European Heart Journal (2016) **37**, 3503–3512
doi:10.1093/eurheartj/ehw225

Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials

George C.M. Siontis[1†], Fabien Praz[1†], Thomas Pilgrim[1], Dimitris Mavridis[2], Subodh Verma[3], Georgia Salanti[2,4,5], Lars Søndergaard[6], Peter Jüni[7], and Stephan Windecker[1*]

[1]Department of Cardiology, INSELSPITAL, Bern University Hospital, University of Bern, Bern 3010, Switzerland; [2]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece; [3]Division of Cardiac Surgery, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; [4]Institute of Social and Preventive Medicine and Clinical Trials Unit, University of Bern, Bern, Switzerland; [5]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland; [6]Department of Cardiology, The Heart Centre, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; and [7]Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada

Received 20 April 2016; revised 2 May 2016; accepted 15 May 2016; online publish-ahead-of-print 7 July 2016

See page 3513 for the editorial comment on this article (doi:10.1093/eurheartj/ehw382)

Aims In view of the currently available evidence from randomized trials, we aimed to compare the collective safety and efficacy of transcatheter aortic valve implantation (TAVI) vs. surgical aortic valve replacement (SAVR) across the spectrum of risk and in important subgroups.

Methods and results Trials comparing TAVI vs. SAVR were identified through Medline, Embase, and Cochrane databases. The primary outcome was death from any cause at 2 years. We performed random-effects meta-analyses to combine the available evidence and to evaluate the effect in different subgroups. This systematic review and meta-analysis is registered with PROSPERO (CRD42016037273). We identified four eligible trials including 3806 participants, who were randomly assigned to undergo TAVI ($n = 1898$) or SAVR ($n = 1908$). For the primary outcome of death from any cause, TAVI when compared with SAVR was associated with a significant 13% relative risk reduction [hazard ratio (95% CI): 0.87 (0.76–0.99); $P = 0.038$] with homogeneity across all trials irrespective of TAVI device ($P_{interaction} = 0.306$) and baseline risk ($P_{interaction} = 0.610$). In subgroup analyses, TAVI showed a robust survival benefit over SAVR for patients undergoing transfemoral access [0.80 (0.69–0.93); $P = 0.004$], but not transthoracic access [1.17 (0.88–1.56); $P = 0.293$] ($P_{interaction} = 0.024$) and in female [0.68 (0.50–0.91); $P = 0.010$], but not male patients [0.99 (0.77–1.28); $P = 0.952$] ($P_{interaction} = 0.050$). Secondary outcomes of kidney injury, new-onset atrial fibrillation, and major bleeding favoured TAVI, while major vascular complications, incidence of permanent pacemaker implantation, and paravalvular regurgitation favoured SAVR.

Conclusion Compared with SAVR, TAVI is associated with a significant survival benefit throughout 2 years of follow-up. Importantly, this superiority is observed irrespective of the TAVI device across the spectrum of intermediate and high-risk patients, and is particularly pronounced among patients undergoing transfemoral TAVI and in females.

Keywords Aortic stenosis • Transcatheter aortic valve replacement • Transcatheter aortic valve implantation • Surgical aortic valve replacement • Meta-analysis • Randomized controlled trial

* Corresponding author. Tel: +41 31 632 44 97, Fax: +41 31 632 47 70, Email: stephan.windecker@insel.ch

† G.C.M.S. and F.P. contributed equally to this study.

Introduction

Transcatheter aortic valve implantation (TAVI) has emerged as valuable treatment for patients with inoperable and high-risk severe, symptomatic aortic stenosis. To date, populations included in randomized controlled trials (RCTs) comparing TAVI with surgical aortic valve replacement (SAVR) have mainly focused on patients at high surgical risk.[1–7] Two trials (NOTION[8] and PARTNER 2B[9]) were designed to also include lower-than-high-risk patients. Furthermore, the majority of studies are designed as non-inferiority trials, and, as such are individually underpowered to evaluate all-cause mortality or provide robust estimates of consistency in patients at various baseline risk categories. Additionally, there is heterogeneity in the trials with respect to the type of TAVI device employed (balloon-expandable vs. self-expandable), as well in the procedural access site employed (transfemoral vs. transapical), making individual trial comparisons difficult to interpret in the context of these important subgroups. Finally, individual trials are too small to determine whether any sex-specific differences in outcomes might exist. Therefore, we performed a meta-analysis of randomized trials to compare TAVI to SAVR with the primary outcome of all-cause mortality, in addition to collectively assessing various important patient and procedural subgroups mentioned above.

Methods

Search methods and resources

In accordance with the Cochrane Handbook recommendations,[10] we performed a systematic review of the literature to identify relevant trials of the competing interventions of our interest. The protocol is available online at http://www.crd.york.ac.uk/PROSPERO/. We identified relevant studies by searching the following databases [Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL)] and websites (www.clinicaltrials.gov, www.cardiosource.com, www.escardio.org, www.tctmd.com), by using keywords and medical subject headings that include all spellings of TAVI and SAVR, with no restrictions on language or year of publication. We scrutinized the reference lists from all eligible studies to identify additional citations that would fit our inclusion criteria. Our search strategy consisted of the terms of 'transcatheter aortic valve implantation', 'transcatheter aortic valve replacement', 'surgical aortic valve replacement', and 'randomized trial'. The detailed search algorithm is provided in the appendix (Supplementary material online, *Box S1*).

Selection of studies

We deemed eligible studies that have a randomized design (random allocation of participants in the competing interventions of interest of TAVI vs. SAVR) and reported on outcomes during a period of at least 1-year or longer of follow-up. We excluded trials that compared different devices (TAVI heart valve system) head-to-head, trials that compared TAVI with medical therapy and trials that reported only short-term outcomes.

Data extraction and management

Following the PRISMA guidelines for systematic reviews and meta-analyses,[11] two investigators (G.C.M.S. and F.P.) scrutinized titles and abstracts of all items independently and identified eligible trials that fulfilled pre-specified inclusion criteria. Potentially eligible studies were subsequently reviewed in duplicate, and consensus was achieved through referral to a third investigator in case of disagreement. An electronic data abstraction form was used to extract and record information related to trials, patients, interventions, and outcomes of interest. Two investigators extracted the following information from the trials' primary texts, supplementary appendixes, and protocols as appropriate: trials' and patients' characteristics [trials' characteristics: trial name, year of publication, number of participated centres, recruitment period, maximum available follow-up, trial design, number of randomized patients, number of patients initially assigned to each treatment group (TAVI and SAVR), and number of patients finally treated with each intervention; patients' characteristics: age, sex, Society of Thoracic Surgeons Predicted Risk Of Mortality (STS) estimate, chronic kidney disease stage 4 or 5, peripheral vascular disease, prior cerebrovascular event, prior coronary artery bypass graft, prior percutaneous coronary intervention, known atrial fibrillation (AF) or flutter, prior pacemaker]; and interventions' characteristics [transcatheter heart valve system, number of patients treated with transfemoral and transthoracic (transapical or transaortic) approach]. The TAVI arm in each trial was considered to have been treated by the transfemoral approach, when >95% of the TAVI interventions had been performed through this access route.

Outcomes

The primary outcome was death from any cause at 2 years; cerebrovascular event (any stroke or transient ischaemic attack), stroke, myocardial infarction, kidney injury, new-onset AF, major bleeding, major vascular complications, valve endocarditis, permanent pacemaker implantation, and the echocardiographic outcome of paravalvular regurgitation (moderate or severe) were secondary outcomes. For all outcomes, information was extracted at a follow-up of up to 2 years according to the Valve Academic Research Consortium (VARC) or the more recent VARC-2 endpoint definitions for consistency across the trials.

For the primary and secondary outcomes, the number of events in each arm and subsequent subgroups, and hazard ratio (HR) with corresponding 95% confidence intervals (CIs) were extracted. Whenever possible, we extracted data based on the intention-to-treat (ITT) principle, considering as-treated data if ITT data were unavailable. We gave HRs precedence over risk ratios (RRs) since they incorporate time-to-event data and allow for censoring. When HRs were unavailable, we calculated RRs from the number of events and participants in each treatment group. Finally, we required additional outcome data from sponsor or principal investigator of trials in which 2-year follow-up data were unavailable at the time of our search.

