2021 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)

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KEYWORDS

- aortic regurgitation
- aortic stenosis
- guidelines
- mitral regurgitation
- mitral stenosis
- percutaneous valve intervention
- prosthetic heart valves
- tricuspid regurgitation
- tricuspid stenosis
- valve disease
- valve surgery
- valvular heart disease

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Councils: Council on Valvular Heart Disease.
Working Groups: Cardiovascular Surgery, Thrombosis.

Vahanian A, Beyersdorf F, Praz F, et al, 2021 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), *European Heart Journal*, 2021; doi:10.1093/eurheartj/ehab395. Reprinted by permission of Oxford University Press on behalf of the European Society of Cardiology.

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EuroIntervention 2022;17:e1126-e1196

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All experts involved in the development of these guidelines have submitted declarations of interest.

These have been compiled in a report and published in a supplementary document simultaneously to the guidelines. The report is also available on the ESC website www.escardio.org/guidelines.

For the Supplementary Data which include background information and detailed discussion of the data that have provided the basis for the guidelines see European Heart Journal online.

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

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Abbreviations and acronyms

2D	Two-dimensional
3D	Three-dimensional
ACEI	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
ARC-HBR	Academic Research Consortium-High Bleeding Risk
ASA	Acetylsalicylic acid
AVA	Aortic valve area
BAV	Balloon aortic valvuloplasty
BHV	Biological heart valve
BVF	Bioprosthetic valve failure
BNP	B-type natriuretic peptide
BP	Blood pressure
BSA	Body surface area
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCT	Cardiac computed tomography
CI	Confidence interval
CMR	Cardiac magnetic resonance
CRT	Cardiac resynchronization therapy
CT	Computed tomography
DAPT	Dual antiplatelet therapy
DPm	Mean pressure gradient
DSE	Dobutamine stress echocardiography
DVI	Doppler velocity index/dimensionless index
EACTS	European Association for Cardio-Thoracic Surgery
ECG	Electrocardiogram
EDV	End-diastolic velocity
EROA	Effective regurgitant orifice area
ESC	European Society of Cardiology
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FFP	Fresh frozen plasma
GDMT	Guideline-directed medical treatment therapy
HALT	Hypo-attenuated leaflet thickening
HTx	Heart transplantation
INR	International normalized ratio
i.v.	Intravenous
LA	Left atrium/left atrial
LAA	Left atrial appendage
LMWH	Low-molecular-weight heparin
LV	Left ventricle/left ventricular
LVAD	Left ventricular assist devices
LVEDD	Left ventricular end-diastolic diameter
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic diameter
LVOT	Left ventricular outflow tract
MAC	Mitral annular calcification
MHV	Mechanical heart valve
MIDA	Mitral Regurgitation International Database
MVA	Mitral valve area
NCS	Non-cardiac surgery
NOAC	Non-vitamin K antagonist oral anticoagulant
NYHA	New York Heart Association
OAC	Oral anticoagulation
PCC	Prothrombin complex concentration
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PISA	Proximal isovelocity surface area
PMC	Percutaneous mitral commissurotomy
PMR	Primary mitral regurgitation
PPM	Patient-prosthesis mismatch
PROM	Predicted risk of mortality
RCT	Randomized controlled trial
RV	Right ventricle/right ventricular
SAPT	Single antiplatelet therapy
SAVR	Surgical aortic valve replacement
SMR	Secondary mitral regurgitation
SVD	Structural valve deterioration
SPAP	Systolic pulmonary arterial pressure
STS	Society of Thoracic Surgeons
SVi	Stroke volume index
TAPSE	Tricuspid annular pulmonary systolic excursion
TAVI	Transcatheter aortic valve implantation
TE	Thromboembolism
TEER	Transcatheter edge-to-edge repair
TTVI	Transcatheter tricuspid valve intervention
TOE	Transoesophageal echocardiography
TTE	Transthoracic echocardiography
TVI	Time-velocity integral
TVR	Tricuspid valve replacement or repair
UFH	Unfractionated heparin
VHD	Valvular heart disease
VKA	Vitamin K antagonist
V_{max}	**Peak** transvalvular velocity

1 Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in proposing the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC) and its partners such as the European Association for Cardio-Thoracic Surgery (EACTS), as well as by other societies and organizations. Because of their impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (https://www.escardio.org/Guidelines). The ESC Guidelines

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

represent the official position of the ESC on a given topic and are regularly updated.

In addition to the publication of Clinical Practice Guidelines, the ESC carries out the EURObservational Research Programme of international registries of cardiovascular diseases and interventions which are essential to assess diagnostic/therapeutic processes, use of resources and adherence to guidelines. These registries aim at providing a better understanding of medical practice in Europe and around the world, based on high-quality data collected during routine clinical practice.

The Members of this Task Force were selected by the ESC and EACTS, including representation from relevant ESC and EACTS sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Clinical Practice Guidelines Committee (CPG). A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk-benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined below.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules and can be found on the ESC website (http://www.escardio.org/guidelines) and have been compiled in a report and published in a supplementary document simultaneously to the guidelines.

This process ensures transparency and prevents potential biases in the development and review processes. Any changes in declarations of interest that arise during the writing period were notified

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.

to the ESC and updated. The Task Force received its entire financial support from the ESC and EACTS without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new guidelines. The Committee is also responsible for the endorsement process of these guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions the guidelines are signed-off by all the experts involved in the Task Force. The finalized document is signed-off by the CPG for publication in the European Heart Journal and the European Journal of Cardio-Thoracic Surgery. The guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC/EACTS Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, summary cards for non-specialists and an electronic version for digital applications (smartphones, etc.). These versions are abridged and thus, for more detailed information, the user should always access to the full text version of the guidelines, which is freely available via the ESC and EACTS website and hosted on the EHJ and EJCTS website. The National Cardiac Societies of the ESC are encouraged to endorse, adopt, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Health professionals are encouraged to take the ESC/EACTS Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC/EACTS Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the healthcare professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription.

2 Introduction

2.1 WHY DO WE NEED NEW GUIDELINES ON VALVULAR HEART DISEASE?

Since the publication of the previous version of the guidelines on the management of valvular heart disease (VHD) in 2017, new evidence has accumulated, particularly on the following topics:

- Epidemiology: the incidence of the degenerative aetiology has increased in industrialized countries while, unfortunately, rheumatic heart disease is still too frequently observed in many parts of the world.[1-3]
- Current practices regarding interventions and medical management have been analysed in new surveys at the national and European level.
- Non-invasive evaluation using three-dimensional (3D) echocardiography, cardiac computed tomography (CCT), cardiac magnetic resonance (CMR), and biomarkers plays a more and more central role.
- New definitions of severity of secondary mitral regurgitation (SMR) based on the outcomes of studies on intervention.
- New evidence on anti-thrombotic therapies leading to new recommendations in patients with surgical or transcatheter bioprostheses for bridging during perioperative periods and over the long term. The recommendation for non- vitamin K antagonist oral anticoagulants (NOACs) was reinforced in patients with native valvular disease, except for significant mitral stenosis, and in those with bioprostheses.
- Risk stratification for the timing of intervention. This applies mostly to (i) the evaluation of progression in asymptomatic patients based on recent longitudinal studies mostly in aortic stenosis, and (ii) interventions in high-risk patients in whom futility should be avoided. Regarding this last aspect, the role of frailty is outlined.
- Results and indication of intervention:
  - The choice of the mode of intervention: current evidence reinforces the critical role of the Heart Team, which should integrate clinical, anatomical, and procedural characteristics beyond conventional scores, and informed patient's treatment choice.
  - Surgery: increasing experience and procedural safety led to expansion of indications toward earlier intervention in asymptomatic patients with aortic stenosis, aortic regurgitation or mitral regurgitation and stress the preference for valve repair when it is expected to be durable. A particular emphasis is put on the need for more comprehensive evaluation and earlier surgery in tricuspid regurgitation.
  - Transcatheter techniques: (i) Concerning transcatheter aortic valve implantation (TAVI), new information from randomized studies comparing TAVI vs. surgery in low-risk patients with a follow-up of 2 years has led to a need to clarify which types of patients should be considered for each mode of intervention. (ii) Transcatheter edge-to-edge repair (TEER) is increasingly used in SMR and has been evaluated against optimal medical therapy resulting in an upgrade of the recommendation. (iii) The larger number of studies on transcatheter valve-in-valve implantation after failure of surgical bioprostheses served as a basis to upgrade its indication. (iv) Finally, the encouraging preliminary experience with transcatheter tricuspid valve interventions (TTVI) suggests a potential role of this treatment in inoperable patients, although this needs to be confirmed by further evaluation.

The new evidence described above made a revision of the recommendations necessary.

2.2 METHODOLOGY

In preparation of the 2021 VHD Guidelines, a methodology group has been created for the first time, to assist the Task Force for the collection and interpretation of the evidence supporting specific

Table 3. What is new.

New or Revised	Recommendations in 2017 version	Class	Recommendations in 2021 version	Class
Section 3. Management of atrial fibrillation in patients with native VHD				
Revised	Surgical excision or external clipping of the LAA may be considered in patients undergoing valve surgery.	IIb	LAA occlusion should be considered to reduce the thromboembolic risk in patients with AF and a CHA_2DS_2VASc score ≥2 undergoing valve surgery.	IIa
Revised	NOACs should be considered as an alternative to VKAs in patients with aortic stenosis, aortic regurgitation and mitral regurgitation presenting with AF.	IIa	For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs in patients with aortic stenosis, aortic and mitral regurgitation.	I
Section 4. Recommendations on indications for surgery in severe aortic regurgitation				
Revised	Surgery is indicated in asymptomatic patients with resting ejection fraction ≤50%.	I	Surgery is recommended in asymptomatic patients with LVESD >50 mm or LVESD >25 mm/m² BSA (in patients with small body size) or resting LVEF ≤50%.	I
	Surgery should be considered in asymptomatic patients with resting ejection fraction >50% with severe LV dilatation: LVEDD >70 mm or LVESD >50 mm (or LVESD >25 mm/m² BSA in patients with small body size).	IIa		
New			Surgery may be considered in asymptomatic patients with LVESD >20 mm/m² BSA (especially in patients with small body size) or resting LVEF ≤55%, if surgery at low-risk.	IIb
Revised	Heart Team discussion is recommended in selected patients in whom aortic valve repair may be a feasible alternative to valve replacement.	I	Aortic valve repair may be considered in selected patients at experienced centres when durable results are expected.	IIb
Section 4. Recommendations on indications for surgery in aortic root or tubular ascending aortic aneurysm (irrespective of the severity of aortic regurgitation)				
Revised	Aortic valve repair, using the reimplantation or remodelling with aortic annuloplasty technique, is recommended in young patients with aortic root dilation and tricuspid aortic valves, when performed by experienced surgeons.	I	Valve-sparing aortic root replacement is recommended in young patients with aortic root dilation, if performed in experienced centres and durable results are expected.	I
Section 5. Recommendations on indications for intervention in symptomatic and asymptomatic aortic stenosis				
Symptomatic aortic stenosis				
Revised	Intervention is indicated in symptomatic patients with severe, high-gradient aortic stenosis (mean gradient ≥40 mmHg or peak velocity ≥4.0 m/s).	I	Intervention is recommended in symptomatic patients with severe, high-gradient aortic stenosis [mean gradient ≥40 mmHg, peak velocity ≥4.0 m/s and valve area ≤1.0 cm² (or ≤0.6 cm²/m²)].	I
Asymptomatic patients with severe aortic stenosis				
New			Intervention should be considered in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF <55%) without another cause.	IIa
Revised	SAVR should be considered in asymptomatic patients with normal ejection fraction and none of the above-mentioned exercise test abnormalities if the surgical risk is low and one of the following findings is present: • Very severe aortic stenosis defined by a V_{max} >5.5 m/s. • Severe valve calcification and a rate of V_{max} progression ≥0.3 m/s/year. • Markedly elevated BNP levels (>3x age- and sex-corrected normal range) confirmed by repeated measurements without other explanations. • Severe pulmonary hypertension (systolic pulmonary artery pressure at rest >60 mmHg confirmed by invasive measurement) without other explanation.	IIa	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 aortic stenosis (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 (>3x age- and sex-corrected normal range) confirmed by repeated measurements and without other explanation.	IIa

Section 5. Recommended mode of intervention in patients with aortic stenosis				
Revised	The choice for intervention must be based on careful individual evaluation of technical suitability and weighing of risks and benefits of each modality. In addition, the local expertise and outcomes data for the given intervention must be taken into account.	I	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
Revised	SAVR is recommended in patients at low surgical risk (STS or EuroSCORE II <4% or logistic EuroSCORE I <10%, and no other risk factors not included in these scores, such as frailty, porcelain aorta, sequelae of chest radiation).	I	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
Revised	TAVI is recommended in patients who are not suitable for SAVR as assessed by the Heart Team.	I	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
Revised	In patients who are at increased surgical risk (STS or EuroSCORE II ≥4% or logistic EuroSCORE I ≥10%, or other risk factors not included in these scores such as frailty, porcelain aorta, sequelae of chest radiation), the decision between SAVR and TAVI should be made by the Heart Team according to the individual patient characteristics, with TAVI being favoured in elderly patients suitable for transfemoral access.	I	SAVR or TAVI are recommended for remaining patients according to individual clinical, anatomical and procedural characteristics.	I
New			Non-transfemoral TAVI may be considered in patients who are inoperable for SAVR and unsuitable for transfemoral TAVI.	IIb
Section 6. Indications for intervention in severe primary mitral regurgitation				
Revised	Surgery is indicated in asymptomatic patients with LV dysfunction (LVESD ≥45 mm and/or LVEF ≤60%).	I	Surgery is recommended in asymptomatic patients with LV dysfunction (LVESD ≥40 mm and/or LVEF ≤60%).	I
Revised	Surgery should be considered in asymptomatic patients with preserved LV function (LVESD <45 mm and LVEF >60%) and AF secondary to mitral regurgitation or pulmonary hypertension (SPAP at rest >50 mmHg).	IIa	Surgery should be considered in asymptomatic patients with preserved LV function (LVESD <40 mm and LVEF >60%) and AF secondary to mitral regurgitation or pulmonary hypertension (SPAP at rest >50 mmHg).	IIa
Revised	Surgery should be considered in asymptomatic patients with preserved LVEF (>60%) and LVESD 40-44 mm when a durable repair is likely, surgical risk is low, the repair is performed in a Heart Valve Centre and at least one of the following findings is present: • flail leaflet or; • presence of significant LA dilatation (volume index ≥60 mL/m^2 BSA) in sinus rhythm.	IIa	Surgical mitral valve 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
Section 6. Indications for mitral valve intervention in chronic severe secondary mitral regurgitation				
New			Valve surgery/intervention is recommended only in patients with severe SMR who remain symptomatic despite GDMT (including CRT if indicated) and has to be decided by a structured collaborative Heart Team.	I
Patients with concomitant coronary artery or other cardiac disease requiring treatment				
New			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
Revised	Surgery is indicated in patients with severe SMR undergoing CABG and LVEF >30%.	I	Valve surgery is recommended in patients undergoing CABG or other cardiac surgery.	I

Patients without concomitant coronary artery or other cardiac disease requiring treatment				
Revised	When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary mitral regurgitation and LVEF >30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have a suitable valve morphology by echocardiography, avoiding futility.	**IIb**	TEER should be considered in selected symptomatic patients, not eligible for surgery and fulfilling criteria suggesting an increased chance of responding to the therapy.	**IIa**
Revised	In patients with severe SMR and LVEF <30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplant according to individual patient characteristics.	**IIb**	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 trans-catheter valve therapy if applicable, after careful evaluation for ventricular assist device or heart transplant.	**IIb**
Section 8. Indications for intervention in primary tricuspid regurgitation				
Revised	Surgery should be considered in asymptomatic or mildly symptomatic patients with severe isolated primary tricuspid regurgitation and progressive RV dilatation or deterioration of RV function.	**IIa**	Surgery should be considered in asymptomatic or mildly symptomatic patients with isolated severe primary tricuspid regurgitation and RV dilatation who are appropriate for surgery.	**IIa**
Revised	After previous left-sided surgery and in absence of recurrent left-sided valve dysfunction, surgery should be considered in patients with severe tricuspid regurgitation who are symptomatic or have progressive RV dilatation/dysfunction, in the absence of severe RV or LV dysfunction and severe pulmonary vascular disease/hypertension.	**IIa**	Surgery should be considered in patients with severe secondary tricuspid regurgitation (with or without previous left-sided surgery) who are symptomatic or have RV dilatation, in the absence of severe RV or LV dysfunction and severe pulmonary vascular disease/hypertension.	**IIa**
New			Transcatheter treatment of symptomatic secondary severe tricuspid regurgitation may be considered in inoperable patients at a Heart Valve Centre with expertise in the treatment of tricuspid valve disease.	**IIb**
Section 11. Recommendations for prosthetic valve selection				
New			A bioprosthesis may be considered in patients already on long-term NOACs due to the high risk for thromboembolism.	**IIb**
Revised	A bioprosthesis should be considered in those (patients) whose life expectancy is lower than the presumed durability of the bioprosthesis.	**IIa**	A bioprosthesis is recommended when good-quality anticoagulation is unlikely (adherence problems, not readily available), contraindicated because of high bleeding risk (previous major bleed, comorbidities, unwillingness, adherence problems, life-style, occupation) and in those patients whose life expectancy is lower than the presumed durability of the bioprosthesis.	**I**
Section 11. Recommendations for perioperative and postoperative antithrombotic management of valve replacement or repair				
Management of antithrombotic therapy in the perioperative period				
New			Bridging of OAC, when interruption is needed, is recommended in patients with any of the following indication: • Mechanical prosthetic heart valve. • AF with significant mitral stenosis. • AF with a 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**
New			It is recommended that VKAs are timely discontinued prior to elective surgery to aim for an INR <1.5.	**I**

New			In patients undergoing surgery, it is recommended that aspirin therapy, if indicated, is maintained during the periprocedural period.	I
New			In patients who have undergone valve surgery with an indication for postoperative therapeutic bridging, it is recommended to start either UFH or LMWH 12-24 hours after surgery.	I
New			In patients with MHVs, it is recommended to (re)-initiate VKAs on the first postoperative day.	I
New			In patients treated with DAPT after recent PCI (within 1 month) who need to undergo heart valve surgery, in the absence of an indication for OAC, it is recommended to resume the $P2Y_{12}$ inhibitor postoperatively, as soon as there is no concern over bleeding.	I
New			In patients treated with DAPT after recent PCI (within 1 month) who need to undergo heart valve surgery, in the absence of an indication for OAC, bridging $P2Y_{12}$ inhibitors with glycoprotein IIb/IIIa inhibitors or cangrelor may be considered.	IIb
Patients with an indication to concomitant antiplatelet therapy				
Revised	In patients undergoing an uncomplicated PCI dual therapy comprising VKA and clopidogrel (75 mg/day) should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk.	IIa	After uncomplicated PCI or ACS in patients requiring long -term OAC, early cessation (≤1 week) of aspirin and continuation of dual therapy with OAC and a $P2Y_{12}$ inhibitor (preferably clopidogrel) for up to 6 months (or up to 12 months in ACS) is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used.	I
New			Discontinuation of antiplatelet treatment in patients treated with an OAC is recommended after 12 months.	I
New			In patients treated with a VKA (e.g. MHVs), clopidogrel alone should be considered in selected patients (e.g. HAS-BLED ≥3 or ARC-HBR met and low risk of stent thrombosis) for up to 12 months.	IIa
New			In patients requiring aspirin and/or clopidogrel in addition to VKA, the dose intensity of VKA should be considered and carefully regulated with a target INR in the lower part of the recommended target range and a time in the therapeutic range >65-70%.	IIa
New			After uncomplicated PCI or ACS in patients requiring both OAC and antiplatelet therapy, triple therapy with aspirin, clopidogrel and OAC for longer than 1 week should be considered when the risk of stent thrombosis outweighs the risk of bleeding, with a total duration (≤1 month) decided according to assessment of these risks and clearly specified at hospital discharge.	IIa
Surgical valve replacement				
New			NOACs should be considered over VKA after 3 months following surgical implantation of a BHV, in patients with AF.	IIa
New			In patients with no baseline indications for OAC, low-dose aspirin (75-100 mg/day) or OAC using a VKA should be considered for the first 3 months after surgical implantation of an aortic BHV.	IIa
New			NOACs may be considered over VKA within 3 months following surgical implantation of a BHV in mitral position in patients with AF.	IIb

Transcatheter Aortic Valve Implantation				
New			OAC is recommended lifelong for TAVI patients who have other indications for OAC.	I
Revised	SAPT may be considered after TAVI in the case of high bleeding risk.	IIb	Lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC.	I
New			Routine use of OAC is not recommended after TAVI in patients with no baseline indication for OAC.	III
Section 11. Recommendations on management of prosthetic valve dysfunction				
Haemolysis and paravalvular leak				
New			Decision on transcatheter or surgical closure of clinically significant paravalvular leaks should be considered based on patient risk status, leak morphology, and local expertise.	IIa
Bioprosthetic thrombosis				
New			Anticoagulation should be considered in patients with leaflet thickening and reduced leaflet motion leading to elevated gradients, at least until resolution.	IIa
Bioprosthetic failure				
New			Transcatheter valve-in-valve implantation in the mitral and tricuspid position may be considered in selected patients at high-risk for surgical re-intervention.	IIb

ACS: acute coronary syndrome; AF: atrial fibrillation; ARC-HBR: Academic Research Consortium - high bleeding risk; BHV: biological heart valve; BNP: B-type natriuretic peptide; BSA: body surface area; CABG: Coronary artery bypass grafting; CCT: cardiac computed tomography; CRT: cardiac resynchronization therapy; DAPT: dual anti-platelet therapy; EuroSCORE: European System for Cardiac Operative Risk Evaluation; GDMT: guideline-directed medical therapy; INR: international normalized ratio; LA: left atrium/left atrial; LAA: left atrial appendage; LMWH: low-molecular-weight heparin; LV: left ventricle/left ventricular; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: Left ventricular end-systolic diameter; MHV: mechanical heart valve; NOAC: non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulation; PCI: percutaneous coronary intervention; RV: right ventricle/right ventricular; SAPT: single antiplatelet therapy; SAVR: surgical aortic valve replacement; SMR: secondary mitral regurgitation; SPAP: systolic pulmonary arterial pressure; STS-PROM: Society of Thoracic Surgeons - predicted risk of mortality; TAVI: transcatheter aortic valve implantation; TEER: transcatheter edge-to-edge repair; UFH: unfractionated heparin; VHD: valvular heart disease; VKA: vitamin K antagonist; V_{max}: peak transvalvular velocity.

recommendations. The group was constituted of two European Society of Cardiology (ESC) and two European Association for Cardio-Thoracic Surgery (EACTS) delegates who were also members of the Task Force. Although the principle activities of the group concerned the chapter on aortic stenosis and SMR, it was not limited to these two domains. The methodology group was at disposal, upon request of the Task Force members, to resolve specific methodological issues.

2.3 CONTENT OF THESE GUIDELINES

Decision making in VHD involves accurate diagnosis, timing of intervention, risk assessment and, based on these, selection of the most suitable type of intervention. These guidelines focus on acquired VHD, are oriented towards management, and do not deal with endocarditis,[4] congenital valve disease[5] (including pulmonary valve disease), or recommendations concerning sports cardiology and exercise in patients with cardiovascular disease,[6] as separate guidelines have been published by the ESC on these topics.

2.4 NEW FORMAT OF THE GUIDELINES

The new guidelines have been adapted to facilitate their use in clinical practice and to meet readers' demands by focusing on condensed, clearly represented recommendations. At the end of the document, key points summarize the essentials. Gaps in evidence are listed to propose topics for future research. The guideline document will be harmonized with the chapter on VHD included in the ESC Textbook of Cardiovascular Medicine (ISBN: 9780198784906). The guidelines and the textbook are complementary. Background information and detailed discussion of the data that have provided the basis for the recommendations will be found in the relevant book chapter.

2.5 HOW TO USE THESE GUIDELINES

The Committee emphasizes that many factors ultimately determine the most appropriate treatment in individual patients within a given community. These factors include the availability of diagnostic equipment, the expertise of cardiologists and surgeons, especially in the field of valve repair and percutaneous intervention, and, notably, the wishes of well-informed patients. Furthermore, owing to the lack of evidence-based data in the field of VHD, most recommendations are largely the result of expert consensus opinion. Therefore, deviations from these guidelines may be appropriate in certain clinical circumstances.

3 General comments

This section defines and discusses concepts common to all the types of VHD including the Heart Team and Heart Valve Centres,

the main evaluation steps of patients presenting with VHD, as well as the most commonly associated cardiac diseases.

3.1 CONCEPTS OF HEART TEAM AND HEART VALVE CENTRE

The main purpose of Heart Valve Centres as centres of excellence in the treatment of VHD is to deliver optimal quality of care with a patient-centred approach. The main requirements of a Heart Valve Centre are presented in **Table 4**.

This is achieved through high procedural volume in conjunction with specialized training, continuous education, and focused clinical interest. Heart Valve Centres should promote timely referral of patients with VHD for comprehensive evaluation before irreversible damage occurs.

Decisions concerning treatment and intervention should be made by an active and collaborative Heart Team with expertise in VHD, comprising clinical and interventional cardiologists, cardiac surgeons, imaging specialists with expertise in interventional imaging,[7,8] cardiovascular anaesthesiologists, and other specialists if necessary (e.g. heart failure specialists or electrophysiologists). Dedicated nursing personnel with expertise in the care of patients with VHD are also an important asset to the Heart Team. The Heart Team approach is particularly advisable for the management of high-risk and asymptomatic patients, as well as in case of uncertainty or lack of strong evidence.

Heart Valve Clinics are an important component of the Heart Valve Centres, aiming to provide standardized organization of care based on guidelines. Access to Heart Valve Clinics improves outcomes.[9]

Table 4. Requirements for a Heart Valve Centre.

Requirements
Centre performing heart valve procedures with institutional cardiology and cardiac surgery departments with 24 h/7-day services.
Heart Team: clinical cardiologist, interventional cardiologist, cardiac surgeon, imaging specialist with expertise in interventional imaging, cardiovascular anaesthesiologist.
Additional specialists if required: heart failure specialist, electrophysiologist, geriatrician and other specialists (intensive care, vascular surgery, infectious disease, neurology). Dedicated nursing personnel is an important asset to the Heart Team. The Heart Team must meet on a frequent basis and work with standard operating procedures and clinical governance arrangements defined locally. A hybrid catheterization laboratory is desirable. The entire spectrum of surgical and transcatheter valve procedures should be available. High volume for hospital and individual operators.
Multimodality imaging including echocardiography, CCT, CMR, and nuclear medicine, as well as expertise on guidance of surgical and interventional procedures.
Heart Valve Clinic for outpatient and follow-up management.
Data review: continuous evaluation of outcomes with quality review and/or local/external audit. Education programmes targeting patient primary care, operator, diagnostic and interventional imager training and referring cardiologist.
CCT: cardiac computed tomography; CMR: cardiac magnetic resonance.

Physicians experienced in the management of VHD and dedicated nurses organize outpatient visits, and referral to the Heart Team, if needed. Earlier referral should be encouraged if patient's symptoms develop or worsen before the next planned visit.[10,11]

Beside the whole spectrum of valvular interventions, expertise in interventional and surgical management of coronary artery disease (CAD), vascular diseases, and complications must be available.

Techniques with a steep learning curve may be performed with better results at hospitals with high procedural volume and experience. The relationship between case volume and outcomes for surgery and transcatheter interventions is complex but should not be denied.[12-14] However, the precise numbers of procedures per individual operator or hospital required to provide high-quality care remain controversial as inequalities exist between high- and middle-income countries.[15] High-volume TAVI programmes are associated with lower mortality at 30 days, particularly at hospitals with a high surgical aortic valve replacement (SAVR) volume.[16,17] The data available on transcatheter mitral valve repair[14,18] and, even more so, transcatheter tricuspid procedures are more limited.

Since performance does not exclusively relate to intervention volume, internal quality assessment consisting of systematic recording of procedural data and patient outcomes at the level of a given Heart Valve Centre is essential, as well as participation in national or ESC/EACTS registries.

A Heart Valve Centre should have structured and possibly combined training programmes for interventionalists, cardiac surgeons, and imaging specialists[13,19,20] (https://ebcts.org/syllabus/). New techniques should be taught by competent mentors to minimize the effects of the learning curve.

Finally, Heart Valve Centres should contribute to optimizing the management of patients with VHD, provide corresponding services at the community level, and promote networks that include other medical departments, referring cardiologists and primary care physicians.

3.2 PATIENT EVALUATION

The aims of the evaluation of patients with VHD are to diagnose, quantify, and assess the mechanism of VHD, as well as its consequences.

3.2.1 CLINICAL EVALUATION

Precise evaluation of the patient's history and symptomatic status, and proper physical examination, in particular auscultation[21] and search for heart failure signs, are crucial. In addition, assessment of their comorbidities and general condition require particular attention. The essential questions in the evaluation of a patient for valvular intervention are summarized in **Figure 1 (Central illustration)**.

3.2.2 ECHOCARDIOGRAPHY

Following adequate clinical evaluation, echocardiography is the key technique used to confirm the diagnosis of VHD, as well as to assess its aetiology, mechanisms, function, severity, and prognosis. It should be performed and interpreted by properly trained imagers.[22,23]

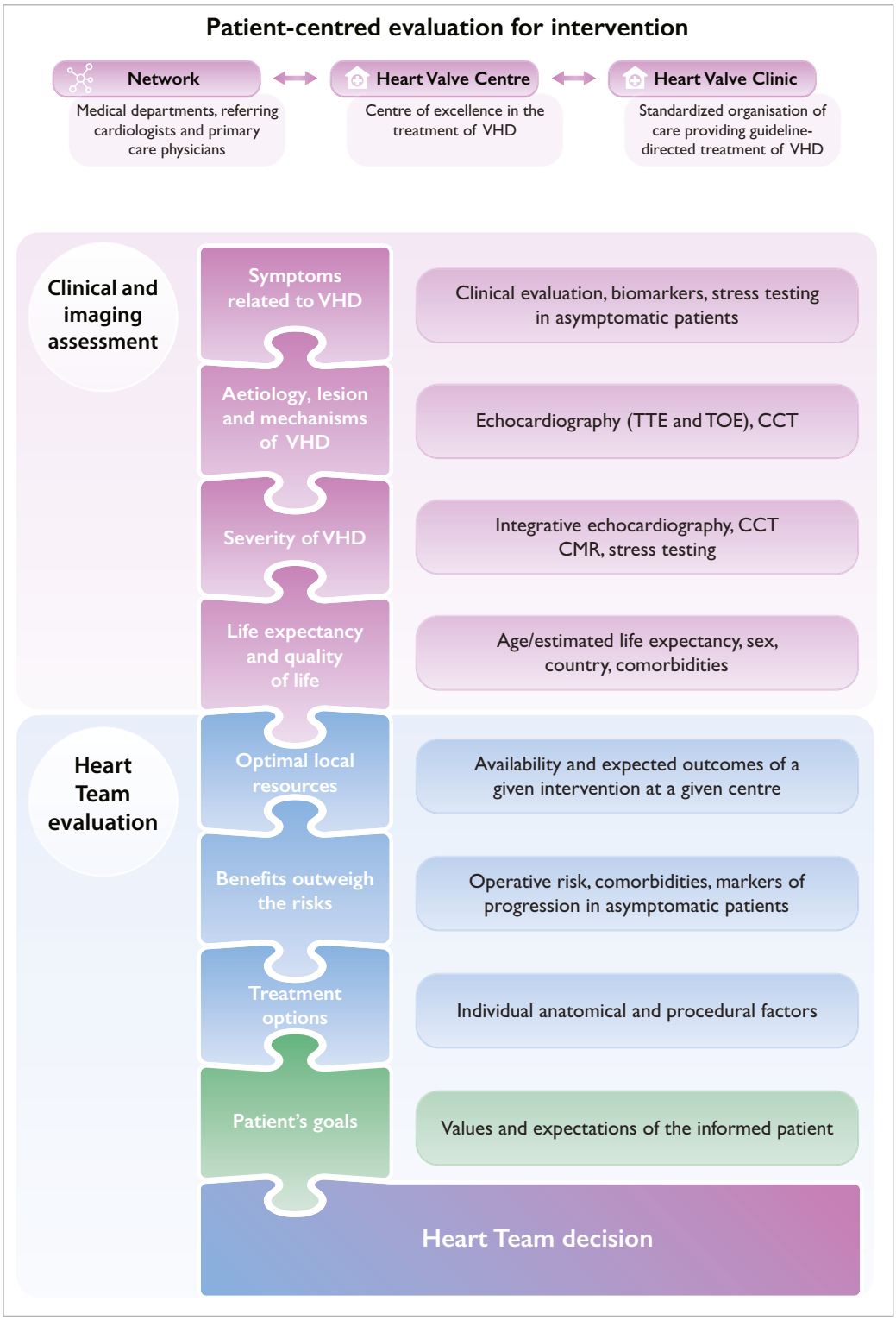

Figure 1. *Central illustration: Patient-centred evaluation for intervention. VHD: valvular heart disease; CCT: cardiac computed tomography; CMR: cardiac magnetic resonance; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography.*

Echocardiographic criteria for the definition of severe valve stenosis and regurgitation are addressed in specific documents[24,25] and summarized in the specific sections of these guidelines. Echocardiography is also key to evaluating the feasibility of a specific intervention.

