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STATE OF THE ART REVIEW
Valvular heart disease

ESC/EACTS vs. ACC/AHA guidelines for the management of severe aortic stenosis

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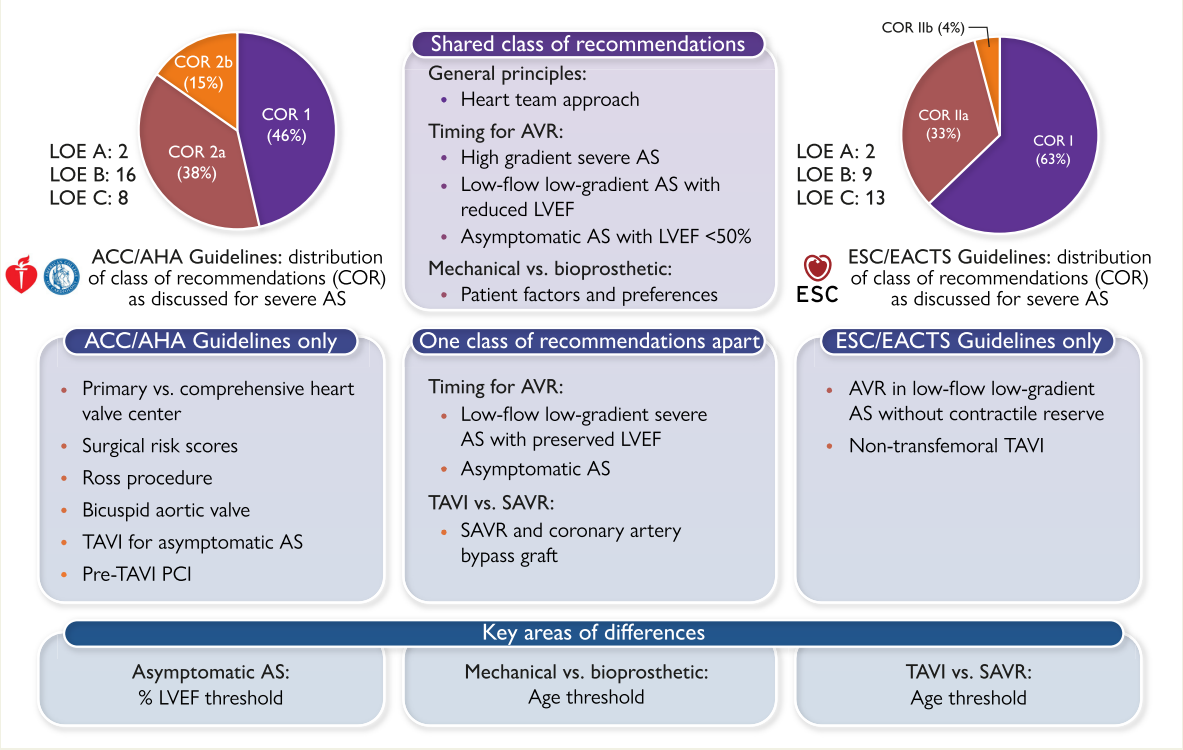
Graphical Abstract



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Key concurrences and divergences of ESC/EACTS and ACC/AHA Guidelines. ACC/AHA, American College of Cardiology/American Heart Association; AS, aortic stenosis; AVR, aortic valve replacement; ESC/EACTS, European Society of Cardiology/European Association for Cardio-Thoracic Surgery; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Abstract

Aortic stenosis (AS) is a serious and complex condition, for which optimal management continues to evolve rapidly. An understanding of current clinical practice guidelines is critical to effective patient care and shared decision-making. This state of the art review of the 2021 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines and 2020 American College of Cardiology/American Heart Association Guidelines compares their recommendations for AS based on the evidence to date. The European and American guidelines were generally congruent with the exception of three key distinctions. First, the European guidelines recommend intervening at a left ventricular ejection fraction of 55%, compared with 60% over serial imaging by the American guidelines for asymptomatic patients. Second, the European guidelines recommend a threshold of ≥65 years for surgical bioprosthesis, whereas the American guidelines employ multiple age categories, providing latitude for patient factors and preferences. Third, the guidelines endorse different age cut-offs for transcatheter vs. surgical aortic valve replacement, despite limited evidence. This review also discusses trends indicating a decreasing proportion of mechanical valve replacements. Finally, the review identifies gaps in the literature for areas including transcatheter aortic valve implantation in asymptomatic patients, the appropriateness of Ross procedures, concomitant coronary revascularization with aortic valve replacement, and bicuspid AS. To summarize, this state of the art review compares the latest European and American guidelines on the management of AS to highlight three areas of divergence: timing of intervention, valve selection, and surgical vs. transcatheter aortic valve replacement criteria.

Keywords Aortic stenosis • TAVI • SAVR • Guidelines • Valvular heart disease • Aortic valve

Introduction

Aortic stenosis (AS) is the most common non-rheumatic valvular heart disease (VHD), affecting 2%–5% of adults over 65 years.[1] The past decade has seen a rapid succession of randomized clinical trials (RCTs) examining transcatheter interventions in high, intermediate, and recently low surgical risk AS patients. Since the 2017 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS)[2] and the 2014 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines,[3] new evidence has shifted how AS is managed in clinical practice. The 2021 ESC/EACTS[4] and 2020 ACC/AHA[5] Guidelines differ on the roles of transcatheter aortic valve implantation (TAVI) and thresholds for intervention, despite being based on a shared body of literature with few exceptions. A critical examination of the evidence supporting these recommendations may assist clinicians caring for patients with AS. This state of the art review will focus on surgical and transcatheter recommendations for managing AS in the 2021 ESC/EACTS and 2020 ACC/AHA Guidelines.

I. Heart team management and decision-making

A. Heart team

Both the ESC/EACTS and ACC/AHA Guidelines emphasize the importance of the Heart Team through a Class of Recommendation (COR) I/1, Level of Evidence (LOE) C statement. The Heart Team is responsible for taking a multidisciplinary appraisal of patient and procedural factors to devise an optimal treatment strategy. Both guidelines refer to the Heart Team as an 'underlying principle' highlighted by a 2019 VHD consensus statement (*Table 1*).[6]

Both the ACC/AHA and ESC/EACTS concur that high volume centres are associated with better outcomes while acknowledging the influence of other performance indicators.[4,5] The ACC/AHA suggests that Heart Valve Centres are particularly useful for complex patients, such as 'asymptomatic patients with severe VHD' or 'patients with multiple comorbidities for whom valve intervention is considered' (COR 2a LOE C-LD).[5] Unlike guidelines from other jurisdictions and the evidence indicating a volume-outcome relationship, neither the American nor European guidelines recommend minimum cases for Heart Valve Centres to perform TAVI and surgical aortic valve replacement (SAVR). The ESC/EACTS Guidelines state that 'the Heart Team approach is particularly advisable for the management of high-risk and asymptomatic patients…' but this is not provided as a formal recommendation. The 2021 ESC/EACTS revised its 2017 criteria to emphasize Heart Team involvement in SAVR vs. TAVI decision-making, stating that the choice 'must be based upon careful evaluation of clinical, anatomical and procedural factors by the Heart Team' (COR I LOE C).[4]

While multidisciplinary care has always existed, the contemporary Heart Team approach was initially designed for eligibility evaluation in the SYNTAX (NCT00114972) and subsequently PARTNER (NCT00530894) trials, as well as the commercially funded Medtronic CoreValve Trial (NCT01240902). In the USA, formalization of the Heart Team approach was incentivized by Medicare and Medicaid reimbursement rules, which required that TAVIs be conducted jointly with an interventional cardiologist and cardiac surgeon.[17] Although the origins and context-specific implementation of the Heart Team may differ between countries, the Heart Team has expanded to become central to both the American and European guidelines on AS.[18]

Observational studies examining the Heart Team approach to coronary artery disease (CAD) have found it results in a formalized decision-making process while introducing perspectives possibly associated with improved clinical outcomes. However, there remains a need to study the potential benefits of a Heart Team approach and factors central to its posited success, which may vary by region and healthcare system.[17,19]

B. Risk stratification

TAVI vs. SAVR decision-making is now mainly based on predicted life expectancy in relation to prosthetic durability and patient preferences.

