ORIGINAL ARTICLE

Single-Arm Meta-Analysis of Argentine Studies Reporting In-Hospital Mortality After Aortic Valve Replacement in Low and Intermediate Risk Patients

Metanálisis sobre la mortalidad hospitalaria del reemplazo valvular aórtico en pacientes con riesgo bajo e intermedio en Argentina

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ABSTRACT

Background: Current evidence favors surgical valve replacement to treat symptomatic aortic disease, except in elderly patients at increased risk for surgery, in whom transcatheter aortic valve implantation (TAVI) may be eligible.
Objectives: Considering that the use of TAVI has been proposed to be extended to other groups at lower risk, the purpose of this study was to perform a single-arm meta-analysis of local studies reporting in-hospital mortality after surgical aortic valve replacement in low and intermediate risk patients in Argentina, as a benchmark for comparing with local TAVI outcomes.
Methods: A systematic review search strategy was performed using controlled trials and observational studies identified in MEDLINE, Embase, SCOPUS, and the Cochrane library to March 2019.
Results: Among 80 studies identified through the search, 4 observational articles reported in-hospital mortality and postoperative complications after aortic valve replacement, divided into intermediate and/or low risk patients according to the STS score or the EuroSCORE II. In 1,192 patients, in-hospital mortality was 3.1%. Weighted pooled estimates were: postoperative stroke1.3%, myocardial infarction 0.4%, need for definite pacemaker 2.7%, mediastinitis 1.4%, and reoperation for bleeding 2.6%.
Conclusions: The proven efficacy of TAVI in high-risk patients is leading to the expansion of its indications toward lower-risk cases; but this shift should be supported by meaningful evidence of its benefit over surgical valve replacement. This single-arm meta-analysis of Argentine studies presents in-hospital mortality and postoperative complications after aortic valve replacement in low and intermediate risk patients. The updated information on local results of surgery could serve as a benchmark for comparing with TAVI performance in our setting.

Key words: Operative Risk - Aortic Valve Replacement - Transcatheter Aortic Valve Implantation - Meta-Analysis - Argentina

RESUMEN

Introducción: La evidencia actual apoya el uso del reemplazo valvular quirúrgico para tratar la enfermedad aórtica sintomática, excepto en los pacientes ancianos con mayor riesgo operatorio, en quienes el implante de una válvula aórtica transcatéter (IVAT) podría ser la técnica de elección.
Objetivos: Considerando que se ha propuesto extender el uso de IVAT a otros grupos de pacientes con riesgo más bajo, el propósito de este estudio fue realizar un metanálisis de estudios locales que informaban la mortalidad hospitalaria después del reemplazo quirúrgico de la válvula aórtica en pacientes de riesgo bajo e intermedio en Argentina, de forma que pueda usarse como punto de referencia para comparar los resultados locales de IVAT.
Material y métodos: Se realizó una búsqueda sistemática de ensayos clínicos controlados y estudios observacionales identificados en MEDLINE, Embase, SCOPUS y Cochrane hasta marzo de 2019.
Resultados: De 80 estudios encontrados, 4 artículos observacionales informaban la mortalidad hospitalaria y las complicaciones postoperatorias después del reemplazo valvular aórtico, dividido en pacientes de riesgo intermedio y/o bajo según la puntuación STS o el EuroSCORE II. En 1192 pacientes la mortalidad hospitalaria fue 3,1%. Las estimaciones ponderadas agrupadas fueron: accidente cerebrovascular 1,3%, infarto de miocardio 0,4%, necesidad de marcapasos definitivo 2,7%, mediastinitis 1,4% y reoperación por hemorragia 2,6%.
Conclusiones: La probada eficacia del IVAT en pacientes de alto riesgo está llevando a indicar este procedimiento en casos de menor riesgo; pero este cambio debe estar respaldado por una evidencia clara de su beneficio por sobre el reemplazo valvular quirúrgico. Este metanálisis de estudios realizados en centros argentinos presenta la mortalidad hospitalaria y las complicaciones postoperatorias después del reemplazo valvular aórtico en pacientes de riesgo intermedio o bajo. La información actualizada sobre los resultados locales de la cirugía podría servir como un punto de referencia para comparar el desempeño futuro del IVAT en nuestro medio.