Risk of bias and quality assessment

To evaluate the risk of bias among included trials, we used the Cochrane risk of bias assessment tool,[12] which assesses the following items: allocation sequence generation, allocation concealment, blinding of participants and investigators, completeness of outcome data, and selective outcome reporting. We considered blinding adequate if outcome assessors were blinded. Because of the invasive nature of the interventions, we did not deem blinding of patients or performing physicians relevant. Two investigators (G.C.M.S. and F.P.) reviewed the studies and judged the risk of bias. For each item, a judgement was made to be of low, unclear, or high risk. Finally, we judged each trial as a whole to ascertain whether there was low, unclear, or high risk of bias, based on whether the level of bias in each of the defined domains could have led to material biases in the risk estimates.

Statistical analysis

The main analysis was focused on 2-year follow-up data since this was the longest follow-up available for all trials, providing a meaningful outcome window in this elderly patient population at an intermediate follow-up before competing causes of death would exert a major influence on estimates and bias estimates towards the null. We used DerSimonian and Laird random-effects meta-analysis.[13] The extent of heterogeneity in each meta-analysis was evaluated using τ^2 as estimated with the restricted maximum likelihood method. Values around 0.04, 0.16, and 0.36 were considered to represent low, moderate, and high heterogeneity, respectively.[14] We stratified the meta-analysis of the primary outcome by access route of valve delivery (transfemoral vs. transthoracic), type of TAVI (balloon-expandable vs. self-expandable), surgical risk (high vs. intermediate risk patients), and sex. A test for subgroup differences based on random effects was performed across the examined subgroups. Evidence for potential publication bias was explored by visually studying funnel plots. All analyses were performed in STATA version 13.0. This study is registered with PROSPERO (CRD42016037273).

Results

The electronic search yielded 407 citations that were initially evaluated for eligibility in title and abstract level (*Figure 1*). Once duplicate and irrelevant publications had been removed, 14 reports were evaluated in full-text for eligibility. Six reports pertaining to RCTs were excluded owing to comparisons other than TAVI vs. SAVR as shown in *Figure 1*. One potentially eligible trial was terminated early by the data safety monitoring board (STACCATO trial[4]) and was excluded from this analysis owing to the lack of follow-up data beyond 30 days. Finally, four trials (eight reports) (PARTNER 1A,[1–3] US CoreValve High Risk,[5–7] NOTION,[8] and PARTNER 2A[9]) fulfilled the pre-specified inclusion criteria and were included in the current meta-analysis.

Characteristics of individual trials and patient populations are summarized in *Table 1*. Overall, 3806 participants were randomly assigned to undergo TAVI ($n = 1898$) or SAVR ($n = 1908$) (*Table 1*). All four eligible studies were multicentre randomized trials, whose results were published between 2011 and 2016. The median time of recruitment was 26 months (interquartile range of 10 months). Two-year follow-up data were available for all trials at the time of this meta-analysis.

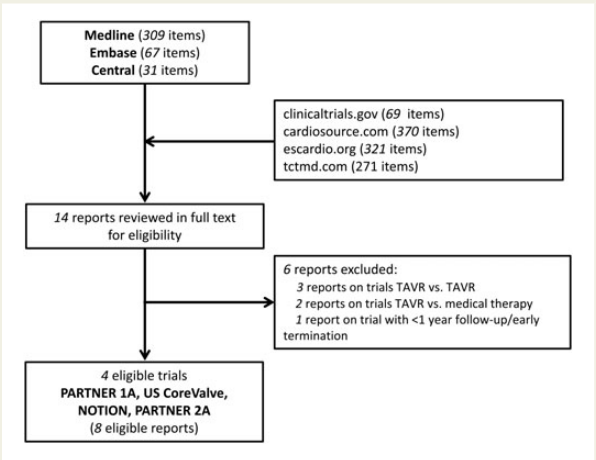

Figure 1 Flow chart of literature search and study selection.

The mean age of patients undergoing TAVI was 82 years, and 45% ($n = 860$) of patients were female. The mean STS score was 8 for patients who were enrolled in high-risk trials (PARTNER 1A[1–3] and US CoreValve High Risk[5–7]), and 4 for those participants who were enrolled in non-high-risk trials (NOTION[8] and PARNTER 2A[9]). Atrial fibrillation or flutter was known before the index interventions in 31 and 34% of participants in the TAVI and SAVR group, respectively; a minority of patients had a permanent pacemaker at baseline before the procedure (15% in each group). Two different types of widely used bioprostheses were compared against SAVR across the four trials; the balloon-expandable bioprosthesis (Edwards Lifesciences)[1,9] and the self-expandable bioprosthesis (Medtronic Inc., Minneapolis, MN, USA).[5,8] Specifically, two different generations of the balloon-expandable TAVI heart valve system were investigated, the Edwards SAPIEN (PARTNER 1A trial[1]) and the Edwards SAPIEN XT (PARTNER 2A trial[9]); the self-expandable TAVI heart valve system, namely Medtronic CoreValve, was used in the other two trials (US CoreValve High Risk[5–7] and NOTION[8]) of this meta-analysis. The transfemoral and transthoracic access site was applied in 75 and 25% of the TAVI interventions, respectively, and applied to the trials of the balloon-expandable Edwards TAVI heart valve systems (1359 participants of PARTNER 1A and 2A trials). In both trials, following assessment for peripheral access, a stratified randomization was performed to TAVI (transfemoral or transthoracic) or SAVR as appropriate.

The overall risk of bias was rated as low in all eligible studies, as assessed by the Cochrane Collaboration's tool (Supplementary material online, *Table S1*). None of the included trials was identified with definite risk of bias in any of the examined domains. However, allocation concealment was judged as unclear risk in three of them because it was not appropriately specified.

Figure 2 presents a meta-analysis of the primary outcome of death from any cause at 2 years of follow-up. Supplementary material online, *Table S2* summarizes the raw data and the given estimates that were extracted from each trial and considered for each outcome of interest. There were a total of 775 deaths (TAVI $n = 378$ vs. SAVR $n = 397$). The summary estimate comparing TAVI and SAVR showed a statistically significant 13% relative risk reduction of death from any cause in favour of TAVI with homogeneity across trials [HR (95% CI): 0.87 (0.76–0.99); $P = 0.038$, $\tau^2 < 0.001$] (*Figure 2*). There was no observed publication bias (Supplementary material online, *Figure S1*). However, the interpretation of the funnel plot is limited by the small numbers of RCTs included.

Figure 3 presents results of stratified meta-analyses for the outcome of death of any cause. For subgroups, appropriate data for synthesis were only available for access route (transfemoral vs. transthoracic), type of TAVI heart valve system (balloon-expandable vs. self-expandable), surgical risk of participants (high vs. lower than high risk), and sex. There was evidence of survival benefit for patients randomized to TAVI through the transfemoral route [0.80 (0.69–0.93); $P = 0.04$], but not for TAVI via transthoracic access [1.17 (0.88–1.56); $P = 0.293$] ($P_{\text{interaction}} = 0.024$). The effect in favour of TAVI was also robust among female patients with a HR

Table 1 Characteristics of trials, patients, and interventions by treatment group of the included randomized trials

