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Systematic Review

Transcatheter versus surgical aortic valve replacement in low- to intermediate-risk patients: a meta-analysis of reconstructed time-to-event data

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Background: Transcatheter aortic valve replacement (TAVR) is an established alternative to surgical aortic valve replacement (SAVR) for severe symptomatic aortic stenosis (AS), including low-risk patients. We aimed to update a systematic review and conduct a meta-analysis of reconstructed time-to-event data from randomized control trials (RCTs) in low-/intermediate-risk patients.

Methods: Systematic searches were performed in PubMed, EMBASE, Cochrane CENTRAL, and specific websites up to November 2023, for RCTs. A meta-analysis was performed using the reconstructed time-to-event data from the provided Kaplan-Meier (KM) curves from the included RCTs. The primary outcome was all-cause mortality, and the secondary outcomes included a composite outcome (all-cause mortality and disabling stroke), and heart failure rehospitalization. Landmark analysis for endpoints beyond 1 year was performed. The study protocol was registered on PROSPERO (CRD42023487893).

Results: Six RCTs with a total of 7,389 patients were included. The survival was comparable between both groups [hazard ratio (HR), 1.03; 95% confidence interval (CI): 0.93–1.14; P=0.57]. The composite outcome and heart failure rehospitalization were comparable between the two groups. Lower mortality with TAVR was observed compared to SAVR before 1 year (HR, 0.82; 95% CI: 0.68–0.98; P=0.03), while TAVR was associated with higher risk of mortality beyond 1 year (HR, 1.13; 95% CI: 1.01–1.27; P=0.04). Similarly, the TAVR group was associated with lower risk for the composite endpoint and heart failure rehospitalization before 1 year, but with higher rates beyond 1 year.

Conclusions: Among low- to intermediate-risk patients, TAVR was found to be associated with favorable outcomes in the short-term (0–1 year). However, our landmark analysis demonstrated TAVR to be associated with poorer outcomes beyond 1 year.

Keywords: Transcatheter aortic valve replacement (TAVR); surgical aortic valve replacement (SAVR); aortic stenosis (AS); meta-analysis

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Introduction

Transcatheter aortic valve replacement (TAVR) has become a well-established alternative to surgical aortic valve replacement (SAVR) for severe symptomatic aortic stenosis (AS) (1,2). Although previous randomized control trials (RCTs) have shown comparable overall mortality for high-, intermediate- and low-risk patient groups (1-8), there remains uncertainty regarding long-term data (9,10). With the exception of the Nordic Aortic Valve Intervention (NOTION) trial, the follow-up periods of no RCTs exceed 5 years (8).

The efficacy of TAVR for low- and intermediate-risk patients remains to be fully elucidated (9,10), and the most recent data from the Evolut Low Risk Trial and the Placement of Aortic Transcatheter Valves 3 (PARTNER 3) trial prompted a reevaluation of the current existing literature (6,7). Given the low event rates in low- and intermediate-risk groups, a meta-analysis would mitigate potential underpowering issues. Furthermore, a previous meta-analysis of RCTs revealed a time-varying association between TAVR and SAVR patients, with a higher mid-term mortality rate with the TAVR group (11). Therefore, a meta-analysis of Kaplan-Meier (KM) derived data, accounting for time-varying effects, holds significance in guiding optimal therapy selection during the decision-making process. Herein, we report a meta-analysis of mid-term outcomes comparing SAVR and TAVR for low- and intermediate-risk patients with severe AS.

Methods

This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement standards (12). Given the nature of our study, Institutional Review Board or Informed Written Consent for Publication was not required. The study protocol was registered on PROSPERO (CRD42023487893).

Literature search strategy

All RCTs comparing TAVR with SAVR for low- and intermediate-risk patients with symptomatic severe AS were identified using a two-level strategy. First, a search of PubMed (MEDLINE), EMBASE, and Cochrane CENTRAL databases was conducted with an experienced medical librarian to identify all the studies published from database inception to November 8th, 2023, that investigated the comparison of TAVR and SAVR in severe symptomatic AS patients. The detailed retrieval strategies are shown in Tables S1-S3. We also searched websites (www.ClinicalTrials.gov, https://www.acc.org, www.escardio.org, https://tctmd.com) for unpublished data.

Eligibility criteria

The included studies met the following criteria: the study design was an RCT, the study population included low- and intermediate-risk patients with symptomatic severe AS, enrolled patients were assigned to the TAVR group or SAVR group, and outcomes included all-cause mortality. Severe AS was defined as AS meeting at least one of the following features: (I) peak velocity 4.0 m/s or greater; (II) mean pressure gradient of 40 mmHg or greater; (III) aortic valve area 1.00 cm^2 or less. Low-risk and intermediate-risk patients were defined using the Society of Thoracic Surgeons (STS) risk score of less than 4% for low-risk and between 4% and 8% for intermediate-risk patients. The latest article was included if there were several publications from one trial.

Data extraction and critical appraisal

Relevant studies were identified through a manual search of secondary sources including references of initially identified articles. All references were downloaded for consolidation, elimination of duplicates, and further analyses. Two independent and blinded authors (T.S. and J.S.) reviewed the search results separately to select the studies based on present inclusion and exclusion criteria with a full-text review. Disagreements were resolved by consensus between the two reviewers, with occasional arbitration by a third reviewer (Toshiki Kuno).

Data items

We sought data according to the following PICOS strategy: P (Population), patients with symptomatic severe AS; I (Intervention), TAVR; C (Comparison), SAVR; O (Outcome), all-cause mortality, all-cause mortality or disabling stroke, cardiovascular mortality, rehospitalization due to heart failure, all stroke, disabling stroke, and bioprosthetic valve failure; and S (Study type), RCTs.

Risk of bias in individual studies

Study quality was assessed by two independent and blinded

authors (T.S. and J.S.) using the Cochrane Collaboration risk of bias 2.0 (RoB) tool for RCTs (13). Disagreements were resolved by consensus.

Summary measures

The primary outcome of interest was all-cause mortality. The secondary outcomes of interest were a composite outcome (all-cause mortality and disabling stroke), cardiovascular mortality, rehospitalization due to heart failure, all stroke, disabling stroke, and bioprosthetic valve failure. Outcomes including strokes, rehospitalizations, and bioprosthetic valve failure were defined according to the Valve Academic Research Consortium-2 (VARC-2) and VARC-3 endpoint definitions (14,15). The definitions of each outcome are summarized in Table S4 (14,15).

Statistical analysis

We analyzed data from included studies based on the approach demonstrated by Liu and colleagues to obtain reconstructed individual time-to-event data from KM curves (16). First, raw data coordinates, including time and event probability, were extracted from KM curves using WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/) (17). KM curves in each study were reconstructed from data coordinates and the numbers at risk at given time points using the R package "IPDfromKM" (version 0.1.10). Reconstructed individual time-to-event data were used to draw KM curves. To assess the accuracy of the calculated data in comparison to the originally extracted data, root mean square error, mean absolute error, and max absolute error were assessed as measures of precision of the estimation based on Liu's algorithm (16). The reconstructed KM curves in our study met the recommended thresholds of root mean square error ≤0.05, mean absolute error ≤0.02, and max absolute error ≤0.05.

We merged the reconstructed KM curves of all eligible studies as demonstrated by Liu and colleagues (16). Cox proportional hazard model with stratification by each study was constructed to compare the outcomes between TAVR and SAVR. The proportionality hazards assumption of each Cox model was checked with the Grambsch and Therneau test (18). The Cox hazard models were also constructed from baseline to 1 year and 1 year and beyond (landmark analysis) for each outcome (19). According to the landmark analysis, we defined the following phases: the initial phase (0–1 year; within the first year) and the late phase (1–5 years; beyond the first year).

As a supplement for the Cox proportional hazards model analysis, the restricted mean survival time (RMST) analysis was performed using the survRM2 package (version 1.0.4) in R (20). RMST is the mean duration where patients are free from the outcome, up to a prespecified time point. RMST difference between two treatment groups can be interpreted as the association between treatment and outcome and RMST is considered a robust and interpretable tool. The difference in RMST between the groups for the outcome all-cause mortality shows the lifetime gain or loss associated with the intervention (TAVR) in comparison with the control (SAVR). We set prespecified time points as five years from the initiation of the trial. The analysis was conducted with R Statistical Software (version 4.2.2, Foundation for Statistical Computing, Vienna, Austria).

Additional analyses

Subgroup analyses were conducted by (I) categorizing included studies into TAVRs using balloon-expandable and self-expanding valves; and (II) low- and intermediate-risk studies. Sensitivity analyses were conducted by (I) only incorporating studies with a follow-up period exceeding 1 year; (II) only incorporating studies with >50% use of the current generation of TAVR devices (SAPIEN 3: Edwards Lifesciences, Irvine, CA, USA; and Evolut R, Evolut PRO: Medtronic, Minneapolis, MN, USA). For subgroup analyses, P values for interaction were calculated. When data from multiple studies were unavailable, subgroup and sensitivity analyses were not performed. Substantial heterogeneity was found to be present when the I^2 index was over 50%.

Results

Study selection and characteristics

Our analysis included 6 RCTs (3-8) which enrolled a total of 7,389 patients with severe AS assigned to the TAVR group (n=3,723) and the SAVR group (n=3,666) (Figure S1).

The study profile and patient characteristics are summarized in *Table 1*. Definitions of symptomatic severe AS for each trial are also summarized in *Table 1*. To validate the precision of the extracted data from KM curves, we showed reconstructed KM curves for each outcome in Figures S2-S8 for each study.

Table 1 Study profiles and patient characteristics

Trial	PARTNER 2A	SURTAVI	UKTAVI	NOTION	PARTNER 3	Evolut
Year	2020	2022	2022	2024	2023	2023
Follow-up (years)	5	5	1	10	5	4
Definition of severe AS	Vmax ≥4, PG ≥40, AVA ≤0.8 cm^2, AVI ≤0.5 cm^2/m^2	Vmax ≥4, PG ≥40, AVA ≤0.6 cm^2, AVI ≤1.0 cm^2/m^2	N/A	Vmax ≥4, PG ≥40, AVA ≤1 cm^2, AVI ≤0.6 cm^2/m^2	Vmax ≥4, PG ≥40, AVA ≤1 cm^2, AVI ≤0.6 cm^2/m^2	Vmax ≥4, PG ≥40, AVA ≤1 cm^2, AVI ≤0.6 cm^2/m^2
Risk	Intermediate	Intermediate	Low	Low	Low	Low
Valve type	Balloon	Self	Both	Self	Balloon	Self
Patients (n)						
All	2,032	1,746	913	280	950	1,468
TAVR	1,011	879	458	145	496	734
SAVR	1,021	867	455	135	454	734
Age (years)						
TAVR	81.5	79.9	81	79.2	73.3	74
SAVR	81.7	79.7	81	79	73.6	73.8
Male (%)						
TAVR	54.2	57.6	53.9	53.8	67.5	63.2
SAVR	54.8	55	52.2	52.6	71.1	66.5
HTN (%)						
TAVR	N/A	N/A	72.1	71	N/A	84.9
SAVR	N/A	N/A	72.3	76.3	N/A	82.9
DM (%)						
TAVR	37.7	34.4	23.4	17.9	31.3	31.1
SAVR	34.2	33.4	24.5	20.7	30.2	30.5
CAD (%)						
TAVR	69.2	62.6	9.5	N/A	27.7	N/A
SAVR	66.5	64.2	8.9	N/A	28	N/A
EuroSCORE (%)						
TAVR	N/A	11.9	2	N/A	N/A	N/A
SAVR	N/A	11.6	2.7	N/A	N/A	N/A
STS-PROM (%)						
TAVR	5.8	4.4	2.6	2.9	1.9	2
SAVR	5.8	4.5	2.7	3.1	1.9	1.9
PG (mmHg)						
TAVR	44.9	N/A	73	N/A	N/A	47.2
SAVR	44.6	N/A	74	N/A	N/A	46.7

Table 1 (*continued*)

Table 1 (*continued*)

Trial	PARTNER 2A	SURTAVI	UKTAVI	NOTION	PARTNER 3	Evolut
AVA (cm^2)						
TAVR	0.7	N/A	0.7	N/A	N/A	0.8
SAVR	0.7	N/A	0.7	N/A	N/A	0.8

PARTNER, Placement of Aortic Transcatheter Valves; SURTAVI, Surgical Replacement and Transcatheter Aortic Valve Implantation; UKTAVI, The UK Transcatheter Aortic Valve Implantation; NOTION, Nordic Aortic Valve Intervention; AS, aortic stenosis; Vmax, peak aortic jet velocity; PG, pressure gradient; AVA, aortic valve area; AVI, aortic valve index; TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; N/A, not available.

