Title: Transcatheter Aortic Valve Implantation With or Without Pre-implantation Balloon Aortic Valvuloplasty: A Systematic Review and Meta-analysis

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Transcatheter Aortic Valve Implantation With or Without Pre-implantation Balloon Aortic Valvuloplasty: A Systematic Review and Meta-analysis

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Short title: TAVI with or without pre-implantation BAV

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Abstract

Objectives: Pre-implantation balloon-aortic valvuloplasty (BAV) is considered routine procedure during transcatheter aortic valve implantation (TAVI) to facilitate prosthesis implantation and expansion; however, it has been speculated that fewer embolic events and/or hemodynamic instability may occur if TAVI is performed without pre-implantation BAV. Hence, the aim of the study was to systematically review the clinical outcomes associated with TAVI undertaken without pre-implantation BAV.

Methods and Results: We conducted a search of MEDLINE and EMBASE to identify studies that evaluated patients who underwent TAVI with/without pre-implantation BAV for predilation. Pooled analysis and random effects meta-analyses were used to estimate the rate and risk of adverse outcomes. Sixteen studies involving 1395 patients (674/721 with/without pre-implantation BAV) fulfilled the inclusion criteria. Crude device success was achieved in 94% (1311/1395) and 30-day all-cause mortality occurred in 6% (72/1282) of patients. Meta-analyses evaluating outcomes between pre-implantation BAV versus without BAV strategies showed no statistically significant differences in terms of mortality (risk ratio [RR]: 0.61, 95% confidence interval [CI]: 0.32-1.14, P=0.12), safety composite endpoint (RR: 0.85, 95%CI: 0.62-1.18, P=0.34), moderate-to-severe paravalvular leaks (RR: 0.68, 95%CI: 0.23-1.99, P=0.48), need for postdilation (RR: 0.86, 95%CI: 0.66-1.13, P=0.58), stroke and/or transient ischemic attack (RR: 0.72, 95%CI: 0.30-1.71, P=0.45), and permanent pacemaker implantation (RR: 0.80, 95%CI: 0.49-1.30, P=0.37).

Conclusion: Our analysis suggests that TAVI procedures with or without pre-implantation BAV were associated with similar outcomes in a number of clinically relevant endpoints. Further

studies including a significant number of patients are needed to ascertain the impact of TAVI without pre-implantation BAV as a standard practice.

Keywords: aortic stenosis - TAVI - TAVR - balloon-expandable - self-expandable - balloon valvuloplasty

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is the definitive alternative option for patients with severe symptomatic aortic stenosis considered either unsuitable or at high-risk for surgical aortic valve replacement.[1,2] Pre-implantation balloon-aortic valvuloplasty (BAV) is considered a standard procedure during TAVI. Predilation BAV creates fractures of calcified leaflets and increases leaflet flexibility, thereby facilitating delivery of the TAVI catheter across the aortic valve, and enhancing prosthesis implantation and expansion within the calcified aortic valve annulus. Importantly, it has been speculated that fewer embolic events and/or hemodynamic instability may occur if TAVI is performed without pre-implantation BAV. Alternatively, there is also a concern that omitting pre-implantation BAV may result in the need for more post-implant BAV postdilation and possible associated complications. Notably, this has only been proposed in single-centre studies with a relatively small sample sizes and therefore, may overestimate the benefits of TAVI without pre-implantation BAV and may be subject to significant selection biases. Hence, we sought to undertake a systematic review and meta-analysis to study the clinical outcomes associated with TAVI procedures performed with and without pre-implantation BAV in order to gain insight into optimal practice during TAVI procedures.

METHODS

Eligibility criteria

We included studies that evaluated patients who underwent TAVI with and without pre-implantation (pre-procedural) BAV for predilation. Studies included in the meta-analysis had to be parallel group in design with one group having TAVI with pre-implantation BAV and the other having TAVI without pre-implantation BAV. We also included single-arm studies that evaluated the feasibility of performing TAVI without pre-implantation BAV. In terms of outcomes, included studies must have evaluated procedural/device success and one or more of

the following events: need for post-implantation balloon postdilation, valve embolization, need for a second valve, vascular complications, bleeding, neurological events (stroke or transient ischemic attack [TIA]), acute kidney injury (AKI), permanent pacemaker implantation (PPI), significant residual aortic regurgitation (AR) or paravalvular leaks (PVL), and mortality. Early safety endpoint, when available, was reported in accordance to Valve Academic Research Consortium-2 (VARC) definitions.[3] Briefly, all-cause mortality (at 30 days), all stroke (disabling and non-disabling), life-threatening bleeding, AKI stage 2 or 3 (including renal replacement therapy), coronary artery obstruction requiring intervention, major vascular complication, valve-related dysfunction requiring repeat procedure (BAV, TAVI or surgical valve replacement). The reporting of outcomes had to include either crude events in each group or any risk/odds estimate (relative risk [RR], hazard ratio, odds ratio) with 95% confidence interval (CI). There was no restriction based on the design of the study or duration of follow-up. We excluded reports where BAV may have been performed weeks/months before TAVI (so called bridge-to-TAVI procedure), as well as isolated case reports, reviews and editorials.

Search strategy

We conducted a search of MEDLINE and EMBASE from conception to September 20th, 2015 using OvidSP. The exact search terms used were: ("transcatheter aortic valve implantation" OR "TAVI" OR "transcatheter aortic valve replacement" OR "TAVR") AND ("Balloon aortic valvuloplasty"). There was no restriction based on language of study and both abstracts and unpublished studies were included. The references of the included studies and relevant reviews were checked for additional studies. A flow diagram is provided following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), Figure 1.

Study selection

Two reviewers (RB and CSK) independently checked all titles and abstracts for studies that met the inclusion criteria. 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 consensus after consulting a third reviewer (MAM).

Quality assessment

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. Publication bias was assessed using funnel plots when there were >10 studies in a meta-analysis and there was no evidence of substantial statistical heterogeneity.[4]

Data analysis

We used RevMan (version 5.1.7, Nordic Cochrane Centre, Copenhagen, Denmark) to perform random effects meta-analysis using the Mantel-Haenszel method to determine pooled risk ratios for dichotomous data. The I^2 statistic was used to assess the consistency among studies, with I^2<25% considered low, $I^2$50% moderate, and I^2>75% high heterogeneity. 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 analyses were further performed according to the access site and type of valve for meta-analysis.

RESULTS

Study population

A total of 16 studies[5-20] including 1395 patients fulfilled the inclusion criteria (Figure 1). The sample size, age, sex, hemodynamic echocardiographic data, predicted operative mortality risk evaluation scores and some of the baseline characteristics are described in Table 1. Among the

studied populations, TAVI was performed without pre-implantation BAV in 721 patients and with pre-implantation BAV in 674 patients. The mean age was 81.3 years and 49.6% were female from 14 studies that reported both age and gender.[5-9,11,14-20] The balloon-expandable Edwards SAPIEN-XT® or SAPIEN-3® valve were implanted in 10 studies[6,10-12,14,16-20] including 793 patients and the self-expandable Medtronic CoreValve® in 7 studies[5,7-9,13,15,17] including 602 patients. One study included both types of bioprostheses.[17] The transfemoral access was exclusively used in 8 studies,[5,7,8,12,14,17,18,20] either transfemoral, trans-subclavian or direct aortic access in 4 studies,[9,10,13,15] transapical access in 3 studies[6,11,16] and transfemoral or transapical access in 1 study.[19] There were 4 prospective cohort studies,[5,7,9,10] 4 cohort studies,[6,8,13,17] 3 retrospective cohort studies,[11,12,19] 2 case-matched studies,[15,18] 2 case-control studies[14,20] and 1 propensity-matched study.[16]

Study designs and quality assessment

The study designs, time frame, country of origin and quality assessment for included studies are reported in Table 2. Ascertainment of outcomes varied from medical record reviews to prospective evaluation with adjudicated clinical end-points. All studies contained reliable data and there was no loss to follow-up. Follow-up of patients varied from in-hospital outcomes, clinical visits, echocardiographic assessment and telephone calls up to 12 months from the date of implant.

Association of pre-implantation BAV versus no-BAV and outcomes

Device type, access site, procedure-related outcomes and follow-up assessment for all included studies reporting crude rate of events are summarized in Table 3. A pooled analysis reporting crude rates outcome of studies without pre-implantation BAV and with BAV according to the valve type is shown in Table 4. Further separate analyses were performed including only studies

undergoing TAVI without pre-implantation BAV (Table 5) and with pre-implantation BAV (Table 6).

In-hospital and 30-day outcomes

Crude device success rate was reported in all studies[5-20] and achieved in 94% (1311/1395) of patients without differences between the valve types. The crude all-cause mortality at 30 days was reported in 15 studies[5-11,13-20] and occurred in 6% (72/1282) of patients. The safety composite endpoint was reported in 6 studies[7,9,11,12,18,19] and occurred in 21% (111/537) of patients. The crude incidence of residual moderate/severe AR or PVL was reported in 9 studies[5-9,12-14] and occurred in 16% (124/757) of patients. In this regard, 4 studies used the balloon-expandable valve[6,12,14,20] with a 3% (9/262) rate and 5 studies the self-expandable valve[5,7-9,13] with a 23% (115/495) rate. Of note, the need for post-implantation postdilation was reported in 14[5-9,11-19] studies and occurred in 18% (210/1177) of patients; 9 studies with the balloon-expandable valve[6,11-14,16-19] with a 14% (118/864) rate and 6 studies with the self-expandable valve,[5,7-9,13,15] with a 29% (92/313) rate. The crude cerebrovascular events, including stroke or TIA, were reported in 12 studies[5,7-11,15-20] and occurred in 3% (28/1014) of patients; 7 studies with the balloon-expandable[10,11,16-20] valve with a 3% (24/701) rate and 5 studies with the self-expandable valve[5,7-9,15] with a 1% (4/313) rate. The need for PPI was reported in 12[5,7-11,14-19] studies and occurred in 12% (117/983) of patients; 7 studies with the balloon-expandable valve[10,11,14,16-19] with a 9% (60/670) rate and 5 studies with the self-expandable valve[5,7-9,15] with an 18% (57/313) rate.

Importantly, meta-analyses evaluating outcomes between pre-implantation BAV versus without BAV strategies showed no statistically significant differences. Notably, device success (RR: 1.02, 95%CI: 0.98-1.06, P=0.24), mortality (RR: 0.61, 95%CI: 0.32-1.14, P=0.12), safety composite endpoint (RR: 0.85, 95%CI: 0.62-1.18, P=0.34), moderate-to-severe PVL (RR: 0.68,

95%CI: 0.23-1.99, P=0.48), need for post-implantation postdilation (RR: 0.86, 95%CI: 0.66-1.13, P=0.28), stroke/TIA (RR: 0.72, 95%CI: 0.30-1.71, P=0.45), PPI (RR: 0.80, 95%CI: 0.49-1.30, P=0.37), or AKI (RR: 1.10, 95%CI: 0.49-2.45, P=0.82). The remaining outcomes can be appreciated in Tables 4 to 6.

Sensitivity analysis

We conducted a sensitivity analysis for clinical outcomes comparing pre-implantation BAV versus without BAV according to the different access sites; thus, comparing the transfemoral with transapical and transfemoral or any other access including the direct aortic and trans-subclavian routes (Table 7, Figures 2 to 4). Those who underwent TAVI without pre-implantation BAV and using the transfemoral or any other access were marginally associated with more cardiac tamponade (RR: 3.61, 95%CI: 1.04-12.56, P=0.04). Studies including the transfemoral access-only were associated with higher mortality among patients who underwent TAVI with pre-implantation BAV (RR, 0.30; 95% CI, 0.11-0.82, P=0.02); however, this difference disappeared when analysed as a whole access-site sample (RR, 0.61; 95% CI, 0.32-1.14, P=0.12).

We also performed sensitivity analysis according to the valve type (Table 8, Figures 5 to 7). The self-expandable valve tended to be associated with more cardiac tamponade (RR: 3.64, 95%CI: 0.94-14.14, P=0.06) when the procedure was performed without pre-implantation BAV and became significant when analysed with the whole type of valve sample (RR: 3.61, 95%CI: 1.04-12.56, P=0.04).

No significant differences were found between the different access sites and valve types in the remaining analyzed variables. Importantly, neither the access site nor the valve type affected the device success rate, safety composite endpoint or mortality (Tables 7 and 8).

DISCUSSION

The results of this meta-analysis show no significant differences between patients undergoing TAVI either with or without pre-implantation BAV with respect to mortality, neurologic events, PPI, or improvement in device success (including repeat procedure, significant residual PVL or AR and the need for post-implantation postdilation).

Rationale and adjunctive utilities of pre-implantation BAV during TAVI

Due to the pathophysiology of the aortic stenosis/calcification, it would be reasonable to hypothesise that crossing the heavy calcified valve by the transapical-antegrade approach would not require predilation.[6,11,16,19] In contrast, in transfemoral or other retrograde procedures, pre-implantation BAV remains important in ensuring a smooth crossing of the TAVI delivery system. Notably, our results show more cardiac tamponade without BAV, although one may be cautious while interpretation the results that are based on two studies-only.[13,14] Certainly, forceful pushing of the device and movement of the stiff-wire inside the ventricle might cause this issue. Importantly, even if the valve is successfully crossed with the TAVI system, failure to fully expand the transcatheter valve may translate into hemodynamic instability due to significant leaflet incompetence, significant PVL, valve migration or further need for postdilation with inherent risk of valve migration.[5,9,21] In fact, some studies reported the need for bailout BAV-predilation when TAVI was initially planned without pre-implantation BAV.[7-9,21] Moreover, partial balloon-tip inflation technique was reported to facilitate crossing the aortic valve.[10,12]

Coronary ostia less than 10-11 mm from the aortic annulus represents a hazardous problem for coronary obstruction,[22,23] especially in narrow/tubular or porcelain aortic roots exhibiting longitudinal remodelling.[22,24] In these cases, simultaneous aortogram at the time of BAV is helpful to assess the behavior of the heavily calcified aortic leaflets, especially the left-leaflet towards the left main.[9,22] Finally, performing pre-implantation BAV also allows confirmation of

reliable pacing-wire capture. Thus, in the case of capture failure, albeit rare, it is preferable to deal with this issue during BAV rather than during balloon-expandable valve deployment.

Residual aortic regurgitation and paravalvular leak

It is well known that the incidence of PVL is associated with worse short and long-term outcomes.[25-27] Our results show a higher pooled incidence of PVL with the self-expanding compared with the balloon-expandable valve, and these percentages remain much higher even if analysing groups with and without pre-implantation BAV separately. Indeed, these results are in line with previous reported evidence.[27,28] Interestingly, Fiorina and colleagues[9] reported a lower incidence of moderate-to-severe PVL without pre-implantation BAV; however, hemodynamics were not statistically different between the two strategies as assessed by aortic regurgitation index, likely due to a low incidence of severe PVL. It is quite provocative to promote that performing TAVI without pre-implantation BAV may reduce PVL, mostly using the self-expandable valve due to its delivery mechanism composed of a self-expanding Nitinol™ frame. With respect of the balloon-expandable bioprosthesis, PVL reduction might have been related due to a better understanding of valve sizing (and slight over-sizing) that progressed along the same learning curve that lead to confidence with direct implantation. In addition, some of the studies included the SAPIEN-3® bioprosthesis that comprises specific anti-PVL sealing design.

