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Saudi Heart Association / National Heart Center / Saudi Arabian Cardiac Interventional Society / Saudi Society for Cardiac Surgeons / Saudi Cardiac Imaging Group 2023 TAVI Guidelines

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GUIDELINE

Saudi Heart Association/National Heart Center/Saudi Arabian Cardiac Interventional Society/Saudi Society for Cardiac Surgeons/Saudi Cardiac Imaging Group 2023 TAVI Guidelines

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Abstract

Saudi Arabia has seen a significant improvement in its healthcare system over the past four decades resulting in an increase in life-expectancy. Transcatheter aortic valve implantation (TAVI) has spread widely in Saudi Arabia and has become a routine procedure in many centers. The expanding clinical indications and the availability of the technology have made it possible for many large and intermediate centers all over the country to commence their own TAVI programs. So, the aim of this document is to standardize TAVI practices in different Saudi Arabian centers through reasonable guidelines based on the evaluation and summarization of the best available evidence. The review committee, composed of different experts in several aspects of the management of patient undergoing TAVI, based their recommendations on the reviewed and analyzed evidence and the class and level of recommendations were discussed until a consensus was reached by the panel.

Keywords: TAVI, Aortic valve, Guidelines, Aortic disease, Saudi Arabia

Contents

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Abbreviations:

COR	Class of Recommendation
LOE	Level of Evidence
NHC	National Hear Center
RCT	randomized controlled trials
SACIS	Saudi Arabian Cardiac Interventional Society
SCIG	Saudi Cardiac Imaging Group
SHA	Saudi Heart Association
SSCS	Saudi Society for Cardiac Surgeons
TAVI	transcatheter aortic valve implantation
MACCE	major adverse cardiac and cerebrovascular events
AV	Aortic Valve
AVR	Aortic Valve Replacement
AS	Aortic stenosis
SAVR	Surgical aortic valve replacement
STS	Society of Thoracic Surgeons
LV	Left Ventricular
EF	Ejection Fraction
ESC	European Society of Cardiology
ACC	American College of Cardiology
LVEF	Left Ventricular Ejection Fraction
PVL	Paravalvular leak
MACE	Major Adverse Cardiac Events
ViV	Valve-in-Valve
LFLG	low flow low gradient
CAD	Coronary Artery Disease
PCI	Percutaneous Coronary Intervention
CABG	Coronary artery bypass graft
AKI	Acute Kidney Injury
CKD	Chronic Kidney Disease
MR	Mitral regurgitation
MS	Mitral stenosis
IE	Infective endocarditis
ESRD	End-stage renal disease

1. Preamble

Guidelines are used to help health practitioners choose the best management strategies for an individual patient with certain conditions. These guidelines are derived from the critical evaluation of the best available evidence to facilitate decision-making for transcatheter aortic valve implantation (TAVI) in daily practice. However, it does not replace individual, case-by-case consensus decisions of the heart team that are deemed appropriate for specific conditions.

2. Introduction

Saudi Arabia has seen a significant improvement in its healthcare system over the past four decades [1] resulting in an increase in life-expectancy [1,2]. In contrast to Europe and northern America where 18% of the total population were above the age of 65 years in 2019, the elderly population in countries of the Gulf region did not account for more than 3.4% of the total population [3,4]. That being said, the percentage of people aged 80 years and above in North Africa and Western Asia is projected to quadruple by 2050 [4]. In Saudi Arabia, demographic indicators also suggest steady increases in life expectancy, with the age group 65 years and older expanding from approximately 1.2 million in 2025 to 10 million by 2050 [5].

It is important to note that 10% of the elderly population suffer from severe aortic stenosis (AS), a type of valvular heart disease [6]. Similar estimates are reported in Saudi Arabia, with both the incidence as well as prevalence of AS expected to rise along with the increased life expectancy. Many chronic medical conditions, such as diabetes mellitus, hypertension, coronary artery disease, lung disease and cancer, frequently coexist in the elderly population; As a result, elderly patients face substantially higher perioperative risk compared to their younger counterparts [7–9].

TAVI is now a routine procedure in many centers in Saudi Arabia. The expanding clinical indications and the availability of the technology have made it possible for many large and intermediate centers all over the country to commence their own TAVI programs. Globally, the indication for TAVI continues to expand to include bicuspid and valve-in-valve procedures. Therefore, it is essential to standardize TAVI practices in different Saudi Arabian centers through reasonable guidelines based on the evaluation and summarization of the best available evidence.

3. Methods

3.1. Review committee members

The National Heart Center (NHC) and the Saudi Heart Association (SHA) strive to ensure that the review committee is representative of different specialties, different health care sectors and different geographic areas of the kingdom with expertise in the management of aortic valve disease in general, and TAVI in particular. The review committee included representative members of the NHC, SHA, Saudi Arabian Cardiac Interventional Society (SACIS), Saudi Society for Cardiac Surgeons (SSCS), and the Saudi Cardiac Imaging Group (SCIG).

3.2. Methodology and evidence review

A number of relevant clinical questions were proposed by the guidelines committee and the evidence was thoroughly reviewed to answer these questions. Literature searches included randomized controlled trials (RCTs), registries, systematic reviews, nonrandomized comparative and descriptive studies, cohort studies and case series. A series of meetings were conducted to review available evidence and formulate recommendations appropriate for clinical practice. The review committee based their recommendations on the reviewed and analyzed evidence and the class and level of recommendations were discussed until a consensus was reached by the panel. The initial draft of the

Table 1. Classes of recommendation (COR) and their definitions.

Classes of Recommendation	Definition
Class I	Strongly supported by evidence or consensus opinion. Such a treatment is strongly recommended.
Class IIa	Evidence or consensus opinion mostly in favor. Such a treatment is reasonable to consider.
Class IIb	Evidence or consensus opinion confliction or less well established. Such a treatment may be reasonable to consider.
Class III	Evidence or consensus opinion is against as the treatment is not effective or harmful. Such a treatment should be avoided.

Table 2. Levels of evidence (LOE) and their definitions.

Level of Evidence	Definition
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 nonrandomized studies
Level of Evidence C	consensus opinion or case reports. Clinical evidence lacking

recommendations was prepared then reviewed again by all members of the review committee, following which it was sent to two external independent reviewers for further review and feedback.

3.3. Class of recommendation and level of evidence

The Class of Recommendation (COR) indicates the strength of recommendation, based on the estimated magnitude of benefit to risk ratio. (Table 1). The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 2).

3.4. Scope

This document is intended for use by general and specialized cardiac practitioners for the management of patients who are planned for, or are candidates for TAVI. Those practitioners are required to form their clinical judgement and manage their patients based on these guidelines, keeping in mind patient specific characteristics. Given that valve practices are standard globally, there may be inevitable similarities between this paper and other published clinical practice guidance documents.

4. Results-Saudi Arabian TAVI guidelines

4.1. TAVI in severe symptomatic AS in patients with prohibitive risk for surgery

Evidence summary:

Overall, evidence shows significantly lower mortality and better long-term survival among TAVI patients compared to standard medical therapy. This advantage is statistically significant starting 1 year after intervention. That being said, TAVI is associated with significantly higher risk of stroke and major adverse cardiac and cerebrovascular events (MACCE). Therefore, TAVI is not recommended for patients who are very frail with less than 1 year expected survival.

Evidence overview:

The PARTNER B trial aimed to compare the effectiveness of TAVI with standard medical therapy [10]. The trial enrolled patients with severe AS who were not suitable candidates for surgery. They were randomly assigned to receive either TAVI or standard medical therapy, which included balloon aortic valvuloplasty. Each group consisted of 179 patients. Initial results showed that the TAVI group had higher rates of overall mortality and cardiovascular-related mortality at 30 days compared to the standard therapy group (5% and 4.5% vs. 2.8% and 1.7%, respectively). While the TAVI group had a significantly greater risk of major stroke and major vascular complications, it also demonstrated a significant survival advantage at one year, with lower rates of all-cause mortality (30.7% vs. 49.7%) and cardiovascular-related mortality (19.6% vs. 41.9%). Despite this advantage, the TAVI group continued to have a higher incidence of stroke and vascular complications compared to the standard therapy group [10]. Subsequent long-term follow-ups at 2, 3, and 5 years revealed sustained survival benefits for patients in the TAVI group, although they remained at a higher risk of stroke and vascular complications [11–13]. TAVI patients also benefited from significant improvement in the New York Heart Association functional class, which persisted during long-term follow-up [11–13].

Another study, the CoreValve US trial, conducted a prospective, multicenter, nonrandomized investigation involving 489 patients with symptomatic severe aortic stenosis who had prohibitive surgical risk. The trial compared self-expanding TAVI to a predetermined objective performance goal of 43% for all-cause mortality or major stroke, using standard therapy (balloon aortic valvuloplasty studies) as a reference [14]. Results revealed the superiority of TAVI to standard therapy in terms of the composite endpoint of all-cause mortality or major stroke at 30 days and 12 months. The rates of this composite endpoint were 9.8% at 30 days and increased to 26.0% at 12 months, remaining significantly lower than the objective performance goal rate of 43.0% ($p < 0.0001$). Adverse events associated with TAVI included a 12.3% rate of MACCE at 30 days and a 29.2% rate at 12 months [14].

Real-world evidence is available from a retrospective cohort study, which included patients diagnosed with severe aortic stenosis who had been turned down for surgery (65 patients) before TAVI

was available (between 1999 and 2009), along with the first 90 TAVI patients once the procedure was implemented. Compared to the medical therapy group, TAVI patients were significantly older (81.8 vs. 79.2) and more likely to be male (59.1% vs. 49.3%). The study found lower mortality in the TAVI group (28%) compared to the surgical turn-down group (70%) after a 1000-day follow-up period [15]. An earlier observational study using propensity score matching [16] and a recent systematic review and meta-analysis [17], which included two of the aforementioned studies ([10,16]), also reported lower mortality rates with TAVI.

Recommendation:

TAVI is recommended for severe symptomatic AS, in patients with prohibitive risk for surgery and suitable for transfemoral TAVI with expected survival of at least 1 year ***(Class I recommendation, Level of evidence A).***

4.2. TAVI in severe symptomatic AS, in patients with high risk for surgery

Evidence summary:

The data from multiple RCTs and a meta-analysis confirmed that TAVI is non-inferior to surgical aortic valve replacement (SAVR) in high-risk patients. The evidence suggests a possible survival advantage with TAVI on the level of all-cause mortality until 3 years. This survival advantage is not clear cut, particularly on the level of cardiovascular mortality, or all-cause mortality after 5 years. TAVI ensures a reduction in MACCE and stroke, and better aortic valve hemodynamics but is associated with higher major vascular complications and moderate or severe residual aortic regurgitation.

Evidence overview:

Clinical outcomes after SAVR and TAVI in patients with severe symptomatic aortic stenosis and high-risk for surgery were compared in two major RCTs (the PARTNER A trial and US CoreValve High-Risk Trial). The CoreValve trial included 750 patients, with a mean age of around 83 years. Results revealed significantly lower 1-year all-cause mortality with TAVI compared to the surgical group (14.2% vs. 19.1%) [18]. Additionally, TAVI showed a reduction in MACCE, with no increased risk of stroke [18]. The three-year analysis revealed that TAVI patients had lower rates of all-cause mortality or stroke, all stroke, and MACCE compared to SAVR patients (all-cause mortality 37.3% vs. 46.7% in SAVR; $p = 0.006$; all stroke (12.6% in TAVI vs. 19.0%, respectively; $p = 0.034$); MACCE (40.2% in TAVI vs. 47.9%, respectively; $p = 0.025$)) [19]. However, these differences were not apparent in the 5-year outcome analysis (all-cause mortality: 55.3% for TAVI and 55.4% for SAVR) [20].

Other outcomes were reported in the 1-year analysis of the CoreValve, revealing the non-inferiority of TAVI to SAVR in terms of echocardiographic indexes of valve stenosis, functional status, and quality of life [18]. At 3 years post-intervention, TAVI patients had better aortic valve hemodynamics (mean aortic valve gradient 7.62 ± 3.57 mm Hg vs. 11.40 ± 6.81 mm Hg in SAVR; $p < 0.001$), but higher moderate or severe residual aortic regurgitation (6.8% vs. 0.0% in SAVR; $p < 0.001$) [19]. That being said, 5-year follow-up results showed that severe structural valve deterioration and valve reinterventions were uncommon in both SAVR and TAVI [20]. Long-term health status was reportedly comparable between self-expanding iliofemoral TAVI and SAVR in the Corevalve trial, despite an initial early health status benefit observed at 1 month with iliofemoral TAVI [21]. The study also reported a five-year survival rate of 44% for iliofemoral TAVI patients and 39% for SAVR patients [21].

In the PARTNER A trial, 699 high-risk patients with severe aortic stenosis underwent either SAVR or TAVI. TAVI was associated with significantly lower 30-day mortality from any cause compared to SAVR (3.4% vs 6.5%; $p = 0.07$). However, 1-year mortality was comparable between the two groups (24.2% and 26.8%; $p = 0.44$) [22]. TAVI showed a lower risk of major stroke at one year (5.1% vs 2.4%; $P = 0.07$) but a higher risk of major vascular complications at 30 days compared to SAVR (11.0% vs. 3.2%, $P < 0.001$) [22]. Adverse events such as major bleeding and new-onset atrial fibrillation were more frequent in the SAVR group [22].

The two-year follow-up revealed comparable rates of death from any cause, strokes, and improvements in valve areas between TAVI and SAVR [23]. However, paravalvular regurgitation was more common after TAVI, with higher late mortality associated even with mild paravalvular regurgitation [23]. In the five-year follow-up, the risk of death was similar between the two groups, with no significant structural valve deterioration requiring surgical valve replacement in either TAVI or SAVR [24]. The incidence of moderate or severe aortic regurgitation was higher in the TAVI group and was associated with an increased risk of mortality at five years (72·4% for moderate or severe aortic regurgitation vs 56·6% for those with mild aortic regurgitation or less; $p = 0{\cdot}003$) [24].

A retrospective sub-analysis focusing on sex-specific differences suggested that TAVI had lower

procedural mortality compared to SAVR (6.8% vs. 13.1%; p = 0.07), particularly among female patients. However, there was no overall survival benefit with TAVI among male patients [25].

A retrospective study comparing TAVI and SAVR in kidney transplant recipients found comparable rates of in-hospital stroke and 30-day readmission between the two approaches. Moreover, TAVI was associated with lower risks of in-hospital mortality, blood transfusion, acute myocardial infarction, acute kidney injury (AKI), sepsis, and discharge with disability compared to SAVR [26].

It is important to note that available studies have their limitations, in that they are based on older-generation TAVI devices. Newer-generation devices and advances in TAVI have been associated with significantly fewer complications. Moreover, there is now a higher level of clinical experience with TAVI. This might lead to TAVI being favored in the future for patients with severe symptomatic AS who are at high risk for surgery, pending the generation of robust clinical data. The anatomical-, patient-, and device-considerations implicated in the choice of TAVI vs SAVR for this patient subset should be mentioned, along with an emphasis on the Heart team discussion.

Recommendation:

TAVI is recommended for severe symptomatic AS, in patients with high risk for surgery and suitable for transfemoral TAVI ***(Class I recommendation, level of evidence A).***

4.3. TAVI for severe symptomatic AS in patients with moderate risk for surgery

Evidence summary:

Overall, evidence shows that TAVI is non-inferior to SAVR in intermediate-risk patients at follow-up extending to 5 years. However, the risk of vascular complications, permanent pacemaker implantation, and paravalvular leak (PVL) is significantly higher with TAVI, while risk of major bleeding and AKI is higher with SAVR. It is also to be noted that the mean age of patients on all published data on moderate risk patient was 75 years or older.

It is therefore debated whether to adjust the age of recommendation to 70 years in order to reflect the lower mean age of Saudi TAVI patients compared to western European/US population. However, there is not enough data to support that notion.

Evidence overview:

Recently, the UK TAVI trial demonstrated that TAVI was as effective as SAVR (non-inferior) in reducing all-cause mortality at 1 year for patients aged 70 years or older with severe, symptomatic aortic stenosis and moderately increased operative risk [27]. However, the TAVI group had a higher incidence of vascular complications, pacemaker implantation, and aortic regurgitation, while experiencing fewer major bleeding events and shorter hospital stays after the procedure [27].

In the SURTAVI trial, which involved intermediate-risk patients with severe, symptomatic aortic stenosis, comparable outcomes were also observed between TAVI and SAVR in terms of a composite of death from any cause or disabling stroke at 24 months [28]. However, the procedures had differing adverse events, with higher rates of acute kidney injury, atrial fibrillation, and transfusion requirements observed after SAVR. On the other hand, TAVI had higher rates of residual aortic regurgitation and pacemaker implantation, but resulted in lower mean gradients and larger aortic valve areas compared to surgery [28]. At the 5-year follow-up, major clinical outcomes remained similar between TAVI and surgery, but TAVI was associated with superior hemodynamic valve performance, albeit with a higher rate of PVL and valve reinterventions [29].

No significant differences in the rates of death from any cause or disabling stroke were observed between TAVI and SAVR after 2 years in the PARTNER 2 trial [30]. However, outcomes differed when considering TAVI access routes; In the transfemoral-access cohort, TAVI was associated lower rate of death or disabling stroke compared to SAVR, while outcomes were similar between SAVR and patients in the transthoracic-access cohort [30]. The 5-year follow-up showed similar incidence rates of death or disabling stroke between the two groups. However, outcomes in the transthoracic-access cohort and SAVR showed a shift to higher incidence of death or disabling stroke was higher after TAVI than after surgery, and now comparable outcomes in the transfemoral-access cohort. Consistently with other trials, TAVI was associated with lower rates of AKI, severe bleeding, and new-onset atrial fibrillation, but higher rates of major vascular complications and paravalvular aortic regurgitation [30]. Health status improvement at 5 years was comparable between TAVI and SAVR, but TAVI was associated with higher rates of repeat hospitalizations and aortic valve reinterventions [31].