	PARTNER 1A[1–3]		US CoreValve High Risk[5–7]		NOTION[8]		PARTNER 2A[9]	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
Trials' characteristics								
Number of centres	25		45		3		57	
Recruitment period	2007–09		2011–12		2009–13		2011–13	
Longest follow-up, year	5		3		2		2	
Design	Non-inferiority		Non-inferiority		Superiority		Non-inferiority	
ITT patients, *n*	348	351	394	401	145	135	1011	1021
As-treated patients, *n*	344	313	391	359	142	134	994	944
Patients' characteristics								
Age, mean (SD)	83.6 ± 6.8	84.5 ± 6.4	83.2 ± 7.1	83.5 ± 6.3	79.2 ± 4.9	79.0 ± 4.7	81.5 ± 6.7	81.7 ± 6.7
Women, *n*	147	153	183	189	67	64	463	461
STS, mean (SD)	11.8 ± 3.3	11.7 ± 3.5	7.3 ± 3.0	7.5 ± 3.2	2.9 ± 1.6	3.1 ± 1.7	5.8 ± 2.1	5.8 ± 1.9
Chronic kidney disease, *n*	38	24	48	52	2	1	51	53
Peripheral vascular disease, *n*	148	142	163	169	6	9	282	336
Prior verebrovascular event, *n*	95	87	51	53	24	22	nd	nd
Prior CABG, *n*	147	152	117	121	nd	nd	239	261
Prior PCI, *n*	116	110	133	152	11	12	274	282
Known atrial fibrillation or flutter, *n*	80	73	161	190	40	34	313	359
Prior pacemaker, *n*	69	76	92	83	5	6	118	123
Intervention's characteristics								
TAVI valve system	Edwards SAPIEN	na	Medtronic CoreValve	na	Medtronic CoreValve	na	Edwards SAPIEN XT	na
Access site, *n*								
Transfemoral	244	na	394	na	145	na	775	na
Transthoracic	104	na	0	na	0	na	236	na

Transthoracic corresponds to transapical or transaortic approach.
TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; SD, standard deviation; STS, Society of Thoracic Surgeons Predicted Risk of Mortality; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; na, not applicable; nd, no data.

(95% CI) of 0.68 (0.50–0.91), $P = 0.010$, whereas no significant difference was detected among male patients [0.99 (0.77–1.28); $P = 0.952$] ($P_{interaction} = 0.050$). We did not detect any variation in the benefit of TAVI over SAVR according to the risk category at baseline ($P_{interaction} = 0.610$).

Results for the secondary outcomes are summarized in *Figure 4*. Kidney injury, new-onset AF, and major bleeding differed significantly between the two groups favouring TAVI (summary point estimates of 0.61, 0.46, and 0.57, respectively) with low detectable heterogeneity. The summary estimates showed no difference between TAVI and SAVR for the secondary outcomes of cerebrovascular event (including stroke or transient ischaemic attack), stroke, myocardial infarction, and valve endocarditis (*Figure 4*). Major vascular complications (*Figure 4*) and incidence of permanent pacemaker implantation (*Figure 5*) were higher in the TAVI group with moderate ($\tau^2 = 0.131$) and high ($\tau^2 = 0.341$) heterogeneity, respectively, between trials. Patients assigned to TAVI were at higher risk of paravalvular regurgitation compared with those allocated to SAVR with considerable heterogeneity across the studies ($\tau^2 = 1.00$) (*Figure 6*).

Discussion

The salient findings of this meta-analysis of the four landmark RCTs comparing directly TAVI with SAVR has the following novel findings summarized as follows:

(1) Compared with SAVR, TAVI results in a 13% relative risk reduction of death from any cause in intermediate to high-risk patients with symptomatic, severe aortic stenosis throughout 2 years of follow-up, with similar outcome with respect to cerebrovascular accidents, stroke, and myocardial infarction.
(2) Mortality benefits with TAVI over SAVR are consistent across the spectrum of intermediate to high-risk without evidence of heterogeneity according to the TAVI heart valve system (balloon-expandable vs. self-expandable).

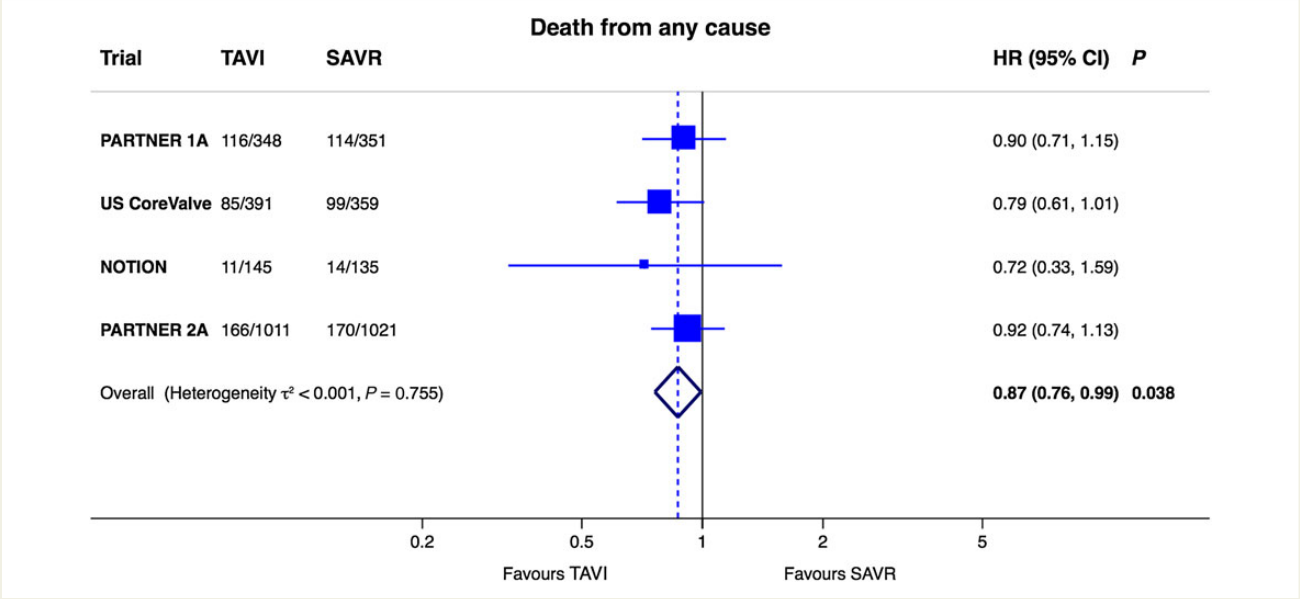

Figure 2 Random-effects meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the primary outcome of death from any cause. Forest plots showing the results of meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the primary outcome of death from any cause at 2 years of follow-up. Hazard ratio estimates according to intention-to-treat principle were retrieved from three trials (PARTNER 1A, NOTION, and PARTNER 2A); whereas one trial (US CoreValve High Risk) contributed with the estimated risk ratio by using the events provided in as-treated populations. The provided number of events and total trial population in each arm correspond to intention-to-treat or as-treated populations, according to the available information in each trial. Boxes and horizontal lines represent the respective hazard ratio and 95% confidence interval for each trial. The vertical solid line on the plot represents the point estimate of hazard ratio = 1. The vertical dashed line on plot represents the point estimate of overall hazard ratio. The size of each box is proportional to weight of that trial result. Diamonds represent the 95% confidence interval for pooled estimates of the effect and are centred on pooled hazard ratios. Heterogeneity estimate of τ^2 accompanies the summary estimate. Values of τ^2 around 0.04 are considered to indicate low heterogeneity. TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; HR, hazard ratio; CI, confidence interval.

(3) The survival benefit of TAVI compared with SAVR is driven at least in part by the subgroup of patients that underwent TAVI by transfemoral access. Conversely, transthoracic TAVI provided similar, but not superior, outcomes in terms of survival compared with SAVR.
(4) There is a significant interaction of sex on the survival benefit of TAVI, with the mortality benefit driven largely in women vs. men undergoing TAVI vs. SAVR.
(5) There are marked reductions (~50%) in various periprocedural morbidities (kidney injury, AF, blood transfusion) in the TAVI compared with SAVR group, whereas the risk of major vascular complications, incidence of permanent pacemaker implantation, and paravalvular regurgitation favoured SAVR.

