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## Meta-analysis of Temporal and Surgical Risk Dependent Associations With Outcomes After Transcatheter Versus Surgical Aortic Valve Implantation

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### Abstract

Temporal and surgical risk dependent associations with clinical outcomes in patients receiving transcatheter versus surgical aortic valve implantation (TAVI vs SAVI) are uncertain. In this meta-analysis, 7 randomized controlled trials (7,771 patients) were included to investigate trends in outcomes in TAVI versus SAVI up to 5 years, and variation in outcomes with respect to low-, intermediate-, and high-surgical risk of the patients up to 1 year. Estimates were calculated as random effects hazard ratios (HRs) with 95% confidence intervals (CI). All-cause mortality was similar in TAVI and SAVI at 30 days (HR 0.81, 95% CI 0.55 to 1.21,  $p = 0.31$ ), 1 year (HR 0.97, 95% CI 0.89 to 1.06,  $p = 0.49$ ), 2 years (HR 0.96, 95% CI 0.85 to 1.09,  $p = 0.54$ ), and 5 years (HR 1.04, 95% CI 0.89 to 1.21,  $p = 0.62$ ). Cardiac mortality, myocardial infarction and stroke were similar in both interventions up to 5 years. TAVI was associated with lower risk of atrial fibrillation, but higher risk of vascular complications, pacemaker implantation, and paravalvular leak up to 5 years. The lower risks of major bleeding and acute kidney injury with TAVI versus SAVI were limited to 1 and 2 years, respectively. Compared with SAVI, TAVI was superior in reducing all-cause mortality in low surgical risk patients at 30 days only, whereas TAVI was noninferior to SAVI in intermediate- and high-risk patients at 30 days and across all risks at 1 year. In conclusion, TAVI was noninferior to SAVI in terms of mortality, myocardial infarction, and stroke up to 5 years. TAVI improved survival versus SAVI in low-risk patients at 30 days.

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#### Disclosures

The authors have no conflicts of interest to disclose.

#### Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2019.07.066>.

Transcatheter aortic valve implantation (TAVI) has revolutionized the management of patients with severe aortic stenosis (AS).<sup>1</sup> Given the increasing number of patients who are potentially eligible to undergo TAVI, it is critical to understand the temporal association between implantation of transcatheter versus surgical aortic prosthesis and clinically relevant complications. In this framework, while TAVI was initially approved for patients considered to be at prohibitive or high risk for surgical aortic valve replacement (SAVI), more recent data have shown the safety and efficacy of TAVI in patients with intermediate risk.<sup>2,3</sup> The recent publication of PARTNER 3 (Placement of Aortic Transcatheter Valves) and Evolut Low Risk (Evolut Surgical Replacement and Transcatheter Aortic Valve Implantation in Low Risk Patients) trials have shifted the paradigm even further for patients at low surgical risk.<sup>4,5</sup> Herein, we performed a meta-analysis of clinical trials comparing TAVI versus SAVI to investigate 2 key issues (1) whether the mortality and clinical outcomes in patients with AS undergoing TAVI versus SAVI vary up to 5 years, and (2) whether mortality and hard cardiovascular end points vary in different surgical risk groups (low, intermediate, and high risk) up to 1 year.

## Methods

This meta-analysis was performed according to the Cochrane Collaboration guidelines and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).<sup>6,7</sup>

Two independent researchers (MUK and MSZ) performed the literature search using Medline, Embase, and CENTRAL (inception-April 2019). Additional online resources included Clinical Trial Results (<http://www.clinicaltrialresults.org>), TCTMD (<https://www.tctmd.com/>) and [ClinicalTrials.gov](http://ClinicalTrials.gov). The search strategy is reported in Table Supplement S1. Two investigators (MUK and MSZ) screened the remaining articles at the title and abstract level and then at full text level based on a prespecified inclusion criteria.

The inclusion criteria were (1) randomized controlled trials comparing TAVI versus SAVI in patients with AS, (2) trials reporting all-cause mortality and clinical outcomes of interest and, (3) trials having sample size of at least 100 patients in each arm.<sup>8</sup> Although trials reporting clinical outcomes at different time lengths were included, post hoc analyses of trials and observational studies were excluded. There was no restriction on the language or follow-up duration.

