Transcatheter Aortic Valve Implantation With or Without Percutaneous Coronary Artery Revascularization Strategy: A Systematic Review and Meta-analysis

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Abstract

Background: Recent recommendations suggest that in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI) and co-existent significant coronary artery disease (CAD), the latter should be treated before the index procedure. However, the evidence basis for such an approach remains limited. We performed a systematic review and meta-analysis to study the clinical outcomes of patients with CAD and underwent revascularization versus without revascularization prior to TAVI.

Methods and Results: We conducted a search of MEDLINE and EMBASE to identify studies evaluating patients who underwent TAVI with/without percutaneous coronary intervention (PCI). Random-effects meta-analyses with the inverse variance method were used to estimate the rate and risk of adverse outcomes. Nine studies involving 3,858 participants were included in the meta-analysis. Patients who underwent revascularization with PCI had a higher rate of major vascular complications (odd ratio [OR]: 1.79, 95% confidence interval [CI]: 1.31-2.45, P=0.0002) and an increased 30-day mortality (OR: 1.39, 95%CI: 1.08-1.79, P=0.010). No statistically significant differences in terms of 1-year mortality (OR: 1.03, 95%CI: 0.79-1.34, P=0.83), cardiovascular mortality (OR: 1.03, 95%CI: 0.37-2.87, P=0.96), myocardial infarction (OR: 0.86, 95%CI: 0.14-5.17, P=0.87), acute kidney injury (OR: 0.89, 95%CI: 0.47-1.71, P=0.73) or stroke (OR: 1.06, 95%CI: 0.39-2.86, P=0.90). The timing, same-setting versus elective did not negatively influence outcomes.

Conclusions: Our analysis suggests that revascularization before TAVI confers no clinical advantage with respect to several patient-important clinical outcomes, and may be associated with an increased risk of major vascular complications and 30-day mortality.

Keywords: transcatheter aortic valve implantation; percutaneous coronary intervention; coronary artery disease

INTRODUCTION

Coronary artery disease (CAD) often co-exists in patients with severe aortic stenosis,[1, 2] and current American and European guidelines recommend combined coronary artery bypass grafting (CABG) at the time of surgical aortic valve replacement (SAVR).[3, 4] Concomitant CABG and SAVR is associated with worse postoperative outcomes, although no negative impact on operative and 1-year mortality.[5, 6] Nevertheless, the role of revascularization on long-term morbidity and mortality is still not clear in octogenarians.[7]

The prevalence of CAD in the population undergoing transcatheter aortic valve implantation (TAVI) is higher than SAVR and, depending on the definition, the presence of significant CAD ranges from 50 to 75%.[8-12] Notably, randomized clinical trials that led to the approval of TAVI devices in United States required revascularization of significant CAD affecting main epicardial vessels within 30 days of TAVI. In this context, it has been recommended to perform percutaneous coronary intervention (PCI) or a hybrid procedure to revascularize patients with significant CAD.[13-15] Favourable outcomes associated with prior-TAVI PCI have been reported in single-centre studies with relatively small sample sizes, although these were often underpowered for the endpoints studied and were also subject to significant selection biases. In addition, data on whether revascularization should be performed before or in the same-setting is still scant. Hence, the aim of this report was to perform a systematic review and meta-analysis to assess the evidence basis and clinical outcomes associated with TAVI procedures performed with and without revascularization of co-existent CAD with PCI.

METHODS

Search Strategy

We conducted a search of MEDLINE, EMBASE, Google Scholar, Science Direct, Web of Science, and conference abstracts, from conception to September 2016 using OvidSP

(Ovid Technologies). The terms used were: ((transcatheter aortic valve implantation OR transfemoral aortic valve implantation OR transapical aortic valve implantation OR trans-subclavian aortic valve implantation OR TAVI OR transcatheter aortic valve replacement OR TAVR) AND (percutaneous coronary intervention OR PCI OR coronary angioplasty)). Institutional review board approval and patient consent were not required as only publication level data published in the public arena was analyzed.

Study selection

The abstract and titles yielded by the search were screened by two independent investigators (RAK and CSK) against the inclusion criteria. Additional studies were retrieved by checking the bibliography of included studies and relevant reviews. The full reports of potentially relevant studies were retrieved, and data was independently extracted on study design, participant characteristics, treatment groups, outcome events, follow-up and results. Any discrepancies between reviewers were resolved by discussion after consulting a third investigator (RB).

Eligibility Criteria

We only included studies published in English that evaluated patients with underlying CAD that underwent PCI as a revascularization strategy prior or concomitant with TAVI versus no revascularization. In terms of outcomes, studies included must have evaluated one or more of the following events: 30-day and 1-year mortality, myocardial infarction (MI), vascular complications, bleeding, neurological events (stroke or transient ischemic attack [TIA]), acute kidney injury (AKI). Endpoints were reported, when available, in accordance to Valve Academic Research Consortium-2 (VARC) definitions.[16] The reporting of outcomes had to include either crude events in each group or any risk/odds estimate (risk-ratio, odds-ratio [OR]) with 95% confidence intervals (CI). There was no restriction based on the design of the study or duration of follow-up. We excluded isolated case reports/case series (≤3

patients), reviews and editorial comments on the subject. When duplicate reports of the same study were identified, only the report with the most complete dataset and detailed methodology description was included. A flow diagram is provided following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),[17] Figure 1.

Quality and risk of bias assessment

To assess the quality of included cohort studies, we employed the Newcastle-Ottawa Scale.[18] The outcomes of interest and follow-up were also extracted on a pre-formatted table. Disagreements were resolved by consensus after consultation with RB. Risk of bias was assessed by considering the ascertainment of treatment groups, ascertainment of outcomes, loss to follow-up and consideration of potential confounders in the data analysis.

Data Analysis

We used RevMan (Review Manager version 5.1.7; Nordic Cochrane Centre, København, Denmark) to perform random-effects meta-analysis using the Mantel-Haenszel method to determine pooled OR for dichotomous data with regards to post-TAVI outcomes with PCI revascularization compared without PCI. To ensure a meta-analysis with clinically transferable results, we only included studies where the methodology or dataset of which permitted adjudication of CAD prevalence in the TAVI alone group. The Cochrane Q-statistic (I^2) was used to assess the consistency among studies with I^2<25% considered low, I^2 25-50% moderate, and I^2>75% high statistical heterogeneity.[19] Where there was insufficient data or studies for meta-analysis, we pooled the studies using weighted average or performed narrative synthesis of studies that were too heterogeneous to pool. Sensitivity analysis were performed to assess the potential influence of any estimates on treatment effect or association that are derived from the mean by excluding the study considered as an outlier[20] and, to further assess for potential differences between random-effects and fixed-effects models and excluding studies where one of the treatment arms had no events. Subgroup analyses were

performed to determine whether studies reporting a population with 100% of the patients with CAD versus those with >50% (but <100%) of the subjects presenting with CAD influenced the treatment effect. Meta-regression was performed to further investigate potential source of clinical heterogeneity[21] and determine the influence of CAD on outcomes. The *metareg* function (STATA 14.0, Stat Corp.) was used to undertake meta-regression with log-risk estimates and the standard error determined from 95%CIs for the log-risk estimates. Prevalence of CAD was calculated by averaging the percentage of patients with CAD in TAVI-PCI and TAVI alone groups. Two-sided P values of 0.05 were considered statistically significant.

RESULTS

Study population

A total of 24 observational studies[9-12, 22-41] including 7,457 participants met the inclusion criteria for the systematic review; among these, 9 studies[9, 10, 12, 25, 31, 32, 35, 37, 40] met criteria for the meta-analysis evaluating 3,858 participants (Figure 1) of which, 983 patients underwent TAVI with PCI revascularization strategy. The mean age was 85.3 years and 48.4% were female from 14 studies that reported both age and gender.[9-12, 23, 26, 28, 31-33, 35, 36, 39, 40] Anatomically significant CAD was inconsistently defined and included at least ≥50% diameter stenosis in 7 studies,[9, 10, 12, 28, 29, 34, 38] >70% stenosis in 5 studies,[11, 24, 31, 36, 37] and >90% stenosis in 1 study.[35] A total of 4 studies,[11, 35, 37, 38] defined >50% stenosis when located in the left main. None of the studies reported on the use of functional assessment for CAD significance. Further details on study design and participants baseline characteristics are presented in Tables 1 and 2.