In this meta-analysis of patients with symptomatic, severe aortic stenosis at intermediate to high surgical risk, we found evidence for a significant benefit of TAVI when compared with SAVR in terms of all-cause mortality at 2 years of follow-up, with a 13% relative risk reduction and no heterogeneity between trials. Previously, only one out of four randomized trials ($n = 795$ patients, US CoreValve High Risk[5–7]) had shown a survival benefit at 2 years ($P = 0.04$), whereas the other three trials had resulted in non-inferiority of TAVI compared with SAVR. As none of the individual trials had sufficient power to detect superiority in terms of all-cause mortality, our analysis is the first report of all randomized trials performed to date providing reliable evidence of a cumulative survival benefit of TAVI (irrespective of access site) over SAVR at 2 years. There were no relevant differences in the risks of other ischaemic outcomes including cerebrovascular accidents, stroke, and myocardial infarction. Of note, the observed reduction in mortality by TAVI when compared with SAVR was independent of the type of TAVI heart valve system (balloon-expandable or self-expandable), suggesting a class effect. Findings were robust and consistent across the different risk categories ranging from high-risk (PARTNER 1A[1] and US CoreValve High Risk trial[5–7]) to lower-than-high-risk (NOTION[8] and PARTNER 2A trial[9]) patients. Of note, all patients included in the randomized clinical trials were evaluated within the Heart Team to ensure eligibility for either procedure.

A key mechanistic insight of our analysis is a significant interaction ($P_{interaction} = 0.02$) between mortality benefit and type of access. We show in our study a robust survival benefit in the subgroup of patients allocated to transfemoral TAVI compared with SAVR. The PARTNER 2A[9] trial had reported a borderline statistically significant benefit of TAVI over SAVR for the composite endpoint of death and disabling stroke at 2 years ($P = 0.05$). However, the difference in terms of all-cause mortality in that study was not significant (14.2 vs. 17.2%, $P = 0.11$), and the study was not powered for the primary

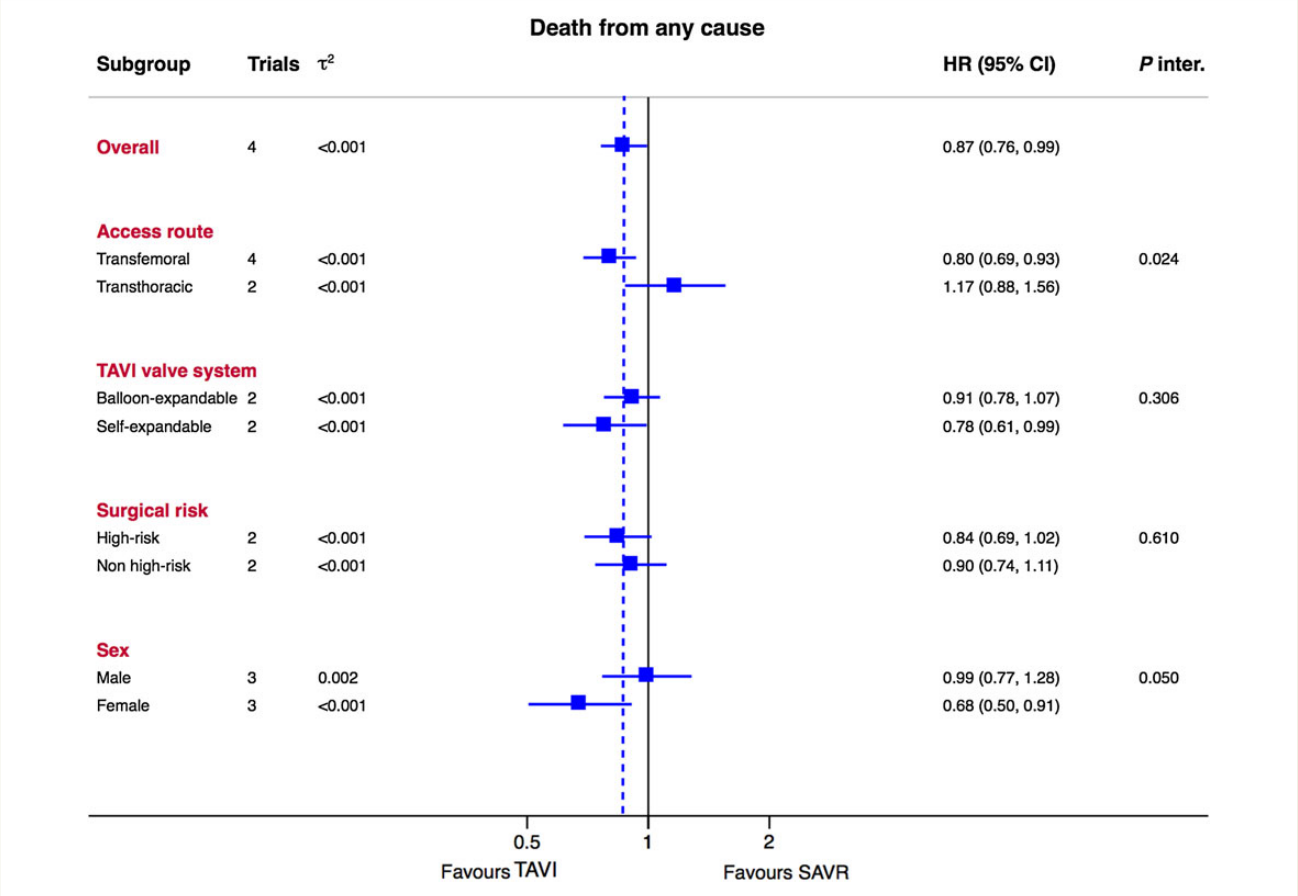

Figure 3 Subgroup analyses for the primary outcome of death from any cause. Hazard ratios and corresponding confidence intervals for patient subgroups from individual trials were pooled and interactions were evaluated by random-effects meta-analyses. Risk ratios were calculated whenever the respective hazard ratios were not reported. Boxes and horizontal lines represent the respective hazard ratio and 95% confidence interval for each trial. The vertical solid line on the plot represents the point estimate of hazard ratio = 1. The vertical dashed line on plot represents the point estimate of the overall hazard ratio. Heterogeneity estimates of τ^2 accompany each estimate. Values of τ^2 around 0.04 are considered to indicate low heterogeneity. Transthoracic corresponds to transapical or transaortic approach. TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; HR, hazard ratio; CI, confidence interval; *P* inter, *P* for interaction.

endpoint nor for all-cause mortality. While transfemoral TAVI was associated with a robust 20% relative risk reduction in mortality when compared with SAVR in our study, we observed similar outcomes among patients allocated to transthoracic TAVI when compared with SAVR. The finding of more favourable outcomes of transfemoral TAVI is consistent with previous reports and may be related at least in part to the less invasive nature of the intervention.[15–17] While TAVI by transthoracic access is an important treatment alternative to SAVR among carefully selected patients (those who cannot undergo transfemoral TAVI), the relevance of transfemoral TAVI will further increase owing to the continued refinement of delivery catheters and downsizing of the introducer sheath diameters with newer-generation devices.[18,19]

Our study shows a robust survival benefit of TAVI over SAVR in the subgroup of female patients, whereas none of the individual trials revealed significant differences at 2 years of follow-up. Several reasons may account for this finding. Female sex has been associated with increased risk of adverse events among patients undergoing SAVR.[20,21] Prosthesis–patient mismatch is more frequent and more often severe after SAVR than TAVI[22] and has been associated with increased all-cause and cardiac mortality.[23] A smaller anatomy of the aortic annulus in female patients with severe aortic stenosis may increase the risk for patient–prosthesis mismatch and contribute to the observed gender effect of TAVI vs. SAVR.