Two investigators (MUK and MSK) independently extracted the data on standard data collection forms, adjudicated the data, and resolved any disagreements with discussion or opinion of third investigator (SUK). Data was abstracted on intention to treat principle and following information was extracted—characteristics of the trials and participants, crude point estimates, number of events and sample sizes in each groups, and follow-up duration. The surgical risk classification was performed at trial level according to STS (Society of Thoracic Surgery) predicted risk of mortality score: mean STS score <4% defined as low risk, 4% to 8% as intermediate risk and >8% as high risk, or if the trial had clearly categorized the patients based on combination of risk estimates (STS score or Logistic EuroScore).<sup>9–11</sup> Data was available at 30 days, 1 year, 2 years, 3 years, and 5 years, however since there was limited data (<2 trials) at 3 years, we omitted this time point from meta-

analyses.<sup>12</sup> The risk of bias assessment was performed at trial level using the Cochrane Risk of Bias Tool (Table S2).<sup>13</sup>

The primary outcome was all-cause mortality. The secondary end points were cardiac mortality, myocardial infarction (MI), stroke, major bleeding, new onset of atrial fibrillation (NOAF), acute kidney injury (AKI), vascular complications, permanent pacemaker (PPM) implantation, paravalvular leak, endocarditis, and repeat hospitalization. Outcomes were defined as reported in selected trials.

Estimates were calculated as random effects hazard ratios (HR) with 95% confidence intervals (CI). For effect size calculation, HRs with 95% CI for each outcome of the trials was extracted when reported. For trials in which HRs were not given, we estimated  $\log(HR)$  and its *variance* using a previously validated method:  $\text{Log-HR} = 2 \times [(\# \text{ observed events Group 1}) - (\# \text{ observed events Group 2})] / [(\# \text{ observed events Group 1}) + (\# \text{ observed events Group 2})]$  and  $\text{Variance}(\log\text{-HR}) = 4 / [(\# \text{ observed events Group 1}) + (\# \text{ observed events Group 2})]$ .<sup>14,15</sup> The SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation)<sup>16</sup> and Evolut Low Risk<sup>4</sup> trials reported outcomes using Bayesian methods. We extracted raw event rates and sample sizes from these trials to estimate  $\log HRs$  and *variances*. Heterogeneity was evaluated via Q statistics with  $I^2 > 75\%$  being consistent with a high degree of heterogeneity (Table S3).<sup>17</sup>

Meta-analyses were performed at 30 days, 1 year, 2 years, and 5 years. For examining outcomes based on surgical risk, analyses were performed at 30 days and 1 year as there was paucity of data on other time points. Publication bias was not performed due to a smaller number of studies (<10). Statistical significance threshold was 5%. Statistical analyses were conducted using Comprehensive Meta-Analysis Software 3.0 (Biostat, Englewood, New Jersey).

## Results

Of 294 identified records, 7 trials (7,771 patients) met inclusion criteria (Table S1). Two trials were of high surgical risk,<sup>11,18–22</sup> 2 trials were of intermediate risk,<sup>16,23</sup> and 3 trials recruited patients with low surgical risk patients.<sup>4,5,24–26</sup> The mean STS score varied from 1.9% to 11.8% and the Log Euro SCORE varied from 1.5% to 29.3% across the trials. Table 1 and Tables S4–S5 show the characteristics of the trials and participants.

TAVI was noninferior to SAVI in terms of all-cause mortality at 30 days (HR 0.81, 95% CI 0.55 to 1.21,  $p = 0.31$ ), 1 year (HR 0.97, 95% CI 0.89 to 1.06,  $p = 0.49$ ), 2 years (HR 0.96, 95% CI 0.85 to 1.09,  $p = 0.54$ ), and 5 years (HR 1.04, 95% CI 0.89 to 1.21,  $p = 0.62$ ; Figure 1). TAVI was noninferior to SAVI in terms of cardiac mortality at 30 days (HR 1.01, 95% CI 0.76 to 1.32,  $p = 0.97$ ), 1 year (HR 0.93, 95% CI 0.83 to 1.04,  $p = 0.22$ ), 2 years (HR 1.03, 95% CI 0.93 to 1.13,  $p = 0.60$ ), and 5 years (HR 1.07, 95% CI 0.91 to 1.26,  $p = 0.42$ ; Figure 2). Similarly, TAVI was noninferior to SAVI in terms of MI, and stroke up to 5 years (Figure S2–S3). Compared with SAVI, TAVI was associated with lower risk of NOAF up to 5 years, and lower risk of AKI up to 2 years (Figure S4–S5). TAVI was associated with lower risk of major bleeding compared with SAVI up to 1 year (Figure S6). TAVI had higher risk of

