A Meta-Analysis of Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement

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Background. Our preliminary meta-analysis suggests that transcatheter aortic valve implantation (TAVI) may not reduce the 30-day mortality rate over surgical aortic valve replacement (AVR) in high-risk patients with severe aortic stenosis (AS). We performed an updated formal meta-analysis of TAVI vs AVR for reduction not only of early but also of late all-cause mortality in AS.

Methods. MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched through October 2012. Eligible studies were randomized controlled trials or adjusted observational comparative studies of TAVI vs AVR enrolling individuals with AS and reporting early (30-day or in-hospital) or late all-cause mortality, or both, as an outcome. Odds ratios or hazard ratios with 95% confidence intervals (adjusted odds ratios or hazard ratios in case of observational studies) were abstracted from each study.

Results. We identified two randomized trials and 15 adjusted observational studies enrolling 4,873 patients with severe AS. Pooled analysis suggested no significant difference in early (odds ratio, 0.92; 95% confidence interval, 0.70 to 1.19) and midterm (3-month to 3-year) total mortality (hazard ratio, 0.99; 95% confidence interval, 0.83 to 1.17) among patients assigned to TAVI vs AVR. Exclusion of any single study from the analysis did not substantively alter the overall result of our analysis. No evidence of significant publication bias was found.

Conclusions. Our meta-analysis of data of approximately 5,000 patients from 17 studies showed that TAVI is likely ineffective in reducing early and midterm all-cause mortality vs AVR in high-risk patients with AS.

Material and Methods

Search Strategy

All randomized controlled trials and adjusted observational comparative studies of TAVI vs AVR enrolling patients with AS were identified using two-level search strategy. First, public-domain databases, including MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials, were searched through October 2012 using Web-based search engines (PubMed and OVID). Keywords included percutaneous, transcatheter, transmural, transarterial, transfemoral, transsubclavian, transaxillary, transapical, or transaortic; aortic; valve; implantation; replacement; and randomized, randomised, randomly, randomization, adjusted, adjusting, adjustment, matched, matching, multivariate, multivariable, multiple, Cox, hazard, logistic, regression, or propensity. Second, relevant studies were identified through a manual search of secondary sources, including references of initially identified articles and a search of reviews and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analysis.

Study Selection and Data Abstraction

Studies considered for inclusion met the following criteria: the design was a randomized controlled trial or adjusted observational comparative study, the study population was patients with AS, patients were assigned to TAVI vs AVR, and main outcomes included early (30-day or in-hospital) or late all-cause mortality, or both. Data for early and late mortality were abstracted from each individual study as odds ratios (ORs) or hazard ratios (HRs), or both, with 95% confidence intervals (CIs). Adjusted ORs or adjusted HRs, or both, were abstracted for observational studies. For studies that did not report an HR for late death with corresponding variance, this was extracted from the Kaplan-Meier survival curve. The method described by Williamson and associates [5] was used to estimate a logarithmic HR with corresponding variance when the number of patients at risk was given at each time frame. If these data were not provided, the method by Parmar and Collaborators [6] was used.

Statistical Analysis

Study-specific estimates were combined using inverse variance-weighted averages of logarithmic ORs/HRs in fixed-effects and random-effects models. Between-study heterogeneity was analyzed by means of standard χ² tests. If no significant statistical heterogeneity was identified, the fixed-effects estimate was used preferentially as the summary measure. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual studies one at a time and recalculating the pooled OR/HR estimates for the remaining studies.