Quality assessment

Ascertainment of outcomes varied from medical record reviews to prospective evaluation with adjudicated clinical end-points. All studies contained no major loss to follow-

up, and the overall quality rate was average. Follow-up of patients varied from in-hospital outcomes, clinical visits, and telephone calls up to 4-year from the date of implant. Whilst follow-up amongst studies was inconsistent, the commonest time-points were at 30 days and 1 year. The Newcastle-Ottawa Quality Assessment is presented Table 3.

In-hospital, 30-day and long-term outcome with PCI versus TAVI alone

Device type, access site, procedure-related outcomes and follow-up assessment for all included studies reporting crude rate of events are summarized in Table 4. Crude outcomes per revascularization-PCI versus without revascularization strategies are shown in Table 5. The crude all-cause 30-day mortality was reported in 18 studies[9-12, 23, 25, 26, 28, 31-37, 39-41] and occurred in 7.2% (401/5,574) of patients; crude cardiovascular 30-day mortality was reported in 5 studies[10, 12, 28, 31, 32] and occurred in 5.0% (52/1,046) of patients. At 30-day, the crude incidence of MI was reported in 10 studies[10-12, 25, 28, 31-33, 35, 39] and occurred in 1.7% (33/1,903) of patients, major or life-threatening bleeding in 12 studies[10-12, 28, 31-36, 39-41] and occurred in 13.8% (608/4,403) of patients, AKI in 14 studies[10, 12, 22, 23, 28, 31-36, 39-41] and occurred in 5.6% (263/4,671) of patients.

Meta-analyses evaluating outcomes showed that patients who underwent revascularization were more likely to experience major vascular complications (OR: 1.86, 95%CI: 1.33-2.60, P=0.0003, I^2=0%) and an increased 30-day mortality (OR: 1.42, 95%CI: 1.08-1.87, P=0.01, I^2=0%). There were no significant differences in point estimates for 30-day MI (OR: 0.86, 95%CI: 0.14-5.17), major or life threatening bleeding (OR: 0.87, 95%CI: 0.58-1.29), AKI and/or need for hemodialysis (OR: 0.89, 95%CI: 0.47-1.71), stroke/TIA (OR: 1.06, 95%CI: 0.39-2.86), combined safety endpoint (OR: 0.84, 95%CI: 0.55-1.27), Figure 2.

A total of 9 studies reported on 1-year[9, 27, 28, 32, 35, 37-39, 41] and 2 studies on 2-year mortality[32, 35] rates. The crude incidence of death at 1 year was 21% (607/2,883), and at 2

years was 57.5% (258/449) of patients. Meta-analyses evaluating 1-year mortality between pre-TAVI PCI versus without revascularization strategies showed no significant differences in point estimate (OR: 1.03, 95%CI: 0.79-1.34), Figure 2.

Notably, whilst most of the included studies were small and reported neutral results, Singh et al.[40] presented a large sample-size and reported adverse outcomes with PCI. In addition, the 95%CI of all the studies except for Singh's overlap 1 (Figure 2), and the 95%CI of the overall effect estimate do not overlap 1. Hence, sensitivity analysis excluding this study showed a decrease in the effect estimates for 30-day mortality (OR: 1.15, 95%CI: 0.69-1.92, P=0.59; heterogeneity P=0.62, I^2=0%) and major vascular complications (OR: 1.38, 95%CI: 0.61-3.10, P=0.44; heterogeneity P=0.90, I^2=0%), though widening the confidence intervals in the latter. The remaining sensitivity-analysed outcomes remained unchanged, Figure 3.

Pre-procedural versus same-setting revascularization

Revascularization PCI was performed either concomitantly with TAVI or *a priori* in 12 studies.[10, 11, 22, 23, 25, 27, 29, 33, 34, 38-40] Eight studies exclusively revascularized patients prior to TAVI,[9, 12, 24, 28, 31, 36, 37, 41] one study in the same-setting[35] and one study reported both strategies.[10] Five studies reported outcomes based on PCI-timing,[10, 22, 23, 33, 36] and those who underwent prior-PCI varied from same-setting[12] to 6 months[41] prior to TAVI.

Meta-analyses evaluating *a priori* PCI versus concomitant revascularization strategies showed comparable point estimates for 30-day mortality (OR: 1.23, 95%CI: 0.46-3.29), major or life threatening bleeding (OR: 0.50, 95%CI: 0.20-1.25), or major vascular complications (OR: 0.32, 95%CI: 0.05-1.94), Figure 4.

Co-existing coronary artery disease

The prevalence of co-existing CAD was reported in both revascularised and non-revascularised groups in 9 studies,[9, 10, 12, 25, 31, 32, 35, 37, 40] and varied from 51.4% to 100%.

Therefore, we conducted a subgroup analysis for clinical outcomes comparing studies reporting a population with 100% of patients with CAD versus those with >50% (but <100%) of the subjects presenting with CAD.

Subgroup analysis including studies in which the prevalence of CAD was 100%, the OR for 30-day mortality among patients that underwent PCI was 0.80 (95%CI: 0.28-2.27), whereas in studies where the prevalence of CAD was >50% (but <100%), patients who received PCI died more often (OR: 1.49, 95%CI: 1.12-1.98, P=0.006; heterogeneity P=0.45, I^2=0%). The overall difference showed statistically significant effect estimates (OR: 1.42, 95%CI: 1.08-1.87, P=0.01; heterogeneity P=0.63, I^2=0%) without significant interaction (P=0.65, I^2=20%). No significant differences in effect estimates were observed in terms of cardiovascular (OR: 1.03, 95%CI: 0.37-2.87) and 1-year (OR: 1.03, 95%CI: 0.79-1.34) mortality rates. Similar effect estimates were found between the two strategies in the remaining analyzed variables (Figure 5).

Sensitivity analysis comparing random- versus fixed-effects model as well as excluding studies with no events in one of the treatment arms is shown in Table 6. The results suggest no differences in effect estimates between the two models or after excluding studies with no events in one of the treatment arms. Meta-regression analysis was conducted to further investigate potential source of clinical heterogeneity based upon the prevalence of CAD. The results rule-out a strong magnitude of the effect to influence any of the analyzed outcomes (Table 7).

DISCUSSION

The results of this meta-analysis of 9 observational studies including 3,858 patients show that PCI-revascularization before (prior to and concomitant) TAVI may be associated with an increased risk of major vascular complications and 30-day mortality, although by one year this association is no longer present. In addition, comparing TAVI with and without

revascularization, there were no significant differences in rates of MI, bleeding, AKI/hemodialysis or cerebrovascular accidents at 30 days. We find that the evidence basis consists of poor quality of the studies confounded by selection bias, emphasising therefore, the need for randomized-controlled trials.