Indices of left ventricular (LV) enlargement and function are strong prognostic factors. Recent studies suggest that global longitudinal strain has greater prognostic value than LV ejection fraction (LVEF), although cut-off values are not uniform.[26,27] Transoesophageal echocardiography (TOE) should be considered

when transthoracic echocardiography (TTE) is of suboptimal quality or when thrombosis, prosthetic valve dysfunction, or endocarditis is suspected. TOE is useful when detailed functional valve anatomy is required to assess repairability. Intraprocedural TOE, preferably 3D, is used to guide transcatheter mitral and tricuspid valve procedures and to assess the immediate result of surgical valve operations. Multimodality imaging may be required in specific conditions for evaluation and/or procedural guidance in TAVI and transcatheter mitral interventions.[28,29]

3.2.3 OTHER NON-INVASIVE INVESTIGATIONS

3.2.3.1 Stress testing

The primary purpose of exercise testing is to unmask the objective occurrence of symptoms in patients who claim to be asymptomatic. It is especially useful for risk stratification in aortic stenosis.[30] Exercise testing will also determine the level of recommended physical activity, including participation in sports. It should be emphasized that stress testing is safe and useful in asymptomatic patients with VHD. Unfortunately, the VHD II survey indicates that it is rarely performed in asymptomatic patients.[1]

Exercise echocardiography may identify the cardiac origin of dyspnoea. Prognostic impact has been shown mainly for aortic stenosis and mitral regurgitation.[31,32]

The use of stress tests to detect CAD associated with severe valvular disease is discouraged because of their low diagnostic value and potential risks in symptomatic patients with aortic stenosis.

3.2.3.2 Cardiac magnetic resonance

In patients with inadequate echocardiographic quality or discrepant results, CMR should be used to assess the severity of valvular lesions, particularly regurgitant lesions, and to assess ventricular volumes, systolic function, abnormalities of the ascending aorta, and myocardial fibrosis.[33] CMR is the reference method for the evaluation of right ventricular (RV) volumes and function and is therefore particularly useful to evaluate the consequences of tricuspid regurgitation.[34] It also has an incremental value for assessing the severity of aortic and mitral regurgitation.

3.2.3.3 Computed tomography

CCT may contribute to the evaluation of valve disease severity, particularly in aortic stenosis[35,36] and possibly associated disease of the thoracic aorta (dilatation, calcification), as well as to evaluate the extent of MAC. CCT should be performed whenever the echocardiographic data indicate an aortic enlargement >40 mm, to clarify aortic diameter and to assess aortic morphology and configuration. CCT is essential in the pre-procedural planning of TAVI and can also be useful to assess patient-prosthesis mismatch (PPM).[37] It is also a prerequisite for pre-procedural planning of mitral and tricuspid valve interventions.[38] Positron emission tomography (PET)/CCT is useful in patients with a suspicion of endocarditis of a prosthetic valve.[39,40]

3.2.3.4 Cinefluoroscopy

Cinefluoroscopy is particularly useful for assessing the kinetics of the leaflet occluders of a mechanical prosthesis.

3.2.3.5 Biomarkers

B-type natriuretic peptide (BNP) serum levels, corrected for age and sex, are useful in asymptomatic patients and may assist selection of the appropriate time point for a given intervention,[41] particularly if the level rises during follow-up. Other biomarkers have been tested, with evidence for fibrosis, inflammation, and adverse ventricular remodelling, which could improve decision making.[42]

3.2.3.6 Multimarkers and staging

In patients with at least moderate aortic stenosis and LVEF >50%, staging according to damage associated with aortic stenosis on LV/RV, left atrium (LA), mitral /tricuspid valve, and pulmonary circulation was predictive of excess mortality after TAVI and SAVR, and may help to identify patients who will benefit from an intervention.[43,44]

3.2.4 INVASIVE INVESTIGATIONS

3.2.4.1 Coronary angiography

Coronary angiography is recommended for the assessment of CAD when surgery or an intervention is planned, to determine if concomitant coronary revascularization is recommended (see recommendations for management of CAD in patients with VHD).[45,46] Alternatively, owing to its high negative predictive value, CCT may be used to rule out CAD in patients who are at low risk of atherosclerosis. The usefulness of fractional flow reserve or instantaneous wave-free ratio in patients with VHD is not well established, and caution is warranted in the interpretation of these measurements when VHD, and in particular aortic stenosis, is present.[47,48]

3.2.4.2 Cardiac catheterization

The measurement of pressures and cardiac output or the assessment of ventricular performance and valvular regurgitation by ventricular angiography or aortography is restricted to situations where non-invasive evaluation by multimodality imaging is inconclusive or discordant with clinical findings. When elevated, pulmonary pressure is the only criterion to support the indication for surgery, and confirmation of echo data by invasive measurement is recommended. Right heart catheterization is also indicated in patients with severe tricuspid regurgitation as Doppler gradient may be impossible or underestimate the severity of pulmonary hypertension.

3.2.5 ASSESSMENT OF COMORBIDITY

The choice of specific examinations to assess comorbidity is guided by the clinical evaluation.

3.3 RISK STRATIFICATION

Risk stratification applies to any sort of intervention and is required for weighing the risk of intervention against the expected natural history of VHD and for choosing the type of intervention. Most experience relates to surgery and TAVI.

3.3.1 RISK SCORES

The Society of Thoracic Surgeons (STS) predicted risk of mortality (PROM) score (http://riskcalc.sts.org/stswebriskcalc/calculate) and the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II; http://www.euroscore.org/calc.html) accurately discriminate high- and low-risk surgical patients and show good calibration to predict postoperative outcome after valvular surgery in the majority of the patients,[49,50] while risk estimation may be less accurate in high-risk patients.[51] The STS-PROM score is dynamic and changes over time. Of note, the risk scores have not been validated for isolated tricuspid surgical interventions.

In isolation, surgical scores have major limitations for practical use in patients undergoing transcatheter intervention because they do not include major risk factors such as frailty, as well as anatomical factors with impact on the procedure, either surgical or transcatheter [porcelain aorta, previous chest radiation, mitral annular calcification (MAC)].

New scores have been developed to estimate the risk in patients undergoing TAVI, with better accuracy and discrimination than the surgical risk scores, despite numerous limitations[52-54] **(Supplementary Table 1)**.

Experience with risk stratification is currently limited for other interventional procedures, such as mitral or tricuspid interventions.

3.3.2 OTHER FACTORS

Other factors should be taken into account:

- Frailty, defined as a decrease of physiologic reserve and ability to maintain homeostasis leading to an increased vulnerability to stresses and conferring an increased risk of morbidity and mortality after both surgery and TAVI.[55] The assessment of frailty should not rely on a subjective approach, such as the 'eyeball test', but rather on a combination of different objective estimates.[55-59] Several tools are available for assessing frailty (**Supplementary Table 2**,[59] and **Supplementary Table 3**).[60]
- Malnutrition[61] and cognitive dysfunction[62] both predict poor prognosis.
- Other major organ failures **(Supplementary Table 4)**, in particular the combination of severe lung disease,[63,64] postoperative pain from sternotomy or thoracotomy and prolonged time under anaesthesia in patients undergoing SAVR via full sternotomy, may contribute to pulmonary complications. There is a positive association between the impairment of renal function and increased mortality after valvular surgery and transcatheter procedures,[65] especially when the glomerular filtration rate is <30 mL/min. Liver disease, is also an important prognostic factor.[66]
- Anatomical aspects affecting procedural performance such as porcelain aorta or severe MAC[67] (see **Table 6** in section 5.1.3, and **Supplementary Figure 1**).

At the extreme of the risk spectrum, futility should be avoided. Therapeutic futility has been defined as a lack of medical efficacy, particularly when the physician judges that the therapy is unlikely to produce its intended clinical results, or lack of meaningful survival according to the personal values of the patient. Assessment of futility goes beyond survival and includes functional recovery. The futility of interventions has to be taken into consideration, particularly for transcatheter interventions.[63]

The high prevalence of comorbidity in the elderly makes assessment of the risk/benefit ratios of interventions more difficult, therefore the role of the Heart Team is essential in this specific population of patients **(Supplementary Table 5)**.

3.4 PATIENT-RELATED ASPECTS

Patient-related life expectancy and expected quality of life should be considered. The patient and their family should be thoroughly informed and assisted in their decision on the best treatment option.[13] A patient-centred approach would take patient-reported outcome measures and patient-reported experience measures into consideration and make these parameters part of the informed choice offered to patients.[68,69]

When benefit in symptom relief aligns with a patient's goals, care is not futile. However, care is futile when no life prolongation or symptom relief is anticipated.[70]

3.5 LOCAL RESOURCES

Even if it is desirable that Heart Valve Centres are able to perform a large spectrum of procedures, either surgical or catheter-based, specialization and thereby expertise in specific domains will vary and should be taken into account when deciding on the orientation of the patient in specific cases, such as complex surgical valve repair or transcatheter intervention.

In addition, penetration of transcatheter interventions is heterogeneous worldwide and highly dependent on socioeconomic inequalities.[15,71] Appropriate stewardship of economic resources is a fundamental responsibility of the Heart Team.

3.6 MANAGEMENT OF ASSOCIATED CONDITIONS

3.6.1 CORONARY ARTERY DISEASE

Recommendations for the management of CAD associated with VHD are provided below and are detailed in specific sections (section 5 and section 6.2) of this guideline document, as well as in other dedicated guideline documents.[45,46,72,73]

3.6.2 ATRIAL FIBRILLATION

Detailed recommendations on the management of patients with atrial fibrillation (AF) including management of anticoagulation are provided in specific guidelines.[74] NOACs are recommended in patients with aortic stenosis, aortic regurgitation or mitral regurgitation presenting with AF[75-78] as subgroup analyses of randomized controlled trials (RCTs) support the use of apixaban, dabigatran, edoxaban, and rivaroxaban. The use of NOACs is not recommended in patients who have AF associated with clinically significant mitral stenosis or those with mechanical prostheses.

Surgical ablation of AF combined with mitral valve surgery effectively reduces the incidence of AF but has no impact on adjusted short-term survival. An increased rate of pacemaker implantation has been observed after surgical ablation (9.5%, vs. 7.6% in the group with AF and no surgical ablation).[79] Concomitant AF ablation should be considered in patients undergoing cardiac surgery, balancing the benefits of freedom from atrial arrhythmias with the risk factors for recurrence, such as age, LA dilatation, years in AF, renal dysfunction, and other cardiovascular risk factors. In addition, left atrial appendage (LAA) occlusion should be considered in combination with valve surgery in patients with AF and a CHA_2DS_2VASc score ≥2 to reduce the thromboembolic risk.[80-82] The selected surgical technique should ensure complete occlusion of the LAA. For patients with AF and risk factors for stroke, long-term oral anticoagulation (OAC) is currently recommended, irrespective of the use of surgical ablation of AF and/or surgical LAA occlusion.

Recommendations for management of CAD in patients with VHD

Recommendations	Class[a]	Level[b]
Diagnosis of CAD		
Coronary angiography is recommended before valve surgery in patients with severe VHD and any of the following: • History of cardiovascular disease. • Suspected myocardial ischaemia.[c] • LV systolic dysfunction. • In men >40 years of age and postmenopausal women. • One or more cardiovascular risk factors.	I	C
Coronary angiography is recommended in the evaluation of severe SMR.	I	C
Coronary CT angiography should be considered as an alternative to coronary angiography before valve surgery in patients with severe VHD and low probability of CAD.[d]	IIa	C
Indications for myocardial revascularization		
CABG is recommended in patients with a primary indication for aortic/mitral/tricuspid valve surgery and coronary artery diameter stenosis ≥70%.[e,f]	I	C
CABG should be considered in patients with a primary indication for aortic/mitral/tricuspid valve surgery and coronary artery diameter stenosis ≥50-70%.	IIa	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 should be considered in patients with a primary indication to undergo transcatheter mitral valve intervention and coronary artery diameter stenosis >70% in proximal segments.	IIa	C

CABG: coronary artery bypass grafting; CAD: coronary artery disease; CT: computed tomography; LV: left ventricle/left ventricular; PCI: percutaneous coronary intervention; SMR: secondary mitral regurgitation; TAVI: transcatheter aortic valve implantation; VHD: valvular heart disease. [a]Class of recommendation. [b]Level of evidence. [c]Chest pain, abnormal non-invasive testing. [d]Coronary CT angiography may also be used in patients requiring emergency surgery with acute infective endocarditis with large vegetations protruding in front of a coronary ostium. [e]Stenosis ≥50% can be considered for left main stenosis. [f]FFR ≤0.8 is a useful cut-off indicating the need for an intervention in patients with mitral or tricuspid diseases, but has not been validated in patients with aortic stenosis. Adapted from[45,72]

Recommendations for the management of AF in native VHD are summarized in the following table. The recommendations concerning patients with valve prostheses, and the combination of anticoagulants and antiplatelet agents in patients undergoing PCI, are described in section 11 (section 11.3.2.2 and related table of recommendations for perioperative and postoperative antithrombotic management of valve replacement or repair).

3.7 ENDOCARDITIS PROPHYLAXIS

Antibiotic prophylaxis should be considered for high-risk procedures in patients with prosthetic valves, including transcatheter valves, or with repairs using prosthetic material, and in patients with previous episode(s) of infective endocarditis.[4] Particular attention to dental and cutaneous hygiene and strict aseptic measures during any invasive procedure are advised in this population. Antibiotic prophylaxis should be considered in dental procedures involving manipulation of the gingival or periapical region of the teeth or manipulation of the oral mucosa.[4]

Recommendations on management of atrial fibrillation in patients with native VHD

Recommendations	Class[a]	Level[b]
Anticoagulation		
For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs in patients with aortic stenosis, aortic and mitral regurgitation.[75-78,83,84]	I	A
The use of NOACs is not recommended in patients with AF and moderate to severe mitral stenosis.	III	C
Surgical interventions		
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).[79,85-90]	IIa	A
LAA occlusion should be considered to reduce the thromboembolic risk in patients, with AF and a CHA_2DS_2VASc score ≥2 undergoing valve surgery.[82]	IIa	B

AF: atrial fibrillation; LA: left atrium/left atrial; LAA: left atrial appendage; NOAC: non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulation; VKA: vitamin K antagonist. [a]Class of recommendation. [b]Level of evidence.

3.8 PROPHYLAXIS FOR RHEUMATIC FEVER

Prevention of rheumatic heart disease should preferably target the first attack of acute rheumatic fever. Antibiotic treatment of group A Streptococcus infection throat is key in primary prevention. Echocardiographic screening in combination with secondary antibiotic prophylaxis in children with evidence of latent rheumatic heart disease is currently investigated to reduce its prevalence in endemic regions.[91] In patients with established rheumatic heart disease, secondary long-term prophylaxis against rheumatic fever is recommended: benzathine benzyl penicillin 1.2 MUI every 3 to 4 weeks over 10 years. Lifelong prophylaxis should be considered in high-risk patients according to the severity of VHD and exposure to group A Streptococcus.[92-95]

4 Aortic regurgitation

Aortic regurgitation can be caused by primary disease of the aortic valve cusps and/or abnormalities of the aortic root and ascending aortic geometry. Degenerative tricuspid and bicuspid aortic regurgitation are the most common aetiologies in high-income countries, accounting for approximately two-thirds of the underlying aetiology of aortic regurgitation in the EURObservational Registry Programme Valvular Heart Disease II registry.[1] Other causes include infective and rheumatic endocarditis. Acute severe aortic regurgitation is mostly caused by infective endocarditis, and less frequently by aortic dissection.

4.1 EVALUATION

4.1.1 ECHOCARDIOGRAPHY

Echocardiography is the key examination used to describe valve anatomy, quantify aortic regurgitation, evaluate its mechanisms, define the morphology of the aorta, and determine the feasibility

of valve-sparing aortic surgery or valve repair.[96,97] Identification of the mechanism follows the same principle such as for mitral regurgitation: normal cusps but insufficient coaptation due to dilatation of the aortic root with central jet (type 1), cusp prolapse with eccentric jet (type 2), or retraction with poor cusp tissue quality and large central or eccentric jet (type 3).[96] Quantification of aortic regurgitation follows an integrated approach considering qualitative, semi-quantitative, and quantitative parameters[24,98] **(Table 5)**. New parameters obtained by 3D echocardiography and two-dimensional (2D) strain imaging as LV global longitudinal strain may be useful, particularly in patients with borderline LVEF where they may help in the decision for surgery.[99] Measurement of the aortic root and ascending aorta in 2D is performed at four levels: annulus, sinuses of Valsalva, sinotubular junction, and tubular ascending aorta.[100,101] Measurements are performed in the parasternal long-axis view from leading edge to leading edge at end diastole, except for the aortic annulus, which is measured in mid systole. As it will have surgical consequences, it is important to differentiate three phenotypes of the ascending aorta: aortic root aneurysms (sinuses of Valsalva >45 mm), tubular ascending aneurysm (sinuses of Valsalva <40-45 mm), and isolated aortic regurgitation (all aortic diameters <40 mm). The calculation of indexed values to account for body size has been suggested,[102] in particular in patients with small stature. Anatomy of the aortic valve cusps and its suitability for valve repair should be provided by preoperative TOE if aortic valve repair or a valve-sparing surgery of the aortic root is considered. Intraoperative evaluation of the surgical result by TOE is mandatory in patients undergoing aortic valve preservation or repair.

Table 5. Echocardiographic criteria for the definition of severe aortic valve regurgitation.

Qualitative	
Valve morphology	Abnormal/flail/large coaptation defect
Colour flow regurgitant jet area[a]	Large in central jets, variable in eccentric jets
CW signal of regurgitant jet	Dense
Other	Holodiastolic flow reversal in descending aorta (EDV >20 cm/s)
Semiquantitative	
Vena contracta width (mm)	>6
Pressure half-time[b] (ms)	<200
Quantitative	
EROA (mm^2)	≥30
Regurgitant volume (mL/beat)	≥60
Enlargement of cardiac chambers	LV dilatation

CW: continuous wave; EDV: end-diastolic velocity; EROA: effective regurgitant orifice area; LV: left ventricle/left ventricular. [a]At a Nyquist limit of 50-60 cm/s. [b]Pressure half-time is shortened with increasing LV diastolic pressure, vasodilator therapy, and in patients with a dilated compliant aorta, or lengthened in chronic aortic regurgitation. Adapted from Lancellotti P et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;14:611-644. Copyright (2013) by permission of Oxford University Press on behalf of the European Society of Cardiology.

4.1.2 COMPUTED TOMOGRAPHY AND CARDIAC MAGNETIC RESONANCE

CMR should be used to quantify the regurgitant fraction when echocardiographic measurements are equivocal or discordant with clinical findings. In patients with aortic dilatation, CCT is recommended to assess the maximum diameter at four levels, as in echocardiography. CMR can be used for follow-up, but indication for surgery should preferably be based on CCT measurements. Different methods of aortic measurements have been reported. To improve reproducibility, it is recommended to measure diameters using the inner-inner-edge technique at end diastole on the strictly transverse plane by double oblique reconstruction perpendicular to the axis of blood flow of the corresponding segment. Maximum root diameter should be taken from sinus-to-sinus diameter rather than sinus-to-commissure diameter, as it correlates more closely to long-axis leading-edge-to-leading-edge echo maximum diameters.[103,104]

4.2 INDICATIONS FOR INTERVENTION

Acute aortic regurgitation may require urgent surgery. It is mainly caused by infective endocarditis and aortic dissection but may also occur after blunt chest trauma and iatrogenic complications during catheter-based cardiac interventions. Specific guidelines deal with these entities.[4,101] The recommendations on indications for surgery in severe aortic regurgitation and aortic root disease may be related to symptoms, status of the LV, or dilatation of the aorta [see table of recommendations on indications for surgery in severe aortic regurgitation and aortic root or tubular ascending aortic aneurysm (irrespective of the severity of aortic regurgitation), and **Figure 2**].

In symptomatic patients, surgery is recommended irrespective of the LVEF as long as aortic regurgitation is severe and the operative risk is not prohibitive.[105-109] Surgery is recommended in symptomatic and asymptomatic patients with severe aortic regurgitation undergoing coronary artery bypass grafting (CABG), or surgery of the ascending aorta or another valve.[110,111] In asymptomatic patients with severe aortic regurgitation, impairment of LV function [LVEF ≤50% or left ventricular end-systolic diameter (LVESD) >50 mm] are associated with worse outcomes and surgery should therefore be pursued when these cut-offs are reached.[107,108,112-114] LVESD should be related to body surface area (BSA) and a cut-off of 25 mm/m^2 BSA appeared to be more appropriate, especially in patients with small body size (BSA <1.68 m^2) or with large BSA who are not overweight.[108,115] Some recent retrospective, non-randomized studies emphasized the role of indexed LVESD and proposed a lower cut-off value of 20 or 22 mm/m^2 BSA for the indexed LVESD.[116-118] One of these studies also suggests a higher cut-off value of 55% for LVEF.[118] Based on these data, low-risk surgery may be discussed in some selected asymptomatic patients with LVESD >20 mm/m^2 or resting LVEF between 50% and 55%. In patients not reaching the thresholds for surgery, close follow-up is needed, and exercise testing should be liberally performed to identify borderline symptomatic patients. Progressive enlargement

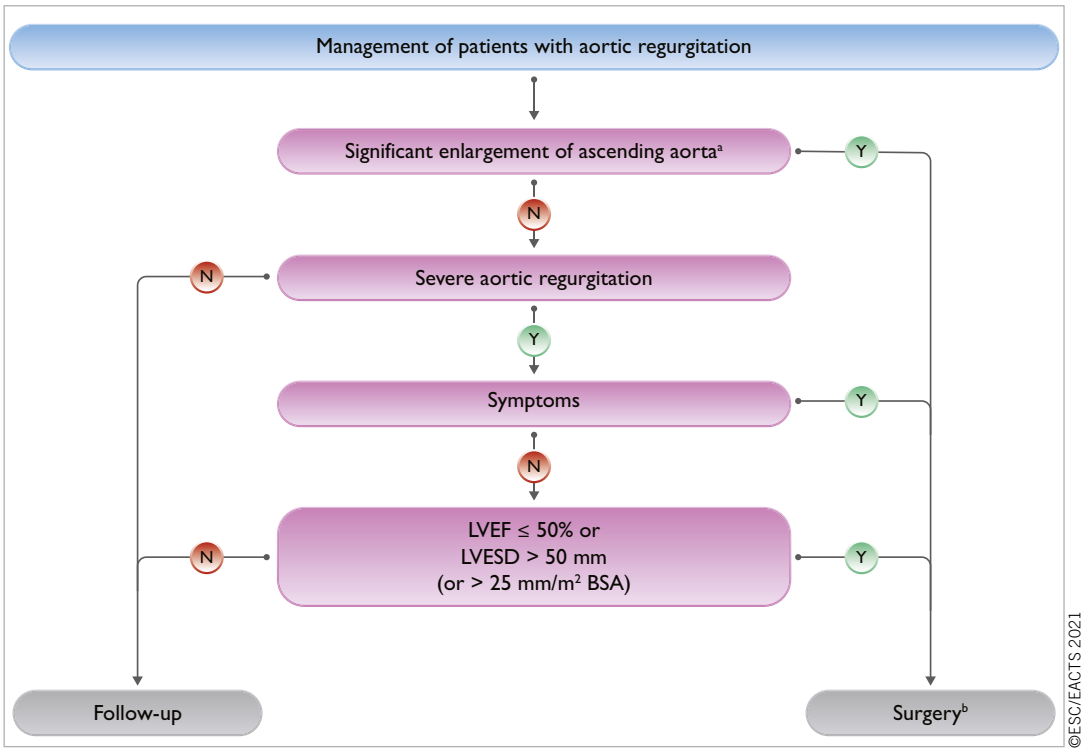

Figure 2. *Management of patients with aortic regurgitation. BSA: body surface area; LV: left ventricle/left ventricular; LVESD: left ventricle end-systolic diameter; LVEF: left ventricular ejection fraction.* [a]*See recommendations on indications for surgery in severe aortic regurgitation and aortic root disease for definition.* [b]*Surgery should also be considered if significant changes in LV or aortic size occur during follow-up.*

of the LV, or a progressive decrease in its function in asymptomatic patients not reaching the thresholds for surgery but with significant LV dilatation [left ventricular end-diastolic diameter (LVEDD) >65 mm], may also be an appropriate indicator for timing operations in asymptomatic patients.

TAVI may be considered in experienced centres for selected patients with aortic regurgitation and ineligible for SAVR.[119,120]

In patients with a dilated aorta, the rationale for surgery has been best defined in patients with Marfan syndrome and root dilation.[121,122] Root aneurysms require root replacement, with or without preservation of the native aortic valve. In contrast, tubular ascending aortic aneurysms in the presence of normal aortic valves require only a supracommissural tube graft replacement. In patients with aortic diameters borderline indicated for aortic surgery, the family history, age, and anticipated risk of the procedure should be taken into consideration. Irrespective of the degree of aortic regurgitation and type of valve pathology, in patients with an aortic diameter ≥55 mm with tricuspid or bicuspid aortic valves, ascending aortic surgery is recommended (see recommendations on indications for surgery in severe aortic regurgitation and aortic root disease) when the operative risk is not prohibitive.[123-125] In individuals with bicuspid aortic valve, when additional risk factors or coarctation[126] are present, surgery should be considered when aortic diameter is ≥50 mm.[127-129] In all patients with Marfan syndrome, aortic surgery is recommended for a maximal aortic diameter ≥50 mm.[5,121,122] When additional risk factors are present in patients with Marfan syndrome and in patients with a TGFBR1 or TGFBR2 mutation (including Loeys-Dietz syndrome), surgery should be considered at a maximal aortic diameter ≥45 mm[121,130] and even earlier (aortic diameter of 40 mm or more) in women with low BSA, patients with a TGFBR2 mutation, or patients with severe extra-aortic features that appear to be at particularly high risk.[130] For patients who have an indication for aortic valve surgery, an aortic diameter ≥45 mm is considered to indicate concomitant surgery of the aortic root or tubular ascending aorta. The patient's stature, the aetiology of the valvular disease (bicuspid valve), and the intraoperative shape and wall thickness of the ascending aorta should be considered for individual decisions.

The choice of the surgical procedure should be adapted according to the experience of the team, the presence of an aortic root aneurysm, characteristics of the cusps, life expectancy, and desired anticoagulation status.

Valve replacement is the standard procedure in the majority of patients with aortic regurgitation. Aortic valve-sparing root replacement and valve repair yield good long-term results in selected patients, with low rates of valve-related events as well as good quality of life[131-140] when performed in experienced centres. Aortic valve-sparing root replacement is recommended in younger patients who have an enlargement of the aortic root with normal cusp motion, when performed by experienced surgeons.[133-136,140] In selected patients, aortic valve repair[132,132,137] or the Ross procedure[138,139] may be an alternative to valve replacement, when performed by experienced surgeons.

4.3 MEDICAL THERAPY

Medical therapy, especially angiotensin-converting enzyme inhibitors (ACEI) or dihydropiridines, may provide symptomatic improvement in individuals with chronic severe aortic regurgitation in whom surgery is not feasible. The value of ACEI or dihydropiridine in delaying surgery in the presence of moderate or severe aortic regurgitation in asymptomatic patients has not been established and their use is not recommended for this indication.

In patients who undergo surgery but continue to suffer from heart failure or hypertension, ACEI, angiotensin receptor blockers (ARBs), and beta-blockers are useful.[141,142]

In patients with Marfan syndrome, beta-blockers remain the mainstay for medical treatment and reducing shear stress and aortic growth rate and should be considered before and after surgery.[143-145] While ARBs did not prove to have a superior effect when compared to beta-blockers, they may be considered as an alternative in patients intolerant to beta-blockers.[146-148] By analogy, while there are no studies that provide supporting evidence, it is common clinical practice to advise beta-blocker or ARBs in patients with bicuspid aortic valve if the aortic root and/or ascending aorta is dilated. Management of aortic regurgitation during pregnancy is discussed in section 13.

Recommendations on indications for surgery in (A) severe aortic regurgitation and (B) aortic root or tubular ascending aortic aneurysm (irrespective of the severity of aortic regurgitation)

Indications for surgery	Class[a]	Level[b]
A) Severe aortic regurgitation		
Surgery is recommended in symptomatic patients regardless of LV function.[105-109]	I	B
Surgery is recommended in asymptomatic patients with LVESD >50mm or LVESD >25 mm/m^2 BSA (in patients with small body size) or resting LVEF ≤50%.[107,108,112,114,115]	I	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
Surgery is recommended in symptomatic and asymptomatic patients with severe aortic regurgitation undergoing CABG or surgery of the ascending aorta or of another valve.	I	C
Aortic valve repair may be considered in selected patients at experienced centres when durable results are expected.	IIb	C
B) Aortic root or tubular ascending aortic aneurysm[c] (irrespective of the severity of aortic regurgitation)		
Valve-sparing aortic root replacement is recommended in young patients with aortic root dilation, if performed in experienced centres and durable results are expected.[133-136,140]	I	B
Ascending aortic surgery is recommended in patients with Marfan syndrome who have aortic root disease with a maximal ascending aortic diameter ≥50 mm.	I	C
Ascending aortic surgery should be considered in patients who have aortic root disease with maximal ascending aortic diameter: • ≥55 mm in all patients. • ≥45 mm in the presence of Marfan syndrome and additional risk factors[d] or patients with a TGFBR1 or TGFBR2 mutation (including Loeys-Dietz syndrome).[e] • ≥50 mm in the presence of a bicuspid valve with additional risk factorsd or coarctation.	IIa	C
When surgery is primarily indicated for the aortic valve, replacement of the aortic root or tubular ascending aorta should be considered when ≥45 mm.[f]	IIa	C

BSA: body surface area; CABG: coronary artery bypass grafting; CCT: cardiac computed tomography; CMR: cardiac magnetic resonance; ECG: electrocardiogram; LV: left ventricle/left ventricular; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter. [a]Class of recommendation. [b]Level of evidence. [c]For clinical decision making, dimensions of the aorta should be confirmed by ECG-gated CCT. [d]Family history of aortic dissection (or personal history of spontaneous vascular dissection), severe aortic or mitral regurgitation, desire for pregnancy, uncontrolled systemic arterial hypertension and/or aortic size increase >3 mm/year (using serial echocardiography or CMR measurements at the same level of the aorta confirmed by ECG-gated CCT). [e]A lower threshold of 40mm may be considered in women with low BSA, in patients with a TGFBR2 mutation or in patients with severe extra-aortic features.[130] [f]Considering age, BSA, aetiology of the valvular disease, presence of a bicuspid aortic valve, and intraoperative shape and thickness of the ascending aorta.

4.4 SERIAL TESTING

All asymptomatic patients with severe aortic regurgitation and normal LV function should be followed up at least every year. In patients with either a first diagnosis or with LV diameter and/or ejection fraction showing significant changes or approaching thresholds for surgery, follow-up should be continued at 3-6-month intervals. Surgery may be considered in asymptomatic patients with significant LV dilatation (LVEDD >65 mm), and with progressive enlargement in the size of LV or progressive decrease of LVEF during follow-up. Patient's BNP levels could be of potential interest as a predictor of outcomes (particularly symptom onset and deterioration of LV function) and may be helpful in the follow-up of asymptomatic patients.[149] Patients with mild-to-moderate aortic regurgitation can be seen on a yearly basis and echocardiography performed every 2 years.

If the ascending aorta is dilated (>40 mm), it is recommended to systematically perform CCT or CMR. Follow-up assessment of the aortic dimension should be performed using echocardiography and/or CMR. Any increase >3 mm should be validated by CCT angiography/CMR and compared with baseline data. After repair of the ascending aorta, Marfan patients remain at risk for dissection of the residual aorta and lifelong regular multidisciplinary follow-up at an expert centre is required.

4.5 SPECIAL PATIENT POPULATIONS

If aortic regurgitation requiring surgery is associated with severe primary and secondary mitral regurgitation, both should be treated during the same operation.

In patients with moderate aortic regurgitation who undergo CABG or mitral valve surgery, the decision to treat the aortic valve is controversial, as data show that progression of moderate aortic regurgitation is very slow in patients without aortic dilation.[150] The Heart Team should decide based on the aetiology of

aortic regurgitation, other clinical factors, the life expectancy of the patient, and the patient's operative risk.

The level of physical and sports activity in the presence of a dilated aorta remains a matter of clinical judgment in the absence of evidence. Current guidelines are very restrictive, particularly regarding isometric exercise, to avoid a catastrophic event.[151] This approach is justified in the presence of connective tissue disease, but a more liberal approach is likely to be appropriate in other patients.

Given the familial risk of thoracic aortic aneurysms, screening and referral for genetic testing of the patient's first-degree relatives with appropriate imaging studies is indicated in patients with connective tissue disease. For patients with bicuspid valves, it is appropriate to have an echocardiographic screening of first-degree relatives.

5 Aortic stenosis

Aortic stenosis is the most common primary valve lesion requiring surgery or transcatheter intervention in Europe[1] and North America. Its prevalence is rising rapidly as a consequence of the ageing population.[2,152]

5.1 EVALUATION

5.1.1 ECHOCARDIOGRAPHY

Echocardiography is key to confirming the diagnosis and severity of aortic stenosis, assessing valve calcification, LV function and wall thickness, detecting other valve disease or aortic pathology, and providing prognostic information.[43,153,154] Assessment should be undertaken when blood pressure (BP) is well controlled to avoid the confounding flow effects of increased afterload. New echocardiographic parameters, stress imaging and CCT provide important adjunctive information when severity is uncertain **(Figure 3)**.

