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META-ANALYSIS

REVIEW

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Five-year outcomes in trials comparing transcatheter aortic valve implantation versus surgical aortic valve replacement: a pooled meta-analysis of reconstructed time-to-event data

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Key question

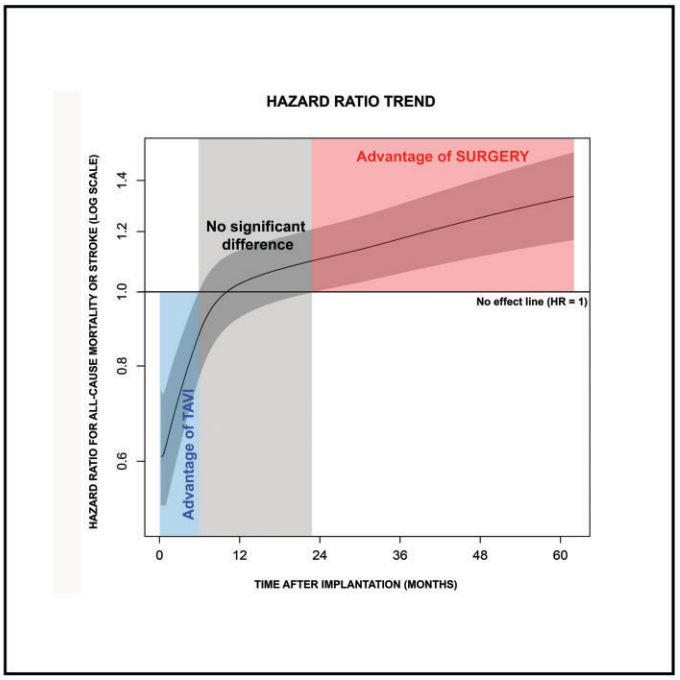
Are midterm results of transcatheter aortic prostheses similar to those of surgical aortic prostheses?

Key finding(s)

TAVI has a protective effect in the short-term that reverses over time, leading to a 25% higher hazard for a composite of death and stroke after 24 months.

Take-home message

Life expectancy is a key factor for selecting the most tailored treatment for aortic valve disease in light of the reversal of TAVI advantages after 2 years.



Abstract

OBJECTIVES: The incidence of outcomes in trials comparing transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR) is expected to be different in the short and long term. We planned a meta-analysis of reconstructed time-to-event data from trials comparing TAVI and SAVR to evaluate their time-varying effects on outcomes.

METHODS: We performed a systematic review of the literature from January 2007 through September 2021 on Medline, Embase, the Cochrane Central Register of Controlled Trials and specialistic websites, including randomized trials with allocation to TAVI or SAVR that reported at least 1-year follow-up and that graphed Kaplan–Meier curves of end points. The comparisons were done with grouped frailty Cox models in a landmark framework and fully parametric models.

RESULTS: Seven trials were included (7770 participants). TAVI showed a lower incidence of the composite of death or stroke in the first 6 months [risk-stratified hazard ratio (HR) 0.66, 95% confidence interval (CI) 0.56–0.77, *P*-value <0.001], with an HR reversal after 24 months favouring SAVR (risk-stratified HR 1.25; 95% CI 1.08–1.46; *P*-value 0.003). These outcomes were confirmed for all-cause death (risk-stratified HR after 24 months 1.18; 95% CI 1.03–1.35; *P*-value 0.01). TAVI was also associated with an increased incidence of rehospitalization after 6 months (risk-stratified HR 1.42; 95% CI 1.06–1.91; *P*-value 0.018) that got worse after 24 months (risk-stratified HR 1.67; 95% CI 1.24–2.24; *P*-value <0.001).

CONCLUSIONS: Although it could appear that there is no difference between TAVI and SAVR in the 5-year cumulative results, TAVI shows a strong protective effect in the short term that runs out after 1 year. TAVI becomes a risk factor for all-cause mortality and the composite end point after 24 months and for rehospitalization after 6 months.

Keywords: Transcatheter aortic valve replacement • Surgical aortic valve replacement • Follow-up • Aortic valve stenosis

ABBREVIATIONS

CI	Confidence interval
HR	Hazard ratio
RCTs	Randomized controlled trials
RTE	Reconstructed time-to-event
SAVR	Surgical aortic valve replacement
TAVI	Transcatheter aortic valve implantation

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has been recognized as the primary choice for the treatment of aortic valve stenosis in prohibitive-risk and high-risk patients and as an alternative to surgery in intermediate-risk patients [1–3]. The encouraging results up to 5 years in the high- [2, 3] and intermediate-risk profiles [4, 5] have led to increased interest also in low-risk patients [6–8], making an appraisal of longer-term outcomes critically important.

The risk of death and comorbidities postoperatively is non-constant over time, because the operation is a factor negatively affecting the early postoperative period. Surgical aortic valve replacement (SAVR) has an intrinsic increased risk of complications in the first months related, for example, to extracorporeal circulation and surgical incisions, risks that decrease soon after surgery. This well-known time-varying incidence of mortality and morbidities moving from short- to mid-term follow-up is driven by different underlying mechanisms:

outcomes are heavily influenced by the surgical procedure in the short term whereas later device durability and other valve-related events intervene in affecting outcomes. We recently performed a meta-analysis of reconstructed time-to-event (RTE) data on all-cause mortality to overcome the limitation of the individually underpowered studies and describe changing relative hazards over time, revealing an early survival advantage of TAVI, followed by a survival disadvantage after 40 months. This result is in contrast with those of single randomized controlled trials (RCTs) and other published meta-analyses that use summary data [9]. The relatively short follow-up time in RCTs on intermediate- and low-risk groups limited results between 2 and 5 years, because only the 2 trials on high risk and 1 small trial on low risk reached the 5-year follow-up [2, 3, 7], leaving open the concerns about intermediate risk [5, 10]. However, in the past months, the 5-year update of the PARTNER 2A trial and the 2-year follow-up of the PARTNER 3 trial have been published or presented [4, 11–13]. These data increased the 5-year sample size 2.14 times, because the PARTNER 2A trial increased the 5-year follow-up population from 1776 patients to 3808 [4], which permitted our analysis to be more informative not only on intermediate-risk but also on low-risk trials.

To date, RCTs in low- and intermediate-risk cohorts have been designed with composite primary outcomes. An advantage of a meta-analysis of multiple trials is that it enables the examination of rarer components of these composite outcomes, such as all-cause mortality and neurological events [2, 4–8, 14, 15]. Another end point that has gained a critical role when comparing TAVI and SAVR is the incidence of rehospitalization, which may provide further insights into the effects of TAVI over time [2, 4, 10, 16].

We planned a pooled meta-analysis of RTE data from trials comparing TAVI and SAVR to evaluate their effects on the long-term composite of death for any cause or stroke, all-cause mortality, stroke and rehospitalization, focusing on the potential time-varying effect and modelling their hazard ratio (HR) over time.

