






# BMJ Open Transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis: a systematic review and meta-analysis

Stephanie Louise Swift ,<sup>1</sup> Thomas Puehler ,<sup>2,3</sup> Kate Misso,<sup>1</sup> Shona Helen Lang ,<sup>1</sup> Carol Forbes,<sup>1</sup> Jos Kleijnen,<sup>1</sup> Marion Danner ,<sup>4</sup> Christian Kuhn,<sup>3,5</sup> Assad Haneya,<sup>2</sup> Hatim Seoudy,<sup>3,5</sup> Jochen Cremer,<sup>2</sup> Norbert Frey,<sup>6</sup> Georg Lutter,<sup>2,3</sup> Robert Wolff ,<sup>1</sup> Fueloep Scheibler,<sup>4</sup> Kai Wehkamp,<sup>7</sup> Derk Frank<sup>3,5</sup>

**To cite:** Swift SL, Puehler T, Misso K, *et al*. Transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis: a systematic review and meta-analysis. *BMJ Open* 2021;**11**:e054222. doi:10.1136/bmjopen-2021-054222

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-054222>).

SLS and TP are joint first authors.

Received 21 June 2021

Accepted 26 October 2021



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

## Correspondence to

Dr Robert Wolff;  
robert@systematic-reviews.com

## ABSTRACT

**Objectives** Patients undergoing surgery for severe aortic stenosis (SAS) can be treated with either transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR). The choice of procedure depends on several factors, including the clinical judgement of the heart team and patient preferences, which are captured by actively informing and involving patients in a process of shared decision making (SDM). We synthesised the most up-to-date and accessible evidence on the benefits and risks that may be associated with TAVI versus SAVR to support SDM in this highly personalised decision-making process.

**Design** Systematic review and meta-analysis.

**Data sources** MEDLINE (Ovid), Embase (Ovid) and the Cochrane Central Register of Controlled Trials (CENTRAL; Wiley) were searched from January 2000 to August 2020 with no language restrictions. Reference lists of included studies were searched to identify additional studies.

**Eligibility criteria** Randomised controlled trials (RCTs) that compared TAVI versus SAVR in patients with SAS and reported on all-cause or cardiovascular mortality, length of stay in intensive care unit or hospital, valve durability, rehospitalisation/reintervention, stroke (any stroke or major/disabling stroke), myocardial infarction, major vascular complications, major bleeding, permanent pacemaker (PPM) implantation, new-onset or worsening atrial fibrillation (NOW-AF), endocarditis, acute kidney injury (AKI), recovery time or pain were included.

**Data extraction and synthesis** Two independent reviewers were involved in data extraction and risk of bias (ROB) assessment using the Cochrane tool (one reviewer extracted/assessed the data, and the second reviewer checked it). Dichotomous data were pooled using the Mantel-Haenszel method with random-effects to generate a risk ratio (RR) with 95% CI. Continuous data were pooled using the inverse-variance method with random-effects and expressed as a mean difference (MD) with 95% CI. Heterogeneity was assessed using the  $I^2$  statistic.

**Results** 8969 records were retrieved and nine RCTs (61 records) were ultimately included (n=8818 participants). Two RCTs recruited high-risk patients, two RCTs recruited intermediate-risk patients, two RCTs recruited low-risk

## Strengths and limitations of this study

- This systematic review (SR) assesses two treatments (transcatheter aortic valve implantation (TAVI) vs surgical aortic valve replacement, SAVR) for patients with severe aortic stenosis.
- Aims to support shared decision making by presenting evidence across a broad range of treatment outcomes, a wide range of surgical risk levels and a uniquely large number of subgroups which can inform decision-making of individual patients.
- Patients were involved in an initial needs assessment based on their priorities and experience, which ultimately evolved into the prespecified outcomes of interest.
- Methods follow guidance by Cochrane, the Centre for Reviews and Dissemination as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guideline and the SR was registered on PROSPERO.
- Includes several new randomised controlled trials or long-term study outcomes that have not yet been incorporated into pooled analysis for TAVI versus SAVR across different risk levels, especially in low-risk patients and in key subgroups of interest.

patients, one RCT recruited high-risk ( $\geq 70$  years) or any-risk ( $\geq 80$  years) patients; and two RCTs recruited all-risk or 'operable' patients. While there was no overall change in the risk of dying from any cause (30 day: RR 0.89, 95% CI 0.65 to 1.22;  $\leq 1$  year: RR 0.90, 95% CI 0.79 to 1.03; 5 years: RR 1.09, 95% CI 0.98 to 1.22), cardiovascular mortality (30 day: RR 1.03, 95% CI 0.77 to 1.39;  $\leq 1$  year: RR 0.90, 95% CI 0.76 to 1.06; 2 years: RR 0.96, 95% CI 0.83 to 1.12);  $\leq 1$  year: RR 0.94, 95% CI 0.72 to 1.23; 5 years: RR 1.07, 95% CI 0.88 to 1.30), the risk of several clinical outcomes was significantly decreased (major bleeding, AKI, NOW-AF) or significantly increased (major vascular complications, PPM implantation) for TAVI vs SAVR. TAVI was associated with a significantly shorter hospital stay vs SAVR (MD  $-3.08$  days, 95% CI  $-4.86$

to -1.29; 4 RCTs, n=2758 participants). Subgroup analysis generally favoured TAVI patients receiving implantation via the transfemoral (TF) route (vs non-TF); receiving a balloon-expandable (vs self-expanding) valve; and those at low-intermediate risk (vs high risk). All RCTs were rated at high ROB, predominantly due to lack of blinding and selective reporting.

**Conclusions** No overall change in the risk of death from any cause or cardiovascular mortality was identified but 95% CIs were often wide, indicating uncertainty. TAVI may reduce the risk of certain side effects while SAVR may reduce the risk of others. Most long-term (5-year) results are limited to older patients at high surgical risk (ie, early trials), therefore more data are required for low risk populations. Ultimately, neither surgical technique was considered dominant, and these results suggest that every patient with SAS should be individually engaged in SDM to make evidence-based, personalised decisions around their care based on the various benefits and risks associated with each treatment.

**PROSPERO registration number** CRD42019138171.

## INTRODUCTION

In the pretranscatheter aortic valve implantation (TAVI) era, patients with severe degenerative symptomatic aortic stenosis (SAS) at high surgical risk had limited access to treatment options, as surgical aortic valve replacement (SAVR) was considered to have an unacceptably elevated risk of complications or death.<sup>1</sup> TAVI was developed as a lower impact, minimally invasive surgical alternative to provide such patients with a much-needed therapeutic option to ameliorate disease symptoms and improve quality of life. TAVI is now being more widely discussed as a useful option for patients at intermediate or even lower levels of surgical risk.

While guidelines do not yet formally recommend TAVI as a first-choice therapy in low-risk patients,<sup>2-4</sup> several new trials have recently reported promising early-term and mid-term data for patients at lower levels of risk. However, current evidence suggests that clinical practice has not yet effectively incorporated TAVI into shared decision making (SDM) processes in patients with SAS who are at lower levels of risk.<sup>5</sup> The use of decision aids in SDM for patients with SAS has been shown to increase patient knowledge and satisfaction.<sup>6</sup> Yet the provision of too little information within decision aids is frequently described by patients as a critical barrier to the SDM process.<sup>5</sup> Therefore, the aim of our systematic review (SR) was to generate a highly accessible and comprehensive dataset that clearly described the current evidence around the risks that may be associated with TAVI versus SAVR.

Several recent SRs and meta-analyses (MAs) have been published that compare patient outcomes following TAVI versus SAVR.<sup>7-9</sup> For example, Barili *et al* and Wang *et al* reported exclusively on all-cause mortality, and indicated similar risks of death for TAVI vs SAVR at early time points<sup>7,8</sup>; Barili *et al* further reported that at late time points (40 months), all-cause mortality was higher for TAVI vs SAVR.<sup>7</sup> In initial consultations carried out in our clinic (which informed the final outcomes investigated by our study), patients indicated that they wanted to consider outcomes beyond the risk of death from any cause. This highlighted a clear need for a SR and MA that included a

broad range of outcomes beyond mortality, and reported results in an accessible way to enable the evidence and conclusions to be used directly in a SDM context. We also identified that extensive subgroup analysis by route of TAVI, level of surgical risk and valve type across all patient outcomes was largely absent in recent SRs and MAs, and yet was considered by our team to be critical, since these three factors can, in large part, be dictated by issues such as patient frailty; anatomical restrictions that limit transfemoral (TF) access, precluding a TF-first approach; and policies and practices that are implemented at either the national or institutional level that govern which valves are available. Finally, we aimed to incorporate new trial data from the UK TAVI study,<sup>10,11</sup> which has not, to our knowledge, been incorporated into any existing MAs.

The ultimate goal of this study was to generate accessible data that could be used by patients, together with their doctors, to make tailored treatment decisions based on the types of benefits and risks they were willing to accept. This SR was performed as part of a wider project to implement a formal decision aid-based SDM process for patients at the University Hospital of Kiel using the most up-to-date, comprehensive and methodologically rigorous evidence available.<sup>12</sup>

## METHODS

This SR was carried out in accordance with the methodologies recommended by Cochrane<sup>13</sup> and the Centre for Reviews and Dissemination<sup>14</sup> following Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines.<sup>15,16</sup>

### Search strategy and selection criteria

In order to identify relevant studies, several databases were searched from January 2000 to August 2020, including MEDLINE, In-Process & Other Non-Indexed Citations, Daily Update, Epub Ahead of Print (Ovid), Embase (Ovid) and Cochrane Central Register of Controlled Trials (CENTRAL; Wiley). The lower search date limit (2000) was set 2 years earlier than the first-in-man report of the TAVI procedure.<sup>17</sup> Searches used a combination of text and database thesaurus terms. The search strategies were adapted to each resource and no limits or restrictions on language or publication status were applied. Reference lists of included articles were searched to identify additional studies. All search strategies are provided in online supplemental appendix S1.

Key inclusion criteria were defined using a Population, Intervention, Comparator, Outcome, Study Design approach. The population of interest was patients with severe aortic valve stenosis. The intervention of interest was TAVI compared with SAVR. Only randomised controlled trials (RCTs) were included to ensure that the conclusions and findings of the review were based on the best available evidence.

Titles and abstracts identified through electronic database and web searching, and subsequently full paper

copies of all potentially eligible references were screened independently by two reviewers; any disagreements were resolved by discussion. No restrictions were placed on language or publication status.

### Data extraction

Microsoft Excel was used to compile data extraction sheets. Data extraction was performed by two reviewers. One reviewer extracted the data while the second reviewer checked the extractions. Any discrepancies were resolved by discussion or the intervention of a third reviewer.

### Outcomes of interest

Primary outcomes included: all-cause or cardiovascular mortality. Secondary outcomes included: length of stay in intensive care unit (ICU) or hospital; valve durability; rehospitalisation/reintervention; stroke (any stroke or major/disabling stroke); myocardial infarction (MI); major vascular complications; major bleeding; permanent pacemaker (PPM) implantation; new-onset or worsening atrial fibrillation (NOW-AF); endocarditis; acute kidney injury (AKI); recovery time and pain. These were included for all time points up to the longest available. Additional methodological details are reported in the online supplemental appendix.

We originally aimed to identify evidence on additional secondary outcomes (including: minor or non-disabling stroke; symptoms such as dyspnoea; 6 min walk test; exercise intensity; exercise duration; impact on activities of daily living; impact on family and carers; health-related quality of life (EQ-5D; KCCQ; SF-12; SF-36); and inconvenience/costs from treatment (eg, need for rehabilitation)), but ultimately had to streamline the final outcomes of interest (after the full-text screening stage) due to budget restraints.

### Risk of bias

The risk of bias (methodological quality) of each included study was assessed using the Cochrane Risk of Bias Tool for RCTs.<sup>18</sup> Risk of bias assessment was performed by one reviewer and checked by a second reviewer. Any discrepancies were resolved by discussion or the intervention of a third reviewer.