Palabras clave: riesgo operatorio - reemplazo valvular aórtico - implante valvular aórtico transcatéter - metaanálisis - Argentina

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INTRODUCTION

At present, valve replacement continues to be the most effective treatment for aortic valve disease after the onset of clinical symptoms (class IA, American Heart Association). (1) Current evidence favors surgical aortic valve replacement except in elderly patients at increased risk for surgery, in whom transcatheter aortic valve implantation (TAVI) may be eligible. (2) TAVI is a novel, less invasive and more expensive technological method for the treatment of aortic valve stenosis, particularly for high risk surgical patients. (3-4) Recently, the use of TAVI has been proposed to be extended to other groups at lower risk. (5-7) Based on preoperative risk stratification scores, the current risk group division considers intermediate in-hospital mortality risk to be between 4% and 7%, and low risk to be under 4%. Despite the intention to treat low risk populations, TAVI has yet to overcome a number of limitations to reach the usual traditional surgical standards, such as paravalvular residual aortic regurgitation (8-9), high rate of permanent pacemaker implantation (10), the impact of residual mismatch considering the traditional threshold of 0.75 cm^2/m^2 effective orifice area (11), the inconvenience of implanting a less durable bioprosthetic valve in patients aged <70 years (10), the risk of subclinical thrombosis (12-14), remote and immediate structural damage secondary to crimping (15), acute renal dysfunction (16), and the cost-effectiveness ratio in our setting. (17) Particularly, the cost of TAVI is a cause for concern among stakeholders, as this procedure can at least double the cost of conventional aortic valve surgery.

We postulated that a pooled analysis of the current local in-hospital outcomes of aortic valve replacement surgery should serve as a benchmark for comparing with the results of TAVI in Argentina. Thus, the objective of this study was to perform a single-arm meta-analysis of local studies reporting in-hospital mortality after aortic valve replacement in low and intermediate risk patients in Argentina.

METHODS

The systematic review search strategy was performed using controlled trials and observational studies identified in MEDLINE, Embase, SCOPUS, and the Cochrane library (to March 17, 2019). Eligible studies included those in which patient cohorts underwent isolated or combined aortic valve replacement surgery in Argentina, and in which outcomes were separately reported as intermediate and low risk, based on the Society of Thoracic Surgeons (STS) (18) score or the EuroSCORE II. (19) Combined surgery was defined as an aortic valve replacement plus coronary artery bypass grafting. Studies that did not include in-hospital mortality or complications as endpoints were excluded. Publication search was limited to Spanish and English languages. The search strategy included the terms: "aortic valve" AND "surgery OR operation OR replacement" AND "Argentina [Affiliation]" as either key words or MeSH terms. All data were extracted from article texts, tables and figures, and primary study authors were personally contacted to request extra information not included in the original publications. Two investigators (R.A.B. and C.C.H.) independently reviewed citations and performed data retrieval, and disagreements were resolved through consensus. The study quality appraisal was performed with the checklist of the Dutch Cochrane Centre proposed by MOOSE. (20)

Statistical analysis

A single-arm meta-analysis of proportions was conducted for the primary endpoints: in-hospital all-cause mortality and postoperative complications. Mean STS/EuroSCORE II scores were calculated, and observed-to-expected (O/E) mortality ratios with their corresponding 95% confidence interval (95% CI) were calculated and compared with the chi square test. Proportions with 95% CI and forest plots were calculated with MedCalc Statistical Software version 18.6 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018) using fixed and random effect models. Heterogeneity among studies was examined using the Cochran Q test and the Higgins I^2 test (25%, 50%, and 75% I^2 values were interpreted as low, moderate, and high heterogeneity). Funnel plots were used as graphical methods to identify studies affecting heterogeneity and to assess publication bias. Since only 4 studies were included in the meta-analysis, we avoided using Begg's method for it was expected to have very low power to detect biases.

Ethical considerations

The protocol was assessed and approved by the local Institutional Review Boards which waived the need for an informed consent to use data.

