Journal of the American Heart Association

ORIGINAL RESEARCH

Surgical Versus Transcatheter Aortic Valve Replacement in Patients Aged >60 Years With Bicuspid Valve Stenosis: A Time-to-Event Data Meta-Analysis

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BACKGROUND: The role of transcatheter aortic valve implantation (TAVI) in bicuspid aortic valve stenosis requires further evaluation, particularly as its use has become comparable to surgical aortic valve replacement. We sought to compare midterm outcomes of TAVI and surgical aortic valve replacement in patients with bicuspid aortic valve stenosis.

METHODS: Systematic searches of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials identified studies reporting TAVI and surgical aortic valve replacement outcomes in patients aged ≥60 years with bicuspid aortic valve stenosis. The primary analysis included only comparative studies with interpretable Kaplan–Meier curves. Individual patient data were reconstructed for time-to-event analysis. Sensitivity analyses incorporated noncomparative single-arm studies. Baseline differences and heterogeneity were addressed using landmark analysis, time-varying hazard ratios (HRs), frailty Cox models, and covariate-adjusted restricted mean survival time. The primary outcome was death with or without unplanned rehospitalization and stroke.

RESULTS: Five comparative, risk-adjusted studies (TAVI, 5901; surgical aortic valve replacement, 12 427) were included. At 48-month follow-up, TAVI was associated with a higher hazard for adverse events (HR, 1.62 [95% CI, 1.46–1.79]; $P<0.0001$ for the composite end point of death, stroke, or rehospitalization at 48 months); landmark analysis showed an initial benefit with TAVI, followed by a reversal at 6 months that was maintained beyond 12 months (12–48 months; $P<0.0001$). Time-varying HRs confirmed this trend. Sensitivity analyses, including frailty Cox models on the full cohort and restricted mean survival time analysis, supported the robustness of the findings.

CONCLUSIONS: This meta-analysis found limited midterm benefits (ie, 48 months) of TAVI in bicuspid aortic valve stenosis. These findings should be interpreted considering patient selection, as younger patients with bicuspid aortic valve stenosis are increasingly referred for TAVI.

Key Words: bicuspid aortic valve ■ SAVR ■ surgical aortic valve replacement ■ TAVI ■ transcatheter aortic valve replacement

See Editorial by Hirji et al.

The indications for transcatheter aortic valve implantation (TAVI) have expanded to include low-risk populations, supported by evidence demonstrating noninferiority or superiority compared with surgical aortic valve replacement (SAVR) in selected patients.[1] However, many relatively young

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This manuscript was sent to Michel Pompeu Sá, MD, MSc, MHBA, PhD, FACC, FAHA, Assistant Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.125.046556

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This is the largest time-to-event meta-analysis of patients with bicuspid aortic valve stenosis comparing transcatheter aortic valve implantation and surgical aortic valve replacement using reconstructed individual patient data from comparative studies.

What Are the Clinical Implications?

- Transcatheter aortic valve implantation shows initial procedural benefit but does not maintain this advantage at midterm follow-up compared with surgical aortic valve replacement, which demonstrates superior outcomes beyond the first year.
- These findings support careful patient selection and underscore the need to avoid premature expansion of transcatheter aortic valve implantation indications in younger patients with bicuspid anatomy.

Nonstandard Abbreviations and Acronyms

BIVOLUTX	Bicuspid Aortic Stenosis With Evolut Platform International Experience
IPD	individual patient data
KM	Kaplan–Meier
NOTION-2	Nordic Aortic Valve Intervention-2
SAVR	surgical aortic valve replacement
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
TAVI	transcatheter aortic valve implantation

patients (ie, aged <75 years) at low risk for surgery may present with bicuspid aortic valve stenosis, and whether TAVI can be equipoised to SAVR in this context remains debated.[2]

Several recent studies have reported conflicting results. The low-risk analysis of the NOTION-2 (Nordic Aortic Valve Intervention-2) trial[2] showed higher composite adverse event rates with TAVI in patients with bicuspid aortic valve stenosis treated with TAVI compared with SAVR, whereas the BIVOLUTX (Bicuspid Aortic Stenosis With Evolut Platform International Experience) registry demonstrated favorable early outcomes for TAVI with the Evolut platform in bicuspid anatomy, although longer-term comparative data remain limited.[3]

Notably, no randomized trials have specifically compared TAVI and SAVR for bicuspid aortic valve, while only a few comparative studies have been performed in this setting.[4]

Despite the paucity of compelling evidence supporting TAVI implementation in younger cohorts, approximately half of the individuals aged <65 years with severe aortic stenosis in the United States are undergoing this procedure, whose results remain uncertain.[5]

This systematic review and meta-analysis aimed to compare the 48-month composite outcome of death, stroke, and unplanned rehospitalization after TAVI versus SAVR in bicuspid aortic valve stenosis.

Noncomparative single-arm studies (reporting either TAVI or SAVR) were included in sensitivity analyses to support and contextualize the main findings.

Time-to-event reconstruction analysis was performed to assess survival and adverse events, providing insights into the relative efficacy of TAVI and SAVR. Early outcomes were also analyzed.

METHODS

Transparency Statement

The data, statistical code, and materials used in this study will be made available to other researchers for purposes of reproducing the results or replicating the procedure upon reasonable request to the corresponding author.

Institutional Review Board Statement

This study used previously published, deidentified data and was exempt from institutional review board approval.

Study Protocol

This study was registered and documented on the International Prospective Register of Systematic Reviews platform (Registration No. CRD42025635173). This systematic review and meta-analysis adhered to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[6] statement, and was based on the Meta-Analysis of Observational Studies in Epidemiology reporting guidelines.[7]

Eligibility Criteria

In adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, inclusion criteria were defined using the Population, Intervention, Control, Outcome, and Study Design framework.

For the primary analysis, we included comparative studies (randomized controlled trials or observational/registry studies) directly comparing outcomes of TAVI (any generation device) versus SAVR (including tissue,

rapid-deployment, and mechanical prostheses) in patients with bicuspid aortic valve stenosis.

Single-arm studies reporting outcomes for TAVI or SAVR in isolation were retained exclusively for sensitivity analyses and were not included in the main effect estimates.

Studies were excluded if they met any of the following criteria: (1) Kaplan–Meier (KM) curves were unavailable or contained insufficient data; (2) follow-up was <6 months; (3) data extraction for patients with bicuspid aortic valve stenosis was not feasible; (4) procedures were carried out in patients with a mean age ≤60 years, (5) procedures were performed in an urgent or endocarditis setting or with aortic regurgitation disease; (6) the study included <40 participants; (7) procedures were carried out in a selected high-risk population; (8) the study included exclusively type 0 aortic valve stenosis; and (9) the study was not written in English. Studies reporting SAVR with adjunctive procedures were included; however, studies with documented aortopathy were excluded.