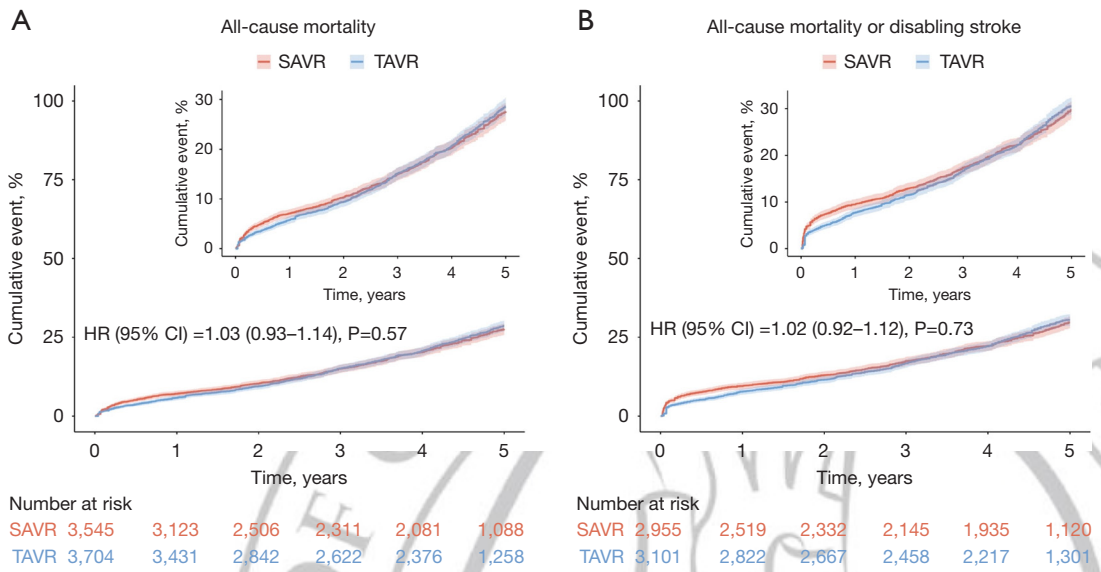

Figure 1 Kaplan-Meier analysis of (A) all-cause mortality and (B) composite outcome of all-cause mortality and disabling stroke. HR, hazard ratio; CI, confidence interval; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Risk of bias

The risk of bias for each of the included RCT is summarized in Figure S9. One study was at low risk of bias and other five studies were at intermediate risk of bias.

Pooled results from stratified cox proportional hazard model

The all-cause mortality after TAVR compared with SAVR was comparable [hazard ratio (HR), 1.03; 95% confidence interval (CI): 0.93–1.14; P=0.57; six studies] (*Figure 1A*). The composite outcome of all-cause mortality and disabling stroke was also similar between the two groups (HR, 1.02; 95% CI: 0.92–1.12; P=0.73; four studies) (*Figure 1B*). The heart failure rehospitalization rates were also similar between the two groups (HR, 1.01; 95% CI: 0.88–1.17; P=0.85; three studies) (*Figure 2A*). The occurrence of disabling stroke, any stroke, bioprosthetic valve failure, and cardiovascular mortality were also comparable (*Figure 2B* and Figure S10).

Landmark analyses

Our analysis of 1 year mortality demonstrated lower

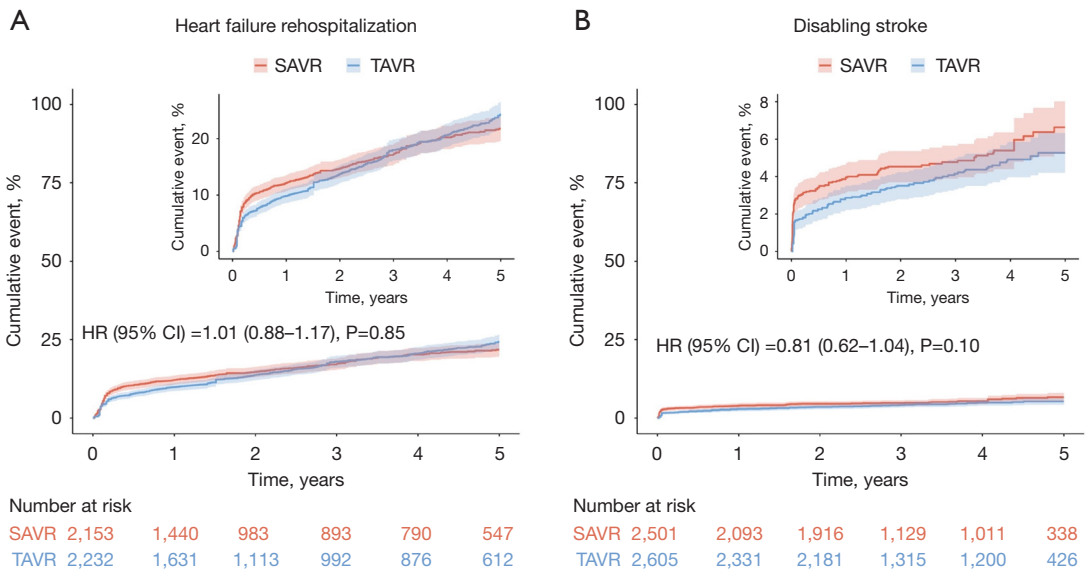

Figure 2 Kaplan-Meier analysis of (A) heart failure rehospitalization rate and (B) disabling stroke rate. HR, hazard ratio; CI, confidence interval; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

mortality in the TAVR group in the initial phase (HR, 0.82; 95% CI: 0.68–0.98; P=0.03) (*Figure 3A*). In contrast, landmark analysis at 1 year demonstrated a higher all-cause mortality in the TAVR group in the late phase (HR, 1.13; 95% CI: 1.01–1.27; P=0.04) (*Figure 3A*). Similarly to all-cause mortality, the TAVR group was associated with lower composite outcome in the initial phase but higher composite outcome in the late phase (HR, 0.81; 95% CI: 0.68–0.96; P=0.01 and HR, 1.14; 95% CI: 1.01–1.29; P=0.03, respectively) (*Figure 3B*). The heart failure rehospitalization followed a similar trend, with initially lower but then higher rates in the TAVR group (HR, 0.81; 95% CI: 0.67–0.97; P=0.02, HR, 1.49; 95% CI: 1.17–1.91; P<0.01, respectively) (Figure S11A).

The rates of disabling stroke demonstrated initial favorable results with TAVR and then comparable results in the late phase (HR, 0.72; 95% CI: 0.53–0.97; P=0.03, and HR, 1.11; 95% CI: 0.68–1.82; P=0.68, respectively) (Figure S11B). The rates of any strokes, bioprosthetic valve failure, and cardiovascular mortality were similar in both initial and late phases (Figure S12).

Heterogeneity for each outcome in all phases (0–5, 0–1, 1–5 years) was summarized in Table S5. There were substantial heterogeneities in heart failure rehospitalization for all time periods, in addition to any stroke in the initial phase.

Additional analyses

Subgroup analyses based on the TAVR valve types and the patient risk groups are summarized in Tables S6,S7, demonstrating the HRs and corresponding CIs with SAVR as the control arm. P values for interaction are summarized in Table S8. Subgroup analyses based on the TAVR valve types revealed mostly consistent results as the main analysis (Figure S13). However, the mortality in the late phase was higher with the TAVR group in the subgroup with balloon-expandable TAVR valves, although such a trend was not observed with self-expanding TAVR valves (HR, 1.22; 95% CI: 1.04–1.44; P=0.01, and HR, 1.02; 95% CI: 0.86–1.22; P=0.80, respectively). Subgroup analyses based on the patient risk group were also consistent with the main analysis, except for heart failure rehospitalization (Table S9). The heart failure rehospitalization with the TAVR arm was less frequent than the SAVR arm for low-risk group, while the opposite trend was observed in intermediate-risk groups (HR, 0.66; 95% CI: 0.50–0.88; P<0.01, and HR, 1.19; 95% CI: 1.00–1.42; P<0.05, respectively).

Results from sensitivity analyses based on duration of follow-up periods and newer generation TAVR valves are summarized in Tables S9,S10, demonstrating the HRs and corresponding CIs with SAVR as the control arm. Sensitivity analyses limited to studies with a follow-up

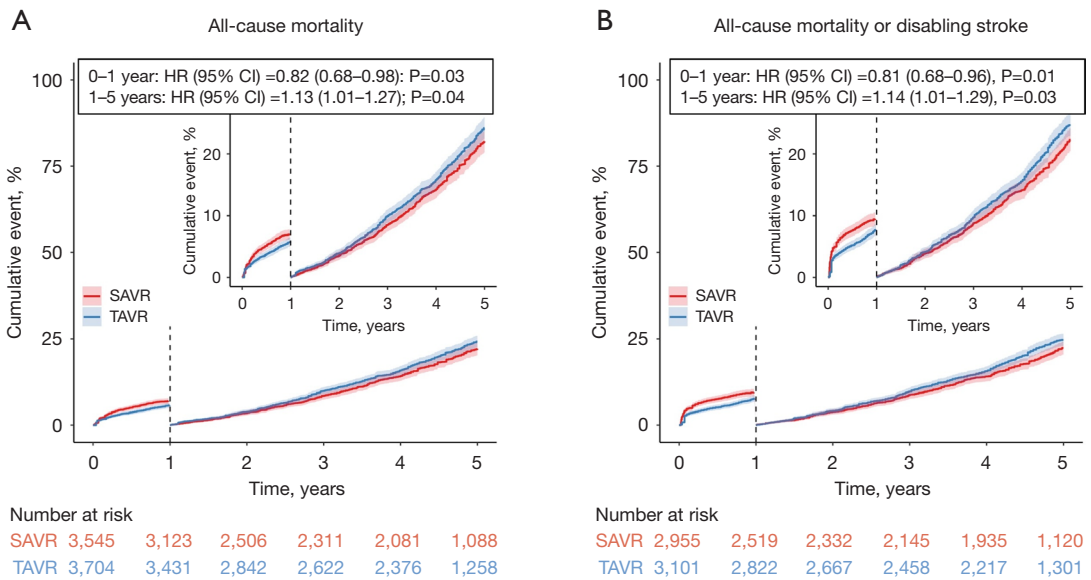

Figure 3 Landmark analysis at 1 year of (A) all-cause mortality and (B) composite outcome of all-cause mortality and disabling stroke. HR, hazard ratio; CI, confidence interval; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

period over 1 year demonstrated consistent findings as the main analysis (Figure S14). However, with regard to the 1-year outcome, the preference toward TAVR disappeared. Lastly, sensitivity analyses with new-generation TAVR devices demonstrated lower heart failure rehospitalization in the TAVR group (HR, 0.66; 95% CI: 0.50–0.88; P<0.01) (Figure S15). In the initial phase, favorable outcomes with the TAVR group were observed for rehospitalizations and composite outcome (HR, 0.58; 95% CI: 0.41–0.80; P<0.01, HR, 0.51; 95% CI: 0.31–0.85; P=0.01, respectively).

Grambsch and Therneau test for time-varying effect demonstrated violation of the proportional hazards assumption for the outcomes of all-cause mortality, the composite outcome, rehospitalization, disabling stroke, any stroke, and cardiovascular mortality, which justifies the need for landmark analyses (Table S11). The differences in RMST at 5 years were calculated between SAVR (a reference group) and TAVR. No significant difference was observed for each outcome (Table S12 and Figure S16).