vascular complications, paravalvular leak, PPM implantation compared with SAVI up to 5 years (Figure S7–S9). Although the risk of repeat hospitalization was comparable between both strategies up to 1 year, TAVI had higher risk at 2 years and 5 years (Figure S10). There were no differences between both interventions in terms of risk of endocarditis up to 5 years (Figure S11).

At 30 days, TAVI reduced the risk of all-cause mortality in low-risk patients (HR 0.46, 95% CI 0.22 to 0.96) compared with SAVI, while TAVI was noninferior to SAVI in high-risk patients (HR 0.66, 95% CI 0.40 to 1.08) and intermediate-risk patients (HR 1.21, 95% CI 0.84 to 1.75) (P-interaction = 0.03; Figure 3). In terms of cardiac mortality, there was a favorable trend toward reduced mortality with TAVI in low-risk candidates, compared with intermediate-risk patients or high-risk patients (P-interaction = 0.04; Figure S12). There was also favorable trend toward TAVI for MI in low-risk patients versus intermediate-risk or high-risk patients, however subgroup interaction was not significant (P-interaction = 0.27; Figure S13). For stroke, risk remained consistently similar in the treatment arms in low-risk, intermediate-risk or high-risk patients (Figure S14). At 1 year, there were no significant differences in terms of all-cause mortality, cardiac mortality, MI, or stroke across different surgical risks between TAVI versus SAVI.

## Discussion

In these analyses, TAVI was noninferior to SAVI in terms of all-cause mortality, cardiac mortality, MI, and stroke up to 5 years. TAVI was consistently associated with lower risk of NOAF, but higher risk of vascular complications, paravalvular leak, and PPM implantation compared with SAVI. The changing trends between TAVI versus SAVI were noticed only in cases of major bleeding and AKI, where lower risks with TAVI versus SAVI were limited up to 2 years. Overall, these findings show that the comparative outcomes data in both interventions are likely to persist during longer term follow up. Whether these observations persist during an even longer term follow up (e.g., 10 years), or whether it would extend to younger and even lower risk populations remain to be seen.

Gargiulo et al suggested nonsignificant differences between TAVI and SAVI for early, mid-term or long-term all-cause mortality.<sup>2</sup> This meta-analysis lacked contemporary clinical trials<sup>4,5,16</sup> and predominantly relied on observational studies, hence was confounded by degree of selection and attrition biases. Khan et al had similar limitations, which showed numerically higher short-term mortality rates with TAVI compared with SAVI in intermediate to low-surgical risk patients,<sup>3</sup> however this analysis included the STACCATO trial (A Prospective, Randomized Trial of Transapical TAVI versus Surgical Aortic Valve Replacement in Operable Elderly Patients with AS) which was prematurely terminated because of higher adverse event rates with TAVI.<sup>27</sup> The STACCATO trial included transapical access, which is rarely used in contemporary practice.

The survival benefit with TAVI versus SAVI at 30 days was most likely secondary to reduction in cardiac mortality and MI in low risk participants. Due to previously limited data and concerns about valve durability,<sup>28</sup> the role of TAVI in low surgical risk patients has been intensely debated, and current guidelines have not yet endorsed it.<sup>1</sup> However, previous

comparative studies in this area were mostly observational, or had modest sample sizes precluding the synthesis of high-quality evidence.<sup>5,29</sup> Nonetheless, given the significant implications of these data and the large number of candidates; long-term data on durability, efficacy, and cost-effectiveness of TAVI in low surgical risk patient will likely remain necessary before a wider application of this technology in these patients. Short-term mortality benefit in low risk TAVI recipients also reflects current practice patterns in the United States.<sup>30</sup> A recent analysis of Transcatheter Valve Therapy Registry reports a major improvement in 30-day mortality with TAVI, from 7.5% in 2012 to 2.5%–3.0% in transfemoral TAVI.<sup>30</sup> These results most likely reflect the use of sophisticated delivery devices which have reduced the incidence of complications such as paravalvular leak.<sup>30</sup>