MATERIALS AND METHODS

Ethics statement

This meta-analysis is exempt from ethics approval because we collected and synthesized data published from previous clinical trials in which informed consent had already been obtained by the trial investigators.

Search strategy and selection criteria

A systematic review of the literature was performed by 2 independent researchers to identify eligible studies published between 1 January 2007 and 30 August 2020 in MEDLINE, Embase and the Cochrane Central Register of Controlled Trials. The systematic review of the literature was updated by a professional librarian (B.M.) to check for further trails, extending the search until 23 September 2021. The search algorithm is detailed in Supplementary Material, Table S1. We also checked websites (www.ClinicalTrials.gov, https://www.acc.org, www.escardio.org) for unpublished data.

The inclusion criteria were (i) RCTs with random allocation to TAVI or SAVR; (ii) at least 1-year follow-up; and (iii) a report of Kaplan–Meier curves of a composite of all-cause mortality or stroke, all-cause-mortality, stroke and rehospitalization in the text or the appendix or presented at selected international meetings.

The meta-analysis end points were the composite of all-cause mortality or stroke at follow-up, death from any cause at follow-up, stroke at follow-up and rehospitalization (procedure-related or valve-related, including heart failure) at follow-up. We planned to consider together in the stroke end point studies that included all strokes or disabling strokes in the composite outcome.

The HR was considered the effect size. HRs were estimated from pooled RTE data with Cox models and fully parametric models. We pooled data from intention-to-treat populations, choosing data from as-treated populations when intention-to-treat data were not available. For each enclosed trial, we selected the longest available follow-up report for each end point.

Data extraction and analysis

Two independent investigators (F.B. and A.P.) identified trials that fulfilled the prespecified inclusion criteria. Eligible trials were then reviewed in duplicate and disagreement was solved by a third investigator (M.R.). Data extracted from the text and appendix were trials characteristics, patient baseline data and comorbidities, device types and implant access.

In a meta-analysis of aggregated time-to-event data across trials, the appropriate effect measurement is the HR. Several extraction methods have been described, including direct and indirect estimation of HRs and 95% confidence interval (CI) [17–27]. Among them, the curve approach with the reconstruction of time-to-event data at the individual level is the more appropriate, because it allows us to overcome the limitation of non-proportional hazards increasingly reported in trials and also affecting the summary effect [26, 27]. Time-to-event data were extracted at the individual level from the Kaplan–Meier graphs. [9, 26–29], employing a dedicated software (Plot Digitizer 2.6.2 for Macintosh, https://sourceforge.net/projects/plotdigitizer/files/plotdigitizer/2.6.2/) to digitize Kaplan–Meier curves and a Kaplan–Meier data reconstruction algorithm for estimating individual patient data.

Risk of bias and quality assessment

The risk of bias among included trials was estimated by 2 authors (M.D.M., M.R.) using the revised Cochrane risk-of-bias tool for RCTs [30].

Statistical analyses

The cumulative incidence of outcomes at follow-up in the 2 treatment arms was evaluated with Kaplan–Meier estimates. Unadjusted HRs in the pooled data set were estimated with the grouped frailty semi-parametric (Cox) model, accounting for heterogeneity among trials with a random-intercept parameter, as previously described [9]. A grouped frailty semi-parametric (Cox) model was used to estimate unadjusted HRs in the pooled data set, accounting for heterogeneity among trials with a random-intercept parameter. The grouped frailty semi-parametric (Cox) model was also stratified by risk profile (high, intermediate and

low, as the risk profile of included patients has been classified by each RCT selected for the meta-analyses). The proportionality of the hazards of the Cox models was checked with the Grambsch–Therneau test and diagnostic plots based on Schoenfeld residuals. We planned to perform a landmark analysis in the case of evidence of non-constant proportional hazards from the test results or from visual inspection of the Kaplan–Meier curves. The time-dependency treatments' effect was approached with the landmark analysis, applying the Kaplan–Meier analysis and Cox regression to evaluate end points in the groups (TAVI/SAVR) at different time points. In the survival analysis setting, landmark analysis refers to the practice of designating a time point occurring during the follow-up period (known as the landmark time) and analysing only those subjects who have survived until the landmark time. The cut-offs were chosen on the basis of visual inspection of the scaled Schoenfeld residuals and of the Kaplan–Meier curves. Moreover, the time-varying HR of end points for TAVI versus SAVR was modelled with fully parametric generalized survival models (Royston–Parmar models) with baseline smoother and time-varying variables based on B-splines.

Quality assessment of RTE data was performed graphically by checking the derived Kaplan–Meier curves with the original ones. Moreover, the accuracy was evaluated by comparing the estimated and reported (when available) HRs. We assessed potential publication bias with visual interpretation of the funnel plots.

Analyses were performed with R language (R 3.6.0; R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2016. ISBN 3-900051-07-0, http://www.R-project.org/).

We adhered to the Preferred Reporting Items for Systematics Reviews and Meta-analyses statement (Preferred Reporting Items for Systematics Reviews and Meta-analyses checklist, Supplementary Material, Table S2) [31]. The meta-analysis protocol has not been registered in the PROSPERO.

Role of funding source

This study was done without funding. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Trials characteristic and risk of bias

After the literature search, eligibility evaluation and exclusion of duplicates, 8 trials were checked for further assessment. We excluded the STACCATO trial because only 30-day follow-up data were reported. Seven trials (PARTNER 1A, PARTNER 2A, PARTNER 3, NOTION, US CoreValve High Risk, SURTAVI and EVOLUT Low-risk trial) fulfilled the prespecified inclusion criteria and were included in the meta-analysis (Supplementary Material, Fig. S1) [2–8, 10–13, 15, 16].

Table 1 shows baseline characteristics of the study groups. All studies were multicentre randomized trials, and the longest available follow-up was published between 2015 and 2020. Four of 7 studies reported 5-year follow-up data (a cohort of 3808 patients). Kaplan–Meier graphs from intention-to-treat data were available from PARTNER 1A, PARTNER 2A and SURTAVI trials. As-treated population data were available from PARTNER 3, CoreValve U.S. Pivotal trial, Evolut R Low-Risk trial and NOTION.

Overall, 7770 patients were randomly assigned to undergo TAVI ($n = 3977$) or SAVR ($n = 3793$). In the 7 trials, both balloon-expanding (Edwards SAPIEN, SAPIEN XT and SAPIEN 3, Edwards Lifesciences, Irvine, CA, USA) and self-expanding TAVI devices (Medtronic CoreValve, Minneapolis, MN, USA) were under study. The TAVI approaches were different; however, the most common access was transfemoral.

The risk of bias of the included trials is detailed in Supplementary Material, Table S3.