Discussion

We performed a meta-analysis of six RCTs including 7,389 low-/intermediate-risk patients to report the mid-term clinical outcomes. Our analysis demonstrated similar all-cause mortality between TAVR and SAVR. Similarly, the composite outcome of all-cause mortality and disabling stroke was also comparable, as well as heart-failure rehospitalization. In the initial phase (0–1 years), TAVR was associated with favorable all-cause mortality, the composite outcome, disabling stroke, and heart failure rehospitalization. However, in the late phase (1–5 years), TAVR was associated with worse outcomes in all-cause mortality, composite outcome, and heart failure rehospitalization. Although we await the long-term outcomes, our data may be useful in guiding optimal therapy selection during the decision-making process.

The current U.S. and European guidelines both recommend shared decision-making with a Heart Team to opt between TAVR and SAVR (9,10). The U.S. guideline recommends TAVR as an equal alternative to SAVR for patients aged between 65 and 80 years, and TAVR is recommended in preference for patients above age 80 years (9). Meanwhile, the European guideline recommends TAVR for patients over 75 years of age, irrespective of the risk group (10). This discrepancy is due to the absence of robust, definitive long-term data, and the publication of mid-term data for the Evolut and PARTNER 3 trial warrants a reappraisal of the up-to-date data.

Previous meta-analyses demonstrated superior short-term outcomes with the TAVR group for low- and intermediate-risk patients (21-23). Our analysis of 1-year

results also demonstrated favorable outcomes with the TAVR arm, congruent to such findings. However, our analysis of mid-term outcomes demonstrated no between-group differences. Additionally, our landmark analysis indicated less favorable outcomes with the TAVR arm in the late phase. This disappearing initial advantage of TAVR coincides with a few meta-analyses employing methods to account for chronological trends, including phase-specific (11) or KM-derived reconstructed time-to-event data approaches (22,24,25). However, such findings in previous reports were likely driven by the high-risk patient groups due to the higher event rates. Our study is the first to demonstrate such a trend specifically for low- and intermediate-risk patients. Notably, our study is the first to also include follow-up data beyond two years for both PARTNER 3 and Evolut Low Risk trials.

The higher mortality initially observed with SAVR can be attributed to its inherently higher procedural invasiveness associated with general anesthesia, full sternotomy, cardioplegic arrest and cardiopulmonary bypass (26). Causes of mortality were previously examined in *post-hoc* analyses of RCTs concerning self-expandable TAVR valves. Deaths in TAVR arm were primarily linked to procedural technical issues, whereas deaths following SAVR were connected to postoperative complications (26-28). Meanwhile, clinical outcome determinants for long-term outcomes are different, including prosthesis-patient mismatch which can increase mortality for both TAVR (29) and SAVR (30,31) in the long run, paravalvular leaks which are associated with higher risk of all-cause mortality, rehospitalization, and cardiovascular mortality (32), structural valve degeneration and permanent pacemaker implantation which is associated with higher risk of mortality and heart failure-related rehospitalization over time (33). These factors are especially important for low- and intermediate-risk groups, where patients are expected to outlive their implanted valves. The development of new-generation TAVR valves protective against such risks could improve the long-term outcomes. Our sensitivity analysis limited to studies with new-generation TAVR valves demonstrated noninferior survival with a landmark analysis after 1 year, with reduced heart failure rehospitalization. Such results may be influenced by superior fluid dynamics associated with newer valves (34,35).

Despite the growing population receiving TAVRs (36), the literature on cardiac reoperations post-TAVR remains sparse. The incidence of post-TAVR cardiac reoperations significantly increased after the approval of TAVR for low-risk patients by the US Food and Drug Administration in 2019 (37,38). TAVR explants constitute nearly half of post-TAVR reoperations (37) and the proportion of patients belonging to the low-/intermediate-risk groups at the initial TAVR exceeded that of high-risk patients in 2021 (39). This warrants caution, as post-TAVR reoperations are associated with high morbidity and mortality (37,39), and careful consideration is warranted during the initial patient selection process.

Regarding heart failure rehospitalizations, our analysis demonstrated overall similar outcomes between groups. However, our landmark analysis yielded initially lower but eventually higher rates for the TAVR group. Heart failure rehospitalization has been associated with heightened mortality in a *post-hoc* analysis of the PARTNER trials (40). Interestingly, the subgroup analysis demonstrated the higher late-phase mortality with balloon-expandable valves, while no such trend was observed with self-expanding valves. However, the mortality in the SAVR arm for PARTNER 3 and Evolut Low Risk trials were different (6,7), rendering any direct comparison between the two low-risk trials less definitive. A direct comparison of self-expanding and balloon expandable valves is out of the scope of this study, and our subgroup results are exploratory and only hypothesis-generating at best.

A cautious approach is imperative before extrapolating our findings to clinical practice. It is worth mentioning that a lack of equity was present between the two groups with respect to the frequency of concomitant procedures. As recently mentioned in the joint statement by the STS and European Association for Cardio-Thoracic Surgery, up to 26% of the SAVR group in the PARTNER 3 and Evolut low risk trials underwent concomitant procedures, including concomitant coronary artery bypass graft (CABG) (6,7). These procedures were not only CABGs, but also mitral, tricuspid valve procedures, and interestingly even ascending aortic replacement and septal myectomy in the SAVR arm (6). In the Evolut low risk trial, a notably high mortality rate was observed in the SAVR arm at four years (12.1%) (7). Meanwhile, five-year mortality with isolated SAVR was 7.1% in the STS database report with 42,586 patients, following the same inclusion/exclusion criteria as the PARTNER 3 and Evolut low risk trials (41). In contrast to the SAVR arm, TAVR was almost exclusively an isolated valve procedure, except for few percutaneous coronary interventions. Notably, concomitant SAVR with CABG has been associated with superior outcomes than concomitant

TAVR with percutaneous coronary intervention (42).

Additionally, the heterogeneity of implanted prostheses in these RCTs represents an inherent bias. A significant number of TAVR valves were earlier generation prostheses (3,4,8). For both balloon expandable and self-expanding TAVR valves, newer generation devices have been associated with superior outcomes (34,35). In contrast, in the SAVR arm, a number of patients received an externally mounted leaflet prosthesis, which is known to be associated with early bioprosthetic valve failure (43). NOTION and SURTAVI trials, in which approximately 30% of patients in the SAVR arm received these valves, demonstrated strikingly higher bioprosthetic valve failure rates in the SAVR group. When opting for the initial treatment modality for severe, symptomatic AS, a careful patient-tailored approach with consideration to the lifetime management with a Heart Team approach is necessary (9).

An aspect we should keep in mind is that RCTs comparing TAVR with SAVR demonstrate conflicting evidence, particularly in low-risk patients. Jacquemyn *et al.* (44) recently reevaluated the evidence using trial sequential analysis, balancing type I and II errors, and compared their findings with conventional meta-analysis. Lower-risk RCTs suggested lower death risk on conventional meta-analysis (relative risk, 0.67, 95% CI: 0.47–0.96, P=0.031), but trial sequential analysis indicated potential spurious evidence (P=0.116), necessitating more data for conclusive benefit. For the composite endpoint of death or disabling stroke at 1 year in lower-risk RCTs, TAVR indicated lower risk in conventional meta-analysis (relative risk, 0.68, 95% CI: 0.50–0.93, P=0.014), but trial sequential analysis suggested potential spurious evidence (P=0.053), necessitating more data for conclusive benefit. Follow-up results provided inconclusive evidence for both primary outcomes across risk categories. The authors concluded that conventional meta-analysis methods may have prematurely declared an early reduction of negative outcomes after TAVR when compared with SAVR.

Limitations

This study has several limitations. First, follow-up data beyond 5 years was only available for the NOTION trial (8). Second, not all cases underwent isolated procedures in the included RCTs. Third, the results from subgroup analyses must be interpreted as exploratory outcomes. Fourth, the valve types used in the SURTAVI, PARTNER 2, and NOTION trials are no longer used in the current clinical practice. Furthermore, there was a substantial amount of bias in the included RCTs. A substantial proportion of deviation from randomly assigned treatment, loss to follow-up, and additionally performed procedures were observed in the SAVR group (45).

The frequent loss to follow-up and deviation from assigned treatment in the SAVR arm was markedly higher in comparison to TAVR arm (45,46). In this study, publication bias was not assessed using the funnel plot owning to the insufficient number of included trials in this meta-analysis. Furthermore, incorporating low and intermediate-risk groups may have generated bias in this study. However, as TAVR application expands to these groups, it's vital to generate relevant evidence, to which this study contributes. Lastly, the SAVR group in the included RCTs contained some portions of patients with concomitant procedures, which could have influenced the results.

Conclusions

This meta-analysis demonstrated that the survival was similar between TAVR and SAVR for low- and intermediate-risk patients with severe symptomatic AS. Our analysis also demonstrated TAVR to be associated with favorable survival in the initial year. However, a landmark analysis indicated suboptimal survival after 1 year in the TAVR arm. Additional RCT results with longer follow-up durations are warranted to confirm this trend.

Acknowledgments

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Footnote

Conflicts of Interest: S.F. is a consultant for Terumo Aortic, Medtronic Inc., Edwards Lifesciences and Artivion. Tsuyoshi Kaneko has received consulting fees from Edwards Lifesciences, Medtronic, 4C Medical, CardioMech, and Cook Medical; and has been a speaker for Abbott and Baylis. The other authors have no conflicts of interest to declare.

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Supplementary

Table S1 The search strategy of MEDLINE via PubMed

#1	"Transcatheter Aortic Valve Replacement"[mh]
#2	"transcatheter aortic valve replacement"[tiab]
#3	"TAVI"[tiab]
#4	"TAVR"[tiab]
#5	#1 OR #2 OR #3 OR #4
#6	"surgical aortic valve replacement"[tiab]
#7	"SAVR"[tiab]
#8	"aortic valve stenosis/surgery"[mh]
#9	#6 OR #7 OR #8
#10	"aortic valve stenosis"[mh]
#11	"aortic valvular stenosis"[tiab]
#12	"AS"[tiab]
#13	#10 OR #11 OR #12
#14	randomized controlled trial[pt]
#15	#5 AND #9 AND #13 AND #14

Table S2 The search strategy of EMBASE

#1	exp aortic valve stenosis
#2	("aortic valve stenosis" or "AS"):ti,ab,kw.
#3	exp transcatheter aortic valve implantation
#4	("transcatheter aortic valve implantation" or "transcatheter aortic valve replacement" or "TAVR" or "TAVI").ti,ab,kw.
#5	("surgical aortic valve replacement" or "SAVR"). ti,ab,kw.
#6	Randomized controlled trial/ or Controlled clinical study/ or Randomized/
#7	("randomized controlled trial").pt. or "randomized". ti,ab,kw. or "randomly".ti,ab,kw.
#8	#1 or #2
#9	#3 or #4
#10	#6 or #7
#11	#5 and #8 and #9 and #10

Table S3 The search strategy of Cochrane CENTRAL

#1	"aortic valve stenosis" OR "AS" OR"aortic valvular stenosis":ti,ab,kw
#2	"transcatheter aortic valve replacement" OR "transcatheter aortic valve implantation" OR "TAVR" OR "TAVI":ti,ab,kw
#3	"surgical aortic valve replacement" OR "SAVR":ti,ab,kw
#4	#1 and #2 and #3

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Table S4 Definitions of outcome in each study

Trial	Death	Stroke	Disabling stroke	Rehospitalization rate	Cardiovascular mortality	Bioprosthetic valve failure
PARTNER 2A	VARC2	VARC2	VARC2	Rehospitalization for symptoms of aortic stenosis and/or complications of the valve procedure If the index hospitalization for a patient is greater than 30 days, then hospital day 31 will count as a re-hospitalization for endpoint analysis	VARC2	NA
SURTAVI	VARC2	VARC2	VARC2	VARC2	VARC2	VARC2
UK TAVI	VARC2	VARC2	VARC2	NA	VARC2	NA
NOTION	VARC2	VARC2	VARC2	VARC2	VARC2	The consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI), the European Society of Cardiology (ESC), and the European Association for Cardio-thoracic Surgery (EACTS)
PARTNER 3	VARC2	VARC2	VARC2	VARC2	VARC2	VARC3
Evoult Low Risk	VARC3	VARC3	VARC3	VARC3	VARC3	NA

VARC, Valve Academic Research Consortium.