Assessing the severity of CAD in patients undergoing TAVI

The optimal treatment of CAD in patients with TAVI remains to be elucidated. While Dewey et al.[8] showed that CAD is an independent predictor of early and mid-term survival, this finding was not further supported by other studies.[37, 38, 42, 43] In addition, Khawaja and colleagues[37] showed that CAD was not predictor of worse outcome; albeit in patients exhibiting a SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) score >9. More recently, Chauhan and colleagues[43] found no significant association between the SYNTAX score or Duke Myocardial Jeopardy score with their pre-specified primary composite endpoint of all-cause mortality, major adverse cardiovascular and cerebrovascular event and postoperative coronary revascularization, nor secondary outcomes of 30-day and 1-year composite endpoint rates. Moreover, the authors went further and questioned the role of coronary angiography as part of the TAVI workup.[43]

As previously mentioned, the reported prevalence of CAD in the population undergoing TAVI varies depending on the definitions used to define significance (Table I, Supplement), and can be as high as 75%.[8-12] The severity of CAD in AS patients has historically been assessed using angiography to further determine the need for revascularisation. However, it is well-known that functionally-guided fractional flow reserve (FFR) PCI strategies have shown improvements in patients' outcome.[44] Nonetheless, functional assessment of CAD in the presence of AS becomes difficult due to diffuse sub-endocardial ischemia leading to myocardial fibrosis, as well as left ventricular remodeling and often severe hypertrophy.[45, 46] Therefore, coronary physiology is altered in patients with severe AS and, although the use of

FFR has not been validated for this group, FFR has been safely performed in contemporaneous studies of patients with severe AS.[47-51]

Coronary revascularization and TAVI outcomes

Our meta-analysis suggests that routine revascularization of patients with severe AS and concomitant CAD undergoing TAVI may be associated with an increased risk of major vascular complications and 30-day mortality, although the latter association was no longer present by 1-year. In this regard, Van Mieghem et al.[29] have shown no significant difference between complete versus incomplete revascularization, but also for SYNTAX scores ≥8 versus <8. One of the theoretical arguments to support revascularization prior to TAVI is the anxiety that peri-procedural MI might occur during the hypotension induced by rapid pacing either for valvuloplasty or during valve delivery. Notably, Griese et al.[33] showed that revascularization was associated with increased 30-day MI compared to TAVI alone. However, the study did not ascertain the prevalence of CAD in the TAVI alone group or indeed the indication for PCI. As such, this study was excluded from our meta-analysis. Singh and colleagues,[40] showed worse 30-day outcomes when PCI was performed during the same admission, though, as above mentioned, this observation might have been driven by the difference in the reported prevalence of CAD between groups, by but also, with a questionable definition of CAD using ICD-9 (international classification of diseases, ninth revision) coding. The higher 30-day mortality could also be associated with a higher pre-operative risk profile, meaning that the PCI group may have been a higher-risk cohort, translating therefore into worse outcome. However, the authors did not report adjusting for pre-procedural risk scoring. Importantly, our analysis shows that when both groups had 100% prevalence of CAD, there was no significant difference in treatment effect estimates, likely due to a small event rates (Figure 2-A). Moreover, meta-regression analysis suggests that differences in the prevalence of CAD did not influence this outcome. Finally, the presence of multiple-comorbid conditions contributes explaining overall 30-day mortality, since the cardiovascular mortality was similar.

Timing for revascularization: concomitant versus *a priori* approach

Performing TAVI shortly after PCI mandates the TAVI procedure be performed while a patient is treated with dual antiplatelet therapy, potentially increasing bleeding risk. However, our analysis shows that major and minor bleeding complications were not significantly different between pre-TAVI PCI and isolated TAVI approaches. Studies which compared a concomitant to *a priori* revascularization approach found no significant differences for AKI and the need for hemodialysis,[10, 23, 33] Interestingly, one would expect that the likelihood of AKI increases with a concomitant approach owing to the larger contrast volumes and higher number of catheter manipulations; however, as previously reported, contrast amount, per-se, was not associated with AKI during TAVI procedures.[52] In addition, most of the studies that reported the incidence of AKI, the PCI was performed *a priori* rather than in the same setting (one study only), Figures 3 and 4. This finding likely reflects the influence of confounding variables as studies were not statistically powered to infer for AKI due to the low event rate.

The revised American guidelines on valvular heart disease have downgraded to Class IIa (Evidence C), the role of coronary revascularization at the time of SAVR.[3] Recommendations focused on TAVI[13-15] while supporting the treatment of significant CAD, do not provide suggestions about the timing of PCI relative to the TAVI procedure. Wenaweser et al.,[10] reported on a combined approach separated into single-stage and staged procedures; later, Van Rosendael et al.[36] found no differences when comparing revascularisation within 30-day prior to TAVI, with PCI performed ≥30 days after TAVI. Thus, there are still very limited data available to inform an optimal strategy with respect to timing of the revascularization.

Limitations

The present study has several limitations. The main limitation lies with the small number of studies, patients and events informing each outcome, and the non-randomized

nature of the included studies that introduced selection bias. Importantly, the decision to perform PCI as revascularization versus medical management for CAD was at the discretion of the heart team and without a consistent selection criteria. In this regard, the decision to undertake PCI may relate to unstable symptoms, limiting angina, or patients considered at higher-risk. Individual-patient level data was not available, precluding therefore, a more robust adjustment for any differences in clinical/anatomical variables or comparisons of severity/risk across the cohorts. Finally, one should bear in mind that once TAVI is extended to lower-risk younger and less morbid patients, also exhibiting a longer life-expectancy, in the case of severe and proximal vessels lesions, it may be beneficial to perform pre-TAVI revascularization to prevent potential problematic coronary arteries accessibility in the future. The results of the ACTIVATION trial[53] will provide further insight into optimal revascularization strategies in patients with CAD undergoing TAVI.

CONCLUSION

Our findings suggest that revascularization before or during TAVI confers no clinical advantage with respect to several patient-important clinical outcomes, and may be associated with an increased risk of major vascular complications and 30-day mortality. These data, however, are based on observational studies including initial high-risk cohorts of patients with limited follow-up and may not be applicable to lower-risk cohorts with greater life expectancy. Randomized-controlled trials are needed to determine the role of routine revascularization in patients with significant CAD undergoing TAVI. Meanwhile, in the absence of definitive evidence, careful evaluation of patients on an individual basis by a dedicated heart team is of paramount importance to identify patients, such as those with significant CAD affecting proximal main epicardial vessels, in which the benefits of elective revascularization are balanced against the potential risks.

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Figures legends

Figure 1. Flow diagram based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).

Figure 2. Meta-analyses evaluating the cumulative risk of **A)** mortality, **B)** clinical outcomes of patients undergoing transcatheter aortic valve implantation (TAVI) plus percutaneous coronary intervention (PCI) versus TAVI alone. AKI: acute kidney injury. M-H: Mantel-Haenszel. CI: confidence interval.

Figure 3. Sensitivity analysis evaluating the cumulative risk of worse outcomes of patients undergoing transcatheter aortic valve implantation (TAVI) plus percutaneous coronary intervention (PCI) versus TAVI alone. AKI: acute kidney injury. M-H: Mantel-Haenszel. CI: confidence interval.

Figure 4. Meta-analyses evaluating outcomes between concomitant (same-setting) versus *a priori* revascularization of patients undergoing transcatheter aortic valve implantation plus percutaneous coronary intervention. M-H: Mantel-Haenszel. CI: confidence interval.

Figure 5. Subgroup analysis according to the percentage in prevalence of significant coronary artery disease (CAD) evaluating the cumulative risk of **A)** 30-day mortality, **B)** cardiovascular mortality, **C)** 1-year mortality, **D)** myocardial infarction, **E)** acute kidney injury and/or need for hemodialysis and **F)** major and life threatening bleeding of patients undergoing transcatheter aortic valve implantation (TAVI) plus percutaneous coronary intervention (PCI) versus TAVI alone. M-H: Mantel-Haenszel. CI: confidence interval.