Quality assessment of estimated reconstructed time-to-event data

No major graphical differences were noted during a visual comparison between the originally reported Kaplan–Meier curves and the estimated Kaplan–Meier curves. HRs estimated from RTE data were compared to HRs in the paper, when available. The NOTION, EVOLUT R Low-Risk and SURTAVI trials did not calculate TAVI versus SAVR HRs, whereas a comparison between reported and estimated HRs was possible for PARTNER 1A, PARTNER 2A, PARTNER 3 and CoreValve US Pivotal trials. As shown in Supplementary Material, Fig. S2, HRs estimated from RTE data were not different from those reported in the trials, confirming a high accuracy of the reconstructing time-to-event data method.

Analysis of composite of death from any cause or stroke up to 5 years

Six of the 7 RCTs reported Kaplan–Meier graphs of the composite end point. The NOTION trial was not included because it reported a composite of death, stroke and myocardial infarction as the primary end point [7]. Moreover, only the 3-year graph of the composite end point was available for the CoreValve U.S. Pivotal trial, although 5-year results have been published [3, 15]. Summarizing, the included trials were PARTNER 1A (5 years), CoreValve U.S. Pivotal trial (3 years), PARTNER 2A (5 years), SURTAVI (2 years), PARTNER 3 (2 years) and EVOLUT LR (2 years) [2, 4, 5, 8, 12, 13, 15]. PARTNER 3 included all strokes as a component of the composite outcomes while all other trials included disabling strokes.

Figure 1A shows the Kaplan–Meier estimates for the composite of all-cause mortality or stroke, based on an estimated follow-up of 192,689 patient-months. The difference between TAVI and SAVR curves was not significant (log-rank P-value 0.7). The risk-stratified Cox modelling (HR 0.98; 95% CI 0.90–1.08; P-value 0.73) was invalidated by the strong departure from constancy of the HR, underscored by the Schoenfeld residuals and the Grambsch–Therneau test for the time-invariant effect (P-value <0.001) that lead to the misleading effect estimation. Therefore we proceeded with the landmark analysis and models accounting for the time-varying effect.

The cut-offs selected for landmarking by visual inspection of the scaled Schoenfeld residuals, and the Kaplan–Meier curves were 6 and 24 months. Figure 1B shows the Kaplan–Meier estimates of all-cause mortality by the landmark analysis. In the first 6 months after implantation, TAVI was related to a significantly lower incidence of the composite outcome (risk profile stratified

Table 1: Baseline characteristics of the 7 trials

Risk profile	High				Low		Intermediate				Low		Low	
Trial name	PARTNER 1A, 5 years		COREVALVE US, 5 years		NOTION		PARTNER 2A, 5 years		SURTAVI, 2 years		PARTNER 3, 2 years		EVOLUT LOW RISK, 2 years	
Treatment group	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
Trial characteristics														
Numbers of centres	25		45		3		57		87		71		86	
Recruitment period	2007–2009		2011–2012		2009–2013		2011–2013		2012–2016		2016–2017		2016–2018	
Longest follow-up, years	5		5		5		2		2		1		1	
Design	Non-inferiority		Non-inferiority		Superiority		Non-inferiority		Non-inferiority		Non-inferiority		Non-inferiority	
ITT patients	348	351	395	402	145	135	1011	1021	864	796			734	734
As-treated patients, *n*	344	313	391	359	142	134	994	944	863	764	496	454	725	678
Patient characteristics														
Age, mean ± SD	83.6 ± 6.8	84.5 ± 6.4	83.2 ± 7.1	83.3 ± 6.3	79.2 ± 4.9	79.0 ± 4.7	81.5 ± 6.7	81.7 ± 6.7	79.9 ± 6.2	79.8 ± 6.0	73.3 ± 5.8	73.6 ± 6.1	74.0 ± 5.9	73.8 ± 6.0
Women, *n* %	147 (42.2)	153 (43.6)	184 (47.1)	171 (47.6)	67 (46.2)	64 (47.4)	463 (45.8)	461 (45.2)	366 (42.4)	438 (55.0)	161 (32.5)	131 (28.9)	266 (36.2)	246 (33.5)
NYHA functional class III or IV, *n* (%)	328 (94.3)	328 (93.4)	334 (85.4)	312 (86.9)	70 (48.3%)	61 (45.2)	782 (77.3)	776 (76.0)	520 (60.2)	463 (58.2)	155 (31.3)	108 (23.8)	181 (24.6)	205 (27.9)
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	4.4 ± 1.5	4.5 ± 1.6	1.9 ± 0.7	1.9 ± 0.6	1.9 ± 0.7	1.9 ± 0.7
Logistic EuroSCORE, mean ± SD	29.3 ± 16.5	29.2 ± 15.6	17.7 ± 13.0	18.8 ± 13.2	8.4 ± 4.0	8.9 ± 5.5	–	–	11.9 ± 7.6	11.6 ± 8.0	–	–	–	–
Logistic EuroSCORE II	–	–	–	–	1.9 ± 1.2	2.0 ± 1.3	–	–	–	–	1.5 ± 1.2	1.5 ± 0.9	–	–
Hypertension, *n* (%)	–	–	372 (95.1)	345 (96.1)	103 (71.0)	103 (76.3)	–	–	801 (92.7)	719 (90.3)	–	–	622 (84.9)	608 (82.9)
Diabetes mellitus, *n* (%)	–	–	136 (34.8)	162 (45.1)	26 (17.9)	28 (20.7)	381 (37.7)	349 (34.2)	295 (34.1)	277 (34.8)	155 (31.3)	137 (30.2)	228 (31.1)	224 (30.5)
Chronic kidney disease	38 (10.9)	24 (6.8)	48 (12.3)	45 (12.5)	2 (1.4)	1 (0.7)	51 (5.0)	53 (5.2)	14 (1.6)	17 (2.1)	1 (0.2)	1 (0.2)	0 (0)	1 (1)
COPD, any, *n* (%)	152 (43.7)	151 (43.0)	–	–	17 (11.7)	16 (11.9)	321 (31.8)	306 (30.0)	–	–	25 (5.1)	28 (6.2)	106 (15.1)	121 (17.2)
COPD, O_2-dependent, *n* (%)	38 (10.9)	38 (10.8)	–	–	–	–	34 (3.4)	32 (3.1)	–	–	–	–	–	–
Peripheral vascular disease, *n* (%)	148 (42.5)	142 (40.5)	159 (40.7)	150 (41.8)	6 (4.1)	9 (6.7)	282 (27.9)	336 (32.9)	266 (30.8)	238 (29.9)	34 (6.9)	33 (7.3)	55 (7.6)	62 (8.5)
Prior cerebrovascular event, *n* (%)	95 (27.3)	87 (24.8)	49 (12.5)	50 (13.9)	24 (16.6)	22 (16.3)	325 (32.1)	317 (31.0)	115 (13.3)	103 (12.9)	17 (3.4)	23 (5.1)	74 (10)	84 (11.4)
Coronary artery disease, *n* (%)	260 (74.7)	266 (75.8)	295 (75.4)	273 (76.0)			700 (69.2)	679 (66.5)	541 (62.6)	511 (64.2)	137 (27.6)	127 (28.0	–	–
Previous myocardial infarction, *n* (%)	92 (26.4)	103 (29.3)	99 (25.3)	91 (25.3)	8 (5.5)	6 (4.4)	185 (18.3)	179 (17.5)	125 (14.5)	111 (13.9)	28 (5.6)	26 (5.7)	49 (6.7)	39 (5.3)
Prior CABG, *n* (%)	147 (42.2)	152 (43.3)	115 (29.4)	113 (31.5)	–	–	239 (23.6)	261 (25.6)	138 (16.0)	137 (17.2)	–	–	18 (2.5)	17 (2.3)
Prior PCI, *n* (%)	116 (33.3)	110 (31.3)	134 (34.3)	135 (37.6)	11 (7.6)	12 (8.9)	274 (27.1)	282 (27.6)	184 (21.3)	169 (21.2)	–	–	102 (13.9)	93 (12.7)
Known atrial fibrillation or flutter, *n* (%)	80 (23.0)	73 (20.8)	160 (40.9)	165 (46.0)	40 (27.6)	34 (25.2)	313 (31.0)	359 (35.2)	243 (28.1)	211 (26.5)	78 (15.7)	85 (18.8)	113 (15.5)	109 (14.9)
Prior pacemaker, *n* (%)	69 (19.8)	76 (21.7)	91 (23.3)	76 (21.2)	5 (3.4)	6 (4.4)	118 (11.7)	123 (12.0)	84 (9.7)	72 (9.0)	12 (2.4)	13 (2.9)	25 (3.4)	28 (3.8)
Pulmonary hypertension, *n* (%)	126 (36.2)	111 (31.6)	–	–	–	–	–	–	–	–	–	–	–	–
Left ventricular ejection fraction, %, mean ± SD	52.5 ± 13.5	53.3 ± 12.8	–	–			56.2 ± 10.8	55.3 ± 11.9			65.7 ± 9.0	66.2 ± 8.6	61.7 ± 7.9	61.9 ± 7.7
Intervention characteristics														
TAVI valve system	Edwards SAPIEN	NA	Medtronic CoreValve	NA	Medtronic CoreValve	NA	Sapien XT	NA	Corevalve or Evolut R	NA	SAPIEN 3	NA	Corevalve, Evolut R or Evolut PRO	NA
Access site, *n* (%)														
Transfemoral	244 (70.1)	NA	394 (99.7)	NA	137 (96.5)	NA	775 (76.7)	NA	808 (93.6)	NA	496 (100.0)	NA	718 (99)	NA
Transthoracic	104 (29.9)	NA	0 (0.0)	NA	0 (0.0)	NA	236 (23.3)	NA	35 (4.1)	NA	0 (0.0)	NA	3 (0.4)	NA
Trans-subclavian	0 (0)	NA	0 (0)	NA	5 (3.5)	NA	0 (0)	NA	20 (2.3)	NA	0 (0)	NA	4 (0.6)	NA

CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; ITT: intention-to-treat; NYHA: New York Heart Association; PCI: percutaneous intervention; SD: standard deviation; STS: Society of Thoracic Surgeons; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

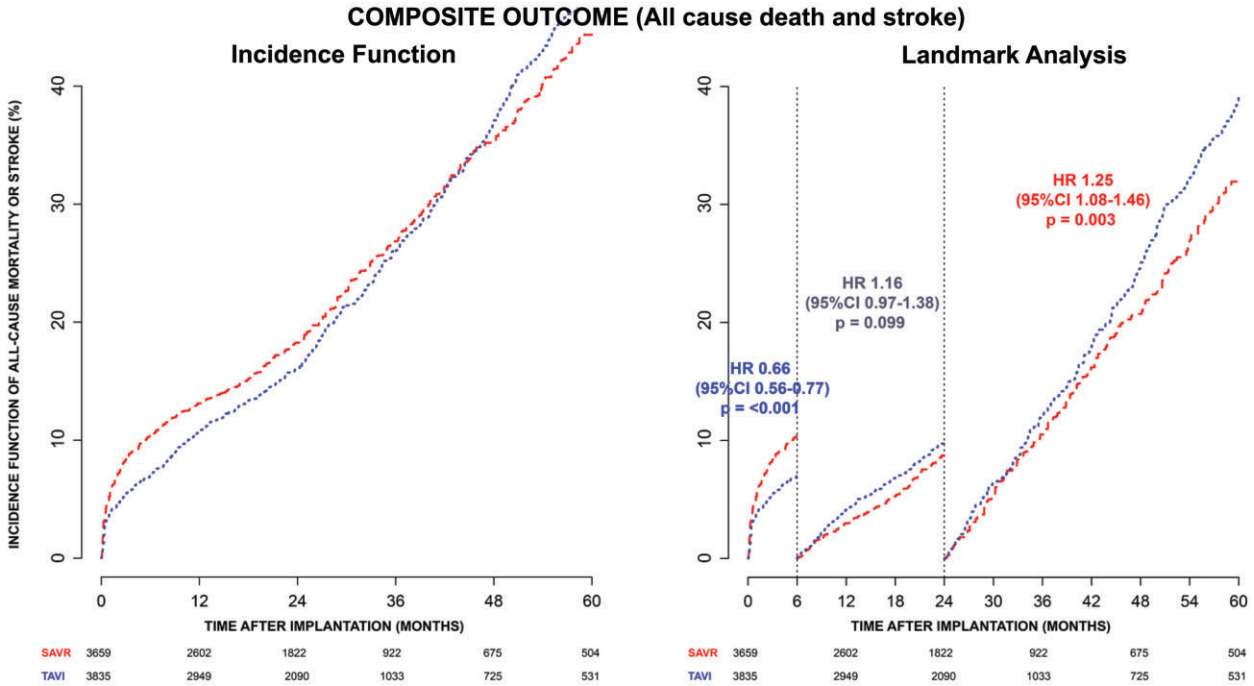


Figure 1: (**A**) Kaplan–Meier incidence function of the composite of all-cause mortality and stroke in transcatheter aortic valve implantation and surgical aortic valve replacement groups. (**B**) Landmark analysis of all-cause mortality or stroke in transcatheter aortic valve implantation and surgical aortic valve replacement groups. CI: confidence interval; HR: hazard ratio; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

Table 2: Risk-stratified hazard ratios of transcatheter aortic valve implantation and surgical aortic valve replacement or the meta-analysis end points by landmark analysis

