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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action 3 WP4

**Rapid assessment of other technologies using the HTA Core Model®
for Rapid Relative Effectiveness Assessment**

TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI) FOR THE TREATMENT OF PATIENTS AT INTERMEDIATE SURGICAL RISK

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Conflict of interest

All authors, dedicated reviewers, and external experts involved in the production of this assessment have declared that they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA Declaration of Interest and Confidentiality Undertaking of Interest (DOICU) statement form.

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LIST OF ABBREVIATIONS

AS	Aortic Stenosis
CE	Conformité Européene
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICD	International Classification of Diseases
ICTRP	International Clinical Trials Registry Platform
KCCQ	Kansas City Cardiomyopathy Questionnaire
MeSH	Medical Subject Headings
NYHA	New York Heart Association
PAVR	Percutaneous aortic valve replacement
PICOD	Population, Intervention, Comparator, Outcome, Design of study
POD	Postoperative delirium
RCT	Randomised Controlled Trial
REA	Relative Effectiveness Assessment
SAVR	Surgical Aortic Valve Replacement
STS-PROM	The Society of Thoracic Surgeons Predicted Risk of Mortality
TAVI	Transcatheter Aortic Valve Implantation. TAVI, TAVR and PAVR are synonyms and just different terms used by different authors
TAVR	Transcatheter aortic valve replacement

SUMMARY OF RELATIVE EFFECTIVENESS OF TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI) IN PATIENTS AT INTERMEDIATE SURGICAL RISK

Scope

The scope of the present assessment can be found here.

Introduction

Description of the technology and comparators

The technology

Transcatheter aortic valve implantation (TAVI), also referred to as transcatheter aortic valve replacement (TAVR), is the deployment of a bioprosthesis in the aortic valve using a catheter. In contrast to traditional open-heart surgery (i.e. surgical aortic valve replacement, SAVR), the procedure is minimally invasive when performed through transfemoral access and can be performed with light sedation and without cardiopulmonary bypass. The diseased valve is not excised, and there is no need for suturing to deploy the valve. The choice of the access route depends on the shape of the arteries and the anatomy of the patient. The most common and preferred route is transfemoral (through the upper leg). Other access routes are transapical (through the wall of the heart), subclavian (beneath the collar bone), direct aortic (transaortic, through a minimally invasive surgical incision into the aorta), and transcaval (through the skin into the inferior vena cava and then into the adjoining abdominal aorta) (B0001). For patients at intermediate surgical risk, claimed benefits of TAVI compared with SAVR are decreased or similar rates of mortality, decreased or similar rates of short-term risks, and improved or similar functional benefits. Other claimed benefits are related to length of hospital stay and recovery time [1–3] (B0002).

The first TAVI systems received the Conformité Européene (CE) mark in 2007. Until 2016, the indication for use covered by CE marking was restricted to treatment of patients with severe symptomatic aortic valve stenosis (referred to here as aortic stenosis) that was either inoperable or put them at high surgical risk of mortality or of complications from SAVR. At the time of scoping for this report (June 2017), two manufacturers (Edwards Lifesciences and Medtronic) were offering TAVI systems where the indication for use, according to the CE mark, also covered treatment of patients with severe aortic stenosis at intermediate surgical risk (Edwards SAPIEN 3 and Medtronic Evolut R) (A0020).

In 2013, reimbursement of TAVI was available in 11 European countries [4]. A survey performed as part of the present assessment between October and November 2017 among EUnetHTA partners showed that TAVI was reimbursed in all 20 responding countries and regions. However, decisions about reimbursement in patients at intermediate risk were pending in some countries (A0011).

The comparators

In most patients, SAVR is the first choice of treatment for severe symptomatic aortic valve stenosis. SAVR is performed under general anaesthesia via an incision in the chest (thoracotomy), through different approaches. Level of invasiveness may vary by approach. he procedure requires patients to be on cardiopulmonary bypass [5, (6).. Recently, sutureless SAVR has been suggested as an alternative to both traditional SAVR and TAVI. Sutureless SAVR resembles TAVI in the way in which the prostheses are deployed, but is based on open surgery (sternotomy or mini-sternotomy) for accessing the aortic valve [7], (B0001).

Health problem

Aortic stenosis, the narrowing of the aortic valve leading to impaired outflow of blood from the left ventricle to the aorta, is the most common valvular heart disease in developed countries (A0002). The impaired heart function is usually progressive and eventually leads to left ventricular hypertrophy and development of heart failure, which, if left untreated, is associated with a poor prognosis. It is a slowly progressive disease and the majority of new diagnoses of clinically

significant aortic stenosis occur among the older patients (age >70 years) (A0004). The most common cause of aortic stenosis in older patients is the calcific degeneration of aortic leaflets, whereas the leading causes in younger patients are congenital heart defects, particularly bicuspid aortic valves [8] (A0002). The prevalence of severe aortic stenosis in Europe is approximately 3.4% among older patients, of whom 75.6% are symptomatic [9]. The overall incidence rate is ~0.49% per year [10] and in those aged above 65 is 2–7% [11]. Approximately 20% of patients over 60 years of age with aortic stenosis have severe aortic stenosis and ~71% of those with severe aortic stenosis are symptomatic [12] (A0023).

Treatment of severe and symptomatic aortic stenosis with medication alone can only be palliative and has limited clinical effect. Timely valve replacement therapy is considered an effective treatment [5]. Given that open-heart surgery involves risks of complications, SAVR might not be suitable for some patients, whereas, for others, the risks might outweigh the benefits. Surgical risk rises with increased age and the presence of comorbidities. The most commonly used risk algorithms include Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), and EuroSCORE II, which has been used since 2011. A surgical risk score <4% (STS-PROM or EuroSCORE II) is normally defined as low risk, risk score 4–8% as intermediate risk, and risk score >8% as high. The most recent update of the European Society of Cariology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines, from August 2017, recommend to consider either TAVI or SAVR in patients at increased surgical risk, defined as STS or EuroSCORE II ≥4% or logistic EuroSCORE I ≥10% or with other risk factors not included in these scores (A0025). Although this includes patients at intermediate risk, SAVR is recommended for lower risk patients. In all cases, a heart team should make the decision between SAVR and TAVI based on assessment of the individual patient and associated risks [5].

Since its introduction in 2007, there has been a rapid but variable rise in the use of TAVI. Use across European countries varies, with annual rates between 20 and nearly 200 procedures per million inhabitants (A0011).

Methods

The selection of assessment elements was based on the HTA Core Model Application for Rapid Relative Effectiveness Assessments (REA) (4.2).

The domains Description and Technical Characteristics of Technology (TEC) and Health Problem and Current Use of the Technology (CUR) were developed by performing *ad hoc* internet searches, reviewing information provided by the manufacturers through a structured questionnaire, and performing a survey among EUnetHTA partners on the use of TAVI and its reimbursement status (October/November 2017).

The domains Clinical Effectiveness (EFF) and Safety (SAF) were developed by systematic literature searches according to the Scope of the present assessment. To identify randomised controlled trials (RCTs), a search for systematic reviews (SRs) and health technology assessment (HTA) reports published in 2013 or later was performed, followed by a search for RCTs published in 2016 or later (update search). The searches were performed between 26th and 27th June 2017. The following sources of information were used: Cochrane Library, Centre for Research and Dissemination (CRD), Embase, and Medline, and Medline Pub status ahead of print. In addition to the systematic searches, a hand search for potentially relevant HTA reports available on the websites of a selected number of HTA agencies was performed. To identify studies of 'real-world data' from prospective national registries, a search for publications from 2013 and later was performed on 5th September 2017. The following sources of information were used: Cochrane Library, Embase, and Medline. To describe upcoming evidence, relevant RCTs registered in 2016 and later were identified by searching the following information sources on 12th January 2018: International Clinical Trials Registry Platform (ICTRP) and Clinicaltrials.gov. Detailed descriptions of the search strategies are provided in Appendix 1.

Internal validity of the included RCTs was assessed in accordance with the criteria established by the Cochrane tool for assessing risk of bias [13]. All analyses, including risk of bias, meta-analyses, and grading of evidence, were performed by the authors and checked by the co-authors. Disagreements were solved by consensus.

The quality of the body of evidence collected was evaluated with The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method [14]. The GRADE method defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. GRADE assessment takes into consideration the within-study risk of bias, consistency of results across the available studies (heterogeneity), precision of the effect estimate, directness of evidence, and the likelihood of publication bias. This method also entails an assessment of the quality of a body of evidence for each individual outcome.

The GRADE system classifies the quality of evidence into four categories: (1) high (we are very confident that the true effect lies close to that of the estimate of the effect); (2) moderate (we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); (3) low (our confidence in the effect estimate is limited: the true effect might be substantially different from the estimate of the effect); and (4) very low (we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect).

For the most important outcomes, summary of findings (SoF) tables were prepared using the GRADE template.

The inclusion criteria for assessing the clinical effectiveness and safety outcomes of TAVI were restricted to studies with a comparison group. For assessing clinical effectiveness outcomes, only RCTs were considered. For assessing safety outcomes, in addition to RCTs, studies reporting real-world data from national registries were also considered.

Results

Available evidence

In total, 56 potentially relevant SRs, out of 377 unique records after the removal of duplicates, were identified by the systematic search for SRs. One additional guideline/HTA report was included based on hand searches. Full-text examination of the SRs identified seven potentially relevant RCTs (Appendix 2), whereas 18 references of potentially relevant RCTs were identified out of 268 unique records. After removing duplicates, the full text of 22 references of potentially relevant RCTs was checked.

Two industry-sponsored multicentre RCTs [PARTNER 2 trial (NCT01314313) and SURTAVI trial (NCT01586910)], with data from three references [2,15,16] involving a total of 3778 patients, were included in accordance to the scope. One of the RCTs (SURTAVI) is ongoing.

The scope (Population, Intervention, Comparator, Outcome, Design; PICOD) for safety in addition to RCTs allowed the inclusion of comparative studies of prospective national registries. In total, 48 records of potentially relevant studies out of 565 unique records from the systematic search were identified. Of these, 41 were noncomparative (Appendix 3). The full text of seven comparative studies was examined and only two studies, one reporting on data from Germany [17] and one from USA [18], were included according to the scope of the study. The full text of excluded noncomparative studies was also examined with the purpose of retrieving any safety outcome data related to the intermediate-risk population; only one study was identified [19] and, given that it was noncomparative, is only described within the *Discussion.*

Excluded but potentially relevant RCTs are presented in Table 2.1; excluded comparative registry studies are presented in Table 2.2; and included RCTs are presented in Table 2.3.

Clinical effectiveness

Evidence was found for most outcomes defined by the scope (PICOD) with exception of procedural success and rehospitalisation for myocardial infarction (>72 h following TAVI). The longest follow-up was 24 months. The most important reported efficacy outcomes were overall mortality at 30-day and 2-year follow-up and cardiac mortality at 30-day and 2-year follow-up (D0001), aortic valve reintervention at 30-day and 2-year follow-up (D0006), hospital length of stay (D0011), and improvement of symptoms [reduction in New York Heart Association (NYHA) class] (D0005) and

quality of life (D0013). Results for the most important outcomes and certainty in estimates (GRADE level of evidence) are detailed in the SoF table for effectiveness data (Table 5.1).

We considered that TAVI is probably non-inferior to SAVR in terms of mortality at 30-day follow-up [3.1% versus 2.9%, risk ratio (RR) 1.07, 95% confidence interval (CI) 0.74–1.55; GRADE evidence: moderate].

We are uncertain whether TAVI is non-inferior to SAVR in terms of mortality at 2-year follow-up (12.9% versus 12.7%, RR 1.01, 95% CI 0.86–1.20; GRADE evidence: very low).

We considered that TAVI is probably non-inferior to SAVR in terms of cardiac mortality at 30-day follow-up (2.6% versus 2.4%, RR 1.11 95% CI 0.75–1.66; GRADE evidence: moderate).

We are uncertain whether TAVI is non-inferior to SAVR in terms of cardiac mortality at 2-year follow-up (12.9% versus 12.7%, RR 1.01, 95% CI 0.86–1.20; GRADE evidence very low).

We concluded that TAVI might increase the risk of aortic valve reintervention at 30-day follow-up compared with SAVR (0.6% versus 0.1%, RR 7.58, 95% CI 1.38–41.55; GRADE evidence: low). However, we are uncertain whether TAVI increases the risk of aortic valve reintervention at 2-year follow-up (1.7% versus 0.4%, RR 3.86, 95% CI 1.76–8.44; GRADE evidence very low).

We are uncertain whether TAVI has any effect on improving symptoms compared with SAVR at 1- and 2-year follow-up (data could not be pooled. GRADE evidence: very low).

We are moderately confident that TAVI probably reduces the length of hospital stay by 2 or 3 days compared with SAVR (data not pooled. GRADE evidence: moderate).

Safety

Any major or minor adverse events were considered important for the assessment of the safety of TAVI compared with SAVR. Most importantly, both RCTs reported the following safety-related events [C0008]: acute kidney injury (30-day follow-up); major vascular complications (30-day follow-up); paravalvular regurgitation (30-day follow-up); stroke (30-day follow-up); stroke (2-year follow-up); atrial fibrillation onset (30-day follow-up), life-threatening and/or disabling bleeding (30-day follow-up); and new permanent pacemaker (30-day follow-up). Results for these outcomes and certainty in estimates (GRADE level of evidence) are shown in the SoF table for effectiveness data (Table 6.1. Summary of findings for the safety comparison of TAVI versus SAVR for patients with aortic stenosis at intermediate surgical risk

Compared with SAVR, we are uncertain whether TAVI has any effect on stroke at 30-day follow-up (4.4% versus 5.6%, RR 0.80, 95% CI 0.58–1.10; GRADE evidence: very low) and at 2-year follow-up (7.4% versus 7.6%, RR 0.97, 95% CI 0.74–1.26; GRADE evidence: very low).

We are moderately confident that TAVI probably reduces the incidence of new atrial fibrillation compared with SAVR (11% versus 34%, RR 0.32, 95% CI 0.27–0.37; GRADE evidence: moderate).

We are uncertain whether TAVI has any effect on life-threatening or disabling bleeding at 30-day follow-up (two studies, data not pooled; GRADE evidence: very low) and 2-year follow-up (one study, RR 1.02, 95% CI 0.74–1.41; GRADE evidence: very low) compared with SAVR.

We are uncertain whether TAVI reduces the risk of acute kidney injury at 30-day follow-up (1.0% versus 2.2%, RR 0.47, 95% CI 0.27–0.80; GRADE evidence: very low) and 2-year follow-up (2.2% versus 3.5%, RR 1.02, 95% CI 0.74–1.41; GRADE evidence: very low) compared with SAVR.

We conclude that, compared with SAVR, TAVI might increase the incidence of major vascular complications at 30-day follow-up (6.9% versus 3.1%, RR 3.03, 95% CI 0.79–11.67; GRADE evidence: low).

Data regarding pacemaker implantation at 30-day follow-up were heterogenous among studies and the results were not pooled. Quality of evidence was rated as very low.

We are moderately confident that TAVI probably increases the risk of paravalvular regurgitation compared with SAVR (3.2% versus 0.3%, RR 9.30, 95% CI 4.02–21.48; GRADE evidence moderate).

In the PARTNER 2 trial, the incidence of endocarditis at 2-year follow-up was 1.2% in the TAVI group and 0.7% in the control group (RR 1.85, 95% CI 0.69–4.99).

None of the trials evaluated rehospitalisation for myocardial infarction (>72 h following TAVI).

Given that more-complete safety data from RCTs with longer follow-up were available, the real-world data studies were only presented narratively, and the level of evidence was not formally graded. The German study [17] reported two safety-related outcomes [in-hospital mortality and postoperative delirium (POD)] in a matched group of 470 patients (out of 3407 patients who underwent valve replacement) with a mean surgical EuroSCORE risk 13.5±2.7. The American study [18] reported the incidence of stroke at 1 year in two groups of 4732 patients each with a median surgical risk of STS 5.6% (IQR: 4.2–8.2%). The patients were matched using propensity scores and results were reported for three different subgroups of surgical risk. Risk of in-hospital mortality in the TAVI group was 3.3% and 5.1% in the SAVR group. The difference was reported as significant ($p < 0.01$) in favour of TAVI. The incidence of POD was 3.9% for TAVI and 12.8% for SAVR ($p < 0.01$). Risk of stroke at 1 year was reported with hazard ratios (HR) revealing no significant differences between the TAVI and SAVR groups at either risk rate.

Ongoing studies

Two active RCTs relevant to the scope of the study were identified. The SURTAVI trial (NCT01586910) had a final completion date of November 2026 and data collection for primary outcome measures was expected in July 2018; however, the results had not been posted at the time of writing (August 2018). The second trial was an ongoing German trial (NCT03112980), with completion expected in 2023. Interestingly, six RCTs comparing TAVI with SAVR or medication in patients at low risk or who were nonsymptomatic were also identified (Appendix 1). For these RCTs, the primary completion date varied from 2018 to 2021.

Discussion

Both TAVI and SAVR are complex procedures under constant development, with both substantial and small incremental changes relating to the devices and all aspects of the procedures being made.

We performed a systematic search oriented towards the identification of SRs and an updated search of primary studies. We identified published data from two RCTs that compared TAVI with open surgery for patients with severe aortic stenosis at intermediate surgical risk. The evidence was rated using the GRADE approach. Given the risk of bias, the level of certainty for important short-term efficacy and safety outcomes (overall mortality at 30-day follow-up, cardiac mortality at 30-day follow-up, length of hospital stay, major vascular complications, paravalvular regurgitation, and atrial fibrillation onset) was regarded as moderate. Further downgrading was done for overall and cardiac mortality at 1- and 2-year follow-up because of serious concerns caused by attrition bias. For the İmprovement of symptoms, aortic valve reintervention, new permanent pacemaker, stroke (at all time points), and life-threatening and/or disabling bleeding outcomes, the evidence was further downgraded by one or more level because of serious or very serious concerns regarding inconsistency and/or imprecision.

In terms of efficacy, based on moderate-level evidence, we considered TAVI to be non-inferior to SAVR in terms of all-cause and cardiac mortality at 30-day follow-up. However, at 2-year follow-up, the evidence regarding non-inferiority was considered very low and no conclusion could be reached. In terms of improvement in symptoms according to the NYHA classification, the evidence for non-inferiority was also considered very low and no conclusion could be reached.

Based on moderate evidence, we found that TAVI probably reduces the duration of hospital stay compared with SAVR. There was a higher proportion of aortic valve reintervention in the TAVI group than in the SAVR group at 30-day and 2-year follow-up. However, the evidence was considered very low and we were not able to determine definitively whether TAVI increases the risk of aortic valve reintervention compared with SAVR.

In terms of safety, based on a moderate level of evidence, we considered that TAVI at 30-day follow-up probably reduces the risk of new atrial fibrillation, but enhances the risk of paravalvular regurgitation. With regard to the stroke, disabling stroke, and risk of acute kidney injury outcomes, we considered the evidence for non-inferiority to be very low and no conclusion could be reached.

Conflicting results between the included trials were observed in terms of life-threatening or disabling bleeding and the need for new permanent pacemaker replacement. Although there was little or no difference in the disabling bleeding outcome between TAVI and SAVR in the SURTAVI trial, the results were in favour of TAVI in the PARTNER 2 trial. Whereas there was little or no difference in the permanent pacemaker replacement outcome in the PARTNER 2 trial, the proportion of implanted pacemakers was in favour of SAVR in the SURTAVI trial. Given the risk of bias and important heterogeneity, we considered the overall quality of evidence for these two outcomes to be very low. Future studies will be needed to confirm whether the observed heterogeneity was related to the TAVI system or if there are alternative explanations.

Limitations of the RCTs included a lack of long-term follow-up, a significant frequency of withdrawals, and uncertain data on quality of life. The ongoing German RCT (NCT03112980) is an industry-independent study that could provide more reliable 5-year follow-up data and quality of life data.

Available evidence (restricted to the inclusion criteria) did not provide answers to the following assessment elements: C0002, C0004, C0005, and C0007. From our search, we were unable to identify published or ongoing RCTs comparing outcomes of one TAVI system with another TAVI system.

The real-world studies identified were not considered relevant to assessing the safety of TAVI in a more extensive way because RCT data with longer follow-up were available and pooled. In addition to patients' data, registries should also collect device-related data and setting information to allow analyses of performance between different products and to assess the impact of different settings on safety outcomes. Upcoming evidence could be derived from more efficient and sophisticated analysis of high-quality real-world data (B0010).

Based on comments from clinical experts, some issues remain. Moreover, the high number of ongoing studies involving patients at low surgical risk could result in an increase in the use of TAVI in future years.

Conclusion

Based on available evidence from two RCTs, we conclude that the effectiveness of TAVI for patients with severe aortic stenosis at intermediate surgical risk is probably non-inferior to SAVR in terms of all-cause mortality and cardiac mortality at 30-day follow-up. Moreover, TAVI probably reduces the length of hospital stay compared with SAVR. However, important uncertainties remain regarding whether TAVI is better or worse than SAVR in terms of symptom improvement.

Moderate-quality evidence suggests that, compared with SAVR, TAVI probably reduces new-onset atrial fibrillation and to enhance the risk of paravalvular regurgitation. However, important uncertainties remain regarding the evidence on the following outcomes: stroke, acute kidney injury, new permanent pacemaker, major vascular complications, aortic valve reintervention, and life-threatening and/or disabling bleeding.

1 SCOPE

Description	Project scope
Population	International Classification of Diseases (ICD)-10 code: I35.0 - Nonrheumatic aortic (valve) stenosis; I35.2 - Nonrheumatic aortic valve stenosis with insufficiency; I06.0 - Rheumatic aortic stenosis; Q23.0 - Congenital stenosis of aortic valve Medical Subject Headings (MeSH) terms: C14.280.484.150, C14.280.955.249 The population of interest in this report is represented by patients with severe aortic stenosis (AS) at intermediate risk of death or complications associated with SAVR. The indication should at least be defined by NYHA class, and either STS risk model score (STS score), EuroSCORE or EuroSCORE II
Intervention	TAVI as a therapeutic intervention for the defined target population. The assessment will be restricted to systems with a CE mark for the defined population MeSH terms: E04.100.376.485.500, E04.650.410.500, E04.928.220.410.500 TAVI involves the insertion of a prosthetic valve, which functionally replaces the damaged aortic valve, using fluoroscopic and echographically guided minimally invasive procedures. The prosthetic valve is compressed within a dedicated delivery system and, once in place within the diseased aortic valve, its deployment allows its expansion and the compression of the native diseased valve against the wall of the aorta. Depending on the anatomy of the patient and device characteristics, the procedure can be performed by one of four different approaches. The transfemoral (TF) route is the most common, whereas the others are performed when the anatomy of the patient precludes access via the TF route. These approaches are the subclavian/transaxillary (S/T) approach, the transapical (TA) approach, and the transaortic (TAo) approach. Subgroup analyses based on the risk assessment tool used, the TAVI system used (i.e., model dependent), and the procedural approach (i.e., TF, S/T, TA, and TAo) will be performed if there are sufficient data
Comparison	SAVR can be performed using different approaches (full sternotomy and more minimally invasive procedures), different kinds of valves, and different kinds of valve-anchoring techniques (i.e., sutured and sutureless). Subgroup analyses based on these comparators will be performed if possible MeSH terms: E04.100.376.485, E04.650.410, E04.928.220.410 Rationale: the comparator has been chosen based on information from relevant published clinical guidelines [20] and EUnetHTA guidelines [21,22]
Outcomes	***Efficacy outcomes:*** • Mortality at 30-day follow-up and at the longest follow-up (all-cause mortality, cardiovascular mortality, and noncardiovascular mortality) • Improvement of symptoms (reduction in NYHA class) • Improvement in health-related quality-of-life indicators [e.g., EQ-5D score, SF-12 score, or Kansas City Cardiomyopathy Questionnaire (KCCQ) score] • Procedural success (i.e., successful valve implantation) • Haemodynamic function of the valve • Intensive care unit (ICU) length of stay (days) • Hospital length of stay (days) • Rehospitalisation for myocardial infarction (>72 h following TAVI) ***Safety outcomes:*** • Any major or minor adverse event (e.g., vascular complications; stroke; TIA; disabling or life-threatening bleeding; aortic valve reintervention; myocardial infarction ≤72

Description	Project scope
	h post procedure; new or worsening atrial fibrillation or atrial flutter; moderate or severe aortic valve regurgitation; acute kidney injury; pain; or need for permanent pacemaker implantation) • Radiation causing harm to both patient and staff Rationale: outcomes have been chosen based on information from relevant published clinical guidelines [20,23] and EUnetHTA guidelines [21,22]
Study design	**Efficacy:** • RCTs (the most recent systematic reviews and/or meta-analysis of RCTs will be used to retrieve potential eligible studies and to compare the overall results) **Safety:** • RCTs (the most recent systematic reviews and/or meta-analysis of RCTs will be used to retrieve potential eligible studies and to compare the overall results) • Real-world data derived from published studies from prospective national registries

2 METHODS AND EVIDENCE INCLUDED

2.1 Assessment team

Description of roles and workload within the assessment team:

1st author (AGENAS):

- Developed the first draft of the EUnetHTA project plan and amended the draft when necessary.
- Carried out the assessment (domains EFF and SAF): answered assessment elements, completed checklist regarding potential 'ethical, organisational, patient and social and legal aspects' of the HTA Core Model® for rapid REA (Table 3.2).
- Sent "draft versions" to reviewers, compiled feedback from reviewers and performed changes according to reviewers' comments (domains EFF and SAF).
- Prepared final assessment and wrote a final summary of the assessment.

Co-author (NIPHNO)

- Assisted to develop the first draft of EUnetHTA project plan.
- Carried out the assessment (domains TEC and CUR): answered assessment elements, filled-in checklist regarding potential "ethical, organisational, patient and social and legal aspects" of the HTA Core Model® for rapid REA (see Table 3.2).
- Compiled feedback from reviewers and performed changes according to reviewers' comments (domains TEC and CUR).
- Performed structured literature searches for domains EFF and SAF.
- Assisted in the preparation of the final assessment and final summary.

Dedicated reviewers (KCE, Onassis Cardiac Surgery Centre, HIQA, SNHTA, Regione Veneto)

- Reviewed the draft and final version of the project plan.
- Reviewed the draft and final version of the assessment.

2.2 Involvement of stakeholders

Stakeholder involvement was restricted to manufacturers and health professionals (external experts). Manufacturers were identified by a call on the author's website according to the internal procedures of the author. Responding companies were involved in the early stages of project development and were invited to contribute to the project by providing information through a structured questionnaire prepared by the author and reviewed by the co-author. Individual face-to-face meetings with the manufacturers were held at AGENAS to present the project objectives and clarify information needs. Both Norwegian and Italian external experts were recruited. The Norwegian Regional Health Services appointed Norwegian experts at commission of the assessment. The Italian expert was recruited through a call to the Italian Regions.

Manufacturers and external experts were involved in the Description and Technical Characteristics of Technology (TEC) and Health Problem and Current Use of the Technology (CUR) domains and in the final draft factual check in relation to the information provided and used within the report. External experts provided input during the scoping phase and final assessment report within the dedicated review process.

2.3 Source of assessment elements

For all domains, the selection of assessment elements was based on the HTA Core Model Application for Rapid Relative Effectiveness (REA) Assessments (ver. 4.2). The selected issues (generic questions) were translated into actual research questions (answerable questions).

2.4 Search

Detailed search strategies for efficacy and safety outcomes (including registry data) are provided in Appendix 1. All search strategies were developed by an information specialist and checked by another information specialist by the co-author.

To identify relevant RCTs, a search of systematic reviews (SRs) published in 2013 or later, followed by a search for RCTs published in 2016 or later (up-date search) were performed by the co-author. The searches were performed between 26th and 27th June 2017. The following sources of information were used: Cochrane Library, Centre for Research and Dissemination (CRD), Embase, and Medline, and Medline Pub status ahead of print. In addition to the systematic search, a hand search of selected members of the International Network of Agencies for Health Technology Assessment (INAHTA) home pages (see Appendix 1 for inspected pages) was also performed. Only reports produced in 2017 and later were included for full-text searches.