In the NOTION trial, which included low- or intermediate-risk patients with severe aortic stenosis (18% of patients had intermediate risk), the non-inferiority of TAVI to SAVR in terms of death, stroke, and myocardial infarction was evident and was maintained for 5 years [32,33].

The OBSERVANT study indicated that TAVI and SAVR had comparable early and midterm mortality rates, in addition to similar rates of survival and MACCE up to 3 years. However, TAVI was associated with higher rates of vascular complications (6.0% vs 0.5%; $p < 0.0001$), permanent pacemaker implantation (13.4% vs 3.7%; $p < 0.0001$), and PVL (8.9% vs 2.4%; $p < 0.0001$), while SAVR had more frequent bleedings needing transfusion (63.2% vs 34.5%; $p < 0.0001$) and AKI (9.6% vs 3.9%; $p = 0.0010$) [34]. In the 5-year follow-up, SAVR was found to lead to better survival and lower rates of MACCE in a real-world population with severe aortic stenosis and at low and intermediate risk compared to transfemoral TAVI performed with first-generation devices [35]. However, further randomized controlled studies with new-generation TAVI devices are needed to confirm these findings.

An observational study of TAVI with SAPIEN 3 in intermediate-risk patients with severe aortic stenosis showed that TAVI is associated with low mortality, strokes, and regurgitation at 1 year. TAVI was favored over surgery by propensity score analysis in terms of the composite outcome of mortality, strokes, and moderate or severe aortic regurgitation, suggesting TAVI as the preferred treatment alternative for intermediate-risk patients [36].

Comparable 3-year mortality was reported between patients undergoing TAVI or SAVR in a large, single center, real world dataset. However, TAVI was associated with a higher incidence of major vascular complications, new pacemaker implantation, and aortic insufficiency, while SAVR carried an increased risk of bleeding [37].

A propensity score-matched comparison of 362 patients with severe symptomatic AS and intermediate-low surgical risk (log Euro Score <20%) revealed shorter hospitalization but comparable in-hospital and 1-year mortality rates with TAVI compared to SAVR. This observation extended to the combined endpoint of stroke and mortality at 1 year [38]. Conversely, a preliminary study involving patients with an intermediate- to high-risk profile associated a higher rate of perioperative complications and decreased survival at the 24-month follow-up with TAVI compared to conventional surgery or sutureless valves [39].

That being said, Registry data, although largely based on older high-/intermediate-risk patients, provide some evidence supporting the long-term durability of TAVI devices up to 8 years [40–43].

Recommendation(s):

- *TAVI is recommended for severe symptomatic AS in patients with moderate risk for surgery that are older than 75 years and suitable for transfemoral TAVI* ***(Class I recommendation, level of evidence A).***

- *TAVI should be considered for severe symptomatic AS in patients with moderate risk for surgery between the age of 65- 75 years and suitable for transfemoral TAVI after heart team discussion* ***(Class IIa recommendation, level of evidence C).***

4.4. TAVI for severe symptomatic AS in patients with low risk for surgery

Evidence summary:

Overall, evidence from RCTs conducted in low-risk patients with severe AS seems to indicate that TAVI is non-inferior to SAVR in terms of survival up to 8-years, albeit differing in terms of adverse events and complications (higher risk of paravalvular regurgitation and pacemaker implantation with TAVI, higher risk of severe bleeding, atrial fibrillation and AKI with SAVR). Emerging data from TAVI with new generation devices suggest potentially lower mortality and complications compared to SAVR. As also was noted in moderate risk patients, data on TAVI in low-risk patients was generated based on a mean age of 75 years or older.

Evidence overview:

TAVI had a significantly lower rate of death, stroke, or rehospitalization at 1 year compared to surgery in patients with severe aortic stenosis and low surgical risk from the PARTNER 3 trial [44]. At the 2-year follow-up, the primary endpoint remained significantly lower with TAVI; however, the advantages of TAVI in terms of death and stroke observed at 1 year diminished, and TAVI patients experienced increased valve thrombosis [45]. That being said, data from the PARTNER 3 trial showed that TAVI provided meaningful early and late health status benefits compared to surgery [46].

In the Evolut Low Risk trial, TAVI proved non-inferior to SAVR for mortality/disabling stroke at 24 months in the treatment of severe symptomatic aortic stenosis among low-risk patients younger than 80 years (mean age 74 years) [47,48].

The NOTION trial, which included patients with severe aortic stenosis and low or intermediate risk (82% low risk), demonstrated the non-inferiority of

TAVI to SAVR in terms of all-cause mortality, stroke, myocardial infarction, and bioprosthetic valve failure. This finding persisted over the course of 8 years of follow-up [32,33,49].

The OBSERVANT study also included patients with low operative risk, among whom SAVR resulted in significantly better 3-year survival and freedom from MACCE compared to TAVI [50]. The final results at the 5-year follow-up were consistent, revealing lower rates of both mortality and MACCE with SAVR in a real-world population with severe aortic stenosis and low to intermediate risk, compared to transfemoral TAVI performed using first-generation devices [35]. However, confirmation of these findings in randomized trials using new-generation TAVI devices was necessary. Accordingly, recent data from the OBSERVANT and OBSERVANT II studies reported 1-year outcomes of patients undergoing TAVI with new-generation devices; These new data showed that TAVI using these devices was associated with lower rates of adverse events and mortality compared to SAVR in a real-world setting [51].

Other real-world evidence is also available. Shorter hospitalization with TAVI, but comparable in-hospital mortality, 1-year mortality and a combined endpoint of stroke and mortality at 1-year, were associated with TAVI in comparison with SAVR in a propensity score-matched comparison of patients with severe symptomatic AS and intermediate-low (logEuroScore <20%) surgical risk [38]. This was confirmed in a prospective multicenter registry involving more than 20 thousand low surgical risk patients (Society of Thoracic Surgeons (STS) score <4%; 14 487 surgical patients and 6062 TAVI patients), which reported that TAVI patients had lower in-hospital and 30-day mortality compared to SAVR, but comparable survival at 1 year [52].

A retrospective propensity score-matched analysis of low-risk patients undergoing SAVR or TAVI (79 patients per group) also showed comparable outcomes in terms of mortality. Moreover, outcomes (all-cause mortality or rehospitalization) were not influenced by treatment strategy at a median follow-up of 4.5 years, with EuroSCORE II remaining the only independent predictor of long-term all-cause mortality [53].

To note that contrasting results were reported by a reconstructed individual patient data meta-analysis in low-risk patients with severe aortic stenosis, comprising six studies (three RCTs and three cohort studies; 4165 total patients); TAVI patients had higher 5-year all-cause mortality rates when compared to SAVR, particularly due to significantly lower survival between 1 and 5 years of follow-up in the TAVI group [54].

Recommendation(s):

*TAVI and SAVR are both recommended for severe symptomatic AS in patients with low risk for surgery that are older than 75 years and suitable for transfemoral TAVI (**Class I recommendation, level of evidence A**).*

4.5. TAVI for severe symptomatic AS in patients younger than 75 years

Evidence summary:

Overall, very few studies have exclusively included/studied young patients <75 years of age. Evidence from RCTs conducted in low-risk patients with severe AS seems to indicate that SAVR and TAVI are comparable in terms of survival, albeit differing in terms of adverse events and complications [28,44,45,47]. Evidence from smaller studies specifically targeting patients <75 years of age is conflicting on the level of survival. However, the studies seem consistent in reporting worse baseline clinical profiles among young patients undergoing TAVI compared to SAVR [55–57]. The higher long-term mortality after TAVI was more likely explained by their baseline surgical risk and frailty as opposed to procedural complications. The choice of intervention should therefore be made based on the heart team discussion and according to individual clinical, anatomical, and procedural characteristics.

Evidence overview:

The PARTNER 3 trial enrolled low surgical risk patients with severe aortic stenosis and found that TAVI had a significantly lower rate of the composite of death, stroke, or rehospitalization at 1 year compared to surgery [44]. The primary endpoint remained significantly lower with TAVI by the second year of follow-up, although the initial differences in death and stroke favoring TAVI were reduced. Moreover, increased valve thrombosis was evident in TAVI patients experienced [45].

The Evolut Low Risk trial reported the non-inferiority of TAVI compared to SAVR in terms of mortality/disabling stroke at 2 years when undertaken for low-risk patients with severe symptomatic aortic stenosis that are younger than 80 years (mean age 74 years) [47].

While the SURTAVI trial had no sub-analysis by age, it included 1660 intermediate-risk patients with severe, symptomatic aortic stenosis, 18.1% and 19.7% of whom were 75 years or younger in the TAVI group and in the surgery group, respectively [28]. At 2 years,

patients in the TAVI and surgery groups had similar outcomes on the level of a composite of death from any cause or disabling stroke. Differences were evident on the level of adverse events (higher rates of AKI, atrial fibrillation, and transfusion requirements with SAVR; higher rates of residual aortic regurgitation and need for pacemaker implantation with TAVI). That being said, TAVI resulted in lower mean gradients and larger aortic-valve areas than surgery [28].

While RCTs generally reported comparable outcomes between TAVI and SAVR, some differences were noted in real-life studies. Patients who underwent SAVR were found to have significantly higher postprocedural adverse events, in-hospital and 30-day mortality compared to TAVI, based on a propensity score-matched analysis (144 patients; aged 75 years or less [55]. However, overall long-term survival (median follow-up 5 years) was significantly lower in TAVI patients compared to those who underwent surgery [55]. Consistently, another propensity-matched comparison of data from close to 7 thousand patients aged 65–74 years (the German AQUA registry) reported higher predicted risk of mortality and comorbidities in patients who underwent Transfemoral-TAVI compared to SAVR [56]. To note that the vast majority of patients included in the analysis had SAVR, which was associated with significantly higher postprocedural delirium. On the other hand, TAVI patients had higher need for a new pacemaker [56]. That is not to say that all real-world studies were in favor of SAVR. Comparable in-hospital mortality, 1-year mortality and a combined endpoint of stroke and mortality were reported in a propensity score-matched analysis of patients with severe symptomatic aortic stenosis and intermediate-low surgical risk (mean age of 73 ± 10.4 years) [38]. While length-of-hospitalization was significantly lower in TAVI, patients in this group experience more aortic regurgitation [38]. It is important to note that patients undergoing TAVI (for example in the OBSERVANT study) had higher risk and more comorbidities compared to those who had SAVR; the higher baseline surgical risk and frailty probably translated into lower long-term survival compared to SAVR, as opposed to complications related to TAVI itself; in fact, the highest rates of 5-year mortality were observed in the youngest age-group of TAVI patients (<65 years), who had the highest baseline risk profile [57].

It is notable to mention a few other studies that were not direct comparisons between TAVI and SAVR. The Young TAVI registry reported comparable 30-day and 1-year mortality rates among TAVI patients from different pre-specified age groups (<75 years (n = 179), 76–86 years (n = 602), and >86 years (n = 221)). Patients aged 76–86 years had significantly lower 2-year mortality compared to those <75 years but not those who were older [58].

Evidence from large-scale, contemporary, real-world, risk-stratified analysis of SAVR outcome (141,905 total patients, 113,377 low risk patients) revealed that patients had an overall lower mean in-hospital mortality compared to predicted rates (2.5% vs 2.95%). However, the significant reductions in operative mortality recently observed in the medium and high risk groups do not extend to the low-risk group [59]. Moreover, a review of the United Kingdom national database showed varied mortality rates by age category for SAVR only, with higher mortality observed in older age groups (2.0% mortality in <60 years, 1.5% in 60–75 years, 2.2% in >75 years [60].

Recommendation(s):

- *SAVR is recommended for severe symptomatic AS, in patients younger than 65 years* ***(Class I recommendation, level of evidence A).***
- *SAVR is recommended for severe symptomatic AS, in patients between 65 and 75 years of age and the decision should be made after heart team discussion* ***(Class I recommendation, level of evidence B).***

- *TAVI should be considered for severe symptomatic AS, in patients between 65 and 75 years of age and the decision should be made after heart team discussion* ***(Class IIa recommendation, level of evidence C).***

4.6. Early replacement vs watchful waiting for severe AS in asymptomatic patients

Evidence summary:

There is currently no evidence to support performing TAVI in asymptomatic patients with severe AS. The current body of evidence recommends early SAVR for patients who have severe AS and are asymptomatic. There is a debate whether to extrapolate data from symptomatic AS and high/intermediate risk and suggest TAVI as alternative to SAVR in patients who are inoperable after Heart team discussion. Results of ongoing/planned clinical trials on TAVI in severe AS patients who are asymptomatic are awaited.

Evidence overview:

While several RCTs are currently ongoing (EASY-AS, EARLY TAVI, DANAVR, EVoLVeD), the results of two RCTs involving patients with asymptomatic

AS, AVATAR and RECOVERY, are published. The AVATAR trial, conducted among 157 asymptomatic patients with severe AS, revealed superior outcomes with early surgery compared to conservative treatment on the level of a primary composite of all-cause death, acute myocardial infarction, stroke, or unplanned hospitalization for heart failure (overall follow-up 32 months) [61]. This randomized trial provided preliminary support for early SAVR once AS becomes severe, regardless of symptoms. The RECOVERY trial was also conducted in a similar patient population (145 asymptomatic patients with very severe aortic stenosis), further supporting the role of early aortic-valve replacement surgery in improving clinical outcomes compared to conservative care; patients undergoing early aortic-valve replacement surgery had a lower incidence of the composite of operative mortality or death from cardiovascular causes during the follow-up period, as opposed to patients receiving conservative care [62].

The benefit of early aortic-valve replacement is also evident in observational studies. Aortic-valve replacement in asymptomatic severe AS patients with preserved left ventricular (LV) function led to significantly reduced mortality in a retrospective cohort [63]. Based on this, early aortic replacement could be justified prior to the onset of ventricular dysfunction or symptom development [63]. A long-term survival advantage (5-year all-cause and cardiovascular mortality) with early SAVR was also reported in another retrospective cohort study, which included patients at low surgical risk with asymptomatic high-gradient severe AS and preserved ejection fraction (EF) without Class I indication and with low comorbidities [64]. The reduction of mortality by early aortic valve replacement in patients with asymptomatic AS was confirmed by several other observational studies [65,66]. Registry data analysis revealed that postoperative survival was comparable between asymptomatic AS patients undergoing aortic valve replacement with or without watchful-waiting. That being said, early aortic valve replacement led to lower mortality in a subgroup of patients with Vmax $\geq$4.5 m/s at diagnosis [67]. By contrast, analysis of data from a different registry associated poor long-term outcomes with conservative management of patients with asymptomatic, but severe AS. Adopting an early aortic valve replacement strategy could lead to better outcomes [68]. Establishing surgical risk could aid in selecting optimal candidates for early aortic valve replacement; patients with severe but asymptomatic AS and an intermediate risk (based on STS score) actually experience significant benefit from early surgery, with improvement in survival rates observed at 1-year postintervention [69]. The survival advantage afforded by aortic valve replacement is consistent with the natural history of asymptomatic AS, which is not benign [70]. In fact, most patients with asymptomatic AS will become symptomatic during follow-up [71]. More importantly, these can benefit with reductions in mortality when aortic valve replacement is undertaken [71].

The clinical advantage afforded by early intervention in patients with asymptomatic severe aortic stenosis is supported by a very recent meta-analysis of two published RCTs, AVATAR and RECOVERY, and eight observational studies; Lower all-cause mortality and better outcomes were associated with early aortic valve replacement compared with the conservative approach [72]. The benefit of early intervention might be more pronounced in patients with severe AS at baseline and peak aortic jet velocity of at least 5.0 m/s or left ventricular ejection fraction (LVEF) less than 60%, owing to their higher risk of all-cause and cardiovascular mortality even after aortic valve replacement [73].

Both the European Society of Cardiology (ESC) and American College of Cardiology (ACC) provided recommendations for aortic valve replacement (AVR) in asymptomatic patients based on LVEF thresholds and other criteria. However, a recent meta-analysis demonstrated that the survival advantage provided by aortic valve replacement was irrespective of LVEF among asymptomatic patients with high-gradient severe AS [74]. Hence, the need of an LVEF threshold for recommending AVR in this patient population becomes questionable.

Recommendation(s):

- *SAVR is recommended for severe AS in patients who are asymptomatic and low or intermediate risk of surgery after heart team discussion* ***(Class I recommendation, level of evidence A).***

- *There is no evidence to support TAVI for severe AS in patients who are asymptomatic. TAVI may be an alternative for SAVR in specific patients after Heart team discussion.*

4.7. TAVI in severe symptomatic AS with bicuspid valve

Evidence summary:

There is no strong evidence on TAVI in severe symptomatic AS with bicuspid valve (no RCTs), but available evidence includes meta-analyses of observational trials comparing SAVR and TAVI, and studies comparing bicuspid and tricuspid aortic

valve. Overall, TAVI in patients with bicuspid aortic valve stenosis has shown satisfactory clinical outcomes compared to SAVR. TAVI with new devices appears to be safe and effective for elderly patients with bicuspid AS. Significant PVL is rarely seen with new-generation TAVI devices.

SAVR is recommended as the primary treatment option for bicuspid valve AS and TAVI should be considered when morphology is favorable. It should be mentioned that results after TAVI are improving with newer devices. There should be a Heart team discussion of anatomical suitability and device choice, in addition of recommending to avoid patients with aortopathy.