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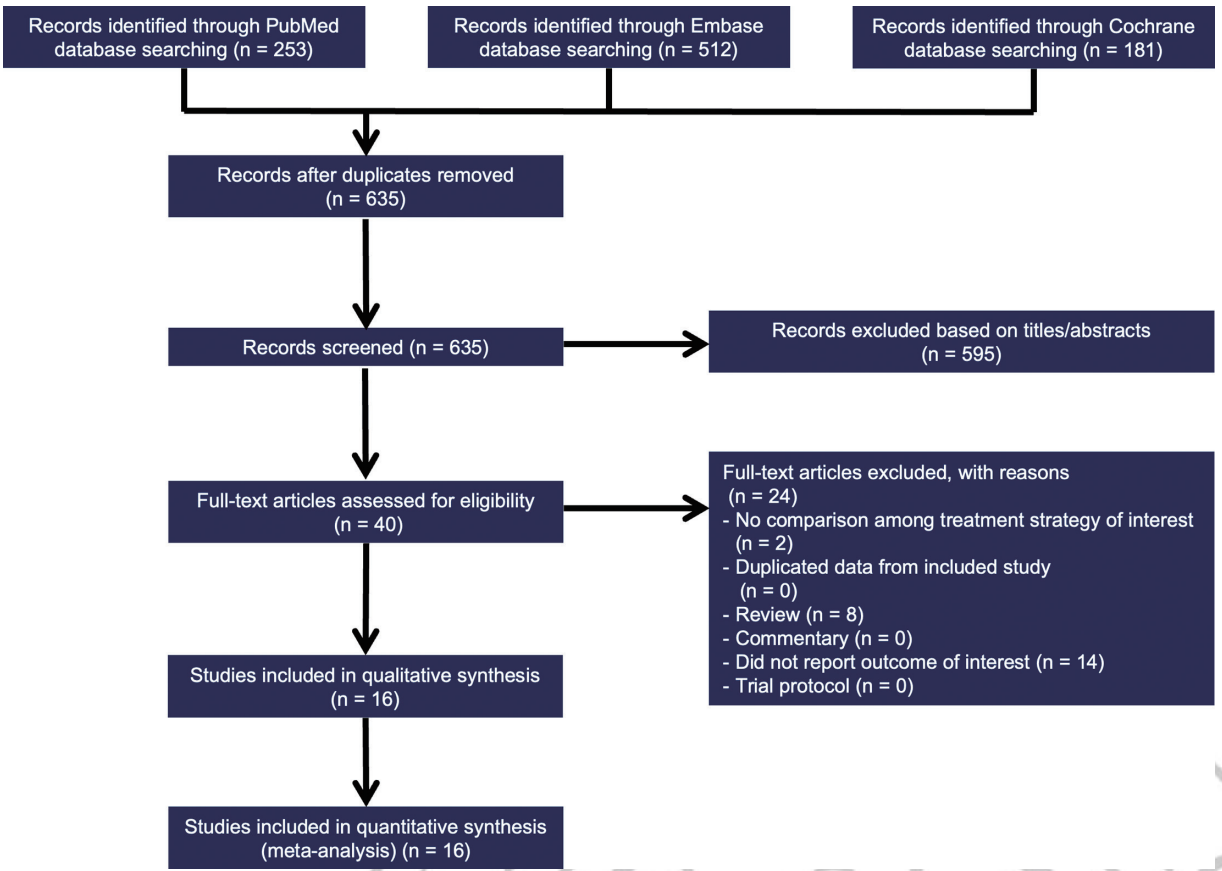

Figure S1 Workflow for selecting eligible papers according to the PRISMA criteria in search of original studies for this meta-analysis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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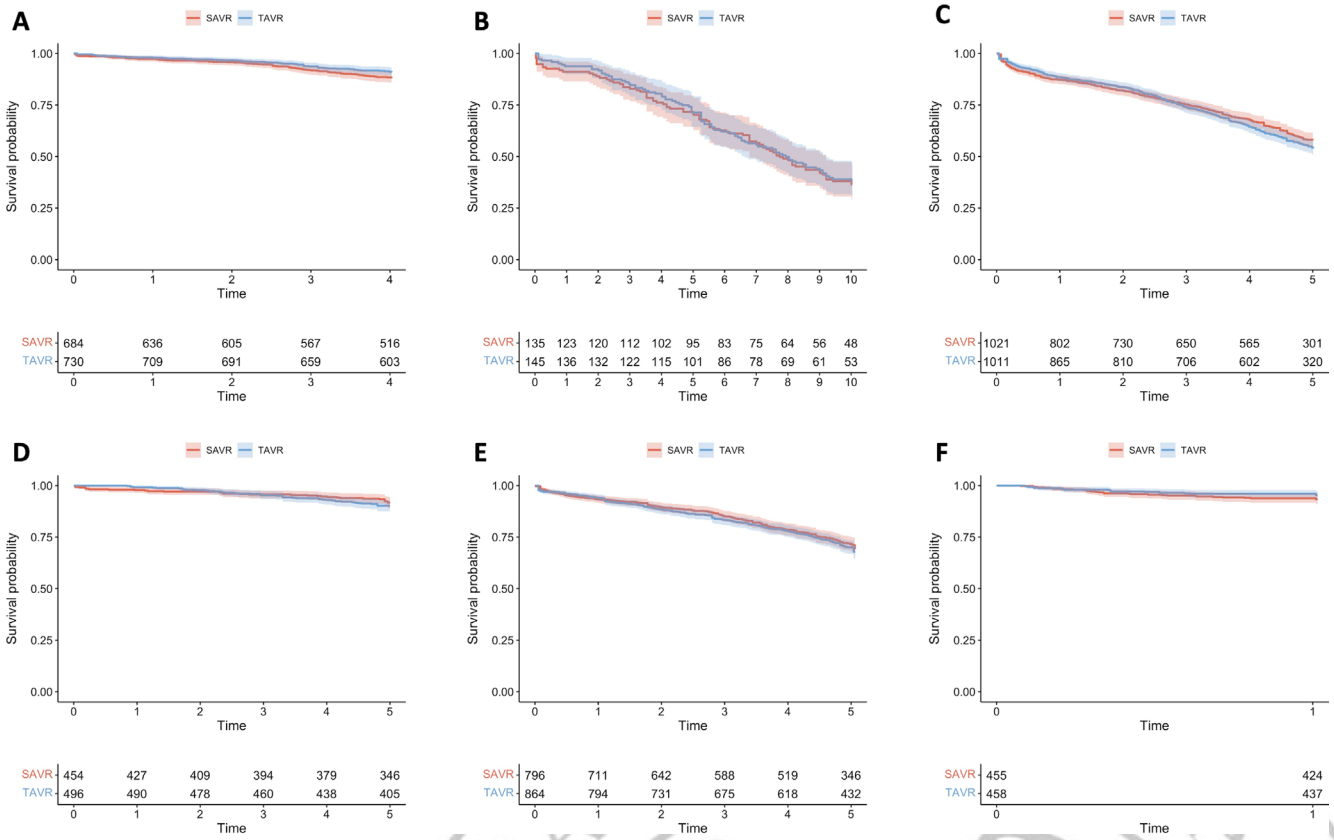

Figure S2 All-cause mortality rate: reconstructed Kaplan-Meier curves from individual studies. Kaplan-Meier analyses of all-cause mortality from individual study (A) Evolut Low Risk Trial, (B) NOTION trial, (C) PARTNER2 trial, (D) PARTNER3 trial, (E) SURTAVI trial, and (F) UKTAVI trial. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

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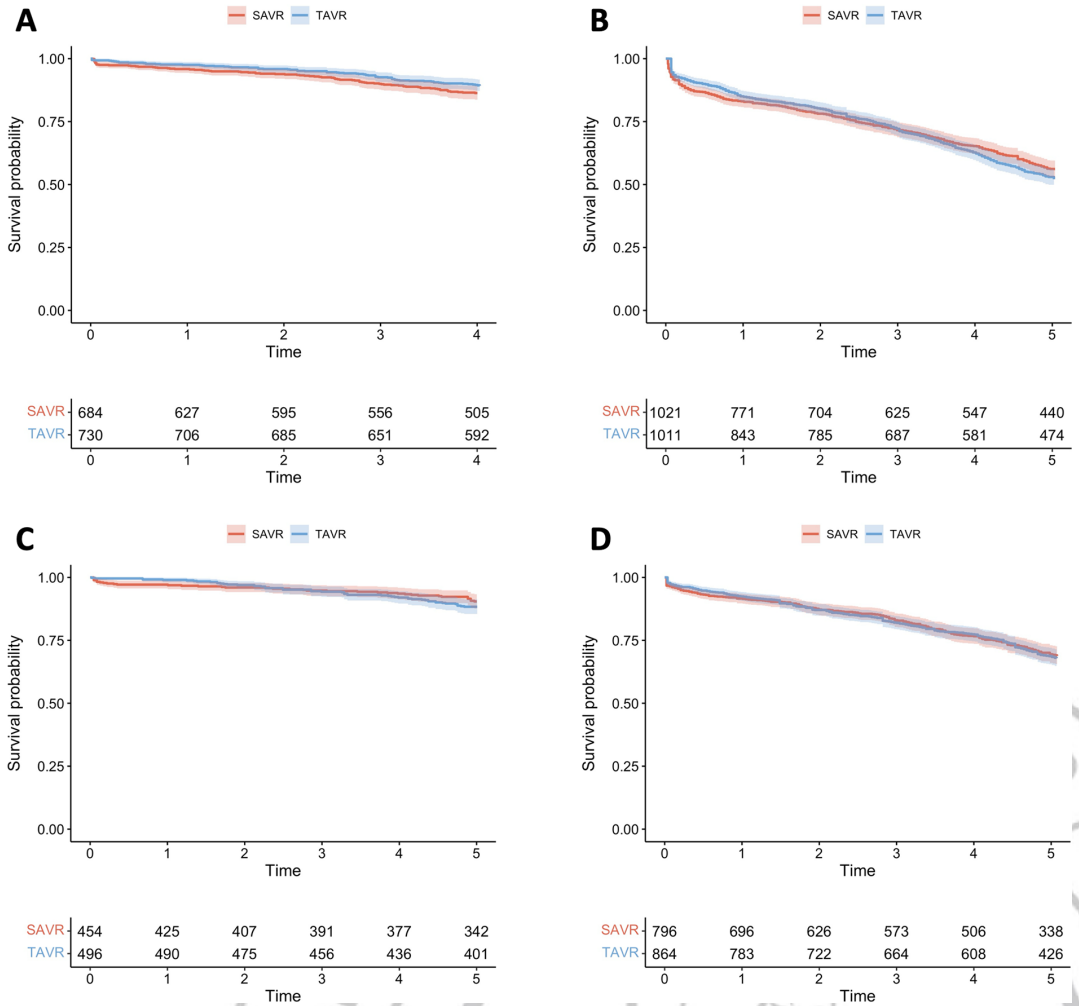

Figure S3 Composite outcome of all-cause mortality and disabling stroke rate: reconstructed Kaplan-Meier curves from individual studies. Kaplan-Meier analyses of composite outcome including all-cause mortality and disabling stroke from individual study (A) Evolut Low Risk Trial, (B) PARTNER2 trial, (C) PARTNER3 trial, and (D) SURTAVI trial. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

