

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

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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 ($P_{\text{interaction}} = 0.306$) and baseline risk ($P_{\text{interaction}} = 0.610$). 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); $P = 0.293$] ($P_{\text{interaction}} = 0.024$) and in female [0.68 (0.50–0.91); $P = 0.010$], but not male patients [0.99 (0.77–1.28); $P = 0.952$] ($P_{\text{interaction}} = 0.050$). 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

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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 (NOTION⁸ and PARTNER 2B⁹) 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 appendices, 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 trial⁴) 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 2A⁹) 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.

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 (NOTION⁸ and PARTNER 2A⁹). 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 trial¹) and the Edwards SAPIEN XT (PARTNER 2A trial⁹); the self-expandable TAVI heart valve system, namely Medtronic CoreValve, was used in the other two trials (US CoreValve High Risk^{5–7} and NOTION⁸) 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

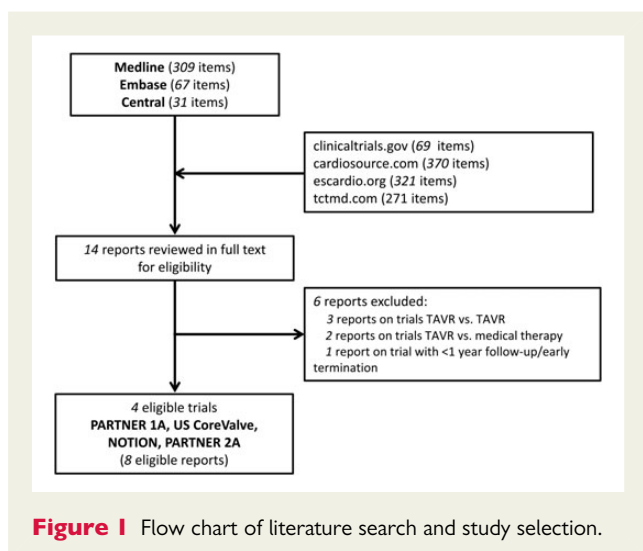


Table 1 Characteristics of trials, patients, and interventions by treatment group of the included randomized trials

	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, <i>n</i>	348	351	394	401	145	135	1011	1021
As-treated patients, <i>n</i>	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, <i>n</i>	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, <i>n</i>	38	24	48	52	2	1	51	53
Peripheral vascular disease, <i>n</i>	148	142	163	169	6	9	282	336
Prior cerebrovascular event, <i>n</i>	95	87	51	53	24	22	nd	nd
Prior CABG, <i>n</i>	147	152	117	121	nd	nd	239	261
Prior PCI, <i>n</i>	116	110	133	152	11	12	274	282
Known atrial fibrillation or flutter, <i>n</i>	80	73	161	190	40	34	313	359
Prior pacemaker, <i>n</i>	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, <i>n</i>								
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); $P = 0.952$] ($P_{\text{interaction}} = 0.050$). We did not detect any variation in the benefit of TAVI over SAVR according to the risk category at baseline ($P_{\text{interaction}} = 0.610$).

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).