RESULTS

Among a total of 80 studies identified through the online database searches, only 4 observational articles reported in-hospital mortality and postoperative complications after aortic valve replacement, divided into intermediate and/or low risk patients based on the STS score or the EuroSCORE II. (21-24) Three studies communicated outcomes in low and intermediate risk patients, while one study reported only results for intermediate risk patients. Baseline characteristics of the studies included in the meta-analysis are shown in Table 1.The overall pooled analysis showed that 59.0% of patients were male, with a weighted mean age of 73.6 years(range, 33-92), and 66.4% underwent isolated aortic valve replacement. According to the Dutch Cochrane Group and MOOSE guidelines, intra-study risk of bias assessment showed that the four selected studies were deemed of high quality. Visual inspection of funnel plots (not shown) did not reveal significant asymmetry for all-cause mortality and complication rates, either for intermediate or low risk patients. These results suggest that publication bias was not a significant influencing factor.

Figure 1a shows the forest plot and pooled-analysis of the three studies reporting in-hospital mortality after isolated or combined aortic valve replacement in low- and intermediate-risk patients. In 1,192 patients, in-hospital mortality was 3.1% when considering the pooled risk. When patients were separated into low- and intermediate risk, mortality rates were 2.7% and

6.1%, respectively (Figures 1b and 1c). Heterogeneity among studies was low when comparing mortality rates for low- and intermediate-risk patients. In the low-risk group, the mean STS score was 1.5% and the O/E ratio was 1.7 (95% CI 0.91-3.11, p=0.090), while in the intermediate-risk group, the mean STS score was 5.1% and the O/E ratio was 1.2 (95% CI 0.52-2.15, p=0.843).

Meta-analyses summarizing postoperative complications are shown in Figures 2 to 4 for the collective risk groups. Weighted pooled estimate of postoperative stroke and myocardial infarction was 1.3% (Figure 2a) and 0.4% (Figure 2b), respectively. Postoperative need for definite pacemaker implantation and the incidence of mediastinitis was 2.7% (Figure 3a) and 1.4% (Figure 3b), respectively. Finally, weighted pooled rate of reoperation for bleeding was 2.6% (Figure 4). Regarding complications, the assessment of heterogeneity among studies was low for myocardial infarction and mediastinitis, moderate for stroke, and high for pacemaker implantation and reoperation for bleeding. Specific Cochran Q test p-values and Higgins I^2 percentages have been associated to each forest plot.

DISCUSSION

Aortic valve stenosis is emerging as a common heart disease in developed and developing countries due to a rapidly aging population. In this context, most experimental and clinical evidence agree on the importance of supporting TAVI as the standard treatment for patients at high surgical risk. (25-26) However, considering that TAVI has started to include moderate and low-risk patients in its protocols, it is essential to have updated comparative information on the local results of aortic valve replacement surgery in those risk strata. This information would constitute a potential benchmark that should be locally taken into account when trying to expand the indication of TAVI in the future.

In the current study, the pooled-analysis of four local observational studies included in the meta-analysis showed updated in-hospital outcomes of aortic valve replacement surgery in high-volume Argentine surgical centers. These results are comparable to those reported by other researchers. Previously, seven international major randomized trials and registries have communicated 30-day outcomes after an aortic valve replacement, separated in intermediate or low risk groups. (5,27-32) Table 2 summarizes the comparison of their results with those of the current study. The data show that for patients at low risk, the current study had a death rate similar to the German GARY registry and higher than the recently published PARTNER 3 and EVOLUT trials; while for patients at intermediate risk, the current pooled analysis presented a higher mortality rate compared with the other two trials. Regarding postoperative complications, in the current meta-analysis, ratios were consistently smaller for almost each comparison; nevertheless, these constant differences could be justified by the potential underreporting of complications in the studies included in the analysis.