The improved survival among patients undergoing TAVI may also be attributed to the lower incidence of several key secondary outcomes, including new-onset AF, acute kidney injury, and major bleeding. Atrial fibrillation has been associated with increased mortality in patients undergoing SAVR[24] as well as TAVI.[25] The implication of a lower risk of AF among patients undergoing TAVI may take effect on the risk of cerebrovascular events during longer term follow-up related to the risk of thromboembolic adverse events particularly among patients without adequate protection by oral anticoagulation. Kidney injury has also been associated with adverse clinical sequelae in patients undergoing either TAVI or SAVR.[26,27] In our analysis, patients treated with TAVI had a lower risk of kidney

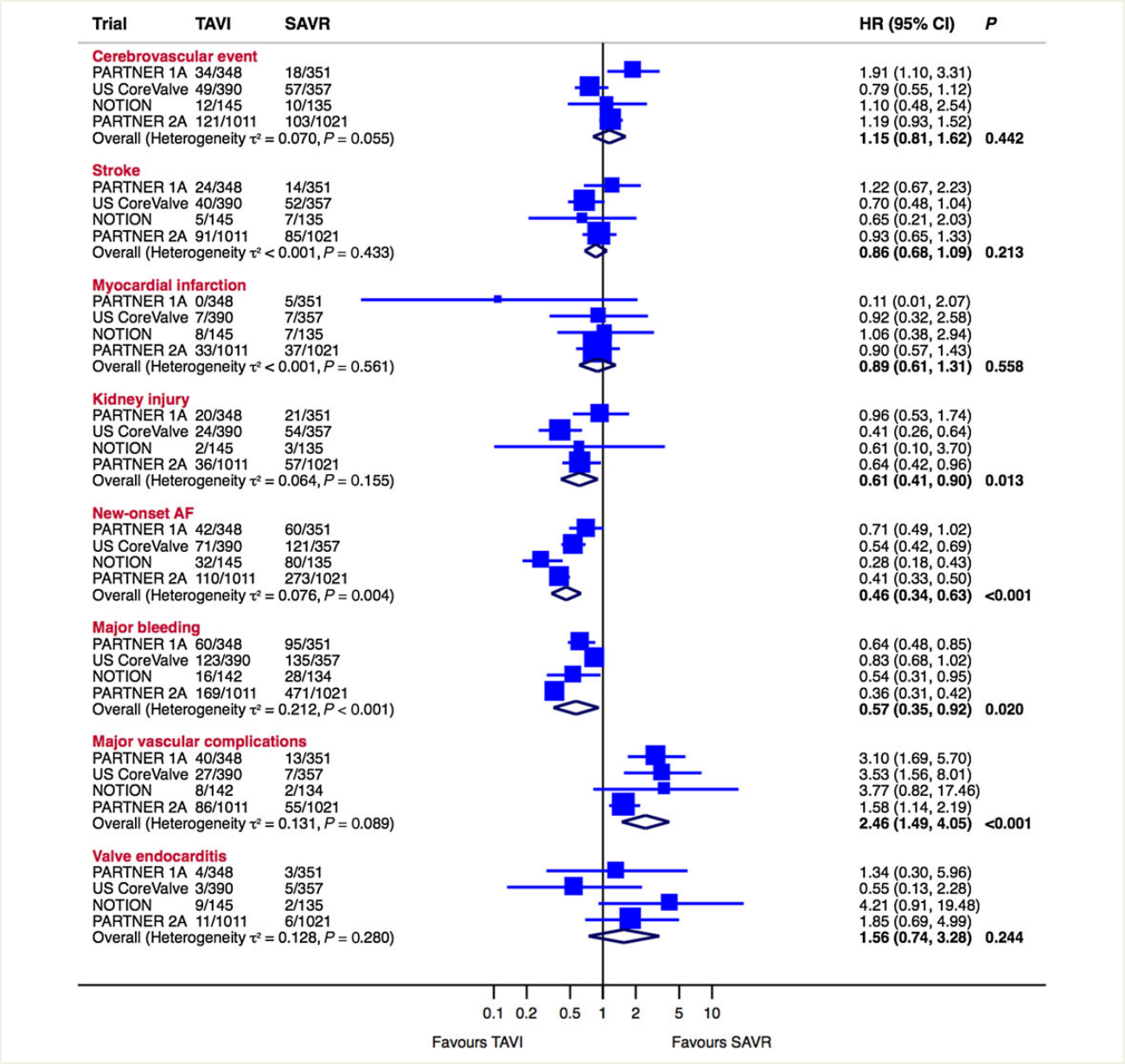

Figure 4 Random-effects meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the secondary outcomes of interest. Forest plots showing the results of meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the secondary outcomes of interest at up to 2 years of follow-up. In the NOTION trial, for the outcomes of major bleeding and major vascular complications, 30-day follow-up data were included. The provided number of events and total trial population in each arm correspond to intention-to-treat or as-treated populations, according to the available information for each outcome and each trial. Boxes and horizontal lines represent the respective hazard ratio and 95% confidence interval for each trial. The vertical solid line on the plot represents the point estimate of hazard ratio = 1. The size of each box is proportional to weight of that trial result. Diamonds represent the 95% confidence interval for pooled estimates of the effect and are centred on pooled hazard ratios. Heterogeneity estimates of τ^2 accompany each summary estimate. Values of τ^2 around 0.04 are considered to indicate low heterogeneity. TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; HR, hazard ratio; CI, confidence interval; AF, atrial fibrillation.

injury compared with SAVR, although we were not able to differentiate this effect by looking into the subgroup of patients with preoperative renal failure. A lower risk of bleeding may further contribute to the improved overall survival in the TAVI when compared with SAVR group. The risk of bleeding is of particular importance in elderly patients and has been associated with mortality in other procedures. Conversely, a higher risk of pacemaker implantation, which was observed in our meta-analysis, may adversely affect longer term outcomes among patients undergoing TAVI compared with SAVR through loss of atrioventricular synchrony, lack of