The primary outcome was the single or composite end point of death (cardiovascular or all-cause), with or without unplanned rehospitalization for cardiovascular causes (including valve reintervention) and stroke at follow-up.

Secondary outcomes included early end points such as intraprocedural or in-hospital or 30-day death, transient ischemic attack/disabling and nondisabling stroke, and need for de novo pacemaker implantation.

Search Strategy

MEDLINE (via PubMed), EMBASE, and Cochrane Central Register of Controlled Trials were systematically searched by a librarian at Kore University of Enna from their inception for SAVR and from 2002 for TAVI. The research was conducted on January 6, 2025.

The following Medical Subject Headings terms were used in combination with the Boolean operators AND/OR: “bicuspid aortic valve,” “surgical aortic valve replacement,” “SAVR,” “transcatheter aortic valve replacement,” “TAVI,” and “TAVR.”

To ensure transparency and reproducibility, the results of the database searches were imported into the meta-analytic software Rayyan.ai (Rayyan,Cambridge,MA).[8] Duplicates and data overlaps were automatically detected and removed. Screening was conducted in blinded mode in Rayyan by 2 independent reviewers at both the title/abstract and full-text stages. Any conflicts were resolved by consensus.

Data Extraction

Data from included records were extracted using a standardized, prespecified, and piloted form. Based on the Population, Intervention, Control, Outcome, and Study Design strategy, we extracted information on the population and study characteristics, intervention, comparison, and outcomes (full data in Data S1). Data extraction and KM plot digitization were performed by a single reviewer (M.M.) using a piloted form and validated reconstruction algorithms. Extracted data were then verified for accuracy by a second author (T.A.).

Statistical Analysis

The analysis used a random-effects model (inverse variance method). DerSimonian–Laird estimators were used to calculate between-study variance.[9] Pooled proportions with 95% CI were estimated for binary outcomes. A continuity correction (=0.5) was applied if any study had 0 (or all) events.

I^2 with 95% CI and χ^2 tests were used to assess heterogeneity. Heterogeneity was considered significant when I^2 was >50% and P was ≤0.05. Prediction intervals accompanying the CIs were calculated using the Higgins–Thompson–Spiegelhalter method due to the large number of included studies. Publication bias was visualized using symmetry of the funnel plot and evaluated using Egger’s test. The “meta” package developed by Schwarzer et al[10] was used (https://cran.r-project.org/web/packages/meta/meta.pdf).

Time-to-Event Reconstruction Analysis

For KM reconstruction analysis, we used an implementation of the iterative KM algorithm proposed by Guyot et al.[11] The modified iterative KM algorithm for individual patient data (IPD) reconstruction is a 2-stage process.[12] First, data coordinates were extracted from KM curves using the R package ‘IPDfromKM’ (https://cran.r project.org/package=IPDfromKM) and the Shiny application developed by Liu et al[12] (https://www.trialdesign.org/one-page-shell.html#IPDfromKM). When multiple KM curves were present, we used Adobe Illustrator to separate the curves before extracting data points to ensure the accuracy of estimation. Second, the IPD reconstruction was carried out using the modified iterative KM algorithm, which improves upon the original iterative KM algorithm by leveraging the KM estimation method, as described in detail by Liu et al (Data S1).

Validation of IPD Reconstruction Accuracy

To assess the accuracy of the modified iterative KM algorithm, we used these metrics.[12]

Survival Probabilities

Estimated survival probabilities at each read-in time point using the reconstructed IPD were compared with the read-in survival probabilities. The estimated

number of patients at risk was also compared with reported values.

Error Metrics

The root mean square error quantified differences between survival probabilities from reconstructed IPD and original data. Mean and maximum absolute errors assessed estimation precision. A restricted mean square error ≤0.05, mean absolute error ≤0.02, and maximum absolute error ≤0.05 indicated sufficiently accurate extracted data points for further analysis.

Kolmogorov–Smirnov Test

This test compared distributions of read-in and reconstructed survival curves. A large *P* value indicated minimal discrepancy between distributions.

The reconstructed IPD from all studies were merged to create the study data set. KM survival curves were generated using the "Survminer" package (https://cran.r-project.org/web/packages/survminer/index.html).

For consistency and to ensure meaningful numbers of patients at risk in each group, KM curves were truncated at 48 months (time point close 90th percentile).

Statistical Models

The primary model estimated the effect of treatment group (TAVI versus SAVR) without covariate adjustment on the basis of the reconstructed IPD form risk-adjusted comparative studies. For sensitivity analysis to account for between-study heterogeneity, a mixed-effects Cox proportional hazards frailty model was fitted using the "coxme" package (https://cran.r-project.org/web/packages/coxme/index.html). A random intercept was included for each study to model unmeasured study-level variability.

To explore whether baseline risk at the study level might influence treatment effect, we also specified a secondary, exploratory model that included study-level mean age, mean Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score, and their interaction terms with treatment group (treatment×age, treatment×STS-PROM). These covariates were assigned uniformly within study arms due to the nature of reconstructed IPD and were interpreted cautiously as between-study effect modifiers, not individual-level predictors.

Multicollinearity was assessed by computing variance inflation factors using the "car" package (https://cran.r-project.org/web/packages/car/index.html).

Proportional Hazards Assumption

The proportional hazards assumption was validated using scaled Schoenfeld residuals and graphical diagnostics, implemented via the 'survival' package (https://cran.r-project.org/web/packages/survival/index.html). For variables violating the proportional hazards assumption, time-varying hazard ratios (HRs) were computed to capture dynamic risks over time.

Landmark Analysis

To further address violation of the proportional hazard assumption, landmark analysis was performed. Survival was divided into 2 time periods (0 to 12 months and 12 to 48 months) and strata compared with the log-rank test.

Heterogeneity and Sensitivity Time-to-Event Analysis

Between-study and within-study heterogeneity were quantified by estimating random-effect variance and residual variance, respectively. Study-level heterogeneity was assessed using the variance of random effects, intraclass correlation/frailty effect, and the median HR.

To further evaluate the robustness of these findings, a sensitivity analysis was conducted using restricted mean survival time at 48 months. The restricted mean survival time analysis was adjusted for study-level covariates (mean age and STS-PROM score) and implemented using the "survRM2" package (https://cran.r-project.org/web/packages/survRM2/index.html), allowing for treatment comparison without the proportional hazards assumption.