### Data synthesis and statistical analysis

All MAs were conducted using random-effects models. Dichotomous outcomes (eg, proportion of patients experiencing each type of outcome) were assessed using the Mantel-Haenszel method applying random-effects models to generate a risk ratio (RR) with 95% CI. Continuous outcomes were assessed using inverse variance applying random-effects models to generate a mean difference with 95% CI. If studies reported time-to-event outcomes, these were planned to be reported as hazard ratios (HRs) with 95% CI; however, this type of data was not identified. The selection of random-effects and fixed-effect models was made based on a judgement of both clinical and statistical heterogeneity.

We further presented our narrative results in an accessible way by calculating the rates from MAs (intervention vs

comparator) and transforming these into absolute numbers (and percentages of these;  $X/100$  (%)) so that patients might be better able to understand them (following the International Patient Decision Aid Standards criteria for patient decision aids).<sup>19</sup> The desire to report our results in a patient-accessible way also informed our choice of effect estimates, since presenting the data in this way would not have been possible with HRs or ORs. For dichotomous outcomes, no evidence of a difference in the effect estimate was set at  $\geq 0.9$  to  $\leq 1.1$ . Statistical significance was considered at  $p \leq 0.05$ . Pooled effect sizes and 95% CIs were only presented where there were two or more trials that were considered to be clinically and statistically homogeneous. The judgement of clinical heterogeneity was based on baseline characteristics of the trial populations (eg, age, gender). Statistical heterogeneity was assessed using the  $I^2$  statistic. For the purposes of this review, a simplified categorisation of heterogeneity was used: low (0% to 25%), moderate (26% to 75%) and high ( $>75\%$ ). Sensitivity analyses were considered in cases where high statistical or clinical heterogeneity was present.

We preferentially used the intention-to-treat (ITT) population, where reported. For major bleeding, we preferentially used the definition of 'life-threatening or disabling bleeding', where available. For AKI, we preferentially used the definition, 'stage 2–3 AKI', where available. All MAs were double-checked by a second reviewer. Forest plots for the main analyses were grouped by the stated study risk level, as defined by the study inclusion criteria; subgroup analyses by level of surgical risk were based exclusively on Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) scores within each study.

Subgroup analysis was prespecified based on TAVI route (TF vs non-TF), level of surgical risk (based on absolute STS-PROM scores) and valve type (balloon vs self-expanding).

All MAs were performed using Review Manager V.5.3. Publication bias was planned to be assessed where there were sufficient numbers of trials (ie, a minimum of ten trials), in line with published recommendations.<sup>20</sup>

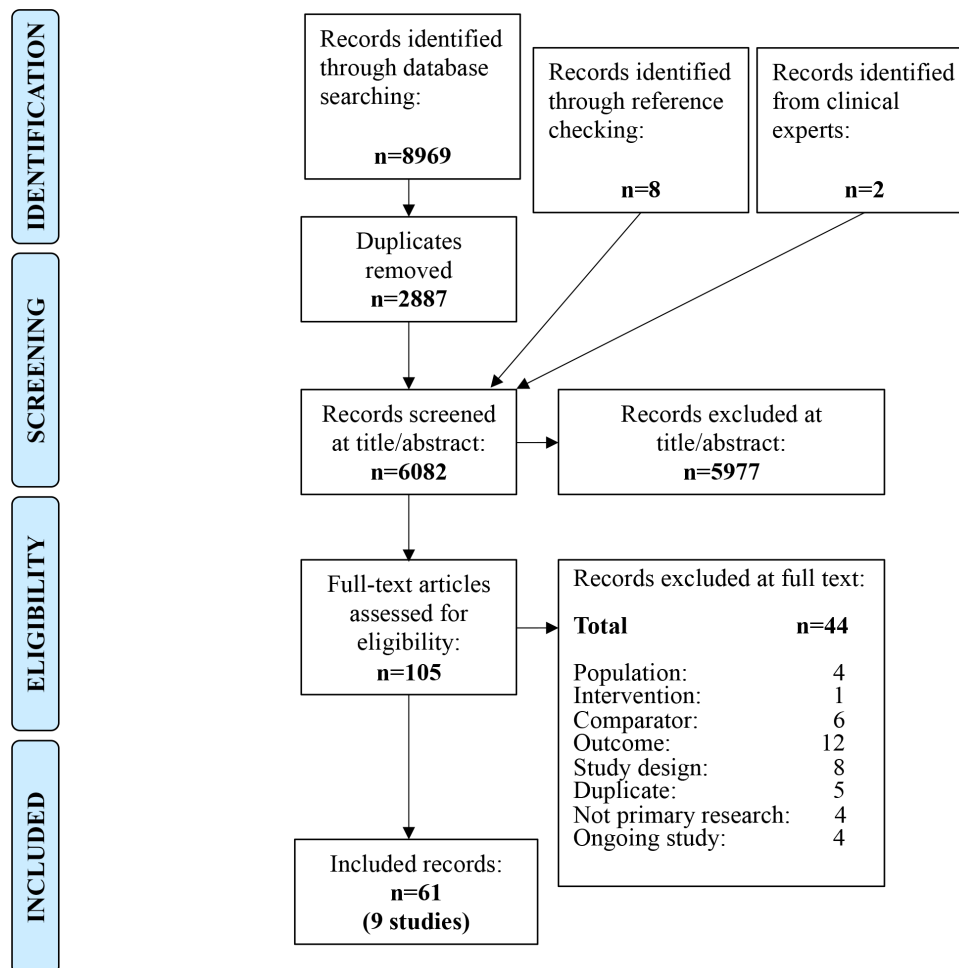
### Patient and public involvement

Patients were involved in an initial needs assessment based on their priorities and experience, which ultimately evolved into our prespecified outcomes of interest. Patients were not involved in the formal design, conduct, analysis or reporting of this study.

## RESULTS

### Search results

We searched three main databases, and retrieved a total of 8969 records. Eight additional records were identified from reference checking included studies, and two records were identified by clinical experts. After deduplication, 6082 records remained. The flow of studies through the search and screening processes is summarised in [figure 1](#).



**Figure 1** PRISMA study flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

In total, 6082 records were screened based on the title and abstracts; 105 were ordered for full text screening and 5977 were excluded. After the full-text screening stage, 61 records (9 studies) were identified for inclusion in the review.

#### Baseline characteristics of included studies

Nine RCTs (61 records; most studies had more than one associated publication) with a total of 8818 patients were identified that fit the inclusion criteria (table 1). Inclusion and exclusion criteria are provided in online supplemental table S1. Primary and secondary outcomes are provided in online supplemental table S2.

In terms of the disease of interest, all nine studies reported recruiting patients with SAS (table 1, online supplemental table S3). In terms of the level of surgical risk at the study level (which was based on the multifaceted, study-specific definitions provided in online supplemental table S3), two studies reported recruiting low-risk patients (EVOLUT, PARTNER 3), two studies reported recruiting intermediate-risk patients (PARTNER 2A, SURTAVI), two studies reported recruiting high-risk patients (PARTNER 1A, US CoreValve), one study reported recruiting intermediate-to-high-risk ( $\geq 70$  years) or any risk ( $\geq 80$  years) patients (UK-TAVI), one

study reported recruiting patients across all levels of risk (NOTION) and one study simply reported that patients should be 'operable' (STACCATO) (table 1, online supplemental table S3). The definitions of surgical risk varied substantially between studies (online supplemental table S3). In terms of the valve type, four of nine studies (50%) reported using a self-expanding valve, four of nine studies (50%) reported using a balloon-expandable valve, and one of nine studies reported using any type of CE-marked valve (table 1).

#### Publication bias

It was not possible to assess publication bias due to the relatively small number of included studies ( $<10$ ).<sup>20</sup>

#### Risk of bias assessment

All nine studies were assessed for risk of bias using the Cochrane risk of bias tool for RCTs, which contains eight assessment domains.<sup>13</sup> Two studies had five domains at high risk of bias (SURTAVI, UK TAVI); five studies had four domains at high risk of bias (NOTION, PARTNER 1A, PARTNER 2A, PARTNER 3, STACCATO); and two studies had three domains at high risk of bias (EVOLUT, US CoreValve) (table 2). All studies were rated at high risk of bias for blinding

**Table 1** Study characteristics

Study ID*, linked publications	Recruit-ment dates	Total sample size	Disease	Patient age (years)†	Level of surgical risk‡	TAVI route	Valve type(s)	Valve name	Funding source
<b>High risk</b>									
PARTNER 1A <sup>26-35</sup> 59-67	May 2007 to Aug 2009	699	SAS and cardiac symptoms	Not prespecified TAVI: 83.6 (6.8) SAVR: 84.5 (6.4)	TAVI: 11.8 (3.3); SAVR: 11.7 (3.5)	TF-first; TA if vascular access was limited	Balloon-expandable	Edwards Sapien	Pharma (EW)
US CoreValve <sup>68-8123</sup>	Feb 2011 to Sep 2012	797	SAS and heart failure symptoms	No limits TAVI: 83.1 (7.1) SAVR: 83.2 (6.4)	TAVI: 7.3 (3.0); SAVR: 7.5 (3.4)	TF or non-TF (SC or direct aortic)	Self-expanding	MDT CoreValve	Pharma (MDT)
<b>High-intermediate risk</b>									
UK TAVI <sup>11</sup> ¶	Apr 2014 to Apr 2018	913	Symptomatic SAS	≥80 or ≥70† TAVI: 81.1 (4.4) SAVR: 81.0 (4.5)	TAVI: 2.6 (2.0 to 3.5); SAVR: 2.7 (2.0 to 3.4)§	TF, TA, SC, direct aortic	Any CE-marked valve	SAPIEN, SAPIEN XT; SAPIEN 3 (all EW); CoreValve, Evolut/ Evolut R, Evolut Pro (all MDT); Lotus, Symetis Acurate/Neo (all BSX); Other (Portico, Direct Flow Medical)	Public/government (NIHR)
<b>Intermediate risk</b>									
PARTNER 2 A2134 <sup>21</sup> 34-82-83	Dec 2011 to Nov 2013	2032	SAS	No limits TAVI: 81.5 (6.7) SAVR: 81.7 (6.7)	TAVI: 5.8 (2.1); SAVR: 5.8 (1.9)	TF or transthoracic (TA or TAO)	Balloon-expandable	SAPIEN XT (EW)	Pharma (EW)
SURTAVI <sup>25-84-92</sup>	Jun 2012 to Jun 2016	1660	Symptomatic SAS	No limits TAVI: 79.9 (6.2) SAVR: 79.7 (6.1)	TAVI: 4.4 (1.5); SAVR: 4.5 (1.6)	TF-first; SC or TAO in the case of unsuitable iliofemoral anatomy	Self-expanding	CoreValve, Evolut R (all MDT)	Pharma (MDT)
<b>Low risk</b>									
EVOLUT <sup>24-93</sup>	Mar 2016 to Nov 2018	1468	SAS	No limits TAVI: 74.0 (5.9) SAVR: 73.8 (6.0)	TAVI: 1.9 (0.7); SAVR: 1.9 (0.7)	TF, subclavian or TAO	Self-expanding	CoreValve, Evolut R, Evolut PRO (all MDT)	Pharma (MDT)
PARTNER 3 <sup>22-94-97</sup>	Mar 2016 to Oct 2017	950	SAS	No limits TAVI: 73.3 (5.8) SAVR: 73.6 (6.1)	TAVI: 1.9 (0.7); SAVR: 1.9 (0.6)	TF	Balloon-expandable	SAPIEN 3 (EW)	Pharma (EW)
<b>All risk</b>									
NOTION <sup>25-98-105</sup>	Dec 2009 to Apr 2014	280	Degenerative SAS	≥70 TAVI: 79.2 (4.9) SAVR: 79.0 (4.7)	TAVI: 2.9 (1.6); SAVR: 3.1 (1.7)	TF-first; left SC access considered when the TF route not accessible	Self-expanding	CoreValve (MDT)	Charity (The Danish Heart Foundation)
STACCATO <sup>27-106-107</sup>	Nov 2008 to May 2011	70	SAS	Initially ≥70; later modified to ≥75 TAVI: 80 (3.6) SAVR: 82 (4.4)	'Operable' TAVI: 3.1 (1.5); SAVR: 3.4 (1.2)	TA	Balloon-expandable	Edwards Sapien	Public/government (University, DHF)

All studies are randomised controlled trials, as per our inclusion criteria.