To assess safety, a search for 'real-world data' from prospective national registries was performed by the co-author. The search was performed on 5th September 2017. Publications from 2013 and later were considered. The following sources of information were used: Cochrane Library, Embase, and Medline.

To describe upcoming evidence, relevant ongoing RCTs were identified by the co-author by searching the following information sources: ICTRP and Clinicaltrials.gov. The search strategy is provided in Appendix 1.

Ad hoc internet searches were performed for the CUR and TEC domains. A survey among EUnetHTA partners was performed in October and November 2017 to receive information on the use of TAVI and on the reimbursement status to be used in the CUR domain.

2.5 Study selection for effectiveness and safety

The systematic searches for the effectiveness (EFF) and safety (SAF) domains were each followed by three rounds of title and abstract screening: the first two rounds were performed by the co-author, and the third round by the author. The two searchers by the co-author included potentially relevant records according to the scope based on the independent screening of abstract and titles (round one), followed by inclusion based on consensus (round two). The co-author sent a list of potentially relevant SRs, RCTs, and real-world studies to the author. The author checked the study selection process (third round) and retrieved potentially relevant records for full-text examination. The author used the included SRs to identify records of potentially relevant RCTs. Final full-text retrieval of all studies was carried out by two independent researchers from the author with final approval from the co-author. Any disagreement was solved through discussions before the final inclusion. Inclusion was limited to articles in English.

The flow chart screening processes in relation to PICOD are revealed detailed in Figures 2.1, 2.2 and 2.3.

Study selection for systematic reviews and HTA reports (2013–June 2017)

In total, 865 unique records were identified using search terms for TAVI and a time limit to the year of publication from 2013 onwards. From these records, 488 were excluded with the use of a search filter for systematic reviews (Appendix 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED). The co-author provided a list of 56 from the remaining 377 records based on screening abstracts and titles. In addition, one guideline with a systematic search for evidence was provided by the co-author based on hand searches. The author included all SRs and the guideline for full-text inspection. The methodological quality of SRs was not assessed by the author but all SRs comparing TAVI with SAVR were checked to identify relevant RCTs (primary studies).

Seven potentially relevant RCTs (CoreValve, PARTNER A, PARTNER 2, Rex 2016, SAPIEN 3, STACCATO, and SURTAVI) were identified based on the SRs. A list of included and excluded SRs is provided in Appendix 2.

Study selection for RCTs (2016–June 2017)

In total, 865 unique records were identified before the use of specific search filters. Of these, 597 records were excluded by restricting the time limit to year of publication from 2016 onwards, and the use of a search filter for RCTs (Appendix 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED). The co-author provided a list of 18 from the remaining 268 records based on screening abstracts and titles. The author removed duplicates between the SR search and the RCT list, leaving 22 records (see Figure 2.2) analysed by the author in full text. Studies in which a population of patients at intermediate operative risk could not be distinguished from patients who were inoperable, at high risk, or at low risk were excluded. Both study eligibility criteria and reported risk scores of included patients were used to determine the relevance. Two RCTs [PARTNER 2 A trial (NCT01314313) and SURTAVI trial (NCT01586910)] with data from three references [2,15,16], involving a total of 3778 patients were included in accordance to the scope. One of the RCTs (SURTAVI) is ongoing. Excluded RCTs are shown in Table 2.1; excluded comparative registry studies are detailed in Table 2.2; included RCTs are detailed in Table 2.3; included registry studies are detailed in Table 2.4.

Study selection for real-world data analysis (2013–September 2017)

In total, 565 unique records were identified by the search. Of those records, the co-author provided a list of 48 potentially relevant titles identified for real-world data from registry studies after the title and abstract screening process. Of the 48 records provided by the co-author, 41 were noncomparative registry studies and were excluded against the defined PICOD (Appendix 3).

The authors identified seven comparative studies for a more in-depth full-text examination. Two comparative (TAVI versus SAVR) prospective studies of national registry data were included, one from Germany [17] and one from USA [18]. The five excluded comparative studies are listed in Table 2.2. In an attempt to identify any safety outcome data related to the intermediate risk population, the author checked the full text of those 41 excluded studies. Only one study reporting relevant data was identified [19] and is briefly described in Section 9.

Study selection for upcoming evidence

Study selection for upcoming evidence was performed by the co-author. One researcher identified those RCTs comparing TAVI with SAVR with completion dates in 2016 or later, and then another researcher checked whether eligibility criteria and outcomes were fulfilled. A list of all identified ongoing RCTs comparing TAVI with SAVR is provided in Appendix 1.

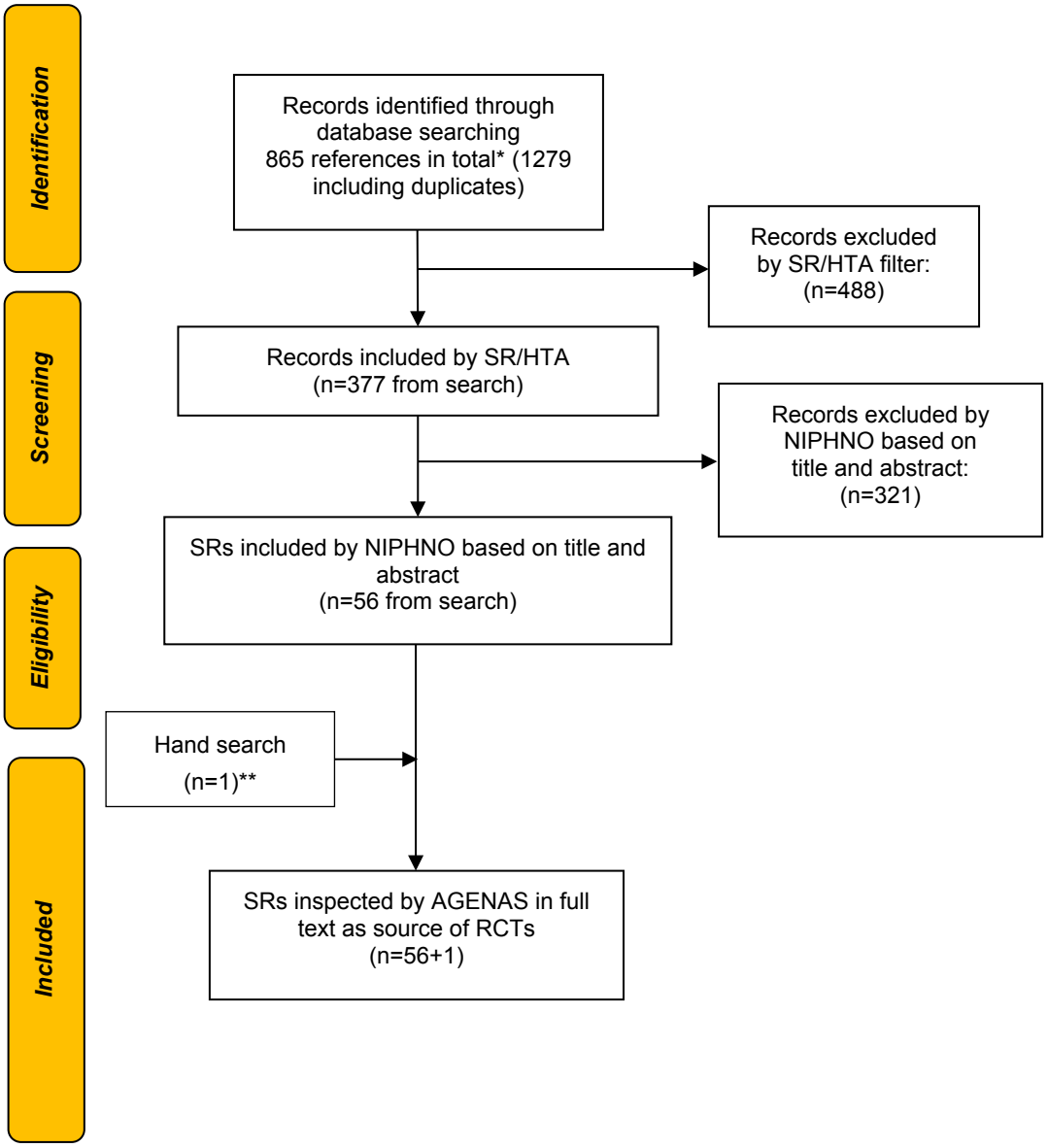


Figure 2.1. Flow chart of efficacy and safety studies: search for SRs published in 2013 onwards

*The same 865 records were identified by both the SR and RCT searches.

**Inspection of HTA agency websites (see list in Appendix 1); only the most updated websites were included.

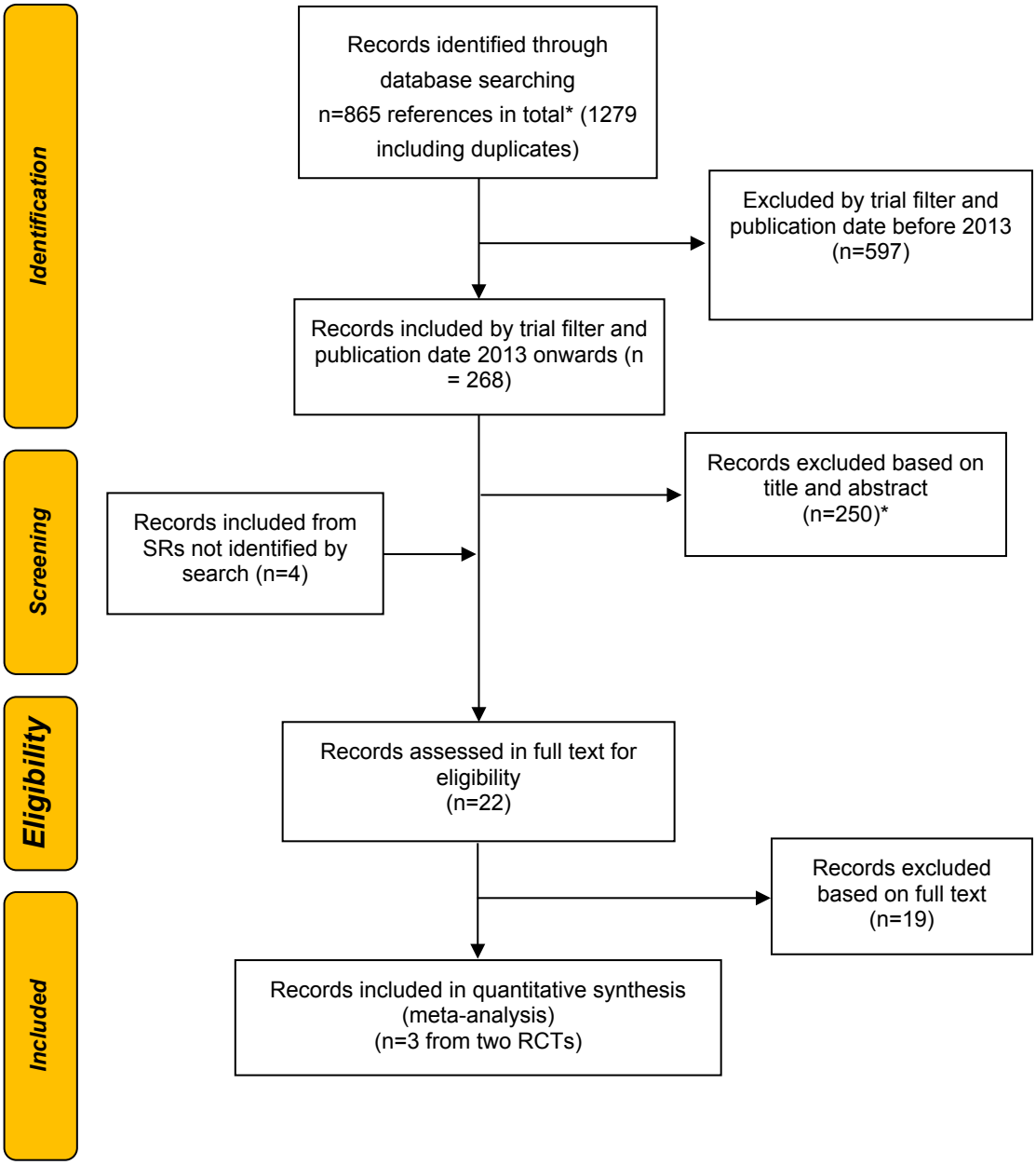


Figure 2.2. Flow chart of efficacy and safety studies: search for RCTs published in 2016 onwards

*The same 865 records were identified by both the SR and RCT searches.

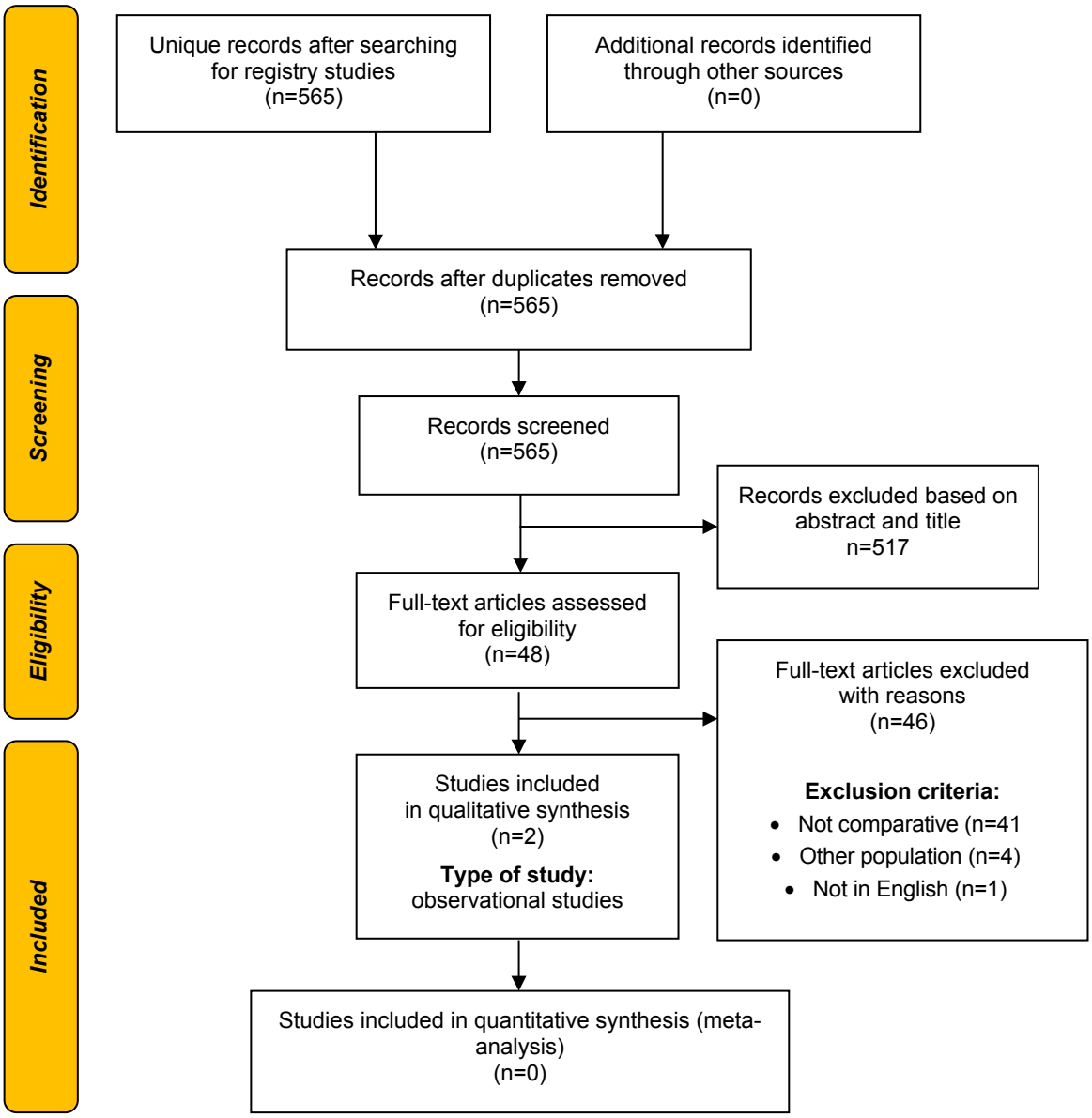


Figure 2.3. Flow chart of registry studies

Table 2.1. Excluded potentially relevant RCTs

Reference	Reason for exclusion
Deeb 2016 [24]	Wrong population: 'Patients with severe aortic stenosis deemed at increased risk for surgery' (mean STS score 7.3±3.0) (Inclusion criteria: patients were considered to be at increased surgical risk if two cardiac surgeons and one interventional cardiologist at the investigative site estimated that the risk of death within 30 days after surgery was 15% or more and the risk of death or irreversible complications within 30 days after surgery was <50%.)
Gleason 2016 [25]	Wrong population: 'High-risk patients (predicted SAVR mortality 15%) with severe aortic stenosis' (mean STS score 7.0±3.0) (NCT01240902)
Gronlykke 2017 [26] (NOTION trial)	Wrong population: post-hoc analysis of NOTION trial (see below)
Gronlykke 2016 [27] (NOTION trial)	Wrong population: post-hoc analysis of NOTION trial (see below)
Jorgensen 2017 (28) (NOTION trial)	Wrong population: post-hoc analysis of NOTION trial (see below)
Kodali 2016 [29] (SAPIEN 3 trial)	Wrong population: post-hoc analysis of SAPIEN 3 trial (Inoperable patients with an estimated probability of death or serious irreversible morbidity after SAVR of >50% [30]
Kodali 2016a [31] (SAPIEN 3 trial)	Wrong population: post-hoc analysis of SAPIEN 3 trial
Kodali 2012 [32] (PARTNER A trial)	Wrong population: high-risk patients with severe aortic stenosis
Little 2016 [33] (CoreValve US High-Risk Clinical Study)	Wrong population: patients with severe aortic stenosis and high surgical risk (mean STS score: 7.3±3.0); Patients were considered by two clinical site cardiac surgeons to have a >15% estimated surgical mortality rate at 30-day follow-up
Mack 2015 [34] (PARTNER A trial)	Wrong population: high-risk patients with severe aortic stenosis
Makkar 2012 [35] (PARTNER A trial)	Wrong population: high-risk patients with severe aortic stenosis
Miller 2012 [36] (PARTNER A trial)	Wrong population: high-risk patients with severe aortic stenosis
NGO 2017 [37] (NOTION trial)	Wrong population: post-hoc analysis: 'This is an echocardiographic sub study of the NOTION trial'
Nielsen 2012 [38] (STACCATO trial)	Unclear population, risk score not reported; in addition: prematurely terminated study because of early adverse events, few participants, and an early version of the TAVI device
Reardon 2016 [39]	Wrong population: post-hoc analysis CoreValve US Pivotal High-Risk Trial; patients at increased risk for surgery

(CoreValve US Pivotal High-Risk Trial)	
Rex 2016 [40]	Wrong population: low-risk patients; long-term health-related quality-of-life (HRQoL) in low-risk patients randomised to TAVI or SAVR
Smith 2011 [41] (PARTNER A trial)	Wrong population: high-risk patients with severe aortic stenosis
Sondergaard 2016 [42] (NOTION trial)	Wrong population: patients with severe aortic valve stenosis; low and intermediate risk (STS-PROM score 3.0±1.7)
Zorn 2016 [43]	Wrong population and outcome: the study aimed to determine the influence of prosthesis–patient mismatch on clinical outcomes; patients at increased risk for surgery

Table 2.2. Excluded comparative registry studies

Reference	Reason for exclusion
Brennan 2014 [44]	Unclear population: safety-related outcome data not reported by risk score of interest (intermediate)
Mohr 2014 [45]	Unclear population: safety-related outcome data not reported by risk score of interest (intermediate)
Eggebrecht 2016 [46]	Unclear population: safety-related outcome data not reported by risk score of interest (intermediate)
Hamm 2014 [47]	Unclear population: safety-related outcome data not reported by risk score of interest (intermediate)
Yucel 2016 [48]	Full text not in English (German).

2.6 Data extraction and analyses

Data extraction was performed by the author and checked by the co-author. Absolute numbers for event rates were based on numbers reported by the studies. For the SURTAVI trial, absolute numbers were provided by authors of the trial; extraction of data was only checked by AGENAS.

Where possible, a meta-analysis of the included RCTs was performed. All analyses were performed by the author and checked by the co-author. Review Manager (Revman 5.3) was used for data synthesis. Data were pooled using both the random-effects model and the fixed-effect model to ensure robustness.

Tables of findings were prepared for presenting results from selected studies using the Summary of Findings template of the GRADE approach [49]. Dichotomous outcomes results were expressed as RRs. When continuous scales of measurement are used to assess the effects of treatment, the mean difference (MD) or standard mean difference (SMD) are used; all RRs, MDs, and SMDs were presented with 95% CIs where possible.

Both studies were of non-inferiority in design and provided analyses based on intention-to-treat and modified intention-to-treat approaches. To perform meta-analyses, data were extracted from both trials using absolute events at different time points. Analyses were based on an intention-to-treat basis.

Heterogeneity was evaluated using a Chi^2 test with n–1 degrees of freedom, with an alpha of 0.10 used for statistical significance and with the I^2 test [13]. Sources of heterogeneity were sought by assessing differences in characteristics of patients, interventions, comparators, and outcomes across the included studies and by visually assessing the forest plots.

No subgroup analysis was performed based on the type of TAVI model and/or systems because there were only two trials, and these used different TAVI systems. Only one of the studies (PARTNER) reported data for two different access routes. Given that the trial was not powered for analysis of the subgroups, data were not evaluated based on the subgroups.

To verify the validity of the document, input was received from experts on the final draft and from manufacturers in terms of factual checks of information used in the report.

Registry studies

Data extraction and analysis were performed by the author. Two reviewers extracted and analysed the studies independently.

2.7 Quality rating

Assessment of the methodological quality of included RCTs was performed by the author and checked by the co-author. Disagreements were resolved by consensus. For RCTs, the

methodological quality of included RCTs was assessed in accordance with the criteria established by the Cochrane tool for assessing risk of bias [14]. The following domains for the risk of bias were considered: (i) random sequence generation (selection bias); (ii) allocation concealment (selection bias); (iii) blinding of patients and personnel (performance bias); (iv) blinding of outcome assessment (detection bias); v) incomplete outcome data (attrition bias); and (vi) selective reporting (reporting bias). Nonrandomised studies were rated by default as at high risk of bias [14,50].

The quality of the body of evidence was evaluated with the GRADE method [14]. The GRADE method defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. GRADE assessment takes into consideration the within-study risk of bias, consistency of results across the available studies (heterogeneity), precision of the effect estimate, directness of evidence, and the likelihood of publication bias. The GRADE method also entails assessment of the quality of a body of evidence for each individual outcome.

The following is how the GRADE system classifies the quality of evidence into four categories, their interpretation, and the wording used in the results to express the efficacy and safety of TAVR versus SAVR for the current report.

(1) high-quality evidence: we are very confident that the true effect lies close to that of the estimate of the effect; this means that the intervention improves and/or reduces a specific outcome;

(2) moderate-quality evidence: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; this means that the intervention probably improves and/or reduces a specific outcome;

(3) low-quality evidence: our confidence in the effect estimate is limited: the true effect might be substantially different from the estimate of the effect: this means that the intervention might improve and/or reduce a specific outcome;

(4) very low-quality evidence: we have little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect; in other words, it is uncertain that the intervention improves and/or reduces a specific outcome.

A ‘Summary of findings’ table was presented to provide key pieces of information in a quick and accessible forma

2.7 Description of the evidence used

Table 2.3. Main characteristics of the effectiveness and safety RCT studies included in the analysis

Author and year and/or study name (number)	Study type	Number of patients	Intervention (s)	Main endpoints	Included in clinical effectiveness and/or safety domain?
Arora 2016 [16] Leon 2016 [15] PARTNER 2 trial (NCT01314313)	RCT, multicentre	2032 intermediate-risk patients with severe aortic stenosis (1011 TAVI; 1021 SAVR)	**Intervention**: TAVI via TF or transthoracic placement of Edwards balloon-expandable SAPIEN XT heart valve (26 mm) **Control**: SAVR	Mortality from any cause Disabling stroke at 2-year follow-up	Effectiveness and safety

Author and year and/or study name (number)	Study type	Number of patients	Intervention (s)	Main endpoints	Included in clinical effectiveness and/or safety domain?
Reardon 2017 [2] SURTAVI trial (NCT01586910)	RCT, multicentre	1746 intermediate-risk patients with severe aortic stenosis (879 TAVI; 867 SAVR)	**Intervention**: Medtronic CoreValve System or Medtronic CoreValve Evolut R System TAVI **Control**: SAVR	Composite of mortality from any cause or disabling stroke at 2-year follow-up	Effectiveness and safety

Table 2.4. Main characteristics of registry studies included in the analysis

Author and year and/or study name	Study type	Number of patients	Intervention (s)	Main endpoints	Included in clinical effectiveness and/or safety domain?
Bestehorn 2015 [17]	Cohort	1526	TAVI versus SAVR	Incidence of POD In-hospital mortality	Safety
Brennan 2017 [18]	Cohort	9464	TAVI versus SAVR	Incidence of stroke	Safety

Evidence included for effectiveness and safety

For effectiveness and safety based on RCTs, the search strategy allowed the identification of 22 articles that evaluated the use of TAVI for aortic stenosis: of these, three were publications of two trials that fulfilled our inclusion [2,15,16]; the other 19 were excluded and are listed in Table 2.1.

Prospective national registries studies presenting analyses of real-world data were used within the safety domain. Two studies were included for the qualitative analysis of safety outcomes [17,18]. However, these two studies were not included in the meta-analysis.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
B0001	What are TAVI and SAVR?
A0020	For which indications has TAVI received marketing authorisation or CE marking?
B0002	What is the claimed benefit of TAVI in relation to SAVR?
B0003	What is the phase of development and implementation of TAVI and SAVR?
A0021	What is the reimbursement status of TAVI?

3.2 Results

[B0001] What are TAVI and SAVR?

TAVI and SAVR differ in both the procedures used and the designs of the implants.

Technology: TAVI

TAVI is the replacement of the aortic valve of the heart with a prosthesis delivered through a blood vessel using a catheter (transluminal via a large artery or vein) or via a small incision through the heart wall (apex of the left ventricle). The prostheses are balloon-expandable or self-expandable bioprostheses compressed in size during delivery and expanded when in place in the aortic heart valve. TAVI is also referred to as TAVR and, for some procedures, can be referred to as percutaneous aortic valve replacement (PAVR). The prosthesis is most commonly delivered via one of several access routes: TF (through the upper leg), TA (through the apex of the left ventricle), S/T (beneath the collar bone), TAo (through a minimally invasive surgical incision into the aorta), and transcaval (through the skin into the inferior vena cava and then into the adjoining abdominal aorta). The choice of access route depends on the shape of the arteries and the anatomy of the patient. The most common and preferred route is TF [3], whereas the others are performed when the anatomy of the patient precludes access via the TF route.

In contrast to SAVR, the diseased valve is not excised and there is no need for suturing. TAVI can be carried out under general anaesthesia, although, in most cases, it is performed under local anaesthesia with sedation. Prophylactic antibiotics and anticoagulation are administrated during the procedure [3,51].

Correct placement of the implant is assured by intraprocedural radiographic imaging using fluoroscopy (angiography). Echocardiography can be used to complement angiographic imaging. Computed tomography (CT) is routinely performed for preprocedural imaging and for long-term postprocedural assessment [52].

An interdisciplinary team with specialist training and experience in complex endovascular cardiac interventions is needed during the TAVI procedure, and for patient selection, choice of implant, and access route. TAVI can be performed either in a catheterisation laboratory or in a hybrid operating theatre. TAVI should be performed in a center with a cardiac surgical division given that cardiac and vascular surgical support for emergency treatment of complications must be in place [3]. The use of a hybrid theatre allows emergency cardiosurgery to be performed in the same room as the TAVI procedure. If performed in a catheterisation laboratory, the patient needs to be transferred to an operating theatre if emergency surgery is required.