Table 1 Heart team management and risk scores

2020 ACC/AHA guideline[5]	2021 ESC/EACTS guideline[4]	Comparison of the evidence
Heart Team Management and Heart Valve Centre		
2.6. COR 1 LOE C-EO: patients with severe VHD should be evaluated by a Multidisciplinary Heart Valve Team when intervention is considered. **2.6.** COR 2a LOE C-LD: consultation with or referral to a Primary or Comprehensive Heart Valve Centre is reasonable when treatment options are being discussed for (i) asymptomatic patients with severe VHD, (ii) patients who may benefit from valve repair vs. valve replacement, or (iii) patients with multiple comorbidities for whom valve intervention is considered.	**5.2.3.** COR I LOE C: 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. **5.2.3.** COR I LOE 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.	Comparable recommendations. Shared Evidence: 2019 Association for Thoracic Surgery, American College of Cardiology, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons expert consensus systems of care document: a proposal to optimize care for patients with valvular heart disease.[6]
Risk scores		
2.5. COR 1 LOE C-EO: for patients with VHD for whom intervention is contemplated, individual risks should be calculated for specific surgical and/or transcatheter procedures, using online tools when available, and discussed before the procedure as a part of a shared decision-making process.	No specific recommendations.	ACC/AHA Evidence: references the Society of Thoracic Surgeons Adult Cardiac Surgery Database for surgical morbidity and mortality risks.[7] References several TAVI risk prediction tools derived from observational cohort and registry studies.[8–12] Cited observational studies and one review to emphasize the importance of frailty assessments.[13–16]

ACC, American College of Cardiology; AHA, American Heart Association; COR, Class of Recommendation; EACTS, European Association for Cardio-Thoracic Surgery; EO, consensus opinion of experts based on clinical experience; ESC, European Society of Cardiology; LD, non-randomized observational studies with limitations in design or execution or meta-analysis of such studies, LOE, level of evidence; TAVI, transcatheter aortic valve implantation; VHD, valvular heart disease.

However, risk scores remain one central aspect of the preprocedural workup in patients with AS. Both the ESC/EACTS and ACC/AHA support the Society of Thoracic Surgeons' Predicted Risk of Mortality (STS-PROM) score, the most widely used risk score throughout both guidelines to assess suitability for surgery. Although this is a COR 1 recommendation by the ACC/AHA (the ESC/EACTS make no formal recommendations regarding the choice of risk scores), both groups acknowledge that risk scores are only one component of overall Heart Team discussions that incorporate clinical status, anatomy and patient preferences (*Table 1*).[4,5]

Another major consideration of risk stratification is frailty when considering SAVR or TAVI intervention. Both the ESC/EACTS and the ACC/AHA guidelines recommend using quantitative and standardized frailty scores, such as the Katz Index of Independence.[4,5] The ACC/AHA goes further to establish a cut-off of two on the Katz Index as 'prohibitive surgical risk'.[5]

The ESC/EACTS and ACC/AHA also concur on their definition of 'futility' for AS patients undergoing evaluation for SAVR as <12 months of life expectancy. This is briefly mentioned by the ACC/AHA but elaborated on by the ESC/EACTS via supplementary tables with detailed factors that impact futility such as STS-PROM, frailty, malnutrition, major organ failure, and cognitive dysfunction.[4]

II. Timing and thresholds for intervention

In the following sections, we present an algorithm that unifies both guidelines for managing AS (*Figure 1*) and deconstructs the sequential approach to the timing of intervention (*Figure 2*).

A. Symptomatic aortic stenosis

Both the ESC/EACTS and ACC/AHA make a COR I/1 for intervention in symptomatic patients with severe high-gradient AS.[4,5] The European guidelines consider this recommendation to be supported with an LOE B instead of its LOE A designation in the American guidelines (*Table 2*). The ESC/EACTS's lower LOE may be explained by its cited evidence of natural history studies from 1988 and 1990.[20,21] In addition to natural history studies, the ACC/AHA guidelines referenced more recent STS risk models and observational studies[20,22,23] and the PARTNER 1B trial, which demonstrated improved survival outcomes with TAVI compared with medical therapy for symptomatic patients at prohibitive surgical risk.[24]

Low-flow low-gradient aortic stenosis with reduced left ventricular ejection fraction

Low-flow low-gradient (LFLG) AS may be categorized as either 'classical AS' or 'paradoxical AS' based on left ventricular ejection fraction (LVEF). In 'classical' LFLG AS with an LVEF <50%, it becomes crucial to distinguish between true-severe and pseudo-severe AS, as the former must be corrected with valve replacement and the latter is treated with medical therapy for underlying cardiomyopathy.[35] Both guidelines require dobutamine stress echocardiography (DSE) to confirm the presence of true-severe AS, upon which the European guidelines concur in a COR I/1 LOE B recommendation for intervention (*Table 2*).[4,5]

Unfortunately, the utility of DSE becomes limited in situations where the contractile reserve is <20% and aortic valve area cannot be accurately predicted using the continuity equation. Other non-invasive modalities

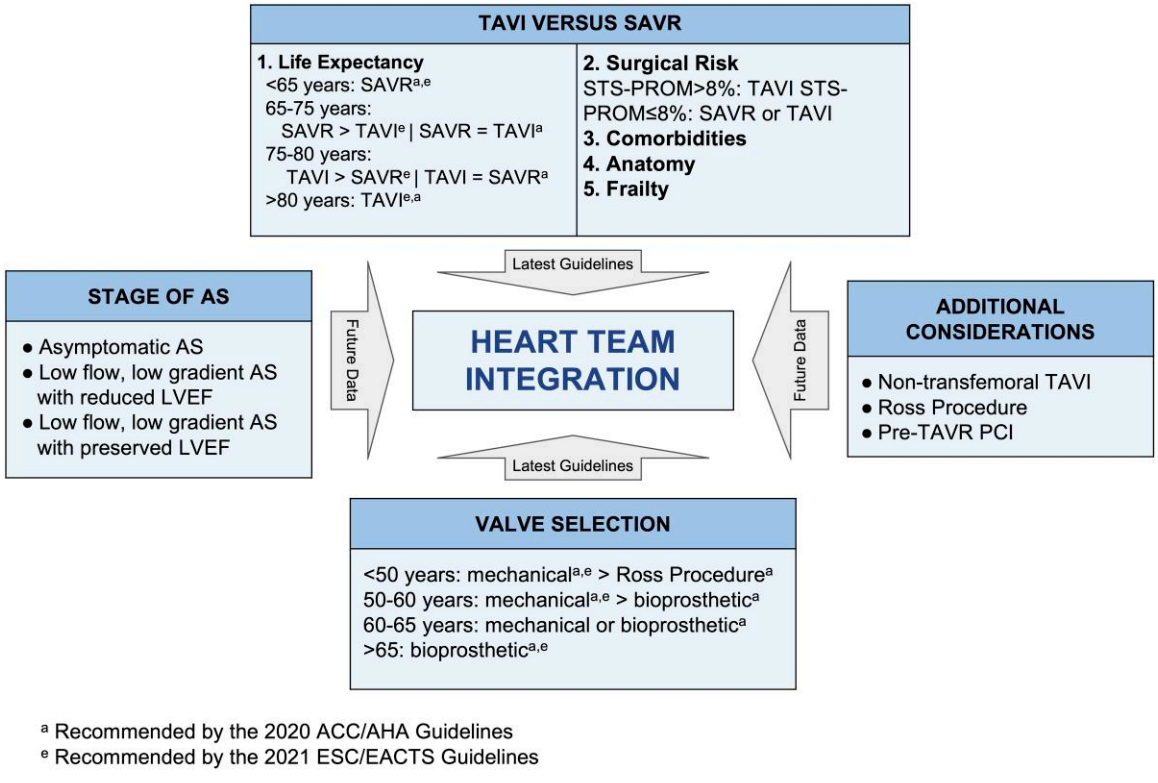

Figure 1 Factors influencing mode of intervention in aortic stenosis. AS, aortic stenosis; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons' Predicted Risk of Mortality; TAVI , transcatheter aortic valve implantation.