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Table 1: Study design and participant characteristics

Study ID	Design; Country; Year	No. of participants; PCI + TAVI; TAVI alone	Participant inclusion criteria and CAD significance definition
Masson et al. 2010[9]	Retrospective cohort study; Canada; 2005-2007	104; 15; 89	Patients for TAVI with ≥50% diameter stenosis in at least one coronary artery & DMJS score
Conradi et al. 2011[23]	Retrospective cohort study; Germany; 2008-2010	28; 28; 0	Patients for TAVI who underwent PCI
Gautier et al. 2011[11]	Retrospective cohort study; France; 2006-2009	83; 11; 72	Patients for TAVI with ≥70% epicardial coronary artery stenosis or ≥ 50% stenosis of left main
Nowakowski et al. 2011[22]	Cohort study; Australia; Unclear	70; 15; 55	Patients for TAVI with no information for determination of CAD significance
Wenaweser et al. 2011[10]	Retrospective cohort study; Switzerland; 2007-2010.	256; 59; 197	TAVI patient with >50% diameter stenosis in at least one coronary artery
Abdel-Wahab et al. 2012[12]	Retrospective cohort study; Germany; 2007-2011	125; 55; 70	TAVI patients with ≥50% stenosis on angiography or previous cardiac event
Bensaid et al. 2012[24]	Cohort study; France; Unclear.	61; 23; 38	TAVI patients with >70% proximal vessel stenosis
Aktug et al. 2013[25]	Cohort study; Germany; 2008-2012	338; 66; 272	Patients for TAVI with CAD defined as clinically significant
Arnold et al. 2013[26]	Retrospective cohort study; Germany; Unclear	300; 73; 227	Patients for TAVI with CAD defined as clinically significant
Codner et al. 2013[27]	Retrospective cohort study; Israel; 2008-2012	153; 36; 117	Patients for TAVI with CAD defined as clinically significant
Czerwinska-Jelonkiewicz et al. 2013[30]	Retrospective cohort study; Poland; 2009-2011	83; 18; 65	Not reported

Gasparetto et al. 2013[28]	Retrospective cohort study; Italy; Unclear	152; 39; 113	Patients for TAVI with ≥50% diameter stenosis of at least one epicardial coronary artery
Van Mieghem et al. 2013[29]	Retrospective cohort study; Netherlands; 2005-2012	138; 39; 99	Patients for TAVI with >50% diameter stenosis in any coronary artery
Abramowitz et al. 2014[31]	Retrospective cohort study; Israel; 2009-2012	144; 61; 83	TAVI patients with >70% stenosis in major epicardial coronary artery
Griese et al. 2014[33]	Retrospective cohort study; Germany; 2009-2012	411; 65; 346	TAVI patients with CAD significance defined as per the institution's current local practice
Paradis et al. 2014[41]	Retrospective cohort study; North America; 2007-2012	383; 98; 285	Patients for TAVI with CAD defined as clinically indicated
Tatar et al. 2014[32]	Retrospective cohort study; France; 2008-2013	141; 38; 103	Patients for TAVI but no information of determination of CAD significance
Khawaja et al. 2015[37]	Retrospective cohort study; United Kingdom; 2008-2012	93; 25; 68	Patients for TAVI with epicardial coronary artery stenosis ≥70% or left main stem stenosis of ≥ 50%
Mancio et al. 2015[34]	Retrospective cohort study; Portugal; 2007-2012	46; 13; 33	Patients for TAVI with ≥50% stenosis in coronary artery
Penkalla et al. 2015[35]	Retrospective cohort study; Germany; 2008-2013	308; 76; 232	>50% stenosis in left main or >90% stenosis in LAD, LCx and RCA
Rosendael et al. 2015[36]	Retrospective cohort study; Netherlands, Unclear	96; 96;0	TAVI patients with ≥70% stenosis of a coronary artery of ≥ 1.5 mm
Snow et al. 2015[38]	Retrospective cohort study; United Kingdom; 2007-2011	1,339; 172; 1,167	TAVI patients with >50% stenosis main, LAD, LCx and RCA
Chakravarty et al. 2016[39]	Retrospective cohort and matched study; International; 2007-2014	204 (cohort); 128; 128	Patients with left main PCI from a TAVI-left main registry and matched controls

Singh et al. 2016[40]	Retrospective cohort study with propensity matching; United States of America; 2011-2013	2,349; 588; 1,761	TAVI patients with CAD according to ICD-9 coding

TAVI: transcatheter aortic valve implantation. PCI: percutaneous coronary intervention. CAD: coronary artery disease. DMJS Duke Myocardial Jeopardy score. LAD: left anterior descending. LCx: left coronary circumflex. RCA: right coronary artery. ICD-9: international classification of diseases, ninth revision.

Table 2: Baseline characteristics for patients who underwent TAVI with and without PCI

Study ID	Strategy	Mean Age (years)	Male	Logistic EuroSCORE	STS score	CAD	Multivessel disease	LVEF	CKD	COPD	PVD
Masson et al. 2010[9]	TAVI + PCI TAVI alone	85.7 84.4	10 (66.6) 60 (57.8)	24.5 31.05	9.5 9.7	15 (100) 104 (100)	N/A	45.0 58.4	0 (0) 93 (89.4)	N/A	3 (20.0) 42 (40.3)
Conradi et al. 2011[23]	TAVI + PCI TAVI alone	80.1 N/A	13 (46.4) N/A	26.8 N/A	9.3 N/A	28 (100) N/A	19 (67.9) N/A	45.6 N/A	8 (28.6) N/A	7 (25.0) N/A	11 (39.3) N/A
Gautier et al. 2011[11]	TAVI + PCI TAVI alone	74±15 N/A	9 (81.8) N/A	25±11 N/A	N/A	11 (100) N/A	7 (63.6) N/A	48±13 N/A	N/A	N/A	N/A
Nowakowski et al. 2011[22]	TAVI + PCI TAVI alone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Wenaweser et al. 2011[10]	TAVI + PCI TAVI alone	83.6±4.8 81.7±6.5	29 (49.2) 83 (42.1)	26.8±16.3 24.2±14.4	7.6±6.2 6.1±4.5	59 (100) 108 (54.8)	N/A	51±12 51±15	N/A	N/A	16 (27.1) 48 (24.4)
Abdel-Wahab et al. 2012[12]	TAVI + PCI TAVI alone	81±7.1 81±6.2	26 (47.0) 34 (48.5)	25.08±12.6 23.62±15.1	N/A	55 (100) 36 (51.4)	18 (32.7) 27 (38.6)	46.9±13.9 48.5±15.3	N/A	N/A	11 (20.0) 10 (14.2)
Bensaid et al. 2012[24]	TAVI + PCI TAVI alone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Aktug et al. 2013[25]	TAVI + PCI TAVI alone	N/A	N/A	N/A	N/A	66 (100) 155 (57)	N/A	N/A	N/A	N/A	N/A
Arnold et al. 2013[26]	TAVI + PCI TAVI alone	82±6 81±6	39 (54) 78 (44)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Codner et al. 2013[27]	TAVI + PCI TAVI alone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Czerwinska-Jelonkiewicz et al. 2013[30]	TAVI + PCI TAVI alone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gasparetto et al. 2013[28]	TAVI + PCI TAVI alone	N/A 80.3±6.3	N/A 57 (50.4)	N/A 23.2±14.1	N/A	39 (100) 113 (100)	N/A	N/A 52.8±12.9	N/A 65 (57.5)	N/A 25 (22.1)	N/A
Van Mieghem et al. 2013[29]	TAVI + PCI TAVI alone	N/A	N/A	N/A	N/A	39 (100) 99 (100)	N/A	N/A	N/A	N/A	N/A

Abramowitz et al. 2014[31]	TAVI + PCI TAVI alone	83.6±5.5 83.1±5.1	33 (50.8) 40 (48.2)	31.3±13.8 29.2±13.8	NA	61 (100) 83 (100)	35 (57.4) 47 (56.7)	54.6±9 55.2±7.5	N/A	7 (11.5) 21 (25.3)	10 (16.4) 14 (16.9)
Griese et al. 2014[33]	TAVI + PCI TAVI alone	82±6 82±5	24 (36.9) 129 (37.3)	21.7±13.9 20.3±14.6	N/A	N/A	N/A	52±15 54±14	36 (55.3) 177 (51.2)	N/A	N/A
Paradis et al. 2017[41]	TAVI + PCI TAVI alone	N/A	39 (39.8) 160 (56.3)	N/A	N/A	SYNTAX 22.0 18.5	N/A	N/A	N/A	N/A	N/A
Tatar et al. 2014[32]	TAVI + PCI TAVI alone	85±5 84±6	18 (47.4) 54 (52.0)	31.3±16.6 31.7±16.8	7.8±5.8 7.5±4.7	38 (100) 54 (52.4)	19 (50.0) 10 (9.7)	N/A	11 (29.0) 41 (39.8)	8 (21.1) 35(34.0)	8 (21.1) 41 (39.8)
Khawaja et al. 2015[37]	TAVI + PCI TAVI alone	N/A	N/A	N/A	N/A	25 (100) 68 (100)	N/A	N/A	N/A	N/A	N/A
Mancio et al. 2015[34]	TAVI + PCI TAVI alone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Penkalla et al. 2015[35]	TAVI + PCI TAVI alone	83 (78-86) 81 (76-85)	21 (27.6) 88 (37.9)	32.1 (19-52) 28.5 (18-45)	11.9 (7-19) 10.1 (6-19)	76 (100) 232 (100)	N/A	55 (40-60) 50 (41-60)	N/A	N/A	50 (65.8) 160 (69.0)
Rosendael et al. 2015[36]	TAVI + PCI TAVI alone	81±5.4 NA	55 (57.3) N/A	23.2±12.9 N/A	N/A	96 (100) N/A	N/A	54±13 N/A	N/A	N/A	N/A
Snow 2015[38]	TAVI + PCI TAVI alone	N/A	N/A	N/A	N/A	172 (100) 1,167 (100)	N/A	N/A	N/A	N/A	N/A
Chakravarty 2016[39]	TAVI + PCI TAVI alone	81.7±6.8 81.0±7.9	81 (63.3) 88 (68.7)	N/A	7.8±4.9 8.0±4.5	128 (100) 128 (100)	N/A	53.5±12.4 55.5±13.6	N/A	N/A	44 (34.4) 50 (41.4)
Singh et al. 2016[40]	TAVI + PCI TAVI alone	83.0±0.59 82.9±0.39	279 (47.4) 812 (46.1)	N/A	N/A	493 (83.9) 1,125 (63.9)	N/A	N/A	N/A	164 (27.9) 560 (31.8)	189 (32.2) 526 (29.9)