TAVI is a less invasive alternative to SAVR, avoiding the need for cardiopulmonary bypass. Specific concerns related to TAVI compared with SAVR have been uncertainties regarding the risk for stroke, the need for a permanent pacemaker implant, access-related complications, and concerns regarding the positioning and lifetime of the implant. Compared with SAVR, TAVI is associated with higher radiation doses for both patient and personnel (see Appendix 4). In addition to being easier to handle, the latest TAVI devices aim to reduce the introducer sheath diameter, to minimise or avoid paravalvular leakage (PVL), and to offer reposition of the valve prosthesis before final deployment [1]. Other improvements aimed at with new designs and techniques are a reduction in complications and in the need for permanent pacemaker implantations.

TAVI systems

There are several TAVI systems commercially available. However, not all have a CE mark and/or marketing authorisation for patients at intermediate surgical risk (see A0020). At the time of writing, to our knowledge, only two manufacturers (Edwards Lifesciences and Medtronic) were offering TAVI systems to be used outside clinical trials for patients at intermediate surgical (operative) risk of death or complications from SAVR ([3,16,53]; manufacturers' websites; submission files from manufacturers; Google search for press releases). The TAVI systems assessed in the present report are described below and in Table 3.1.

Edwards SAPIEN 3™ system

Edwards SAPIEN TAVI systems are delivered by Edwards Lifesciences (www.edwards.com) and are available in both the USA and Europe for use outside clinical trials. The first-generation Edwards TAVI system received a CE mark in 2007 for patients at high surgical risk. Edwards SAPIEN was approved by the US Food and Drug Administration (FDA) in 2012 for patients at high surgical risk. The first-generation SAPIEN system was replaced by the second-generation Edwards SAPIEN-XT (S-XT) and then by the third-generation Edwards SAPIEN 3 (S3). Both S-XT and S3 received FDA approval in 2016 for patients at intermediate surgical risk. The Edwards SAPIEN prostheses are balloon expandable and comprise a cobalt-chromium frame and bovine (made from cow heart tissue) pericardium transcatheter heart valves. The S-XT and S3 systems are improvements to the original Cribier and Edwards SAPIEN systems. According to the supplier's submission file, there are differences in the stent-frame design of the two systems. S3 is given a high radial strength, based on its stent frame. The S3 also has an additional outer polyethylene terephthalate cuff to enhance paravalvular leak sealing. Both S-XT and S3 are available in four diameter sizes: 20 mm, 23 mm, 26 mm, and 29 mm, although S-XT 20 mm is only available for TF use. The European Medical Device Risk Class for Edwards S3 is Risk Class III.

Medtronic Evolut™ R and Evolut™ Pro Systems

The Evolut systems are delivered by Medtronic (www.medtronic.com) and are available in both the USA and Europe for use outside clinical trials. The first-generation CoreValve systems received a CE mark in 2007 for patients at high surgical risk and FDA approval for the same patient group in 2014. The second-generation CoreValve Evolut R System received a CE mark in 2014 and FDA approval in 2015 for treating patients at high or extreme risk for surgery. In Europe, this indication was extended in 2016 to patients with aortic stenosis at intermediate risk for open-heart surgery as determined by a heart team. In the USA in 2017, the FDA approved the use of Evolut™ R to treat patients at intermediate surgical risk. Furthermore, in 2017, a new Evolut R 34-mm valve received a CE mark for patients with severe aortic stenosis at intermediate, high, or extreme risk for surgery. In July 2017, while the assessment was ongoing, Medtronic launched Evolut PRO, a new TAVI system with a CE mark and FDA approval for patients at intermediate risk.

The Medtronic CoreValve Evolut R system is a recapturable transcatheter aortic valve implantation system that includes the CoreValve Evolut R transcatheter aortic valve, the EnVeo R delivery catheter system, and the EnVeo™ R loading system. The bioprosthesis comprises a self-expandable, nitinol frame with porcine (made from pig heart tissue) pericardial transcatheter heart valves. Both systems can be delivered via the TF or alternative access routes, such as S/T and TAo. Evolut R valves are provided with a specific anticalcification treatment; they can be recaptured and repositioned if needed and are available in four diameter sizes (23 mm, 26 mm, 29 mm, and 34 mm). The European Medical Device Risk Class for Evolut R is Risk Class III.

The Evolut PRO valve has an outer wrap that adds surface area contact between the valve and the native aortic annulus to further improve valve sealing performance. Evolut Pro is available in three sizes (23 mm, 26 mm, and 29 mm). The European Medical Device Risk Class for Evolut Pro is Risk Class III.

Table 3.1. Features of TAVI systems available for use outside clinical trials in Europe for patients with severe symptomatic aortic stenosis at intermediate surgical risk

Proprietary name	Manufacturer	Indications	Expansion	Valve	Stent	Delivery approach
Edwards SAPIEN 3 Valve*	Edwards Life Sciences	Inoperable; high risk; intermediate risk	Balloon expanding	Bovine pericardium	Cobalt chromium	TF, TA, TAo
CoreValve Evolut R*	Medtronic (formerly delivered by CoreValve)	Inoperable; high risk; intermediate risk	Self-expanding	Porcine pericardium	Nitinol	TF, SC, DA
Medtronic Evolut Pro	Medtronic	Extreme high risk; high risk; intermediate risk	Self-expanding	Porcine pericardium	Nitinol (with an outer wrap)	TF, SC, DA

Abbreviations: DA=direct aortic access, SC=subclavian, TA=transapical, TAo=transaortic, TF=transfemoral.
*Information from 2017.

Comparator: SAVR

The existing standard treatment of patients with symptomatic aortic stenosis at intermediate surgical risk is SAVR. The surgery is performed under general anaesthesia and cardiopulmonary bypass. Access to the heart is either by full sternotomy or via less invasive approaches. A minimally invasive approach can be carried out via mini-thoracotomy and/or port access using direct vision, thoracoscopic, or robotic assistance. During SAVR, a cardiac surgeon removes the native aortic valve and replaces it with a prosthetic valve. There are many different prostheses and generations of prostheses available for SAVR. Although the prosthetic valve can be a mechanical valve, the use of bioprosthetic valves is the most common choice. Conventional prostheses for SAVR are anchored using surgical sutures (i.e., sutured valves) [5,54].

More recent approaches to SAVR include sutureless valves and rapid deployment valves. In the same manner as traditional sutured SAVR, these approaches require surgical incisions and can be performed with either full sternotomy or minimally invasive approaches under general anaesthesia and cardiopulmonary bypass. As in TAVI, there is no need for surgical sutures when fitting valves. The potential benefits of sutureless valves compared with conventional SAVR can include a reduction in operation time. Unlike TAVI, the diseased valve is excised during the procedure [7,55].

[A0020] For which indications has TAVI received marketing authorisation or CE marking?

Several TAVI systems are holders of a CE mark for use in inoperable patients and patients with high surgical risk. To our knowledge, only two manufacturers of TAVI devices hold a CE mark for use in patients with intermediate operative risk. These are Edwards Lifesciences (SAPIEN 3) and Medtronic (Evolut R and Evolut Pro).

Table 3.2. CE marking of TAVI systems

Device	Manufacturer	CE mark for inoperable patients and patients with high surgical risk	CE mark for patients with intermediate surgical risk
SAPIEN 3	Edwards Lifesciences	2014	2016

SAPIEN XT		2010	No
Evolut R	Medtronic (formerly CoreValve)	2014	2016
Evolut Pro*	Medtronic	2017	2017
CENTERA*	Edwards Lifesciences	2018	No
CoreValve	Medtronic: (formerly CoreValve)	2007	No
ACURATE TA ACURATE TF	Boston Scientific (formerly Symetis)	2011 2014	No No
Engager	Medtronic	2013	No
Lotus Edge**	Boston Scientific	2013 (Lotus Valve)* 2016 (Edge Valve)*	No
Direct Flow***	Direct Flow Medical (company closed in 2017)	2013	No
JenaValve***	Jena Technology	2011 (stenosed and calcified valves) 2013	No
Portico	St. Jude Medical	2012 2015 (update)	No

*Launched during assessment.

**Voluntarily recalled from the market in 2017; possible re-introduction after improvements in 2018.

***JenaValve and Direct Flow Medical (DFM) aortic valve are no longer on the market.

[B0002] What is the claimed benefit of TAVI in relation to SAVR?

SAVR is a high-risk procedure and can be contraindicated in some patients for medical and anatomical reasons. TAVI provides a less invasive alternative to SAVR and can be undertaken without the use of cardiopulmonary bypass and thoracotomy. For patients with intermediate surgical risk, the claimed benefits of TAVI compared with SAVR are decreased or similar rates of mortality, decreased or similar rates of short-term risks, and improved or similar functional benefits. Other claimed benefits are related to the length of hospital stay, recovery time, and post-discharge rehabilitation.

[B0003] What is the phase of development and implementation of the technology and the comparator(s)?

TAVI

The first-in-human TAVI implantations were performed in 2002 using the balloon-expandable bioprosthetic Cribier–Edwards valve (Edwards Lifesciences), followed by first-in-human studies with the self-expandable bioprosthetic CoreValve (Medtronic) in 2004. Both systems were awarded CE marks in 2007. The first FDA approvals came in 2012 (Edwards) and 2014 (CoreValve). Since these first CE marks and FDA approvals, there have been substantial and incremental developments for both systems. Although there are other TAVI systems and manufacturers,

currently only Edwards Lifesciences and Medtronic provide systems for patients at intermediate risk available for use outside clinical trials.

Between 2006 and 2016, over 100 000 TAVI procedures were performed worldwide [51]. Until recently, TAVI was primarily indicated for patients with symptomatic aortic stenosis considered ineligible for SAVR or at high surgical risk [3,20], There is variation in use across Europe. In 2011, 46% of all TAVI procedures in Europe were performed in Germany, and 40% of all aortic valve replacement procedures in Germany were carried out with the use of TAVI [51]. The rate of adoption in other countries has been slower. Lack of evidence on improved effectiveness, uncertainty with regard to prosthesis lifetime and uncertainty with regard to risks of early complications and long-term outcomes, as well as higher device costs and need for organisational changes, influence the use of TAVI, and have restricted its use in particular for younger patients and those at lower surgical risk. However, at least in some countries, there has been a shift towards the use of TAVI for patients at intermediate or low surgical risk [12].

Manufacturers have been focussing on improvements related to specific risks associated with the implants, such as aortic regurgitation, the need for a permanent pacemaker, risk of stroke, access-related complications, and the need to reposition the valve prosthesis before final deployment.

SAVR

The first successful aortic valve replacement was performed in 1960. Since then, SAVR has been the established and preferred treatment for patients with severe symptomatic aortic stenosis. The benefits, risks, and long-term outcomes of SAVR using conventional sutured valves are considered to be well documented. By contrast, SAVR with sutureless valves is less documented and not considered an established treatment [5,6].

[A0021] What is the reimbursement status of the technology/comparator?

According to a publication from 2016, TAVI had reimbursement available in 11 European countries in 2013 (Table 3.3). Diagnosis-related groups (DRG) for entire hospitalisation, add-on reimbursement, and fee-for-services and devices were the main payment models in Europe in 2013 [51].

Table 3.3. Payment models in European Countries in 2013

European country	Payment model
Sweden, Norway, Germany, Denmark, Switzerland, Austria, the Netherlands	DRG
Belgium	Fee for services and device
UK, France	DRG + add-on reimbursement
Italy	DRG + (regional) add-on reimbursement

In most of these 11 countries, reimbursement was established for the class of device, except in Belgium and France, where brand-specific reimbursement was available. In France, Germany, and Switzerland, the reimbursement varied according to the type of access for the procedure; for example, there was a higher reimbursement for procedures with transapical access in Germany and Switzerland. The use of TAVI and reimbursement has steadily increased since 2013 and TAVI is now available and reimbursed in several other European countries in addition to those mentioned here (for more information, see A0011).

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
A0002	What is severe symptomatic aortic stenosis with intermediate operative risk (intermediate risk for death or complications associated with SAVR)? How is the condition defined?
A0003	What are the known risk factors for severe aortic stenosis?
A0004	What is the natural course of severe aortic stenosis?
A0005	What are the symptoms and the burden of severe aortic stenosis for the patient?
A0025	Are there European professional society guidelines describing best practice for the treatment of patients with severe aortic stenosis at intermediate operative risk?
A0023	How many people with both severe aortic stenosis and intermediate operative risk are there in Europe?
A0011	How much is TAVI used in Europe?

4.2 Results

Overview of the disease or health condition

[A0002] What is severe symptomatic aortic stenosis with intermediate operative risk? How is the condition defined?

The aortic valve is one of four valves in the human heart. It is placed between the left ventricle and the main artery (aorta). The aortic valve regulates blood flow from the heart to the aorta. The valve normally has three cusps or leaflets, although ~1.4% of the population congenitally have two (bicuspid aortic valve) leaflets [8].

Aortic stenosis is the thickening, fibrosis, and calcification of aortic leaflets that impair outflow of blood to the rest of the circulation. The narrowing of the aortic valve increases workload to the heart as it attempts to maintain normal circulation. The impaired heart function is usually progressive and eventually leads to left ventricular hypertrophy and heart failure [8,56].

The NYHA Functional Classification provides a simple way of classifying the extent of heart failure [57]. It places patients into one of four categories based on how much they are limited during physical activity. NYHA classification is widely used as a measure of patient functionality in study eligibility criteria and study outcomes. The following classes are recognised:

NYHA class I: no symptoms and no limitation in ordinary physical activity (e.g., no shortness of breath when walking or climbing stairs).

NYHA class II: mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.

NYHA class III: marked limitation in activity because of symptoms, even during less-than-ordinary activity [e.g., walking short distances (20–100 m)]. Comfortable only at rest.

NYHA class IV: severe limitations; experience symptoms even when at rest; mostly bedbound patients.

Assessment of the severity of aortic stenosis utilises echocardiographic examinations and function tests together with age, symptoms, and comorbidities. Doppler, 2D, and M-mode echocardiography are the preferred tools for assessing major indicators of severity, such as valve area, transvalvular pressure gradients, flow rate, ventricular function, size and wall thickness, degree of valve

calcification, and blood pressure [20]. Severe aortic stenosis is typically described as the presence of severe leaflet calcification, severely reduced leaflet opening (≤1.0 cm^2), significantly increased mean pressure gradient (≥40 mmHg), and a peak transvalvular velocity ≥4 m/s. Exercise testing is recommended in physically active patients for unmasking symptoms [5,58,59].

Risk stratification is required for weighing the risk of intervention against the expected natural history of valvular heart disease. Aortic valve replacement by open-heart surgery (SAVR) is an established and effective treatment for severe symptomatic aortic stenosis. The procedure requires thoracotomy and takes place under general anaesthesia and cardiopulmonary bypass. Therefore, SAVR might not be suitable for some patients and, for others, the risks might outweigh the benefits [5,58,59].

A contraindication for SAVR is a high surgical risk of 30-day mortality because of medical and anatomical causes as well as frailty and comorbidity. Surgical risk rises with increased age and the presence of comorbidities.

Most commonly used risk algorithms include STS Predicted Risk of Mortality (STS-PROM), logistic EuroSCORE and EuroSCORE II (http://euroscore.org/calc.html). These systems aim to identify and quantify several risk factors that help to predict mortality from cardiac surgery. STS-PROM calculates the risk on the basis of the demographic and clinical characteristics of each patient. It is available as an online statistical tool. EuroSCORE assigns scores to patient-related, cardiac-related, and surgery-related risk factors. In its first version, published in 1999, the predicted mortality (in percent) was simply a sum of weights assigned to the risk factors. The tool was later refined into a logistic regression equation (logistic EuroSCORE). The latest version of the model (EuroSCORE II) was launched in 2011 as an online tool and is constantly updated and enhanced. The exact cut-off values for risk scores vary across the literature and can be arbitrary. However, for STS-Prom and EuroSCORE II, intermediate and low risk are defined by the ESC/EACTS guidelines as shown in Table 4.1.

Table 4.1. Surgical risk for 30-day mortality in patient stratification for SAVR and TAVI

Surgical risk for 30-day mortality based on STS-PROM or EuroSCORE II	Classification of risk
4–8%	Intermediate
<4%	Low

To estimate overall risks in individual patients and to stratify them to receive either palliative medical treatment (no valve replacement), medical treatment with reassessment on follow-up, SAVR, or TAVI, the surgical risk scores are used along with assessment of frailty as well as major organ complications not covered by the scores. This assessment is normally conducted by a specialised team [5,59].

A clear definition of what is understood by severe symptomatic aortic stenosis with intermediate surgical risk might not be possible because the criteria vary across different classification systems. Stratification will always depend on the classification system used as well as on subjective input from the specialised team, and can vary across different studies and contexts.

[A0003] What are the known risk factors for severe aortic stenosis?

The most common cause of aortic stenosis in patients older than 70 is the calcific degeneration of aortic leaflets, leading to narrowing and/or leaking of the valve. The leading causes in younger patients are congenital heart defects, particularly a bicuspid aortic valve. Other causes include previous rheumatic fever and infections, such as infective endocarditis [60,61].

Increased age, male gender, chronic renal insufficiency, and cardiovascular risk factors can also be associated with the progression of aortic stenosis [3].

[A0004] What is the natural course of severe aortic stenosis?

Aortic stenosis is a chronic, slowly progressive disease. Patients can remain asymptomatic for a long period until the disease is fairly advanced. Duration of the latent period varies widely among patients. However, once symptoms develop, there is a rapid increase in mortality rate for untreated patients [20]. Progressing stenosis causes an increase in pressure in the left ventricle, leading to compensatory left ventricular hypertrophy, impaired heart function, and eventually heart failure [60]. The only curative treatment is timely valve replacement therapy [62]. Treatment with medication alone for symptomatic aortic stenosis has limited clinical effect and can only be palliative (easing some symptoms). Patients with severe, symptomatic, untreated aortic stenosis have a mean life expectancy of <5 years from the onset of symptoms [3,60].

Effects of the disease or health condition

[A0005] What are the symptoms and burden of severe aortic stenosis for the patient?

Patients with aortic stenosis are initially asymptomatic with an incidental finding of crescendo-decrescendo heart murmur. Symptoms usually appear late during the course of the illness. Aortic stenosis resulting from age-related calcification typically occurs in normal tricuspid valves in patients aged 70 or over. In patients with bicuspid valve, age-related calcification typically appears earlier, during their fourth or fifth decade [61]. Fatigue and intolerance of exercise are some of the early symptoms. Depending on the degree of left ventricular hypertrophy and heart function insufficiency, patients can develop dyspnoea (shortness of breath) and angina pectoris (chest pain) if the heart becomes ischaemic. Some patients can experience syncope (episodes of fainting), or presyncope (dizziness) on exertion. Without treatment, pressure overload on the left ventricle leads to systolic dysfunction and left ventricular failure, and patients can report symptoms of pulmonary oedema, including shortness of breath, fatigue, and palpitations [60].

Current clinical management of the disease or health condition

[A0025] Are there European professional society guidelines describing best practice for the treatment of patients with severe aortic stenosis at intermediate operative risk?

According to the latest guidelines from ESC/EACTS [5], either TAVI or SAVR can be considered for patients at increased surgical risk, defined as STS or EuroSCORE II ≥4% or logistic EuroSCORE I ≥10% (class of recommendation: I). SAVR is recommended for lower risk patients with absence of other risks not included in these scores, such as frailty, porcelain aorta (extensive calcification of the aorta),or sequelae of chest radiation (class of recommendation: I).

The guidelines also recommend that a heart team should make the decision between SAVR and TAVI according to assessment of the individual risk and characteristics of the patient. The guidelines list aspects for consideration for the individual decision, and make recommendations in favour of either TAVI or SAVR [5].

Selection of aspects in favour of TAVI:

- STS or EuroSCORE II ≥4% or logistic EuroSCORE I ≥10%
- Presence of severe comorbidity
- Age ≥75
- Previous cardiac surgery
- Frailty
- Favourable access for transfemoral TAVI
- Porcelain aorta

Selection of aspects in favour of SAVR:

- STS or EuroSCORE II <4% or logistic EuroSCORE I <10%
- Age <75
- Suspicion of endocarditis
- Unfavourable access (any) for TAVI
- Size of aortic valve annulus out of range for TAVI
- Presence of thrombi in aorta or left ventricle
- Presence of cardiac conditions in addition to aortic stenosis that require consideration for concomitant intervention

Based on the above, we conclude that the 2017 ESC/EATC guidelines recommend that TAVI can be considered a treatment alternative for patients with severe symptomatic aortic stenosis at intermediate risk in conjunction with other aspects.

Target population

[A0023] How many people with severe aortic stenosis and intermediate risk are there in Europe?

Aortic stenosis is the most common valvular heart disease, accounting for nearly half of cases in developed countries. It is a slowly progressive disease and most new diagnoses of clinically significant aortic stenosis occur among older people [63]. Prevalence increases with age, reflecting an accelerated progression of the aortic mean gradient as the disease advances [10]. Various prevalence estimates have been reported in literature, with approximate average values being: 0.02% in people aged 18–44 years, 0.2% in the 50–59-year-old cohort, 1.3% in the 60–69-year-old cohort [3], 3.9% in the 70–79-year-old cohort, and 9.8% in the 80–89-year-old cohort [10]. Among older patients (>70), the prevalence of severe aortic stenosis in Europe is ~3.4%. It is reported that 75.6% of people with severe aortic stenosis are symptomatic [9]. Overall incidence rate is reported to be ~0.49% per year [10]. The annual incidence in the population over the age 65 is 2–7% [11].

A model calculation assuming the overall prevalence of aortic stenosis among people aged >60 to be 4.5%, suggested that 7.5 million people in Europe are likely to have aortic stenosis. Approximately 20% of these have severe aortic stenosis and ~71% of those with severe aortic stenosis are symptomatic. Based on this model, it is estimated that 873 700 patients in Europe are eligible for open-heart surgery. The calculated proportion of these patients with intermediate surgical risk is ~28.9% [12], resulting in an estimate of 252 500 patients.

The prevalence of aortic stenosis is likely to increase with progressive ageing of the population in Europe. Currently, 20% of this population is ≥65, with predictions that this proportion will rise to 24% by 2030 [64].

[A0011] How much is TAVI used in Europe?

Since the introduction of CE marked systems in 2007, there has been a rapid increase in the adoption of TAVI. In 2012 expert guidelines, the technology was recommended only for selected inoperable patients and patients with high surgical risk. However, in many countries, the use has extended to patients at intermediate and low risk, that is, not included by 2012 guideline recommendations [12,65].

Despite the rapid adoption of TAVI in most parts of Europe, there are important discrepancies in practice, particularly when it comes to patient selection. According to a survey performed in 2016 by the European Association of Percutaneous Coronary Interventions (EAPCI), 89% of European centres performed TAVI in inoperable patients; 95% in patients at high surgical risk, 45% in intermediate-risk patients, and 10% in low-risk patients. TAVI was restricted only to inoperable patients in 5% of centres [65].

An analysis of registry data revealed an overall increase in the number of aortic valve replacement procedures in recent years, whereas numbers of SAVR procedures are moderately but steadily declining [46,51]. This decline is most prominent in younger groups of patients with lower risk profiles. There is a suggestion that, in older patient groups (≥80 years), TAVI and SAVR are complementary procedures, with older patients treated with TAVI who otherwise would not have been able to have a heart valve replacement. However, in younger cohorts, the increase in TAVI offsets the reduction in the number of SAVR procedures, suggesting that TAVI competes with open-heart surgery in younger patients at lower risk [12,66].

In several European countries, most patients who undergo TAVI are included in national databases on cardiac surgery and Germany, UK, France, Italy, Spain, Switzerland, and Belgium have set up national TAVI registries to follow up patients who undergo the procedure.

For the purpose of this assessment, the authors performed a survey among the EUnetHTA partners taking part in WP4. The survey included questions about the reimbursement status of TAVI in the respondents' country or region as well as the number of TAVI procedures performed in 2015 and/or

2016. EUnetHTA partners from 19 countries and one region (Scotland) responded to the survey. The results show that the use of TAVI varied across these 20 European countries or regions (Table 4.2). Germany had the highest annual rate per million inhabitants, followed closely by Switzerland and France. These three countries accounted for >60% of all TAVI procedures performed in Europe.

Table 4.2. Reimbursement status of TAVI among EUnetHTA partners

Country/Region (million inhabitants, 2015*)	Reimbursement status	Number of procedures 2015/2016	Number of procedures per million inhabitants*
Austria (8.7)	Reimbursed	807 (2015)	93
Belgium (11.3)	Reimbursed for patients with severe symptomatic AS with high risk or inoperable	500	44
Czech Republic (10.6)	Reimbursed for patients with severe symptomatic AS with high risk or inoperable	382 (2015); 528 (2016)	50
Finland (5.5)	Reimbursed	419 (2015)	76
France (64.5)	Reimbursed for patients with severe, symptomatic AS contraindicated for surgery or at high surgical risk. For patients with intermediate risk, HAS also recommended reimbursement (September 2017) but decision remains to be taken	10 000 (2016)	155
Germany (81.7)	Reimbursed	15 277 (2015)	187
Greece (11.2)	Reimbursed only for inoperable and high-risk patients	295 (2016)	26
Ireland (4.7)	Reimbursed for inoperable and high-risk patients	192 (2015)	41
Malta (0.43)	Reimbursed for patients with severe symptomatic AS turned down for SAVR	21 (2015); 26 (2016)	60
Netherlands (16.9)	Reimbursed for patients for whom SAVR is unsuitable	995 (2012)	59
Norway (5.2)	Reimbursed for patients with severe symptomatic aortic stenosis, mainly used for high risk and patients >80 years	356 (2015); 524 (2016)	100
Poland (38.3)	Reimbursed	625 (2015); 867 (2016)	22
Portugal (10.4)	Reimbursed	313 (2015)	30
Scotland, UK (5.3**)	Reimbursed for inoperable and high-risk patients	180/year	34
Slovenia (20.1)	Partly reimbursed	120 (2016)	6
Spain (46.4)	Reimbursed for patients with severe AS evaluated by a multidisciplinary clinical committee from a clinical centre with a cardiovascular surgery unit and a written protocol for selection of TAVI candidate available	1586 (2015); 2026 (2016)	43

Sweden (9.8)	Reimbursed	577 (2015); 661 (2016)	67
Switzerland (8.3)	Reimbursed for inoperable and high-risk patients, re-evaluation ongoing	1300	156
UK (65.4)	Reimbursed based on NICE guidance IPG 506	3250 (2016)	50
Italy (60.7**)	Some regions introduced supplementary payment in addition to standard DRG; some others used procedure-specific payments	3466 (2015) 4592 (2016)	76

* Inhabitants of countries based on: World Population Prospects, the 2017 Revision, United Nations Department of Economic and Social Affairs, Population Division.

** Inhabitants of country/region based on Google search.

5 CLINICAL EFFECTIVENESS (EFF)

5.1 Research questions

Element ID	Research question
D0001	What is the expected beneficial effect of TAVI on mortality (disease specific and all cause) in patients with severe aortic stenosis at intermediate surgical risk?
D0005	How does TAVI affect the symptoms and findings (severity and frequency) of aortic stenosis?
D0006	How does TAVI affect the progression of aortic stenosis?
D0011	What is the effect of TAVI on the physiological functions of patients?
D0016	How does TAVI affect activities of daily living?
D0012	What is the effect of TAVI on generic health-related quality of life?
D0013	What is the effect of TAVI on disease-specific quality of life?

5.2 Results

Included studies

The two included trials (PARTNER 2a) [15, 16][a] and SURTAVI [2] were multicentre trials conducted in several countries (USA, Europe, and Canada) and included 3778 patients with 2 years of follow-up. The mean age of patients (mean 80 and 82, respectively) and female percentage (43% and 45%, respectively) were similar between the two trials.

The patient eligibility criteria of the PARTNER 2 trial were: symptomatic severe aortic valve stenosis and intermediate surgical risk according to the Society of Thoracic Surgeons (STS) score of at least 4% with an (not prespecified) upper limit of 8%. Patients with an STS score <4% could also be included if there were coexisting conditions not represented in the STS risk score algorithm. Patients included in the trial had a mean STS score of 5.8±2.1 for the TAVI group and 5.8±1.8 for the SAVR group [15].

Patient eligibility criteria of the SURTAVI were: symptomatic severe aortic stenosis and intermediate surgical risk according to an STS score of 3–15% [2]. Patients included in the trial had a mean STS score of 4.5±1.6 [2].