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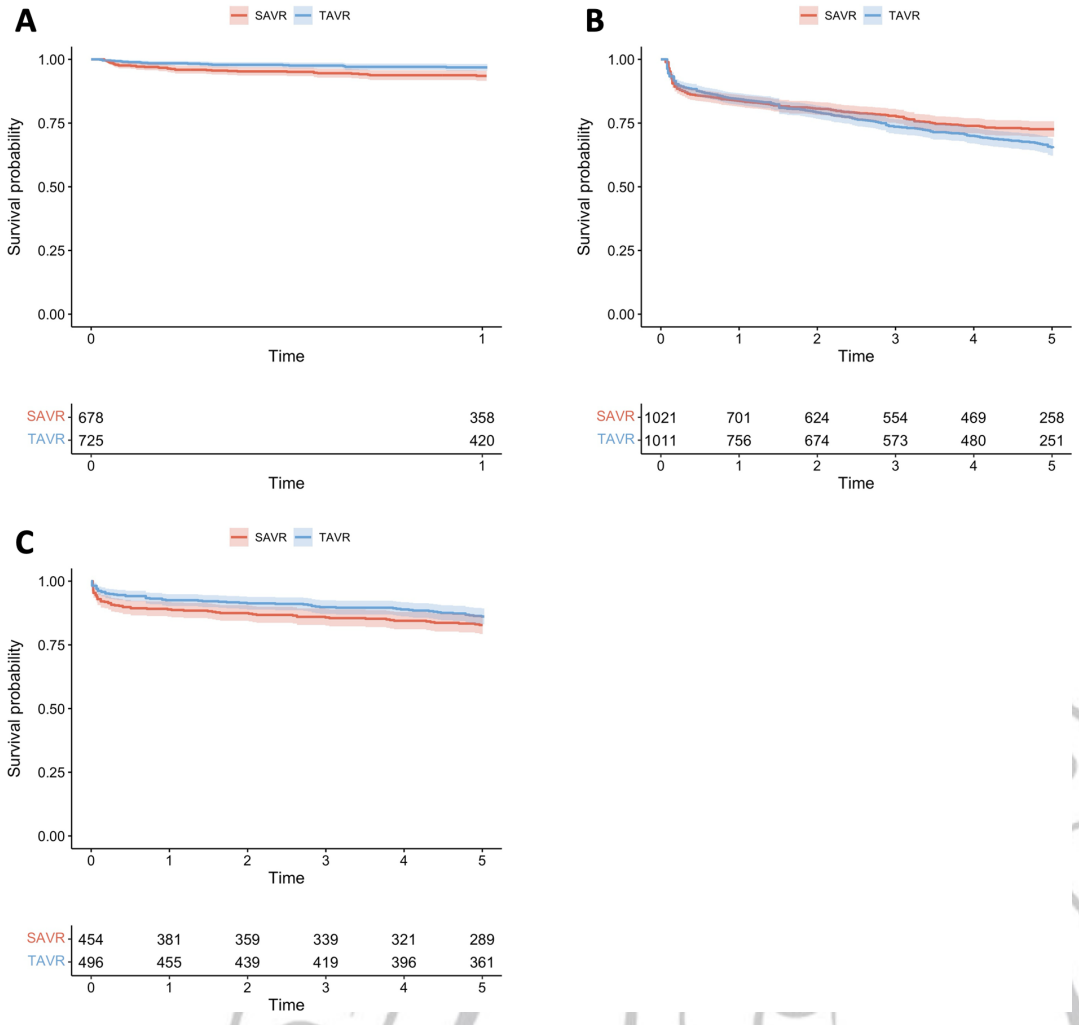

Figure S4 Heart-failure rehospitalization rates: reconstructed Kaplan-Meier curves from individual studies. Kaplan-Meier analyses of heart failure rehospitalizations from individual study (A) Evolut Low Risk Trial, (B) PARTNER2 trial, and (C) PARTNER3 trial. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

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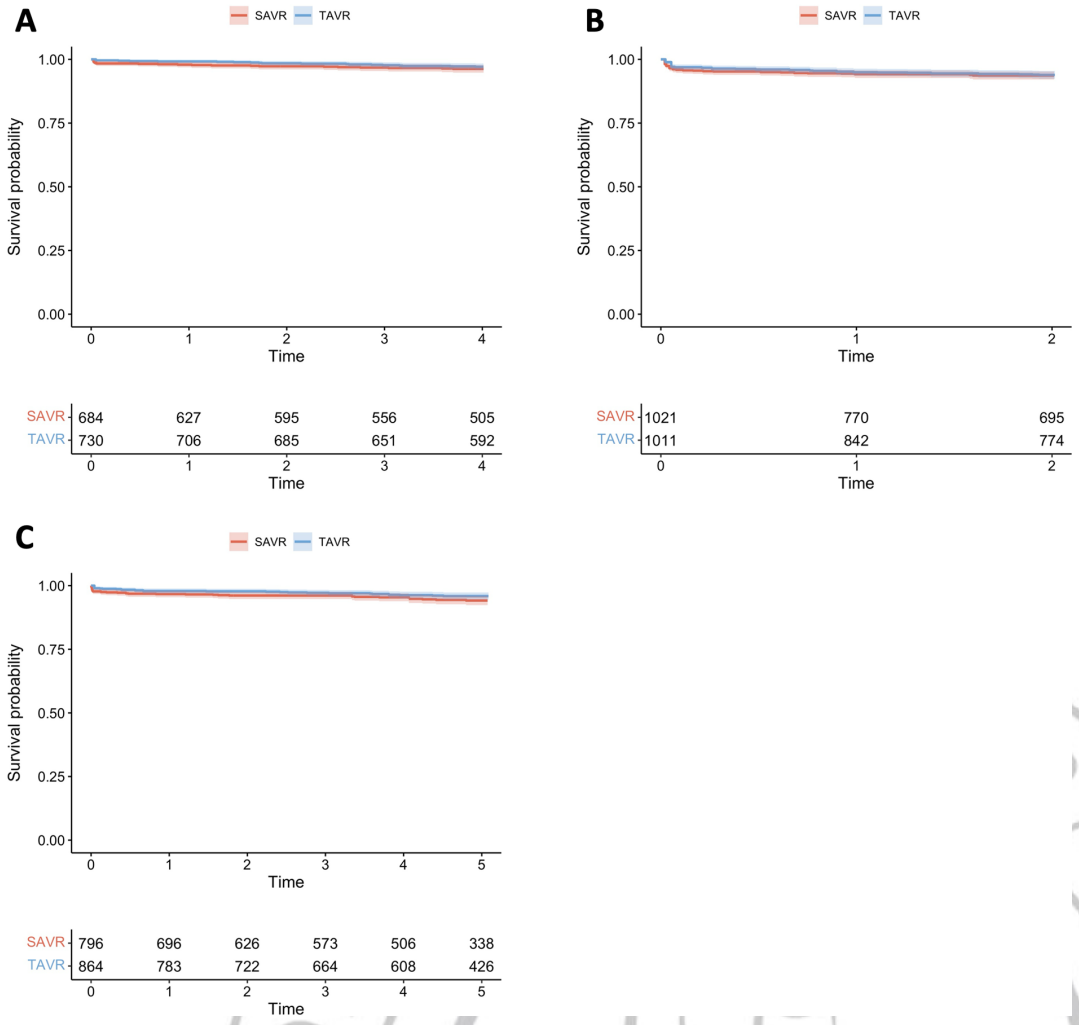

Figure S5 Disabling stroke rate: reconstructed Kaplan-Meier curves from individual studies. Kaplan-Meier analyses of disabling stroke from individual study (A) Evolut Low Risk trial, (B) PARTNER2 trial, and (C) SURTAVI trial. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

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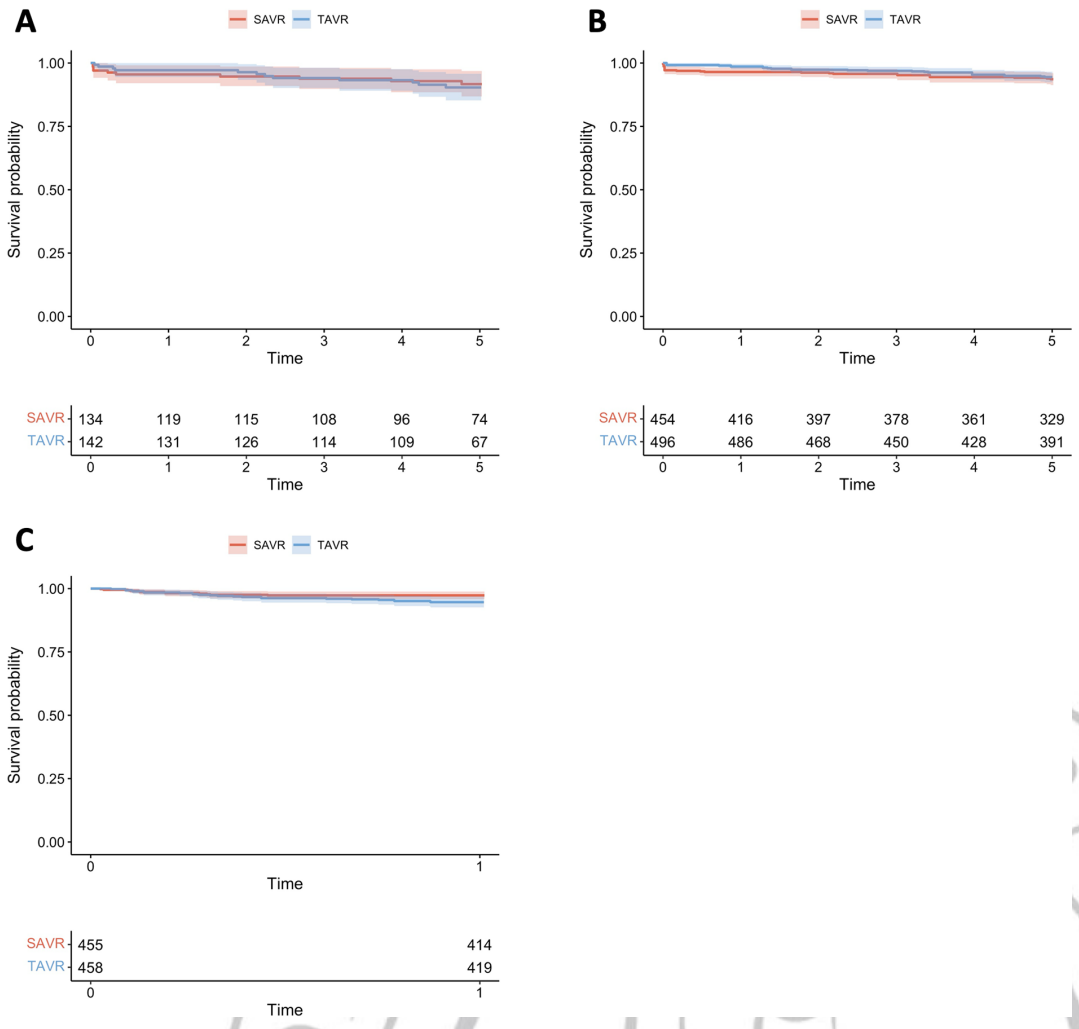

Figure S6 All stroke rate: reconstructed Kaplan-Meier curves from individual studies. Kaplan-Meier analyses of any stroke from individual study (A) NOTION Trial, (B) PARTNER3 trial, and (C) UKTAVI trial. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

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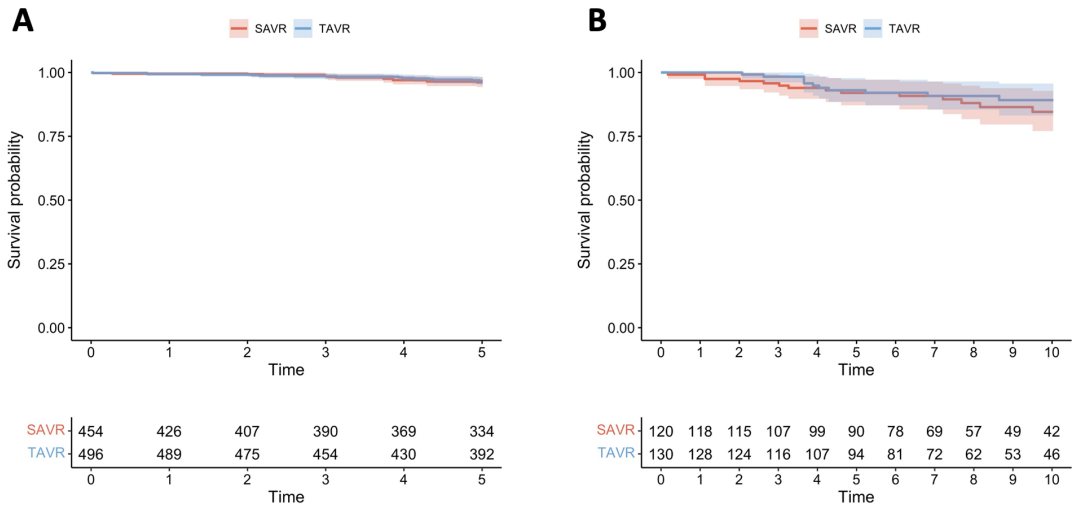