Current international recommendations for the echocardiographic evaluation of patients with aortic stenosis[25] depend upon measurement of mean pressure gradient (the most robust parameter), peak transvalvular velocity (V_{max}), and valve area. Although valve area is the theoretically ideal measurement for assessing severity, there are numerous technical limitations. Clinical decision making in discordant cases should therefore take account of additional parameters: functional status, stroke volume, Doppler velocity index,[156] degree of valve calcification, LV function, the presence or absence of LV hypertrophy, flow conditions, and the adequacy of BP control.[25] Low flow is arbitrarily defined by a stroke volume index (SVi) ≤35 mL/m² – a threshold that is under current debate.[155,157,158] The use of sex -specific thresholds has been recently proposed.[159] Four broad categories can be defined:

- High-gradient aortic stenosis [mean gradient ≥40 mmHg, peak velocity ≥4.0 m/s, valve area ≤1 cm² (or ≤0.6 cm²/m²)]. Severe aortic stenosis can be assumed irrespective of LV function and flow conditions.
- Low-flow, low-gradient aortic stenosis with reduced ejection fraction (mean gradient <40 mmHg, valve area ≤1 cm², LVEF <50%, SVi ≤35 mL/m²). Low-dose dobutamine stress echocardiography (DSE) is recommended to distinguish between true severe and pseudo-severe aortic stenosis (increase in valve area to >1.0 cm² with increased flow) and identify patients with no flow (or contractile) reserve.[160] However, utility in elderly patients has only been evaluated in small registries.[161]
- Low-flow, low-gradient aortic stenosis with preserved ejection fraction (mean gradient <40 mmHg, valve area ≤1 cm², LVEF ≥50%, SVi ≤35 mL/m²). Typically encountered in hypertensive elderly subjects with small LV size and marked hypertrophy.[157,162] This scenario may also result from conditions associated with low stroke volume (e.g. moderate/severe mitral regurgitation, severe tricuspid regurgitation, severe mitral stenosis, and large ventricular septal defect and severe RV dysfunction). Diagnosis of severe aortic stenosis is challenging and requires careful exclusion of measurement errors and other explanations for the echocardiographic findings,[25] as well as the presence or absence of typical symptoms (with no other explanation), LV hypertrophy (in the absence of coexistent hypertension) or reduced LV longitudinal strain (with no other cause). CCT assessment of the degree of valve calcification provides important additional information [thresholds (Agatston units) for severe aortic stenosis: men >3000, women >1600=highly likely; men >2000, women >1200=likely; men <1600, women <800=unlikely].[35,36,163,164]
- Normal-flow, low-gradient aortic stenosis with preserved ejection fraction (mean gradient <40 mmHg, valve area ≤1 cm², LVEF≥50%, SVi >35 mL/m²). These patients usually have only moderate aortic stenosis.[36,165-167]

5.1.2 ADDITIONAL DIAGNOSTIC AND PROGNOSTIC PARAMETERS

The resting Doppler velocity index (DVI, also termed 'dimensionless index') – the ratio of the left ventricular outflow tract (LVOT) time-velocity integral (TVI) to that of the aortic valve jet – does not require calculation of LVOT area and may assist evaluation when other parameters are equivocal (a value <0.25 suggests that severe aortic stenosis is highly likely).[156] Assessment of global longitudinal strain provides additional information concerning LV function and a threshold of 15% may help to identify patients with severe asymptomatic aortic stenosis who are at higher risk of clinical deterioration or premature mortality.[26,168] TOE allows evaluation of concomitant mitral valve disease and may be of value for periprocedural imaging during TAVI and SAVR.[169]

Natriuretic peptides predict symptom-free survival and outcome in normal and low-flow severe aortic stenosis.[170,171] They can be used to arbitrate the source of symptoms in patients with multiple potential causes and identify those with high-risk asymptomatic aortic stenosis who may benefit from early intervention (section 5.2.2, **Table 6** and **Figure 3**).

Exercise testing may unmask symptoms and is recommended for risk stratification of asymptomatic patients with severe aortic stenosis.[172] Exercise echocardiography provides additional prognostic information by assessing the increase in mean pressure gradient and change in LV function.[173]

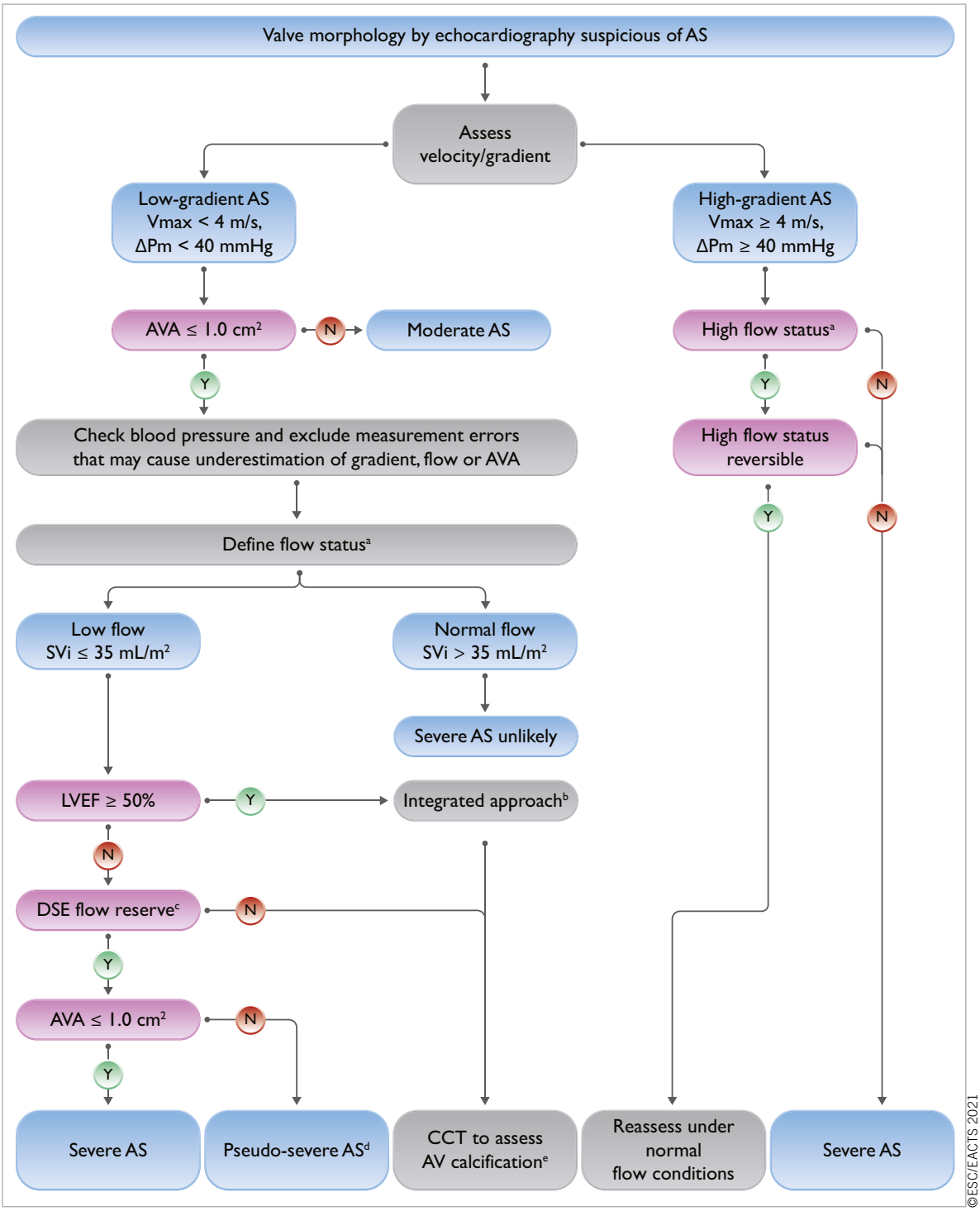

Figure 3. *Integrated imaging assessment of aortic stenosis. AS: aortic stenosis; AV: aortic valve; AVA: aortic valve area; CT: computed tomography; ΔPm: mean pressure gradient; DSE: dobutamine stress echocardiography; LV: left ventricle/left ventricular; LVEF: left ventricular ejection fraction; SVi: stroke volume index; V_{max}: peak transvalvular velocity. [a]High flow may be reversible in patients with anaemia, hyperthyroidism or arterio-venous fistulae, and may also be present in patients with hypertrophic obstructive cardiomyopathy. Upper limit of normal flow using pulsed Doppler echocardiography: cardiac index 4.1 L/min/m² in men and women, SVi 54 mL/m² in men, 51 mL/m² in women).[155] [b]Consider also: typical symptoms (with no other explanation), LV hypertrophy (in the absence of coexistent hypertension) or reduced LV longitudinal function (with no other cause). [c]DSE flow reserve: >20% increase in stroke volume in response to low-dose dobutamine. [d]Pseudo-severe aortic stenosis: AVA >1.0 cm² with increased flow. [e]Thresholds for severe aortic stenosis assessed by means of CT measurement of aortic valve calcification (Agatston units): men >3000, women >1600: highly likely; men >2000, women >1200: likely; men <1600, women <800: unlikely.*

Table 6. Clinical, anatomical and procedural factors that influence the choice of treatment modality for an individual patient.

	Favours TAVI	Favours SAVR
Clinical characteristics		
Lower surgical risk	–	+
Higher surgical risk	+	–
Younger age[a]	–	+
Older age[a]	+	–
Previous cardiac surgery (particularly intact coronary artery bypass grafts at risk of injury during repeat sternotomy)	+	–
Severe frailty[b]	+	–
Active or suspected endocarditis	–	+
Anatomical and procedural factors		
TAVI feasible via transfemoral approach	+	–
Transfemoral access challenging or impossible and SAVR feasible	–	+
Transfemoral access challenging or impossible and SAVR inadvisable	+[c]	–
Sequelae of chest radiation	+	–
Porcelain aorta	+	–
High likelihood of severe patient-prosthesis mismatch (AVA <0.65 cm^2/m^2 BSA)	+	–
Severe chest deformation or scoliosis	+	–
Aortic annular dimensions unsuitable for available TAVI devices	–	+
Bicuspid aortic valve	–	+
Valve morphology unfavourable for TAVI (e.g. high risk of coronary obstruction due to low coronary ostia or heavy leaflet/LVOT calcification)	–	+
Thrombus in aorta or LV	–	+
Concomitant cardiac conditions requiring intervention		
Significant multi-vessel CAD requiring surgical revascularization[d]	–	+
Severe primary mitral valve disease	–	+
Severe tricuspid valve disease	–	+
Significant dilatation/aneurysm of the aortic root and/or ascending aorta	–	+
Septal hypertrophy requiring myectomy	–	+

AVA: aortic valve area, BSA: body surface area, CAD: coronary artery disease; ESC: European Society of Cardiology; LV: left ventricle/left ventricular; LVOT: left ventricular outflow tract; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation. Integration of these factors provides guidance for the Heart Team decision (indications for intervention are provided in the table of recommendations on indications for intervention in symptomatic and asymptomatic aortic stenosis and recommended mode of intervention). [a]Life expectancy is highly dependent on absolute age and frailty, differs between men and women, and may be a better guide than age alone. There is wide variation across Europe and elsewhere in the world (http://ghdx.healthdata.org/record/ihme-data/gbd-2017-life-tables-1950-2017). [b]Severe frailty: >2 factors according to Katz index[59] (see section 3.3 for further discussion). [c]Via non-transfemoral approach. [d] According to the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.

CCT provides information concerning the anatomy of the aortic root and ascending aorta, and the extent and distribution of valve and vascular calcification, and feasibility of vascular access.[174] Quantification of valve calcification predicts disease progression and clinical events[164] and may be useful when combined with geometric assessment of valve area in assessing the severity of aortic stenosis in patients with low valve gradient.[35,36,163,164]

Myocardial fibrosis is a major driver of LV decompensation in aortic stenosis (regardless of the presence or absence of CAD), which can be detected and quantified using CMR. Amyloidosis is also frequently associated with aortic stenosis in elderly patients (incidence 9-15%).[175] When cardiac amyloidosis is clinically suspected, based on symptoms (neuropathy and hematologic data), diphosphonate scintigraphy and/or CMR should be considered. Both entities persist following valve intervention and are associated with poor long-term prognosis.[176-179]

Coronary angiography is essential prior to TAVI and SAVR to determine the potential need for concomitant revascularization (see section 3.2.4.1 and section 5.5). Retrograde LV catheterization is not recommended unless there are symptoms and signs of severe aortic stenosis and non-invasive investigations are inconclusive.

5.1.3 TAVI DIAGNOSTIC WORKUP

Prior to TAVI, CCT is the preferred imaging tool to assess: (i) aortic valve anatomy, (ii) annular size and shape, (iii) extent and distribution of valve and vascular calcification, (iv) risk of coronary ostial obstruction, (v) aortic root dimensions, (vi) optimal fluoroscopic projections for valve deployment, and (vii) feasibility of vascular access (femoral, subclavian, axillary, carotid, transcaval or transapical). Adverse anatomical findings may suggest that SAVR is a better treatment option **(Table 6)**. TOE is more operator-dependent but may be considered when CCT is difficult to interpret or relatively contraindicated (e.g. chronic renal failure).

5.2 INDICATIONS FOR INTERVENTION (SAVR OR TAVI)

Indications for aortic valve intervention are summarized in the table of recommendations on indications for intervention in symptomatic and asymptomatic aortic stenosis and recommended mode of intervention and in **Figure 4**.

5.2.1 SYMPTOMATIC AORTIC STENOSIS

Symptomatic severe aortic stenosis has dismal prognosis and early intervention is strongly recommended in all patients. The only exceptions are for those in whom intervention is unlikely to improve quality of life or survival (due to severe comorbidities) or for those with concomitant conditions associated with survival <1 year (e.g. malignancy) (section 3).

Intervention is recommended in symptomatic patients with high-gradient aortic stenosis, regardless of LVEF. However, management of patients with low-gradient aortic stenosis is more challenging:

- LV function usually improves after intervention in patients with low-flow, low-gradient aortic stenosis, when reduced ejection fraction is predominantly caused by excessive afterload.[32,180] Conversely, improvement is uncertain if the primary cause of

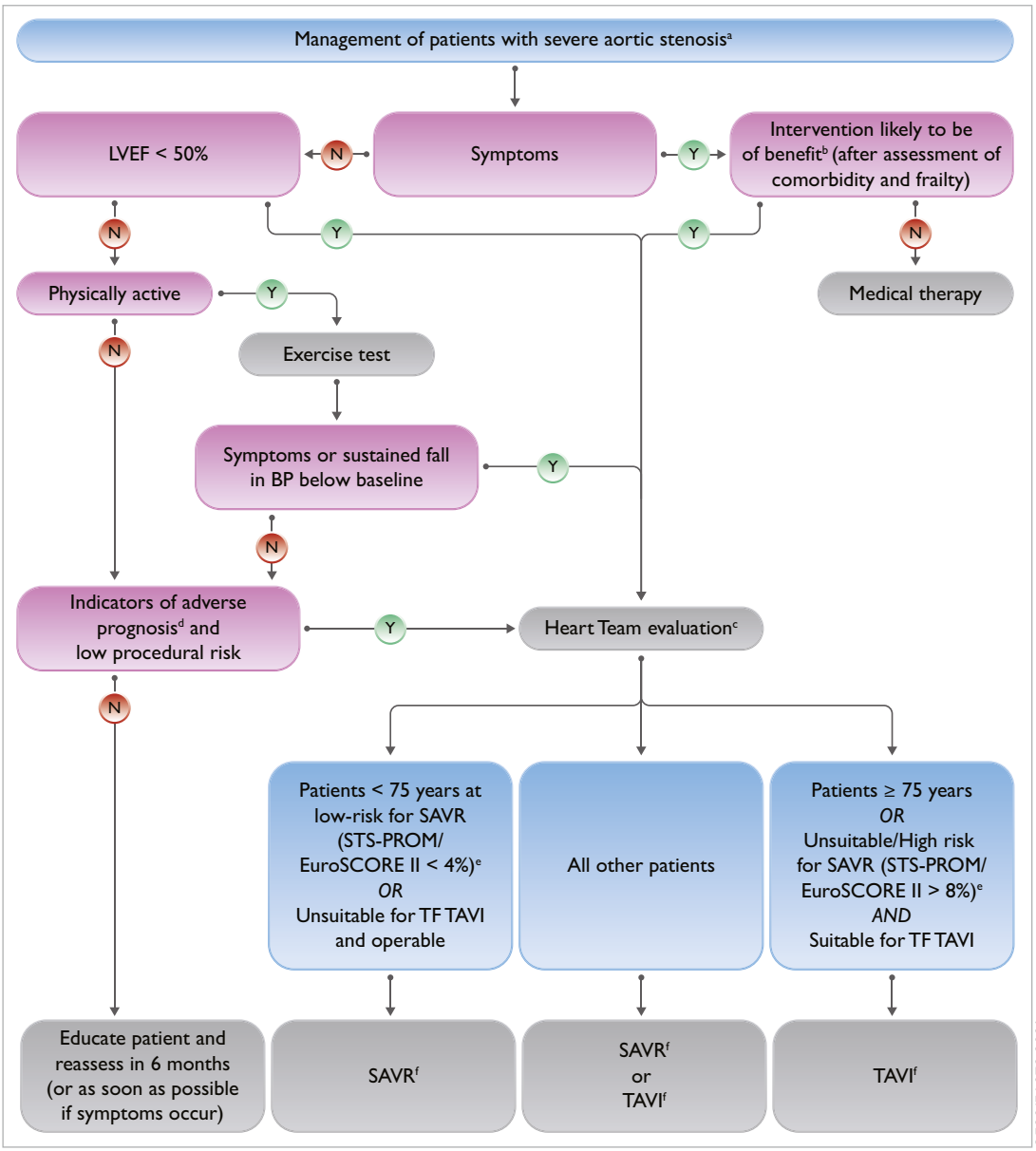

Figure 4. *Management of patients with severe aortic stenosis. BP: blood pressure; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LVEF: left ventricular ejection fraction; SAVR: surgical aortic valve replacement; STS-PROM: Society of Thoracic Surgeons – predicted risk of mortality; TAVI: transcatheter aortic valve implantation; TF: transfemoral. [a]See* **Figure 3***: Integrated imaging assessment of aortic stenosis. [b]Prohibitive risk is defined in* **Supplementary Table 5***. [c]Heart Team assessment based upon careful evaluation of clinical, anatomical, and procedural factors (see* **Table 6** *and table on Recommendations on indications for intervention in symptomatic and asymptomatic aortic stenosis and recommended mode of intervention). The Heart Team recommendation should be discussed with the patient who can then make an informed treatment choice. [d]Adverse features according to clinical, imaging (echocardiography/CT), and/or biomarker assessment. [e]STS-PROM: http://riskcalc.sts.org/stswebriskcalc/#/calculate, EuroSCORE II: http://www.euroscore.org/calc.html. [f]If suitable for procedure according to clinical, anatomical, and procedural factors* **(Table 6)**.

reduced ejection fraction is scarring due to myocardial infarction or cardiomyopathy. Intervention is recommended when severe aortic stenosis is confirmed by stress echocardiography (true severe aortic stenosis; **Figure 3**),[32] while patients with pseudo-severe aortic stenosis should receive conventional heart failure treatment.[142,181] The presence or absence of flow reserve (increase in stroke volume ≥20%) does not appear to influence prognosis in contemporary series of patients undergoing TAVI or SAVR,[182-184] and although those with no flow reserve show increased procedural mortality, both modes of intervention improve ejection fraction and clinical outcomes.[32,180,182] Decision making for such patients should take account of comorbidities, degree of valve calcification, extent of CAD, and feasibility of revascularization.

- Data concerning the natural history of low-flow, low-gradient aortic stenosis and preserved ejection fraction, and outcomes after SAVR and TAVI remain controversial.[162,165,167] Intervention should only be considered in those with symptoms and significant valve obstruction (see table of recommendations on indications for intervention in symptomatic and asymptomatic aortic stenosis and recommended mode of intervention and **Figure 4**).
- The prognosis of patients with normal-flow, low-gradient aortic stenosis and preserved ejection fraction is similar to that of moderate aortic stenosis – regular clinical and echocardiographic surveillance is recommended.[165,166,185]

5.2.2 ASYMPTOMATIC AORTIC STENOSIS

Intervention is recommended in asymptomatic patients with severe aortic stenosis and impaired LV function of no other cause,[9] and those who are asymptomatic during normal activities but develop symptoms during exercise testing.[172,186] Management of asymptomatic severe aortic stenosis is otherwise controversial and the decision to intervene requires careful assessment of the benefits and risks in an individual patient.

In the absence of adverse prognostic features, watchful waiting has generally been recommended with prompt intervention at symptom onset.[187] Data from a single RCT have shown significant reduction in the primary endpoint (death during or within 30 days of surgery or cardiovascular death during the entire follow-up period) following early SAVR compared with conservative management [1% vs. 15%; hazard ratio 0.09; 95% confidence interval (CI), 0.01-0.67; P=0.003].[188] However, subjects were selected per inclusion criteria (median age 64 years, minimal comorbidities, low operative risk) and follow-up in the conservative group was limited. Further randomized trials [EARLY TAVR (NCT03042104), AVATAR (NCT02436655), EASY-AS (NCT04204915), EVOLVED (NCT03094143)] will help determine future recommendations.

Predictors of symptom development and adverse outcomes in asymptomatic patients include clinical characteristics (older age, atherosclerotic risk factors), echocardiographic parameters (valve calcification, peak jet velocity[189,190]), LVEF, rate of haemodynamic progression,[189] increase in mean gradient >20 mmHg with exercise,[172] severe LV hypertrophy,[191] indexed stroke volume,[158] LA volume,[192] LV global longitudinal strain,[26,168,193] and abnormal biomarker levels (natriuretic peptides, troponin, and fetuin-A).[170,171,194,195] Early intervention may be considered in asymptomatic patients with severe aortic stenosis and one or more of these predictors if procedural risk is low (although application of TAVI in this setting has yet to be formally evaluated) (**Table 6** and **Figure 4**). Otherwise, watchful waiting is a safer and more appropriate strategy.

5.2.3 THE MODE OF INTERVENTION

Use of SAVR and TAVI as complementary treatment options has allowed a substantial increase in the overall number of patients with aortic stenosis undergoing surgical or transcatheter intervention in the past decade.[196] RCTs have assessed the two modes of intervention across the spectrum of surgical risk in predominantly elderly patients and a detailed appraisal of the evidence base is provided in Supplementary Section 5. In brief, these trials used surgical risk scores to govern patient selection and demonstrate that TAVI is superior to medical therapy in extreme-risk patients,[197] and non-inferior to SAVR in high-[198-201] and intermediate-risk patients at follow-up extending to 5 years.[202-208] The more recent PARTNER 3 and Evolut Low Risk trials demonstrate that TAVI is non-inferior to SAVR in low-risk patients at 2-year follow-up.[209-212] Importantly, patients in the low-risk trials were predominantly male and relatively elderly (e.g. PARTNER 3: mean age 73.4 years, <70 years 24%, 70-75 years 36%, >75 years 40%, >80 years 13%) whilst those with low-flow aortic stenosis or adverse anatomical characteristics for either procedure (including bicuspid aortic valves or complex coronary disease) were excluded.

Rates of vascular complications, pacemaker implantation, and paravalvular regurgitation are consistently higher after TAVI, whereas severe bleeding, acute kidney injury, and new-onset AF are more frequent after SAVR. Although the likelihood of paravalvular regurgitation has been reduced with newer transcatheter heart valve designs, pacemaker implantation (and new-onset left bundle branch block) may have long-term consequences[213-215] and further refinements are required. Most patients undergoing TAVI have a swift recovery, short hospital stay, and rapidly return to normal activities.[216,217] Despite these benefits, there is wide variation in worldwide access to the procedure as a result of high device costs and differing levels of healthcare resources.[71,218,219]

The Task Force has attempted to address the gaps in evidence and provide recommendations concerning the indications for intervention and mode of treatment (Recommendations on indications for intervention in symptomatic and asymptomatic aortic stenosis and recommended mode of intervention, **Figure 4**) that are guided by the RCT findings and compatible with real-world Heart Team decision making for individual patients (many of whom fall outside the RCT inclusion criteria). Aortic stenosis is a heterogeneous condition and selection of the most appropriate mode of intervention should be carefully considered by the Heart Team for all patients, accounting for individual age and estimated life expectancy, comorbidities (including frailty and overall quality of life, section 3), anatomical and procedural characteristics **(Table 6)**, the relative risks of SAVR and TAVI and their long-term outcomes, prosthetic heart valve durability, feasibility of transfemoral TAVI, and local experience and outcome data. These factors should be discussed with the patient and their family to allow informed treatment choice.

The interplay between estimated life expectancy and prosthetic heart valve durability is a key consideration in these discussions. Age is a surrogate for life expectancy but had no impact on the outcomes of the low-risk RCTs at 1-2 year follow-up. Life expectancy varies widely across the world and is highly dependent on absolute age, sex, frailty, and the presence of comorbidities (http://ghdx.healthdata.org/record/ihme-data/gbd-2017-life-tables-1950-2017); it may be a better guide than age alone but is difficult to determine in individual patients. Although

some (now abandoned) surgical bioprosthetic designs have failed early, the durability of contemporary surgical bioprosthetic valves beyond 10 years is well established.[220] Conversely, registry data provide some reassurance concerning the long-term durability of TAVI devices up to 8 years but largely relate to older high-/intermediate-risk patients,[221-224] whereas information concerning durability in low-risk patients is currently limited to 2-year follow-up.

Recommendations on indications for intervention[a] in symptomatic (A) and asymptomatic (B) aortic stenosis and recommended mode of intervention (C)

A) Symptomatic aortic stenosis	Class[b]	Level[c]
Intervention is recommended in symptomatic patients with severe, high-gradient aortic stenosis [mean gradient ≥40 mmHg, peak velocity ≥4.0 m/s, and valve area ≤1.0 cm² (or ≤0.6 cm²/m²)].[235,236]	I	B
Intervention is recommended in symptomatic patients with severe low-flow (SVi ≤35 mL/m²), low-gradient (<40 mmHg) aortic stenosis with reduced ejection fraction (<50%), and evidence of flow (contractile) reserve.[32,237]	I	B
Intervention should be considered in symptomatic patients with low-flow, low-gradient (<40 mmHg) aortic stenosis with normal ejection fraction after careful confirmation that the aortic stenosis is severed **(Figure 3)**.	IIa	C
Intervention should be considered in symptomatic patients with low-flow, low-gradient severe aortic stenosis and reduced ejection fraction without flow (contractile) reserve, particularly when CCT calcium scoring confirms severe aortic stenosis.	IIa	C
Intervention is not recommended in patients with severe comorbidities when the intervention is unlikely to improve quality of life or prolong survival >1 year.	III	C
B) Asymptomatic patients with severe aortic stenosis		
Intervention is recommended in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF <50%) without another cause.[9,238,239]	I	B
Intervention is recommended in asymptomatic patients with severe aortic stenosis and demonstrable symptoms on exercise testing.	I	C
Intervention should be considered in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF <55%) without another cause.[9,240,241]	IIa	B
Intervention should be considered in asymptomatic patients with severe aortic stenosis and a sustained fall in BP (>20 mmHg) during exercise testing.	IIa	C
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 aortic stenosis (mean gradient ≥60 mmHg or V_{max} >5 m/s).[9,242] • Severe valve calcification (ideally assessed by CCT) and V_{max} progression ≥0.3 m/s/year.[164,189,243] • Markedly elevated BNP levels (>3- age- and sex-corrected normal range) confirmed by repeated measurements and without other explanation.[163,171]	IIa	B
C) Mode of intervention		
Aortic valve interventions must be performed in Heart Valve Centres that declare their local expertise and outcomes data, have active interventional cardiology and cardiac surgical programmes on site, and a structured collaborative Heart Team approach.	I	C
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
SAVR is recommended in younger patients who are low risk for surgery (<75 years[e] and STSPROM/ EuroSCORE II <4%)[e,f], or in patients who are operable and unsuitable for transfemoral TAVI.[244]	I	B
TAVI is recommended in older patients (≥75 years), or in those who are high risk (STSPROM/ EuroSCORE II[f] >8%) or unsuitable for surgery.[197-206,245]	I	A
SAVR or TAVI are recommended for remaining patients according to individual clinical, anatomical, and procedural characteristics.[202-205,207,209,210,212 f,g]	I	B
Non-transfemoral TAVI may be considered in patients who are inoperable and unsuitable for transfemoral TAVI.	IIb	C
Balloon aortic valvotomy may be considered as a bridge to SAVR or TAVI in haemodynamically unstable patients and (if feasible) in those with severe aortic stenosis who require urgent highrisk NCS **(Figure 11)**.	IIb	C
D) Concomitant aortic valve surgery at the time of other cardiac/ascending aorta surgery		
SAVR is recommended in patients with severe aortic stenosis undergoing CABG or surgical intervention on the ascending aorta or another valve.	I	C
SAVR should be considered in patients with moderate aortic stenosish undergoing CABG or surgical intervention on the ascending aorta or another valve after Heart Team discussion.	IIa	C

BNP: B-type natriuretic peptide; BP: blood pressure; CABG: coronary artery bypass grafting; CCT: cardiac computed tomography; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LV: left ventricle/left ventricular; LVEF: left ventricular ejection fraction; NCS: non-cardiac surgery; 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]SAVR or TAVI. [b]Class of recommendation. [c]Level of evidence. [d]Explanations other than severe aortic stenosis for a small valve area but low gradient despite preserved LVEF are frequent and must be carefully excluded **(Figure 3)**. [e]STS-PROM: http://riskcalc.sts.org/stswebriskcalc/#/calculate, EuroSCORE II: http://www.euroscore.org/calc.html. [f]If suitable for surgery (see **Table 6**). [g]If suitable for transfemoral TAVI (see **Table 6**). [h]Moderate aortic stenosis is defined as a valve area of 1.0-1.5 cm² (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.

Data comparing the durability of transcatheter heart valves and surgical bioprostheses directly remain limited. Rates of aortic valve re-intervention were higher after TAVI using a balloon-expandable valve compared to SAVR at 5-year follow-up in the PARTNER 2A trial (3.2% vs. 0.8%; hazard ratio, 3.3; 95% CI,

1.3-8.1),[206] whereas rates of structural valve deterioration (SVD) were not statistically different following SAVR and TAVI using the third generation SAPIEN 3 device in a parallel observational registry over the same time frame.[225]

Valve-in-valve TAVI is an established treatment option for surgical bioprosthetic valve deterioration but may not be appropriate or feasible in all patients due to the increased likelihood of PPM in patients with a small aortic root (or undersized original prosthesis), incompatible surgical valve designs associated with increased risk of coronary occlusion, or difficult vascular access; re-do SAVR should also be considered in these settings.[226-228] Favourable short-term outcomes of redo-TAVI have been demonstrated in selected older patients with transcatheter heart valve deterioration,[229] despite theoretical concerns relating to maintained coronary access.[230]

A bicuspid aortic valve is more frequent in younger patients with aortic stenosis. While several registries have reported excellent outcomes of TAVI in patients with a bicuspid valve who were unsuitable for surgery,[231-233] SAVR remains more appropriate in patients with aortic stenosis affecting a bicuspid valve and in those with associated disease (e.g. aortic root dilatation, complex coronary disease, or severe mitral regurgitation) requiring a surgical approach.

In summary, prosthetic heart valve durability is a key consideration in younger patients (<75 years) at low surgical risk and SAVR (if feasible) is therefore the preferred treatment option. Conversely, durability is a lower priority in older patients (≥75 years), or those who are inoperable or high risk for surgery, and TAVI is preferred in these groups (particularly if feasible via transfemoral approach). The Heart Team should make tailored recommendations for remaining patients based upon their individual characteristics **(Table 6)**. This guidance should be re-addressed when further data concerning the long-term durability of TAVI become available.

Balloon aortic valvuloplasty (BAV) may be considered as a bridge to TAVI or SAVR in patients with decompensated aortic stenosis and (when feasible) in those with severe aortic stenosis who require urgent high-risk non-cardiac surgery (NCS) (section 12). The procedure carries significant risk of complications[234] and should only be undertaken after Heart Team discussion.

5.3 MEDICAL THERAPY

No medical therapies influence the natural history of aortic stenosis. Statins (which demonstrated favourable effects in preclinical studies) do not affect disease progression[246] and clinical trials targeting calcium metabolic pathways are ongoing. Patients with heart failure who are unsuitable (or waiting) for SAVR or TAVI should be medically treated according to ESC heart failure Guidelines.[247] ACEI are safe in aortic stenosis (provided that BP is monitored carefully) and may have beneficial myocardial effects before the onset of symptoms, and after TAVI and SAVR.[248-250] Coexisting hypertension should be treated to avoid additional afterload, although medication (particularly vasodilators) should be titrated to avoid symptomatic hypotension.

Antithrombotic therapy after TAVI is discussed in section 11.

5.4 SERIAL TESTING

Rate of progression of aortic stenosis varies widely. Asymptomatic patients, their family and medical carers need careful education, with emphasis on the importance of regular follow-up (ideally in a Heart Valve Clinic[9]) and prompt reporting of symptoms. Those with severe aortic stenosis should be followed up every 6 months (at least) to allow earliest symptom detection (using exercise testing if symptoms are doubtful) and any change in echocardiographic parameters (particularly LVEF). Measurement of natriuretic peptides may be considered.

Several studies suggest that the prognosis of moderate degenerative aortic stenosis is worse than previously considered[251-254] (particularly if there is significant valve calcification) and these patients should be re-evaluated at least annually. Younger patients with mild aortic stenosis and no significant calcification may be followed up every 2-3 years.

5.5 SPECIAL PATIENT POPULATIONS

Women with aortic stenosis have higher mortality than men, resulting from late diagnosis and initial specialist assessment followed by less frequent and delayed referral for intervention.[255-257] Measures are needed to improve this situation and ensure that both sexes receive equivalent care.