Need for post-implantation postdilation

According to our results, the self-expanding valve was associated with a crude 2-fold greater need for postdilation. Importantly, post-implantation postdilation can also cause device migration and thereby increase PVL,[9] as well as increasing the risk for annular rupture with a postdilation than with a predilation. Although avoiding BAV minimizes manipulating the severely calcified aortic annulus/native valve, it must be balanced with the potential need for more postdilation to

correct a significant residual PVL. Furthermore, the impact of postdilation on the long-term valve outcome remains unknown.

Aortic valve calcification assessment to plan TAVI without pre-implantation BAV

The degree and distribution of aortic valve calcification and annular morphology has been correlated with post-procedural PVL.[29-32] Moreover, the location and/or asymmetry of this calcification, more often located at the non-coronary cusp and/or device-landing zone, is more important than the total calcium load.[20,29,31] Interestingly, Mollmann and colleagues[14] showed no differences in the extent of valve calcification as assessed by Agatston score among patients treated with the two strategies. In addition, they found no correlation between the aortic valve area and load of calcification with the duration of the procedure, fluoroscopy time, radiation dose, or contrast amount. Similarly, Fiorina et al.[9] found no correlation between residual PVL and the degree of calcification in the device-landing zone among those who received TAVI without pre-implantation BAV. Of note, the authors also reported that among patients who received pre-implantation BAV, the bigger the prosthesis size, the higher incidence of significant PVL although that relationship was not observed in patients where TAVI was undertaken without pre-implantation BAV.[9]

Islas and colleagues[17] reported favourable/unfavourable features relevant to the decision to perform TAVI without pre-implantation BAV using 3-dimentional transesophageal echocardiography. Notably, unfavourable features include: a heavy or severely aortic valve calcification defined as leaflet thickness >5 mm, with large nodules and diffuse calcification of the aortic annulus; an asymmetric and bulky calcification distribution; valve area <0.4 cm^2 with an eccentric and/or irregular orifice; moderate or severe restricted mobility; presence of calcification nodules at the left ventricle outflow tract or close to coronary ostia; moderate AR. In this regard, Bijuklic et al.[20] also reported that in cases of severe, asymmetric aortic valve

calcification or a tight aortic effective orifice area (planimetry ≤0.5 cm^2) as assessed by intra-procedural transesophageal echocardiography, pre-implantation BAV was performed even if the newest-generation lower profile Edwards SAPIEN-3 was available.

Neurologic events

It has been hypothesized that TAVI without pre-implantation BAV may be associated with fewer embolic events, especially less cerebrovascular accidents. Strikingly, relatively low stroke rates have been reported with the two strategies and by the two TAVI devices. The different technique by which the balloon-expandable valve is deployed, more often oversized, as compared with the self-expandable (less aggressive expansion technique) may explain the higher potential for calcific embolization. In this regard, the new-generation balloon-expandable Edwards SAPIEN-3 requires less over expansion compared to SAPIEN-XT. However, most of the analysed studies failed to support avoiding pre-implantation BAV strategy with reduced neurological complications. Moreover, Aggarwal and colleagues[12] reported no differences between groups in terms of embolic load based on transcranial Doppler; including number in solid, gaseous or total emboli (P>0.05 for all). In addition, Bijuklic et al.[20] showed no difference in terms of silent embolic events as assessed by diffusion-weighted cerebral magnetic resonance. Interestingly, a large volume was observed among those undergoing TAVI without pre-implantation BAV. Importantly, the authors reported that 4 patients experienced stroke, 3 of them without pre-implantation BAV and 1 patient with pre-implantation BAV. Nonetheless, due to the exclusion criteria stated in their methodology, these patients were excluded from their analysis due to a clinical apparent stroke within 3 days after TAVI.[20]

Potential benefits of TAVI without pre-implantation BAV

Pre-implantation BAV might be poorly tolerated in certain patients. The time between BAV predilation and TAVI is a particularly crucial period, especially in patients with pre-existing

severe left ventricular systolic dysfunction and/or pulmonary hypertension. Moreover, the temporary interruption in ventricular output during rapid ventricular pacing and BAV outflow occlusion itself can result in hemodynamic compromise. Furthermore, significant AR following BAV can precipitate clinically significant instability even in patients with normal left ventricular function and this hemodynamic deterioration can be sudden, profound, and not entirely predictable. Thus, the special subset of patients presenting with and/or prone to a significant hemodynamic instability, can certainly experience multi-organ hypoperfusion, mainly cerebral and renal. Hence, avoiding a rapid pacing run for BAV may prevent an unnecessary period of hypotension in certain cases.

On the other hand, it is logical that performing TAVI without pre-implantation BAV is associated with a reduction in contrast volume,[6,11,14,18,20] fluoroscopy time,[12,16,18] radiation dose[14] or total procedural time.[6,17,20] However, the clinical impact of these differences is uncertain.

Limitations

The present study has several limitations. The main limitation lies with the small number of patients within each study, and the non-randomized nature of the included studies that may introduce selection bias. Importantly, the decision to predilate or not was at the discretion of the TAVI team operator/s, and may relate to the complexity of the valve anatomy and the operator's perception of successful valve delivery; hence, it is possible that BAV was undertaken in more complex and challenging cases making comparison of outcomes subject to selection bias. Also, patient-level data was not available for this analysis, precluding therefore a more robust adjustment for any differences in clinical/anatomical variables. Nevertheless, in studies where clinical demographics and anatomical features of the patients were reported, these variables were relatively well matched in both BAV/non-BAV studied cohorts. Notably, many of the studies included in this analysis lack data around whether patients had hemodynamic compromise and/or

poor left ventricle function necessitating BAV prior to the index TAVI event (bridge-to-TAVI). Finally, patients exhibiting major comorbidities and clinical uncertain benefit from TAVI may have been offered BAV as a potential bridge or palliation due to an adverse profile, with subsequent definitive treatment (TAVI) offered after significant improvement.

CONCLUSION

Our analysis suggests that TAVI procedures with or without pre-implantation BAV were associated with similar outcomes in a number of clinically relevant endpoints. Further studies including large number of patients are needed to ascertain the impact of TAVI without pre-implantation BAV as a standard practice. Meanwhile, our findings provide real-world data that may contribute to the current practice of TAVI operators as well as influence future perspectives. Notably, a more "simplified procedure" can be safely performed and achieving comparable results.

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Table 1. Characteristics of the study population

Study ID	Without BAV	Age Female	Mean gradient AVA (cm^2) LVEF	EuroSCORE STS-PROM	With BAV	Age Female	Mean gradient AVA (cm^2) LVEF	EuroSCORE STS-PROM	Differences between baseline characteristics
Grube et al.[5] 2011	60	80.1±6.4 53.3%	47.8±15.5 0.66±0.2 NA	23.3±15.2 NA	-	-	-	-	-
Wendler et al.[6] 2012	6	82±3 33%	49±5 0.6±0.18 NA	30±12 NA	-	-	-	-	-
Mendiz et al.[7] 2013	51	79±8 65%	80±22 (peak) 0.7±0.2 56±10%	20±15 NA	-	-	-	-	-
Ruck et al.[8] 2013	78	NA	NA	19 NA	-	-	-	-	-
Fiorina et al.[9] 2014	55	83±7 51%	44±13 0.39±0.1* 49±13%	27±18 10±8*	45	83±8 44%	48±16 0.36±0.1* 49±13%	22±14 7±4*	- Indexed AVA, P=0.09. - STS score, P=0.03 - Prior MI 20% no-BAV vs. 6% in BAV, P=0.05
Davies et al.[10] 2014	12	83±3 50%	56±19 (peak) 0.7±0.2 56±19%	23±12 6±3	-	-	-	-	-
Conradi et al.[11] 2014	50	78±8 46%	28±14 0.9±0.4 NA	21±14 8±7	50	81±7 52%	31±17 0.8±0.2 NA	23±13 8±5	Similar
Aggarwal et al.[12] 2014	52	NA	NA	NA NA	61	NA	NA	NA NA	NA
Giustino et al.[13] 2014	73	NA	NA	NA NA	133	NA	NA	NA NA	Similar
Möllmann et al.[14] 2014	26	81.6±6.5 42.3%	36.0±17.3* 0.7±0.2 55%*	24.6±8.7 6.2±2.7	30	82.2±5.4 43.3%	48.5±17.7* 0.6±0.2 60%*	21.4±12.1 6.2±3.1	- LVEF 55% [IQR 35.0-60.0%] in non-BAV vs. 60% [IQR 53.8-65.0%] in BAV group, P=0.01 - Mean gradient, P=0.01

Kochman et al.[15] 2014	8	78.1±8.4 50%	46.0±14.1 0.58±0.15 38.4%	20±6 NA	16	83.3±3.7 31.3%	55.9±12.0 0.59±0.17 46.8%	19±7 NA	Similar
Kempfert et al.[16] 2015	40	79 30%	42 NA 52%	NA 7.62	40	80 30%	40 NA 51%	NA 7.22	Differences were observed between the no-BAV and BAV group before adjustment for variables male sex (52% vs. 70%, P=0.05), stroke (23% vs. 7%, P=0.01). The cohorts were similar after propensity score matching.
Islas et al.[17] 2015	79†	82.4±5.5 65.7%	47.3±14.7 0.6±0.2 56.9±12.5%	18.6±9.8 NA	170¥	82.8±5.7 64.7%	50.1±17.7 0.7±0.2 58.7±13.4%	17.9±9.6 NA	Similar
Conradi et al.[18] 2015	26	81.3±6.3 61.5%	38±14 0.8±0.2 19% ≤45%†	15±13 6±3	26	81.7±5.2 61.4%	42±17 0.7±0.2 15% ≤45%†	15±12 5±2	Similar
Wong et al.[19] 2015	50	84.3±6.6 58%	44±13 0.7±0.2 50±14%	NA 8.5±4.6	71	84.4±7.5 46%	51±14 0.7±0.2 49±15%	NA 9.4±5.3	In the transfemoral BAV group, smoking was 42% vs. 68% in transapical no-BAV (P=0.005), peripheral vascular disease was 20% vs. 38% in transapical no-BAV (P=0.03). AV calcification tended to be higher (P=007) in the transfemoral BAV vs. the transapical no-BAV group. Conversely, the transfemoral no-BAV tended to have more (P=007) porcelain aorta than the transfemoral BAV group.
Bijuklic et al.[20] 2015	55	82.9±6.8 47.3%	40.0±12.7 0.71±0.2 53.0±13.8%	21.4±15.1 NA	32	83.8±5.2 56.2%	40.5±13.4 0.71±0.2 57.2±11.9%	23.7±16.0 NA	Similar

Values are expressed as number of patients for NO-BAV: without pre-implantation balloon-aortic valvuloplasty and BAV: with pre-implantation balloon-aortic valvuloplasty. Values are expressed as mean±SD for age, mean gradient (mmHg), AVA: aortic valve area. LVEF: left ventricle ejection fraction, †percentage of

patients with LVEF ≤45%. Log-EuroSCORE: logistic European system for cardiac operative risk evaluation and STS-PROM: Society of Thoracic Surgeons Score for Prediction of Mortality. NA: not available. MI: myocardial infarction. †Edwards SAPIEN-XT, n=51 and Medtronic CoreValve, n=28. ¥Edwards SAPIEN-XT, n=115 and Medtronic CoreValve, n=55. Asterisk (*) highlights variables where some difference was encountered. IQR: interquartile range.

Table 2. Design and quality assessment of included studies

Study ID and year of publication	Design; dates; country	Ascertainment of treatment group	Ascertainment of outcomes	Loss to follow-up	Adjustment for confounders
Grube et al.[5] 2011	Prospective cohort study; 2009 to 2010; International	Reliable	Follow-up by clinical visits and echocardiography	None	None, crude results
Wendler et al.[6] 2012	Cohort study; Unclear; United Kingdom	Reliable	Assessment at 30 days	None	None, crude results
Mendiz et al.[7] 2013	Prospective cohort study; May 2010 to May 2012; Argentina	Reliable	Follow-up by clinical visits, echocardiography and telephone calls	None	None, crude results
Ruck et al.[8] 2013	Cohort study; started September 2012; Sweden	Reliable	Unclear	None	None, crude results
Fiorina et al.[9] 2014	Prospective cohort study; June 2012 to June 2013; Italy	Reliable	Follow-up by clinical visits and echocardiography	None	None, crude results
Davies et al.[10] 2014	Prospective cohort study; Unclear; United Kingdom	Reliable	Unclear	None	None, crude results
Conradi et al.[11] 2014	Retrospective cohort study; May 2011 to December 2012; Germany	Reliable	Clinical endpoints were adjudicated	None, retrospective	None, crude results
Aggarwal et al.[12] 2014	Retrospective cohort; March 2012 to April 2014; United Kingdom	Reliable	Unclear	None, retrospective	None, crude results
Giustino et al.[13] 2014	Cohort study; November 2007 to September 2013; Italy	Reliable	Assessment at 30 days and 12 months	None	None, crude results
Möllmann et al.[14] 2014	Case-control study; Unclear; Germany	Reliable	Assessment at 30 days	None	None, crude results
Kochman et al.[15] 2014	Case-matched study; March 2010 to April 2013; Poland	Reliable	Follow-up by clinical visits at 30 days, 6 months and 12 months	None	Case-matched analysis
Kempfert et al.[16] 2015	Propensity-matched analysis; March 2012 to July 2013; Germany	Reliable	Clinical follow-up at 30 days	None	Propensity matched analysis

Islas et al.[17] 2015	Cohort study; January 2009 to August 2014; Spain	Reliable	Clinical follow-up at 30 days	None	None, crude results
Conradi et al.[18] 2015	Case-matched study; Unclear; Germany	Reliable	Clinical endpoints were adjudicated	None, retrospective	Matched by logistic regression and nearest neighbours
Wong et al.[19] 2015	Retrospective cohort; May 2012 to December 2013; United States	Reliable	Follow-up by clinical visits	None, retrospective	None, crude results
Bijuklic et al.[20] 2015	Case-control study; Unclear; Germany	Reliable	Follow-up at 30 days	None, retrospective	None, crude results

Table 3. Procedure-related and clinical outcomes

Study ID and year of publication	Type of valve Approach	Time-frame of assessment	Assessment definitions	Outcomes	NO-BAV	BAV
Grube et al.[5] 2011	CoreValve Transfemoral	30-day	VARC	Procedural success Need for a second valve Conversion to surgery Postdilation Moderate/severe AR Myocardial infarction Stroke/TIA Pacemaker implantation Major vascular complication All-cause mortality	58/60 (96.7) 1/60 (1.7) 1/60 (1.7) 10/60 (16.7) 0/60 (0) 0/60 (0) 3/60 (50) 7/60 (11.7) 6/60 (10) 4/60 (6.7)	NA
Wendler et al.[6] 2012	SAPIEN-XT Transapical	30-day	VARC	Procedural success Postdilation Moderate/severe AR Trivial or mild AR Acute kidney injury All-cause mortality	6/6 (100) 0/6 (0) 0/6 (0) 3/6 (50) 1/6 (16.7) 0/6 (0)	NA
Mendiz et al.[7] 2013	CoreValve Transfemoral	12-month	VARC	Device success Need for bailout BAV predilation[#] Postdilation Moderate AR Pacemaker implantation Major vascular complication Cardiac tamponade Conversion to surgery Stroke Combined safety endpoint 30-day mortality 7-month (median time) mortality	48/51 (94.2) 1/51 (1.96) 16/51 (31.4) 1/51 (1.96) 14/49 (28.6) 3/51 (5.9) 1/51 (1.96) 1/51 (1.96) 1/51 (1.96) 8/51 (15.7) 2/51 (3.9) 7/51 (13.7)	NA
Ruck et al.[8]	CoreValve	In-hospital or	Unclear	Procedural success	77/78 (98.7)	NA