	Number of patients (trials)	Hazard ratio			Random parameter θ	*P*-value
		Value (95% CI)	*P*-value	GTt *P*[a]		
Composite of death and stroke	7494 (6)	0.98 (0.90–1.08)	0.73	<0.001*	0.050	<0.001*
0–6 months		0.66 (0.56–0.77)	<0.001*	0.951	0.052	0.002*
6–24 months		1.16 (0.97–1.38)	0.099	0.083	0.037	0.079
24–60 months		1.25 (1.08–1.46)	0.003*	0.172	0.001	0.7
All-cause mortality	7770 (7)	1.00 (0.92–1.1)	0.94	0.001*	0.100	<0.001*
0–6 months		0.70 (0.59–0.83)	<0.001*	0.225	0.139	<0.001*
6–24 months		1.09 (0.91–1.31)	0.33	0.003*	0.045	0.066
24–60 months		1.18 (1.03–1.35)	0.01*	0.964	0.017	0.047*
Stroke	5738 (6)	0.73 (0.58–0.93)	0.01*	0.03*	0.095	0.019*
0–6 months		0.63 (0.47–0.87)	0.003*	0.108	0.151	0.023*
6–24 months		0.94 (0.58–1.51)	0.79	0.07	0.083	0.17
24–60 months		0.91 (0.50–1.67)	0.87	0.01*	0.001	0.87
Rehospitalization	5084 (4)	1.07 (0.93–1.22)	0.34	<0.001*	0.246	<0.001*
0–6 months		0.80 (0.67–0.96)	0.018*	0.384	0.320	<0.001*
6–24 months		1.42 (1.06–1.91)	0.018*	0.359	0.001	0.80
24–60 months		1.67 (1.24–2.24)	<0.001*	0.63	0.001	0.99

CI: confidence interval; GTt: grambsch-therneau test for time-invariant effect.

[a]Grambsch–Therneau test for time-invariant effect. When the proportionality of hazards is violated, the Cox model is invalidated and methods for integrating time-varying effects should be considered.

**P*-value <0.05.

HR 0.66, 95% CI 0.56–0.77; *P*-value <0.001). Although randomization to SAVR was associated with a numerically improved survival in 6–24 months, this difference in the incidence of the composite outcome between TAVI and SAVR was not statistically significant (6–24 months risk-stratified HR 1.16, 95% CI 0.97–1.38; *P*-value 0.099). A landmark analysis of the composite outcome after 24 months yielded a significant reversal of HR (risk-stratified HR 1.25; 95% CI 1.08–1.46; *P*-value 0.003) favouring SAVR (Table 2).

The analysis of the HR trend over time of TAVI versus SAVR estimated by fully parametric generalized survival models confirmed the results of the landmark analysis (Fig. 2). TAVI was superior to surgery in the early months with the advantage

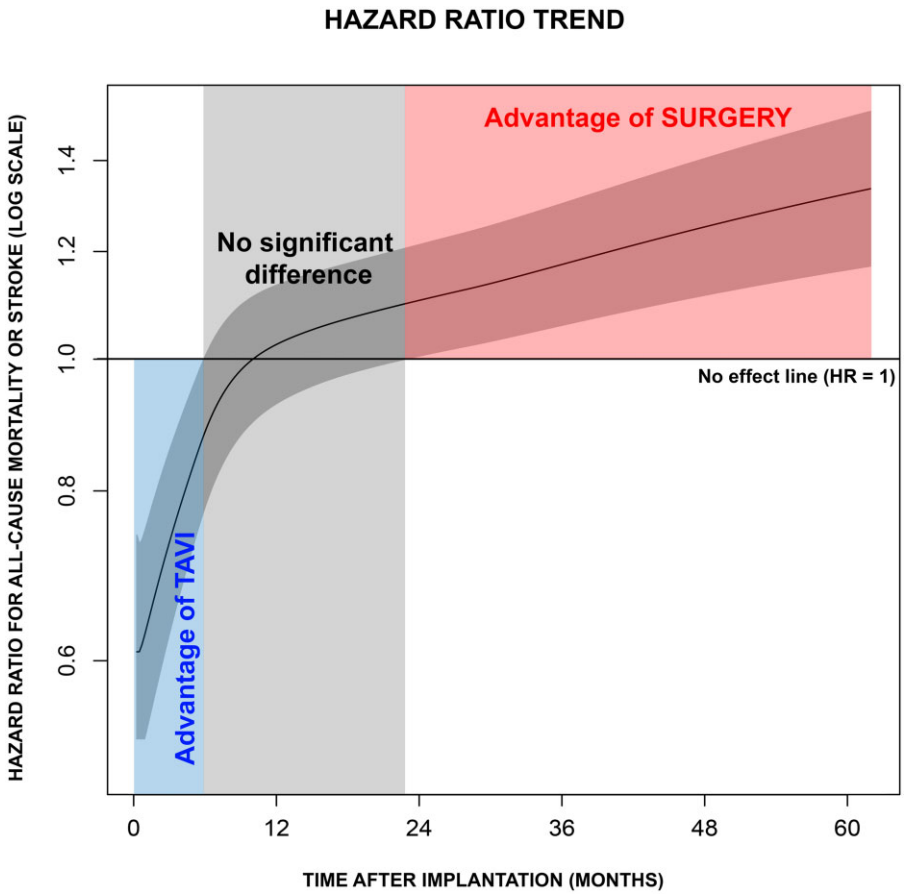


Figure 2: Hazard ratio trend over time for all-cause mortality or stroke of transcatheter aortic valve implantation versus surgical aortic valve replacement estimated by fully parametric generalized survival models. CI: confidence interval; HR: hazard ratio; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

decreasing over time to 2 years, when SAVR became clearly superior.

Analysis of all-cause mortality up to 5 years

All 7 RCTs reported Kaplan–Meier graphs of all-cause mortality. Summarizing, the included trials were PARTNER 1A (5 years), CoreValve U.S. Pivotal trial (5 years), NOTION trial (5 years), PARTNER 2A (5 years), SURTAVI (2 years), PARTNER 3 (2 years) and EVOLUT LR (1 year) [2, 3, 5, 7, 11–13, 16].

Figure 3A shows the Kaplan–Meier estimates for all-cause mortality (log-rank *P*-value 0.9). Also in the risk-stratified Cox-estimated HR for all-cause mortality, the assumption of hazard proportionality was not fulfilled (Grambsch–Therneau test, *P*-value 0.001), invalidating the results (HR 1.00; 95% CI 0.92–1.1; *P*-value 0.94) and requesting further analysis for investigating the time-varying effect.

The Kaplan–Meier estimates of all-cause mortality by the landmark analysis show results similar to those of the composite outcome (Supplementary Material, Fig. S3). TAVI was associated with a survival advantage over surgery in the first 6 months (HR 0.70, 95% CI 0.59–0.83; *P*-value <0.001), whereas no difference in mortality was shown between 6 and 24 months (HR 1.09, 95% CI 0.91–1.31; *P*-value 0.33). Again, a reversal of HR (risk-stratified HR 1.18; 95% CI 1.03–1.35; *P*-value 0.01) favouring SAVR over TAVI was evident after 24 months (Table 2).