In the PARTNER 2 trial, 2032 patients were stratified into cohorts according to access route (TF or transthoracic) and then randomised in a 1:1 ratio to either TAVI or SAVR. Of these, 1550 patients were deemed suitable for TF access and 775 were then allocated to TAVI; 482 patients (23.7%) were deemed suitable for transthoracic access and 236 were then allocated to TAVI. Patients assigned to TAVI cohorts received an Edwards balloon-expandable SAPIEN XT heart valve (26 mm). Details for the SAVR procedures were not provided in the publications.

In the SURTAVI trial, 84% of the patients in the TAVI group received CoreValve self-expanding valves, whereas the remaining 16% received the Evolut R self-expanding valves. Most patients in

[a]The main author and co-author disagreed as to whether Aurora 2016 [16] should be included as a study presenting data from the PARTNER2 trial. Given that no information presented in Leon 2016 [15] can be found in Aurora 2016 [16], the decision by the main author to include this publication does not change any results or conclusions.

the TAVI group were treated iliofemorally (93.6%). The choice of implant and access route was decided after randomisation.

Primary outcomes in both trials were composite of death from any cause and disabling stroke at 2-year follow-up; however, both studies reported most outcomes at follow-ups after 30 days, 1 year, and 2 years. Secondary outcomes and basic characteristics of the included studies are provided in Table A1 in Appendix 1. The follow-up time was 2 years for both studies. Both studies were funded by the manufacturers.

Both studies reported a secured central randomisation method and were considered to be at low risk of selection bias. Given the nature of the interventions, patients and investigators could not be blinded, but performance bias was not taken into account when the outcome of interest (e.g., mortality) was objective. The PARTNER 2 trial was considered at low risk of detection bias because all patients were visited by trained neurologists who were unaware of treatment allocation. In the SURTAVI trial, it was unclear whether the outcome assessor was blinded to the treatment assignment.

In the PARTNER 2 trial, 1011 patients were enrolled in the TAVI cohort and 1021 in the SAVR cohort (intention-to-treat population). Ninety-four patients [17 (1.7%) in the TAVI group and 77 (7.6%) in the SAVR group] were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery. It is unclear whether differences in withdrawal between the two groups might have created an imbalance in the prognostic characteristics of the two groups. In the PARTNER 2 trial, outcomes were reported using Kaplan Meier time-to-event analyses on available evidence at each time point. For various outcomes, the population at risk varied at each time point. As an example, at 2-year follow-up, 774 patients in the TAVI group and 695 patients in the SAVR group were available for the overall mortality outcome. This important attrition generated serious concerns regarding the available evidence at the 2-year follow-up.

In the SURTAVI trial, 1746 patients were randomised (879 in the TAVI group and 867 in the SAVR group); of these 1660 (864 in the TAVI group and 796 in the SAVR group) received the intervention. For the SURTAVI trial, the reported data represented the results of a Bayesian statistical method interim analysis after 1 year. Most patients reached this follow-up point; however, at the 2-year follow-up, there were considerably fewer patients. Thus, data for patients without a known outcome were used at the 2-year follow-up. As an example, for the mortality outcome at the 2-year follow-up, 280 patients were available for outcome measures in the TAVI group and 249 in the SAVR group. The SURTAVI trial reported both standard and modified intention-to-treat analysis with outcome imputation and sensitivity analysis. Hence, the study was considered at low risk of attrition bias at 30-day and 1-year follow-up but not at the 2-year follow-up.

No concerns were identified in terms of selective reporting. Risk of bias for the two included trials is reported in Appendix 1.

Mortality

[D0001] What is the expected beneficial effect of TAVI on mortality (disease specific and all cause) in patients with severe aortic stenosis at intermediate surgical risk?

All-cause mortality

All-cause mortality was reported by both trials. At 30-day follow-up, 3.1% of patients in the TAVI group had died, whereas 2.9% of patients had died in the control group: TAVI was probably non-inferior to SAVR in terms of mortality [RR 1.07, 95% CI 0.74–1.55; GRADE evidence: moderate). We downgraded the quality for this outcome at 30-day follow-up because of risk of bias (i.e., imbalance in withdrawals between the groups). See Table 5.1 for the efficacy comparison.

At 2-year follow-up, 12.9% of patients had died in the TAVI group, whereas 12.7% had died in the control group: it is uncertain whether TAVI is non-inferior to SAVR [RR 1.01, 95% CI 0.86–1.20; GRADE evidence: very low) (Figure 5.1). We downgraded the quality for this outcome at 2-year follow-up because of a serious concern of risk of bias (i.e., important attrition). See Table 5.1 for the efficacy comparison.

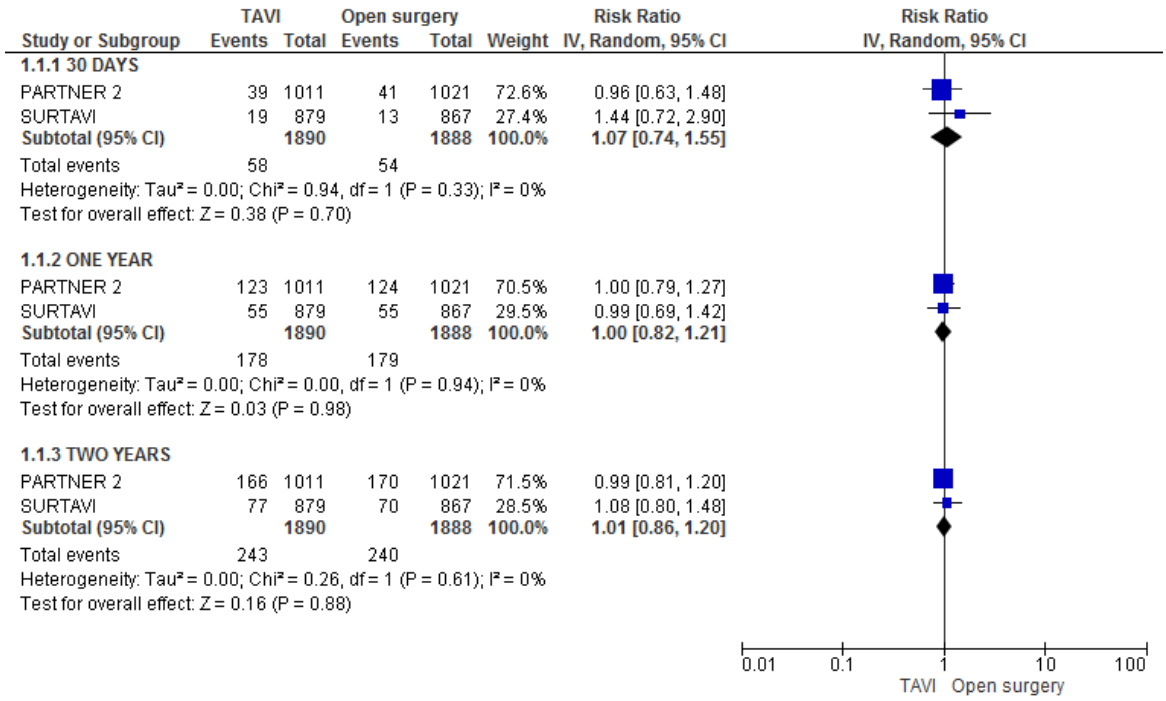


Figure 5.1. All-cause mortality at 30-day, 1-year, and 2-year follow-up

Cardiac mortality

Cardiac mortality was reported by both trials at 30-day, 1-year, and 2-year follow-up. At 30-day follow-up, cardiac mortality was reported for 2.6% of patients in the TAVI group compared with 2.4% of patients in the control group: TAVI is probably non-inferior to SAVR in terms of cardiac mortality (RR 1.11, 95% CI 0.75–1.66; GRADE evidence: moderate) (Figure 5.2). We downgraded the quality for this outcome at 30-day follow-up because of a risk of bias (i.e., imbalance in withdrawals between the groups). See Table 5.1 for the efficacy comparison.

At 2-year follow-up, cardiac mortality was reported for 7.9% of patients in the TAVI group, compared with 8.2% in the control group. In terms of cardiac mortality at patients -year follow-up, it is uncertain whether TAVI is non-inferior to SAVR [RR 0.96, 95% CI 0.78–1.19; GRADE evidence: very low) (Figure 5.2). We downgraded the quality for this outcome at 2-year follow-up because of serious concerns of a risk of bias (i.e., important attrition). See Table 5.1 for the efficacy comparison.

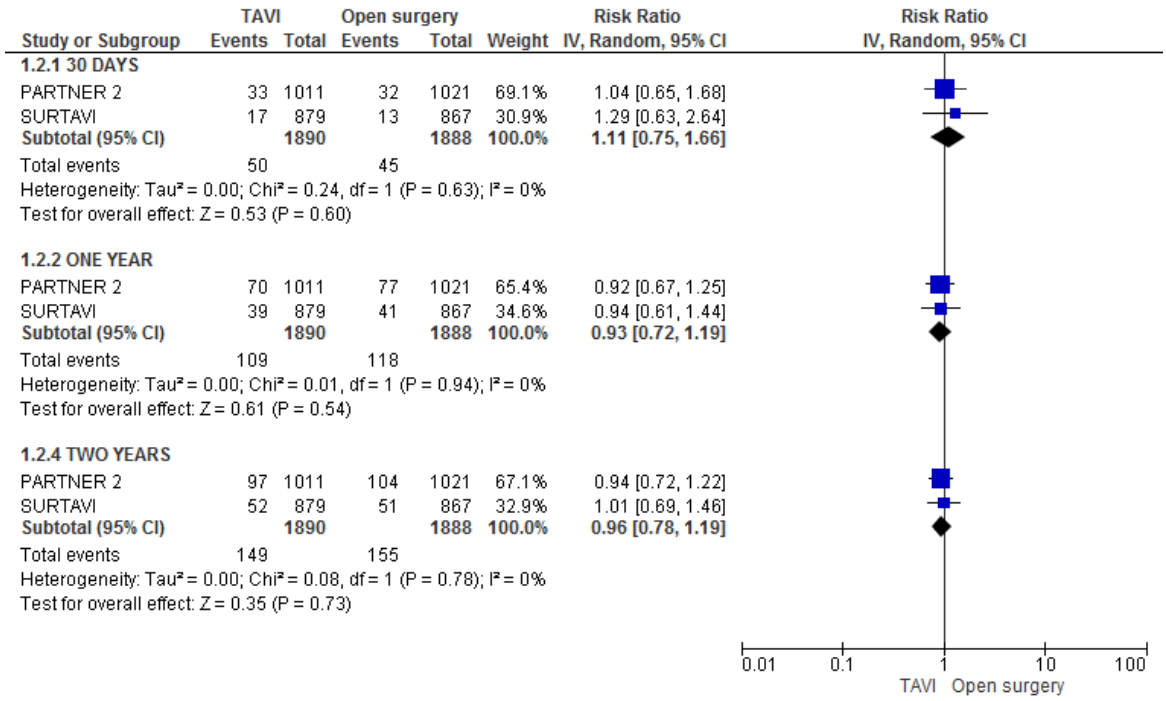


Figure 4.2. Cardiac mortality at 30-day, 1-year, and 2-year follow-up

Morbidity

[D0005] How does TAVI affect the symptoms and findings (severity and frequency) of aortic stenosis?

Improvement of symptoms (reduction in NYHA class)

In the PARTNER 2 trial, 80% of patients were NYHA class III or higher at baseline. The investigators reported a significant reduction in symptoms to NYHA class II or I at 30-day follow-up in both the TAVI and control groups, and the NYHA class was maintained for 2 years (p <0.001). At 2-year follow-up, ~48% of patients in the TAVI group and ~52% in the surgery group remained in NYHA class I. No differences in effect was observed between the two groups at 1- or 2-year follow-up.

In the SURTAVI trial, 60% of the TAVI group and 58% of the SAVR group were NYHA class III or higher at baseline. After 2-year follow-up, there was a significant reduction to NYHA class II or I, with 62% NYHA class I in the TAVI and 58% in the SAVR group. No differences in effect were observed between the two groups at 1- or 2-year follow-up.

Thus, we conclude that it is uncertain whether TAVI has any effect on improving symptoms compared with SAVR at 1- or 2-year follow-up (GRADE evidence: very low). We downgraded the quality for this outcome because of serious concerns of risk of bias (i.e., imbalance in withdrawals between the groups, important attrition, and performance bias) and imprecision (i.e., no evidence of effect).

[D0006] How does TAVI affect the progression of aortic stenosis?

The outcome 'Rehospitalisation for myocardial infarction (>72 h following TAVI)' reported in our protocol was not evaluated by either study. However, the PARTNER 2 trial assessed any rehospitalisation at 30-day, 1-year, and 2-year follow-up, with no reported differences between the TAVI and SAVR groups.

Aortic valve reintervention

At 30-day follow-up, aortic valve reintervention was performed in 0.6% of patients in the TAVI group and 0.1% in the SAVR group: thus, TAVI might increase the risk of aortic valve reintervention compared with SAVR (RR 7.58, 95% CI 1.38–41.55; GRADE evidence: low) (Figure 5.3). We

downgraded the quality for this outcome at 30-day follow-up because of a risk of bias (i.e., imbalance in withdrawals between the groups) and serious concerns regarding imprecision (i.e., few events and wide CIs). See Table 5.1 for the efficacy comparison.

At 2-year follow-up, aortic valve reintervention was performed in 1.7% of the TAVI group and 0.4% of the SAVR group: thus, compared with SAVR, it is uncertain whether TAVI increases the risk of aortic valve reintervention (RR 3.86, 95% CI 1.76–8.44; GRADE evidence: very low) (Figure 5.3). We downgraded the quality for this outcome at 2-year follow-up because of serious concerns regarding a risk of bias (i.e., owing to important attrition) and imprecision (i.e., very few events with wide CIs). See Table 5.1 for the efficacy comparison.

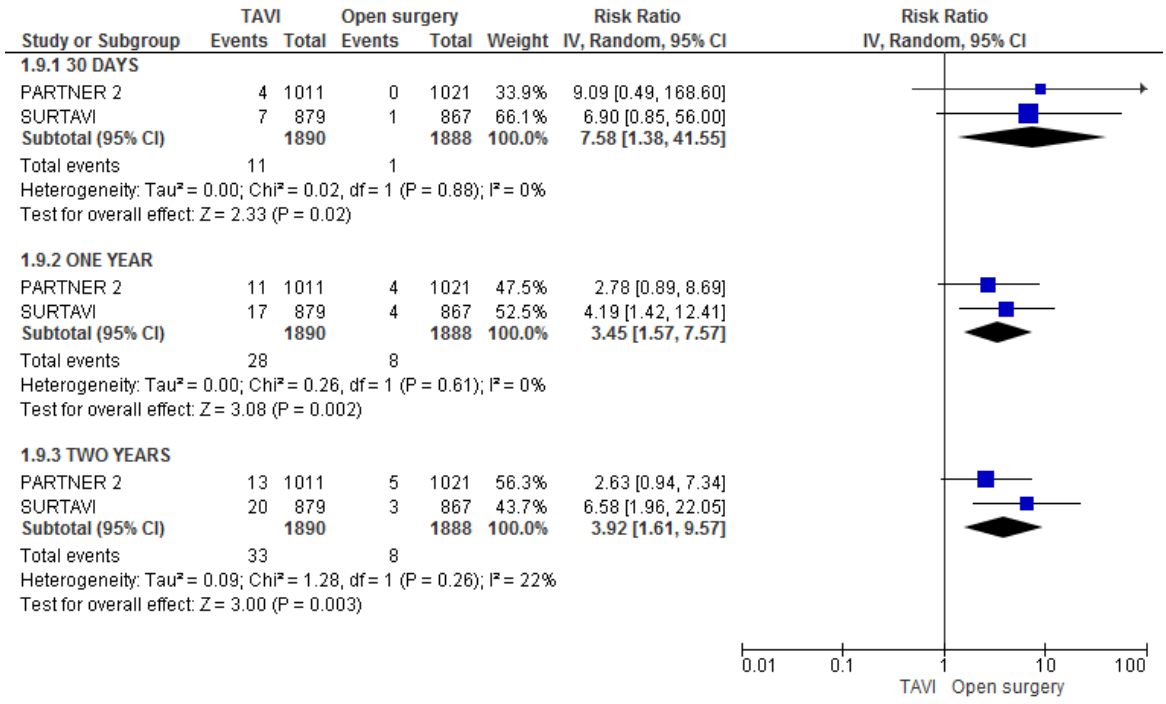


Figure 5.3. Aortic reintervention at 30-day, 1-year, and 2-year follow-up

In addition, the SURTAVI trial assessed rehospitalisations because of aortic valve dysfunction at 30-day, 1-year, and 2-year follow-up with no reported difference between the TAVI and SAVR groups.

[D0011] What is the effect of TAVI on the physiological functions of patients?

Evidence for the following outcomes was identified: haemodynamic function of the valve, and hospital and intensive care unit length of stay. For procedural success and rehospitalisation for myocardial infarction (>72 h following TAVI), no evidence was found from either of the included studies.

Haemodynamic function of the valve

In the SURTAVI trial, from baseline to discharge, the mean aortic gradient improved in both the TAVI group (8.9±4.1 mmHg) and the SAVR group (12.4±5.7 mmHg); the difference between the two groups was statistically significant (p <0.001). This difference persisted throughout the 2-year follow-up. In addition, from baseline to discharge, the TAVI group had larger aortic valve areas than the SAVR group (2.1±0.6 cm^2 versus 1.8±0.6 cm^2, respectively) with a statistically significant difference. These improvements persisted throughout the 2-year follow-up.

In the PARTNER 2 trial, in both the TAVI and SAVR groups, there was an improvement in the aortic valve area (1.7±0.5 cm^2 versus 1.5 cm^2 ± 0.4, respectively; p <0.001) and LVEF (56.9±10.2% versus 55.0±11.0%, respectively; p <0.004) as well as a decrease in the mean aortic valve gradients

(9.7±3.5 mmHg versus 10.9±4.3 mmHg, respectively; p <0.001). These improvements persisted throughout the 2-year follow-up.

Hospital and intensive care unit length of stay

In the PARTNER 2 trial, patients in the TAVI group had a significantly shorter duration of the index of hospitalisation (median, 6 versus 9 days; p <0.001) as well as a shorter duration of stay in the intensive care unit than those in the surgery group (median, 2 versus 4 days; p <0.001).

In the SURTAVI trial, the duration of the index of hospitalisation was shorter in the TAVI than in the SAVR group (5.75±4.85 days versus 9.75±8.03 days, respectively). No data regarding intensive care unit stays were provided.

The overall GRADE level of evidence for hospital stay was considered moderate. We downgraded the quality for this outcome because of risk of bias (i.e., imbalance in withdrawals between the groups).

Health-related quality of life

[D0016] How does TAVI affect activities of daily living?

[D0012] What is the effect of TAVI on generic health-related quality of life?

[D0013] What is the effect of TAVI on disease-specific quality of life?

Improvement in health-related quality of life indicators

In the PARTNER 2 trial, 80% of patients were NYHA class III or higher at baseline. Investigators reported a significant reduction in symptoms to NYHA class II or I at 30-day follow-up in both the TAVI group and the SAVR group, and the NYHA class was maintained for 2 years (p <0.001). At 2-year follow-up, ~48% of patients in the TAVI group and ~52% in the SAVR group maintained NYHA class I. No difference of effect was observed between the two groups at 1- or 2-year follow-up.

In the SURTAVI trial, 60% in the TAVI group and 58% in the SAVR group were NYHA class III or higher at baseline (KCCQ). After 2-year follow-up, there was a significant reduction to NYHA class II or I, with 62% in the TAVI and 58% in the SAVR group in NYHA class I. No difference of effect was observed between the two groups at 1- or 2-year follow-up. The overall GRADE level of certainty was considered to be low.

Hence, we conclude that it is uncertain whether TAVI has any effect on improving symptoms compared with SAVR at 1- or 2-year follow-up (GRADE evidence: low).

No other generic or disease-specific quality-of-life instrument data were reported in either of the two trials.

Table 5.1. Summary of findings for the efficacy comparison of TAVI versus SAVR for patients with aortic stenosis at intermediate surgical risk

Certainty assessment							№ of patients (%)		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TAVI**	**SAVR**	**Relative (95% CI)**	**Absolute (95% CI)**	
Mortality from any cause: 30-day follow-up											
2	Randomised trials	Serious [a]	Not serious	Not serious	Not serious [b]	None	58/1890 (3.1%)	54/1888 (2.9%)	RR 1.07 (0.74–1.55)	2 more per 1000 (from 6 fewer to 16 more)	⊕⊕⊕◯ moderate
Mortality from any cause: 2-year follow-up											
2	Randomised trials	Very serious [c]	Not serious	Not serious	Not serious [b]	None	243/1890 (12.9%)	240/1888 (12.7%)	RR 1.01 (0.86–1.20)	0 fewer per 1000 (from 21 fewer to 24 more)	⊕⊕◯◯ low
Cardiac mortality: 30-day follow-up											
2	Randomised trials	Serious [a]	Not serious	Not serious	Not serious [b]	None	50/1890 (2.6%)	45/1888 (2.4%)	RR 1.11 (0.75–1.66)	3 more per 1000 (from 6 fewer to 16 more)	⊕⊕⊕◯ moderate
Cardiac mortality: 2-year follow-up											
2	Randomised trials	Very serious [c]	Not serious	Not serious	Not serious [b]	None	149/1890 (7.9%)	155/1888 (8.2%)	RR 0.96 (0.78–1.19)	3 fewer per 1000 (from 16 fewer to 18 more)	⊕⊕◯◯ low
Improvement of symptoms (reduction in NYHA class)											

Certainty assessment							№ of patients (%)		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TAVI**	**SAVR**	**Relative (95% CI)**	**Absolute (95% CI)**	
2	Randomised trials	Very serious [d]	Not serious	Not serious	Serious[e]	Not serious	PARTNER 2 trial: at baseline, 80% of patients were NYHA class III or higher; at 30-day follow-up, both groups had significant reduction of symptoms; at 2-year follow-up, ~48% of patients in the TAVI group and 52% in the SAVR group maintained NYHA class I. There was no significant difference between the two groups. SURTAVI trial: at baseline, 60% in the TAVI group and 58% in the SAVR group were NYHA class III or higher. After 2-year follow-up, there was a significant reduction to NYHA class II or I in the TAVI (63%) and SAVR (58%) groups. There was no significant difference between the two groups				⊕◯◯◯ very low
Aortic valve reintervention: 30-day follow-up											
2	Randomised trials	Serious [f]	Not serious	Not serious	Serious[g]	None	11/1890 (0.6%)	1/1888 (0.1%)	RR 7.58 (1.38 to 41.55)	3 more per 1000 (from 0 fewer to 21 more)	⊕⊕◯◯ low
Aortic valve reintervention: 2-year follow-up											
2	Randomised trials	Very serious [h]	Not serious	Not serious	Very serious[g]	None	33/1890 (1.7%)	8/1888 (0.4%)	RR 3.86 (1.76 to 8.44)	12 more per 1000 (from 3 more to 32 more)	⊕◯◯◯ very low
Length of hospital stay											
2	Randomised trials	Serious [i]	Not serious	Not serious	Not serious	None	Both trials reported significantly shorter durations of hospital stay in the TAVI group, but data could not be pooled. PARTNER 2 reported a median of 6 days for TAVI and 9 days for SAVR (p <0.001). In the SURTAVI trial, length of hospital stay was shorter by 4 days in the TAVI group than in the SAVR group (media: –4.00 days, 95% CI –4.58 to –3.42)				⊕⊕⊕◯ moderate
Quality of life (improvement of symptoms only)											

Certainty assessment							№ of patients (%)		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAVI	SAVR	Relative (95% CI)	Absolute (95% CI)	
2	Randomised trials	Very serious [d]	Not serious	Not serious	Serious[e]	Not serious	PARTNER 2 trial: at baseline, 80% of patients were NYHA class III or higher; at 30-day follow-up, both groups had significant reduction of symptoms; at 2-year follow-up, ~48% of patients in the TAVI group and 52% in the SAVR group maintained NYHA class I. There was no significant difference between the two groups. SURTAVI trial: at baseline, 60% of the TAVI group and 58% of the SAVR group were NYHA class III or higher. After 2-year follow-up, there was a significant reduction to NYHA class II or I for the TAVI (63%) and SAVR (58%) groups. There was no significant difference between the two groups.				⊕◯◯◯ very low

GRADE Working Group grades of evidence:

High evidence: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate evidence: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low evidence: our confidence in the effect estimate is limited: the true effect might be substantially different from the estimate of the effect.

Very low evidence: we have little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Serious concern regarding risk of bias: blinding patients and personnel was not possible because of the type of intervention. Given that mortality was considered an objective outcome, we considered that absence of blinding could not introduce any performance bias and, therefore, there was no downgrading. However, the quality of evidence was downgraded by one level because, in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this imbalance in withdrawals between the two groups might have introduced bias.

b. We did not downgrade for imprecision: the sample size was sufficiently large (N=3778) and rates of events were low; the absolute difference in mortality rates between the two procedures was very small (absolute difference of +0.2% with a 95% CI of –0.7% to 1.6%).

c. Very serious concern regarding risk of bias: blinding patients and personnel was not possible because of the type of intervention. Given that mortality was considered an objective outcome, we considered that absence of blinding could not introduce the performance bias and, therefore, no downgrading was done. However, the quality of evidence was downgraded by two levels given that: (i) in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this imbalance in withdrawals between the two groups might have introduced bias; and (ii) at 2-year follow-up, >30% and >50% of patients were lost to follow-up in each trial, respectively.

d. Very serious concern regarding risk of bias: blinding patients and personnel was not possible because of the type of intervention. The quality of evidence was downgraded by two levels given that: (i) in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this imbalance in withdrawals between the two groups might have introduced bias; (b) at 2-year follow-up, >30% and >50% of patients were lost to follow-up in each trial, respectively; and (c) performance bias or detection bias might affect the results because the outcome was considered subjective.

e. No effect of treatment.

f. Serious concern regarding risk of bias: blinding patients and personnel was not because of the type of intervention. Given that aortic valve intervention was an objective outcome, we considered that absence of blinding could not introduce the performance bias and, therefore, no downgrading was done. However, the quality of evidence was downgraded by one level because, in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this imbalance in withdrawals between the two groups might have introduced bias.

g. Large CI.

h. Very serious concern regarding risk of bias: blinding patients and personnel was not possible because of the type of intervention. Given that aortic valve reintervention was an objective outcome, we considered that absence of blinding could not introduce the performance bias and, therefore, no downgrading was done. However, the quality of evidence was downgraded by two levels given that: (i) in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this imbalance in withdrawals between the two groups might have introduced bias; and (ii) at 2-year follow-up, >30% and >50% of patients were lost to follow-up in each trial, respectively.

i. Serious concern regarding risk of bias: blinding patients and personnel was not possible because of the type of intervention. Given that length of hospital stay was an objective outcome, we considered that absence of blinding could not introduce the performance bias and, therefore, no downgrading was done. However, the quality of evidence was downgraded by one level because, in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this imbalance in withdrawals between the two groups might have introduced bias.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
C0008	How safe is TAVI compared with SAVR?
C0002	Are the harms device related?
C0004	How does the frequency or severity of harm change in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through TAVI?
C0007	Are TAVI and SAVR associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of TAVI?

6.2 Results

Included studies

Other than the studies presented in the EFF domain, comparative prospective national registries studies presenting analyses of real-world data were included for the SAF domain. Overall, two RCTs [2,15,16] and two registry studies [17,18] were included for the analysis of safety outcomes.

RCT studies

The included RCTs are described in detail within the EFF domain.

Real-world data studies

Given that data on safety outcomes were available from RCTs, the real-world data studies were only presented narratively and the level of evidence was not graded. The two registry studies were not included in any meta-analysis. Results were only presented and discussed narratively.

The study by Bestehorn *et al.* [17] presented the analysis of the incidence of POD and in-hospital mortality in patients with comparable risk treated with either SAVR or TAVI (TF route only) in Germany during 2013. From a data set of 3407 procedures performed in patients with a EuroSCORE between 10% and 20%, two homogeneous groups of 763 patients each with EuroSCORE 13.5±2.7 were extracted for a first analysis. A second analysis was performed using two groups of 470 patients each matched according to sex, ASA classification, left ventricular ejection fraction, previous PCI, previous cardiac surgery, peripheral artery disease, lung disease, neurological disease, and diabetes mellitus.

