioprosthetic aortic valve replacement: a network meta-analysis. *J Am Heart Assoc* 2023;**12**:e8066. https://doi.org/10.1161/jaha.122.027715
263. El-Hamamsy I, Toyoda N, Itagaki S, Stelzer P, Varghese R, Williams EE, *et al.* Propensity-matched comparison of the Ross procedure and prosthetic aortic valve replacement in adults. *J Am Coll Cardiol* 2022;**79**:805–15. https://doi.org/10.1016/j.jacc.2021.11.057
264. Sawaya FJ, Deutsch MA, Seiffert M, Yoon SH, Codner P, Wickramarachchi U, *et al.* Safety and efficacy of transcatheter aortic valve replacement in the treatment of pure aortic regurgitation in native valves and failing surgical bioprostheses: results from an international registry study. *JACC Cardiovasc Interv* 2017;**10**:1048–56. https://doi.org/10.1016/j.jcin.2017.03.004
265. Yoon SH, Schmidt T, Bleiziffer S, Schofer N, Fiorina C, Munoz-Garcia AJ, *et al.* Transcatheter aortic valve replacement in pure native aortic valve regurgitation. *J Am Coll Cardiol* 2017;**70**:2752–63. https://doi.org/10.1016/j.jacc.2017.10.006
266. Poletti E, De Backer O, Scotti A, Costa G, Bruno F, Fiorina C, *et al.* Transcatheter aortic valve replacement for pure native aortic valve regurgitation: the PANTHEON international project. *JACC Cardiovasc Interv* 2023;**16**:1974–85. https://doi.org/10.1016/j.jcin.2023.07.026
267. Garcia S, Ye J, Webb J, Reardon M, Kleiman N, Goel S, *et al.* Transcatheter treatment of native aortic valve regurgitation: the North American experience with a novel device. *JACC Cardiovasc Interv* 2023;**16**:1953–60. https://doi.org/10.1016/j.jcin.2023.05.018
268. Adam M, Tamm AR, Wienemann H, Unbehaun A, Klein C, Arnold M, *et al.* Transcatheter aortic valve replacement for isolated aortic regurgitation using a new self-expanding TAVR system. *JACC Cardiovasc Interv* 2023;**16**:1965–73. https://doi.org/10.1016/j.jcin.2023.07.038
269. Vahl TP, Thourani VH, Makkar RR, Hamid N, Khalique OK, Daniels D, *et al.* Transcatheter aortic valve implantation in patients with high-risk symptomatic native aortic regurgitation (ALIGN-AR): a prospective, multicentre, single-arm study. *Lancet* 2024;**403**:1451–9. https://doi.org/10.1016/s0140-6736(23)02806-4
270. Borger MA, Preston M, Ivanov J, Fedak PW, Davierwala P, Armstrong S, *et al.* Should the ascending aorta be replaced more frequently in patients with bicuspid aortic valve disease? *J Thorac Cardiovasc Surg* 2004;**128**:677–83. https://doi.org/10.1016/j.jtcvs.2004.07.009
271. Coady MA, Rizzo JA, Hammond GL, Mandapati D, Darr U, Kopf GS, *et al.* What is the appropriate size criterion for resection of thoracic aortic aneurysms? *J Thorac Cardiovasc Surg* 1997;**113**:476–91; discussion 489–491. https://doi.org/10.1016/S0022-5223(97)70360-X
272. Davies RR, Goldstein LJ, Coady MA, Tittle SL, Rizzo JA, Kopf GS, *et al.* Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. *Ann Thorac Surg* 2002;**73**:17–27; discussion 27–18. https://doi.org/10.1016/s0003-4975(01)03236-2
273. Zafar MA, Li Y, Rizzo JA, Charilaou P, Saeyeldin A, Velasquez CA, *et al.* Height alone, rather than body surface area, suffices for risk estimation in ascending aortic aneurysm. *J Thorac Cardiovasc Surg* 2018;**155**:1938–50. https://doi.org/10.1016/j.jtcvs.2017.10.140
274. Popović ZB, Desai MY, Griffin BP. Decision making with imaging in asymptomatic aortic regurgitation. *JACC Cardiovasc Imaging* 2018;**11**:1499–513. https://doi.org/10.1016/j.jcmg.2018.05.027
275. Evangelista A, Sitges M, Jondeau G, Nijveldt R, Pepi M, Cuellar H, *et al.* Multimodality imaging in thoracic aortic diseases: a clinical consensus statement from the European Association of Cardiovascular Imaging and the European Society of Cardiology working group on aorta and peripheral vascular diseases. *Eur Heart J Cardiovasc Imaging* 2023;**24**:e65–85. https://doi.org/10.1093/ehjci/jead024
276. Weisenberg D, Omelchenko A, Shapira Y, Vaturi M, Monakier D, Bental T, *et al.* Mid-term echocardiographic progression of patients with moderate aortic regurgitation: implications for aortic valve surgery. *J Heart Valve Dis* 2013;**22**:192–4.
277. Budts W, Pieles GE, Roos-Hesselink JW, Sanz de la Garza M, D'Ascenzi F, Giannakoulas G, *et al.* Recommendations for participation in competitive sport in adolescent and adult athletes with Congenital Heart Disease (CHD): position statement of the Sports Cardiology & Exercise Section of the European Association of Preventive Cardiology (EAPC), the European Society of Cardiology (ESC) Working Group on Adult Congenital Heart Disease and the Sports Cardiology, Physical Activity and Prevention Working Group of the Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2020;**41**:4191–9. https://doi.org/10.1093/eurheartj/ehaa501
278. Robertson EN, van der Linde D, Sherrah AG, Vallely MP, Wilson M, Bannon PG, *et al.* Familial non-syndromal thoracic aortic aneurysms and dissections—incidence and family screening outcomes. *Int J Cardiol* 2016;**220**:43–51. https://doi.org/10.1016/j.ijcard.2016.06.086
279. Bray JJH, Freer R, Pitcher A, Kharbanda R. Family screening for bicuspid aortic valve and aortic dilatation: a meta-analysis. *Eur Heart J* 2023;**44**:3152–64. https://doi.org/10.1093/eurheartj/ehad320
280. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation* 2005;**111**:920–5. https://doi.org/10.1161/01.Cir.0000155623.48408.C5

281. Verma S, Siu SC. Aortic dilatation in patients with bicuspid aortic valve. *N Engl J Med* 2014;**370**:1920–9. https://doi.org/10.1056/NEJMra1207059
282. Zühlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, *et al.* Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J* 2015;**36**:1115–22a. https://doi.org/10.1093/eurheartj/ehu449
283. Willner N, Prosperi-Porta G, Lau L, Nam Fu AY, Boczar K, Poulin A, *et al.* Aortic stenosis progression: a systematic review and meta-analysis. *JACC Cardiovasc Imaging* 2023;**16**:314–28. https://doi.org/10.1016/j.jcmg.2022.10.009
284. Dweck MR, Loganath K, Bing R, Treibel TA, McCann GP, Newby DE, *et al.* Multi-modality imaging in aortic stenosis: an EACVI clinical consensus document. *Eur Heart J Cardiovasc Imaging* 2023;**24**:1430–43. https://doi.org/10.1093/ehjci/jead153
285. Jaiswal V, Agrawal V, Khulbe Y, Hanif M, Huang H, Hameed M, *et al.* Cardiac amyloidosis and aortic stenosis: a state-of-the-art review. *Eur Heart J Open* 2023;**3**:oead106. https://doi.org/10.1093/ehjopen/oead106
286. Desai MY, Alashi A, Popovic ZB, Wierup P, Griffin BP, Thamilarasan M, *et al.* Outcomes in patients with obstructive hypertrophic cardiomyopathy and concomitant aortic stenosis undergoing surgical myectomy and aortic valve replacement. *J Am Heart Assoc* 2021;**10**:e018435. https://doi.org/10.1161/JAHA.120.018435
287. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, *et al.* Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr* 2017;**30**:372–92. https://doi.org/10.1016/j.echo.2017.02.009
288. Rusinaru D, Bohbot Y, Djelaili F, Delpierre Q, Altes A, Serbout S, *et al.* Normative reference values of cardiac output by pulsed-wave Doppler echocardiography in adults. *Am J Cardiol* 2021;**140**:128–33. https://doi.org/10.1016/j.amjcard.2020.10.046
289. Annabi MS, Touboul E, Dahou A, Burwash IG, Bergler-Klein J, Enriquez-Sarano M, *et al.* Dobutamine stress echocardiography for management of low-flow, low-gradient aortic stenosis. *J Am Coll Cardiol* 2018;**71**:475–85. https://doi.org/10.1016/j.jacc.2017.11.052
290. Clavel MA, Burwash IG, Mundigler G, Dumesnil JG, Baumgartner H, Bergler-Klein J, *et al.* Validation of conventional and simplified methods to calculate projected valve area at normal flow rate in patients with low flow, low gradient aortic stenosis: the multicenter TOPAS (True or Pseudo Severe Aortic Stenosis) study. *J Am Soc Echocardiogr* 2010;**23**:380–6. https://doi.org/10.1016/j.echo.2010.02.002
291. Ash J, Sandhu GS, Arriola-Montenegro J, Agakishiev D, Clavel MA, Pibarot P, *et al.* Performance of computed tomographic angiography-based aortic valve area for assessment of aortic stenosis. *J Am Heart Assoc* 2023;**12**:e029973. https://doi.org/10.1161/jaha.123.029973
292. Guzzetti E, Poulin A, Annabi MS, Zhang B, Kalavrouziotis D, Couture C, *et al.* Transvalvular flow, sex, and survival after valve replacement surgery in patients with severe aortic stenosis. *J Am Coll Cardiol* 2020;**75**:1897–909. https://doi.org/10.1016/j.jacc.2020.02.065
293. Mehrotra P, Jansen K, Flynn AW, Tan TC, Elmariah S, Picard MH, *et al.* Differential left ventricular remodelling and longitudinal function distinguishes low flow from normal-flow preserved ejection fraction low-gradient severe aortic stenosis. *Eur Heart J* 2013;**34**:1906–14. https://doi.org/10.1093/eurheartj/eht094
294. Tribouilloy C, Rusinaru D, Marechaux S, Castel AL, Debry N, Maizel J, *et al.* Low-gradient, low-flow severe aortic stenosis with preserved left ventricular ejection fraction: characteristics, outcome, and implications for surgery. *J Am Coll Cardiol* 2015;**65**:55–66. https://doi.org/10.1016/j.jacc.2014.09.080
295. Jander N, Minners J, Holme I, Gerdts E, Boman K, Brudi P, *et al.* Outcome of patients with low-gradient "severe" aortic stenosis and preserved ejection fraction. *Circulation* 2011;**123**:887–95. https://doi.org/10.1161/CIRCULATIONAHA.110.983510
296. Bohbot Y, Kubala M, Rusinaru D, Maréchaux S, Vanoverschelde JL, Tribouilloy C. Survival and management of patients with discordant high-gradient aortic stenosis: a propensity-matched study. *JACC Cardiovasc Imaging* 2021;**14**:1672–4. https://doi.org/10.1016/j.jcmg.2021.02.010
297. Unger P, Powers A, Le Nezet E, Lacasse-Rioux E, Galloo X, Clavel MA. Prevalence and outcomes of patients with discordant high-gradient aortic stenosis. *J Am Coll Cardiol* 2024;**83**:1109–19. https://doi.org/10.1016/j.jacc.2024.01.025
298. Ito S, Oh JK, Michelena HI, Egbe AC, Connolly HM, Pellikka PA, *et al.* High-gradient aortic stenosis with valve area >1.0 cm^2: the "forgotten" discordant hemodynamic phenotype. *JACC Cardiovasc Imaging* 2025;**18**:166–76. https://doi.org/10.1016/j.jcmg.2024.07.025
299. Ribeiro HB, Lerakis S, Gilard M, Cavalcante JL, Makkar R, Herrmann HC, *et al.* Transcatheter aortic valve replacement in patients with low-flow, low-gradient aortic stenosis: the TOPAS-TAVI registry. *J Am Coll Cardiol* 2018;**71**:1297–308. https://doi.org/10.1016/j.jacc.2018.01.054
300. Clavel MA, Pibarot P, Messika-Zeitoun D, Capoulade R, Malouf J, Aggarval S, *et al.* Impact of aortic valve calcification, as measured by MDCT, on survival in patients with aortic stenosis: results of an international registry study. *J Am Coll Cardiol* 2014;**64**:1202–13. https://doi.org/10.1016/j.jacc.2014.05.066
301. Tastet L, Enriquez-Sarano M, Capoulade R, Malouf J, Araoz PA, Shen M, *et al.* Impact of aortic valve calcification and sex on hemodynamic progression and clinical outcomes in AS. *J Am Coll Cardiol* 2017;**69**:2096–8. https://doi.org/10.1016/j.jacc.2017.02.037
302. Clavel MA, Messika-Zeitoun D, Pibarot P, Aggarwal SR, Malouf J, Araoz PA, *et al.* The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. *J Am Coll Cardiol* 2013;**62**:2329–38. https://doi.org/10.1016/j.jacc.2013.08.1621
303. Pawade T, Clavel MA, Tribouilloy C, Dreyfus J, Mathieu T, Tastet L, *et al.* Computed tomography aortic valve calcium scoring in patients with aortic stenosis. *Circ Cardiovasc Imaging* 2018;**11**:e007146. https://doi.org/10.1161/CIRCIMAGING.117.007146
304. Shen M, Oh JK, Guzzetti E, Singh GK, Pawade T, Tastet L, *et al.* Computed tomography aortic valve calcium scoring in patients with bicuspid aortic valve stenosis. *Struct Heart* 2022;**6**:100027. https://doi.org/10.1016/j.shj.2022.100027
305. Shen M, Tastet L, Capoulade R, Larose É, Bédard É, Arsenault M, *et al.* Effect of age and aortic valve anatomy on calcification and haemodynamic severity of aortic stenosis. *Heart* 2017;**103**:32–9. https://doi.org/10.1136/heartjnl-2016-309665
306. Wanchaitanawong W, Kanjanavanit R, Srisuwan T, Wongcharoen W, Phrommintikul A. Diagnostic role of aortic valve calcium scoring in various etiologies of aortic stenosis. *Sci Rep* 2023;**13**:8019. https://doi.org/10.1038/s41598-023-34118-7
307. Ye Z, Clavel MA, Foley TA, Pibarot P, Enriquez-Sarano M, Michelena HI. Computed tomography calcium scoring in aortic stenosis: bicuspid versus tricuspid morphology. *Heart* 2024;**110**:594–602. https://doi.org/10.1136/heartjnl-2023-323281
308. Maznyczka A, Tomii D, Angellotti D, Baekke PS, Nakase M, Samim D, *et al.* Fibrotic vs calcific aortic stenosis: characteristics and outcomes in patients undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2024;**17**:2969–71. https://doi.org/10.1016/j.jcin.2024.09.041
309. Rusinaru D, Malaquin D, Marechaux S, Debry N, Tribouilloy C. Relation of dimensionless index to long-term outcome in aortic stenosis with preserved LVEF. *JACC Cardiovasc Imaging* 2015;**8**:766–75. https://doi.org/10.1016/j.jcmg.2015.01.023
310. Thellier N, Altes A, Rietz M, Menet A, Layec J, Outteryck F, *et al.* Additive prognostic value of left ventricular dispersion and deformation in patients with severe aortic stenosis. *JACC Cardiovasc Imaging* 2023;**17**:235–45. https://doi.org/10.1016/j.jcmg.2023.09.010
311. Vollema EM, Amanullah MR, Prihadi EA, Ng ACT, van der Bijl P, Sin YK, *et al.* Incremental value of left ventricular global longitudinal strain in a newly proposed staging classification based on cardiac damage in patients with severe aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2020;**21**:1248–58. https://doi.org/10.1093/ehjci/jeaa220
312. Ternacle J, Bodez D, Guellich A, Audureau E, Rappeneau S, Lim P, *et al.* Causes and consequences of longitudinal LV dysfunction assessed by 2D strain echocardiography in cardiac amyloidosis. *JACC Cardiovasc Imaging* 2016;**9**:126–38. https://doi.org/10.1016/j.jcmg.2015.05.014
313. Harada K, Saitoh T, Tanaka J, Shibayama K, Berdejo J, Shiota T. Valvuloarterial impedance, but not aortic stenosis severity, predicts syncope in patients with aortic stenosis. *Circ Cardiovasc Imaging* 2013;**6**:1024–31. https://doi.org/10.1161/circimaging.113.000584
314. Hachicha Z, Dumesnil JG, Pibarot P. Usefulness of the valvuloarterial impedance to predict adverse outcome in asymptomatic aortic stenosis. *J Am Coll Cardiol* 2009;**54**:1003–11. https://doi.org/10.1016/j.jacc.2009.04.079
315. Pibarot P, Salaun E, Dahou A, Avenatti E, Guzzetti E, Annabi MS, *et al.* Echocardiographic results of transcatheter versus surgical aortic valve replacement in low-risk patients: the PARTNER 3 trial. *Circulation* 2020;**141**:1527–37. https://doi.org/10.1161/circulationaha.119.044574
316. Zamorano JL, Badano LP, Bruce C, Chan KL, Goncalves A, Hahn RT, *et al.* EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. *Eur Heart J* 2011;**32**:2189–214. https://doi.org/10.1093/eurheartj/ehr259
317. Bergler-Klein J, Klaar U, Heger M, Rosenhek R, Mundigler G, Gabriel H, *et al.* Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation* 2004;**109**:2302–8. https://doi.org/10.1161/01.CIR.0000126825.50903.18
318. Rafique AM, Biner S, Ray I, Forrester JS, Tolstrup K, Siegel RJ. Meta-analysis of prognostic value of stress testing in patients with asymptomatic severe aortic stenosis. *Am J Cardiol* 2009;**104**:972–7. https://doi.org/10.1016/j.amjcard.2009.05.044
319. Lancellotti P, Lebois F, Simon M, Tombeux C, Chauvel C, Pierard LA. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. *Circulation* 2005;**112**:I377–82. https://doi.org/10.1161/circulationaha.104.523274
320. Le VD, Jensen GV, Kjøller-Hansen L. Prognostic usefulness of cardiopulmonary exercise testing for managing patients with severe aortic stenosis. *Am J Cardiol* 2017;**120**:844–9. https://doi.org/10.1016/j.amjcard.2017.05.047
321. Hoedemakers S, Verwerft J, Reddy YNV, Delvaux R, Stroobants S, Jogani S, *et al.* Cardiac dysfunction rather than aortic valve stenosis severity drives exercise intolerance and adverse hemodynamics. *Eur Heart J Cardiovasc Imaging* 2023;**25**:302–12. https://doi.org/10.1093/ehjci/jead276

322. Bing R, Cavalcante JL, Everett RJ, Clavel MA, Newby DE, Dweck MR. Imaging and impact of myocardial fibrosis in aortic stenosis. *JACC Cardiovasc Imaging* 2019;**12**:283–96. https://doi.org/10.1016/j.jcmg.2018.11.026
323. Everett RJ, Treibel TA, Fukui M, Lee H, Rigolli M, Singh A, *et al.* Extracellular myocardial volume in patients with aortic stenosis. *J Am Coll Cardiol* 2020;**75**:304–16. https://doi.org/10.1016/j.jacc.2019.11.032
324. Thornton GD, Vassiliou VS, Musa TA, Aziminia N, Craig N, Dattani A, *et al.* Myocardial scar and remodelling predict long-term mortality in severe aortic stenosis beyond 10 years. *Eur Heart J* 2024;**45**:2019–22. https://doi.org/10.1093/eurheartj/ehae067
325. Nitsche C, Scully PR, Patel KP, Kammerlander AA, Koschutnik M, Dona C, *et al.* Prevalence and outcomes of concomitant aortic stenosis and cardiac amyloidosis. *J Am Coll Cardiol* 2021;**77**:128–39. https://doi.org/10.1016/j.jacc.2020.11.006
326. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, *et al.* Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. *Circ Heart Fail* 2019;**12**:e006075. https://doi.org/10.1161/circheartfailure.119.006075
327. Cannata F, Chiarito M, Pinto G, Villaschi A, Sanz-Sánchez J, Fazzari F, *et al.* Transcatheter aortic valve replacement in aortic stenosis and cardiac amyloidosis: a systematic review and meta-analysis. *ESC Heart Fail* 2022;**9**:3188–97. https://doi.org/10.1002/ehf2.13876
328. Blanke P, Weir-McCall JR, Achenbach S, Delgado V, Hausleiter J, Jilaihawi H, *et al.* Computed tomography imaging in the context of Transcatheter Aortic Valve Implantation (TAVI)/Transcatheter Aortic Valve Replacement (TAVR). *JACC Cardiovasc Imaging* 2019;**12**:1–24. https://doi.org/10.1016/j.jcmg.2018.12.003
329. Khan JM, Kamioka N, Lisko JC, Perdoncin E, Zhang C, Maini A, *et al.* Coronary obstruction from TAVR in native aortic stenosis: development and validation of multivariate prediction model. *JACC Cardiovasc Interv* 2023;**16**:415–25. https://doi.org/10.1016/j.jcin.2022.11.018
330. Reindl M, Lechner I, Holzknecht M, Tiller C, Fink P, Oberhollenzer F, *et al.* Cardiac magnetic resonance imaging versus computed tomography to guide transcatheter aortic valve replacement: a randomized, open-label, noninferiority trial. *Circulation* 2023;**148**:1220–30. https://doi.org/10.1161/CIRCULATIONAHA.123.066498
331. Gleitman S, Elbaz-Greener G, Ghanim D, Kusniec F, Rabin A, Sudarsky D, *et al.* Similar procedural success of transcutaneous aortic valve replacement with prosthesis valve sizing by either three-dimensional transesophageal echocardiography modeling or computed tomography. *J Am Soc Echocardiogr* 2020;**33**:1149–51. https://doi.org/10.1016/j.echo.2020.05.026
332. Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, *et al.* Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008;**359**:1343–56. https://doi.org/10.1056/NEJMoa0804602
333. Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, Northridge DB, *et al.* A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med* 2005;**352**:2389–97. https://doi.org/10.1056/NEJMoa043876
334. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. *Circulation* 2010;**121**:306–14. https://doi.org/10.1161/CIRCULATIONAHA.109.900027
335. Pawade TA, Doris MK, Bing R, White AC, Forsyth L, Evans E, *et al.* Effect of denosumab or alendronic acid on the progression of aortic stenosis: a double-blind randomized controlled trial. *Circulation* 2021;**143**:2418–27. https://doi.org/10.1161/CIRCULATIONAHA.121.053708
336. Diederichsen ACP, Lindholt JS, Möller S, Øvrehus KA, Auscher S, Lambrechtsen J, *et al.* Vitamin K2 and D in patients with aortic valve calcification: a randomized double-blinded clinical trial. *Circulation* 2022;**145**:1387–97. https://doi.org/10.1161/CIRCULATIONAHA.121.057008
337. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, *et al.* 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J* 2024;**45**:3912–4018. https://doi.org/10.1093/eurheartj/ehae178
338. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, *et al.* 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–337. https://doi.org/10.1093/eurheartj/ehab484
339. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2021;**42**:3599–726. https://doi.org/10.1093/eurheartj/ehab368
340. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2023 Focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2023;**44**:3627–39. https://doi.org/10.1093/eurheartj/ehad195
341. Monin JL, Quéré JP, Monchi M, Petit H, Baleynaud S, Chauvel C, *et al.* Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation* 2003;**108**:319–24. https://doi.org/10.1161/01.CIR.0000079171.43055.46
342. Tribouilloy C, Levy F, Rusinaru D, Gueret P, Petit-Eisenmann H, Baleynaud S, *et al.* Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. *J Am Coll Cardiol* 2009;**53**:1865–73. https://doi.org/10.1016/j.jacc.2009.02.026
343. Quere JP, Monin JL, Levy F, Petit H, Baleynaud S, Chauvel C, *et al.* Influence of preoperative left ventricular contractile reserve on postoperative ejection fraction in low-gradient aortic stenosis. *Circulation* 2006;**113**:1738–44. https://doi.org/10.1161/circulationaha.105.568824
344. Fougeres E, Tribouilloy C, Monchi M, Petit-Eisenmann H, Baleynaud S, Pasquet A, *et al.* Outcomes of pseudo-severe aortic stenosis under conservative treatment. *Eur Heart J* 2012;**33**:2426–33. https://doi.org/10.1093/eurheartj/ehs176
345. Levy F, Laurent M, Monin JL, Maillet JM, Pasquet A, Le Tourneau T, *et al.* Aortic valve replacement for low-flow/low-gradient aortic stenosis operative risk stratification and long-term outcome: a European multicenter study. *J Am Coll Cardiol* 2008;**51**:1466–72. https://doi.org/10.1016/j.jacc.2007.10.067
346. Maes F, Lerakis S, Barbosa Ribeiro H, Gilard M, Cavalcante JL, Makkar R, *et al.* Outcomes from transcatheter aortic valve replacement in patients with low-flow, low-gradient aortic stenosis and left ventricular ejection fraction less than 30%: a substudy from the TOPAS-TAVI registry. *JAMA Cardiol* 2019;**4**:64–70. https://doi.org/10.1001/jamacardio.2018.4320
347. Sato K, Sankaramangalam K, Kandregula K, Bullen JA, Kapadia SR, Krishnaswamy A, *et al.* Contemporary outcomes in low-gradient aortic stenosis patients who underwent dobutamine stress echocardiography. *J Am Heart Assoc* 2019;**8**:e011168. https://doi.org/10.1161/JAHA.118.011168
348. Ueyama H, Kuno T, Harrington M, Takagi H, Krishnamoorthy P, Sharma SK, *et al.* Impact of surgical and transcatheter aortic valve replacement in low-gradient aortic stenosis: a meta-analysis. *JACC Cardiovasc Interv* 2021;**14**:1481–92. https://doi.org/10.1016/j.jcin.2021.04.038
349. Clavel MA, Dumesnil JG, Capoulade R, Mathieu P, Senechal M, Pibarot P. Outcome of patients with aortic stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. *J Am Coll Cardiol* 2012;**60**:1259–67. https://doi.org/10.1016/j.jacc.2011.12.054
350. Chadha G, Bohbot Y, Rusinaru D, Marechaux S, Tribouilloy C. Outcome of normal-flow low-gradient severe aortic stenosis with preserved left ventricular ejection fraction: a propensity-matched study. *J Am Heart Assoc* 2019;**8**:e012301. https://doi.org/10.1161/JAHA.119.012301
351. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, *et al.* Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation* 2005;**111**:3290–5. https://doi.org/10.1161/circulationaha.104.495903
352. Heuvelman HJ, van Geldorp MW, Kappetein AP, Geleijnse ML, Galema TW, Bogers AJ, *et al.* Clinical course of patients diagnosed with severe aortic stenosis in the Rotterdam area: insights from the AVARIJN study. *Neth Heart J* 2012;**20**:487–93. https://doi.org/10.1007/s12471-012-0309-3
353. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, *et al.* Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation* 1997;**95**:2262–70. https://doi.org/10.1161/01.cir.95.9.2262
354. Bohbot Y, de Meester de Ravenstein C, Chadha G, Rusinaru D, Belkhir K, Trouillet C, *et al.* Relationship between left ventricular ejection fraction and mortality in asymptomatic and minimally symptomatic patients with severe aortic stenosis. *JACC Cardiovasc Imaging* 2019;**12**:38–48. https://doi.org/10.1016/j.jcmg.2018.07.029
355. Capoulade R, Le Ven F, Clavel MA, Dumesnil JG, Dahou A, Thebault C, *et al.* Echocardiographic predictors of outcomes in adults with aortic stenosis. *Heart* 2016;**102**:934–42. https://doi.org/10.1136/heartjnl-2015-308742
356. Dahl JS, Eleid MF, Michelena HI, Scott CG, Suri RM, Schaff HV, *et al.* Effect of left ventricular ejection fraction on postoperative outcome in patients with severe aortic stenosis undergoing aortic valve replacement. *Circ Cardiovasc Imaging* 2015;**8**:e002917. https://doi.org/10.1161/CIRCIMAGING.114.002917
357. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, *et al.* Prognostic impact of left ventricular ejection fraction in patients with severe aortic stenosis. *JACC Cardiovasc Interv* 2018;**11**:145–57. https://doi.org/10.1016/j.jcin.2017.08.036
358. Ito S, Miranda WR, Nkomo VT, Connolly HM, Pislaru SV, Greason KL, *et al.* Reduced left ventricular ejection fraction in patients with aortic stenosis. *J Am Coll Cardiol* 2018;**71**:1313–21. https://doi.org/10.1016/j.jacc.2018.01.045
359. De Azevedo D, Boute M, Tribouilloy C, Maréchaux S, Pouleur AC, Bohbot Y, *et al.* Quantifying the survival loss linked to late therapeutic indication in high-gradient severe aortic stenosis. *JACC Adv* 2024;**3**:100830. https://doi.org/10.1016/j.jacadv.2024.100830
360. Généreux P, Schwartz A, Oldemeyer JB, Pibarot P, Cohen DJ, Blanke P, *et al.* Transcatheter aortic-valve replacement for asymptomatic severe aortic stenosis. *N Engl J Med* 2024;**392**:217–27. https://doi.org/10.1056/NEJMoa2405880
361. Loganath K, Craig NJ, Everett RJ, Bing R, Tsampasian V, Molek P, *et al.* Early intervention in patients with asymptomatic severe aortic stenosis and myocardial fibrosis: the