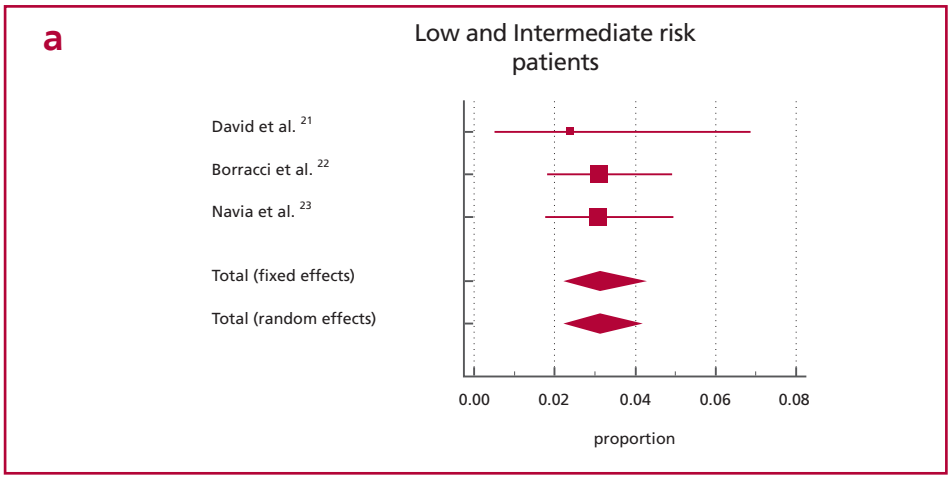
Contemporary Argentine reports on TAVI results in low and intermediate risk patients are scarce. For intermediate-risk patients, Raleigh et al. (33) communicated a 30-day all-cause mortality of 5.4% with transfemoral TAVI; whereas Abud et al. (34) reported a 30-day mortality rate of 5.0% with the same procedure. Using a minimally invasive approach for TAVI in 229 patients with a mean STS score of 6.8%, Fava et al. (35) observed 30-day mortality: 3.9%, stroke: 1.8%, myocardial infarction: 0.9%, need for definite pacemaker implantation: 35.8%, moderate to severe leak: 13.1%, and major bleeding: 6.1%. Except for death, post TAVI complications rates were higher than those observed with aortic valve replacement in the present meta-analysis. Since surgical aortic valve replacement is a well-known effective technique to treat valve disease, a potential positioning of TAVI as first-choice treatment for moderate and low risk patients with symptomatic aortic stenosis will raise the problem of how stakeholders de-implement an effective and less expensive procedure that is in widespread use.

Scientific evidence supporting high-cost technologies can be overly influenced by industry that usually avoids to investigate costs, missing the opportunity to provide some realistic direction for local health systems. Locally, cost-effectiveness analyses will become more important as TAVI indications expand to lower risk patients. (36) An early analysis from the Netherlands demonstrated higher 1-year costs of TAVI versus surgical valve replacement in intermediate-risk patients (37), and this cost difference was mainly driven by the variation in device prices. Although local differences in reimbursement and device costs hamper the generalization of these results, health economic

Table 1. Baseline characteristics of the studies included in the meta-analysis.

Study	Number of centers	Period	Risk stratification	Reported risk	Mean age	Isolated AVR
David et al.[21]	two centers	2015-2017	STS	low/intermediate	71 years	70%
Borracci et al.[22]	multicenter	2012-2017	EuroSCORE 2	low/intermediate	70 years	77%
Navia et al.[23]	single center	2010-2017	STS	low/intermediate	77 years	60%
Fortunato et al.[24]	single center	2007-2017	STS	intermediate	79 years	37%

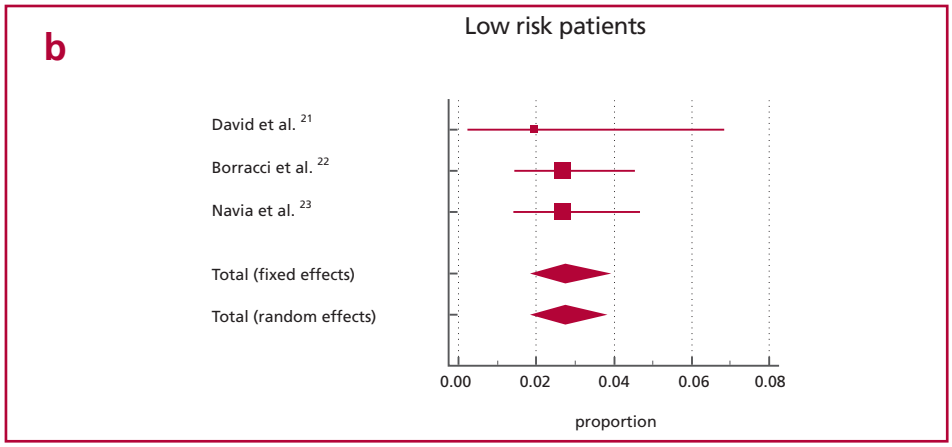
AVR, aortic valve replacement



Studies	Sample	Death	Proportion (%)	95% CI
David et al.[21]	125	3	2.40	0.498 to 6.854
Borracci et al.[22]	547	17	3.11	1.821 to 4.929
Navia et al.[23]	520	16	3.08	1.769 to 4.949
Total (fixed effects)	1,192	36	3.14	2.222 to 4.287
Total (random effects)	1,192	36	3.14	2.223 to 4.197