Evidence overview:

Overall, results of a very recent meta-analysis based on time-to-event data shows that TAVI can be used safely in selected patients with bicuspid aortic valves. Although TAVI and SAVR had comparable mortality and immediate outcomes, a time-varying risk becomes apparent with TAVI; the analysis shows that SAVR is favored over TAVI at later timepoints, most likely due to the higher rates of permanent pacemaker implantation experienced by TAVI patients [75]. Comparable outcomes between TAVI and SAVR in terms of in-hospital mortality, rates of cardiac arrest, cardiogenic shock, AKI, hemopericardium, cardiac tamponade, or acute stroke were reported from a large-scale propensity-matched analysis of hospitalizations with bicuspid aortic stenosis (1055 (3.3%) underwent TAVI and 30,840 (96.7%) underwent SAVR) [76]. While patients undergoing TAVI more frequently suffered from complete heart block and permanent pacemaker insertion, SAVR patients more commonly experienced acute myocardial infarction, postoperative bleeding, vascular complications, discharge to nursing facility, and length of hospital stay [76]. Another propensity-matched analysis of around 17 thousand adult patients with bicuspid aortic valve stenosis treated with TAVI or SAVR (1629 (9.5%) patients underwent TAVI and 15,439 (90.5%) underwent SAVR) reported comparable 30-day and 6-month outcomes in terms of major adverse cardiovascular events (MACE) and PVL between the two groups, but lower in-hospital mortality with TAVI [77]. Patients with bicuspid aortic valve and higher-risk also experience comparable outcomes after TAVI and SAVR, with the exception of periprocedural complication which were more frequent with SAVR [78]. While similar clinical results were reported between TAVI and SAVR in a single center cross sectional study involving patients with aortic stenosis and bicuspid valve, better functional recovery and functional capacity were associated with SAVR [79]. That being said, newer-generation TAVI devices seem to have comparable rates of paravalvular regurgitation with SAVR; A retrospective analysis of the FinnValve registry confirmed that SAVR and TAVR have similar results in patients with stenotic BAV both at 30 days and 2 years. While an overall higher rate of paravalvular regurgitation was observed with TAVI, newer-generation devices yielded outcomes similar to SAVR [80].

Recently, 2 nonrandomized studies presented their results evaluating TAVI in low-risk patients with bicuspid valves: LRT Bicuspid [81] and Evolut Low Risk Bicuspid [82]. Both studies showed excellent outcomes at 30 days. In the LRT Bicuspid study, there were no deaths or disabling strokes at 30 days, and only 1 patient had moderate PVL at 30 days [81]. In the Evolut Low Risk Bicuspid study, 30-day all-cause mortality was 0.7%, the rate of disabling stroke was 0.7%, and no patient had moderate or severe PVL [82]. The recent state of the art review of the ESC on the indication for TAVI vs SAVR concluded that "*transcatheter aortic valve implantation with contemporary devices appears to be safe and effective for elderly patients with bicuspid AS; however, SAVR should remain the primary treatment option for bicuspid AS in young patients and independent of age when the bicuspid aortic valve morphology is unfavorable or significant aortopathy coexists*" [83].

Recommendation(s):

- *SAVR is recommended for severe symptomatic AS with bicuspid valve and unfavorable morphology for TAVI or aortopathy regardless of age* ***(Class I recommendation, level of evidence A).***

- *TAVI should be considered for severe symptomatic AS with bicuspid valve with favorable morphology for TAVI and no aortopathy after heart team discussion* ***(Class IIa recommendation, level of evidence B).***

4.8. TAVI for aortic valve reintervention

Evidence summary:

Overall, evidence shows that valve-in-valve (ViV) TAVI is associated with lower 30-day mortality and major bleeding, while redo SAVR had lower PVL, severe patient-prosthesis mismatch, and postoperative gradients. Mid to long-term (6 months–5 years) outcomes seem to be comparable, but more long-term data are still needed. It is important to highlight that ViV-TAVI could be used for reintervention due to stenosis or regurgitation, but not due to prosthesis mismatch in high-risk patients. Patients with a small valve are most likely not suitable

for ViV-TAVI. Heart team discussion is recommended for patients who have suitable anatomy for ViV-TAVI and have high risk or prohibitive risk for surgery.

Evidence overview:

When compared to redo-SAVR, meta-analysis findings (11 studies comprising 8326 patients (ViV-TAVI = 4083 and redo-SAVR = 4243) revealed better short-term, but comparable mid to long-term outcomes, with ViV-TAVI; a 30-day survival advantage was apparent with ViV-TAVI in addition to lower rates of major bleeding, although mortality (all-cause and cardiovascular) and stroke were similar up to 5 years [84]. The 30-day survival advantage was confirmed in another meta-analysis, and was reportedly persistent despite the higher baseline risk of patients undergoing ViV-TAVI [85]. That being said, and consistent with previous studies on TAVI, PVL was more common in TAVI patients, in addition to lower rates of severe patient-prosthesis mismatch, and better postoperative gradients [85]. ViV-TAVI remains a valid treatment option for high-risk patients, but confirmation of these results in randomized trials remains necessary.

In fact, real-world studies confirm that both redo-SAVR and ViV-TAVI carry acceptable operative results and similar operative outcomes after previous SAVR, despite the high-risk of this patient population [86]. To note that redo-SAVR is consistently associated with improved valve hemodynamics compared with ViV-TAVI [86]. The most recently published retrospective study showed that although the ViV-TAVI group had higher risk patients, there were significantly fewer procedural complications, shorter length of stay, and similar mortality outcomes up to 1-year follow-up [87]. However, it becomes evident that the results of observational studies are generally variable, with some reports of comparable survival between redo-SAVR and ViV-TAVI [88,89], while others demonstrate a significant advantage to ViV-TAVI in terms of short-term outcomes such as mortality, morbidity, in-hospital MACE, and length of hospital stay [89–91].

When specifically considering ViV-transfemoral TAVI compared to redo-SAVR, evidence is limited. That being said, a retrospective cohort study found similar rates of 1-year-mortality, albeit with a higher incidence of bleeding and renal failure with redo-SAVR but higher postoperative transvalvular gradients after VinV-transfemoral TAVI [92]. This suggests that while VinV-transfemoral TAVI could be considered for the management of degenerated aortic bioprostheses in patients at increased surgical risk, redo-SAVR may be favored when surgical risk is low owing to its better clinical efficacy and safety in this setting [92]. Femoral ViV-TAVI was actually associated with a higher incidence of mild PVLs [93] and elevated transvalvular gradients with consequent lower rate of device success [94], but similar early mortality despite worse baseline risk profiles compared to surgery [94]. In one study, valve implantation was reported to be successful in all surgical cases and in around 89% of transcatheter cases (93% *trans*-femoral, 56% balloon-expandable) [95].

Recommendation(s):

Patients who are at high operative risk or inoperable and have favorable anatomic considerations for TAVI should be considered for ViV-TAVI after discussion by the heart team ***(Class IIa recommendation, level of evidence B).***

4.9. TAVI for severe symptomatic AS with LV systolic dysfunction

Evidence summary:

There are no head-to-head comparisons (RCTs) between SAVR and TAVI in this patient population (severe symptomatic AS with LV systolic dysfunction). There is a lack of recommendations for AVR in patients with moderate AS and left ventricular systolic dysfunction despite the substantial morbidity and mortality because there is insufficient evidence that supports early AVR in those patients. Patients with low flow low gradient (LFLG) AS are difficult to characterize and confirming the diagnosis is complicated. Low ejection fraction will be defined based on the criteria of the RCT subgroup analysis (<50%). Sub-analysis of the COREVALVE US trial in high risk AS patients showed no difference between SAVR and TAVI in terms of mortality when LVEF <50%. This was corroborated by a meta-analysis of 32 studies supporting early AVR, with no difference between SAVR and TAVI. However, 2 studies suggested better survival with *trans*-femoral TAVI compared to SAVR. Evidence also shows that both SAVR and TAVI ensure early LVEF improvement. However, there are contradictory data on whether SAVR or TAVI ensure higher LVEF improvement.

The choice of implantation approach falls to the Heart Team. To note that TAVI should be done in highly specialized centers only and patients should be on a maximal medical therapy. TAVI-UNLOAD is an ongoing clinical trial that is expecting to clarify the need for an eventual redefinition of the criteria to establish the need for AVR in the setting of impaired LVEF.

Evidence overview:

A sub-analysis of the Core Valve US Pivotal High-Risk Trial, which randomized patients to TAVI (n = 389) or SAVR (n = 353) revealed the influence of ejection fraction on mortality; there was no difference in mortality between the two groups in patients with LVEF of 50% or higher, while patients with LVEF lower than 50% (18.1% of TAVI patients; 19.6% of SAVR patients) had lower mortality when undergoing TAVI if stroke volume index was preserved (9.8% vs 18.6% in SAVR; P=.01) [96].

A small study showed that patients with high gradient severe AS and LVEF ≤35% waiting for an intervention have a very high and premature risk of death. However, these patients have relatively low postoperative mortality irrespective of LVEF and should therefore be rapidly scheduled for aortic valve replacement, preferably TAVI, after Heart Team decision [97].

Similarly, the TOPAS prospective observational cohort study (including 481 consecutive patients; age 75 ± 10 years; 71% men) with LFLG AS (aortic valve area ≤0.6 cm^2/m2 and mean gradient <40 mm Hg) supported early AVR for both classic and paradoxical LFLG AS based on the major mortality reduction with the intervention. The subgroup of patients with pseudo-severe AS also seemed to have better survival with early AVR. This study also preferred TAVI, specifically using femoral access, as the optimal strategy for patient survival compared to conservative management and SAVR [98].

In patients with HFrEF (LVEF<50%) and moderate AS from a retrospective cohort, extant risk of mortality can be reduced with TAVI, but not SAVR, during follow-up [99]. By contrast, registry data analysis revealed both TAVI and SAVR as valid options for the improvement of 1-year survival in patients with low ejection fraction low-grade aortic stenosis compared to medical therapy [100]. No significant differences were observed between the two AVR approaches, although adjusted clinical outcomes were numerically better in SAVR at 1 year (all-cause death 13.9 % vs 25.1% in TAVI, cardiovascular death 9.6% vs 22.6%, all-cause death, major stroke or myocardial infarction 17.5% vs 27.9%) [100]. It seems that based on overall evidence from 32 studies, aortic valve replacement through either TAVI or SAVR can significantly decrease all-cause mortality in all subclasses of low-gradient AS (classical LFLG, paradoxical LFLG), compared with conservative management [101]. No significant difference was observed between the surgical and transcatheter approaches [101].

The TOPAS-TAVI registry demonstrated positive periprocedural outcomes in patients with LFLG-AS who underwent TAVI. However, at the 2-year follow-up, mortality was high among LFLG-AS TAVI recipients (1/3 of patients). Predictors of worse outcomes included pulmonary disease, anemia, and residual PVLs [102]. That being said, a sub-study of this registry revealed comparable clinical outcomes with TAVI between patients with severe left ventricular dysfunction (LVEF<30%) and those with milder LV dysfunction [103]. Moreover, the increase in LVEF observed with TAVI was irrespective of contractile reserve, which supports TAVI for patients with LF-LG AS regardless of the severity of left ventricular dysfunction and dobutamine stress echocardiography results [103]. Registry data demonstrated only low flow to be an independent predictor of all-cause and cardiovascular mortality in patients undergoing TAVI for AS [104]. By contrast, LV ejection fraction and mean pressure gradient could not predict survival; The significant increase in mortality among low flow AS patients with LVEF of 50% did not persist in multivariate analysis [104]. Overall, TAVI is supported in patients with low flow severe AS due to high procedural success and exceptional functional improvement, despite worse long-term survival [104]. Contrasting results were observed in real-world data from the TVT registry (11,292 patients who underwent TAVI), where higher mortality and recurrent heart failure were associated with low aortic valve gradient, but not LV dysfunction. Despite the implications of the above-mentioned findings on the evaluation of TAVI on a case-by-case basis, treatment with TAVI should not be excluded bases on severe LV dysfunction and/or low aortic valve gradient [105].

When considering early hemodynamic changes and long-term outcome of patients with severe low-gradient AS after TAVI, classical LFLG-AS (representing the heart failure with reduced ejection fraction (HFrEF) form of AS) carries the worst prognosis but is still associated with early hemodynamic reverse response after TAVI [106]. Another imaging study reported that long-term mortality after TAVI can be predicted by longitudinal LV systolic function assessment by tissue Doppler imaging. This can guide risk stratification in such patient populations, noting that clinically meaningful reductions in longitudinal systolic function are best defined by an average S′ below 6.5 cm/s [107]. Moreover, LV reverse modeling after TAVI seems to be similar to SAVR, but reductions in valvular pressure gradient and myocardial fibrosis were higher in TAVI [108].

As for transcatheter approaches, transfemoral TAVI is less invasive than transapical TAVI and SAVR, with less intraoperative trauma and

pericardial adhesions to the heart. Moreover, early improvement of LVEF was superior with transfemoral TAVI compared to transapical TAVI among patients with a pre-existing reduced LV-function. Patients with a preoperative reduced LVEF undergoing SAVR also experience an increase in LV function [109]. 1 in 3 patients undergoing TAVI can experience early LVEF improvement (defined as ≥10% points increase over baseline LVEF at 30 days), and by extension, better 5-year survival (all-cause and cardiac death). This was shown in a sub-analysis of the PARTNER trials which included high- or intermediate-risk patients with symptomatic severe aortic stenosis and LVEF less than 50% [110].

However, the comparison of TAVI and SAVR in terms of LVEF recovery is inconsistent in the literature; a prospective study of echocardiographic data reported that in patients with severe aortic stenosis and depressed LV systolic function, LVEF recovery was better with TAVI compared with SAVR [111]. On the other hand, a sub-study of the NOTION trial reported a larger LV mass regression at 1 year after SAVR compared with TAVI. This difference could be caused by the higher rates of PVL and pacemakers in the TAVI group [112].

The coexistence of severe AS and impaired LVEF always concerns the Heart Team specialists and pushes towards a transcatheter approach that currently seems to guarantee a lower perioperative risk than the surgical treatment. To date, there are not enough data available about long-term outcome of TAVI. Therefore, especially in young subjects who are expected to gain a significant benefit from AVR and with a good life expectancy, the choice of the best treatment has to be carefully evaluated, even discussing with the patient themself about the risk/benefit of both solutions. Finally, the decision between TAVI and SAVR imposes a comprehensive short-term and long-term risk evaluation, especially when pre-existent factors can predispose to a suboptimal transcatheter treatment.

There are not currently large-scale clinical trials specifically designed to assess TAVI in patients with paradoxical low flow, low-gradient aortic stenosis (PLFLG-AS). This is because PLFLG-AS is a complex condition and diagnosing who will benefit from TAVI requires careful evaluation. However, there is growing evidence from observational studies that TAVI can be an effective treatment for some patients with PLFLG-AS. These studies found that TAVI improved symptoms and valve function in most patients. Additionally, some patients with PLFLG-AS derived similar clinical benefits from TAVI as patients with high-gradient aortic stenosis.

In a meta-analysis of 32 studies with a total of 6515 patients which assessed the impact of aortic valve replacement (AVR) on survival in patients with each subclass of low-gradient (LG) aortic stenosis (AS) and to compare outcomes following SAVR and TAVI. Overall, AVR was associated with a significant decrease in all-cause mortality in classical LF-LG (hazard ratio [HR]: 0.42; 95% confidence interval [CI]: 0.36 to 0.48), paradoxical LF-LG (HR: 0.41; 95% CI: 0.29 to 0.57), and NF-LG (HR: 0.41; 95% CI: 0.27 to 0.62) AS compared with conservative management. No significant difference was observed between SAVR and TAVI [101].

These findings suggest that TAVI may be a viable option for some patients with PLFLG-AS. However, more research is needed to determine the best way to select patients who are likely to benefit from the procedure as patients with PLFLG-AS often present a great challenge in the assessment and that multidimensional evaluation is required to select the appropriate patients for TAVI. Thus, heart team should be actively involved in selecting the best management pathway for patients with PLFLG-AS.

Recommendation(s):

- *TAVI and SAVR are both recommended for patients with confirmed AS and low ejection fraction (<50%)* ***(Class I recommendation, level of evidence B)***

- *TAVI and SAVR should both be considered for patients with severe low flow low gradient AS* ***(Class IIa recommendation, level of evidence B)***

- *TAVI may be considered for selected patients with paradoxical low-flow, low-gradient aortic stenosis* ***(Class IIb recommendation, level of evidence C)***

4.10. TAVI for severe symptomatic AS with concomitant coronary artery disease (CAD)

Evidence summary:

Overall, evidence suggests that a percutaneous transcatheter approach confers similar short-term outcomes compared to a surgical approach in patients with severe AS and CAD. However, survival rates and MACCE might be worse at long-term follow-up. Additional high-quality trials, especially RCTs, are still needed. One published trial (ACTIVATION) showed that in patients with severe AS and asymptomatic CAD, outcomes were similar after TAVI with percutaneous coronary intervention

(PCI) vs medical therapy [113]. Revascularization might not be necessary in the absence of a compelling indication and TAVI alone should be sufficient. This will be clear when the results of ongoing trials are published. 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.