To assess the effect of the differential approach (transfemoral or transapical) of TAVI among the studies on the study-specific estimate, we performed mixed-effects (unrestricted maximum likelihood) meta-regression analyses. Meta-regression graphs depict the effect of TAVI on the outcome (plotted as a logarithmic OR for early death or logarithmic HR for late death on the y-axis) as a function of a given factor (plotted as percentage of patients undergoing transapical TAVI on the x-axis). Meta-regression coefficients (slopes of meta-regression lines) show the estimated increase in logarithmic OR/HR per unit increase in the covariate. Because logarithmic OR/HR exceeding 0 corresponds to OR/HR exceeding 1 and logarithmic OR/HR of less than 0 corresponds to OR/HR of less than 1, a negative coefficient would indicate that as a given factor (percentage of patients undergoing transapical TAVI) increases, the OR/HR decreases; that is, TAVI is more beneficial in reducing the outcome of interest. Publication bias was assessed graphically using a funnel plot and mathematically using an adjusted rank-correlation and linear regression test. All analyses were conducted using Review Manager 5.1 software (Nordic Cochrane Centre, Copenhagen, Denmark) and Comprehensive Meta-Analysis 2 software (Biostat, Englewood, NJ).

Results

Search Results

Our comprehensive search identified only two randomized controlled trials (Placement of Aortic Transcatheter Valves [PARTNER] [7, 8] and A Prospective, Randomised Trial of Transapical Transcatheter Aortic Valve Implantation vs Surgical Aortic Valve Replacement in Operable Elderly Patients With Aortic Stenosis [STACCATO] [9]) and 15 adjusted observational comparative studies [10–24] of TAVI vs AVR enrolling high-risk (~10 to >30 of EuroSCORE) patients with AS. The study design, predicted mortality rate, and risk estimate for all-cause mortality are summarized in Appendices A and B. We excluded a study by Appel and colleagues [25] because the EuroSCORE and STS-PROM were significantly higher in the TAVI than AVR group despite matching for age, sex, and systolic left ventricular function.

Early Death

Pooled analysis of the 17 studies (representing 4,873 patients) demonstrated no statistically significant difference in early (30-day or in-hospital) all-cause mortality among patients assigned to TAVI vs AVR in the fixed-effects model (OR, 0.92; 95% CI, 0.70 to 1.19; p = 0.52; Fig 1). There was minimal study heterogeneity (p = 0.57) and, accordingly, no difference in the pooled result from random-effects modeling. To assess the effect of qualitative heterogeneity in study design and patient selection on the pooled estimate, we performed several sensitivity analyses. Exclusion of any single study from the analysis did not substantively alter the overall result of our analysis. The meta-regression coefficient (slope of the meta-regression line) was not statistically significant for the percentage of patients undergoing transapical TAVI (coefficient, −0.00054; 95% CI, −0.00783 to 0.00675; p = 0.88; Fig 2). To assess publication bias, we generated a funnel plot of the logarithm of effect size vs the
precision (reciprocal of standard error) for each study (Fig 3). There was no evidence of significant publication bias by the adjusted rank-correlation ($p = 0.90$) and linear regression ($p = 0.84$) tests.

**Late Death**

Pooled analysis of the 11 studies (representing 2,724 patients) demonstrated no statistically significant difference in midterm (3-months to 3-year) all-cause mortality among patients assigned to TAVI vs AVR in the fixed-effects model (HR, 0.99; 95% CI, 0.83 to 1.17; $p = 0.89$; Fig 4). There was minimal study heterogeneity ($p = 0.72$) and, accordingly, no difference in the pooled result from random-effects modeling. Exclusion of any single study from the analysis did not substantively alter the overall result of our analysis. The meta-regression coefficient (slope of the meta-regression line) for the percentage of patients undergoing transapical TAVI was not statistically significant, but a trend toward positive (slope, 0.00468; 95% CI, −0.00044 to 0.0979; $p = 0.07$; Fig 5). We generated a funnel plot of the logarithm of effect size vs the precision (reciprocal of standard error) for each study (Fig 6). There was no evidence of significant publication bias by the adjusted rank-correlation ($p = 0.09$) and linear regression ($p = 0.37$) tests.