CAD and aortic stenosis frequently coexist and the combination confers higher risk of clinical events, therefore the need to consider revascularization in conjunction with aortic valve intervention is common. The impact of coronary revascularization in patients with silent CAD accompanying aortic stenosis is unclear and further studies are warranted in this context (section 3). Both simultaneous SAVR and CABG, and SAVR late after CABG, carry a higher procedural risk than isolated SAVR. Nevertheless, retrospective data indicate that patients with moderate aortic stenosis, in whom CABG is indicated, benefit from concomitant SAVR. Patients aged <70 years with mean gradient progression ≥5 mmHg/year benefit from SAVR at the time of CABG once baseline peak gradient exceeds 30 mmHg.[258] Decisions for individual patients should take into account haemodynamic data, rate of progression, extent of leaflet calcification, life expectancy, and associated comorbidities, as well as the individual risk of concomitant SAVR or deferred TAVI.[244]

Percutaneous coronary intervention (PCI) and TAVI may be undertaken as combined or staged procedures according to the clinical situation, pattern of CAD, and extent of myocardium at risk.[259] In the SURTAVI trial, there was no significant difference in the primary endpoint (all-cause mortality or stroke at 2-year follow-up) in intermediate-risk patients with severe aortic stenosis and non-complex CAD (SYNTAX score <22) undergoing either TAVI and PCI or SAVR and CABG [16.0% (95% CI, 11.1-22.9) vs. 14% (95% CI, 9.2-21.1); P=0.62].[260] Assessing the clinical value of systematic PCI in TAVI patients with significant associated CAD is the objective of ongoing RCTs. Patients with severe symptomatic aortic stenosis and diffuse CAD unsuitable for revascularization should receive

optimal medical therapy and undergo SAVR or TAVI according to individual characteristics.

Severity of mitral regurgitation accompanying severe aortic stenosis may be overestimated as a result of elevated LV pressures and careful quantification is required. In patients with severe primary mitral regurgitation (PMR), mitral valve surgery is required at the time of SAVR. In patients with severe SMR, surgery may also be considered in the presence of significant annular dilatation and marked LV enlargement. In high-risk or inoperable patients with severe aortic stenosis and severe mitral regurgitation, combined (or more often sequential) TAVI and TEER may be feasible, but there is insufficient experience to allow robust recommendations.[261-263] In patients with severe PMR, TEER should be considered early if the patient remains symptomatic and mitral regurgitation is still severe after TAVI. In patients with severe SMR, TAVI should be followed by careful clinical and echocardiographic reassessment to determine whether further mitral intervention is required.[264]

Section 4 provides recommendations for the management of aneurysm/dilatation of the ascending aorta accompanying aortic stenosis. Assessment and management of congenital aortic stenosis is addressed in ESC Guidelines on adult congenital heart disease.[265]

6 Mitral regurgitation

Mitral regurgitation is the second-most frequent VHD in Europe.[1,3] The underlying mechanism (primary or secondary) determines the therapeutic approach.

6.1 PRIMARY MITRAL REGURGITATION

Primary lesion of one or more components of the mitral valve apparatus characterizes PMR. Degenerative aetiology (fibroelastic deficiency and Barlow disease) is most frequent in Western countries.[1,2,266] In low-income countries, rheumatic aetiology is the most frequent cause of mitral regurgitation.[267] Endocarditis can cause PMR and is addressed in the corresponding ESC Guidelines.[4]

6.1.1 EVALUATION

Echocardiography is the first choice of imaging technique to grade PMR **(Table 7)**. An integrative approach including qualitative, semi-quantitative, and quantitative measures of mitral regurgitation (besides quantification of LV and LA dimensions) is recommended.[24,268] Routinely measured effective regurgitant orifice area (EROA) is strongly associated with all-cause mortality, and compared with the general population an excess mortality appears for an EROA ≥20 mm^2 and steadily increases beyond 40 mm^2.[269] Evaluation of the specific lesion leading to mitral regurgitation has prognostic implications[266,270] and is fundamental to determine

Table 7. Severe mitral regurgitation criteria based on 2D echocardiography.

	Primary mitral regurgitation	Secondary mitral regurgitation
Qualitative		
Mitral valve morphology	Flail leaflet, ruptured papillary muscle, severe retraction, large perforation	Normal leaflets but with severe tenting, poor leaflet coaptation
Colour flow jet area	Large central jet (>50% of LA) or eccentric wall impinging jet of variable size	Large central jet (>50% of LA) or eccentric wall impinging jet of variable size
Flow convergence	Large throughout systole	Large throughout systole
Continuous wave Doppler jet	Holosystolic/dense/triangular	Holosystolic/dense/triangular
Semiquantitative		
Vena contracta width (mm)	≥7 (≥8 mm for biplane)	≥7 (≥8 mm for biplane)
Pulmonary vein flow	Systolic flow reversal	Systolic flow reversal
Mitral inflow	E-wave dominant (>1.2 m/s)	E-wave dominant (>1.2 m/s)
TVI mitral/TVI aortic	>1.4	>1.4
Quantitative		
EROA (2D PISA, mm^2)	≥40 mm^2	≥40 mm^2 (may be ≥30 mm^2 if elliptical regurgitant orifice area)
Regurgitant volume (mL/beat)	≥60 mL	≥60 mL (may be ≥45 mL if low flow conditions)
Regurgitant fraction (%)	≥50%	≥50%
Structural		
Left ventricle	Dilated (ESD ≥40 mm)	Dilated
Left atrium	Dilated (diameter ≥55 mm or volume ≥60 mL/m^2)	Dilated

2D: two-dimensional; ESD: endsystolic diameter; EROA: effective regurgitant orifice area; LA: left atrium; PMR: primary mitral regurgitation; SMR: secondary mitral regurgitation; PISA: proximal isovelocity surface area; TVI: time-velocity integral. Adapted from Lancellotti P et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;14:611-644. Copyright (2013) by permission of Oxford University Press on behalf of the European Society of Cardiology. Reproduced from Zoghbi WA 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;30:303-371. Copyright (2017), with permission from the American Society of Echocardiography.

the feasibility of surgical and transcatheter valve repair[271-273] **(Supplementary Figure 1)**. Three-dimensional TOE provides an '*en face*' view of the mitral leaflets resembling the surgical inspection of the valve, thereby facilitating Heart Team discussion.[24,268] In addition, 3D echocardiography has shown better agreement with CMR in quantifying the regurgitant volume than 2D echocardiography, particularly in eccentric, multiple and late-systolic regurgitant jets.[274-277] When various echocardiographic parameters used to grade mitral regurgitation are inconsistent, CMR is a valid alternative to quantify the regurgitant volume and is the reference standard to quantify LV and LA volumes.[278] In addition, quantification of mitral regurgitation with CMR has shown prognostic implications.[277] Finally, preliminary data show that myocardial fibrosis assessed with CMR is frequent in PMR and has been associated with sudden cardiac death and ventricular arrhythmias.[279]

Exercise echocardiography permits evaluation of changes in mitral regurgitant volume and pulmonary pressures during peak exercise and is particularly helpful in patients with discordant symptoms and regurgitation grade at rest.[280,281] In asymptomatic patients with severe PMR and non-dilated LV and LA, low BNP values are associated with low mortality and can be useful during follow-up.[41,282]

LV dimensions and ejection fraction are considered to guide the management of patients with severe PMR. However, there is cumulative evidence showing that LV global longitudinal strain has incremental prognostic value in patients treated with surgical repair.[283,284] Recently, the Mitral Regurgitation International Database (MIDA) score has been proposed to estimate the risk of all-cause mortality in patients with severe PMR due to flail leaflet, who are under medical treatment or surgically treated.[285] Among the variables included in the score, LA diameter ≥55 mm and LVESD ≥40 mm are new thresholds that have been included in the current recommendations.

Right heart catheterization is systematically used to confirm pulmonary hypertension diagnosed by echocardiography when this is the only criterion to refer the patient for surgery.

6.1.2 INDICATIONS FOR INTERVENTION

Urgent surgery is indicated in patients with acute severe mitral regurgitation. In the case of papillary muscle rupture as the underlying disease, valve replacement is generally required.

Indications for surgery in severe chronic PMR are shown in the following table of recommendations and in **Figure 5**. Surgery is recommended in patients with symptomatic severe PMR and acceptable surgical risk according to the Heart Team decision. The presence of LVEF ≤60%, LVESD ≥40 mm,[285,286] LA volume ≥60 mL/m^2 or diameter ≥55 mm,[287,288] systolic pulmonary arterial pressure (SPAP) >50 mmHg,[289] and AF[290,291] have been associated with worse outcomes and are considered triggers for intervention regardless of symptomatic status.[292] In the absence of these criteria, watchful waiting is a safe strategy in asymptomatic patients with severe PMR and ideally should be performed in a Heart Valve Clinic.

When surgery is considered, mitral valve repair is the surgical intervention of first choice when the results are expected to be durable according to the Heart Team evaluation since it is associated with better survival compared to mitral valve replacement.[293,294] PMR due to segmental valve prolapse can be repaired with a low risk of recurrence and reoperation.[294-296] The reparability of rheumatic lesions, extensive valve prolapse and to a greater extent leaflet calcification or extensive annular calcification is more challenging.[297,298] Patients requiring a predictably complex repair should undergo surgery in experienced repair centres with high repair rates, low operative mortality, and a record of durable results. When repair is not feasible, mitral valve replacement with preservation of the subvalvular apparatus is favoured.

Transcatheter mitral valve implantation for severe PMR is a safe alternative in patients with contraindications for surgery or high operative risk.[299-302] TEER is the most evidenced, while the safety and efficacy of other techniques have been demonstrated in smaller series.[303-306] The efficacy of more recent TEER system iterations[307] will be investigated in high-risk (MITRA-HR study NCT03271762)[308] and intermediate-risk patients (REPAIR-MR study NCT04198870).

6.1.3 MEDICAL THERAPY

In acute mitral regurgitation, nitrates and diuretics are used to reduce filling pressures. Sodium nitroprusside reduces afterload

Recommendations on indications for intervention in severe primary mitral regurgitation

Recommendations	Class[a]	Level[b]
Mitral valve repair is the recommended surgical technique when the results are expected to be durable.[293-296]	I	B
Surgery is recommended in symptomatic patients who are operable and not high risk.[293-296]	I	B
Surgery is recommended in asymptomatic patients with LV dysfunction (LVESD ≥40 mm and/or LVEF ≤60%).[277,286,292]	I	B
Surgery should be considered in asymptomatic patients with preserved LV function (LVESD <40 mm and LVEF >60%) and AF secondary to mitral regurgitation or pulmonary hypertensionc (SPAP at rest >50 mmHg).[285,289]	IIa	B
Surgical mitral valve repair should be considered in low-risk asymptomatic patients with LVEF >60%, LVESD <40 mmd 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.[285,288]	IIa	B
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.[299-302]	IIb	B

AF: atrial fibrillation; LA: left atrium/left atrial; LV: left ventricle/left ventricular; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; SPAP: systolic pulmonary arterial pressure; TEER: transcatheter edge-to-edge repair. [a]Class of recommendations. [b]Level of evidence. [c]If an elevated SPAP is the only indication for surgery, the value should be confirmed by invasive measurement. [d]Cut-offs refer to average-size adults and may require adaptations in patients with unusually small or large stature.

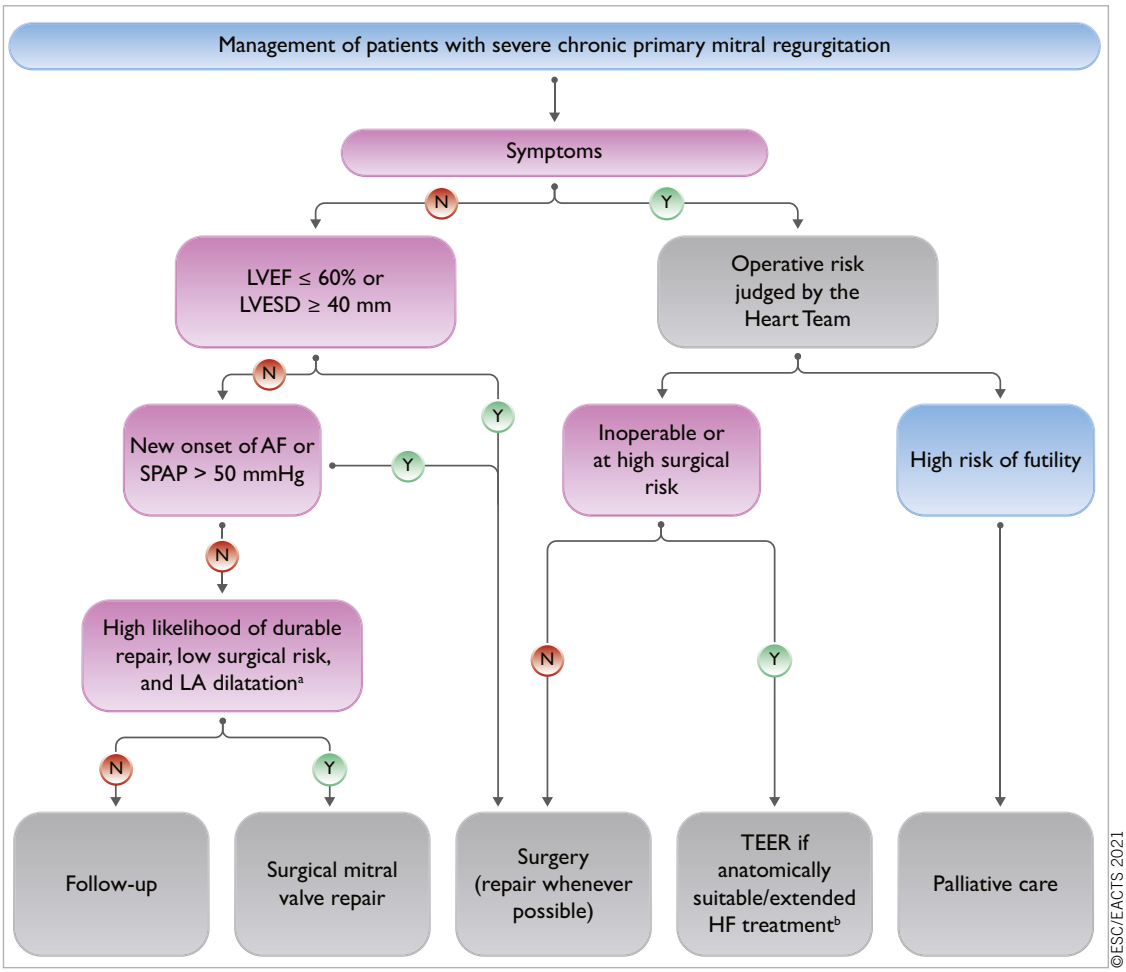

Figure 5. *Management of patients with severe chronic primary mitral regurgitation. AF: atrial fibrillation; HF: heart failure; LA: left atrium/left atrial; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; SPAP: systolic pulmonary arterial pressure; TEER: transcatheter edge-to-edge repair. [a]LA dilatation: volume index ≥60 mL/m² or diameter ≥55 mm at sinus rhythm. [b]Extended heart failure treatment includes the following: CRT; ventricular assist devices; heart transplantation.*[247]

and regurgitant fraction. Inotropic agents and an intra-aortic balloon pump are of use in hypotension and haemodynamic instability.

In chronic PMR with preserved LVEF, there is no evidence to support the prophylactic use of vasodilators. In patients with overt heart failure, medical treatment as per current heart failure guidelines applies.[247]

6.1.4 SERIAL TESTING

Asymptomatic patients with severe mitral regurgitation and LVEF >60% should be followed clinically and by echocardiography every 6 months, ideally in the setting of a Heart Valve Centre.[309] Measurement of BNP levels, exercise echocardiography, electrocardiogram-Holter monitoring and CMR are useful complementary diagnostic and risk stratification tools.[268] The association between PMR, sudden cardiac death and ventricular arrhythmias remains controversial.[310-312] The presence of mitral annulus disjunction (abnormal atrial displacement of the hinge point of the mitral valve away from the ventricular myocardium) has been also associated with increased risk of ventricular arrhythmias.[310,311,313] Interestingly, the majority of these patients did not have severe mitral regurgitation. In asymptomatic patients with severe PMR and progressive increase of LV size (LVESD approaching 40 mm) or decrease of LVEF on serial studies, surgical mitral valve repair should be discussed. Asymptomatic patients with moderate mitral regurgitation and preserved LV function can be followed on a yearly basis and echocardiography should be performed every 1-2 years. After intervention, serial follow-up focuses on evaluation of symptomatic status, presence of arrhythmic events, assessment of valve function,[314] and recurrence of mitral regurgitation. After surgical mitral valve repair, high-volume centres have reported good durability with a recurrence rate of moderate or severe mitral regurgitation of 12.5% at 20 years of follow-up.[296] After transcatheter mitral valve repair, the currently reported rates of residual moderate and severe mitral regurgitation (23-30%) would suggest that yearly echocardiogram is appropriate.[14,300,301]

6.1.5 SPECIAL POPULATIONS

Sex differences in terms of prevalence of underlying aetiology of PMR and management have been reported.[298,315,316] Despite the

reduction in the prevalence of rheumatic disease in Western countries, women still have higher rates of rheumatic mitral regurgitation than men and emerging aetiologies such as radiation heart disease are also more frequent in women.[297] These aetiologies are often characterized by severe calcification of the mitral valve apparatus and associated with mitral stenosis precluding durable repair. Women with PMR referred for surgical treatment received mitral valve repair at a similar rate to men.[316] However, women more frequently present with post-operative heart failure, probably related to a later referral and more advanced disease as compared to men.

6.2 SECONDARY MITRAL REGURGITATION

In SMR, the valve leaflets and chordae are structurally normal and mitral regurgitation results from an imbalance between closing and tethering forces secondary to alterations in LV and LA geometry.[317,318] It is most commonly seen in dilated or ischaemic cardiomyopathies, both in severely dilated LV with markedly depressed LV function or after an isolated infero-basal myocardial infarction leading to posterior leaflet tethering, despite almost normal LV size and ejection fraction. SMR may also arise as a consequence of LA enlargement and mitral annular dilatation in patients with longstanding AF, in whom LVEF is usually normal and LV dilatation less pronounced (so called 'atrial functional mitral regurgitation').[319]

6.2.1 EVALUATION

The echocardiographic criteria to define severe SMR do not differ from those used in PMR and an integrative approach should be used **(Table 7)**.[24,268] However, it should be acknowledged that when quantifying EROA and regurgitant volume in SMR, lower thresholds may be applied to define severe SMR. In heart failure patients, the total forward LV stroke volume is lower and that may lead to lower estimated regurgitant volume (<60 mL/beat). Calculation of regurgitant fraction in those circumstances could account for lower flows and has shown prognostic implications.[320] In addition, the crescent shape of the regurgitant orifice, characteristic of SMR, may lead to underestimation of the vena contracta width and of the EROA. An EROA ≥30 mm^2 by 2D proximal isovelocity surface area (PISA) likely corresponds to severe SMR. In contrast, whether an EROA ≥20 mm^2 defines severe SMR remains controversial. In heart failure patients, even mild mitral regurgitation is associated with poor prognosis[321] and evidence that surgical or transcatheter treatment of moderate SMR does not seem to improve patient outcomes[322,323] supports the change in definition of severe SMR. Caution is required, therefore, when labelling severe SMR based solely on prognostic implications. Other factors such as the extent of myocardial scar, as assessed with CMR, have been associated with poor prognosis.[324] In addition, LVEF has been shown to be misleading in patients with severe SMR, while LV global longitudinal strain has been shown to have incremental prognostic value.[325,326] The use of 3D echocardiography, CMR and exercise echocardiography may help to identify patients with severe mitral regurgitation when 2D echocardiography at rest is inconclusive.[24,268]

6.2.2 MEDICAL THERAPY

Optimal medical therapy in line with the guidelines for the management of heart failure[247] should be the first and essential step in the management of all patients with SMR and should include replacement of ACEI or ARB with sacubitril/valsartan, sodium-glucose co-transporter 2 inhibitors and/or ivabradine, whenever indicated.[247,327] Indications for cardiac resynchronization therapy (CRT) should be evaluated in accordance with related guidelines.[247] If symptoms persist after optimization of conventional heart failure therapy, options for mitral valve intervention should be promptly evaluated before further deterioration of LV systolic function or cardiac remodelling occur.

6.2.3 INDICATIONS FOR INTERVENTION

Chronic SMR is associated with impaired prognosis[321,328] and its interventional management is complex (see recommendations on indications for mitral valve intervention in chronic severe SMR, and **Figure 6**). The detailed analysis of the available level of evidence made by the methodology group of the task force is available in Supplementary Section 5. The importance of decision making by a multidisciplinary Heart Team needs to be emphasized in this setting. The Heart Team, including a heart failure specialist, should optimize guideline-directed medical therapy (GDMT) and consider the indications of electrophysiological, transcatheter and surgical interventions, their priority and order of implementation.

The evidence supporting surgical intervention remains limited. Mitral valve surgery is recommended in patients with severe SMR undergoing CABG or other cardiac surgery.[329,330] The surgical approach has to be tailored to the individual patient.[247,331] In selected patients without advanced LV remodelling, mitral valve repair with an undersized complete rigid ring restores valve competence, improves symptoms, and results in reverse LV remodelling.[331] Additional valvular/subvalvular techniques or chordal sparing valve replacement may be considered in patients with echocardiographic predictors of repair failure.[332] Valve replacement avoids recurrence of mitral regurgitation, although this does not translate into better LV reverse remodelling or survival.[333] Indications for isolated mitral valve surgery in SMR are particularly restrictive, owing to significant procedural risk, high rates of recurrent mitral regurgitation, and the absence of proven survival benefit.[333-335] In patients with atrial functional mitral regurgitation, LVEF is usually normal, LV dilatation less pronounced and mitral annular dilatation represents the main mechanism of mitral regurgitation. This subgroup may be more effectively treated by ring annuloplasty often associated with ablation of AF but evidence is still limited.[319]

TEER with the MitraClip system is a minimal-invasive treatment option for SMR. Two RCTs (COAPT and MITRA-FR)[323,336,337] have evaluated its safety and efficacy in patients with symptomatic heart failure and severe SMR persisting despite medical therapy, who were considered either ineligible or not appropriate for surgery by the Heart Team **(Supplementary Table 7)**. The results indicate that the procedure is safe and effectively reduces SMR up to 3 years.[338] However, in the MITRA-FR trial,[323,336] MitraClip implantation had no impact on the primary endpoint of all-cause

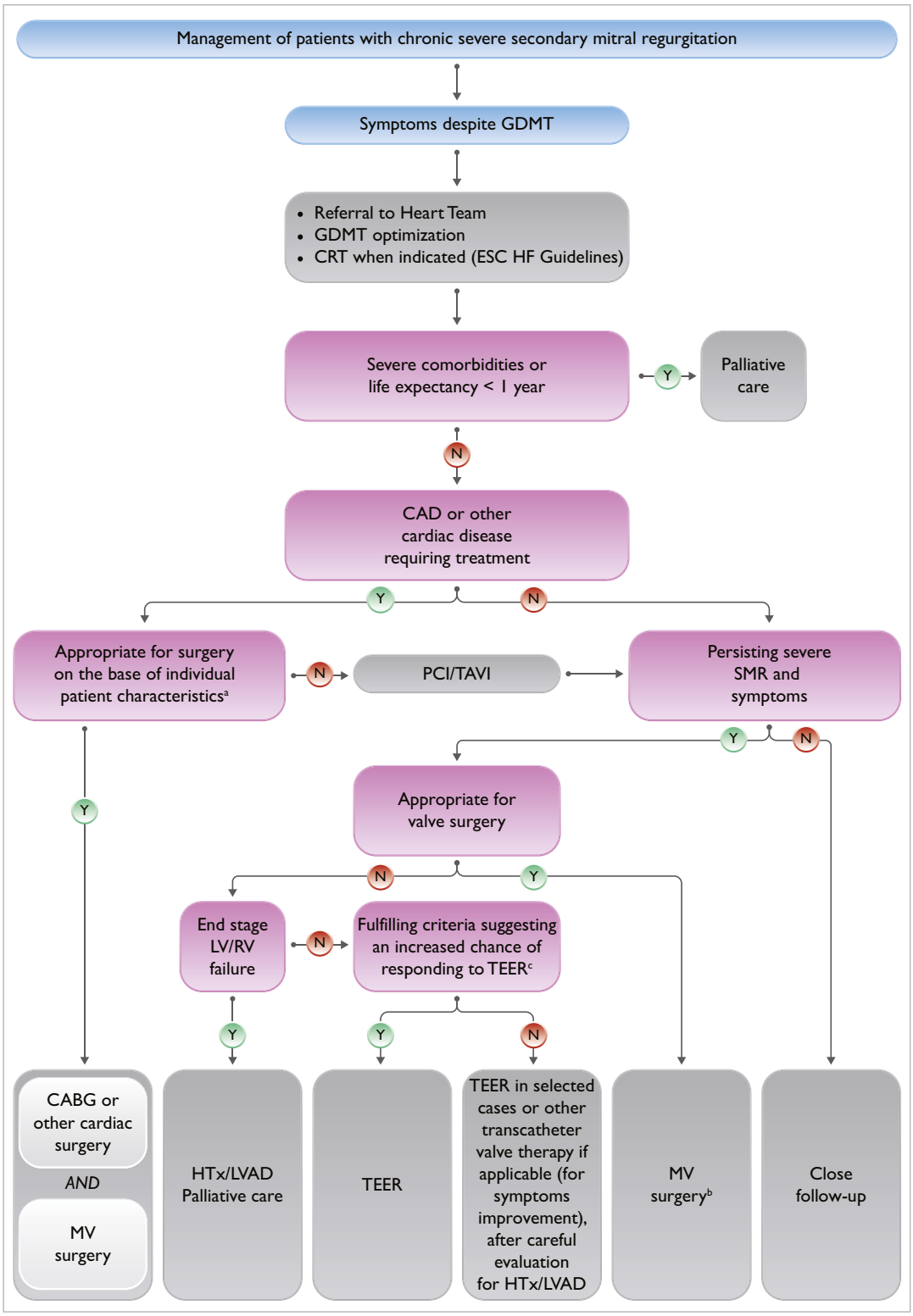

Figure 6. *Management of patients with chronic severe secondary mitral regurgitation. CAD: coronary artery disease; CABG: coronary artery bypass grafting; CRT: cardiac resynchronization therapy; ESC: European Society of Cardiology; GDMT: guideline-directed medical therapy; HF: heart failure; HTx: heart transplantation; LVAD: left ventricular assist devices; LV: left ventricle/left ventricular; LVEF: left ventricular ejection fraction; MV: mitral valve; PCI: percutaneous coronary intervention; RV: right ventricle/right ventricular; SMR: secondary mitral regurgitation; TAVI: transcatheter aortic valve implantation; TEER: transcatheter edge-to-edge repair.* [a]*LVEF, predicted surgical risk, amount of myocardial viability, coronary anatomy/target vessels, type of concomitant procedure needed, TEER eligibility, likelihood of durable surgical repair, need of surgical mitral replacement, local expertise.* [b]*Particularly when concomitant tricuspid valve surgery is needed.* [c]*COAPT criteria (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation): see* **Supplementary Table 7**.

mortality or heart failure hospitalization at 12 months and 2 years compared to GDMT alone. In the COAPT trial,[337] MitraClip implantation substantially reduced the primary endpoint of cumulative hospitalizations for heart failure, as well as several pre-specified secondary endpoints, including all-cause mortality at 2 years.

Subanalyses of the COAPT trial confirm the positive response to TEER in several patient subgroups;[339-343] conversely, the effect of the interventional treatment was neutral throughout all subgroups in an echocardiographic subanalyses of the MITRA-FR trial.[344]

The conflicting results of these two trials have generated considerable discussion. These diverging results might be partially explained by effect size of the trials, differences in trial design, patient selection, echocardiographic assessment of SMR severity, use of medical therapy, and technical factors. Patients in COAPT demonstrated greater severity of SMR (EROA 41±15 mm^2 vs. 31±10 mm^2) and less LV dilatation (mean indexed LV end-diastolic volume 101±34 mL/m^2 vs. 135±35 mL/m^2) than those enrolled in MITRA-FR. Perhaps reflecting greater severity of SMR in relation to LV dimensions ('disproportionate' mitral regurgitation), patients in COAPT were overall more likely to benefit from TEER in terms of reduced mortality and heart failure hospitalization.[345]

Additional studies are needed to identify patients who will benefit the most from TEER.

Therefore, TEER should be considered in selected patients with severe SMR fulfilling the COAPT inclusion criteria,[346-348] who receive optimal medical therapy supervised by a heart failure specialist and are as close as possible to the patients actually enrolled in the study. Optimization of the procedural result should also be pursued. In addition, TEER may be considered only in selected cases when the COAPT criteria are not fulfilled with the aim of improving symptoms and quality of life.[349-353] In patients with less severe SMR (EROA <30 mm^2) and advanced LV dilatation/dysfunction, the prognostic benefit of MitraClip remains unproven.[323,354,355] Patients with end-stage LV and/or RV failure and no option for revascularization may be better served by cardiac transplantation or LV assist device implantation. Valve intervention is generally not an option when LVEF is <15%.[247]

The management of moderate ischaemic SMR in patients undergoing CABG remains an object of debate.[322,330] Surgery is more likely to be considered if myocardial viability is present and if comorbidity is low. Exercise-induced dyspnoea and a large increase in mitral regurgitation severity and SPAP favour combined surgery.

Transcatheter mitral valve repair systems other than TEER, as well as transcatheter mitral valve replacement devices, are currently the subject of intense investigation but clinical data are still limited.

Recommendations on indications for mitral valve intervention in chronic severe secondary mitral regurgitation[a]

Recommendations	Class[b]	Level[c]
Valve surgery/intervention is recommended only in patients with severe SMR who remain symptomatic despite GDMT (including CRT if indicated) and has to be decided by a structured collaborative Heart Team.[247,323,336,337]	I	B
Patients with concomitant coronary artery or other cardiac disease requiring treatment		
Valve surgery is recommended in patients undergoing CABG or other cardiac surgery.[329,330,333]	I	B
In symptomatic patients, who are judged not appropriate for surgery by the Heart Team on the basis of their individual characteristics,[d] PCI (and/or TAVI) possibly followed by TEER (in case of persisting severe SMR) should be considered.	IIa	C
Patients without concomitant coronary artery or other cardiac disease requiring treatment		
TEER should be considered in selected symptomatic patients, not eligible for surgery and fulfilling criteria suggesting an increased chance of responding to the treatment.[337,338,356,357][e]	IIa	B
Valve surgery may be considered in symptomatic patients judged appropriate for surgery by the Heart Team.	IIb	C
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.[e]	IIb	C

2D: two-dimensional; CABG: coronary artery bypass grafting; CRT: cardiac resynchronization therapy; EROA: effective regurgitation orifice area; GDMT: guideline-directed medical therapy; LVEF: left ventricular ejection fraction; SMR: secondary mitral regurgitation; PCI: percutaneous coronary intervention; SMR: secondary mitral regurgitation; TAVI: transcatheter aortic valve implantation; TEER: transcatheter edge-to-edge repair. [a]See **Table 7** for SMR quantification (an EROA ≥30 mm^2 by 2D proximal isovelocity surface area corresponds likely to severe SMR). Quantification of SMR must always be performed under optimal guidelines-directed medical treatment. [b]Class of recommendation. [c]Level of evidence. [d]LVEF, predicted surgical risk, amount of myocardial viability, coronary anatomy/target vessels, type of concomitant procedure needed, TEER eligibility, likelihood of durable surgical repair, need of surgical mitral replacement, local expertise. [e]COAPT criteria (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation): see **Supplementary Table 7**.

7 Mitral stenosis

Aetiology of mitral stenosis is mostly rheumatic or degenerative. Rheumatic fever is the most common cause of mitral stenosis worldwide. Its prevalence has greatly decreased in industrialized countries, but it remains a significant healthcare problem in developing countries and affects young patients.[2,267,358] Degenerative mitral stenosis related to MAC is a distinct pathology and its prevalence significantly increases with age.[359,360] Both types of mitral stenosis are more frequent in females.[361] In rare cases, mitral stenosis due to valve rigidity but without commissural fusion, may be related to chest radiation, carcinoid heart disease, or inherited metabolic diseases.

7.1 RHEUMATIC MITRAL STENOSIS

7.1.1 EVALUATION

Clinically significant mitral stenosis is defined by a mitral valve area (MVA) ≤1.5 cm^2. Commissural fusion with thickening of

the posterior leaflet is the most important mechanism of stenosis. Echocardiography is the preferred method for diagnosis, assessment of severity, and haemodynamic consequences of mitral stenosis. Valve area using 2D planimetry is the reference measurement of mitral stenosis severity, whereas mean transvalvular gradient and pulmonary pressures reflect its consequences and have a prognostic role.[362] 3D-TTE planimetry may have an additional diagnostic value. TTE usually provides sufficient information for routine management. Scoring systems have been developed to help assess suitability for percutaneous mitral commissurotomy (PMC; **Supplementary Table 8**),[363-365] TOE should be performed to exclude LA thrombus before PMC or after an embolic episode, and to obtain detailed information on mitral anatomy (commissural zones and subvalvular apparatus) before intervention when TTE is suboptimal. Stress testing is indicated in patients with no symptoms or symptoms equivocal or discordant with the severity of mitral stenosis. Exercise echocardiography may provide objective information by assessing changes in mitral gradient and pulmonary artery pressure and is superior to DSE. Echocardiography plays an important role in the periprocedural monitoring of PMC and follow-up.