Evidence overview:

Evidence on clinical outcomes after TAVI + PCI or SAVR + coronary artery bypass graft surgery (CABG) in patients with severe AS and concomitant CAD are generally conflicting. Some studies found comparable outcomes between the two approaches, while others favor one over the other. No differences in either 30-day or 2-year mortality were observed in the SURTAVI trial between patients undergoing TAVI + PCI and those undergoing SAVR + CABG. That being said, the TAVI + PCI group had a significantly higher risk of permanent pacemaker implantation and vascular complications at 30 days, while the SAVR + CABG group were more likely to suffer an AKI and atrial fibrillation [114]. In a similar vein, comparable outcomes in terms of MACCE, all-cause mortality, myocardial infarction and stroke were reported after a median follow-up period of 3 years in a propensity-matched analysis of patients with severe AS and complex CAD (156 pairs) who had TAVI + PCI or SAVR + CABG. However, TAVI + PCI recipients were more likely to need repeat coronary revascularization [115]. This confirmed results from earlier propensity-matched analysis [116]. The Italian OBSERVANT study also showed that in patients with associated severe AS and CAD, percutaneous treatment (TAVI and staged or concomitant PCI), early and mid-term risk of death from any cause, myocardial infarction, stroke and unplanned revascularization occur in similar rates as in patients treated surgically (SAVR and concomitant CABG) [117]. When looking at overall evidence from different studies, two meta-analyses (3 studies, 1380 total patients; 6 studies, 1770 total patients) found no significant difference in short-term safety outcomes or early and late mortality between the total percutaneous and total surgical approaches [118,119]. That being said, these findings are based on studies of low quality, emphasizing the need for adequately powered studies.

However, clinical outcomes were not comparable in all studies investigating this patient population. A prospective registry analysis of SAVR + CABG patients (n = 464), TAVI + off-pump/minimally-invasive coronary artery bypass patients (n = 50), and TAVI + PCI patients (n = 112) showed that while in-hospital mortality was comparable between TAVI + PCI and SAVR + CABG groups (9.0 and 6.9%; p = 0.009), 1-year survival and risk of rehospitalization was higher in the TAVI + PCI group. The highest levels of in-hospital mortality (18.0%), 1-year mortality and rehospitalization were observed among patients who underwent TAVI + off-pump/minimally-invasive CABG. To note that patients in the TAVI groups were older than those in the SAVR group, and prior cardiac surgery was more common in TAVI + PCI [120]. The most recently published meta-analysis at the time of writing (8 studies, 33,286 total patients (3448 for TAVI plus PCI and 29,838 for SAVR plus CABG) corroborated these results, showing that TAVI + PCI (in comparison with SAVR plus CABG) lead to lower in-hospital death and AKI but significantly worse survival rates and more MACCE at 5-year follow up [121]. By contrast, other large-scale data from close to 31 thousand patients revealed better survival and lower rates of periprocedural complications among patients who underwent TAVI + PCI compared to those who had SAVR + CABG. These outcomes were observed despite worse baseline characteristics, as recipients of TAVI + PCI were older, had higher proportions of females and higher prevalence of congestive heart failure and chronic renal failure [122]. Similar results favoring TAVI and PCI were reported in a small retrospective single center study, involving 52 age and sex-matched patients/group [123].

In a recent registry, The REVASC-TAVI registry, 1603 patients undergoing TAVI with significant, stable CAD were scheduled to undergo PCI before, after or concomitantly with TAVI. Performance of PCI after TAVI was associated with improved 2-year clinical outcomes including all-cause death and a composite of all-cause death, stroke, myocardial infarction or rehospitalization for congestive heart failure [124].

Recommendation(s):

- *TAVI+PCI or SAVR+CABG should be considered for severe AS with associated CAD* ***(Class IIa recommendation, level of evidence B).***

- *If TAVI+PCI is chosen as a strategy then PCI should be considered after the TAVI (excluding left main coronary disease)* ***(Class IIa recommendation, level of evidence B).***

4.11. TAVI for severe symptomatic AS with concomitant significant mitral valve disease

Evidence summary:

Significant early improvement in mitral regurgitation (MR) can be observed after both TAVI and SAVR, but there is no clear evidence this improvement from either approach to better survival. Primary and secondary MR should be differentiated when making decision regarding the appropriate intervention. Treatment should be considered with worsening symptoms (NYHA or II/IV), LV dysfunction, pulmonary hypertension and/or persistent moderate-severe MR.

For primary MR and AS patients, heart team should decide the appropriate intervention between TAVI vs. SAVR depending on the patient's age and risk profile. For secondary MR and AS, possibility of MR improvement after TAVI should be considered. TAVI should be done for mitral stenosis and AS if Mitral Balloon Valvoplasty is feasible, and then the patient should be reassessed. If Mitral balloon valvoplasty is not feasible, then double valve replacement is recommended. If the patient has prohibitive risk for surgery, then TAVI ± percutaneous mitral valve replacement should be considered.

In AS with concomitant mitral stenosis, improvement can be expected after both TAVI and SAVR. That being said, TAVI is a safe and attractive option for patients undergoing AVR with less complications compared with SAVR. Ultimately, the decision should be case-dependent, with concerns on anatomical and clinical features.

Evidence overview:

There are no head-to-head studies comparing TAVI and SAVR in severe symptomatic AS with concomitant mitral regurgitation by the time of writing. Improvement in preoperative moderate to severe mitral regurgitation was observed in the PARTNER trial following both SAVR and TAVR; of 21% of SAVR patients and 20% of TAVI patients who had preoperative moderate to severe mitral regurgitation, 69% of SAVR patients and 58% of TAVI patients experienced improvement at 30 days. However, this significant early improvement in MR did not translate to improved survival with SAVR, which was associated with increased mortality at 2 years. By contrast, this associated was not observed with TAVI, which suggests that TAVI may be a reasonable option in selected patients with combined aortic and mitral valve disease [125]. A local Saudi study also reported significant improvement in MR after TAVI that is more pronounced in severe types. This improvement was irrespective of MR etiology, implanted valve type, and operative risk, which calls for confirmation of these results in a larger multi-center study [126]. A large study (n = 1100 patients) confirmed that significant MR is not uncommon in patients undergoing TAVI for severe AS, and that significant improvement in the degree of MR can be expected in more than 50% of patients. This is important considering that significant MR is associated with worsened survival and could persist after TAVI. That being said, after dedicated pre-imaging evaluation, percutaneous mitral procedures could be beneficial for at least 1 in 10 patients with persistent MR, while Mitral Clip could have even wider applications in this patient population [127]. Long-term follow-up data (up to 12 years) after SAVR also revealed improvement in secondary MR after AVR. While this improvement is observed even without mitral surgery, it is greater with concomitant mitral surgery albeit with no impact on survival. That being said, compromised survival was observed in patients who did not experience immediate improvement after AVR, and concomitant atrial fibrillation calls for mitral valve repair at the time of surgery [128]. In a similar vein, increased late and early mortality was reported in a meta-analysis of patients who underwent TAVI for AS with concomitant moderate-severe MR, despite half of patients exhibiting a significant improvement in MR severity after the procedure. The use of a balloon-expandable valve was associated with a greater degree of improvement [129]. When looking at a physiological level, real-time three-dimensional transesophageal echocardiography evidence reveals immediate improvement in mitral leaflet tethering after TAVI in patients with mitral leaflet tenting regardless of mitral annular geometry. Global left ventricular hemodynamics and mitral leaflet tethering change are the main predictors of acute improvement in mitral regurgitation after TAVI [130]. Retrospective data showed that improvement in MR can be expected in 60% of patients undergoing isolated (either TAVI or SAVR). MR improvement can be predicted by greater ventricular dimensions and is in turn associated with lower long-term mortality. However, the need to adopt a staged approach remains debatable, especially considering the comparable 2-year survival rates of patients who had TAVI, SAVR, or a double aortic-mitral valve procedure [131]. That being said, transcatheter mitral valve interventions (particularly percutaneous edge-to-edge mitral valve repair) post-TAVI have been shown to be feasible, safe, and could lead to significant improvement in MR grade and NYHA functional class in patients with persistent significant MR and symptoms with post-TAVI,

who are anatomically suitable for these interventions. Although mortality was lower with a stage percutaneous edge-to-edge mitral valve repair strategy, this improvement in survival did not reach statistical significance [132]. In general, registry data (German transcatheter mitral valve interventions (TRAMI) registry; STS registry) reveal higher mortality and morbidity following double (mitral-aortic) valve interventions compared to isolated AVR [133–135]. However, double valve interventions may be indicated in some cases; moderate MR can lead to worsened clinical outcomes, such as higher mortality, if left untreated at the time of SAVR [136,137]. That said, the adverse effect of untreated moderate functional MR in patients undergoing SAVR was not consistently reported, as Ruel et al. found no independent adverse effect on survival even at mean follow-up of 5.4 ± 3.4 years [138]. Risk factors other than moderate functional AS could play an important role, as patients with one other risk factor (left atrial diameter >5 cm, mean/peak gradient <40/60 mmHg or atrial fibrillation) were at increased risk for the composite outcome of heart failure symptoms, cardiac death or subsequent mitral repair or replacement (hazard ratio 2.7; $p = 0.004$) [138].

Mitral stenosis (MS) is also not uncommon in TAVI patients with severe symptomatic AS, affecting approximately one fifth of these patients. Concomitant MS (particularly rheumatic MS) led to worsened clinical outcomes, evident on the level of a higher risk of cardiovascular adverse events at 1 year as well as increased risk of cardiovascular death [139]. Consistently, a meta-analysis confirmed higher frequency of at least moderate paravalvular aortic regurgitation early all-cause mortality, early incidence of myocardial infarction, and midterm all-cause mortality after TAVI in patients with MS compared to those without [140]. TAVI is safe in patients with severe AS and concomitant mitral stenosis based on a retrospective large-scale data (almost 4500 patients). Moreover, TAVI is associated with less complications, better in-hospital mortality, and shorter length of stay in this patient population compared with SAVR, despite worse baseline characteristics in the TAVI group [141]. That being said, both SAVR and TAVI can lead to improvement in mitral valve area in nearly half of patients with severe aortic stenosis and mitral stenosis. However, this means that half of patients will have persistent true mitral stenosis (mitral valve area <2 cm^2) after AVR, and by extension, worse survival [142]. TAVI was an independent predictor of improvement in mitral valve area, potentially due to an increase in stroke volume after TAVI [142].

According to the current guidelines, bi-valvular surgery is indicated in the presence of mitral valve area ≤1.5 cm^2. Compared to isolated AVR, double valvular surgery is associated with higher operative mortality and poorer long term. Significantly worse prognosis is associated with MS, even when mild and not leading to secondary pulmonary hypertension or manifest valvular atrial fibrillation [139].

Balloon dilatation may not be helpful in mitral calcific degenerative disease and can be dangerous in the case of annular calcifications [143]. In patients at high surgical risk and not suitable for balloon valvuloplasty, *trans*-catheter mitral valve replacement is now possible with proven efficacy and safety either alone [141], or in combination with or subsequently to TAVI (74). When comparing the outcomes of the off-label use of TAVI devices in mitral annular calcification for mitral stenosis, valve-in-valve (ViV), and valve-in-ring procedures, worse 30-day and 1-year survival as well as lower rate of technical success were associated with valve in mitral annular calcification procedures [144].

Recommendation(s):

- *Heart team discussion is recommended to decide for TAVI in patients with primary severe MR and severe symptomatic AS who are at high surgical risk or inoperable* ***(Class I recommendation, level of evidence C)***

- *For patients with secondary severe MR and severe AS it is recommended to assess the possibility of improvement of mitral valve regurgitation after TAVI according to proposed predictors* ***(Class I recommendation, level of evidence B).***

- *If transcatheter repair is feasible, TAVI should be considered for patients with secondary severe MR and severe AS who are at high surgical risk or inoperable.* ***(Class IIa recommendation, level of evidence C)***

- *If Transcatheter repair is not feasible, TAVI with or without staged percutaneous mitral valve replacement should be considered for patients with severe secondary MR and severe AS who are at high surgical risk or inoperable* ***(Class IIa recommendation, level of evidence C)***

- *TAVI is recommended in patients with severe mitral stenosis and severe AS if mitral valve balloon is feasible,* ***(Class I recommendation, level of evidence B).***

- *TAVI with or without staged percutaneous mitral valve replacement may be considered in patients with severe mitral stenosis and severe AS who are at high surgical risk or inoperable* ***(Class IIb recommendation, level of evidence C).***

4.12. TAVI with alternate access for severe symptomatic AS with peripheral vascular disease

Evidence summary:

Overall, studies have yet to clearly define the relative risks and benefits of TAVI using alternative, non-transfemoral arterial approaches. The most superior non-femoral access for TAVI remains debated and available data are potentially limited by several confounding factors, being derived from TAVI registries. The choice of which alternative access to be used has to rely on the individualized decision of each center in the absence of no data from randomized trials on the relative safety and efficacy among non-femoral approaches.

Evidence from RCTs, observational studies, registries and meta-analyses show that central *trans*-axillary/transaortic access has higher mortality, higher morbidity and lower stroke and vascular complications vs transfemoral or other alternative access. In recent years, multiple studies from high volume centers, registries and several meta-analyses have demonstrated the safety and efficacy of alternative access strategies, especially *trans*-axillary, *trans*-carotid and transcaval access. There is also emerging evidence on methods facilitating transfemoral access (shock wave dilation of iliac, smaller sheaths, etc.). It preserves the benefit of transfemoral TAVI, is less invasive, safe with very low complication rate, and avoids long learning curve of alternative accesses. With the increased use of these techniques, the need for alternative access is becoming more limited. Important considerations include relative expertise of each non-femoral approach by the heart team in concern and patient-related factors, including anatomical characteristics and frailty. Heart team discussion is therefore needed for decisions regarding alternative access for TAVI on a case-by-case basis.

Evidence overview:

A transapical TAVI strategy did not compare favorably with SAVR in the PARTNER 2 and STACCATO trials. In the PARTNER 2 trial, 76.3% of the patients were included in the transfemoral-access cohort and 23.7% in the transthoracic-access cohort (either transapical access (174 patients) or transaortic access (62 patients)). The rate of death or disabling stroke was lower in the transfemoral-access TAVI cohort than surgery (hazard ratio, 0.79; 95% CI, 0.62 to 1.00; P = 0.05), but not in the transthoracic-access cohort, (hazard ratio in the intention-to-treat analysis, 1.21; 95% CI, 0.84 to 1.74; P = 0.31; hazard ratio in the as-treated analysis, 1.14; 95% CI, 0.79 to 1.65; P = 0.47). Although the differences between SAVR and transthoracic-TAVI were not statistically significant, it can be said that outcomes after transthoracic TAVI are similar to or worse than those with surgery, but appear to be inferior to those with transfemoral TAVI [30]. The STACCATO trial was a small prematurely terminated study whose results suggested comparable or inferior rates of device success and higher complications with transapical-TAVI in low-risk patients compared to high-risk patients with aortic valve stenosis [145]. A previous study involving high-risk patients treated with TAVI also showed higher rates of adverse periprocedural events and death among propensity-matched patients who underwent transapical access than among those who underwent transfemoral access [146]. Overall, it seems that transapical access has consistently been linked to increased procedural complication and increased morbidity and mortality, rendering this approach of primarily historical significance in TAVI at this point [147–149].

When comparing different TAVI approaches and SAVR, results of a meta-analysis from 2017 (4 RCTs (n = 2319) and 14 propensity-matched cohorts (n = 7217)) revealed comparable results between transfemoral TAVI and SAVR in terms of early and mid-term deaths. While transfemoral-TAVI and transapical TAVI were associated with similar rates of early deaths, Transapical TAVI could lead to a higher (but not statistically significant) number of mid-term deaths [150]. Of non-femoral approaches, *trans*-axillary and subclavian TAVI were associated with a higher risk of perioperative stroke based on data from the STS/ACC TVT registry (*trans*-axillary and *trans*-subclavian TAVI stroke risk of 6.3%, significantly higher than transthoracic approaches (odds ratio of 2.1) [149].

Similarly, *trans*-axillary and *trans*-subclavian TAVI have been shown to be associated with higher stroke risks when compared to *trans*-carotid and *trans*-caval approaches [151,152]. In a retrospective analysis, outcomes were similar among 102 patients with comparable baseline characteristics (except higher surgical risk in *trans*-carotid TAVI) who were treated with alternative TAVI accesses (*trans*-carotid; n = 49 and *trans*-apical; n = 53). Both approaches were safe to use in appropriately selected patients; While the rates of procedural success, rate of Valve Academic Research Consortium-2 defined clinical events, new-onset rhythm disturbances and permanent pacemaker implantation and 30-day mortality were comparable between the two approaches, significantly more cases of pneumonia and blood transfusions were observed in the *Trans*-apical-TAVI group (11% vs. 0%; p = 0.01 and 30.2%

vs. 12.2%; p = 0.03) [153]. Better outcomes were observed with the *trans*-carotid approach compared with transapical and transaortic access for TAVI in other studies. This was evident on the level of several clinical variables, including shorter length of stay, fewer transfusions, more frequent discharge to home, better 2-year survival, less new-onset atrial fibrillation, less major or life-threatening bleeding (4.3% versus 19.9%; P = 0.002), and less AKI [147,148]. Non-transfemoral *trans*-arterial approaches were also found to be safe and feasible, as they were associated with similar outcomes (major perioperative complications and midterm mortality) to the transthoracic approach for TAVI [154]. In an observational multicenter study from France and the United States, 20% of patients had an alternative access TAVI (of which 26% *trans*-apical, 39% *trans*-aortic, 10% *trans*-subclavian, and 25% *trans*-carotid [155]. All examined approaches yielded similar frequency of PVL, intra-procedural bleeding, vascular complications, conversion to open-heart surgery, and development of AKI. However, while *Trans*-aortic TAVI was associated with higher in-hospital mortality than other non-TF approaches, this could be due to patient-related rather than procedural factors [155]. Alternative access techniques lead to comparable clinical outcomes and could be safe and feasible when conducted in centers with high technical expertise. Finally, there is limited evidence to suggest that *trans*-caval TAVI might be superior to *trans*-axillary access with respect to stroke risk, with a tendency towards lower mortality and acute renal failure risk compared to *trans*-axillary access [152].