**Comment**

**Early and Late Mortality Rates**

It never would be surprising that early mortality rates after TAVI are compatible with those after AVR because observed TAVI mortality rates are similar to predicted AVR mortality rates not using the EuroSCORE but using the STS-PROM [3]. The EuroSCORE has been well known to overestimate the risks for AVR [26–29]; however, the STS-PROM is superior to the logistic

### Table 1: Study or Subgroup Analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Total</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>SE</th>
<th>Total</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
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<tr>
<td>Conradi 2012</td>
<td>−0.1674</td>
<td>0.5797</td>
<td>82</td>
<td>82</td>
<td>5.4%</td>
<td>0.85 [0.27, 2.63]</td>
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<tr>
<td>D’Onofrio 2012</td>
<td>1.6628</td>
<td>1.5664</td>
<td>38</td>
<td>38</td>
<td>0.7%</td>
<td>5.27 [0.24, 113.62]</td>
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<tr>
<td>Fusari 2012</td>
<td>−1.6773</td>
<td>1.5709</td>
<td>30</td>
<td>30</td>
<td>0.7%</td>
<td>0.19 [0.01, 4.06]</td>
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<tr>
<td>Higgins 2011</td>
<td>0.4543</td>
<td>0.6823</td>
<td>46</td>
<td>46</td>
<td>3.9%</td>
<td>1.58 [0.41, 6.00]</td>
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<tr>
<td>Holzhey 2012</td>
<td>−0.2778</td>
<td>0.3745</td>
<td>167</td>
<td>167</td>
<td>12.9%</td>
<td>0.76 [0.36, 1.68]</td>
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<td>Johansson 2011</td>
<td>−0.7472</td>
<td>0.8967</td>
<td>40</td>
<td>40</td>
<td>2.3%</td>
<td>0.47 [0.08, 2.75]</td>
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<tr>
<td>OBSEVANT 2012</td>
<td>0</td>
<td>0.64468985</td>
<td>133</td>
<td>133</td>
<td>4.4%</td>
<td>1.00 [0.28, 3.54]</td>
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<tr>
<td>Osnabrugge 2012</td>
<td>−0.4308</td>
<td>0.9402</td>
<td>42</td>
<td>42</td>
<td>2.1%</td>
<td>0.65 [0.10, 4.10]</td>
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</tr>
<tr>
<td>PARTNER 2011</td>
<td>−0.6272</td>
<td>0.3672</td>
<td>348</td>
<td>351</td>
<td>13.5%</td>
<td>0.53 [0.26, 1.10]</td>
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<tr>
<td>Piazza 2009</td>
<td>0.22311155</td>
<td>0.55644985</td>
<td>114</td>
<td>1008</td>
<td>5.9%</td>
<td>1.25 [0.42, 3.72]</td>
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<tr>
<td>STACCATO 2012</td>
<td>1.72551008</td>
<td>1.5678541</td>
<td>34</td>
<td>36</td>
<td>0.7%</td>
<td>5.62 [0.26, 121.32]</td>
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<tr>
<td>Stöhr 2011</td>
<td>0.49130714</td>
<td>0.34389855</td>
<td>175</td>
<td>175</td>
<td>15.3%</td>
<td>1.63 [0.83, 3.21]</td>
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<tr>
<td>Tamburino 2012</td>
<td>−0.70962273</td>
<td>0.58185031</td>
<td>218</td>
<td>400</td>
<td>5.4%</td>
<td>0.49 [0.16, 1.54]</td>
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<tr>
<td>Walther 2010</td>
<td>−1.14434109</td>
<td>1.2052348</td>
<td>100</td>
<td>100</td>
<td>1.2%</td>
<td>0.32 [0.03, 3.38]</td>
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<tr>
<td>Wenaweser 2011</td>
<td>−0.29389333</td>
<td>0.34621698</td>
<td>257</td>
<td>107</td>
<td>15.1%</td>
<td>0.75 [0.38, 1.47]</td>
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<tr>
<td>Wendt 2012</td>
<td>0.4581</td>
<td>0.4736</td>
<td>59</td>
<td>184</td>
<td>8.1%</td>
<td>1.58 [0.62, 4.00]</td>
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<tr>
<td>Zierer 2009</td>
<td>0.4055</td>
<td>0.8714</td>
<td>21</td>
<td>30</td>
<td>2.4%</td>
<td>1.50 [0.27, 8.28]</td>
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</tbody>
</table>