To address potential heterogeneity in primary end point definitions across studies, we performed an additional sensitivity analysis restricted to studies reporting all-cause death as the sole outcome.

Risk of Bias

The risk of bias was assessed by 2 independent authors (M.M. and T.A.) using the Risk of Bias in Non-randomized Studies–of Exposures, which recognizes 7 different domains with the package "robvis" (https://cran.r-project.org/web/packages/robvis/index.html). Each domain was assessed through signaling questions whose answers were yes/probably yes/probably no/no/no information. Therefore, a judgment of the risk of bias was made (low/some concerns/high) and plotted using the Risk-of-Bias visualization tool. We used the Non-randomized Studies–of Exposures instead of the Newcastle–Ottawa Scale because many KM estimates were extracted from comparative studies (bicuspid versus tricuspid aortic valve), making the Non-randomized Studies–of Exposures more appropriate for accounting for confounding and bias in observational comparative studies. The certainty in the body of evidence for each outcome was further

evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation approach.

Software

All statistical analyses were performed using R Statistical Software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics

This systematic review and meta-analysis used data from previously published studies and did not involve interactions with human subjects or access to individual patient data. Therefore, ethical approval was not required in this study.

RESULTS

Thirty-nine studies with interpretable KM curves were included in the quantitative analysis[2,3,13–48] (Figure 1,), of which 5 provided comparative, risk-adjusted cohorts of TAVI versus SAVR.[22,27,33,41,49]

Studies were published from 2014 to 2024. There were excellent metrics of accuracy for the reconstructed KM curves (restricted mean square error, 0.007±0.001; mean absolute error, 0.004±0.008; maximum absolute error, 0.01±0.03; Kolmogorov–Smirnov test for each study reported in Table). Weighted mean ages were 72.7 (95% CI, 72.6–72.8) and 69 (95% CI, 69.0–69.1) years, and weighted mean STS-PROM scores were 2.73 (95% CI, 2.70–2.76) and 1.43 (95% CI, 1.43–1.44) TAVI and SAVR, respectively. The youngest cohort included had a mean age of 68.3 years in the TAVI group[33] and 62 years in the SAVR group.[28]

Twenty-seven studies were multicentric.[2,3,13–15,18–22,24–27,29,31,33,34,39–41,44,45,47–49] The NOTION-2 trial was the only low-risk randomized study that did not exclude bicuspid anatomy from the randomization process. Weighted follow-up was 15.5 (95% CI, 15.3–15.7) and 33.5 (95% CI, 33.2–33.8) months for TAVI and SAVR, respectively. All-cause death was the primary end point of 28 studies. Two studies assessed cardiovascular death, whereas 5 studies analyzed a composite outcome of all-cause death, stroke, and rehospitalization. Additionally, 2 studies investigated all-cause death and rehospitalization, and 2 others examined all-cause death and stroke (Table). Type of prosthesis implanted is also reported in the Table.

Comparative Studies

Five studies included a comparative risk-adjusted cohort[22,27,33,41,49] with pooled samples of patients undergoing TAVI (n=5901) and SAVR (n=12 427) (Figure 2). At the truncated follow-up of 48 months, TAVI was associated with a significantly reduced freedom from composite events compared with SAVR (log-rank $P<0.001$). The univariable Cox model yielded an estimated HR of 1.62 (95% CI, 1.46–1.79; $P<0.0001$), indicating a persistently higher event risk in the TAVI group across comparative studies.

Sensitivity Analysis: Frailty Model

In the overall cohort (TAVI, 16698 patients; SAVR, 24087 patients) with a truncated follow-up of 48 months, patients in the TAVI group exhibited a significantly higher hazard for adverse events (death, stroke, or rehospitalization) than those in the SAVR group (frailty model HR, 1.58 [95% CI, 1.35–1.85]; $P<0.0001$; Figure 3A). Age and Society of Thoracic Surgeons Predicted Risk of Mortality were not significantly associated with adverse events (age: frailty model HR, 1.04 [95% CI, 0.99–1.08]; $P=0.14$; STS-PROM: frailty model HR, 1.04 [95% CI: 0.94–1.16]; $P=0.43$).
There was moderate variance (0.126±0.355), moderate study-level variability (intraclass correlation, 3.7%), and a moderate study effect (median HR, 1.65).

A comparison of the full and reduced models, along with the variance metrics, is provided in Data S1.

In a sensitivity analysis restricted to the 28 studies (comprising 10 206 patients undergoing TAVI and 15 090 patients undergoing SAVR) reporting all-cause death as the primary outcome, the results remained consistent with the main findings (frailty model HR, 1.54 [95% CI, 1.33–1.82]; $P<0.0001$).

Landmark Analysis

Landmark analysis demonstrated significant differences in freedom from combined adverse events between TAVI and SAVR across 2 intervals (0–12 months and 12–48 months). In the early postoperative period (0–12 months; Figure 3B), a significant difference was observed between groups (log-rank $P<0.0001$), with the KM curves showing an initial numerical advantage for TAVI that diminished and reversed around the 6-month mark. In the subsequent interval (12–48 months; TAVI n=9357, SAVR n=19 984), SAVR maintained significantly higher freedom from adverse events (log-rank $P<0.0001$; Figure 3C).

Covariate-Adjusted Restricted Mean Survival Time

After adjustment for study-level age and STS, SAVR demonstrated a higher restricted mean survival time than TAVI (HR, 0.88 [95% CI, 0.80–0.97]; $P=0.013$; Figure 4A). Restricted mean time lost was lower for TAVI (HR, 0.79 [95% CI, 0.71–0.89]; $P<0.001$),