7.1.2 INDICATIONS FOR INTERVENTION

The type of treatment (PMC or surgery), as well as its timing, should be decided based on clinical characteristics, anatomy of valve and subvalvular apparatus, and local expertise.[366-369] In general, indication for intervention should be limited to patients with clinically significant (moderate-to-severe) rheumatic mitral stenosis (valve area ≤1.5 cm^2) in whom PMC has had a significant impact on its management. In Western countries where incidence of rheumatic fever and number of PMC is low, this treatment should be restricted to expert operators in specialized centres to improve safety and procedural success rate.[366] Efforts should be made to increase availability of PMC in developing countries where access to treatment is limited due to economic reasons.[267] PMC should be considered as an initial treatment for selected patients with mild to moderate calcification or impaired subvalvular apparatus, but who have otherwise favourable clinical characteristics.[360]

The management of clinically significant rheumatic mitral stenosis is summarized in **Figure 7** and the indications and contraindications for PMC are provided in the table of recommendations below, and **Table 8**.

Recommendations on indications for percutaneous mitral commissurotomy and mitral valve surgery in clinically significant (moderate or severe) mitral stenosis (valve area ≤1.5 cm^2)

Recommendations	Class[a]	Level[b]
PMC is recommended in symptomatic patients without unfavourable characteristics[c] for PMC.[360,363-365,367]	I	B
PMC is recommended in any symptomatic patients with a contraindication or a high risk for surgery.	I	C
Mitral valve surgery is recommended in symptomatic patients who are not suitable for PMC in the absence of futility.	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[c] 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 (systolic pulmonary pressure >50 mmHg at rest, need for major NCS, desire for pregnancy).	IIa	C

AF: atrial fibrillation; LA: left atrium/left atrial; MVA: mitral valve area; NCS: non-cardiac surgery; PMC: percutaneous mitral commissurotomy. [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, New York Heart Association class IV, permanent AF, severe pulmonary hypertension. Anatomical characteristics: echocardiographic score >8, Cormier score 3 (calcification of mitral valve of any extent as assessed by fluoroscopy), very small MVA, severe tricuspid regurgitation. For the definition of scores, see **Supplementary Table 8**.

Table 8. Contraindications for percutaneous mitral commissurotomy in rheumatic mitral stenosis[a].

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

CAD: coronary artery disease; LA: left atrium/left atrial; MVA: mitral valve area; PMC: percutaneous mitral commissurotomy. [a]PMC may be considered in patients with valve area >1.5 cm^2 with symptoms that cannot be explained by another cause and if the anatomy is favourable.

7.1.3 MEDICAL THERAPY

Diuretics, beta-blockers, digoxin, non-dihydropyridine calcium channel blockers and ivabradine can improve symptoms. Anticoagulation with vitamin K antagonist (VKA) with a target international normalized ratio (INR) between 2 and 3 is indicated in patients with AF. Patients with moderate-to-severe mitral stenosis and AF should be kept on VKA and not receive NOACs. Currently there is no solid evidence to support the use of NOACs in this setting[370] and a randomized clinical trial is underway (INVICTUS VKA NCT 02832544). Neither cardioversion nor catheter pulmonary vein isolation are indicated before intervention in patients with significant mitral stenosis, as they do not durably restore sinus rhythm. If AF is of recent onset and the LA is only moderately enlarged, cardioversion should be performed soon after successful intervention, it should also be considered in patients

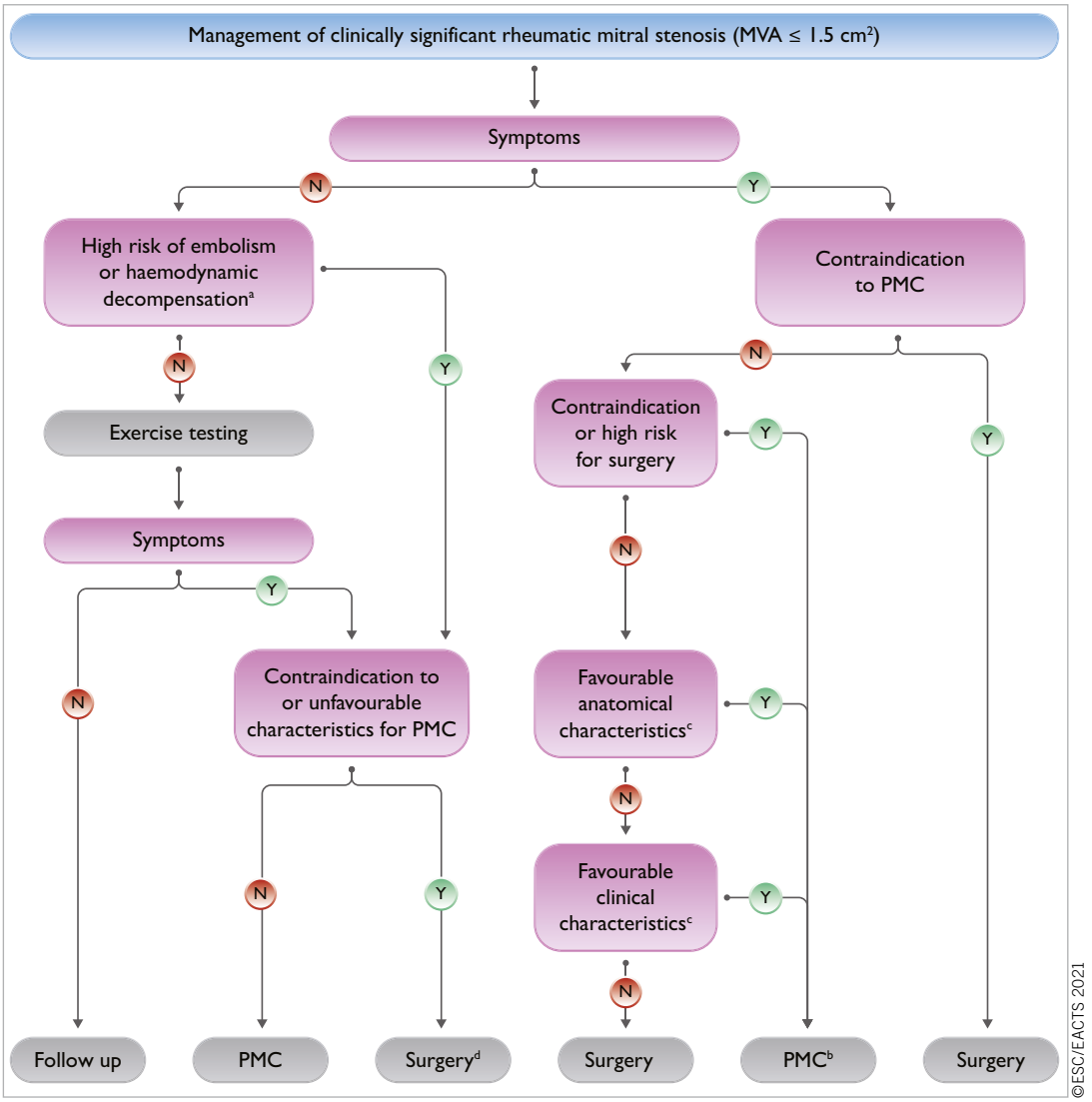

Figure 7. *Management of clinically significant rheumatic mitral stenosis (MVA ≤1.5 cm²). AF: atrial fibrillation; LA: left atrium/left atrial; MVA: mitral valve area; NCS: non-cardiac surgery; PMC: percutaneous mitral commissurotomy. [a]High thromboembolic risk: history of systemic embolism, dense spontaneous contrast in the LA, new-onset AF. High-risk of haemodynamic decompensation: systolic pulmonary pressure >50 mmHg at rest, need for major NCS, desire for pregnancy. [b]Surgical commissurotomy may be considered by experienced surgical teams in patients with contraindications to PMC. [c]See recommendations on indications for PMC and mitral valve surgery in clinically significant mitral stenosis in section 7.2. [d]Surgery if symptoms occur for a low level of exercise and operative risk is low.*

with less than severe mitral stenosis. Amiodarone is most effective in maintaining the sinus rhythm after cardioversion. In patients in sinus rhythm, OAC is recommended when there has been a history of systemic embolism or 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/m²).

7.1.4 SERIAL TESTING

Asymptomatic patients with clinically significant mitral stenosis should be followed up yearly by clinical and echocardiographic examinations; and at longer intervals (2-3 years) in case of moderate stenosis. Follow-up of patients after successful PMC is similar to that of asymptomatic patients and should be more frequent if asymptomatic restenosis occurs.

7.1.5 SPECIAL PATIENT POPULATIONS

When symptomatic restenosis occurs after surgical commissurotomy or PMC, re-intervention in most cases requires valve replacement, but PMC can be proposed in selected candidates with favourable characteristics if the predominant mechanism is commissural refusion.[369]

In patients with severe rheumatic mitral stenosis combined with severe aortic valve disease, surgery is preferable when it is not contraindicated. The management of patients in whom surgery is contraindicated is difficult and requires a comprehensive and individualized evaluation by the Heart Team. In cases with severe mitral stenosis associated with moderate aortic valve disease, PMC can be performed to postpone the surgical treatment of both valves. In patients with severe tricuspid regurgitation, PMC

may be considered in selected patients with sinus rhythm, moderate atrial enlargement, and severe functional tricuspid regurgitation secondary to pulmonary hypertension. In other cases, surgery on both valves is preferred.[371]

In the elderly population with rheumatic mitral stenosis when surgery is high risk, PMC is a useful option, even if as palliative care.[364,367,368] Treatment of patients with low-gradient severe mitral stenosis (MVA ≤1.5 cm^2, mean gradient <10 mmHg) is difficult, as these patients are older and have less optimal anatomy.[372]

7.2 DEGENERATIVE MITRAL STENOSIS WITH MITRAL ANNULAR CALCIFICATION

MAC is a distinct entity that differs from rheumatic mitral stenosis. Usually, these patients are elderly and may have significant comorbidities including disease of other valves. Overall, the prognosis is poor due to high-risk profile and technical anatomic challenges resulting from the presence of annular calcification.[373] Between 9% and 15% of the general population may have MAC, with higher frequency in elderly patients (40%).[67,374-376] Furthermore, almost half of patients with aortic stenosis undergoing TAVI have MAC, and the disease is severe in 9.5% of cases.[359,377] Severe MAC may result in mitral stenosis (more frequently) or mitral regurgitation, or both.

7.2.1 EVALUATION

In patients with degenerative mitral stenosis and MAC, the echocardiographic evaluation of the disease severity is difficult and the usual parameters lack validation. Planimetry is less reliable due to diffuse calcium and irregular orifice. The mean transmitral gradient has been shown to have prognostic value.[378] For the evaluation of severity, it is necessary to take into account the abnormalities of LA and LV compliance before indicating an intervention. If an intervention is planned, echocardiography is used for initial evaluation and CCT is necessary to assess the degree and location of calcification and to evaluate the feasibility of an intervention.[379]

7.2.2 INDICATIONS FOR INTERVENTION

Treatment options, including transcatheter and surgical approaches, are high-risk procedures and evidence from randomized trials is lacking. Even if the procedure is done successfully and the transvalvular gradient is reduced, due to low compliance of the LA and LV the mean atrial pressure may remain elevated.

In elderly patients with degenerative mitral stenosis and MAC, surgery is technically challenging and high risk.[380] As there is no commissural fusion, degenerative mitral stenosis is not amenable to PMC.[359] In symptomatic inoperable patients with suitable anatomy, preliminary experience showed that transcatheter mitral valve implantation (in mitral position, using an inverted balloon-expandable TAVI prosthesis), is feasible in selected patients with severe mitral stenosis, when performed by experienced operators after careful pre-planning using multimodality imaging.[379] The largest case series reported to date included only 116 patients.[381] However, operative mortality is high, in particular due to the risk of LVOT obstruction and mid-term results are less favourable compared to mitral valve-in-valve procedures.[382,383] The most recent case series show that results are improving owing to better patient selection and the use of different accesses, as well as concomitant or preventive measures such as alcohol septal ablation[384] or laceration/resection of the anterior leaflet.[385-387]

Recently, a preliminary case series suggested that transcatheter mitral valve replacement using a dedicated prosthesis is feasible and can result in symptom improvement.[388]

8 Tricuspid regurgitation

Moderate or severe tricuspid regurgitation is observed in 0.55% of the general population and its prevalence increases with age, affecting about 4% of the patients aged 75 years or more.[389] Aetiology is secondary in ≥90% of cases, due to pressure and/or volume overload mediated RV dilatation or enlarged right atrium and tricuspid annulus due to chronic AF. Secondary tricuspid regurgitation is associated with left-sided valvular or myocardial dysfunction in most cases, whereas it is isolated in 8.1% of subjects and independently related to mortality.[389] Secondary tricuspid regurgitation may also develop late after left-sided valve surgery.[390,391]

Causes of primary tricuspid regurgitation include infective endocarditis [especially in intravenous (i.v.) drug addicts], rheumatic heart disease, carcinoid syndrome, myxomatous disease, endomyocardial fibrosis, congenital valve dysplasia (e.g. Ebstein's anomaly), thoracic trauma, and iatrogenic valve damage.

Atrial fibrillation induces annular remodelling even in the absence of left-heart disease.[392] Cardiac implantable electronic device-lead implantation leads to progressive tricuspid regurgitation in 20-30% of the patients[393-395] and predicts its progression over time.[396]

In patients with heart failure and reduced LVEF, secondary tricuspid regurgitation is a very frequent finding and is an independent predictor of clinical outcomes.[397]

8.1 EVALUATION

Tricuspid regurgitation should be evaluated first by echocardiography. In primary tricuspid regurgitation, specific abnormalities of the valve can be identified. In secondary tricuspid regurgitation, annular dilatation, along with RV and right atrium dimensions, as well as RV function should be measured, owing to their prognostic relevance.[398] In experienced laboratories, RV strain[27] and/or 3D measurements of RV volumes[399,400] may be considered to overcome the existing limitations of conventional RV function indices.[102] When available, CMR is the preferred method to assess the RV[400] due to its high accuracy and reproducibility.[401]

Echocardiographic evaluation of tricuspid regurgitation severity is based on an integrative approach considering multiple qualitative and quantitative parameters **(Table 9)**. Due to the non-circular and non-planar shape of the regurgitant orifice, biplane vena contracta width should be considered in addition to the conventional

Table 9. Echocardiographic criteria for grading severity of tricuspid regurgitation.

Qualitative	
Tricuspid valve morphology	Abnormal/flail
Colour flow regurgitant jet	Very large central jet or eccentric wall impinging jet[a]
CW signal of regurgitant jet	Dense/triangular with early peaking
Semiquantitative	
Vena contracta width (mm)	>7[a,b]
PISA radius (mm)	>9[c]
Hepatic vein flow[c]	Systolic flow reversal
Tricuspid inflow	E-wave dominant ≥1 m/s[d]
Quantitative	
EROA (mm^2)	≥40
Regurgitant volume (mL/beat)	≥45
Enlargement of cardiac chambers/vessels	RV, RA, inferior vena cava

CW: continuous wave; EROA: effective regurgitant orifice area; PISA: proximal isovelocity surface area; RA: right atrium/right atrial; RV: right ventricle/right ventricular; TR: tricuspid regurgitation.
[a]At a Nyquist limit of 50-60 cm/s. [b]Preferably biplane. [c]Baseline Nyquist limit shift of 28 cm/s. [d]In the absence of other causes of elevated RA pressure.

2D measurement.[402] Similarly, underestimation of tricuspid regurgitation severity by the PISA method may occur.[403] In case of inconsistent findings, the 3D vena contracta area may be evaluated, although diverging cut-offs have been reported.[402,404-406] Recently, a new grading scheme including two additional grades ('massive' and 'torrential') has been proposed[407] and used in clinical studies on transcatheter interventions.[408,409] Studies showed an incremental prognostic value of the two additional grades (massive and torrential) in terms of mortality and rehospitalization for heart failure in patients with advanced disease.[410-412]

Alternatively, calculation of the tricuspid regurgitant volume by CMR using RV volumetry may be helpful.

Importantly, estimation of pulmonary pressures using Doppler gradient may be impossible or might underestimate the severity of pulmonary hypertension in the presence of severe tricuspid regurgitation, justifying cardiac catheterization to evaluate pulmonary vascular resistances.[413]

8.2 INDICATIONS FOR INTERVENTION

Severe tricuspid regurgitation is associated with impaired survival[389,414-416] and worsening heart failure.[397,417] In clinical practice, tricuspid valve interventions are underused and often initiated too late.[418-420] Appropriate timing of intervention is crucial to avoid irreversible RV damage and organ failure with subsequent increased surgical risk[421,422] (see table of recommendations on indications for intervention in tricuspid valve disease in section 9 and **Figure 8**).

Surgery is recommended in symptomatic patients with severe primary tricuspid regurgitation. In selected asymptomatic or mildly symptomatic patients who are appropriate for surgery, an intervention should also be considered when RV dilatation or declining RV function is observed. However, exact thresholds have not yet been defined.

According to observational data, tricuspid valve repair should be performed liberally during left-sided surgery in patients with secondary tricuspid regurgitation. Indeed, it does not increase operative risk, but promotes reverse remodelling of the RV and improves functional status when annular dilatation is present, even in the absence of severe tricuspid regurgitation.[423-427]

The benefit of surgical correction of isolated secondary tricuspid regurgitation compared to medical treatment is not well established[428] and the procedure has a non-negligible risk of periprocedural mortality and morbidity when patients present late.[429-432] However, in carefully selected candidates, surgery can be performed safely with good long-term survival.[418,433] It should therefore be considered early in selected symptomatic patients appropriate for surgery, as well as in those with no or mild symptoms, RV dilatation and severe tricuspid regurgitation. Although a tricuspid annular pulmonary systolic excursion (TAPSE) <17 mm has been associated with worse prognosis in patients with secondary tricuspid regurgitation,[398,434] thresholds for severe RV dysfunction making intervention futile have not yet been defined.

Reoperation on the tricuspid valve in new-onset or worsening secondary tricuspid regurgitation after left-sided surgery carries a high procedural risk, possibly due to late referral and subsequent poor clinical condition.[435] To improve prognosis, treatment of severe tricuspid regurgitation in this challenging scenario should be considered even in asymptomatic patients if there are signs of RV dilatation or decline in RV function (after exclusion of left-sided valve dysfunction, severe RV or LV dysfunction and severe pulmonary vascular disease/hypertension).

Whenever possible, annuloplasty with prosthetic rings is preferable to valve replacement,[423,430,436] which should only be considered when the tricuspid valve leaflets are tethered and the annulus severely dilated. In presence of a cardiac implantable electronic device lead, the technique used should be adapted to the patient's condition and the surgeon's experience.[437]

TTVI are under clinical development. Early registry and study data demonstrated the feasibility to reduce tricuspid regurgitation using various systems, enabling either leaflet approximation[408,438-440] direct annuloplasty,[409,441] or valve replacement,[442-444] with subsequent symptomatic and haemodynamic improvement.[445,446] In a propensity-score-matched study comparing medical treatment to TTVI, all-cause mortality and rehospitalizations at 1 year were lower among the patients who received the interventional treatment.[447] Several RCTs will investigate the efficacy of TTVI against medical treatment.

Therefore, TTVI may be considered by the Heart Team at experienced Heart Valve Centres in symptomatic, inoperable, anatomically eligible patients in whom symptomatic or prognostic improvement can be expected. For detailed anatomical evaluation, TOE and CCT may be preferred owing to higher spatial resolution.[448,449]

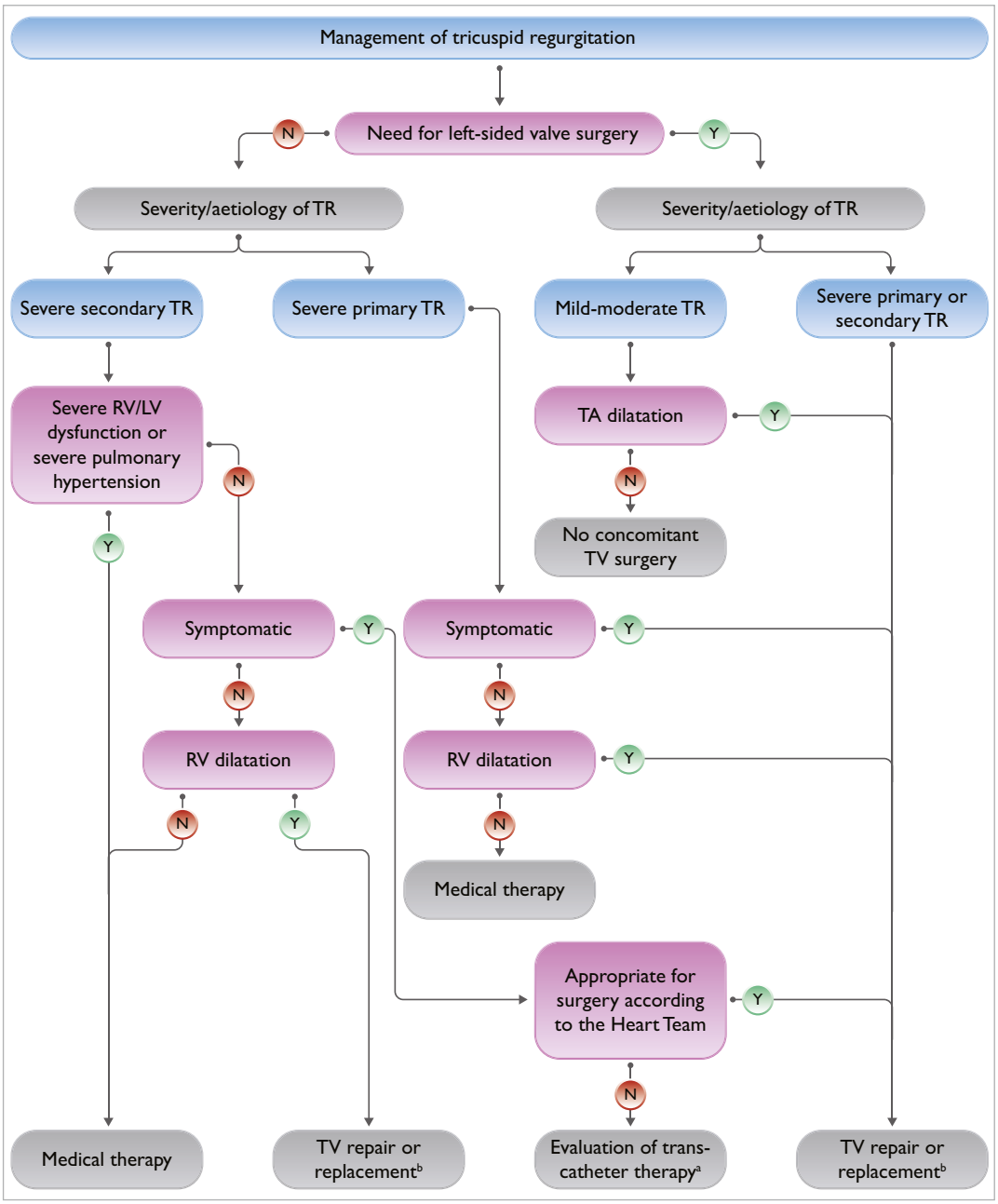

Figure 8. *Management of tricuspid regurgitation. LV: left ventricle/left ventricular; RV: right ventricle/right ventricular; TA: tricuspid annulus; TR: tricuspid regurgitation; TV: tricuspid valve. [a]The Heart Team with expertise in the treatment of tricuspid valve disease evaluates anatomical eligibility for transcatheter therapy including jet location, coaptation gap, leaflet tethering, potential interference with pacing lead. [b]Replacement when repair is not feasible.*

8.3 MEDICAL THERAPY

Diuretics are useful in the presence of right heart failure. To counterbalance the activation of the renin-angiotensin-aldosterone system associated with hepatic congestion, the addition of an aldosterone antagonist may be considered.[247] Dedicated treatment of pulmonary hypertension is indicated in specific cases. Although data are limited, rhythm control may help to decrease tricuspid regurgitation and contain annular dilatation in patients with chronic AF.[450] Importantly, in the absence of advanced RV dysfunction or severe pulmonary hypertension, none of the above-mentioned therapies should delay referral for surgery or transcatheter therapy.

9 Tricuspid stenosis

Tricuspid stenosis is often combined with tricuspid regurgitation and most frequently of rheumatic origin. It is therefore usually associated with left-sided valve lesions, particularly mitral stenosis. Other causes are rare, including congenital, carcinoid and

drug-induced valve diseases, Whipple's disease, endocarditis, and large right atrial tumour.

9.1 EVALUATION

Echocardiography provides the most useful information. Tricuspid stenosis is often overlooked and requires careful evaluation. Echocardiographic evaluation of valve anatomy and subvalvular apparatus is important to assess valve reparability. No generally accepted grading of tricuspid stenosis severity exists, but a mean echocardiographic transvalvular gradient ≥5 mmHg at normal heart rate is considered indicative of significant tricuspid stenosis.[362]

9.2 INDICATIONS FOR INTERVENTION

Intervention on the tricuspid valve is usually performed concomitantly during procedures for left-sided valve disease in patients who are symptomatic despite medical therapy. Although the lack of pliable leaflet tissue is a main limitation for valve repair, the choice between repair and replacement depends on anatomy and surgical expertise. Owing to satisfactory long-term durability, biological prostheses are usually preferred over mechanical valves, which have a high risk of thrombosis.[451]

Percutaneous tricuspid balloon valvuloplasty has been performed in a limited number of cases, either alone or in combination with PMC. It frequently induces significant regurgitation and long-term results are lacking.[452] It can be considered in rare cases with anatomically suitable valves, when tricuspid stenosis is isolated or additional mitral stenosis can also be treated interventionally (see recommendations on indications for PMC and mitral valve surgery in clinically significant mitral stenosis in section 7).

9.3 MEDICAL THERAPY

Diuretics are useful in the presence of heart failure symptoms but are of limited long-term efficacy.

10 Combined and multiple-valve diseases

Significant stenosis and regurgitation can be found on the same valve. Disease of multiple valves may be encountered in several conditions, particularly in rheumatic and congenital heart disease, but also less frequently in degenerative valve disease. There is a lack of data on combined or multiple-valve disease.[453-460] This does not allow for evidence-based recommendations. The general principles for the management of combined or multiple-valve disease are as follows:

- When either stenosis or regurgitation is predominant, management follows the recommendations concerning the predominant VHD. When the severity of both stenosis and regurgitation is balanced, indications for interventions should be based on symptoms and objective consequences rather than on the indices of severity of stenosis or regurgitation.[453-456] In this setting, Doppler pressure gradient reflects the global haemodynamic burden (stenosis and regurgitation) of the valve lesion.[453]
- Besides the separate assessment of each valve lesion, it is necessary to consider the interaction between the different valve lesions. As an illustration, associated mitral regurgitation may lead to underestimation of the severity of aortic stenosis, as decreased stroke volume due to mitral regurgitation lowers the flow across the aortic valve and hence the aortic gradient.[453] This underlines the need to combine different measurements, including assessment of valve areas, if possible using methods that are less dependent on loading conditions, such as planimetry.[457]

Recommendations on indications for intervention in tricuspid valve disease

Recommendations	Class[a]	Level[b]
Recommendations on tricuspid stenosis		
Surgery is recommended in symptomatic patients with severe tricuspid stenosis.[c]	I	C
Surgery is recommended in patients with severe tricuspid stenosis undergoing left-sided valve intervention.[d]	I	C
Recommendations on primary tricuspid regurgitation		
Surgery is recommended in patients with severe primary tricuspid regurgitation undergoing leftsided valve surgery.	I	C
Surgery is recommended in symptomatic patients with isolated severe primary tricuspid regurgitation without severe RV dysfunction.	I	C
Surgery should be considered in patients with moderate primary tricuspid regurgitation undergoing left-sided valve surgery.	IIa	C
Surgery should be considered in asymptomatic or mildly symptomatic patients with isolated severe primary tricuspid regurgitation and RV dilatation who are appropriate for surgery.	IIa	C
Recommendations on secondary tricuspid regurgitation		
Surgery is recommended in patients with severe secondary tricuspid regurgitation undergoing left-sided valve surgery.[423-427]	I	B
Surgery should be considered in patients with mild or moderate secondary tricuspid regurgitation with a dilated annulus (≥40 mm or >21 mm/m^2 by 2D echocardiography) undergoing left-sided valve surgery.[423,425-427]	IIa	B
Surgery should be considered in patients with severe secondary tricuspid regurgitation (with or without previous left-sided surgery) who are symptomatic or have RV dilatation, in the absence of severe RV or LV dysfunction and severe pulmonary vascular disease/ hypertension.[418,433 e]	IIa	B
Transcatheter treatment of symptomatic secondary severe tricuspid regurgitation may be considered in inoperable patients at a Heart Valve Centre with expertise in the treatment of tricuspid valve disease.[f]	IIb	C

2D: two-dimensional; LV: left ventricle/left ventricular; PMC: percutaneous mitral commissurotomy; RV: right ventricle/right ventricular. [a]Class of recommendation. [b]Level of evidence. [c]Percutaneous balloon valvuloplasty can be attempted as a first approach if tricuspid stenosis is isolated. [d]Percutaneous balloon valvuloplasty can be attempted if PMC can be performed on the mitral valve. [e]In patients with previous surgery recurrent left-sided valve dysfunction needs to be excluded. [f]Transcatheter treatment can be performed according to Heart Team at experienced valve centres in anatomically eligible patients in whom improvement of quality of life or survival can be expected.

- Indications for intervention are based on global assessment of the consequences of the different valve lesions (i.e. symptoms or presence of LV dilatation or dysfunction). Intervention can be considered for non-severe multiple lesions associated with symptoms or leading to LV impairment.[453]
- The decision to intervene on multiple valves should take into account the age, comorbidities, and risk of combined procedures, and should be made by the Heart Team after precise and comprehensive evaluation of valve lesions and their interactions with each other.[453,461] The risk of combined intervention should be weighed against the evolution of untreated valve disease and the inherent risk of subsequent intervention.
- The choice of surgical technique/interventional procedure should take into account the presence of the other VHD.[453,458,459,461]
- When interventional procedures are considered, staged procedures may be preferable in cases with aortic stenosis and mitral regurgitation (see section 5.5). Improved 1-year survival after combined transcatheter treatment of mitral and tricuspid regurgitation has been reported compared to mitral regurgitation alone.[263] PMC may delay surgery, in situations such as severe mitral stenosis associated with moderate aortic regurgitation.

The management of specific associations of VHD is detailed in the individual sections of this document.

11 Prosthetic valves

11.1 CHOICE OF PROSTHETIC VALVE

Factors for valve selection are the patient's life expectancy, lifestyle, and environmental factors, bleeding and thromboembolic risks related to anticoagulation, potential for surgical or transcatheter re-intervention, and, importantly, informed patient preference. Generally, biological heart valves (BHVs) should be preferred in patients with shorter anticipated survival or comorbidities that may lead to further surgical procedures, and those who are at increased risk for bleeding complications. Thromboembolic complications are less frequent in pregnant women with BHVs.

In a nationwide observational study, patients aged 45 to 54 with surgical aortic BHV implantation and those aged 40 to 70 years with surgical mitral BHV implantation had a significantly higher 15-year mortality than those with a mechanical heart valve (MHV). An analysis of patients 55 to 64 years of age showed no difference in mortality between aortic BHV and MHV prosthesis.[462] However, an earlier systematic review[463] and a recent meta-analysis[464] of studies comparing aortic MHVs and BHVs showed a significant mortality reduction with MHVs in patients ≤60 and in those 50-70 years of age, respectively. All these studies are limited by their predominantly observational nature and missing information on the type of prostheses implanted. There is no new high-quality evidence supporting a decrease in the established age cut-off for prosthesis selection.

The best aortic valve substitute for younger adults remains unclear. In appropriately selected patients, replacement of the aortic valve using an autograft may be performed, with long-term

Recommendations for prosthetic valve selection

Recommendations	Class[a]	Level[b]
Mechanical prostheses		
A mechanical prosthesis is recommended according to the desire of the informed patient and if there are no contraindications to longterm anticoagulation.[c]	I	C
A mechanical prosthesis is recommended in patients at risk of accelerated SVD.[d]	I	C
A mechanical prosthesis should be considered in patients already on anticoagulation because of a mechanical prosthesis in another valve position.	IIa	C
A mechanical prosthesis should be considered in patients aged <60 years for prostheses in the aortic position and aged <65 years for prostheses in the mitral position.[462,464 e]	IIa	B
A mechanical prosthesis should be considered in patients with a reasonable life expectancy for whom future redo valve surgery or TAVI (if appropriate) would be at high risk.[f]	IIa	C
A mechanical prosthesis may be considered in patients already on long-term anticoagulation due to the high risk for thromboembolism.[f]	IIb	C
Biological prostheses		
A bioprosthesis is recommended according to the desire of the informed patient.	I	C
A bioprosthesis is recommended when goodquality anticoagulation is unlikely (adherence problems, not readily available), contraindicated because of high bleeding risk (previous major bleed, comorbidities, unwillingness, adherence problems, lifestyle, occupation) and in those patients whose life expectancy is lower than the presumed durability of the bioprosthesis.[g]	I	C
A bioprosthesis is recommended in case of reoperation for mechanical valve thrombosis despite good long-term anticoagulant control.	I	C
A bioprosthesis should be considered in patients for whom there is a low likelihood and/or a low operative risk of future redo valve surgery.	IIa	C
A bioprosthesis should be considered in young women contemplating pregnancy.	IIa	C
A bioprosthesis should be considered in patients aged >65 years for a prosthesis in the aortic position or aged >70 years in a mitral position.	IIa	C
A bioprosthesis may be considered in patients already on long-term NOACs due to the high risk for thromboembolism.[466-469 f]	IIb	B

AF: atrial fibrillation; NOAC: non-vitamin K antagonist oral anticoagulant; SVD: structural valve deterioration; TAVI: transcatheter aortic valve implantation. [a]Class of recommendation. [b]Level of evidence. [c]Increased bleeding risk because of comorbidities, adherence concerns or geographic, lifestyle or occupational conditions. [d]Young age (<40 years), hyperparathyroidism, haemodialysis. [e]In patients 60-65 years of age who should receive an aortic prosthesis and those between 65 and 70 years of age in the case of mitral prosthesis, both valves are acceptable and the choice requires careful analysis of factors other than age. [f]Risk factors for thromboembolism are AF, previous unprovoked proximal deep venous thromboembolism and/or symptomatic pulmonary embolism, hypercoagulable state, antiphospholipid antibody. [g]Life expectancy should be estimated at >10 years according to age, sex, comorbidities, and country-specific life expectancy.

survival rates and valve-related reoperation that are comparable to those achieved with a MHV, but high expertise in aortic root surgery is required.[465] Strategies for patients with small aortic annulus include root enlargement and use of stentless valves. Although the use of sutureless and rapid-deployment aortic valves may reduce invasiveness, cross-clamp and cardiopulmonary bypass times, and potentially lower perioperative complications of SAVR, there is a lack of a large-scale randomized comparison on both short- and long-term safety, efficacy, and haemodynamic performance of this approach against conventional aortic valve replacement, which remains the gold standard of procedure.