EVOLVED randomized clinical trial. *JAMA* 2024;**333**:213–21. https://doi.org/10.1001/jama.2024.22730
362. Kang DH, Park SJ, Lee SA, Lee S, Kim DH, Kim HK, *et al.* Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med* 2020;**382**:111–9. https://doi.org/10.1056/NEJMoa1912846
363. Banovic M, Putnik S, Penicka M, Doros G, Deja MA, Kockova R, *et al.* Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis: the AVATAR Trial. *Circulation* 2022;**145**:648–58. https://doi.org/10.1161/CIRCULATIONAHA.121.057639
364. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, *et al.* Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med* 2000;**343**:611–7. https://doi.org/10.1056/NEJM200008313430903
365. Nakatsuma K, Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, *et al.* B-type natriuretic peptide in patients with asymptomatic severe aortic stenosis. *Heart* 2019;**105**:384–90. https://doi.org/10.1136/heartjnl-2018-313746
366. Parikh V, Kim C, Siegel RJ, Arsanjani R, Rader F. Natriuretic peptides for risk stratification of patients with valvular aortic stenosis. *Circ Heart Fail* 2015;**8**:373–80. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001649
367. Banovic M, Putnik S, Da Costa BR, Penicka M, Deja MA, Kotrc M, *et al.* Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis: long-term follow-up of the AVATAR trial. *Eur Heart J* 2024;**45**:4526–35. https://doi.org/10.1093/eurheartj/ehae585
368. Généreux P, Banovic M, Kang DH, Giustino G, Prendergast BD, Lindman BR, *et al.* Aortic valve replacement vs clinical surveillance in asymptomatic severe aortic stenosis: a systematic review and meta-analysis. *J Am Coll Cardiol* 2024;**85**:912–22. https://doi.org/10.1016/j.jacc.2024.11.006
369. Smith WTI, Ferguson TBJ, Ryan T, Landolfo CK, Peterson ED. Should coronary artery bypass graft surgery patients with mild or moderate aortic stenosis undergo concomitant aortic valve replacement? A decision analysis approach to the surgical dilemma. *J Am Coll Cardiol* 2004;**44**:1241–7. https://doi.org/10.1016/j.jacc.2004.06.031
370. Jean G, Van Mieghem NM, Gegenava T, van Gils L, Bernard J, Geleijnse ML, *et al.* Moderate aortic stenosis in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol* 2021;**77**:2796–803. https://doi.org/10.1016/j.jacc.2021.04.014
371. Jacquemyn X, Strom JB, Strange G, Playford D, Stewart S, Kutty S, *et al.* Moderate aortic valve stenosis is associated with increased mortality rate and lifetime loss: systematic review and meta-analysis of reconstructed time-to-event data of 409 680 patients. *J Am Heart Assoc* 2024;**13**:e033872. https://doi.org/10.1161/jaha.123.033872
372. Amanullah MR, Pio SM, Ng ACT, Sin KYK, Marsan NA, Ding ZP, *et al.* Prognostic implications of associated cardiac abnormalities detected on echocardiography in patients with moderate aortic stenosis. *JACC Cardiovasc Imaging* 2021;**14**:1724–37. https://doi.org/10.1016/j.jcmg.2021.04.009
373. Van Mieghem NM, Elmariah S, Spitzer E, Pibarot P, Nazif TM, Bax JJ, *et al.* Transcatheter aortic valve replacement in patients with systolic heart failure and moderate aortic stenosis: TAVR UNLOAD. *J Am Coll Cardiol* 2024;**85**:878–90. https://doi.org/10.1016/j.jacc.2024.10.070
374. Graversen PL, Butt JH, Østergaard L, Jensen AD, Warming PE, Strange JE, *et al.* Changes in aortic valve replacement procedures in Denmark from 2008 to 2020. *Heart* 2023;**109**:557–63. https://doi.org/10.1136/heartjnl-2022-321594
375. Johnston DR, Soltesz EG, Vakil N, Rajeswaran J, Roselli EE, Sabik JF 3rd, *et al.* Long-term durability of bioprosthetic aortic valves: implications from 12,569 implants. *Ann Thorac Surg* 2015;**99**:1239–47. https://doi.org/10.1016/j.athoracsur.2014.10.070
376. Goldstone AB, Chiu P, Baiocchi M, Lingala B, Patrick WL, Fischbein MP, *et al.* Mechanical or biologic prostheses for aortic-valve and mitral-valve replacement. *N Engl J Med* 2017;**377**:1847–57. https://doi.org/10.1056/NEJMoa1613792
377. Mazine A, David TE, Stoklosa K, Chung J, Lafreniere-Roula M, Ouzounian M. Improved outcomes following the Ross procedure compared with bioprosthetic aortic valve replacement. *J Am Coll Cardiol* 2022;**79**:993–1005. https://doi.org/10.1016/j.jacc.2021.12.026
378. Notenboom ML, Melina G, Veen KM, De Robertis F, Coppola G, De Siena P, *et al.* Long-term clinical and echocardiographic outcomes following the Ross procedure: a post hoc analysis of a randomized clinical trial. *JAMA Cardiology* 2023;**9**:6–14. https://doi.org/10.1001/jamacardio.2023.4090
379. Alkhouli M, Zack CJ, Sarraf M, Bashir R, Nishimura RA, Eleid MF, *et al.* Morbidity and mortality associated with balloon aortic valvuloplasty: a national perspective. *Circ Cardiovasc Interv* 2017;**10**:e004481. https://doi.org/10.1161/CIRCINTERVENTIONS.116.004481
380. Sharma T, Krishnan AM, Lahoud R, Polomsky M, Dauerman HL. National trends in TAVR and SAVR for patients with severe isolated aortic stenosis. *J Am Coll Cardiol* 2022;**80**:2054–6. https://doi.org/10.1016/j.jacc.2022.08.787
381. Gaede L, Blumenstein J, Eckel C, Grothusen C, Tiyerili V, Sötemann D, *et al.* Transcatheter-based aortic valve replacement vs. isolated surgical aortic valve replacement in 2020. *Clin Res Cardiol* 2022;**111**:924–33. https://doi.org/10.1007/s00392-022-02006-1
382. Nguyen V, Willner N, Eltchaninoff H, Burwash IG, Michel M, Durand E, *et al.* Trends in aortic valve replacement for aortic stenosis: a French nationwide study. *Eur Heart J* 2022;**43**:666–79. https://doi.org/10.1093/eurheartj/ehab773
383. Mori M, Gupta A, Wang Y, Vahl T, Nazif T, Kirtane AJ, *et al.* Trends in transcatheter and surgical aortic valve replacement among older adults in the United States. *J Am Coll Cardiol* 2021;**78**:2161–72. https://doi.org/10.1016/j.jacc.2021.09.855
384. Pilgrim T, Windecker S. Expansion of transcatheter aortic valve implantation: new indications and socio-economic considerations. *Eur Heart J* 2018;**39**:2643–45. https://doi.org/10.1093/eurheartj/ehy228
385. Durko AP, Osnabrugge RL, Van Mieghem NM, Milojevic M, Mylotte D, Nkomo VT, *et al.* Annual number of candidates for transcatheter aortic valve implantation per country: current estimates and future projections. *Eur Heart J* 2018;**39**:2635–42. https://doi.org/10.1093/eurheartj/ehy107
386. Barbato E, Noc M, Baumbach A, Dudek D, Bunc M, Skalidis E, *et al.* Mapping interventional cardiology in Europe: the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Atlas project. *Eur Heart J* 2020;**41**:2579–88. https://doi.org/10.1093/eurheartj/ehaa475
387. Benfari G, Essayagh B, Michelena HI, Ye Z, Inojosa JM, Ribichini FL, *et al.* Severe aortic stenosis: secular trends of incidence and outcomes. *Eur Heart J* 2024;**45**:1877–86. https://doi.org/10.1093/eurheartj/ehad887
388. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, *et al.* Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;**363**:1597–607. https://doi.org/10.1056/NEJMoa1008232
389. Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, *et al.* 5-Year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. *J Am Coll Cardiol* 2018;**72**:2687–96. https://doi.org/10.1016/j.jacc.2018.08.2146
390. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, *et al.* 5-Year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;**385**:2477–84. https://doi.org/10.1016/S0140-6736(15)60308-7
391. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, *et al.* Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;**364**:2187–98. https://doi.org/10.1056/NEJMoa1103510
392. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, *et al.* Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;**374**:1609–20. https://doi.org/10.1056/NEJMoa1514616
393. Toff WD, Hildick-Smith D, Kovac J, Mullen MJ, Wendler O, Mansouri A, *et al.* Effect of transcatheter aortic valve implantation vs surgical aortic valve replacement on all-cause mortality in patients with aortic stenosis: a randomized clinical trial. *JAMA* 2022;**327**:1875–87. https://doi.org/10.1001/jama.2022.5776
394. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, *et al.* Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019;**380**:1706–15. https://doi.org/10.1056/NEJMoa1816885
395. Blankenberg S, Seiffert M, Vonthein R, Baumgartner H, Bleiziffer S, Borger MA, *et al.* Transcatheter or surgical treatment of aortic-valve stenosis. *N Engl J Med* 2024;**390**:1572–83. https://doi.org/10.1056/NEJMoa2400685
396. Makkar RR, Thourani VH, Mack MJ, Kodali SK, Kapadia S, Webb JG, *et al.* Five-year outcomes of transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2020;**382**:799–809. https://doi.org/10.1056/NEJMoa1910555
397. Van Mieghem NM, Deeb GM, Søndergaard L, Grube E, Windecker S, Gada H, *et al.* Self-expanding transcatheter vs surgical aortic valve replacement in intermediate-risk patients: 5-year outcomes of the SURTAVI randomized clinical trial. *JAMA Cardiol* 2022;**7**:1000–8. https://doi.org/10.1001/jamacardio.2022.2695
398. Thyregod HGH, Jørgensen TH, Ihlemann N, Steinbrüchel DA, Nissen H, Kjeldsen BJ, *et al.* Transcatheter or surgical aortic valve implantation: 10-year outcomes of the NOTION trial. *Eur Heart J* 2024;**45**:1116–24. https://doi.org/10.1093/eurheartj/ehae043
399. Ahmad Y, Howard JP, Arnold AD, Madhavan MV, Cook CM, Alu M, *et al.* Transcatheter versus surgical aortic valve replacement in lower-risk and higher-risk patients: a meta-analysis of randomized trials. *Eur Heart J* 2023;**44**:836–52. https://doi.org/10.1093/eurheartj/ehac642
400. Barili F, Brophy JM, Ronco D, Myers PO, Uva MS, Almeida RMS, *et al.* Risk of bias in randomized clinical trials comparing transcatheter and surgical aortic valve replacement: a systematic review and meta-analysis. *JAMA Netw Open* 2023;**6**:e2249321. https://doi.org/10.1001/jamanetworkopen.2022.49321
401. Siontis GCM, Overtchouk P, Cahill TJ, Modine T, Prendergast B, Praz F, *et al.* Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. *Eur Heart J* 2019;**40**:3143–53. https://doi.org/10.1093/eurheartj/ehz275
402. Pibarot P, Hahn RT, Weissman NJ, Arsenault M, Beaudoin J, Bernier M, *et al.* Association of paravalvular regurgitation with 1-year outcomes after transcatheter aortic valve replacement with the SAPIEN 3 valve. *JAMA Cardiol* 2017;**2**:1208–16. https://doi.org/10.1001/jamacardio.2017.3425
403. Kodali S, Pibarot P, Douglas PS, Williams M, Xu K, Thourani V, *et al.* Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. *Eur Heart J* 2015;**36**:449–56. https://doi.org/10.1093/eurheartj/ehu384

404. Lerman TT, Levi A, Kornowski R. Meta-analysis of short- and long-term clinical outcomes of the self-expanding Evolut R/pro valve versus the balloon-expandable Sapien 3 valve for transcatheter aortic valve implantation. *Int J Cardiol* 2023;**371**:100–8. https://doi.org/10.1016/j.ijcard.2022.09.035
405. Faroux L, Chen S, Muntané-Carol G, Regueiro A, Philippon F, Sondergaard L, *et al.* Clinical impact of conduction disturbances in transcatheter aortic valve replacement recipients: a systematic review and meta-analysis. *Eur Heart J* 2020;**41**:2771–81. https://doi.org/10.1093/eurheartj/ehz924
406. Greason KL, Lahr BD, Stulak JM, Cha YM, Rea RF, Schaff HV, *et al.* Long-term mortality effect of early pacemaker implantation after surgical aortic valve replacement. *Ann Thorac Surg* 2017;**104**:1259–64. https://doi.org/10.1016/j.athoracsur.2017.01.083
407. Rück A, Saleh N, Glaser N. Outcomes following permanent pacemaker implantation after transcatheter aortic valve replacement: SWEDEHEART observational study. *JACC Cardiovasc Interv* 2021;**14**:2173–81. https://doi.org/10.1016/j.jcin.2021.07.043
408. Baron SJ, Wang K, House JA, Magnuson EA, Reynolds MR, Makkar R, *et al.* Cost-effectiveness of transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at intermediate risk. *Circulation* 2019;**139**:877–88. https://doi.org/10.1161/CIRCULATIONAHA.118.035236
409. Tam DY, Azizi PM, Fremes SE, Chikwe J, Gaudino M, Wijeysundera HC. The cost-effectiveness of transcatheter aortic valve replacement in low surgical risk patients with severe aortic stenosis. *Eur Heart J Qual Care Clin Outcomes* 2021;**7**:556–63. https://doi.org/10.1093/ehjqcco/qcaa058
410. Pibarot P, Ternacle J, Jaber WA, Salaun E, Dahou A, Asch FM, *et al.* Structural deterioration of transcatheter versus surgical aortic valve bioprostheses in the PARTNER-2 trial. *J Am Coll Cardiol* 2020;**76**:1830–43. https://doi.org/10.1016/j.jacc.2020.08.049
411. Fatima B, Mohananey D, Khan FW, Jobanputra Y, Tummala R, Banerjee K, *et al.* Durability data for bioprosthetic surgical aortic valve: a systematic review. *JAMA Cardiol* 2019;**4**:71–80. https://doi.org/10.1001/jamacardio.2018.4045
412. Kedhi E, Hermanides RS, Dambrink JE, Singh SK, Ten Berg JM, van Ginkel D, *et al.* TransCatheter aortic valve implantation and fractional flow reserve-guided percutaneous coronary intervention versus conventional surgical aortic valve replacement and coronary bypass grafting for treatment of patients with aortic valve stenosis and complex or multivessel coronary disease (TCW): an international, multicentre, prospective, open-label, non-inferiority, randomised controlled trial. *Lancet* 2025;**404**:2593–602. https://doi.org/10.1016/s0140-6736(24)02100-7
413. Martinsson A, Nielsen SJ, Milojevic M, Redfors B, Omerovic E, Tonnessen T, *et al.* Life expectancy after surgical aortic valve replacement. *J Am Coll Cardiol* 2021;**78**:2147–57. https://doi.org/10.1016/j.jacc.2021.09.861
414. Glaser N, Persson M, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Loss in life expectancy after surgical aortic valve replacement: SWEDEHEART study. *J Am Coll Cardiol* 2019;**74**:26–33. https://doi.org/10.1016/j.jacc.2019.04.053
415. Attinger-Toller A, Ferrari E, Tueller D, Templin C, Muller O, Nietlispach F, *et al.* Age-related outcomes after transcatheter aortic valve replacement: insights from the SwissTAVI registry. *JACC Cardiovasc Interv* 2021;**14**:952–60. https://doi.org/10.1016/j.jcin.2021.01.042
416. Jørgensen TH, Thyregod HGH, Savontaus M, Willemen Y, Bleie Ø, Tang M, *et al.* Transcatheter aortic valve implantation in low-risk tricuspid or bicuspid aortic stenosis: the NOTION-2 trial. *Eur Heart J* 2024;**45**:3804–14. https://doi.org/10.1093/eurheartj/ehae331
417. Dahle TG, Kaneko T, McCabe JM. Outcomes following subclavian and axillary artery access for transcatheter aortic valve replacement: Society of the Thoracic Surgeons/American College of Cardiology TVT registry report. *JACC Cardiovasc Interv* 2019;**12**:662–9. https://doi.org/10.1016/j.jcin.2019.01.219
418. Gleason TG, Schindler JT, Hagberg RC, Deeb GM, Adams DH, Conte JV, *et al.* Subclavian/axillary access for self-expanding transcatheter aortic valve replacement renders equivalent outcomes as transfemoral. *Ann Thorac Surg* 2018;**105**:477–83. https://doi.org/10.1016/j.athoracsur.2017.07.017
419. Kirker E, Korngold E, Hodson RW, Jones BM, McKay R, Cheema M, *et al.* Transcarotid versus subclavian/axillary access for transcatheter aortic valve replacement with SAPIEN 3. *Ann Thorac Surg* 2020;**110**:1892–7. https://doi.org/10.1016/j.athoracsur.2020.05.141
420. Debry N, Trimech TR, Gandet T, Vincent F, Hysi I, Delhaye C, *et al.* Transaxillary compared with transcarotid access for TAVR: a propensity-matched comparison from a French multicentre registry. *EuroIntervention* 2020;**16**:842–9. https://doi.org/10.4244/eij-d-20-00117
421. Beurtheret S, Karam N, Resseguier N, Houel R, Modine T, Folliguet T, *et al.* Femoral versus nonfemoral peripheral access for transcatheter aortic valve replacement. *J Am Coll Cardiol* 2019;**74**:2728–39. https://doi.org/10.1016/j.jacc.2019.09.054
422. Greenbaum AB, Babaliaros VC, Chen MY, Stine AM, Rogers T, O'Neill WW, *et al.* Transcaval access and closure for transcatheter aortic valve replacement: a prospective investigation. *J Am Coll Cardiol* 2017;**69**:511–21. https://doi.org/10.1016/j.jacc.2016.10.024
423. Lederman RJ, Babaliaros VC, Lisko JC, Rogers T, Mahoney P, Foerst JR, *et al.* Transcaval versus transaxillary TAVR in contemporary practice: a propensity-weighted analysis. *JACC Cardiovasc Interv* 2022;**15**:965–75. https://doi.org/10.1016/j.jcin.2022.03.014
424. Okuno T, Asami M, Heg D, Lanz J, Praz F, Hagemeyer D, *et al.* Impact of left ventricular outflow tract calcification on procedural outcomes after transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2020;**13**:1789–99. https://doi.org/10.1016/j.jcin.2020.04.015
425. Barbanti M, Yang TH, Rodès Cabau J, Tamburino C, Wood DA, Jilaihawi H, *et al.* Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement. *Circulation* 2013;**128**:244–53. https://doi.org/10.1161/circulationaha.113.002947
426. Kirmani BH, Jones SG, Muir A, Malaisrie SC, Chung DA, Williams RJ, *et al.* Limited versus full sternotomy for aortic valve replacement. *Cochrane Database Syst Rev* 2023;**12**:CD011793. https://doi.org/10.1002/14651858.CD011793.pub3
427. Paparella D, Malvindi PG, Santarpino G, Moscarelli M, Guida P, Fattouch K, *et al.* Full sternotomy and minimal access approaches for surgical aortic valve replacement: a multicentre propensity-matched study. *Eur J Cardiothorac Surg* 2020;**57**:709–16. https://doi.org/10.1093/ejcts/ezz286
428. Vincent F, Ternacle J, Denimal T, Shen M, Redfors B, Delhaye C, *et al.* Transcatheter aortic valve replacement in bicuspid aortic valve stenosis. *Circulation* 2021;**143**:1043–61. https://doi.org/10.1161/CIRCULATIONAHA.120.048048
429. Alperi A, Voisine P, Kalavrouziotis D, Dumont E, Dagenais F, Perron J, *et al.* Aortic valve replacement in low-risk patients with severe aortic stenosis outside randomized trials. *J Am Coll Cardiol* 2021;**77**:111–23. https://doi.org/10.1016/j.jacc.2020.10.056
430. Makkar RR, Yoon SH, Leon MB, Chakravarty T, Rinaldi M, Shah PB, *et al.* Association between transcatheter aortic valve replacement for bicuspid vs tricuspid aortic stenosis and mortality or stroke. *JAMA* 2019;**321**:2193–202. https://doi.org/10.1001/jama.2019.7108
431. Halim SA, Edwards FH, Dai D, Li Z, Mack MJ, Holmes DR, *et al.* Outcomes of transcatheter aortic valve replacement in patients with bicuspid aortic valve disease: a report from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. *Circulation* 2020;**141**:1071–9. https://doi.org/10.1161/CIRCULATIONAHA.119.040333
432. Forrest JK, Kaple RK, Ramlawi B, Gleason TG, Meduri CU, Yakubov SJ, *et al.* Transcatheter aortic valve replacement in bicuspid versus tricuspid aortic valves from the STS/ACC TVT registry. *JACC Cardiovasc Interv* 2020;**13**:1749–59. https://doi.org/10.1016/j.jcin.2020.03.022
433. Montalto C, Sticchi A, Crimi G, Laricchia A, Khokhar AA, Giannini F, *et al.* Outcomes after transcatheter aortic valve replacement in bicuspid versus tricuspid anatomy: a systematic review and meta-analysis. *JACC Cardiovasc Interv* 2021;**14**:2144–55. https://doi.org/10.1016/j.jcin.2021.07.052
434. Yoon SH, Bleiziffer S, De Backer O, Delgado V, Arai T, Ziegelmueller J, *et al.* Outcomes in transcatheter aortic valve replacement for bicuspid versus tricuspid aortic valve stenosis. *J Am Coll Cardiol* 2017;**69**:2579–89. https://doi.org/10.1016/j.jacc.2017.03.017
435. Jilaihawi H, Chen M, Webb J, Himbert D, Ruiz CE, Rodés-Cabau J, *et al.* A bicuspid aortic valve imaging classification for the TAVR era. *JACC Cardiovasc Imaging* 2016;**9**:1145–58. https://doi.org/10.1016/j.jcmg.2015.12.022
436. Sá MPBO, Zhigalov K, Cavalcanti LRP, Escorel Neto AC, Rayol SC, Weymann A, *et al.* Impact of aortic annulus enlargement on the outcomes of aortic valve replacement: a meta-analysis. *Semin Thorac Cardiovasc Surg* 2021;**33**:316–25. https://doi.org/10.1053/j.semtcvs.2020.06.046
437. Head SJ, Reardon MJ, Deeb GM, Van Mieghem NM, Popma JJ, Gleason TG, *et al.* Computed tomography-based indexed aortic annulus size to predict prosthesis-patient mismatch. *Circ Cardiovasc Interv* 2019;**12**:e007396. https://doi.org/10.1161/circinterventions.118.007396
438. Herrmann HC, Mehran R, Blackman DJ, Bailey S, Möllmann H, Abdel-Wahab M, *et al.* Self-expanding or balloon-expandable TAVR in patients with a small aortic annulus. *N Engl J Med* 2024;**390**:1959–71. https://doi.org/10.1056/NEJMoa2312573
439. Yokoyama Y, Kuno T, Zaid S, Kaneko T, Takagi H, Tang GHL, *et al.* Surgical explantation of transcatheter aortic bioprosthesis: a systematic review and meta-analysis. *JTCVS Open* 2021;**8**:207–27. https://doi.org/10.1016/j.xjon.2021.09.023
440. Marin-Cuartas M, Tang GHL, Kiefer P, Fukuhara S, Lange R, Harrington KB, *et al.* Transcatheter heart valve explant with infective endocarditis-associated prosthesis failure and outcomes: the EXPLANT-TAVR international registry. *Eur Heart J* 2024;**45**:2519–32. https://doi.org/10.1093/eurheartj/ehae292
441. Hirji SA, Percy ED, McGurk S, Malarczyk A, Harloff MT, Yazdchi F, *et al.* Incidence, characteristics, predictors, and outcomes of surgical explantation after transcatheter aortic valve replacement. *J Am Coll Cardiol* 2020;**76**:1848–59. https://doi.org/10.1016/j.jacc.2020.08.048
442. Jawitz OK, Gulack BC, Grau-Sepulveda MV, Matsouaka RA, Mack MJ, Holmes DR Jr, *et al.* Reoperation after transcatheter aortic valve replacement: an analysis of the Society of Thoracic Surgeons database. *JACC Cardiovasc Interv* 2020;**13**:1515–25. https://doi.org/10.1016/j.jcin.2020.04.029
443. Hawkins RB, Deeb GM, Sukul D, Patel HJ, Gualano SK, Chetcuti SJ, *et al.* Redo surgical aortic valve replacement after prior transcatheter versus surgical aortic valve replacement. *JACC Cardiovasc Interv* 2023;**16**:942–53. https://doi.org/10.1016/j.jcin.2023.03.015
444. Bapat VN, Zaid S, Fukuhara S, Saha S, Vitanova K, Kiefer P, *et al.* Surgical explantation after TAVR failure: mid-term outcomes from the EXPLANT-TAVR international