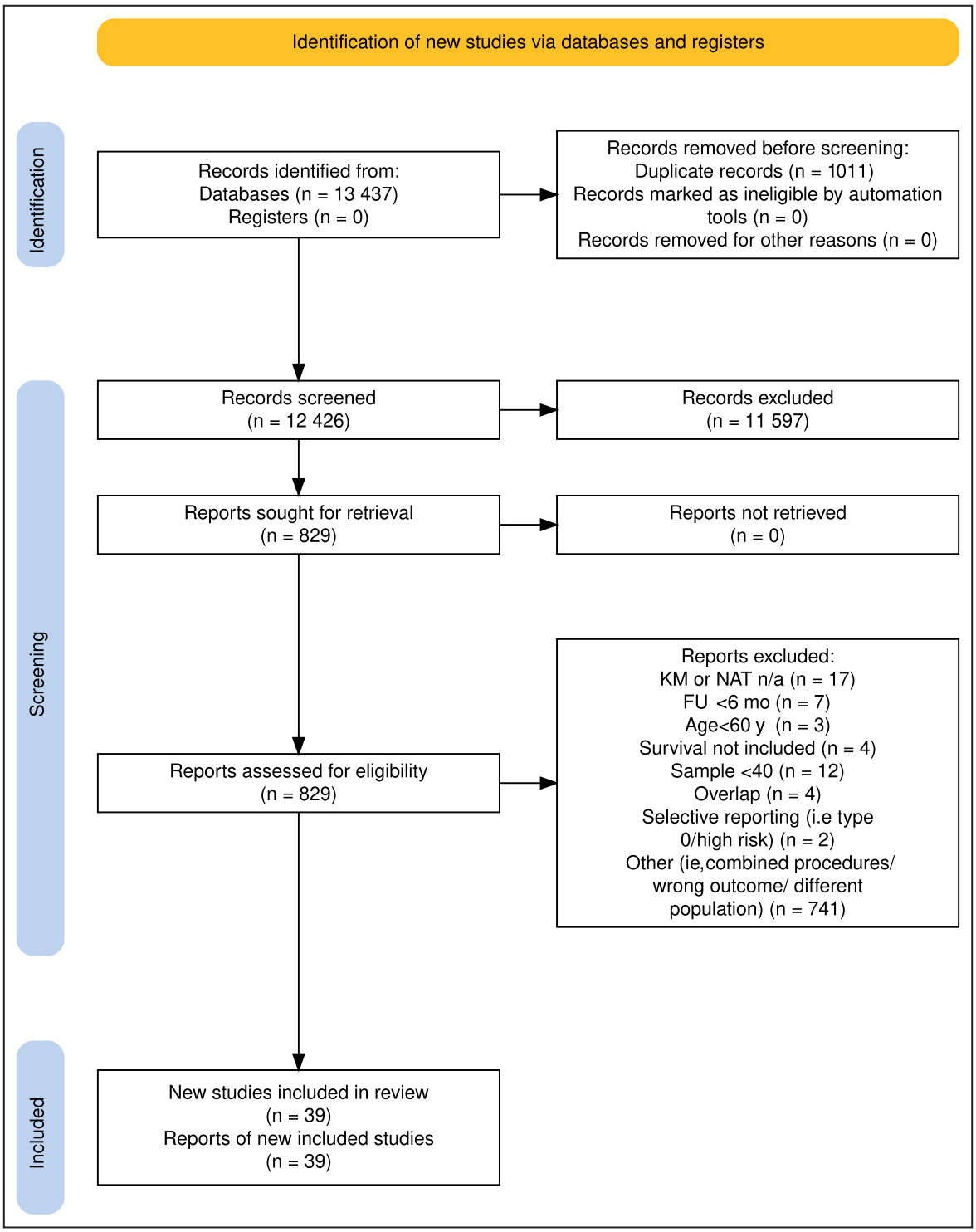

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.
A single study may have met multiple exclusion criteria. FU indicates follow-up; KM, Kaplan–Meier; n/a, not applicable; and NAT, number of patient at risk.

suggesting fewer events in the early period (Figure 4B). Age had a modest positive association with restricted mean survival time (+0.13 months per year [95% CI, −0.06 to +0.32]; *P*=0.19), while STS-PROM score was a strong negative predictor (−3.82 months per unit increase [95% CI, −5.04 to −2.60]; *P*<0.001), indicating that higher-risk patients had significantly worse survival outcomes.

Table. Study Characteristics

Study ID, name (year)	Study period	Comparative (SAVR vs TAVI)	Multicenter/ single center	Type of valve	N Bicuspid TAVI	N Bicuspid SAVR	Mean Age TAVI	Mean Age SAVR	STS TAVI	STS SAVR	Primary outcome analyzed
Mylotte[13] (2014)	2005–2014	No	Multicenter	BE/SE	139	…	78	…	NR (ES II)	…	All-cause death
Jilaihawi[14] (2016)	2005–2014	No	Multicenter	BE/SE	130	…	76.6	…	4.7	…	All-cause death
Sannino[15] (2017)	2012–2016	No	Multicenter	BE/SE	82	…	80.2	…	7.4	…	All-cause death
Huntley[16] (2018)	2010–2012	No	Single center	Tissue/Mechanical	…	198	…	68	…	NR	All-cause death
Liao[17] (2018)	2012–2017	No	Single center	SE	87	…	73.4	…	7.9	…	All-cause death
Song[18] (2018)	2012–2015	No	Multicenter	SE	44	…	73.8	…	5	…	All-cause death
Attinger-Toller[19] (2020)	2012–2017	No	Multicenter	BE	76	…	76	…	3.8	…	All-cause death
Yoon[20] (2020)	2012–2019	No	Multicenter	BE/SE	1034	…	74.7	…	3.7		Cardiovascular death
Mangieri[21] (2020)	2013–2018	No	Multicenter	BE/SE	353	…	77.8	…	4.4	…	Cardiovascular death
Mentias[22] (2020)	2015–2017	Yes	Multicenter	NR	1026	2609	NR	NR	NR	NR	All-cause death
Pineda[23] (2020)	2011–2016	No	Single center	BE/SE	50	…	70	…	4.6	…	All-cause death
HalimSTS-TVT[24] (2020)	2011–2018	No	Multicenter	BE/SE	2449	…	74	…	3.8	…	All-cause death
Fu[25] (2020)	2017–2019	No	Multicenter	SE	44	…	73.5	…	6.7	…	All-cause death
Holmgren[26] (2021)	2005–2016	No	Multicenter	Tissue/ Mechanical	…	1131	…	63	…	NR	All-cause death
Husso[27] (2021)	2008–2017	Yes	Multicenter	BE/SE Tissue/ Mechanical	75	75	75.8	75.7	2.9	3.1	All-cause death
Brown[28] (2021)	1992–2014	No	Single center	Tissue	…	330	…	62	…	NR	All-cause death
Makkar[29] (2021)	2015–2020	No	Multicenter	BE	3168	…	68.8	…	1.7	…	All-cause death, stroke
Michel[30] (2021)	2014–2019	No	Single center	BE	78	…	77	…	NR (ES II)		All-cause death, rehospitalization
Gasecka[31] (2022)	2009–2017	No	Multicenter	BE/SE	130	…	79	…	NR (ES II)	…	All-cause death
Jin[32] (2022)	2017–2019	No	Single center	SE	195	…	72.9 Type 0 76.3 Type 1	…	4.1 Type 0 4.5 Type 1	…	All-cause death, rehospitalization
Majmundar[33] (2022)	2016–2018	Yes	Multicenter	NR	837	823	68.3	68.1	NR	NR	All-cause death, stroke rehospitalization
PARTNER-3 bic[34] (2022)	–2022	No	Multicenter	BE	148	…	71	…	1.4	…	All-cause death, stroke rehospitalization
Coti[35] (2022)	2010–2020	No	Single center	Tissue	…	107	…	68	…	1.4	All-cause death
He[36] (2022)	2012–2021	No	Single center	SE	362	…	72.1 m 72 f	…	4.9 m 5.6 f	…	All-cause death
Zhou[37] (2022)	2013–2018	No	Single center	BE/SE	109	…	75	…	5.09	…	All-cause death
Wedin[38] (2022)	2014–2021	No	Single center	NR	…	152	…	65	…	NR	All-cause death
STABILITY[39] (2023)	2011–2017	No	Multicenter	NR	109	…	78	-	5.1	…	All-cause death