11.2 BASELINE ASSESSMENT AND FOLLOW-UP

All patients with prosthetic valves require lifelong follow-up to detect early deterioration in prosthetic function or ventricular function, or progressive disease of another heart valve.[314] Clinical assessment should be performed yearly or as soon as possible if new cardiac symptoms occur. TTE should be performed if any new symptoms occur or if complications are suspected. After transcatheter, as well as surgical implantation of a BHV, echocardiography, including measurement of transprosthetic gradients, should be performed within 30 days after valve implantation (i.e. baseline), at 1 year, and annually thereafter.[470] TOE should be considered if TTE is of poor quality and in all cases of suspected prosthetic dysfunction (especially if the prosthesis is in the mitral position) or endocarditis.[314,471] Cinefluoroscopy for MHVs and CCT scanning provide useful additional information if valve thrombus or pannus are suspected to impair valve function.[314]

11.3 ANTITHROMBOTIC MANAGEMENT

11.3.1 MECHANICAL PROSTHESES

11.3.1.1 Postoperative anticoagulation management

MHVs require lifelong treatment with VKA guided by the INR.[472,473] NOACs currently have no role in patients with MHVs.[474] Treatment with VKA should be started on the first postoperative day in combination with bridging therapy [with therapeutic doses of either unfractionated heparin (UFH) or off-label use of low-molecular-weight heparin (LMWH)] until therapeutic INR is achieved.[475] Similar safety and efficacy outcomes have been reported following bridging with either UFH or LMWH.[476] Once a stable therapeutic INR is reached for ≥24 h, bridging can be discontinued. The postoperative risk of thromboembolism peaks about 1 month after implantation, but risks are substantially increased up to 6 months.[477,478] Long-term prevention of valve thrombosis and thromboembolism after MHV implantation involves effective antithrombotic medication and risk factor modification for thromboembolism.[479]

11.3.1.2 Target international normalized ratio

Target INR should be based upon prosthesis thrombogenicity and patient-related risk factors **(Table 10)**.[479] It is recommended to target a median INR value rather than a range to avoid considering extreme values in the target range as a valid target INR. High INR variability is a strong independent predictor of adverse events after valve replacement. Although some studies have supported lowering a target INR for aortic MHVs,[480,481] further evaluation in larger cohorts is warranted before updating current recommendations. The use of self-monitoring INR is associated with a lower rate of VKA-related complications in all ages.[482] In a trial of lower intensity warfarin plus aspirin (INR 1.5-2.0) or standard warfarin plus aspirin (INR 2.0-3.0) after implantation of the On-X MHV in the aortic position, the similar safety of the two approaches was partly attributed to use of home INR monitoring and high degree of adherence among patients.[481] Patient's education plays an important role for achieving stable anticoagulation in the therapeutic range. Effective management of patients with unstable INR requires frequent in-clinic testing and dose titration. Because of the lack of good-quality evidence, pharmacogenetic testing cannot be recommended to guide the dosing of VKAs.

Table 10. Target international normalized ratio for mechanical prostheses.

Prosthesis thrombogenicity	Patient-related risk factors[a]	
	None	≥1 risk factor
Low[b]	2.5	3.0
Medium[c]	3.0	3.5
High[d]	3.5	4.0

AF: atrial fibrillation; LVEF: left ventricular ejection fraction. [a]Mitral or tricuspid valve replacement; previous thromboembolism; AF; mitral stenosis of any degree; LVEF <35%. [b]Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St Jude Medical, Sorin Bicarbon. [c]Other bileaflet valves with insufficient data. [d]Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Bjork-Shiley and other tilting-disc valves.

11.3.1.3 Management of vitamin K antagonist (VKA) overdose and bleeding

Bleeding increases exponentially with INR >4.5.[483] In case of major and/or life-threatening bleeding and in patients who need to undergo urgent surgery, the VKA should be discontinued and 10 mg vitamin K should be administrated by slow i.v. infusion and repeated every 12 h if needed. Until the anticoagulation effect is reversed, administration of prothrombin complex concentration (PCC) and/or fresh frozen plasma (FFP) therapy should be initiated according to body weight and pre-treatment INR. The efficacy should be monitored by re-check of INR at 30 min and every 4-6 h until normalization. The optimal time to restart anticoagulation should be discussed in relation to location of the bleeding event and interventions performed to stop bleeding and/or to treat an underlying cause.[484]

In the absence of bleeding, the use of PCC and/or FFP therapy is not recommended and the decision to start vitamin K should be individualized. In asymptomatic patients with INR >10, the VKA must be stopped and oral vitamin K (2.5-5 mg) prescribed, while the INR must be monitored on a daily base for 2 weeks. Multiple RCTs in patients with INR between 4.5 and 10 suggest no difference in bleeding events with vitamin K vs. placebo.[483,485] Therefore, in such patients, warfarin should be stopped temporarily, and a small dose of oral vitamin K (1-2 mg) can be considered on an individual basis balancing between the risks. Finally,

asymptomatic patients with INR <4.5 require careful down-titration and/or skipping one or more doses. In all patients with MHVs, VKAs must be resumed once the INR achieves the therapeutic range or is slightly elevated.

11.3.1.4 Combination of oral anticoagulation (OAC) with antiplatelet drugs

The addition of low-dose (75-100 mg) acetylsalicylic acid (ASA) to VKA may reduce the incidence of thromboembolism at the cost of bleeding.[477] Therefore, addition of antiplatelets to VKAs should be reserved for patients at very high risk of thromboembolism where advantages clearly outweigh the risks.[486,487] In patients with thromboembolism despite adequate INR, low dose (75-100 mg) ASA should be added to VKAs. Management of oral antithrombotic therapy in patients with CAD is summarized in **Supplementary Figure 2**.

11.3.1.5 Interruption of anticoagulant therapy for planned invasive procedures

In patients with MHVs, preoperative bridging with UFH or LMWH before surgery imposes a risk of perioperative bleeding while interrupting anticoagulation results in an increased risk of thromboembolism.[488] Therefore, anticoagulation in patients with MHVs undergoing elective NCS requires careful management by multidisciplinary consensus.[478,489] For minor surgical procedures (e.g. dental, cataract, skin incision) in which blood loss is usually small and easily controlled, it is recommended that OAC is not interrupted. Major surgeries require temporary interruption and therapeutic bridging with either UFH or LMWH, aiming for an INR <1.5 **(Supplementary Figure 3)**. Fondaparinux should not be routinely used for bridging, but may have a role in patients with history of heparin-induced thrombocytopenia.[490]

11.3.2 BIOPROSTHESES

11.3.2.1 Patients with no baseline indication to oral anticoagulation (OAC)

Surgical bioprostheses: The optimal antithrombotic strategy early after surgical implantation of an aortic BHV remains controversial due to lack of high-quality evidence. Multiple observational studies support the use of VKAs to reduce the risk of thromboembolism.[491-493] A small randomized trial found that VKA for 3 months significantly increased major bleeding compared with ASA, without reducing the rate of deaths or thromboembolic events, but the statistical power was low for demonstrating a thrombotic benefit.[494] VKA for 3 months should be considered in all patients with a mitral or tricuspid BHV and ASA or VKA should be considered for 3 months after surgical implantation of an aortic bioprosthesis.

Transcatheter bioprostheses: A meta-analysis of three small RCTs showed a significant increase in major or life-threatening bleeding with dual antiplatelet therapy (DAPT) over ASA at 30 days, with no difference in ischaemic outcomes.[495] Consistently, the more recent POPular TAVI trial (cohort A) found reduced bleeding and the composite of bleeding or thromboembolic events with ASA compared with DAPT.[496] A randomized trial was halted prematurely due to safety concerns with a rivaroxaban-based regimen as compared with DAPT, including a higher risk of death or thromboembolic complications and a higher risk of bleeding.[497] There is a lack of data on the management of antithrombotic therapy after implantation of transcatheter mitral BHVs (e.g. valve-in-valve or valve-in-ring) for which 3 months of VKA is commonly prescribed.[498]

11.3.2.2 Patients with baseline indication to oral anticoagulation (OAC)

Surgical bioprostheses: OAC is recommended lifelong for patients with surgical BHVs who have other indications for anticoagulation. The evidence supporting the use of NOACs in preference to VKA has increased since the publication of the 2017 VHD Guidelines. In the RIVER trial, including patients with AF and a BHV in the mitral position, the NOAC rivaroxaban was non-inferior to warfarin with respect to a net benefit endpoint at 12 months.[499] The benefit of NOAC was consistent among subgroups. However, only 20% of patients were enrolled in the trial before the third postoperative month, which raises a note of caution and calls for additional data in this particular subgroup. In the small ENAVLE trial (N=220), including patients with and without AF, edoxaban was non-inferior to warfarin for preventing thromboembolism and the

Recommendations for management of antithrombotic therapy after prosthetic valve implantation or valve repair in the perioperative and postoperative periods

Recommendations	Class[a]	Level[b]
Management of antithrombotic therapy in the perioperative period		
It is recommended that VKAs are timely discontinued prior to elective surgery to aim for an INR <1.5.[c]	I	C
Bridging of OAC, when interruption is needed, is recommended in patients with any of the following indications: • Mechanical prosthetic heart valve. • AF with significant mitral stenosis. • AF with a CHA_2DS_2-VASc score ≥3 for women or 2 for men.[d] • Acute thrombotic event within the previous 4 weeks. • High acute thromboembolic risk.[e]	I	C
Therapeutic doses of either UFH or subcutaneous LMWH are recommended for bridging.[476,504]	I	B
In patients with MHVs, it is recommended to (re)-initiate the VKA on the first postoperative day.	I	C
In patients who have undergone valve surgery with an indication for postoperative therapeutic bridging, it is recommended to start either UFH or LMWH 12-24 h after surgery.	I	C
In patients undergoing surgery, it is recommended that aspirin therapy, if indicated, is maintained during the periprocedural period.	I	C
In patients treated with DAPT after recent PCI (within 1 month) who need to undergo heart valve surgery in the absence of an indication for OAC, it is recommended to resume the $P2Y_{12}$ inhibitor postoperatively, as soon as there is no concern over bleeding.	I	C

In patients treated with DAPT after recent PCI (within 1 month) who need to undergo heart valve surgery in the absence of an indication for OAC, bridging $P2Y_{12}$ inhibitors with short-acting glycoprotein IIb/IIIa inhibitors or cangrelor may be considered.	IIb	C
Patients with an indication to concomitant antiplatelet therapy		
After uncomplicated PCI or ACS in patients requiring long-term OAC, early cessation (≤1 week) of aspirin and continuation of dual therapy with OAC and a $P2Y_{12}$ inhibitor (preferably clopidogrel) for up to 6 months (or up to 12 months in ACS) is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used.[505-509]	I	B
Discontinuation of antiplatelet treatment in patients treated with an OAC is recommended after 12 months.[74,510-512]	I	B
After uncomplicated PCI or ACS in patients requiring both OAC and antiplatelet therapy, triple therapy with aspirin, clopidogrel and OAC for longer than 1 week should be considered when the risk of stent thrombosis outweighs the risk of bleeding, with the total duration (≤1 month) decided according to assessment of these risks and clearly specified at hospital discharge.	IIa	C
In patients treated with a VKA (e.g. MHVs), clopidogrel alone should be considered in selected patients (e.g. HAS-BLED ≥3 or ARC-HBR met and low risk of stent thrombosis) for up to 12 months.[512,513]	IIa	B
In patients requiring aspirin and/or clopidogrel in addition to VKA, the dose intensity of VKA should be considered and carefully regulated with a target INR in the lower part of the recommended target range and a time in the therapeutic range >65-70%.[505,514]	IIa	B
Surgical valve replacement		
OAC using a VKA is recommended lifelong for all patients with an MHV prosthesis.[472,473]	I	B
For patients with a VKA, INR self-management is recommended provided appropriate training and quality control are performed.[482]	I	B
OAC is recommended for patients undergoing implantation of a surgical BHV who have other indications for anticoagulation.[f]	I	C
NOACs should be considered over VKA after 3 months following surgical implantation of a BHV in patients with AF.[74,499,500,515-518]	IIa	B
In patients with no baseline indications for OAC, low-dose aspirin (75-100 mg/day) or OAC using a VKA should be considered for the first 3 months after surgical implantation of an aortic BHV.[491,494]	IIa	B
In patients with no baseline indications for OAC, OAC using a VKA should be considered for the first 3 months after surgical implantation of a bioprosthesis in the mitral or tricuspid position.[519,520]	IIa	B
The addition of low-dose aspirin (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 aspirin (75-100 mg/day) to VKA should be considered after thromboembolism despite an adequate INR.	IIa	C
NOACs may be considered over VKA within 3 months following surgical implantation of a BHV in mitral position in patients with AF.[499]	IIb	C
NOACs are not recommended in patients with a mechanical valve prosthesis.[474]	III	B
Surgical valve repair		
OAC with VKA should be considered during the first 3 months after mitral and tricuspid repair.	IIa	C
SAPT with low-dose ASA (75-100 mg/day) should be considered for the first 3 months after valve-sparing aortic surgery when there are no other baseline indications to OAC.	IIa	C
Transcatheter aortic valve implantation		
OAC is recommended lifelong for TAVI patients who have other indications for OAC.[501 f]	I	B
Lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC.[495,496,521]	I	A
Routine use OAC is not recommended after TAVI in patients with no baseline indication for OAC.[497]	III	B

ACS: acute coronary syndrome; AF: atrial fibrillation; ARC-HBR: Academic Research Consortium - high bleeding risk; ASA: acetylsalicylic acid; BHV: biological heart valve; DAPT: dual antiplatelet therapy; INR: international normalized ratio; LMWH: low-molecular-weight heparin; LV: left ventricle/left ventricular; PCI: percutaneous coronary intervention; MHV: mechanical heart valve; NOAC: non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulation; SAPT: single antiplatelet therapy; TAVI: transcatheter aortic valve implantation; UFH: unfractionated heparin; VKA: vitamin K antagonist. [a]Class of recommendation. [b]Level of evidence. [c]≤5 days for warfarin and ≤3 days for acenocoumarol. [d]CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (2 points), diabetes, prior stroke (2 points) - vascular disease, age 65-74, sex category (female). [e]LV apex thrombus, antithrombin 3 deficit and proteins C and/or S deficit. [f]AF, venous thromboembolism, hypercoagulable state or, with a lesser degree of evidence, severely impaired LV dysfunction (ejection fraction <35%).

occurrence of major bleeding in the first 3 months after aortic or mitral surgical bioprosthetic valve implantation or repair, which warrants confirmation in larger investigations.[500]

Transcatheter bioprostheses: 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.[501] OAC alone was non-inferior to OAC plus clopidogrel with respect to ischaemic events, but the non-inferiority margin was large. An observational study suggested that there is a higher risk of ischaemic events at 1 year with NOACs compared with VKAs, after adjustment for potential confounders.[502] Randomized trials comparing NOACs vs. VKAs are ongoing (NCT02943785, NCT02664649). Data on the management of antithrombotic therapy after transcatheter mitral or tricuspid valve implantation are scant.[498]

11.3.3 VALVE REPAIR

Observational data suggest comparable risk of thromboembolism with ASA or VKAs following mitral valve repair,[503] but randomized data are lacking. The high incidence of new-onset AF and its recurrence, the thrombogenic tendency of the non-endothelialized repair components, and a relatively high rate of patients who are resistant

to ASA establish VKAs as a preferable option for the initial period (e.g. 3 months). However, the potential for bleeding complications in the postoperative phase dictates careful patient selection.

The management of antithrombotic treatment after prosthetic valve implantation or valve repair is summarized in the table of recommendations for management of antithrombotic therapy after prosthetic valve implantation or valve repair and in **Figure 9**.

11.4 MANAGEMENT OF PROSTHETIC VALVE DYSFUNCTION AND COMPLICATIONS

11.4.1 STRUCTURAL VALVE DETERIORATION

Definitions of SVD and bioprosthetic valve failure (BVF) were standardized by recent consensus.[470,522] The comparative durability of TAVI and SAVR BHVs must be ascertained at longer term. Reversible causes of BVF (e.g. endocarditis, thrombosis) should be excluded, and considerations on timing of dysfunction (e.g. for BHV obstruction, mismatch in early phases, thrombosis in later phases) and location of malfunction (e.g. endocarditis or SVD in case of central regurgitation, endocarditis or anatomical/technical factors in case of paravalvular regurgitation) may reveal the most plausible underlying cause and guide clinical decision making.

Percutaneous balloon interventions should be avoided in the treatment of stenotic left-sided bioprostheses. Transcatheter valve-in-valve implantation is an option for treating degenerated BHVs in patients with increased surgical risk.[227,523-525] Redo-TAVI is a safe and feasible option in selected patients, but the risk of PPM in small valves and that of coronary occlusion, as well the possibility for future access to the coronary arteries need to be considered.[229,526-528] Experience is mostly in aortic BHVs and remains limited for BHVs in the mitral position and even more so in the tricuspid position[529-532] for which valve-in-valve procedures may be reasonable in patients at increased surgical risk.[531,533] Valve-in-ring mitral procedures are also acceptable in selected candidates, while the role of valve-in-ring tricuspid procedures remains uncertain. It is necessary for the Heart Team to discuss every patient and choose the best individualized approach. Careful pre-procedural planning is needed to minimize the risk of coronary artery obstruction and enable future coronary re-access in aortic BHV

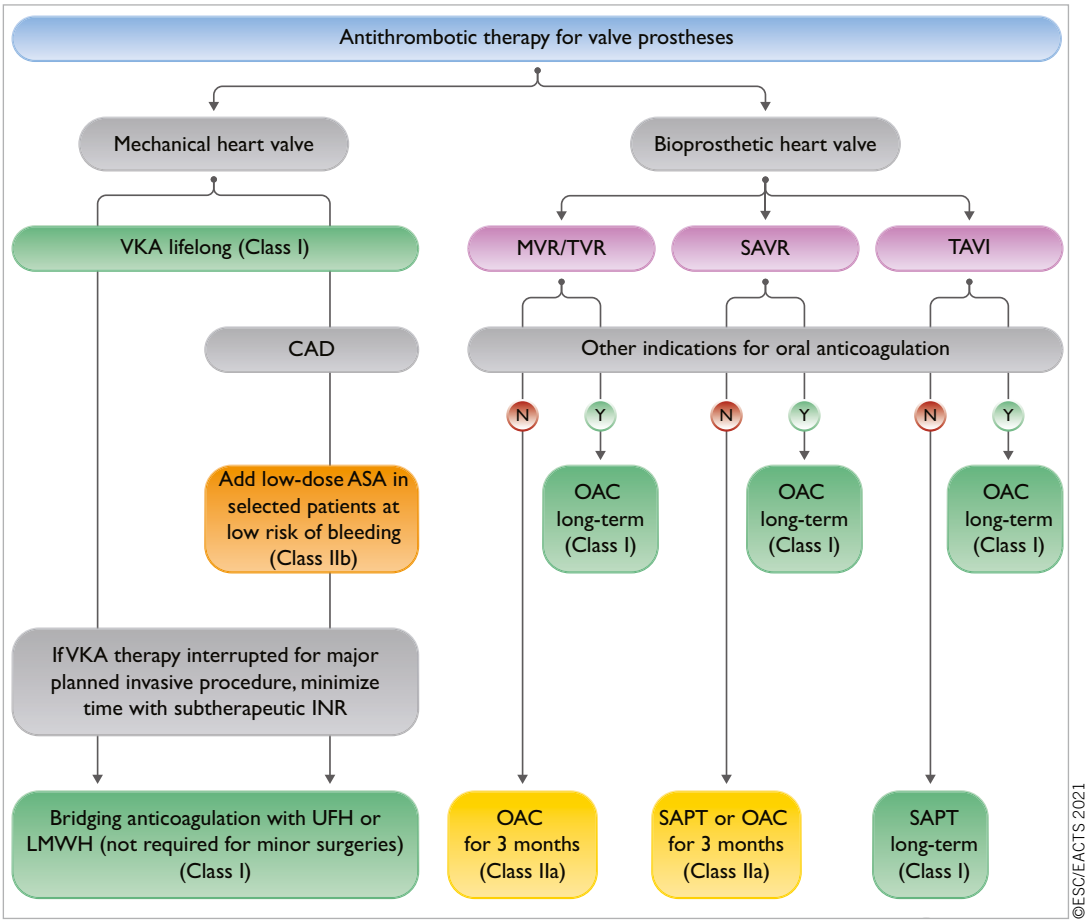

Figure 9. *Antithrombotic therapy for valve prostheses. AF: atrial fibrillation; ASA: acetylsalicylic acid; CAD: coronary artery disease; DAPT: dual antiplatelet therapy; INR: international normalized ratio; LMWH: low-molecular-weight heparin; LV: left ventricle/left ventricular; MHV: mechanical heart valve; MVR: mitral valve replacement or repair; OAC: oral anticoagulation; SAPT: single antiplatelet therapy; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation; TVR: tricuspid valve replacement or repair; UFH: unfractionated heparin; VKA: vitamin K antagonist. Colour coding corresponds to class of recommendation.*

re-interventions if necessary. For mitral re-interventions the risk of LVOT obstruction should be carefully evaluated.[534]

11.4.2 NON-STRUCTURAL VALVE DYSFUNCTION

11.4.2.1 Patient-prosthesis mismatch

Patient-prosthesis mismatch (PPM) significantly decreases long-term survival, correlates with SVD and increases readmission rates for both heart failure and reoperation.[535-537] Efforts to prevent PPM should receive more emphasis to improve long-term survival after either SAVR or TAVI.[538]

11.4.2.2 Paravalvular leak and haemolysis

Blood tests for haemolysis should be part of routine follow-up after valve replacement. Diagnosis of haemolytic anaemia requires TOE to detect paravalvular leaks for prostheses in the mitral position if TTE is not contributory. Reoperation is recommended if the paravalvular leak is related to endocarditis or causes haemolysis requiring repeated blood transfusions or leading to severe symptoms. Transcatheter closure of a paravalvular leak is feasible, but experience is limited and there is presently no conclusive evidence to show consistent efficacy.[539] Transcatheter closure of paravalvular leaks should be considered for anatomically suitable paravalvular leaks in candidates selected by the Heart Team.[540] Medical therapy (including iron supplementation, beta-blockers, and erythropoietin) is indicated in patients with severe haemolytic anaemia when contraindications to surgical or transcatheter closure are present.[540]

11.4.3 ENDOCARDITIS

The management of patients with endocarditis should follow the relevant guidelines.[4]

11.4.4 THROMBOSIS

11.4.4.1 General comments

Obstructive valve thrombosis should be suspected promptly in any patient with any type of prosthetic valve who presents with recent dyspnoea or an embolic event. The diagnosis should be confirmed by TTE and TOE, cinefluoroscopy, or CCT if promptly available.[268,314] Valve thrombosis occurs mainly in MHVs. However, cases of thrombosis of BHVs have also been reported after surgery or transcatheter valve implantation.[541] Thrombus on BHVs can present as hypo-attenuated leaflet thickening (HALT) with relatively normal leaflet motion, HALT with reduced leaflet motion but normal gradients, and clinical valve thrombosis with elevated gradients. Distinguishing between thrombus and pannus by means of CCT is important to guide decision making.

11.4.4.2 Valve thrombosis

The management of MHVs thrombosis is high risk, whatever the option taken. Fibrinolysis carries risks of bleeding, systemic embolism, and recurrent thrombosis.[542] Emergency valve replacement is recommended for obstructive prosthetic valve thrombosis in critically ill patients without a contraindication to surgery. Management of non-obstructive thrombosis of an MHV 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 anticoagulation.[543]

Fibrinolysis may be considered if surgery is not an option or is very high risk for the treatment of thrombosis of right-sided prostheses, but carries a risk of bleeding and thromboembolism. Anticoagulation using a VKA and/or UFH is the first-line treatment of BHV thrombosis. Because BHV thrombosis is associated with recurrence and early prosthetic degeneration, indefinite anticoagulation should be considered after a confirmed episode, but this strategy must be balanced against an increased risk of bleeding[544,545] **(Figure 10)**.

11.4.4.3 Subclinical leaflet thrombosis

HALT is detected by CCT in 12.4% and 32.4% of TAVI patients on OAC or DAPT at 3 months, respectively.[546] The clinical significance of these findings is uncertain. Selective use of oral anticoagulants in patients with confirmed HALT and restricted leaflet motion with elevated gradients should be considered.

11.4.5 HEART FAILURE

Heart failure after valve surgery should lead to a quick search for SVD or PPM, deterioration of repair, LV dysfunction, or progression of another valve disease. Non-valvular-related causes such as CAD, hypertension, or sustained arrhythmias should also be considered. The management of patients with heart failure should follow the relevant guidelines and consensus documents.[142,247]

Recommendations on management of prosthetic valve dysfunction

Recommendations	Class[a]	Level[b]
Mechanical prosthetic thrombosis		
Urgent or emergency valve replacement is recommended for obstructive thrombosis in critically ill patients without serious comorbidity.[542]	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.[542]	IIa	B
Surgery should be considered for large (>10 mm) non-obstructive prosthetic thrombus complicated by embolism.	IIa	C
Bioprosthetic thrombosis		
Anticoagulation using a VKA and/or UFH is recommended in bioprosthetic valve thrombosis before considering re-intervention.	I	C
Anticoagulation should be considered in patients with leaflet thickening and reduced leaflet motion leading to elevated gradients, at least until resolution.[541,546]	IIa	B
Haemolysis and paravalvular leak		
Reoperation is recommended if a paravalvular leak is related to endocarditis or causes haemolysis requiring repeated blood transfusions or leading to severe heart failure symptoms.	I	C
Transcatheter closure should be considered for suitable paravalvular leaks with clinically significant regurgitation and/or haemolysis in patients at high or prohibitive surgical risk.[547]	IIa	B

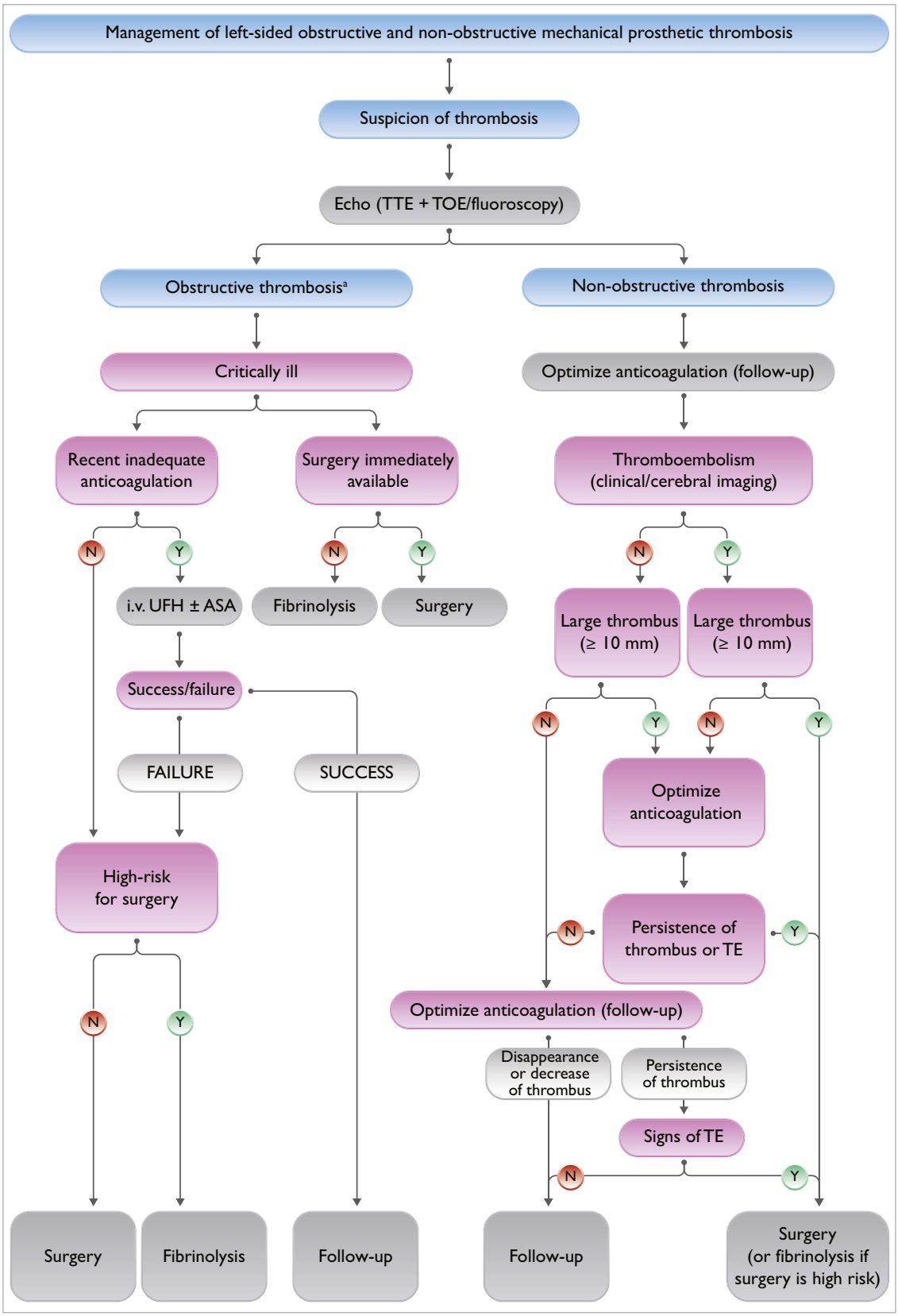

Figure 10. *Management of left-sided obstructive and non-obstructive mechanical prosthetic thrombosis. ASA: acetylsalicylic acid; CCT: cardiac computed tomography; i.v.: intravenous; TOE: transoesophageal echocardiography; TE: thromboembolism; TTE: transthoracic echocardiography; UFH: unfractionated heparin. Risk and benefits of both treatments should be individualized. The presence of a first-generation prosthesis is an incentive to surgery. [a]Refer to recommendations for the imaging assessment of prosthetic heart valves. Evaluation generally includes TTE plus TOE or CCT and occasionally fluoroscopy.*

Decision on transcatheter or surgical closure of clinically significant paravalvular leaks should be considered based on patient risk status, leak morphology, and local expertise.	IIa	C
Bioprosthetic failure		
Reoperation is recommended in symptomatic patients with a significant increase in transprosthetic gradient (after exclusion of valve thrombosis) or severe regurgitation.	I	C
Transcatheter, transfemoral valve-in-valve implantation in the aortic position should be considered by the Heart Team depending on anatomic considerations, features of the prosthesis, and in patients who are at high operative risk or inoperable.[529]	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.[382,531,532]	IIb	B
Reoperation should be considered in asymptomatic patients with significant prosthetic dysfunction if reoperation is low risk.	IIa	C

UFH: unfractionated heparin; VKA: vitamin K antagonist. [a]Class of recommendation. [b]Level of evidence.

12 Management during non-cardiac surgery

Cardiovascular morbidity and mortality are increased in patients with VHD who undergo NCS. Symptomatic severe aortic stenosis or mitral stenosis may require valve replacement or percutaneous intervention before NCS. A detailed description of recommendations in the setting is available in specific ESC Guidelines.[489]

12.1 PREOPERATIVE EVALUATION

Patient and surgical specific factors dictate the strategy.[489,548,549] The cardiologist provides recommendations on pre- and perioperative management, surveillance, and continuation of chronic cardiovascular medical treatment. Echocardiography should be performed in any patient with VHD requiring NCS. Determination of functional capacity is a pivotal step in preoperative risk assessment, measured either by ability to perform activities in daily life or by exercise test. The decision for management should be taken after multidisciplinary discussion involving cardiologists, surgeons, and cardiac anaesthesiologists, as well as the team who will be in charge of NCS.

Patients receiving anticoagulation treatment should be managed as discussed in section 11.

12.2 SPECIFIC VALVE LESIONS

12.2.1 AORTIC STENOSIS

In patients with severe aortic stenosis, urgent NCS should be performed under careful haemodynamic monitoring. In case of high risk of NCS, balloon valvuloplasty may be considered before NCS.[549] Management related to elective NCS depends on the presence of symptoms and the type of surgery.[489,549-553] In symptomatic patients, aortic valve procedure should be considered before NCS. The type of procedure, TAVI or SAVR, is decided by the Heart Team. In asymptomatic patients, elective NCS, if at low to moderate risk, can be performed safely, albeit with a risk of worsening heart failure.[489,552,553] If NCS implies large volume shifts, aortic valve procedure (TAVI or SAVR) should be considered first according to the Heart Team's decision **(Figure 11)**.

12.2.2 MITRAL STENOSIS

NCS can be performed safely in patients with non-significant mitral stenosis (valve area >1.5 cm^2) and in asymptomatic patients with significant mitral stenosis and an SPAP <50 mmHg. In symptomatic patients or in patients with SPAP >50 mmHg, correction of mitral stenosis, by means of PMC whenever possible, should be attempted before NCS if it is high risk.