\*Main publication provided.

†Mean (SD) are provided.

‡STS-PROM scores are provided (mean (SD)).

§Median and IQR.

¶If patients are considered at intermediate or high operative risk from conventional AVR by a multidisciplinary heart team.

AWR, aortic valve replacement; BSX, Boston Scientific; CE, Conformité européenne; DHF, Danish Heart Foundation; EW, Edward Lifesciences; MDT, Medtronic; NA, not applicable; NIHR, National Institute for Health Research; NYHA, New York Heart Association; SAS, severe aortic stenosis; SAVR, surgical aortic valve replacement; SC, subclavian; STS, society for thoracic surgeons; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TA, transcatheter aortic valve implantation; TF, transfemoral.

Table 2 Risk of bias assessment

Study ID	Level of surgical risk	Randomisation	Allocation concealment	Are participants blinded?	Are personnel blinded?	Blinding of assessors	Incomplete outcome data	Selective reporting	Other biases	N High	N Low	N Unclear
PARTNER 1 A <sup>26</sup>	High	Low	Unclear	High	High	Unclear	Low	High	High	4	2	2
US CoreValve <sup>23</sup>	High	Low	Unclear	High	High	Unclear	Low	Low	High	3	3	2
PARTNER 2 A <sup>21</sup>	Intermediate	Low	Unclear	High	High	Unclear	Low	High	High	4	2	2
SURTAVI <sup>28</sup>	Intermediate	Low	Unclear	High	High	High	Low	High	High	5	2	1
EVOLUT <sup>24</sup>	Low	Low	Unclear	High	High	Low	Low	Low	High	3	4	1
PARTNER 3 <sup>22</sup>	Low	Low	Unclear	High	High	Unclear	Low	High	High	4	2	2
UK TAVI <sup>10</sup>	Intermediate-high ( $\geq 70$ y) or any ( $\geq 80$ years)	Low	Unclear	High	High	High	Low	High	High	5	2	1
NOTION <sup>25</sup>	All	Low	Low	High	High	Low	Low	High	High	4	4	0
STACCATO <sup>27</sup>	'Operable'	Low	Unclear	High	High	Unclear	High	Low	High	4	2	2

TAVI, transcatheter aortic valve implantation.

of participants, blinding of personnel and other biases. Other biases were typically based on a disparity between the number of patients randomised versus the number of patients implanted per treatment arm (where a greater proportion of TAVI patients tended to receive their assigned implant compared with SAVR patients) or a disparity between the numbers of patients who crossed over per treatment arm.

### Clinical outcomes

A visual overview of all main results is presented in figure 2, and a tabular overview of all main results is presented in table 3.

### Mortality

#### All-cause mortality

The risk of dying from any cause either within the periprocedural period (which was typically defined as before, during or soon after surgery) or during the in-hospital stay was numerically increased by 16% for TAVI compared with SAVR (RR 1.16, 95% CI 0.52 to 2.27,  $p=0.67$ ,  $I^2$  0%; 3 studies,  $n=3732$  patients<sup>21-23</sup>); however, this was not a statistically significant difference (figure 3). No heterogeneity was evident in this analysis.

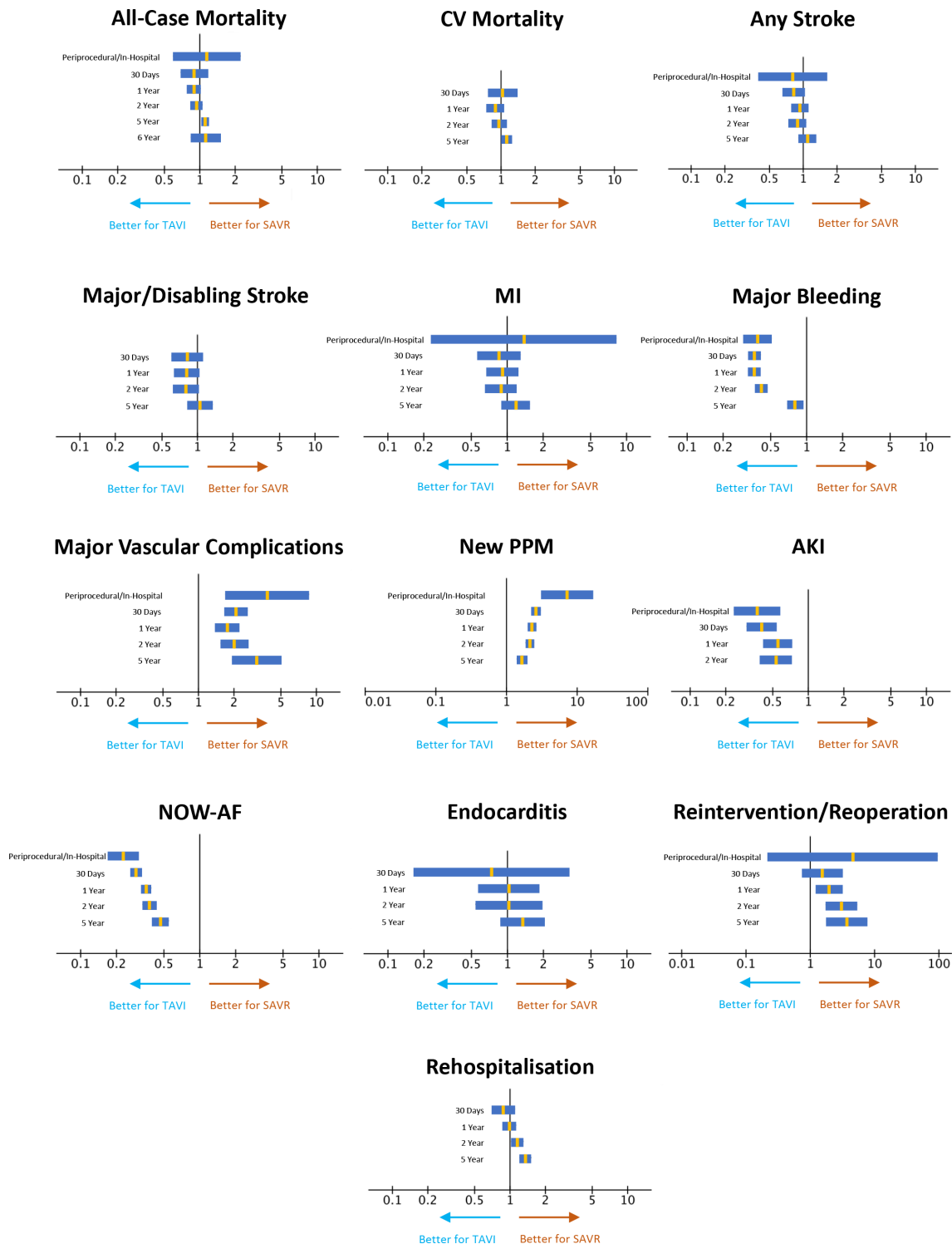
The risk of dying from any cause by 30 days following surgery was numerically decreased by 15% for TAVI compared with SAVR (RR 0.89, 95% CI 0.65 to 1.22,  $p=0.48$ ,  $I^2$  14%; 9 studies,  $n=8873$  patients<sup>10 21-28</sup>); however, this was not a statistically significant difference. Heterogeneity was moderate for intermediate-risk and all-risk studies at 30 days.

There was no evidence of a difference in the overall risk of dying from any cause by 1 year following surgery (RR 0.90, 95% CI 0.79 to 1.03,  $p=0.13$ ,  $I^2$  0%; 9 studies,  $n=8936$  patients<sup>10 21-28</sup>) by 2 years (RR 0.95, 95% CI 0.85 to 1.06,  $p=0.38$ ,  $I^2$  0%; 8 studies,  $n=6648$  patients<sup>21-28</sup>) or by 5 years (RR 1.09, 95% CI 0.98 to 1.22,  $p=0.10$ ,  $I^2$  48%; 5 studies,  $n=3866$  patients<sup>21 23 25-27</sup>). Heterogeneity was moderate at 2 years and 5 years in high-risk studies.

At 6 years following surgery, a single small study reported that the risk of dying from any cause was numerically increased by 12% for all-risk TAVI patients compared with all-risk SAVR patients (RR 1.12, 95% CI 0.84 to 1.50,  $p=0.43$ ,  $I^2$  N/A; 1 study,  $n=274$ <sup>25</sup>); however, this was not a statistically significant difference. Across study risk groups (defined by the criteria reported in online supplemental table S3, which were not exclusively based on STS-PROM scores), the CIs overlapped between each group at all time points, suggesting no significant difference between study risk groups (figure 3).

#### Cardiovascular mortality

There was no evidence of a difference in the risk of dying from cardiovascular or cardiac causes for TAVI compared with SAVR by 30 days following surgery (RR 1.03, 95% CI 0.77 to 1.39,  $p=0.83$ ,  $I^2$  0%; 8 studies,  $n=8803$  patients<sup>10 21-26 28</sup>), by 1 year (RR 0.90, 95% CI 0.76 to 1.06,  $p=0.20$ ,  $I^2$  0%; 8 studies,  $n=8831$  patients<sup>10 21-26 28</sup>) or by



**Figure 2** Visual summary of key findings over time. The blue bars represent the uncertainty in the result (wide bars mean more uncertainty) while the yellow bars represent the relative risk. A yellow bar to the right of 1 means that the risk of the outcome is lower for SAVR, while a yellow bar to the left of 1 means that the risk of the outcome is lower for TAVI. If the yellow and blue bars are all to the left of 1, this means that the result is statistically significant in favour of TAVI. If the yellow and blue bars are all to the right of 1, this means that the result is statistically significant in favour of SAVR. AKI, acute kidney injury; CV, cardiovascular; MI, myocardial infarction; NOW-AF, new-onset or worsening atrial fibrillation; PPM, permanent pacemaker; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

2 years (RR 0.96, 95% CI 0.83 to 1.12,  $p=0.61$ ,  $I^2$  0%; 5 studies,  $n=5503$  patients<sup>21 23 25 26 28</sup>) (figure 4). Heterogeneity was low at 30 days and moderate for high-risk studies at 1 and 2 years.