(*Continued*)

Table. Continued

Study ID, name (year)	Study period	Comparative (SAVR vs TAVI)	Multicenter/ single center	Type of valve	N Bicuspid TAVI	N Bicuspid SAVR	Mean Age TAVI	Mean Age SAVR	STS TAVI	STS SAVR	Primary outcome analyzed
BIVOLUTX[3] (2023)	2018–2020	No	Multicenter	SE	149		78.4		2.6		All-cause death
Hirji[40] (2023)	2011–2018	No	Multicenter	BE/SE	…	9131	…	70	…	1.28	All-cause death
Chen[41] (2024)	2012–2019	Yes	Multicenter	NR	797	797	73	73	NR	NR	All-cause death
Mehaffey[49] (2024)	2018–2022	Yes	Multicenter	BE/SE Tissue/ Mechanical	3166	8123	71	69	1.9	1.7	All-cause death, stroke reintervention
Nagasaka[42] (2024)	2016–2020	No	Single center	BE	229	…	73.1	…	3.04	…	All-cause death
NOTION-2[2] (2024)	2016–2023	Yes	Multicenter	BE/SE Tissue	49	51	69.7	70	1	1.1	All-cause death, stroke rehospitalization
Makkinejad[43] (2024)	2020–2022	No	Single center	Tissue	…	560	…	67	…	NR	All-cause death
Buono[44] (2024)	2016–2023	No	Multicenter	BE/SE	602	…	78	…	2.5	…	All-cause death, stroke rehospitalization
EvolutLowRisk[45] (2024)	2018–2019	No	Multicenter	SE	150	…	70.3	…	1.3	…	All-cause death, stroke
Wang[46] (2024)	2016–2023	No	Single center	BE/SE	262	…	72	…	2.03	…	All-cause death
De Felice[47] (2024)	2009–20022	No	Multicenter	SE	106	…	82	…	3.7	…	All-cause death
Yamanaka[48] (2024)	2013–2019	No	Multicenter	BE/SE	503	…	84	…	5.7	…	All-cause death

BE indicates balloon-expandable; ES, EuroSCORE; NR, not reported; SAVR, surgical aortic valve replacement; SE, self-expandable; STS, Society of Thoracic Surgeons; and TAVI, transcatheter aortic valve implantation.

Time Varying HR

The time-varying HR model, corrected for age and STS-PROM score, was used due to the violation of the proportionality assumption (Schoenfeld residuals test, $P<0.001$). Initially, the time-varying HR for the TAVI group was 0.72 (95% CI, 0.61–0.85]; $P<0.001$), indicating a lower mortality risk compared with SAVR. However, time-varying HR for TAVI increased significantly over time to 1.50 (95% CI, 1.40–1.60; $P<0.001$), reflecting a rising relative risk of death as follow-up progressed (Figure 5). A study-level forest plot of HRs is provided in Figure S1.

Postoperative Outcome

The pooled proportions of early death (intraprocedural, in-hospital, and 30-day) were 1.82% (95% CI, 1.33–2.48) after TAVI and 1.70% (95% CI, 1.33–2.18) after SAVR, with substantial heterogeneity (Egger's test, $P<0.008$; Figures S2 and S3). Similarly, the pooled proportions of early neurological events (disabling and nondisabling stroke) were 2.39% (95% CI, 2.02–2.82) after TAVI and 1.84% (95% CI, 1.15–2.94) after SAVR, again with evidence of substantial heterogeneity (Egger's test, $P<0.008$; Figures S4 and S5). In contrast, the pooled proportions of de novo pacemaker implantation were considerably higher after TAVI, at 12.57% (95% CI, 10.66–14.76), compared with 4.85% (95% CI, 3.23–7.23) after SAVR (Figures S6 and S7).

Risk of Bias

Risk-of-bias assessment for the comparative and noncomparative studies showed an overall substantially moderate quality of the included studies (Figure S8). The certainty in the body of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation approach is summarized in Tables S2 and S3.

DISCUSSION

This time-to-event meta-analysis based on reconstructed patient-level data, with comparative studies informing the primary analysis and noncomparative studies included as a sensitivity analysis, represents the largest evaluation to date of the midterm outcomes of TAVI and SAVR in patients with bicuspid aortic valve stenosis.

The findings suggest that while TAVI may provide initial benefit, its midterm advantage remains uncertain. This has important implications for clinical trial design: Reliance on single or composite 1-year outcomes may obscure the later survival advantage of SAVR.