2013	Transfemoral	30-day		Need for bailout BAV predilation[#] Postdilation Need for a second valve Moderate AR Severe AR Myocardial infarction Stroke Pacemaker implantation 30-day mortality	1/78 (1.3) 19/78 (24.4) 14/78 (17.9) 11/78 (14.1) 0/78 (0) 0/78 (0) 0/78 (0) 20/78 (25.6) 5/78 (6.4)	
Fiorina et al.[9] 2014	CoreValve Transfemoral or Direct Aortic	30-day	VARC-2	Device success Need for bailout BAV predilation[#] Need for a second valve Moderate or severe PVL Postdilation Myocardial infarction Stroke Acute kidney injury Major vascular complication Minor vascular complication Major bleeding Pacemaker implantation Safety endpoint All-cause mortality	47/55 (85.5)* 1/55 (1.8) 2/55 (3.6) 5/55 (9.1) 19/55 (34.5) 0/55 (0) 0/55 (0) 3/55 (5.5) 2/55 (3.6) 0/55 (0) 3/55 (5.5) 3/55 (5.5) 8/55 (14.5) 1/55 (1.8)	29/45 (64.4) - 2/45 (4.4) 15/45 (33)** 23/45 (51.1)¶ 0/45 (0) 0/45 (0) 1/45 (2.2) 1/45 (2.2) 4/45 (8.9) 1/45 (2.2) 7/45 (15.6)¶ 4/45 (8.9) 2/45 (4.4)
Davies et al.[10] 2014	SAPIEN-XT Transfemoral or Direct Aortic	Unclear	Unclear	Device success Bleeding needing transfusion Stroke Pacemaker implantation All-cause mortality	12/12 (100) 0/12 (0) 1/12 (8.3) 0/12 (0) 0/12 (0)	NA
Conradi et al.[11] 2014	SAPIEN-XT Transapical	30-day	VARC-2	Device success Postdilation Need for a second valve Conversion to surgery Stroke Myocardial infarction Major bleeding	47/50 (94) 4/50 (8) 1/50 (2) 1/50 (2) 1/50 (2) 0/50 (0) 1/50 (2)	43/50 (86) 2/50 (4) 1/50 (2) 0/50 (0) 3/50 (6) 0/50 (0) 1/50 (2)

				Major access site complications	1/50 (2)	1/50 (2)
				Acute kidney injury	1/50 (2)	2/50 (4)
				Pacemaker implantation	5/50 (10)	4/50 (8)
				Early safety endpoint	7/50 (14)	12/50 (24)
				All-cause mortality	2/50 (4)	5/50 (10)
Aggarwal et al.[12] 2014	SAPIEN-XT and SAPIEN-3 Transfemoral	NA	VARC-2	Device success	50/52 (96.1)	60/61 (98.3)
				Moderate or severe AR	3/52 (5.8)	3/61 (4.9)
				Postdilation	2/52 (4.0)	2/61 (3.4)
				Procedural safety	18/52 (34.6)	31/61 (50.8)
Giustino et al.[13] 2014	CoreValve Transfemoral, Direct Aortic or Subclavian	30-day and 12-month	VARC-2	Device success	73/73 (100)	133/133 (100)
				Cardiac tamponade	6/73 (8.2)§	3/133 (2.3)
				Moderate AR needing postdilation	36/73 (49.3)§§	47/133 (35.6)
				Acute kidney injury	14/73 (19.4)	43/133 (32.3)‡
				30-day all-cause mortality	4/73 (5.5)	4/133 (3.0)
				30-day cardiovascular mortality	4/73 (5.5)	2/133 (1.5)
				Long-term† all-cause mortality	17/73 (23.3)	24/133 (17.8)
				Long-term† cardiovascular mortality	13/73 (17.6)	18/133 (13.3)
Möllmann et al.[14] 2014	SAPIEN-XT Transfemoral	In-hospital and 30-day	VARC-2	Procedural success	26/26 (100)	30/30 (100)
				Postdilation	3/26 (11.5)	3/30 (10)
				Cardiac tamponade	1/26 (3.8)	0/30 (0)
				Moderate PVL	0/26 (0)	0/30 (0)
				Major vascular complication	2/26 (7.7)	0/30 (0)
				Pacemaker implantation	2/26 (7.7)	0/30 (0)
				Acute kidney injury	1/26 (3.8)	0/30 (0)
				30-day mortality	0/26 (0)	3/30 (10)
Kochman et al.[15] 2014	CoreValve Transfemoral or Subclavian	12-month	VARC-2	Device success	8/8 (100)	15/16 (93.8)
				Postdilation	3/8 (37.5)	2/16 (12.5)
				Life-threatening bleeding	1/8 (12.5)	0/16 (0)
				Major vascular complication	2/8 (25)	6/16 (37.5)
				Minor vascular complication	5/8 (62.5)	12/16 (75)
				Pacemaker implantation	2/8 (25)	4/16 (25)
				Myocardial infarction	0/8 (0)	1/16 (6)
				Stroke	0/8 (0)	0/16 (0)
				In-hospital mortality	0/8 (0)	1/16 (6)
				12-month mortality	1/8 (12.5)	2/16 (12.5)

Kempfert et al.[16] 2015	SAPIEN-XT Transapical	30-day	Unclear	Device success	40/40 (100)	40/40 (100)
				Need for a second valve	1/40 (2.5)	1/40 (2.5)
				Postdilation	4/40 (10)	6/40 (15)
				Mild or more residual PVL	4/40 (10)	3/40 (7.5)
				Stroke	0/40 (0)	0/40 (0)
				TIA	3/40 (7.5)	3/40 (7.5)
				Pacemaker implantation	1/40 (2.5)	2/40 (5)
				30-day mortality	1/40 (2.5)	3/40 (7.5)
Islas et al.[17] 2015	SAPIEN-XT (n=166) and CoreValve (n=83) Transfemoral	30-day	VARC-2	Procedural success	73 (92.3)	153 (90.1)
				Need for a second valve	3 (3.8)	9 (5.3)
				Conversion to surgery	2 (2.3)	9 (5.3)
				Postdilation	14 (17.7)	32 (18.8)
				Mild or more residual PVL	3 (3.8)	6 (3.5)
				Stroke	1 (1.2)	3 (1.7)
				Pacemaker implantation	5 (6.3)	24 (14.1)∫
				30-day mortality	2 (2.5)	20 (11.8)∫∫
Conradi et al.[18] 2015	SAPIEN-XT and SAPIEN-3 Transfemoral	30-day	VARC-2	Device success	25/26 (96.2)	24/26 (92.3)
				Need for a second valve	1/26 (3.8)	1/26 (3.8)
				Annular rupture	0/26 (0)	1/26 (3.8)
				Postdilation	0/26 (0)	3/26 (11.5)
				Myocardial infarction	0/26 (0)	0/26 (0)
				Stroke	1/26 (3.8)	2/26 (7.7)
				Major or life-threatening bleeding	2/26 (7.7)	2/26 (7.7)
				Major access site complications	2/26 (7.7)	3/26 (11.5)
				Acute kidney injury	3/26 (11.5)	0/26 (0)
				Pacemaker implantation	4/26 (15.4)	4/26 (15.4)
				30-day mortality	2/26 (7.7)	2/26 (7.7)
				Early safety	4/26 (15.4)	5/26 (19.2)
Wong et al.[19] 2015	SAPIEN and SAPIEN-XT Transfemoral or Transapical	30-day	VARC-2	Device success	47/50 (94)	63/71 (88.7)
				Valve embolization	1/50 (2)	0/71 (0)
				Annular rupture	0/50 (0)	1/71 (1.4)
				Postdilation	15/50 (30)	24/71 (34)
				Myocardial infarction	0/50 (0)	0/71 (0)
				Stroke	0/50 (0)	2/71 (2.8)
				Bleeding complications	4/50 (8.0)	2/71 (2.8)

				Vascular complications	2/50 (4)	2/71 (2.8)
				Transfusions	28/50 (56)√	17/71 (23.9)
				Acute kidney injury	3/50 (6)	2/71 (2.8)
				Pacemaker implantation	5/50 (10)	4/71 (5.6)
				30-day all cause mortality	4/50 (8)	3/71 (4.2)
				Cardiac mortality	3/50 (6)	3/71 (4.2)
				Composite safety	7/50 (14)	7/71 (9.9)
Bijuklic et al.[20] 2015	SAPIEN-XT and SAPIEN-3 Transapical	30-day	VARC-2	Device success	54/55 (98.2)	30/32 (93.5)
				Postdilation	3/55 (5.5)	1/32 (3.1)
				Moderate PVL	1/55 (1.8)	2/32 (6.5)
				Myocardial infarction	0/55 (0)	0/32 (0)
				Stroke	3/58 (5.2)	1/33 (3.0)
				30-day all cause mortality	0/55 (0)	2/32 (2.8)

Values are expressed as the occurrence of an event/sample size and (%). NO-BAV: without pre-implantation balloon-aortic valvuloplasty. BAV: with pre-implantation balloon-aortic valvuloplasty. NA: not available. TIA: transient ischemic attack. AR: aortic regurgitation. PVL: paravalvular leakage. VARC-2: Valve Academic Research Consortium. *VARC-2 definitions: Device success:* absence of procedural mortality-correct positioning of a single prosthetic heart valve into the proper anatomical position-intended performance of the prosthetic heart valve (no prosthesis-patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s and no moderate or severe prosthetic valve regurgitation). *Early safety at 30 days:* all-cause mortality (at 30 days)-all stroke (disabling and non-disabling)-life-threatening bleeding-acute kidney injury stage 2 or 3 (including renal replacement therapy)-coronary artery obstruction requiring intervention-major vascular complication-valve-related dysfunction requiring repeat procedure (BAV-TAVI-or surgical aortic replacement).

[#]Bailout BAV predilation due to difficulties in crossing the aortic valve. *P=0.014. **P=0.02. ¶P=0.09. §P=0.078. §§P=0.056. ‡P=0.049. †Median time of 429 days. √P<0.001. ∫P=0.03. ∫∫P=0.018.

Table 4. Pooled analysis for adverse outcomes without and with pre-implantation BAV according to the valve type

Outcome	Studies	Cumulative	%	Studies	Edwards SAPIEN-XT or SAPIEN-3	%	Studies	Medtronic CoreValve	%
Device success	16	1311/1395	94%	10	823/876	94%	6	488/519	94%
Postdilation	14	210/1177	18%	9	118/864	14%	5	92/313	29%
Need for second valve	7	37/719	5%	4	18/481	4%	3	19/238	8%
Conversion to surgery	4	14/460	3%	2	12/349	3%	2	2/111	2%
Moderate or severe AR/PVL	9	124/757	16%	4	9/262	3%	5	115/495	23%
Mild AR/PVL	3	19/335	6%	3	19/335	6%	NA	NA	NA
Stroke/TIA	12	28/1014	3%	7	24/701	3%	5	4/313	1%
Myocardial infarction	8	1/622	0.2%	4	0/360	0%	4	1/262	0.4%
Major or life-threatening bleeding	6	17/409	4%	4	12/285	4%	2	5/124	4%
Annulus rupture	2	2/173	1%	2	2/173	1%	NA	NA	NA
Cardiac tamponade	3	11/313	4%	1	1/56	2%	2	10/257	4%
Acute kidney injury	7	74/641	12%	5	13/335	4%	2	61/306	20%
Pacemaker implantation	12	117/983	12%	7	60/670	9%	5	57/313	18%
Major vascular complications	6	26/412	6%	2	6/177	3%	4	20/235	9%
Minor vascular complications	2	21/124	17%	NA	NA	NA	2	21/124	17%
Safety composite endpoint	6	111/537	21%	4	91/386	24%	2	20/151	13%
Mortality	15	72/1282	6%	9	49/763	6%	6	23/519	4%

AR: aortic regurgitation. PVL: paravalvular leakage. TIA: transient ischemic attack.

Table 5. Analysis for adverse outcomes without pre-implantation BAV according to the valve type

Outcome	Studies	Cumulative	%	Studies	Edwards SAPIEN-XT or SAPIEN-3	%	Studies	Medtronic CoreValve	%
Device success	16	691/721	96%	10	380/396	96%	6	311/325	96%
Postdilation	14	112/636	18%	9	45/384	12%	5	67/252	27%
Need for second valve	7	23/388	6%	4	6/195	3%	3	17/193	9%
Conversion to surgery	4	5/240	2%	2	3/129	2%	2	2/111	2%
Moderate or severe AR/PVL	9	57/456	13%	4	4/139	3%	5	53/317	17%
Mild AR/PVL	3	10/125	8%	3	10/125	8%	NA	NA	NA
Stroke/TIA	12	14/564	2%	7	10/312	3%	5	4/252	2%
Myocardial infarction	8	0/382	0%	4	0/181	0%	4	0/201	0%
Major or life-threatening bleeding	6	11/201	5%	4	7/138	5%	2	4/63	6%
Annulus rupture	2	0/76	0%	2	0/76	0%	NA	NA	NA
Cardiac tamponade	3	8/150	5%	1	1/26	4%	2	7/124	2%
Acute kidney injury	7	26/286	9%	5	9/158	6%	2	17/128	13%
Pacemaker implantation	12	68/535	13%	7	22/283	8%	5	46/252	18%
Major vascular complications	6	17/250	7%	2	4/76	5%	4	13/174	7%
Minor vascular complications	2	5/63	8%	NA	NA	NA	2	5/63	8%
Safety composite endpoint	6	52/284	18%	4	36/178	20%	2	16/106	15%
Mortality	15	27/669	4%	9	11/344	3%	6	16/325	5%

AR: aortic regurgitation. PVL: paravalvular leakage. TIA: transient ischemic attack.