Data presented as number/sample size (percentage), mean±SD or median (interquartile range). CAD: coronary artery disease. CKD: chronic kidney disease. COPD: chronic obstructive pulmonary disease. Log-EuroSCORE: logistic European system for cardiac operative risk evaluation. LVEF: left ventricle ejection fraction (%). Mean gradient (mmHg). TAVI: transcatheter aortic valve implantation. PCI: percutaneous coronary intervention. PVD: peripheral vascular disease. STS score: Society of Thoracic Surgeons Score for Prediction of Mortality score. N/A: not available.

Table 3: Newcastle-Ottawa Quality Assessment Scale

		Selection Bias				Comparability	Ascertainment and attrition bias			Overall Quality
Study ID	**Sample size >50 in each arm**	**Representativeness of exposed cohort for TAVI population**	**Selection of non-exposed cohort**	**Method of exposure ascertainment**	**Outcome of interest present at start?**	**Adjustment for important confounders**	**Outcome Ascertainment (source, criteria)**	**Adequate length of follow-up**	**Loss to follow-up <10%**	
Masson et al. 2010[9]	No, 15 and 89	Yes	All in our analysis had CAD of varying severity	Pre-operative coronary angiography and Duke Myocardial Jeopardy Score	No	Both groups in our analysis had 100% CAD, but no other adjustments	Clinical appointment follow-up but adjudication not according to standardized end-points	Yes	Yes, unclear	Average
Conradi et al. 2011[23]	No, 28	Yes	All had CAD	Pre-operative coronary angiography	No	Both groups had 100% CAD but no other adjustments	Telephone interviews but no adjudication according to guidelines	Yes	Yes, none	High
Gautier et al. 2011[11]	No, 11 and 72	Yes	All had CAD	Pre-operative coronary angiography	No	No adjustment	Unclear, but adjudicated according to guidelines for reporting mortality and morbidity in TAVI	Yes	Yes, none	Average
Nowakowski et al. 2011[22]	No, 15 and 55	Yes	No information on CAD prevalence	Unclear	Unclear	No reporting of CAD% in each arm or other adjustments	Unclear	Unclear.	Unclear	Low

Wenaweser et al. 2011[10]	Yes, 59 and 197	Yes	Dissimilar CAD distribution between exposed and non-exposed cohorts	Pre-procedural left heart catheterization	No	No adjustments, imbalance in CAD between arms	Data from municipal civil registries and hospital records. Data recorded in accordance with VARC guidelines, but which version is unclear	Yes	Yes, none	Average
Abdel-Wahab et al. 2012 [12]	Yes, 55 and 70	Yes	Non-exposed cohort had different rate of CAD	Pre-operative coronary angiography	No	No, not controlling for CAD	No information on source employed. Outcomes adjudicated in accordance with VARC-1 guidelines	Yes	Yes, 0.8% loss to follow up	Average
Bensaid et al. 2012[24]	No, 23 and 38	Yes	No information on CAD prevalence	Pre-operative coronary angiography	Unclear	CAD % same in both groups but no other adjustments	Unclear source and adjudication guidelines	Yes	Unclear	Low
Aktug et al. 2013[25]	Yes, 66 and 272	Yes	Dissimilar CAD distribution between exposed and non-exposed cohorts	Unclear	No	No, not controlling for CAD or other factors	Unclear source and adjudication guidelines	Yes	Unclear	Low
Arnold et al. 2013[26]	Yes, 73 and 227	Yes	No information on CAD prevalence	Unclear	Unclear	No, not controlling for CAD or other factors	Unclear	Yes	Unclear	Low
Codner et al. 2013[27]	No, 36 and 117	Yes	No separate information on CAD prevalence	Pre-operative coronary angiography	No	No adjustments	Participants prospectively examined. Data recorded in accordance with VARC-1 criteria	Yes	Yes, none	Average

Czerwinska-Jelonkiewicz et al. 2013 [30]	No, 18 and 65	Yes	No information on CAD prevalence	Unclear	No	No adjustments	Telephone interviews. Data recorded in accordance with VARC-1 criteria	Yes	Yes, 2.4% loss to follow up	Low
Gasparetto et al. 2013[28]	No, 39 and 113	Yes	All had CAD	Pre-operative coronary angiography or history	No	No adjustments	Unclear. Data recorded in accordance with VARC-1 criteria	Yes	Yes, none.	Average
Van Mieghem et al. 2013[29]	No, 39 and 99	Yes	Unclear	Pre-operative coronary angiography	No	No adjustments	Clinical follow-up. VARC-1 criteria	Yes	Yes, none	Average
Abramowitz et al. 2014 [31]	Yes, 61 and 83	Yes	Non-exposed cohort similar to exposed in terms of CAD	Pre-procedural coronary angiography	No	Yes, controlling for CAD	Outcomes prospectively recorded in clinical assessments employing VARC-1 guidelines	Yes	Yes, none	High
Griese et al. 2014[33]	Yes 65 and 346	Yes	No information on CAD prevalence	Pre-operative cardiac catheterisation	No	No adjustment and CAD % unreported	Yes, Phone calls. Data recorded in accordance with VARC-2 criteria	Yes	Yes, 100% follow up	Average
Paradis et al. 2017[41]	Yes, 98 and 285	Yes	No information on CAD prevalence	Pre-TAVI coronary angiogram	Unclear	Multivariate analysis for mortality but not for other outcomes. Not data on variables included in the model	Adjudicated outcomes according to VARC-1 definition by clinical event committee	Yes	Unclear	Average
Tatar et al. 2014[32]	Yes, 38 and 103	Yes	Non-exposed cohort had different rate of CAD	Unclear	No	No adjustments, imbalance in CAD between arms	Unclear	Yes	Yes, none	Low

Khawaja et al. 2015[37]	No, 25 and 68	Yes	All patients in analysed sub-group had CAD	Pre-TAVI coronary angiogram and SYNTAX score calculation	No	In the subgroup analysis all patients had CAD, but no other adjustments	Database, with outcomes reported according to VARC-2 criteria	Yes	Yes, none	High
Mancio et al. 2015[34]	No, 13 and 33	Yes	All had CAD	Pre-procedural coronary angiography	No	100% CAD in both groups, no other adjustments	Unclear	Yes	Yes, none	High
Penkalla et al. 2015[35]	Yes, 76 and 232	Yes	Information on CAD present and stratified according to significance	Pre-TAVI coronary angiogram and SYNTAX score calculation	No	Adjusted for comparison between group II and III as they all had CAD, no other adjustments	Mortality ascertained from German Register of Residents and clinical outcomes from prospective e-database. Ascertainment according to VARC-2 consensus guidelines	Yes	Unclear	High
Rosendael et al. 2015[36]	No, 96	Yes	All had CAD	Pre-operative coronary angiograms with SYNTAX score calculation	No	No adjustments	Electronic record keeping, using VARC-2 criteria	Yes	Yes, none	Average
Snow et al. 2015[38]	Yes, 172 and 2,416	Yes	Unequal CAD distribution between exposed and non-exposed	Pre-TAVI coronary angiogram	No	No adjustments	Prospectively entered data from electronic BCIS and SCTS database. Data linked to the Office of National Statistics and National Records of Scotland	Yes	Unclear	Average