registry. *JACC Cardiovasc Interv* 2021;**14**:1978–91. https://doi.org/10.1016/j.jcin.2021.07.015
445. Bowdish ME, Habib RH, Kaneko T, Thourani VH, Badhwar V. Cardiac surgery after transcatheter aortic valve replacement: trends and outcomes. *Ann Thorac Surg* 2024;**118**:155–62. https://doi.org/10.1016/j.athoracsur.2024.03.024
446. Landes U, Webb JG, De Backer O, Sondergaard L, Abdel-Wahab M, Crusius L, *et al.* Repeat transcatheter aortic valve replacement for transcatheter prosthesis dysfunction. *J Am Coll Cardiol* 2020;**75**:1882–93. https://doi.org/10.1016/j.jacc.2020.02.051
447. Tam DY, Dharma C, Rocha RV, Ouzounian M, Wijeysundera HC, Austin PC, *et al.* Transcatheter ViV versus redo surgical AVR for the management of failed biological prosthesis: early and late outcomes in a propensity-matched cohort. *JACC Cardiovasc Interv* 2020;**13**:765–74. https://doi.org/10.1016/j.jcin.2019.10.030
448. Sá MBPO, Van den Eynde J, Simonato M, Cavalcanti LRP, Doulamis IP, Weixler V, *et al.* Valve-in-valve transcatheter aortic valve replacement versus redo surgical aortic valve replacement: an updated meta-analysis. *JACC Cardiovasc Interv* 2021;**14**:211–20. https://doi.org/10.1016/j.jcin.2020.10.020
449. Percy ED, Harloff MT, Hirji S, McGurk S, Yazdchi F, Newell P, *et al.* Nationally representative repeat transcatheter aortic valve replacement outcomes: report from the centers for Medicare and Medicaid services. *JACC Cardiovasc Interv* 2021;**14**:1717–26. https://doi.org/10.1016/j.jcin.2021.06.011
450. Makkar RR, Kapadia S, Chakravarty T, Cubeddu RJ, Kaneko T, Mahoney P, *et al.* Outcomes of repeat transcatheter aortic valve replacement with balloon-expandable valves: a registry study. *Lancet* 2023;**402**:1529–40. https://doi.org/10.1016/s0140-6736(23)01636-7
451. Deharo P, Bisson A, Herbert J, Lacour T, Etienne CS, Porto A, *et al.* Transcatheter valve-in-valve aortic valve replacement as an alternative to surgical re-replacement. *J Am Coll Cardiol* 2020;**76**:489–99. https://doi.org/10.1016/j.jacc.2020.06.010
452. Dismorr M, Glaser N, Franco-Cereceda A, Sartipy U. Effect of prosthesis-patient mismatch on long-term clinical outcomes after bioprosthetic aortic valve replacement. *J Am Coll Cardiol* 2023;**81**:964–75. https://doi.org/10.1016/j.jacc.2022.12.023
453. Head SJ, Mokhles MM, Osnabrugge RL, Pibarot P, Mack MJ, Takkenberg JJ, *et al.* The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. *Eur Heart J* 2012;**33**:1518–29. https://doi.org/10.1093/eurheartj/ehs003
454. Herrmann HC, Daneshvar SA, Fonarow GC, Stebbins A, Vemulapalli S, Desai ND, *et al.* Prosthesis–patient mismatch in patients undergoing transcatheter aortic valve replacement: from the STS/ACC TVT registry. *J Am Coll Cardiol* 2018;**72**:2701–11. https://doi.org/10.1016/j.jacc.2018.09.001
455. Ternacle J, Pibarot P, Herrmann HC, Kodali S, Leipsic J, Blanke P, *et al.* Prosthesis-patient mismatch after aortic valve replacement in the PARTNER 2 trial and registry. *JACC Cardiovasc Interv* 2021;**14**:1466–77. https://doi.org/10.1016/j.jcin.2021.03.069
456. Akodad M, Sellers S, Landes U, Meier D, Tang Gilbert HL, Gada H, *et al.* Balloon-expandable valve for treatment of Evolut valve failure. *JACC Cardiovasc Interv* 2022;**15**:368–77. https://doi.org/10.1016/j.jcin.2021.12.021
457. Ribeiro HB, Rodés-Cabau J, Blanke P, Leipsic J, Kwan Park J, Bapat V, *et al.* Incidence, predictors, and clinical outcomes of coronary obstruction following transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: insights from the VIVID registry. *Eur Heart J* 2018;**39**:687–95. https://doi.org/10.1093/eurheartj/ehx455
458. Ochiai T, Oakley L, Sekhon N, Komatsu I, Flint N, Kaewkes D, *et al.* Risk of coronary obstruction due to sinus sequestration in redo transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2020;**13**:2617–27. https://doi.org/10.1016/j.jcin.2020.09.022
459. Akodad M, Sellers S, Gulsin GS, Tzimas G, Landes U, Chatfield Andrew G, *et al.* Leaflet and neoskirt height in transcatheter heart valves. *JACC Cardiovasc Interv* 2021;**14**:2298–300. https://doi.org/10.1016/j.jcin.2021.07.034
460. Tang GH, Spencer J, Rogers T, Grubb KJ, Gleason P, Gada H, *et al.* Feasibility of coronary access following redo-TAVR for Evolut failure: a computed tomography simulation study. *Circ Cardiovasc Interv* 2023;**16**:e013238. https://doi.org/10.1161/CIRCINTERVENTIONS.123.013238
461. De Backer O, Landes U, Fuchs A, Yoon SH, Mathiassen ON, Sedaghat A, *et al.* Coronary access after TAVR-in-TAVR as evaluated by multidetector computed tomography. *JACC Cardiovasc Interv* 2020;**13**:2528–38. https://doi.org/10.1016/j.jcin.2020.06.016
462. Fukui M, Okada A, Thao KR, Burns MR, Koike H, Wang C, *et al.* Feasibility of redo-transcatheter aortic valve replacement in Sapien valves based on in vivo computed tomography assessment. *Circ Cardiovasc Interv* 2023;**16**:e013497. https://doi.org/10.1161/CIRCINTERVENTIONS.123.013497
463. Chhatriwalla AK, Allen KB, Depta JP, Rodriguez E, Thourani VH, Whisenant BK, *et al.* Outcomes of bioprosthetic valve fracture in patients undergoing valve-in-valve TAVR. *JACC Cardiovasc Interv* 2023;**16**:530–9. https://doi.org/10.1016/j.jcin.2022.12.019
464. Khan JM, Babaliaros VC, Greenbaum AB, Spies C, Daniels D, Depta JP, *et al.* Preventing coronary obstruction during transcatheter aortic valve replacement: results from the multicenter international BASILICA registry. *JACC Cardiovasc Interv* 2021;**14**:941–8. https://doi.org/10.1016/j.jcin.2021.02.035
465. Jørgensen TH, Thyregod HGH, Ihlemann N, Nissen H, Petursson P, Kjeldsen BJ, *et al.* Eight-year outcomes for patients with aortic valve stenosis at low surgical risk randomized to transcatheter vs. surgical aortic valve replacement. *Eur Heart J* 2021;**42**:2912–9. https://doi.org/10.1093/eurheartj/ehab375
466. O'Hair D, Yakubov SJ, Grubb KJ, Oh JK, Ito S, Deeb GM, *et al.* Structural valve deterioration after self-expanding transcatheter or surgical aortic valve implantation in patients at intermediate or high risk. *JAMA Cardiol* 2023;**8**:111–9. https://doi.org/10.1001/jamacardio.2022.4627
467. Rodriguez-Gabella T, Voisine P, Puri R, Pibarot P, Rodés-Cabau J. Aortic bioprosthetic valve durability: incidence, mechanisms, predictors, and management of surgical and transcatheter valve degeneration. *J Am Coll Cardiol* 2017;**70**:1013–28. https://doi.org/10.1016/j.jacc.2017.07.715
468. Pibarot P, Magne J, Leipsic J, Cote N, Blanke P, Thourani VH, *et al.* Imaging for predicting and assessing prosthesis-patient mismatch after aortic valve replacement. *JACC Cardiovasc Imaging* 2019;**12**:149–62. https://doi.org/10.1016/j.jcmg.2018.10.020
469. Freitas-Ferraz Afonso B, Tirado-Conte G, Dagenais F, Ruel M, Al-Atassi T, Dumont E, *et al.* Aortic stenosis and small aortic annulus. *Circulation* 2019;**139**:2685–702. https://doi.org/10.1161/CIRCULATIONAHA.118.038408
470. Tang GHL, Zaid S, Fuchs A, Yamabe T, Yazdchi F, Gupta E, *et al.* Alignment of transcatheter aortic-valve neo-commissures (ALIGN TAVR): impact on final valve orientation and coronary artery overlap. *JACC Cardiovasc Interv* 2020;**13**:1030–42. https://doi.org/10.1016/j.jcin.2020.02.005
471. Kapadia SR, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, *et al.* 5-Year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;**385**:2485–91. https://doi.org/10.1016/S0140-6736(15)60290-2
472. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, *et al.* Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med* 2012;**366**:1696–704. https://doi.org/10.1056/NEJMoa1202277
473. Turina J, Hess O, Sepulcri F, Krayenbuehl HP. Spontaneous course of aortic valve disease. *Eur Heart J* 1987;**8**:471–83. https://doi.org/10.1093/oxfordjournals.eurheartj.a062307
474. Pellikka PA, Nishimura RA, Bailey KR, Tajik AJ. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. *J Am Coll Cardiol* 1990;**15**:1012–7. https://doi.org/10.1016/0735-1097(90)90234-g
475. Mangner N, Stachel G, Woitek F, Haussig S, Schlotter F, Hollriegel R, *et al.* Predictors of mortality and symptomatic outcome of patients with low-flow severe aortic stenosis undergoing transcatheter aortic valve replacement. *J Am Heart Assoc* 2018;**7**:e007977. https://doi.org/10.1161/JAHA.117.007977
476. Eleid MF, Padang R, Al-Hijji M, Pislaru SV, Greason KL, Maltais S, *et al.* Hemodynamic response in low-flow low-gradient aortic stenosis with preserved ejection fraction after TAVR. *J Am Coll Cardiol* 2019;**73**:1731–2. https://doi.org/10.1016/j.jacc.2019.01.034
477. Rusinaru D, Bohbot Y, Ringle A, Marechaux S, Diouf M, Tribouilloy C. Impact of low stroke volume on mortality in patients with severe aortic stenosis and preserved left ventricular ejection fraction. *Eur Heart J* 2018;**39**:1992–9. https://doi.org/10.1093/eurheartj/ehy123
478. Zheng Q, Djohan AH, Lim E, Ding ZP, Ling LH, Shi L, *et al.* Effects of aortic valve replacement on severe aortic stenosis and preserved systolic function: systematic review and network meta-analysis. *Sci Rep* 2017;**7**:5092. https://doi.org/10.1038/s41598-017-05021-9
479. Salaun E, Clavel MA, Hahn RT, Jaber WA, Asch FM, Rodriguez L, *et al.* Outcome of flow-gradient patterns of aortic stenosis after aortic valve replacement: an analysis of the PARTNER 2 trial and registry. *Circ Cardiovasc Interv* 2020;**13**:e008792. https://doi.org/10.1161/CIRCINTERVENTIONS.119.008792
480. Annabi MS, Côté N, Dahou A, Bartko PE, Bergler-Klein J, Burwash IG, *et al.* Comparison of early surgical or transcatheter aortic valve replacement versus conservative management in low-flow, low-gradient aortic stenosis using inverse probability of treatment weighting: results from the TOPAS prospective observational cohort study. *J Am Heart Assoc* 2020;**9**:e017870. https://doi.org/10.1161/jaha.120.017870
481. Mosleh W, Amer MR, Ding Y, Megaly M, Mather JF, McMahon S, *et al.* Benefit of transcatheter aortic valve replacement in patients with paradoxical low-flow low-gradient versus high-gradient aortic stenosis and preserved left ventricular function. *Circ Cardiovasc Interv* 2021;**14**:e010042. https://doi.org/10.1161/circinterventions.120.010042
482. Bohbot Y, Kowalski C, Rusinaru D, Ringle A, Marechaux S, Tribouilloy C. Impact of mean transaortic pressure gradient on long-term outcome in patients with severe aortic stenosis and preserved left ventricular ejection fraction. *J Am Heart Assoc* 2017;**6**:e005850. https://doi.org/10.1161/JAHA.117.005850
483. Costa GNF, Cardoso JFL, Oliveiros B, Gonçalves L, Teixeira R. Early surgical intervention versus conservative management of asymptomatic severe aortic stenosis: a systematic review and meta-analysis. *Heart* 2023;**109**:314–21. https://doi.org/10.1136/heartjnl-2022-321411
484. Bohbot Y, Rusinaru D, Delpierre Q, Marechaux S, Tribouilloy C. Risk stratification of severe aortic stenosis with preserved left ventricular ejection fraction using peak aortic

jet velocity: an outcome study. *Circ Cardiovasc Imaging* 2017;**10**:e006760. https://doi.org/10.1161/CIRCIMAGING.117.006760
485. Adams DH, Popma JJ, Reardon MJ. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;**371**:967–8. https://doi.org/10.1056/NEJMc1408396
486. Thyregod HGH, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, *et al.* Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. *J Am Coll Cardiol* 2015;**65**:2184–94. https://doi.org/10.1016/j.jacc.2015.03.014
487. Thourani VH, Suri RM, Gunter RL, Sheng S, O'Brien SM, Ailawadi G, *et al.* Contemporary real-world outcomes of surgical aortic valve replacement in 141,905 low-risk, intermediate-risk, and high-risk patients. *Ann Thorac Surg* 2015;**99**:55–61. https://doi.org/10.1016/j.athoracsur.2014.06.050
488. Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, *et al.* Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet* 2016;**387**:2218–25. https://doi.org/10.1016/s0140-6736(16)30073-3
489. Coylewright M, Grubb KJ, Arnold SV, Batchelor W, Dhoble A, Horne A Jr, *et al.* Outcomes of balloon-expandable transcatheter aortic valve replacement in younger patients in the low-risk era. *JAMA Cardiol* 2025;**10**:127–35. https://doi.org/10.1001/jamacardio.2024.4237
490. Ullah W, DiMeglio M, Sana MK, Muhammadzai HZU, Kochar K, Zahid S, *et al.* Outcomes after transcatheter aortic valve implantation in patients excluded from clinical trials. *JACC Adv* 2023;**2**:100271. https://doi.org/10.1016/j.jacadv.2023.100271
491. Reents W, Barth S, Griese DP, Winkler S, Babin-Ebell J, Kerber S, *et al.* Transfemoral versus transapical transcatheter aortic valve implantation: a single-centre experience. *Eur J Cardiothorac Surg* 2019;**55**:744–50. https://doi.org/10.1093/ejcts/ezy363
492. Allen KB, Chhatriwalla AK, Cohen D, Saxon J, Hawa Z, Kennedy KF, *et al.* Transcarotid versus transapical and transaortic access for transcatheter aortic valve replacement. *Ann Thorac Surg* 2019;**108**:715–22. https://doi.org/10.1016/j.athoracsur.2019.02.007
493. Overtchouk P, Folliguet T, Pinaud F, Fouquet O, Pernot M, Bonnet G, *et al.* Transcarotid approach for transcatheter aortic valve replacement with the Sapien 3 prosthesis. *JACC Cardiovasc Interv* 2019;**12**:413–9. https://doi.org/10.1016/j.jcin.2018.11.014
494. Kumar N, Khera R, Fonarow GC, Bhatt DL. Comparison of outcomes of transfemoral versus transapical approach for transcatheter aortic valve implantation. *Am J Cardiol* 2018;**122**:1520–6. https://doi.org/10.1016/j.amjcard.2018.07.025
495. van Wely M, van Nieuwkerk AC, Rooijakkers M, van der Wulp K, Gehlmann H, Verkroost M, *et al.* Transaxillary versus transfemoral access as default access in TAVI: a propensity matched analysis. *Int J Cardiol* 2024;**394**:131353. https://doi.org/10.1016/j.ijcard.2023.131353
496. Allen KB, Watson D, Vora AN, Mahoney P, Chhatriwalla AK, Schwartz JG, *et al.* Transcarotid versus transaxillary access for transcatheter aortic valve replacement with a self-expanding valve: a propensity-matched analysis. *JTCVS Tech* 2023;**21**:45–55. https://doi.org/10.1016/j.xjtc.2023.07.019
497. Salihu A, Ferlay C, Kirsch M, Shah PB, Skali H, Fournier S, *et al.* Outcomes and safety of transcaval transcatheter aortic valve replacement: a systematic review and meta-analysis. *Can J Cardiol* 2024;**40**:2054–62. https://doi.org/10.1016/j.cjca.2024.05.016
498. Abraham B, Sous M, Sedhom R, Megaly M, Roman S, Sweeney J, *et al.* Meta-analysis on transcarotid versus transfemoral and other alternate accesses for transcatheter aortic valve implantation. *Am J Cardiol* 2023;**192**:196–205. https://doi.org/10.1016/j.amjcard.2023.01.023
499. Williams MR, Jilaihawi H, Makkar R, O'Neill WW, Guyton R, Malaisrie SC, *et al.* The PARTNER 3 bicuspid registry for transcatheter aortic valve replacement in low-surgical-risk patients. *JACC Cardiovasc Interv* 2022;**15**:523–32. https://doi.org/10.1016/j.jcin.2022.01.279
500. Waksman R, Craig PE, Torguson R, Asch FM, Weissman G, Ruiz D, *et al.* Transcatheter aortic valve replacement in low-risk patients with symptomatic severe bicuspid aortic valve stenosis. *JACC Cardiovasc Interv* 2020;**13**:1019–27. https://doi.org/10.1016/j.jcin.2020.02.008
501. Elbadawi A, Saad M, Elgendy IY, Barssoum K, Omer MA, Soliman A, *et al.* Temporal trends and outcomes of transcatheter versus surgical aortic valve replacement for bicuspid aortic valve stenosis. *JACC Cardiovasc Interv* 2019;**12**:1811–22. https://doi.org/10.1016/j.jcin.2019.06.037
502. Tchétché D, Ziviello F, De Biase C, De Backer O, Hovasse T, Leroux L, *et al.* Transcatheter aortic valve implantation with the Evolut platform for bicuspid aortic valve stenosis: the international, multicentre, prospective BIVOLUTX registry. *EuroIntervention* 2023;**19**:502–11. https://doi.org/10.4244/eij-d-23-00021
503. Yang L-T, Boler A, Medina-Inojosa Jose R, Scott Christopher G, Maurer Matthew J, Eleid Mackram F, *et al.* Aortic stenosis progression, cardiac damage, and survival. *JACC Cardiovasc Imaging* 2021;**14**:1113–26. https://doi.org/10.1016/j.jcmg.2021.01.017
504. Strange G, Stewart S, Celermajer D, Prior D, Scalia GM, Marwick T, *et al.* Poor long-term survival in patients with moderate aortic stenosis. *J Am Coll Cardiol* 2019;**74**:1851–63. https://doi.org/10.1016/j.jacc.2019.08.004
505. Samad Z, Vora AN, Dunning A, Schulte PJ, Shaw LK, Al-Enezi F, *et al.* Aortic valve surgery and survival in patients with moderate or severe aortic stenosis and left ventricular dysfunction. *Eur Heart J* 2016;**37**:2276–86. https://doi.org/10.1093/eurheartj/ehv701
506. Oz A, Tsoumas I, Lampropoulos K, Xanthos T, Karpettas N, Papadopoulos D. Cardiac rehabilitation after TAVI—a systematic review and meta-analysis. *Curr Probl Cardiol* 2023;**48**:101531. https://doi.org/10.1016/j.cpcardiol.2022.101531
507. Monteagudo Ruiz JM, Galderisi M, Buonauro A, Badano L, Aruta P, Swaans MJ, *et al.* Overview of mitral regurgitation in Europe: results from the European Registry of mitral regurgitation (EuMiClip). *Eur Heart J Cardiovasc Imaging* 2018;**19**:503–7. https://doi.org/10.1093/ehjci/jey011
508. Nalliah CJ, Mahajan R, Elliott AD, Haqqani H, Lau DH, Vohra JK, *et al.* Mitral valve prolapse and sudden cardiac death: a systematic review and meta-analysis. *Heart* 2019;**105**:144–51. https://doi.org/10.1136/heartjnl-2017-312932
509. Van der Bijl P, Stassen J, Haugaa KH, Essayagh B, Basso C, Thiene G, *et al.* Mitral annular disjunction in the context of mitral valve prolapse: identifying the at-risk patient. *JACC Cardiovasc Imaging* 2024;**17**:1229–45. https://doi.org/10.1016/j.jcmg.2024.03.006
510. Antoine C, Benfari G, Michelena HI, Maalouf JF, Nkomo VT, Thapa P, *et al.* Clinical outcome of degenerative mitral regurgitation. *Circulation* 2018;**138**:1317–26. https://doi.org/10.1161/CIRCULATIONAHA.117.033173
511. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, Detaint D, Capps M, Nkomo V, *et al.* Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med* 2005;**352**:875–83. https://doi.org/10.1056/NEJMoa041451
512. O'Gara PT, Grayburn PA, Badhwar V, Afonso LC, Carroll JD, Elmariah S, *et al.* 2017 ACC Expert Consensus Decision Pathway on the management of mitral regurgitation: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol* 2017;**70**:2421–49. https://doi.org/10.1016/j.jacc.2017.09.019
513. Dziadzko V, Dziadzko M, Medina-Inojosa JR, Benfari G, Michelena HI, Crestanello JA, *et al.* Causes and mechanisms of isolated mitral regurgitation in the community: clinical context and outcome. *Eur Heart J* 2019;**40**:2194–202. https://doi.org/10.1093/eurheartj/ehz314
514. Samad Z, Shaw LK, Phelan M, Glower DD, Ersboll M, Toptine JH, *et al.* Long-term outcomes of mitral regurgitation by type and severity. *Am Heart J* 2018;**203**:39–48. https://doi.org/10.1016/j.ahj.2018.05.001
515. Bakkestrom R, Banke A, Christensen NL, Pecini R, Irmukhamedov A, Andersen M, *et al.* Hemodynamic characteristics in significant symptomatic and asymptomatic primary mitral valve regurgitation at rest and during exercise. *Circ Cardiovasc Imaging* 2018;**11**:e007171. https://doi.org/10.1161/CIRCIMAGING.117.007171
516. Utsunomiya H, Hidaka T, Susawa H, Izumi K, Harada Y, Kinoshita M, *et al.* Exercise-stress echocardiography and effort intolerance in asymptomatic/minimally symptomatic patients with degenerative mitral regurgitation combined invasive-noninvasive hemodynamic monitoring. *Circ Cardiovasc Imaging* 2018;**11**:e007282. https://doi.org/10.1161/CIRCIMAGING.117.007282
517. Butcher SC, Essayagh B, Steyerberg EW, Benfari G, Antoine C, Grigioni F, *et al.* Factors influencing post-surgical survival in degenerative mitral regurgitation. *Eur Heart J* 2023;**44**:871–81. https://doi.org/10.1093/eurheartj/ehad004
518. Grigioni F, Clavel MA, Vanoverschelde JL, Tribouilloy C, Pizarro R, Huebner M, *et al.* The MIDA mortality risk score: development and external validation of a prognostic model for early and late death in degenerative mitral regurgitation. *Eur Heart J* 2018;**39**:1281–91. https://doi.org/10.1093/eurheartj/ehx465
519. Del Rio-Pertuz G, Nugent K, Argueta-Sosa E. Right heart catheterization in clinical practice: a review of basic physiology and important issues relevant to interpretation. *Am J Cardiovasc Dis* 2023;**13**:122–37.
520. Mentias A, Patel K, Patel H, Gillinov AM, Rodriguez LL, Svensson LG, *et al.* Prognostic utility of brain natriuretic peptide in asymptomatic patients with significant mitral regurgitation and preserved left ventricular ejection fraction. *Am J Cardiol* 2016;**117**:258–63. https://doi.org/10.1016/j.amjcard.2015.10.040
521. Cawley PJ, Hamilton-Craig C, Owens DS, Krieger EV, Strugnell WE, Mitsumori L, *et al.* Prospective comparison of valve regurgitation quantitation by cardiac magnetic resonance imaging and transthoracic echocardiography. *Circ Cardiovasc Imaging* 2013;**6**:48–57. https://doi.org/10.1161/CIRCIMAGING.112.975623
522. Penicka M, Vecera J, Mirica DC, Kotrc M, Kockova R, Van Camp G. Prognostic implications of magnetic resonance-derived quantification in asymptomatic patients with organic mitral regurgitation: comparison with Doppler echocardiography-derived integrative approach. *Circulation* 2018;**137**:1349–60. https://doi.org/10.1161/CIRCULATIONAHA.117.029332
523. Naoum C, Blanke P, Cavalcante JL, Leipsic J. Cardiac computed tomography and magnetic resonance imaging in the evaluation of mitral and tricuspid valve disease. *Circ Cardiovasc Imaging* 2017;**10**:e005331. https://doi.org/10.1161/CIRCIMAGING.116.005331
524. Kitkungvan D, Nabi F, Kim RJ, Bonow RO, Khan MA, Xu J, *et al.* Myocardial fibrosis in patients with primary mitral regurgitation with and without prolapse. *J Am Coll Cardiol* 2018;**72**:823–34. https://doi.org/10.1016/j.jacc.2018.06.048

525. Garg P, Swift AJ, Zhong L, Carlhall CJ, Ebbers T, Westenberg J, *et al.* Assessment of mitral valve regurgitation by cardiovascular magnetic resonance imaging. *Nat Rev Cardiol* 2020;**17**:298–312. https://doi.org/10.1038/s41569-019-0305-z
526. Feuchtner GM, Alkadhi H, Karlo C, Sarwar A, Meier A, Dichtl W, *et al.* Cardiac CT angiography for the diagnosis of mitral valve prolapse: comparison with echocardiography. *Radiology* 2010;**254**:374–83. https://doi.org/10.1148/radiol.2541090393
527. Gollmann-Tepeköylü C, Nägele F, Höfer D, Holfeld J, Hirsch J, Oezpeker CU, *et al.* A qualitative improvement program for minimally invasive mitral surgery: technical advancements ameliorate outcome and operative times. *Interdiscip Cardiovasc Thorac Surg* 2023;**36**:ivad030. https://doi.org/10.1093/icvts/ivad030
528. Tarzia P, Ciampi P, Lanza O, Canali E, Canestrelli S, Calò L. Multi-modality imaging for pre-procedural planning of transcatheter mitral valve interventions. *Eur Heart J Suppl* 2023;**25**:C205–11. https://doi.org/10.1093/eurheartjsupp/suad021
529. Eleid MF, Foley TA, Said SM, Pislaru SV, Rihal CS. Severe mitral annular calcification: multimodality imaging for therapeutic strategies and interventions. *JACC Cardiovasc Imaging* 2016;**9**:1318–37. https://doi.org/10.1016/j.jcmg.2016.09.001
530. Roselli C, Yu M, Nauffal V, Georges A, Yang Q, Love K, *et al.* Genome-wide association study reveals novel genetic loci: a new polygenic risk score for mitral valve prolapse. *Eur Heart J* 2022;**43**:1668–80. https://doi.org/10.1093/eurheartj/ehac049
531. Badhwar V, Chikwe J, Gillinov AM, Vemulapalli S, O'Gara PT, Mehaffey JH, *et al.* Risk of surgical mitral valve repair for primary mitral regurgitation. *J Am Coll Cardiol* 2023;**81**:636–48. https://doi.org/10.1016/j.jacc.2022.11.017
532. Lazam S, Vanoverschelde JL, Tribouilloy C, Grigioni F, Suri RM, Avierinos JF, *et al.* Twenty-year outcome after mitral repair versus replacement for severe degenerative mitral regurgitation: analysis of a large, prospective, multicenter, international registry. *Circulation* 2017;**135**:410–22. https://doi.org/10.1161/CIRCULATIONAHA.116.023340
533. David TE, David CM, Tsang W, Lafreniere-Roula M, Manlhiot C. Long-term results of mitral valve repair for regurgitation due to leaflet prolapse. *J Am Coll Cardiol* 2019;**74**:1044–53. https://doi.org/10.1016/j.jacc.2019.06.052
534. Deja MA, Malinowski M, Widenka K, Stozynski N, Bartus K, Kapelak B, *et al.* Comparison of repair vs replacement in calcific and rheumatic mitral disease. *Ann Thorac Surg* 2023;**116**:954–61. https://doi.org/10.1016/j.athoracsur.2023.04.048
535. Brescia AA, Watt TMF, Murray SL, Rosenbloom LM, Kleeman KC, Allgeyer H, *et al.* Rheumatic mitral valve repair or replacement in the valve-in-valve era. *J Thorac Cardiovasc Surg* 2022;**163**:591–602.e1. https://doi.org/10.1016/j.jtcvs.2020.04.118
536. Chen SW, Chen CY, Chien-Chia Wu V, Chou AH, Cheng YT, Chang SH, *et al.* Mitral valve repair versus replacement in patients with rheumatic heart disease. *J Thorac Cardiovasc Surg* 2022;**164**:57–67.e11. https://doi.org/10.1016/j.jtcvs.2020.07.117
537. Yun KL, Sintek CF, Miller DC, Pfeffer TA, Kochamba GS, Khonsari S, *et al.* Randomized trial comparing partial versus complete chordal-sparing mitral valve replacement: effects on left ventricular volume and function. *J Thorac Cardiovasc Surg* 2002;**123**:707–14. https://doi.org/10.1067/mtc.2002.121048
538. Makkar RR, Chikwe J, Chakravarty T, Chen Q, O'Gara PT, Gillinov M, *et al.* Transcatheter mitral valve repair for degenerative mitral regurgitation. *JAMA* 2023;**329**:1778–88. https://doi.org/10.1001/jama.2023.7089
539. von Bardeleben RS, Mahoney P, Morse MA, Price MJ, Denti P, Maisano F, *et al.* 1-Year outcomes with fourth-generation mitral valve transcatheter edge-to-edge repair from the EXPAND G4 study. *JACC Cardiovasc Interv* 2023;**16**:2600–10. https://doi.org/10.1016/j.jcin.2023.09.029
540. Zahr F, Smith RL, Gillam LD, Chadderdon S, Makkar R, von Bardeleben RS, *et al.* One-year outcomes from the CLASP IID randomized trial for degenerative mitral regurgitation. *JACC Cardiovasc Interv* 2023;**15**:2803–16. https://doi.org/10.1016/j.jcin.2023.10.002
541. Kaneko T, Hirji S, Zaid S, Lange R, Kempfert J, Conradi L, *et al.* Mitral valve surgery after transcatheter edge-to-edge repair: mid-term outcomes from the CUTTING-EDGE international registry. *JACC Cardiovasc Interv* 2021;**14**:2010–21. https://doi.org/10.1016/j.jcin.2021.07.029
542. Wild MG, Kreidel F, Hell MM, Praz F, Mach M, Adam M, *et al.* Transapical mitral valve implantation for treatment of symptomatic mitral valve disease: a real-world multicentre experience. *Eur J Heart Fail* 2022;**24**:899–907. https://doi.org/10.1002/ejhf.2434
543. Ludwig S, Perrin N, Coisne A, Ben Ali W, Weimann J, Duncan A, *et al.* Clinical outcomes of transcatheter mitral valve replacement: two-year results of the CHOICE-MI Registry. *EuroIntervention* 2023;**19**:512–25. https://doi.org/10.4244/EIJ-D-22-01037
544. Suri RM, Vanoverschelde JL, Grigioni F, Schaff HV, Tribouilloy C, Avierinos J-F, *et al.* Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. *JAMA* 2013;**310**:609–16. https://doi.org/10.1001/jama.2013.8643
545. Tribouilloy C, Grigioni F, Avierinos JF, Barbieri A, Rusinaru D, Szymanski C, *et al.* Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets a long-term follow-up multicenter study. *J Am Coll Cardiol* 2009;**54**:1961–68. https://doi.org/10.1016/j.jacc.2009.06.047
546. Tribouilloy C, Rusinaru D, Grigioni F, Avierinos JF, Vanoverschelde JL, Benfari G, *et al.* Indexing left ventricular end-systolic dimension to body size: association with mortality in patients with degenerative mitral regurgitation. *Eur J Heart Fail* 2024;**26**:2563–9. https://doi.org/10.1002/ejhf.3393
547. Essayagh B, Antoine C, Benfari G, Messika-Zeitoun D, Michelena H, Le Tourneau T, *et al.* Prognostic implications of left atrial enlargement in degenerative mitral regurgitation. *J Am Coll Cardiol* 2019;**74**:858–70. https://doi.org/10.1016/j.jacc.2019.06.032
548. Abadie BQ, Cremer PC, Vakamudi S, Gillinov AM, Svensson LG, Cho L. Sex-specific prognosis of left ventricular size and function following repair of degenerative mitral regurgitation. *J Am Coll Cardiol* 2024;**83**:303–12. https://doi.org/10.1016/j.jacc.2023.10.033
549. Dejgaard LA, Skjolsvik ET, Lie OH, Ribe M, Stokke MK, Hegbom F, *et al.* The mitral annulus disjunction arrhythmic syndrome. *J Am Coll Cardiol* 2018;**72**:1600–9. https://doi.org/10.1016/j.jacc.2018.07.070
550. Essayagh B, Sabbag A, Antoine C, Benfari G, Batista R, Yang LT, *et al.* The mitral annular disjunction of mitral valve prolapse: presentation and outcome. *JACC Cardiovasc Imaging* 2021;**14**:2073–87. https://doi.org/10.1016/j.jcmg.2021.04.029
551. Essayagh B, Sabbag A, Antoine C, Benfari G, Yang LT, Maalouf J, *et al.* Presentation and outcome of arrhythmic mitral valve prolapse. *J Am Coll Cardiol* 2020;**76**:637–49. https://doi.org/10.1016/j.jacc.2020.06.029
552. Weiner MM, Boateng P, Pandis D, Miller MA, Adams DH. Impact of mitral valve repair on the Pickelhaube sign. *Eur Heart J* 2019;**40**:2267. https://doi.org/10.1093/eurheartj/ehy458
553. Pandis D, David N, Ei-Eshmawi A, Miller MA, Boateng P, Costa AC, *et al.* Noncomplex ventricular arrhythmia associated with greater freedom from recurrent ectopy at 1 year after mitral repair surgery. *JTCVS Open* 2024;**19**:94–113. https://doi.org/10.1016/j.xjon.2024.04.005
554. Bonaros N, Hoefer D, Oezpeker C, Gollmann-Tepekoylu C, Holfeld J, Dumfarth J, *et al.* Predictors of safety and success in minimally invasive surgery for degenerative mitral disease. *Eur J Cardiothorac Surg* 2022;**61**:637–44. https://doi.org/10.1093/ejcts/ezab438
555. Berretta P, Kempfert J, Van Praet F, Salvador L, Lamelas J, Nguyen TC, *et al.* Risk-related clinical outcomes after minimally invasive mitral valve surgery: insights from the Mini-Mitral International Registry. *Eur J Cardiothorac Surg* 2023;**63**:ezad090. https://doi.org/10.1093/ejcts/ezad090
556. Pfannmueller B, Misfeld M, Verevkin A, Garbade J, Holzhey DM, Davierwala P, *et al.* Loop neochord versus leaflet resection techniques for minimally invasive mitral valve repair: long-term results. *Eur J Cardiothorac Surg* 2021;**59**:180–6. https://doi.org/10.1093/ejcts/ezaa255
557. Akowuah EF, Maier RH, Hancock HC, Kharatikoopaei E, Vale L, Fernandez-Garcia C, *et al.* Minithoracotomy vs conventional sternotomy for mitral valve repair: a randomized clinical trial. *JAMA* 2023;**329**:1957–66. https://doi.org/10.1001/jama.2023.7800
558. Olsthoorn JR, Heuts S, Houterman S, Maessen JG, Sardari Nia P. Effect of minimally invasive mitral valve surgery compared to sternotomy on short- and long-term outcomes: a retrospective multicentre interventional cohort study based on Netherlands Heart Registration. *Eur J Cardiothorac Surg* 2022;**61**:1099–106. https://doi.org/10.1093/ejcts/ezab507
559. Lang M, Vitanova K, Voss B, Feirer N, Rheude T, Krane M, *et al.* Beyond the 10-year horizon: mitral valve repair solely with chordal replacement and annuloplasty. *Ann Thorac Surg* 2023;**115**:96–103. https://doi.org/10.1016/j.athoracsur.2022.05.036
560. Newell P, Percy E, Hirji S, Harloff M, McGurk S, Malarczyk A, *et al.* Outcomes of mitral valve repair among high- and low-volume surgeons within a high-volume institution. *Ann Thorac Surg* 2023;**115**:412–19. https://doi.org/10.1016/j.athoracsur.2022.05.057
561. Rosenhek R, Rader F, Klaar U, Gabriel H, Krejc M, Kalbeck D, *et al.* Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation* 2006;**113**:2238–44. https://doi.org/10.1161/CIRCULATIONAHA.105.599175
562. Grigioni F, Benfari G, Vanoverschelde JL, Tribouilloy C, Avierinos JF, Bursi F, *et al.* Long-term implications of atrial fibrillation in patients with degenerative mitral regurgitation. *J Am Coll Cardiol* 2019;**73**:264–74. https://doi.org/10.1016/j.jacc.2018.10.067
563. Ratwatte S, Strange G, Playford D, Stewart S, Celermajer DS. Prevalence of pulmonary hypertension in mitral regurgitation and its influence on outcomes. *Open Heart* 2023;**10**:e002268. https://doi.org/10.1136/openhrt-2023-002268
564. Essayagh B, Antoine C, Benfari G, Maalouf J, Michelena HI, Crestanello JA, *et al.* Functional tricuspid regurgitation of degenerative mitral valve disease: a crucial determinant of survival. *Eur Heart J* 2020;**41**:1918–29. https://doi.org/10.1093/eurheartj/ehaa192
565. Essayagh B, Benfari G, Antoine C, Grigioni F, Le Tourneau T, Roussel JC, *et al.* The MIDA-Q mortality risk score: a quantitative prognostic tool for the mitral valve prolapse spectrum. *Circulation* 2023;**147**:798–811. https://doi.org/10.1161/CIRCULATIONAHA.122.062612
566. Benfari G, Sorajja P, Pedrazzini G, Taramasso M, Gavazzoni M, Biasco L, *et al.* Association of transcatheter edge-to-edge repair with improved survival in older patients with severe, symptomatic degenerative mitral regurgitation. *Eur Heart J* 2022;**43**:1626–35. https://doi.org/10.1093/eurheartj/ehab910
567. Speziale G, Nasso G, Esposito G, Conte M, Greco E, Fattouch K, *et al.* Results of mitral valve repair for Barlow disease (bileaflet prolapse) via right minithoracotomy versus conventional median sternotomy: a randomized trial. *J Thorac Cardiovasc Surg* 2011;**142**:77–83. https://doi.org/10.1016/j.jtcvs.2010.08.033