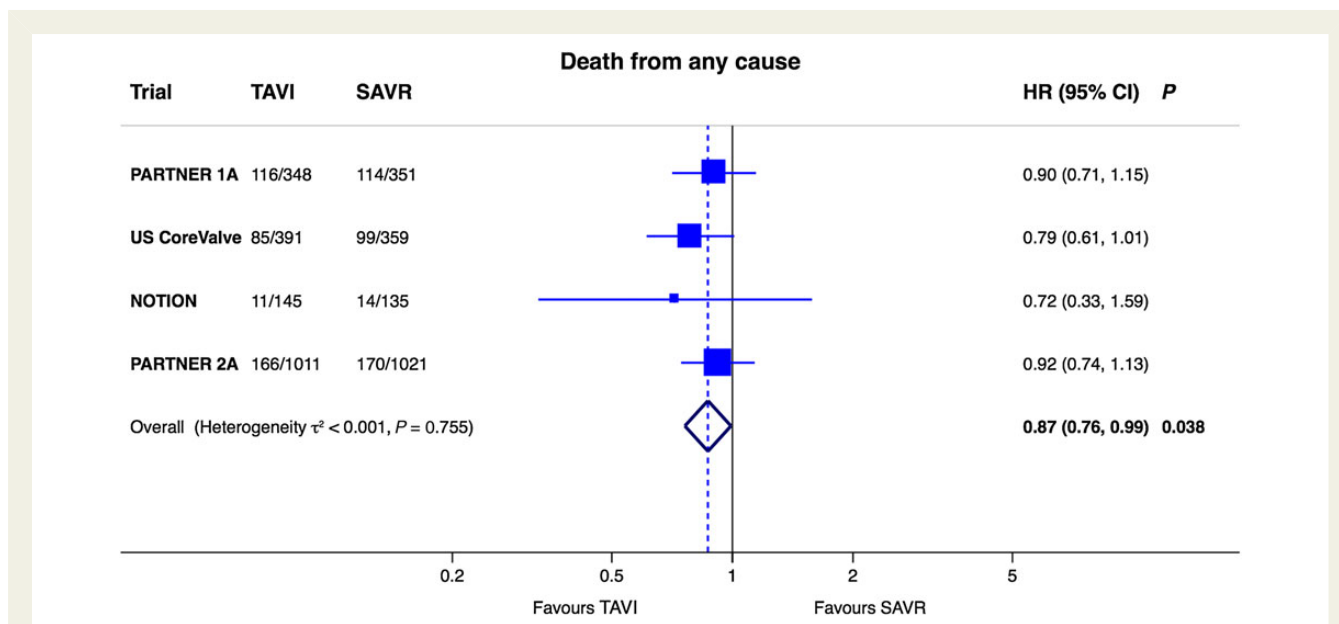


Figure 2 Random-effects meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the primary outcome of death from any cause. Forest plots showing the results of meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for 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 peri-procedural 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 Risk⁵⁻⁷) 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 1A¹ and US CoreValve High Risk trial⁵⁻⁷) to lower-than-high-risk (NOTION⁸ and PARTNER 2A trial⁹) 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 ($P_{\text{interaction}} = 0.02$) 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 2A⁹ 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