Chakravarty et al. 2016 [39]	Yes, 128 and 128	Yes	No information on CAD prevalence but matched for unprotected left main stem	Pre-operative coronary angiography and CT scans	No	Matched control subjects	Data from registry, recorded in accordance with VARC-2 guidelines	Yes	Yes, none	High
Singh et al. 2016[40]	Yes, 588 and 1,761	Yes	Unequal CAD distribution between the two groups	No information on how significance was determined	Unclear	Propensity matching for some confounders but not for CAD	Outcomes ascertained via the Nationwide Inpatient sample. ICD-9 codes used	Unclear	Yes, none	Average

BCIS: British Cardiovascular Intervention Society. CAD: coronary artery disease. ICD-9: International Classification Disease-9. SCTS: Society of Cardiothoracic Surgeons. TAVI: trans-catheter aortic valve implantation. VARC: Valve academic research consortium.

Table 4: Procedural-related complications and follow-up clinical outcome

Author, Year	Type of Valve Approach	Timing of PCI	Outcomes	TAVI + PCI		TAVI alone
Masson et al. 2010[9]	Edwards- SAPIEN (100%) Transfemoral: 82/119 (69%)	*a priori* Median 26 days range 3-100 days	30-day mortality	0/15 (0)		12/89 (14)
			1-year mortality	3/15 (20)		26/89 (29)
Conradi et al. 2011[23]	Medtronic CoreValve Edwards SAPIEN Transapical: 17/28 (61%) Transfemoral: 11/28 (39%)	Concomitant and *a priori* up to 4 weeks before TAVI		**Concomitant**	***a priori***	
			Procedural & 30-day mortality	2/7 (29)	0/21 (0)	N/A
			AKI	2/7 (29)	0/21(0)	
			Non-severe bleeding	0/7 (0)	2/21 (10)	
Gautier et al. 2011[11]	Medtronic CoreValve Edwards SAPIEN Transfemoral Trans-subclavian	Concomitant and *a priori*, mean delay 6±6 weeks	30-day mortality	8/83 (9.6)		
			Stroke	2/83 (2.4)		
			MI	8/83 (9.6)		
			Severe bleeding	5/83 (6.0)		
			Vascular complications	9/83 (11)		
Nowakowski et al. 2011[22]	N/A	Concomitant and *a priori*, at least 6 weeks prior to TAVI in all but 6 patients		**Concomitant**	***a priori***	
			Stroke	0/6 (0)	1/9 (11.1)	N/A
			AKI	0/6 (0)	2/9 (22)	
			Vascular complications	1/6 (17)	0/9 (0)	
Wenaweser et al. 2011[10]	Medtronic CoreValve Edwards SAPIEN Transfemoral Trans-subclavian Transapical	Concomitant and *a priori*		**Concomitant**	***a priori***	
			30-day mortality	4/36 (11)	2/23 (8.7)	11/197 (5.6)
			30-day cardiovascular mortality	3/59 (5.1)		0/9 (0)
			30-day stroke	2/36 (5.6)	0/23 (0)	8/197 (4.1)

			30-day MI	0/36 (0) | 0/23 (0)	1/197 (0.5)
			Life threatening bleeding	2/36 (5.6) | 3/23 (13)	24/197 (12)
			Major bleeding	21/59 (36)	57/197 (29)
			Major access site related complication	1/36 (2.8) | 3/23 (13)	12/197 (6.1)
			Minor access site related complication	5/59 (8.5)	18/197 (9.1)
			Combined safety end-point	8/36 (22) | 6/36 (17)	61/197 (31)
			AKI (I, II & III)	8/59 (14)	35/197 (18)
			Permanent pacemaker implantation	14/59 (24)	46/197 (23)
Abdel-Wahab et al. 2012 [12]	Medtronic CoreValve Transfemoral: 124/125 (99.2%) Trans-subclavian: 1/125 (0.8%)	*a priori* Median 10 days range 0 to 90 days	30-day mortality	1/55 (1.8)	4/70 (5.7)
			30-day cardiovascular mortality	1/55 (1.8)	3/70 (4.3)
			30-day stroke	1/55 (1.8)	4/70 (5.7)
			30-day life threatening bleeding	4/55 (7.3)	4/70 (5.7)
			30-day major bleeding	6/55 (11)	8/70 (11)
			30-day minor bleeding	4/55 (7.3)	3/70 (4.3)
			30-day major vascular complications	3/55 (5.5)	2/70 (2.9)
			30-day minor vascular complications	8/55 (15)	10/70 (14)
			30-day combined safety end-point	6/55 (11)	9/70 (13)

			30-day permanent pacemaker	16/55 (30)	11/70 (16)
			30-day hemodialysis	0/55 (0)	2/70 (2.9)
			6-month mortality	4/48 (8.3)	8/59 (14)
			6-month coronary events	2/48 (4.2)	0/59 (0)
			6-month stroke	2/48 (4.2)	3/59 (5.1)
			6-month bleeding	10/48 (21)	13/59 (22)
			6-month permanent pacemaker	16/48 (33)	11/59 (19)
			6-month hemodialysis	0/48 (0)	1/59 (1.7)
Bensaid et al. 2012[24]	Medtronic CoreValve	*a priori* One month prior to TAVI	Composite of heart failure, MI and mortality	6/23 (26)	12/38 (32)
Aktug et al. 2013[25]	Medtronic CoreValve: 183/338 (54.1%) Edwards SAPIEN: 146/338 (43.2%) Symetis Acurate: 9/338 (2.7%)	Concomitant and *a priori* Mean 13±9 days	30-day mortality	8/66 (12)	27/272 (9.9)
Arnold et al. 2013[26]	Balloon-expandable valve Transapical: 200/300 (66.7%) Transfemoral: 100/300 (33.3%)	N/A	30-day mortality	8/73 (11)	26/227 (12)
			Long-term mortality	25/73 (34)	59/227 (26)

Codner et al. 2013[27]	Medtronic CoreValve Edwards-SAPIEN Transfemoral: 112/153 (73.2%) Transapical: 27/153 (17.6%) Transaxillary: 13/153 (8.5%) Transaortic: 1/153 (0.6%)	Concomitant and *a priori*	1-year mortality	5/36 (14)	8/117 (6.8)
Czerwinska-Jelonkiewicz et al. 2013[30]	Medtronic CoreValve Edwards SAPIEN/SAPIEN-XT Transfemoral 59/83 (71%) Trans-subclavian 8/83 (9.6%) Transapical 16/83 (19.2%)	N/A	Bleeding complications	17/18 (94)	34/65 (52)
Gasparetto et al. 2013[28]	Medtronic CoreValve Edwards SAPIEN/SAPIEN-XT Transfemoral Trans-subclavian	*a priori*, median 27 (IQR 8-51) days	30-day mortality	N/A	5/113 (4.4)
			30-day cardiovascular mortality	N/A	6/113 (5.3)
			30-day stroke	N/A	3/113 (2.7)
			30-day MI	N/A	5/113 (4.4)
			30-day life threatening bleeding	N/A	4/113 (3.5)
			30-day major vascular complications	N/A	7/113 (6.2)
			30-day combined safety end-point	N/A	12/113 (11)
			30-day AKI (Stage III)	N/A	6/113 (5.3)