Figure S7 Bioprosthetic valve failure rates: reconstructed Kaplan-Meier curves from individual studies. Kaplan-Meier analyses of bioprosthetic valve failure from individual study (A) PARTNER3 Trial and (B) NOTION trial. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

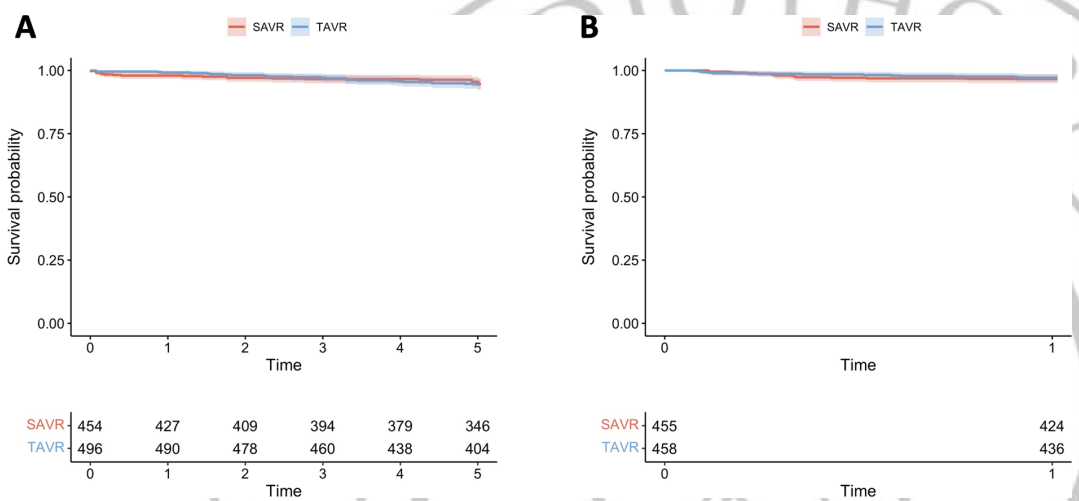

Figure S8 Cardiovascular mortality rate: reconstructed Kaplan-Meier curves from individual studies. Kaplan-Meier analyses of cardiovascular mortality from individual study (A) PARTNER3 Trial and (B) UKTAVI trial. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

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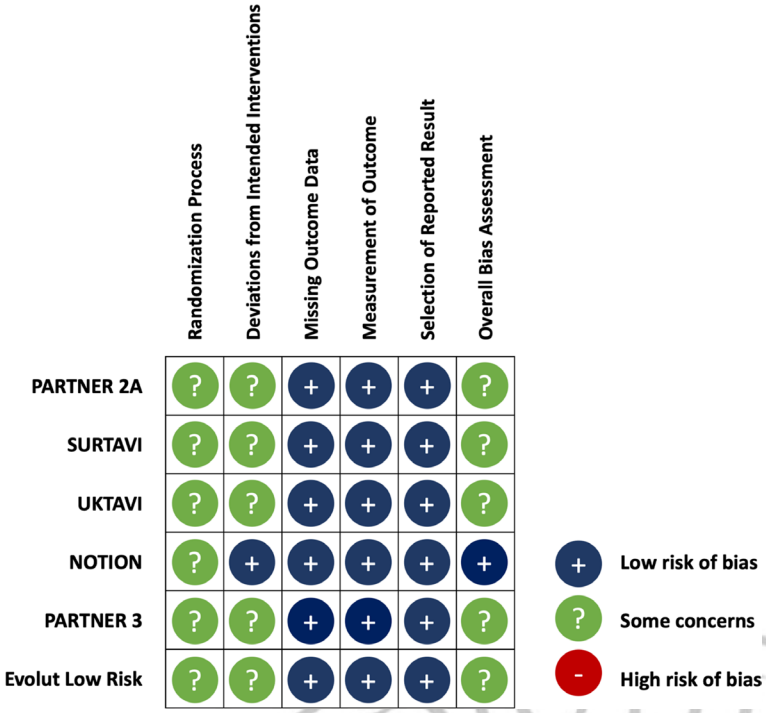

Figure S9 Risk of bias summary according to the Cochrane Collaboration Manual. PARTNER, Placement of Aortic Transcatheter Valves; SURTAVI, Surgical Replacement and Transcatheter Aortic Valve Implantation; UKTAVI, The UK Transcatheter Aortic Valve Implantation; NOTION, Nordic Aortic Valve Intervention.

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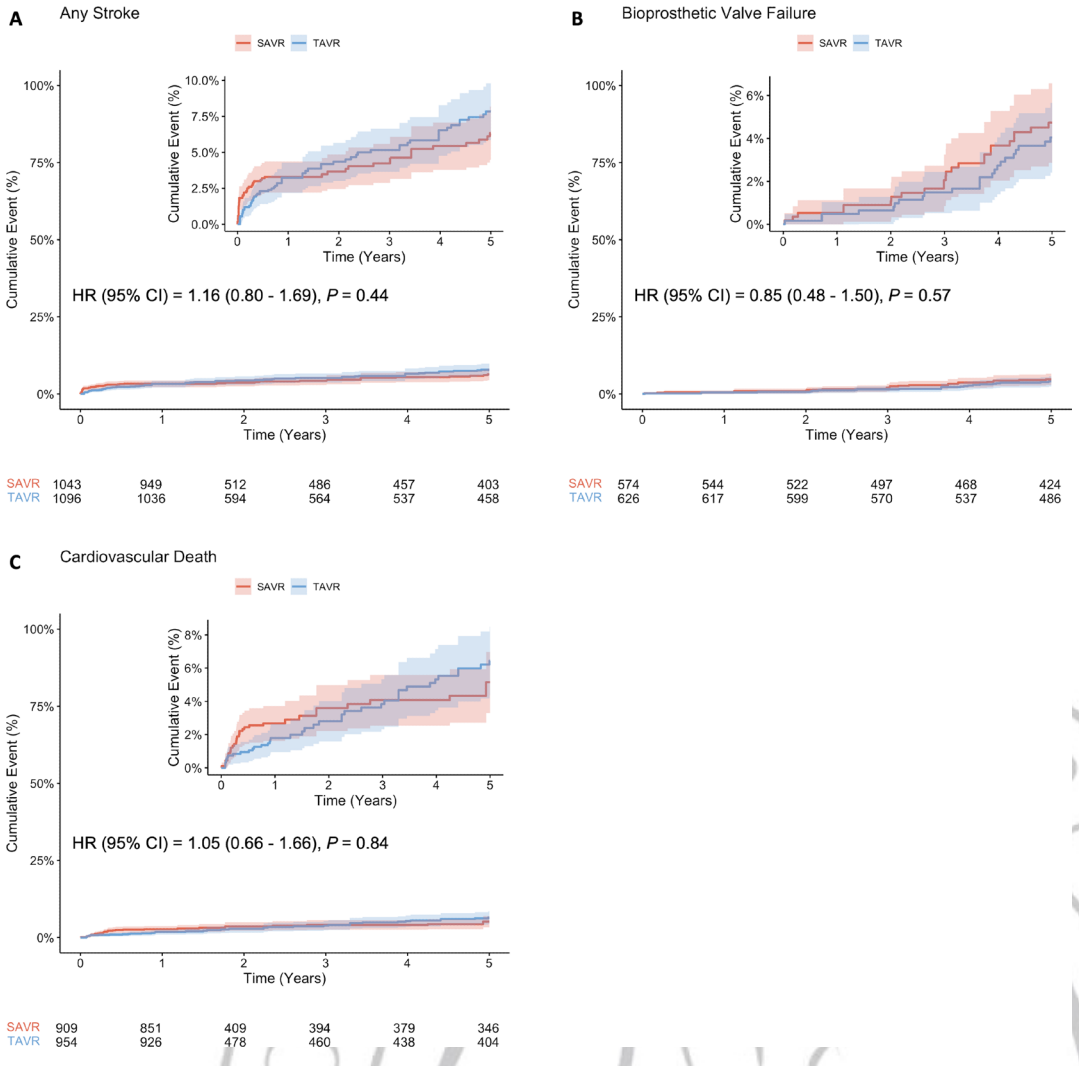

Figure S10 Rates of any stroke, bioprosthetic valve failure, and cardiovascular mortality. Kaplan-Meier analyses of (A) any stroke, (B) bioprosthetic valve failure, and (C) cardiovascular mortality. Solid lines represent the estimates, and the surrounding bands represent the 95% confidence intervals. CI, confidence interval; HR, hazard ratio; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

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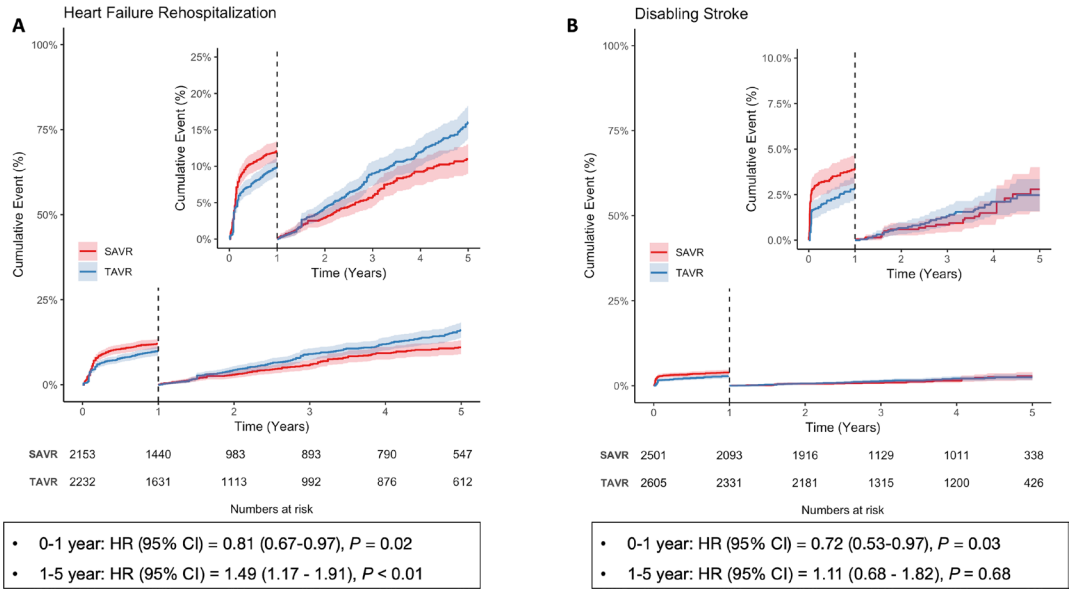

Figure S11 Landmark analyses of heart failure rehospitalization and disabling stroke rates. Landmark analyses at 1 year of (A) heart failure rehospitalization and (B) disabling stroke. Solid lines represent the estimates, and the surrounding bands represent the 95% confidence intervals. CI, confidence interval; HR, hazard ratio; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