| Total (95% CI) | 1904 | 2969 | 100.0% | 0.92 [0.70, 1.19] |

Heterogeneity: Chi² = 14.43, df = 16 ($P = 0.57$); $I^2 = 0$
Test for overall effect: $Z = 0.64$ ($P = 0.52$)

**Fig 1.** Primary meta-analysis of early all-cause mortality among patients with aortic stenosis assigned to transcatheter aortic valve implantation (TAVI) vs surgical aortic valve replacement (AVR). (CI = confidence interval; IV = inverse variance; SE = standard error.)

**Fig 2.** Meta-regression of percentage of patients undergoing transapical transcatheter aortic valve implantation (TAVI) on logarithmic odds ratio for early mortality is shown. The area of each circle is inversely proportional to the variance of the logarithmic odds ratio.
EuroSCORE in predicting death in high-risk patients with severe AS [30]. Our previous pooled analysis [3] of 26 single-arm observational studies (representing 1,956 patients) showed significantly lower observed TAVI mortality rates than predicted AVR mortality rates with the logistic EuroSCORE (risk ratio, 0.45; 95% CI, 0.38 to 0.53; \( p < 0.00001 \)) but no significant difference between observed TAVI mortality rates and predicted AVR mortality rates with the STS-PROM (risk ratio, 1.15; 95% CI, 0.89 to 1.47; \( p = 0.28 \)).

**Causes of Death**

The causes of death after TAVI were widely variable and of cardiac and noncardiac origin. In a recent pooled analysis by Moreno and coworkers [31] of 12 published studies with information about the causes of death in patients undergoing TAVI, the mortality rate was 2.3% during the procedure and 9.7% at 1 month. The proportion of cardiac deaths was 56% before 1 month compared with 34% after 1 month (\( p = 0.001 \)). The most frequent causes of death during the procedure were cardiac tamponade (39%), cardiac failure (21%), cardiac arrest (18%), and vascular or bleeding complications (18%). The most frequent causes of death at 1 month were cardiac failure or multiorgan failure (24%), sudden death or cardiac arrest (17%), vascular and bleeding complications (17%), stroke (11%), sepsis (11%), and cardiac tamponade (10%).

There were some important differences among devices in the cause of death [31]. In patients treated with the CoreValve system (Medtronic, Minneapolis, MN) vs those treated with Cribier-Edwards, Edwards-SAPIEN, or SAPIEN XT valves (Edward Lifesciences, Irvine, CA), deaths at 1 month due to vascular and bleeding complications were less frequent (3% vs 22%, respectively; \( p = 0.019 \)), but those due to cardiac tamponade (26% vs 6%, respectively; \( p = 0.019 \)) and because of aortic regurgitation (10% vs 0%, respectively; \( p = 0.03 \)) were more frequent. The significantly higher proportion of deaths due to vascular or bleeding complications with Edwards valves is probably related to the larger catheter size of this device compared with the CoreValve system.