			1-year mortality	N/A	16/106 (15)
			1-year cardiovascular mortality	N/A	4/106 (3.8)
			1-year major stroke	N/A	1/106 (0.9)
			1-year MI	N/A	2/106 (1.9)
			1-year major bleeding	N/A	1/106 (0.94)
Van Mieghem et al. 2013[29]	Medtronic CoreValve Edwards SAPIEN Transfemoral Transaxillary, Transapical	Concomitant and *a priori*	N/A	N/A	N/A
Abramowitz et al. 2014[31]	Medtronic CoreValve Edwards SAPIEN Transfemoral Trans-subclavian	*a priori* Mean 56.5±29.4 days	30-day mortality	1/61(1.6)	2/83 (2.4)
			30-day stroke	2/61 (3.3)	2/83 (2.4)
			30-day MI	0/61 (0)	0/83 (0)
			30-day major bleeding	2/61 (3.3)	1/83 (1.2)
			30-day major vascular complications	3/61 (4.9)	2/83 (2.4)
			30-day minor vascular complications	9/61 (15)	4/83 (4.8)
			30-day combined safety end-point	5/61 (8.2)	5/83 (6.0)
			30-day permanent pacemaker	13/61 (21.3)	22/83 (26.5)
			30-day hemodialysis	0/61 (0)	0/83 (0)
Griese et al. 2014[33]	Medtronic CoreValve Edwards SAPIEN-XT Symetis Acurate Transfemoral: 190/411 (46.2%) Transapical: 221/411	Concomitant and *a priori*, 36±38 days		**Concomitant**	***a priori***
			30-day mortality	3/17 (18)	7/48 (15)
			30-day cardiovascular mortality	3/17 (18)	7/48 (15)
			30-day stroke	0/17 (0)	0/48 (0)

	18/346 (5.2)
	18/346 (5.2)
	6/346 (1.7)

	(53.8%)		30-day MI	2/17 (12)	2/48 (4.2)	3/346 (0.9)
			30-day major bleeding	3/17 (17)	7/48 (15)	93/346 (27)
			30-day major vascular complications	0/10 (0)	1/23 (4.4)	8/157 (5.1)
			30-day permanent pacemaker	0/17 (0)	0/48 (0)	76/346 (22)
			30-day Stage III AKI	1/17 (5.9)	2/48 (4.2)	20/346 (5.8)
Paradis et al. 2014[41]	Edwards SAPIEN Transfemoral: 200/383 (52.2%) Transapical: 183/383 (47.8%)	*a priori* Up to 6 months before TAVI	30-day mortality	4/98 (4.1)		27/285 (9.5)
			Major bleeding complications	6/98 (6.1)		21/285 (7.4)
			Major vascular complications	3/98 (3.1)		22/285 (7.7)
			AKI stage III	1/98 (1.0)		3/285 (1.1)
			1-year mortality	10/98 (10)		69/285 (24)
Tatar et al. 2014[32]	Medtronic CoreValve: 8/141 (5.7%) Edwards SAPIEN: 126/141 (89.4%) St. Jude Portico: 7/141 (4.96%) Transfemoral: 141/141 (100%)		In hospital mortality	2/38 (5.3)		2/103 (1.9)
			Cardiovascular mortality	1/38 (2.6)		1/103 (1.0)
			Stroke	2/38 (5.3)		1/103 (1.9)
			Myocardial infarction	0/38 (0)		0/103 (0)
			Life threatening bleeding	0/38 (0)		2/103 (1.9)
			Major bleeding	0/38 (0)		1/103 (1.0)
			Minor bleeding	0/38 (0)		0/103 (0)
			Major vascular complications	1/38 (2.6)		3/103 (2.9)
			Minor vascular complications	0/38 (0)		2/103 (1.9)
			New Pacemaker	2/38 (5.3)		10/103 (9.7)

			AKI stage I, II & III	13/38 (34)	17/103 (17)
			1-year mortality	11/38 (29)	21/103 (20)
			2-year mortality	13/38 (34)	48/103 (47)
Khawaja et al. 2015[37]	Edwards SAPIEN Transfemoral 47/93 (50.5%) Transapical: 29/93 (31.2%) Trans-aortic: 17/93 (18.3%)	*a priori* Median 49.5 (IQR 25-127) days	30-day mortality	2/25 (8)	5/68 (7.4)
			1-year mortality	6/25 (24)	15/68 (22)
Mancio et al. 2015[34]	Medtronic CoreValve Edwards SAPIEN Transfemoral Transapical Trans-subclavian	Concomitant (2/13) and *a priori* (11/13) Median 56 (IQR 3-166) days	30-day mortality	2/13 (15)	4/33 (12)
			30-day stroke	1/13 (7.7)	1/33 (3.0)
			30-day life threatening bleeding	2/13 (15)	10/33 (30)
			30-day major vascular complications	2/13 (15)	11/33 (33)
			30-day AKI	4/13 (31)	10/33 (30)
			30-day permanent pacemaker	3/13 (23)	13/33 (39)
Penkalla et al. 2015[35]	Edwards SAPIEN (100%) Transapical (100%)	Concomitant	30-day mortality	2/76 (2.6)	9/232 (3.9)
			Peri and post procedural MI	1/76 (1.3)	4/232 (1.7)
			AKI stage I & III	16/76 (21)	43/232 (19)
			1-year mortality	30/76 (40)	94/232 (41)
			2-year mortality	46/76 (61)	151/232 (65)
			3-year mortality	63/76 (83)	188/232 (81)
			4-year mortality	73/76 (96)	221/232 (95)

van Rosendael et al. 2015[36]	Medtronic CoreValve Edwards SAPIEN Transfemoral Transapical	*A priori*		***a priori* ≥30 days**	***a priori* <30 days**	
			In-hospital death	4/48 (8.3)	2/48 (4.2)	N/A
			30-day stroke	1/48 (2.1)	1/48 (2.1)	
			30-day major bleeding	4/48 (8.3)	4/48 (8.3)	
			30-day minor bleeding	0/48 (0)	6/48 (13)	
			30-day major vascular injury	3/48 (7.3)	5/48 (10)	
			30-day minor vascular injury	1/48 (2.1)	8/48 (17)	
			30-day combined safety endpoint	9/48 (19)	6/48 (13)	
			30-day AKI	8/48 (17)	8/48 (17)	
			30-day Atrioventricular block	7/48 (7.3)	2/48 (4.2)	
Snow et al. 2015[38]	NA	Concomitant and *a priori*	1-year mortality	36/172 (21)		246/1,167 (21)
Chakravarty et al. 2016[39]	Medtronic CoreValve Edwards SAPIEN Direct Flow Transfemoral/Trans-subclavian: 194/256 (75.8%) Alternative Access: 44/256 (17.2%)	Concomitant and *a priori*	30-day mortality	4/128 (3.1)		3/128 (2.3)
			30-day stroke	1/128 (0.8)		2/128 (1.6)
			30-day MI	0/128 (0)		0/128 (0)
			Procedural death	0/128 (0)		1/128 (0)
			Procedural major or life threatening bleeding	22/128 (17)		33/128 (26)
			Procedural major vascular complications	21/128 (16)		5/128 (3.9)
			Permanent pacemaker	34/128 (27)		18/128 (14)
			AKI	6/128 (4.7)		7/128 (5.5)
			1-year mortality	12/128 (9.4)		13/128 (10)

			1-year stroke	1/128 (0.8)	3/128 (2.3)
			1-year MI	3/128 (2.3)	1/128 (0.8)
Singh et al. 2016[40]	Transfemoral/transaortic (84.6%) Transapical (15.4%)	Concomitant and *a priori*	In-hospital mortality	60/588 (10)	120/1,761 (6.8)
			In-hospital neurological complications	20/588 (3.4)	128/1,761 (7.3)
			In-hospital bleeding requiring transfusion	45/588 (7.7)	217/1,761 (12)
			In-hospital major vascular complications	50/588 (8.5)	79/1,761 (4.5)
			In-hospital AKI requiring dialysis	5/588 (0.9)	44/1,761 (2.5)
			In-hospital permanent pacemaker	34/588 (5.8)	190/1,761 (11)

Data presented as the occurrence of an event/sample size (percentage). AKI: acute kidney injury. IQR: Interquartile range. MI: myocardial infarction. PCI: percutaneous coronary intervention. TAVI: Transcatheter Aortic Valve Implantation.