By 5 years following surgery, the overall risk of dying from cardiovascular or cardiac causes was significantly increased by 11% for TAVI compared with SAVR (RR 1.11, 95% CI 1.01 to 1.23,  $p=0.04$ ,  $I^2$  0%; 4 studies,  $n=3761$

**Table 3** Summary of key findings

Outcome	In-hospital/periprocedural (RR (95% CI))	30 days (RR (95% CI))	1 year (RR (95% CI))	2 years (RR (95% CI))	5 years (RR (95% CI))
All-cause mortality	Favours SAVR 1.16 (0.59 to 2.27; 3 studies, n=3732)	Favours TAVI 0.89 (0.65 to 1.22; 9 studies, n=8873)	No difference 0.90 (0.79 to 1.03; 9 studies, n=8936)	No difference 0.95 (0.85 to 1.06; 8 studies, n=6648)	No difference 1.09 (0.98 to 1.22; 5 studies, n=3866)
Cardiovascular mortality	NR	No difference 1.03 (0.77 to 1.39; 8 studies, n=8803)	No difference 0.90 (0.76 to 1.06; 8 studies, n=8831)	No difference 0.96 (0.83 to 1.12; 5 studies, n=5503)	<b>Favours SAVR 1.11 (1.01 to 1.23; 4 studies, n=3761)</b>
All stroke	Favours TAVI 0.80 (0.40 to 1.62; 1 study, n=750)	Favours TAVI 0.83 (0.61 to 1.14; 9 studies, n=8873)	No difference 0.94 (0.72 to 1.23; 8 studies, n=8831)	Favours TAVI 0.88 (0.67 to 1.16; 6 studies, n=6453)	No difference 1.07 (0.88 to 1.30; 4 studies, n=3761)
Major or disabling stroke	NR	Favours TAVI 0.85 (0.56 to 1.29; 7 studies, n=7712)	Favours TAVI 0.80 (0.53 to 1.20; 6 studies, n=7642)	Favours TAVI 0.79 (0.60 to 1.04; 4 studies, n=4665)	No difference 1.05 (0.82 to 1.34; 2 studies, n=2782)
Myocardial infarction	Favours SAVR 1.38 (0.23 to 8.20; 1 study, n=750)	Favours TAVI 0.84 (0.55 to 1.28; 9 studies, n=8877)	No difference 0.92 (0.68 to 1.25; 9 studies, n=8901)	No difference 0.91 (0.68 to 1.23; 6 studies, n=6453)	No difference 1.08 (0.73 to 1.61; 4 studies, n=3761)
Major bleeding	<b>Favours TAVI 0.41 (0.28 to 0.60; 2 studies, n=1026)</b>	<b>Favours TAVI 0.37 (0.21 to 0.64; 8 studies, n=8446)</b>	<b>Favours TAVI 0.38 (0.31 to 0.48; 6 studies, n=6744)</b>	<b>Favours TAVI 0.46 (0.34 to 0.64; 3 studies, n=3481)</b>	<b>Favours TAVI 0.80 (0.69 to 0.93; 2 studies, n=1449)</b>
Major vascular complications	<b>Favours SAVR 3.83 (1.69 to 8.67; 2 studies, n=1026)</b>	<b>Favours SAVR 2.42 (1.55 to 3.80; 7 studies, n=8376)</b>	<b>Favours SAVR 2.05 (1.38 to 3.04; 6 studies, n=6744)</b>	<b>Favours SAVR 2.39 (1.36 to 4.18; 3 studies, n=3480)</b>	<b>Favours SAVR 3.14 (1.95 to 5.07; 2 studies, n=1449)</b>
Permanent pacemaker implantation	<b>Favours SAVR 7.19 (3.11 to 16.62; 1 study, n=750)</b>	<b>Favours SAVR 2.47 (1.55 to 3.93; 7 studies, n=7767)</b>	<b>Favours SAVR 2.23 (1.44 to 3.46; 7 studies, n=7767)</b>	<b>Favours SAVR 2.11 (1.31 to 3.42; 6 studies, n=6367)</b>	<b>Favours SAVR 1.90 (1.14 to 3.16; 4 studies, n=3761)</b>
Acute kidney injury	Favours TAVI 0.30 (0.10 to 0.93; 2 studies, n=1026)	Favours TAVI 0.40 (0.30 to 0.53; 6 studies, n=7441)	Favours TAVI 0.58 (0.34 to 1.00; 4 studies, n=4831)	Favours TAVI 0.52 (0.33 to 0.80; 2 studies, n=2782)	NR
New-onset or worsening atrial fibrillation	<b>Favours TAVI 0.23 (0.06 to 0.91; 2 studies, n=1536)</b>	<b>Favours TAVI 0.29 (0.23 to 0.38; 7 studies, n=7767)</b>	<b>Favours TAVI 0.36 (0.28 to 0.47; 7 studies, n=7767)</b>	<b>Favours TAVI 0.36 (0.25 to 0.52; 4 studies, n=4008)</b>	<b>Favours TAVI 0.45 (0.36 to 0.56; 2 studies, n=2312)</b>
Endocarditis	NR	Favours TAVI 0.79 (0.21 to 3.04; 6 studies, n=6310)	No difference 1.02 (0.55 to 1.89; 7 studies, n=7088)	No difference 0.99 (0.43 to 2.24; 4 studies, n=4431)	Favours SAVR 1.34 (0.87 to 2.05; 4 studies, n=3761)
Reintervention/reoperation	Favours SAVR 4.59 (0.22 to 95.32; 1 study, n=750)	Favours SAVR 1.54 (0.50 to 4.77; 6 studies, n=7828)	Favours SAVR 1.95 (0.92 to 4.13; 6 studies, n=7856)	<b>Favours SAVR 2.78 (1.35 to 5.71; 4 studies, n=5478)</b>	<b>Favours SAVR 3.67 (1.76 to 7.63; 3 studies, n=3062)</b>

Continued



Table 3 Continued

Outcome	In-hospital/periprocedural (RR (95% CI))	30 days (RR (95% CI))	1 year (RR (95% CI))	2 years (RR (95% CI))	5 years (RR (95% CI))
Rehospitalisation	NR	Favours TAVI 0.88 (0.70 to 1.10; 6 studies, n=7645)	No difference 0.95 (0.76 to 1.20; 6 studies, n=7645)	Favours SAVR 1.14 (0.94 to 1.38; 5 studies, n=6177)	<b>Favours SAVR 1.35 (1.20 to 1.51; 3 studies, n=3481)</b>
Length of hospital stay	<b>Favours TAVI* -3.08 days (-4.86 to -1.29; 4 studies, n=2758)</b>	NA	NA	NA	NA
Valve durability	NR	NR	NR	NR	NE†
Recovery time	NR	NR	NR	NR	NR
Pain	NR	NR	NR	NR	NR

Values in bold that are coloured blue (favours TAVI) or yellow (favours SAVR) represent statistically significant ( $p < 0.05$ ) results.

\*Mean difference.

†Three studies reported on this outcome, but one reported zero events in both arms (ie, could not be incorporated into a RR).

NA, not applicable; NE, not estimable; NR, not reported; RR, risk ratio; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

patients).<sup>21 23 25 26</sup> Heterogeneity was low at 5 years. By study risk group (defined by the criteria reported in online supplemental table S3), which were not exclusively based on STS-PROM scores), the CIs overlapped between each group at all time points, suggesting no significant difference between study risk groups (figure 4).

#### All stroke

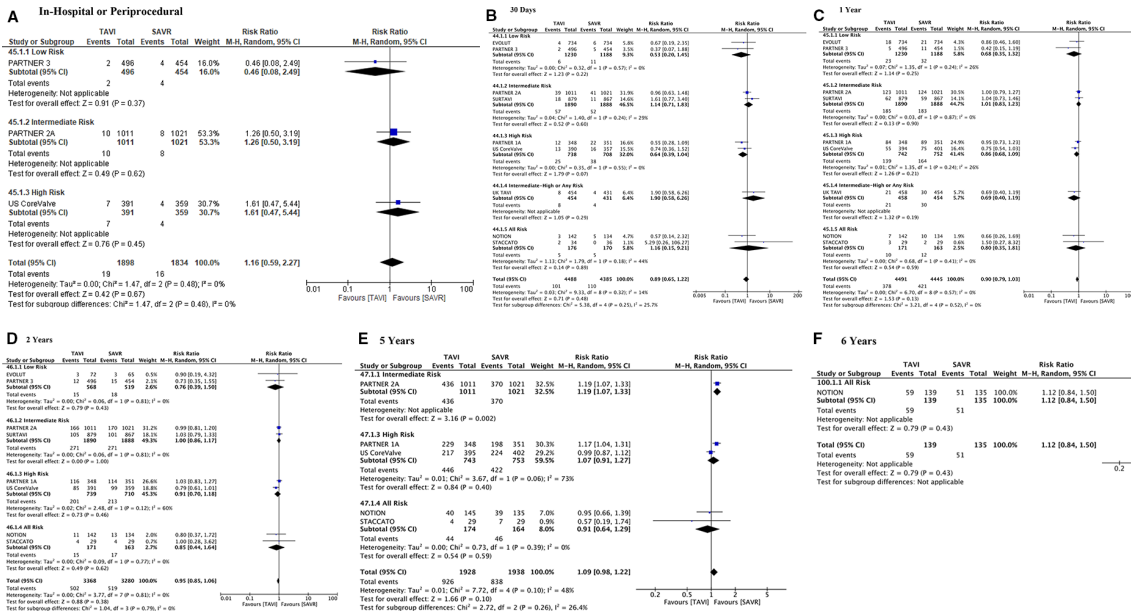
A single study reported that the risk of having any type of stroke at periprocedural time points was numerically decreased by 20% for TAVI compared with SAVR (RR 0.80, 95% CI 0.4 to 1.62,  $p=0.54$ ,  $I^2$  N/A; 1 study,  $n=750$  patients<sup>23</sup>); however, this was not a statistically significant difference (figure 5).

The risk of having any type of stroke was numerically decreased by 18% for TAVI compared with SAVR by 30 days following surgery (RR 0.83, 95% CI 0.61 to 1.14,  $p=0.26$ ,  $I^2$  36%; 9 studies,  $n=8873$  patients<sup>10 21-28</sup>) and by 12% by 2 years (RR 0.88, 95% CI 0.67 to 1.16,  $p=0.37$ ,  $I^2$  48%; 6 studies,  $n=6,453$  patients<sup>21-23 25 26 28</sup>); however, these differences were not statistically significant.

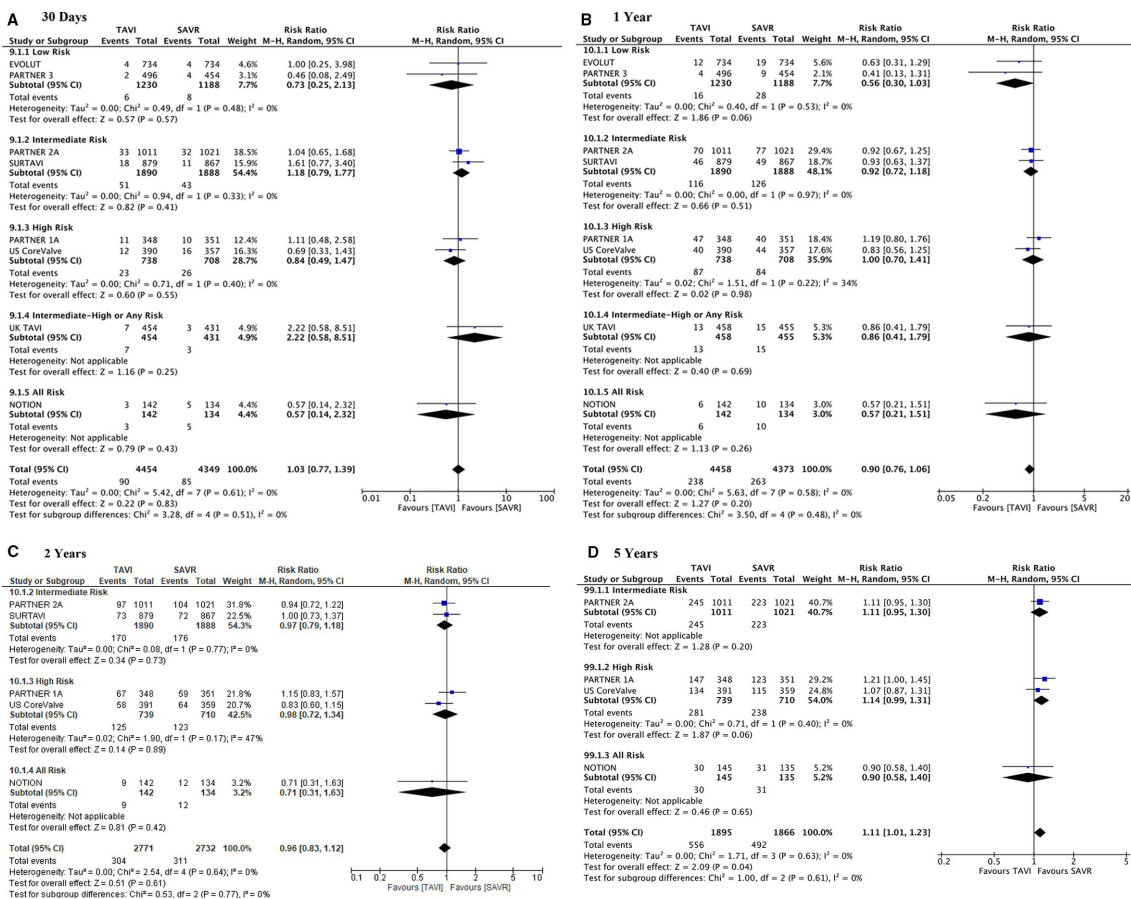
There was no evidence of a difference in the risk of having any type of stroke by 1 year following surgery (RR 0.94, 95% CI 0.72 to 1.23,  $p=0.65$ ,  $I^2$  48%; 8 studies,  $n=8831$  patients<sup>10 21-26 28</sup>) or by 5 years (RR 1.07, 95% CI 0.88 to 1.30,  $p=0.51$ ,  $I^2$  11%; 4 studies,  $n=3761$  patients).<sup>21 23 25 26</sup> Heterogeneity was moderate at 30 days, at 1 year; high for high-risk studies and moderate for intermediate-risk studies at 2 years; and low at 5 years. By study risk group (defined by the criteria reported in online supplemental table S3, which were not exclusively based on STS-PROM scores), the CIs overlapped between each group at all time points, suggesting no significant difference in the risk of all stroke between study risk groups (figure 5).