These findings align with and support those of smaller pairwise meta-analyses, given the larger sample size and extended follow-up of our study.[4]

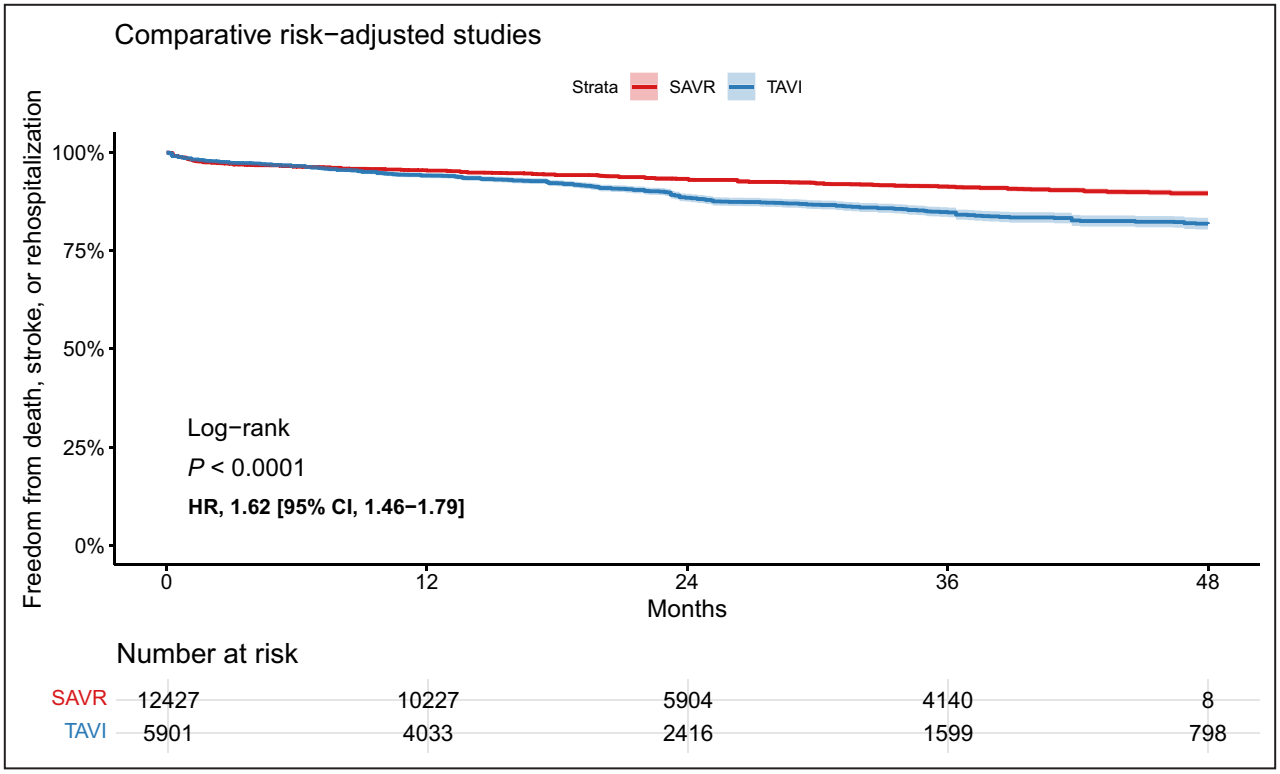

Figure 2. Primary outcome, comparative risk-adjusted cohort (TAVI, n=5901; SAVR, n=12427) survival analysis (log-rank test, *P*<0.0001).
SAVR indicates surgical aortic valve replacement; and TAVI, transcatheter aortic valve implantation.

TAVI may be associated with suboptimal performance in bicuspid aortic valves due to factors including (1) nonuniform prosthesis expansion/deformation, occurring due to the eccentric native aortic valve annulus, leading to (2) incomplete or asymmetrical leaflet expansion, potentially contributing to (3) early formation of hypoattenuated leaflet thickening/subclinical thrombosis; (4) multiple resheathing attempts, which may cause leaflet microlesions and impact durability; and (5) significant paravalvular regurgitation, resulting from suboptimal sealing.[50,51]

The heterogeneous progression of bicuspid aortic valve stenosis, manifesting at varying ages, must be acknowledged. Although TAVI was associated with lower midterm survival compared with SAVR, it may remain a solid option in older patients.

In the analysis of early events, the pooled proportions of complications were not statistically different between TAVI and SAVR. However, this should not be interpreted as proof of equivalence or safety parity, particularly in light of observed heterogeneity and the nonrandomized nature of the underlying data.

This early benefit of TAVI is corroborated by the time-varying hazard model and restricted mean survival time analysis, which confirmed a significantly lower risk of events in the initial period after TAVI. This likely reflects the lower procedural risk associated with transcatheter intervention compared with the inherent risk of surgery.

Notably, the incidence of de novo pacemaker implantation was significantly higher in the TAVI group. Given the relatively young patient population, the mid- and long-term impact of permanent pacemaker implantation on clinical outcomes warrants further investigation.

Study Limitations

This study has important limitations. The primary drawback for sensitivity analysis is the inclusion of non–risk-adjusted studies and baseline differences between TAVI and SAVR populations, with patients undergoing SAVR being younger and at lower surgical risk. These differences may have led to treatment allocation bias, potentially influencing outcomes. Our analysis includes single-arm studies necessitating an indirect comparison approach, an inherent limitation of this methodology. Nevertheless, results from the sensitivity analysis aligned with the primary analysis on the basis of comparative, risk-adjusted studies, supporting the robustness of the overall findings.

Multiple statistical methodologies were used to mitigate this issue: (1) mixed-effects model to compare groups while accounting for study heterogeneity; (2)