Recommendation(s):

- *Alternative access selection should be based on heart team discussion considering the patient's anatomy, excellent preprocedural planning, local experience and the risk/benefit of each access* ***(Class I recommendation, level of evidence A)***

- *Facilitated TAVI (Intravascular lithotripsy or angioplasty in suitable peripheral arteries) should be considered* ***(Class IIa recommendation, level of evidence C)***

- *The choice of Trans-carotid, trans-caval, Trans-subclavian/trans-axillary depends on local experience and anatomy* ***(Class IIa recommendation, level of evidence B)***

- *Trans-aortic/trans-apical access may be considered if there are no other alternative access* ***(Class IIb recommendation, level of evidence A)***

4.13. TAVI for severe symptomatic AS in patients with chronic renal failure

Evidence summary:

Overall, evidence suggests that patients with severe symptomatic AS and concomitant chronic kidney disease (CKD) have good outcomes after both SAVR and TAVI. TAVI is at least comparable to SAVR, if not better. However, evidence to the superiority of TAVI over SAVR remains inconsistent. Compared to SAVR, TAVI carries the advantage of a decreased incidence of worsening of renal failure or AKI, of new dialysis, and of intensive care unit stay but the disadvantage of increased vascular complications. Patients on dialysis and advanced CKD will benefit more from lower hospitalization such as in TAVI. However, the choice between SAVR and TAVI should be decided by the heart team based on patient risk.

Evidence overview:

Long-term outcomes at 5 years from a pooled analysis of patients from the PARTNER 2A RCT and the SAPIEN 3 Intermediate Risk Registry reflect comparable results with SAPIEN 3 TAVI and SAVR in intermediate-risk patients with AS and CKD. This was observed on the level of the risk for the primary endpoint of death, stroke, rehospitalization, and new hemodialysis. It is important to note that the durability of the SAPIEN 3 valve was comparable to surgical bioprotheses, but TAVI was associated with less postprocedural AKI compared to SAVR [156]. When retrospectively examined, results from the CoreValve US Pivotal High-Risk Trial also showed similar rates of all-cause mortality, myocardial infarction or all stroke/TIA or need for new dialysis between TAVI and SAVR in high-risk patients with moderate/severe CKD. That being said, 3-year major adverse cardiovascular and renal events were lower with TAVI versus SAVR. Moreover, patients undergoing TAVI and experiencing worsening CKD had higher mid-term mortality and major adverse cardiovascular and renal events [157].

Observational data show that patients with advanced CKD and concomitant atrial fibrillation and dialysis therapy are at an unacceptably high risk of death after TAVI (up to 71% in the first year), in addition to the risk of bleeding events carried by this procedure [158]. This should be carefully considered during patient risk assessment. That being said, the in-hospital mortality of patients with AS and end-stage renal disease (ESRD) who are on hemodialysis is high, regardless of the AVR

approach (TAVI or SAVR), as shown in a propensity score-matched analysis of 175 pairs of patients. While no differences were evident between TAVI and SAVR on the level of in-hospital mortality, patients undergoing TAVI had shorter length of stay, lower hospitalization costs, lower in-hospital complications, and a higher rates of home discharge [159]. By contrast, a larger propensity matched analysis of 2485 pairs found significantly worse survival and higher periprocedural complications (higher AKI, dialysis requirement, blood transfusion, atrial fibrillation, iatrogenic cardiac complications, pericardial complications, perioperative stroke, perioperative infections, and postoperative shock) in patients who underwent SAVR and had advanced kidney disease, as compared with TAVI [160]. However, the survival advantage of TAVI might be restricted to the short-term. An observational study of close to 9000 patients who underwent TAVI, SAVR or conservative management found comparable mid-term, but not short-term, mortality between TAVI and SAVR in patients with ESRD undergoing hemodialysis. Compared to conservative management, survival of these patients can be improved by both AVR approaches (TAVI and SAVR). Moreover, heart failure hospitalizations can be reduced with AVR, albeit significantly more with TAVI compared to SAVR [161].

A sub-analysis of 170 propensity-matched pairs from the OBSERVANT study confirmed the higher risk of AKI after SAVR compared to TAVI in patients with advanced CKD (stages 3b to 5). While all patients with advanced CKD had lower survival after AVR, early and late mortality was somewhat lower after SAVR in this analysis [162]. TAVI is at least comparable to SAVR in patients with moderate to severe CKD, as both approached led to excellent results in an intermediate-risk population from the large nationwide German Aortic Valve Registry [163]. This was confirmed by several meta-analyses, which suggested that TAVI yields similar outcomes to SAVR with the advantage of a decreased incidence of worsening of renal failure or AKI, new dialysis, and intensive care unit stay but the disadvantage of increased vascular complications [164–166]. The most recent meta-analysis (21 studies, 38,989 total patients) noted a survival advantage with TAVI in terms of in-hospital and 1-year mortality in patients with advanced CKD, particularly those on dialysis [167]. TAVI was associated with several other positive outcomes, such as lower risk of stroke, AKI, bleeding, blood transfusion, AKI requiring dialysis, infection, major vascular damage, new-onset AF, cardiac tamponade, intensive care unit stay and length of stay. That being said, the risk of permanent pacemaker implantation and major vascular damage in this patient population was lower after SAVR [167].

A large study including 12,500 AS patients with ESRD also reported results in favor of TAVI over SAVR on the level of in-patient mortality, length of stay, cost of care, and home discharge, despite patients having a higher comorbidity burden [168].

Recommendation(s):

- *TAVI or SAVR is both recommended for patients with severe symptomatic AS and chronic renal failure not on dialysis. Final choice should be based on heart team discussion* ***(Class I recommendation, level of evidence B).***

- *TAVI is recommended for patients with advanced chronic renal failure and patients on dialysis after heart team discussion* ***(Class I recommendation, level of evidence B).***

- *SAVR should be considered for patients with advanced chronic renal failure and patients on dialysis after heart team discussion* ***(Class IIa recommendation, level of evidence B).***

4.14. TAVI for treated (healed) aortic valve endocarditis

Evidence summary:

The majority of evidence suggests comparable incidence of infective endocarditis after SAVR and TAVI, but some studies suggest a higher risk after SAVR. SAVR remains the golden standard for the treatment of endocarditis in international guidelines. There are no RCTs or observational studies comparing SAVR to TAVI for treated aortic valve endocarditis. Data on the use of TAVI for healed infective endocarditis remains scant, limited to one controversial study and 2 case reports. However, evidence suggests TAVI to be feasible for patients at prohibitive risk for surgery. Heart team discussion is therefore needed for infective endocarditis: there is a need to differentiate between infective endocarditis in severe AS without prior intervention, infective endocarditis post TAVI, infective endocarditis bioprosthetic aortic valve, recurrent endocarditis, and active vs healed endocarditis. To note that imaging can't be used to differentiate between healed or not healed endocarditis but can reveal presence of complications.

Evidence overview:

A limited number of published reports describe the use of percutaneous treatment for residual lesions after infective endocarditis as peri-prosthetic leakage or mitral damage, with good outcomes

[169,170]. Also, treatment of residual lesions with TAVI have been published in several anecdotal cases, with ideal outcomes at follow-up [169–172]. However, the actual risk and predictors of relapse or other complications remain unknown, which prompted a group of researchers (Santos-Martínez et al., 2020) [173] to establish and analyze data from a multicenter consecutive registry of TAVI cases including all those with prior aortic valve infective endocarditis (-IE) considered healed after antibiotic therapy but with residual severe valvular lesion treated with TAVI. The incidence of prior AV IE with residual valvular lesion and healed infection was found to be 1.8% (54/2920 patients). These patients were more likely to have a valvular prosthesis rather than a native valve, and had worse surgical risk, and a higher rate of multivalvular disease. After conducting a matched comparison of 46 pairs of patients, both in-hospital and 1-year mortality rates (5.6 and 11.1%, respectively) were worse in patients with prior AV IE with residual valvular lesion and healed infection compared to the control group. The authors considered TAVI to be a safe therapeutic alternative for residual valvular lesion after successfully healed AV IE based on the low risk of IE relapse and comparable survival in patients with or without prior IE, despite significant aortic regurgitation being observed in 25% of patients, and re-admission being needed in half [173]. However, these results were highly criticized due to several important limitations, such as highly selected patient population, lack of indication for TAVI, differences in baseline characteristics, small sample size, and lack of comparator (medical therapy) [174]. While TAVI could be feasible in this setting, medical therapy remains the standard of care for such patients and the two approaches should be investigated in a prospective randomized trial, powered for hard endpoints before comparing TAVR to SAVR.

Several case reports are also worth mentioning.

Kuehl et al. (2009) presented the case of a highly symptomatic 64-year-old male with severe hemolysis caused by paravalvular leakages after reoperation of a mechanical mitral valve replacement due to recurrent endocarditis [169]. In this patient, the percutaneous closure approach was favored over the surgical approach seing as a reoperation would have entailed significant perioperative risk due to patient comorbidity (pulmonary hypertension, renal dysfunction) and the high chance of recurrence of PVLs (67%) [169]. Park et al. (2017) described transcatheter mitral valve repair for subacute infective endocarditis [170]. The patient was a 75-year-old man with a recent diagnosis of Enterococcus faecalis native mitral valve IE four weeks prior on outpatient parenteral antimicrobial therapy. Cardiogenic shock and renal failure requiring hemodynamic support occurred despite continued medical therapy. Based on a heart team discussion, the patients was deemed inoperable but suitable for transcatheter mitral valve repair based on his hemodynamic instability. The patient then had a successful transcutaneous mitral valve repair with 2 Mitra Clip placement in the A2-P2 and A3-P3 scallops without complications [170]. Albu et al. (2013) [172] reported a case of a patient with endocarditis by severe homograft aortic stenosis for which a TAVI procedure was performed with an excellent result. After developing a *Staphylococcus aureus* sepsis during a pre-SAVR standard screening, aortic valve vegetation was observed on transesophageal echocardiography. This was followed by a stroke several days later, possibly due to embolization of a vegetation. Considering the high surgical risk in this case, TAVI was therefore undertaken and led to fast normalization of the septic shock parameters and clinical status. The patient continued to be completely asymptomatic 6 months post discharge, with normally functioning aortic valve without indications of endocarditis on echocardiography [172]. Nguyen et al. (2015) described the case of a patient who was successfully treated by transcatheter aortic valve-in-valve-in-valve replacement with a favorable 1-year outcome, despite severe early complications [171]. Another case report described the use of TAVI to treat infective endocarditis in an 88-year-old man with small lymphocytic lymphoma and incident heart failure [175]. Staphylococcus epidermidis endocarditis was evident upon blood screening and was complicated by severe aortic regurgitation. The patient decompensated into cardiogenic shock despite intravenous antibiotic therapy and aggressive intravenous diuresis therapy. TAVI with palliative intent was preferred over SAVR following multidisciplinary discussion involving the patient and his children, leading to symptomatic and functional improvement as well as resolution of cardiogenic shock [175]. Finally, one case described a 69-year-old man with a history of bioprosthetic aortic valve replacement who presented with Corynebacterium striatum prosthetic valve endocarditis complicated by severe aortic insufficiency with refractory cardiogenic shock despite antibiotic therapy [176]. After multidisciplinary evaluation, the patient was deemed at prohibitive risk for surgery and underwent off-label ViV-TAVI. The patient had a good recovery, with

normal functioning prosthetic valve evident on transthoracic echocardiogram at 12 months.

However, not all evidence supports positive outcomes after TAVI in this setting. In a registry analysis of 584 patients who developed infective endocarditis after TAVI, patients were treated with surgery (19%) or antibiotics alone (81%). Survival was not improved by cardiac surgery (both on the level of in-hospital or 1-year mortality) and high mortality was strongly predicted by patients' characteristics, pathogen, and infective endocarditis-related complications (logistic Euro SCORE I, *Staphylococcus aureus*, acute renal failure, persistent bacteremia, and septic shock) [177]. Another retrospective database analysis also showed the lack of a mortality benefit with surgical vs medical management of infective endocarditis post TAVI [178]. SAVR was performed for 2.21% of a total of 906 hospitalizations for infective endocarditis following TAVI, with no significant advantage in terms of in-hospital mortality and 30-day readmissions compared to medical therapy despite higher cost and longer length of stay [178].

However, SAVR could result in better survival in patients with Staphylococcus Aureus infective endocarditis undergoing surgery at the time of index Staphylococcus Aureus IE episode compared with medical therapy alone. This is important considering the high rate of both in-hospital mortality and late mortality associated with Staphylococcus Aureus infective endocarditis, which accounts for approximately 25% of IE cases after TAVI [179].

Several studies have compared the incidence of IE after SAVR and TAVI. Observational analyses using the United States Readmissions Database [180], Danish National Patient Registry [181], the FinnValve Registry [182] and a pooled analysis from the PARTNER trials [183] identified no difference in the incidence of IE after SAVR and TAVI over a follow-up period of 5–44 months. This was confirmed in a meta-analysis of 19 studies (84,288 total patients), both on the level of short and long-term risk of prosthetic valve endocarditis appears to be identical in patients undergoing TAVI. The comparability of both approaches was observed irrespective of the type of valve, duration of follow-up, study design and surgical risk of the patients [184]. By contrast, more than one study reported a higher incidence of IE after SAVR compared to TAVI, including a pooled analysis from three randomized controlled trials of the self-expanding Core Valve transcatheter heart valve family against SAVR [185], and an English study of an unselected consecutive nationwide population [186].

In a single-center cohort, only ten out of 494 definite cases of prosthetic valve IE were confirmed to have TAVI-IE [187]. In most cases, TAVI-IE occurred after 2–12 months of the procedures and was most commonly caused by *Staphylococcus aureus*. Conservative management was the preferred approach for the majority of cases, with a 37.5% survival rate over a mean follow-up of 709 ± 453 days [187].

Recommendation(s):

- *TAVI may be considered for the treatment of healed aortic valve endocarditis with uncomplicated vegetation* ***(Class IIb recommendation, level of evidence C)***

- *Heart team discussion is recommended to establish the optimal management of all cases of healed infective endocarditis* ***(Class I recommendation, level of evidence C)***

- *In cases of complicated healed infective endocarditis on imaging (e.g, perforation, abscess, heart block) TAVI is not recommended* ***(Class III recommendation, level of evidence C)***

4.15. TAVI for asymptomatic severe AS in patients going for non-cardiac surgery

Evidence summary:

There are no studies comparing TAVI/Balloon Valvuloplasty to SAVR. Other evidence is available on the impact of asymptomatic severe AS in patients going for non-cardiac surgery (NCS), suggesting worse outcomes in these patients. However, the risk of mortality and MACE is mainly significant in patients who are symptomatic. Postoperative adverse events after NCS might be less likely in patients with prior AVR. 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). To note that available evidence supports intervention in general rather than TAVI specifically. It is very important to establish that the patient is truly asymptomatic before making clinical decisions.

Evidence overview:

When considering available evidence, a meta-analysis (9 studies, 29,327 total patients) found that patients with AS did not have worsened survival, myocardial infarction, heart failure or stroke after NCS compared to patients without AS. That being said, patients with AS experience a significantly higher rate of adverse cardiovascular events [188].

This confirmed the results of several smaller studies, one of which reported comparable survival at 30 days and 1 year as well as similar occurrence of MACE in patients with severe asymptomatic AS who are undergoing intermediate or high-risk surgical intervention [189]. The same could not be said about symptomatic patients, which had significantly worse survival and experienced more MACE compared to their controls [189,190]. Symptomatic severe AS was actually identified as an independent predictor of adverse outcomes after NCS, as opposed to asymptomatic severe AS which was associated with comparable outcomes to controls (with the exception of borderline significantly higher risk of MI) [191]. There is also evidence confirming the relative safety of performing intermediate-to-low-risk NCS for patients with severe, asymptomatic AS [192]. To note that the comparability of clinical outcomes in patients with AS after NCS could be limited to elective surgery, as higher MACE and mortality were observed in AS patients undergoing emergency surgeries compared to non-AS patients [190]. The risks of worse survival and increased incidence of new or worsening HF in patients with severe AS who are symptomatic or asymptomatic could be reduced by conducting AVR before NCS, as shown in one study; asymptomatic patients who did not undergo preoperative AVR actually had the second worst prognosis, experiencing more complications and mortality compared to symptomatic and asymptomatic AVR patients [193]. In a similar vein, analysis of data from the CURRENT AS registry showed that severe AS, be it symptomatic or asymptomatic, results in a higher rate of 30-day mortality if left untreated before elective intermediate- and high-risk NCS [194]. Data from a prospective TAVI registry of patients also revealed that noncardiac surgery may be safely performed early after successful TAVI in the absence of suboptimal device performance (prosthesis-patient mismatch and paravalvular regurgitation) which increases the risk of adverse outcomes [195]. It should be noted that AS itself is an independent risk factor for adverse events after noncardiac surgery, in addition to being associated to 30-day in-hospital mortality, acute renal failure, pneumonia, stroke, and intensive care unit stay. When looking at factors that could affect clinical outcomes in patients with AS, neuraxial anesthesia was associated with fewer postoperative complications compared to general anesthesia [196].