Table 6. Analysis for adverse outcomes with pre-implantation BAV according to the valve type

Outcome	Studies	Cumulative	%	Studies	Edwards SAPIEN-XT or SAPIEN-3	%	Studies	Medtronic CoreValve	%
Device success	11	620/674	92%	8	443/480	92%	3	177/194	91%
Postdilation	10	98/541	18%	8	73/480	15%	2	25/61	41%
Need for second valve	5	14/331	4%	4	12/286	4%	1	2/45	4%
Conversion to surgery	2	9/220	4%	2	9/220	4%	NA	NA	NA
Moderate or severe AR/PVL	5	67/301	22%	3	5/123	4%	2	62/178	35%
Mild AR/PVL	2	9/210	4%	2	9/210	4%	NA	NA	NA
Stroke/TIA	8	14/450	3%	6	14/389	4%	2	0/61	0%
Myocardial infarction	6	1/240	0.4%	4	0/179	0%	2	1/61	2%
Major or life-threatening bleeding	5	6/208	3%	3	5/147	3%	2	1/61	2%
Annulus rupture	2	2/97	2%	2	2/97	2%	NA	NA	NA
Cardiac tamponade	2	3/163	2%	1	0/30	0%	1	3/133	2%
Acute kidney injury	6	48/355	14%	4	4/177	2%	2	44/178	25%
Pacemaker implantation	8	49/448	11%	6	38/387	10%	2	11/61	18%
Major vascular complications	4	9/162	6%	2	2/101	2%	2	7/61	6%
Minor vascular complications	2	16/61	26%	NA	NA	NA	2	16/61	26%
Safety composite endpoint	5	59/253	23%	4	55/208	26%	1	4/45	9%
Mortality	10	45/613	7%	7	38/419	9%	3	7/194	4%

AR: aortic regurgitation. PVL: paravalvular leakage. TIA: transient ischemic attack.

Table 7. Sensitivity analysis with risk of outcomes without or with pre-implantation BAV according to the access site

Outcome or Subgroup	Studies	Patients	Risk Ratio (95%CI)
Device success	11	1188	1.02 (0.98-1.06)
Transfemoral	5	557	1.01 (0.97-1.04)
Transapical	2	180	1.04 (0.90-1.19)
Transfemoral or any other access	4	451	1.09 (0.87-1.36)
Postdilation	10	982	0.86 (0.66-1.13)
Transfemoral	5	557	0.95 (0.58-1.56)
Transapical	2	180	0.99 (0.35-2.78)
Transfemoral or any other access	3	245	0.87 (0.53-1.43)
Need for a second valve	5	581	0.82 (0.34-1.98)
Transfemoral	2	301	0.76 (0.24-2.42)
Transapical	2	180	1.00 (0.14-6.94)
Transfemoral or any other access	1	100	0.82 (0.12-5.58)
Conversion to surgery	2	349	0.69 (0.16-2.89)
Transfemoral	1	249	0.48 (0.11-2.16)
Transapical	1	100	3.00 (0.13-71.92)
Moderate or severe AR/PVL	4	506	0.68 (0.23-1.99)
Transfemoral	2	200	0.77 (0.21-2.82)
Transfemoral or any other access	2	306	0.65 (0.13-3.39)
Mild AR/PVL	2	329	1.19 (0.44-3.19)
Transfemoral	1	249	1.08 (0.28-4.19)
Transapical	1	80	1.33 (0.32-5.58)
Stroke/TIA	6	689	0.72 (0.30-1.71)
Transfemoral	3	388	0.87 (0.24-3.23)
Transapical	2	180	0.70 (0.20-2.49)
Transfemoral or any other access	1	121	0.28 (0.01-5.76)
Myocardial infarction	1	24	0.63 (0.03-13.93)
Transfemoral or any other access	1	24	0.63 (0.03-13.93)
Major or life-threatening bleeding	5	397	1.98 (0.76-5.18)
Transfemoral	1	52	1.00 (0.15-6.57)
Transapical	1	100	1.00 (0.06-15.55)
Transfemoral or any other access	3	245	3.03 (0.89-10.28)
Annulus rupture	2	173	0.40 (0.04-3.72)
Transfemoral	1	52	0.33 (0.01-7.82)
Transfemoral or any other access	1	121	0.47 (0.02-11.32)
Cardiac tamponade	2	262	3.61 (1.04-12.56)
Transfemoral	1	56	3.44 (0.15-81.09)
Transfemoral or any other access	1	206	3.64 (0.94-14.14)

Acute kidney injury	6	635	1.10 (0.49-2.45)
Transfemoral	2	108	5.05 (0.59-43.03)
Transapical	1	100	0.50 (0.05-5.34)
Transfemoral or any other access	3	427	0.98 (0.37-2.58)
Pacemaker implantation	8	782	0.80 (0.49-1.30)
Transfemoral	3	357	0.79 (0.29-2.17)
Transapical	2	180	1.02 (0.34-3.09)
Transfemoral or any other access	3	245	0.85 (0.32-2.25)
Major vascular complications	4	301	1.15 (0.45-2.99)
Transfemoral	1	56	5.74 (0.29-114.41)
Transfemoral or any other access	3	245	0.96 (0.35-2.63)
Minor vascular complications	2	124	0.38 (0.03-4.92)
Transfemoral or any other access	2	124	0.38 (0.03-4.92)
Safety composite endpoint	4	434	0.85 (0.62-1.18)
Transfemoral	1	113	0.68 (0.44-1.07)
Transapical	1	100	0.58 (0.25-1.36)
Transfemoral or any other access	2	221	1.02 (0.66-1.58)
Mortality	10	1075	0.61 (0.32-1.14)
Transfemoral	4	357	0.30 (0.11-0.82)
Transapical	2	180	0.38 (0.10-1.37)
Transfemoral or any other access	4	451	1.38 (0.58-3.32)

CI: confidence interval. AR: aortic regurgitation. PVL: paravalvular leakage. TIA: transient ischemic attack. Any other access: trans-subclavian or direct aortic

Table 8. Sensitivity analysis with risk of outcomes without or with pre-implantation BAV according to the valve type

Outcome or Subgroup	Studies	Patients	Risk Ratio (95%CI)
Device success	10	1101	1.02 (0.98-1.07)
SAPIEN	7	609	1.01 (0.98-1.04)
CoreValve	3	330	1.11 (0.69-1.78)
Postdilation	9	733	0.84 (0.62-1.14)
SAPIEN	7	609	0.92 (0.60-1.40)
CoreValve	2	124	1.17 (0.28-4.82)
Need for a second valve	4	332	0.92 (0.27-3.12)
SAPIEN	3	232	1.00 (0.21-4.84)
CoreValve	1	100	0.82 (0.12-5.58)
Conversion to surgery	1	100	3.00 (0.13-71.92)
SAPIEN	1	100	3.00 (0.13-71.92)
Moderate or severe AR/PVL	4	506	0.68 (0.23-1.99)
SAPIEN	2	200	0.77 (0.21-2.82)
CoreValve	2	306	0.65 (0.13-3.39)
Mild AR/PVL	1	80	1.33 (0.32-5.58)
SAPIEN	1	80	1.33 (0.32-5.58)
Stroke/TIA	5	440	0.72 (0.28-1.84)
SAPIEN	5	440	0.72 (0.28-1.84)
Myocardial infarction	1	24	0.63 (0.03-13.93)
CoreValve	1	24	0.63 (0.03-13.93)
Major or life-threatening bleeding	5	397	1.98 (0.76-5.18)
SAPIEN	3	273	1.63 (0.52-5.06)
CoreValve	2	124	3.27 (0.53-19.93)
Annulus rupture	2	173	0.40 (0.04-3.72)
SAPIEN	2	173	0.40 (0.04-3.72)
Cardiac tamponade	2	262	3.61 (1.04-12.56)
SAPIEN	1	56	3.44 (0.15-81.09)
CoreValve	1	206	3.64 (0.94-14.14)
Acute kidney injury	6	635	1.10 (0.49-2.45)
SAPIEN	4	329	1.93 (0.60-6.27)
CoreValve	2	306	0.79 (0.26-2.41)
Pacemaker implantation	7	533	0.98 (0.56-1.72)
SAPIEN	5	409	1.30 (0.66-2.57)
CoreValve	2	124	0.56 (0.20-1.56)
Major vascular complications	4	301	1.15 (0.45-2.99)
SAPIEN	2	177	2.14 (0.42-10.80)
CoreValve	2	124	0.83 (0.26-2.70)

Minor vascular complications	2	124	0.38 (0.03-4.92)
CoreValve	2	124	0.38 (0.03-4.92)
Safety composite endpoint	4	434	0.85 (0.62-1.18)
SAPIEN	3	334	0.79 (0.52-1.20)
CoreValve	1	100	1.64 (0.53-5.08)
Mortality	9	826	0.78 (0.41-1.48)
SAPIEN	6	496	0.52 (0.28-1.40)
CoreValve	3	330	1.15 (0.38-3.47)

CI: confidence interval. AR: aortic regurgitation. PVL: paravalvular leakage. TIA: transient ischemic attack. SAPIEN: includes SAPIEN-XT and SAPIEN-3 valves.

Figure legends

Figure 1. Flow diagram upon PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses). www.prisma-statement.org. BAV: balloon-aortic valvuloplasty. TAVI: transcatheter aortic valve implantation.

Figure 2. Meta-analyses evaluating A) device success, B) mortality, C) safety composite endpoint, D) need for a second valve, E) postdilation and F) major or life-threatening bleeding, between pre-implantation balloon-aortic valvuloplasty (BAV) versus without BAV according to the access site. M-H: Mantel-Haenszel, CI: confidence interval.

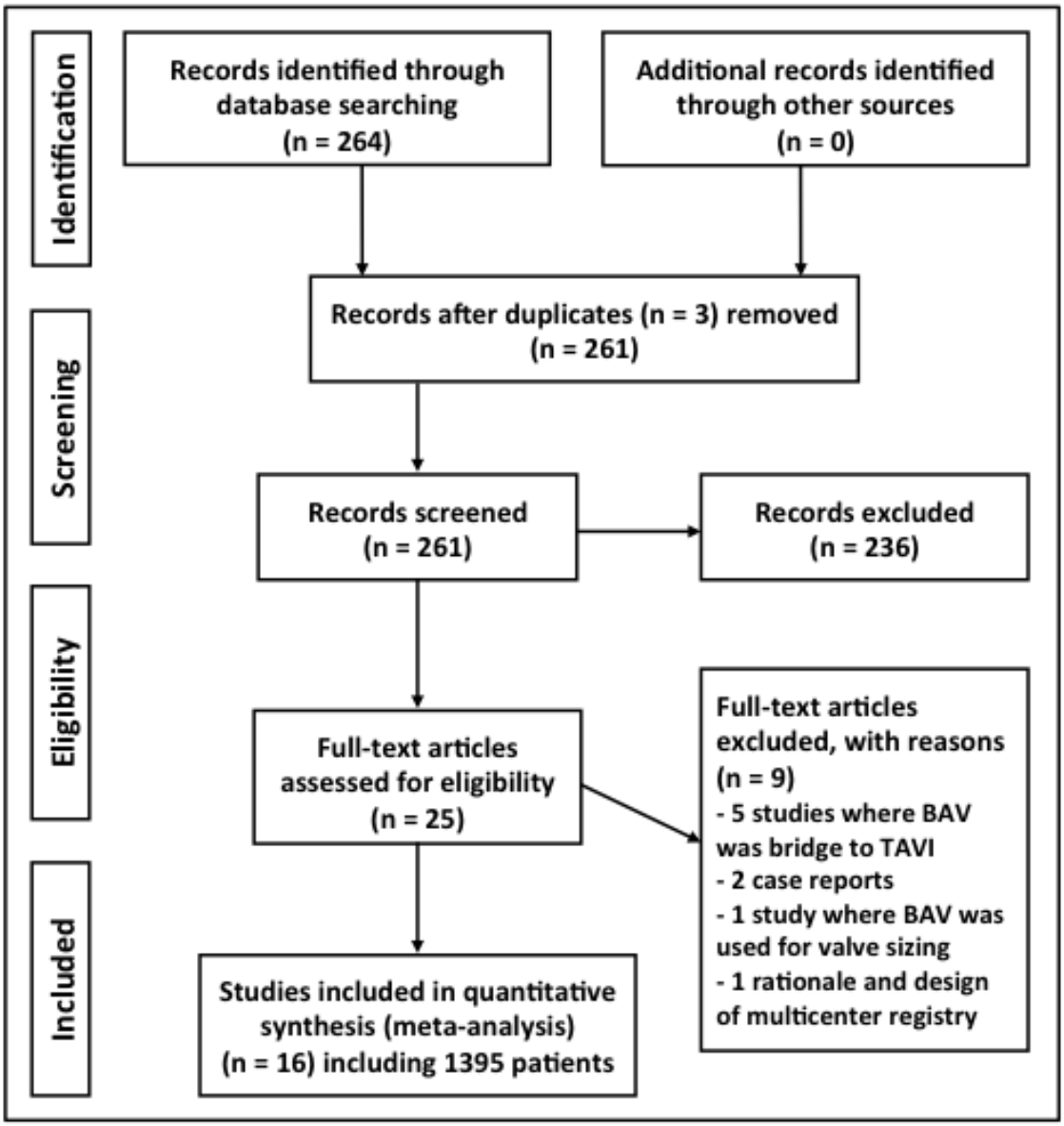
Figure 3. Meta-analyses evaluating the risk of A) annulus rupture, B) cardiac tamponade, C) conversion to surgery, D) major vascular complications, E) stroke or transient ischemic attack and F) acute kidney injury, between pre-implantation balloon-aortic valvuloplasty (BAV) versus without BAV according to the access site. M-H: Mantel-Haenszel, CI: confidence interval.

Figure 4. Meta-analyses evaluating the risk of A) significant paravalvular leakage, B) pacemaker implantation, C) minor vascular compilations and D) myocardial infarction, between pre-implantation balloon-aortic valvuloplasty (BAV) versus without BAV according to the access site. M-H: Mantel-Haenszel, CI: confidence interval.

Figure 5. Meta-analyses evaluating A) device success, B) mortality, C) safety composite endpoint, D) need for a second valve, E) postdilation and F) major or life-threatening bleeding, between pre-implantation balloon-aortic valvuloplasty (BAV) versus without BAV according to the valve type. M-H: Mantel-Haenszel, CI: confidence interval.

Figure 6. Meta-analyses evaluating the risk of A) cardiac tamponade, B) annulus rupture, C) conversion to surgery, D) stroke or transient ischemic attack, E) major vascular complications and F) acute kidney injury, between pre-implantation balloon-aortic valvuloplasty (BAV) versus without BAV according to the valve type. M-H: Mantel-Haenszel, CI: confidence interval.