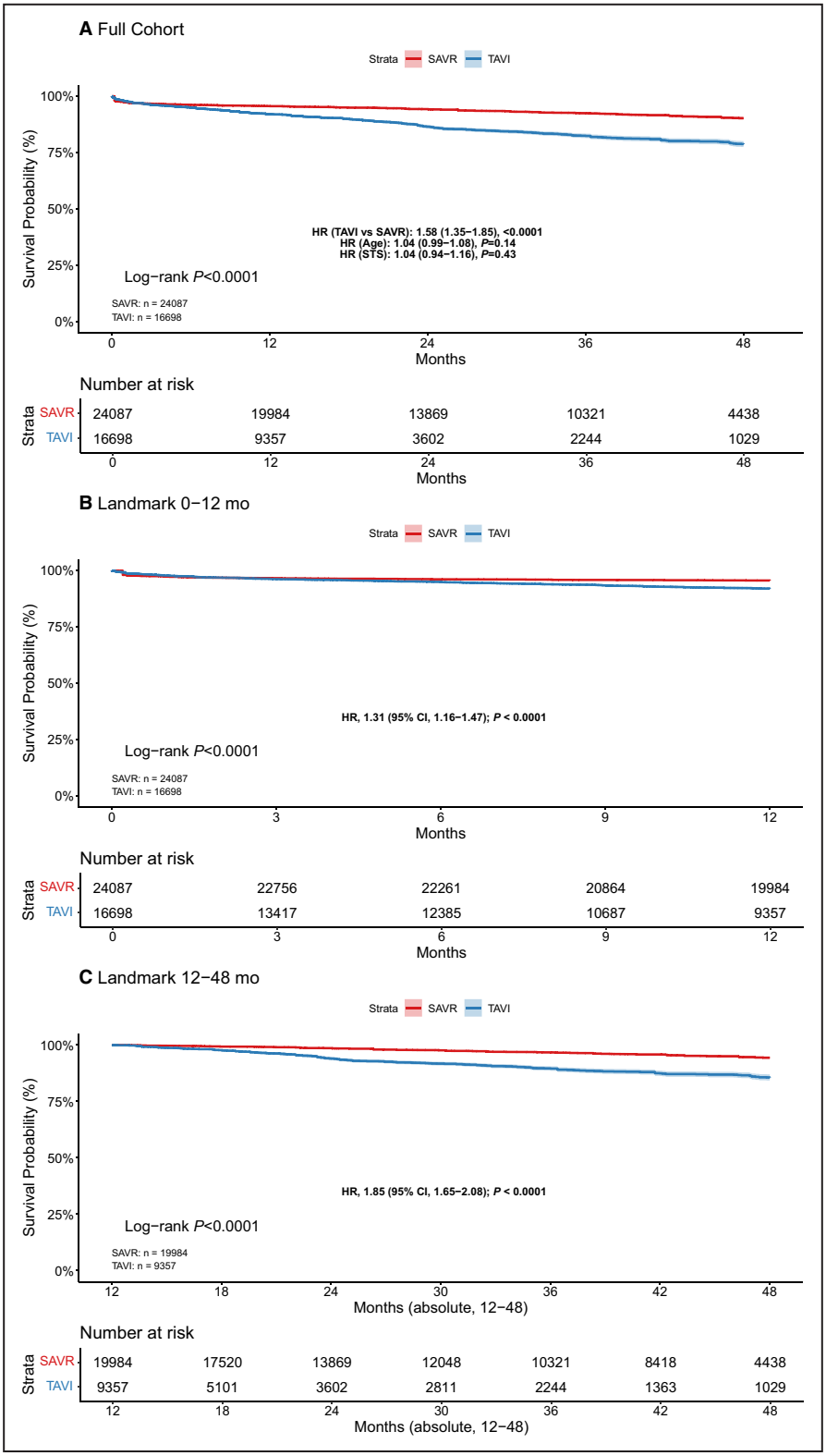

Figure 3. Sensitivity analysis.
A, Overall cohort, comparative and noncomparative studies (TAVI, n=16698; SAVR, n=24087) frailty model. (TAVI: frailty model HR, 1.58 [95% CI, 1.35–1.85]; *P*<0.0001; age: frailty model HR, 1.04 [95% CI, 0.99–1.08]; *P*=0.14; STS-PROM: frailty model HR,1.04 [95% CI, 0.94–1.16]; *P*=0.43). Landmark analysis at 2 intervals: **B**, 0 to 12 months and (**C**) 12 to 48 months. HR indicates hazard ratio; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; and TAVI, transcatheter aortic valve implantation.

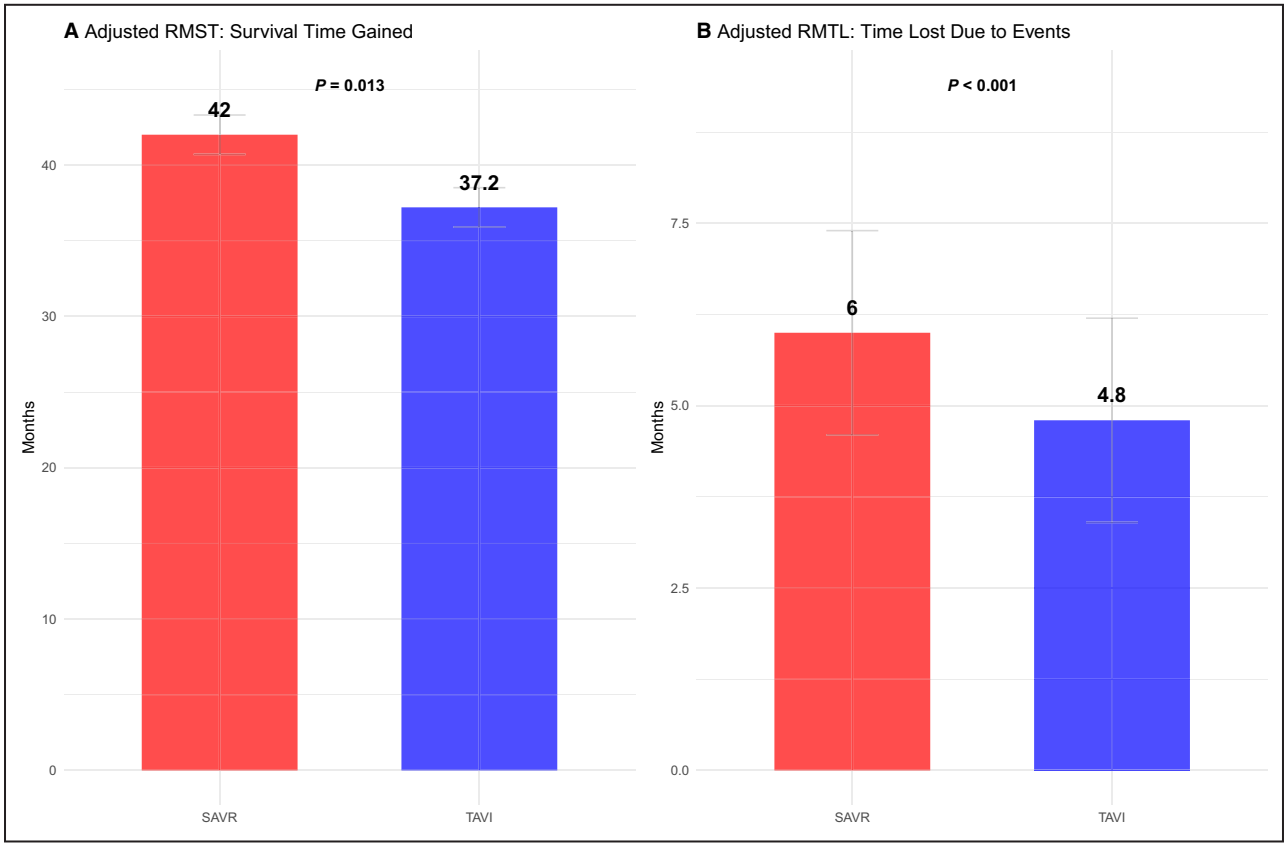

Figure 4. Covariate-adjusted RMST at 48 months for TAVI and SAVR.
A, Survival time gained. **B**, Time lost due to events. Time gained (= $RMST_{SAVR} - RMST_{TAVI}$) represents the absolute difference in RMST, indicating that despite an early disadvantage, SAVR provided longer event-free survival over time compared with TAVI; time lost (= $\int_0^t (Survival_{TAVI(t)} - Survival_{SAVR(t)} dt$) reflects the cumulative impact of adverse events, which was initially higher for SAVR but later reversed in favor of SAVR as follow-up progressed. RMST indicates restricted mean survival time; SAVR, surgical aortic valve implantation; and TAVI, transcatheter aortic valve implantation.

landmark analyses to address violation of proportionality assumptions; (3) time-varying HRs incorporating weighted age and STS-PROM; and (4) exclusion of studies with a mean patients age of ≤60 years to limit confounding from younger population.