Current report is profoundly affected by the changing trends occurring in TAVI practice between the timing of different risk trials spanning over the last 10 years. The major changes that occurred included reduction of valve and sheath profile and improved delivery systems, considerable dominance of transfemoral approach and practical elimination of transapical approach, repositioning and recapture options in self-expandable valves, sealing skirts to mitigate paravalvular regurgitation, and considerable reduction in pre-TAVI balloon dilatation. Hence, first and second generation TAVI valves matched up to SAVI third generation valves and promoted TAVI superiority in the low risk trials. Similarly, the trial population is biased by excluding considerable proportions of patients in all risk categories that are deemed not suitable for SAVI (frailty or special exclusive conditions) but amenable for TAVI, whereas it is quite unusual to see the opposite scenario. The design of most clinical trials also mandated a single TAVI device but allowed the surgeon to use the SAVI device and procedure versatility. TAVI clinical practice fortunately is less restrictive and allows the operator to tailor the most suitable device for his individual patient based on a series of measurements and clinical and anatomical considerations.

This meta-analysis has several limitations. First, this is a trial level meta-analysis and we lacked access to individual patient data. Second, the summary estimates at different time points were derived from clinical trials having patients with different TAVI devices, delivery systems, and device access. Third, we could not assess the association of surgical risk with hard outcomes beyond 1 year due to limited data. Fourth, we could not perform subgroup analysis with respect to balloon expandable versus self-expandable valves, access (such as transfemoral, subclavian, and apical) or age due to smaller number of studies. Finally, since our focus was to evaluate hard end points, this analysis did not evaluate some important outcomes, such as length of hospital-stay, quality of life indicators, procedural and post-procedural cost, incidence of prosthetic mismatch, residual gradient, and effective valvular orifice.

In summary, TAVI was noninferior to SAVI in terms of all-cause mortality, cardiac mortality, MI, and stroke up to 5 years. TAVI was associated with survival benefit compared with SAVI in low surgical risk patients at 30 days. Overall, both TAVI and SAVI were associated with their own array of adverse events.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