12.2.3 AORTIC AND MITRAL REGURGITATION

NCS can be performed safely in asymptomatic patients with severe mitral regurgitation or aortic regurgitation and preserved LV function. The presence of symptoms or LV dysfunction should lead to consideration of valvular surgery, but this is seldom needed before NCS. If LV dysfunction is severe (ejection fraction <30%) and/or SPAP is >50/60 mmHg, NCS should be performed only if strictly necessary and after optimization of medical therapy for heart failure.

12.3 PERIOPERATIVE MONITORING

Heart rate control (particularly in mitral stenosis) and careful fluid management (particularly in aortic stenosis) are needed. TOE monitoring may be considered.

13 Management during pregnancy

Detailed guidelines on the management of cardiovascular disease during pregnancy are available in another document.[554] The decision for management before and during pregnancy should be taken after multidisciplinary discussion in the pregnancy Heart Team involving cardiologists, cardiac surgeons, obstetricians, neonatologists, and anaesthesiologists.

13.1 MANAGEMENT BEFORE PREGNANCY

Valve disease should be evaluated before pregnancy and treated if necessary.[554,555]

Pregnancy should be discouraged, and intervention should be recommended before pregnancy in the following cases:

- Patients with mitral stenosis and a valve area <1.5 cm² (especially if <1.0 cm²).[554,556]
- All symptomatic patients with severe AS or asymptomatic patients with impaired LV function (LVEF <50%) or an abnormal exercise test should be counselled against pregnancy, and surgery should be performed pre-pregnancy.[554,557]
- Women with Marfan syndrome and an aortic diameter >45 mm should be strongly discouraged from becoming pregnant without prior aortic repair because of the high risk of aortic dissection. Although an aortic diameter <40 mm is rarely associated with aortic dissection, a completely safe diameter does not exist. With an aortic diameter between 40 and 45 mm, previous aortic growth and family history are important for advising pregnancy with or without aortic repair.[558] Although the actual risk of dissection is not well documented in the setting of bicuspid valves,

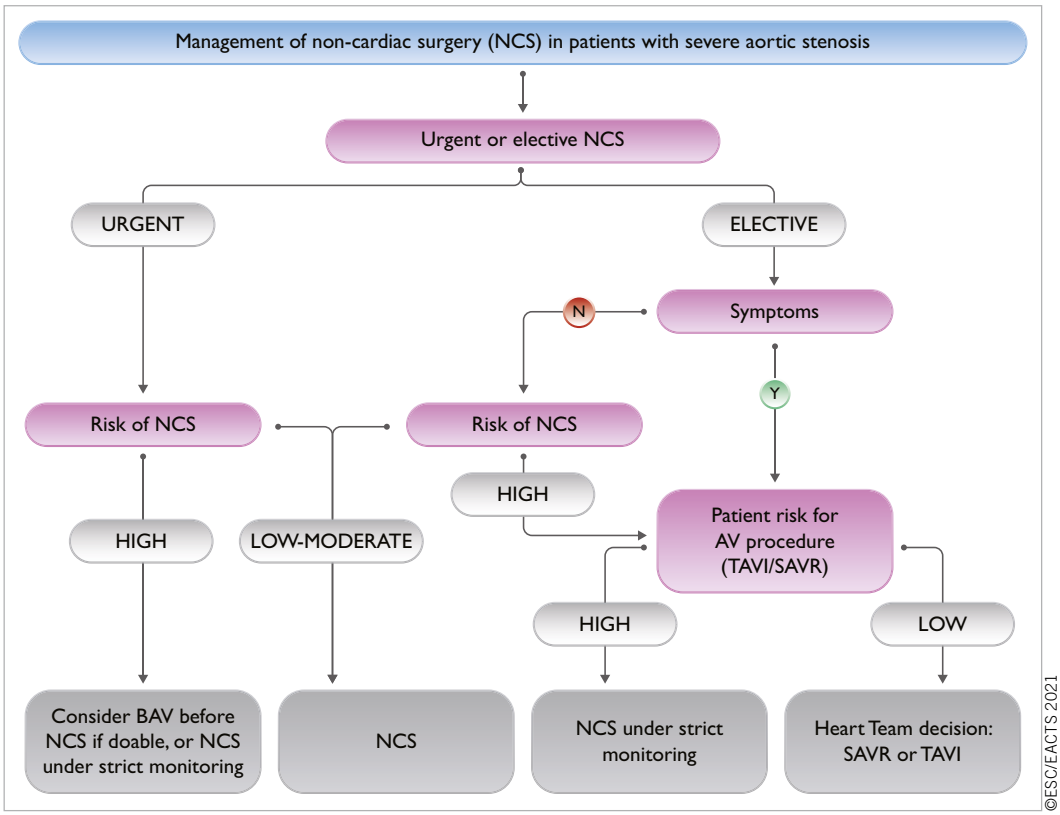

Figure 11. *Management of non-cardiac surgery (NCS) in patients with severe aortic stenosis. AV: aortic valve; BAV: balloon aortic valvuloplasty; NCS: non cardiac surgery; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.*

counselling against pregnancy is recommended in the setting of aortic diameters >50 mm (>27 mm² BSA).[559] Finally, an aortic diameter >25 mm/m² BSA in Turner syndrome and all patients with vascular Ehlers-Danlos syndrome are also contraindications for pregnancy.

In women considering pregnancy and requiring heart valve replacement, it is recommended to choose the prosthesis in consultation with a pregnancy Heart Team.[554,560]

Pregnancy in women with a mechanical valve, especially in the mitral position, is associated with a high risk of maternal and foetal complications,[554,561] which should be carefully discussed with the patient and family.

13.2 MANAGEMENT DURING PREGNANCY

13.2.1 PATIENTS WITH NATIVE VALVE DISEASE

Moderate or severe mitral stenosis with a valve area <1.5 cm² in pregnant women is usually poorly tolerated. PMC should be considered in severely symptomatic patients [New York Heart Association (NYHA) class III-IV] and/or those with SPAP >50 mmHg despite optimal therapy. PMC should preferably be performed after the 20th week of pregnancy in experienced centres.[554]

In patients who are severely symptomatic despite medical therapy, BAV for severe aortic stenosis can be undertaken by an experienced operator.[557] TAVI is a promising alternative, but experience during pregnancy is very limited.[554]

Surgery under cardiopulmonary bypass is associated with a foetal mortality rate of 15-56%[562] and should be restricted to the rare conditions that threaten the mother's life if transcatheter intervention is not possible or has failed. Valve replacement should be considered after early delivery by caesarean section.

Caesarean section is recommended for patients with severe mitral or aortic stenosis, ascending aortic diameter >45 mm, severe pulmonary hypertension, or if delivery starts while treated with a VKA or <2 weeks after discontinuation of a VKA.

13.2.2 MECHANICAL PROSTHESIS

It is recommended to manage pregnancy in patients with MHV in a centre with a pregnancy Heart Team.[554]

Therapeutic anticoagulation during pregnancy is of utmost importance to avoid complications in these patients, keeping in mind that no anticoagulation regimen is ideal and management will require a careful balance between maternal and foetal risks.

In patients requiring <5 mg/day warfarin, oral anticoagulants throughout pregnancy and a change to UFH before delivery is favoured. In patients requiring higher doses, switching to LMWH during the first trimester with strict anti-Xa monitoring (therapeutic range 0.8-1.2 IU/mL, aortic valve prosthesis; and 1.0-1.2 IU/mL, mitral and right sided valve prosthesis) and the use of oral anticoagulants afterwards is favoured with a change to UFH before delivery.[554]

14 Key messages

GENERAL COMMENTS

1. Precise evaluation of the patient's history and symptomatic status, as well as proper physical examination, are crucial for the diagnosis and management of VHD.
2. Echocardiography is the key technique to diagnose VHD and assess its severity and prognosis. Other non-invasive investigations such as CMR, CCT, fluoroscopy, and biomarkers provide important additional information in selected patients. Stress testing should be widely used in asymptomatic patients. Invasive investigation, beyond preoperative coronary angiography, is restricted to situations where non-invasive evaluation is inconclusive.
3. Decision making in elderly patients requires the integration of multiple parameters, including estimation of life expectancy and anticipated quality of life, evaluation of comorbidities, and general condition (including frailty).
4. Decision making in asymptomatic patients weighs the risk of intervention against the expected natural history of VHD. Stress testing should be liberally performed.
5. Informed patient's expectations and values are an important part of the decision-making process.
6. Interventions (surgery or transcatheter) are indicated in symptomatic patients (spontaneous or exercise induced) in the absence of futility. In selected asymptomatic patients, presence of predictors of rapid symptom progression justifies early intervention when procedural risk is low.
7. Heart Valve Centres with multidisciplinary Heart Teams, Heart Valve Clinics, comprehensive equipment, and sufficient volumes of procedures are required to deliver high-quality care and provide adequate training.
8. Careful follow-up of symptomatic status, LV/RV size, and function is mandatory in asymptomatic patients with severe VHD if an intervention is not yet indicated.
9. In patients with AF, NOACs are contraindicated in patients with clinically significant mitral stenosis or mechanical valves. For stroke prevention in patients who are eligible for OAC, NOACs are recommended in preference to VKAs in patients with aortic stenosis, aortic and mitral regurgitation, or aortic bioprostheses >3 months after implantation.

AORTIC REGURGITATION

10. The evaluation of aortic regurgitation requires careful assessment of potentially associated aortic dilatation to guide the timing and type of surgery.

AORTIC STENOSIS

11. Diagnosis of severe aortic stenosis requires integrative evaluation of pressure gradients (the most robust measurements), AVA, extent of valve calcification, flow conditions, and LV function.
12. Selection of the most appropriate mode of intervention by the Heart Team should take into account clinical characteristics (age and estimated life expectancy, general condition), anatomical characteristics, the relative risks of SAVR and TAVI, the feasibility of transfemoral TAVI, local experience and outcome data, as well as informed patient preference.

MITRAL REGURGITATION

13. Regarding imaging, routine quantification of EROA is an important part of the integrative evaluation for quantification and risk stratification in patients with PMR. 3D transoesophageal echocardiography is more accurate than 2D echocardiography for defining the underlying mechanism of PMR. CMR is useful when echocardiographic evaluation of severe PMR grade is inconclusive.
14. Surgical mitral valve repair is the preferred method of treatment in PMR if a durable repair can be achieved. TEER is a safe but less efficacious alternative that may be considered in patients with contraindications for surgery or high operative risk.
15. In patients with severe SMR, GDMT (including CRT if indicated) should be the first step. If the patient remains symptomatic: mitral surgery is recommended concomitantly in patients with an indication for CABG or other cardiac surgery. Isolated valve surgery may be considered in selected patients. TEER should be considered in patients not eligible for surgery and fulfilling criteria indicating an increased chance of responding to the treatment. Circulatory support devices, cardiac transplantation, or palliative care should be considered as an alternative in patients with end-stage LV and/or RV failure.

MITRAL STENOSIS

16. PMC is currently the standard of care in patients with severe rheumatic mitral stenosis and favourable valve anatomy.
17. Decision making as to the type of intervention used in patients with unfavourable anatomy is still a matter of debate and must take into account the multifactorial nature of predicting the results of PMC.

TRICUSPID REGURGITATION

18. Relevant tricuspid regurgitation requires early intervention to avoid secondary damage of the RV.
19. Tricuspid regurgitation should be liberally treated at the time of left-sided valve surgery. Isolated surgery of severe secondary tricuspid regurgitation (with or without previous left-sided valve surgery) requires comprehensive assessment of the underlying disease, pulmonary haemodynamics, and RV function.

PROSTHETIC VALVES

20. The choice between a mechanical prosthesis and a bioprosthesis should be patient-centred and multifactorial based on patient characteristics, the indication for lifelong anticoagulation, the potential and risks of a re-intervention, and the informed patient preference.

21. Clinical assessment of prosthetic valves should be performed yearly and as soon as possible if new cardiac symptoms occur.

15 Gaps in evidence

Important gaps in evidence exist in the following aspects of VHD:

GENERAL COMMENTS

1. Prognostic value of CMR-derived indices in patients with aortic regurgitation, aortic stenosis, and mitral regurgitation.
2. Tools for risk stratification for the decision for intervention (including the avoidance of futile interventions) and the choice of the type of intervention (TAVI vs. SAVR for aortic stenosis, repair vs. replacement for mitral and aortic regurgitation).
3. In asymptomatic patients with aortic regurgitation, aortic stenosis, and mitral regurgitation, identification and evaluation of earlier markers of LV dysfunction (biomarkers, imaging, multimodality) as well as longitudinal and translational studies on progression.
4. Gender issues regarding pathophysiology, indications, and timing of treatment.
5. Minimum volumes of procedures that are required to achieve optimal results of intervention.
6. Safety and efficacy of NOACs in patients with surgical or transcatheter bioprostheses in the first 3 months after implantation.
7. Patient education for shared decision making and timely evaluation.
8. Systematic epidemiological data addressing the burden of rheumatic heart disease.
9. Advocacy of VHD.

AORTIC REGURGITATION

10. Potential differences in the risk of aortic complications depending on subtypes of aortic aneurysms (site and morphology), as well as in patients with bicuspid aortic valves.
11. Further evaluation of surgical aortic valve repair.

AORTIC STENOSIS

12. Pathophysiology of progression and novel therapeutic targets for medical treatment.
13. Further research to evaluate the role of intervention:
    - a. Long-term durability of transcatheter heart valves in comparison with surgical bioprostheses.
    - b. Role of intervention (SAVR or TAVI) in asymptomatic patients.
    - c. Role of TAVI in younger low-risk patients, patients with aortic stenosis affecting bicuspid valves, and patients with moderate aortic stenosis and LV impairment.
    - d. Results of re-intervention (valve or coronary) after TAVI or SAVR.
    - e. The role of revascularization in patients with severe aortic stenosis and asymptomatic concomitant CAD.

MITRAL REGURGITATION

14. Association between PMR and sudden cardiac death and ventricular arrhythmias.
15. Role of genetic testing to mitral valve prolapse.
16. Further evaluation of the role of intervention:
    - a. Long-term results of transcatheter intervention.
    - b. Indications of transcatheter intervention in patients with severe PMR at lower surgical risk.
    - c. Potential impact of mitral valve intervention (surgery and catheter intervention) on survival in patients with SMR.
    - d. Selection of criteria to identify responders to TEER for SMR (severity criteria, concept of 'disproportionate mitral regurgitation').
    - e. The role of newer transcatheter treatment options (annuloplasty, combined repair techniques, valve replacement).

MITRAL STENOSIS

17. Scores predicting the results and complications of PMC, particularly that of severe mitral regurgitation.
18. Role of transcatheter mitral valve implantation in high-risk patients, particularly in patients with severe degenerative mitral stenosis and MAC.

TRICUSPID REGURGITATION

19. Quantification of tricuspid regurgitation severity and evaluation of RV function.
20. Further research to evaluate the role of intervention:
    - a. Criteria for optimal timing of surgery in primary tricuspid regurgitation.
    - b. Evidence on the clinical impact, timing, and treatment modality of isolated severe secondary tricuspid regurgitation.
    - c. Criteria for concomitant tricuspid valve surgery at the time of left-sided surgery in patients without severe tricuspid regurgitation.
    - d. Results and indications of transcatheter tricuspid valve treatment.

COMBINED AND MULTI-VALVE DISEASES

21. Further evaluation of the impact on outcomes and modalities of transcatheter intervention to better define the indications for intervention.

PREGNANCY

22. Optimal management of pregnant women with MHVs regarding antithrombotic regimens.

NON-CARDIAC SURGERY

23. Evaluation of the role of 'urgent TAVI' in the management of patients with severe aortic stenosis undergoing NCS.

16 To Do and Not To Do

Recommendations	Class[a]	Level[b]
Recommendations for management of CAD in patients with VHD		
Diagnosis of CAD		
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 postmenopausal women. • One or more cardiovascular risk factors.	I	C
Coronary angiography is recommended in the evaluation of severe SMR.	I	C
Indications for myocardial revascularization		
CABG is recommended in patients with a primary indication for aortic/mitral/tricuspid valve surgery and coronary artery diameter stenosis ≥70%.	I	C
Recommendations on management of atrial fibrillation in patients with native VHD		
Anticoagulation		
For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs in patients with aortic stenosis, aortic and mitral regurgitation.	I	A
The use of NOACs is not recommended in patients with AF and moderate to severe mitral stenosis.	III	C
Recommendations on indications for surgery in (A) severe aortic regurgitation and (B) aortic root or tubular ascending aortic aneurysm (irrespective of the severity of aortic regurgitation)		
A) Severe aortic regurgitation		
Surgery is recommended in symptomatic patients regardless of LV function.	I	B
Surgery is recommended in asymptomatic patients with LVESD >50mm or LVESD >25 mm/m^2 BSA (in patients with small body size) or resting LVEF ≤50%.	I	B
Surgery is recommended in symptomatic and asymptomatic patients with severe aortic regurgitation undergoing CABG or surgery of the ascending aorta or of another valve.	I	C
B) Aortic root or tubular ascending aortic aneurysm (irrespective of the severity of aortic regurgitation)		
Valve-sparing aortic root replacement is recommended in young patients with aortic root dilation, if performed in experienced centres and durable results are expected.	I	B
Ascending aortic surgery is indicated in patients with Marfan syndrome who have aortic root disease with a maximal ascending aortic diameter ≥50 mm.	I	C
Recommendations on indications for intervention in symptomatic (A) and asymptomatic (B) aortic stenosis and recommended mode of intervention (C)		
A) Symptomatic aortic stenosis		
Intervention is recommended in symptomatic patients with severe, high-gradient aortic stenosis [mean gradient ≥40 mmHg, peak velocity ≥4.0 m/s and valve area ≤1.0 cm^2 (or ≤0.6 cm^2/m^2)].	I	B
Intervention is recommended in symptomatic patients with severe low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) aortic stenosis with reduced ejection fraction (<50%) and evidence of flow (contractile) reserve.	I	B
Intervention is not recommended in patients with severe comorbidities when the intervention is unlikely to improve quality of life or prolong survival >1 year.	III	C
B) Asymptomatic patients with severe aortic stenosis		
Intervention is recommended in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF <50%) without another cause.	I	B
Intervention is recommended in asymptomatic patients with severe aortic stenosis and demonstrable symptoms on exercise testing.	I	C
C) Mode of intervention		
Aortic valve interventions must be performed in Heart Valve Centres that declare their local expertise and outcomes data, have active interventional cardiology and cardiac surgical programmes on site, and a structured collaborative Heart Team approach.	I	C
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
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

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
SAVR or TAVI are recommended for remaining patients according to individual clinical, anatomical, and procedural characteristics.	I	B
D) Concomitant aortic valve surgery at the time of other cardiac/ascending aorta surgery		
SAVR is recommended in patients with severe aortic stenosis undergoing CABG or surgical intervention on the ascending aorta or another valve.	I	C
Recommendations on indications for intervention in severe primary mitral regurgitation		
Mitral valve repair is the recommended surgical technique when the results are expected to be durable.	I	B
Surgery is recommended in symptomatic patients who are operable and not high risk.	I	B
Surgery is recommended in asymptomatic patients with LV dysfunction (LVESD ≥40 mm and/or LVEF ≤60%).	I	B
Recommendations on indications for mitral valve intervention in chronic severe secondary mitral regurgitation		
Valve surgery/intervention is recommended only in patients with severe SMR who remain symptomatic despite GDMT (including CRT if indicated) and has to be decided by a structured collaborative Heart Team.	I	B
Patients with concomitant coronary artery or other cardiac disease requiring treatment		
Valve surgery is recommended in patients undergoing CABG or other cardiac surgery.	I	B
Recommendations on indications for percutaneous mitral commissurotomy and mitral valve surgery in clinically significant (moderate or severe) mitral stenosis (valve area ≤1.5 cm2)		
PMC is recommended in symptomatic patients without unfavourable characteristics for PMC.	I	B
PMC is recommended in any symptomatic patients with a contraindication or a high risk for surgery.	I	C
Mitral valve surgery is recommended in symptomatic patients who are not suitable for PMC in the absence of futility.	I	C
Recommendations on indications for intervention in tricuspid valve disease		
Recommendations on tricuspid stenosis		
Surgery is recommended in symptomatic patients with severe tricuspid stenosis.	I	C
Surgery is recommended in patients with severe tricuspid stenosis undergoing left-sided valve intervention.	I	C
Recommendations on primary tricuspid regurgitation		
Surgery is recommended in patients with severe primary tricuspid regurgitation undergoing left-sided valve surgery.	I	C
Surgery is recommended in symptomatic patients with isolated severe primary tricuspid regurgitation without severe RV dysfunction.	I	C
Recommendations on secondary tricuspid regurgitation		
Surgery is recommended in patients with severe secondary tricuspid regurgitation undergoing left-sided valve surgery.	I	B
Recommendations for prosthetic valve selection		
Mechanical prostheses		
A mechanical prosthesis is recommended according to the desire of the informed patient and if there are no contraindications to long-term anticoagulation.	I	C
A mechanical prosthesis is recommended in patients at risk of accelerated SVD.	I	C
Biological prostheses		
A bioprosthesis is recommended according to the desire of the informed patient.	I	C
A bioprosthesis is recommended when good-quality anticoagulation is unlikely (adherence problems, not readily available), contraindicated because of high bleeding risk (previous major bleed, comorbidities, unwillingness, adherence problems, lifestyle, occupation), and in those patients whose life expectancy is lower than the presumed durability of the bioprosthesis.	I	C
A bioprosthesis is recommended in case of reoperation for mechanical valve thrombosis despite good long-term anticoagulant control.	I	C
Recommendations for perioperative and postoperative antithrombotic management of valve replacement or repair		
Management of antithrombotic therapy in the perioperative period		
It is recommended that VKAs are timely discontinued prior to elective surgery to aim for an INR <1.5.	I	C
Bridging of OAC, when interruption is needed, is recommended in patients with any of the following indications: • Mechanical prosthetic heart valve. • AF with significant mitral stenosis. • AF with a 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
Therapeutic doses of either UFH or subcutaneous LMWH are recommended for bridging.	I	B
In patients with MHVs, it is recommended to (re)-initiate the VKA on the first postoperative day.	I	C

In patients who have undergone valve surgery with an indication for postoperative therapeutic bridging, it is recommended to start either UFH or LMWH 12-24 h after surgery.	I	C
In patients undergoing surgery, it is recommended that aspirin therapy, if indicated, is maintained during the periprocedural period.	I	C
In patients treated with DAPT after recent PCI (within 1 month) who need to undergo heart valve surgery in the absence of an indication for OAC, it is recommended to resume the $P2Y_{12}$ inhibitor postoperatively as soon as there is no concern over bleeding.	I	C
Patients with an indication to concomitant antiplatelet therapy		
After uncomplicated PCI or ACS in patients requiring long-term OAC, early cessation (≤1 week) of aspirin and continuation of dual therapy with OAC and a $P2Y_{12}$ inhibitor (preferably clopidogrel) for up to 6 months (or up to 12 months in ACS) is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used.	I	B
Discontinuation of antiplatelet treatment in patients treated with an OAC is recommended after 12 months.	I	B
Surgical valve replacement		
OAC using a VKA is recommended lifelong for all patients with a MHV prosthesis.	I	B
For patients with a VKA, INR self-management is recommended provided appropriate training and quality control are performed.	I	B
OAC is recommended for patients undergoing implantation of a surgical BHV who have other indications for anticoagulation.	I	C
NOACs are not recommended in patients with an MHV.	III	B
Transcatheter aortic valve implantation		
OAC is recommended lifelong for TAVI patients who have other indications for anticoagulation.	I	B
Lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC.	I	A
Routine use of OAC is not recommended after TAVI in patients who have no baseline indication for OAC.	III	B
Recommendations on management of prosthetic valve dysfunction		
Mechanical prosthetic thrombosis		
Urgent or emergency valve replacement is recommended for obstructive thrombosis in critically ill patients without serious comorbidity.	I	B
Bioprosthetic thrombosis		
Anticoagulation using a VKA and/or UFH is recommended in bioprosthetic valve thrombosis before considering reintervention.	I	C
Haemolysis and paravalvular leak		
Reoperation is recommended if a paravalvular leak is related to endocarditis or causes haemolysis requiring repeated blood transfusions or leading to severe heart failure symptoms.	I	C
Bioprosthetic failure		
Reoperation is recommended in symptomatic patients with a significant increase in transprosthetic gradient (after exclusion of valve thrombosis) or severe regurgitation.	I	C

ACS: acute coronary syndrome; AF: atrial fibrillation; BHV: biological heart valve; BSA: body surface area; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CRT: cardiac resynchronization therapy; DAPT: dual antiplatelet therapy; EuroSCORE: European System for Cardiac Operative Risk Evaluation; GDMT: guidelinedirected medical therapy; h: hours; INR: international normalized ratio; LMWH: low-molecular-weight heparin; LV: left ventricle/left ventricular; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MHV: mechanical heart valve; MR: mitral regurgitation; NOAC: non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulation; PCI: percutaneous coronary intervention; PMC: percutaneous mitral commissurotomy; RV: right ventricle/right ventricular; SAPT: single antiplatelet therapy; SAVR: surgical aortic valve replacement; SMR: secondary mitral regurgitation; STS-PROM: Society of Thoracic Surgeons – predicted risk of mortality; SVD: structural valve deterioration; SVi: stroke volume index; TAVI: transcatheter aortic valve implantation; UFH: unfractionated heparin; VHD: valvular heart disease; VKA: vitamin K antagonist.

17 Supplementary data

Supplementary Table 1. Cardiovascular and non-cardiovascular factors linked with transcatheter aortic valve implantation-related futility featured within the PARTNER and FRANCE 2 transcatheter aortic valve implantation-risk score models.

Supplementary Table 2. Katz Index of Independence in Activities of Daily Living.

Supplementary Table 3. Essential frailty toolset in older adults undergoing aortic valve replacement.

Supplementary Table 4. Medical comorbidities and factors predicting poorer outcomes post transcatheter aortic valve implantation.

Supplementary Table 5. Integrated approach for estimating transcatheter aortic valve implantation-specific risk and futility.

Supplementary Table 6. Risk-of-bias judgments for all evaluated trials.

Supplementary Table 7. Main inclusion/exclusion criteria suggesting an increased chance of responding to TEER in patients with SMR.

Supplementary Table 8. Echocardiographic scores used for assessing the feasibility of percutaneous mitral commissurotomy: Wilkins score, Cormier score, and Echo score 'Revisited'.

Supplementary Figure 1. Criteria for patients selection for MitraClip procedure.

Supplementary Figure 2. Peri- and post-procedural management of antithrombotic therapy in patients with indication to OAC and ACS/PCI.

Supplementary Figure 3. Management of OAC in patients with an indication for preoperative bridging.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-E-21-00009

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19 Appendix

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of Cardiology, Aicha Aouad; *Netherlands:* Netherlands Society of Cardiology, Renée van den Brink; *North Macedonia:* North Macedonian Society of Cardiology, Emilija Antova; *Norway:* Norwegian Society of Cardiology, Jan Otto Beitnes; *Poland:* Polish Cardiac Society, Andrzej Ochala; *Portugal:* Portuguese Society of Cardiology, Regina Ribeiras; *Romania:* Romanian Society of Cardiology, Dragos Vinereanu; *Russian Federation:* Russian Society of Cardiology, Olga Irtyuga; *Serbia:* Cardiology Society of Serbia, Branislava Ivanovic; *Slovakia:* Slovak Society of Cardiology, Iveta Simkova; *Spain:* Spanish Society of Cardiology, Ariana González Gómez; *Sweden:* Swedish Society of Cardiology, Giovanna Sarno; *Switzerland:* Swiss Society of Cardiology, Giovanni B. Pedrazzini; *Syrian Arab Republic:* Syrian Cardiovascular Association, Walid Bsata; *Tunisia:* Tunisian Society of Cardiology and Cardio-Vascular Surgery, Lilia Zakhama; *Turkey:* Turkish Society of Cardiology, Levent Korkmaz; *Ukraine:* Ukrainian Association of Cardiology, Sergii Cherniuk; *United Kingdom of Great Britain and Northern Ireland:* British Cardiovascular Society, Mohammed Y. Khanji; *Uzbekistan:* Association of Cardiologists of Uzbekistan, Islamjan Sharipov.

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ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–12
doi:10.1093/eurheartj/ehab395

2021 ESC/EACTS Guidelines for the management of valvular heart disease Supplementary data

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)

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All experts involved in the development of these guidelines have submitted declarations of interest. These have been compiled in a report and published in a supplementary document simultaneously to the guidelines. The report is also available on the ESC website www.escardio.org/guidelines

Keywords Guidelines • valvular heart disease • valve disease • valve surgery • percutaneous valve intervention • aortic regurgitation • aortic stenosis • mitral regurgitation • mitral stenosis • tricuspid regurgitation • tricuspid stenosis • prosthetic heart valves

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1. Abbreviations and acronyms

6MWT	6-minute walk test
ACEI	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor–neprilysin inhibitors
ASA	Acetylsalicylic acid
BMI	Body mass index
CABG	Coronary artery bypass grafting
CI	Confidence interval
DLCO	Diffusing Capacity of lung for carbon monoxide
DMR	Diastolic mitral regurgitation
EACTS	European Association for Cardio-Thoracic Surgery
EFT	Essential Frailty Toolset
ESC	European Society of Cardiology
FEV1	Forced expiratory volume in 1 second
FMR	Functional mitral regurgitation
GDMT	Guideline-directed medical therapy
Heart Tx	Heart transplantation
INR	International normalized ratio
LAA	Left atrial appendage
LMWH	Low-molecular-weight heparin
LTFU	Lost to follow-up
LV	Left ventricle/left ventricular
LVAD	Left ventricular assist devices
LVEF	Left ventricular ejection fraction
MR	Mitral regurgitation
MVA	Mitral valve area
NOAC	Non-vitamin K antagonist oral anticoagulant
NYHA	New York Heart Association
OAC	Oral anticoagulation
PAP	Pulmonary artery pressure
PCI	Percutaneous coronary intervention
PH	Pulmonary hypertension
QOL	Quality of life
RCT	Randomized controlled trial
RV	Right ventricle/right ventricular
SAVR	Surgical aortic valve replacement
SMR	Secondary mitral regurgitation
SPAP	Systolic pulmonary arterial pressure
TAVI	Transcatheter aortic valve implantation
TAVR	Transcatheter aortic valve replacement
TEER	Transcatheter edge-to-edge repair
TMVR	Transcatheter mitral valve repair
TTE	Transthoracic echocardiography
UFH	Unfractionated heparin
VHD	Valvular heart disease
VKA	Vitamin K antagonist

2. Introduction

There is no supplementary material for this section.

3. General comments

Supplementary Table 1 Cardiovascular and non-cardiovascular factors linked with transcatheter aortic valve implantation-related futility featured within the PARTNER and FRANCE 2 transcatheter aortic valve implantation-risk score models

	PARTNER risk score	FRANCE 2 risk score
Non-cardiovascular factors		Age ≥90 years
		BMI <30 kg/m^2
	Higher serum creatinine	Dialysis
	Oxygen-dependent chronic lung disease	Respiratory insufficiency
	Lower mini-mental status exam	
		Non-transfemoral access
Cardiovascular factors	Major arrhythmia (AF)	NYHA Class IV
	Lower mean trans-aortic gradient	Critical haemodynamic state ≥2 pulmonary oedemas/year
	Lower 6MWT distance	Pulmonary hypertension
	High-prohibitive risk	
	>50% mortality or lack of quality-of-life improvement at 6 months	>15% 30-day mortality

AF = atrial fibrillation; 6MWT = 6-minute walk test; BMI = body mass index; NYHA = New York Heart Association.