**Fig 4. Primary meta-analysis of midterm all-cause mortality among patients with aortic stenosis assigned to transcatheter aortic valve implantation (TAVI) vs surgical aortic valve replacement (AVR).**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Total</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Fixed, 95% CI</td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>Conradi 2012</td>
<td>0.0448</td>
<td>0.0438</td>
<td>82</td>
<td>82</td>
<td>4.1%</td>
<td>1.05 [0.44, 2.46]</td>
</tr>
<tr>
<td>Fusari 2012</td>
<td>-0.4392</td>
<td>0.6667</td>
<td>30</td>
<td>30</td>
<td>1.7%</td>
<td>0.64 [0.17, 2.38]</td>
</tr>
<tr>
<td>Holzhey 2012</td>
<td>0.23030747</td>
<td>0.18171488</td>
<td>167</td>
<td>167</td>
<td>23.5%</td>
<td>1.26 [0.88, 1.80]</td>
</tr>
<tr>
<td>Johansson 2011</td>
<td>0.05355</td>
<td>0.40</td>
<td>40</td>
<td>40</td>
<td>2.7%</td>
<td>1.00 [0.35, 2.86]</td>
</tr>
<tr>
<td>Osnabrugg 2012</td>
<td>0.392</td>
<td>0.6312</td>
<td>42</td>
<td>42</td>
<td>2.0%</td>
<td>1.48 [0.43, 5.10]</td>
</tr>
<tr>
<td>PARTNER 2012</td>
<td>-0.10136418</td>
<td>0.12302579</td>
<td>348</td>
<td>351</td>
<td>51.3%</td>
<td>0.90 [0.71, 1.15]</td>
</tr>
<tr>
<td>STACCATO 2012</td>
<td>2.37681015</td>
<td>1.51079127</td>
<td>34</td>
<td>36</td>
<td>0.3%</td>
<td>10.77 [0.56, 208.08]</td>
</tr>
<tr>
<td>Tamburino 2012</td>
<td>-0.26557723</td>
<td>0.42281193</td>
<td>218</td>
<td>400</td>
<td>4.3%</td>
<td>0.77 [0.33, 1.75]</td>
</tr>
<tr>
<td>Walther 2010</td>
<td>0.00314012</td>
<td>0.63318229</td>
<td>100</td>
<td>100</td>
<td>1.9%</td>
<td>1.00 [0.29, 3.47]</td>
</tr>
<tr>
<td>Wenaweser 2011</td>
<td>-0.29389333</td>
<td>0.34621698</td>
<td>257</td>
<td>107</td>
<td>6.5%</td>
<td>0.75 [0.38, 1.47]</td>
</tr>
<tr>
<td>Zierer 2009</td>
<td>0.4463</td>
<td>0.7089</td>
<td>21</td>
<td>30</td>
<td>1.5%</td>
<td>1.56 [0.39, 6.27]</td>
</tr>
</tbody>
</table>

**Fig 4. Primary meta-analysis of midterm all-cause mortality among patients with aortic stenosis assigned to transcatheter aortic valve implantation (TAVI) vs surgical aortic valve replacement (AVR).** (CI = confidence interval; IV = inverse variance; SE = standard error.)
Deaths due to aortic regurgitation in patients treated with the CoreValve system are probably due to the self-expandable design of this prosthesis, which may be associated with a higher rate of significant paravalvular regurgitation compared with the Edwards device. Significantly higher cardiac tamponade as the cause of death with the CoreValve system could be related to reasons inherent to the procedure itself and also with the more frequent need for prolonged use of a transvenous pacemaker with the CoreValve system; however, the explanation for this finding is not clear [31].

In the large (699 patients) randomized PARTNER trial [7, 8] included in the present meta-analysis, TAVI and AVR were associated with similar rates of death from cardiac causes: 3.2% in the TAVI group and 3.0% in the AVR group at 30 days (p = 0.90), 14.3% and 13.0%, at 1 year (p = 0.63), and 21.4% and 20.5% at 2 years (p = 0.80). At 30 days, 92% of deaths (11 of 12) were due to cardiac causes in the TAVI group, whereas 45% of any deaths (10 of 22) were due to cardiac causes in the AVR group. At 1 and 2 years, respectively 56% (47 of 84) and 58% (67 of 116) of all deaths were due to cardiac causes in the TAVI group, which was somewhat higher than, respectively, 45% (40 of 89) and 52% (59 of 114) in the AVR group.