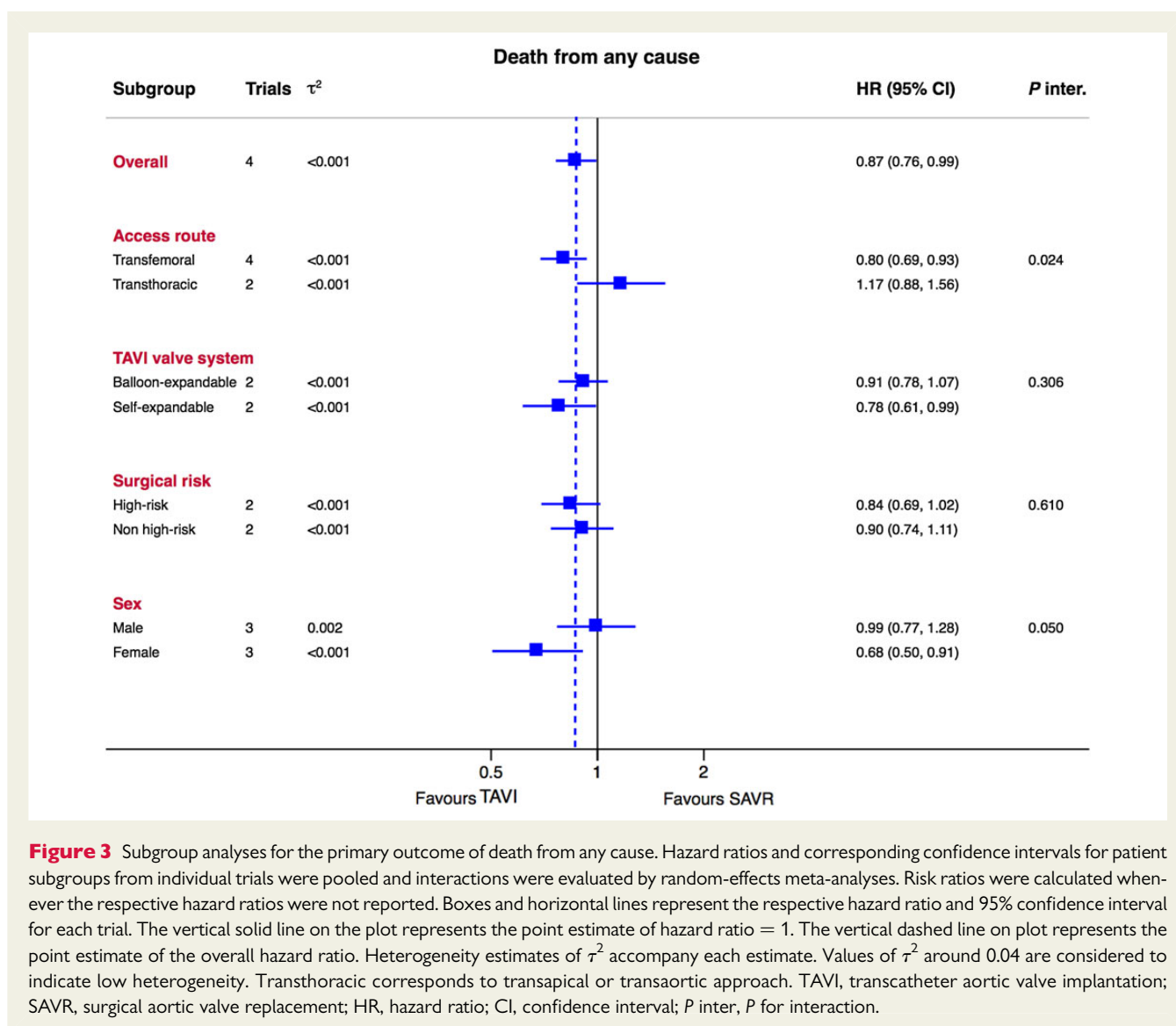


Figure 3 Subgroup analyses for the primary outcome of death from any cause. Hazard ratios and corresponding confidence intervals for patient subgroups from individual trials were pooled and interactions were evaluated by random-effects meta-analyses. Risk ratios were calculated whenever the respective 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 TAVI²² 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 SAVR²⁴ 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