Several studies reported the feasibility of BAV as bridge to SAVR or TAVI, with generally comparable outcomes in patients who underwent TAVI with pre-BAV and those who had no prior BAV [197–200]. While direct TAVI without prior BAV was non inferior to TAVI with prior BAV, there is still a role for BAV determined by upstream selection on the basis of patient anatomy [201].

Recommendation(s):

- *TAVI/SAVR should be considered for asymptomatic severe AS patients going for high-risk non-cardiac surgery* ***(Class IIa recommendation, level of evidence B)***

- *TAVI is not recommended for severe AS patients going for low/intermediate non-cardiac surgery* ***(Class III recommendation, level of evidence B)***

- *Heart Team Discussion is recommended for the choice of SAVR vs TAVI* ***(Class I recommendation, level of evidence C)***

4.16. Coronary angiogram vs. CTA for coronary assessment for TAVI patients

Evidence summary:

There are no RCTs specifically comparing CTA with coronary angiogram pre-TAVI, but there are many observational studies (retrospective/prospective) conducted. Although no direct comparisons are available between CTA and coronary angiography before TAVI, overall evidence supports CCTA as a tool with excellent diagnostic accuracy for assessing obstructive CAD in patients referred for TAVI. CT has high sensitivity and negative predictive value, low specificity and Positive Predictive Value, with no significant difference to coronary angiogram. Evidence also showed no significant differences in mortality and MACE over the short term or long term. In fact, some studies showed that Major procedure related complications occurred less often in the CT group than in the ICA group. Few studies suggest that the role of CTA may be questionable in patients with severe coronary calcifications.

Evidence overview:

Studies report on the diagnostic accuracy of CTA for patients referred to TAVI. A meta-analysis (14 small retrospective observational studies; 2533 total patients) found that CCTA has an excellent diagnostic accuracy for assessing obstructive CAD in patients referred for TAVI (sensitivity 97%, specificity 68%, area under the HSROC curve 0.96) and could save 41% of ICAs if done routinely [202]. Single-heartbeat scanners afforded significantly higher specificity compared to other scanners (82% vs. 60%) [202]. The specificity, sensitivity and

negative/positive predictive values of CTA vary from study to study. Strong et al. (2019) reported that on a per-patient analysis (assuming non-evaluable segments as stenotic), CTA showed sensitivity of 100%, specificity of 42%, and positive and negative predictive values of 48% and 100% (95% CI, 92–100%), respectively [203]. Schicchi et al. (2020) conducted a prospective study among 223 patients who underwent Dual Source CT (DSCT) for TAVI, and found that CT sensitivity, specificity, positive and negative predictive values and diagnostic accuracy on patient-based analysis were 97.8 %, 88.8 %, 68.8 %, 99.4 % and 90.6 %, respectively [204]. Gohmann et al. (2020) reported on 460 consecutive patients undergoing pre-TAVI CT. coronary CTA (cCTA) was negative for CAD in 40.2% cases, with a Sensitivity, specificity, PPV, and NPV of 97.8%, 45.2%, 49.6%, and 97.4%, respectively [205]. Meier et al. (2021) studied 127 patients, comparing CTA to ICA results. NPV of CTA was 97.5% for significant CAD and 96.3% for severe CAD, with lower values for significant CAD when looking at a patient level (88.6%). Positive predictive value and accuracy were 44.8% and 87.1% for significant CAD and 56.3% and 94.4% for severe CAD. Malebranche et al. (2022) retrospectively studied 100 consecutive patients and reported that on a per-patient analysis, where patients with low image quality were classified as CAD, CTA showed a sensitivity of 100%, specificity of 11.4%, PPV of 32.6%, NPV of 100% and diagnostic accuracy of 38% for obstructive CAD [206].

Overall, it seems that CT is feasible for TAVI planning, with one study demonstrating better performance in patients with lower coronary artery calcium score and no severe coronary calcifications [204]. In a retrospective data analysis, it was found that obstructive CAD can be ruled out in 20% of patients when combining coronary artery calcium score in patients with low image quality, and quantitative CTA assessment in patients with good image quality [206]. However, another study reported no correlation between median coronary artery calcium score and classification of patients with cCTA [205]. Regardless, cCTA could potentially exclude significant CAD in a large proportion of high-risk patients planned for TAVI without need for additional contrast medium, which could lead to safer and faster pre-procedural evaluation in selected patients [205–207]. Coronary CTA can safely exclude obstructive CAD and avoid the need for ICA in at least 25% of patients [203]. Higher proportions were reported in a prospective cohort study of 354 consecutive TAVI patients; pre-procedural invasive angiography could be avoided in at least 70% of cases with the evaluation of CAD via CTA, while rarely missing high risk findings [208]. These results suggest that patients for whom conservative CAD management is optimal, a CTA-first strategy for disease assessment should be considered [208]. Other earlier studies also supported CTA in this setting [209–219].

Recommendation(s):

*CTA should be considered for coronary assessment as alternative to ICA for TAVI patients with low to intermediate pretest probability of CAD) (**Class IIa recommendation, level of evidence C**).*

4.17. CTA vs echo for aortic valve calcium scoring and annular sizing for TAVI

Evidence summary:

Overall, CT is the gold standard of aortic valve calcium scoring and annular sizing for TAVI. Evidence shows that CT is superior to 2D echocardiography as well as 3D echocardiography in the presence of calcification. SCCT guidelines clearly recommend CT for aortic valve calcium scoring and annular sizing for TAVI. Without evidence suggesting CT is inferior to other modalities, CT should be recommended for TAVI. CT is already done in clinical practice for all patients undergoing TAVI except when contraindicated (i.e. CKD, contrast allergy, contrast nephropathy). Of note that calcium scoring can differ by ethnicity as shown in the MESA registry but there are no data in this regard from local populations.

Evidence overview:

The anatomy of the aortic root and ascending aorta can be examined by CT, in addition to the extent and distribution of valve and vascular calcification, and the feasibility of vascular access [220]. Valve calcification is directly associated with disease progression and clinical events (such as predicted aortic valve replacement and death), with excellent discrimination for severe AS reported with the use of CT in a large registry-based study [221]. Data generated from quantitative Doppler echocardiographic and MDCT assessment of AS revealed that the prognostic value of aortic valve calcification extends beyond diagnosis into risk-stratification purposes; Low survival following AS diagnosis can be predicted by the presence of severe AVC, and this high mortality can be reduced by AVR [222]. Quantification of valve calcification may also be useful when combined with geometric assessment of valve area in assessing the severity of aortic stenosis in patients with low valve gradient [223,224].

One study conducted in 185 patients reported that both 2D and 3D-TEE underestimate the aortic annulus measurements compared to CTA, with 2D-TEE being relatively more precise than 3D-TEE technology [225]. The presence of a discrepancy between echocardiographic and CTA measurements of the aortic annulus is associated with a lower survival rate [225].

CT vs 2D echo:

When comparing aortic annulus diameter (AAD) between 2D TEE and MSCT, it was evident that each imaging modality was measuring different landmarks and could therefore not be used interchangeably [226]. MDCT-based annular sizing yields lower incidence of postprocedural PVL and in patients undergoing TAVI compared to 2D TEE, with a pivotal role of Transcatheter heart valve oversizing [227].

In a study of 256 patients undergoing balloon-expandable TAVI for severe symptomatic AS, high cross-sectional discriminatory ability for post-TAVI aortic regurgitation was observed with 3D-TEE, compared to intermediate with 2D-TEE, rendering 3D-TEE a good alternative in case CT data are unavailable for aortic annulus sizing [228].

CT vs 3D echo (TEE, TOE):

In a comparative study of novel automated 3-dimensional (3D) transesophageal echocardiography (TEE) software and multidetector row computed tomography (MDCT) for aortic annulus sizing, slight underestimation of aortic annulus dimensions was observed with 3D-TEE compared to MDCT, although both had excellent interobserver variability. Aortic valve calcium (AVC) affected the agreement between the two modalities, with superior agreement in patients with low aortic valve calcium burden, but not those with high aortic valve calcium burden. Prosthesis size selection was identical between 3D TEE and MDCT in 88% or the total population. This proportion increase to 95% in patients with low aortic valve calcium burden, but decrease to 81% in those with a high burden [229]. Other studies similarly reported slight underestimation, but comparable and consistent evaluation of the aortic annulus in TAVI patients with 3D TEE in relation to CT [230], leading the similar prediction of aortic prosthetic valve size [231]. These results were confirmed in a meta-analysis, where 3D-TEE was found to be comparable to MDCT for pre-TAVI planning [232].

Recommendation(s):

*CT is recommended for aortic valve calcium scoring and annular sizing for TAVI (**Class I recommendation, level of evidence B**).*

4.18. CTA vs cath to determine angles of deployment for TAVI

Evidence summary:

Computed tomography (CT) is now the non-invasive imaging gold standard tool to provide co-planar fluoroscopic angle prediction in advance of the TAVI/TAVI procedure. It has surpassed more traditional imaging modalities including echocardiography, angiography, and magnetic resonance. Use of CT-derived angulations allows optimization of initial pre-deployment fluoroscopic angulation, reducing the need for repeat pre-deployment root shots and thereby reducing radiation exposure, contrast usage and procedural time.

Evidence overview:

A Prospective randomized trial including 80 TAVI patients with symptomatic severe aortic valve stenosis and normal renal function evaluated a CT-predicted suitable angulation compared to angiography-acquired aortogram. The CT cohort had a significantly lower number of aortic angiograms needed to achieve a satisfactory fluoroscopic position were less likely to require further aortograms and needed significantly lower total procedural amount of the contrast agent compared with the angiography cohort. No significant differences were observed in the dose area product, fluoroscopy time and procedure duration [233].

Another study also showed that a significant reduction of implantation time, radiation exposure, amount of contrast delivered and risk of valve malposition and/or AR grade $\geq$2 can be achieved with the use of MDCT for the derivation of the position of the C-arm in TAVI patients, compared with ad-hoc angiography [234]. The 3D angiographic reconstruction of the aortic root captured from rotational C-arm fluoroscopic images has also been shown to be safe, practical, and accurate when compared with MDCT in another study, with significant correlation between the two methods for prediction of perpendicular valve projections [235].

Retrospective data showed [236] that MSCT-guided deployment projections were more frequently correct in the MSCT-guided lead to 90% excellent or satisfactory projections compared to only 65% in the non-MSCT group. That being said, the accuracy of angle prediction depends on image quality, and is highest with optimal images (73% of predicted angles were poor with suboptimal images) [237]. Pre-procedural MDCT imaging also allows prediction of X-ray angiographic planes before TAVI [238]. The accuracy of MDCT in predicting c-

arm angulation was also demonstrated in several retrospective studies; coplanar fluoroscopic angles prediction can be achieved with MDCT prior to TAVI with good accuracy and reproducibility [239]. CTA correctly predicts the 3-CSA plane used intraoperatively for implantation of the device in the vast majority (96%) of TAVI patients, with no statistically significant difference in the mean LAO/RAO deviation between CTA and the intraoperative implantation projection [240]. Novel automated CT software can also yield accurate optimal fluoroscopic viewing angles that are nearly identical to manual readings (difference <5°) albeit with significantly shorter time [241]. According to recommendations provided by the Society of Cardiovascular Computed Tomography (SCCT), image acquisition should cover the entire cardiac cycle and acquisition parameters should comply the 'As low as reasonably achievable' (ALARA) principle. This means that the amount of radiation delivered varies from 100 kV for patients with BMI 30 or less or weight 90 kg or less, to 120 kV for patients with BMI more than 30 kg or weight more than 90 kg. Furthermore, total contrast volume commonly varies between 50 and 100 ml, with a flow rate of 4–6 ml/s. These values need to be customized on habitus of patient and contrast agent concentration [236]. In patients with impaired kidney function, total amount of contrast should be reduced to a minimum, and this can be achieved using lower flow rates as low as 3 ml/s, low tube potential (down to 80 kVp), multiphasic contrast injection protocols and diligent optimization of the scanning protocol and timing [242,243]. Novel protocols for procedural CT assessment of TAVI patients can further reduce radiation doses, as shown by a comparative study assessing a 3-phase protocol compared to a combined ECG-synchronized and non-ECG-synchronized spiral CT protocol. That being said, both tested protocols yield good to excellent average subjective image quality ratings and near perfect to substantial interrater agreement [244].

Recommendation(s):

*CT is recommended for pre-deployment fluoroscopic angulation in TAVI (**Class I recommendation, level of evidence B**).*

4.19. Balloon-expandable vs self-expandable valve for TAVI

Evidence summary:

Evidence from RCTs demonstrate comparable outcomes between early-generation and newer-generation balloon-expandable valve and self-expandable valves. Propensity-score matched studies suggest possibly lower early and midterm mortality in BEV than SEV, but the contribution of unmeasured confounders cannot be excluded. The specific choice of a balloon-expandable valve or self-expanding valve depends on patient anatomy and other considerations acknowledging that some patients are a better fit for balloon-expandable valve or self-expanding valve.

Evidence overview:

Despite the higher device success rate with the balloon-expandable valve, 1-year follow-up of patients in CHOICE Trial, with limited statistical power, revealed comparable clinical outcomes after transfemoral transcatheter aortic valve replacement with both balloon- and self-expandable prostheses [245]. Similarly, five-year follow-up of patients in the CHOICE trial revealed comparable clinical outcomes after transfemoral TAVI with early-generation BE and SE valves, with limited statistical power. That being said, SE valves were associated with significantly better forward flow hemodynamics and a lower frequency of moderate or severe structural valve deterioration [246]. In the SOLVE-TAVI trial, 30-day and 1-year outcomes supported the safety of newer generation SEV and BEV in terms of the primary valve-related efficacy endpoint in most intermediate- to high-risk patients undergoing transfemoral TAVI, with some specific preferences based on individual valve anatomy. SEV and BEV were equivalent in the individual components of the primary endpoint, namely all-cause mortality, stroke, moderate/severe PVL, and permanent pacemaker implantation [247].

However, another randomized non-inferiority trial of TAVI with the self-expanding ACURATE neo did not its meet non-inferiority endpoint compared to the balloon-expandable SAPIEN 3 device in terms of early safety and clinical efficacy outcomes [248]. The primary composite safety and efficacy endpoint comprised all-cause death, any stroke, life-threatening or disabling bleeding, major vascular complications, coronary artery obstruction requiring intervention, AKI (stage 2 or 3), rehospitalization for valve-related symptoms or congestive heart failure, valve-related dysfunction requiring repeat procedure, moderate or severe prosthetic valve regurgitation, or prosthetic valve stenosis within 30 days of the procedure.

A recent meta-analysis (3 RCTs, 1418 total patients; 12 propensity score-matched studies, 36,540 total patients) found that lower early and midterm mortality in BEV compared to SEV is observed in propensity score-matched, although the

contribution of unmeasured confounders cannot be excluded [249]. However, the survival advantage observed with BEV in propensity score-matched studies could not be demonstrated based on RCTs, which were insufficiently powered for this outcome [249]. 30-day and 1-year cardiovascular mortality, 30-day incidences of moderate to severe PVL, procedural contrast agent volume, and procedure time were lower, but transvalvular pressure gradient was higher in BEV than SEV in propensity score-matched studies [249]. When considering valve generations and SEV types, permanent pacemaker implantation was higher at 30 days in early-generation SEV compared to corresponding BEV comparators. Moreover, PPI risk was lower in ACURATE neo (Boston Scientific, Natick, MA) but higher in Evolut R SEV (Medtronic Inc., Minneapolis, MN), both compared with SAPIEN 3 BEV (Edwards Lifesciences, Irvine, CA) [249].

Another meta-analysis of observational studies (8 studies, 1080 total patients; 620 BEV, 460 SEV) found no statistically significant difference in survival between the two modalities up to 1 year after the procedure [250]. That being said, risk of annulus rupture was higher with BEV, although PVL was lower with new generation BEVs when compared to new generation SEVs [250].

Recommendation(s):

The specific choice of a balloon-expandable valve or self-expanding valve should be tailored to different patient characteristics, depending on patient anatomy and other considerations.

4.20. Use of cerebral protection devices for TAVI

Evidence summary:

Overall, evidence on the use of cerebral protection devices for TAVI remains controversial; RCTs have reported the safety but failed to demonstrate the efficacy of cerebral protection devices in TAVI, including the large-scale PROTECTED-TAVI trial. Data from observational studies suggest otherwise, reporting significant benefit on the level of stroke-free survival, inpatient mortality, neurological, and clinical complications. That being said, results from observational studies are not consistent. While the radiological efficacy of cerebral protection devices is debatable, their clinical efficacy could not be demonstrated by RCTs. Based on clinical practice, cerebral protection devices are useful in highly selected cases (high risk patients e.g. renal failure, previous stroke, significant calcification of the aorta (porcelain aorta), atrial fibrillation, bicuspid aortic valve, valve in valve, etc.).

Evidence overview:

Several RCTs of varying size investigated the use of cerebral protection devices in TAVI. A small RCT randomizing 30 high-risk patients to undergo *transaortic* TAVI with the SAPIEN XT prosthesis (Edwards Lifesciences) either combined with or without the EMBOL-X protection device found evidence to support intra-aortic protection; it seems that a reduced incidence and volume of new cerebral lesions can be ensured by intra-aortic protection, although no neurologic events were document after transaortic TAVI in either group [251].