#### Other outcomes

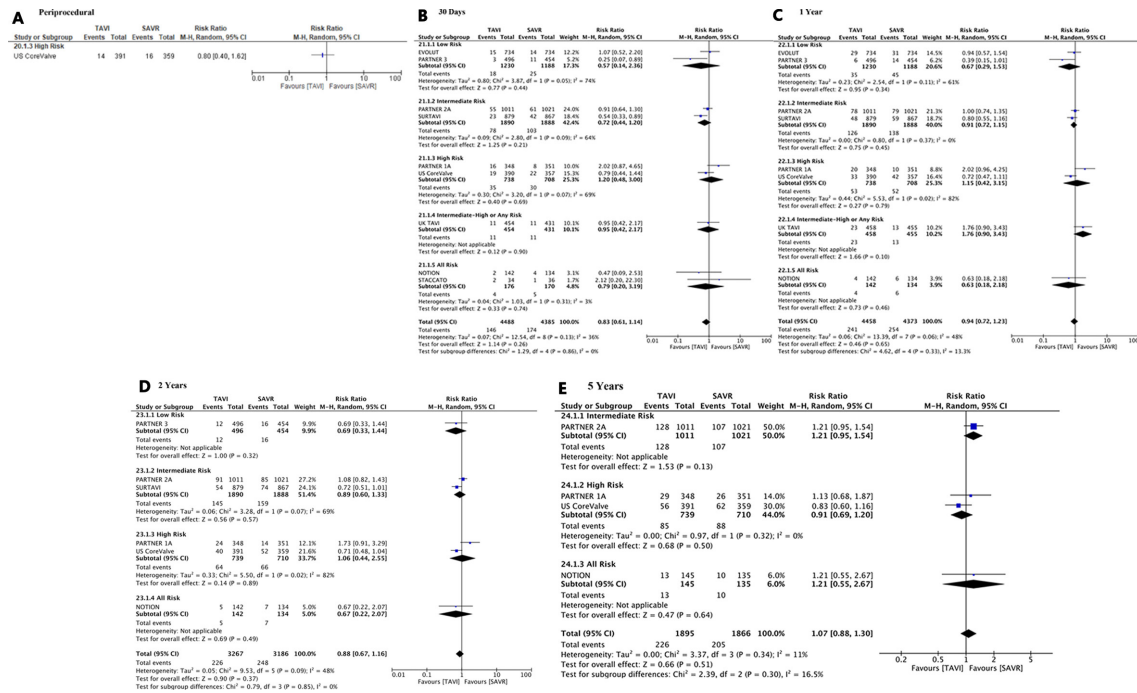
The risk of major or disabling stroke was numerically decreased by 15%–21% for TAVI compared with SAVR between 30 days to 2 years following surgery (although this was not a statistically significant difference); there was no evidence of a difference in risk at 5 years (online supplemental figure 1). The risk of MI was numerically increased by 38% at periprocedural time points, but numerically decreased by 16% at 30 days following surgery; there was no evidence of a difference in risk of MI between 1 and 5 years following surgery (online supplemental figure 2). The risk of major bleeding was significantly decreased by between 20% and 63% for TAVI compared with SAVR at all time points between periprocedural and 5 years following surgery (online supplemental figure 3; sensitivity analysis based on definition of major bleeding presented in online supplemental figure 4). The risk of major vascular complications was significantly increased by between 205% and 383% for TAVI compared with SAVR at all time points between periprocedural and 5 years following surgery (online supplemental figure 5). The risk of PPM implantation was significantly increased by between 190% and 719%



**Figure 3** Forest plots for death from any cause. (A) In-hospital or periprocedural, (B) 30 days, (C) 1 year, (D) 2 years, (E) 5 years, and (F) 6 years time points are presented. Risk subgroups represent the study risk level and not necessarily the patient risk level. M-H, Mantel-Haenszel; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.



**Figure 4** Forest plots for death from cardiovascular causes. (A) 30 days, (B) 1 year, (C) 2 years and (D) 5 years time points are presented. Risk subgroups represent the study risk level and not necessarily the patient risk level. M-H, Mantel-Haenszel; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.



**Figure 5** Forest plots for any stroke. (A) Periprocedural, (B) 30 days, (C) 1 year, (D) 2 years and (E) 5 years time points are presented. Risk subgroups represent the study risk level and not necessarily the patient risk level. M-H, Mantel-Haenszel; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

for TAVI compared with SAVR at all time points between periprocedural and 5 years following surgery (online supplemental figure 6). The risk of AKI was significantly decreased by between 42% and 70% for TAVI compared with SAVR at all time points between periprocedural time points and 2 years following surgery (online supplemental figure 7). The risk of NOW-AF was significantly decreased by between 55% and 77% for TAVI compared with SAVR for all time points between periprocedural and 5 years following surgery (online supplemental figure 8). The risk of endocarditis varied between being numerically reduced (30 days), no different (1 year, 2 years, 6 years) or numerically increased (5 years) for TAVI compared with SAVR (online supplemental figure 9). The risk of reintervention or reoperation was numerically increased by 154%–459% for TAVI versus SAVR from periprocedural time points up to 1 year following surgery; and was significantly increased by 278% for TAVI vs SAVR by 2 years following surgery (online supplemental figure 10). The risk of rehospitalisation varied between being numerically reduced (30 days), no different (1 year), numerically increased (2 years) or significantly increased (5 years) for TAVI compared with SAVR (online supplemental figure 11). The length of stay in the ICU and the overall length of hospital stay were generally shorter for TAVI compared with SAVR (online supplemental figure 12, tables S4 and S5).

### Subgroup analysis

For the primary outcome of all-cause mortality, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone)

had a significantly lower risk of dying from any cause after TAVI compared with patients at high risk from 1 to 5 years following surgery (online supplemental table S6); and that patients who had TAVI through the TF route had a significantly lower risk of dying from any cause compared with patients who had TAVI through a non-TF route from 30 days to 5 years following surgery (online supplemental table S7).

For the primary outcome of cardiovascular mortality, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone) had a significantly higher risk of dying from cardiovascular causes after TAVI compared with patients at high risk by 1 year following surgery (online supplemental table S6); and that patients who had TAVI through the TF route had a significantly lower risk of dying from cardiovascular causes than patients who had TAVI through a non-TF route from 30 days to 5 years following surgery (online supplemental table S7). Results for the subgroup analysis by valve type for the outcome ‘new PPM implantation’ are presented in online supplemental table S8, showing higher rates for self-expanding TAVI compared with balloon expandable TAVI.

For any-stroke outcomes, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone) had a significantly higher risk of any type of stroke after TAVI compared with patients at high risk by 1 year following surgery (online supplemental table S6); and that patients who had TAVI through the TF route had a lower risk of any type of stroke than patients who had TAVI through

a non-TF route from 30 days to 5 years following surgery (online supplemental table S7).

Valve durability of the two treatments was comparable. However, NOTION reported a statistically significantly lower rate of moderate/severe haemodynamic structural valve deterioration after 6 years follow-up, see online supplemental table S9.

### Sensitivity analysis

As we noted an inconsistency in how studies reported subgroup data by level of surgical risk, we performed sensitivity analyses to address this. Most studies reported two subgroups based on low-intermediate vs high risk (NOTION (STS <4 vs STS ≥4); PARTNER 1A (STS ≤11 vs STS >11); US CoreValve (STS-PROM ≤7 vs STS-PROM >7); however, one study reported three subgroups based on low-risk, intermediate-risk and high-risk (SURTAVI (STS <3% vs STS ≥3% to <5% vs STS ≥5%). Therefore, we combined low-risk and intermediate-risk groups to make the data more comparable across studies.

To test whether this affected the outcome, we performed sensitivity analyses where we assigned subgroups to low vs high instead of low-intermediate versus high for the SURTAVI study. For most outcomes, this did not change the direction of the effect or push the result into or out of significance. However, for reintervention/reoperation, the comparison of low versus high was significant (RR 5.79, 95% CI 1.19 to 28.31,  $p=0.03$ ; 1 study,  $n=384$  patients<sup>28</sup>) whereas the comparison of low-intermediate versus high was not (RR 3.11, 95% CI 0.72 to 13.48,  $p=0.13$ ; 1 study,  $n=864$  patients).<sup>28</sup> Conversely, for all stroke, the comparison of low-intermediate versus high was significant (RR 0.54, 95% CI 0.31 to 0.97,  $p=0.04$ ; 1 study,  $n=864$  patients<sup>28</sup>) whereas the comparison of low vs high was not (RR 0.51, 95% CI 0.19 to 1.33,  $p=0.17$ ; 1 study,  $n=384$  patients).<sup>28</sup> Similarly, for PPM implantation, the comparison of low-intermediate versus high was significant (RR 1.41, 95% CI 1.08 to 1.83,  $p=0.01$ ; 1 study,  $n=864$  patients<sup>28</sup>) whereas the comparison of low versus high was not (RR 1.12, 95% CI 0.77 to 1.65,  $p=0.55$ ; 1 study,  $n=384$  patients).<sup>28</sup>

## DISCUSSION

### Strengths and limitations

SDM is a critical form of professional–patient interaction that enables patients to make informed and uniquely personal decisions on their own care using evidence-based medical information. SRs and MAs provide important evidence to inform and generate a comprehensive overview pertaining to a particular research question, and therefore may naturally feed into decision aids and SDM-based patient–physician communication. This SR includes data from a new study (UK TAVI), plus long-term data from several other studies (EVOLUT, PARTNER 2, PARTNER 3). Our MAs have revealed several critical differences in clinical outcomes for TAVI compared with SAVR that should be highlighted and carefully considered

when patients, together with their physicians, are making decisions regarding treatment options for SAS.

While the STACCATO trial was terminated early due to safety concerns, we nevertheless included these data in our analysis as the study met our inclusion/exclusion criteria. This is in line with the approaches of several other SRs.<sup>29–33</sup> We performed sensitivity analyses to test whether the inclusion of the STACCATO study impacted any main analyses; this did not change the direction or statistical significance of any results (data not shown).

Regarding study-level surgical risk, the two high-risk studies included in our analyses (PARTNER 1A, US CoreValve) recruited elderly (mean age >83 years) patients at increased risk of intraoperative death or death within 30 days of the procedure. These risk levels were further elevated by including high proportions of patients who had undergone previous coronary artery bypass graft (CABG) surgeries in the SAVR arms of both studies (44.2% (PARTNER 1A) or 30.2% (US CoreValve)). The two intermediate-risk studies included in our analyses (PARTNER 2A, SURTAVI) might be expected to produce more representative results based on recruiting larger numbers of slightly younger patients (mean age >79 years), fewer of whom in the SAVR arm had previously undergone CABG (25.6% (PARTNER 2A) or 16.7% (SURTAVI)). The results from the two low-risk studies included in our analyses (EVOLUT, PARTNER 3), which recruited relatively young patients (mean age >73 years), are of key interest to the field. While these studies actively excluded patients with prior cardiac surgery, they nevertheless included patients who underwent concomitant surgical procedures (26.4% (PARTNER 3) or 13.6% (EVOLUT)). Therefore, in all studies, the inclusion of patients who had undergone prior cardiac procedures may have introduced bias (or at least clinical heterogeneity) that may have been disadvantageous to the SAVR arm, as surgical redo aortic valve procedures typically confer a higher risk of mortality compared with primary surgeries, a difference that does not manifest *per se* in patients receiving the TAVI procedure.