568. Zilberszac R, Heinze G, Binder T, Laufer G, Gabriel H, Rosenhek R. Long-term outcome of active surveillance in severe but asymptomatic primary mitral regurgitation. *JACC Cardiovasc Imaging* 2018;**11**:1213–21. https://doi.org/10.1016/j.jcmg.2018.05.014
569. Sengupta A, Yazdchi F, Alexis SL, Percy E, Premkumar A, Hirji S, *et al.* Reoperative mitral surgery versus transcatheter mitral valve replacement: a systematic review. *J Am Heart Assoc* 2021;**10**:e019854. https://doi.org/10.1161/JAHA.120.019854
570. Simonato M, Whisenant B, Ribeiro HB, Webb JG, Kornowski R, Guerrero M, *et al.* Transcatheter mitral valve replacement after surgical repair or replacement: comprehensive midterm evaluation of valve-in-valve and valve-in-ring implantation from the VIVID registry. *Circulation* 2021;**143**:104–16. https://doi.org/10.1161/CIRCULATIONAHA.120.049088
571. Sugiura A, Kavsur R, Spieker M, Iliadis C, Goto T, Öztürk C, *et al.* Recurrent mitral regurgitation after MitraClip: predictive factors, morphology, and clinical implication. *Circ Cardiovasc Interv* 2022;**15**:e010895. https://doi.org/10.1161/CIRCINTERVENTIONS.121.010895
572. Zaid S, Avvedimento M, Vitanova K, Akansel S, Bhadra OD, Ascione G, *et al.* Impact of mitral regurgitation etiology on mitral surgery after transcatheter edge-to-edge repair: from the CUTTING-EDGE registry. *JACC Cardiovasc Interv* 2023;**16**:1176–88. https://doi.org/10.1016/j.jcin.2023.02.029
573. Bartkowiak J, Reineke D, Tomii D, Brugger N, Pilgrim T, Terbeck S, *et al.* Electrosurgical laceration and stabilization of MitraClip followed by valve implantation for iatrogenic mitral stenosis. *JACC Cardiovasc Interv* 2022;**15**:110–12. https://doi.org/10.1016/j.jcin.2021.10.011
574. Lisko JC, Greenbaum AB, Guyton RA, Kamioka N, Grubb KJ, Gleason PT, *et al.* Electrosurgical detachment of MitraClips from the anterior mitral leaflet prior to transcatheter mitral valve implantation. *JACC Cardiovasc Interv* 2020;**13**:2361–70. https://doi.org/10.1016/j.jcin.2020.06.047
575. Huang AL, Dal-Bianco JP, Levine RA, Hung JW. Secondary mitral regurgitation: cardiac remodeling, diagnosis, and management. *Struct Heart* 2022;**7**:100129. https://doi.org/10.1016/j.shj.2022.100129
576. Bartko PE, Heitzinger G, Pavo N, Heitzinger M, Spinka G, Prausmüller S, *et al.* Burden, treatment use, and outcome of secondary mitral regurgitation across the spectrum of heart failure: observational cohort study. *BMJ* 2021;**373**:n1421. https://doi.org/10.1136/bmj.n1421
577. Deferm S, Bertrand PB, Verbrugge FH, Verhaert D, Rega F, Thomas JD, *et al.* Atrial functional mitral regurgitation: *JACC* review topic of the week. *J Am Coll Cardiol* 2019;**73**:2465–76. https://doi.org/10.1016/j.jacc.2019.02.061
578. Mori M, Zogg CK, Amabile A, Fereydooni S, Agarwal R, Weininger G, *et al.* Impact of secondary mitral regurgitation on survival in atrial and ventricular dysfunction. *PLoS One* 2022;**17**:e0277385. https://doi.org/10.1371/journal.pone.0277385
579. Moonen A, Ng MKC, Playford D, Strange G, Scalia GM, Celermajer DS. Atrial functional mitral regurgitation: prevalence, characteristics and outcomes from the National Echo Database of Australia. *Open Heart* 2023;**10**:e002180. https://doi.org/10.1136/openhrt-2022-002180
580. Okamoto C, Okada A, Nishimura K, Moriuchi K, Amano M, Takahama H, *et al.* Prognostic comparison of atrial and ventricular functional mitral regurgitation. *Open Heart* 2021;**8**:e001574. https://doi.org/10.1136/openhrt-2021-001574
581. Farhan S, Silbiger JJ, Halperin JL, Zhang L, Dukkipati SR, Vogel B, *et al.* Pathophysiology, echocardiographic diagnosis, and treatment of atrial functional mitral regurgitation: *JACC* state-of-the-art review. *J Am Coll Cardiol* 2022;**80**:2314–30. https://doi.org/10.1016/j.jacc.2022.09.046
582. Naser JA, Michelena HI, Lin G, Scott CG, Lee E, Kennedy AM, *et al.* Incidence, risk factors, and outcomes of atrial functional mitral regurgitation in patients with atrial fibrillation or sinus rhythm. *Eur Heart J Cardiovasc Imaging* 2023;**24**:1450–7. https://doi.org/10.1093/ehjci/jead199
583. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, *et al.* Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;**379**:2307–18. https://doi.org/10.1056/NEJMoa1806640
584. Stone GW, Abraham WT, Lindenfeld J, Kar S, Grayburn PA, Lim DS, *et al.* Five-year follow-up after transcatheter repair of secondary mitral regurgitation. *N Engl J Med* 2023;**388**:2037–48. https://doi.org/10.1056/NEJMoa2300213
585. Cavalcante JL, Kusunose K, Obuchowski NA, Jellis C, Griffin BP, Flamm SD, *et al.* Prognostic impact of ischemic mitral regurgitation severity and myocardial infarct quantification by cardiovascular magnetic resonance. *JACC Cardiovasc Imaging* 2020;**13**:1489–501. https://doi.org/10.1016/j.jcmg.2019.11.008
586. Kim K, Kitai T, Kaji S, Pak M, Toyota T, Sasaki Y, *et al.* Outcomes and predictors of cardiac events in medically treated patients with atrial functional mitral regurgitation. *Int J Cardiol* 2020;**316**:195–202. https://doi.org/10.1016/j.ijcard.2020.06.042
587. Mesi O, Gad MM, Crane AD, Ramchand J, Puri R, Layoun H, *et al.* Severe atrial functional mitral regurgitation: clinical and echocardiographic characteristics, management and outcomes. *JACC Cardiovasc Imaging* 2021;**14**:797–808. https://doi.org/10.1016/j.jcmg.2021.02.008
588. Doldi P, Stolz L, Orban M, Karam N, Praz F, Kalbacher D, *et al.* Transcatheter mitral valve repair in patients with atrial functional mitral regurgitation. *JACC Cardiovasc Imaging* 2022;**15**:1843–51. https://doi.org/10.1016/j.jcmg.2022.05.009
589. Masiero G, Montonati C, Rubbio AP, Adamo M, Grasso C, Denti P, *et al.* Impact of transcatheter edge-to-edge mitral valve repair on atrial functional mitral regurgitation from the GIOTTO registry. *Am J Cardiol* 2024;**211**:219–27. https://doi.org/10.1016/j.amjcard.2023.11.007
590. Yoon SH, Makar M, Kar S, Chakravarty T, Oakley L, Sekhon N, *et al.* Outcomes after transcatheter edge-to-edge mitral valve repair according to mitral regurgitation etiology and cardiac remodeling. *JACC Cardiovasc Interv* 2022;**15**:1711–22. https://doi.org/10.1016/j.jcin.2022.07.004
591. Chen QF, Zhou X, Katsouras CS, Ni C, Zhu H, Liu C, *et al.* Atrial and ventricular functional mitral regurgitation: prevalence, characteristics, outcomes, and disease progression. *Eur Heart J Cardiovasc Imaging* 2024;**26**:545–56. https://doi.org/10.1093/ehjci/jeae309
592. von Stein P, von Stein J, Hohmann C, Wienemann H, Guthoff H, Körber MI, *et al.* Atrial functional mitral regurgitation subtypes undergoing transcatheter edge-to-edge repair: suboptimal outcomes in atriogenic hamstringing. *JACC Cardiovasc Imaging* 2025;**18**:16–29. https://doi.org/10.1016/j.jcmg.2024.06.019
593. Rosano GMC, Moura B, Metra M, Böhm M, Bauersachs J, Ben Gal T, *et al.* Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2021;**23**:872–81. https://doi.org/10.1002/ejhf.2206
594. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, *et al.* Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet* 2022;**400**:1938–52. https://doi.org/10.1016/s0140-6736(22)02076-1
595. Spinka G, Bartko PE, Heitzinger G, Prausmuller S, Winter MP, Arfsten H, *et al.* Guideline directed medical therapy and reduction of secondary mitral regurgitation. *Eur Heart J Cardiovasc Imaging* 2022;**23**:755–64. https://doi.org/10.1093/ehjci/jeac068
596. Pagnesi M, Adamo M, Sama IE, Anker SD, Cleland JG, Dickstein K, *et al.* Clinical impact of changes in mitral regurgitation severity after medical therapy optimization in heart failure. *Clin Res Cardiol* 2022;**111**:912–23. https://doi.org/10.1007/s00392-022-01991-7
597. Di Biase L, Auricchio A, Mohanty P, Bai R, Kautzner J, Pieragnoli P, *et al.* Impact of cardiac resynchronization therapy on the severity of mitral regurgitation. *Europace* 2011;**13**:829–38. https://doi.org/10.1093/europace/eur047
598. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, *et al.* 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2021;**42**:3427–520. https://doi.org/10.1093/eurheartj/ehab364
599. Michalski B, Stankovic I, Pagourelias E, Ciarka A, Aarones M, Winter S, *et al.* Relationship of mechanical dyssynchrony and LV remodeling with improvement of mitral regurgitation after CRT. *JACC Cardiovasc Imaging* 2022;**15**:212–20. https://doi.org/10.1016/j.jcmg.2021.08.010
600. Ypenburg C, Lancellotti P, Tops LF, Bleeker GB, Holman ER, Pierard LA, *et al.* Acute effects of initiation and withdrawal of cardiac resynchronization therapy on papillary muscle dyssynchrony and mitral regurgitation. *J Am Coll Cardiol* 2007;**50**:2071–7. https://doi.org/10.1016/j.jacc.2007.08.019
601. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, *et al.* Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;**379**:2297–306. https://doi.org/10.1056/NEJMoa1805374
602. Iung B, Armoiry X, Vahanian A, Boutitie F, Mewton N, Trochu JN, *et al.* Percutaneous repair or medical treatment for secondary mitral regurgitation: outcomes at 2 years. *Eur J Heart Fail* 2019;**21**:1619–27. https://doi.org/10.1002/EJHF.1616
603. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc Imaging* 2019;**12**:353–62. https://doi.org/10.1016/j.jcmg.2018.11.006
604. Senni M, Adamo M, Metra M, Alfieri O, Vahanian A. Treatment of functional mitral regurgitation in chronic heart failure: can we get a 'proof of concept' from the MITRA-FR and COAPT trials? *Eur J Heart Fail* 2019;**21**:852–61. https://doi.org/10.1002/EJHF.1491
605. Pibarot P, Delgado V, Bax JJ. MITRA-FR vs. COAPT: lessons from two trials with diametrically opposed results. *Eur Heart J Cardiovasc Imaging* 2019;**20**:620–24. https://doi.org/10.1093/ehjci/jez073
606. Anker SD, Friede T, von Bardeleben RS, Butler J, Khan MS, Diek M, *et al.* Transcatheter valve repair in heart failure with moderate to severe mitral regurgitation. *N Engl J Med* 2024;**391**:1799–809. https://doi.org/10.1056/NEJMoa2314328
607. Anker MS, Porthun J, Bonnet G, Schulze PC, Rassaf T, Landmesser U. Percutaneous transcatheter edge-to-edge repair for functional mitral regurgitation in heart failure: a meta-analysis of 3 randomized controlled trials. *J Am Coll Cardiol* 2024;**84**:2364–68. https://doi.org/10.1016/j.jacc.2024.08.026
608. Koell B, Orban M, Weimann J, Kassar M, Karam N, Neuss M, *et al.* Outcomes stratified by adapted inclusion criteria after mitral edge-to-edge repair. *J Am Coll Cardiol* 2021;**78**:2408–21. https://doi.org/10.1016/j.jacc.2021.10.011
609. Scotti A, Latib A, Rubbio AP, Testa L, Adamo M, Denti P, *et al.* Derivation and validation of a clinical risk score for COAPT-ineligible patients who underwent transcatheter edge-to-edge repair. *Am J Cardiol* 2023;**186**:100–8. https://doi.org/10.1016/j.amjcard.2022.10.024

610. Godino C, Munafò A, Scotti A, Estevez-Loureiro R, Portoles Hernandez A, Arzamendi D, *et al.* MitraClip in secondary mitral regurgitation as a bridge to heart transplantation: 1-year outcomes from the International MitraBridge registry. *J Heart Lung Transplant* 2020;**39**:1353–62. https://doi.org/10.1016/j.healun.2020.09.005
611. Ailawadi G, Lim DS, Mack MJ, Trento A, Kar S, Grayburn PA, *et al.* One-year outcomes after MitraClip for functional mitral regurgitation. *Circulation* 2019;**139**:37–47. https://doi.org/10.1161/CIRCULATIONAHA.117.031733
612. Goel K, Lindenfeld J, Makkar R, Naik H, Atmakuri S, Mahoney P, *et al.* Transcatheter edge-to-edge repair in 5,000 patients with secondary mitral regurgitation: COAPT post-approval study. *J Am Coll Cardiol* 2023;**82**:1281–97. https://doi.org/10.1016/j.jacc.2023.07.015
613. Adamo M, Tomasoni D, Stolz L, Stocker TJ, Pancaldi E, Koell B, *et al.* Impact of transcatheter edge-to-edge mitral valve repair on guideline-directed medical therapy uptitration. *JACC Cardiovasc Interv* 2023;**16**:896–905. https://doi.org/10.1016/j.jcin.2023.01.362
614. Witte KK, Lipiecki J, Siminiak T, Meredith IT, Malkin CJ, Goldberg SL, *et al.* The REDUCE FMR trial: a randomized sham-controlled study of percutaneous mitral annuloplasty in functional mitral regurgitation. *JACC Heart Fail* 2019;**7**:945–55. https://doi.org/10.1016/j.jchf.2019.06.011
615. Anker SD, Starling RC, Khan MS, Friede T, Filippatos G, Lindenfeld J, *et al.* Percutaneous mitral valve annuloplasty in patients with secondary mitral regurgitation and severe left ventricular enlargement. *JACC Heart Fail* 2021;**9**:453–62. https://doi.org/10.1016/j.jchf.2021.03.002
616. Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2005;**45**:381–7. https://doi.org/10.1016/j.jacc.2004.09.073
617. Baldus S, Doenst T, Pfister R, Gummert J, Kessler M, Boekstegers P, *et al.* Transcatheter repair versus mitral-valve surgery for secondary mitral regurgitation. *N Engl J Med* 2024;**391**:1787–98. https://doi.org/10.1056/NEJMoa2408739
618. Acker MA, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P, *et al.* Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med* 2014;**370**:23–32. https://doi.org/10.1056/NEJMoa1312808
619. von Stumm M, Dudde F, Holst T, Sequeira-Gross T, Pausch J, Muller L, *et al.* Predicting clinical outcome by indexed mitral valve tenting in functional mitral valve regurgitation. *Open Heart* 2021;**8**:e001483. https://doi.org/10.1136/openhrt-2020-001483
620. Girdauskas E, Pausch J, Reichenspurner H, Kempfert J, Kuntze T, Owais T, *et al.* Subannular repair for functional mitral regurgitation with reduced systolic ventricle function: rationale and design of REFORM-MR registry. *J Cardiothorac Surg* 2022;**17**:343. https://doi.org/10.1186/s13019-022-02045-9
621. Pausch J, Sequeira Gross T, Müller L, von Stumm M, Kloth B, Reichenspurner H, *et al.* Subannular repair for functional mitral regurgitation type IIIb in patients with ischaemic versus dilated cardiomyopathy. *Eur J Cardiothorac Surg* 2021;**60**:122–30. https://doi.org/10.1093/ejcts/ezab048
622. Kopjar T, Gasparovic H, Mestres CA, Milicic D, Biocina B. Meta-analysis of concomitant mitral valve repair and coronary artery bypass surgery versus isolated coronary artery bypass surgery in patients with moderate ischaemic mitral regurgitation. *Eur J Cardiothorac Surg* 2016;**50**:212–22. https://doi.org/10.1093/ejcts/ezw022
623. Altarabsheh SE, Deo SV, Dunlay SM, Erwin PJ, Obeidat YM, Navale S, *et al.* Meta-analysis of usefulness of concomitant mitral valve repair or replacement for moderate ischemic mitral regurgitation with coronary artery bypass grafting. *Am J Cardiol* 2017;**119**:734–41. https://doi.org/10.1016/j.amjcard.2016.11.024
624. Michler RE, Smith PK, Parides MK, Ailawadi G, Thourani V, Moskowitz AJ, *et al.* Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med* 2016;**374**:1932–41. https://doi.org/10.1056/NEJMoa1602003
625. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, *et al.* SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet* 2022;**400**:757–67. https://doi.org/10.1016/S0140-6736(22)01429-5
626. Soulat-Dufour L, Lang S, Addetia K, Ederhy S, Adavane-Scheuble S, Chauvet-Droit M, *et al.* Restoring sinus rhythm reverses cardiac remodeling and reduces valvular regurgitation in patients with atrial fibrillation. *J Am Coll Cardiol* 2022;**79**:951–61. https://doi.org/10.1016/j.jacc.2021.12.029
627. Kagiyama N, Kaneko T, Amano M, Sato Y, Ohno Y, Obokata M, *et al.* Clinical outcomes of mitral valve surgery in atrial functional mitral regurgitation in the REVEAL-AFMR registry. *JAMA Netw Open* 2024;**7**:e2428032. https://doi.org/10.1001/jamanetworkopen.2024.28032
628. Wagner CM, Brescia AA, Watt TMF, Bergquist C, Rosenbloom LM, Ceniza NN, *et al.* Surgical strategy and outcomes for atrial functional mitral regurgitation: all functional mitral regurgitation is not the same! *J Thorac Cardiovasc Surg* 2024;**167**:647–55. https://doi.org/10.1016/j.jtcvs.2022.02.056
629. Balogh Z, Mizukami T, Bartunek J, Collet C, Beles M, Albano M, *et al.* Mitral valve repair of atrial functional mitral regurgitation in heart failure with preserved ejection fraction. *J Clin Med* 2020;**9**:3432. https://doi.org/10.3390/jcm9113432
630. Ye Q, Li Y, Zhang W, Zhao Y, Zhao C, Li Z, *et al.* Catheter ablation or surgical therapy in severe atrial functional mitral regurgitation caused by long-standing persistent atrial fibrillation-propensity score analysis. *J Am Heart Assoc* 2024;**13**:e035695. https://doi.org/10.1161/jaha.124.035695
631. Chen J, Wang Y, Lv M, Yang Z, Zhu S, Wei L, *et al.* Mitral valve repair and surgical ablation for atrial functional mitral regurgitation. *Ann Transl Med* 2020;**8**:1420. https://doi.org/10.21037/atm-20-2958
632. Benito-González T, Carrasco-Chinchilla F, Estévez-Loureiro R, Pascual I, Arzamendi D, Garrote-Coloma C, *et al.* Clinical and echocardiographic outcomes of transcatheter mitral valve repair in atrial functional mitral regurgitation. *Int J Cardiol* 2021;**345**:29–35. https://doi.org/10.1016/j.ijcard.2021.09.056
633. Popolo Rubbio A, Testa L, Grasso C, Sisinni A, Tusa M, Agricola E, *et al.* Transcatheter edge-to-edge mitral valve repair in atrial functional mitral regurgitation: insights from the multi-center MITRA-TUNE registry. *Int J Cardiol* 2022;**349**:39–45. https://doi.org/10.1016/j.ijcard.2021.11.027
634. Rudolph F, Geyer M, Baldus S, De Luca VM, Doenst T, Pfister R, *et al.* Transcatheter repair versus surgery for atrial versus ventricular functional mitral regurgitation: a post hoc analysis of the MATTERHORN trial. *Circulation* 2024;**151**:418–20. https://doi.org/10.1161/circulationaha.124.072648
635. Tanaka T, Sugiura A, Vogelhuber J, Öztürk C, Böhm L, Wilde N, *et al.* Outcomes of transcatheter edge-to-edge repair for atrial functional mitral regurgitation. *EuroIntervention* 2024;**20**:e250–60. https://doi.org/10.4244/eij-d-23-00819
636. Gemelli M, Gallo M, Addonizio M, Van den Eynde J, Pradegan N, Danesi TH, *et al.* Surgical ablation for atrial fibrillation during mitral valve surgery: a systematic review and meta-analysis of randomized controlled trials. *Am J Cardiol* 2023;**209**:104–13. https://doi.org/10.1016/j.amjcard.2023.09.088
637. Suwalski P, Kowalewski M, Jasiński M, Staromlynski J, Zembala M, Widenka K, *et al.* Survival after surgical ablation for atrial fibrillation in mitral valve surgery: analysis from the Polish National Registry of Cardiac Surgery Procedures (KROK). *J Thorac Cardiovasc Surg* 2019;**157**:1007–18.e1004. https://doi.org/10.1016/j.jtcvs.2018.07.099
638. Hamada S, Ueyama H, Aikawa T, Kampaktsis PN, Misumida N, Takagi H, *et al.* Outcomes of transcatheter edge-to-edge repair for atrial functional mitral regurgitation: a meta-analysis of observational studies. *Catheter Cardiovasc Interv* 2023;**102**:751–60. https://doi.org/10.1002/ccd.30806
639. Sodhi N, Asch FM, Ruf T, Petrescu A, von Bardeleben S, Lim DS, *et al.* Clinical outcomes with transcatheter edge-to-edge repair in atrial functional MR from the EXPAND study. *JACC Cardiovasc Interv* 2022;**15**:1723–30. https://doi.org/10.1016/j.jcin.2022.07.023
640. Deja MA, Grayburn PA, Sun B, Rao V, She L, Krejca M, *et al.* Influence of mitral regurgitation repair on survival in the surgical treatment for ischemic heart failure trial. *Circulation* 2012;**125**:2639–48. https://doi.org/10.1161/CIRCULATIONAHA.111.072256
641. Chan KM, Punjabi PP, Flather M, Wage R, Symmonds K, Roussin I, *et al.* Coronary artery bypass surgery with or without mitral valve annuloplasty in moderate functional ischemic mitral regurgitation: final results of the Randomized Ischemic Mitral Evaluation (RIME) trial. *Circulation* 2012;**126**:2502–10. https://doi.org/10.1161/circulationaha.112.143818
642. Virk SA, Tian DH, Sriravindrarajah A, Dunn D, Wolfenden HD, Suri RM, *et al.* Mitral valve surgery and coronary artery bypass grafting for moderate-to-severe ischemic mitral regurgitation: meta-analysis of clinical and echocardiographic outcomes. *J Thorac Cardiovasc Surg* 2017;**154**:127–36. https://doi.org/10.1016/j.jtcvs.2017.03.039
643. Adamo M, Fiorelli F, Melica B, D'Ortona R, Lupi L, Giannini C, *et al.* COAPT-like profile predicts long-term outcomes in patients with secondary mitral regurgitation undergoing MitraClip implantation. *JACC Cardiovasc Interv* 2021;**14**:15–25. https://doi.org/10.1016/J.JCIN.2020.09.050
644. Coffey S, Roberts-Thomson R, Brown A, Carapetis J, Chen M, Enriquez-Sarano M, *et al.* Global epidemiology of valvular heart disease. *Nat Rev Cardiol* 2021;**18**:853–64. https://doi.org/10.1038/s41569-021-00570-z
645. Kingue S, Ba SA, Balde D, Diarra MB, Anzouan-Kacou JB, Anisubia B, *et al.* The VALVAFRIC study: a registry of rheumatic heart disease in Western and Central Africa. *Arch Cardiovasc Dis* 2016;**109**:321–9. https://doi.org/10.1016/j.acvd.2015.12.004
646. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, *et al.* European Society of Cardiology: cardiovascular disease statistics 2021. *Eur Heart J* 2022;**43**:716–99. https://doi.org/10.1093/eurheartj/ehab892
647. Churchill TW, Yucel E, Deferm S, Levine RA, Hung J, Bertrand PB. Mitral valve dysfunction in patients with annular calcification: *JACC* review topic of the week. *J Am Coll Cardiol* 2022;**80**:739–51. https://doi.org/10.1016/j.jacc.2022.05.032
648. Andell P, Li X, Martinsson A, Andersson C, Stagmo M, Zoller B, *et al.* Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. *Heart* 2017;**103**:1696–703. https://doi.org/10.1136/heartjnl-2016-310894
649. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, *et al.* Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr* 2009;**22**:1–23; quiz 101–102. https://doi.org/10.1016/j.echo.2008.11.029