Transfemoral vs Transapical Approach
In the randomized PARTNER trial [7], as in observational studies [32-36], the rates of death at 30 days were higher among patients who had undergone transapical placement (8.7% in the as-treated analysis) than among those who had undergone transfemoral placement (3.7% in the as-treated analysis). Possible reasons for these increased rates in the transapical cohort include an increased rate of coexisting disorders, a more protracted learning curve for surgeons, a smaller number of patients who were evaluated, and important procedural differences. Multivariable analysis in a study by Wenaweser and associates [37] showed neither transfemoral (HR, 2.39; 95% CI, 0.59 to 9.62) nor transapical (HR, 2.77; 95% CI, 0.73 to 11.12) balloon-expandable Edwards SAPIEN valve implantation vs transfemoral/transsubclavian self-expandable Medtronic CoreValve implantation emerged as independent risk factors for 30-day mortality. With respect to late mortality, multivariate analysis in a study by Himbert and collaborators [34] showed that the transapical vs transfemoral approach was not a significant predictor of late death with models using the EuroSCORE (HR, 2.7; 95% CI, 0.9 to 8.1; p = 0.08) or using the STS-PROM (HR, 2.5; 95% CI, 0.8 to 7.7; p = 0.12). By multivariate analysis in a study by Webb and colleagues [35], however, transapical...
access was significantly associated with increased late death (HR, 1.85; 95% CI, 0.99 to 3.43). Although the present meta-regression analyses suggest that the transapical approach may be responsible for the treatment effects on not early but midterm survival observed across studies, further investigation should be required.

Limitations
Our analysis must be viewed in the context of its limitations. We used data from only two randomized controlled trials and 15 adjusted observational comparative studies. Patients enrolled in randomized trials may not be representative of those typically seen in clinical practice. Because randomized trials balance known and unknown confounders across treatment groups, however, this is the study design least vulnerable to bias.

Although the PARTNER [7, 8] trial is the highest in weight (51.3% for late mortality) and larger in the two randomized trials, it has a limitation. Withdrawals and decisions to forgo the procedure among patients who were assigned to undergo AVR were unexpectedly frequent, and approximately 5% of patients who were assigned to the TAVI group did not undergo the procedure [7]. Nonetheless, no significant differences were found in clinical outcomes between the intention-to-treat cohort and the as-treated cohort [8]. Potential biases are likely to be greater for observational studies compared with randomized trials, however, so results should always be interpreted with caution when they are included in reviews and meta-analyses [38].

Particular concerns arise with respect to differences between patients in different intervention groups (selection bias) and studies that do not explicitly report having had a protocol (reporting bias). Unlike for randomized trials, it would usually be appropriate to analyze adjusted, rather than unadjusted, effect estimates (ie, analyses that attempt to control for confounding) [38]. To reduce the effect of treatment-selection bias and potential confounding in observational studies, rigorous adjustment for significant differences in the baseline characteristics of patients should be conducted.

Further, not unadjusted but adjusted estimates ought to be pooled in a meta-analysis that includes observational studies. In the present meta-analysis, we strictly selected and then included only adjusted ORs or HRs for all-cause mortality, using appropriate statistical methods from observational studies.

Furthermore, our results may be influenced by a publication bias favoring TAVI. This risk was minimized through an exhaustive search of the available literature in our analysis. Although the statistical tests did not indicate publication bias, there is clearly limited power to detect such bias given the small number of studies examined.

Conclusions
In conclusion, TAVI may reduce neither early (30-day or in-hospital) nor midterm (3-month to 3-year) all-cause mortality over AVR in high-risk patients with AS. To confirm the present results and to determine whether TAVI is equivalent to AVR with respect to long-term mortality for high-risk patients or in clinical benefit for not only high-risk but also lower-risk patients, additional randomized controlled trials would be required.

References
3. Takagi H, Umemoto T. Transcatheter aortic valve implanta-