The study by Brennan *et al.* [18] presented the analysis of the incidence of stroke at 1 year in patients treated with either SAVR or TAVI in the USA between 2011 and 2015. From a data set of 40 528 procedures, two groups of 4732 patients each were matched using propensity scores: median age: 82 years (IQR: 77–85 years); sex: 47.9% women; median STS PROM score: 5.6% (IQR: 4.2–8.2%).

Patient safety

Analysis of RCT data

[C0008] How safe is TAVI in relation to SAVR?

Stroke and disabling stroke

Stroke and disabling stroke were reported by both trials at 30-day, 1-year, and 2-year follow-up.

At 30-day follow-up, stroke occurred in 4.4% of patients in the TAVI group and 5.6% in the SAVR group: compared with SAVR, it is uncertain whether TAVI has any effect on stroke at 30-day follow-up (RR 0.80, 95% CI 0.58–1.10; GRADE evidence: very low) (Figure 6.1). We downgraded the quality for this outcome at 30-day follow-up because of the risk of bias (i.e., imbalance in withdrawals between the groups), inconsistency (i.e., substantial heterogeneity: I^2 = 64), and imprecision (i.e., wide CIs that crossed the line of no effect). See Table 6.1 for the safety comparison.

At 2-year follow-up, the overall stroke occurrence was 7.4% in the TAVI group and 7.6% in the SAVR group: it is uncertain whether TAVI is non-inferior to SAVR in terms of stroke (RR 0.97, 95% CI 0.74–1.26; GRADE evidence: very low) (Figure 6.1). We downgraded the quality for this outcome at 2-year follow-up because of a risk of bias (i.e., very serious concern owing to important attrition), and imprecision (i.e., wide CIs that crossed the line of no effect). See Table 6.1 for the safety comparison.

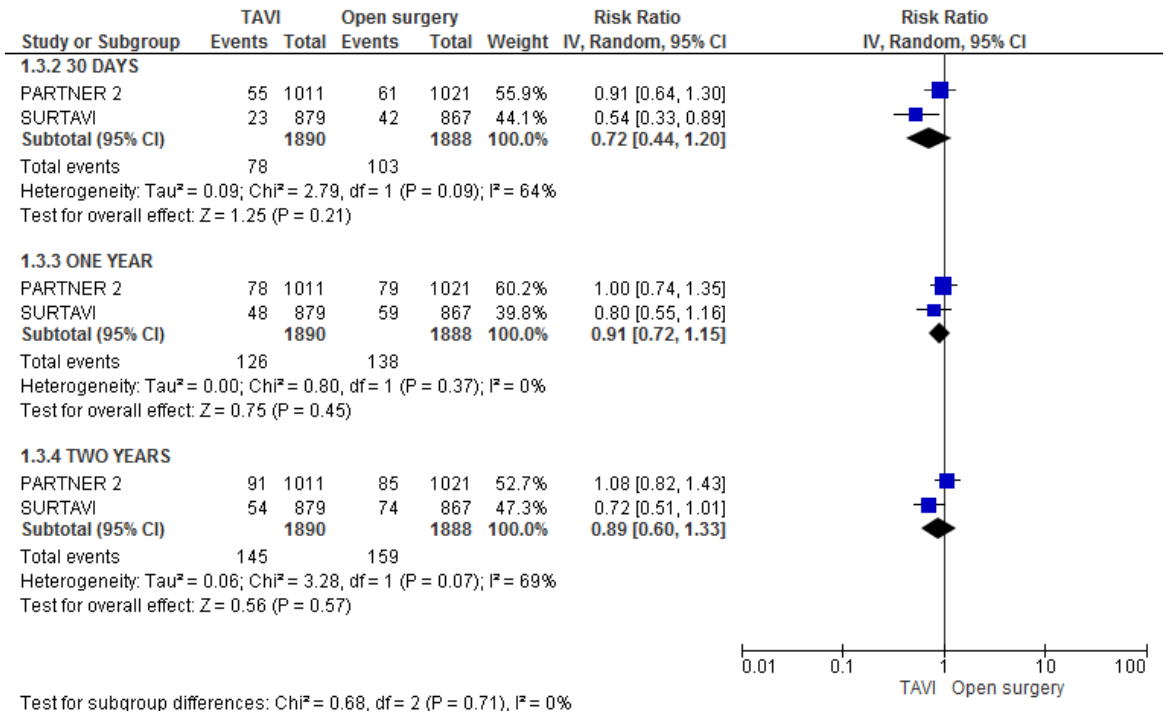


Figure 6.1. Incidence of stroke at 30-day, 1-year, and 2-year follow-up

At 30-day follow-up, disabling stroke occurred in 2.3% of patients in the TAVI group and 3.3% in the SAVR group: it is uncertain whether TAVI has any effect on disabling stroke compared with SAVR (RR 0.70, 95% CI 0.48–1.02; GRADE evidence: low) (Figure 6.2).

We downgraded the quality for this outcome at 30-day follow-up because of a risk of bias (i.e., imbalance in withdrawals between the groups) and imprecision (i.e., wide CIs that crossed the line of no effect). See Table 6.1 for the safety comparison.

At 2- year follow-up, the overall disabling stroke occurrence was 4.2% in the TAVI group and 4.9% in the SAVR group: it is uncertain whether TAVI has any effect on disabling stroke compared with SAVR (RR 0.83, 95% CI 0.56–1.25; GRADE evidence: very low) (Figure 6.1).

We downgraded the quality for this outcome at 2-year follow-up because of the risk of bias (i.e., very serious concern owing to important attrition), and imprecision (i.e., wide CIs that crossed the line of no effect). See Table 6.1 for the safety comparison.

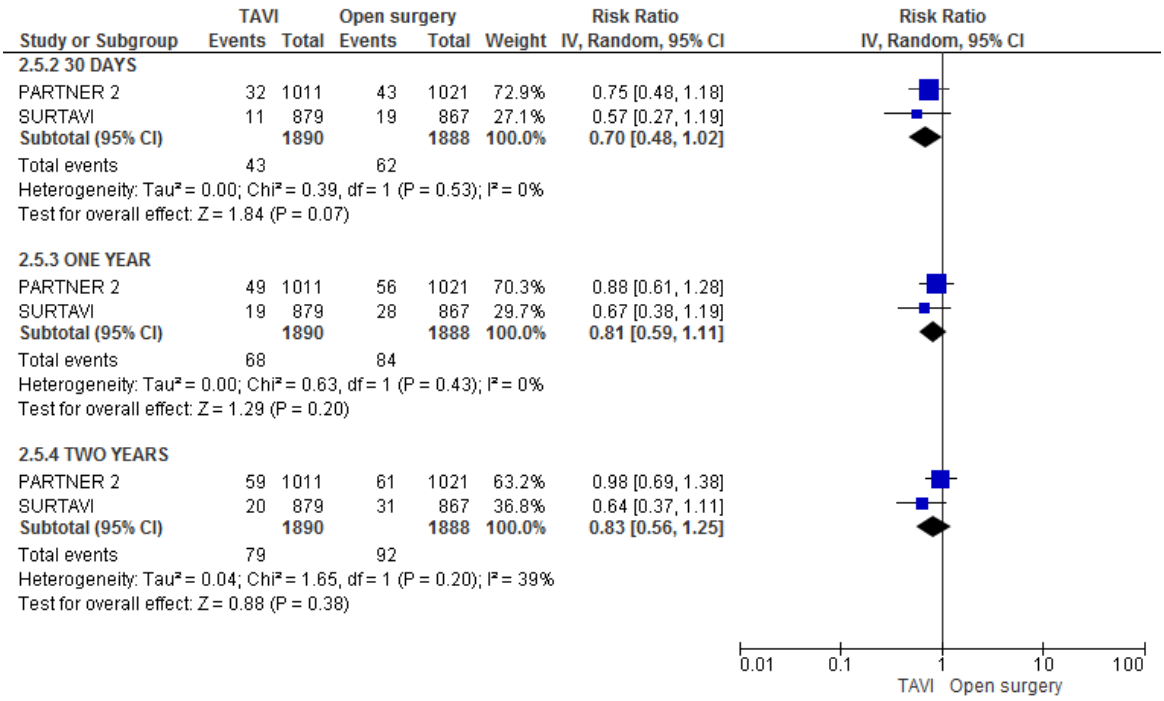
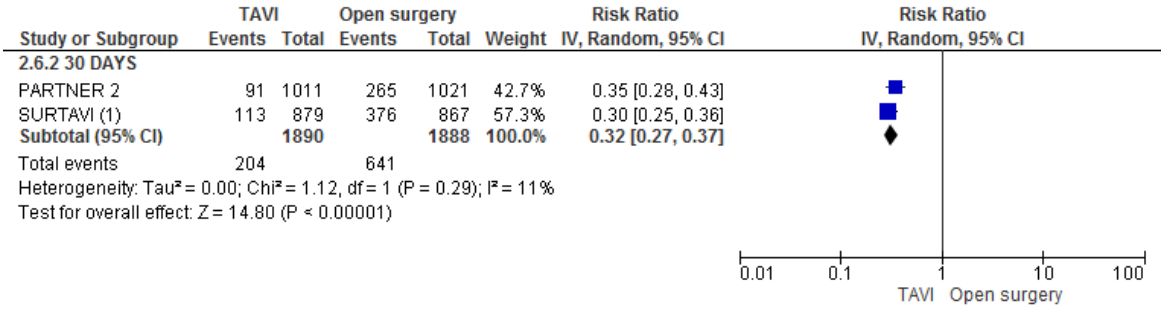


Figure 6.2. Incidence of disabling stroke at 30-day, 1-year, and 2-year follow-up

New atrial fibrillation

New atrial fibrillation occurred in 11% of patients in the TAVI group and 34% in the SAVR group. Moderate-quality evidence suggested that TAVI is probably superior to SAVR in terms of new atrial fibrillation occurrence (RR 0.32, 95% CI 0.27–0.37; I^2 = 11%) (Figure 6.3).

We downgraded the quality for this outcome only because of risk of bias (i.e., imbalance in withdrawals between the groups). See Table 6.1 for the safety comparison.



Footnotes
(1) Events for AF in the SURTAVI trial obtained from percentages calculated by Bayesian approach

Figure 6.3. Incidence of new atrial fibrillation at 30-day follow-up

Life-threatening or disabling bleeding

In the PARTNER 2 trial, life-threatening or disabling bleeding at 30-day follow-up occurred in 10% of the TAVI group compared with 43% of patients in the SAVR group (pooled RR 0.24, 95% CI 0.20–0.29).

In the SURTAVI, there was no evidence of differences between the two treatments at 30-day, 1-year, and 2-year follow-up in terms of life-threatening or disabling bleeding. Data were not pooled because the heterogeneity was high (I^2 = 99%) (Figure 6.4).

The overall GRADE level of certainty for this outcome at 30-day follow-up was rated as very low. We downgraded the quality because of a risk of bias (i.e., imbalance in withdrawals between the groups), inconsistency (i.e., very serious concern owing to considerable heterogeneity), and imprecision (i.e., wide CIs that crossed the line of no effect). See Table 6.1 for the safety comparison.

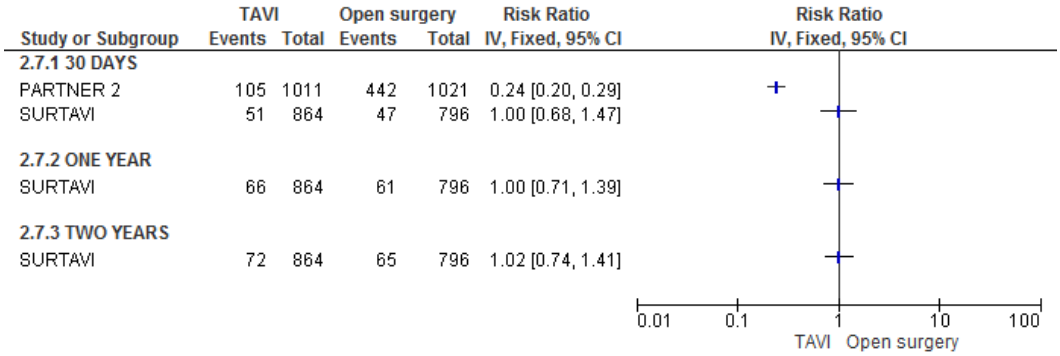


Figure 6.4. Incidence of life-threatening or disabling bleeding at 30-day, 1-year, and 2-year follow-up

Acute kidney injury

Acute kidney injury was reported by both trials at 30-day, 1-year, and 2-year follow-up.

At 30-day follow-up, acute kidney injury occurred in 1.0% of patients in the TAVI group and 2.2% in the SAVR group: compared with SAVR it is uncertain whether TAVI reduces the occurrence of acute kidney injury (RR 0.47, 95% CI 0.27–0.80); GRADE evidence: very low) (Figure 6.5). We downgraded the quality for this outcome at 30-day follow-up because of a risk of bias (i.e., imbalance in withdrawals between the groups), and imprecision (i.e., few events and wide CI). See Table 6.1 for the safety comparison.

At 2-year follow-up, the overall acute kidney injury occurrence was 2.2% in the TAVI group and 3.5% in the SAVR group: compared with SAVR, it is uncertain whether TAVI reduces the occurrence of acute kidney injury (RR 0.63, 95% CI 0.43–0.92; GRADE evidence: very low) (Figure 6.5). We downgraded the quality for this outcome at 2 years follow-up because of a risk of bias (i.e., very serious concern owing to important attrition) and imprecision (i.e., wide CI). See Table 6.1 for the safety comparison.

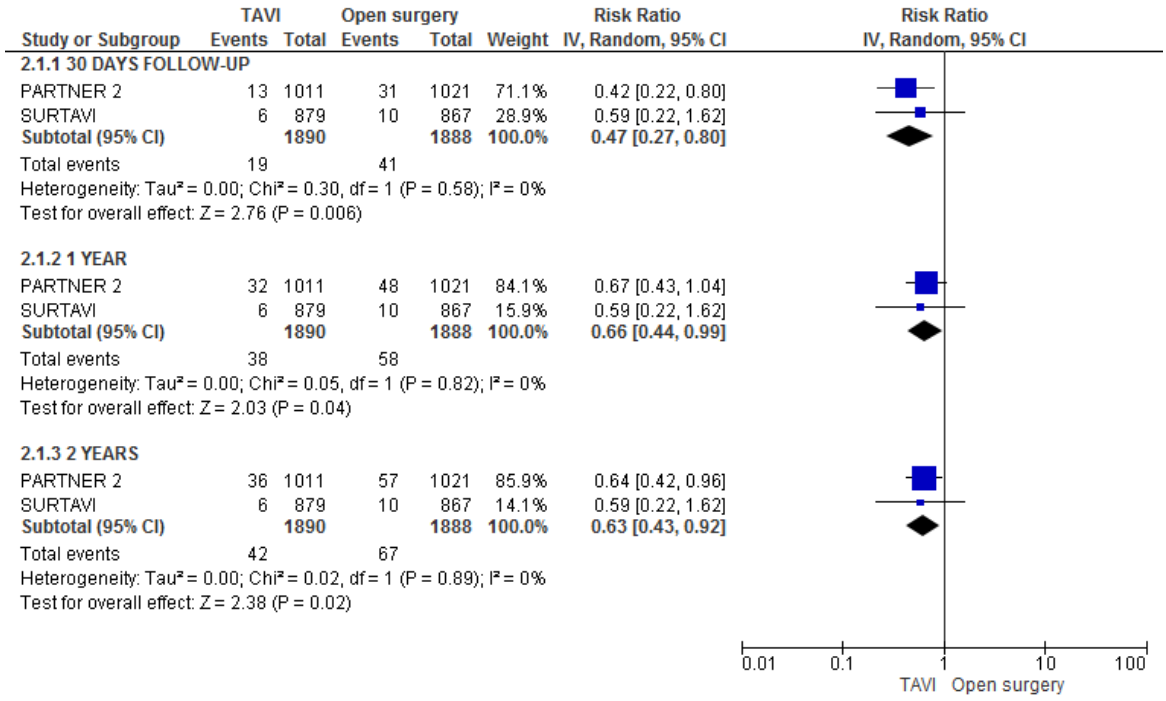


Figure 6.5. Incidence of acute kidney injury at 30-day, 1-year, and 2-year follow-up.

Major vascular complications

At 30-day follow-up, major vascular complications occurred in 6.9% of patients in the TAVI group and 3.1% in the SAVR group: compared with SAVR, TAVI might increase the incidence of major vascular complications (RR 3.03, 95% CI 0.79–11.67; GRADE evidence: low) (Figure 6.6). We downgraded the quality for this outcome at 30-day follow-up because of a risk of bias (i.e., imbalance in withdrawals between the groups), and imprecision (i.e., wide CI). We did not downgrade for inconsistency even though heterogeneity was substantial (I^2 = 90%) because the direction of the effect of treatment was the same for the two trials with statistically significant results: the inconsistency was between studies that showed moderate and large effects. See Table 6.1 for the safety comparison.

At 2-year follow-up, the overall occurrence of major vascular complications increased modestly in both groups (7.7% in the TAVI group and 3.3% in the SAVR group) and the treatment effect remained substantially the same (RR 3.27, 95% CI 0.73–14.57) (Figure 6.6).

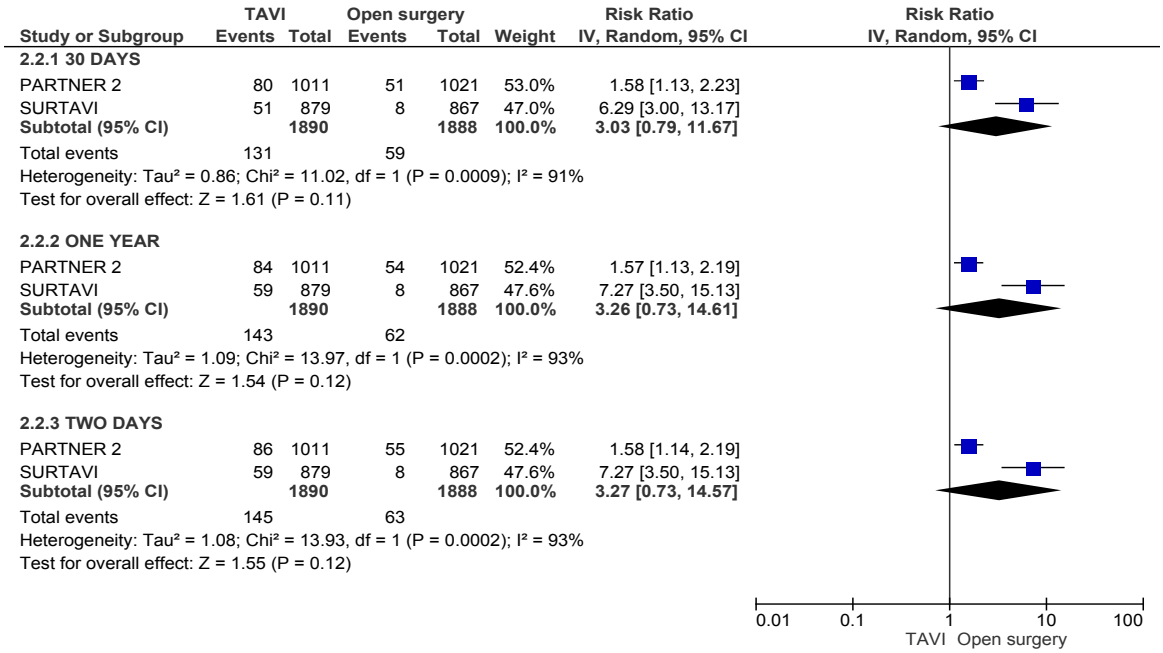


Figure 6.6. Incidence of major vascular complications at 30-day, 1-year, and 2-year follow-up

Permanent pacemaker implantation

Pacemaker implantation at 30-day follow-up was performed in 6.7% of patients in the SAVR groups in both studies. Data were not pooled because of considerable heterogeneity (I^2 >90%). In the PARTNER 2 trial, the incidence of permanent pacemaker implantation was higher in the TAVI group than in the SAVR group; however, there was no statistically significant difference between the groups at any follow-up point. In the SURTAVI trial, the incidence of permanent pacemaker implantation was significantly higher in the TAVI group (25.9%) than in the control group (6.6%) at all follow-up points (Figure 6.7).

The overall GRADE level of certainty was considered very low. We downgraded the quality for this outcome at 30-day follow-up because of a risk of bias (i.e., imbalance in withdrawals between the groups), inconsistency (i.e., very serious concern owing to substantial heterogeneity), and imprecision (i.e., wide CI). See Table 6.1 for the safety comparison.

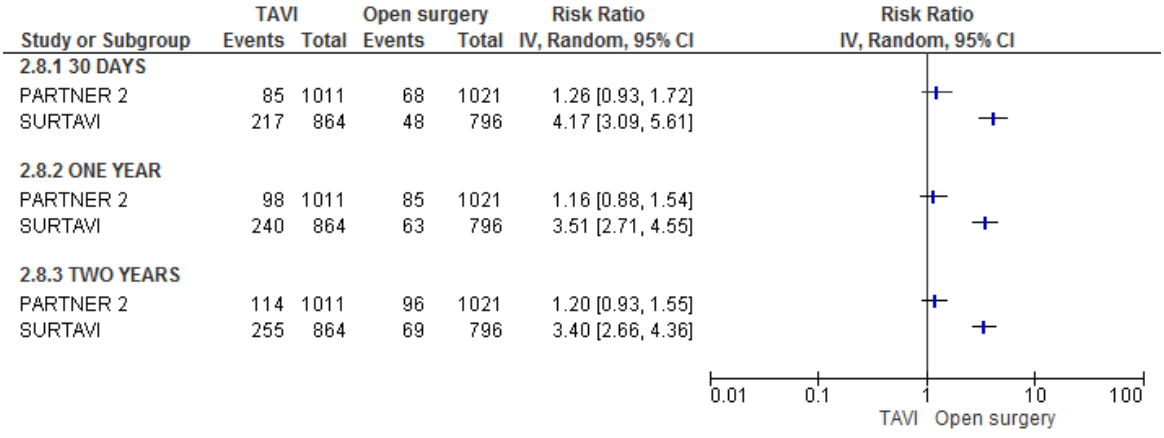


Figure 6.7. Incidence of permanent pacemaker implantation at 30-day, 1-year, and 2-year follow-up

Paravalvular regurgitation

Paravalvular aortic regurgitation was reported in both trials.

At 30-day follow-up, paravalvular regurgitation occurred in 3.2% of patients in the TAVI group and 0.3% in the SAVR group: compared with SAVR, TAVI probably increases the risk of paravalvular regurgitation (RR 9.30, 95% CI 4.02–21.48; GRADE evidence: Moderate) (Figure 6.8). We downgraded the quality for this outcome at 30-day follow-up because of a risk of bias (i.e., imbalance in withdrawals between the groups). See Table 6.1 for the safety comparison.

At 1- and 2-year follow-up, additional paravalvular regurgitation occurred in similar proportions. At 2-year follow-up, compared with SAVR, TAVI might increase the risk of paravalvular regurgitation (RR 14.74, 95% CI 5.04–43.08; GRADE evidence: low). (Figure 6.8).

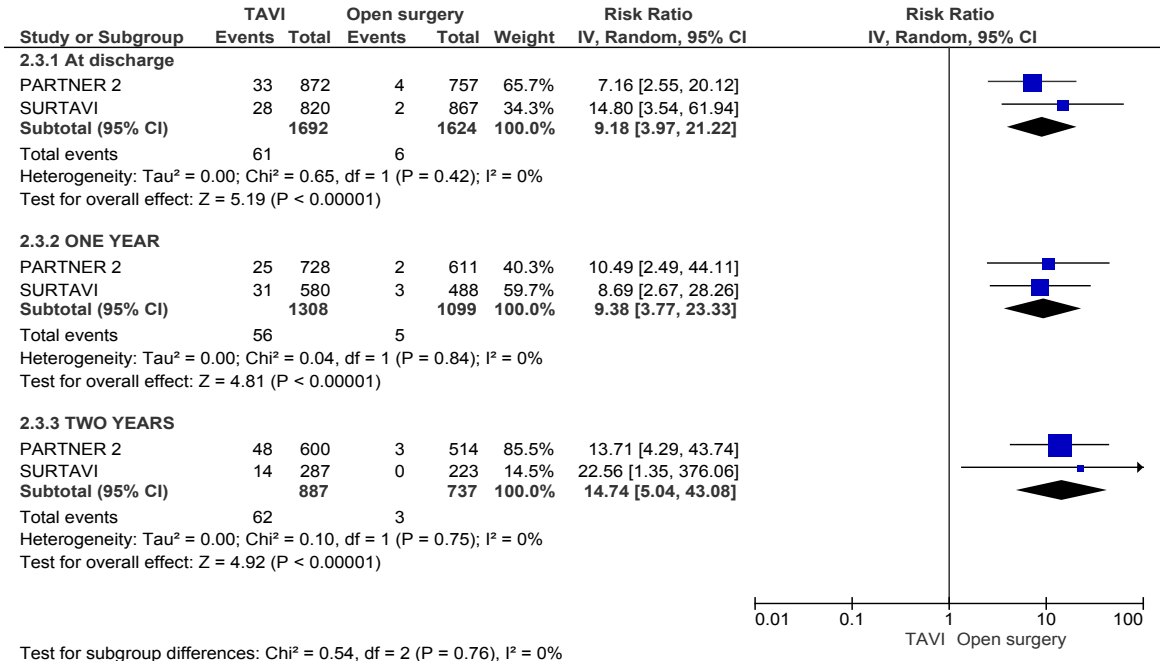


Figure 6.8. Incidence of severe or moderate paravalvular aortic regurgitation at 30-day, 1-year and 2-year follow-up

Endocarditis

In the PARTNER 2 trial, the occurrence of endocarditis at 2-year follow-up was 1.2% in the TAVI group and 0.7% in the control group (RR 1.85, 95% CI 0.69–4.99).

Rehospitalisation for myocardial infarction (>72 h following TAVI)

Neither of the trials assessed this outcome.

Analysis of real-world data

Three safety outcomes identified were reported by the two real-world data studies included: risk of POD and in-hospital mortality in the German study [17] and risk of stroke in the US study [18].

The authors of the German study reported that, in the homogeneous groups (EuroSCORE 13.5±2.7) the incidence of POD was around three times higher after SAVR compared with TAVI: 12.8% for SARV versus 3.9% for TAVI (p <0.01). In-hospital mortality was higher in the SAVR group than in the TAVI group: 5.1% versus 3.3%, respectively (p <0.01). In accordance with this, the results from a second analysis of two groups matched according to other parameters and the authors reported that the incidence of POD as well as in-hospital mortality were higher in the SAVR versus TAVI groups (14.5% versus 4.9% and 6.2% versus 2.3%, respectively; p <0.001).

Risk of stroke at 1 year follow-up, presented in one study [18], was reported for three subgroups but differences were not significant between the two procedures. In particular, the group with STS PROM ≥3% and <5% (1953 TAVI versus 1850 SAVR patients) showed a risk of stroke at 1-year follow-up of 3.8 versus 3.3; HR 1.06 (95% CI: 0.73–1.54). The group with STS PROM ≥5% and <8% (1596 TAVI versus 1545 SAVR patients) showed a risk of stroke at 1-year follow-up of 4.5 versus 3.5; HR 1.22 (95% CI: 0.83–1.79), whereas the group with STS PROM >8% (1183 TAVI versus 1337 SAVR patients) showed a risk of stroke at 1 year follow-up of 4.4 versus 3.1; HR 1.33 (95% CI: 0.8–-2.03).

[C0002] Are the harms device related?

It is not possible to confirm or exclude whether the reported adverse events, such as new pacemaker implantation, paravalvular regurgitation, or major vascular complications, could be related to the type of device used. The devices were not directly compared in the same study for the same patients; therefore, further research is required.

TAVI is potentially associated with high radiation doses for both patient and personnel. Details concerning TAVI and radiation doses in terms of the risk of radiation-induced cancer are described in Appendix 4.