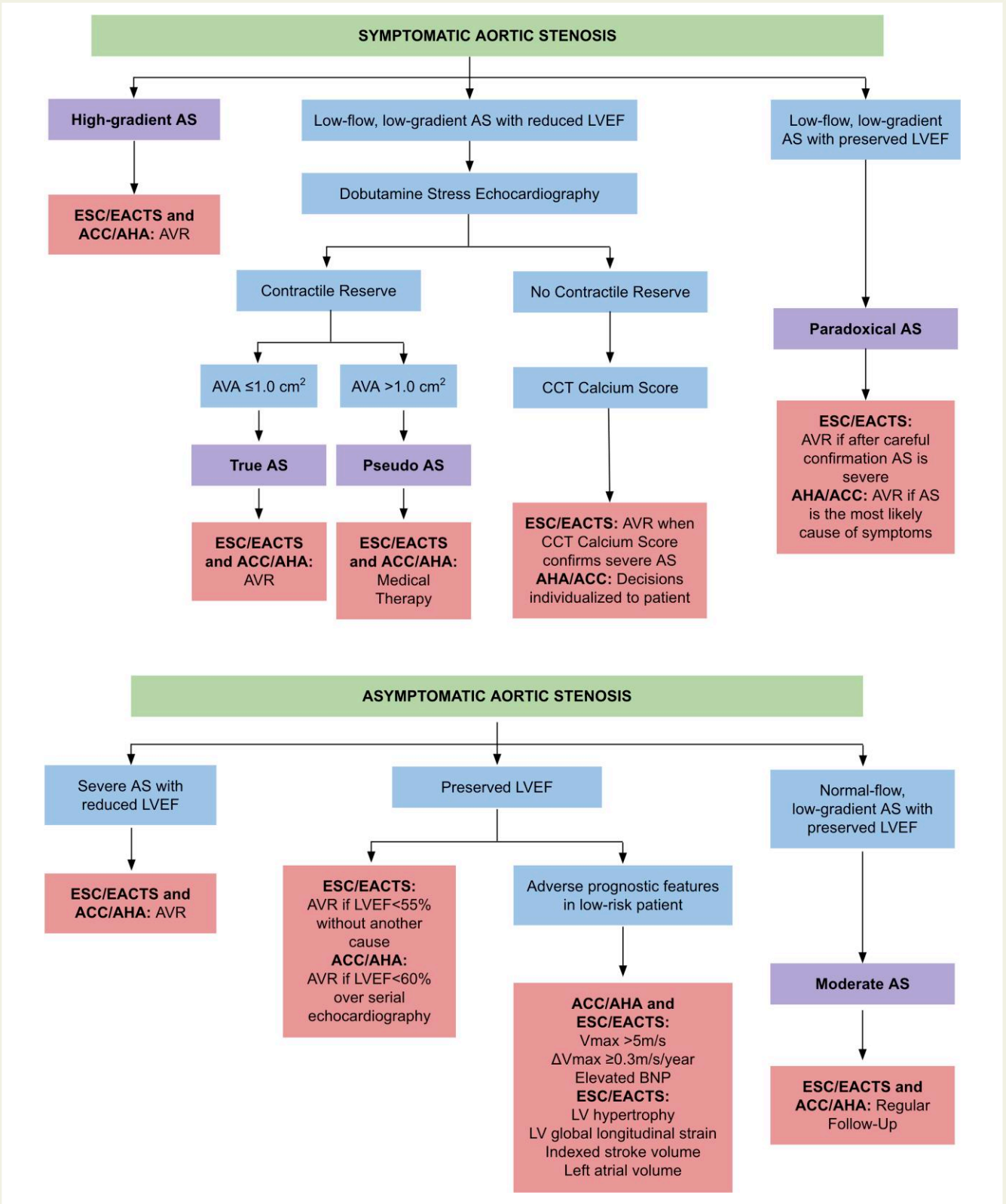

Figure 2 ESC/EACTS vs. ACC/AHA on timing of intervention. AS, aortic stenosis; BNP, blood natriuretic peptide; CCT, Cardiac CT; LVEF, left ventricular ejection fraction.

Table 2 Symptomatic aortic stenosis

2020 ACC/AHA guideline[5]	2021 ESC/EACTS guideline[4]	Comparison of the evidence
High-gradient severe AS		
3.2.3. COR 1 LOE A: in adults with severe high-gradient AS and symptoms of exertional dyspnoea, HF, angina, syncope, or presyncope by history or on exercise testing, AVR is indicated.	**5.2.1.** COR I LOE B: intervention is recommended in symptomatic patients with severe, high-gradient AS.	Shared Evidence: natural history studies of symptomatic AS.[20,21] ACC/AHA Evidence: O'Brien et al. (2009): STS risk models for isolated valve surgery, including AVR.[22] Kvidal et al. (2000): observational study of 2359 patients which found excellent long-term survival after AVR.[23] PARTNER 1B Trial[24]
Low-flow low-gradient severe as with reduced LVEF		
3.2.3. COR 1 LOE B-NR: AVR is recommended in symptomatic patients with LFLG severe AS with reduced LVEF.	**5.2.1.** COR I LOE B: intervention is recommended in symptomatic patients with severe LFLG AS with reduced LVEF and evidence of flow (contractile) reserve. **5.2.1.** COR IIa LOE C: intervention should be considered in symptomatic patients with severe LFLG AS with reduced LVEF without flow (contractile) reserve, particularly when CCT calcium scoring confirms severe AS.	ESC/EACTS Evidence: Monin et al. (2003): prospective cohort study of 136 patients with low-gradient AS undergoing AVR. Found no contractile reserve to be a predictor of periprocedural mortality.[25] Tribouilloy et al. (2009): prospective cohort of 81 patients with LFLG AS found AVR to be associated with higher 5-year survival compared with medical therapy.[26] TOPAS-TAVI registry for possible role of TAVI.[27] ACC/AHA Evidence: no specific recommendations for low contractile reserve. The role of TAVI is unclear.
Low-flow low-gradient severe AS with preserved LVEF		
3.2.3. COR 1 LOE B-NR: in symptomatic patients with LFLG severe AS with normal LVEF, AVR is recommended if AS is the most likely cause of symptoms. E.g. a severely calcified aortic valve, an aortic velocity <4.0 m/s (mean pressure gradient <40 mmHg), and a valve area ≤1.0 cm^2 when stroke volume index is <35 mL/m^2. Requires additional testing e.g. aortic valve area index, Doppler and CCT calcium score.	**5.2.1.** COE IIa LOE C: intervention should be considered in symptomatic patients with LFLG (<40 mmHg) AS with normal ejection fraction after careful confirmation that the aortic stenosis is severe.	ESC/EACTS Evidence: four prospective studies performed before 2015:[28–31] Jander et al. (2011) Retrospective cohort study comparing patients with LFLG severe AS and preserved LVEF ($n = 435$) to patients with low-gradient moderate AS ($n = 184$) with preserved LVEF. Outcome: aortic valvular events: congestive heart failure due to AS, aortic valve replacement, cardiovascular mortality. Conclusion: patients with LFLG 'severe' AS and preserved LVEF have similar outcomes as 'moderate' AS. Clavel et al. (2012) Prospective cohort study comparing paradoxical LFLG severe AS with preserved LVEF (187 patients) to those with high-gradient severe AS with preserved LVEF ($n = 187$) and moderate AS ($n = 187$) Outcome: patients with LFLG severe AS had reduced overall 1-year survival. AVR in the LFLG severe AS group was associated with improved survival. Mehrotra et al. 2013 Retrospective cohort study comparing LFLG severe AS ($n = 38$) with preserved LVEF vs. normal-flow LG severe AS ($n = 75$) vs. moderate AS ($n = 70$). Outcome: all-cause mortality after 3 years Conclusions: 3-year survival significantly lower in LFLG severe AS compared with both other groups Tribouilloy et al. (2015) Prospective study of 809 AS patients (57 patients had LFLG AS and preserved LVEF) undergoing real-world treatment Outcome: patients with LFLG AS with preserved LVEF had similar prognosis to moderate-severe AS ACC/AHA Evidence: 3 post-2015 prospective cohort studies:[32–34] Zheng et al. (2017): network meta-analysis comparing (a) LFLG severe AS vs. (b) low-flow high-gradient AS vs. (c) moderate AS vs. (d) normal-flow high-gradient AS

Continued

Table 2 *Continued*

2020 ACC/AHA guideline[5]	2021 ESC/EACTS guideline[4]	Comparison of the evidence
		vs. (e) normal-flow low-gradient AS in 15 studies and 9737 patients. Outcome: all-cause mortality. Conclusions: low-flow states of AS were associated with increased risk of mortality compared with moderate AS and normal-flow AS. Rusinaru et al. (2018): prospective cohort study comparing low-flow aortic stenosis ($n = 190$) vs. moderate ($n = 221$) and high-flow AS ($n = 1039$) in patients with preserved LVEF. Outcome: 5-year all-cause mortality. Conclusions: low-flow severe AS with preserved LVEF is associated with a higher mortality rate. Eleid et al. (2019): prospective cohort study evaluating TAVI for LFLG severe AS with LVEF. Outcome: increase in flow post-TAVI, indicating positive hemodynamic benefits.