The analysis of the HR trend over time for all-cause death is concordant with the landmark outputs, showing that the TAVI survival advantage in the first few months turns into a significant disadvantage after 2 years (Fig. 3B). As expected, the HR trend including only trials with 5 years of follow-up was largely superimposable on that of the total group (Supplementary Material, Fig. S6).

Analysis of stroke incidence up to 5 years

Six of the 7 RCTs reported Kaplan–Meier graphs of stroke; the PARTNER 2A trial was not included [4]. Moreover, the 3-year graph of stroke was available for the CoreValve U.S. Pivotal trial, and the 1-year Kaplan–Meier graph of stroke was available for the EVOLUT LR Trial [3, 8, 14, 15]. Summarizing, the included trials were PARTNER 1A (5 years), CoreValve U.S. Pivotal trial (3 years), NOTION (5 years), SURTAVI (2 years), PARTNER 3 (2 years) and EVOLUT LR (1 years) [2, 5, 7, 12, 13, 15, 16]. Analysis of stroke in the 2 groups was limited by the low incidence and the reduced sample size.

Figure 4A shows the Kaplan–Meier estimates for stroke (log-rank *P*-value 0.01, showing the advantage of TAVI). Also in the risk-stratified Cox-estimated HR for stroke, the assumption of hazard proportionality was not fulfilled (Grambsch–Therneau test; *P*-value 0.03), invalidating the results of the Cox model (HR 0.73; 95% CI 0.58–0.93; *P*-value 0.01) and requiring further analysis for investigating the time-varying effect.

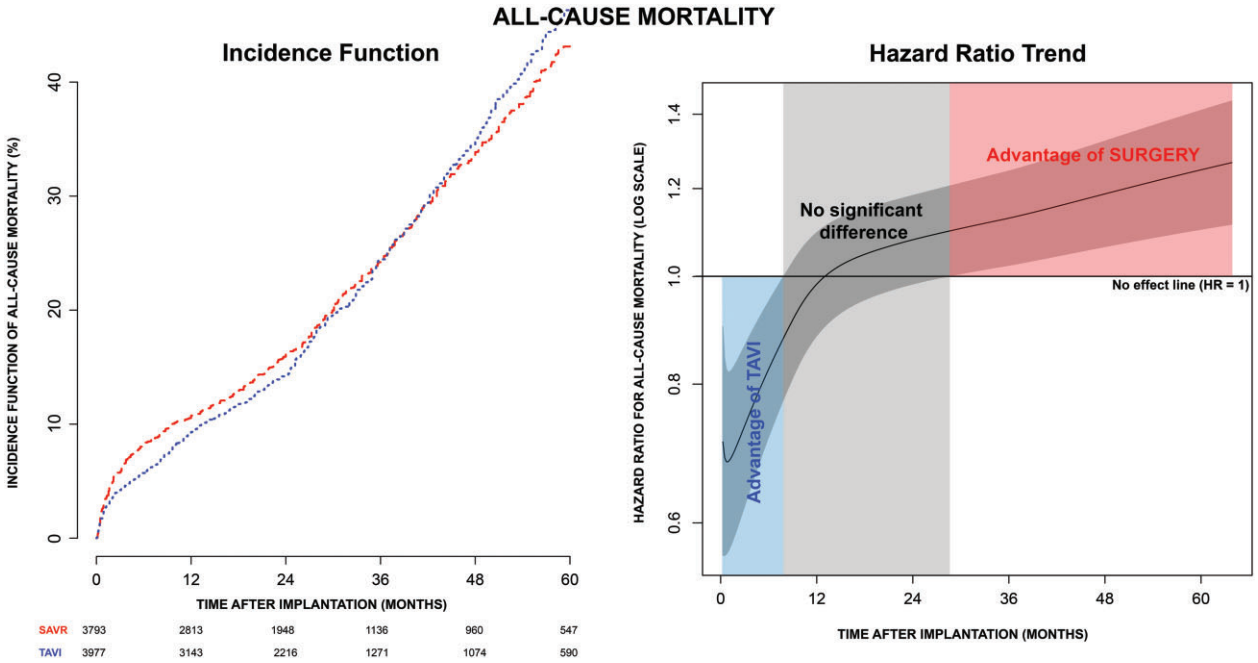


Figure 3: (**A**) Kaplan–Meier incidence function of all-cause mortality in transcatheter aortic valve implantation and surgical aortic valve replacement groups. (**B**) Hazard ratio trend over time for mortality of transcatheter aortic valve implantation versus surgical aortic valve replacement. HR: hazard ratio; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

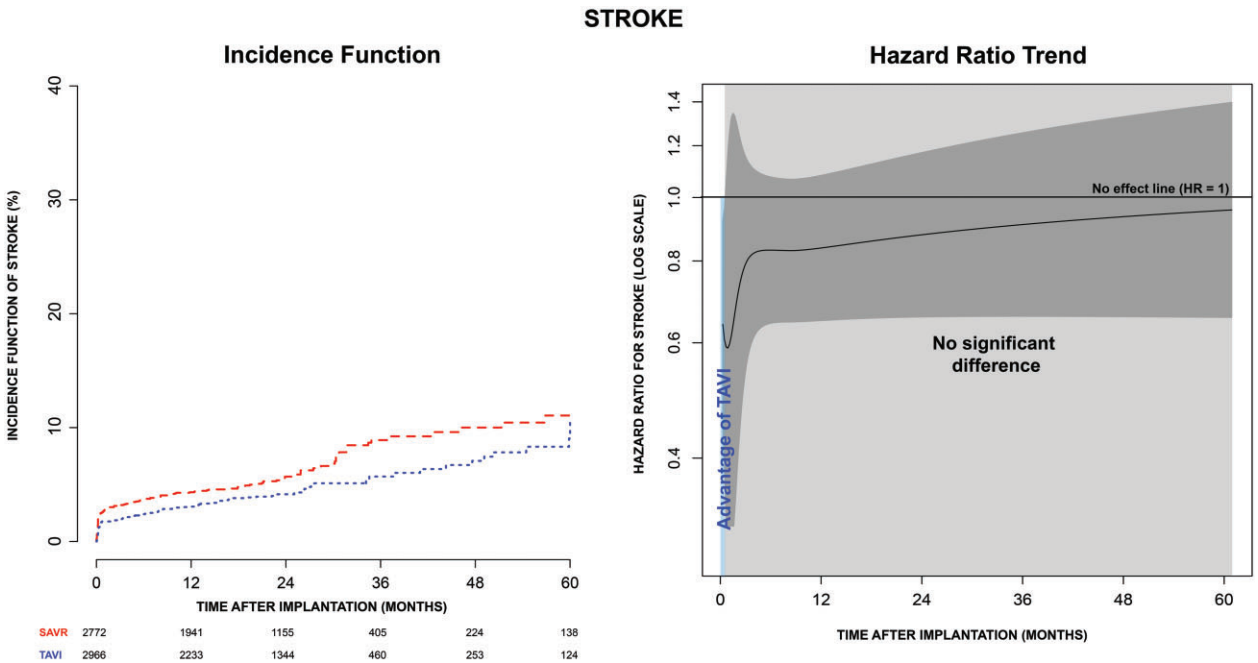


Figure 4: (**A**) Kaplan–Meier incidence function of stroke in transcatheter aortic valve implantation and surgical aortic valve replacement groups. (**B**) Hazard ratio trend over time for stroke with transcatheter aortic valve implantation versus surgical aortic valve replacement. HR: hazard ratio; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