[C0004] How does the frequency or severity of harms change in different settings?

[C0005] What are the susceptible patient groups that are more likely to be harmed through TAVI?

Neither the included RCT nor the real-world data studies included in our analysis provided data to answer either of these questions.

[C0007] Are TAVI and SAVR associated with user-dependent harms?

Long learning curves and procedural volume in the operating centre or the specific user could be important factors that might influence the clinical outcomes of TAVI and SAVR. However, neither the included RCT nor the real-world data studies included in our analysis provided data to answer this question directly.

Safety risk management

[B0010] What kind of data/records and/or registry is needed to monitor the use of TAVI?

The real-world data studies included in our analysis did not provide relevant data that enabled us to assess the technology more extensively. To compare different TAVI systems, registries should also collect, other than patient data, device-related data, such as mean aortic valve gradient, risk of paravalvular leak, need for pacemaker implantation, vascular complications, reintervention rate, and durability of the prosthesis. For this latter outcome, it is important to agree and adopt the same definitions of structural deterioration and valve failure across the different registries [67]. Moreover, setting information should also be collected to assess the impact of different settings on safety outcomes.

Table 6.1. Summary of findings for the safety comparison of TAVI versus SAVR for patients with aortic stenosis at intermediate surgical risk

Certainty assessment							№ of patients (%)		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TAVI**	**SAVR**	**Relative (95% CI)**	**Absolute (95% CI)**	
Stroke: 30-day follow-up											
2	Randomised trials	Serious [a]	Serious	Not serious	Serious[b]	None	78/1890 (4.1%)	103/1888 (5.5%)	RR 0.72 (0.44 to 1.20)	15 fewer per 1000 (from 11 more to 31 fewer)	⊕◯◯◯ very low
Stroke: 2-year follow-up											
2	Randomised trials	Serious [c]	Not serious	Not serious	Serious[b]	None	145/1890 (7.7%)	159/1888 (8.4%)	RR 0.89 (0.60 to 1.33)	9 fewer per 1000 (from 28 more to 34 fewer)	⊕◯◯◯ very low
Atrial fibrillation onset: 30-day follow-up											
2	Randomised trials	Serious [d]	Not serious	Not serious	Not serious	None	204/1890 (10.8%)	641/1888 (34.0%)	RR 0.32 (0.27 to 0.37)	231 fewer per 1000 (from 214 fewer to 248 fewer)	⊕⊕⊕◯ moderate
Life threatening/disabling bleeding: 30-day follow-up											
2	Randomised trials	Serious [e]	Serious[f]	Not serious	Serious[g]	None	In the PARTNER 2 trial: the risk of life-threatening or disabling bleeding occurred in 10% of the TAVI group versus 43% of the SAVR group (RR 0.24, 95% CI 0.20–0.29; at 30-day follow-up). In the SURTAVI trial: the risk of life-threatening or disabling bleeding was higher in the TAVI group (12.2%) than in the SAVR group (9.3%) with no statistical significance (RR 1.31, 95% CI 0.99–1.73).				⊕◯◯◯ very low
Acute kidney injury: 30-day follow-up											
2	Randomised trials	Serious [h]	Not serious	Not serious	Very serious[i]	none	19/1890 (2.3%)	41/1888 (0.3%)	RR 0.47 (0.27 to 0.80)	12 fewer per 1000 (from 4 fewer to 16 fewer)	⊕◯◯◯ very low

Certainty assessment							№ of patients (%)		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TAVI**	**SAVR**	**Relative (95% CI)**	**Absolute (95% CI)**	
Acute kidney injury: 2-year follow-up											
2	Randomised trials	Very serious [j]	Not serious	Not serious	Very serious[i]	none	42/1890 (1.5%)	67/1888 (3.5%)	RR 0.63 (0.43 to 0.92)	13 fewer per 1000 (from 3 fewer to 20 fewer)	⊕◯◯◯ very low
Major vascular complications: 30-day follow-up											
2	Randomised trials	Serious [k]	Not serious[l]	Not serious	Serious[m]	none	131/1890 (6.9%)	59/1888 (3.1%)	RR 3.03 (0.79 to 11.67)	63 more per 1000 (from 7 more to 333 more)	⊕⊕◯◯ low
New permanent pacemaker: 30-day follow-up											
2	Randomised trials	Serious [n]	Very serious[o]	Not serious	Not serious	none	In the PARTNER 2 trial, the proportion of new permanent pacemakers was 8.4% in the TAVI group and 6.7% in the control group with no evidence of significant differences (RR 1.26, 95% CI 0.93– 1.72). In the SURTAVI trial, the proportion of implanted pacemakers was higher in the TAVI group (25.1%) than in the SAVR group (6.7%) with a statistically significant difference (RR 3.78, 95% CI 2.84–5.02).				⊕◯◯◯ very low
Paravalvular regurgitation: 30-day follow-up											
2	Randomised trials	Serious [p]	Not serious	Not serious	Not serious	none	255/1890 (13.5%)	32/1888 (1.7%)	RR 7.93 (5.54 to 11.35)	117 more per 1000 (from 77 more to 175 more)	⊕⊕⊕◯ moderate

GRADE Working Group grades of evidence:

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: the true effect might be substantially different from the estimate of the effect.

Very low quality: we have little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious concern regarding risk of bias: blinding patients and personnel was not possible because of the type of intervention. Given that stroke was an objective outcome, we considered that absence of blinding could not introduce the performance bias and, therefore, no downgrading was done. However, the quality of evidence was downgraded by one level because, in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this might have generated an imbalance between the two trials.

b. Wide CI.

c. Very serious concern regarding risk of bias: blinding patients and personnel was not possible because of the type of intervention. However, because stroke was an objective outcome, we considered that absence of blinding could not introduce the performance bias and, therefore, no downgrading was done. However, the quality of evidence was downgraded by two levels given that: (i) in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this might have generated an imbalance between the two trials; and (ii) at 2-year follow-up, >30% and >50% of patients were lost to follow-up in each trial, respectively.

d. serious concern regarding risk of bias: blinding patients and personnel was not possible because of the type of intervention. However, because atrial fibrillation was an objective outcome, we considered that absence of blinding could not introduce the performance bias and, therefore, no downgrading was done. However, the quality of evidence was downgraded by one level because, in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this might have generated an imbalance between the two trials.

e. Serious concern regarding risk of bias: blinding patients and personnel was not possible because of the type of intervention. However, because bleeding was an objective outcome, we considered that absence of blinding could not introduce the performance bias and, therefore, no downgrading was done. However, the quality of evidence was downgraded by one level because, in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this might have generated an imbalance between the two trials.

f. Considerable heterogeneity.

g. One study had a wide CI crossing the null effect.

h. serious concern regarding risk of bias: blinding patients and personnel was not possible because of the type of intervention. Given that acute kidney injury was an objective outcome, we considered that absence of blinding could not introduce the performance bias and, therefore, no downgrading was done. However, the quality of evidence was downgraded by one level because, in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this might have generated an imbalance between the two trials.

i. Wide CI and/or very few events.

j. Very serious concern regarding risk of bias: blinding patients and personnel was not possible because of the type of intervention. Given that acute kidney injury was an objective outcome, we considered that absence of blinding could not introduce the performance bias and, therefore, no downgrading was done. However, the quality of evidence was downgraded by two levels given that: (i) in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this imbalance in withdrawals between the two groups might have introduced bias; and (ii) at 2-year follow-up, >30% and >50% of patients were lost to follow-up in each trial, respectively.

k. Serious concern regarding risk of bias: blinding patients and personnel was not possible because of the type of intervention. However, because vascular complication was an objective outcome, we considered that absence of blinding could not introduce the performance bias and, therefore, no downgrading was done. However, the quality of evidence was downgraded by one level because, in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this imbalance in withdrawals between the two groups might have introduced bias.

l. We found an unexplained important heterogeneity (I^2 = 90%) because of the lower frequency of the outcome in the SAVR group in one of the two trials. However, we decided not to downgrade because the direction of the treatment was consistent between the trials and the inconsistency was between studies that showed moderate and large effects.

m. Wide CI.

n. Serious concern regarding risk of bias: blinding patients and personnel was not possible because of the type of intervention. However, because pacemaker implantation was an objective outcome, we considered that absence of blinding could not introduce the performance bias and, therefore, no downgrading was done. However, the quality of evidence was downgraded by one level because, in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; we are uncertain whether this might have generated an imbalance between the two trials.

o. Very serious concern regarding heterogeneity.

p. Serious concern regarding risk of bias: blinding patients and personnel was not possible because of the type of intervention. Downgrading by one level was done because of a risk of bias: (i) paravalvular regurgitation was considered a subjective outcome and the trial could be subject to performance and detection bias; (ii) in one of the two trials, 94 enrolled patients (4.6%; 17 patients in the TAVI group and 77 in the SAVR group) were withdrawn from the study mainly owing to a decision after randomisation not to undergo surgery; despite the minimal percentage of attrition, there was an imbalance between the two groups in terms of withdrawal.

7 UPCOMING EVIDENCE (ONGOING STUDIES)

Two active relevant RCTs were identified according to the PICOD (Table 7.1). One of these was the SURTAVI trial (NCT01586910), for which we assessed an interim analysis published in 2017. The final completion date of the SURTAVI trial is October 2018. The planed number of patients to be recruited was 2500. The entry was last updated in November 2017.

The second trial was an ongoing German trial (NCT03112980), which appears to be the first independent RCT aiming to answer questions relevant to the present assessment. A total of 17 German university hospitals will contribute to the trial. Its estimated completion is 2023, with no information available on possible publications of interim analyses. The entry was last updated on October 2017. The trial is still recruiting patients.

Interestingly, six RCTs comparing TAVI versus SAVR or medication in patients at low risk or non-symptomatic were also identified (Appendix 1). For these RCTs, primary completion dates varied from 2018 to 2021.

Table 7.1. Ongoing RCTs according to PICOD

Trial (trial number and name)	Number of patients	P (study inclusion criteria)	I	C	O	Estimated completion date
NCT01586910: Safety and Efficacy Study of the Medtronic CoreValve® System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement (SURTAVI)	2500	Severe AS, comorbidities such that the heart team agrees predicted risk of operative mortality is ≥3% and <15% at 30-day follow-up	Medtronic CoreValve® Evolut R System	SAVR	All-cause mortality or disabling stroke (time frame: 2 years); safety and efficacy outcomes; QoL (not specified)	2018 (published Interim results included in this report)
NCT03112980: Randomized Trial of TAVI versus SAVR in Patients with Severe Aortic Valve Stenosis at Intermediate Risk of Mortality (PARTNER 2)	1600	Severe symptomatic AS; intermediate risk (STS-score 2–6%)	TAVI using most appropriate CE marked device available	SAVR	Overall survival 5 years after last patient enrolled; safety and efficacy outcomes; QoL (EQ-5D)	2023

8 POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT, SOCIAL, AND LEGAL ASPECTS (ETH, ORG, SOC, LEG)

8.1 Research questions

1. Ethical		
1.2	Does comparing the new technology to the defined, existing comparators point to any differences that might be ethically relevant?	Yes
	Patient autonomy might be an issue. Currently, the indication for TAVI does not include low-risk patients. However, patients with indication for SAVR do increasingly demand TAVI regardless of risk. Denying TAVI to low-risk patients might challenge patient autonomy.	
2. Organisational		
2.1	Does the introduction of the new technology and its potential use and/or non-use instead of the defined, existing comparator(s) require organisational changes?	Yes
	According to the latest guidelines from ESC/EACTS [5], aortic valve interventions should only be performed in centres with both departments of cardiology and cardiac surgery on site and with structured collaboration between the two. In the case of TAVI, the presence of a heart team is considered crucial to perform proper patient selection. In particular, in patients who are at increased surgical risk, the decision between SAVR and TAVI should be made by the heart team according to the characteristics of the individual patient. The presence of a heart team could be particularly complex from an organisational point of view because it typically involves cardiologists, cardiac surgeons, imaging specialists, anaesthetists and, if needed, general practitioners, geriatricians, and heart failure, electrophysiology, or intensive care specialists. Moreover, centres performing TAVI should have the proper imaging equipment, hybrid operating rooms, or catheterisation laboratory facilities.	
2.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that might be organisationally relevant?	Yes
	The RCTs included in the present assessment indicate that TAVI is linked to shorter length of hospital stay. This should impact the availability of beds within the health centre.	

9 DISCUSSION

TAVI and SAVR are both complex procedures under constant development in terms of both substantial and small incremental changes related to the devices and all aspects of the procedures. When initiating the present assessment, only two TAVI systems had the CE mark with indication for intermediate-risk patients (received in during 2016). Another TAVI system, Medtronic's Evolut PRO, received the CE mark for intermediate-risk patients when this assessment was ongoing (Summer 2017). Thus, it is possible that the TAVI systems used in the included clinical trials might not be identical to those currently used across Europe. We performed a search for published and registered RCTs of TAVI compared with SAVR or another TAVI system. No RCTs involving Evolut Pro were either excluded or identified. Thus, evidence on the newly introduced TAVI system is likely to be limited to nonrandomised studies and does not meet the criteria defined within the scope of this assessment

TAVI is widely available and reimbursed across European countries. Our survey from October to November 2017 revealed substantial variations in use (a factor of 10 in difference) and reimbursement policies across European countries. To investigate the reasons for this variation is outside the scope of this assessment. However, among the factors potentially influencing the diffusion we can list the local presence of skilled health professionals and reimbursement schemes.

The two included studies showed non-inferiority in design and had comparable outcome measures that allowed meta-analyses to be performed for most outcomes. Limitations associated with both studies were a high frequency of unplanned withdrawals in the SAVR group and the lack of long-term follow-up data. Limitations of the SURTAVI study included the fact that results were based on an interim analysis with only a fraction of the included patients followed for 2 years. Thus, event rates for the meta-analysis, in particular for the 2-year results, depend on a model for imputation of data. Furthermore, the newest generation of the CoreValve device (CoreValve Evolut R) was only used in 20% of patients. The PARTNER 2 trial was planned as a cohort trial with randomisation based on access route. In the PARTNER 2 trial, the SAPIEN XT device was used, whereas the newest CE marked device (SAPIEN 3) was not. In the SURTAVI trial, patients were randomised before access route determination; thus, there might be differences in the characteristics of the enrolled patients that were not addressed in our meta-analysis. Despite these limitations, we did not downgrade with respect to any uncertainties these limitations might provide, except for attrition bias when outcomes were evaluated at 1- and 2-year follow-up.

Given that both systems are widely used in Europe, we looked at results across the two RCTs and pooled the data for outcomes using a random effects model if there was no substantial heterogeneity observed in the meta-analysis (I^2 <50). For outcomes with heterogeneity between the data reported by the trials, unpooled results were provided. There are arguments for and against the pooling of data from two trials, in particular if differences in risk of bias are observed. According to the *Cochrane Handbook*, a random-effects meta-analysis model involves an assumption that the effects being estimated in the different studies are not identical but follow some distribution (ref). Pooling or not a pooling data is a matter of decision for the meta-analyst. We cannot exclude that reasons for the observed heterogeneity are associated with the choice of system, procedures, or differences in the population. Although the imprecision will be somewhat higher, the main conclusions with regard to the most important outcomes (i.e., confidence in estimates either pooled or un-pooled) is unlikely to be greatly affected by pooling or not pooling the results.

Making a clear and unequivocal definition of severe symptomatic aortic stenosis with intermediate risk is challenging. Patient stratification builds on team-based overall assessment of the patient (i.e., a heart team approach) and can vary across different studies and clinical contexts. Therefore, the exact number of patients with severe symptomatic aortic stenosis at intermediate surgical risk eligible for TAVI is hard to estimate, but it is likely to increase as the population ages.

Our search strategies were oriented towards the identification of all RCTs and studies of national registries that compared TAVI with SAVR or another TAVI system. After thorough evaluation of the characteristics of the patient eligibility criteria of the studies and the patient characteristics, we considered eligible the PARTNER 2 and the SURTAVI trials. The eligibility criteria of SURTAVI was a STS score of 3–15%. Given that the included patients for the interim analysis all had an STS score of 4.5±1.6%, we considered the study to be in compliance in terms of including only patients at intermediate risk. By contrast, the NOTION trial included intermediate and low-risk patients with

a STS mean score of 3.1 (1.7), resulting in 81% of patients at low risk [37] and this trial was subsequently excluded.

We used the GRADE approach for rating the quality of evidence. We rated the quality as moderate only for outcomes evaluated at 30-day follow-up (e.g., mortality, new atrial fibrillation onset, hospital stay, and paraventricular regurgitation). At 30-day follow-up, the quality of the following outcomes was further downgraded because of imprecision: stroke, acute kidney failure, and major vascular complications. For the remaining outcomes, further downgrading was performed when the outcomes were evaluated at 2-year follow-up mainly owing to serious concerns caused by attrition bias (mortality, improvement of symptoms, aortic valve intervention) or to serious or very serious concerns regarding inconsistency and/or imprecision (life-threatening and/or disabling bleeding)

Given that our protocol did not foresee a non-inferiority trial, we did not provide any non-inferiority margin. In this context, the PARTNER II trial estimated that a sample of 2000 patients would provide the trial with a power of at least 80% to show the non-inferiority of TAVI compared with SAVR with respect to the primary endpoint at 2 years, assuming an event rate of 30% in each group, with a non-inferiority margin of 0.20. Conversely, the SURTAVI trial used Bayesian methods and calculated a sample size of 4000 based on a standard frequentist non-inferiority power analysis and used a non-inferiority margin of 0.07. To provide judgment regarding the certainty of the evidence, we used the more conservative margin, which was that of the PARTNER II trial, also being aware that it is difficult to propose a delta in mortality that is not ‘clinically meaningful’. Hence, because there was no difference in rates of all-cause mortality (or cardiac specific mortality) between the two groups, we considered TAVI to be non-inferior to SAVR in terms of these outcomes at 30-day follow-up based on moderate-level evidence. The downgrading by one level was performed because, in one of the two trials, there was an imbalance of withdrawals between the groups. Conversely, for the same outcomes at 2-year follow-up, we concluded that there was uncertainty about whether TAVI is non-inferior to SAVR owing to very low-level evidence. The downgrading by two levels was because of important attrition that occurred in both trials. In conclusion, the evidence is very limited regarding the most important outcomes at 2-year follow-up.

Other efficacy outcomes evaluated by both trials were aortic valve reintervention, improvement of symptoms, and length of hospital stay.

The proportion of aortic valve reintervention was higher in the TAVI group than in the SAVR group at 30-day follow-up, but the overall number of events was 12. This led to downgrading by two levels because of imprecision resulting in very low-quality evidence. At 2-year follow-up, the number of events was 41, with a higher proportion in the TAVI group than in the SAVR group, but we graded the level of evidence as very low because of a risk of bias and imprecision.

Regarding the outcome of improvement of symptoms (according to the NYHA classification), within each group in both trials, there was an improvement at 30-day follow-up and this improvement was maintained during the 2-year follow-up. No significant difference was observed between the two groups during follow-up, but we graded the level of evidence as very low because of the risk of bias and imprecision.

In terms of length of hospital stay, the data could not be pooled because of different data reporting, although both trials reported significant shorter duration in favour of TAVI compared with SAVR. Our confidence in the treatment effect was graded as moderate quality of evidence. However, this outcome is relevant when there is a strong evidence in favour of a clinically important outcome.

With regard to the stroke and disabling stroke outcomes, there were only small differences in the number of events in each group reported by the trials. Given the risk of bias and imprecision, our confidence in the estimates was very low and we were not able to conclude with regard to non-inferiority.

In the TAVI group compared with the SAVR group, there were fewer reported cases of acute kidney injury and atrial fibrillation, but more cases of major vascular complications and of paravalvular regurgitation. However, our confidence in estimates of the effects was either very low (acute kidney injury, atrial fibrillation, and paravalvular regurgitation) or low (major vascular complications), reflecting the uncertainty about whether TAVI reduces the risk of acute kidney injury and atrial fibrillation or enhances the risk of paravalvular regurgitation and major vascular complications.

Conflicting results between the included trials were observed in terms of life-threatening or disabling bleeding and the need for new permanent pacemaker replacement. Although there was little or no difference in the disabling bleeding outcome between TAVI and SAVR in the SURTAVI trial, the results were in favour of TAVI in the PARTNER 2 trial. In addition, although there was little or no difference in the permanent pacemaker replacement outcome in the PARTNER 2 trial, the proportion of implanted pacemakers was in favour of SAVR in the SURTAVI trial. Given the risk of bias and important heterogeneity, we considered the overall quality of evidence for these two outcomes to be very low and we were unable to provide a conclusion. The two trials used different TAVI systems and had slightly different inclusion criteria. Whether the observed heterogeneity is related to the TAVI system used, or if there are other explanations, such as differences in the population, will require additional studies.

In both trials, the improvement in aortic valve haemodynamics increased significantly from baseline to 30-day and 2-year follow-up. Haemodynamic findings were significantly better in the TAVI group than in the SAVR group. This in contrast to the finding that paravalvular regurgitation was significantly higher in the TAVI group. A better haemodynamic performance of TAVI compared with SAVR could translate in a lower incidence of structural valve deterioration over time and better clinical outcome, especially in patients with small annulus size, reducing the risk of prosthesis–patient mismatch. However, because our confidence in estimates for these outcomes was very low, future studies will need to clarify these issues.

Limitations of the RCTs include lack of long-term follow-up, a significant frequency of withdrawals, and uncertain data on quality of life. The ongoing German RCT (NCT03112980) is an industry independent study that could provide more-reliable 5-year follow-up data and quality-of-life data.

Available evidence (restricted to the inclusion criteria) did not provide answers to the following assessment elements: (C0002), (C0004), (C0005), and (C0007).

We found an extensive number of systematic reviews compared with the number of trials addressing the effectiveness of TAVI for patients with aortic stenosis. During the preparation of the present assessment (July 2017), NICE published its interventional procedures guidance (IPG) on transcatheter aortic valve implantation for aortic stenosis [61] and an update of the ECT/EASCT guidelines [5] was published.

Most importantly, the evidence evaluations supporting the guidelines preclude the publication of results from the SURTAVI trial. Furthermore, neither the NICE nor ECT/EACST guidelines are based on the GRADE approach to evaluate confidence in each outcome. In our assessment, we included data from the SURTAVI trial and used the GRADE approach for the most important outcomes. Our confidence in TAVI being non-inferior to SAVR with regard to 30-day mortality across the two trials is moderate. However, we report substantial uncertainty (low and very low-quality evidence) for several important outcomes, making us unable to provide a firm conclusion with regard to the benefits of TAVI versus SAVR for patients at intermediate surgical risk.

The number of trials included differed between the reviews depending on the inclusion criteria applied. In particular, Arora *et al.* [68] performed a meta-analysis including data from the PARTNER 2 trial and three propensity-matched observational studies. No significant differences were observed in terms of 30-day mortality and stroke between the two groups. Patients undergoing TAVI were less likely to have bleeding complications and acute kidney injury, but were more likely to have vascular complications, paravalvular regurgitation, and a need for pacemaker implantation.

The choice of access route depends on the patient anatomy and TF access is less invasive than the transapical approach. Neither the NICE nor ECT/EASCT guidelines provide recommendations with regard to access route or choice of system device. The systematic review by Siemieniuk [69] included four RCTs for which only one fulfilled our inclusion criteria. Analysis of data was performed based on access routes, and the authors concluded that patients at low and intermediate surgical risk were likely to perceive a net benefit with TF TAVI compared with SAVR, but that SAVR performs better than transapical TAVI. These analyses were mainly based on data from the PARTNER trial. Another meta-analysis performed by Singh *et al.* [70] included eight comparative studies, three of which had a randomised design. The 30-day all-cause mortality, 30-day cardiac mortality, and 1-year all-cause mortality were similar between the two groups. However, TAVI performed via TF access had a significantly lower mortality than SAVR, whereas the incidence of moderate aortic incompetence and pacemaker implantation was higher in the TAVI group.

Mainly because of the risk of bias, and uncertainty related to directness (patient inclusion criteria) and imprecision (lack of power), we do not consider that the additional results presented by the identified systematic reviews would influence our confidence in any estimates of outcomes.

The analysis of real-world comparative data from national registries did not allow us to add significant elements to the safety analysis performed using RCTs that had 2 years of follow-up. Only two comparative national registry studies were identified and presented data on a limited number of safety outcomes (i.e., incidence of POD and incidence of stroke) with limited follow-up (up to 1 year). In one German study [17], incidence of POD was three times higher after SAVR compared with TAVI (12.8% versus 3.9%) when two groups of 763 patients were matched according to EuroSCORE values. Such a safety outcome was not reported in the included RCTs. Risk of stroke assessed in one American registry study [18] did not show significant differences between the two procedures. This finding is in line with evidence from RCTs. Moreover, extending inclusion criteria outside the defined PICOD added no value. We reviewed in full-text the noncomparative registry studies identified and found that only one study [19] presented safety data relevant to the population of interest (i.e., patients at intermediate surgical risk). The study by Holmes *et al.* [19] presented outcomes following TAVI in the USA between 2011 and 2014. Outcomes from a total of 12 182 patients were reported at 1 year of follow-up. Of those patients, 6988 (57.4%) had an STS-PROM score <8%. Incidence of stroke and heart failure for this specific group of patients was 3.8% (239) and 11.1% (676), respectively. By comparison, pooled incidence of stroke from the included RCTs was 4.1% in the TAVI group, whereas heart failure was not reported in the RCTs. In the other registry studies, either the cumulative data or the surgical risk score of the observed population ranging from low to high risk with no stratification according to risk were reported. In addition to patient data, registries should also collect device-related data and setting information to allow analyses of performance between different products and to assess the impact of the different settings on safety outcomes. Upcoming evidence could be derived from more efficient and sophisticated analysis of high-quality real-world data.

In general, the additional risk of radiation-induced cancer () (i.e., stochastic effect) following TAVI procedures can be considered small in relation to the natural risk of cancer morbidity and mortality. However, patient's age is a key variable. Patients at intermediate surgical risk are expected to be younger, with a slightly increased risk of stochastic effects as a result. The radiation dose from preoperative investigations and follow-up also needs to be considered. The average skin dose (i.e., deterministic effect) for coronary angiography and TAVI gives no cause for concern. However, in complex cases, doses might exceed values where acute effects can be observed. Personnel closest to the patient will be exposed to the highest radiation doses. Radiated tissues include fingers (especially during a transapical approach) and the lenses of the eye.

Patient autonomy be an issue. Currently, the indication for TAVI does not include low-risk patients. However, patients with an indication for SAVR do increasingly demand TAVI regardless of risk. Denying TAVI to low-risk patients might challenge patient autonomy. The excluded NOTION trial as well as six ongoing RCTs were identified to be studying low-risk populations and/or symptom-free populations (Appendix 1). Given that the use of TAVI might rapidly include more patients at lower risk and in lower age groups, a more extensive (re-)assessment of TAVI for all populations with subgroup analyses for different populations should be planned.

As emerged from the comments from clinical experts, some issues at the moment remain uncovered and hardly can be incorporated within a health technology assessment. It is difficult to reach conclusions on the diffusion of the different models of TAVI in different settings or to assess whether the diffusion of a specific model is related to the availability of (good-quality) supporting evidence. In fact, some centres show a preference for a specific model or a specific manufacturer; however, analysis of these variations was not within the scope of the present assessment. We acknowledge that the convalescence phase can be another key element in the choice of TAVI. However, only length of hospital stay is commonly reported within the studies. Equal durability of the prosthetic valves used for TAVI and SAVR is another important issue; however, given that long-term data are not available for TAVI, it remains theoretical. Moreover, the various ongoing studies on patients at low surgical risk might predict an increasing trend in the use of TAVI and the continuous and rapid development and introduction of new TAVI models will necessarily require periodic evidence reviews in the near future.

10 CONCLUSION

TAVI is a procedure for the deployment of bioprostheses in the aortic valve using a catheter. TAVI aims to constitute a less invasive alternative to SAVR, avoiding the need for cardiopulmonary bypass. At the time of writing, there were two manufacturers offering TAVI systems that are CE marked to be used for the treatment of patients with severe aortic stenosis at intermediate surgical risk.