No overall change in the risk of death from any cause was identified for TAVI compared with SAVR; however, CIs around the point estimates for low risk and all-risk studies were often wide, which introduced substantial uncertainty. Follow-up duration is currently relatively short for low-risk studies, and longer-term data will be of great relevance to future updates of this review. For example, 5-year all-cause mortality data have recently been published for the intermediate-risk PARTNER 2A study,<sup>34</sup> however, 5-year data for the intermediate-risk SURTAVI study are still outstanding. A significant increase was observed in the risk of dying from cardiovascular or cardiac causes for TAVI vs SAVR at 5 years.

Of note, TAVI was associated with a significantly lower risk of major bleeding, NOW-AF and AKI compared with SAVR. Patients also spent fewer days in the ICU and in hospital overall after TAVI compared with SAVR. In contrast, TAVI appeared to be associated with a

significantly increased risk of major vascular complications and new PPM implantations at all time points following surgery; and a significantly increased risk of rehospitalisation or reintervention/reoperation at late time points compared with SAVR.

Based on subgroup analyses, patients undergoing TAVI via the TF route generally had improved outcomes compared with patients undergoing TAVI via the non-TF route (with the exception of major vascular complications); and patients at low or intermediate risk (based exclusively on STS-PROM scores) generally had improved outcomes compared with patients at high risk (with the exception of new PPM implantation or reintervention/reoperation).

In terms of valve durability, we identified three studies (NOTION, PARTNER 1A, US CoreValve) that either reported no cases of structural valve deterioration in TAVI or SAVR patients at 5 years (PARTNER 1A); mixed outcomes depending on the definition of valve deterioration used (ranging from significantly lower rate of haemodynamic structural valve deterioration for TAVI patients compared with SAVR patients at 6 years (based on one definition) to no difference between TAVI vs SAVR (based on three separate definitions) at 6 years (NOTION); or no cases of valve frame fracture in 21 TAVI patients who had undergone implant explantation or autopsy after death a median of 17 days (range: 0–503 days) after implantation (US CoreValve). Thus, there was only limited and heterogeneous evidence to inform this outcome, and further research into the long-term durability of the TAVI valves is clearly required.

No evidence comparing TAVI vs SAVR was identified for recovery time or pain, therefore further research is needed to address these areas of interest.

We noted several study limitations. A major limitation was a discrepancy in the number of events reported for the same time point in different publications within the same study series. For example, in the PARTNER study, Smith 2011 reported 1-year MI as one event in the TAVI arm (out of  $n=348$ ) and two events in the SAVR arm (out of  $n=351$ ),<sup>26</sup> while Kodali *et al* reported 1-year MI as zero events in the TAVI arm (out of  $n=348$ ) and two events in the SAVR arm (out of  $n=351$ ).<sup>35</sup> In these cases, we chose to use the first published set of numbers reported for consistency. Several studies (EVOLUT, SURTAVI) only reported percentages of patients experiencing an event based on an estimated incidence derived from a Bayesian analysis rather than absolute numbers. This was an issue for pooled data analysis, as absolute values had to be estimated from already-estimated values, compounding any potential numerical variation.

Multiple studies that prespecified reporting the ITT population in a sensitivity analysis failed to do this across all published time points. While we used ITT as our preferred analysis population, this meant that in some cases, only the as-treated population was available for pooled analysis, which may have contributed to heterogeneity.

Most studies were only powered for the primary outcome, which was generally read out at 12 or 24 months. This meant that long-term results and durability analyses in particular may have been underpowered. For all outcomes except all-cause mortality, subgroup analysis by level of surgical risk was also only reported at 1 year, preventing any longitudinal analyses.

The clinical relevance of some of the acute procedural outcomes, such as NOW-AF, was in some cases uncertain. It was often not clearly reported whether such clinical symptoms had recovered, such as converting to a sinus rhythm, or whether long-term sequelae were present.

There was substantial variation in the definitions used by each study for certain outcomes, which impacted study comparability and increased clinical heterogeneity. For example, ‘major bleeding’ was reported under several definitions, including life-threatening or disabling bleeding (EVOLUT, PARTNER 2A, PARTNER 3, US CoreValve), major bleeding (PARTNER 1A, US CoreValve), life-threatening, disabling or major bleeding (PARTNER 3), life-threatening or major bleeding (SURTAVI) or simply ‘bleeding’ (STACCATO). Only two studies reported two different definitions of bleeding (PARTNER 3 (life-threatening or disabling bleeding and life-threatening, disabling or major bleeding; and US CoreValve (life-threatening or disabling bleeding and major bleeding)).

Finally, we have only focused on RCTs in our SR, as we considered this to be the highest level of available evidence. We acknowledge that other levels of evidence (such as large registries and propensity-score matched datasets<sup>36–39</sup>) are available, with more patients reported, especially for longer follow-up periods. However, only one of these sources reported information for low-risk patients. The number of patients at risk is rather small at 5 years and this evidence is based on studies with considerable differences in baseline characteristics (e.g. post malignant disease) that might account for the long-term differences in outcomes.<sup>39</sup> The other two sources provide data for high-risk patients only and do not include many more patients than the RCTs identified in our SR.<sup>36–37</sup> Several potential sources of bias (miscoding, no data/deaths out of hospital, different time intervals for outcome assessments) could lower the level of evidence even further, especially when compared with results obtained in RCTs.

### Ongoing studies

Three ongoing studies with no published data at the time of our literature searches were identified during screening: DEDICATE,<sup>40–41</sup> RHEIA<sup>42</sup> and VIVA.<sup>43</sup> The DEDICATE study is currently recruiting patients with SAS at low-to-intermediate levels of surgical risk to analyse whether TAVI is non-inferior to SAVR. The RHEIA study will recruit female patients with SAS who are at any level of surgical risk to determine whether TAVI may be more effective than SAVR. The VIVA study will recruit patients with SAS and a small aortic annulus to compare TAVI vs SAVR in this specific subpopulation.

## Comparison with other SRs

We identified at least 18 previous SRs that compared TAVI vs SAVR in patients with SAS.<sup>9 29–33 44–55</sup> One SR/MA was identified that reported a difference in findings in terms of mortality based on a pooled analysis of RCT and observational studies. However, this discrepancy disappeared when only RCT study data were considered (ie, results were similar when based on the most robust evidence base).<sup>55</sup> None of these studies incorporated new UK TAVI study data; none analysed the same broad range of outcomes we have presented; and most tended to focus on a specific risk level (low or intermediate low) rather than comparing across and within all levels of risk. Only one SR reported results for more than one outcome stratified by route subgroup.<sup>56</sup> The results of these SRs were broadly in line with those we have reported.

Overall, this SR highlights that the choice between TAVI versus SAVR will undoubtedly be a highly personalised one, which in most cases will include a trade-off between an increase in the risk of certain outcomes and a decrease in the risk of others. The findings of this SR support the growing approach to enable patients to make physician-guided choices on their own care based on their personal preferences and values in the context of the Heart Team's assessment of their inherent anatomical features, comorbidities and frailties, life expectancy and valve durability rather than the classical approach of assigning treatments simply based on estimated surgical risk.<sup>57 58</sup>

## Conclusions

Current evidence suggests that while all-cause or cardiovascular mortality may not be different for TAVI compared with SAVR, TAVI may reduce the risk of certain side effects (such as major bleeding, AKI, NOW-AF) and reduce the length of hospital stay, while SAVR may reduce the risk for other side effects (such as major vascular complications, new PPM implantation or reinterventions/rehospitalisations). Consequently, each individual patient should be engaged in a SDM framework to enable highly personalised trade-off decisions to be made based on a carefully balanced review of this evidence.

## Author affiliations

<sup>1</sup>Kleijnen Systematic Reviews Ltd, York, UK

<sup>2</sup>Department of Cardiac and Vascular Surgery, Universitätsklinikum Schleswig-Holstein, Kiel, Germany

<sup>3</sup>German Centre for Cardiovascular Research, Kiel, Germany

<sup>4</sup>National Competency Center for Shared Decision Making, Universitätsklinikum Schleswig-Holstein, Kiel, Germany

<sup>5</sup>Department of Cardiology and Angiology, Universitätsklinikum Schleswig-Holstein, Kiel, Germany

<sup>6</sup>Department of Cardiology, Angiology, and Pneumology, University Hospital Heidelberg, Heidelberg, Germany

<sup>7</sup>Department of Internal Medicine I, Universitätsklinikum Schleswig-Holstein, Kiel, Germany

**Twitter** Stephanie Louise Swift @swiftsciwriting, Shona Helen Lang @ShonaHLang and Robert Wolff @wolffrr

**Acknowledgements** Technical Support: Project support was provided by Caro M. Noake, Heath White, Gill Worthy, Annette Chalker, Heike Raatz, Vanesa Huertas Carrera, Titas Buksnys and Debra Fayter, all from KSR.

**Contributors** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. SLS, KM, JK, MD, RW and FS were involved in the planning, conduct and reporting of the work. SLS wrote the main manuscript text and prepared all the figures and tables. SHL and CF were involved in the conduct and reporting of the work. TP and DF were involved in the planning and reporting of the work. CK, AH, HS, JC, NF, GL and KW were involved in the reporting of the work and in contextualising the results from a clinical perspective (cardiology and heart surgery). The corresponding author attests that all listed authors meet authorship criteria and that no other individuals meeting the criteria have been omitted.

**Funding** This study was sponsored and funded by the German Innovationsfonds (hosted by the Federal Joint Committee), grant number 01NVF17009. The researchers worked independently from the funding agency. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. Project support was provided by Caro M. Noake, Heath White, Gill Worthy, Annette Chalker, Heike Raatz, Vanesa Huertas Carrera, Titas Buksnys and Debra Fayter, all from KSR.

**Disclaimer** All authors have completed the ICMJE uniform disclosure form. SLS, KM, SHL, CAF, JK and RFW are employees of KSR Ltd., which received financial support from University Medical Center Schleswig-Holstein in connection with the development of this manuscript; they have no other conflicts of interest. AH, JC, MD, NF, CK, TP, HS, FS and KW have no conflicts of interest. DF is a proctor and consultant for Medtronic Inc. and Edwards Lifesciences, and has received speaker's honoraria as well as travel support. GL is a consultant for Abbott. SLS, RW, and FS accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

**Competing interests** SLS, KM, SHL, CF, JK and RW are employees of KSR, which received financial support from University Medical Center Schleswig-Holstein in connection with the development of this manuscript; they have no other conflicts of interest. TP, MD, AH, HS, JC and KW have no conflicts of interest. FS is managing partner of the SHARE TO CARE. CK and DF are consultants for Medtronic Inc. and Edwards Lifesciences, DF has received speaker's honoraria as well as travel support. NF is a consultant for Edwards Lifesciences. GL is a consultant for Abbott.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

## ORCID iDs

Stephanie Louise Swift <http://orcid.org/0000-0002-8545-8322>

Thomas Puehler <http://orcid.org/0000-0002-4990-1892>

Shona Helen Lang <http://orcid.org/0000-0002-4883-8393>

Marion Danner <http://orcid.org/0000-0002-0653-4092>

Robert Wolff <http://orcid.org/0000-0003-3270-7791>

## REFERENCES

- MacCarthy P, Smith D, Muir D, *et al*. Extended statement by the British cardiovascular intervention Society president regarding transcatheter aortic valve implantation. *Interv Cardiol* 2021;16:e03.
- Aortic Stenosis Writing Group, Bonow RO, Brown AS, *et al*. ACC/AATS/AHA/ASE/EACTS/HVS/SCA/SCAI/SCCT/SCMR/STS 2017 appropriate use criteria for the treatment of patients with severe aortic stenosis: a report of the American College of