Abbreviations as in *Table 1*. AS, aortic stenosis; AVR, aortic valve replacement; BNP, B-type natriuretic peptide; BP, blood pressure; CCT, cardiac computed tomography; LVEF, left ventricular ejection fraction; LFLG, low-flow, low-gradient; NR, non-randomized evidence.

have been suggested for these patients, such as multi-slice computed tomography (CT), cardiac magnetic resonance imaging, positron emission tomography scan, and B-type natriuretic peptide (BNP) levels.[36] Unlike their American counterparts, the ESC/EACTS makes an additional COR IIa LOE C recommendation for intervention in LFLG AS without contractile reserve, 'particularly when cardiac CT (CCT) calcium scoring confirms severe AS' (*Table 2*).[4] Overall, there is sparse and conflicting evidence in patients with LFLG AS without contractile reserve, as exemplified by small registries such as the TOPAS-TAVI study by Ribeiro and colleagues which found DSE to be an unreliable predictor of severe AS, and thus clinical outcomes.[37] The European guidelines acknowledge historical evidence indicating that LFLG AS patients without contractile reserve who undergo TAVI or SAVR have higher periprocedural mortality, but also emphasize findings from Tribouilloy and colleagues that patients who survive intervention have enjoyed better LVEF and long-term outcomes than traditional medical management.[4,25,26] The COR IIa recommendation can be seen as tolerating greater operative risk to avoid underestimating the severity of AS. Nonetheless, it is contextualized by stating that 'decision-making for such patients should take account of co-morbidities, degree of valve calcification, extent of CAD, and feasibility of revascularization'.[4] In contrast, the ACC/AHA speculates these high-risk patients may also benefit from SAVR but decisions 'must be individualized because outcomes are poor with either surgical or medical therapy'.[5]

Regarding the mode of intervention, the ACC/AHA primarily recommends SAVR for LFLG AS with reduced LVEF, stating 'the role TAVI in these patients is under investigation'.[5] The ESC/EACTS cites a substudy of the TOPAS-TAVI Registry, implying that TAVI can be used for this patient population, but this lacked a SAVR comparison group.[27] A 2014 GARY registry study reported higher rates of post-TAVI mortality in those with low-gradient AS with reduced ejection fraction compared with patients with high-gradient AS.[38]

Low-flow low-gradient aortic stenosis with preserved left ventricular ejection fraction

Approximately 10%–15% of patients have LFLG AS with preserved LVEF, classified as 'paradoxical AS'. Much remains uncertain about paradoxical AS, which is reflected by the ESC/EACTS' recommendation for an 'integrated approach' in their *Figure 3* algorithm ending in CCT assessment, and intervention 'after careful confirmation that the AS is severe' (COR IIa LOE C).[4] The ACC/AHA guidelines more specifically state 'aortic valve replacement is recommended if AS is the most likely cause of symptoms', which may be suspected for a 'severely calcified aortic valve and a valve area $\leq 1.0\ cm^2$' (COR 1 LOE B-NR).[5] The ESC/EACTS states that data surrounding valve intervention is 'controversial' in paradoxical AS which contrasts the ACC/AHA's stronger COR 1 (*Table 2*).[4] Three cohort studies are cited as providing unclear implications by the ESC/EACTS guidelines, which likely contributed to the COR IIa.[28–30] Two of these studies, by Clavel and colleagues and Mehrotra and colleagues, compared LFLG severe AS to either moderate- or high-gradient severe AS. Both reported that LFLG AS was associated with significantly worse survival, but Clavel and colleagues additionally found that survival could be improved with intervention.[29,30] The third study by Jander and colleagues found LFLG AS with preserved LVEF to have similar outcomes to moderate AS.[28] Another study by Tribouilloy and colleagues was referenced by the European guidelines for normal-flow low-gradient (NFLG) AS, but also supported LFLG AS with preserved LVEF as having a comparable prognosis to mild-to-moderate AS that was not improved with surgery.[31]

By contrast, the ACC/AHA guidelines cite more recent literature to support their COR 1, including a 2018 prospective cohort which found low-flow AS with preserved LVEF to be associated with greater 5-year mortality than moderate or high-flow AS.[32] Finally, while the benefit of TAVI is deemed unclear by the ESC/EACTS, the ACC/AHA cites a small prospective cohort of patients with paradoxical AS who exhibited an increase in post-TAVI valvular flow, thus indicating its positive hemodynamic benefits.[33]

B. Asymptomatic aortic stenosis

Left ventricular ejection fraction

Asymptomatic AS presents ongoing challenges to the timing of the intervention. The potential benefits of valve replacement in asymptomatic AS must be weighed against the risks of surgery. One major consideration is LVEF.

NFLG AS with preserved LVEF is the most common form of low-gradient AS and can present with or without symptoms. When asymptomatic, NFLG AS is considered to be 'moderate' by both European and North American guidelines.[4,5] Regular follow-up is recommended as the patient can deteriorate rapidly into symptomatic severe AS, at which point intervention is necessary.

Both the ESC/EACTS and ACC/AHA guidelines recommend valve intervention in patients with asymptomatic severe AS and LVEF <50% (COR I/1 LOE B).[4,5] Notably, both guidelines introduced recommendations for intervention in patients with asymptomatic AS and LVEF >50%, which were not specifically defined in previous versions. The ACC/AHA states that aortic valve replacement may also be considered in those with severe high-gradient AS (Stage C1) and progressive decrease in LVEF over three serial imaging studies to <60% (COR 2b LOE B-NR).[5] Likewise, a COR IIa was added to the 2021 ESC/EACTS guidelines specifying that asymptomatic AS with an LVEF <55% could be considered for intervention 'in the absence of another cause' (*Table 3*).[4]

In the absence of adverse features (see below), the optimal LVEF threshold for asymptomatic patients remains controversial and both groups reference the same cohort studies.[39,40] The ESC/EACTS recommends a threshold of LVEF <55% based on Bohbot and colleagues' findings that patients with LVEF <55% displayed higher mortality compared with LVEF ≥60%'.[40] The ACC/AHA establishes a higher LVEF cut-off of <60% (outlined by Lancellotti and colleagues[39]) but requires echocardiography to show a progressive decline in LVEF over three serial examinations which may reduce the impact of inter-rater differences in performing and interpreting imaging. As such, the serial decline required for intervention by the ACC/AHA guidelines may be considered by some to be more conservative despite having a higher LVEF threshold than the European guidelines.

The new ESC/EACTS recommendation for intervention with low-risk patients with an LVEF >55% and an aortic Vmax of ≥5 m/s reflect the potential survival benefits of early SAVR in asymptomatic AS, shown by the RECOVERY trial.[41] The 2021 AVATAR trial was the first RCT to implement systematic exercise testing and conventional echocardiographic assessments to isolate truly asymptomatic severe AS. Although its results were published after the most recent guidelines were released, AVATAR found that early SAVR likewise reduced major adverse cardiovascular and cerebrovascular events compared with conservative management.[56] These trials align with previous studies that informed the decision to lower Vmax from ≥5.5 m/s to ≥5 m/s[57] and establish a 60 mmHg mean gradient cut-off,[39,48] marking the first time the ESC/EACTS and ACC/AHA have aligned in their definitions of very severe AS. In Europe, the new criteria will allow more low-risk patients to receive early intervention.

Adverse prognostic features

In asymptomatic patients, the ACC/AHA and ESC/EACTS endorse exercise stress testing and subsequent intervention with decreased exercise tolerance, irrespective of LVEF. Both guidelines also identify other adverse prognosticators for early intervention such as Vmax >5 m/s, Vmax progression ≥0.3 m/s/year, or elevated BNP (COR II/2a LOE B for both guidelines), but only when procedural risk is low.[4,5] Although not official recommendations, the ESC/EACTS also consider left ventricular hypertrophy and global longitudinal strain, indexed stroke volume, and left atrial volume as additional criteria for intervention in low-risk patients.[4]

Regular follow-up

For asymptomatic patients with severe AS who are deemed inappropriate for intervention, follow-up via serial testing is strongly recommended by the ESC/EACTS due to the potential for rapid deterioration. Although not official recommendations, the European guidelines emphasize a minimum of 6-month follow-ups for severe AS, serial echocardiograms, exercise testing for early symptom detection, and BNP levels.[4]

C. Concomitant cardiac surgery

The American guidelines advise patients with asymptomatic severe AS already undergoing cardiac surgery to receive concomitant SAVR, as it may diminish the risks associated with late intervention and redo TAVI (COR 1 LOE B-NR).[5] The ESC/EACTS does not directly recommend intervention with cardiac surgery for patients with asymptomatic AS (*Table 3*).[4] However, the European guidelines provide a general recommendation of SAVR for patients with severe AS (COR 1 LOE C) and or moderate AS (COR 2a LOE C) undergoing coronary artery bypass grafting (CABG) or surgical intervention on the ascending aorta or another valve.[4]

D. Tavi vs. savr

The decision-making algorithm for TAVI vs. SAVR is discussed in detail in Section V. In the context of asymptomatic AS, the ACC/AHA applies the same TAVI vs. SAVR treatment selection algorithm as symptomatic patients despite lacking randomized evidence (COR 1 LOE B-NR).[5] The ESC/EACTS avoids this liberal approach by stating that suitability for TAVI is determined by the Heart Team once the intervention has already been decided and defers to future RCT evidence from EARLY TAVR (NCT03042104), EASY-AS (NCT04204915) and EVoLVeD (NCT03094143) for guidance (*Table 4*).[4] Notably, whereas the presence of adverse prognosticators was previously an indication for SAVR alone, the 2021 ESC/EACTS guidelines have expanded intervention options to include TAVI.