Figure 7. Meta-analyses evaluating the risk of A) significant paravalvular leakage, B) pacemaker implantation, C) minor vascular compilations and D) myocardial infarction, between pre-implantation balloon-aortic valvuloplasty (BAV) versus without BAV according to the valve type. M-H: Mantel-Haenszel, CI: confidence interval.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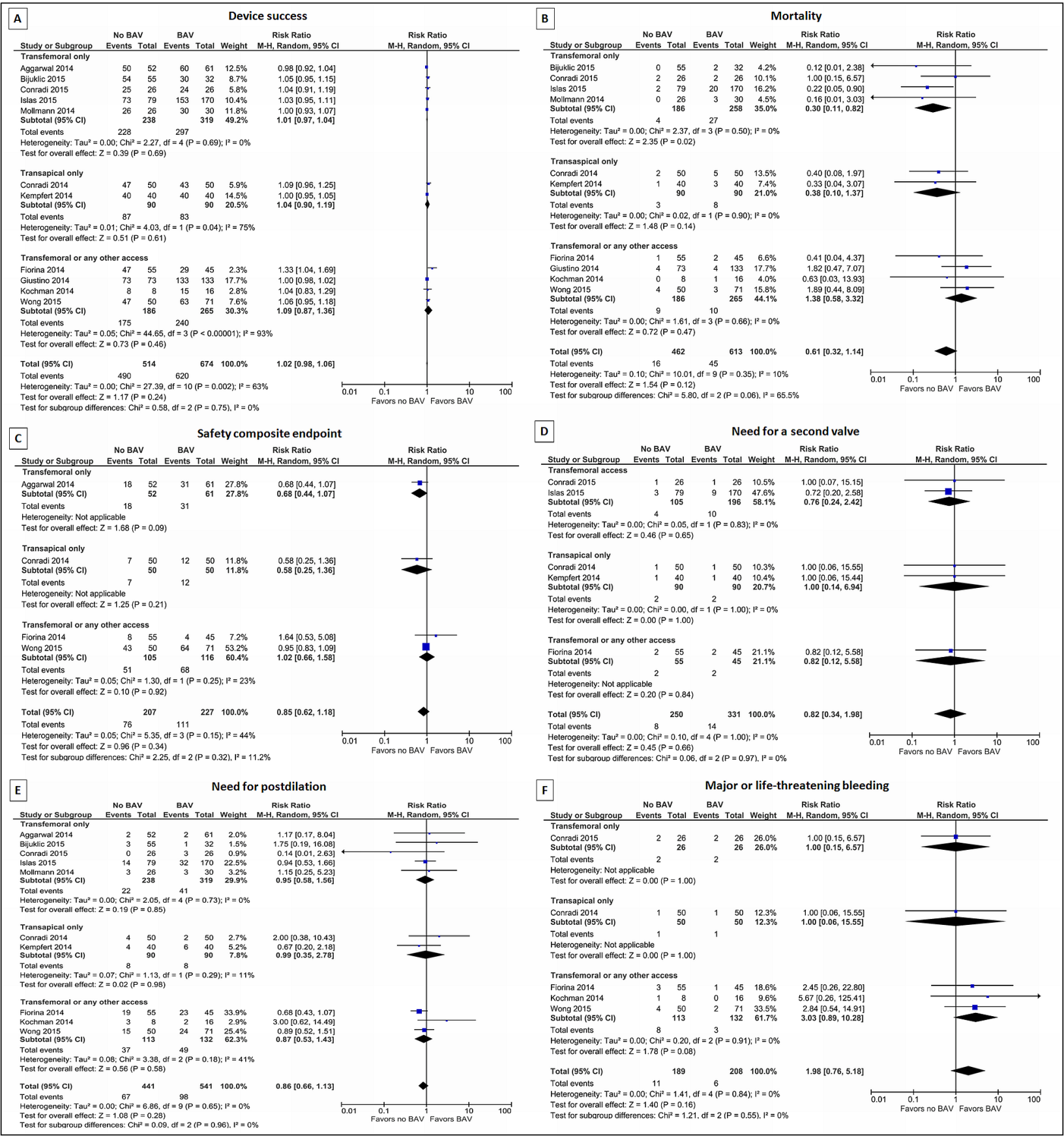
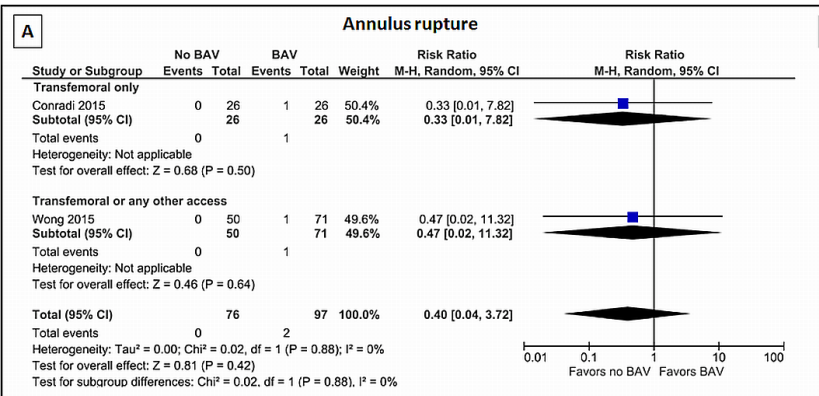
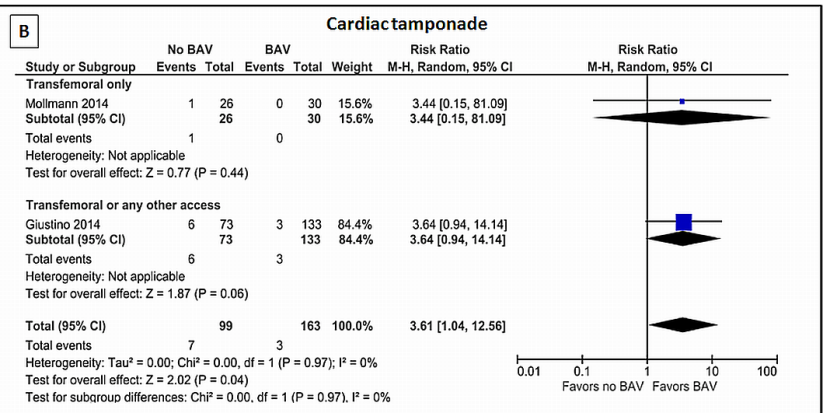
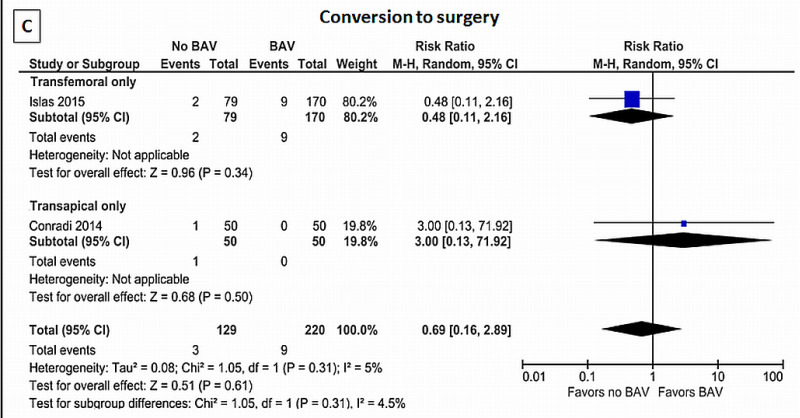
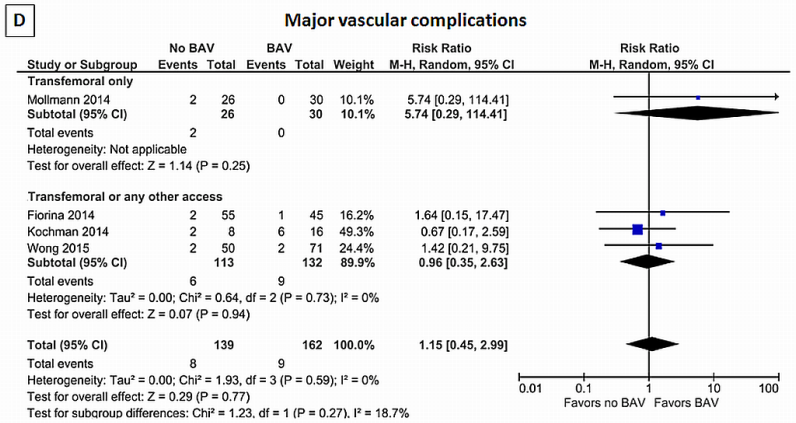
Records identified through database searching (n = 264)
Additional records identified through other sources (n = 0)
Screening
Records after duplicates (n = 3) removed (n = 261)
Records screened (n = 261)
Records excluded (n = 236)
Eligibility
Full-text articles assessed for eligibility (n = 25)
Full-text articles excluded, with reasons (n = 9)
- 5 studies where BAV was bridge to TAVI
- 2 case reports
- 1 study where BAV was used for valve sizing
- 1 rationale and design of multicenter registry
Included
Studies included in quantitative synthesis (meta-analysis) (n = 16) including 1395 patients

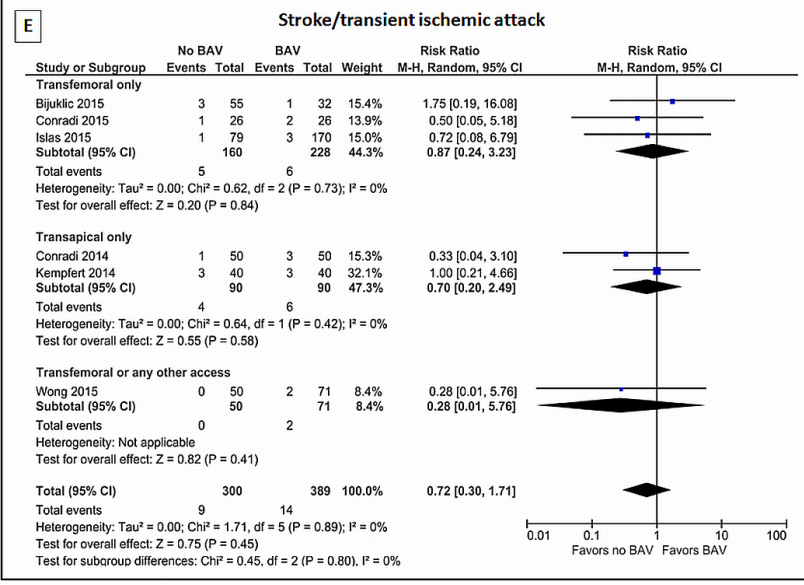

A
Device success
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral only
Aggarwal 2014 50 52 60 61 12.5% 0.98 [0.92, 1.04]
Bijuklic 2015 54 55 30 32 8.7% 1.05 [0.95, 1.15]
Conradi 2015 25 26 24 26 5.8% 1.04 [0.91, 1.19]
Islas 2015 73 79 153 170 10.4% 1.03 [0.95, 1.11]
Mollmann 2014 26 26 30 30 11.8% 1.00 [0.93, 1.07]
Subtotal (95% CI) 238 319 49.2% 1.01 [0.97, 1.04]
Total events 228 297
Heterogeneity: Tau² = 0.00; Chi² = 2.27, df = 4 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.69)
Transapical only
Conradi 2014 47 50 43 50 5.9% 1.09 [0.96, 1.25]
Kempfert 2014 40 40 40 40 14.5% 1.00 [0.95, 1.05]
Subtotal (95% CI) 90 90 20.5% 1.04 [0.90, 1.19]
Total events 87 83
Heterogeneity: Tau² = 0.01; Chi² = 4.03, df = 1 (P = 0.04); I² = 75%
Test for overall effect: Z = 0.51 (P = 0.61)
Transfemoral or any other access
Fiorina 2014 47 55 29 45 2.3% 1.33 [1.04, 1.69]
Giustino 2014 73 73 133 133 17.7% 1.00 [0.98, 1.02]
Kochman 2014 8 8 15 16 2.8% 1.04 [0.83, 1.29]
Wong 2015 47 50 63 71 7.6% 1.06 [0.95, 1.18]
Subtotal (95% CI) 186 265 30.3% 1.09 [0.87, 1.36]
Total events 175 240
Heterogeneity: Tau² = 0.05; Chi² = 44.65, df = 3 (P < 0.00001); I² = 93%
Test for overall effect: Z = 0.73 (P = 0.46)
Total (95% CI) 514 674 100.0% 1.02 [0.98, 1.06]
Total events 490 620
Heterogeneity: Tau² = 0.00; Chi² = 27.39, df = 10 (P = 0.002); I² = 63%
Test for overall effect: Z = 1.17 (P = 0.24)
Test for subgroup differences: Chi² = 0.58, df = 2 (P = 0.75), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
B
Mortality
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral only
Bijuklic 2015 0 55 2 32 4.2% 0.12 [0.01, 2.38]
Conradi 2015 2 26 2 26 10.1% 1.00 [0.15, 6.57]
Islas 2015 2 79 20 170 16.2% 0.22 [0.05, 0.90]
Mollmann 2014 0 26 3 30 4.5% 0.16 [0.01, 3.03]
Subtotal (95% CI) 186 258 35.0% 0.30 [0.11, 0.82]
Total events 4 27
Heterogeneity: Tau² = 0.00; Chi² = 2.37, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 2.35 (P = 0.02)
Transaspical only
Conradi 2014 2 50 5 50 13.5% 0.40 [0.08, 1.97]
Kempfert 2014 1 40 3 40 7.4% 0.33 [0.04, 3.07]
Subtotal (95% CI) 90 90 21.0% 0.38 [0.10, 1.37]
Total events 3 8
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.48 (P = 0.14)
Transfemoral or any other access
Fiorina 2014 1 55 2 45 6.6% 0.41 [0.04, 4.37]
Giustino 2014 4 73 4 133 17.7% 1.82 [0.47, 7.07]
Kochman 2014 0 8 1 16 4.0% 0.63 [0.03, 13.93]
Wong 2015 4 50 3 71 15.8% 1.89 [0.44, 8.09]
Subtotal (95% CI) 186 265 44.1% 1.38 [0.58, 3.32]
Total events 9 10
Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 3 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)
Total (95% CI) 462 613 100.0% 0.61 [0.32, 1.14]
Total events 16 45
Heterogeneity: Tau² = 0.10; Chi² = 10.01, df = 9 (P = 0.35); I² = 10%
Test for overall effect: Z = 1.54 (P = 0.12)
Test for subgroup differences: Chi² = 5.80, df = 2 (P = 0.06), I² = 65.5%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
C
Safety composite endpoint
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral only
Aggarwal 2014 18 52 31 61 27.8% 0.68 [0.44, 1.07]
Subtotal (95% CI) 52 61 27.8% 0.68 [0.44, 1.07]
Total events 18 31
Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)
Transapical only
Conradi 2014 7 50 12 50 11.8% 0.58 [0.25, 1.36]
Subtotal (95% CI) 50 50 11.8% 0.58 [0.25, 1.36]
Total events 7 12
Heterogeneity: Not applicable
Test for overall effect: Z = 1.25 (P = 0.21)
Transfemoral or any other access
Fiorina 2014 8 55 4 45 7.2% 1.64 [0.53, 5.08]
Wong 2015 43 50 64 71 53.2% 0.95 [0.83, 1.09]
Subtotal (95% CI) 105 116 60.4% 1.02 [0.66, 1.58]
Total events 51 68
Heterogeneity: Tau² = 0.05; Chi² = 1.30, df = 1 (P = 0.25); I² = 23%
Test for overall effect: Z = 0.10 (P = 0.92)
Total (95% CI) 207 227 100.0% 0.85 [0.62, 1.18]
Total events 76 111
Heterogeneity: Tau² = 0.05; Chi² = 5.35, df = 3 (P = 0.15); I² = 44%
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Chi² = 2.25, df = 2 (P = 0.32), I² = 11.2%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
D
Need for a second valve
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral access
Conradi 2015 1 26 1 26 10.5% 1.00 [0.07, 15.15]
Islas 2015 3 79 9 170 47.6% 0.72 [0.20, 2.58]
Subtotal (95% CI) 105 196 58.1% 0.76 [0.24, 2.42]
Total events 4 10
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.65)
Transapical only
Conradi 2014 1 50 1 50 10.3% 1.00 [0.06, 15.55]
Kempfert 2014 1 40 1 40 10.4% 1.00 [0.06, 15.44]
Subtotal (95% CI) 90 90 20.7% 1.00 [0.14, 6.94]
Total events 2 2
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Transfemoral or any other access
Fiorina 2014 2 55 2 45 21.1% 0.82 [0.12, 5.58]
Subtotal (95% CI) 55 45 21.1% 0.82 [0.12, 5.58]
Total events 2 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)
Total (95% CI) 250 331 100.0% 0.82 [0.34, 1.98]
Total events 8 14
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 4 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.66)
Test for subgroup differences: Chi² = 0.06, df = 2 (P = 0.97), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
E
Need for postdilation
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral only
Aggarwal 2014 2 52 2 61 2.0% 1.17 [0.17, 8.04]
Bijuklic 2015 3 55 1 32 1.5% 1.75 [0.19, 16.08]
Conradi 2015 0 26 3 26 0.9% 0.14 [0.01, 2.63]
Islas 2015 14 79 32 170 22.5% 0.94 [0.53, 1.66]
Mollmann 2014 3 26 3 30 3.2% 1.15 [0.25, 5.23]
Subtotal (95% CI) 238 319 29.9% 0.95 [0.58, 1.56]
Total events 22 41
Heterogeneity: Tau² = 0.00; Chi² = 2.05, df = 4 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)
Transapical only
Conradi 2014 4 50 2 50 2.7% 2.00 [0.38, 10.43]
Kempfert 2014 4 40 6 40 5.2% 0.67 [0.20, 2.18]
Subtotal (95% CI) 90 90 7.8% 0.99 [0.35, 2.78]
Total events 8 8
Heterogeneity: Tau² = 0.07; Chi² = 1.13, df = 1 (P = 0.29); I² = 11%
Test for overall effect: Z = 0.02 (P = 0.98)
Transfemoral or any other access
Fiorina 2014 19 55 23 45 33.9% 0.68 [0.43, 1.07]
Kochman 2014 3 8 2 16 2.9% 3.00 [0.62, 14.49]
Wong 2015 15 50 24 71 25.4% 0.89 [0.52, 1.51]
Subtotal (95% CI) 113 132 62.3% 0.87 [0.53, 1.43]
Total events 37 49
Heterogeneity: Tau² = 0.08; Chi² = 3.38, df = 2 (P = 0.18); I² = 41%
Test for overall effect: Z = 0.56 (P = 0.58)
Total (95% CI) 441 541 100.0% 0.86 [0.66, 1.13]
Total events 67 98
Heterogeneity: Tau² = 0.00; Chi² = 6.86, df = 9 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.08 (P = 0.28)
Test for subgroup differences: Chi² = 0.09, df = 2 (P = 0.96), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
F
Major or life-threatening bleeding
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral only
Conradi 2015 2 26 2 26 26.0% 1.00 [0.15, 6.57]
Subtotal (95% CI) 26 26 26.0% 1.00 [0.15, 6.57]
Total events 2 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Transapical only
Conradi 2014 1 50 1 50 12.3% 1.00 [0.06, 15.55]
Subtotal (95% CI) 50 50 12.3% 1.00 [0.06, 15.55]
Total events 1 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Transfemoral or any other access
Fiorina 2014 3 55 1 45 18.6% 2.45 [0.26, 22.80]
Kochman 2014 1 8 0 16 9.6% 5.67 [0.26, 125.41]
Wong 2015 4 50 2 71 33.5% 2.84 [0.54, 14.91]
Subtotal (95% CI) 113 132 61.7% 3.03 [0.89, 10.28]
Total events 8 3
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.78 (P = 0.08)
Total (95% CI) 189 208 100.0% 1.98 [0.76, 5.18]
Total events 11 6
Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 4 (P = 0.84); I² = 0%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Chi² = 1.21, df = 2 (P = 0.55), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV

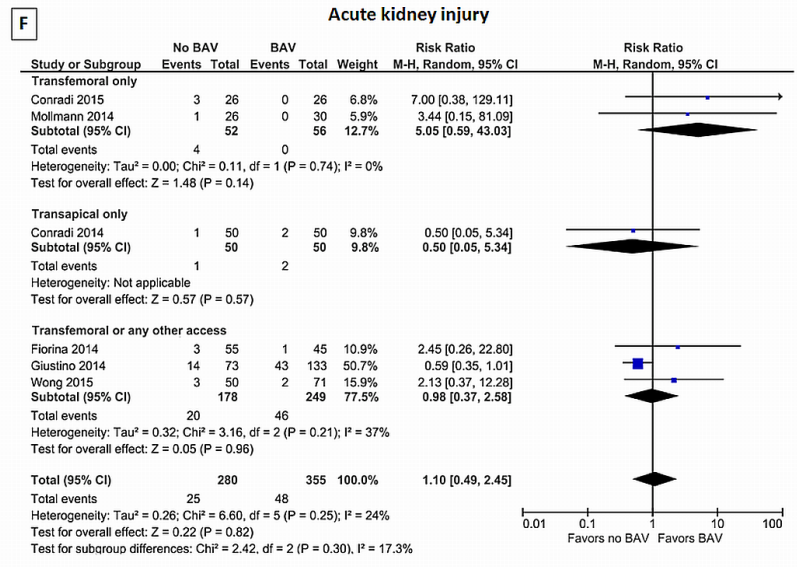

A
Annulus rupture
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral only
Conradi 2015 0 26 1 26 50.4% 0.33 [0.01, 7.82]
Subtotal (95% CI) 26 26 50.4% 0.33 [0.01, 7.82]
Total events 0 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Transfemoral or any other access
Wong 2015 0 50 1 71 49.6% 0.47 [0.02, 11.32]
Subtotal (95% CI) 50 71 49.6% 0.47 [0.02, 11.32]
Total events 0 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)
Total (95% CI) 76 97 100.0% 0.40 [0.04, 3.72]
Total events 0 2
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV

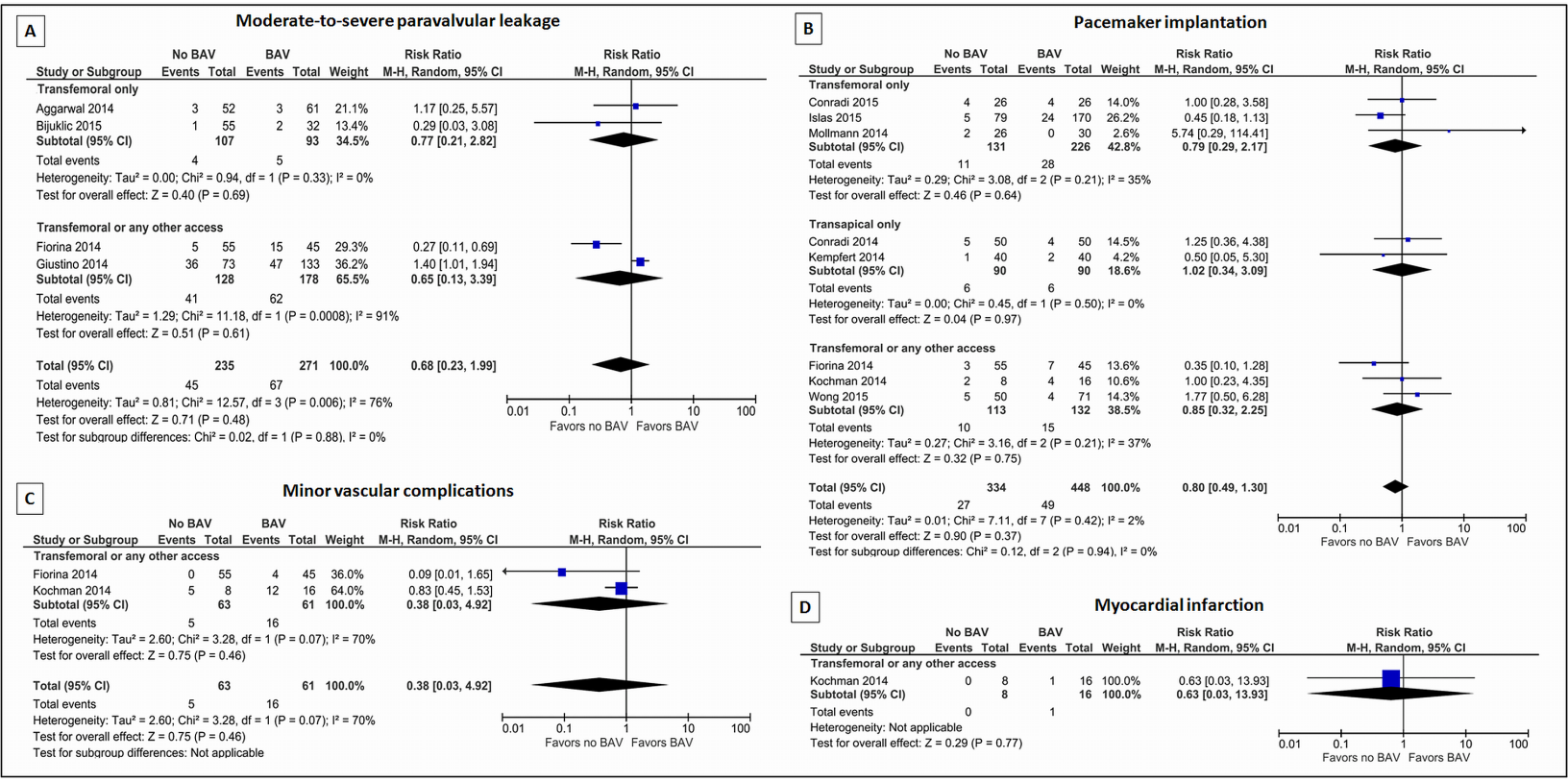

B
Cardiac tamponade
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral only
Mollmann 2014 1 26 0 30 15.6% 3.44 [0.15, 81.09]
Subtotal (95% CI) 26 30 15.6% 3.44 [0.15, 81.09]
Total events 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)
Transfemoral or any other access
Giustino 2014 6 73 3 133 84.4% 3.64 [0.94, 14.14]
Subtotal (95% CI) 73 133 84.4% 3.64 [0.94, 14.14]
Total events 6 3
Heterogeneity: Not applicable
Test for overall effect: Z = 1.87 (P = 0.06)
Total (95% CI) 99 163 100.0% 3.61 [1.04, 12.56]
Total events 7 3
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 2.02 (P = 0.04)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV

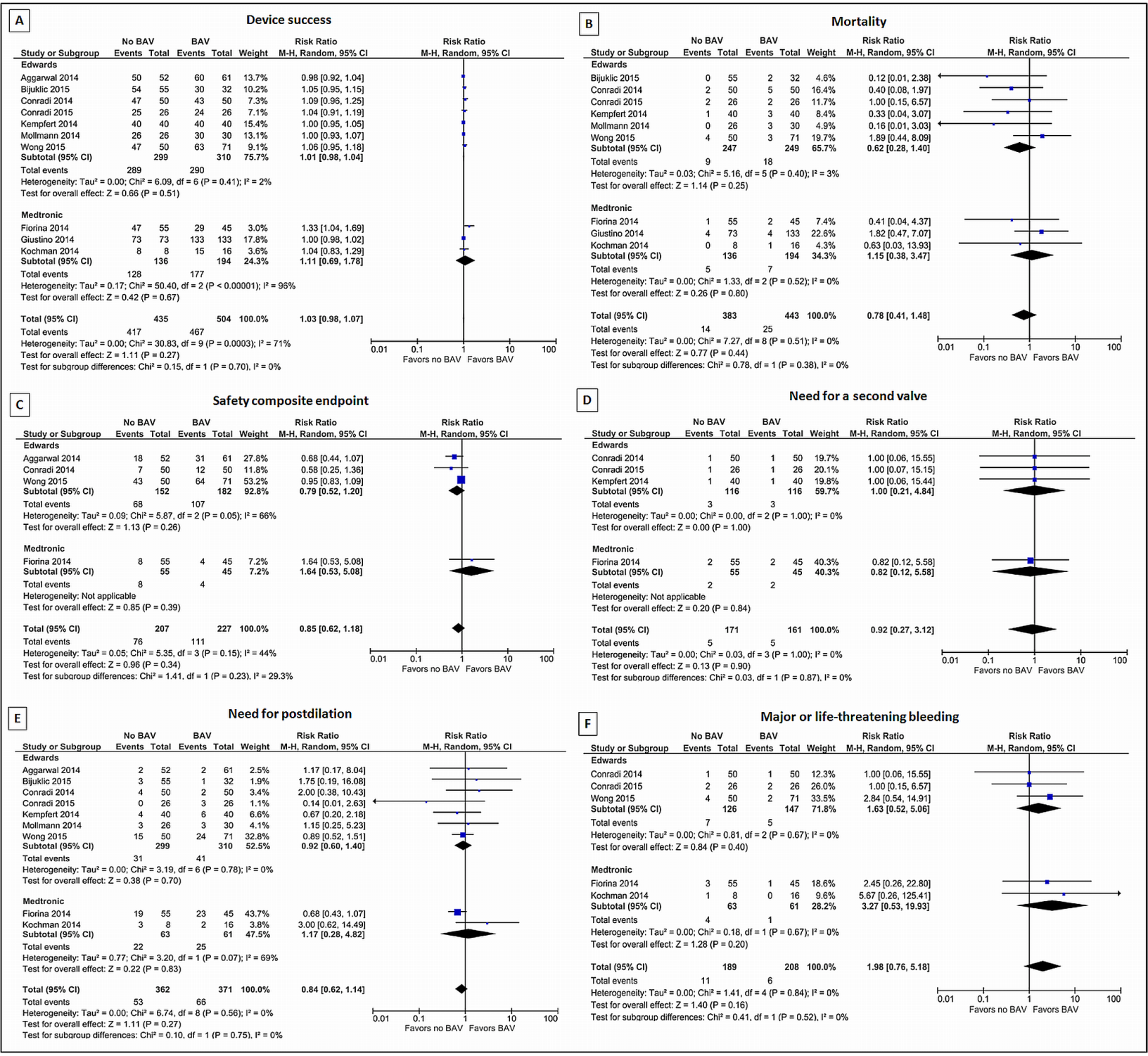

C
Conversion to surgery
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral only
Islas 2015 2 79 9 170 80.2% 0.48 [0.11, 2.16]
Subtotal (95% CI) 79 170 80.2% 0.48 [0.11, 2.16]
Total events 2 9
Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)
Transapical only
Conradi 2014 1 50 0 50 19.8% 3.00 [0.13, 71.92]
Subtotal (95% CI) 50 50 19.8% 3.00 [0.13, 71.92]
Total events 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Total (95% CI) 129 220 100.0% 0.69 [0.16, 2.89]
Total events 3 9
Heterogeneity: Tau² = 0.08; Chi² = 1.05, df = 1 (P = 0.31); I² = 5%
Test for overall effect: Z = 0.51 (P = 0.61)
Test for subgroup differences: Chi² = 1.05, df = 1 (P = 0.31), I² = 4.5%
0.01 0.1 1 10 100
Favors no BAV Favors BAV