Reproduced from Puri R et al., TAVI or no TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. *Eur Heart J* 2016;**37**:2217–2225, by permission of Oxford University Press on behalf of the European Society of Cardiology.[1]

Supplementary Table 2 Katz Index of Independence in Activities of Daily Living

Patient's name and last name:			
	Activities point (1 or 0)	**Independence (1 point)**	**Dependence (0 points)**
Bathing		Bathes himself/herself completely or needs partial help while cleaning her back or genital region	Needs help while getting in or out of the tub or shower, and while cleaning more than one part of the body
Dressing		Dress himself/herself completely. May sometimes need help when tying shoes	Completely needs help while dressing
Toileting		Goes to toilet, gets on and off, clean genital area and puts on his/her clothing without help	Needs help while going to the toilet, cleaning self, and dressing
Mobilization		Gets up from the bed and chair on his/her own. May need help for carrying loads	Needs help while getting up from bed to the chair
Incontinence		May control himself/herself while urinating and defecating	Partially or completely incontinent of bowel or bladder
Feeding		Gets foods from plate into mouth without help. May need help while preparing food	Needs complete or partial help with feeding or requires parenteral nutrition
TOTAL SCORE:			

Adapted from Katz S., Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. *J Am Geriatr Soc* 1983;31:721–727. Copyright (1983), with permission from Wiley.[2]

Supplementary Table 3 Essential frailty toolset in older adults undergoing aortic valve replacement

EFT Score	
Five Chair rises <15 seconds	0 Points
Five Chair rises ≥15 seconds	1 Point
Unable to complete	2 Points
No cognitive impairment	0 Points
Cognitive impairment	1 Point
Haemoglobin ≥13.0 g/dL ♂ Haemoglobin ≥12.0 g/dL ♀	0 Points
Haemoglobin <13.0 g/dL ♂ Haemoglobin <12.0 g/dL ♀	1 Point
Serum albumin ≥3.5 g/dL	0 Points
Serum albumin <3.5 g/dL	1 Point
TOTAL SCORE:	

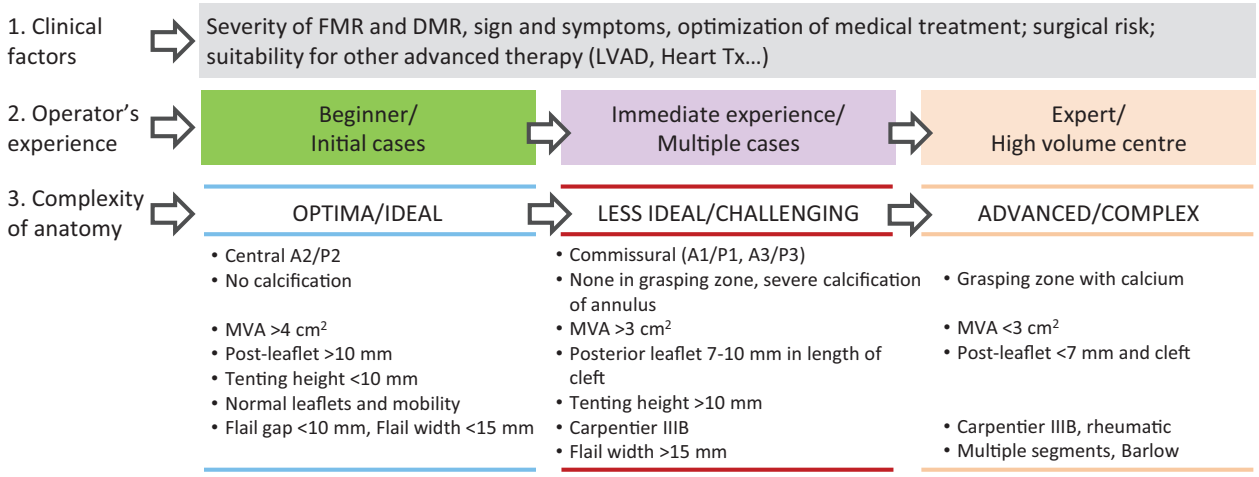
Score interpretation		
EFT Score	**1-Year Mortality**	
	TAVI	**SAVR**
0–1	6%	3%
2	15%	7%
3	28%	16%
4	30%	38%
5	65%	50%

EFT = Essential Frailty Toolset; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation.
Reprinted from Afilalo J et al. Frailty in older adults undergoing aortic valve replacement: the FRAILTY-AVR Study. *J Am Coll Cardiol* 2017;**70**:689–700. Copyright (2017), with permission from the American College of Cardiology Foundation.[3]

Supplementary Table 4 Medical comorbidities and factors predicting poorer outcomes post transcatheter aortic valve implantation

Medical comorbidity	**Factors specifically associated with futility**
Chronic lung disease	6MWT <150 m Oxygen-dependency
Advanced chronic kidney disease	Atrial fibrillation Dialysis dependence
Frailty	>2 frailty indices (Katz activities of daily living + mobility status[a])
Cardiovascular conditions	LVEF <30% Pre-capillary or combined PH[b] (mean PAP >25 mmHg) Low trans-aortic gradient Impaired contractile reserve Low flow state (<35 mL/m^2) Severe primary MR

6MWT = 6-minute walk test; LV = left ventricle/left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; PAP = pulmonary artery pressure; PH = pulmonary hypertension; TAVI = transcatheter aortic valve implantation.
[a]Time taken to walk 5 m is >6 seconds. Katz indices are: independence in feeding, bathing, dressing, transferring, toileting, urinary incontinence.
[b]Measured invasively. Combined PH defined as post-capillary PH (measured by LV end-diastolic pressure >15 mmHg) with a diastolic PAP ≥7 mmHg than LV end-diastolic pressure.
Reproduced from Puri R et al., TAVI or no TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. *Eur Heart J* 2016;**37**:2217–2225, by permission of Oxford University Press on behalf of the European Society of Cardiology.[1]



Supplementary Figure 1 Criteria for patients selection for MitraClip procedure. DMR = Degenerative mitral regurgitation; FMR = functional mitral regurgitation; Heart Tx = heart transplantation; LVAD = left ventricular assist devices; MVA = mitral valve area. Reproduced from Gavazzoni M et al., Conceiving MitraClip as a tool: percutaneous edge-to-edge repair in complex mitral valve anatomies. *Eur Heart J Cardiovasc Imaging* 2020;**21**:1059–1067, by permission of Oxford University Press on behalf of the European Society of Cardiology.[4]

Supplementary Table 5 Integrated approach for estimating transcatheter aortic valve implantation-specific risk and futility

Criteria	Low risk	Intermediate risk	High risk	Prohibitive risk
PARTNER TAVI score[a] OR FRANCE 2 TAVI score	<25% risk of mortality or lack of QOL improvement at 6 months Risk score: 0 (30-day mortality risk <5%)	25–50% risk of mortality or lack of QOL improvement at 6 months Risk score: 1–5 (30-day mortality risk 5–15%)	>50% risk of mortality or lack of QOL improvement at 6 months Risk score: 6–7 (30-day mortality risk 15–25%)	Risk score ≥8 (30-day mortality risk >25%)
Frailty[b]	None	1 index	≥2 indices	≥4 indices
Specific major organ system compromise not to be improved post-TAVI[c]	None	1 organ system	2 organ systems	≥3 organ systems

DLCO = diffusing capacity of lung carbon monoxide; FEV1 = forced expiratory volume in 1 second; INR = international normalized ratio; LV = left ventricle/left ventricular; QOL = quality of life; RV = right ventricle/right ventricular; TAVI = transcatheter aortic valve implantation; VKA = vitamin K antagonist.
[a]http://h-outcomes.com/tavi-risk-calculator/.
[b]Frailty based on Katz Index (independence in feeding, bathing, dressing, transferring, toileting, and urinary incontinence) and independence in ambulation (walk 5 m in <6 seconds).
[c]Examples of major organ system compromise: Cardiac (severe LV systolic or diastolic dysfunction or RV dysfunction, and fixed pulmonary hypertension); chronic kidney disease stage 3 or worse; pulmonary dysfunction with FEV1 <50% or DLCO <50% of predicted; central nervous system dysfunction (dementia, Alzheimer's disease, Parkinson's disease, and cerebrovascular accident with persistent physical limitation); gastrointestinal dysfunction (Crohn's disease, ulcerative colitis, nutritional impairment, or serum albumin <3.0); cancer (active malignancy); and liver (any history of cirrhosis, variceal bleeding, or elevated INR in the absence of VKA therapy).

Reproduced from Puri R et al., TAVI or no TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. *Eur Heart J* 2016;**37**:2217–2225, by permission of Oxford University Press on behalf of the European Society of Cardiology.[1]

4. Aortic regurgitation

There is no supplementary material for this section.

5. Aortic stenosis

Indications for intervention (SAVR or TAVI)

Assessment of methodological quality of studies and randomized controlled trials (RCTs) by the Methodology Group of the 2021 European Society of Cardiology (ESC)/ European Association for Cardio-Thoracic Surgery (EACTS) Guidelines for the management of valvular heart disease (VHD).

Methodology group

In preparation of the 2021 VHD Guidelines, a methodology group has been created for the first time to assist the Task Force for the collection and interpretation of the evidence supporting specific recommendations. The group was constituted by 2 ESC delegates and 2 EACTS delegates who were also members of the Task Force. Although the main activity of the group concerned the chapter on aortic stenosis and secondary mitral regurgitation (SMR), it was not limited to these two domains. The group was at disposal upon request of the Task Force members to resolve other specific methodological issues.

Assessment of methodological quality of studies and RCTs

The quality of the eligible RCTs was assessed systematically using the revised Cochrane risk-of-bias tool for randomized trials 2.0.[5] The

present document reflects the consensus achieved during the group's deliberations. Agreement among the members of the group could be achieved for all sections, except for the randomization process (in particular concealment of allocation). Trials are listed by topic and in chronological order according to their respective recruitment period. Only published results were considered, and the longest follow-up was given priority. Published manuscripts, supplementary appendices, and protocols were reviewed for each trial.

The five following domains were assessed for their specific risk of bias: i) randomization process, ii) deviations from the intended

Supplementary Table 6 Risk-of-bias judgments for all evaluated trials

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of outcome	Selection of reported result	Overall
Treatment of aortic stenosis						
PARTNER A – overall population*						
Non-inferiority primary outcome at 5 years[a]	?	−	−	−	+	−
CoreValve U.S. Pivotal High Risk						
Non-inferiority primary outcome at 5 years (ESC)	+	−	−	−	+	−
Non-inferiority primary outcome at 5 years (EACTS)	?	−	−	−	+	−
Superiority primary outcome at 1 year (ESC)	+	−	−	−	+	−
Superiority primary outcome at 1 year (EACTS)	?	−	−	−	+	−
NOTION						
Similarity primary outcome at 5 years (ESC)	+	+	+	+	+	+
Similarity primary outcome at 5 years (EACTS)	?	+	+	+	+	?
PARTNER 2						
Non-inferiority primary outcome at 2 years (ESC)	+	?	+	+	+	?
Non-inferiority primary outcome at 2 years (EACTS)	?	?	+	+	+	?
SURTAVI						
Non-inferiority at 2 years (ESC)	+	?	+	+	+	?
Non-inferiority at 2 years (EACTS)	?	?	+	+	+	?
PARTNER 3						
Non-inferiority primary outcome at 2 years	?	?	+	+	+	?
Superiority primary outcome at 2 years[a]	?	?	−	−	+	−
Evolut Low Risk						
Non-inferiority primary outcome at 2 years (ESC)	+	?	+	+	+	?
Non-inferiority primary outcome at 2 years (EACTS)	?	?	+	+	+	?
Treatment of secondary mitral regurgitation						
COAPT						
Superiority primary outcome at 2 years (ESC)	+	?	+	+	+	?
Superiority primary outcome at 2 years (EACTS)	?	?	+	+	+	?
Superiority secondary outcomes at 2 years (ESC)	+	?	?	?	+	?
Superiority secondary outcomes at 2 years (EACTS)	?	?	?	?	+	?
MITRA-FR						
Primary outcome at 2 years (ESC)	+	+	+	+	+	+
Primary outcome at 2 years (EACTS)	?	+	+	+	+	?

ESC = delegates of the European Society of Cardiology; EACTS = delegates of the European Association for Cardio-Thoracic Surgery.

+ = low risk of bias; ? = some concerns; − = high risk of bias

[a] Two separate statements are included where no consensus could be reached. Initials indicate the members of the group endorsing each risk-of-bias judgment.

Non-inferiority at longer term follow-up was assessed using the same criteria as used for the primary non-inferiority analysis of the respective trial.

*ROB only applicable to the overall population – there was an access route by treatment interaction.

interventions, iii) missing outcome data, iv) measurement of outcome, and v) selection of reported results. For each domain, the overall risk of bias was derived according to pre-specified algorithms[5] and quantified using three categories: low risk of bias, some concerns, and high risk of bias. Only domains with some concerns or high risk of bias will be discussed in the present document.

If appropriate, robustness to missing data was explored using a worst-case scenario that assumed no primary endpoint event in all missing patients of the control group [surgical aortic valve replacement (SAVR) or guideline-directed medical therapy (GDMT)] and the occurrence of an event in all patients of the experimental group [transcatheter aortic valve implantation (TAVI) or transcatheter mitral valve repair (TMVR)]. Supplementary Table 6 below summarizes the risk-of-bias judgments for all evaluated trials.

Treatment of severe aortic stenosis

PARTNER A (5 years)[6]

***Domain 1*:** The group indicates that *some concerns* exist due to the lack of description of a central randomization process.

***Domains 2, 3, and 4*:** A substantial proportion of the randomized patients did not undergo the intended procedure and were not followed up, particularly in the surgical group [38 patients (10.8%) vs. 4 (1.1%) in the transcatheter aortic valve replacement (TAVR) group]. The main reason for this was patient's decision not to undergo SAVR. In addition, there was an imbalance between the number of lost to follow-up (LTFU) at 5 years (9 patients in the TAVI group vs. 23 patients for SAVR). This translates into a *high risk of bias* for the overall population for non-inferiority at 5 years since the worst-case scenario suggests SAVR to be superior to TAVI. However, there is a clear access route by treatment interaction, with worse prognosis for transapical access to TAVI that needs to be considered when interpreting the trial results. The published hazard ratio for transapical access is 1.37 at 5 years [95% confidence interval (CI) 0.98−1.92] whereas the published hazard ratio for transfemoral is 0.91 at 5 years (95% CI, 0.72−1.14), *P* for interaction = 0.05, and the distinction is valid as randomization was stratified by intended access route.

Overall risk of bias:

High risk of bias regarding non-inferiority at 5 years for the overall population due to missing outcome data. Correct interpretation of the results requires distinction between transfemoral and transapical access; for transfemoral access TAVI and SAVR appeared similar at 5 years.

CoreValve U.S. Pivotal High-Risk Trial (5 years)[7]

Domain 1: *The group was not able to reach an agreement concerning this domain*. EACTS delegates indicate *some concerns*, as there is a theoretical risk of selection bias of unclear magnitude and direction because of stratification by site and blocking with randomly varied block sizes. In contrast, ESC delegates follow the published algorithm of the Cochrane risk-of-bias tool and classify this domain as *low risk of bias*, as they consider the potential for selection bias of a relevant magnitude through the combination of stratification by site and blocking to be small and of theoretical nature only.

Domains 2, 3, and 4: A substantial proportion of the randomized patients did not undergo the intended procedure and were not followed up, particularly in the surgical group [38 patients (9%) vs. 4 (1%) in the TAVI group]. The main reason for this was patient's consent withdrawal. In addition, there was an imbalance between the number of LTFU at 5 years (29 patients in the TAVI group vs. 48 patients for SAVR). This results in a *high risk of bias* for the overall population for both the non-inferiority and superiority at 5 years, since the worst-case scenario suggests SAVR to be superior to TAVI. In addition, there is a *high risk of bias* regarding previous claims of superiority at 1 year on the primary outcome.

Overall risk of bias:

High risk of bias regarding both non-inferiority at 1 and 5 years, as well as previous claims of superiority at 1 year due to missing outcome data.

NOTION[8]

Domain 1: The group was not able to reach an agreement concerning this domain. EACTS delegates indicate *some concerns*, as there is a theoretical risk of selection bias of unclear magnitude and direction because of stratification by site and blocking with randomly varied block sizes. In contrast, ESC delegates follow the published algorithm of the Cochrane risk-of-bias tool and classify this domain as *low risk of bias*, as they consider the potential for selection bias of a relevant magnitude through the combination of stratification by site and blocking to be small and of theoretical nature only.

Overall risk of bias:

- *The group was not able to reach an agreement.*
- *Low risk of bias* regarding similarity of the primary endpoint according to *ESC delegates*; *some concerns* according to *EACTS delegates*.

PARTNER 2[9]

Domain 1: *The group was not able to reach an agreement concerning this domain*. EACTS delegates indicate *some concerns*, as there is a theoretical risk of selection bias of unclear magnitude and direction because of stratification by site and blocking with randomly varied block sizes. In contrast, ESC delegates follow the published algorithm of the Cochrane risk-of-bias tool and classify this domain as *low risk of bias*, as they consider the potential for selection bias of a relevant magnitude through the combination of stratification by site and blocking to be small and of theoretical nature only.

Domain 2: *Some concerns* exist because of imbalances in concomitant procedures [coronary artery bypass grafting (CABG) 14.5% vs. 3.9% percutaneous coronary intervention (PCI); 9.1% of patients had other surgical concomitant procedures]. This may have favoured the experimental group (TAVI) due to the incremental risk of stroke and death associated with concomitant surgical procedures, while differences in revascularization rates could also favour the control group (SAVR) due to the higher frequency of revascularization in this group. Importantly, this reflects clinical reality and may not explain the

numerical difference of 18 neurological events in favour of TAVI observed at 2 years of follow-up.

Domains 3 and 4: Some of the randomized patients did not undergo the intended procedure and were not followed up, particularly in the surgical group [77 patients (7.5%) vs. 17 (1.7%) in the TAVI group]. The main reason for this was patient's decision not to undergo SAVR. In addition, there were an imbalance between the number of LTFU at 2 years (31 patients in the TAVI group vs. 45 patients for SAVR). Despite these imbalances, there is a *low risk of bias for the non-inferiority analysis* since even considering the worst-case scenario non-inferiority was still demonstrated for the primary endpoint at 2 years.

Overall risk of bias:

Some concerns regarding non-inferiority of the primary outcome at 2 years due to imbalances in concomitant procedures.

SURTAVI[10]

Domain 1: *The group was not able to reach an agreement concerning this domain.* EACTS delegates indicate *some concerns*, as there is a theoretical risk of selection bias of unclear magnitude and direction because of stratification by site and blocking with randomly varied block sizes. In contrast, ESC delegates follow the published algorithm of the Cochrane risk-of-bias tool and classify this domain as *low risk of bias*, as they consider the potential for selection bias of a relevant magnitude through the combination of stratification by site and blocking to be small and of theoretical nature only.

Domain 2: Some concerns exist because of imbalances in concomitant procedures [CABG (22.1%) vs. PCI (14.5%); cardiac ablation (8%); and root enlargement (1.6%)]. This may have favoured the experimental group (TAVI) due to the incremental risk of stroke and death associated with concomitant surgical procedures, while differences in revascularization rates could also favour the control group (SAVR) due to the higher frequency of revascularization in this group. Importantly, this reflects clinical reality and is unlikely to explain differences observed at 2 years of follow-up.

Domains 3 and 4: A substantial proportion of the randomized patients did not undergo the intended procedure and were not followed up, particularly in the surgical group [71 patients (8.1%) vs. 15 (1.7%) in the TAVI group]. Despite these imbalances, there is a low risk of bias for the non-inferiority analysis since even considering the worst-case scenario, non-inferiority was still demonstrated for the primary endpoint at 2 years.

Overall risk of bias:

Some concerns regarding non-inferiority of the primary outcome at 2 years due to imbalances in concomitant procedures.

PARTNER 3[11]

Domain 1: The group agreed that there are *some concerns* regarding undermining of concealment due to stratification by site and block randomization with a fixed block size of four. If this had been known to sites, allocation would have been fully predictable for sites in case of a difference of 2 participants between groups. Therefore, there is a theoretical possibility of selection bias of unclear magnitude and direction.

Domain 2: *Some concerns* exist because of imbalances in left atrial appendage (LAA) ligation [43 patients (9.5%)] as concomitant procedure (which was allowed according to the protocol) and Maze [22 patients (4.8%)] as non-protocol co-intervention (which was a protocol deviation). This may have favoured the experimental group (TAVI) due to the incremental risk of stroke and death associated with concomitant surgical procedures, while differences in revascularization rates could also favour the control group (SAVR) due to the higher frequency of revascularization in this group. No appropriate statistical method was used to account for these discrepancies. However, both procedures seem unlikely to be associated with a greater than 5% risk of peri-procedural stroke[12,13] and therefore may not explain the difference of 8 strokes in favour of TAVI observed at 1 year.

Domains 3 and 4: A substantial proportion of the randomized patients did not undergo the intended procedure and were not followed up, particularly in the surgical group [43 patients (8.6%) vs. 7 (1.4%) in the TAVI group]. The main reason for this was patients' decisions not to undergo SAVR. The number of LTFU at 1 year was low for both groups (3 patients in the TAVI group vs. 12 patients for SAVR). Despite imbalances in the number of patients who did not receive the intended treatment, there is a *low risk of bias for the non-inferiority analysis* since even considering the worst-case scenario non-inferiority was still demonstrated for the primary endpoint at 1 year. In contrast, there is a *high risk of bias for the superiority analysis* since the 95% CI of the primary outcome crosses the line of no difference in the worst-case scenario.

Overall risk of bias:

Some concerns regarding non-inferiority on the primary outcome at 2 years due to the use of a fixed block size of 4 for the randomization process and imbalances in concomitant procedures; *high risk of bias* regarding superiority on the primary outcome at 2 years due to missing data in the patients who did not receive the intended intervention.

Evolut low risk[14]

Domain 1: *The group was not able to reach an agreement concerning this domain.* EACTS delegates indicate *some concerns*, as there is a theoretical risk of selection bias of unclear magnitude and direction because of stratification by site and blocking with randomly varied block sizes. In contrast, ESC delegates follow the published algorithm of the Cochrane risk-of-bias tool and classify this domain as *low risk of bias*, as they consider the potential for selection bias of a relevant magnitude through the combination of stratification by site and blocking to be small and of theoretical nature only.

Domain 2: *Some concerns* exist because of imbalances in LAA ligation [42 patients (6.2%)] and Maze [24 patients (3.5%)] as concomitant procedures (which were both allowed according to the protocol). This may have favoured the experimental group (TAVI) due to the incremental risk of stroke and death associated with concomitant surgical procedures, while differences in revascularization rates could

also favour the control group (SAVR) due to the higher frequency of revascularization in this group. No appropriate statistical method was used to account for these discrepancies. However, both procedures are unlikely to be associated with a greater than 5% risk of peri-procedural stroke[12,13] and do not therefore explain differences between groups.

Domains 3 and 4: A substantial proportion of the randomized patients did not undergo the intended procedure and were not followed up, particularly in the surgical group [53 patients (7.2%) vs. 12 (1.6%) in the TAVI group]. In addition, there was an imbalance between the number of LTFU at 2 years (9 patients in the TAVI group vs. 27 patients for SAVR). Despite imbalances in the number of patients who did not receive the intended treatment, there is a *low risk of bias for the non-inferiority analysis* since even considering the worst-case scenario non-inferiority was still demonstrated for the primary endpoint at 2 years.

Overall risk of bias:

Some concerns regarding non-inferiority on the primary outcome due to imbalances in concomitant procedures.

Treatment of secondary mitral regurgitation

COAPT[15]

Domain 1: *The group was not able to reach an agreement concerning this domain*. EACTS delegates indicate *some concerns*, as there is a theoretical risk of selection bias of unclear magnitude and direction because of stratification by site and blocking with randomly varied block sizes. In contrast, ESC delegates follow the published algorithm of the Cochrane risk-of-bias tool and classify this domain as *low risk of bias*, as they consider the potential for selection bias of a relevant magnitude through the combination of stratification by site and blocking to be small and of theoretical nature only.

Domain 2: The group acknowledges that *some concerns* exist due to the significantly lower use of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), or angiotensin receptor–neprilysin inhibitors (ARNI) at baseline in the patients of the GDMT group (62.8% vs. 71.5% in the TMVR group). This could indicate failure to implement medical treatment in the control group and may have favoured the TMVR group. However, considerable efforts were made to optimize GDMT at study entry through control by a clinical eligibility committee, the evolution of the medical therapy was strictly monitored for both groups, and the percentage of patients with major changes was low in both groups. In addition, patients in the control group had worse heart failure symptoms as reflected by New York Heart Association (NYHA) classes III and IV.

Domains 3 and 4: There was an imbalance between the number of LTFU at 2 years (25 patients in the TMVR group vs. 47 patients in the GDMT group). An attempt to account for missing data was made using multiple imputation, but resulting estimates may not be robust. There was a *low risk of bias* regarding superiority on the primary outcome as findings were robust to missing data considering the worst-case scenario. In contrast, *some concerns* exist for superiority on secondary outcomes due to missing data and lower use of ACEI, ARB, or ARNI at baseline.

Overall risk of bias:

Some concerns regarding superiority on the primary outcome due to lower use of ACEI, ARB, or ARNI at baseline; *some concerns* for superiority on secondary outcomes due to missing data and lower use of ACEI, ARB, or ARNI at baseline.

MITRA-FR[16]

Domain 1: *The group was not able to reach an agreement concerning this domain*. EACTS delegates indicate *some concerns*, as there is a theoretical risk of selection bias of unclear magnitude and direction because of stratification by site and blocking with randomly varied block sizes. In contrast, ESC delegates follow the published algorithm of the Cochrane risk-of-bias tool and classify this domain as *low risk of bias*, as they consider the potential for selection bias of a relevant magnitude through the combination of stratification by site and blocking to be small and of theoretical nature only.

Domains 2, 3, and 4: *Low concerns* for the primary endpoint (99% follow-up). Analyses of secondary endpoints were deemed *inconclusive* due to the high level of missing data.

Overall risk of bias:

- *The group was not able to reach an agreement.*
- *Low risk* of bias according to the *ESC delegates* regarding the superiority analysis of the primary outcome; *some concerns* according to the *EACTS delegates* regarding the superiority analysis of the primary outcome due to the randomization process. Consensus that analyses of secondary endpoints were *inconclusive* due to the high level of missing data.

6. Mitral regurgitation

Supplementary Table 7 Main inclusion/exclusion criteria suggesting an increased chance of responding to TEER in patients with SMR

Inclusion criteria:
• Severe SMR
• Symptomatic heart failure (NYHA class II, III or ambulatory IV) despite optimized GDMT
• LVEF 20–50%
• LV end-systolic diameter ≤70 mm
• At least one heart failure hospitalization within the previous year or increased natriuretic peptide levels
• Anatomy judged suitable for TEER
Exclusion criteria:
• Severe disability/frailty
• Hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischaemic etiology
• Infiltrative cardiomyopathies (e.g. amyloidosis, haemochromatosis, sarcoidosis)

Continued

- Estimated SPAP >70 mmHg assessed by echocardiography or right heart catheterization
- Haemodynamic instability defined as systolic pressure <90 mmHg with or without afterload reduction, cardiogenic shock or the need for inotropic support or intra-aortic balloon pump or other haemodynamic support device
- Physical evidence of right-sided congestive heart failure with echocardiographic evidence of moderate or severe RV dysfunction
- Mitral valve orifice area <4.0 cm^2 by site-assessed TTE
- Coronary, aortic or tricuspid valve disease requiring surgery

GDMT = guideline-directed medical therapy; LV = left ventricle/left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RV = right ventricle/right ventricular; SMR = secondary; SPAP = systolic pulmonary arterial pressure; TTE = transthoracic echocardiography; TEER = transcatheter edge-to-edge repair.
Adapted from Mack MJ et al., Cardiovascular outcomes assessment of the MitraClip in patients with heart failure and secondary mitral regurgitation: design and rationale of the COAPT trial. Am Heart J. 2018;205:1–11, Copyright (2018), with permission from Elsevier.[17]

7. Mitral stenosis

8. Tricuspid regurgitation

There is no supplementary material for this section.

9. Tricuspid stenosis

There is no supplementary material for this section.

10. Combined and multiple-valve diseases

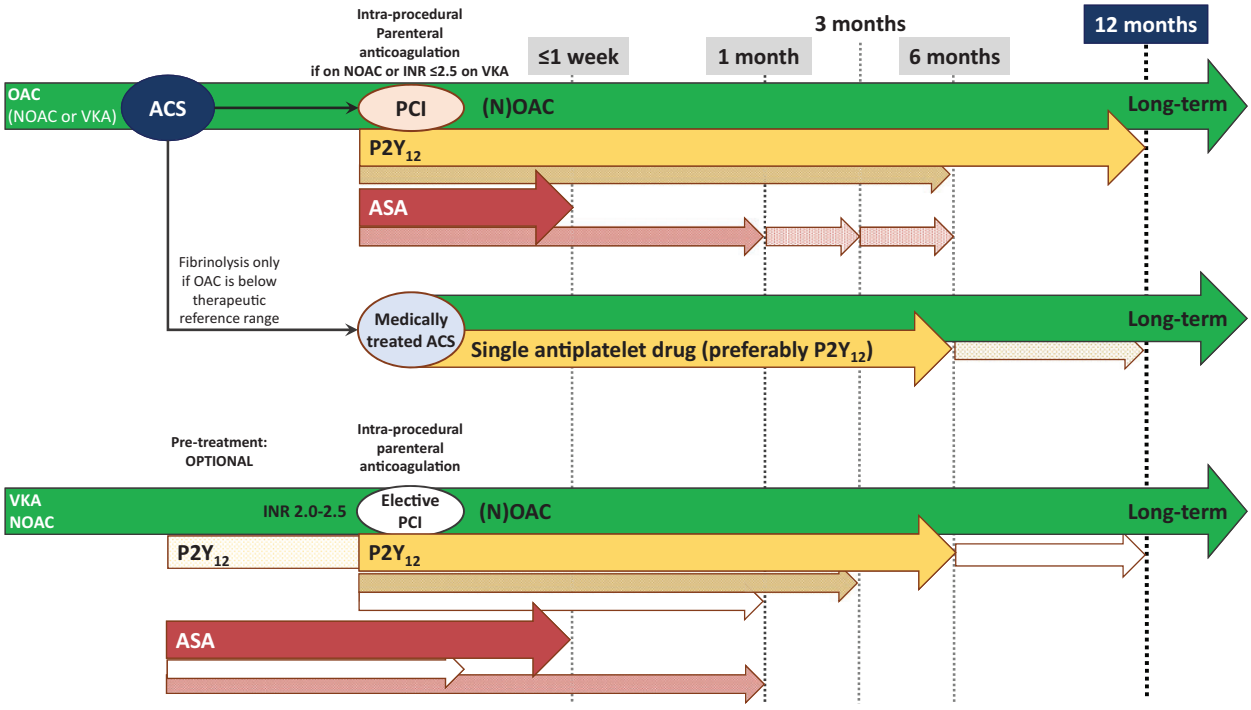
There is no supplementary material for this section.

Supplementary Table 8 Echocardiographic scores used for assessing the feasibility of percutaneous mitral commissurotomy: Wilkins score, Cormier score, and Echo score 'Revisited'

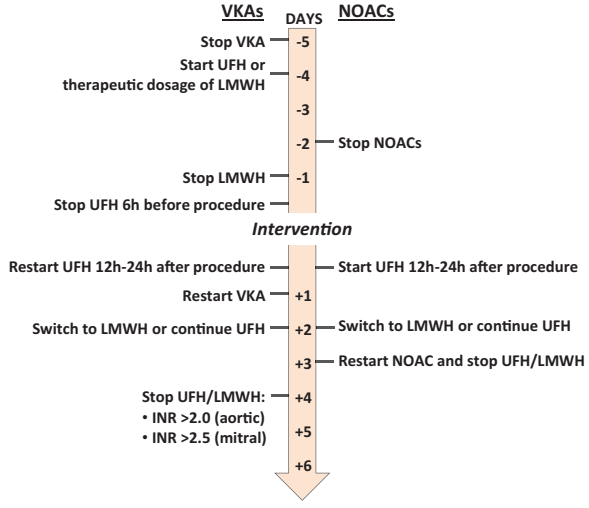
Assessment of mitral valve anatomy according to the Wilkins score[18]				
Grade	**Mobility**	**Thickening**	**Calcification**	**Subvalvular thickening**
1	Highly mobile valve with only leaflet tips restricted	Leaflets near normal in thickness (4–5 mm)	A single area of increased echo brightness	Minimal thickening just below the mitral leaflets
2	Leaflet mid and base portions have normal mobility	Mid leaflets normal, considerable thickening of margins (5–8 mm)	Scattered areas of brightness confined to leaflet margins	Thickening of chordal structures extending to one third of the chordal length
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending through the entire leaflet (5–8 mm)	Brightness extending into the mid portions of the leaflets	Thickening extended to distal third of the chords
4	No or minimal forward movement of the leaflets in diastole	Considerable thickening of all leaflet tissue (>8–10 mm)	Extensive brightness throughout much of the leaflet tissue	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles
The total score is the sum of the four items and ranges between 4 and 16.				
Assessment of mitral valve anatomy according to the Cormier score[19]				
Echocardiographic group	Mitral valve anatomy			
Group 1	Pliable non-calcified anterior mitral leaflet and mild subvalvular disease (i.e. thin chordae ≥10 mm long)			
Group 2	Pliable non-calcified anterior mitral leaflet and severe subvalvular disease (i.e. thickened chordae <10 mm long)			
Group 3	Calcification of mitral valve of any extent, as assessed by fluoroscopy, whatever the state of subvalvular apparatus			
Echo score 'Revisited' for immediate outcome prediction[20]				
Echocardiographic variables	**Points for score (0 to 11)**			
Mitral valve area ≤1 cm^2	2			
Maximum leaflet displacement ≤12 mm	3			
Commissural area ratio ≥1.25	3			
Subvalvular involvement	3			

Risk groups for Echo score 'Revisited': low (score 0–3); intermediate (score 4–5); high (score 6–11).
Reproduced from Baumgartner H et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–2791, by permission of Oxford University Press on behalf of the European Society of Cardiology.[21]

11. Prosthetic valves



Supplementary Figure 2 Peri- and post-procedural management of antithrombotic therapy in patients with indication to OAC and ACS/PCI. ACS = acute coronary syndrome; ASA = acetylsalicylic acid; INR = international normalized ratio; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; VKA = vitamin K antagonist. Adapted from Hindricks G et al., 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498. Copyright (2021) by permission of Oxford University Press on behalf of the European Society of Cardiology.[22]



Supplementary Figure 3 Management of OAC in patients with an indication for preoperative bridging. INR = international normalized ratio; LMWH = low-molecular-weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; UFH = unfractionated heparin; VKA = vitamin K antagonist. [a]Bridging with UFH/LMWH should start when INR values are below specific therapeutic ranges. [b]Discontinuation should be prolonged to >72 h if creatinine clearance is 50–79 mL/min/1.73 m^2 or >96 h if creatinine clearance is <50 mL/min/1.73 m^2. Of note, VKA should be stopped 5 days before intervention if warfarin is used but only 3 days in the case of acenocumarol. Reproduced from Sousa-Uva M et al., 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. *Eur J Cardiothorac Surg* 2018;**53**:5–33, by permission of Oxford University Press on behalf of the European Association for Cardio-Thoracic Surgery.[23]

12. Management during non-cardiac surgery

There is no supplementary material for this section.

13. Management during pregnancy

There is no supplementary material for this section.

14. Key messages

There is no supplementary material for this section.

15. Gaps in evidence

There is no supplementary material for this section.

16. To Do and Not to Do

There is no supplementary material for this section.

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