IV. Bioprosthetic vs. mechanical valve

A. Age thresholds

The choice between bioprosthetic vs. mechanical aortic valve repair has become increasingly complicated with the rise of TAVI, especially the potential for valve-in-valve interventions following bioprosthetic failure. The ESC/EACTS and ACC/AHA guidelines agree that valve choice is influenced by Heart Team discussion, informed patient preferences, and contraindications to anticoagulation (COR I/1 LOE C) but differ in

Table 3 Asymptomatic aortic stenosis

2020 ACC/AHA guideline[5]	2021 ESC/EACTS guideline[4]	Comparison of the evidence
3.2.3. COR 1 LOE B-NR: in asymptomatic patients with severe AS and LVEF < 50%, AVR may be considered. **3.2.3.** COR 2b LOE B-NR: in asymptomatic patients with severe high-gradient AS and a progressive decrease in LVEF on at least 3 serial imaging studies to <60%, AVR may be considered.	**5.2.2.** COR I LOE B: intervention is recommended in asymptomatic AS and systolic LV dysfunction (LVEF <50%) without another cause. **5.2.2.** COR IIa LOE B: intervention should be considered in asymptomatic AS and LV systolic dysfunction (LVEF <55%) without another cause.	Shared Evidence: Bohbot et al. (2019) and Lancellotti et al. (2018).[39,40] Bohbot et al. (2019): cohort study examining conservative vs. surgical management in patients with asymptomatic AS and various LVEFs: < 55% ($n = 239$), 55%–59% ($n = 331$) and ≥ 60% ($n = 1108$). Outcomes: 5-year mortality Conclusions: patients with LVEF <55% had higher mortality rates compared with both LVEF 55%–60% ($P < 0.001$) and LVEF >60% ($P < 0.001$). Patients with LVEF 55%–60% and >60% had a comparable prognosis. In patients with LVEF <55%, initial surgical management reduces all-cause mortality risk ($P < 0.001$). Lancellotti et al. (2018): registry cohort study of the natural history of 1375 patients with asymptomatic AS. Outcomes: patients with severe AS at baseline, Vmax >5 m/s and LVEF <60% were at increased risk of all-cause mortality. Anticipating trials on the suitability of TAVI for asymptomatic disease such as RECOVERY.[41]
Exercise testing		
3.2.3. COR 2a LOE B-NR: in apparently asymptomatic patients with severe AS and low surgical risk, AVR is reasonable when: (1) Exercise test demonstrates decreased exercise tolerance (normalized for age and sex) or a fall in SBP of ≥10 mm Hg from baseline to peak exercise. (2) Serum B-type natriuretic peptide (BNP) level is >3 times normal 3. At least 3 serial imaging studies shows an increase in aortic velocity ≥0.3 m/s per year. **3.2.3.** COR 2a LOE B-R: In asymptomatic patients with very severe AS (defined as an aortic velocity of ≥5 m/s) and low surgical risk, AVR is reasonable.	**5.2.2.** COR I LOE C: intervention is recommended in asymptomatic patients with demonstrable symptoms on exercise testing. **5.2.2.** COR IIa LOE B: intervention should be considered in asymptomatic patients with LVEF >55% and a normal exercise test if the procedural risk is low and one the following parameters is present: (1) very severe aortic stenosis (mean gradient ≥60 mmHg or Vmax >5 m/s). (2) Severe valve calcification (ideally assessed by CCT) and Vmax progression ≥ 0.3 m/s/year. (3) Markedly elevated BNP levels (>3 × age- and sex-corrected normal range) confirmed by repeated measurements and without other explanation. **5.2.2.** COR IIa LOE C: intervention should be considered in asymptomatic patients with a sustained fall in BP (>20 mmHg) during exercise testing.	ACC/AHA Evidence: prospective cohort studies and registry studies to support use of exercise testing and BNP levels.[42–46] Peak aortic Vmax supported by registry studies and the RECOVERY trial which set the inclusion criteria for early surgery as Vmax ≥4.5 m/s.[39,41,47] ESC/EACTS Evidence: recommendations surrounding peak aortic Vmax and mean gradient were supported by prospective cohort and retrospective database studies.[39,48] CCT scoring and progression of Vmax recommendations supported by a 2018 registry study[49] and historical studies from 2000 to 1997.[48,50,51] BNP recommendations supported by 2 large studies completed in 2014 (one registry study and one prospective cohort study).[52,53]
Concomitant cardiac surgery		
3.2.3. COR 1 LOE B-NR: in asymptomatic patients with severe AS who are undergoing cardiac surgery for other indications, AVR is indicated.	No specific recommendations.	ACC/AHA Evidence: prospective cohort studies examining the risk factors for asymptomatic AS are cited to suggest a lower risk associated with concomitant AVR than future reoperation.[39,41,54,55]

Abbreviations as in *Tables 1* and *2*. LV, left ventricular; SBP, systolic blood pressure.

recommended age thresholds.[4,5] The ACC/AHA states that 'patients <50 years without contraindications to anticoagulation should get mechanical aortic prosthesis', 'patients >65 years should get a bioprosthetic valve' and shared decision-making and patient factors should determine valve choice for 50–65 years (COR 2a LOE B-NR).[5] Meanwhile, the ESC/EACTS guidelines state that mechanical valves should be considered in patients <60 years (COR IIa LOE B), and bioprosthetic valves in patients >65 years (COR IIa LOE C) (*Table 5*).[4]

Both the ACC/AHA and ESC/EACTS reference a 2017 retrospective cohort study by Goldstone and colleagues that found mechanical prostheses were associated with lower 15-year mortality for ages 45–54 but similar survival in ages >55.[58] Additionally, retrospective data showed comparable long-term survival in ages 50–65[96] and an RCT by Stassano and colleagues in ages 55–70 found a long-term survival advantage but increased risk of bioprosthetic valve failure beginning at 10 years of follow-up.[62] Of note, this was not performed with contemporary