- cardiology appropriate use criteria Task force, American association for thoracic surgery, American heart association, American Society of echocardiography, European association for Cardio-Thoracic surgery, heart valve Society, society of cardiovascular Anesthesiologists, Society for cardiovascular angiography and interventions, society of cardiovascular computed tomography, Society for cardiovascular magnetic resonance, and society of thoracic surgeons. *J Am Soc Echocardiogr* 2018;31:117–47.
- 3 Baumgartner H, Falk V, Bax JJ, *et al.* 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739–91.
  - 4 Kuck K-H, Eggebrecht H, Elsässer A. *Qualitätskriterien Zur Durchführung Der kathetergestützten Aortenklappenimplantation (TAVI): Aktualisierung des Positionspapiers Der Deutschen Gesellschaft für Kardiologie.* Berlin: Springer-Verlag, 2016.
  - 5 van Beek-Peeters JJAM, van Noort EHM, Faes MC, *et al.* Shared decision making in older patients with symptomatic severe aortic stenosis: a systematic review. *Heart* 2020;106:647–55.
  - 6 Coylewright M, O'Neill E, Sherman A, *et al.* The learning curve for shared decision-making in symptomatic aortic stenosis. *JAMA Cardiol* 2020;5:442–8.
  - 7 Barili F, Freemantle N, Pillozzi Casado A, *et al.* Mortality in trials on transcatheter aortic valve implantation versus surgical aortic valve replacement: a pooled meta-analysis of Kaplan-Meier-derived individual patient data. *Eur J Cardiothorac Surg* 2020;58:221–9.
  - 8 Wang D, Huang L, Zhang Y, *et al.* Transcatheter aortic valve implantation versus surgical aortic valve replacement for treatment of severe aortic stenosis: comparison of results from randomized controlled trials and real-world data. *Braz J Cardiovasc Surg* 2020;35:346–67.
  - 9 Siontis GCM, Overtchouk P, Cahill TJ, *et al.* Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. *Eur Heart J* 2019;40:3143–53.
  - 10 Toff WD. United Kingdom Transcatheter Aortic Valve Implantation - UK TAVI. Presented at ACC 2020 (World Congress of Cardiology); 28-30 March 2020; Chicago, IL [online] Washington, DC: American College of Cardiology, 2020. Available: <https://www.acc.org/latest-in-cardiology/clinical-trials/2020/03/26/21/14/uk-tavi> [Accessed 14 Aug 2020].
  - 11 University of Leicester. The United Kingdom Transcatheter Aortic Valve Implantation (UK TAVI) Trial. A multi-centre randomised controlled trial to assess the clinical effectiveness and cost utility of TAVI, compared with conventional surgical aortic valve replacement (AVR), in patients with severe symptomatic aortic stenosis at intermediate or high operative risk, 2013. Available: <http://apps.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN57819173CN-01856898>
  - 12 Share to Care Gemeinsam entscheiden. Willkommen bei SHARE TO CARE: homepage [online], 2019. Available: <https://abnahme-kiel.share-to-care.de/> [Accessed 19 Jun 2019].
  - 13 Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions [online]. Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011.*
  - 14 Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care [online].* York: University of York, 2009.
  - 15 PRISMA Group. PRISMA (Preferred reporting items for systematic reviews and meta-analyses) statement [online]. Available: <http://prisma-statement.org/> [Accessed 18 Jun 2015].
  - 16 Swift S, Wolff R, Misso K. Comparative effectiveness and safety of transcatheter aortic valve implantation (TAVI) versus surgical aortic valve replacement (SAVR) in elderly (>75 years) patients with severe aortic stenosis: a systematic review and meta-analysis. PROSPERO protocol: CRD42019138171 [online], 24th June 2019.
  - 17 Cribier A, Eltchaninoff H, Bash A, *et al.* Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation* 2002;106:3006–8.
  - 18 Higgins JPT, Altman DG, Gøtzsche PC, *et al.* The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
  - 19 Elwyn G, O'Connor A, Stacey D, *et al.* Developing a quality criteria framework for patient decision AIDS: online international Delphi consensus process. *BMJ* 2006;333:417.
  - 20 Sterne JAC, Sutton AJ, Ioannidis JPA, *et al.* Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
  - 21 Leon MB, Smith CR, Mack MJ, *et al.* Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374:1609–20.
  - 22 Mack MJ, Leon MB, Thourani VH, *et al.* Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;380:1695–705.
  - 23 Adams DH, Popma JJ, Reardon MJ, *et al.* Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;370:1790–8.
  - 24 Popma JJ, Deeb GM, Yakubov SJ, *et al.* Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019;380:1706–15.
  - 25 Thyregod HGH, Steinbrüchel DA, Ihlemann N, *et al.* Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the All-Comers NOTION randomized clinical trial. *J Am Coll Cardiol* 2015;65:2184–94.
  - 26 Smith CR, Leon MB, Mack MJ, *et al.* Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187–98.
  - 27 Nielsen HHM, Klaaborg KE, Nissen H, *et al.* A prospective, randomised trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve replacement in operable elderly patients with aortic stenosis: the STACCATO trial. *EuroIntervention* 2012;8:383–9.
  - 28 Reardon MJ, Van Mieghem NM, Popma JJ, *et al.* Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017;376:1321–31.
  - 29 Ando T, Ashraf S, Villablanca P, *et al.* Meta-Analysis of effectiveness and safety of transcatheter aortic valve implantation versus surgical aortic valve replacement in low-to-intermediate surgical risk cohort. *Am J Cardiol* 2019;124:580–5.
  - 30 Dagan M, Yeung T, Stehli J, *et al.* Transcatheter versus surgical aortic valve replacement: an updated systematic review and meta-analysis with a focus on outcomes by sex. *Heart Lung Circ* 2021;30:86–99.
  - 31 Khan MR, Kayani WT, Manan M, *et al.* Comparison of surgical versus transcatheter aortic valve replacement for patients with aortic stenosis at low-intermediate risk. *Cardiovasc Diagn Ther* 2020;10:135–44.
  - 32 Mc Morrow R, Kriza C, Urbán P, *et al.* Assessing the safety and efficacy of TAVR compared to SAVR in low-to-intermediate surgical risk patients with aortic valve stenosis: an overview of reviews. *Int J Cardiol* 2020;314:43–53.
  - 33 Zhang X, Wang T, Lan R, *et al.* Meta-analysis comparing results of transcatheter versus surgical aortic-valve replacement in patients with severe aortic stenosis. *Am J Cardiol* 2020;125:449–58.
  - 34 Makkar RR, Thourani VH, Mack MJ. Five-year outcomes of transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2020;382.
  - 35 Kodali SK, Williams MR, Smith CR, *et al.* Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;366:1686–95.
  - 36 Armoiry X, Obadia J-F, Pascal L, *et al.* Comparison of transcatheter versus surgical aortic valve implantation in high-risk patients: a nationwide study in France. *J Thorac Cardiovasc Surg* 2018;156:1017–25.
  - 37 Barbanti M, Tamburino C, D'Errigo P, *et al.* Five-year outcomes of transfemoral transcatheter aortic valve replacement or surgical aortic valve replacement in a real world population. *Circ Cardiovasc Interv* 2019;12:e007825.
  - 38 Kuss O, Blettner M, Börgemann J. Propensity score: an alternative method of analyzing treatment effects - part 23 of a series on evaluation of scientific publications]. *Dtsch Arztebl Int* 2016;113:597–603.
  - 39 Schaefer A, Schofer N, Goßling A, *et al.* Transcatheter aortic valve implantation versus surgical aortic valve replacement in low-risk patients: a propensity score-matched analysis. *Eur J Cardiothorac Surg* 2019;56:1131–9.
  - 40 Universitätsklinikum Hamburg-Eppendorf, Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK). *Randomized trial of TAVI vs. SAVR in patients with severe aortic valve stenosis at intermediate risk of mortality [online].* Bethesda, MD: National Library of Medicine, 2017. <https://clinicaltrials.gov/show/nct03112980CN-01563392>
  - 41 Seiffert M, Walther T, Hamm C, *et al.* The DEDICATE trial: an independent all-comers trial of transcatheter aortic valve implantation vs. surgical aortic valve replacement in patients at low to intermediate operative risk is recruiting patients. *Eur Heart J* 2019;40:331–3.
  - 42 Eltchaninoff H, Bonaros N, Prendergast B, *et al.* Rationale and design of a prospective, randomized, controlled, multicenter study to evaluate the safety and efficacy of transcatheter heart valve replacement in female patients with severe symptomatic aortic stenosis requiring aortic valve intervention (Randomized research