Aortic stenosis is the most common valvular heart disease in developed countries. Treatment of symptomatic aortic stenosis with medication alone can only be palliative and has limited clinical effect. SAVR is an established, effective, first-choice treatment for aortic stenosis. The most recent guidelines from ESC/EACTS recommend either TAVI or SAVR in patients at increased surgical risk. According to these guidelines, a heart team should make the treatment decision based on assessments of individual risk and patient characteristics.

Moderate-quality evidence suggests that TAVI for patients with severe aortic stenosis at intermediate surgical risk is non-inferior to SAVR in terms of all-cause mortality and cardiac mortality at 30-day follow-up. Moderate-quality evidence also suggests that TAVI reduces hospital stay compared with SAVR. However, important uncertainties remain in terms of whether TAVI is better or worse than SAVR in terms of the improvement of symptoms.

Moderate-quality evidence suggests that, compared with SAVR, TAVI reduces new-onset atrial fibrillation and enhances the risk of paravalvular regurgitation. Important uncertainties remain regarding evidence on the following outcomes: stroke, acute kidney injury, new permanent pacemaker, major vascular complications, aortic valve reintervention, and life-threatening and/or disabling bleeding.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

Documentation of the Search Strategies

1.1 Literature search - TAVI Collaborative Assessment

Databases: Embase (Ovid), Ovid MEDLINE(R), Cochrane Library: Cochrane Database of Systematic Reviews (CDSR), Other Reviews, Cochrane Central Register of Controlled Trials (CENTRAL). Centre for Reviews and Dissemination (CRD): Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessments (HTA) database. Epistemonikos, PubMed (publication status ahead of print publications).
Search filter: Systematic reviews (SR) and Health Technology Assessments (HTA) amended, based on Ovid's clinical queries and Cochrane Highly Sensitive Search Strategy for identifying randomized trials (Cochrane Handbook, ch. 6.4.11.1, Box 6.4.d).

Date Run: 2017.06.26-27
Results: 865 references in total (1279 including duplicates)
377 Systematic reviews/ Health Technology Assessments (publication year 2013-2017)
268 Trials (publication year 2016-2017)
220 Publication status ahead of print (non-indexed) publications (publication year 2013-2017)

Performed by: Ingrid Harboe, research librarian; peer review: Ingvild Kirkehei, research librarian
Embase 1980 to 2017 Week 24
Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date run: 2017.06.27

#	Searches	Results
1	heart valve prosthesis implantation/ use ppez	18532
2	heart valve replacement/ use ppez or aorta valve replacement/ use emez or transcatheter aortic valve implantation/ use emez or aorta valve prosthesis/ use emez	31001
3	Aortic Valve/ use ppez or aorta valve/ use emez or percutaneous aortic valve/ use emez	28941
4	((aortic valv* or aorta* valv* or heart valv*) adj4 (prosthe* or implant* or insert* or replac*)).ti,ab.	55296
5	or/1-4	90174
6	(percutaneous or transapical or trans-apical or transarterial or trans-arterial or transcatheter or trans-catheter or transcutaneous or trans-cutaneous or transfemoral or trans-femoral or transaxillary or trans-axillary or transluminal or trans-luminal or transaortic or trans-aortic or transcarotid or trans-carotid or transsubclavian or trans-subclavian or transiliac or trans-iliac or transiliofemoral or trans-iliofemoral or TAVI or TAVR).ti,ab.	387824
7	5 and 6	23663
8	percutaneous aortic valve/ use emez and (prosthe* or implant* or insert* or replac*).ti,ab.	1613
9	transcatheter aortic valve replacement/ use emez	11315

10	or/7-9	24882
11	exp animals/ not humans.sh.	27210271
12	10 not 11	9911
13	((systematic* adj2 review*) or meta-anal* or technology assessment*).mp,pt. or (review.mp. and (pubmed or medline).ab.) or ((systematic* or database* or literature) adj2 search*).mp.	716322
14	12 and 13	298
15	limit 14 to yr="2013 -Current" (SR 2013 -2017)	264
16	remove duplicates from 15	247
17	(randomized controlled trial or controlled clinical trial).pt. or random*.mp. or placebo.ab. or double-blind*.ti,ab. or trial.ti.	2816368
18	12 and 17	736
19	limit 18 to yr="2016 -Current"	210
20	remove duplicates from 19	191
21	registries/ use ppez or register/ use emez or (registries or register or registry).mp.	399044
22	12 and 21	713
23	limit 22 to yr="2013 -Current"	555
24	remove duplicates from 23	520

Comments to the search strategy after revision from co-author (KCE):

MeSH Aortic Valve Stenosis: we considered this MeSH as too broad. We could have combined the term with valve implantation/replacement but assumed it was covered by the other search terms. A test search did not seem to add relevant unique hits (please contact NIPHNO for test search strategy).

MeSH Transcatheter Aortic Valve Replacement*:* The MeSH *Transcatheter Aortic Valve Replacement* should have been included in the search strategy instead of the previous version Heart Valve Prosthesis Implantation (line 1) from a previous search strategy. The subject heading ***is*** included (line 9) but coded as Embase subject heading (emez) not MEDLINE MeSH (ppez). In Embase *transcatheter aortic valve* ***implantation*** is used for *transcatheter aortic valve* ***replacement****. Nevertheless, w*e think the required MeSH is covered by **free text terms** (line 4).
MeSH Heart valve prosthesis implantation: included in the search strategy (line 1) A quick revised search including the suggested MeSH (1, 2) retrieved 6 unique hits, none of which met the inclusion criteria.

Ovid search syntax:
.pt. denotes a Publication Type term;
.ab. denotes a word in the abstract;
.fs. denotes a 'floating' subheading;
.sh. denotes a Medical Subject Heading (MeSH) term;
.ti. denotes a word in the title.
* (asterisk) denotes truncation (e.g. random* for random or randomised or randomized or randomly, etc)

Database: Cochrane library
Date Run: 2017.06.26
Results: 55 Systematic Reviews/ Health Technology Assessments (publication year 2013-2017)
240 Trials (publication year 2016-2017)

ID	Search	Hits
#1	MeSH descriptor: (Heart Valve Prosthesis Implantation) this term only	684
#2	MeSH descriptor: (Aortic Valve) this term only	451
#3	((aortic valv* or aorta* valv* or heart valv*) near/4 (prosthe* or implant* or insert* or replac*)):ti,ab,kw in Cochrane Reviews (Reviews and Protocols)	7
#4	((aortic valv* or aorta* valv* or heart valv*) near/4 (prosthe* or implant* or insert* or replac*)) in Other Reviews, Trials and Technology Assessments	1985
#5	#1 or #2 or #3 or #4	2091
#6	(percutaneous or transapical or trans-apical or transarterial or trans-arterial or transcatheter or trans-catheter or transcutaneous or trans-cutaneous or transfemoral or trans-femoral or transaxillary or trans-axillary or transluminal or trans-luminal or transaortic or trans-aortic or transcarotid or trans-carotid or transsubclavian or trans-subclavian or transiliac or trans-iliac or transiliofemoral or trans-iliofemoral or TAVI or TAVR):ti,ab,kw in Cochrane Reviews (Reviews and Protocols)	173
#7	(percutaneous or transapical or trans-apical or transarterial or trans-arterial or transcatheter or trans-catheter or transcutaneous or trans-cutaneous or transfemoral or trans-femoral or transaxillary or trans-axillary or transluminal or trans-luminal or transaortic or trans-aortic or transcarotid or trans-carotid or transsubclavian or trans-subclavian or transiliac or trans-iliac or transiliofemoral or trans-iliofemoral or TAVI or TAVR) in Other Reviews, Trials and Technology Assessments	17886
#8	#6 or #7	18059
#9	MeSH descriptor: (Transcatheter Aortic Valve Replacement) this term only	73
#10	(#5 and #8) or #9 Publication Year from 2013 to 2017	505
#11	(#5 and #8) or #9 Publication Year from 2016 to 2017	244
#12	MeSH descriptor: (Registries) this term only	955
#13	registries or register or registry in Trials	8716
#15	#12 or #13	1055457
#16	#10 and #15 Publication Year from 2013 to 2017	450

Database: Centre for Reviews and Dissemination
Date run: 2017.06.27
Results: 56 Systematic Reviews/ Health Technology Assessments (publication year 2013-2017)

Line	Search	Hits
1	MeSH DESCRIPTOR Heart Valve Prosthesis Implantation	138
2	MeSH DESCRIPTOR Aortic Valve	82
3	(((aortic valv* or aorta* valv* or heart valv*) near4 (prosthe* or implant* or insert* or replac*)))	240
4	#1 OR #2 OR #3	250
5	((percutaneous or transapical or trans-apical or transarterial or trans-arterial or transcatheter or trans-catheter or transcutaneous or trans-cutaneous or transfemoral or trans-femoral or transaxillary or trans-axillary or transluminal or trans-luminal or transaortic or trans-aortic or transcarotid or trans-carotid or transsubclavian or trans-subclavian or transiliac or trans-iliac or transiliofemoral or trans-iliofemoral or TAVI or TAVR))	2241
6	#4 AND #5	118
7	MeSH DESCRIPTOR Transcatheter Aortic Valve Replacement	9
8	(#6 OR #7) FROM 2013 TO 2017	68
9	(#6 OR #7) IN HTA FROM 2013 TO 2017	29

10	(#6 OR #7) IN DARE FROM 2013 TO 2017	27

Database: **Epistemonikos**
Date run: 2017.06.27
Results: 279 Systematic Reviews (publication year 2013-2017)
Search: (title:((title:(TAVI OR TAVR OR transcatheter aortic valve replacement) OR abstract:(TAVI OR TAVR OR transcatheter aortic valve replacement)) OR (title:(TAVI OR TAVR OR transcatheter aortic valve implantation) OR abstract:(TAVI OR TAVR OR transcatheter aortic valve implantation)) (title:(heart valve prosthesis implantation) OR abstract:(heart valve prosthesis implantation))))

Database: **PubMed**
Date run: 2017.06.27
Results: 272 references (publication year 2016-2017)

Search: ((("heart valve prosthesis implantation"(MeSH Terms)) AND pubstatusaheadofprint)) OR ((("transcatheter aortic valve replacement"(MeSH Terms)) OR (TAVI(Title/Abstract) OR TAVR(Title/Abstract) OR transcatheter aortic valve replacement(Title/Abstract))) AND pubstatusaheadofprint)
OR
Search ((((((percutaneous(Title/Abstract) OR transapical(Title/Abstract) OR trans-apical(Title/Abstract) OR transarterial(Title/Abstract) OR trans-arterial(Title/Abstract) OR transcatheter(Title/Abstract) OR trans-catheter(Title/Abstract) OR transcutaneous(Title/Abstract) OR trans-cutaneous(Title/Abstract) OR transfemoral(Title/Abstract) OR trans-femoral(Title/Abstract) OR transaxillary(Title/Abstract) OR trans-axillary(Title/Abstract) OR transluminal(Title/Abstract) OR trans-luminal(Title/Abstract) OR transaortic(Title/Abstract) OR trans-aortic(Title/Abstract) OR transcarotid(Title/Abstract) OR trans-carotid(Title/Abstract) OR transsubclavian(Title/Abstract) OR trans-subclavian(Title/Abstract) OR transiliac(Title/Abstract) OR trans-iliac(Title/Abstract) OR transiliofemoral(Title/Abstract) OR trans-iliofemoral(Title/Abstract)))
AND (aortic valve Replace*(Title/Abstract) OR aortic valve implant*(Title/Abstract))) AND pubstatusaheadofprint)))
OR
((((((percutaneous(Title/Abstract) OR transapical(Title/Abstract) OR trans-apical(Title/Abstract) OR transarterial(Title/Abstract) OR trans-arterial(Title/Abstract) OR transcatheter(Title/Abstract) OR trans-catheter(Title/Abstract) OR transcutaneous(Title/Abstract) OR trans-cutaneous(Title/Abstract) OR transfemoral(Title/Abstract) OR trans-femoral(Title/Abstract) OR transaxillary(Title/Abstract) OR trans-axillary(Title/Abstract) OR transluminal(Title/Abstract) OR trans-luminal(Title/Abstract) OR transaortic(Title/Abstract) OR trans-aortic(Title/Abstract) OR transcarotid(Title/Abstract) OR trans-carotid(Title/Abstract) OR transsubclavian(Title/Abstract) OR trans-subclavian(Title/Abstract) OR transiliac(Title/Abstract) OR trans-iliac(Title/Abstract) OR transiliofemoral(Title/Abstract) OR trans-iliofemoral(Title/Abstract)))
AND (aorta valve Replace*(Title/Abstract) OR aorta valve implant*(Title/Abstract))) AND pubstatusaheadofprint)))

1.2 Literature search for “TAVI Collaborative Assessment” (Registry studies)

Search for Registry studies:

Date Run: 2017.09.05
Databases: Embase (Ovid), Ovid MEDLINE(R), Cochrane Central Register of Controlled Trials (CENTRAL), PubMed (ahead of print articles).

Hits: 565 after removal of duplicates (1059 including duplicates)

Comment: We searched for registry studies using a combination of subject headings and text words. In MEDLINE and Embase we searched for text words in title, original title, abstract, and subject heading using the code ".mp" (multi-purpose field).
We used the subject headings *Registries* (in MEDLINE, Cochrane Library, PubMed) and *Register* (in Embase), and the text words *register, registry, and registries.*
We combined the search terms using the Boolean OR operator (see search strategy in Embase and MEDLINE, line 21).

We added these search terms to the subject search used also for RCTs, SR and HTA (line 1-10 in Embase and MEDLINE) using the AND operator (12 AND 13). Line 11 is used to exclude animal studies.

Embase 1980 to 2017 Week 24
Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date run: 2017.09.05
Hits: 557

#	Searches (Embase and Ovid MEDLINE)	Results
1	heart valve prosthesis implantation/ use ppez	18532
2	heart valve replacement/ use ppez or aorta valve replacement/ use emez or transcatheter aortic valve implantation/ use emez or aorta valve prosthesis/ use emez	31001
3	Aortic Valve/ use ppez or aorta valve/ use emez or percutaneous aortic valve/ use emez	28941
4	((aortic valv* or aorta* valv* or heart valv*) adj4 (prosthe* or implant* or insert* or replac*)).ti,ab.	55296
5	or/1-4	90174
6	(percutaneous or transapical or trans-apical or transarterial or trans-arterial or transcatheter or trans-catheter or transcutaneous or trans-cutaneous or transfemoral or trans-femoral or transaxillary or trans-axillary or transluminal or trans-luminal or transaortic or trans-aortic or transcarotid or trans-carotid or transsubclavian or trans-subclavian or transiliac or trans-iliac or transiliofemoral or trans-iliofemoral or TAVI or TAVR).ti,ab.	387824
7	5 and 6	23663
8	percutaneous aortic valve/ use emez and (prosthe* or implant* or insert* or replac*).ti,ab.	1613
9	transcatheter aortic valve replacement/ use emez	11315
10	or/7-9	24882
11	exp animals/ not humans.sh.	27210271
12	10 not 11	9911
13	registries/ use ppez or register/ use emez or (registries or register or registry).mp.	399044
14	12 and 13	713
15	limit 14 to yr="2013 -Current"	601
16	remove duplicates from 15	557

Ovid search syntax

.pt. denotes a Publication Type term;

.ab. denotes a word in the abstract;
.fs. denotes a 'floating' subheading;
.sh. denotes a Medical Subject Heading (MeSH) term;
.ti. denotes a word in the title.
emez denotes Embase
ppez denotes MEDLINE
* (asterisk) denotes truncation (e.g. random* for random or randomised or randomized or randomly, etc)

Database: **Cochrane** Central Register of Controlled Trials
Date Run: 2017.09.05
Hits: 450

ID	Search	Hits
#1	MeSH descriptor: (Heart Valve Prosthesis Implantation) this term only	684
#2	MeSH descriptor: (Aortic Valve) this term only	451
#3	((aortic valv* or aorta* valv* or heart valv*) near/4 (prosthe* or implant* or insert* or replac*)):ti,ab,kw in Cochrane Reviews (Reviews and Protocols)	7
#4	((aortic valv* or aorta* valv* or heart valv*) near/4 (prosthe* or implant* or insert* or replac*)) in Other Reviews, Trials and Technology Assessments	1985
#5	#1 or #2 or #3 or #4	2091
#6	(percutaneous or transapical or trans-apical or transarterial or trans-arterial or transcatheter or trans-catheter or transcutaneous or trans-cutaneous or transfemoral or trans-femoral or transaxillary or trans-axillary or transluminal or trans-luminal or transaortic or trans-aortic or transcarotid or trans-carotid or transsubclavian or trans-subclavian or transiliac or trans-iliac or transiliofemoral or trans-iliofemoral or TAVI or TAVR):ti,ab,kw in Cochrane Reviews (Reviews and Protocols)	173
#7	(percutaneous or transapical or trans-apical or transarterial or trans-arterial or transcatheter or trans-catheter or transcutaneous or trans-cutaneous or transfemoral or trans-femoral or transaxillary or trans-axillary or transluminal or trans-luminal or transaortic or trans-aortic or transcarotid or trans-carotid or transsubclavian or trans-subclavian or transiliac or trans-iliac or transiliofemoral or trans-iliofemoral or TAVI or TAVR) in Other Reviews, Trials and Technology Assessments	17886
#8	#6 or #7	18059
#9	MeSH descriptor: (Transcatheter Aortic Valve Replacement) this term only	73
#10	(#5 and #8) or #9	704
#11	MeSH descriptor: (Registries) this term only	955
#12	registries or register or registry in Trials	8716
#13	#11 or #12	1055457
#14	#10 and #13 Publication Year from 2013 to 2017	450

Database: **PubMed**
Date run: 2017.09.05
Hits: 52
Search: (("heart valve prosthesis implantation"(MeSH Terms))
OR (("transcatheter aortic valve replacement"(MeSH Terms)) OR (TAVI(Title/Abstract) OR TAVR(Title/Abstract) OR transcatheter aortic valve replacement(Title/Abstract))) OR
(((percutaneous(Title/Abstract) OR transapical(Title/Abstract) OR trans-apical(Title/Abstract) OR transarterial(Title/Abstract) OR trans-arterial(Title/Abstract) OR transcatheter(Title/Abstract) OR trans-catheter(Title/Abstract) OR transcutaneous(Title/Abstract) OR trans-cutaneous(Title/Abstract) OR transfemoral(Title/Abstract) OR trans-femoral(Title/Abstract) OR transaxillary(Title/Abstract) OR trans-axillary(Title/Abstract) OR transluminal(Title/Abstract) OR trans-luminal(Title/Abstract) OR transaortic(Title/Abstract) OR trans-aortic(Title/Abstract) OR transcarotid(Title/Abstract) OR trans-carotid(Title/Abstract) OR

transsubclavian(Title/Abstract) OR trans-subclavian(Title/Abstract) OR transiliac(Title/Abstract) OR trans-iliac(Title/Abstract) OR transiliofemoral(Title/Abstract) OR trans-iliofemoral(Title/Abstract)))
AND (aortic valve Replace*(Title/Abstract) OR aortic valve implant*(Title/Abstract))))
OR ((transcatheter aortic valve replac*(Title/Abstract) OR transcatheter aortic valve implant*(Title/Abstract)
AND registries(Title/Abstract) OR register(Title/Abstract) OR registry(Title/Abstract)
AND pubstatusaheadofprint))

DESCRIPTION OF THE EVIDENCE USED

Evidence tables of individual studies included for clinical effectiveness and safety

Table A1. Characteristics of randomised controlled studies

Study ID	Study design (country)	Participants	Interventions	*Primary* Outcomes	Funding
PARTNER 2 (USA (15, 16)	RCT, multicentre	- 2032 intermediate-risk patients with severe aortic stenosis (1011 TAVI; 1021 SAVR); - Mean age 82 years (TAVI 82 ±6.7; SAVR 82 ±6.7) - 45.5% female INCLUSION CRITERIA: - symptomatic degenerative aortic valve stenosis (NYHA Functional Class II or greater) - heart team agreed that valve implantation would likely benefit the patient - STS >4 or <4 if the Heart Team determines intermediate risk patient profile with important comorbidities not represented in the STS risk score algorithm	**Intervention**: TAVI underwent by transfemoral or transthoracic placement of the Edwards balloon-expandable SAPIEN XT heart-valve (26 mm). **Control**: Surgical aortic-valve replacement (Following a thorough assessment of the iliofemoral vasculature, patients were categorised into either a transfemoral or transthoracic cohort)	- mortality from any cause - disabling stroke at 2 years Other assessed outcomes: - severe bleeding - atrial fibrillation - intensive care unit stay - index hospitalization - vascular complication - paravalvular regurgitation - pacemaker implantation - repeat hospitalisation (2-year follow-up)	Sponsored by Edwards SAPIEN Lifesciences (Irvine, CA, USA), was
SURTAVI Reardon 2017 (2)	RCT, multicentre	- 1746 intermediate-risk patients with severe aortic stenosis (879 TAVI; 867 SAVR) - 80 years± 6.2 (TAVI 80±6.2, SAVR 80±6.0); 43% Female Definition of intermediate: estimated risk of 30-day surgical mortality of 3 to 15% (Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), Definition of severe AS: aortic valve area <1cm2 or <0.6 cm2/m2 body surface area and a mean gradient >40 mm Hg or a	**Intervention**: TAVI **Control**: Surgical aortic-valve replacement	- composite of death from any cause or disabling stroke at 24 months Other assessed outcomes: - mortality (overall; cardiac) - stroke - severe bleeding - atrial fibrillation	Medtronic

		maximum velocity >4m/second at rest or with dobutamine in patients with a left ventricular ejection fraction <55% or Doppler velocity index < 0.25 on resting echocardiography.			

List of ongoing and planned studies

Emerging evidence

The co-author (NIPHNO) searched ClinicalTrials.gov and WHO ICTRP for entries on studies on TAVI entered in 2012 and later (search strategy provided below). 443 unique entries were identified after removal of duplicates.

282 entries with completion date 2016 and later were considered as emerging evidence. 42 of these were excluded based on title and study name not being TAVI and one was excluded as information only was available in Chinese. Of the remaining 239 entries 59 were RCTs. All entries for RCTs were inspected for Population, Intervention and Comparator. (See below Search strategy for ongoing studies. The entry data for the SURTAVI trial data was last updated in November 2017.

Literature search for ongoing studies

Database: ClinicalTrials.gov, first posted from 01/01/2012 to 07/12/2020

Date: 2018.01.12

Search strategy:

1. (Transcatheter aortic valve implant* OR Transcatheter aortic valve replacement OR TAVI)
2. Aortic valve stenosis AND (Transcatheter aortic valve replacement, Transcatheter aortic valve implantation)
3. ((Edwards SAPIEN) OR CoreValve OR Evolut OR ACURATE OR JenaValve OR (Jena Valve) OR Portico):

Results: 417 trials identified (duplicates removed)
Database: WHO ICTRP, 01/01/2012

Date: 2018.01.12

Search strategy:

1. (Transcatheter aortic valve implant* OR Transcatheter aortic valve replacement OR TAVI)
2. ((Edwards SAPIEN) OR CoreValve OR Evolut OR ACURATE OR JenaValve OR (Jena Valve) OR Portico)

Results: 210 trials identified (duplicates removed)

After removal of duplicates, the total number entries were 443

Included	Excluded (reason for exclusion)
443 Unique	184 (duplicates)
282 Completion date => 2016	161 (completion date < 2016)
239 TAVI	43 (42 non-TAVI, 1 Chinese language)
59 RCT	180 non-RCT
59	**568**

Two RCTs were identified where the eligibility criteria clearly stated that the patients should have severe aortic stenosis with an intermediate surgical risk (table A2 below). One of these was the SURTAVI trial, for which we have assessed interim analysis published in 2017. The final completion date of the SURTAVI trial is October 2018. Number of patients planned to be recruited was 2500.

The second trial was an ongoing German trial NCT03112980, which seems to be the first RCT on relevant questions for this assessment to be developer independent. A total of 17 German University hospitals contribute to the trial. Estimated completion is 2023 with no information possible publications of interim analysis. The last update on the trial was from October 2017, the trial is still recruiting participants.

A small Chinese trial (NCT03163329, see Table A4) also reported on intermediate risk patients, but the trial was restricted inclusion to patients with bi-cuspid AS, which was not a predefined population of this assessment.

Additional emerging evidence includes six RCTs comparing TAVI with SAVR or medication were the patients are at low risk or non-symptomatic (Table A3 List of ongoing trials). For these RCTs primary completion date vary from 2018 to 2021. There were also five RCTs were the patients are at high or unspecified risks comparing one TAVI system with another TAVI system (see tableA4). The additional (excluded) 46 RCTs with TAVI relevant emerging evidence, had either studied various aspects of TAVI such as medication, sedation prehab and rehab or a specific sub-population (see Table A5 or excluded RCTs on TAVI relevant emerging evidence).