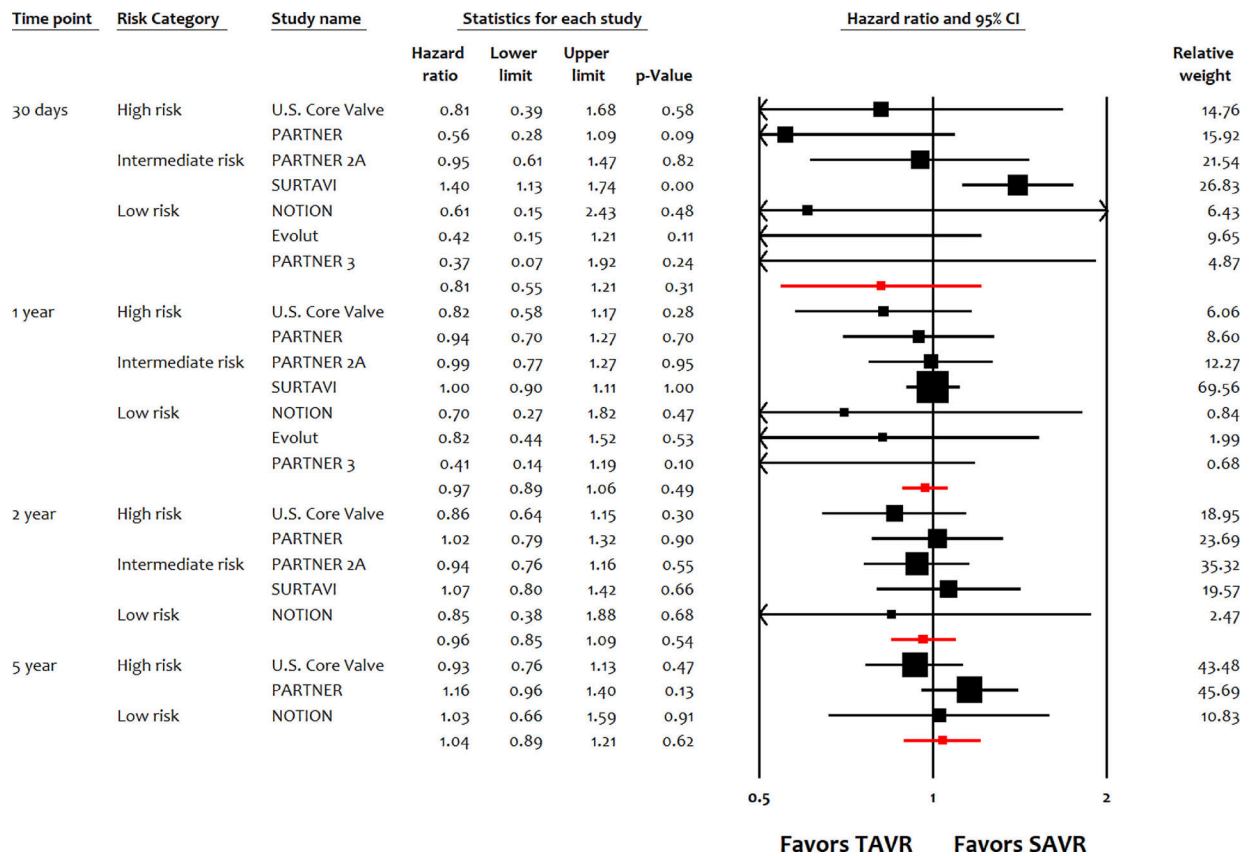
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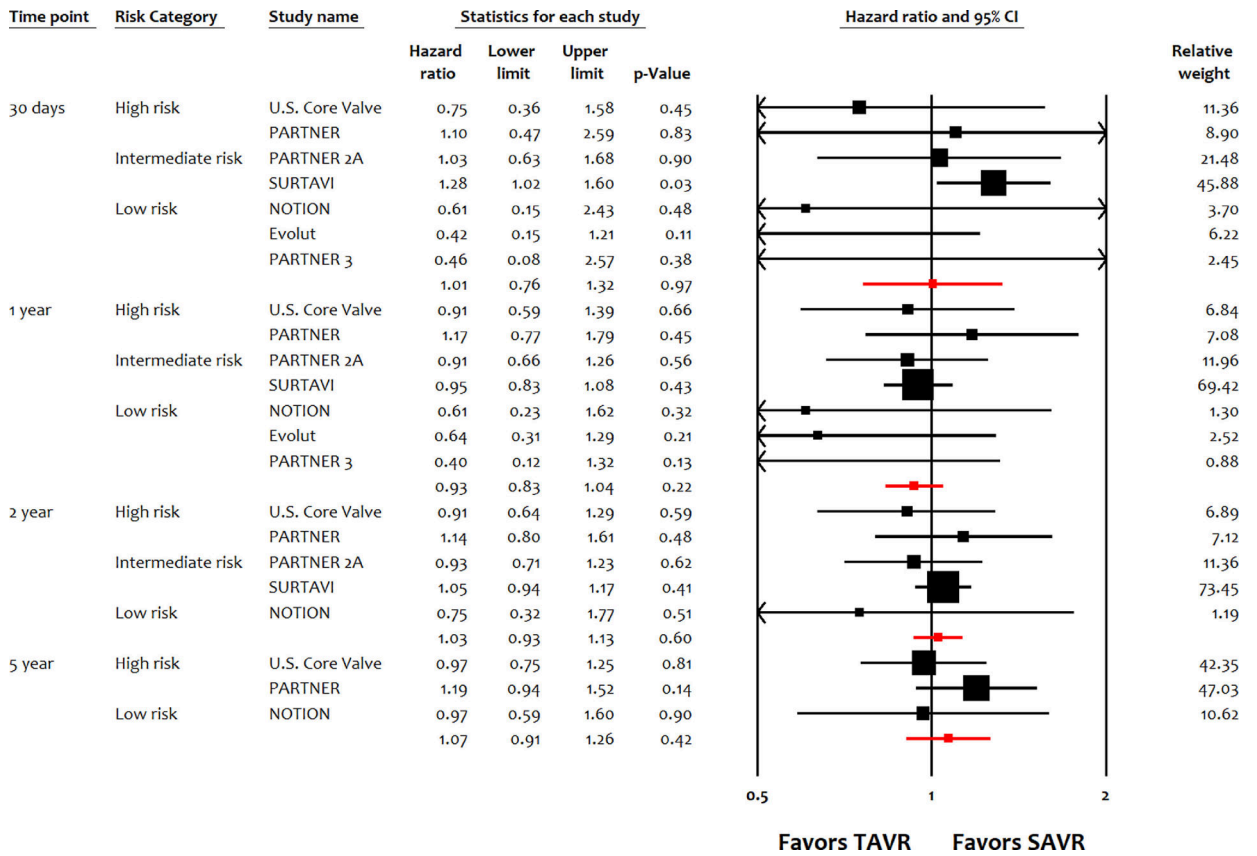