The MISTRAL-C trial in turn investigated the influence of the filter-based Sentinel™ Cerebral Protection System (CPS) during TAVI in 65 patients. By capturing debris en route to the brain, filter-based embolic protection might decrease the number and volume of new brain lesions, as assessed by MRI. This approach could also potentially preserve neurocognitive performance early after TAVI [252]. The CLEAN-TAVI trial had a slightly larger patient population (n = 100) and also reported a reduced number of cerebral lesions in potentially protected regions with the use of a cerebral protection device in TAVI [253]. The DEFLECT III trial included 85 patients who underwent TAVI with or without the TriGuard™ HDH Embolic Deflection Device (TriGuard) [254]. The study demonstrated the safety of TriGuard cerebral protection during TAVI, with complete cerebral vessel coverage achieved in 89% of cases. Although the study was exploratory in nature, the use of the cerebral protection device afforded patients more freedom from ischemic brain lesions, fewer neurologic deficits, and improved cognitive function in some domains at discharge and 30 days compared with controls [254]. The SENTINEL trial examined the safety and efficacy of transcatheter cerebral embolic protection (TCEP) and demonstrated is safe and efficacy in capturing embolic debris in 99% of patients without any change in neurocognitive function. That being said, the reduction in new lesion volume on MRI failed to reach statistical significance [255]. The TriGUARD 3 (TG3) cerebral embolic protection was found to be safe but did not meet its pre-specified primary superiority efficacy endpoint in both the REFLECT I trial [256] and the REFLECT II trial [257]. The PROTECTED TAVI trial is the most recently published RCT with the largest number of patients (n = 3000 patients) which assigned patients to the cerebral embolic protection (CEP) group or to the control group [258]. The study failed to demonstrate any significant effect with the use of CEP in patients with AS undergoing transfemoral TAVI in terms of the incidence of periprocedural stroke [258].

However, these results do not rule out a benefit of CEP during TAVI.

When RCT results are taken collectively, meta-analysis outcomes (7 RCTs) reveal comparable risk of stroke, disabling stroke, all-cause mortality, new ischemic lesions on imaging, major vascular complications, and AKI in patients who underwent TAVI with CEP or without [259]. To note that it remains unclear whether the lack of benefit with CEP is due to true lack of efficacy, or design flaws in RCTs (i.e. insufficient follow-up) or the devices used (i.e. no protection to all cerebral territories). Moreover, the large-scale RCT, BHF PROTECTTAVI (the British Heart Foundation Randomized Trial of Routine Cerebral Embolic Protection in Transcatheter Aortic Valve Implantation) was not included in this meta-analysis. That being said, another meta-analysis of RCTs also concluded that cerebral embolic protection during TAVI is safe but there is no evidence of a statistically significant benefit on clinical outcomes or neuroimaging parameters [260]. By contrast, a meta-analysis including both RCTs (n = 6) and observational cohort studies (n = 5) found a benefit with cerebral protection device use in TAVI [261]; patients who underwent TAVI with cerebral protection device had lower rates of MACE, mortality, and stroke compared with patients undergoing TAVI without the device. However, the significant reduction in mortality is driven mainly by observational studies.

That is not to say that the results of observational studies are consistently positive. For example, two studies using nationwide evidence on cerebral embolic protection devices (CPD) in the US reported contrasting results; Khan et al. (2021) analyzed data from both the National Inpatient Sample and Nationwide Readmissions Database between 2017 and 2018 [262]. A 1:3 ratio propensity score matched model was created, and 108,315 weighted encounters were considered. CPD was used in 4380 patients (4.0%) and led to decreased inpatient mortality, as well as lower neurological and clinical complications as compared to TAVI without CPD [262]. By contrast, Kolte et al. (2021) employed overlap propensity score weighted logistic regression models to determine the association between CEPD use and outcome using data from the Nationwide Readmissions Databases alone, albeit in the same time frame as the previous study (2017–2018) [263]. This study failed to demonstrate any statistically significant reduction in the rates of in-hospital stroke, TIA, or mortality with the use of CEPD in TAVI [263]. Similarly, a registry-based nationally representative observational study including a total of 123 186 patients from 599 sites did not find an association between EPD use for TAVI and in-hospital stroke in its primary instrumental variable analysis, and found only a modestly lower risk of in-hospital stroke in our secondary propensity-weighted analysis [264].

Other studies had more positive outcomes; stroke-free survival was significantly higher in patients who underwent TAVI with the Sentinel cerebral protection device (2.1% vs 6.8% in the no cerebral protection group). Propensity matched analysis of this non-randomized trial also revealed a significantly lower rate of disabling and nondisabling stroke with the use of cerebral embolic protection [265].

This was similar to another study, which found that patients who underwent TAVI with filter-based CEP had significantly less disabling strokes at 30 days, as well as fewer neurological events at 24 hours and at 30-days [266]. A dataset analysis of a total of 41,654 TAVI procedures showed that cerebral embolic protection devices were used in only 3.8% of TAVI cases, and were associated with lower mortality but not a reduction in stroke or delirium [267].

Recommendation(s):

- *Cerebral protection devices should be considered in high-risk groups (renal failure, previous stroke, significant calcification of the aorta, porcelain aorta, bicuspid, valve in valve, etc.)* ***(Class IIa recommendation, level of evidence B)***

- *Cerebral protection devices may be recommended for routine use in TAVI* ***(Class IIb recommendation, level of evidence C)***

4.21. Conscious sedation vs general anesthesia for TAVI

Evidence summary:

Evidence from one RCT suggests conscious sedation to be comparable in terms of safety to general anesthesia. Observational studies consistently report the superior effectiveness of conscious sedation in terms of procedure time, need for inotropic support, ICU and hospital length of stay. Moreover, they all report conscious sedation to be comparable or superior to general anesthesia in terms of mortality and safety. A meta-analysis of observational studies suggests conscious sedation might have lower 30-day mortality compared to general anesthesia. The choice of general anesthesia vs conscious sedation should be guided by patient preference, anatomical factors and the expertise of the anesthesia team. The definition of conscious

sedation should be clearly provided. It is important for a cardiac anesthetist to review studies on which the recommendation was based in order to determine whether the method used is consistent with the definition of conscious sedation (or as now referred to, monitored anesthesia care).

Evidence overview:

Conscious sedation and general anesthesia led to comparable efficacy outcomes in the SOLVE-TAVI trial, which included patients with AS undergoing transfemoral TAVI [268]. 1-year results were consistent, also demonstrating the safety and efficacy of conscious sedation compared to general anesthesia in this setting [247].

A large meta-analysis (26 studies, 10,572 total patients) suggested that the use of local anesthesia for TAVI might be preferable as it is associated with a lower 30-day mortality, shorter procedure time, fluoroscopy time, ICU LOS, hospital length of stay, and reduced need for inotropic support [269].

Comparable outcomes on the level of all-cause mortality, cardiovascular mortality, and stroke were observed up to 2 years of follow-up after TAVI using general or non-general anesthesia, in a propensity matched analysis of data from Core Valve ADVANCE Study [270]. Outcomes of both approaches are equally good and the choice between them seems to be predominately dependent on local and national practice, rather than superior safety or efficacy. Another study employed propensity matching and found that patients undergoing TAVI with conscious sedation had less bleeding and vascular events, lower procedural radiation exposure, reduced length of hospitalization and ICU stay, and lower direct costs compared to TAVI with general anesthesia. More importantly, both procedural efficacy and safety were preserved [271].

Evidence from large registry datasets is also available, such as the National Cardiovascular Data Registry Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. While conscious sedation was used in 15.8% (1737/10,997) of TAVI cases, it is safe and leads to shorter hospital stays as well as lower mortality (both in-hospital and 30-day mortality) compared to TAVI with general anesthesia. That being said, the superiority of conscious sedation over general anesthesia cannot be definitely established based on observational data alone [272]. Another large analysis of registry data including 1694 TAVI patients reported comparable outcomes between conscious sedation and general anesthesia on the level of hospital length of stay, 30-day all-cause death and myocardial infarction [273]. However, conscious sedation was associated with less need for intra-procedural transesophageal echocardiography and post implantation dilatations, lesser contrast medium and fewer kidney injury at 7 days, albeit with more frequent moderate PVLs compared to general anesthesia [273]. Compared with TAVI under GA, TAVI under monitored anesthesia care can increase the efficiency of medical resources, reducing the lengths of ICU stay and the occurrence of postoperative pulmonary complications [274]. Several smaller studies also reported conscious sedation as a safe and feasible alternative to general anesthesia, in addition to its efficiency in reducing hospital and ICU length of stay [275–278].

Recommendation(s):

*Both conscious sedation and general anesthesia are recommended for sedation for TAVI procedure. (**Class I recommendation, level of evidence B**).*

4.22. Pacemaker insertion vs extended monitoring for heart block post TAVI

Evidence summary:

No head-to-head comparisons of permanent pacemaker insertion (PPI) vs extended monitoring for heart block post TAVI are currently available. There is a lack of consensus and large variability in the management of conduction disturbances post-TAVI. Continuous electrocardiogram monitoring allows the detection of arrhythmic events post TAVI; patients with new-onset left bundle branch block (LBBB) post-TAVI exhibited a very high burden of arrhythmic events within the 2 years post-procedure. The vast majority of conduction abnormalities necessitating permanent pacing occur within 48 hours of TAVI. Pre-existing right bundle branch block (RBBB) is consistently associated with poor clinical outcomes. New-onset LBBB after TAVI is a significant predictor of permanent pacemaker implantation. Permanent pacemaker implantation carries significant risks (increased mortality and rehospitalization). Future studies need to determine the role of EP studies, ambulatory continuous ECG monitoring, and prophylactic pacemaker in the management of conduction disturbance in post-TAVI patients.

Evidence overview:

No RCTs are available comparing PPI and extended monitoring for heart block post TAVI. However, a sub-analysis of the PARTNER study and registry showed that 8.8% of patients undergoing

balloon-expandable TAVI without prior pacemaker required PPI [279]. The need for PPI after TAVI could be predicted by pre-existing right bundle branch block, the prosthesis to LV outflow tract diameter ratio and the LV end-diastolic diameter. Moreover, patients who had new PPI had longer hospital length of stay and were more likely to experience repeat hospitalization or death at 1 year [279].

The occurrence of intraprocedural- high-degree atrioventricular block (HAVB) or complete heart block (CHB) was assessed in 676 consecutive patients undergoing TAVI, revealing that 7.4% of cases experienced intraprocedural HAVB/CHB, but most cases had persistent HAVB/CHB [280]. Early PPI and close monitoring is therefore warranted, particularly considering the very high ventricular pacing rate at the 1 month and 12 month follow-up, and its subsequent impact on LVEF [280]. 10% of TAVI recipients in one study were found to have pre-existing RBBB, which was associated with poorer clinical outcomes. The risk of high-degree atrioventricular block and/or sudden cardiac death during follow-up was highest in patients who had baseline RBBB but no permanent pacemaker at discharge [281]. Patients undergoing TAVI can experience periprocedural high-degree AVB (8.7% of cases) and delayed high-degree AVB (6.7% of cases), up to 8 days post-procedure [282]. Men and patients with pre-existing conduction disorders are more likely to experience delayed high-degree AVB, and could benefit from monitoring until ECG is stable for at least 2 days. On the other hand, delayed high-degree AVB did not occur in patients in sinus rhythm without conduction disorders and was infrequent in patients with AF but no other conduction disorders [282]. The MARE study was a multicenter prospective study including 103 consecutive patients with new-onset persistent LBBB post-TAVI that were subjected to continuous electrocardiogram monitoring via an implantable cardiac monitor for 12 months. Patients with LBBB post-TAVI had a high incidence (almost 50%) of arrhythmic events at the 1-year follow-up, while significant brady-arrhythmias occurred in one-fifth of the patients, and PPM was required in nearly one-half of them [283]. 2-year outcomes of the MARE study showed that 15% of new arrhythmic events occurred beyond the first year post-TAVI, irrespective of valve type [284]. While the majority of late (>1 year) arrhythmic events were asymptomatic (94%), 19% of patients had a subsequent treatment change. That being said, PPI was predominately undertaken early after the procedure as a result of new HAVB events occurring in the first year post-TAVI [284]. Continuous implantable cardiac monitoring also showed that patients with new-onset persistent LBBB following TAVI have a high arrhythmic burden, with at least one third of patients experiencing 1 or more significant arrhythmic episode within 12 months; 10% of patients exhibited HAVB/CHB, and around 50% of brady-arrhythmic events occurred within 4 weeks after discharge [285].

When considering the causes of death in patients undergoing TAVI, it was found that advanced HF accounts for 46.1% of deaths from cardiac causes, while sudden cardiac death accounts for 16.9% of cardiac deaths [286]. The risk of sudden cardiac death can be predicted by reduced LVEF $\leq$40%, a QRS duration >160 ms and new-onset persistent left bundle-branch block following TAVI [286]. Consistently, a study showed that removal of temporary pacemaker immediately following TAVI is potentially safe in patients without RBBB who are in sinus rhythm with PR interval <240 ms and QRS interval <150 ms; or are in atrial fibrillation with a QRS interval <140 ms [287]. Retrospective data reported a PPI rate of 15.6% in patients who underwent TAVI, with the vast majority of PPI being done for class I indications [288]; 91.3% of patients had PPI for complete heart block/high-grade atrioventricular block, 3.8% for severe sinus node dysfunction, and 3.8% for alternating bundle branch block. More than half of conduction abnormalities were intraprocedural (55%), and 88.8% occurred within 72 hours of the procedure. Very few conduction abnormalities necessitating PPI occur beyond the very early periprocedural period, suggesting the safety of early mobilization and discharge of these patients [288]. That being said, the European Heart Rhythm Association (EHRA) survey revealed variability in contemporary clinical practice for conduction disorders after TAVI [289]. Most centers (63%) had a standardized management protocol for advanced conduction disorders such as LBBB or atrioventricular block (AVB) after TAVI. Patients with new-onset or pre-existing LBBB were most often managed via telemetry, with a variable duration; most respondents monitored patients for 48 hours, but telemetry was continued for at least 72 hours in other cases. PPI was considered significantly more frequently in new-onset LBBB vs pre-existing LBBB, with a heterogenous HV interval cut-off point

leading to PPI between centers. Risk stratification strategies were also found to vary substantially, and underuse of conduction system pacing in patients with LBBB after TAVI was evident [289]. Standardized protocols for the management of conduction abnormalities after TAVI have been assessed and shown to be safe for the management of conduction disturbance, with high compliance among healthcare providers and decreased duration of hospitalization [285]. Stable patients can be discharged, supported by ambulatory monitoring.

When taken collectively in a meta-analysis, available data on new-onset LBBB (17 studies, 4756 total patients) and periprocedural PPI (11 studies, 7032 patients) post TAVI showed that patients with new-onset LBBB had a higher risk of PPI and cardiac death. A tendency towards worse survival was also evident. However, periprocedural PPI tended to have a protective effect in terms of cardiac death at 1 year follow-up, with no worsening of survival [290]. However, a more recent meta-analysis had conflicting results, showing increased risk of all-cause death, heart failure hospitalization, risk of cardiac death and PPI in the year following the procedure among patients with new-onset persistent LBBB and PPI after TAVI [291].

Recommendation(s):

- *Permanent pacing is recommended in patients with complete or high-degree AVB that persists for 24 − 48 h after TAVI.* ***(Class I recommendation, level of evidence C)***

- *Permanent pacing is recommended in patients with new-onset alternating BBB after TAVI* ***(Class I recommendation, level of evidence C)***

- *Early permanent pacing should be considered in patients with pre-existing RBBB who develop any further conduction disturbance during or after TAVI* ***(Class IIa recommendation, level of evidence C)***

- *Ambulatory ECG monitoring or EPS should be considered for patients with new LBBB with QRS >150 ms or PR > 240 ms with no further prolongation during the >48 h after TAVI* ***(Class IIa recommendation, level of evidence C)***

- *Ambulatory ECG monitoring or EPS may be considered for patients with a pre-existing conduction abnormality who develop prolongation of QRS or PR > 20 ms.* ***(Class IIb recommendation, level of evidence C)***

- *Prophylactic permanent pacemaker implantation is not indicated before TAVI in patients with RBBB and no indication for permanent pacing* ***(Class III recommendation, level of evidence C)***

4.23. DAP vs SAP for antiplatelet therapy post TAVI

Evidence summary:

Overall, evidence consistently shows that single antiplatelet therapy (SAPT) is the preferred therapeutic strategy when there is no indication for oral anticoagulation (OAC) or dual antiplatelet therapy (DAPT) as it reduces thromboembolic and bleeding events after transcatheter aortic valve implantation. However, guideline recommendations are inconsistent. The ESC 2021 guidelines have a class I recommendation for lifelong OAC for TAVI patients who have other indications for OAC, and lifelong SAPT for those who don't have a baseline indication for OAC. On the other hand, the ACC 2020 guidelines give aspirin a class IIa recommendation for TAVI patients with no other indication for OAC, and a Class IIb recommendation for DAPT as well as vitamin K antagonist (VKA) for patients with TAVI and low risk of bleeding.