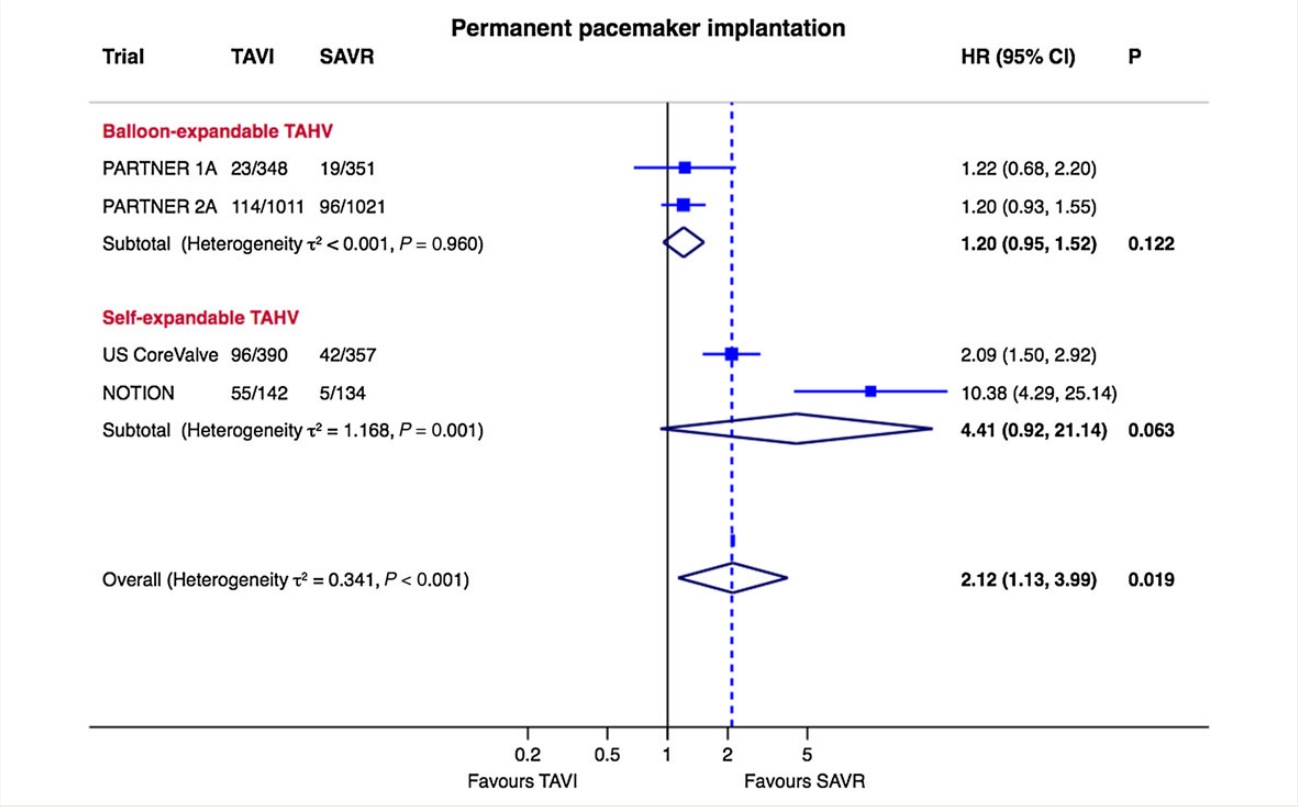

Figure 5 Random-effects meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the outcome of permanent pacemaker implantation stratified according to transcatheter heart valve system. Forest plot showing the results of meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the outcome of permanent pacemaker implantation at 2 years of follow-up. The provided number of events and total trial population in each arm correspond to as-treated populations, according to the available information for each outcome and each trial. Boxes and horizontal lines represent the respective hazard ratio and 95% confidence interval for each trial. The vertical solid line on the plot represents the point estimate of hazard ratio = 1. The vertical dashed line on plot represents the point estimate of the overall hazard ratio. The size of each box is proportional to weight of that trial result. Diamonds represent the 95% confidence interval for pooled estimates of the effect and are centred on pooled hazard ratios. Heterogeneity estimates of τ^2 accompany each summary estimate. Values of τ^2 around 0.04 are considered to indicate low heterogeneity. TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; HR, hazard ratio; CI, confidence interval; TAHV, transcatheter heart valve system.

physiological rate control, and right ventricular stimulation.[28] However, permanent pacemaker implantation does not always correspond to true atrioventricular node disturbances,[29] as the latter may recover over time and obviate the need for chronic right ventricular pacing[30,31] explaining at least in part conflicting evidence regarding the long-term effects of pacemaker implantation on mortality after TAVI.[32,33] Of note, self-expandable prostheses have an increased risk of atrioventricular conductance disturbances when compared with balloon-expandable devices.[29]

Patients allocated to SAVR had a lower risk of moderate-to-severe paravalvular regurgitation at 2 years than patients allocated to TAVI in our analysis. Of note, only early-generation transcatheter heart valve systems had been used in PARTNER 1A,[1–3] PARTNER 2A,[9] US CoreValve,[5–7] and NOTION[8] and are included in this meta-analysis. Moreover, this meta-analysis did not evaluate differences in terms of other haemodynamic outcomes including effective orifice area. On one hand, TAVI bioprosthetic heart valves consistently achieve greater effective orifice area compared with SAVR. Conversely, TAVI in our analysis is inferior to SAVR with respect to paravalvular regurgitation, which has been shown to adversely affect long-term outcomes if more than mild. Of note, newer-generation transcatheter bioprostheses provide significantly reduced rates of moderate-to-severe paravalvular regurgitation compared with early-generation devices used in this meta-analysis and have been associated with improved clinical outcomes.[9,34]

This meta-analysis has several limitations. First, the main analysis is focused on 2 years of follow-up. Excess mortality during long-term follow-up due to non-valvular causes of death may conceal the therapeutic effect of valvular replacement. The competing effect of non-valve-related mortality in a predominantly elderly and high-risk patient population may camouflage potential differences between the two treatment strategies and bias potentially important between/group differences towards the null. Of note, data regarding the long-term outcome of TAVI when compared with SAVR beyond 5 years are not available at this point in time. Second, RCTs included

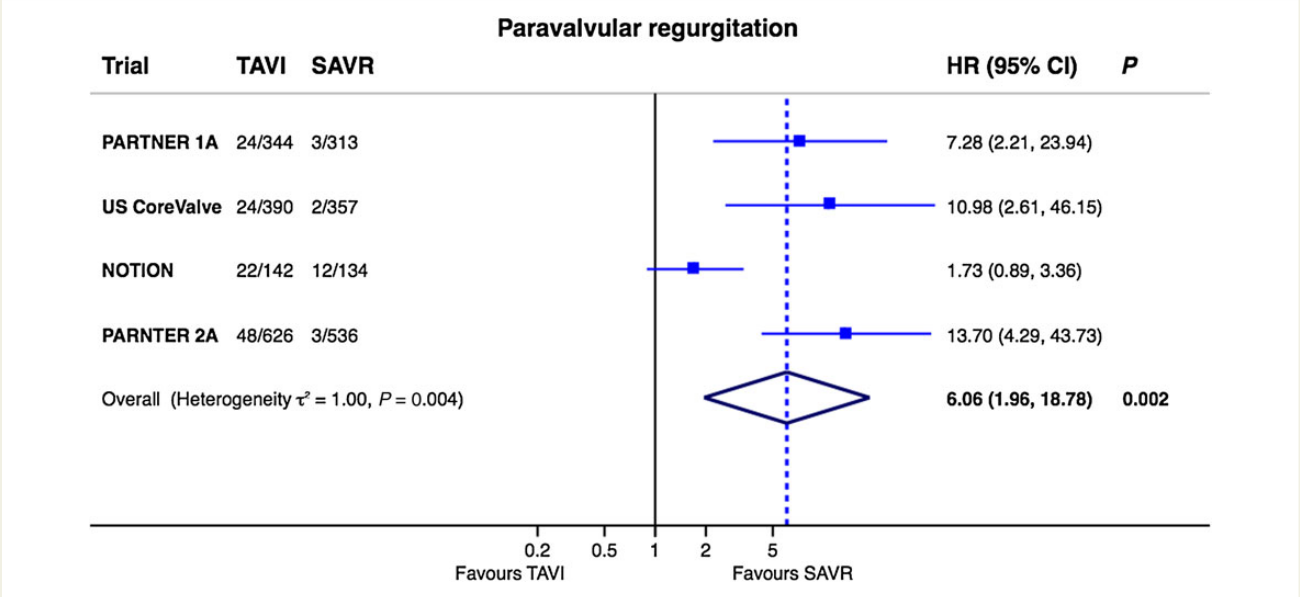

Figure 6 Random-effects meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the echocardiographic outcome of paravalvular regurgitation (moderate or severe). Forest plot showing the results of meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the echocardiographic outcome of paravalvular regurgitation (moderate or severe) at 2 years of follow-up. The provided number of events and total trial population in each arm correspond to as-treated populations, according to the available information for each outcome and each trial. Boxes and horizontal lines represent the respective hazard ratio and 95% confidence interval for each trial. The vertical solid line on the plot represents the point estimate of hazard ratio = 1. The vertical dashed line on plot represents the point estimate of the overall hazard ratio. The size of each box is proportional to weight of that trial result. Diamonds represent the 95% confidence interval for pooled estimates of the effect and are centred on pooled hazard ratios. Heterogeneity estimates of τ^2 accompany each summary estimate. Values of τ^2 around 0.04 are considered to indicate low heterogeneity. TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; HR, hazard ratio; CI, confidence interval.

in the meta-analysis used early-generation transcatheter bioprostheses, which underwent substantial improvements in recent device iterations. Newer generation are associated with a significant reduction of paravalvular regurgitation due to the features of repositionability and/or the use of internal skirts or external cuffs.[34–36] In addition, downsizing of the delivery sheaths from 18–24 French to 14–16 French in newer iterations of TAVI prostheses has resulted in a further reduction of vascular access site complications.[35–37] Along this line, a recent propensity-score-matched comparison of an observational study using a new balloon-expandable transcatheter heart valve prosthesis (Edwards Sapien S3) among intermediate risk patients with severe aortic stenosis with a historical cohort of patients undergoing SAVR within the PARTNER 2A trial suggested superior outcomes of TAVI in terms of the composite of mortality, stroke, and moderate-to-severe aortic regurgitation at 1 year.[34] Third, due to lack of individual patient-level data, we were unable to perform all analyses in pre-specified subgroups of patients such as age, left ventricular ejection fraction, and other characteristics that might yield additional clinical insights. Fourth, only four trials were available, which limits the power of the interaction tests accompanying the subgroup analyses. Therefore, we cannot exclude that the two non-significant interaction tests are false negatives. Moreover, an investigation of the impact and mutual association of patient-level covariates requires individual patient data to which we had no access. Finally, patients recruited in RCTs are carefully selected and may not reflect routine clinical practice. However, results of numerous large-scale and carefully conducted nationwide registries attest to the external validity of the findings in the randomized trials.[38–41] Overall, there has been the consistent observation of decreasing mortality and stroke rates with increasing experience and improved patient evaluation and selection as well as device iteration.[42–44]

In conclusion, in this meta-analysis of the four landmark RCTs comparing TAVI with SAVR among patients with symptomatic, severe aortic stenosis, TAVI showed a mortality benefit when compared with SAVR at 2 years of follow-up. The effect was consistent across high-risk and lower-risk categories, was independent of device type, and was driven by the subgroup of TAVI patients undergoing transfemoral access and the pronounced effect found in females.