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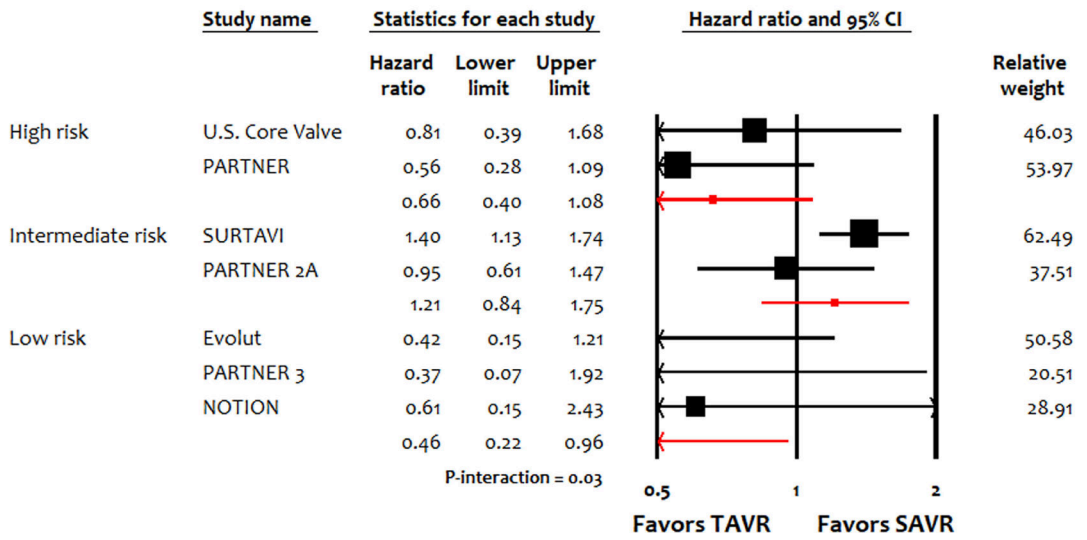