Table 4 Mechanical vs bioprosthetic valve

2020 ACC/AHA guideline[5]	2021 ESC/EACTS guideline[4]	Comparison of the evidence
3.2.4. COR 1 LOE C-EO: the choice of prosthetic valve should be based on a shared decision-making process that accounts for the patient's values and preferences and includes a discussion of the indications for and risks of anticoagulant therapy and the potential need for and risks associated with valve reintervention. **3.2.4.** COR 1 LOE C-EO: for patients of any age requiring AVR for whom VKA anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired, a bioprosthetic AVR is recommended	**11.1.** COR I LOE C: a mechanical prosthesis is recommended according to the desire of the informed patient and if there are no contraindications to long-term anticoagulation. **11.1.** COR I LOE C: a bioprosthesis is recommended according to the desire of the informed patient. **11.1.** COR I LOE C: a bioprosthesis is recommended when good-quality anticoagulation is unlikely and in those patients whose life expectancy is lower than the presumed durability of the bioprosthesis.	Recommendations based largely on expert opinion instead of evidence for both guidelines.
3.2.4. COR 2a LOE B-R: for patients <50 years without contraindications to anticoagulation, it is reasonable to choose a mechanical aortic prosthesis over a bioprosthetic valve. **3.2.4.** COR 2a LOE B-R: for patients >65 years of age who require AVR, it is reasonable to choose a bioprosthesis over a mechanical valve. **3.2.4.** COR 2a LOE B-NR: for patients 50–65 years of age who require AVR and who do not have a contraindication to anticoagulation, it is reasonable to individualize the choice of either a mechanical or bioprosthetic AVR with consideration of individual patient factors and after informed shared decision-making.	**11.1.** COR IIa LOE B: a mechanical prosthesis should be considered in patients aged <60 years. **11.1.** COR IIa LOE C: a bioprosthetic valve should be considered in patients >65 years of age.	Shared Evidence: Goldstone et al. (2017):[58] prospective cohort study following close to 10 000 patients from 1996 to 2013. Outcome: mechanical prosthesis was associated with lower 15-year mortality for patients of 45–54 years only. ACC/AHA Evidence: large retrospective studies examining older valves for 50–65 range, with all studies published near or before 2010.[59–61] For >60 age group: supported by a randomized trial by Stassano et al. examining mechanical AVR vs. bioprosthetic AVR in patients 55–70 years of age. Found that 10-year risk of bioprosthetic valve failure was significantly increased.[62] Acknowledges lack of definitive data about anticoagulation vs. deterioration for 50–65 age group. ESC/EACTS Evidence: more contemporary studies; 2 systematic reviews by Head et al. (2017) and Diaz et al. (2019) to support age thresholds.[63,64]
11.2. COR 2a LOE B-R: for patients with a bioprosthetic TAVI, aspirin 75–100 mg daily is reasonable in the absence of other indications for oral anticoagulants. **11.2.** COR 2b LOE B-NR: for patients with a bioprosthetic TAVI who are at low risk of bleeding, anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after valve implantation.	**11.3.** COR I LOE B: OAC is recommended lifelong for TAVI patients who have other indications for OAC. **11.3.** COR I LOE A: lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC.	Shared Evidence: Maes et al. (2018): SAPT vs. DAPT showed higher rates of adverse events with DAPT with a lack of clinical benefits on ischaemic events.[65] ACC/AHA Evidence: Rodés-Cabau et al. (2017): ARTE trial of SAPT vs. DAPT ($n = 222$) following TAVI indicating SAPT was superior in reducing adverse events.[66] Zuo et al. (2019): meta-analysis of SAPT vs. DAPT showing decreased 30-day mortality associated with SAPT.[67] Jochheim et al. (2019): prospective cohort studies ($n = 962$) showed NOACs and VKAs had comparable 1-year bleeding but VKAs had fewer events.[68] Jose et al. (2017): retrospective cohort study showing that OACs prevented transcatheter valve thrombosis.[69] Makkar et al. (2015) and Chakravarty et al. (2019): secondary analyses RCTs showing that OACs improved valve hemodynamics after TAVI.[70,71] ESC/EACTS Evidence: Brouwer et al. (2020): RCT ($n = 331$) of SAPT vs. DAPT in TAVI patients with no other indication for anticoagulation showed fewer adverse bleeding events with SAPT.[72] Nijenhuis et al. (2020): RCT ($n = 157$) of SAPT vs. DAPT in TAVI patients showed that 1-month and 1-year bleeding was lower in SAPT.[73]

Continued

Table 4 *Continued*

2020 ACC/AHA guideline[5]	2021 ESC/EACTS guideline[4]	Comparison of the evidence
3.2.4. COR 2b LOE B-NR: in patients <50 years of age who prefer a bioprosthetic AVR and have appropriate anatomy, replacement of the aortic valve by a pulmonic autograft (the Ross procedure) may be considered at a Comprehensive Valve Centre.	No specific recommendations. '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 survival rates and valve-related reoperation that are comparable to those achieved with a mechanical heart valve, but high expertise in aortic root surgery is required.'	ACC/AHA Evidence: three observational studies support increased survival benefits of the Ross procedure over a wide age range and long follow-up times.[74–76] ESC/EACTS Evidence: David et al. (2019): observational study of young patients for 18 years.[77] Newer observational studies contribute mounting evidence which may impact future recommendations.

Abbreviations as in *Tables 1–3*. VKA , vitamin K antagonist; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy; OAC, oral anticoagulant; NOAC, non-vitamin K antagonist oral anticoagulant.

bioprosthetic valves and more recent studies were not cited in the ACC/AHA guidelines.[97,98] The European guidelines include more contemporary literature, such as a 2017 systematic review of observational studies by Head and colleagues which favours mechanical valves for patients <60 years of age.[63] Another meta-analysis by Diaz and colleagues stated that mechanical valves had a mortality benefit between 50 and 70 years (*Table 5*).[64] Although mechanical prostheses have demonstrated lower long-term reoperation risk, the overall survival benefit has only been shown in few studies that predominantly examined young patients.

The shift towards patient-centred care combined with greater confidence in the durability of bioprosthetic valves has led to a surge in the number of bioprosthetic AVRs, with Goldstone and colleagues reporting an increase from 11.5% in 1996 to 51.6% in 2013.[58] Similarly, an analysis of the STS Adult Cardiac Surgery Database found that the percentage of mechanical AVRs declined dramatically from 2004 to 2016.[99] Part of this change may be attributed to a shifting attitude toward avoiding lifelong anticoagulation in younger patients. This is likely combined with assumptions that newer generation bioprosthetic valves are long-lasting and that valve-in-valve TAVI can be performed to salvage a degenerated valve. The ACC/AHA emphasizes the importance of shared decision-making that considers patient preferences, anticoagulation, and reintervention risk (COR 1 LOE C-EO) (*Table 5*).[5] With regard to anticoagulation, the ACC/AHA guidelines recommend aspirin of 75–100 mg daily following TAVI as a COR 2a recommendation. VKA anticoagulation is only COR 2b for TAVI indicating greater uncertainty.[5] On the other hand, the ESC/EACTS does not provide specific recommendations for TAVI patients other than recommending lifelong single antiplatelet therapy, with oral anticoagulation reserved for patients with other indications as COR I.[4] The importance of patient preference may be greatest in treatment decisions where there is uncertainty in long-term risks and benefits. In this scenario, a careful explanation of different strategies should be clearly presented to the patient and their preference may be the ultimate arbitrator in decision-making.

B. Ross procedure

Renewed interest in the Ross procedure highlights another option in young-to-middle aged patients with AS. The Ross procedure involves implanting the patient's own pulmonary valve in the aortic position and replacing the right ventricular outflow with a cadaveric pulmonary homograft.[100–103] The ACC/AHA and ESC/EACTS, respectively, state that a Ross procedure may be considered 'in patients <50 years of age [with] appropriate anatomy […] at a comprehensive valve centre' (COR 2b LOE B-NR)[5] or in 'selected patients […] but high expertise in aortic root surgery is required'[4] (*Table 5*). Although early iterations of the Ross procedure suffered from higher rates of valve failure, observational studies since have suggested improved long-term survival when compared with mechanical or bioprosthetic SAVR.[100–103] The ESC/EACTS and ACC/AHA both cite observational studies but generally consider the evidence insufficient for a strong recommendation given concerns for confounding and bias. While outcomes have been excellent from centres of expertise, observations from the STS Adult Cardiac Surgical Database show that early mortality is 2.7% across American centres; more than double that of conventional SAVR.[104] Thus, poor generalizability of this procedure limits its COR. Thus, the ESC/EACTS and ACC/AHA guideline statements that a Ross procedure 'may be performed' is appropriate given the current state of evidence but may strengthen should encouraging data continue to accumulate (*Table 5*).

V. Tavi vs. SAVR

Supplementary material online, *Figure S1* summarizes key considerations in the decision-making process between TAVI and SAVR.