Although a few studies may have enrolled individuals aged <60 years, the reported mean or median age and dispersion measures suggest that the proportion of younger patients is likely negligible. Most TAVI studies included recent/latest-generation devices, whereas the SAVR group also comprised prostheses with known suboptimal performance, some eventually withdrawn from the market (eg, Trifecta). Many studies evaluating bicuspid aortic valve and SAVR included patients who underwent combined procedures, potentially influencing outcomes.

Subgroup analysis based on aortic stenosis type was not feasible. We did not account for the type of prosthesis implanted.

The primary outcome assessed was all-cause death, while a competing risk analysis for cardiovascular death was not performed. We acknowledge that comparing separately pooled proportions from nonrandomized studies may be misleading due to potential confounding and the lack of independence between treatment arms within studies. The incidence of stroke and rehospitalization could not be analyzed separately. Analysis of structural and not structural valve deterioration incidence was not performed. Paravalvular leak is a known risk factor following TAVI, particularly in bicuspid anatomy. However, due to inconsistent reporting across studies, we were unable to include para valvular leak in the meta-analysis. We did not perform standard meta-regression due to inconsistent reporting of time-specific HRs across studies. This limits our ability to explore effect modification and should be addressed in future analyses. Finally, we acknowledge that IPD, while enabling flexible modeling and exploration of treatment–covariate interactions, may lack the granularity and precision of true IPD and should be interpreted with appropriate caution.

CONCLUSIONS

This systematic review and meta-analysis found weak evidence supporting the midterm benefits of TAVI in patients with bicuspid aortic valve stenosis. These

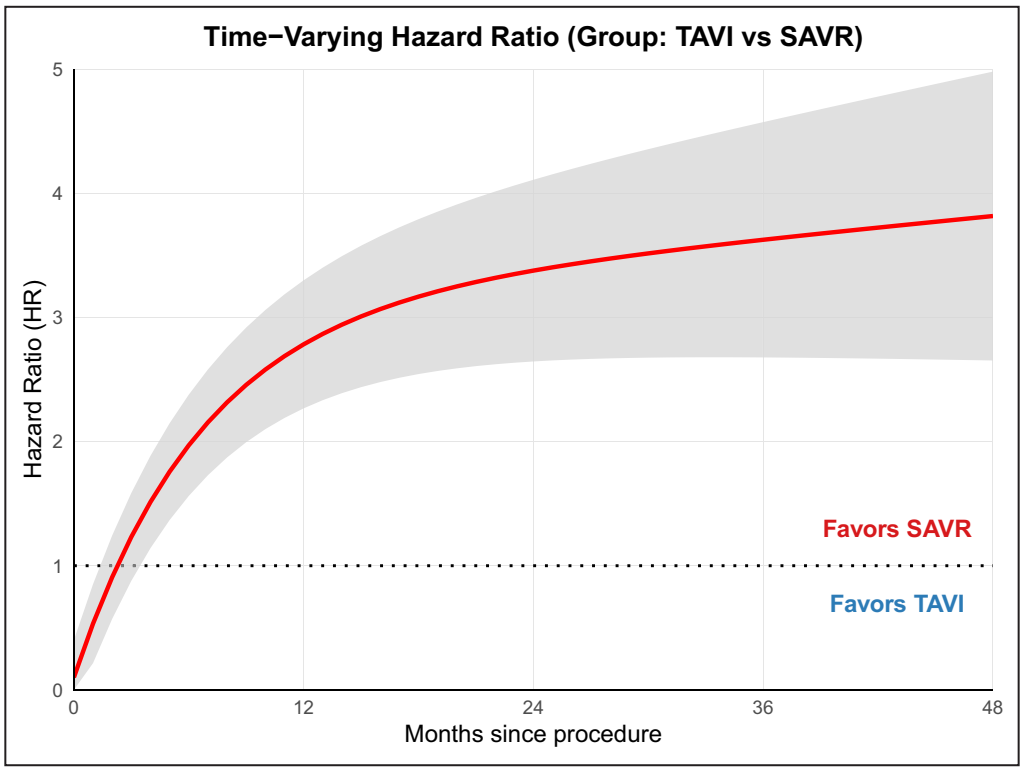

Figure 5. Time-varying HR model corrected for age and STS-PROM score.
Initial time-varying HR for the TAVI, 0.72 (95% CI, 0.61–0.85; *P*<0.001); later time-varying HR for TAVI, 1.50 (95% CI, 1.40–1.60, *P*<0.001). HR indicates hazard ratio; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; and TAVI, transcatheter aortic valve implantation.

findings should be interpreted in the context of patient selection, as many relatively young patients with bicuspid aortic valve stenosis are nowadays referred for TAVI. However, the moderate study-level variability, driven by differences in patient selection, prosthesis type, follow-up duration, and study design, underscores the need for careful interpretation of group differences across diverse clinical settings.

ARTICLE INFORMATION

Received September 14, 2025; accepted December 9, 2025.

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Acknowledgments

Drs Moscarelli and Lancellotti had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; concept and design: all authors; acquisition, analysis, or interpretation of data: Drs Moscarelli, Athanasiou, Lancellotti, and Gaudino; drafting of the manuscript: Drs Moscarelli and Lancellotti. Critical review of the manuscript for important intellectual content: all authors; statistical analysis: Drs Moscarelli, Athanasiou, and Gaudino; administrative, technical, or material support: Dr Speziale; supervision: Drs Fattouch and Casula.

Sources of Funding

This research was funded by a European grant ("EndoTAVI," PO-FESR 2014–2020; www.endotavi.it).

Disclosures

None.

Supplemental Material

Supplemental Methods
Tables S1–S3
Figures S1–S8

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