Table 5. Pooled analysis for adverse outcomes with and without revascularization

Outcome	Studies	Cumulative	%	References	Studies	TAVI PCI	%	References	Studies	TAVI alone	%	References
30-day Mortality	18	401/5,574	7.2%	9-12, 23, 25, 26, 28, 29, 31-37, 39-41	16	118/1,484	7.95%	9, 10, 12, 23, 25, 26, 29, 31-37, 39-41	16	275/4,007	6.9%	9-12, 25-29, 31-35, 37, 39-41
30-day cardiovascular mortality	5	52/1,046	5.0%	10, 12, 28, 31, 32	4	15/217	6.9%	10, 12, 31, 32	5	37/829	4.5%	10, 12, 28, 31, 32
1-year Mortality	9	607/2,883	21%	9, 27, 28, 32, 35, 37-39, 41	8	113/588	19.2%	9, 27, 32, 35, 37-39, 41	9	494/2,295	21.5%	9, 27, 28, 32, 35, 37-39, 41
2-year Mortality	2	258/449	57.5%	32, 35	2	59/114	51.8%	32, 35	2	199/335	59.4%	32, 35
Myocardial infarction	10	33/1,903	1.7%	10-12, 25, 28, 31-33, 35, 39	8	12/548	2.2%	10, 12, 25, 31-33, 35, 39	8	13/1,272	1.02%	10, 12, 28, 31-33, 35, 39
Major or life-threatening bleeding	13	608/4,403	13.8%	10-12, 28, 31-36, 39-41	10	140/1,201	11.6%	10, 12, 31-34, 36, 39-41	10	463/3,119	14.8%	10, 12, 28, 31-34, 39-41
Major vascular complications	11	247/4,099	6.02%	10, 12, 28, 31-34, 36, 39-41	10	96/1,169	8.2%	10, 12, 31-34, 36, 39-41	10	151/2,930	5.2%	10, 12, 28, 31-34, 39-41
Acute kidney injury	14	263/4,671	5.6%	10, 12, 22, 23, 28, 31-36, 39-41	13	76/1,320	5.8%	10, 12, 22, 23, 31-36, 39-41	11	187/3,351	5.6%	10, 12, 28, 31-35, 39-41
Stroke/transient ischemic attack	12	43/1,752	2.45%	10-12, 22, 25, 28, 31-34, 36, 39	10	14/596	2.3%	10, 12, 22, 25, 31-34, 36, 39	8	27/1,073	2.5%	10, 12, 28, 31-34, 39
Pacemaker implantation	8	519/3,728	13.9%	10, 12, 31-34, 39, 40	8	133/1,007	13.2%	10, 12, 31-34, 39, 40	8	386/2,721	14.2%	10, 12, 31-34, 39, 40

TAVI: transcatheter aortic valve implantation. PCI: percutaneous coronary intervention. Values are expressed as the occurrence of an event/sample size.

Table 6: Sensitivity Analysis for Clinical Outcomes Comparing the Percentage of Reported Coronary Artery Disease in Studies Without Revascularization

Outcome	Random effects odds ratio [95%CI]	Fixed effects odds ratio [95%CI]	Random effects odds ratio excluding studies with no events in at least one arm
30-day mortality	1.39 [1.08-1.79]	1.34 [1.04-1.71]	1.41 [1.10-1.81]
100% CAD in TAVI alone group	0.82 [0.30-2.20]	0.80 [0.30-2.16]	0.82 [0.30-2.20]
>50% CAD in TAVI alone group	1.44 [1.11-1.87]	1.39 [1.08-1.80]	1.47 [1.13-1.90]
1-year mortality	1.03 [0.79-1.34]	1.03 [0.79-1.33]	1.03 [0.79-1.34]
100% CAD in TAVI alone group	0.99 [0.73-1.33]	0.99 [0.74-1.34]	0.99 [0.73-1.33]
>50% CAD in TAVI alone group	1.12 [0.57-2.20]	1.13 [0.66-1.93]	1.12 [0.57-2.20]
Cardiovascular mortality	1.03 [0.37-2.87]	0.98 [0.36-2.65]	1.03 [0.37-2.87]
>50% CAD in TAVI alone group	1.03 [0.37-2.87]	0.98 [0.36-2.65]	1.03 [0.37-2.87]
Myocardial infarction	0.86 [0.14-5.17]	0.85 [0.14-5.11]	0.76 [0.09-6.72]
100% CAD in TAVI alone group	0.76 [0.09-6.72]	0.76 [0.09-6.72]	0.76 [0.09-6.72]
>50% CAD in TAVI alone group	1.10 [0.05-26.65]	1.10 [0.05-26.65]	Not estimable
Major or life threatening bleeding	0.87 [0.58-1.29]	0.76 [0.61-0.95]	0.89 [0.58-1.35]
100% CAD in TAVI alone group	2.72 [0.25-29.33]	2.72 [0.25-29.33]	2.72 [0.25-29.33]
>50% CAD in TAVI alone group	0.84 [0.56-1.26]	0.75 [0.60-0.94]	0.86 [0.55-1.32]
Major vascular or access site complication	1.79 [1.31-2.45]	1.78 [1.31-2.43]	1.79 [1.31-2.45]
100% CAD in TAVI alone group	2.04 [0.35-11.84]	2.04 [0.35-11.84]	2.04 [0.35-11.84]
>50% CAD in TAVI alone group	1.79 [1.30-2.45]	1.77 [1.29-2.43]	1.79 [1.30-2.45]
Acute kidney injury and/or dialysis	0.89 [0.47-1.71]	0.90 [0.65-1.23]	0.94 [0.48-1.84]
100% CAD in TAVI alone group	1.14 [0.68-1.90]	1.14 [0.68-1.90]	1.14 [0.68-1.90]
>50% CAD in TAVI alone group	0.77 [0.29-2.06]	0.79 [0.53-1.19]	0.85 [0.29-2.43]
Stroke	1.06 [0.39-2.86]	1.00 [0.42-2.40]	1.06 [0.39-2.86]
100% CAD in TAVI alone group	1.36 [0.20-9.39]	1.36 [0.20-9.39]	1.36 [0.20-9.39]
>50% CAD in TAVI alone group	1.02 [0.25-4.21]	0.92 [0.34-2.46]	1.02 [0.25-4.21]
Pacemaker implantation	0.87 [0.54-1.39]	0.72 [0.57-0.92]	0.87 [0.54-1.39]
100% CAD in TAVI alone group	0.80 [0.44-1.47]	0.80 [0.44-1.47]	0.80 [0.44-1.47]
>50% CAD in TAVI alone group	0.89 [0.48-1.66]	0.71 [0.55-0.92]	0.89 [0.48-1.66]
Combined safety	0.84 [0.55-1.27]	0.84 [0.56-1.28]	0.84 [0.55-1.27]
100% CAD in TAVI alone group	1.36 [0.41-4.49]	1.36 [0.41-4.49]	1.36 [0.41-4.49]
>50% CAD in TAVI alone group	0.78 [0.50-1.22]	0.78 [0.50-1.23]	0.78 [0.50-1.22]

CI: confidence interval. TAVI: transcatheter aortic valve implantation. CAD: coronary artery disease.

Table 7: Meta-regression Examining the Influence of Coronary Artery Disease on Outcomes

Outcome	Exp(b) (95%CI)	P-value
30-day mortality	0.98 (0.94-1.02)	0.23
1-year mortality	0.99 (0.94-1.04)	0.36
Cardiovascular mortality	0.92 (0.15-5.71)	0.68
Myocardial infarction	insufficient observations	-
Major or life threatening bleeding	1.05 (0.99-1.10)	0.074
Major vascular or access site complication	0.99 (0.91-1.07)	0.72
Acute kidney injury or hemodialysis	1.01 (0.90-1.13)	0.77
Stroke	0.98 (0.74-1.31)	0.81
Permanent pacemaker	1.01 (0.94-1.09)	0.64
Combined safety	1.03 (0.65-1.64)	0.57

CI: confidence interval.