650. Otto CM, Davis KB, Reid CL, Slater JN, Kronzon I, Kisslo KB, *et al.* Relation between pulmonary artery pressure and mitral stenosis severity in patients undergoing balloon mitral commissurotomy. *Am J Cardiol* 1993;**71**:874–8. https://doi.org/10.1016/0002-9149(93)90844-3
651. Bouleti C, Iung B, Laouenan C, Himbert D, Brochet E, Messika-Zeitoun D, *et al.* Late results of percutaneous mitral commissurotomy up to 20 years: development and validation of a risk score predicting late functional results from a series of 912 patients. *Circulation* 2012;**125**:2119–27. https://doi.org/10.1161/CIRCULATIONAHA.111.055905
652. Nunes MC, Tan TC, Elmariah S, do Lago R, Margey R, Cruz-Gonzalez I, *et al.* The echo score revisited: impact of incorporating commissural morphology and leaflet displacement to the prediction of outcome for patients undergoing percutaneous mitral valvuloplasty. *Circulation* 2014;**129**:886–95. https://doi.org/10.1161/CIRCULATIONAHA.113.001252
653. Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. *Br Heart J* 1988;**60**:299–308. https://doi.org/10.1136/hrt.60.4.299
654. Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, *et al.* The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2016;**17**:1191–229. https://doi.org/10.1093/ehjci/jew190
655. Brochet E, Détaint D, Fondard O, Tazi-Mezalek A, Messika-Zeitoun D, Iung B, *et al.* Early hemodynamic changes versus peak values: what is more useful to predict occurrence of dyspnea during stress echocardiography in patients with asymptomatic mitral stenosis? *J Am Soc Echocardiogr* 2011;**24**:392–8. https://doi.org/10.1016/j.echo.2011.01.006
656. Al Rawahi MN, Al-Maqbali JS, Al Noumani J, Al Alawi AM, Essebag V. Novel oral anticoagulants in patients with atrial fibrillation and moderate to severe mitral stenosis: a systematic review. *Cureus* 2023;**15**:e33222. https://doi.org/10.7759/cureus.33222
657. Kim JY, Kim SH, Myong JP, Kim YR, Kim TS, Kim JH, *et al.* Outcomes of direct oral anticoagulants in patients with mitral stenosis. *J Am Coll Cardiol* 2019;**73**:1123–31. https://doi.org/10.1016/j.jacc.2018.12.047
658. Vilvanathan VK, Srinivas Prabhavathi Bhat BC, Nanjappa MC, Pandian B, Bagi V, Kasturi S, *et al.* A randomized placebo-controlled trial with amiodarone for persistent atrial fibrillation in rheumatic mitral stenosis after successful balloon mitral valvuloplasty. *Indian Heart J* 2016;**68**:671–7. https://doi.org/10.1016/j.ihj.2016.02.013
659. Sharma G, Anantha Krishnan R, Bohra V, Ramakrishnan S, Naik N, Seth S, *et al.* Evaluation of early direct current cardioversion for maintenance of sinus rhythm in rheumatic atrial fibrillation following successful balloon mitral valvotomy. *Indian Heart J* 2016;**68**:486–92. https://doi.org/10.1016/j.ihj.2015.11.013
660. Keenan NG, Cueff C, Cimadevilla C, Brochet E, Lepage L, Detaint D, *et al.* Usefulness of left atrial volume versus diameter to assess thromboembolic risk in mitral stenosis. *Am J Cardiol* 2010;**106**:1152–6. https://doi.org/10.1016/j.amjcard.2010.06.024
661. Badheka AO, Shah N, Ghatak A, Patel NJ, Chothani A, Mehta K, *et al.* Balloon mitral valvuloplasty in the United States: a 13-year perspective. *Am J Med* 2014;**127**:1126.e1121–1126.e1112. https://doi.org/10.1016/j.amjmed.2014.05.015
662. Tomai F, Gaspardone A, Versaci F, Ghini AS, Altamura L, De Luca L, *et al.* Twenty year follow-up after successful percutaneous balloon mitral valvuloplasty in a large contemporary series of patients with mitral stenosis. *Int J Cardiol* 2014;**177**:881–5. https://doi.org/10.1016/j.ijcard.2014.10.040
663. Bouleti C, Iung B, Himbert D, Messika-Zeitoun D, Brochet E, Garbarz E, *et al.* Relationship between valve calcification and long-term results of percutaneous mitral commissurotomy for rheumatic mitral stenosis. *Circ Cardiovasc Interv* 2014;**7**:381–9. https://doi.org/10.1161/CIRCINTERVENTIONS.113.000858
664. Bouleti C, Iung B, Himbert D, Brochet E, Messika-Zeitoun D, Detaint D, *et al.* Reinterventions after percutaneous mitral commissurotomy during long-term follow-up, up to 20 years: the role of repeat percutaneous mitral commissurotomy. *Eur Heart J* 2013;**34**:1923–30. https://doi.org/10.1093/eurheartj/eht097
665. Desnos C, Iung B, Himbert D, Ducrocq G, Urena M, Cormier B, *et al.* Temporal trends on percutaneous mitral commissurotomy: 30 years of experience. *J Am Heart Assoc* 2019;**8**:e012031. https://doi.org/10.1161/JAHA.119.012031
666. Ambari AM, Setianto B, Santoso A, Dwiputra B, Radi B, Alkatiri AA, *et al.* Survival analysis of patients with rheumatic MS after PBMV compared with MVS in a low-to-middle-income country. *Neth Heart J* 2019;**27**:559–64. https://doi.org/10.1007/s12471-019-01315-x
667. Song H, Kang DH, Kim JH, Park KM, Song JM, Choi KJ, *et al.* Percutaneous mitral valvuloplasty versus surgical treatment in mitral stenosis with severe tricuspid regurgitation. *Circulation* 2007;**116**:I246–50. https://doi.org/10.1161/CIRCULATIONAHA.107.678151
668. Soesanto AM, Roeswita D, Atmosudigdo IS, Adiarto S, Sahara E. Clinical and hemodynamic factors associated with low gradient severe rheumatic mitral stenosis. *Int J Angiol* 2022;**32**:43–7. https://doi.org/10.1055/s-0042-1751231
669. El Sabbagh A, Reddy YNV, Barros-Gomes S, Borlaug BA, Miranda WR, Pislaru SV, *et al.* Low-gradient severe mitral stenosis: hemodynamic profiles, clinical characteristics, and outcomes. *J Am Heart Assoc* 2019;**8**:e010736. https://doi.org/10.1161/JAHA.118.010736
670. Okura H, Nakada Y, Nogi M, Ishihara S, Okamura A, Okayama S, *et al.* Prevalence of mitral annular calcification and its association with mitral valvular disease. *Echocardiography* 2021;**38**:1907–12. https://doi.org/10.1111/echo.15236
671. Kato N, Padang R, Scott CG, Guerrero M, Pislaru SV, Pellikka PA. The natural history of severe calcific mitral stenosis. *J Am Coll Cardiol* 2020;**75**:3048–57. https://doi.org/10.1016/j.jacc.2020.04.049
672. Chehab O, Roberts-Thomson R, Bivona A, Gill H, Patterson T, Pursnani A, *et al.* Management of patients with severe mitral annular calcification: *JACC* state-of-the-art review. *J Am Coll Cardiol* 2022;**80**:722–38. https://doi.org/10.1016/j.jacc.2022.06.009
673. Okuno T, Brugger N, Asami M, Heg D, Siontis GCM, Winkel MG, *et al.* Clinical impact of mitral calcium volume in patients undergoing transcatheter aortic valve implantation. *J Cardiovasc Comput Tomogr* 2021;**15**:356–65. https://doi.org/10.1016/j.jcct.2020.10.003
674. Bertrand PB, Churchill TW, Yucel E, Namasivayam M, Bernard S, Nagata Y, *et al.* Prognostic importance of the transmitral pressure gradient in mitral annular calcification with associated mitral valve dysfunction. *Eur Heart J* 2020;**41**:4321–8. https://doi.org/10.1093/eurheartj/ehaa819
675. Urena M, Himbert D, Brochet E, Carrasco JL, Iung B, Nataf P, *et al.* Transseptal transcatheter mitral valve replacement using balloon-expandable transcatheter heart valves: a step-by-step approach. *JACC Cardiovasc Interv* 2017;**10**:1905–19. https://doi.org/10.1016/j.jcin.2017.06.069
676. Guerrero ME, Grayburn P, Smith RLI, Sorajja P, Wang DD, Ahmad Y, *et al.* Diagnosis, classification, and management strategies for mitral annular calcification. *JACC Cardiovasc Interv* 2023;**16**:2195–210. https://doi.org/10.1016/j.jcin.2023.06.044
677. Uchimuro T, Fukui T, Shimizu A, Takanashi S. Mitral valve surgery in patients with severe mitral annular calcification. *Ann Thorac Surg* 2016;**101**:889–95. https://doi.org/10.1016/j.athoracsur.2015.08.071
678. Fukui M, Cavalcante JL, Ahmed A, Bae R, Bapat VN, Gössl M, *et al.* Clinical outcomes of mitral valve disease with mitral annular calcification. *Am J Cardiol* 2022;**174**:107–13. https://doi.org/10.1016/j.amjcard.2022.03.041
679. Kato N, Pellikka PA, Scott CG, Lee AT, Jain V, Eleid MF, *et al.* Impact of mitral intervention on outcomes of patients with mitral valve dysfunction and annulus calcification. *Catheter Cardiovasc Interv* 2022;**99**:1807–16. https://doi.org/10.1002/ccd.30093
680. Brener MI, Hamandi M, Hong E, Pizano A, Harloff MT, Garner EF, *et al.* Early outcomes following transatrial transcatheter mitral valve replacement in patients with severe mitral annular calcification. *J Thorac Cardiovasc Surg* 2024;**167**:1263–1275.e3. https://doi.org/10.1016/j.jtcvs.2022.07.038
681. Guerrero ME, Eleid MF, Wang DD, Pursnani A, Kodali SK, George I, *et al.* 5-Year prospective evaluation of mitral valve-in-valve, valve-in-ring, and valve-in-MAC outcomes: MITRAL trial final results. *JACC Cardiovasc Interv* 2023;**16**:2211–27. https://doi.org/10.1016/j.jcin.2023.06.041
682. Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, Maalouf J, *et al.* Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging* 2019;**12**:433–42. https://doi.org/10.1016/j.jcmg.2018.06.014
683. Chorin E, Rozenbaum Z, Topilsky Y, Konigstein M, Ziv-Baran T, Richert E, *et al.* Tricuspid regurgitation and long-term clinical outcomes. *Eur Heart J Cardiovasc Imaging* 2020;**21**:157–65. https://doi.org/10.1093/ehjci/jez216
684. Topilsky Y, Inojosa JM, Benfari G, Vaturi O, Maltais S, Michelena H, *et al.* Clinical presentation and outcome of tricuspid regurgitation in patients with systolic dysfunction. *Eur Heart J* 2018;**39**:3584–92. https://doi.org/10.1093/eurheartj/ehy434
685. Kadri AN, Menon V, Sammour YM, Gajulapalli RD, Meenakshisundaram C, Nusairat L, *et al.* Outcomes of patients with severe tricuspid regurgitation and congestive heart failure. *Heart* 2019;**105**:1813–7. https://doi.org/10.1136/heartjnl-2019-315004
686. Dreyfus J, Ghalem N, Garbarz E, Cimadevilla C, Nataf P, Vahanian A, *et al.* Timing of referral of patients with severe isolated tricuspid valve regurgitation to surgeons (from a French nationwide database). *Am J Cardiol* 2018;**122**:323–6. https://doi.org/10.1016/j.amjcard.2018.04.003
687. Hoke U, Auger D, Thijssen J, Wolterbeek R, van der Velde ET, Holman ER, *et al.* Significant lead-induced tricuspid regurgitation is associated with poor prognosis at long-term follow-up. *Heart* 2014;**100**:960–8. https://doi.org/10.1136/heartjnl-2013-304673
688. Andreas M, Burri H, Praz F, Soliman O, Badano L, Barreiro M, *et al.* Tricuspid valve disease and cardiac implantable electronic devices. *Eur Heart J* 2024;**45**:346–65. https://doi.org/10.1093/eurheartj/ehad783
689. Praz F, Muraru D, Kreidel F, Lurz P, Hahn RT, Delgado V, *et al.* Transcatheter treatment for tricuspid valve disease. *EuroIntervention* 2021;**17**:791–808. https://doi.org/10.4244/EIJ-D-21-00695
690. Song H, Kim MJ, Chung CH, Choo SJ, Song MG, Song JM, *et al.* Factors associated with development of late significant tricuspid regurgitation after successful left-sided valve surgery. *Heart* 2009;**95**:931–6. https://doi.org/10.1136/hrt.2008.152793
691. Galloo X, Dietz MF, Fortuni F, Prihadi EA, Cosyns B, Delgado V, *et al.* Prognostic implications of atrial vs. ventricular functional tricuspid regurgitation. *Eur Heart J Cardiovasc Imaging* 2023;**24**:733–41. https://doi.org/10.1093/ehjci/jead016

692. Schlotter F, Dietz MF, Stolz L, Kresoja KP, Besler C, Sannino A, *et al.* Atrial functional tricuspid regurgitation: novel definition and impact on prognosis. *Circ Cardiovasc Interv* 2022;**15**:e011958. https://doi.org/10.1161/CIRCINTERVENTIONS.122.011958
693. Adamo M, Chioncel O, Pagnesi M, Bayes-Genis A, Abdelhamid M, Anker SD, *et al.* Epidemiology, pathophysiology, diagnosis and management of chronic right-sided heart failure and tricuspid regurgitation. A clinical consensus statement of the Heart Failure Association (HFA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC. *Eur J Heart Fail* 2024;**26**:18–33. https://doi.org/10.1002/ejhf.3106
694. Fortuni F, Dietz MF, Prihadi EA, van der Bijl P, De Ferrari GM, Knuuti J, *et al.* Prognostic implications of a novel algorithm to grade secondary tricuspid regurgitation. *JACC Cardiovasc Imaging* 2021;**14**:1085–95. https://doi.org/10.1016/j.jcmg.2020.12.011
695. Peri Y, Sadeh B, Sherez C, Hochstadt A, Biner S, Aviram G, *et al.* Quantitative assessment of effective regurgitant orifice: impact on risk stratification, and cut-off for severe and torrential tricuspid regurgitation grade. *Eur Heart J Cardiovasc Imaging* 2020;**21**:768–76. https://doi.org/10.1093/ehjci/jez267
696. Dreyfus J, Galloo X, Taramasso M, Heitzinger G, Benfari G, Kresoja KP, *et al.* TRI-SCORE and benefit of intervention in patients with severe tricuspid regurgitation. *Eur Heart J* 2024;**45**:586–97. https://doi.org/10.1093/eurheartj/ehad585
697. Hahn RT, Lawlor MK, Davidson CJ, Badhwar V, Sannino A, Spitzer E, *et al.* Tricuspid Valve Academic Research Consortium definitions for tricuspid regurgitation and trial endpoints. *Eur Heart J* 2023;**44**:4508–32. https://doi.org/10.1093/eurheartj/ehad653
698. Petersen SE, Khanji MY, Plein S, Lancellotti P, Bucciarelli-Ducci C. European Association of Cardiovascular Imaging expert consensus paper: a comprehensive review of cardiovascular magnetic resonance normal values of cardiac chamber size and aortic root in adults and recommendations for grading severity. *Eur Heart J Cardiovasc Imaging* 2019;**20**:1321–31. https://doi.org/10.1093/ehjci/jez232
699. Kawel-Boehm N, Hetzel SJ, Ambale-Venkatesh B, Captur G, Francois CJ, Jerosch-Herold M, *et al.* Reference ranges ("normal values") for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update. *J Cardiovasc Magn Reson* 2020;**22**:87. https://doi.org/10.1186/s12968-020-00683-3
700. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233–70. https://doi.org/10.1093/ehjci/jev014
701. Addetia K, Miyoshi T, Citro R, Daimon M, Gutierrez Fajardo P, Kasliwal RR, *et al.* Two-dimensional echocardiographic right ventricular size and systolic function measurements stratified by sex, age, and ethnicity: results of the World Alliance of Societies of Echocardiography study. *J Am Soc Echocardiogr* 2021;**34**:1148–1157.e1. https://doi.org/10.1016/j.echo.2021.06.013
702. Addetia K, Miyoshi T, Amuthan V, Citro R, Daimon M, Gutierrez Fajardo P, *et al.* Normal values of three-dimensional right ventricular size and function measurements: results of the World Alliance Societies of Echocardiography study. *J Am Soc Echocardiogr* 2023;**36**:858–866.e1. https://doi.org/10.1016/j.echo.2023.04.011
703. Dietz MF, Prihadi EA, van der Bijl P, Goedemans L, Mertens BJA, Gursoy E, *et al.* Prognostic implications of right ventricular remodeling and function in patients with significant secondary tricuspid regurgitation. *Circulation* 2019;**140**:836–45. https://doi.org/10.1161/CIRCULATIONAHA.119.039630
704. Eriksen-Volnes T, Grue JF, Hellum Olaisen S, Letnes JM, Nes B, Løvstakken L, *et al.* Normalized echocardiographic values from guideline-directed dedicated views for cardiac dimensions and left ventricular function. *JACC Cardiovasc Imaging* 2023;**16**:1501–15. https://doi.org/10.1016/j.jcmg.2022.12.020
705. Lurz P, Orban M, Besler C, Braun D, Schlotter F, Noack T, *et al.* Clinical characteristics, diagnosis, and risk stratification of pulmonary hypertension in severe tricuspid regurgitation and implications for transcatheter tricuspid valve repair. *Eur Heart J* 2020;**41**:2785–95. https://doi.org/10.1093/eurheartj/ehaa138
706. Stocker TJ, Hertell H, Orban M, Braun D, Rommel KP, Ruf T, *et al.* Cardiopulmonary hemodynamic profile predicts mortality after transcatheter tricuspid valve repair in chronic heart failure. *JACC Cardiovasc Interv* 2021;**14**:29–38. https://doi.org/10.1016/j.jcin.2020.09.033
707. Brener MI, Lurz P, Hausleiter J, Rodés-Cabau J, Fam N, Kodali SK, *et al.* Right ventricular-pulmonary arterial coupling and afterload reserve in patients undergoing transcatheter tricuspid valve repair. *J Am Coll Cardiol* 2022;**79**:448–61. https://doi.org/10.1016/j.jacc.2021.11.031
708. Stolz L, Weckbach LT, Karam N, Kalbacher D, Praz F, Lurz P, *et al.* Invasive right ventricular to pulmonary artery coupling in patients undergoing transcatheter edge-to-edge tricuspid valve repair. *JACC Cardiovasc Imaging* 2023;**16**:564–6. https://doi.org/10.1016/j.jcmg.2022.10.004
709. Dreyfus J, Juarez-Casso F, Sala A, Carnero-Alcazar M, Eixerés-Esteve A, Bohbot Y, *et al.* Benefit of isolated surgical valve repair or replacement for functional tricuspid regurgitation and long-term outcomes stratified by the TRI-SCORE. *Eur Heart J* 2024;**45**:4512–22. https://doi.org/10.1093/eurheartj/ehae578
710. Thourani VH, Bonnell L, Wyler von Ballmoos MC, Mehaffey JH, Bowdish M, Kurlansky P, *et al.* Outcomes of isolated tricuspid valve surgery: a Society of Thoracic Surgeons analysis and risk model. *Ann Thorac Surg* 2024;**118**:873–81. https://doi.org/10.1016/j.athoracsur.2024.04.014
711. Anguita-Gámez M, Giraldo MA, Nombela-Franco L, Eixeres Esteve A, Cuerpo G, Lopez-Menendez J, *et al.* Validation of the TRI-SCORE in patients undergoing surgery for isolated tricuspid regurgitation. *Heart* 2023;**109**:1401–6. https://doi.org/10.1136/heartjnl-2022-322067
712. Nassif ME, Qintar M, Windsor SL, Jermyn R, Shavelle DM, Tang F, *et al.* Empagliflozin effects on pulmonary artery pressure in patients with heart failure: results from the EMBRACE-HF trial. *Circulation* 2021;**143**:1673–86. https://doi.org/10.1161/circulationaha.120.052503
713. Sorajja P, Whisenant B, Hamid N, Naik H, Makkar R, Tadros P, *et al.* Transcatheter repair for patients with tricuspid regurgitation. *N Engl J Med* 2023;**388**:1833–42. https://doi.org/10.1056/NEJMoa2300525
714. Dreyfus J, Flagiello M, Bazire B, Eggenspieler F, Viau F, Riant E, *et al.* Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes. *Eur Heart J* 2020;**41**:4304–17. https://doi.org/10.1093/eurheartj/ehaa643
715. Scotti A, Sturla M, Granada JF, Kodali SK, Coisne A, Mangieri A, *et al.* Outcomes of isolated tricuspid valve replacement: a systematic review and meta-analysis of 5,316 patients from 35 studies. *EuroIntervention* 2022;**18**:840–51. https://doi.org/10.4244/EIJ-D-22-00442
716. Chen Q, Bowdish ME, Malas J, Roach A, Gill G, Rowe G, *et al.* Isolated tricuspid operations: the Society of Thoracic Surgeons adult cardiac surgery database analysis. *Ann Thorac Surg* 2023;**115**:1162–70. https://doi.org/10.1016/j.athoracsur.2022.12.041
717. Hahn RT, Wilkoff BL, Kodali S, Birgersdotter-Green UM, Ailawadi G, Addetia K, *et al.* Managing implanted cardiac electronic devices in patients with severe tricuspid regurgitation: *JACC* state-of-the-art review. *J Am Coll Cardiol* 2024;**83**:2002–14. https://doi.org/10.1016/j.jacc.2024.02.045
718. Taramasso M, Gavazzoni M, Pozzoli A, Dreyfus GD, Bolling SF, George I, *et al.* Tricuspid regurgitation: predicting the need for intervention, procedural success, and recurrence of disease. *JACC Cardiovasc Imaging* 2019;**12**:605–21. https://doi.org/10.1016/j.jcmg.2018.11.034
719. Bannehr M, Edlinger CR, Kahn U, Liebchen J, Okamoto M, Hähnel V, *et al.* Natural course of tricuspid regurgitation and prognostic implications. *Open Heart* 2021;**8**:e001529. https://doi.org/10.1136/openhrt-2020-001529
720. Park SJ, Oh JK, Kim SO, Lee SA, Kim HJ, Lee S, *et al.* Determinants of clinical outcomes of surgery for isolated severe tricuspid regurgitation. *Heart* 2021;**107**:403–10. https://doi.org/10.1136/heartjnl-2020-317715
721. McCarthy PM, Bhudia SK, Rajeswaran J, Hoercher KJ, Lytle BW, Cosgrove DM, *et al.* Tricuspid valve repair: durability and risk factors for failure. *J Thorac Cardiovasc Surg* 2004;**127**:674–85. https://doi.org/10.1016/j.jtcvs.2003.11.019
722. Kwak JJ, Kim YJ, Kim MK, Kim HK, Park JS, Kim KH, *et al.* Development of tricuspid regurgitation late after left-sided valve surgery: a single-center experience with long-term echocardiographic examinations. *Am Heart J* 2008;**155**:732–7. https://doi.org/10.1016/j.ahj.2007.11.010
723. Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? *Ann Thorac Surg* 2005;**79**:127–32. https://doi.org/10.1016/j.athoracsur.2004.06.057
724. Dreyfus GD, Essayagh B, Benfari G, Dulguerov F, Haley SR, Dommerc C, *et al.* Outcome of consistent guideline-based tricuspid management in patients undergoing degenerative mitral regurgitation correction. *JTCVS Open* 2021;**7**:125–38. https://doi.org/10.1016/j.xjon.2021.07.010
725. Gammie JS, Chu MWA, Falk V, Overbey JR, Moskowitz AJ, Gillinov M, *et al.* Concomitant tricuspid repair in patients with degenerative mitral regurgitation. *N Engl J Med* 2022;**386**:327–39. https://doi.org/10.1056/NEJMoa2115961
726. Pettinari M, De Kerchove L, Lazam S, Pasquet A, Gerber B, Vanoverschelde JL, *et al.* Mid-term results of a randomized trial of tricuspid annuloplasty for less-than-severe functional tricuspid regurgitation at the time of mitral valve surgery. *Eur J Cardiothorac Surg* 2019;**55**:851–8. https://doi.org/10.1093/ejcts/ezy378
727. Ailawadi G, Voisine P, Raymond S, Gelijns AC, Moskowitz AJ, Falk V, *et al.* Pacemaker implantation associated with tricuspid repair in the setting of mitral valve surgery: insights from a Cardiothoracic Surgical Trials Network randomized trial. *J Thorac Cardiovasc Surg* 2022;**167**:2104–16.e5. https://doi.org/10.1016/j.jtcvs.2022.11.031
728. Ragnarsson S, Taha A, Nielsen SJ, Amabile A, Geirsson A, Krane M, *et al.* Pacemaker implantation following tricuspid valve annuloplasty. *JTCVS Open* 2023;**16**:276–89. https://doi.org/10.1016/j.xjon.2023.08.017
729. Iribarne A, Alabbadi SH, Moskowitz AJ, Ailawadi G, Badhwar V, Gillinov M, *et al.* Permanent pacemaker implantation and long-term outcomes of patients undergoing concomitant mitral and tricuspid valve surgery. *J Am Coll Cardiol* 2024;**83**:1656–68. https://doi.org/10.1016/j.jacc.2024.02.042
730. Kassab J, Harb SC, Desai MY, Gillinov AM, Layoun H, El Dahdah J, *et al.* Incidence, risk factors, and outcomes associated with permanent pacemaker implantation following tricuspid valve surgery. *J Am Heart Assoc* 2024;**13**:e032760. https://doi.org/10.1161/jaha.123.032760
731. Chikwe J, Itagaki S, Anyanwu A, Adams DH. Impact of concomitant tricuspid annuloplasty on tricuspid regurgitation, right ventricular function, and pulmonary artery