**Figure 1.** Meta-analysis for all-cause mortality up to 5 years. EVOLUT, Transcatheter Aortic Valve Replacement With the Medtronic Transcatheter Aortic Valve Replacement System In Patients at Low Risk for Surgical Aortic Valve Replacement Trial; NOTION, Nordic Aortic Valve Intervention Trial; PARTNER, Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve Trial; SURTAVI, the Surgical Replacement and Transcatheter Aortic Valve Implantation trial; U.S. CoreValve, Medtronic CoreValve U.S. Pivotal Trial.

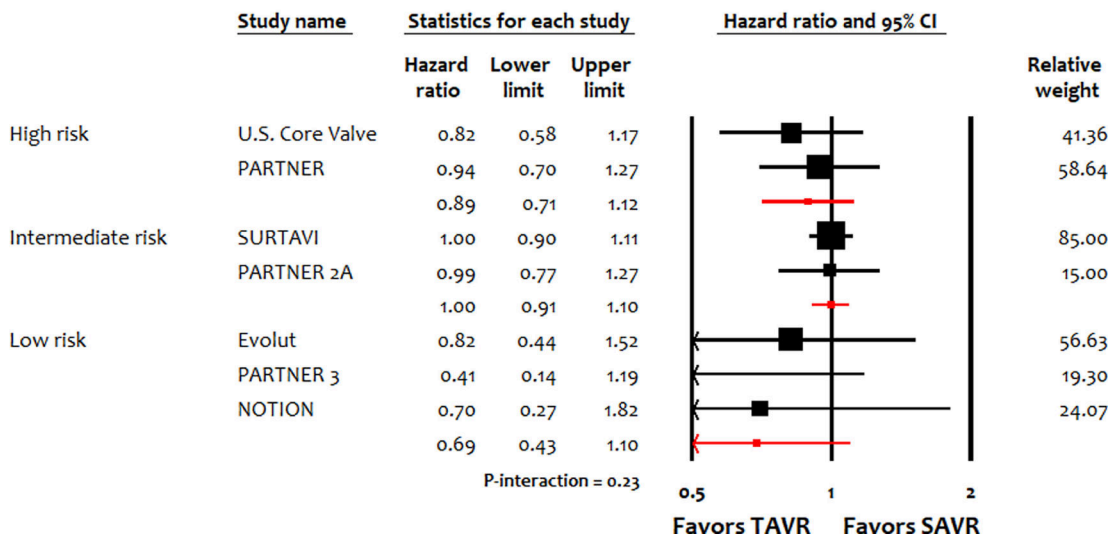


**Figure 2.** Meta-analysis for cardiac mortality up to 5 years. EVOLUT, Transcatheter Aortic Valve Replacement With the Medtronic Transcatheter Aortic Valve Replacement System In Patients at Low Risk for Surgical Aortic Valve Replacement Trial; NOTION, Nordic Aortic Valve Intervention Trial; PARTNER, Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve Trial; SURTAVI, the Surgical Replacement and Transcatheter Aortic Valve Implantation trial; U.S. CoreValve, Medtronic CoreValve U.S. Pivotal Trial.

**A. 30 days**



**B. 1-year**



**Figure 3.**

Meta-analysis for all-cause mortality stratified by surgical risk of patients at 30 days and 1 year. EVOLUT, Transcatheter Aortic Valve Replacement With the Medtronic Transcatheter Aortic Valve Replacement System In Patients at Low Risk for Surgical Aortic Valve Replacement Trial; NOTION, Nordic Aortic Valve Intervention Trial; PARTNER, Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve Trial; SURTAVI, the Surgical Replacement and Transcatheter Aortic Valve Implantation trial; U.S. CoreValve, Medtronic CoreValve U.S. Pivotal Trial.

Characteristics of randomized trials

Table 1.

Characteristics	U.S Core Valve <sup>11,18,19</sup>	PARTNER <sup>20-22</sup>	PARTNER 2A <sup>23</sup>	SURTAVI <sup>16</sup>	NOTION <sup>24-26</sup>	EVOLUT <sup>1</sup>	PARTNER 3 <sup>5</sup>
End of enrollment	2012	2009	2013	2012	2013	2016	2016
Year of publication	2014	2011	2016	2017	2015	2019	2019
No. of patient	795	699	2031	1660	280	1468	950
No. of countries	1	3	2	9	2	7	5
Valve type	Core Valve (Medtronic)	Sapien (Edwards)	Sapien XT (Edwards)	Core Valve and Evolut R. (Medtronic)	Core Valve (Medtronic)	Core Valve, Evolut R, Evolut PRO (Medtronic)	Sapien 3 (Edwards)
Design	Noninferiority and superiority	Noninferiority	Noninferiority	Noninferiority	Superiority	Noninferiority	Noninferiority and Superiority
Primary end point	All-cause mortality	All-cause mortality	All-cause mortality or disabling stroke	All-cause mortality or disabling stroke	All-cause mortality, stroke or Myocardial Infarction	All-cause mortality or disabling stroke	All-cause mortality, stroke, or re-hospitalization
Length of study (years)	1	1	2	2	1	2	1
Result	Noninferiority and superiority shown.	Noninferiority shown	Noninferiority shown	Noninferiority	Superiority not shown.	Noninferiority shown	Superiority shown.

EVOLUT, Transcatheter Aortic Valve Replacement With the Medtronic Transcatheter Aortic Valve Replacement System In Patients at Low Risk for Surgical Aortic Valve Replacement Trial; NOTION, Nordic Aortic Valve Intervention Trial; PARTNER, Placement of Aortic Transcatheter Valve Trial; Edwards SAPIEN Transcatheter Heart Valve Trial; SURTAVI, the Surgical Replacement and Transcatheter Aortic Valve Implantation trial; U.S. Core Valve, Medtronic Core Valve® U.S. Pivotal Trial.