At landmark analysis (Supplementary Material, Fig. S4), TAVI showed a significantly lower incidence of stroke (risk-stratified HR 0.63, 95% CI 0.47–0.87; *P*-value 0.003) in the first 6 months after implantation (Fig. 3A). There was no difference in stroke incidence between the groups after 6 months (risk-stratified HR 0.94, 95% CI 0.58–1.51; *P*-value 0.79 between 6 and 24 months; risk-stratified HR 0.91, 95% CI 0.50–1.67; *P*-value 0.87 after 24 months; Table 2).

The landmark analysis results were concordant with the HR trend analysis shown in Fig. 4B. The weight of the protective effect of TAVI in the first postoperative period accounts for the unvalidated Cox estimated HR considering all the time points.

Analysis of rehospitalization incidence up to 5 years

Four of the 7 RCTs reported Kaplan–Meier graphs for rehospitalization. The included trials were PARTNER 1A (5 years), PARTNER 2A (5 years), PARTNER 3 (2 years) and EVOLUT LRT (1 year) [2, 4, 12, 13, 16].

Figure 5A shows the Kaplan–Meier estimates for rehospitalization (log-rank *P*-value 0.5). Also in the risk-stratified Cox-estimated HR for rehospitalization, the assumption of hazard-proportionality was not fulfilled (Grambsch–Therneau test; *P*-value <0.001), invalidating the results of the Cox model (HR 1.07; 95% CI 0.93–1.22; *P*-value 0.34) and requesting further analysis for investigating the time-varying effect.

The risk-stratified Cox-estimated HR showed a strong departure from constancy (*P*-value <0.001); therefore, we moved to a landmark analysis. In the first 6 months after the implant, TAVI was related to a significantly lower incidence of rehospitalization (risk-stratified HR 0.80, 95% CI 0.67–0.96, *P*-value 0.02; Supplementary Material, Fig. S5). The incidence of rehospitalization was significantly favourable for surgery between 6 and 24 months (risk-stratified HR 1.42; 95% CI 1.06–1.91; *P*-value 0.018) and this advantage was maintained and amplified after 24 months (risk-stratified HR 1.67; 95% CI 1.24–2.24; *P*-value <0.001), as shown in Supplementary Material, Fig. S5 and Table 2.

The landmark analysis results were concordant with those of the HR trend analysis (Fig. 5B). The advantage of TAVI appears to be limited to the first few months after the implant whereas the hazard of rehospitalization is significantly lower in the surgical group after 1 year.

DISCUSSION

The rapid development and wider indication for TAVI in younger and lower-risk patients have led to increased attention to long-term follow-up, because the feasibility and short-term safety of the procedure are increasingly well documented in clinical trials [2–8, 10–13, 15, 16]. Short-term results have shown that the appeal of a less invasive approach is not only aesthetic but it also leads to lower complication rates and faster 'recovery', which may be particularly valuable in older and frail patients [2–8, 10–13, 15, 16]. A shorter in-hospital stay, as well as a lower incidence of readmission in the first months after the procedure, is a direct confirmation of the better outcomes of TAVI within the first months [6]. Nonetheless, the short-term outcome cannot necessarily be confirmed at the longer follow-up because the forces that drive outcomes are different and the durability of a new prosthesis compared to the gold standard should be evaluated over a prolonged period of time, usually >5 years and, ideally, at least 10 years. Our results indicate that the advantage of TAVI over SAVR is not constant over time and might be reversed with a longer follow-up, favouring surgery. The increase in patient numbers of the 5-year cohort, as well as the follow-up to 2 years of low-risk trials, stabilized the results of our previous analyses of all-cause death [9] and gave more precise estimates, indicating that the reversal of HR favouring surgery may be anticipated at about 2 years and that most of the TAVI advantage on survival can be confined to the first months. This message is reinforced also by the analysis of the composite of all-cause mortality and stroke at follow-up and rehospitalization at follow-up. Their HRs trend to have the same pattern and overturn the widespread hypothesis that good short-term results indicate good long-term results [32].

Our results contrast with those of most of the meta-analyses performed on the same issue and with almost the same included

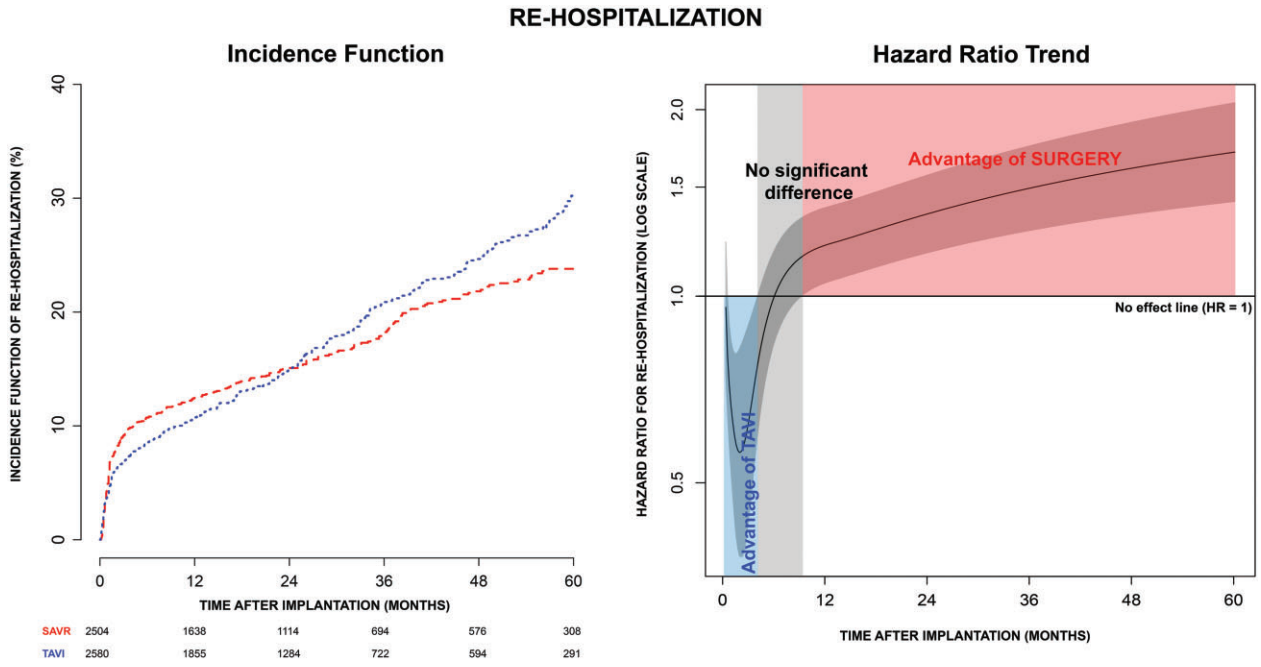


Figure 5: (**A**) Kaplan–Meier incidence function of stroke in transcatheter aortic valve implantation and surgical aortic valve replacement groups. (**B**) Hazard ratio trend over time for rehospitalization of transcatheter aortic valve implantation versus surgical aortic valve replacement. HR: hazard ratio; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