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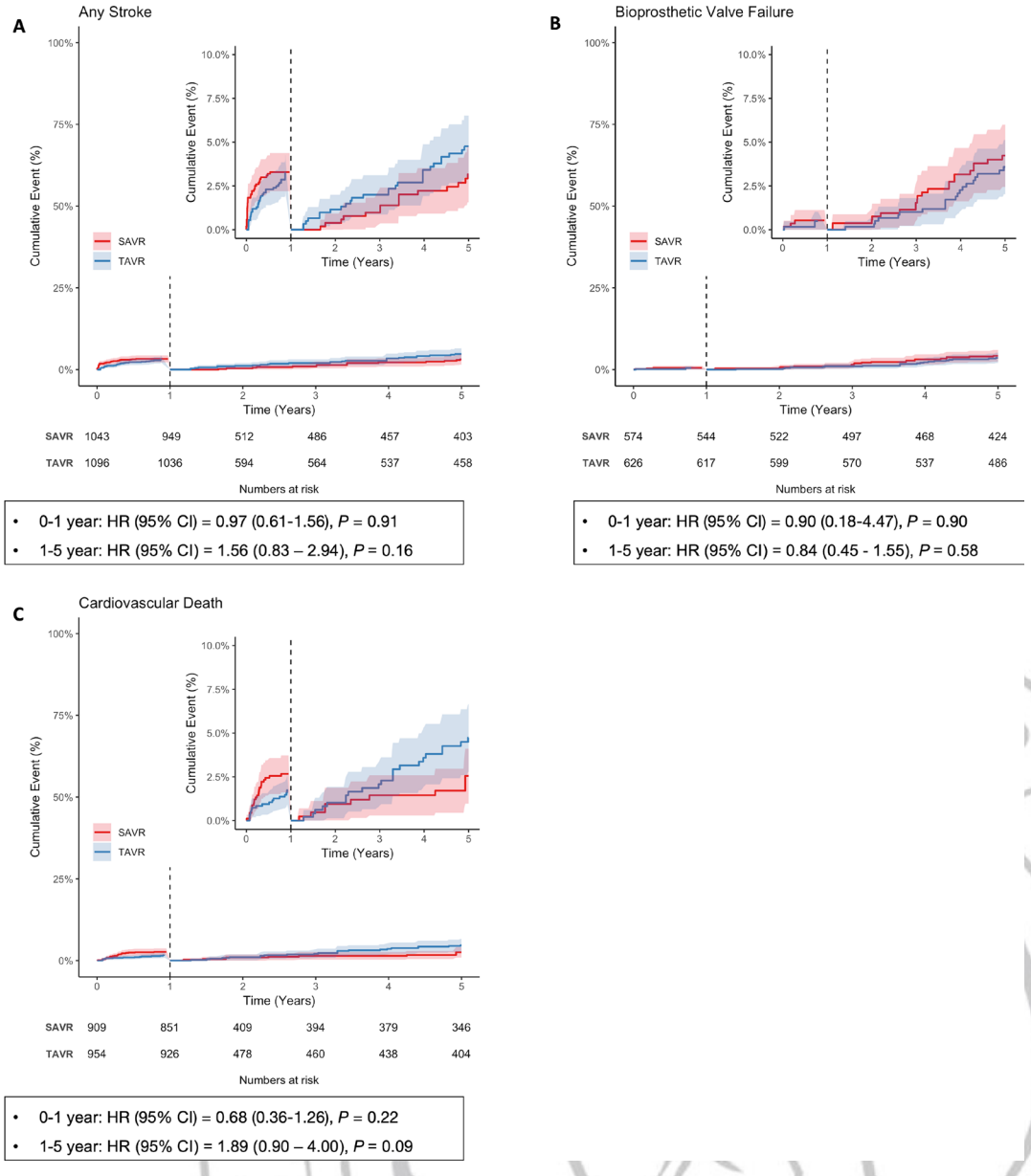

Figure S12 Landmark analyses of any stroke, bioprosthetic valve failure, and cardiovascular mortality rates. Landmark analyses at 1 year of (A) any stroke, (B) bioprosthetic valve failure, and (C) cardiovascular mortality. Solid lines represent the estimates, and the surrounding bands represent the 95% confidence intervals. CI, confidence interval; HR, hazard ratio; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

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Table S5 Heterogeneity of each outcome

Outcome	Overall	0–1 year	1–5 year
All-cause Mortality	22.54	0	28.63
All-cause Mortality or Disabling Stroke	10.72	0	45.75
Bioprosthetic Valve Failure	0	0	0
Cardiovascular Mortality	0	11.77	NA
Disabling Stroke	0	12.35	0
Heart Failure Rehospitalization	86.59	69.84	65.4
Any Stroke	47.12	73.49	0

I^2 values for each outcome are summarized in the table below. NA, not available.

Table S6 Subgroup analyses for each outcome based on the TAVR valve type

Outcome	Subgroup	HR	Lower 95% CI	Upper 95% CI	P value
All-cause Mortality	Balloon-Expandable TAVR Valve	1.098	0.961	1.255	0.17
All-cause Mortality	Self-Expanding TAVR Valve	0.974	0.835	1.136	0.739
All-cause Mortality or Disabling Stroke	Balloon-Expandable TAVR Valve	1.074	0.945	1.22	0.275
All-cause Mortality or Disabling Stroke	Self-Expanding TAVR Valve	0.938	0.802	1.098	0.425
Disabling Stroke	Self-Expanding TAVR Valve	0.705	0.488	1.019	0.063
Heart Failure Rehospitalization	Balloon-Expandable TAVR Valve	1.084	0.932	1.262	0.295

CI, confidence interval; HR, hazard ratio; TAVR, transcatheter aortic valve replacement.

Table S7 Subgroup analyses for each outcome based on patient risk group

Outcome	Subgroup	HR	Lower 95% CI	Upper 95% CI	P value
All-cause Mortality	Low-Risk Patient Group	0.872	0.707	1.075	0.200
All-cause Mortality	Intermediate-Risk Patient Group	1.080	0.965	1.208	0.183
All-cause Mortality or Disabling Stroke	Low-Risk Patient Group	0.894	0.700	1.142	0.369
All-cause Mortality or Disabling Stroke	Intermediate-Risk Patient Group	1.044	0.937	1.164	0.436
Disabling Stroke	Intermediate-Risk Patient Group	0.824	0.619	1.097	0.184
Heart Failure Rehospitalization	Low-Risk Patient Group	0.664	0.502	0.877	0.004
Heart Failure Rehospitalization	Intermediate-Risk Patient Group	1.190	1.003	1.412	0.046

CI, confidence interval; HR, hazard ratio.

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Table S8 P-interaction values between subgroups

Outcomes	Number of studies	Overall outcome		Initial 1 year		Landmark analysis after 1 year	
		Valve types	Risk groups	Valve types	Risk groups	Valve types	Risk groups
All-cause Mortality	6	0.395	0.776	0.873	0.494	0.612	0.732
All-cause Mortality or Disabling Stroke	4	0.567	0.734	0.904	0.261	0.408	0.921
Bioprosthetic Valve Failure	2	NA	NA	NA	NA	NA	NA
Cardiovascular Mortality	2	NA	NA	NA	NA	NA	NA
Disabling Stroke	3	0.641	0.891	0.447	0.411	0.408	0.937
Heart Failure Rehospitalization	3	0.180	0.151	0.335	0.284	NA	NA
Any Stroke	3	0.279	0.298	0.067	0.069	NA	NA

NA, not available.

https://dx.doi.org/10.21037/acs-2024-etavr-0096

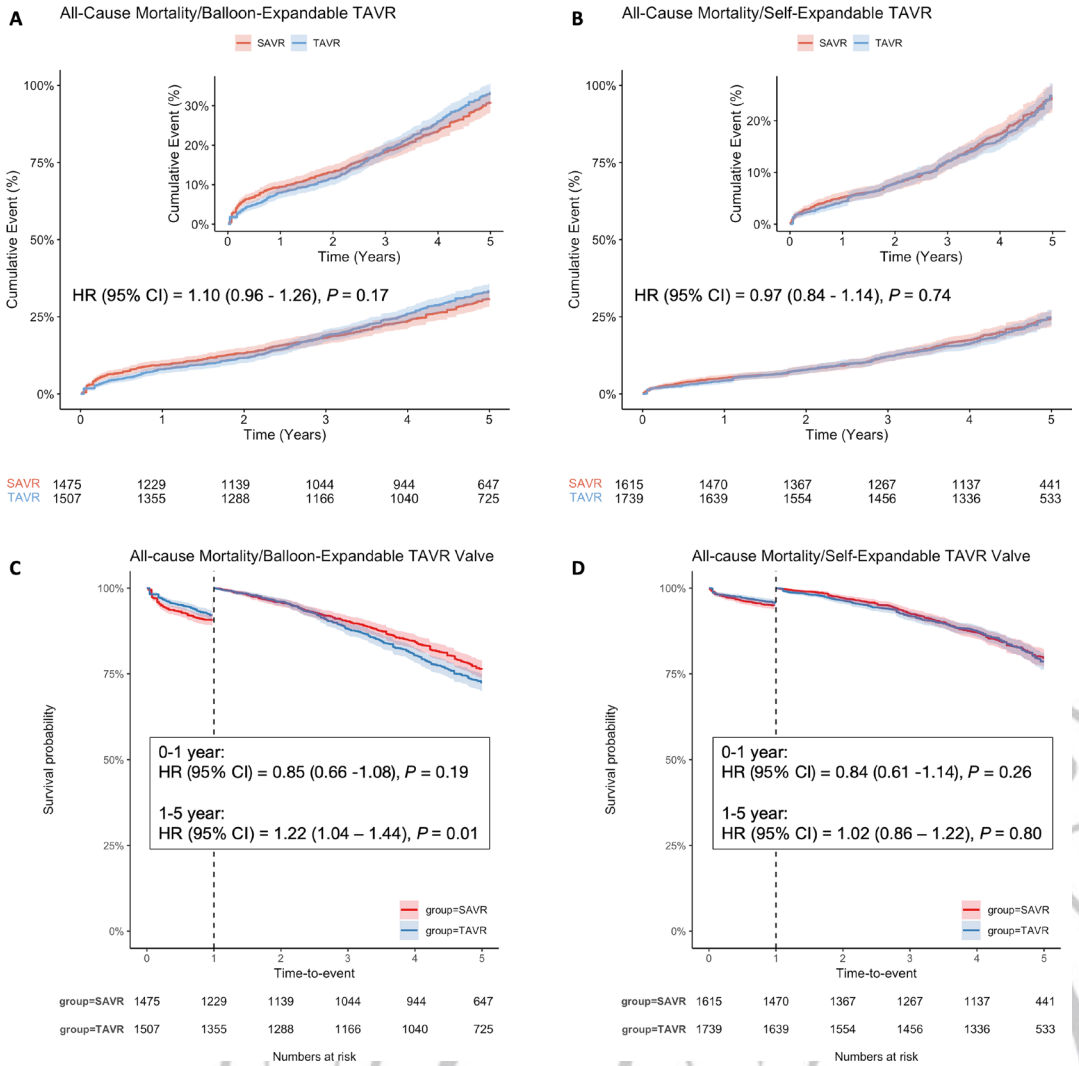

Figure S13 Subgroup analyses based on TAVR valve types. Subgroup analyses of all-cause mortality for (A) balloon-expandable TAVR valves and (B) self-expanding TAVR valves. Landmark analyses for each of the subgroup are shown in (C) and (D), in the same order. Solid lines represent the estimates, and the surrounding bands represent the 95% confidence intervals. CI, confidence interval; HR, hazard ratio; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

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Table S9 Sensitivity analyses for each outcome for studies with follow-up >1 year

Outcomes	Overall				Initial 1 year				Landmark analysis after 1 year			
	HR	Lower 95% CI	Upper 95% CI	P value	HR	Lower 95% CI	Upper 95% CI	P value	HR	Lower 95% CI	Upper 95% CI	P value
All-cause Mortality	1.043	0.943	1.154	0.412	0.843	0.694	1.022	0.083	1.13	1.004	1.273	0.043
Any Stroke	0.907	0.577	1.427	0.674	0.451	0.219	0.930	0.031	1.565	0.832	2.942	0.165

CI, confidence interval; HR, hazard ratio.

Table S10 Sensitivity analyses for each outcome for studies with new generation TAVR valves

Outcomes	Overall				Initial 1 year				Landmark analysis after 1 year			
	HR	Lower 95% CI	Upper 95% CI	P value	HR	Lower 95% CI	Upper 95% CI	P value	HR	Lower 95% CI	Upper 95% CI	P value
All-cause Mortality	0.842	0.663	1.069	0.159	0.618	0.345	1.107	0.106	0.970	0.719	1.308	0.841
All-cause Mortality or Disabling Stroke	0.894	0.700	1.142	0.369	0.512	0.307	0.854	0.010	1.071	0.806	1.422	0.638
Heart Failure Rehospitalization	0.664	0.502	0.877	0.004	0.575	0.413	0.800	0.001	0.979	0.570	1.681	0.937
Any Stroke	1.171	0.770	1.780	0.461	0.390	0.161	0.948	0.038	1.458	0.694	3.064	0.319

CI, confidence interval; HR, hazard ratio.