Evidence overview:

An early open-label RCT including 79 patients was published in 2011, revealing that the addition of maintenance clopidogrel to aspirin (100 mg lifelong) for 3 months after TAVI was not superior to aspirin alone [292]; comparable outcomes were observed between the two groups on the level of the cumulative incidence of MACCE and the primary endpoint (composite of major adverse cardiac and cerebrovascular events, defined as death from any cause, myocardial infarction, major stroke, urgent or emergency conversion to surgery, or life-threatening bleeding). The SAT-TAVI trial had a larger patient pool (n = 120) and also demonstrated that aspirin alone is sufficient for TAVI procedures, with no impact on morbidity or mortality noted by choosing aspirin alone over DAPT (aspirin and Clopidogrel 75 mg/qd or ticlopidine 500 mg/bid) [293]. To note that the study found a significantly lower rate of 30-day vascular complications in the aspirin only group, compared to the DAPT group. A reduction in the risk of major or life-threatening adverse events post TAVI was found with SAPT compared to DAPT in the ARTE trial, without compromising the risk of myocardial infarction or stroke [294]. That being said, the trial was small and underpowered as it was prematurely stopped after the inclusion of 74% of the planned study population (because of slow enrollment and lack of continued financial support). The most recent RCT, the POPular TAVI, randomized 665 patients to either receive aspirin alone or aspirin with clopidogrel [295]. Results were consistent with previous

trials in that aspirin alone among patients undergoing TAVI who did not have an indication for oral anticoagulation led to significantly less bleeding as well as lower frequency of the composite of bleeding or thromboembolic events at 1 year compared to DAPT (aspirin plus clopidogrel for 3 months) [295].

Evidence from non-randomized studies consistently show the superiority of SAPT over DAPT.

Propensity-matched analyses report better safety outcomes (reduced risk of periprocedural complications) and no compromise of valve function or survival in patients undergoing TAVI and discharged with aspirin alone compared to those discharge with aspirin and DAPT [296,297]. Similar results were published in an earlier prospective comparative study [298]; SAPT after TAVI reduces LTB and major bleedings without increasing the risk of stroke and myocardial infarction compared to DAPT. Large-scale evidence from the STS/ACC TVT Registry (16,694 total patients, 13,546 on DAPT, 3148 discharged on SAPT) also reported an increased bleeding risk with DAPT, but comparable risk of mortality, stroke and myocardial infarction compared with SAPT [299]. Some insights from the OCEAN-TAVI (Optimized trans CathEter vAlvular iNtervention) registry suggests that bleeding risk is lowest in patients who receive no antithrombotic therapy after TAVI, compared to those who receive either SAPT or DAPT [300].

Several meta-analyses have been published, assessing DAPT versus SAPT for patients post-TAVI.

A patient level meta-analysis published in 2021 included the above-mentioned 4 RCTs and confirmed their results; aspirin alone is safe and effective in patients without an indication for oral anticoagulation undergoing TAVI [301]. Another meta-analysis from the same year included both RCTS and observational studies (4 RCTs, 8 observational studies; 20,766 total patients) but had similar results; DAPT, compared with SAPT, increased the risk for combined life threatening and major bleeding without any significant improvements in terms of MACE, cardiovascular mortality or stroke [302]. The increased bleeding risk associated with DAPT compared with SAPT is persistent regardless of the duration of DAPT (3 or 6 months), as demonstrated by a network meta-analysis [303]. Other meta-analyses also support SAPT as the preferred antithrombotic regimen post TAVI compared with other regimens (DAPT, OAC/SAPT) in patients who do not have other indications for anticoagulation of DAPT [304–306].

Recommendation(s):

- *Lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC. (**Class I recommendation, level of evidence A**)*
- *Clopidogrel is preferred over aspirin for SAPT after TAVI (**Class I recommendation, Class of evidence B**)*
- *DAPT is not recommended after TAVI in the absence of other indications for oral anticoagulants. (**Class III recommendation, level of evidence A**)*

4.24. OAC/NOAC or no anticoagulation post TAVI

Evidence summary:

Overall, current evidence does not support the use of short- or long-term OAC with VKAs or NOACs after TAVI unless concomitant conditions require its use. By contrast, OAC alone has an important benefit in a significantly lower risk of all bleeding and major and/life-threatening bleeding events compared to OAC + SAPT. As with DAP vs SAP, guideline recommendations on OAC/NOAC are inconsistent. The ESC 2021 guidelines have a class I recommendation for lifelong OAC for TAVI patients who have other indications for OAC. On the other hand, the ACC 2020 guidelines give a Class IIb recommendation for VKA for patients with TAVI and low risk of bleeding. Although some studies showed the potential benefit of NOAC on preventing subclinical leaflet thrombosis in some TAVI patients, their use may result in worse outcomes which outweigh their benefits.

Evidence overview:

Patients without an indication for long-term OAC

The GALILEO trial demonstrated that in patients without an established indication for oral anticoagulation after successful TAVI, antiplatelet-based therapy leads to a lower risk of death or thromboembolic complications and a lower risk of bleeding than OAC (rivaroxaban/10 mg daily) [307]. This led to the premature termination of the trial due to safety concerns. The reasons underlying these findings remain unclear, particularly in light of the main mortality difference occurring remotely after study drug discontinuation and the results of the GALILEO-4D sub-study, which revealed a lower incidence of subclinical leaflet motion abnormalities and leaflet thrombosis in the rivaroxaban arm [308]. Consistently, the ATLANTIS (Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis) trial failed to find a significant

advantage with OAC (full-dose apixaban) compared to standard antiplatelet therapy in 1049 TAVI patients without indications for OAC [309]. In fact, no significant improvement was observed in the composite primary end point of thrombotic and bleeding events and non-cardiovascular mortality was higher with OAC, irrespective of an indication for oral anticoagulation [309]. While the ATLANTIS-4D-CT Randomized Clinical Trial Sub-study was not powered for clinical outcomes, it found reduced subclinical obstructive valve thrombosis with apixaban [310]. Similar results also emerged from the FRANCE-TAVI registry, where full-dose OAC at discharge (predominately VKAs) increased mortality independently of AF and other confounders, despite a lower risk of bioprosthetic valve dysfunction and subclinical leaflet thrombosis [311]. Evidence from a small study (n = 94) among low-risk patients undergoing transfemoral TAVI also found no efficacy benefit with the addition of warfarin to aspirin, although this approach may prevent transcatheter heart valve dysfunction (hypo-attenuated leaflet thickening) in the short term without excess bleeding [312]. Numerically lower incidence of leaflet thrombosis was evident with Edoxaban in the underpowered ADAPT-TAVI trial compared with DAPT, although this did not reach statistical significance. Otherwise, the study reported comparable outcomes between the two groups in terms of new cerebral thromboembolism and neurological or neurocognitive function [313].

Patients with an indication for long-term OAC

Conversely, results were favorable in patients with an indication for long-term OAC. In the POPular TAVI trial (Cohort B), the use of OAC alone as opposed to the addition of an antiplatelet agent in patients who underwent TAVI with an indication for long-term OAC lowered the risk of the 2 co-primary end points of all bleeding and non−procedure-related bleeding, with no evident increase in the incidence of major adverse ischemic events [314]. While not statistically significant, subgroup analysis of a propensity-matched study revealed 30-day all-cause death to be lower in patients receiving OAC alone compared to those also receiving aspirin. Patients receiving concomitant OAC and aspirin had a significantly higher risk of life-threatening bleedings, minor vascular complications, and major bleeding. However, comparable risk of prosthetic heart dysfunction and rate of stroke/TIA were observed between the two groups [296]. Other studies also showed that VKA therapy alone is effective and safe for patients with AF undergoing TAVI, and the addition of antiplatelet therapy increases the risk of major or life-threatening bleeding [315,316].

Limited evidence exists on the use of NOACs in TAVI patients who have an indication for OAC. In the ATLANTIS trial, apixaban 5 mg twiced was similarly effective and safe compared with VKAs in 451 TAVI patients requiring long-term OAC [309]. In the POPular TAVI (Cohort B), the results for the co-primary and secondary outcomes were consistent in the subgroup of patients on NOACs (24% of the entire study population) and therefore reassuring, although nonconclusive [314].

A meta-analysis of the GALILEO, ATLANTIS and ADAPT-TAVI trials and their sub-studies confirmed that although controversial, DOACs can decrease reduced leaflet motion and hypo-attenuated leaflet thickening; however, this effect comes at the cost of efficacy and safety, including worse all-cause mortality [317]. When considering data from 5 studies (1 RCT, 4 retrospective cohort studies, 1344 total patients), a meta-analysis found comparable all-cause mortality and ischemic stroke, but lower risk of bleeding (all bleeding events and major/life-threatening bleeding events) when OAC was used alone after TAVI in patients with an indication for OAC, compared to OAC plus SAPT [318]. These results were confirmed by a similar meta-analysis, which showed that OAC plus SAPT was ranked the worst among all antithrombotic regimens in patients undergoing TAVI owing to an increased risk of all-cause mortality and all bleeding [305].

Recommendation(s):

- *Life-long OAC/NOAC is recommended for TAVI patients who have other indications for anticoagulation.* ***(Class I recommendation, level of evidence B)***

- *Routine use of OAC/NOAC is not recommended after TAVI in patients with no baseline indication for anticoagulation.* ***(Class III recommendation, level of evidence B)***

4.25. Timing of follow-up echocardiography post TAVI

Evidence summary:

Overall, there are no studies comparing 1-year vs 2-year follow-up with echocardiography after TAVI. There is a general consensus in all available guidelines and consensus recommendations that echocardiography is the principal imaging modality for the detection of structural valve deterioration and the best and most accessible way to detect serial

changes in valve function. After TAVI, echocardiography should be performed before discharge or within 30–90 days after valve implantation (i.e. baseline imaging), at 1 year after valve implantation and annually thereafter (with additional follow up assessments and/or integration of other imaging modalities as necessary and/or determined by the attending physician).

Evidence overview:

There are no studies directly investigating the optimal timing for echo post TAVI. Evidence is mainly limited to expert opinion and derived from data on time to complications post TAVI. Studies report that the incidence of thrombosis is relatively low (0.61–1%), and the events mostly occur in the first-year post TAVI. In a systematic review of 4266 patients from 12 centers, 0.61% thrombosis rate was found after TAVI. The peak incidence of bioprosthetic valve thrombosis (BPVT) was between 13 and 24 months, although the median time to occurrence of a thrombotic event was 181 days [319]. A higher incidence of 1% was reported in a retrospective analysis of BPVT cases occurring over a 15-year period at Mayo Clinic, with 65% of these cases occurring at least 12 months post-implantation. The median bioprosthetic valve longevity was 24 months [320]. Another retrospective case-control study of all suspected (imaging diagnosis) or confirmed (histopathological diagnosis) cases of BPVT (n = 94) found that thrombosis was the predominant event recorded in the first year after implantation; structural failure due to degeneration becomes prevalent after 5 years of implantation [321].

The pooled estimated structural valve deterioration found in a Meta-analysis of 13 studies (8914 total patients) was 28 per 10,000 patient years. Individual studies had variable estimates of structural valve deterioration after TAVI, with numbers varying between 0 and 1.34 per 100 patient years [322]. In an analysis of two multi center registries, 4.5% of patients treated with TAVI presented with valve hemodynamic deterioration (defined as an absolute increase in mean G 10 mmHg). Moreover, it was evident that the incidence of structural valve deterioration increases with time (almost 10 mmHg per year), and is highest 4–5 years post TAVI [323].

In a meta-analysis of 45 studies including more than 12,000 patients between 2008 and 2012, it was shown that at a follow-up of 6 months to 2.5 years, the incidence of moderate or severe AR was around 11.7%, while the incidence of mild PVL ranged from 7 to 70% [324]. As for endocarditis, a large multicenter registry reported that the incidence of prosthetic valve endocarditis after TAVI was estimated to be 1.1%, and the majority of patients present within 1 year after the procedure [325].

Available consensus guidelines on follow-up echo post TAVI are generally concordant, recommending it be done before discharge or at baseline (at 30 days), at 6 months, at 1 year, then yearly thereafter [326–328]. The ESC/EACTS 2017 VHD guidelines also recommend a follow-up echo be done earlier (at 1 month) for patients who had alternative access TAVI.

Recommendation(s):

*Follow-up echocardiography after TAVI is recommended at baseline (1–3 months), at 1 year, then yearly thereafter. (**Class I recommendation, level of evidence C**).*

4.26. CMR vs echo for the assessment of PVL post TAVI

Evidence summary:

Overall, the majority of available evidence shows that TTE evaluation is semiquantitative and with a degree of subjectivity. CMR approach is more quantitative and has low interobserver variability. Moreover, the physiologically variable shape of the PVL defect limits accurate quantitative evaluation through TTE. CMR RV or regurgitant fraction quantification is not limited by the variable change of the orifice during the cardiac cycle. Studies comparing CMR and echo for PVL assessment post TAVI reveal better prediction of clinical outcomes with CMR. The general consensus is that TTE should be the first modality of choice to investigative post TAVI PVL. However, CMR should be considered for further evaluation of PVL in case of inconsistencies between clinical presentation and TTE results, particularly if considering a therapeutic intervention.

Evidence overview:

Moderate to severe post-TAVI paravalvular aortic regurgitation is associated with a 2.12-fold increase in overall all-cause mortality 1 or more years after the procedure [329]; the prognostic value of post-TAVI paravalvular aortic regurgitation was demonstrated in a meta-analysis of 17 studies (15,131 total patients). When comparing CMR and TTE post-TAVI, a small study noted only a modest correlation between the prosthetic AR severity assessed by TTE and regurgitant volume and fraction measured by CMR, with TTE underestimating jet AR severity in 61.9% of patients [330]. The best correlation between TTE and CMR findings was observed on the level of jet diameter and the

multiparametric echocardiography integrative approach, but not the circumferential extent of the leaks [330]. By assessing the value of CMR in quantifying PVL in AVR or mitral valve replacement, a small study including 31 patients with a preliminary diagnosis of significant PVL showed moderate agreement between CMR and semi-quantitative-TEE [331]; the latter led to the underestimation of a notable number of AVR or mitral valve replacement PVL.

One observational study compared 2D and 3D echo and found limitations in the grading of AR severity after TAVI with 2D TTE based on the VARC-2 criteria when compared to CMR. The accuracy of 3D TTE, but not observer variability on regurgitant volume, was higher than that of 2D TTE for the quantification of aortic regurgitation. Meanwhile, CMR was associated with very low observer variability [332]. Consistently, low correlation between 2D TTE and CMR for the measurement of AR post-TAVI was evident in 6 out of 7 studies included in a meta-analysis, irrespective of AR grade [333]. That being said, TTE has a good ability to discriminate mild from moderate or severe AR [333].

The quantification of AR with CMR could have greater prognostic value compared with echocardiography, as one observational multicenter study of 135 patients demonstrated; increased mortality and worse clinical outcomes following TAVI were found in patients with worse CMR-quantified aortic regurgitation [334]. This was also evident in a smaller study (n = 23) where CMR had superior prognostic value compared to both qualitative and semi-qualitative echocardiography; patients with greater than mild PVL detected by CMR experience more adverse events than those assessed by echocardiography [335]. The correlation between MRI-RF and echocardiographic grades of paravalvular regurgitation is also modest [336]. That being said, agreement on paravalvular regurgitation classification between MRI-RF (≥20% to define ≥ moderate paravalvular regurgitation) and echocardiography was observed in 97.2% of cases [336]. Patients with moderate or higher grade of paravalvular regurgitation had worse rates of 5-year mortality or reintervention, assessed by either MRI-RF or echocardiography. That being said, patients with less than moderate paravalvular regurgitation on echocardiography, but moderate-to-severe paravalvular regurgitation on MRI-RF (MRI-RF ≥20%) had significantly higher 5-year mortality or reintervention as compared with those who had less than moderate paravalvular regurgitation on MRI-RF (<20%) [336].

Recommendation(s):

- *Echocardiography is recommended for the evaluation of patients with suspected PVL post TAVI* ***(Class I recommendation, level of evidence A)***

- *CMR should be considered (if available) in case of clinical suspicion of significant regurgitation and inconclusive estimation of regurgitation severity by echocardiography* ***(Class IIa recommendation, level of evidence B)***

5. Conclusion

These guidelines provide guidance for the standardization of TAVI practices in Saudi Arabia based on best available evidence. Such clinical guidance is needed considering the recent wide spread of TAVI as a routine procedure and the establishment of local TAVI programs in many large and intermediate centers in Saudi Arabia. Recommendations are provided on the indication for TAVI (vs. SAVR) in different patient populations, in addition to recommendations on other topics relevant to clinical practice such as TAVI access route, pre-TAVI assessment, as well as post-op follow-up and management.

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Author contribution

Conception and design of Study, Acquisition of data, Supervision of the research, Research coordination and management, Funding for the research: TA. Literature review, Drafting of manuscript, Revising and editing the manuscript critically for important intellectual contents, Data preparation and presentation: TA, AT, HA, MA, WA, FA, FA, AA, UA, GA, MB, FM.

Conflict of interest

None declared.

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Supplementary Material

SHA/NHC/SACIS/SSCS/SCIG 2023 TAVI guidelines recommendations summary.

Supplementary Table 1. SHA/ NHC / SACIS / SSCS / SCIG 2023 TAVI guidelines recommendations summary

AS: Aortic Stenosis; AVB: Atrioventricular Block; BBB: Bundle Branch Block; CABG: Coronary Artery Bypass Graft; CAD: Coronary Artery Disease; CMR: Cardiac Magnetic Resonance Imaging; COR: Class Of Recommendation; CT: Computed Tomography; DAPT: Dual Antiplatelet Therapy; ECG: Electrocardiogram; EPS: Electrophysiologic Study; ICA: Invasive Coronary Angiography; LOE: Level Of Evidence; LV: Left Ventricular; MR: Mitral Regurgitation; NOAC: Novel Oral Anticoagulant; OAC: Oral Anticoagulation; PCI: Percutaneous Coronary Intervention; PVL: Paravalvular Leak; RBBB: Right Bundle Branch Block; SAPT: Single Antiplatelet Therapy; SAVR: Surgical Aortic Valve Replacement; TAVI: Transcatheter Aortic Valve Interventions; TEE: Transesophageal Echocardiogram; TTE: Transthoracic Echocardiogram; ViV: Valve-In-Valve.

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