Supplementary material

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

Authors' contributions

G.C.M.S., G.S., D.M., P.J., and S.W. conceived and designed the study. G.C.M.S. and F.P. scrutinized the potentially eligible items and performed data extraction. L.S. contributed by providing additional

data. G.C.M.S. and D.M. analysed the data. G.C.M.S., F.P., T.P., P.J., and S.W. wrote the first draft of the report. All authors reviewed the final version. All authors read and met the ICMJE criteria for authorship. All authors agree with the results and conclusions of the report.

Funding

The study was funded by intramural funds of the Department of Cardiology, Bern University Hospital, Bern, Switzerland. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest: T.P. has received speaker fees from Medtronic and Biotronik, outside the submitted work. L.S. is proctor for Medtronic, St Jude Medical, and Boston Scientific; and has received research grants to his institution (Rigshospitalet) from Medtronic, St Jude Medical, Boston Scientific, and Symetis, outside the submitted work. P.J. has received research grants to the institution from Astra Zeneca, Biotronik, Biosensors International, Eli Lilly, and The Medicines Company; and serves as unpaid member of the steering group of trials funded by Astra Zeneca, Biotronik, Biosensors, St Jude Medical, and The Medicines Company. S.W. has received research grants to his institution (Bern University Hospital) from Abbott, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, Medicines Company, and St Jude Medical. All other authors declare no competing interests.

References

1. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;**364**:2187–2198.
2. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;**366**:1686–1695.
3. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG; PARTNER 1 Trial Investigators. 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**:2477–2484.
4. Nielsen HH, Klaaborg KE, Nissen H, Terp K, Mortensen PE, Kjeldsen BJ, Jakobsen CJ, Andersen HR, Egeblad H, Krusell LR, Thuesen L, Hjortdal VE. 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**:383–389.
5. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK; U.S. CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;**370**:1790–1798.
6. Reardon MJ, Adams DH, Kleiman NS, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Lee JS, Hermiller JB Jr, Chetcuti S, Heiser J, Merhi W, Zorn GL III, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Maini B, Mumtaz M, Conte JV, Resar JR, Aharonian V, Pfeffer T, Oh JK, Qiao H, Popma JJ. 2-year outcomes in patients undergoing surgical or self-expanding transcatheter aortic valve replacement. *J Am Coll Cardiol* 2015;**66**:113–121.
7. Deeb GM, Reardon MJ, Chetcuti S, Patel HJ, Grossman PM, Yakubov SJ, Kleiman NS, Coselli JS, Gleason TG, Lee JS, Hermiller JB Jr, Heiser J, Merhi W, Zorn GL III, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Maini B, Mumtaz M, Conte J, Resar J, Aharonian V, Pfeffer T, Oh JK, Qiao H, Adams DH, Popma JJ; CoreValve US Clinical Investigators. Three-year outcomes in high-risk patients who underwent surgical or transcatheter aortic valve replacement. *Eur Heart J* 2016;**67**:2565–2574.
8. Thyregod HG, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrøm T, Clemmensen P, Hansen PB, Andersen LW, Olsen PS, Søndergaard L. 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**:2184–2194.
9. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG; PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;**374**:1609–1620.
10. Higgins JJ, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
11. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;**349**:g7647.
12. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–188.
14. Da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. *Eur Heart J* 2014;**35**:3336–3345.
15. Thomas M, Schymik G, Walther T, Himbert D, Lefèvre T, Treede H, Eggebrecht H, Rubino P, Colombo A, Lange R, Schwarz RR, Wendler O. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation* 2011;**124**:425–433.
16. van der Boon RM, Marcheix B, Tchetche D, Chieffo A, Van Mieghem NM, Dumonteil N, Vahdat O, Maisano F, Serruys PW, Kappetein AP, Fajadet J, Colombo A, Carrié D, van Domburg RT, de Jaegere PP. Transapical versus transfemoral aortic valve implantation: a multicenter collaborative study. *Ann Thorac Surg* 2014;**97**:22–28.
17. Panchal HB, Ladia V, Amin P, Patel P, Veeranki SP, Albalbissi K, Paul T. A meta-analysis of mortality and major adverse cardiovascular and cerebrovascular events in patients undergoing transfemoral versus transapical transcatheter aortic valve implantation using edwards valve for severe aortic stenosis. *Am J Cardiol* 2014;**114**:1882–1890.
18. Webb JG, Doshi D, Mack MJ, Makkar R, Smith CR, Pichard AD, Kodali S, Kapadia S, Miller DC, Babaliaros V, Thourani V, Herrmann HC, Bodenhamer M, Whisenant BK, Ramee S, Maniar H Jr, Kereiakes D, Xu K, Jaber WA, Menon V, Tuzcu EM, Wood D, Svensson LG, Leon MB. A randomized evaluation of the SAPIEN XT transcatheter heart valve system in patients with aortic stenosis who are not candidates for surgery. *JACC Cardiovasc Interv* 2015;**8**:1797–1806.
19. Nijhoff F, Abawi M, Agostoni P, Ramjankhan FZ, Doevendans PA, Stella PR. Transcatheter aortic valve implantation with the new balloon-expandable Sapien 3 versus Sapien XT valve system: a propensity score-matched single-center comparison. *Circ Cardiovasc Interv* 2015;**8**:e002408.
20. Fuchs C, Mascherbauer J, Rosenhek R, Pernicka E, Klaar U, Scholten C, Heger M, Wollenek G, Czerny M, Maurer G, Baumgartner H. Gender differences in clinical presentation and surgical outcome of aortic stenosis. *Heart* 2010;**96**:539–545.
21. Kodali S, Williams MR, Doshi D, Hahn RT, Humphries KH, Nkomo VT, Cohen DJ, Douglas PS, Mack M, Xu K, Svensson L, Thourani VH, Tuzcu EM, Weissman NJ, Leon M, Kirtane AJ. Sex-specific differences at presentation and outcomes among patients undergoing transcatheter aortic valve replacement: a cohort study. *Ann Intern Med* 2016;**164**:377–384.
22. Pibarot P, Weissman NJ, Stewart WJ, Hahn RT, Lindman BR, McAndrew T, Kodali SK, Mack MJ, Thourani VH, Miller DC, Svensson LG, Herrmann HC, Smith CR, Rodés-Cabau J, Webb J, Lim S, Xu K, Hueter I, Douglas PS, Leon MB. Incidence and sequelae of prosthesis-patient mismatch in transcatheter versus surgical valve replacement in high-risk patients with severe aortic stenosis: a PARTNER trial cohort-A analysis. *J Am Coll Cardiol* 2014;**64**:1323–1334.
23. Head SJ, Mokhles MM, Osnabrugge RL, Pibarot P, Mack MJ, Takkenberg JJ, Bogers AJ, Kappetein AP. The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. *Eur Heart J* 2012;**33**:1518–1529.