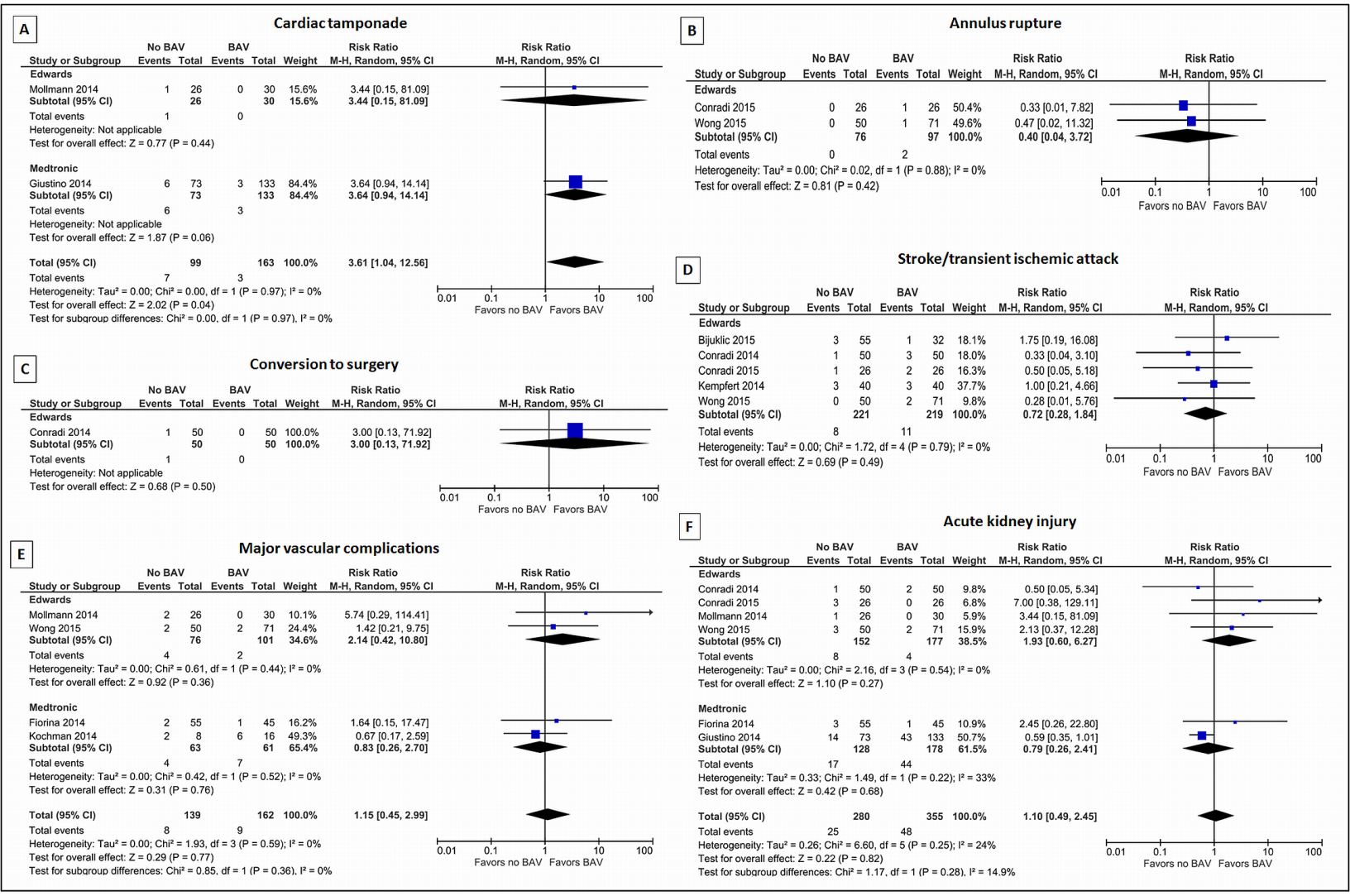

D
Major vascular complications
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral only
Mollmann 2014 2 26 0 30 10.1% 5.74 [0.29, 114.41]
Subtotal (95% CI) 26 30 10.1% 5.74 [0.29, 114.41]
Total events 2 0
Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)
Transfemoral or any other access
Fiorina 2014 2 55 1 45 16.2% 1.64 [0.15, 17.47]
Kochman 2014 2 8 6 16 49.3% 0.67 [0.17, 2.59]
Wong 2015 2 50 2 71 24.4% 1.42 [0.21, 9.75]
Subtotal (95% CI) 113 132 89.9% 0.96 [0.35, 2.63]
Total events 6 9
Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)
Total (95% CI) 139 162 100.0% 1.15 [0.45, 2.99]
Total events 8 9
Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 3 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)
Test for subgroup differences: Chi² = 1.23, df = 1 (P = 0.27), I² = 18.7%
0.01 0.1 1 10 100
Favors no BAV Favors BAV

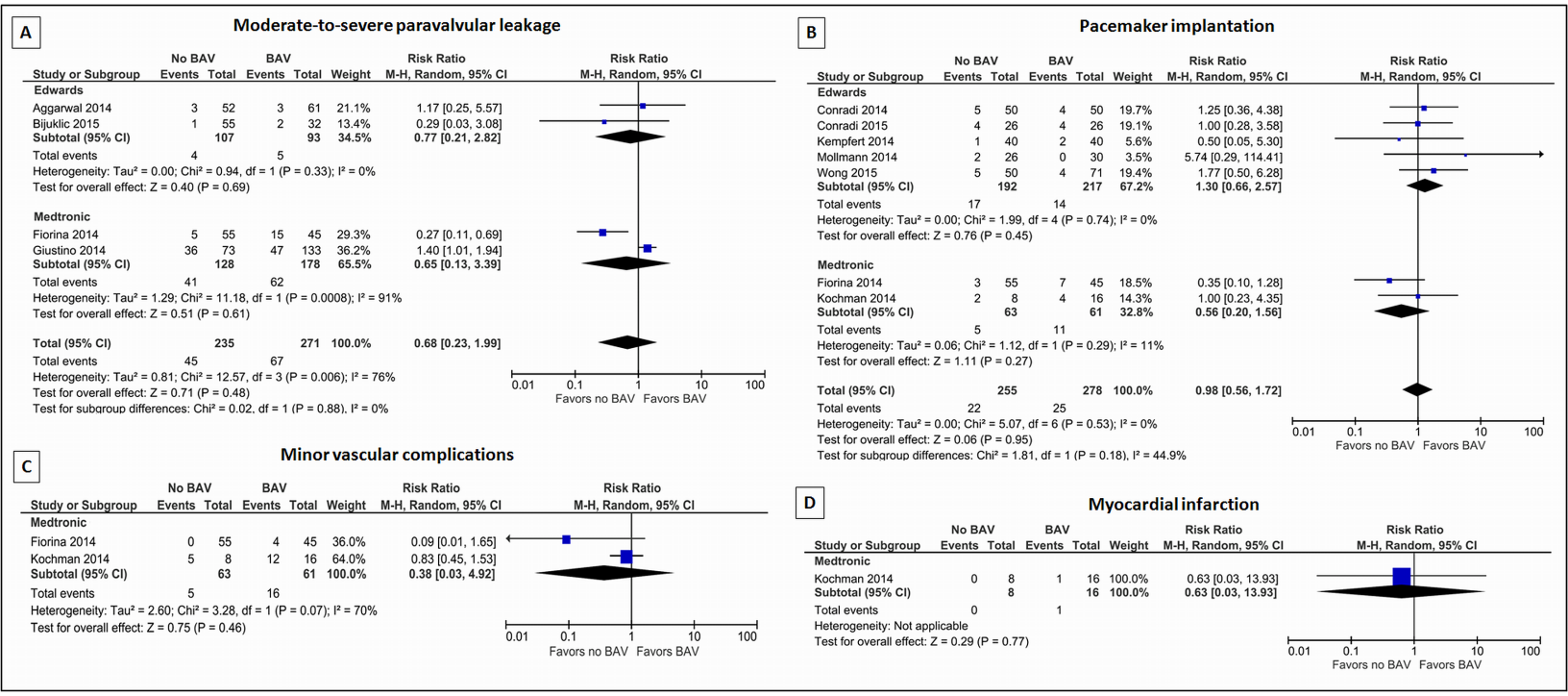

E
Stroke/transient ischemic attack
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral only
Bijuklic 2015 3 55 1 32 15.4% 1.75 [0.19, 16.08]
Conradi 2015 1 26 2 26 13.9% 0.50 [0.05, 5.18]
Islas 2015 1 79 3 170 15.0% 0.72 [0.08, 6.79]
Subtotal (95% CI) 160 228 44.3% 0.87 [0.24, 3.23]
Total events 5 6
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)
Transapical only
Conradi 2014 1 50 3 50 15.3% 0.33 [0.04, 3.10]
Kempfert 2014 3 40 3 40 32.1% 1.00 [0.21, 4.66]
Subtotal (95% CI) 90 90 47.3% 0.70 [0.20, 2.49]
Total events 4 6
Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.55 (P = 0.58)
Transfemoral or any other access
Wong 2015 0 50 2 71 8.4% 0.28 [0.01, 5.76]
Subtotal (95% CI) 50 71 8.4% 0.28 [0.01, 5.76]
Total events 0 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)
Total (95% CI) 300 389 100.0% 0.72 [0.30, 1.71]
Total events 9 14
Heterogeneity: Tau² = 0.00; Chi² = 1.71, df = 5 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.75 (P = 0.45)
Test for subgroup differences: Chi² = 0.45, df = 2 (P = 0.80), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV


F
Acute kidney injury
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral only
Conradi 2015 3 26 0 26 6.8% 7.00 [0.38, 129.11]
Mollmann 2014 1 26 0 30 5.9% 3.44 [0.15, 81.09]
Subtotal (95% CI) 52 56 12.7% 5.05 [0.59, 43.03]
Total events 4 0
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.48 (P = 0.14)
Transapical only
Conradi 2014 1 50 2 50 9.8% 0.50 [0.05, 5.34]
Subtotal (95% CI) 50 50 9.8% 0.50 [0.05, 5.34]
Total events 1 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)
Transfemoral or any other access
Fiorina 2014 3 55 1 45 10.9% 2.45 [0.26, 22.80]
Giustino 2014 14 73 43 133 50.7% 0.59 [0.35, 1.01]
Wong 2015 3 50 2 71 15.9% 2.13 [0.37, 12.28]
Subtotal (95% CI) 178 249 77.5% 0.98 [0.37, 2.58]
Total events 20 46
Heterogeneity: Tau² = 0.32; Chi² = 3.16, df = 2 (P = 0.21); I² = 37%
Test for overall effect: Z = 0.05 (P = 0.96)
Total (95% CI) 280 355 100.0% 1.10 [0.49, 2.45]
Total events 25 48
Heterogeneity: Tau² = 0.26; Chi² = 6.60, df = 5 (P = 0.25); I² = 24%
Test for overall effect: Z = 0.22 (P = 0.82)
Test for subgroup differences: Chi² = 2.42, df = 2 (P = 0.30), I² = 17.3%
0.01 0.1 1 10 100
Favors no BAV Favors BAV


A
Moderate-to-severe paravalvular leakage
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral only
Aggarwal 2014 3 52 3 61 21.1% 1.17 [0.25, 5.57]
Bijuklic 2015 1 55 2 32 13.4% 0.29 [0.03, 3.08]
Subtotal (95% CI) 107 93 34.5% 0.77 [0.21, 2.82]
Total events 4 5
Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)
Transfemoral or any other access
Fiorina 2014 5 55 15 45 29.3% 0.27 [0.11, 0.69]
Giustino 2014 36 73 47 133 36.2% 1.40 [1.01, 1.94]
Subtotal (95% CI) 128 178 65.5% 0.65 [0.13, 3.39]
Total events 41 62
Heterogeneity: Tau² = 1.29; Chi² = 11.18, df = 1 (P = 0.0008); I² = 91%
Test for overall effect: Z = 0.51 (P = 0.61)
Total (95% CI) 235 271 100.0% 0.68 [0.23, 1.99]
Total events 45 67
Heterogeneity: Tau² = 0.81; Chi² = 12.57, df = 3 (P = 0.006); I² = 76%
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
B
Pacemaker implantation
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral only
Conradi 2015 4 26 4 26 14.0% 1.00 [0.28, 3.58]
Islas 2015 5 79 24 170 26.2% 0.45 [0.18, 1.13]
Mollmann 2014 2 26 0 30 2.6% 5.74 [0.29, 114.41]
Subtotal (95% CI) 131 226 42.8% 0.79 [0.29, 2.17]
Total events 11 28
Heterogeneity: Tau² = 0.29; Chi² = 3.08, df = 2 (P = 0.21); I² = 35%
Test for overall effect: Z = 0.46 (P = 0.64)
Transapical only
Conradi 2014 5 50 4 50 14.5% 1.25 [0.36, 4.38]
Kempfert 2014 1 40 2 40 4.2% 0.50 [0.05, 5.30]
Subtotal (95% CI) 90 90 18.6% 1.02 [0.34, 3.09]
Total events 6 6
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)
Transfemoral or any other access
Fiorina 2014 3 55 7 45 13.6% 0.35 [0.10, 1.28]
Kochman 2014 2 8 4 16 10.6% 1.00 [0.23, 4.35]
Wong 2015 5 50 4 71 14.3% 1.77 [0.50, 6.28]
Subtotal (95% CI) 113 132 38.5% 0.85 [0.32, 2.25]
Total events 10 15
Heterogeneity: Tau² = 0.27; Chi² = 3.16, df = 2 (P = 0.21); I² = 37%
Test for overall effect: Z = 0.32 (P = 0.75)
Total (95% CI) 334 448 100.0% 0.80 [0.49, 1.30]
Total events 27 49
Heterogeneity: Tau² = 0.01; Chi² = 7.11, df = 7 (P = 0.42); I² = 2%
Test for overall effect: Z = 0.90 (P = 0.37)
Test for subgroup differences: Chi² = 0.12, df = 2 (P = 0.94), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
C
Minor vascular complications
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral or any other access
Fiorina 2014 0 55 4 45 36.0% 0.09 [0.01, 1.65]
Kochman 2014 5 8 12 16 64.0% 0.83 [0.45, 1.53]
Subtotal (95% CI) 63 61 100.0% 0.38 [0.03, 4.92]
Total events 5 16
Heterogeneity: Tau² = 2.60; Chi² = 3.28, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 0.75 (P = 0.46)
Total (95% CI) 63 61 100.0% 0.38 [0.03, 4.92]
Total events 5 16
Heterogeneity: Tau² = 2.60; Chi² = 3.28, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 0.75 (P = 0.46)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favors no BAV Favors BAV
D
Myocardial infarction
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Transfemoral or any other access
Kochman 2014 0 8 1 16 100.0% 0.63 [0.03, 13.93]
Subtotal (95% CI) 8 16 100.0% 0.63 [0.03, 13.93]
Total events 0 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)
0.01 0.1 1 10 100
Favors no BAV Favors BAV