Tests for heterogeneity: Cochran Q = 0.068, p = 0.966; I^2 = 0.0% (95% CI 0.00 to 1.78)
CI, confidence interval

Fig. 1. Proportion meta-analysis of single-arm local studies reporting in-hospital mortality after isolated or combined aortic valve replacement in (a) pooled low and intermediate risk patients, (b) low risk patients, and (c) intermediate risk patients.



Studies	Sample	Death	Proportion (%)	95% CI
David et al.[21]	103	2	1.94	0.236 to 6.839
Borracci et al.[22]	486	13	2.68	1.432 to 4.531
Navia et al.[23]	445	12	2.70	1.401 to 4.663
Total (fixed effects)	1,034	27	2.74	1.837 to 3.930
Total (random effects)	1,034	27	2.74	1.838 to 3.825

Tests for heterogeneity: Cochran Q = 0.062, p = 0.970; I^2 = 0.0% (95% CI 0.00 to 0.00)
CI, confidence interval

Fig. 1. Continuation

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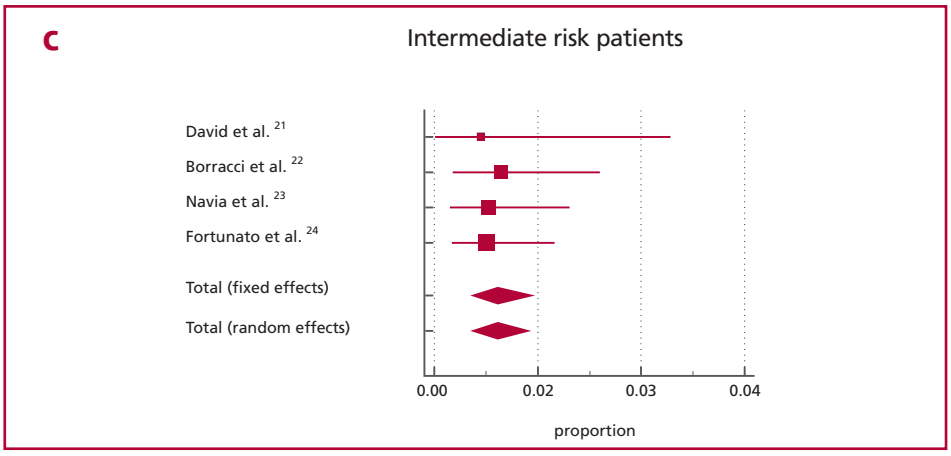


Studies	Sample	Death	Proportion (%)	95% CI
David et al.[21]	22	1	4.55	0.115 to 22.84
Borracci et al.[22]	61	4	6.56	1.815 to 15.95
Navia et al.[23]	75	4	5.33	1.472 to 13.10
Fortunato et al.[24]	97	5	5.16	1.695 to 11.62
Total (fixed effects)	255	14	6.13	3.538 to 9.784
Total (random effects)	255	14	6.13	3.543 to 9.373

Tests for heterogeneity: Cochran Q = 0.181, p = 0.981; I^2 = 0.0% (95% CI 0.00 to 0.00)
CI, confidence interval

analyses will be mandatory as the field expands.

In order to improve outcomes and increase the indication of surgical treatment for high-risk patients who are otherwise inoperable, another less invasive alternative approach using innovative technologies has been developed. Thus, in addition to TAVI, sutureless aortic valve replacement is beginning to emerge as an alternative method for treating aortic valve disease, even in high-risk patients. (38-39) This method should be contrasted against TAVI in future randomized trials.