24. Tanawuttiwat T, O'Neill BP, Cohen MG, Chinthakanan O, Heldman AW, Martinez CA, Alfonso CE, Mitrani RD, Macon CJ, Carrillo RG, Williams DB, O'Neill WW, Myerburg RJ. New-onset atrial fibrillation after aortic valve replacement: comparison of transfemoral, transapical, transaortic, and surgical approaches. *J Am Coll Cardiol* 2014;**63**:1510–1519.
25. Stortecky S, Buellesfeld L, Wenaweser P, Heg D, Pilgrim T, Khattab AA, Gloekler S, Huber C, Nietlispach F, Meier B, Jüni P, Windecker S. Atrial fibrillation and aortic stenosis: impact on clinical outcomes among patients undergoing transcatheter aortic valve implantation. *Circ Cardiovasc Interv* 2013;**6**:77–84.
26. Bagur R, Webb JG, Nietlispach F, Dumont E, De Larochellière R, Doyle D, Masson JB, Gutiérrez MJ, Clavel MA, Bertrand OF, Pibarot P, Rodés-Cabau J. Acute kidney injury following transcatheter aortic valve implantation: predictive factors, prognostic value, and comparison with surgical aortic valve replacement. *Eur Heart J* 2010;**31**:865–874.
27. Karkouti K, Wijeysundera DN, Yau TM, Callum JL, Cheng DC, Crowther M, Dupuis JY, Fremes SE, Kent B, Laflamme C, Lamy A, Legare JF, Mazer CD, McCluskey SA, Rubens FD, Sawchuk C, Beattie WS. Acute kidney injury after cardiac surgery: focus on modifiable risk factors. *Circulation* 2009;**119**:495–502.
28. Tops LF, Schalij MJ, Bax JJ. The effects of right ventricular apical pacing on ventricular function and dyssynchrony implications for therapy. *J Am Coll Cardiol* 2009;**54**:764–776.
29. Siontis GC, Jüni P, Pilgrim T, Stortecky S, Büllesfeld L, Meier B, Wenaweser P, Windecker S. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVI: a meta-analysis. *J Am Coll Cardiol* 2014;**64**:129–140.
30. Gutiérrez M, Rodés-Cabau J, Bagur R, Doyle D, DeLarochellière R, Bergeron S, Lemieux J, Villeneuve J, Côté M, Bertrand OF, Poirier P, Clavel MA, Pibarot P, Dumont E. Electrocardiographic changes and clinical outcomes after transapical aortic valve implantation. *Am Heart J* 2009;**158**:302–308.
31. Guetta V, Goldenberg G, Segev A, Dvir D, Kornowski R, Finckelstein A, Hay I, Goldenberg I, Glikson M. Predictors and course of high-degree atrioventricular block after transcatheter aortic valve implantation using the CoreValve Revalving System. *Am J Cardiol* 2011;**108**:1600–1605.
32. Buellesfeld L, Stortecky S, Heg D, Hausen S, Mueller R, Wenaweser P, Pilgrim T, Gloekler S, Khattab AA, Huber C, Carrel T, Eberle B, Meier B, Boekstegers P, Jüni P, Gerckens U, Grube E, Windecker S. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. *J Am Coll Cardiol* 2012;**60**:493–501.
33. Nazif TM, Dizon JM, Hahn RT, Xu K, Babaliaros V, Douglas PS, El-Chami MF, Herrmann HC, Mack M, Makkar RR, Miller DC, Pichard A, Tuzcu EM, Szeto WY, Webb JG, Moses JW, Smith CR, Williams MR, Leon MB, Kodali SK; PARTNER Publications Office. Predictors and clinical outcomes of permanent pacemaker implantation after transcatheter aortic valve replacement: the PARTNER (Placement of AoRtic TraNscathetER Valves) trial and registry. *JACC Cardiovasc Interv* 2015;**8**:60–69.
34. Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, Smalling R, Lim S, Malaisrie SC, Kapadia S, Szeto WY, Greason KL, Kereiakes D, Ailawadi G, Whisenant BK, Devireddy C, Leipsic J, Hahn RT, Pibarot P, Weissman NJ, Jaber WA, Cohen DJ, Suri R, Tuzcu EM, Svensson LG, Webb JG, Moses JW, Mack MJ, Miller DC, Smith CR, Alu MC, Parvataneni R, D'Agostino RB Jr, Leon MB. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet* 2016;**387**:2218–2225.
35. Rampat R, Khawaja MZ, Byrne J, MacCarthy P, Blackman DJ, Krishnamurthy A, Gunarathne A, Kovac J, Banning A, Kharbanda R, Firoozi S, Brecker S, Redwood S, Bapat V, Mullen M, Aggarwal S, Manoharan G, Spence MS, Khogali S, Dooley M, Cockburn J, de Belder A, Trivedi U, Hildick-Smith D. Transcatheter aortic valve replacement using the repositionable LOTUS valve: United Kingdom experience. *JACC Cardiovasc Interv* 2016;**9**:367–372.
36. Généreux P, Head SJ, Van Mieghem NM, Kodali S, Kirtane AJ, Xu K, Smith C, Serruys PW, Kappetein AP, Leon MB. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. *J Am Coll Cardiol* 2012;**59**:2317–2326.
37. Barbanti M, Binder RK, Freeman M, Wood DA, Leipsic J, Cheung A, Ye J, Tan J, Toggweiler S, Yang TH, Dvir D, Maryniak K, Lauck S, Webb JG. Impact of low-profile sheaths on vascular complications during transfemoral transcatheter aortic valve replacement. *EuroIntervention* 2013;**9**:929–935.
38. Walther T, Hamm CW, Schuler G, Berkowitsch A, Kötting J, Mangner N, Mudra H, Beckmann A, Cremer J, Welz A, Lange R, Kuck KH, Mohr FW, Möllmann H; GARY Executive Board. Perioperative results and complications in 15,964 transcatheter aortic valve replacements: prospective data from the GARY registry. *J Am Coll Cardiol* 2015;**65**:2173–2180.
39. Van Belle E, Juthier F, Susen S, Vincentelli A, Iung B, Dallongeville J, Eltchaninoff H, Laskar M, Leprince P, Lievre M, Banfi C, Auffray JL, Delhaye C, Donzeau-Gouge P, Chevreul K, Fajadet J, Leguerrier A, Prat A, Gilard M, Teiger E; FRANCE 2 Investigators. Postprocedural aortic regurgitation in balloon-expandable and self-expandable transcatheter aortic valve replacement procedures: analysis of predictors and impact on long-term mortality: insights from the FRANCE2 Registry. *Circulation* 2014;**129**:1415–1427.
40. Duncan A, Ludman P, Banya W, Cunningham D, Marlee D, Davies S, Mullen M, Kovac J, Spyt T, Moat N. Long-term outcomes after transcatheter aortic valve replacement in high-risk patients with severe aortic stenosis: the U.K. Transcatheter Aortic Valve Implantation Registry. *JACC Cardiovasc Interv* 2015;**8**:645–653.
41. Holmes DR Jr, Brennan JM, Rumsfeld JS, Dai D, O'Brien SM, Vemulapalli S, Edwards FH, Carroll J, Shahian D, Grover F, Tuzcu EM, Peterson ED, Brindis RG, Mack MJ; STS/ACC TVT Registry. Clinical outcomes at 1 year following transcatheter aortic valve replacement. *JAMA* 2015;**313**:1019–1028.
42. Pilgrim T, Windecker S. Transcatheter aortic valve replacement: lessons gained from extreme-risk patients. *J Am Coll Cardiol* 2015;**66**:1335–1338.
43. Binder RK, Stortecky S, Heg D, Tueller D, Jeger R, Toggweiler S, Pedrazzini G, Amann FW, Ferrari E, Noble S, Nietlispach F, Maisano F, Räber L, Roffi M, Grünenfelder J, Jüni P, Huber C, Windecker S, Wenaweser P. Procedural results and clinical outcomes of transcatheter aortic valve implantation in Switzerland: an observational cohort study of Sapien 3 versus Sapien XT transcatheter heart valves. *Circ Cardiovasc Interv* 2015;**8**:e002653.
44. Manoharan G, Walton AS, Brecker SJ, Pasupati S, Blackman DJ, Qiao H, Meredith IT. Treatment of symptomatic severe aortic stenosis with a novel resheathable supra-annular self-expanding transcatheter aortic valve system. *JACC Cardiovasc Interv* 2015;**8**:1359–1367.