Table A2. Included ongoing trials relevant for research questions of this assessment

Inclusion criteria
P: AS Intermediate risk
I: TAVI any system/model
C: SAVR; TAVI another system/model; Clinical surveillance (medication)
O: Relevant for this assessment

Trial (trial number and name)	Number of participants	P (study inclusion criteria)	I	C	O	Estimated Completion
NCT01586910 Safety and Efficacy Study of the Medtronic CoreValve® System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement (SURTAVI). 2017.	2500	Severe AS, co-morbidities such that Heart Team agrees predicted risk of operative mortality is ≥3% and <15% at 30-day follow-up	Medtronic CoreValve® Evolut R System	SAVR	All-cause mortality or disabling stroke (Time Frame: 24 months); Safety and efficacy outcomes; QoL (not specified)	2018 (Published Interim results included in this report)
NCT03112980 Randomized Trial of TAVI vs. SAVR in Patients with Severe Aortic Valve Stenosis at Intermediate Risk of Mortality.	1600	AS –severe symptomatic Intermediate risk STS-score 2-6%	TAVI using the most appropriate CE marked device available	SAVR	Overall survival five years after last patient in; Safety and efficacy outcomes; QoL (EQ-5D)	2023

Table A3. Excluded due to P: Non-symptomatic or low risk

P: AS Non-symptomatic or low risk
I: TAVI any system/model
C: SAVR; TAVI another system/model; Clinical surveillance (medication)
O: Not extracted

Trial (Number and name)	P (study inclusion criteria)	I	C	Estimated Completion
1. NCT03042104 Edwards L. Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis.	AS- Non-symptomatic	Transcatheter aortic valve replacement (TAVR) arm will have intervention with the Edwards SAPIEN 3 THV.	Clinical surveillance	2021/2031
2. NCT03094143. Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients with Severe AS.	AS - Non-symptomatic	TAVI (type not specified)	No-intervention (3 arms)	2020

Trial (Number and name)	P (study inclusion criteria)	I	C	Estimated Completion
3. NCT02825134 • Comparison of Transcatheter Versus Surgical Aortic Valve Replacement in Younger Low Surgical Risk Patients with Severe Aortic Stenosis.	AS –low risk 75 or younger STS Score <4%	TAVR, Retrograde transfemoral transcatheter aortic valve replacement with any CE mark approved aortic bioprosthesis with or without concomitant percutaneous coronary intervention	SAVR	2020
4. NCT02675114The Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients with Aortic Stenosis.	Severe Calc. AS, STS <4	Edwards Sapien3	SAVR Any commercially available	2018/2027
5. NCT02701283 Medtronic Transcatheter Aortic Valve Replacement in Low Risk Patients. 2018.	Severe AS, symptomatic or asymptomatic, Risk of mortality <3% at 30-day follow-up	Medtronic TAVR Systems	SAVR (any commercially available)	2018
6. NCT03011346 Safety and Efficacy of the Symetis ACURATE Neo/TF Compared to the Edwards SAPIEN 3 Bioprosthesis.	AS symptomatic, Increased risk (STS>10%) or other reasons considered by heart team not covered by risk score, frailty and life expectancy	Symetis ACURATE neo/TF transfemoral TAVI	Edwards SAPIEN 3	2017

Table A4. Excluded due to P being High risk or risk not specified

P: AS High risk or risk not specified
I: TAVI any system/model
C: SAVR; TAVI another system/model;
O: Not extracted

Trial (Number and name)	P (study inclusion criteria)	I	C	Estimated Completion
1. NCT03192813 Safety and Efficacy Comparison of Two TAVI Systems in a Prospective Randomized Evaluation II.	AS – Symptomatic high risk	Symetis ACURATE neo™ transfemoral TAVI system	Medtronic CoreValve Evolut R TAVI System	2019
2. NCT02668484 Repositionable Versus Balloon-expandable Prosthesis for Trans-catheter Aortic Valve Implantation.	AS symptomatic, trans-femoral TAVI is appropriate	Lotus, repositionable valve	Balloon expandable, Edwards SAPIEN	2017/2019
3. NCT02163850 SALUS trial, Transcatheter Aortic Valve Replacement System Pivotal Trial. 2017.	AS symptomatic, Extreme or High risk	Direct Flow Medical TAVR	Commercially available TAVR	2017/2021
4. NCT02000115 Portico Re-sheathable Transcatheter Aortic Valve System US IDE Trial:	Severe AS, Extreme risk or High risk	Portico transcatheter aortic valve	Commercially Available Valve	2018/2021
5. NCT02668484 Repositionable Versus Balloon-expandable Prosthesis for Trans-catheter Aortic Valve Implantation.	AS symptomatic, trans-femoral TAVI is appropriate	Lotus, repositionable valve	Balloon expandable, Edwards SAPIEN	2017/2019

Table A5. Excluded due to either the population (P) not being aortic stenosis per se, or the intervention (I) not being TAVI alone or per se and/ or comparator (C) not being SAVR or another TAVI system/model

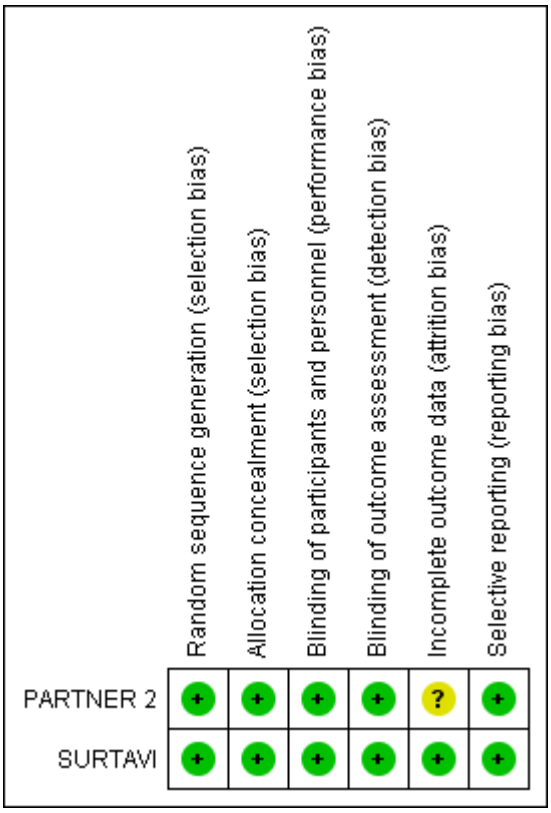
Trial (Number and name)	Reason for exclusion
1. NCT03163329 The Safety and Effectiveness of Transcatheter Aortic Valve Replacement in Intermediate Risk Patients with Bicuspid Aortic Stenosis.	P (AS-bicuspid)
2. NCT03058627 Revascularization in Patients Undergoing Transcatheter Aortic Valve Implantation. 2021/2025	C
3. NCT03315832 Efficacy of Angiotensin Receptor Blocker Following Aortic Valve Intervention for Aortic Stenosis: a Randomized multicentric Double-blind Phase II Study.	I+C
4. NCT03360591 Functional Assessment In TAVI: FATAVI.	I+C

Trial (Number and name)	Reason for exclusion
5. NCT02838199 Transcatheter or Surgical Aortic Valve Replacement in All-Comers with Severe Aortic Valve Stenosis.	Withdrawn
6. NCT03173534 WATCH-TAVR, WATCHMAN for Patients with Atrial Fibrillation Undergoing Transcatheter Aortic Valve Replacement.	I + C
7. NCT02943785 Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation (ENVISAGE-TAVI AF).	P, I and C
8. NCT02735902 Anticoagulation Alone Versus Anticoagulation and Aspirin Following Transcatheter Aortic Valve Interventions (1:1).	I+C
9. NCT03303612 Clinical Monitoring Strategy vs EP-guided Algorithmic in LBBB Patients Post-TAVI.	I +C
10. NCT03084978 Conscious Sedation vs General Anesthesia in TAVR Patients.	I
11. NCT03201185 Renin-angiotensin System Blockade Benefits in Clinical Evolution and Ventricular Remodeling After Transcatheter Aortic Valve Implantation (RASTAVI).	C
12. NCT02895737 Prospective Randomized Outcome Study in TAVI Patients Undergoing Periprocedural Embolic Cerebral Protection with the Claret Sentinel™ Device. 2019.	I + C + O
13. NCT02664649 Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis. 2019.	I + C
14. NCT03107897 Prehabilitation for Patients Undergoing Transcatheter Aortic Valve Replacement. 2018.	I + C
15. NCT02247128 Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation. 2018.	I+C
16. NCT03121053 Preventing Contrast Induced Nephropathy After Transcatheter Aortic Valve Replacement. 2018.	I
17. NCT03291210 O2 Tension During TAVI. 2018.	I+C
18. NCT02974660 Protamine Sulfate During Transcatheter Aortic Valve Implantation. 2018.	I + C
19. NCT02541877 Sizing-Strategy of Bicuspid Aortic Valve Stenosis with Transcatheter Self-expandable Valve. 2018.	I
20. NCT03347032 Remote Ischemic Preconditioning for Renal Protection in TAVI. 2018.	C
21. NCT02768064 Temporary Pacemaker in Transcatheter Aortic Valve Implantation Patients. 2018.	I + C
22. NCT02781896 Direct Left Ventricular Rapid Pacing Via the Valve Delivery Guide-wire in TAVI. 2018.	I+C
23. NCT03284827Anticoagulant Versus Dual Antiplatelet Therapy for Preventing Leaflet Thrombosis and Cerebral Embolization After Transcatheter Aortic Valve Replacement. 2018.	C
24. NCT03001960 Dual Antiplatelet Therapies for Prevention of Periinterventional Embolic Events in TAVI. 2018.	I+C
25. NCT03383445 Transcatheter Aortic Valve Replacement versus Surgical Aortic Valve Replacement for Treating Elderly Patients with Severe Aortic Stenosis and Small Aortic Annuli: A Prospective Randomized Study The VIVA Trial. 2018.	P (small aortic annuli)
26. nct02661451 Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients with Advanced Heart Failure (TAVR UNLOAD). 2018.	P
27. NCT02805309 Home-Based Exercise Program for Recovery After Transcatheter Aortic Valve Replacement. 2018.	I + C
28. NCT02556203 Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes 2018.	I + C

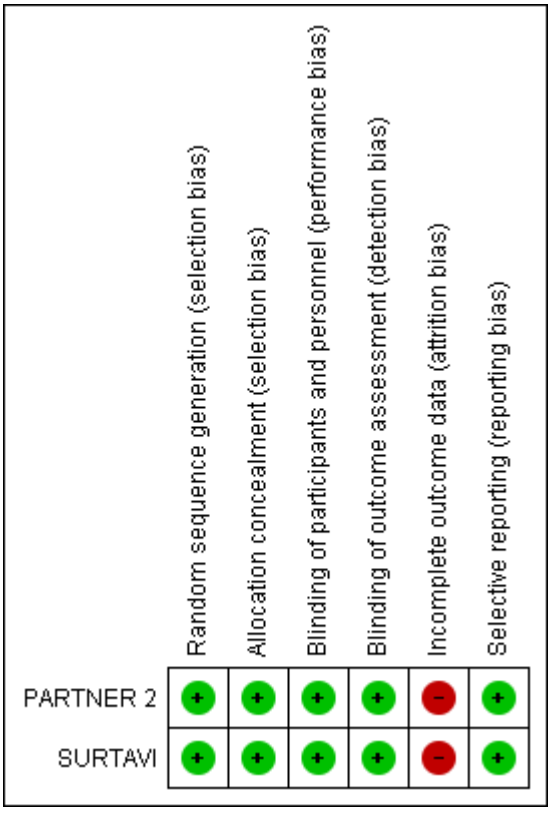
Trial (Number and name)	Reason for exclusion
29. NCT01982032 Edwards SAPIEN Periprosthetic Leakage Evaluation Versus Medtronic CoreValve in Transfemoral Aortic Valve Implantation (the ELECT Trial). 2017.	Terminated
30. NCT02448927 The Predilatation in Transcatheter Aortic Valve Implantation Trial. 2017.	I+C
31. NCT02080299 117 Protection by Remote Ischemic Preconditioning During Transcatheter Aortic Valve Implantation. 2017.	C
32. NCT02696226 Frequency of Reduced Leaflet Motion After Surgical Aortic Valve Replacement and Transcatheter Aortic Valve Replacement. 2017.	Terminated
33. NCT02855099 Can Rehabilitation after TAVI Precipitate Recovery and Improve Prognosis. 2017.	Withdrawn
34. NCT01866800 The Effect of the Forced Diuresis with Matched Hydration in Reducing Acute Kidney Injury During TAVI. 2017.	I + C
35. NCT02766075 A STEP for Patients Prior to Undergoing TAVR: A Pilot Study. 2017.	I + C
36. NCT02921880 Does Cardiac Rehabilitation Improve Functional, Independence, Frailty and Emotional Outcomes Following Trans Catheter Aortic Valve Replacement? 2017.	I + C
37. NCT02597985 Functional and Clinical Outcomes in Patients with Aortic Stenosis. NCT02597985 2017.	I
38. NCT02536196 The REFLECT Trial: Cerebral Protection to Reduce Cerebral Embolic Lesions After Transcatheter Aortic Valve Implantation. 2017.	C
39. NCT02468219 Assessment and Cardiovascular Rehabilitation in Patients with Severe Aortic Stenosis. 2017.	I+ C
40. NCT02640794Aspirin Versus Aspirin+Clopidogrel as Antithrombotic Treatment Following TAVI. 2017.	I+C
41. NCT02833948 Comparison of a Rivaroxaban-based Strategy with an Antiplatelet-based Strategy Following Successful TAVR for the Prevention of Leaflet Thickening and Reduced Leaflet Motion as Evaluated by Four-dimensional, Volume-rendered Computed Tomography (4DCT). 2017.	I + C
42. NCT02224066 Platelet Reactivity After TAVI: A Multicenter Pilot Study. 2017.	I+C
43. NCT01642134 Dual Antiplatelet Therapy Versus Oral Anticoagulation for a Short Time to Prevent Cerebral Embolism After TAVI. 2017.	I+C
44. NCT02721758 Understanding and Promoting Health Behaviour Change Amid Transition to Cardiac Rehabilitation. 2016.	I+C
45. NCT02283398 Cardioprotective Effect of RIPC in Patients Undergoing TAVI. 2016.	I+C
46. NCT02214277 Cerebral Protection in Transcatheter Aortic Valve Replacement. 2016.	I+C

Risk of bias tables

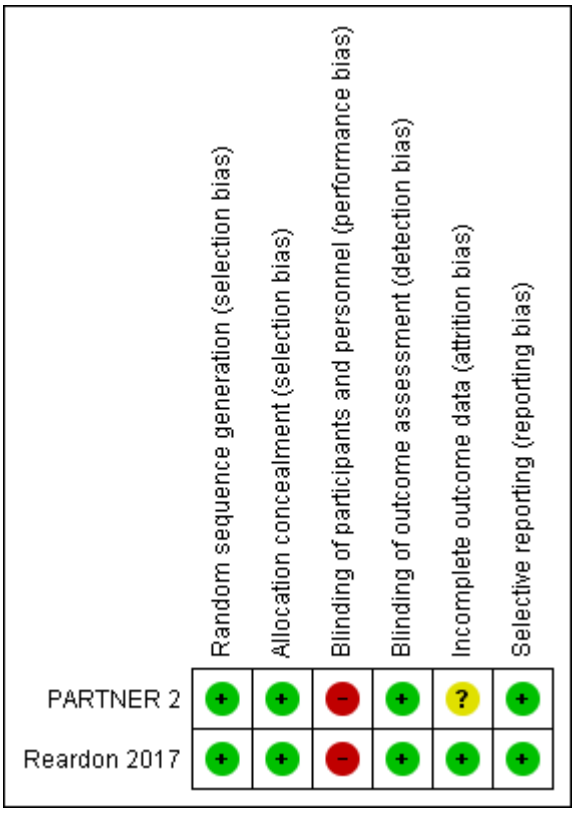
Table A6. Risk of bias study level (RCTs) summary: review authors' judgements about each risk of bias item for each included study according to type of outcome and time follow-up.



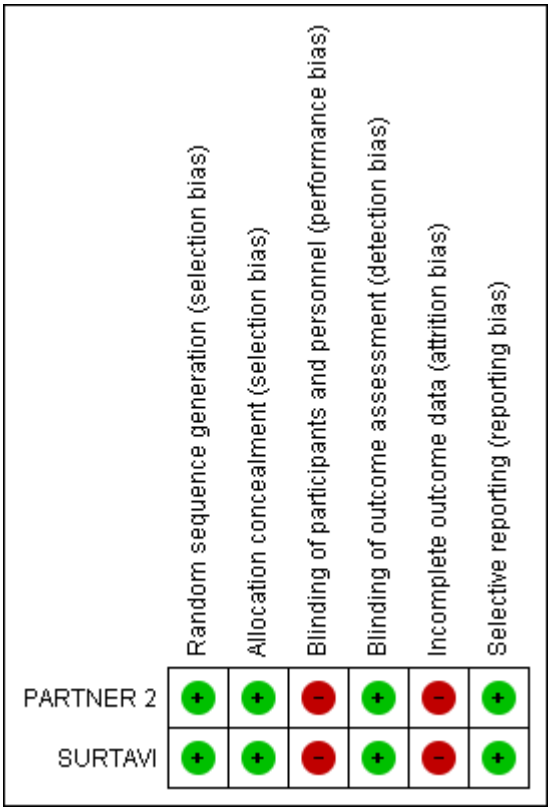
(a) Objective outcomes at 30-day follow-up



(b) Objective outcomes at 2-year follow-up



Subjective outcomes (30-day follow-up)



Subjective outcomes (2-year follow-up)

For the purpose of transparency, a separate document with comments on the 2nd draft assessment from external experts and the MAH/manufacturer(s) (fact check), as well as responses from authors, is available on the EUnetHTA website.

APPENDIX 2. SYSTEMATIC REVIEWS CROSS-MATCHED WITH THE TRIALS

Author year	CoreValve	NOTION	PARTNER A	PARTNER 2	SAPIEN 3	STACCATO	SURTAVI	Notes
AK 2017 [71]								Not found
Amato 2016 [72]		x	x			x		
Ando 2017 [73]			x	x		x		
Ando 2017 [74]	x	x	x	x				
Arora 2016 [75]		x						
Arora 2017 [76]		x						
Athappan 2013 [77]			x		x			
Biondi-Zoccai 2014 [78]	x		x			x		
Boothroyd 2013 [79]			x					
Burrage 2017 [80]	x	x	x	x		x		
Cadth. 2013 [81]			x					
Cao 2013 [82]	x		x			x		
Cao 2016 [83]	x		x			x		
Cao 2015 [84]								Excluded: Abstract
Cardoso 2015 [85]	x	x	x					
Enezate 2017 [86]		x		x		x		
Ferrari 2016 [87]			x					
Garg 2017 [88]		x		x		x	x	
Garg 2016 [89]		x		x		x	x	
Gargiulo 2016 [90]	x	x	x	x		x		

Health 2016 [91]	x	x	x			x		
Herial 2015 [92]								Excluded: abstract
Holzhey 2013 [93]								Excluded: commentary
Indraratna 2016 [94]	x	x	x	x		x		
Jilaihawi 2013 [95]			x					
Khan 2016 [96]						x		
Kim 2014 [97]			x					
Kularatna 2016 [98]								Not found
Mattos 2016 [99]								Not found
Mohammadi 2016 [100]	x		x					Narrative review.
Munkholm-Larsen 2013 [101]								Not found
Nagaraja 2014 [102]	x		x			x		
Panchal 2013 [103]			x			x		
Panoulas 2016 [104]	x	x				x		Excluded: Abstract (citing Partner A, Corevalve, STACCATO and NOTION)
Paone 2016 [105]								Excluded: HTA report on sutureless aortic valve replacement.
Praz 2017 [106]	x	x	x	x		x		
Ribeiro 2017 [107]								Excluded: post hoc analysis in a rehab centre.
Saji 2016 [108]	**x**	**x**	**x**	**x**			**x**	

Sardar 2017 [109]				x		x		
Sehatzadeh 2013 [110]			x					
Shan 2013 [111]								Excluded: aortic valve replacement (no TAVI).
Siemieniuk 2016 [69]	x	x		x		x		
Singh 2017 [112]		x		x		x		
Siontis 2016 [113]	x	x	x	x		x		
Spaccarotella 2017 [114]		x		x			x	
Spinetto 2015 [115]	x			x		x		
Takagi 2017 [116]	x	x	x	x		x		
Takagi 2013 [117]			x			x		
Tsu 2017 [118]	x		x					Narrative review.
Turagam 2016 [119]								Abstract
Villablanca 2016 [120]	x	x	x	x			x	
Wang 2016 [121]								Excluded: matched or propensity score matched studies
Wong 2015 [122]								Not found
Wu 2013 [123]								Not found
Zhou 2017 [124]		x		x		x		

APPENDIX 3. EXLCUDED NONCOMPARATIVE REGISTRY STUDIES

Excluded noncomparative Registry Studies
1. Amat-Santos IJ, Messika-Zeitoun D, Eltchaninoff H, et al. Infective endocarditis after transcatheter aortic valve implantation: results from a large multicenter registry. Circulation 2015;131(18):1566-74 (125).
2. Arnold SV, Spertus JA, Vemulapalli S, et al. Association of Patient-Reported Health Status With Long-Term Mortality After Transcatheter Aortic Valve Replacement: Report From the STS/ACC TVT Registry. Circ Cardiovasc Interv 2015;8(12):e002875 (126).
3. Arsalan M, Szerlip M, Vemulapalli S, et al. Should Transcatheter Aortic Valve Replacement Be Performed in Nonagenarians?: insights From the STS/ACC TVT Registry. J Am Coll Cardiol 2016; 67(12). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/190/CN-01200190/frame.html (127).
4. Auffret V, Lefevre T, Van Belle E, et al. Temporal Trends in Transcatheter Aortic Valve Replacement in France: FRANCE 2 to FRANCE TAVI. J Am Coll Cardiol 2017;70(1):42-55 (128).
5. Bernardi FL, Ribeiro HB, Carvalho LA, et al. Direct Transcatheter Heart Valve Implantation Versus Implantation with Balloon Predilatation: Insights From the Brazilian Transcatheter Aortic Valve Replacement Registry. Circ Cardiovasc Interv 2016;9(8) (129).
6. Bestehorn K, Eggebrecht H, Fleck E, et al. Volume-Outcome Relationship with Transfemoral Transcatheter Aortic Valve Implantation (TAVI) - Insights from the Compulsory German Quality Assurance Registry on Aortic Valve Replacement (AQUA). EuroIntervention 2017;06:06 (130).
7. Biere L, Durfort A, Fouquet O, et al. Baseline characteristics and outcomes after transcatheter aortic-valve implantation in patients with or without previous balloon aortic valvuloplasty: Insights from the FRANCE 2 registry. Arch Cardiovasc Dis 2017;03:03 (131).
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APPENDIX 4. RISK OF RADIATION-INDUCED CANCER IN TAVI

Input to assessment of TAVI - A radiation protection view

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TAVI is a catheter-based administration of an aortic valve and replaces open surgery, primarily for patients with high operational risk or patients who cannot undergo open surgery (method introduced in 2008). The method is now being evaluated for patients with intermediate surgical risk. There are several manufacturers of cardiac valves and equipment. TAVI is potentially associated with high radiation doses for both patient and personnel.

Radiation doses for patients and personnel depend on several factors such as equipment (technical possibilities, mono- or bi-plane), working techniques, experience and competence of personnel, use of protective equipment and shielding of X-ray room, complexity of the procedure, route of administration and equipment (type of catheters). In addition, presurgery investigation and postsurgery follow-up with assumed coronary angiography will contribute, but their frequency is not known at this stage.

The Radiation Protection Regulation have requirements for all medical use of radiation, and it is a prerequisite for implementing the method that the requirements of the Radiation Protection Regulations are respected.

Contraindication in patients with renal failure and / or anaphylaxis must also be included in the overall risk assessment for all identified risks associated with TAVI and contrast media administration.

Stochastic risk for patients

Dose statistics have been collected for all nine cardiological interventional departments that offer coronary angiography from the Norwegian Registry for Invasive Cardiology (NORIC) for 2016. There are also statistics for TAVI for Haukeland University Hospital, Rikshospitalet and partly the Feiring clinic for 2016 (Table A7). Haukeland and Rikshospitalet are reported to undertake approximately 50% of all TAVI procedures in Norway. The remaining hospitals are expected to report dose data for their TAVI procedures to the NORIC registry within 2017.

Table A7. Statistical data for coronary angiography and TAVI obtained from NORIC. Angiography data contains some children, but this only affects the minimum value due to the high number of procedures. * Conversion factors between dose area product (DAP), effective dose and skin dose respectively are obtained from Karambatsakidou et al. (163).

	No.	Average DAP [Gycm^2]	Median DAP [Gycm^2]	Effective dose [mSv] *	Skin dose [mGy]
Coronary angio	13 601	16.5 (0.1-241)	11.9	4.0 (0.1-57.8)	160 (1-2336)
TAVI	245	56.9 (0.4-385)	40.7	13.7 (0.1-92.3)	552 (3.7-3732)

The statistics do not contain age-related data for the patients, so a risk calculation presented in table 2 includes risk of morbidity and mortality for different age groups and dose levels (Table A8).

Table A8. General natural risk of morbidity and mortality in cancer for Norwegian population, compared to additional risk from TAVI for different age groups.

	General fatal cancer before 75 yrs age (%) **		General incidence of cancer before 75 yrs age (%) **		Increased risk of fatal cancer after TAVI. Comes in addition to the general risk.		
	Female	Male	Female	Male	Risk coefficient [% per Sievert]	Average increased fatal risk [%]	Worst case [%] (max value tab. 1)
Population	9.6	12.1	27.2	33.6	5	0.0685	0.462
50-59	9.6	12.1	27.2	33.6	4	0.0548	0.369
60-69	9.6	12.1	27.2	33.6	3.1	0.0425	0.286
70-79	9.6	12.1	27.2	33.6	1.6	0.0219	0.148
80+					0.75	0.0103	0.069

*Risk coefficients obtained from NRPB** (164). General risk of cancer incidence and fatal cancer before 75 years of age for 2010 and 2011, respectively, are taken from NORDCAN (165).*

In general, the additional risk of radiation induced cancer following a TAVI procedure will be small, in relation to the natural risk of morbidity and mortality in cancer. Typically, an increase in the first or second decimal. However, the age of patients will be important. Patients with intermediate risk are expected to be younger, with a slightly increased risk of stochastic effects as a result. Women in general have also a higher risk of radiation induced cancer. Probably since the breast glandules are quite radio-sensitive. There will also be a dose contribution from the presurgery investigation and postsurgery follow-up. If e.g. a preoperative coronary angiography and three postoperative angiographs are being performed, the fatal risk are assumed to be doubled.

Epidemiological and experimental studies have also shown a risk of damage to cardiovascular systems, etc. Preston et al. (166), finds that 0.8% of mortality in the Hiroshima and Nagasaki population are due to radiation-induced non-cancer, such as heart disease, stroke and respiratory disease. However, no effects were found below 500 mSv, but more research has to be done in this area. It is also uncertain whether the radiation-induced non-cancer effects are of stochastic or deterministic nature, i.e. are the risk increasing with increasing dose or has the dose to be over a certain threshold to develop the certain effect?

The risk of genetic damage is negligible and does not have to be estimated.

Deterministic effects of the patient

Deterministic effects will primarily include tissue reactions such as erythema, hair loss and more serious skin lesions. Typical for deterministic effects are that the dose must exceed a certain threshold value for a certain effect (Table A9). The indicated effects in table 3 occur with 1% incidence for the given dose level, and there will be large variations in tissue sensitivity between different persons and possibly also between different ethnicities. The average skin dose for coronary angiography and TAVI give no general cause for concern. However, in difficult procedures with coronary angiography, followed by a difficult TAVI procedure, doses may exceed values where acute deterministic effects can be seen (see max values in Table A7).

Table A9. Acute skin effects at different dose levels with latency to develop the certain effect. The table is modified from Wagner *et al.* (167).

Effect	Typical threshold dose [Gy]	Time to onset of effect
Transient erythema	2	Hours
Temporary epilation	3	3 wk
Permanent erythema	6	10 d
Permanent epilation	7	3 wk
Dry desquamation	10	4 wk
Dermal atrophy	11	
Teleangiectasia	12	>14 wk
Late erythema	15	>52 wk
Dermal necrosis	18	>10 wk
Secondary ulceration	20	>6 wk

Radiation risk personnel

Personnel closest to the patient will be exposed to the highest radiation doses, and cardiologists are the occupational group receiving the highest radiation doses in Norway. Radiated tissue will be fingers (especially in transapical administration) and eye lenses (usually is the left lens most exposed). Periodic monitoring of finger and eye lens doses should be performed. A personal dose meter attached to the left shoulder will give a good indication of the eye lens dose if no safety goggles are used. The induction of postcapsular opacities and cataracts seems to have a stochastic nature, that is, a small dose means a small risk, and an increasing dose an increasing risk. The EURALOC project (www.euraloc.eu) conducted a dose-response analysis of 318 interventional cardiologists, compared to 235 non-exposed persons in a control group (168). It was found that radiation had a significant effect on the induction of postcapsular opacities, with a relative risk for interventional cardiologists with an odds ratio of 2.62 (95% confidence interval 1.35-5.08).

The thyroid gland has low radio-sensitivity for men over 45 years and women over 50 years. It is important that adequate shielding equipment is used and that the personnel have competence to use it properly. Lead aprons should be adapted to the current work situation and be personal. Careful selection of lead aprons should be made for thickness and design. Use of safety goggles will significantly reduce the risk of induction of postcapsular opacities and cataracts, if the goggles are ergonomically shaped and suitable for the cardiologist concerned. Lead curtains should be used on the side of the x-ray board, and ceiling mounted screens should be optimally positioned.

Personnel must also comply with regulatory dose limits, as proposed by The International Commission on Radiological Protection (ICRP) (169), (170).

- Skin / hands: 500 mSv (equivalent dose).
- Eye lens: 20 mSv (equivalent dose).
- Whole body dose: 20 mSv (effective dose).

Some publications recommend that the TAVI procedures should be performed by several different (many) cardiologists, in order to reduce the radiation dose to the individual. It is doubtful whether

this is a good solution, since TAVI is a highly specialized procedure and cardiologists need many procedures for maintaining and building expertise.

Definitions

Effective dose - A radiation dose taking into account all radiation-sensitive organs that have received a radiation dose. Effective dose gives an estimate of cancer risk but should not be used on individuals. Used primarily to compare different irradiation situations. Specified in the unit milliSievert (mSv) or decadian prefixes.

Skin dose - The radiation dose to a skin area. Says something about the likelihood of developing an acute (deterministic) injury. Specified in the unit milliGray (mGy) or decadian prefixes.

Dose area product - A measure of the total amount of radiation (energy) that hits the patient. Indicated in unit $Gycm^2$ (dose x area).

Stochastic effect - A random effect (injury, here cancer), where the likelihood of injury, but not the severity of the effect, increases with increasing radiation dose. Biological cause is damage to DNA.

Deterministic effect (also called tissue reactions) - An effect that occurs when a given threshold is exceeded for a certain effect. Increasing the dose also increases the effect. Biological cause is massive cell death.

Conversion Factor - A numerical factor used to calculate (here) effective dose or skin dose based on dose-area product.

Postcapsular opacity or cataract - An injury to the eye lens that is typical for radiation. Can also be found to some degree in the population