A. Risk categories and age thresholds

In the past two decades, landmark trials such as PARTNER 1A and the CoreValve High Risk Study have shown that TAVI is an effective alternative for patients at high surgical risk. Based on this evidence, both the ESC/EACTS and ACC/AHA guidelines recommend TAVI over medical therapy for patients for whom surgery is prohibitive or with STS-PROM/EuroSCORE II >8% (COR I/1 LOE A) (*Table 4*).[4,5] More recently, PARTNER 3 and the Evolut Low Risk Trial demonstrated 1-year superiority and 2-year non-inferiority of TAVI in low-risk groups, respectively.[78,80]

Previous ACC/AHA and ESC/EACTS guidelines based their TAVI recommendations on risk scores. With TAVI now considered across the risk spectrum in elderly patients, both guidelines have highlighted age (surrogate for life expectancy) as the main consideration after accounting for patient preferences, comorbidities, and anatomical characteristics.[4,5] The ACC/AHA strongly recommends SAVR for ages <65 or with life expectancy >20 years, TAVI for ages >80 or with life expectancy <10 years, and shared decision-making about the'balance between expected patient longevity and valve durability' for ages 65–80 (COR 1

Table 5 SAVR vs. TAVI

2020 ACC/AHA guideline[5]	2021 ESC/EACTS guideline[4]	Comparison of the evidence
Age thresholds		
3.2.4.2. COR 1 LOE A: in symptomatic and asymptomatic patients with severe AS: (1) < 65 years of age or with a life expectancy >20 years, SAVR is recommended. (2) 65–80 years of age and with no anatomic contraindication to transfemoral TAVI, SAVR or transfemoral TAVI is recommended after shared decision-making about the balance between expected patient longevity and valve durability. Consider vascular access, cardiac and non-cardiac factors, function, mechanical vs. prosthetic. 1. > 80 years or for younger patients with a life expectancy <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to SAVR. Consider patient anatomy for balloon-expandable or self-expanding valve.	**5.2.3.** COR I LOE B: SAVR is recommended in younger patients (<75 years) and who are low risk for surgery (STS-PROM/EuroSCORE II <4%) or in patients who are operable and unsuitable for transfemoral TAVI. **5.2.3.** COR I LOE A: TAVI is recommended in older patients (≥75 years), or in those who are high risk (STS-PROM/EuroSCORE II >8%) or unsuitable for surgery. **5.2.3.** COR I LOE B: SAVR or TAVI are recommended for the remaining patients according to individual clinical, anatomical, and procedural characteristics.	ACC/AHA Evidence: PARTNER-3: randomized trial reporting 1-year TAVI superiority compared with SAVR.[78,79] Evolut Low Risk Trial: randomized trial supporting non-inferiority of TAVI at 2 years.[80] Siemieniuk et al. (2016): meta-analysis of 4 RCTs in comparing TAVI to SAVR.[81] Kumer et al. (2019): prospective cohort study ($n = 276$) finding higher rates of valve deterioration amongst young patients.[82] Siontis et al. (2019): meta-analysis of 7 major RCTs and 8020 patients finding that overall TAVI was associated with a reduction of 2-year all-cause mortality regardless of the STS risk score and method of TAVI.[83] ESC/EACTS Evidence: registry data for intermediate and high-risk patients, most of whom were elderly, indicate valve integrity up to 8 years. However, the data for the durability of TAVI for low-risk patients is only available for up to 2 years. Barbanti et al. (2018): REPLACE registry of bioprosthetic valves in 288 patients with a mean age of 80 years. At 8 years after TAVI, bioprosthetic valve failure and severe structural valve dysfunction occurred in 4.5% and 2.4% of patients, respectively.[84] Didier et al. (2018): FRANCE-2 Registry study showing that the rate of severe structural valve deterioration was 2.5% at 5 years and moderate deterioration was 13.3%.[85]
Bicuspid aortic valve		
5.1.2.2. COR 2b LOE B-NR: 2. In patients with BAV and symptomatic, severe AS, TAVI may be considered as an alternative to SAVR after consideration of patient-specific procedural risks, values, trade-offs, and preferences, and when the surgery is performed at a Comprehensive Valve Centre.	No specific recommendations.	ACC/AHA Evidence: Makkar et al. 2019: registry study of 2691 propensity-score matched patients undergoing TAVI for bicuspid vs. tricuspid AS.[86] Takagi et al. (2019): systematic review and meta-analysis of 12 TAVI studies comparing bicuspid vs. tricuspid aortic valves.[87] Kanjanahattakij et al. (2018): systematic review and meta-analysis of nine studies reporting TAVI outcomes in bicuspid vs. tricuspid AS.[88] ESC/EACTS Evidence: Forrest et al. (2020): STS/ACC Transcatheter Valve Therapy Registry study of 932 bicuspid valve patients vs. 26 154 tricuspid valve patients undergoing TAVI.[89] Halim et al. (2020): STS/ACC Transcatheter Valve Therapy Registry study of 5412 bicuspid valve patients tricuspid valve patients undergoing TAVI.[90] Yoon et al. (2017): observational study of 561 patients undergoing TAVI for bicuspid vs. tricuspid AS.[91]
TAVI for asymptomatic AS		
3.2.4.2. COR 1 LOE B-NR: in asymptomatic patients with severe AS and an LVEF <50% who are ≤80 years of age and have no anatomic contraindication to transfemoral TAVI, the decision between TAVI and SAVR should follow	No specific recommendations.	ACC/AHA Evidence: cites the same studies used to inform TAVI vs. SAVR decision-making in symptomatic AS.

Continued

Table 5 *Continued*

2020 ACC/AHA guideline[5]	2021 ESC/EACTS guideline[4]	Comparison of the evidence
the same recommendations as for symptomatic patients. **3.2.4.2.** COR 1 LOE B-NR: for asymptomatic patients with severe AS and an abnormal exercise test, very severe AS, rapid progression, or an elevated BNP (COR 2a indications for AVR), SAVR is recommended in preference to TAVI.		
Non-transfemoral TAVI		
No specific recommendations.	**5.2.3.** COR IIb LOE C: non-transfemoral TAVI may be considered in patients who are inoperable and unsuitable for transfemoral TAVI.	ACC/AHA Evidence: PARTNER-1 substudy by Elmariah et al. in 2017 showed a disproportionately higher risk of cardiac mortality in patients with LV dysfunction who underwent transapical TAVI.[92]
Bystander coronary artery disease		
14.1.2. COR 2a LOE C-LD: in patients undergoing valve repair or replacement with significant proximal CAD, CABG is reasonable for selective patients. **14.1.1.** COR 2a LOE C-LD: in patients undergoing TAVI with significant left main or proximal CAD with or without angina, revascularization by PCI before TAVI is reasonable. **14.1.1.** COR 2a LOE C-LD: in patients with significant AS and significant CAD consisting of complex bifurcation left main and/or multivessel CAD with a SYNTAX score >33, SAVR and CABG are reasonable and preferred over TAVI and PCI.	**5.2.3.** COR I LOE C: SAVR is recommended in patients with severe aortic stenosis undergoing CABG or surgical intervention on the ascending aorta or another valve. **5.2.3.** COR IIa LOE C: SAVR should be considered in patients with moderate aortic stenosis undergoing CABG or surgical intervention on the ascending aorta or another valve after Heart Team discussion. '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'	ACC/AHA Evidence: references a systematic review by Bajaj et al. (2017) and the TAVR-LM Registry by Chakravarty et al. (2016).[93,94] References an observational study by Thalji et al. that shows favourable results for those with concomitant coronary artery disease with CABG and SAVR over SAVR alone.[95] ESC/EACTS Evidence: does not address pre-TAVI PCI. Both guidelines await data from ACTIVATION and TAVR-PCI.

Abbreviations as in *Tables 1–4*. CAD, coronary artery disease; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; SAVR , surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons' Predicted Risk of Mortality.

LOE A).[5] The ESC/EACTS uses a blanket age cut-off, stating that 'SAVR is recommended in younger patients <75 years who are low risk for surgery (STS-PROM/EuroSCORE II <4%)' and 'TAVI is recommended in patients ≥75 years' (COR I LOE A) (*Table 4*).[4] The authors indicate that the age cut-off is meant to substitute life expectancy and is only relevant when considering overall surgical risk and frailty.

The age disparities between guidelines and the perceived crudeness of this approach have incited some controversy. The ACC/AHA cites a mix of systematic reviews, RCTs, and observational studies to recommend SAVR for <65 years based on a lack of TAVI follow-up data beyond 5 years. Siemieniuk and colleagues' 2016 meta-analysis of four randomized trials, which proposed a cut-off of 65 and 80 years for TAVI and SAVR, respectively, found the longest study follow-up time to be 3 years.[81] The only cited evidence of TAVI inferiority for patients <65 years was a prospective cohort study by Kumar and colleagues, which found that amongst 276 TAVI recipients, higher rates of valve deterioration were prominent amongst younger patients.[82] PARTNER 3 and the Evolut Low Risk Trial are referred by the ACC/AHA as evidence supporting 'no difference' between SAVR and TAVI for patients 65–80 years of age.[5] While PARTNER 3 demonstrated a lower risk of 1-year mortality, stroke, and rehospitalization associated with TAVI, the longer term outcomes of the PARTNER 3 trial remain uncertain.[78] This trend may be anticipated based on the Evolut Low Risk Trial, which reported non-inferiority between TAVI and SAVR after 2 years.[78,80] Finally, the ACC/AHA appeared to base its recommendation in patients >80 years on a 2019 meta-analysis of seven major RCTs by Siontis and colleagues, which found a reduction in 2-year all-cause mortality in TAVI regardless of STS risk score; this study was acknowledged but not considered as supporting evidence under ESC/EACTS guidelines.[83]