hypertension after repair of mitral valve prolapse. *J Am Coll Cardiol* 2015;**65**:1931–8. https://doi.org/10.1016/j.jacc.2015.01.059
732. Chang JD, Manning WJ, Ebrille E, Zimetbaum PJ. Tricuspid valve dysfunction following pacemaker or cardioverter-defibrillator implantation. *J Am Coll Cardiol* 2017;**69**: 2331–41. https://doi.org/10.1016/j.jacc.2017.02.055
733. von Bardeleben RS, Lurz P, Sorajja P, Ruf T, Hausleiter J, Sitges M, *et al.* Two-year outcomes for tricuspid repair with a transcatheter edge-to-edge valve repair from the transatlantic TRILUMINATE trial. *Circ Cardiovasc Interv* 2023;**16**:e012888. https://doi.org/10.1161/CIRCINTERVENTIONS.122.012888
734. Lurz P, Besler C, Schmitz T, Bekeredjian R, Nickenig G, Möllmann H, *et al.* Short-term outcomes of tricuspid edge-to-edge repair in clinical practice. *J Am Coll Cardiol* 2023;**82**: 281–91. https://doi.org/10.1016/j.jacc.2023.05.008
735. Kodali SK, Hahn RT, Davidson CJ, Narang A, Greenbaum A, Gleason P, *et al.* 1-Year outcomes of transcatheter tricuspid valve repair. *J Am Coll Cardiol* 2023;**81**:1766–76. https://doi.org/10.1016/j.jacc.2023.02.049
736. Kar S, Makkar RR, Whisenant BK, Hamid N, Naik H, Tadros P, *et al.* (March 30, 2025) Two-year outcomes of transcatheter edge-to-edge repair for severe tricuspid regurgitation: the TRILUMINATE pivotal randomized trial. *Circulation*, https://doi.org/10.1161/CIRCULATIONAHA.125.074536
737. Donal E, Dreyfus J, Leurent G, Coisne A, Leroux PY, Ganivet A, *et al.* Transcatheter edge-to-edge repair for severe isolated tricuspid regurgitation: the Tri.Fr randomized clinical trial. *JAMA* 2025;**333**:124–32. https://doi.org/10.1001/jama.2024.21189
738. Hahn RT, Makkar R, Thourani VH, Makar M, Sharma RP, Haeffele C, *et al.* Transcatheter valve replacement in severe tricuspid regurgitation. *N Engl J Med* 2024;**392**:115–26. https://doi.org/10.1056/NEJMoa2401918
739. Park SJ, Gentry JLI, Varma N, Wazni O, Tarakji KG, Mehta A, *et al.* Transvenous extraction of pacemaker and defibrillator leads and the risk of tricuspid valve regurgitation. *JACC Clin Electrophysiol* 2018;**4**:1421–8. https://doi.org/10.1016/j.jacep.2018.07.011
740. Aboulhosn J, Cabalka AK, Levi DS, Himbert D, Testa L, Latib A, *et al.* Transcatheter valve-in-ring implantation for the treatment of residual or recurrent tricuspid valve dysfunction after prior surgical repair. *JACC Cardiovasc Interv* 2017;**10**:53–63. https://doi.org/10.1016/j.jcin.2016.10.036
741. Chen S, Dershowitz L, George I. Transcatheter valve implantation for degenerated tricuspid bioprosthesis and failed tricuspid ring. *Ann Cardiothorac Surg* 2021;**10**:651–7. https://doi.org/10.21037/acs-2021-tviv-11
742. Rao VN, Giczewska A, Chiswell K, Felker GM, Wang A, Glower DD, *et al.* Long-term outcomes of phenoclusters in severe tricuspid regurgitation. *Eur Heart J* 2023;**44**: 1910–23. https://doi.org/10.1093/eurheartj/ehad133
743. Van de Veire NR, Braun J, Delgado V, Versteegh MI, Dion RA, Klautz RJ, *et al.* Tricuspid annuloplasty prevents right ventricular dilatation and progression of tricuspid regurgitation in patients with tricuspid annular dilatation undergoing mitral valve repair. *J Thorac Cardiovasc Surg* 2011;**141**:1431–9. https://doi.org/10.1016/j.jtcvs.2010.05.050
744. Brescia AA, Ward ST, Watt TMF, Rosenbloom LM, Baker M, Khan S, *et al.* Outcomes of guideline-directed concomitant annuloplasty for functional tricuspid regurgitation. *Ann Thorac Surg* 2020;**109**:1227–32. https://doi.org/10.1016/j.athoracsur.2019.07.035
745. Hamandi M, Smith RL, Ryan WH, Grayburn PA, Vasudevan A, George TJ, *et al.* Outcomes of isolated tricuspid valve surgery have improved in the modern era. *Ann Thorac Surg* 2019;**108**:11–5. https://doi.org/10.1016/j.athoracsur.2019.03.004
746. Russo M, Di Mauro M, Saitto G, Lio A, Berretta P, Taramasso M, *et al.* Outcome of patients undergoing isolated tricuspid repair or replacement surgery. *Eur J Cardiothorac Surg* 2022;**62**:ezac230. https://doi.org/10.1093/ejcts/ezac230
747. Abdelbar A, Kenawy A, Zacharias J. Minimally invasive tricuspid valve surgery. *J Thorac Dis* 2021;**13**:1982–92. https://doi.org/10.21037/jtd-20-1331
748. Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L, *et al.* Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;**74**:2998–3008. https://doi.org/10.1016/j.jacc.2019.09.028
749. Kodali S, Hahn RT, Makkar R, Makar M, Davidson CJ, Puthumana JJ, *et al.* Transfemoral tricuspid valve replacement and one-year outcomes: the TRISCEND study. *Eur Heart J* 2023;**44**:4862–73. https://doi.org/10.1093/eurheartj/ehad667
750. Donal E, Sitges M, Panis V, Schueler R, Lapp H, Moellmann H, *et al.* Characterization of tricuspid valve anatomy and coaptation gap in subjects receiving tricuspid transcatheter edge-to-edge repair: observations from the bRIGHT TriClip study. *J Am Soc Echocardiogr* 2024;**37**:397–404. https://doi.org/10.1016/j.echo.2023.12.002
751. Wild MG, Löw K, Rosch S, Gercek M, Higuchi S, Massberg S, *et al.* Multicenter experience with the transcatheter leaflet repair system for symptomatic tricuspid regurgitation. *JACC Cardiovasc Interv* 2022;**15**:1352–63. https://doi.org/10.1016/j.jcin.2022.05.041
752. Sarralde JA, Bernal JM, Llorca J, Pontón A, Diez-Solorzano L, Giménez-Rico JR, *et al.* Repair of rheumatic tricuspid valve disease: predictors of very long-term mortality and reoperation. *Ann Thorac Surg* 2010;**90**:503–8. https://doi.org/10.1016/j.athoracsur.2010.03.105
753. Saran N, Dearani JA, Said SM, Greason KL, Pochettino A, Stulak JM, *et al.* Long-term outcomes of patients undergoing tricuspid valve surgery. *Eur J Cardiothorac Surg* 2019;**56**:950–8. https://doi.org/10.1093/ejcts/ezz081
754. McElhinney DB, Cabalka AK, Aboulhosn JA, Eicken A, Boudjemline Y, Schubert S, *et al.* Transcatheter tricuspid valve-in-valve implantation for the treatment of dysfunctional surgical bioprosthetic valves: an international, multicenter registry study. *Circulation* 2016;**133**:1582–93. https://doi.org/10.1161/CIRCULATIONAHA.115.019353
755. Pereyra M, Farina JM, Chao CJ, Ayoub C, Arsanjani R. Percutaneous transcatheter pulmonary and tricuspid valve replacements in a patient with carcinoid heart disease. *Eur Heart J Case Rep* 2023;**7**:ytad511. https://doi.org/10.1093/ehjcr/ytad511
756. Connolly HM, Schaff HV, Abel MD, Rubin J, Askew JW, Li Z, *et al.* Early and late outcomes of surgical treatment in carcinoid heart disease. *J Am Coll Cardiol* 2015;**66**: 2189–96. https://doi.org/10.1016/j.jacc.2015.09.014
757. Yunoki K, Naruko T, Itoh A, Ohashi J, Fujimoto K, Shirai N, *et al.* Percutaneous transcatheter balloon valvuloplasty for bioprosthetic tricuspid valve stenosis. *Circulation* 2006;**114**:e558–9. https://doi.org/10.1161/CIRCULATIONAHA.106.618611
758. Tribouilloy C, Bohbot Y, Kubala M, Ruschitzka F, Popescu B, Wendler O, *et al.* Characteristics, management, and outcomes of patients with multiple native valvular heart disease: a substudy of the EURObservational Research Programme Valvular Heart Disease II Survey. *Eur Heart J* 2022;**43**:2756–66. https://doi.org/10.1093/eurheartj/ehac209
759. Iung B, Baron G, Tornos P, Gohlke-Bärwolf C, Butchart EG, Vahanian A. Valvular heart disease in the community: a European experience. *Curr Probl Cardiol* 2007;**32**:609–61. https://doi.org/10.1016/j.cpcardiol.2007.07.002
760. Cutter DJ, Schaapveld M, Darby SC, Hauptmann M, van Nimwegen FA, Krol AD, *et al.* Risk of valvular heart disease after treatment for Hodgkin lymphoma. *J Natl Cancer Inst* 2015;**107**:djv008. https://doi.org/10.1093/jnci/djv008
761. Unger P, Pibarot P, Tribouilloy C, Lancellotti P, Maisano F, Iung B, *et al.* Multiple and mixed valvular heart diseases. *Circ Cardiovasc Imaging* 2018;**11**:e007862. https://doi.org/10.1161/CIRCIMAGING.118.007862
762. Ajmone Marsan N, Delgado V, Shah DJ, Pellikka P, Bax JJ, Treibel T, *et al.* Valvular heart disease: shifting the focus to the myocardium. *Eur Heart J* 2023;**44**:28–40. https://doi.org/10.1093/eurheartj/ehac504
763. de Marchi SF, Windecker S, Aeschbacher BC, Seiler C. Influence of left ventricular relaxation on the pressure half time of aortic regurgitation. *Heart* 1999;**82**:607–13. https://doi.org/10.1136/hrt.82.5.607
764. Unger P, Tribouilloy C. Aortic stenosis with other concomitant valvular disease: aortic regurgitation, mitral regurgitation, mitral stenosis, or tricuspid regurgitation. *Cardiol Clin* 2020;**38**:33–46. https://doi.org/10.1016/j.ccl.2019.09.002
765. Unger P, Clavel M-A. Mixed aortic valve disease: a diagnostic challenge, a prognostic threat. *Structural Heart* 2020;**4**:468–74. https://doi.org/10.1080/24748706.2020.1817643
766. Flachskampf FA, Weyman AE, Gillam L, Liu CM, Abascal VM, Thomas JD. Aortic regurgitation shortens Doppler pressure half-time in mitral stenosis: clinical evidence, in vitro simulation and theoretic analysis. *J Am Coll Cardiol* 1990;**16**:396–404. https://doi.org/10.1016/0735-1097(90)90592-d
767. Tribouilloy C, Shen WF, Rey JL, Adam MC, Lesbre JP. Mitral to aortic velocity-time integral ratio: a non-geometric pulsed-Doppler regurgitant index in isolated pure mitral regurgitation. *Eur Heart J* 1994;**15**:1335–9. https://doi.org/10.1093/oxfordjournals.eurheartj.a060390
768. Benfari G, Clavel M-A, Nistri S, Maffeis C, Vassanelli C, Enriquez-Sarano M, *et al.* Concomitant mitral regurgitation and aortic stenosis: one step further to low-flow preserved ejection fraction aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2018;**19**: 569–73. https://doi.org/10.1093/ehjci/jex172
769. Mohan JC, Mukherjee S, Kumar A, Arora R, Patel AR, Pandian NG. Does chronic mitral regurgitation influence Doppler pressure half-time–derived calculation of the mitral valve area in patients with mitral stenosis? *Am Heart J* 2004;**148**:703–9. https://doi.org/10.1016/j.ahj.2003.12.043
770. Hauge SW, Estensen ME, Persson R, Abebe S, Mekonnen D, Nega B, *et al.* The importance of concomitant mitral regurgitation for estimates of mitral valve area by pressure half time in patients with chronic rheumatic heart disease. *Int J Cardiol* 2024;**398**: 131600. https://doi.org/10.1016/j.ijcard.2023.131600
771. Dahou A, Magne J, Clavel MA, Capoulade R, Bartko PE, Bergler-Klein J, *et al.* Tricuspid regurgitation is associated with increased risk of mortality in patients with low-flow low-gradient aortic stenosis and reduced ejection fraction: results of the multicenter TOPAS study (True or Pseudo-Severe Aortic Stenosis). *JACC Cardiovasc Interv* 2015; **8**:588–96. https://doi.org/10.1016/j.jcin.2014.08.019
772. Shiran A, Sagie A. Tricuspid regurgitation in mitral valve disease: incidence, prognostic implications, mechanism, and management. *J Am Coll Cardiol* 2009;**53**:401–8. https://doi.org/10.1016/j.jacc.2008.09.048
773. Naeije R, Badagliacca R. The overloaded right heart and ventricular interdependence. *Cardiovasc Res* 2017;**113**:1474–85. https://doi.org/10.1093/cvr/cvx160
774. Furukawa A, Abe Y, Ito K, Hosogi S, Yamamoto K, Ito H. Mechanisms of changes in functional mitral regurgitation by preload alterations. *J Cardiol* 2018;**71**:570–6. https://doi.org/10.1016/j.jjcc.2017.12.005
775. Wunderlich NC, Beigel R, Siegel RJ. Management of mitral stenosis using 2D and 3D echo-Doppler imaging. *JACC Cardiovasc Imaging* 2013;**6**:1191–205. https://doi.org/10.1016/j.jcmg.2013.07.008

776. Cho IJ, Lee SE, Jeong H, Chang HJ. Determinants of clinical outcomes in patients with mixed mitral valve disease. *Echocardiography* 2020;**37**:1164–70. https://doi.org/10.1111/echo.14673
777. Pawade T, Sheth T, Guzzetti E, Dweck Marc R, Clavel M-A. Why and how to measure aortic valve calcification in patients with aortic stenosis. *JACC Cardiovasc Imaging* 2019;**12**:1835–48. https://doi.org/10.1016/j.jcmg.2019.01.045
779. Bandera F, Generati G, Pellegrino M, Garatti A, Labate V, Alfonzetti E, *et al.* Mitral regurgitation in heart failure: insights from CPET combined with exercise echocardiography. *Eur Heart J Cardiovasc Imaging* 2017;**18**:296–303. https://doi.org/10.1093/ehjci/jew096
780. Bissessor N, Shanahan L, Wee YS, Stewart R, Lowe B, Kerr A, *et al.* The role of natriuretic peptides in patients with chronic complex (mixed or multiple) heart valve disease. *Congest Heart Fail* 2010;**16**:50–4. https://doi.org/10.1111/j.1751-7133.2009.00132.x
781. Myerson SG. CMR in evaluating valvular heart disease: diagnosis, severity, and outcomes. *JACC Cardiovasc Imaging* 2021;**14**:2020–32. https://doi.org/10.1016/j.jcmg.2020.09.029
782. Grafton G, Cascino TM, Perry D, Ashur C, Koelling TM. Resting oxygen consumption and heart failure: importance of measurement for determination of cardiac output with the use of the Fick principle. *J Card Fail* 2020;**26**:664–72. https://doi.org/10.1016/j.cardfail.2019.02.004
783. Singh AD, Mian A, Devasenapathy N, Guyatt G, Karthikeyan G. Percutaneous mitral commissurotomy versus surgical commissurotomy for rheumatic mitral stenosis: a systematic review and meta-analysis of randomised controlled trials. *Heart* 2020;**106**:1094–101. https://doi.org/10.1136/heartjnl-2019-315906
784. Winter MP, Bartko PE, Krickl A, Gatterer C, Donà C, Nitsche C, *et al.* Adaptive development of concomitant secondary mitral and tricuspid regurgitation after transcatheter aortic valve replacement. *Eur Heart J Cardiovasc Imaging* 2021;**22**:1045–53. https://doi.org/10.1093/ehjci/jeaa106
785. Khan F, Okuno T, Malebranche D, Lanz J, Praz F, Stortecky S, *et al.* Transcatheter aortic valve replacement in patients with multivalvular heart disease. *JACC Cardiovasc Interv* 2020;**13**:1503–14. https://doi.org/10.1016/j.jcin.2020.03.052
786. Adamo M, Pagnesi M, Ghizzoni G, Estévez-Loureiro R, Raposeiras-Roubin S, Tomasoni D, *et al.* Evolution of tricuspid regurgitation after transcatheter edge-to-edge mitral valve repair for secondary mitral regurgitation and its impact on mortality. *Eur J Heart Fail* 2022;**24**:2175–84. https://doi.org/10.1002/ejhf.2637
787. Kavsur R, Iliadis C, Spieker M, Brachtendorf BM, Tiyerili V, Metze C, *et al.* Predictors and prognostic relevance of tricuspid alterations in patients undergoing transcatheter edge-to-edge mitral valve repair. *EuroIntervention* 2021;**17**:827–34. https://doi.org/10.4244/eij-d-20-01094
788. Mehr M, Karam N, Taramasso M, Ouarrak T, Schneider S, Lurz P, *et al.* Combined tricuspid and mitral versus isolated mitral valve repair for severe MR and TR: an analysis from the TriValve and TRAMI registries. *JACC Cardiovasc Interv* 2020;**13**:543–50. https://doi.org/10.1016/j.jcin.2019.10.023
789. Besler C, Blazek S, Rommel KP, Noack T, von Roeder M, Luecke C, *et al.* Combined mitral and tricuspid versus isolated mitral valve transcatheter edge-to-edge repair in patients with symptomatic valve regurgitation at high surgical risk. *JACC Cardiovasc Interv* 2018;**11**:1142–51. https://doi.org/10.1016/j.jcin.2018.04.010
790. Egbe AC, Luis SA, Padang R, Warnes CA. Outcomes in moderate mixed aortic valve disease: is it time for a paradigm shift? *J Am Coll Cardiol* 2016;**67**:2321–9. https://doi.org/10.1016/j.jacc.2016.03.509
791. Egbe AC, Poterucha JT, Warnes CA. Mixed aortic valve disease: midterm outcome and predictors of adverse events. *Eur Heart J* 2016;**37**:2671–8. https://doi.org/10.1093/eurheartj/ehw079
792. Zilberszac R, Gabriel H, Schemper M, Zahler D, Czerny M, Maurer G, *et al.* Outcome of combined stenotic and regurgitant aortic valve disease. *J Am Coll Cardiol* 2013;**61**:1489–95. https://doi.org/10.1016/j.jacc.2012.11.070
793. Isaza N, Desai MY, Kapadia SR, Krishnaswamy A, Rodriguez LL, Grimm RA, *et al.* Long-term outcomes in patients with mixed aortic valve disease and preserved left ventricular ejection fraction. *J Am Heart Assoc* 2020;**9**:e014591. https://doi.org/10.1161/jaha.119.014591
794. Saijo Y, Isaza N, Conic JZ, Desai MY, Johnston D, Roselli EE, *et al.* Left ventricular longitudinal strain in characterization and outcome assessment of mixed aortic valve disease phenotypes. *JACC Cardiovasc Imaging* 2021;**14**:1324–34. https://doi.org/10.1016/j.jcmg.2021.01.020
795. Bernard J, Jean G, Bienjonetti-Boudreau D, Jacques F, Tastet L, Salaun E, *et al.* Prognostic utility of N-terminal pro B-type natriuretic peptide ratio in mixed aortic valve disease. *Open Heart* 2023;**10**:e002361. https://doi.org/10.1136/openhrt-2023-002361
796. Onishi H, Naganuma T, Izumo M, Ouchi T, Yuki H, Mitomo S, *et al.* Prognostic relevance of B-type natriuretic peptide in patients with moderate mixed aortic valve disease. *ESC Heart Fail* 2022;**9**:2474–83. https://doi.org/10.1002/ehf2.13946
797. Carpentier AF, Pellerin M, Fuzellier JF, Relland JY. Extensive calcification of the mitral valve anulus: pathology and surgical management. *J Thorac Cardiovasc Surg* 1996;**111**:718–29; discussion 729–730. https://doi.org/10.1016/s0022-5223(96)70332-x
798. World Health Organization. *Life Expectancy at Birth*. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/3131 (28 March 2025, date last accessed).
799. Johansson I, Benz AP, Kovalova T, Balasubramanian K, Fukakusa B, Lynn MJ, *et al.* Outcomes of patients with a mechanical heart valve and poor anticoagulation control on warfarin. *Thromb Haemost* 2024;**124**:613–24. https://doi.org/10.1055/s-0043-1777827
800. Persson M, Glaser N, Nilsson J, Friberg O, Franco-Cereceda A, Sartipy U. Comparison of long-term performance of bioprosthetic aortic valves in Sweden from 2003 to 2018. *JAMA Netw Open* 2022;**5**:e220962. https://doi.org/10.1001/jamanetworkopen.2022.0962
801. Jiang Y, Wang S, Bian J, Chen S, Shao Y. Mechanical versus bioprosthetic aortic valve replacement in middle-aged adults: a systematic review and meta-analysis. *J Cardiovasc Dev Dis* 2023;**10**:90. https://doi.org/10.3390/jcdd10020090
802. Kim MS, Kim HR, Lee SH, Lee S, Joo HC. Aortic valve replacement in patients aged 50 to 69 years: analysis using Korean National Big Data. *J Card Surg* 2022;**37**:3623–30. https://doi.org/10.1111/jocs.16908
803. Vogt F, Santarpino G, Fujita B, Frerker C, Bauer T, Beckmann A, *et al.* Surgical aortic valve replacement in patients aged 50–69 years—insights from the German Aortic Valve Registry (GARY). *Eur J Cardiothorac Surg* 2022;**62**:ezac286. https://doi.org/10.1093/ejcts/ezac286
804. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50–69 years. *Eur Heart J* 2016;**37**:2658–67. https://doi.org/10.1093/eurheartj/ehv580
805. Kiyose AT, Suzumura EA, Laranjeira L, Buehler AM, Santo JAE, Berwanger O, *et al.* Comparison of biological and mechanical prostheses for heart valve surgery: a systematic review of randomized controlled trials. *Arq Bras Cardiol* 2019;**112**:292–301. https://doi.org/10.5935/abc.20180272
806. Bouhout I, Ghoneim A, Poirier N, Cartier R, Demers P, Perrault LP, *et al.* Impact of the learning curve on early outcomes following the Ross procedure. *Can J Cardiol* 2017;**33**:493–500. https://doi.org/10.1016/j.cjca.2016.11.014
807. Tasoudis PT, Varvoglis DN, Vitkos E, Mylonas KS, Sá MP, Ikonomidis JS, *et al.* Mechanical versus bioprosthetic valve for aortic valve replacement: systematic review and meta-analysis of reconstructed individual participant data. *Eur J Cardiothorac Surg* 2022;**62**:ezac268. https://doi.org/10.1093/ejcts/ezac268
808. Leviner DB, Witberg G, Levi A, Landes U, Schwartz N, Shiran A, *et al.* Mechanical vs bioprosthetic aortic valve replacement in patients younger than 70 years of age: a hazard ratio meta-analysis. *Can J Cardiol* 2022;**38**:355–64. https://doi.org/10.1016/j.cjca.2021.12.008
809. Yu J, Qiao E, Wang W. Mechanical or biologic prostheses for mitral valve replacement: a systematic review and meta-analysis. *Clin Cardiol* 2022;**45**:701–16. https://doi.org/10.1002/clc.23854
810. Yanagawa B, Lee J, Ouzounian M, Bagai A, Cheema A, Verma S, *et al.* Mitral valve prosthesis choice in patients <70 years: a systematic review and meta-analysis of 20 219 patients. *J Card Surg* 2020;**35**:818–25. https://doi.org/10.1111/jocs.14478
811. Ahmed A, Awad AK, Varghese KS, Sehgal VS, Hisham K, George J, *et al.* Bioprosthetic versus mechanical valves for mitral valve replacement in patients <70 years: an updated pairwise meta-analysis. *Gen Thorac Cardiovasc Surg* 2024;**72**:95–103. https://doi.org/10.1007/s11748-023-01956-1
812. Capodanno D, Petronio AS, Prendergast B, Eltchaninoff H, Vahanian A, Modine T, *et al.* Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2017;**38**:3382–90. https://doi.org/10.1093/eurheartj/ehx303
813. Meskin M, Dimasi A, Votta E, Jaworek M, Fusini L, Muratori M, *et al.* A novel multiparametric score for the detection and grading of prosthetic mitral valve obstruction in cases with different disc motion abnormalities. *Ultrasound Med Biol* 2019;**45**:1708–20. https://doi.org/10.1016/j.ultrasmedbio.2019.03.011
814. Passaglia LG, de Barros GM, de Sousa MR. Early postoperative bridging anticoagulation after mechanical heart valve replacement: a systematic review and meta-analysis. *J Thromb Haemost* 2015;**13**:1557–67. https://doi.org/10.1111/jth.13047
815. Li BX, Liu SD, Qi L, Sun S, Sun W, Li YM, *et al.* Comparison of different bridging anticoagulation therapies used after mechanical heart valve replacement in Chinese patients—a prospective cohort study. *J Cardiothorac Surg* 2020;**15**:40. https://doi.org/10.1186/s13019-020-1084-7
816. Tao E, Luo YL, Tao Z, Wan L. A meta-analysis of bridging anticoagulation between low molecular weight heparin and heparin. *Medicine (Baltimore)* 2020;**99**:e18729. https://doi.org/10.1097/MD.0000000000018729
817. Baudet EM, Puel V, McBride JT, Grimaud JP, Roques F, Clerc F, *et al.* Long-term results of valve replacement with the St. Jude Medical prosthesis. *J Thorac Cardiovasc Surg* 1995;**109**:858–70. https://doi.org/10.1016/s0022-5223(95)70309-8