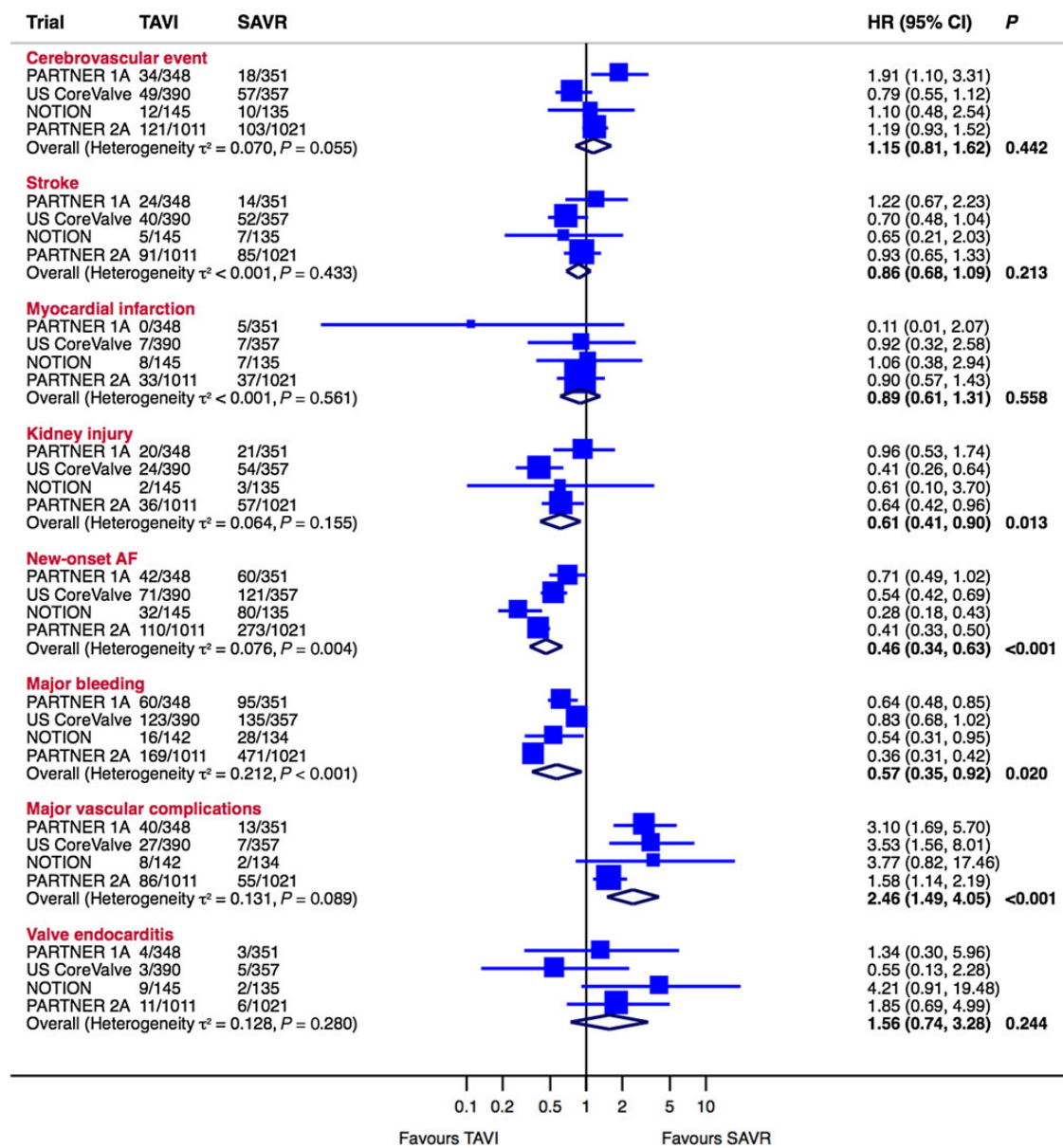


Figure 4 Random-effects meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the secondary outcomes of interest. Forest plots showing the results of meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the secondary 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 pre-operative 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

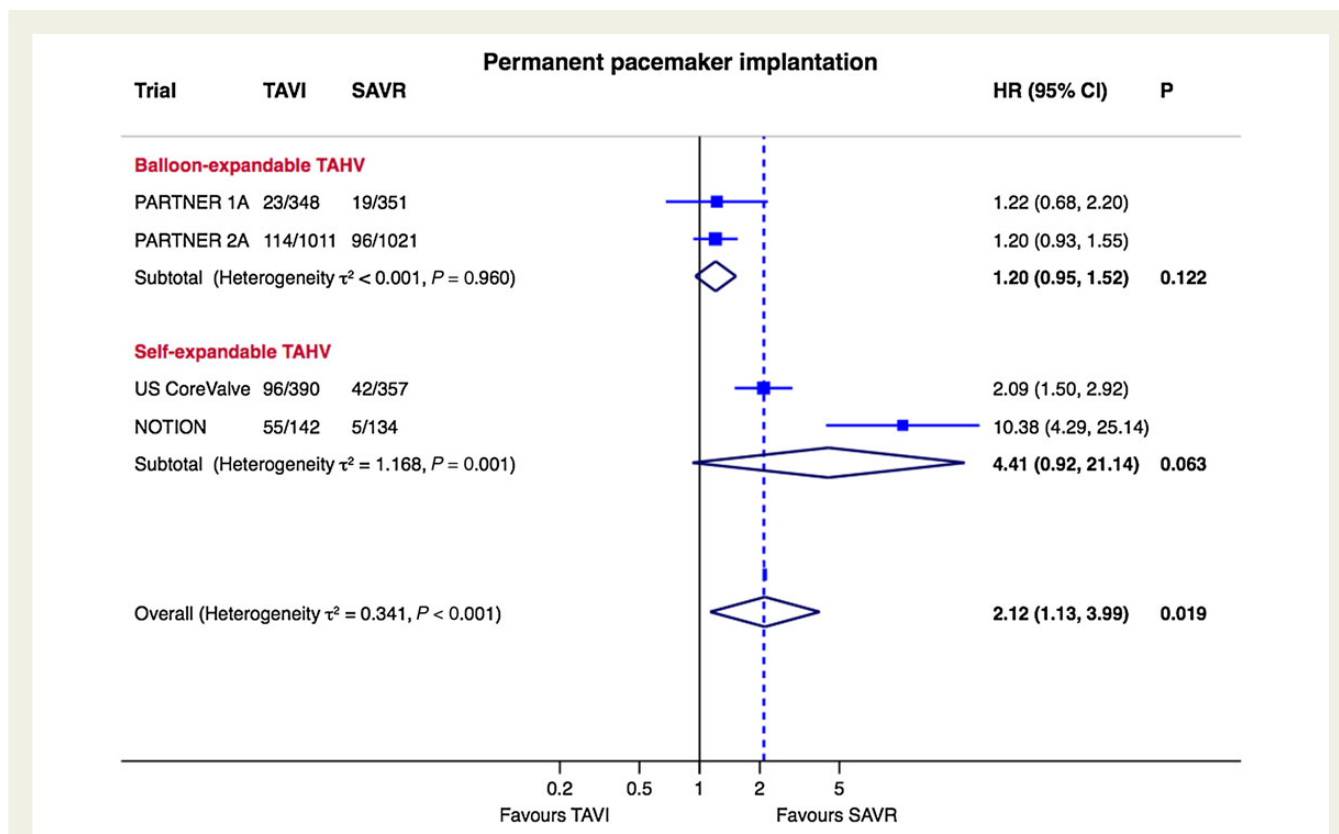


Figure 5 Random-effects meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the outcome of permanent pacemaker implantation stratified according to transcatheter heart valve system. Forest plot showing the results of meta-analysis of transcatheter aortic 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 conduction 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 NOTION⁸ 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