studies [33–35], which showed superiority or at least no inferiority of TAVI at follow-up. As we previously demonstrated, these contrasting results are related to the use of standard meta-analytic methods for time-to-event outcomes that are used when the data are front-loaded in short-term trials. For the evidence syntheses, pooling the treatment effect over trials with reported HR is limited and unsatisfactory, because it requires proportional hazards, an assumption that is seldom checked and sometimes implausible on inspection [9, 25, 26]. Moreover, mixing HRs and ORs in the same meta-analysis can substantially bias the summary effect [33]. In addition, heterogeneity due to effects that vary with time could be highly misleading when treatment effects are estimated with traditional meta-analytic methods [9].

Our meta-analytic estimates are congruent with those of the individual studies but provide greater statistical precision. The graphical analysis of Kaplan–Meier curves as well as the landmark analysis performed in some studies reveals a varying effect of TAVI versus SAVR over time [2–4]. In the PARTNER 2A at 5 years, TAVI was associated with a significant survival disadvantage of 2–5 years in the overall cohort (HR 1.27, 95% CI 1.06–1.53; $P < 0.05$) and in the transfemoral (HR 1.23 95% CI 1.00–1.52) and transapical subgroups (1.45, 95% CI 1.01–2.07) [4, 11, 36]. The pooled estimates after 2 years in the meta-analysis are consistent with those derived by comparing the transfemoral cohort and SAVR and diverge from the higher HR of transapical TAVI versus SAVR, suggesting that they are more representative of the comparison between the transfemoral cohort and SAVR and are little affected by the outcomes of transapical TAVI. It is a key point because one of the limitations related to the comparison between TAVI and SAVR is the case mix in both groups. The transapical TAVI have significantly worse outcomes compared to the transfemoral TAVI, and the pooled analysis of TA and TF groups can lead to less reliable results. In the surgical arm of all RCTs, there is a significantly higher proportion of associated procedures compared to TAVI that holds an intrinsically higher risk of mortality and morbidities, which is also shown by the existing risk score calculators. Although an unbiased analysis should compare isolated transfemoral TAVI and isolated SAVR, the case mix of the 2 treatments in RCTs moves the outcomes in the same direction and could not affect their ratio. The difference between TAVI and SAVR at follow-up is also more marked in the 5-year outcomes of the German Aortic Valve Registry, with a 50% higher risk for mortality in the TAVI group that remains constant over time [37]. The worse scenario of the registry can reflect the different meaning of observation studies, because RCTs cannot reflect the real world, and their internal validity may be gained at the price of their general applicability [38].

The explanation for the time-varying effect of TAVR/SAVR on outcomes at 5 years is far beyond the scope of the present study. Durability of the prosthesis, paravalvular leaks and the higher incidence of pacemaker implants have been considered potential factors affecting midterm outcomes [39]. Newer prostheses are claimed to have better performance and a lower incidence of structural and non-structural valve deterioration, although the evidence supporting these arguments is limited. Further, a latest-generation device in low-risk patients has been associated with an increased risk of valve thrombosis at 2 years compared with surgery (2.6% vs 0.7%; P-value 0.02) [12].

Limitations

Our pooled meta-analysis of RTE data has limitations. The duration of follow-up is limited to 5 years, and midterm outcomes are representative of intermediate-risk and high-risk groups. The longer follow-up is available for older devices, and results should be validated also in trials with newer devices that potentially could demonstrate improved outcomes due to improvement in valve design, technical aspects and procedural learning curve. Moreover, on top of device changes, procedures are systematically improving over time for both TAVR and SAVR, and studies performed a few years ago cannot intercept these continuous advances [40, 41]. Nonetheless, the open concerns about durability and the outcomes at longer follow-up times overcome by far the expectations associated with newer TAVI prostheses. A comparison between balloon-expanding and self-expanding TAVI devices was not performed. Moreover, this analysis was stratified only for risk profile by STS score and EuroSCORE at the study level, and the potential impact of comorbidities on both heterogeneity and outcomes in individual patients cannot be extrapolated.

CONCLUSIONS

Although it could appear that there is no difference between TAVI and SAVR in the 5-year cumulative results, there is an evident time-varying trend of the HR concordant with the survival crossing curves. TAVI shows a strong protective effect in the first months after implantation. This advantage reverses over time, and TAVI becomes a risk factor for all-cause mortality alone and the composite for all-cause mortality or stroke after 24 months. TAVI is also associated with a 69% increased hazard of rehospitalization beginning 1 year after implantation.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: Fabio Barili reports personal fees from Abbott Medical, outside the submitted work. Nicholas Freemantle reports grants from the European Association of Cardiothoracic Surgery, outside the submitted work.

Data Availability Statement

Data underlying the meta-analysis are retrieved from published randomized clinical trials and hence already available in literature; no unpublished data were employed. However, the collected data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Fabio Barili: Conceptualization; Formal analysis; Investigation; Methodology; Software; Writing—original draft; Writing—review & editing. **Nicholas Freemantle:** Conceptualization; Formal analysis; Investigation; Supervision; Writing—review & editing. **Francesco Musumeci:** Data curation; Resources; Visualization; Writing—review & editing. **Barbara Martin:** Methodology; Writing—review & editing. **Amedeo Anselmi:** Investigation; Project administration; Writing—original draft; Writing—review & editing. **Mauro Rinaldi:** Data curation; Investigation; Project administration; Resources; Writing—review & editing. **Sanjay Kaul:** Software; Supervision; Visualization; Writing—review & editing. **Jorge Rodriguez-Roda:** Investigation; Supervision; Writing—review & editing. **Michele Di Mauro:** Data curation; Project administration; Writing—original draft; Writing—review & editing. **Thierry Folliguet:** Methodology; Software; Writing—review & editing. **Jean-**

Philippe Verhoye: Project administration; Resources; Writing—original draft; Writing—review & editing. **Miguel Sousa Uva:** Conceptualization; Supervision; Validation; Writing—review & editing. **Alessandro Parolari:** Conceptualization; Methodology; Software; Supervision; Writing—review & editing.

Reviewer information

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