818. Massel DR, Little SH. Antiplatelet and anticoagulation for patients with prosthetic heart valves. *Cochrane Database Syst Rev* 2013;**2013**:CD003464. https://doi.org/10.1002/14651858.CD003464.pub2
819. Torella M, Torella D, Chiodini P, Franciulli M, Romano G, De Santo L, *et al.* LOWERing the INtensity of oral anticoaGulant therapy in patients with bileaflet mechanical aortic valve replacement: results from the "LOWERING-IT" Trial. *Am Heart J* 2010;**160**:171–8. https://doi.org/10.1016/j.ahj.2010.05.005
820. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, *et al.* Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 2008;**118**:2029–37. https://doi.org/10.1161/CIRCULATIONAHA.107.750000
821. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, *et al.* Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;**369**:1206–14. https://doi.org/10.1056/NEJMoa1300615
822. Puskas JD, Gerdisch M, Nichols D, Fermin L, Rhenman B, Kapoor D, *et al.* Anticoagulation and antiplatelet strategies after On-X mechanical aortic valve replacement. *J Am Coll Cardiol* 2018;**71**:2717–26. https://doi.org/10.1016/j.jacc.2018.03.535
823. Schlitt A, von Bardeleben RS, Ehrlich A, Eimermacher A, Peetz D, Dahm M, *et al.* Clopidogrel and aspirin in the prevention of thromboembolic complications after mechanical aortic valve replacement (CAPTA). *Thromb Res* 2003;**109**:131–35. https://doi.org/10.1016/s0049-3848(03)00143-9
824. Wang TY, Svensson LG, Wen J, Vekstein A, Gerdisch M, Rao VU, *et al.* Apixaban or warfarin in patients with an On-X mechanical aortic valve. *NEJM Evid* 2023;**2**:EVIDoa2300067. https://doi.org/10.1056/EVIDoa2300067
825. Wang M, Zeraatkar D, Obeda M, Lee M, Garcia C, Nguyen L, *et al.* Drug–drug interactions with warfarin: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2021;**87**:4051–100. https://doi.org/10.1111/bcp.14833
826. Tan CSS, Lee SWH. Warfarin and food, herbal or dietary supplement interactions: a systematic review. *Br J Clin Pharmacol* 2021;**87**:352–74. https://doi.org/10.1111/bcp.14404
827. Heneghan CJ, Garcia-Alamino JM, Spencer EA, Ward AM, Perera R, Bankhead C, *et al.* Self-monitoring and self-management of oral anticoagulation. *Cochrane Database Syst Rev* 2016;**7**:CD003839. https://doi.org/10.1002/14651858.CD003839.pub3
828. Khouja C, Brunton G, Richardson M, Stokes G, Blanchard L, Burchett H, *et al.* Oral anticoagulants: a systematic overview of reviews on efficacy and safety, genotyping, self-monitoring, and stakeholder experiences. *Syst Rev* 2022;**11**:232. https://doi.org/10.1186/s13643-022-02098-w
829. Park YK, Lee MJ, Kim JH, Lee JS, Park RW, Kim GM, *et al.* Genetic and non-genetic factors affecting the quality of anticoagulation control and vascular events in atrial fibrillation. *J Stroke Cerebrovasc Dis* 2017;**26**:1383–90. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.02.022
830. Praxedes MFDS, Silva JLPD, Cruz AJAD, Viana CC, Barbosa HC, Guimaraes NS, *et al.* Assessment of the relationship between the level of patient knowledge on warfarin therapy and the quality of oral anticoagulation: a systematic review and meta-analysis. *PLoS One* 2023;**18**:e0289836. https://doi.org/10.1371/journal.pone.0289836
831. Marx N, Federici M, Schütt K, Muller-Wieland D, Ajjan RA, Antunes MJ, *et al.* 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J* 2023;**44**:4043–140. https://doi.org/10.1093/eurheartj/ehad192
832. Meurin P, Tabet JY, Weber H, Renaud N, Ben Driss A. Low-molecular-weight heparin as a bridging anticoagulant early after mechanical heart valve replacement. *Circulation* 2006;**113**:564–9. https://doi.org/10.1161/circulationaha.105.575571
833. Ferreira I, Dos L, Tornos P, Nicolau I, Permanyer-Miralda G, Soler-Soler J. Experience with enoxaparin in patients with mechanical heart valves who must withhold acenocumarol. *Heart* 2003;**89**:527–30. https://doi.org/10.1136/heart.89.5.527
834. Caldeira D, David C, Santos AT, Costa J, Pinto FJ, Ferreira JJ. Efficacy and safety of low molecular weight heparin in patients with mechanical heart valves: systematic review and meta-analysis. *J Thromb Haemost* 2014;**12**:650–9. https://doi.org/10.1111/jth.12544
835. Pengo V, Palareti G, Cucchini U, Molinatti M, Del Bono R, Baudo F, *et al.* Low-intensity oral anticoagulant plus low-dose aspirin during the first six months versus standard-intensity oral anticoagulant therapy after mechanical heart valve replacement: a pilot study of low-intensity warfarin and aspirin in cardiac prostheses (LIWACAP). *Clin Appl Thromb Hemost* 2007;**13**:241–8. https://doi.org/10.1177/1076029607302544
836. Meschengieser SS, Fondevila CG, Frontroth J, Santarelli MT, Lazzari MA. Low-intensity oral anticoagulation plus low-dose aspirin versus high-intensity oral anticoagulation alone: a randomized trial in patients with mechanical prosthetic heart valves. *J Thorac Cardiovasc Surg* 1997;**113**:910–6. https://doi.org/10.1016/s0022-5223(97)70264-2
837. Puskas J, Gerdisch M, Nichols D, Quinn R, Anderson C, Rhenman B, *et al.* Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized On-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. *J Thorac Cardiovasc Surg* 2014;**147**:1202–10; discussion 1210–1201. https://doi.org/10.1016/j.jtcvs.2014.01.004
838. Hanigan S, Kong X, Haymart B, Kline-Rogers E, Kaatz S, Krol G, *et al.* Standard versus higher intensity anticoagulation for patients with mechanical aortic valve replacement and additional risk factors for thromboembolism. *Am J Cardiol* 2021;**159**:100–6. https://doi.org/10.1016/j.amjcard.2021.08.023
839. Ray WA, Chung CP, Murray KT, Smalley WE, Daugherty JR, Dupont WD, *et al.* Association of proton pump inhibitors with reduced risk of warfarin-related serious upper gastrointestinal bleeding. *Gastroenterology* 2016;**151**:1105–12.e1110. https://doi.org/10.1053/j.gastro.2016.08.054
840. Kurlander JE, Barnes GD, Fisher A, Gonzalez JJ, Helminski D, Saini SD, *et al.* Association of antisecretory drugs with upper gastrointestinal bleeding in patients using oral anticoagulants: a systematic review and meta-analysis. *Am J Med* 2022;**135**:1231–43.e1238. https://doi.org/10.1016/j.amjmed.2022.05.031
841. Crowther MA, Ageno W, Garcia D, Wang L, Witt DM, Clark NP, *et al.* Oral vitamin K versus placebo to correct excessive anticoagulation in patients receiving warfarin: a randomized trial. *Ann Intern Med* 2009;**150**:293–300. https://doi.org/10.7326/0003-4819-150-5-200903030-00005
842. Khatib R, Ludwikowska M, Witt DM, Ansell J, Clark NP, Holbrook A, *et al.* Vitamin K for reversal of excessive vitamin K antagonist anticoagulation: a systematic review and meta-analysis. *Blood Adv* 2019;**3**:789–96. https://doi.org/10.1182/bloodadvances.2018025163
843. Gunther KE, Conway G, Leibach L, Crowther MA. Low-dose oral vitamin K is safe and effective for outpatient management of patients with an INR>10. *Thromb Res* 2004;**113**:205–9. https://doi.org/10.1016/j.thromres.2004.03.004
844. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;**3**:692–4. https://doi.org/10.1111/j.1538-7836.2005.01204.x
845. Brekelmans MPA, van Ginkel K, Daams JG, Hutten BA, Middeldorp S, Coppens M. Benefits and harms of 4-factor prothrombin complex concentrate for reversal of vitamin K antagonist associated bleeding: a systematic review and meta-analysis. *J Thromb Thrombolysis* 2017;**44**:118–29. https://doi.org/10.1007/s11239-017-1506-0
846. Chai-Adisaksopha C, Hillis C, Siegal DM, Movilla R, Heddle N, Iorio A, *et al.* Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal. A systematic review and meta-analysis. *Thromb Haemost* 2016;**116**:879–90. https://doi.org/10.1160/TH16-04-0266
847. Hood C, Goldstein JN, Milling TJ, Refaai MA, Bajcic P, Goldstein B, *et al.* INR and vitamin K-dependent factor levels after vitamin K antagonist reversal with 4F-PCC or plasma. *Blood Adv* 2023;**7**:2206–13. https://doi.org/10.1182/bloodadvances.2022009015
848. Sarode R, Milling TJJ, Refaai MA, Mangione A, Schneider A, Durn BL, *et al.* Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation* 2013;**128**:1234–43. https://doi.org/10.1161/CIRCULATIONAHA.113.002283
849. Erdoes G, Koster A, Ortmann E, Meesters MI, Bolliger D, Baryshnikova E, *et al.* A European consensus statement on the use of four-factor prothrombin complex concentrate for cardiac and non-cardiac surgical patients. *Anaesthesia* 2021;**76**:381–92. https://doi.org/10.1111/anae.15181
850. Eichinger S. Reversing vitamin K antagonists: making the old new again. *Hematology Am Soc Hematol Educ Program* 2016;**2016**:605–11. https://doi.org/10.1182/asheducation-2016.1.605
851. Birnie DH, Healey JS, Wells GA, Verma A, Tang AS, Krahn AD, *et al.* Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med* 2013;**368**:2084–93. https://doi.org/10.1056/NEJMoa1302946
852. Di Biase L, Burkhardt JD, Santangeli P, Mohanty P, Sanchez JE, Horton R, *et al.* Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) randomized trial. *Circulation* 2014;**129**:2638–44. https://doi.org/10.1161/CIRCULATIONAHA.113.006426
853. Engelen ET, Schutgens RE, Mauser-Bunschoten EP, van Es RJJ, van Galen KPM. Antifibrinolytic therapy for preventing oral bleeding in people on anticoagulants undergoing minor oral surgery or dental extractions. *Cochrane Database Syst Rev* 2018;**7**:CD012293. https://doi.org/10.1002/14651858.CD012293.pub2
854. Ghanbari H, Phard WS, Al-Ameri H, Latchamsetty R, Jongnarngsin K, Crawford T, *et al.* Meta-analysis of safety and efficacy of uninterrupted warfarin compared to heparin-based bridging therapy during implantation of cardiac rhythm devices. *Am J Cardiol* 2012;**110**:1482–8. https://doi.org/10.1016/j.amjcard.2012.06.057
855. Makuloluwa AK, Tiew S, Briggs M. Peri-operative management of ophthalmic patients on anti-thrombotic agents: a literature review. *Eye (Lond)* 2019;**33**:1044–59. https://doi.org/10.1038/s41433-019-0382-6
856. Nagata N, Yasunaga H, Matsui H, Fushimi K, Watanabe K, Akiyama J, *et al.* Therapeutic endoscopy-related GI bleeding and thromboembolic events in patients using warfarin or direct oral anticoagulants: results from a large nationwide database analysis. *Gut* 2018;**67**:1805–12. https://doi.org/10.1136/gutjnl-2017-313999

857. Dohler I, Roder D, Schlesinger T, Nassen CA, Germer CT, Wiegering A, *et al.* Risk-adjusted perioperative bridging anticoagulation reduces bleeding complications without increasing thromboembolic events in general and visceral surgery. *BMC Anesthesiol* 2023;**23**:56. https://doi.org/10.1186/s12871-023-02017-z
858. Shah S, Nayfeh T, Hasan B, Urtecho M, Firwana M, Saadi S, *et al.* Perioperative management of vitamin K antagonists and direct oral anticoagulants: a systematic review and meta-analysis. *Chest* 2023;**163**:1245–57. https://doi.org/10.1016/j.chest.2022.11.032
859. Gigante B, Tamargo J, Agewall S, Atar D, Ten Berg J, Campo G, *et al.* Update on antithrombotic therapy and body mass: a clinical consensus statement of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and the European Society of Cardiology Working Group on Thrombosis. *Eur Heart J Cardiovasc Pharmacother* 2024;**10**:614–45. https://doi.org/10.1093/ehjcvp/pvae064
860. Jeppsson A, Rocca B, Hansson EC, Gudbjartsson T, James S, Kaski JK, *et al.* 2024 EACTS Guidelines on perioperative medication in adult cardiac surgery. *Eur J Cardiothorac Surg* 2024;**67**:ezae355. https://doi.org/10.1093/ejcts/ezae355
861. Kovacs MJ, Wells PS, Anderson DR, Lazo-Langner A, Kearon C, Bates SM, *et al.* Postoperative low molecular weight heparin bridging treatment for patients at high risk of arterial thromboembolism (PERIOP2): double blind randomised controlled trial. *BMJ* 2021;**373**:n1205. https://doi.org/10.1136/bmj.n1205
862. Kuo HC, Liu FL, Chen JT, Cherng YG, Tam KW, Tai YH. Thromboembolic and bleeding risk of periprocedural bridging anticoagulation: a systematic review and meta-analysis. *Clin Cardiol* 2020;**43**:441–9. https://doi.org/10.1002/clc.23336
863. Siegal D, Yudin J, Kaatz S, Douketis JD, Lim W, Spyropoulos AC. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation* 2012;**126**:1630–9. https://doi.org/10.1161/CIRCULATIONAHA.112.105221
864. Yong JW, Yang LX, Ohene BE, Zhou YJ, Wang ZJ. Periprocedural heparin bridging in patients receiving oral anticoagulation: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2017;**17**:295. https://doi.org/10.1186/s12872-017-0719-7
865. Brennan JM, Edwards FH, Zhao Y, O'Brien S, Booth ME, Dokholyan RS, *et al.* Early anticoagulation of bioprosthetic aortic valves in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. *J Am Coll Cardiol* 2012;**60**:971–7. https://doi.org/10.1016/j.jacc.2012.05.029
866. Rafiq S, Steinbrüchel DA, Lilleør NB, Moller CH, Lund JT, Thiis JJ, *et al.* Antithrombotic therapy after bioprosthetic aortic valve implantation: warfarin versus aspirin, a randomized controlled trial. *Thromb Res* 2017;**150**:104–10. https://doi.org/10.1016/j.thromres.2016.11.021
867. Butnaru A, Shaheen J, Tzivoni D, Tauber R, Bitran D, Silberman S. Diagnosis and treatment of early bioprosthetic malfunction in the mitral valve position due to thrombus formation. *Am J Cardiol* 2013;**112**:1439–44. https://doi.org/10.1016/j.amjcard.2013.06.014
868. Russo A, Grigioni F, Avierinos JF, Freeman WK, Suri R, Michelena H, *et al.* Thromboembolic complications after surgical correction of mitral regurgitation incidence, predictors, and clinical implications. *J Am Coll Cardiol* 2008;**51**:1203–11. https://doi.org/10.1016/j.jacc.2007.10.058
869. Dangas GD, Tijssen JGP, Wöhrle J, Søndergaard L, Gilard M, Mollmann H, *et al.* A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med* 2020;**382**:120–9. https://doi.org/10.1056/NEJMoa1911425
870. Alkhalil M, Edwards R, Puri R, Kalra A, Zaman A, Das R. Aspirin versus dual antiplatelet therapy in patients undergoing trans-catheter aortic valve implantation, updated meta-analysis. *Cardiovasc Drugs Ther* 2022;**36**:279–83. https://doi.org/10.1007/s10557-021-07146-6
871. El Bèze N, Himbert D, Suc G, Brochet E, Ajzenberg N, Cailliau A, *et al.* Comparison of direct oral anticoagulants vs vitamin K antagonists after transcatheter mitral valve replacement. *J Am Coll Cardiol* 2024;**83**:334–46. https://doi.org/10.1016/j.jacc.2023.10.031
872. Carnicelli AP, De Caterina R, Halperin JL, Renda G, Ruff CT, Trevisan M, *et al.* Edoxaban for the prevention of thromboembolism in patients with atrial fibrillation and bioprosthetic valves. *Circulation* 2017;**135**:1273–5. https://doi.org/10.1161/CIRCULATIONAHA.116.026714
873. Guimarães HP, Lopes RD, de Barros E Silva PGM, Liporace IL, Sampaio RO, Tarasoutchi F, *et al.* Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. *N Engl J Med* 2020;**383**:2117–26. https://doi.org/10.1056/NEJMoa2029603
874. Philippart R, Brunet-Bernard A, Clementy N, Bourguignon T, Mirza A, Angoulvant D, *et al.* Oral anticoagulation, stroke and thromboembolism in patients with atrial fibrillation and valve bioprosthesis. The Loire Valley Atrial Fibrillation Project. *Thromb Haemost* 2016;**115**:1056–63. https://doi.org/10.1160/TH16-01-0007
875. Shim CY, Seo J, Kim YJ, Lee SH, De Caterina R, Lee S, *et al.* Efficacy and safety of edoxaban in patients early after surgical bioprosthetic valve implantation or valve repair: a randomized clinical trial. *J Thorac Cardiovasc Surg* 2023;**165**:58–67.e54. https://doi.org/10.1016/j.jtcvs.2021.01.127
876. Siontis KC, Yao X, Gersh BJ, Noseworthy PA. Direct oral anticoagulants in patients with atrial fibrillation and valvular heart disease other than significant mitral stenosis and mechanical valves: a meta-analysis. *Circulation* 2017;**135**:714–6. https://doi.org/10.1161/CIRCULATIONAHA.116.026793
877. Suppah M, Kamal A, Saadoun R, Baradeiya AMA, Abraham B, Alsidawi S, *et al.* An evidence-based approach to anticoagulation therapy comparing direct oral anticoagulants and vitamin K antagonists in patients with atrial fibrillation and bioprosthetic valves: a systematic review, meta-analysis, and network meta-analysis. *Am J Cardiol* 2023;**206**:132–50. https://doi.org/10.1016/j.amjcard.2023.07.141
878. Nijenhuis VJ, Brouwer J, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, *et al.* Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med* 2020;**382**:1696–707. https://doi.org/10.1056/NEJMoa1915152
879. Van Mieghem NM, Unverdorben M, Hengstenberg C, Mollmann H, Mehran R, Lopez-Otero D, *et al.* Edoxaban versus vitamin K antagonist for atrial fibrillation after TAVR. *N Engl J Med* 2021;**385**:2150–60. https://doi.org/10.1056/NEJMoa2111016
880. Collet JP, Van Belle E, Thiele H, Berti S, Lhermusier T, Manigold T, *et al.* Apixaban vs. standard of care after transcatheter aortic valve implantation: the ATLANTIS trial. *Eur Heart J* 2022;**43**:2783–97. https://doi.org/10.1093/eurheartj/ehac242
881. Brouwer J, Nijenhuis VJ, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, *et al.* Aspirin with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med* 2020;**383**:1447–57. https://doi.org/10.1056/NEJMoa2017815
882. Maes F, Stabile E, Ussia GP, Tamburino C, Pucciarelli A, Masson JB, *et al.* Meta-analysis comparing single versus dual antiplatelet therapy following transcatheter aortic valve implantation. *Am J Cardiol* 2018;**122**:310–5. https://doi.org/10.1016/j.amjcard.2018.04.006
883. Rodés-Cabau J, Masson JB, Welsh RC, Garcia Del Blanco B, Pelletier M, Webb JG, *et al.* Aspirin versus aspirin plus clopidogrel as antithrombotic treatment following transcatheter aortic valve replacement with a balloon-expandable valve: the ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) randomized clinical trial. *JACC Cardiovasc Interv* 2017;**10**:1357–65. https://doi.org/10.1016/j.jcin.2017.04.014
884. Meurin P, Tabet JY, Iliou MC, Pierre B, Corone S, Cristofini P, *et al.* Thromboembolic events early after mitral valve repair: incidence and predictive factors. *Int J Cardiol* 2008;**126**:45–52. https://doi.org/10.1016/j.ijcard.2007.03.115
885. van der Wall SJ, Olsthoorn JR, Heuts S, Klautz RJM, Tomsic A, Jansen EK, *et al.* Antithrombotic therapy after mitral valve repair: VKA or aspirin? *J Thromb Thrombolysis* 2018;**46**:473–81. https://doi.org/10.1007/s11239-018-1724-0
886. Mazur PK, Arghami A, Macielak SA, Nei SD, Viehman JK, King KS, *et al.* Apixaban for anticoagulation after robotic mitral valve repair. *Ann Thorac Surg* 2023;**115**:966–73. https://doi.org/10.1016/j.athoracsur.2022.07.045
887. Paparella D, Di Mauro M, Bitton Worms K, Bolotin G, Russo C, Trunfio S, *et al.* Antiplatelet versus oral anticoagulant therapy as antithrombotic prophylaxis after mitral valve repair. *J Thorac Cardiovasc Surg* 2016;**151**:1302–8.e1301. https://doi.org/10.1016/j.jtcvs.2015.12.036
888. Trevis J, Akowuah E. Which antithrombotic strategy provides the best outcomes after mitral valve repair in patients who remain in sinus rhythm? *Interact Cardiovasc Thorac Surg* 2022;**35**:ivac085. https://doi.org/10.1093/icvts/ivac085
889. Moser N, Omar MA, Koshman SL, Lin M, Youngson E, Kent W, *et al.* Direct oral anticoagulants for atrial fibrillation in early postoperative valve repair or bioprosthetic replacement. *J Thorac Cardiovasc Surg* 2023;**168**:523–32.e3. https://doi.org/10.1016/j.jtcvs.2023.03.004
890. Mentias A, Saad M, Michael M, Nakhla S, Menon V, Harb S, *et al.* Direct oral anticoagulants versus warfarin in patients with atrial fibrillation and valve replacement or repair. *J Am Heart Assoc* 2022;**11**:e026666. https://doi.org/10.1161/jaha.122.026666
891. Philippart R, Brunet-Bernard A, Clementy N, Bourguignon T, Mirza A, Babuty D, *et al.* Prognostic value of CHA_2DS_2-VASc score in patients with 'non-valvular atrial fibrillation' and valvular heart disease: the Loire Valley Atrial Fibrillation Project. *Eur Heart J* 2015;**36**:1822–30. https://doi.org/10.1093/eurheartj/ehv163
892. Jochheim D, Barbanti M, Capretti G, Stefanini GG, Hapfelmeier A, Zadrozny M, *et al.* Oral anticoagulant type and outcomes after transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2019;**12**:1566–76. https://doi.org/10.1016/j.jcin.2019.03.003
893. Didier R, Lhermusier T, Auffret V, Eltchaninoff H, Le Breton H, Cayla G, *et al.* TAVR patients requiring anticoagulation: direct oral anticoagulant or vitamin K antagonist? *JACC Cardiovasc Interv* 2021;**14**:1704–13. https://doi.org/10.1016/j.jcin.2021.05.025
894. Tanawuttiwat T, Stebbins A, Marquis-Gravel G, Vemulapalli S, Kosinski AS, Cheng A. Use of direct oral anticoagulant and outcomes in patients with atrial fibrillation after transcatheter aortic valve replacement: insights from the STS/ACC TVT registry. *J Am Heart Assoc* 2022;**11**:e023561. https://doi.org/10.1161/jaha.121.023561
895. VARC-3 Writing Committee; Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, *et al.* Valve academic research consortium 3: updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol* 2021;**77**:2717–46. https://doi.org/10.1016/j.jacc.2021.02.038
896. Pibarot P, Herrmann HC, Wu C, Hahn RT, Otto CM, Abbas AE, *et al.* Standardized definitions for bioprosthetic valve dysfunction following aortic or mitral valve replacement: *JACC* state-of-the-art review. *J Am Coll Cardiol* 2022;**80**:545–61. https://doi.org/10.1016/j.jacc.2022.06.002
897. Kaneko T, Bapat VN, Alakhtar AM, Zaid S, George I, Grubb KJ, *et al.* Transcatheter heart valve explantation for transcatheter aortic valve replacement failure: a Heart

Valve Collaboratory expert consensus document on operative techniques. *J Thorac Cardiovasc Surg* 2024;**169**:878–89. https://doi.org/10.1016/j.jtcvs.2024.04.025
898. Bleiziffer S, Rudolph TK. Patient prosthesis mismatch after SAVR and TAVR. *Front Cardiovasc Med* 2022;**9**:761917. https://doi.org/10.3389/fcvm.2022.761917
899. Hirji SA, Percy ED, Zogg CK, Malarczyk A, Harloff MT, Yazdchi F, *et al.* Comparison of in-hospital outcomes and readmissions for valve-in-valve transcatheter aortic valve replacement vs. reoperative surgical aortic valve replacement: a contemporary assessment of real-world outcomes. *Eur Heart J* 2020;**41**:2747–55. https://doi.org/10.1093/eurheartj/ehaa252
900. Tam DY, Vo TX, Wijeysundera HC, Dvir D, Friedrich JO, Fremes SE. Transcatheter valve-in-valve versus redo surgical aortic valve replacement for the treatment of degenerated bioprosthetic aortic valve: a systematic review and meta-analysis. *Catheter Cardiovasc Interv* 2018;**92**:1404–11. https://doi.org/10.1002/ccd.27686
901. Bleiziffer S, Simonato M, Webb JG, Rodes-Cabau J, Pibarot P, Kornowski R, *et al.* Long-term outcomes after transcatheter aortic valve implantation in failed bioprosthetic valves. *Eur Heart J* 2020;**41**:2731–42. https://doi.org/10.1093/eurheartj/ehaa544
902. Guerrero M, Vemulapalli S, Xiang Q, Wang DD, Eleid M, Cabalka AK, *et al.* Thirty-day outcomes of transcatheter mitral valve replacement for degenerated mitral bioprostheses (valve-in-valve), failed surgical rings (valve-in-ring), and native valve with severe mitral annular calcification (valve-in-mitral annular calcification) in the United States: data from the Society of Thoracic Surgeons/American College of Cardiology/Transcatheter Valve Therapy Registry. *Circ Cardiovasc Interv* 2020;**13**:e008425. https://doi.org/10.1161/CIRCINTERVENTIONS.119.008425
903. Eleid MF, Whisenant BK, Cabalka AK, Williams MR, Nejjari M, Attias D, *et al.* Early outcomes of percutaneous transvenous transseptal transcatheter valve implantation in failed bioprosthetic mitral valves, ring annuloplasty, and severe mitral annular calcification. *JACC Cardiovasc Interv* 2017;**10**:1932–42. https://doi.org/10.1016/j.jcin.2017.08.014
904. Little SH, Bapat V, Blanke P, Guerrero M, Rajagopal V, Siegel R. Imaging guidance for transcatheter mitral valve intervention on prosthetic valves, rings, and annular calcification. *JACC Cardiovasc Imaging* 2021;**14**:22–40. https://doi.org/10.1016/j.jcmg.2019.10.027
905. Fallon JM, DeSimone JP, Brennan JM, O'Brien S, Thibault DP, DiScipio AW, *et al.* The incidence and consequence of prosthesis-patient mismatch after surgical aortic valve replacement. *Ann Thorac Surg* 2018;**106**:14–22. https://doi.org/10.1016/j.athoracsur.2018.01.090
906. Flameng W, Herregods MC, Vercalsteren M, Herijgers P, Bogaerts K, Meuris B. Prosthesis-patient mismatch predicts structural valve degeneration in bioprosthetic heart valves. *Circulation* 2010;**121**:2123–9. https://doi.org/10.1161/CIRCULATIONAHA.109.901272
907. Zorn GLI, Little SH, Tadros P, Deeb GM, Gleason TG, Heiser J, *et al.* Prosthesis–patient mismatch in high-risk patients with severe aortic stenosis: a randomized trial of a self-expanding prosthesis. *J Thorac Cardiovasc Surg* 2016;**151**:1014–23.e3, 1023.e1011–1013. https://doi.org/10.1016/j.jtcvs.2015.10.070
908. Thourani VH, Abbas AE, Ternacle J, Hahn RT, Makkar R, Kodali SK, *et al.* Patient-prosthesis mismatch after surgical aortic valve replacement: analysis of the PARTNER trials. *Ann Thorac Surg* 2024;**117**:1164–71. https://doi.org/10.1016/j.athoracsur.2024.01.023
909. Tomii D, Okuno T, Heg D, Nakase M, Lanz J, Praz F, *et al.* Long-term outcomes of measured and predicted prosthesis-patient mismatch following transcatheter aortic valve replacement. *EuroIntervention* 2023;**19**:746–56. https://doi.org/10.4244/eij-d-23-00456
910. Vriesendorp MD, De Lind Van Wijngaarden RAF, Head SJ, Kappetein AP, Hickey GL, Rao V, *et al.* The fallacy of indexed effective orifice area charts to predict prosthesis–patient mismatch after prosthesis implantation. *Eur Heart J Cardiovasc Imaging* 2020;**21**:1116–22. https://doi.org/10.1093/ehjci/jeaa044
911. Sorajja P, Bae R, Lesser JA, Pedersen WA. Percutaneous repair of paravalvular prosthetic regurgitation: patient selection, techniques and outcomes. *Heart* 2015;**101**:665–73. https://doi.org/10.1136/heartjnl-2014-306270
912. Ruiz CE, Hahn RT, Berrebi A, Borer JS, Cutlip DE, Fontana G, *et al.* Clinical trial principles and endpoint definitions for paravalvular leaks in surgical prosthesis. *Eur Heart J* 2018;**39**:1224–45. https://doi.org/10.1093/eurheartj/ehx211
913. Laplace G, Lafitte S, Labèque JN, Perron JM, Baudet E, Deville C, *et al.* Clinical significance of early thrombosis after prosthetic mitral valve replacement: a postoperative monocentric study of 680 patients. *J Am Coll Cardiol* 2004;**43**:1283–90. https://doi.org/10.1016/j.jacc.2003.09.064
914. Symersky P, Budde RPJ, de Mol BAJM, Prokop M. Comparison of multidetector-row computed tomography to echocardiography and fluoroscopy for evaluation of patients with mechanical prosthetic valve obstruction. *Am J Cardiol* 2009;**104**:1128–34. https://doi.org/10.1016/j.amjcard.2009.05.061
915. Egbe AC, Pislaru SV, Pellikka PA, Poterucha JT, Schaff HV, Maleszewski JJ, *et al.* Bioprosthetic valve thrombosis versus structural failure: clinical and echocardiographic predictors. *J Am Coll Cardiol* 2015;**66**:2285–94. https://doi.org/10.1016/j.jacc.2015.09.022
916. Rheude T, Pellegrini C, Stortecky S, Marwan M, Xhepa E, Ammon F, *et al.* Meta-analysis of bioprosthetic valve thrombosis after transcatheter aortic valve implantation. *Am J Cardiol* 2021;**138**:92–9. https://doi.org/10.1016/j.amjcard.2020.10.018
917. Blanke P, Leipsic JA, Popma JJ, Yakubov SJ, Deeb GM, Gada H, *et al.* Bioprosthetic aortic valve leaflet thickening in the Evolut Low Risk sub-study. *J Am Coll Cardiol* 2020;**75**:2430–42. https://doi.org/10.1016/j.jacc.2020.03.022
918. Chakravarty T, Sondergaard L, Friedman J, De Backer O, Berman D, Kofoed KF, *et al.* Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet* 2017;**389**:2383–92. https://doi.org/10.1016/S0140-6736(17)30757-2
919. Makkar RR, Blanke P, Leipsic J, Thourani V, Chakravarty T, Brown D, *et al.* Subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves: PARTNER 3 cardiac computed tomography substudy. *J Am Coll Cardiol* 2020;**75**:3003–15. https://doi.org/10.1016/j.jacc.2020.04.043
920. De Backer O, Dangas GD, Jilaihawi H, Leipsic JA, Terkelsen CJ, Makkar R, *et al.* Reduced leaflet motion after transcatheter aortic-valve replacement. *N Engl J Med* 2020;**382**:130–9. https://doi.org/10.1056/NEJMoa1911426
921. Montalescot G, Redheuil A, Vincent F, Desch S, De Benedictis M, Eltchaninoff H, *et al.* Apixaban and valve thrombosis after transcatheter aortic valve replacement: the ATLANTIS-4D-CT randomized clinical trial substudy. *JACC Cardiovasc Interv* 2022;**15**:1794–804. https://doi.org/10.1016/j.jcin.2022.07.014
922. Ruile P, Jander N, Blanke P, Schoechlin S, Reinöhl J, Gick M, *et al.* Course of early subclinical leaflet thrombosis after transcatheter aortic valve implantation with or without oral anticoagulation. *Clin Res Cardiol* 2017;**106**:85–95. https://doi.org/10.1007/s00392-016-1052-3
923. Günduz S, Özkan M, Kalçik M, Gürsoy OM, Astarcioglu MA, Karakoyun S, *et al.* Sixty-four-section cardiac computed tomography in mechanical prosthetic heart valve dysfunction: thrombus or pannus. *Circ Cardiovasc Imaging* 2015;**8**:e003246. https://doi.org/10.1161/CIRCIMAGING.115.003246
924. Lancellotti P, Pibarot P, Chambers J, Edvardsen T, Delgado V, Dulgheru R, *et al.* Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging endorsed by the Chinese Society of Echocardiography, the Inter-American Society of Echocardiography, and the Brazilian Department of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016;**17**:589–90. https://doi.org/10.1093/ehjci/jew025
925. Tanis W, Habets J, van den Brink RBA, Symersky P, Budde RP, Chamuleau SA. Differentiation of thrombus from pannus as the cause of acquired mechanical prosthetic heart valve obstruction by non-invasive imaging: a review of the literature. *Eur Heart J Cardiovasc Imaging* 2014;**15**:119–29. https://doi.org/10.1093/ehjci/jet127
926. Karthikeyan G, Senguttuvan NB, Joseph J, Devasenapathy N, Bahl VK, Airan B. Urgent surgery compared with fibrinolytic therapy for the treatment of left-sided prosthetic heart valve thrombosis: a systematic review and meta-analysis of observational studies. *Eur Heart J* 2013;**34**:1557–66. https://doi.org/10.1093/eurheartj/ehs486
927. Castilho FM, De Sousa MR, Mendonca AL, Ribeiro AL, Caceres-Loriga FM. Thrombolytic therapy or surgery for valve prosthesis thrombosis: systematic review and meta-analysis. *J Thromb Haemost* 2014;**12**:1218–28. https://doi.org/10.1111/jth.12577
928. Chopard R, Vidoni C, Besutti M, Ismail M, Ecarnot F, Favoulet B, *et al.* Surgery versus thrombolytic therapy for the management of left-sided prosthetic valve thrombosis without hemodynamic compromise: a systematic review and meta-analysis. *J Am Heart Assoc* 2024;**13**:e035143. https://doi.org/10.1161/jaha.124.035143
929. Özkan M, Günduz S, Güner A, Kalcik M, Gursoy MO, Uygur B, *et al.* Thrombolysis or surgery in patients with obstructive mechanical valve thrombosis: the multicenter HATTUSHA study. *J Am Coll Cardiol* 2022;**79**:977–89. https://doi.org/10.1016/j.jacc.2021.12.027
930. Özkan M, Günduz S, Gürsoy OM, Karakoyun S, Astarcioglu MA, Kalcik M, *et al.* Ultraslow thrombolytic therapy: a novel strategy in the management of PROsthetic MEchanical valve thrombosis and the prEdictors of outcomE: the ultra-slow PROMETEE trial. *Am Heart J* 2015;**170**:409–18. https://doi.org/10.1016/j.ahj.2015.04.025
931. Sadeghipour P, Saedi S, Saneei L, Rafiee F, Yoosefi S, Parsaee M, *et al.* Fast vs. ultraslow thrombolytic infusion regimens in patients with obstructive mechanical prosthetic valve thrombosis: a pilot randomized clinical trial. *Eur Heart J Cardiovasc Pharmacother* 2022;**8**:668–76. https://doi.org/10.1093/ehjcvp/pvab083
931a. Karthikeyan G, Rajashekar P, Devasenapathy N, Biswas S, Kidambi B, Singal A, *et al.* Urgent surgery vs fibrinolytic therapy for left-sided prosthetic valve thrombosis: a randomized trial. *Eur Heart J* 2025:ehaf391. https://doi.org/10.1093/eurheartj/ehaf391
932. Bemurat LR, Laffort PR, Deville CJ, Roques XG, Baudet EM, Roudaut RP. Management of nonobstructive thrombosis of prosthetic mitral valve in asymptomatic patients in the early postoperative period: a study in 20 patients. *Echocardiography* 1999;**16**:339–46. https://doi.org/10.1111/j.1540-8175.1999.tb00823.x
933. Mutuberría-Urdaniz M, Rodríguez-Palomares JF, Ferreira I, Bañeras J, Teixidó G, Gutiérrez L, *et al.* Non-obstructive prosthetic heart valve thrombosis (NOPVT): really a benign entity? *Int J Cardiol* 2015;**197**:16–22. https://doi.org/10.1016/j.ijcard.2015.06.021