- in womEn all comers with Aortic stenosis [RHEIA] trial). *Am Heart J* 2020;228:27–35.
- 43 Centre de Recherche de l'Institut Universitaire de Cardiologie et de Pneumologie de Quebec. *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*. NCT03383445. In: *ClinicalTrials.gov [online]*. Bethesda, MD: National Library of Medicine (US), 2017. <https://clinicaltrials.gov/show/nct03383445>
  - 44 Ler A, Ying YJ, Sazzad F, et al. Structural durability of early-generation transcatheter aortic valve replacement valves compared with surgical aortic valve replacement valves in heart valve surgery: a systematic review and meta-analysis. *J Cardiothorac Surg* 2020;15:127.
  - 45 Takagi H, Hari Y, Nakashima K, et al. Mortality after transcatheter versus surgical aortic valve replacement: an updated meta-analysis of randomised trials. *Neth Heart J* 2020;28:320–33.
  - 46 Takagi H, Hari Y, Nakashima K, et al. A meta-analysis of ≥5-year mortality after transcatheter versus surgical aortic valve replacement. *J Cardiovasc Surg* 2020;61:107–16.
  - 47 Ueyama H, Kuno T, Ando T, et al. Network meta-analysis of surgical aortic valve replacement and different transcatheter heart valve systems for symptomatic severe aortic stenosis. *Can J Cardiol* 2021;37:27–36.
  - 48 Zhang X-L, Zhang X-W, Xu Wet al. Response to the comment on "long-term and temporal outcomes of transcatheter versus surgical aortic-valve replacement in severe aortic stenosis: a meta-analysis". *Ann Surg* 2020. doi:10.1097/SLA.0000000000004516
  - 49 Kheiri B, Osman M, Bakhit A, et al. Meta-analysis of transcatheter aortic valve replacement in low-risk patients. *Am J Med* 2020;133:e38–41.
  - 50 Kolkailah AA, Doukky R, Pelletier MP, et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis in people with low surgical risk. *Cochrane Database Syst Rev* 2019;12:CD013319.
  - 51 Kundu A, Sardar P, Malhotra R, et al. Cardiovascular outcomes with transcatheter vs. surgical aortic valve replacement in low-risk patients: an updated meta-analysis of randomized controlled trials. *Cardiovasc Revasc Med* 2020;21:453–60.
  - 52 Malik AH, Zaid S, Ahmad H, et al. A meta-analysis of 1-year outcomes of transcatheter versus surgical aortic valve replacement in low-risk patients with severe aortic stenosis. *J Geriatr Cardiol* 2020;17:43–50.
  - 53 Polimeni A, Sorrentino S, De Rosa S. Transcatheter versus surgical aortic valve replacement in low-risk patients for the treatment of severe aortic stenosis. *J Clin Med* 2020;9:439.
  - 54 Vipparthy SC, Ravi V, Avula S, et al. Meta-Analysis of transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with low surgical risk. *Am J Cardiol* 2020;125:459–68.
  - 55 Gargiulo G, Sannino A, Capodanno D, et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement: a systematic review and meta-analysis. *Ann Intern Med* 2016;165:334–44.
  - 56 Liu Z, Kidney E, Bem D, et al. Transcatheter aortic valve implantation for aortic stenosis in high surgical risk patients: a systematic review and meta-analysis. *PLoS One* 2018;13:e0196877.
  - 57 Otto CM. Informed shared decisions for patients with aortic stenosis. *N Engl J Med* 2019;380:1769–70.
  - 58 Costa G, Fukutomi M, Sondergaard L. The role of the heart team in the planning of aortic valve replacement. *EuroIntervention* 2019;15:e1027–9.
  - 59 Daubert MA, Weissman NJ, Hahn RT, et al. Long-term valve performance of TAVR and SAVR: a report from the partner I trial. *JACC Cardiovasc Imaging* 2016. doi:10.1016/j.jcmg.2016.11.004. [Epub ahead of print:
  - 60 Edwards Lifesciences. *The partner trial: placement of aortic transcatheter valve trial*. Bethesda, MD: National Library of Medicine, 2010. <https://ClinicalTrials.gov/show/NCT00530894>
  - 61 Gada H, Kirtane AJ, Wang K, et al. Temporal trends in quality of life outcomes after transapical transcatheter aortic valve replacement: a placement of aortic transcatheter valve (partner) trial substudy. *Circ Cardiovasc Qual Outcomes* 2015;8:338–46.
  - 62 Généreux P, Cohen DJ, Williams MR, et al. Bleeding complications after surgical aortic valve replacement compared with transcatheter aortic valve replacement: insights from the partner I trial (placement of aortic transcatheter valve). *J Am Coll Cardiol* 2014;63:1100–9.
  - 63 Genereux P, Svensson L, Kodali S. Incidence, predictors and impact of bleeding events after transcatheter aortic valve replacement (TAVR) compared to surgical aortic valve replacement (SAVR): insights from the partner trial. *J Am Coll Cardiol* 2012;59:E2.
  - 64 Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;385:2477–84.
  - 65 Miller DC, Blackstone EH, Mack MJ, et al. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. *J Thorac Cardiovasc Surg* 2012;143:832–43.
  - 66 Reynolds MR, Magnuson EA, Wang K, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (placement of aortic transcatheter valve) trial (cohort a). *J Am Coll Cardiol* 2012;60:548–58.
  - 67 Svensson LG, Blackstone EH, Rajeswaran J, et al. Comprehensive analysis of mortality among patients undergoing TAVR: results of the PARTNER trial. *J Am Coll Cardiol* 2014;64:158–68.
  - 68 Arnold SV, Reynolds MR, Wang K, et al. Health status after transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis at increased surgical risk: results from the CoreValve US pivotal trial. *JACC Cardiovasc Interv* 2015;8:1207–17.
  - 69 Baron SJ, Arnold SV, Reynolds MR. Durability of the quality of life benefit of transcatheter or surgical aortic valve replacement in high risk patients with aortic stenosis: two-year results from the Corevalve US pivotal high risk trial. *J Am Coll Cardiol* 2015;66:B54–5.
  - 70 Conte JV, Hermiller J, Resar JR, et al. Complications after self-expanding transcatheter or surgical aortic valve replacement. *Semin Thorac Cardiovasc Surg* 2017;29:321–30.
  - 71 Deeb GM, Reardon MJ, Chetcuti S, et al. 3-year outcomes in high-risk patients who underwent surgical or transcatheter aortic valve replacement. *J Am Coll Cardiol* 2016;67:2565–74.
  - 72 Gaudiani V, Deeb GM, Popma JJ, et al. Causes of death from the randomized CoreValve US pivotal high-risk trial. *J Thorac Cardiovasc Surg* 2017;153:1293–301.
  - 73 Gleason TG, Reardon MJ, Popma JJ, et al. 5-year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. *J Am Coll Cardiol* 2018;72:2687–96.
  - 74 Gleason TG, Schindler JT, Adams DH, et al. The risk and extent of neurologic events are equivalent for high-risk patients treated with transcatheter or surgical aortic valve replacement. *J Thorac Cardiovasc Surg* 2016;152:85–96.
  - 75 Little SH, Oh JK, Gillam L, et al. Self-expanding transcatheter aortic valve replacement versus surgical valve replacement in patients at high risk for surgery: a study of echocardiographic change and risk prediction. *Circ Cardiovasc Interv* 2016;9.
  - 76 Medtronic Cardiovascular. Safety and efficacy study of the Medtronic CoreValve® system in the treatment of symptomatic severe aortic stenosis in high risk and very high risk subjects who need aortic valve replacement. NCT01240902. In: *ClinicalTrials.gov [Internet]*. Bethesda (MD): National Library of Medicine (US) 2014 [accessed 4.6.19] [ Order SS]. Available from: Available: <https://ClinicalTrials.gov/show/NCT01240902>
  - 77 Reardon MJ, Adams D, Kleiman N. Outcomes in the CoreValve us high-risk pivotal trial in patients with a Society of thoracic surgeons predicted risk of mortality less than or equal to 7. *J Am Coll Cardiol* 2016;67:121.
  - 78 Reardon MJ, Adams DH, Kleiman NS, et al. 2-year outcomes in patients undergoing surgical or self-expanding transcatheter aortic valve replacement. *J Am Coll Cardiol* 2015;66:113–21.
  - 79 Reardon MJ, Kleiman NS, Adams DH, et al. Outcomes in the randomized CoreValve US pivotal high risk trial in patients with a Society of Thoracic Surgeons risk score of 7% or less. *JAMA Cardiol* 2016;1:945–9.
  - 80 Yahagi K, Torii S, Ladich E, et al. Pathology of self-expanding transcatheter aortic valves: findings from the CoreValve us pivotal trials. *Catheter Cardiovasc Interv* 2018;91:947–55.
  - 81 Arnold S, Chinnakondepalli K, Magnuson E. 5-year health status outcomes after self-expanding transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis. Presented at the ACC 20 - World Congress of Cardiology. *J Am Coll Cardiol* 2020;75:1109.
  - 82 Baron SJ, Arnold SV, Wang K, et al. Health status benefits of transcatheter vs surgical aortic valve replacement in patients with severe aortic stenosis at intermediate surgical risk: results from the PARTNER 2 randomized clinical trial. *JAMA Cardiol* 2017;2:837–45.
  - 83 Edwards Lifesciences. *The PARTNER II Trial: Placement of AoRTic TraNscatheteR Valves - PII A [online]*. Bethesda, MD: National Library of Medicine, 2016. <https://ClinicalTrials.gov/show/NCT01314313>



- 84 Amrane H, Deeb GM, Popma JJ, *et al.* Causes of death in intermediate-risk patients: the randomized surgical replacement and transcatheter aortic valve implantation trial. *J Thorac Cardiovasc Surg* 2019;158:718–28.
- 85 Durko AP, Reardon MJ, Kleiman NS, *et al.* Neurological Complications After Transcatheter Versus Surgical Aortic Valve Replacement in Intermediate-Risk Patients. *J Am Coll Cardiol* 2018;72:2109–19.
- 86 Kiaii B, Reardon M, Popma J. Clinical impact of atrial fibrillation following surgical or transcatheter aortic valve replacement in patients at intermediate surgical risk: results from the SURTAVI trial. *J Am Coll Cardiol* 2018.
- 87 Medtronic Cardiovascular. *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)*. Bethesda, MD: National Library of Medicine, 2018. <https://ClinicalTrials.gov/show/NCT01586910>
- 88 Popma JJ, Van Mieghem N, Reardon MJ. Functional status after transcatheter and surgical aortic valve replacement: a two-year analysis from the SURTAVI trial. *J Am Coll Cardiol* 2017.
- 89 Serruys P, Abdelghani M, Popma JJ. Clinical outcomes of surgical or transcatheter aortic-valve replacement in intermediate-risk patients stratified by STS score: results from the SURTAVI trial. *J Am Coll Cardiol* 2017.
- 90 Serruys PW, Modolo R, Reardon M, *et al.* One-year outcomes of patients with severe aortic stenosis and an STS PROM of less than three percent in the SURTAVI trial. *EuroIntervention* 2018;14:877–83.
- 91 Van Mieghem N, Reardon MJ, Popma JJ. Transcatheter aortic valve replacement with a self-expanding prosthesis or surgical aortic valve replacement in intermediate-risk patients: complete 1-year outcomes from the surtavi trial. *J Am Coll Cardiol* 2017.
- 92 Van Mieghem NM, Popma JJ, Deeb GM, *et al.* Complete 2-year results confirm Bayesian analysis of the SURTAVI trial. *JACC Cardiovasc Interv* 2020;13:323–31.
- 93 Medtronic Cardiovascular. *Medtronic evolut transcatheter aortic valve replacement in low risk patients [online]*. Bethesda, MD: National Library of Medicine, 2016. <https://clinicaltrials.gov/show/nct02701283CN-01576135>
- 94 National Library of Medicine. *Edwards Lifesciences The PARTNER 3 trial: the safety and effectiveness of the SAPIEN 3 transcatheter heart valve in low risk patients with aortic stenosis [online]*. Bethesda, MD: National Library of Medicine, 2016. <https://clinicaltrials.gov/show/nct02675114CN-01555589>
- 95 Baron SJ, Magnuson EA, Lu M, *et al.* Health status after transcatheter versus surgical aortic valve replacement in low-risk patients with aortic stenosis. *J Am Coll Cardiol* 2019;74:2833–42.
- 96 Pibarot P, Salaun E, Dahou A, *et al.* Echocardiographic results of transcatheter versus surgical aortic valve replacement in low-risk patients: the partner 3 trial. *Circulation* 2020;141:1527–37.
- 97 Mack MJ, Leon MB. *Two year clinical and echocardiographic outcomes from the PARTNER 3 low risk randomized trial. Presented at ACC 2020 (World Congress of Cardiology); 28-30 March 2020; Chicago, IL [online]*. Washington, DC: American College of Cardiology, 2020. <https://www.acc.org/latest-in-cardiology/clinical-trials/2019/03/15/18/29/partner-3>
- 98 Jorgensen TH, Thygesen JB, Thyregod HG. Temporal changes in new-onset atrial fibrillation after TAVI or SAVR for aortic stenosis: a randomised study. *EuroIntervention* 2013;9.
- 99 Jørgensen TH, Thyregod HGH, Tarp JB, *et al.* Temporal changes of new-onset atrial fibrillation in patients randomized to surgical or transcatheter aortic valve replacement. *Int J Cardiol* 2017;234:16–21.
- 100 Ngo A, Hassager C, Thyregod HGH, *et al.* Differences in left ventricular remodelling in patients with aortic stenosis treated with transcatheter aortic valve replacement with CoreValve prostheses compared to surgery with porcine or bovine biological prostheses. *Eur Heart J Cardiovasc Imaging* 2018;19:39–46.
- 101 Rigshospitalet Denmark, Odense University Hospital, Sahlgrenska University Hospital Sweden. *The nordic aortic valve intervention trial [online]*. Bethesda, MD: National Library of Medicine, 2014. <https://ClinicalTrials.gov/show/NCT01057173>
- 102 Søndergaard L, Ihlemann N, Capodanno D, *et al.* Durability of transcatheter and surgical bioprosthetic aortic valves in patients at lower surgical risk. *J Am Coll Cardiol* 2019;73:546–53.
- 103 Søndergaard L, Steinbrüchel DA, Ihlemann N, *et al.* Two-year outcomes in patients with severe aortic valve stenosis randomized to transcatheter versus surgical aortic valve replacement: the all-comers nordic aortic valve intervention randomized clinical trial. *Circ Cardiovasc Interv* 2016;9.
- 104 Thyregod HG, Søndergaard L, Ihlemann N, *et al.* The Nordic aortic valve intervention (NOTION) trial comparing transcatheter versus surgical valve implantation: study protocol for a randomised controlled trial. *Trials* 2013;14:11.
- 105 Thyregod HGH, Ihlemann N, Jørgensen TH, *et al.* Five-year clinical and echocardiographic outcomes from the Nordic aortic valve intervention (NOTION) randomized clinical trial in lower surgical risk patients. *Circulation* 2019 doi:10.1161/CIRCULATIONAHA.118.036606
- 106 Aarhus University Hospital Skejby, Odense University Hospital, Danish Heart Foundation. *Transapical transcatheter treatment versus conventional surgery in patients with native aortic valve stenosis [online]*. Bethesda, MD: National Library of Medicine, 2011. <https://ClinicalTrials.gov/show/NCT00986193>
- 107 Rex CE, Heiberg J, Klaborg K-E, *et al.* Health-related quality-of-life after transapical transcatheter aortic valve implantation. *Scand Cardiovasc J* 2016;50:377–82.