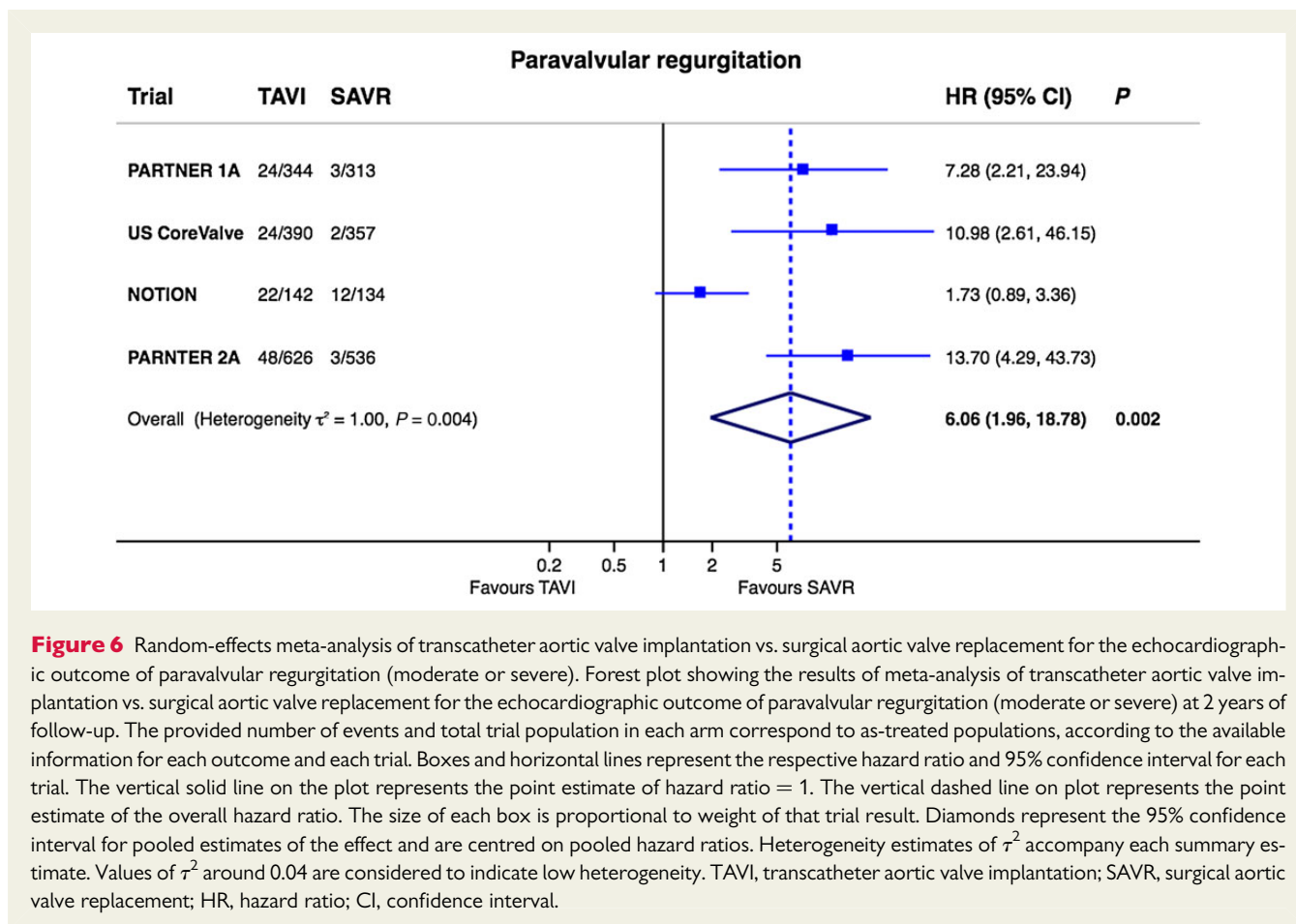


Figure 6 Random-effects meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the echocardiographic outcome of paravalvular regurgitation (moderate or severe). Forest plot showing the results of meta-analysis of transcatheter aortic valve implantation vs. 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.

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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.

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