934. Egbe AC, Connolly HM, Pellikka PA, Schaff HV, Hanna R, Maleszewski JJ, *et al.* Outcomes of warfarin therapy for bioprosthetic valve thrombosis of surgically implanted valves: a prospective study. *JACC Cardiovasc Interv* 2017;**10**:379–87. https://doi.org/10.1016/j.jcin.2016.11.027
935. Jose J, Sulimov DS, El-Mawardy M, Sato T, Allali A, Holy EW, *et al.* Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. *JACC Cardiovasc Interv* 2017;**10**:686–97. https://doi.org/10.1016/j.jcin.2017.01.045
936. Petrescu I, Egbe AC, Ionescu F, Nkomo VT, Greason KL, Pislaru C, *et al.* Long-term outcomes of anticoagulation for bioprosthetic valve thrombosis. *J Am Coll Cardiol* 2020;**75**:857–66. https://doi.org/10.1016/j.jacc.2019.12.037
937. Pislaru SV, Hussain I, Pellikka PA, Maleszewski JJ, Hanna RD, Schaff HV, *et al.* Misconceptions, diagnostic challenges and treatment opportunities in bioprosthetic valve thrombosis: lessons from a case series. *Eur J Cardiothorac Surg* 2015;**47**:725–32. https://doi.org/10.1093/ejcts/ezu201
938. Puri R, Auffret V, Rodés-Cabau J. Bioprosthetic valve thrombosis. *J Am Coll Cardiol* 2017;**69**:2193–211. https://doi.org/10.1016/j.jacc.2017.02.051
939. Sellers SL, Turner CT, Sathananthan J, Cartlidge TRG, Sin F, Bouchareb R, *et al.* Transcatheter aortic heart valves: histological analysis providing insight to leaflet thickening and structural valve degeneration. *JACC Cardiovasc Imaging* 2019;**12**:135–45. https://doi.org/10.1016/j.jcmg.2018.06.028
940. Alkhouli M, Rihal CS, Zack CJ, Eleid MF, Maor E, Sarraf M, *et al.* Transcatheter and surgical management of mitral paravalvular leak: long-term outcomes. *JACC Cardiovasc Interv* 2017;**10**:1946–56. https://doi.org/10.1016/j.jcin.2017.07.046
941. Dvir D, Webb JG, Bleiziffer S, Pasic M, Waksman R, Kodali S, *et al.* Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA* 2014;**312**:162–70. https://doi.org/10.1001/jama.2014.7246
942. Yoon SH, Whisenant BK, Bleiziffer S, Delgado V, Dhoble A, Schofer N, *et al.* Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. *Eur Heart J* 2019;**40**:441–51. https://doi.org/10.1093/eurheartj/ehy590
943. Whisenant B, Kapadia SR, Eleid MF, Kodali SK, McCabe JM, Krishnaswamy A, *et al.* One-year outcomes of mitral valve-in-valve using the SAPIEN 3 transcatheter heart valve. *JAMA Cardiol* 2020;**5**:1245–52. https://doi.org/10.1001/jamacardio.2020.2974
944. McElhinney DB, Aboulhosn JA, Dvir D, Whisenant B, Zhang Y, Eicken A, *et al.* Mid-term valve-related outcomes after transcatheter tricuspid valve-in-valve or valve-in-ring replacement. *J Am Coll Cardiol* 2019;**73**:148–57. https://doi.org/10.1016/j.jacc.2018.10.051
945. Muratori M, Montorsi P, Teruzzi G, Celeste F, Doria E, Alamanni F, *et al.* Feasibility and diagnostic accuracy of quantitative assessment of mechanical prostheses leaflet motion by transthoracic and transesophageal echocardiography in suspected prosthetic valve dysfunction. *Am J Cardiol* 2006;**97**:94–100. https://doi.org/10.1016/j.amjcard.2005.07.112
946. Barbetseas J, Nagueh SF, Pitsavos C, Toutouzas PK, Quiñones MA, Zoghbi WA. Differentiating thrombus from pannus formation in obstructed mechanical prosthetic valves: an evaluation of clinical, transthoracic and transesophageal echocardiographic parameters. *J Am Coll Cardiol* 1998;**32**:1410–7. https://doi.org/10.1016/s0735-1097(98)00385-4
947. Suchá D, Symersky P, Vonken EJPA, Provoost E, Chamuleau SA, Budde RP. Multidetector-row computed tomography allows accurate measurement of mechanical prosthetic heart valve leaflet closing angles compared with fluoroscopy. *J Comput Assist Tomogr* 2014;**38**:451–6. https://doi.org/10.1097/RCT.0b013e3182ab5f15
948. Daniel WG, Mügge A, Grote J, Hausmann D, Nikutta P, Laas J, *et al.* Comparison of transthoracic and transesophageal echocardiography for detection of abnormalities of prosthetic and bioprosthetic valves in the mitral and aortic positions. *Am J Cardiol* 1993;**71**:210–5. https://doi.org/10.1016/0002-9149(93)90740-4
949. Özkan M, Çakal B, Karakoyun S, Gürsoy OM, Çevik C, Kalçık M, *et al.* Thrombolytic therapy for the treatment of prosthetic heart valve thrombosis in pregnancy with low-dose, slow infusion of tissue-type plasminogen activator. *Circulation* 2013;**128**:532–40. https://doi.org/10.1161/circulationaha.113.001145
950. Taherkhani M, Hashemi SR, Hekmat M, Safi M, Taherkhani A, Movahed MR. Thrombolytic therapy for right-sided mechanical pulmonic and tricuspid valves: the largest survival analysis to date. *Tex Heart Inst J* 2015;**42**:543–7. https://doi.org/10.14503/THIJ-14-4659
951. Roudaut R, Roques X, Lafitte S, Choukroun E, Laborde N, Madona F, *et al.* Surgery for prosthetic valve obstruction. A single center study of 136 patients. *Eur J Cardiothorac Surg* 2003;**24**:868–72. https://doi.org/10.1016/s1010-7940(03)00568-2
952. Nishanth KR, Shankar M, Srinivasa KH, Manjunath CN, Ravindranath KS. Fibrinolysis in left-sided mechanical prosthetic valve thrombosis with high INR. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:S58–62. https://doi.org/10.1177/2048872619846329
953. Separham A, Ghaffari S, Aslanabadi N, Sohrabi B, Ghojazadeh M, Anamzadeh E, *et al.* Prosthetic valve thrombosis. *J Card Surg* 2015;**30**:246–50. https://doi.org/10.1111/jocs.12510
954. Farzaneh K, Mortazavi SH, Oraii A, Abbasi K, Salehi Omran A, Ahmadi Tafti SH, *et al.* Safety of thrombolytic therapy in patients with prosthetic heart valve thrombosis who have high international normalized ratio levels. *J Card Surg* 2020;**35**:2522–8. https://doi.org/10.1111/jocs.14777
955. Jander N, Kienzle RP, Kayser G, Neumann FJ, Gohlke-Baerwolf C, Minners J. Usefulness of phenprocoumon for the treatment of obstructing thrombus in bioprostheses in the aortic valve position. *Am J Cardiol* 2012;**109**:257–62. https://doi.org/10.1016/j.amjcard.2011.08.038
956. Oliver JM, Gallego P, Gonzalez A, Dominguez FJ, Gamallo C, Mesa JM. Bioprosthetic mitral valve thrombosis: clinical profile, transesophageal echocardiographic features, and follow-up after anticoagulant therapy. *J Am Soc Echocardiogr* 1996;**9**:691–9. https://doi.org/10.1016/s0894-7317(96)90066-8
957. Agarwal S, Rajamanickam A, Bajaj NS, Griffin BP, Catacutan T, Svensson LG, *et al.* Impact of aortic stenosis on postoperative outcomes after noncardiac surgeries. *Circ Cardiovasc Qual Outcomes* 2013;**6**:193–200. https://doi.org/10.1161/CIRCOUTCOMES.111.000091
958. Taniguchi T, Morimoto T, Shiomi H, Ando K, Shirai S, Kanamori N, *et al.* Elective noncardiac surgery in patients with severe aortic stenosis — observations from the CURRENT AS registry. *Circ J* 2020;**84**:1173–82. https://doi.org/10.1253/circj.CJ-20-0026
959. Luis SA, Dohaei A, Chandrashekar P, Scott CG, Padang R, Lokineni S, *et al.* Impact of aortic valve replacement for severe aortic stenosis on perioperative outcomes following major noncardiac surgery. *Mayo Clin Proc* 2020;**95**:727–37. https://doi.org/10.1016/j.mayocp.2019.10.038
960. Halvorsen S, Mehilli J, Cassese S, Hall TS, Abdelhamid M, Barbato E, *et al.* 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing noncardiac surgery. *Eur Heart J* 2022;**43**:3826–924. https://doi.org/10.1093/eurheartj/ehac270
961. Okuno T, Demirel C, Tomii D, Erdoes G, Heg D, Lanz J, *et al.* Risk and timing of noncardiac surgery after transcatheter aortic valve implantation. *JAMA Netw Open* 2022;**5**:e2220689. https://doi.org/10.1001/jamanetworkopen.2022.20689
962. Tashiro T, Pislaru SV, Blustin JM, Nkomo VT, Abel MD, Scott CG, *et al.* Perioperative risk of major non-cardiac surgery in patients with severe aortic stenosis: a reappraisal in contemporary practice. *Eur Heart J* 2014;**35**:2372–81. https://doi.org/10.1093/eurheartj/ehu044
963. Okuno T, Yahagi K, Horiuchi Y, Sato Y, Tanaka T, Koseki K, *et al.* The role of transcatheter aortic valve replacement in the patients with severe aortic stenosis requiring major non-cardiac surgery. *Cardiovasc Interv Ther* 2019;**34**:345–51. https://doi.org/10.1007/s12928-019-00575-z
964. Calleja AM, Dommaraju S, Gaddam R, Cha S, Khandheria BK, Chaliki HP. Cardiac risk in patients aged >75 years with asymptomatic, severe aortic stenosis undergoing noncardiac surgery. *Am J Cardiol* 2010;**105**:1159–63. https://doi.org/10.1016/j.amjcard.2009.12.019
965. Sohrabi B, Kazemi B, Mehryar A, Teimouri-Dereshki A, Toufan M, Aslanabadi N. Correlation between pulmonary artery pressure measured by echocardiography and right heart catheterization in patients with rheumatic mitral valve stenosis (a prospective study). *Echocardiography* 2016;**33**:7–13. https://doi.org/10.1111/echo.13000
966. Smilowitz NR, Armanious A, Bangalore S, Ramakrishna H, Berger JS. Cardiovascular outcomes of patients with pulmonary hypertension undergoing noncardiac surgery. *Am J Cardiol* 2019;**123**:1532–7. https://doi.org/10.1016/j.amjcard.2019.02.006
967. Bajaj NS, Agarwal S, Rajamanickam A, Parashar A, Poddar KL, Griffin BP, *et al.* Impact of severe mitral regurgitation on postoperative outcomes after noncardiac surgery. *Am J Med* 2013;**126**:529–35. https://doi.org/10.1016/j.amjmed.2012.12.005
968. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundqvist C, Cifkova R, De Bonis M, *et al.* 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2018;**39**:3165–241. https://doi.org/10.1093/eurheartj/ehy340
969. Roos-Hesselink J, Baris L, Johnson M, De Backer J, Otto C, Marelli A, *et al.* Pregnancy outcomes in women with cardiovascular disease: evolving trends over 10 years in the ESC Registry Of Pregnancy And Cardiac disease (ROPAC). *Eur Heart J* 2019;**40**:3848–55. https://doi.org/10.1093/eurheartj/ehz136
970. Pande SN, Yavana Suriya J, Ganapathy S, Pillai AA, Satheesh S, Mondal N, *et al.* Validation of risk stratification for cardiac events in pregnant women with valvular heart disease. *J Am Coll Cardiol* 2023;**82**:1395–406. https://doi.org/10.1016/j.jacc.2023.07.023
971. van Hagen IM, Thorne SA, Taha N, Youssef G, Elnagar A, Gabriel H, *et al.* Pregnancy outcomes in women with rheumatic mitral valve disease: results from the Registry of Pregnancy and Cardiac Disease. *Circulation* 2018;**137**:806–16. https://doi.org/10.1161/CIRCULATIONAHA.117.032561
972. Orwat S, Diller GP, van Hagen IM, Schmidt R, Tobler D, Greutmann M, *et al.* Risk of pregnancy in moderate and severe aortic stenosis: from the multinational ROPAC registry. *J Am Coll Cardiol* 2016;**68**:1727–37. https://doi.org/10.1016/j.jacc.2016.07.750
973. Meijboom LJ, Vos FE, Timmermans J, Boers GH, Zwinderman AH, Mulder BJ. Pregnancy and aortic root growth in the Marfan syndrome: a prospective study. *Eur Heart J* 2005;**26**:914–20. https://doi.org/10.1093/eurheartj/ehi103
974. McKellar SH, MacDonald RJ, Michelena HI, Connolly HM, Sundt TMI. Frequency of cardiovascular events in women with a congenitally bicuspid aortic valve in a single

community and effect of pregnancy on events. *Am J Cardiol* 2011;**107**:96–9. https://doi.org/10.1016/j.amjcard.2010.08.061
975. Wichert-Schmitt B, Grewal J, Malinowski AK, Pfaller B, Losenno KL, Kiess MC, *et al.* Outcomes of pregnancy in women with bioprosthetic heart valves with or without valve dysfunction. *J Am Coll Cardiol* 2022;**80**:2014–24. https://doi.org/10.1016/j.jacc.2022.09.019
976. van Hagen IM, Roos-Hesselink JW, Ruys TPE, Merz WM, Goland S, Gabriel H, *et al.* Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation* 2015;**132**:132–42. https://doi.org/10.1161/CIRCULATIONAHA.115.015242
977. Pfaller B, Dave Javier A, Grewal J, Gabarin N, Colman J, Kiess M, *et al.* Risk associated with valvular regurgitation during pregnancy. *J Am Coll Cardiol* 2021;**77**:2656–64. https://doi.org/10.1016/j.jacc.2021.03.327
978. Hameed A, Karaalp IS, Tummala PP, Wani OR, Canetti M, Akhter MW, *et al.* The effect of valvular heart disease on maternal and fetal outcome of pregnancy. *J Am Coll Cardiol* 2001;**37**:893–9. https://doi.org/10.1016/s0735-1097(00)01198-0
979. Hoover E, Corlin T, Lohr J, Sabol B, Yamamura Y, Jacobs K, *et al.* TAVR beyond fetal viability: an alternative to preterm delivery in symptomatic severe aortic stenosis. *JACC Case Rep* 2023;**27**:102104. https://doi.org/10.1016/j.jaccas.2023.102104
980. Sajja A, Dassanayake M, Morales IA, Wenger NK, Smith C, Xie J, *et al.* Valve-in-valve transcatheter aortic valve replacement during second trimester of pregnancy. *JACC Case Rep* 2023;**27**:102074. https://doi.org/10.1016/j.jaccas.2023.102074
981. D'Souza R, Ostro J, Shah PS, Silversides CK, Malinowski A, Murphy KE, *et al.* Anticoagulation for pregnant women with mechanical heart valves: a systematic review and meta-analysis. *Eur Heart J* 2017;**38**:1509–16. https://doi.org/10.1093/eurheartj/ehx032
982. Fuchs A, Urena M, Chong-Nguyen C, Kikoine J, Brochet E, Abtan J, *et al.* Valve-in-valve and valve-in-ring transcatheter mitral valve implantation in young women contemplating pregnancy. *Circ Cardiovasc Interv* 2020;**13**:e009579. https://doi.org/10.1161/CIRCINTERVENTIONS.120.009579
983. Mascherbauer J, Kammerlander A, Nitsche C, Bax J, Delgado V, Evangelista A, *et al.* Sex-related differences in severe native valvular heart disease: the ESC-EORP Valvular Heart Disease II survey. *Eur Heart J* 2024;**45**:3818–33. https://doi.org/10.1093/eurheartj/ehae523
984. Cote N, Clavel MA. Sex differences in the pathophysiology, diagnosis, and management of aortic stenosis. *Cardiol Clin* 2020;**38**:129–38. https://doi.org/10.1016/j.ccl.2019.09.008
985. Habib G, Erba PA, Iung B, Donal E, Cosyns B, Laroche C, *et al.* Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study. *Eur Heart J* 2019;**40**:3222–32. https://doi.org/10.1093/eurheartj/ehz620
986. Avierinos JF, Inamo J, Grigioni F, Gersh B, Shub C, Enriquez-Sarano M. Sex differences in morphology and outcomes of mitral valve prolapse. *Ann Intern Med* 2008;**149**:787–95. https://doi.org/10.7326/0003-4819-149-11-200812020-00003
987. Brown JM, O'Brien SM, Wu C, Sikora JA, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. *J Thorac Cardiovasc Surg* 2009;**137**:82–90. https://doi.org/10.1016/j.jtcvs.2008.08.015
988. O'Brien SM, Feng L, He X, Xian Y, Jacobs JP, Badhwar V, *et al.* The Society of Thoracic Surgeons 2018 adult cardiac surgery risk models: part 2—statistical methods and results. *Ann Thorac Surg* 2018;**105**:1419–28. https://doi.org/10.1016/j.athoracsur.2018.03.003
989. Shan Y, Pellikka PA. Aortic stenosis in women. *Heart* 2020;**106**:970–6. https://doi.org/10.1136/heartjnl-2019-315407
990. Voisine M, Hervault M, Shen M, Boilard AJ, Filion B, Rosa M, *et al.* Age, sex, and valve phenotype differences in fibro-calcific remodeling of calcified aortic valve. *J Am Heart Assoc* 2020;**9**:e015610. https://doi.org/10.1161/JAHA.119.015610
991. Capoulade R, Clavel MA, Le Ven F, Dahou A, Thebault C, Tastet L, *et al.* Impact of left ventricular remodelling patterns on outcomes in patients with aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2017;**18**:1378–87. https://doi.org/10.1093/ehjci/jew288
992. Simard L, Côté N, Dagenais F, Mathieu P, Couture C, Trahan S, *et al.* Sex-related discordance between aortic valve calcification and hemodynamic severity of aortic stenosis: is valvular fibrosis the explanation? *Circ Res* 2017;**120**:681–91. https://doi.org/10.1161/CIRCRESAHA.116.309306
993. Bienjonetti-Boudreau D, Fleury MA, Voisine M, Paquin A, Chouinard I, Tailleur M, *et al.* Impact of sex on the management and outcome of aortic stenosis patients. *Eur Heart J* 2021;**42**:2683–91. https://doi.org/10.1093/eurheartj/ehab242
994. Tribouilloy C, Bohbot Y, Rusinaru D, Belkhir K, Diouf M, Altes A, *et al.* Excess mortality and undertreatment of women with severe aortic stenosis. *J Am Heart Assoc* 2021;**10**:e018816. https://doi.org/10.1161/JAHA.120.018816
995. Hartzell M, Malhotra R, Yared K, Rosenfield HR, Walker JD, Wood MJ. Effect of gender on treatment and outcomes in severe aortic stenosis. *Am J Cardiol* 2011;**107**:1681–6. https://doi.org/10.1016/j.amjcard.2011.01.059
996. Lowenstern A, Sheridan P, Wang TY, Boero I, Vemulapalli S, Thourani VH, *et al.* Sex disparities in patients with symptomatic severe aortic stenosis. *Am Heart J* 2021;**237**:116–26. https://doi.org/10.1016/j.ahj.2021.01.021
997. Onorati F, D'Errigo P, Barbanti M, Rosato S, Covello RD, Maraschini A, *et al.* Different impact of sex on baseline characteristics and major periprocedural outcomes of transcatheter and surgical aortic valve interventions: results of the multicenter Italian OBSERVANT registry. *J Thorac Cardiovasc Surg* 2014;**147**:1529–39. https://doi.org/10.1016/j.jtcvs.2013.05.039
998. Tchetche D, Pibarot P, Bax JJ, Bonaros N, Windecker S, Dumonteil N, *et al.* Transcatheter vs. surgical aortic valve replacement in women: the RHEIA trial. *Eur Heart J* 2025:ehaf133. https://doi.org/10.1093/eurheartj/ehaf133
999. Saad M, Nairooz R, Pothineni NVK, Almomani A, Kovelamudi S, Sardar P, *et al.* Long-term outcomes with transcatheter aortic valve replacement in women compared with men: evidence from a meta-analysis. *JACC Cardiovasc Interv* 2018;**11**:24–35. https://doi.org/10.1016/j.jcin.2017.08.015
1000. Akintoye E, Saijo Y, Braghieri L, Badwan O, Patel H, Dabbagh MM, *et al.* Impact of age and sex on left ventricular remodeling in patients with aortic regurgitation. *J Am Coll Cardiol* 2023;**81**:1474–87. https://doi.org/10.1016/j.jacc.2023.02.037
1001. Kammerlander AA, Donà C, Nitsche C, Koschutnik M, Zafar A, Eslami P, *et al.* Sex differences in left ventricular remodeling and outcomes in chronic aortic regurgitation. *J Clin Med* 2020;**9**:4100. https://doi.org/10.3390/jcm9124100
1002. Basso C, Iliceto S, Thiene G, Perazzolo Marra M. Mitral valve prolapse, ventricular arrhythmias, and sudden death. *Circulation* 2019;**140**:952–64. https://doi.org/10.1161/CIRCULATIONAHA.118.034075
1003. Stolfo D, Uijl A, Vedin O, Stromberg A, Faxen UL, Rosano GMC, *et al.* Sex-based differences in heart failure across the ejection fraction spectrum: phenotyping, and prognostic and therapeutic implications. *JACC Heart Fail* 2019;**7**:505–15. https://doi.org/10.1016/j.jchf.2019.03.011
1004. El Sabbagh A, Al-Hijji M, Wang DD, Eleid M, Urena M, Himbert D, *et al.* Predictors of left ventricular outflow tract obstruction after transcatheter mitral valve replacement in severe mitral annular calcification: an analysis of the Transcatheter Mitral Valve Replacement in Mitral Annular Calcification Global Registry. *Circ Cardiovasc Interv* 2021;**14**:e010854. https://doi.org/10.1161/CIRCINTERVENTIONS.121.010854
1005. Willner N, Burwash IG, Beauchesne L, Chan V, Vulesevic B, Ascah K, *et al.* Natural history of mitral annular calcification and calcific mitral valve disease. *J Am Soc Echocardiogr* 2022;**35**:925–32. https://doi.org/10.1016/j.echo.2022.05.007
1006. Offen S, Playford D, Strange G, Stewart S, Celermajer DS. Adverse prognostic impact of even mild or moderate tricuspid regurgitation: insights from the National Echocardiography Database of Australia. *J Am Soc Echocardiogr* 2022;**35**:810–17. https://doi.org/10.1016/j.echo.2022.04.003
1007. Mutlak D, Khalil J, Lessick J, Kehat I, Agmon Y, Aronson D. Risk factors for the development of functional tricuspid regurgitation and their population-attributable fractions. *JACC Cardiovasc Imaging* 2020;**13**:1643–51. https://doi.org/10.1016/j.jcmg.2020.01.015
1008. Prihadi EA, van der Bijl P, Gursoy E, Abou R, Mara Vollema E, Hahn RT, *et al.* Development of significant tricuspid regurgitation over time and prognostic implications: new insights into natural history. *Eur Heart J* 2018;**39**:3574–81. https://doi.org/10.1093/eurheartj/ehy352
1009. Beale AL, Nanayakkara S, Segan L, Mariani JA, Maeder MT, van Empel V, *et al.* Sex differences in heart failure with preserved ejection fraction pathophysiology: a detailed invasive hemodynamic and echocardiographic analysis. *JACC Heart Fail* 2019;**7**:239–49. https://doi.org/10.1016/j.jchf.2019.01.004
1010. Dietz MF, Prihadi EA, van der Bijl P, Fortuni F, Marques AI, Ajmone Marsan N, *et al.* Sex-specific differences in etiology and prognosis in patients with significant tricuspid regurgitation. *Am J Cardiol* 2021;**147**:109–15. https://doi.org/10.1016/j.amjcard.2021.02.016
1011. Pfannmueller B, Eifert S, Seeburger J, Misfeld M, Borger M, Mende M, *et al.* Gender-dependent differences in patients undergoing tricuspid valve surgery. *Thorac Cardiovasc Surg* 2013;**61**:37–41. https://doi.org/10.1055/s-0032-1324406
1012. Fortmeier V, Lachmann M, Körber MI, Unterhuber M, Schober AR, Stolz L, *et al.* Sex-related differences in clinical characteristics and outcome prediction among patients undergoing transcatheter tricuspid valve intervention. *JACC Cardiovasc Interv* 2023;**16**:909–23. https://doi.org/10.1016/j.jcin.2023.01.378
1013. Scotti A, Coisne A, Taramasso M, Granada JF, Ludwig S, Rodes-Cabau J, *et al.* Sex-related characteristics and short-term outcomes of patients undergoing transcatheter tricuspid valve intervention for tricuspid regurgitation. *Eur Heart J* 2023;**44**:822–32. https://doi.org/10.1093/eurheartj/ehac735