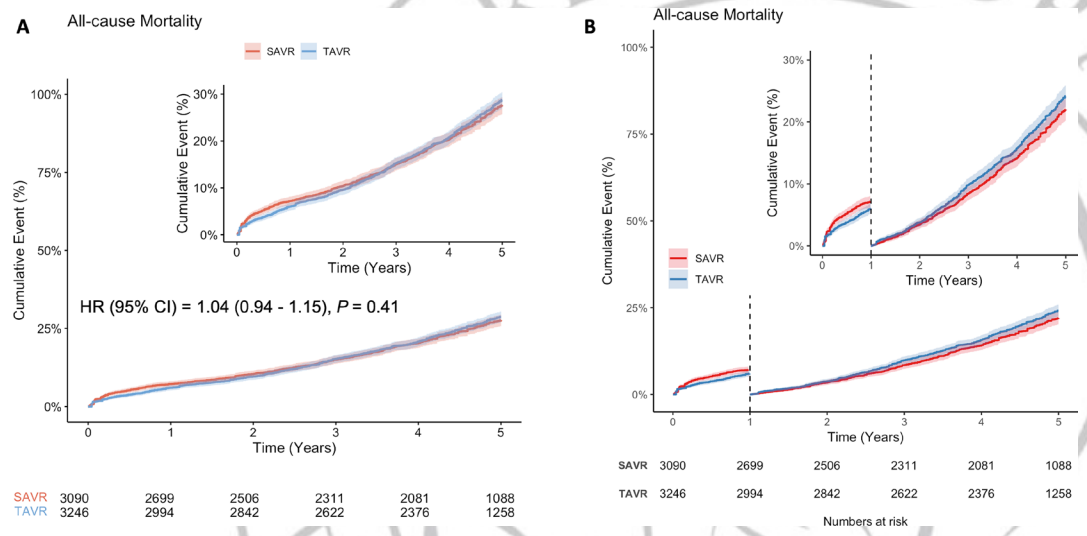

Figure S14 Sensitivity analyses with inclusion of studies reporting >1 year of follow-up. Sensitivity analyses of all-cause mortality for studies reporting >1 year of follow-up (A) all-cause mortality and (B) landmark analysis of all-cause mortality. Solid lines represent the estimates, and the surrounding bands represent the 95% confidence intervals. CI, confidence interval; HR, hazard ratio; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

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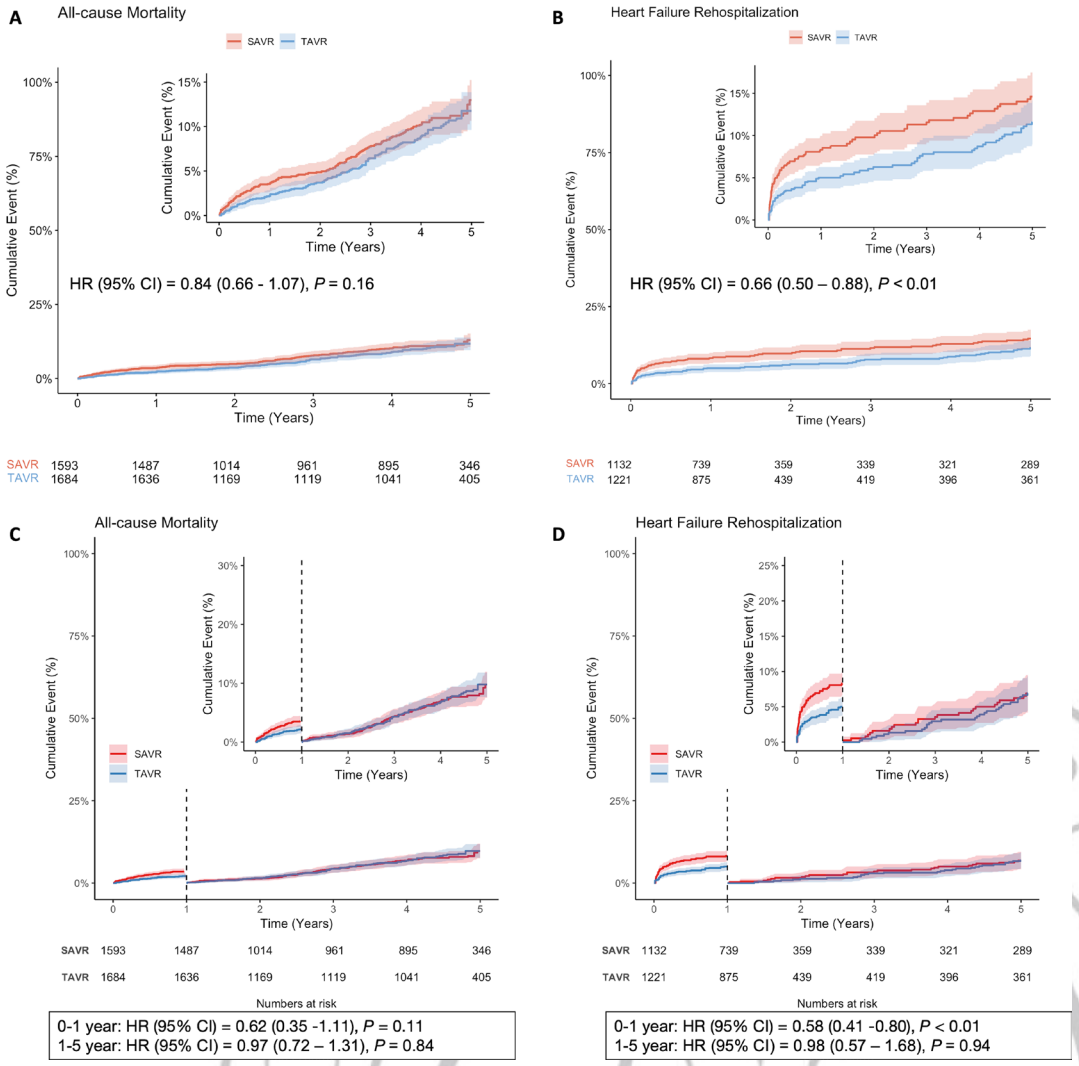

Figure S15 Sensitivity analyses with inclusion of studies with new generation TAVR devices. Sensitivity analyses of studies with the use of new generation TAVR devices (A) all-cause mortality and (B) heart failure rehospitalization rates. (C) and (D) indicate the results of landmark analysis at 1 year. Solid lines represent the estimates, and the surrounding bands represent the 95% confidence intervals. CI, confidence interval; HR, hazard ratio; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

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Table S11 Grambsch and Therneau test for time-invariant effect	
Outcome	P value
All-cause Mortality	0.034
All-cause Mortality or Disabling Stroke	0.001
Bioprosthetic Valve Failure	0.421
Cardiovascular Death	0.032
Disabling Stroke	0.001
Heart Failure Rehospitalization	<0.001
Any Stroke	0.014

Table S12 The difference in restricted mean survival time for each outcome

Outcome	RMST difference (days)	Lower 95% CI (days)	Upper 95% CI (days)	P value
All-cause Mortality	6.48	–17.49	30.45	0.60
All-cause Mortality or Disabling Stroke	15.36	–12.44	43.16	0.28
Bioprosthetic Valve Failure	9.35	–11.74	30.45	0.38
Cardiovascular Death	0.92	–29.31	31.16	0.95
Disabling Stroke	17.84	–1.7	37.38	0.07
Heart Failure Rehospitalization	12.12	–26.21	50.44	0.54
Any Stroke	–9.65	–40.69	21.39	0.54

CI, confidence interval; RMST, restricted mean survival.

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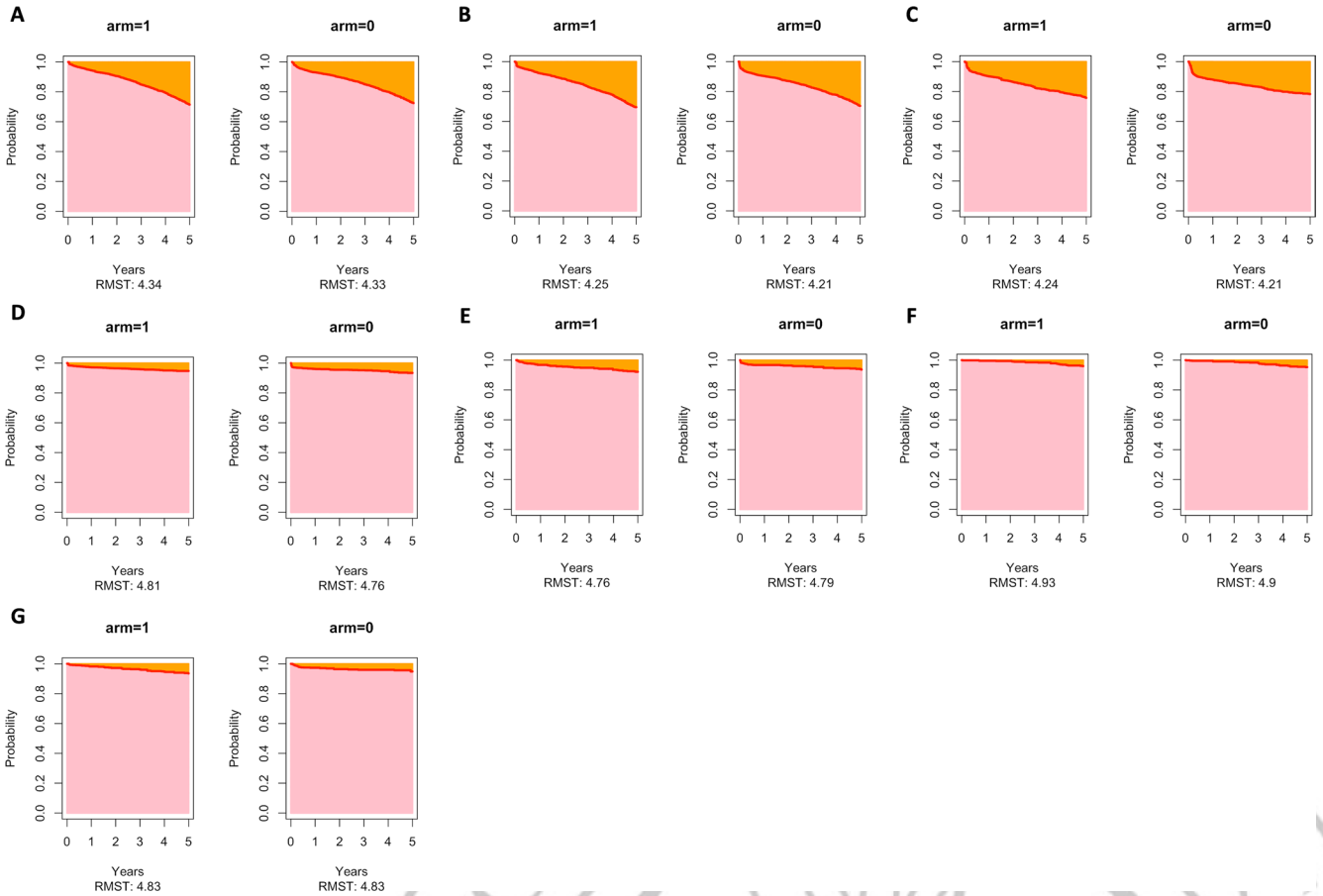

Figure S16 Restricted mean survival time as area under the Kaplan-Meier curve in each outcome. Arm 1 = transcatheter aortic valve replacement, Arm 0 = surgical aortic valve replacement. Red bold lines indicate Kaplan-Meier curve. The pink-shaded area below each Kaplan-Meier curve is restricted mean survival time with the follow-up period of 5 years. The number shown below each Kaplan Meier curve shows restricted mean survival time (years) in the corresponding treatment groups. (A) all-cause mortality, (B) all-cause mortality or disabling stroke, (C) heart-failure rehospitalization, (D) disabling stroke, (E) any stroke, (F) bioprosthetic valve failure, and (G) cardiovascular mortality. RMST, restricted mean survival time.

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