A
Device success
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Edwards
Aggarwal 2014 50 52 60 61 13.7% 0.98 [0.92, 1.04]
Bijuklic 2015 54 55 30 32 10.2% 1.05 [0.95, 1.15]
Conradi 2014 47 50 43 50 7.3% 1.09 [0.96, 1.25]
Conradi 2015 25 26 24 26 7.1% 1.04 [0.91, 1.19]
Kempfert 2014 40 40 40 40 15.4% 1.00 [0.95, 1.05]
Mollmann 2014 26 26 30 30 13.1% 1.00 [0.93, 1.07]
Wong 2015 47 50 63 71 9.1% 1.06 [0.95, 1.18]
Subtotal (95% CI) 299 310 75.7% 1.01 [0.98, 1.04]
Total events 289 290
Heterogeneity: Tau² = 0.00; Chi² = 6.09, df = 6 (P = 0.41); I² = 2%
Test for overall effect: Z = 0.66 (P = 0.51)
Medtronic
Fiorina 2014 47 55 29 45 3.0% 1.33 [1.04, 1.69]
Giustino 2014 73 73 133 133 17.8% 1.00 [0.98, 1.02]
Kochman 2014 8 8 15 16 3.6% 1.04 [0.83, 1.29]
Subtotal (95% CI) 136 194 24.3% 1.11 [0.69, 1.78]
Total events 128 177
Heterogeneity: Tau² = 0.17; Chi² = 50.40, df = 2 (P < 0.00001); I² = 96%
Test for overall effect: Z = 0.42 (P = 0.67)
Total (95% CI) 435 504 100.0% 1.03 [0.98, 1.07]
Total events 417 467
Heterogeneity: Tau² = 0.00; Chi² = 30.83, df = 9 (P = 0.0003); I² = 71%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
B
Mortality
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Edwards
Bijuklic 2015 0 55 2 32 4.6% 0.12 [0.01, 2.38]
Conradi 2014 2 50 5 50 16.4% 0.40 [0.08, 1.97]
Conradi 2015 2 26 2 26 11.7% 1.00 [0.15, 6.57]
Kempfert 2014 1 40 3 40 8.4% 0.33 [0.04, 3.07]
Mollmann 2014 0 26 3 30 4.9% 0.16 [0.01, 3.03]
Wong 2015 4 50 3 71 19.7% 1.89 [0.44, 8.09]
Subtotal (95% CI) 247 249 65.7% 0.62 [0.28, 1.40]
Total events 9 18
Heterogeneity: Tau² = 0.03; Chi² = 5.16, df = 5 (P = 0.40); I² = 3%
Test for overall effect: Z = 1.14 (P = 0.25)
Medtronic
Fiorina 2014 1 55 2 45 7.4% 0.41 [0.04, 4.37]
Giustino 2014 4 73 4 133 22.6% 1.82 [0.47, 7.07]
Kochman 2014 0 8 1 16 4.3% 0.63 [0.03, 13.93]
Subtotal (95% CI) 136 194 34.3% 1.15 [0.38, 3.47]
Total events 5 7
Heterogeneity: Tau² = 0.00; Chi² = 1.33, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)
Total (95% CI) 383 443 100.0% 0.78 [0.41, 1.48]
Total events 14 25
Heterogeneity: Tau² = 0.00; Chi² = 7.27, df = 8 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Chi² = 0.78, df = 1 (P = 0.38), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
C
Safety composite endpoint
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Edwards
Aggarwal 2014 18 52 31 61 27.8% 0.68 [0.44, 1.07]
Conradi 2014 7 50 12 50 11.8% 0.58 [0.25, 1.36]
Wong 2015 43 50 64 71 53.2% 0.95 [0.83, 1.09]
Subtotal (95% CI) 152 182 92.8% 0.79 [0.52, 1.20]
Total events 68 107
Heterogeneity: Tau² = 0.09; Chi² = 5.87, df = 2 (P = 0.05); I² = 66%
Test for overall effect: Z = 1.13 (P = 0.26)
Medtronic
Fiorina 2014 8 55 4 45 7.2% 1.64 [0.53, 5.08]
Subtotal (95% CI) 55 45 7.2% 1.64 [0.53, 5.08]
Total events 8 4
Heterogeneity: Not applicable
Test for overall effect: Z = 0.85 (P = 0.39)
Total (95% CI) 207 227 100.0% 0.85 [0.62, 1.18]
Total events 76 111
Heterogeneity: Tau² = 0.05; Chi² = 5.35, df = 3 (P = 0.15); I² = 44%
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Chi² = 1.41, df = 1 (P = 0.23), I² = 29.3%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
D
Need for a second valve
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Edwards
Conradi 2014 1 50 1 50 19.7% 1.00 [0.06, 15.55]
Conradi 2015 1 26 1 26 20.1% 1.00 [0.07, 15.15]
Kempfert 2014 1 40 1 40 19.8% 1.00 [0.06, 15.44]
Subtotal (95% CI) 116 116 59.7% 1.00 [0.21, 4.84]
Total events 3 3
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Medtronic
Fiorina 2014 2 55 2 45 40.3% 0.82 [0.12, 5.58]
Subtotal (95% CI) 55 45 40.3% 0.82 [0.12, 5.58]
Total events 2 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)
Total (95% CI) 171 161 100.0% 0.92 [0.27, 3.12]
Total events 5 5
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
E
Need for postdilation
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Edwards
Aggarwal 2014 2 52 2 61 2.5% 1.17 [0.17, 8.04]
Bijuklic 2015 3 55 1 32 1.9% 1.75 [0.19, 16.08]
Conradi 2014 4 50 2 50 3.4% 2.00 [0.38, 10.43]
Conradi 2015 0 26 3 26 1.1% 0.14 [0.01, 2.63]
Kempfert 2014 4 40 6 40 6.6% 0.67 [0.20, 2.18]
Mollmann 2014 3 26 3 30 4.1% 1.15 [0.25, 5.23]
Wong 2015 15 50 24 71 32.8% 0.89 [0.52, 1.51]
Subtotal (95% CI) 299 310 52.5% 0.92 [0.60, 1.40]
Total events 31 41
Heterogeneity: Tau² = 0.00; Chi² = 3.19, df = 6 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)
Medtronic
Fiorina 2014 19 55 23 45 43.7% 0.68 [0.43, 1.07]
Kochman 2014 3 8 2 16 3.8% 3.00 [0.62, 14.49]
Subtotal (95% CI) 63 61 47.5% 1.17 [0.28, 4.82]
Total events 22 25
Heterogeneity: Tau² = 0.77; Chi² = 3.20, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 0.22 (P = 0.83)
Total (95% CI) 362 371 100.0% 0.84 [0.62, 1.14]
Total events 53 66
Heterogeneity: Tau² = 0.00; Chi² = 6.74, df = 8 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
F
Major or life-threatening bleeding
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Edwards
Conradi 2014 1 50 1 50 12.3% 1.00 [0.06, 15.55]
Conradi 2015 2 26 2 26 26.0% 1.00 [0.15, 6.57]
Wong 2015 4 50 2 71 33.5% 2.84 [0.54, 14.91]
Subtotal (95% CI) 126 147 71.8% 1.63 [0.52, 5.06]
Total events 7 5
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)
Medtronic
Fiorina 2014 3 55 1 45 18.6% 2.45 [0.26, 22.80]
Kochman 2014 1 8 0 16 9.6% 5.67 [0.26, 125.41]
Subtotal (95% CI) 63 61 28.2% 3.27 [0.53, 19.93]
Total events 4 1
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.28 (P = 0.20)
Total (95% CI) 189 208 100.0% 1.98 [0.76, 5.18]
Total events 11 6
Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 4 (P = 0.84); I² = 0%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV


A
Cardiac tamponade
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Edwards
Mollmann 2014 1 26 0 30 15.6% 3.44 [0.15, 81.09]
Subtotal (95% CI) 26 30 15.6% 3.44 [0.15, 81.09]
Total events 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)
Medtronic
Giustino 2014 6 73 3 133 84.4% 3.64 [0.94, 14.14]
Subtotal (95% CI) 73 133 84.4% 3.64 [0.94, 14.14]
Total events 6 3
Heterogeneity: Not applicable
Test for overall effect: Z = 1.87 (P = 0.06)
Total (95% CI) 99 163 100.0% 3.61 [1.04, 12.56]
Total events 7 3
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 2.02 (P = 0.04)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
B
Annulus rupture
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Edwards
Conradi 2015 0 26 1 26 50.4% 0.33 [0.01, 7.82]
Wong 2015 0 50 1 71 49.6% 0.47 [0.02, 11.32]
Subtotal (95% CI) 76 97 100.0% 0.40 [0.04, 3.72]
Total events 0 2
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)
0.01 0.1 1 10 100
Favors no BAV Favors BAV
C
Conversion to surgery
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Edwards
Conradi 2014 1 50 0 50 100.0% 3.00 [0.13, 71.92]
Subtotal (95% CI) 50 50 100.0% 3.00 [0.13, 71.92]
Total events 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
0.01 0.1 1 10 100
Favors no BAV Favors BAV
D
Stroke/transient ischemic attack
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Edwards
Bijuklic 2015 3 55 1 32 18.1% 1.75 [0.19, 16.08]
Conradi 2014 1 50 3 50 18.0% 0.33 [0.04, 3.10]
Conradi 2015 1 26 2 26 16.3% 0.50 [0.05, 5.18]
Kempfert 2014 3 40 3 40 37.7% 1.00 [0.21, 4.66]
Wong 2015 0 50 2 71 9.8% 0.28 [0.01, 5.76]
Subtotal (95% CI) 221 219 100.0% 0.72 [0.28, 1.84]
Total events 8 11
Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 4 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)
0.01 0.1 1 10 100
Favors no BAV Favors BAV
E
Major vascular complications
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Edwards
Mollmann 2014 2 26 0 30 10.1% 5.74 [0.29, 114.41]
Wong 2015 2 50 2 71 24.4% 1.42 [0.21, 9.75]
Subtotal (95% CI) 76 101 34.6% 2.14 [0.42, 10.80]
Total events 4 2
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.92 (P = 0.36)
Medtronic
Fiorina 2014 2 55 1 45 16.2% 1.64 [0.15, 17.47]
Kochman 2014 2 8 6 16 49.3% 0.67 [0.17, 2.59]
Subtotal (95% CI) 63 61 65.4% 0.83 [0.26, 2.70]
Total events 4 7
Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.76)
Total (95% CI) 139 162 100.0% 1.15 [0.45, 2.99]
Total events 8 9
Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 3 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)
Test for subgroup differences: Chi² = 0.85, df = 1 (P = 0.36), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
F
Acute kidney injury
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Edwards
Conradi 2014 1 50 2 50 9.8% 0.50 [0.05, 5.34]
Conradi 2015 3 26 0 26 6.8% 7.00 [0.38, 129.11]
Mollmann 2014 1 26 0 30 5.9% 3.44 [0.15, 81.09]
Wong 2015 3 50 2 71 15.9% 2.13 [0.37, 12.28]
Subtotal (95% CI) 152 177 38.5% 1.93 [0.60, 6.27]
Total events 8 4
Heterogeneity: Tau² = 0.00; Chi² = 2.16, df = 3 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)
Medtronic
Fiorina 2014 3 55 1 45 10.9% 2.45 [0.26, 22.80]
Giustino 2014 14 73 43 133 50.7% 0.59 [0.35, 1.01]
Subtotal (95% CI) 128 178 61.5% 0.79 [0.26, 2.41]
Total events 17 44
Heterogeneity: Tau² = 0.33; Chi² = 1.49, df = 1 (P = 0.22); I² = 33%
Test for overall effect: Z = 0.42 (P = 0.68)
Total (95% CI) 280 355 100.0% 1.10 [0.49, 2.45]
Total events 25 48
Heterogeneity: Tau² = 0.26; Chi² = 6.60, df = 5 (P = 0.25); I² = 24%
Test for overall effect: Z = 0.22 (P = 0.82)
Test for subgroup differences: Chi² = 1.17, df = 1 (P = 0.28), I² = 14.9%
0.01 0.1 1 10 100
Favors no BAV Favors BAV


A
Moderate-to-severe paravalvular leakage
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Edwards
Aggarwal 2014 3 52 3 61 21.1% 1.17 [0.25, 5.57]
Bijuklic 2015 1 55 2 32 13.4% 0.29 [0.03, 3.08]
Subtotal (95% CI) 107 93 34.5% 0.77 [0.21, 2.82]
Total events 4 5
Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)
Medtronic
Fiorina 2014 5 55 15 45 29.3% 0.27 [0.11, 0.69]
Giustino 2014 36 73 47 133 36.2% 1.40 [1.01, 1.94]
Subtotal (95% CI) 128 178 65.5% 0.65 [0.13, 3.39]
Total events 41 62
Heterogeneity: Tau² = 1.29; Chi² = 11.18, df = 1 (P = 0.0008); I² = 91%
Test for overall effect: Z = 0.51 (P = 0.61)
Total (95% CI) 235 271 100.0% 0.68 [0.23, 1.99]
Total events 45 67
Heterogeneity: Tau² = 0.81; Chi² = 12.57, df = 3 (P = 0.006); I² = 76%
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
B
Pacemaker implantation
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Edwards
Conradi 2014 5 50 4 50 19.7% 1.25 [0.36, 4.38]
Conradi 2015 4 26 4 26 19.1% 1.00 [0.28, 3.58]
Kempfert 2014 1 40 2 40 5.6% 0.50 [0.05, 5.30]
Mollmann 2014 2 26 0 30 3.5% 5.74 [0.29, 114.41]
Wong 2015 5 50 4 71 19.4% 1.77 [0.50, 6.28]
Subtotal (95% CI) 192 217 67.2% 1.30 [0.66, 2.57]
Total events 17 14
Heterogeneity: Tau² = 0.00; Chi² = 1.99, df = 4 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)
Medtronic
Fiorina 2014 3 55 7 45 18.5% 0.35 [0.10, 1.28]
Kochman 2014 2 8 4 16 14.3% 1.00 [0.23, 4.35]
Subtotal (95% CI) 63 61 32.8% 0.56 [0.20, 1.56]
Total events 5 11
Heterogeneity: Tau² = 0.06; Chi² = 1.12, df = 1 (P = 0.29); I² = 11%
Test for overall effect: Z = 1.11 (P = 0.27)
Total (95% CI) 255 278 100.0% 0.98 [0.56, 1.72]
Total events 22 25
Heterogeneity: Tau² = 0.00; Chi² = 5.07, df = 6 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Chi² = 1.81, df = 1 (P = 0.18), I² = 44.9%
0.01 0.1 1 10 100
Favors no BAV Favors BAV
C
Minor vascular complications
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Medtronic
Fiorina 2014 0 55 4 45 36.0% 0.09 [0.01, 1.65]
Kochman 2014 5 8 12 16 64.0% 0.83 [0.45, 1.53]
Subtotal (95% CI) 63 61 100.0% 0.38 [0.03, 4.92]
Total events 5 16
Heterogeneity: Tau² = 2.60; Chi² = 3.28, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 0.75 (P = 0.46)
0.01 0.1 1 10 100
Favors no BAV Favors BAV
D
Myocardial infarction
No BAV
BAV
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Medtronic
Kochman 2014 0 8 1 16 100.0% 0.63 [0.03, 13.93]
Subtotal (95% CI) 8 16 100.0% 0.63 [0.03, 13.93]
Total events 0 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)
0.01 0.1 1 10 100
Favors no BAV Favors BAV