The ESC/EACTS guidelines cite observational registries such as REPLACE and FRANCE-2, the latter of which demonstrated a 5-year rate of severe structural valve deterioration of 2.5% and moderate deterioration of 13.3% after TAVI.[85] These studies contrasted against a 2015 study of >12 500 SAVR patients that revealed a 10-year explant rate of only 5.6% for patients <60% and 8.1% for patients 60–80 years (*Table 4*).[105]

None of the aforementioned data provides robust evidence for the age thresholds established by the ACC/AHA and ESC/EACTS guidelines. Since the release of the 2021 ESC/EACTS guidelines, results from the NOTION and UK TAVI trials provided more clarity about low-to-intermediate risk patients ≥70 years of age with a EuroSCORE II <4%. As the first pragmatic, investigator-initiated trial allowing the use of any CE-marked valve, the UK TAVI trial's findings of TAVI non-inferiority compared with SAVR at 1-year reinforced that TAVI can be applicable to low-risk patients in real-world settings.[106] Eight-year follow-up data from the NOTION trial, which reported no difference

in all-cause mortality, stroke, myocardial infarction, or valve failure between TAVI and SAVR, indicates that the benefits of TAVI results may extend long-term.[107] Finally, the 5-year results of the SURTAVI trial also support the durability of TAVI in intermediate-risk patients.[108] These findings, in addition to the 5-year UK TAVI and 10-year NOTION results expected shortly, may provide greater clarity to guidelines and the current uncertainty regarding the optimal age threshold for TAVI and the degree to which age should play a factor in the overall decision-making process after considering patient comorbidities, preferences, and anatomical presentation.

B. Bicuspid aortic valve

TAVI is increasingly considered for low-risk and younger patients, many of which may have bicuspid valve anatomy. The ACC/AHA guidelines continue to recommend these patients be treated with SAVR, with TAVI receiving a COR 2b (LOE B-NR) as an alternative.[5] This is because all large RCTs comparing SAVR and TAVI have specifically excluded bicuspid valve disease. While ESC/EACTS offer no official recommendations for bicuspid aortic valves specifically, their guidelines state that 'SAVR remains more appropriate' in bicuspid AS and in those with associated aortopathy (*Table 4*).[4] To date, NOTION-2 (NCT02825134) is the only TAVI vs. SAVR trial that includes patients with bicuspid AS, which highlights the need for randomized trials specifically examining the role of TAVI in this population.

C. Non-transfemoral tavi

While transfemoral access is preferred, patients with contraindications to transfemoral access may benefit from alternative approaches such as axillary access. Still, there is no robust evidence supporting their safety and effectiveness.[109] The ESC/EACTS guidelines acknowledge the limited role of alternative access through a new recommendation that 'non-transfemoral TAVI may be considered in patients who are inoperable and unsuitable for transfemoral TAVI' (COR IIb LOE C).[4] The ACC/AHA does not make direct recommendations but warns that based on a 2017 PARTNER I substudy, transapical TAVI is associated with increased mortality and should be a last resort (*Table 4*).[5,92]

VI. Other considerations

A. Bystander coronary artery disease

Observational studies have suggested that the prevalence of CAD with severe AS may range from 40%–75%, depending on the definition of CAD used.[110,111] However, large RCTs such as NOTION, SURTAVI, and the Evolut Low Risk Trial have traditionally excluded patients with left main CAD (LMCAD), SYNTAX score >22 or percutaneous coronary intervention (PCI) within 30 days, resulting in an unremarkable number of revascularized patients.[80,112,113] The recent PARTNER 3 trial excluded patients with a SYNTAX score >32, complex CAD, and LMCAD, but a small subset of the TAVI (6.5%) and SAVR cohorts (12.8%) underwent revascularization.[78] Based on longstanding observational data, the ESC/EACTS and ACC/AHA guidelines support performing SAVR for moderate or asymptomatic AS during CABG when appropriate. The ESC/EACTS lists severe (COR I LOE C) and moderate AS (COR IIa LOE C) as indications for concomitant SAVR with CABG.[4] However, they opt not to address pre-TAVI PCI, instead suggesting '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'.[4] In contrast, the ACC/AHA states that pre-TAVI PCI is reasonable in patients with significant LMCAD or proximal CAD (COR 2a LOE C-LD), and references a meta-analysis by Bajaj and colleagues of observational studies and the TAVR-LM Registry study.[5,93,94] Ultimately, the evidence for TAVI plus PCI remains uncertain. The ACC/AHA adds that in 'significant CAD (luminal reduction >70% diameter, fractional flow reserve <0.8, instantaneous wave-free ratio <0.89), complex bifurcation LMCAD and/or multivessel CAD with a SYNTAX score >33', CABG and SAVR remains the preferred intervention (COR 2a LOE C) (*Table 5*).[4] Although the ACC/AHA is more specific in defining parameters of CAD amenable to intervention in VHD, both guidelines await data from the ongoing ACTIVATION (ISRCTN75836930) and TAVR-PCI (NCT04310046) trials. Furthermore, while there is comparatively more evidence for SAVR plus CABG, it is chiefly observational and indicates greater early perioperative risk with the potential for better long-term outcomes compared with those who are not revascularized at the time of SAVR.[95]

B. Concomitant mitral valve disease

Mitral stenosis and regurgitation can be observed with severe AS, either as a primary valvular condition or secondary to increased left ventricular pressures. Both guidelines recommend transthoracic echocardiography to differentiate between primary and secondary mitral disease. Severe primary mitral regurgitation is an indication for mitral valve surgery alongside SAVR, which is not supported by official recommendations but described in both guidelines.[4,5]

Summary of evidence comparison

The optimal approach to managing AS continues to evolve. TAVI has played a key role in disrupting long-held notions about patients suitable for intervention, their options, and their prognosis. As expected, the ACC/AHA and ESC/EACTS guidelines were generally congruent where evidence was available. Areas of divergence represent fields where emerging evidence may have substantial implications (*Figure 1*). Both guidelines relied heavily on observational data in these areas, which are subject to confounding and bias and therefore have limited reliability in informing treatment recommendations.

Variations in COR and LOE definitions may also have influenced the ACC/AHA and ESC/EACTS recommendations. The ACC/AHA guidelines offered more granularity between LOEs in specifying whether non-randomized studies (B-NR), randomized studies (B-R), limited data (C-LD), or expert opinions (C-EO) informed the recommendation. Nevertheless, of approximately 25 categories of recommendations that were discussed, 12 were classified with the same COR, and eight also shared identical LOEs. When the guidelines diverged, they mainly differed by small degrees, with five CORs being one level apart. We found one instance where the same COR and cited evidence resulted in a higher LOE by the ACC/AHA than the ESC/EACTS.

Overall, citations were sparser in the ESC/EACTS guidelines, making it difficult to ascertain the rationale for some recommendations. Furthermore, the ESC/EACTS makes fewer official recommendations than the ACC/AHA, as exemplified by its generalized approach to pre-TAVI PCI, TAVI in asymptomatic patients, bicuspid AS, and the Ross procedure. This review highlighted 26 ACC/AHA and 24 ESC/EACTS recommendations. The ACC/AHA made six recommendations not discussed by the ESC/EACTS, compared with three ESC/EACTS recommendations not discussed by the ACC/AHA.

Conclusions

New evidence continues to overturn current recommendations for AS management. The 2021 ESC/EACTS and 2020 ACC/AHA guidelines

were largely congruent and differed mainly on (i) LVEF intervention thresholds in asymptomatic AS, (ii) age thresholds for SAVR vs. TAVI, and (iii) age thresholds for mechanical vs. bioprosthetic valves (*Graphical abstract*). What remains constant is the importance of adapting population-level frameworks to serve individuals by unifying patient preferences with Heart Team recommendations.

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Supplementary data

Supplementary data is available at *European Heart Journal* online.

Data availability

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

Conflict of interest: G.B.-Z. has consulted for Cardionovum, Crannmedical, Innovheart, Guidotti, Meditrial, Opsens Medical, Replycare, Teleflex, and Terumo. D.Y.T. has consulted for Medtronics Inc (Canada) and Edwards Life Sciences (Canada). M.G. has received research grants from the Canadian Institute of Health Research and the National Institute of Health. S.F. has received grants from the the Canadian Institute of Health Research and is the site co-Principal Investigator for the Medtronic SURTAVI, Medtronic Low Risk, and Boston NeoAccurate IDE trials. The other authors have no conflicts to disclose.

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