Short- and long-term monitoring to track the new devices and techniques related with TAVI are crucial to focus on the right balance between innovation and evaluation. In order to assess and regulate safe implementation of any type of surgical innovation, a three-component approach should be accepted, including the following items: central registration of treated patients on a unique open-source database, individual patient tracking, and longitudinal monitoring. Furthermore, while low-risk innovations could be rolled out over a larger scale in multiple centers for prospective evaluation, high-risk innovations like TAVI should be released at only a few medical centers for early assessment. (40)

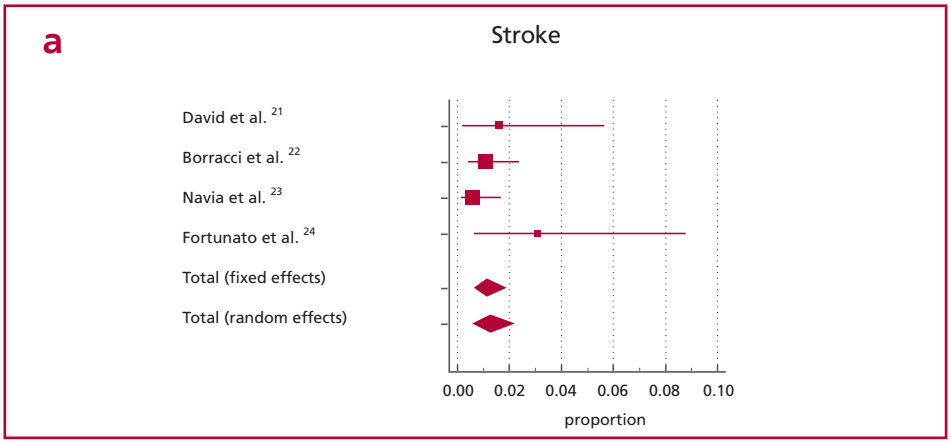
The principal limitation of the current study is given by the natural restriction associated to a single-arm meta-analysis, which in this case is lack of a TAVI control group. A second limitation is that this pooled analysis does not represent the whole population of patients undergoing aortic valve replacement annually in Argentina. Finally, since current data include patients with isolated or combined aortic valve replacement, comparison with isolated TAVI outcomes could generate some bias. Nevertheless, a significant proportion of patients undergoing TAVI has previous or concomitant coronary angioplasty due to associated coronary disease.

CONCLUSIONS

The proven efficacy of TAVI in high-risk patients is leading to the expansion of its indication toward lower-risk cases; but this shift should be supported by meaningful evidence of its benefit over surgical valve replacement. The current single-arm meta-analysis of Argentine studies presented in-hospital mortality and postoperative complications after aortic valve replacement in low and intermediate risk patients. This updated information on the local results of aortic valve replacement surgery could serve as a benchmark for comparing TAVI performance in our setting.

Conflicts of interest

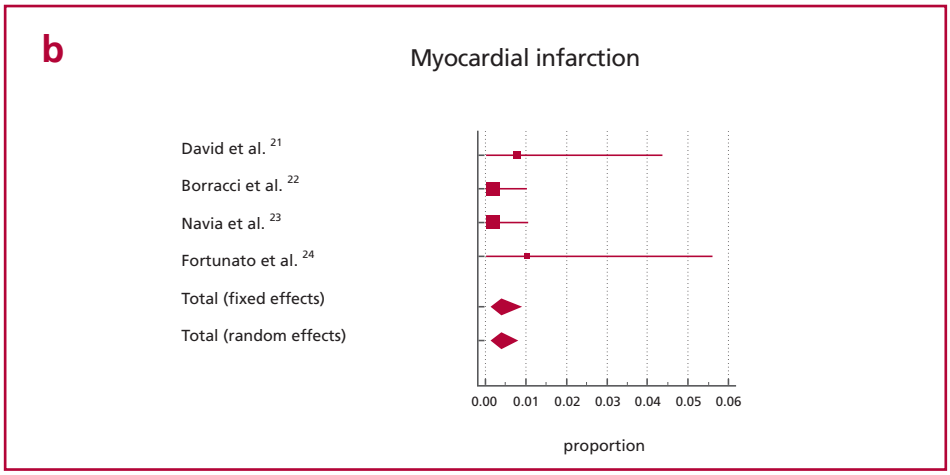
None declared. (See authors' conflicts of interest forms on the website/Supplementary material).



Studies	Sample	Stroke	Proportion (%)	95% CI
David et al.[21]	125	2	1.60	0.194 to 5.660
Borracci et al.[22]	547	6	1.10	0.404 to 2.372
Navia et al.[23]	520	3	0.58	0.472 to 13.10
Fortunato et al.[24]	97	3	3.09	1.119 to 1.677
Total (fixed effects)	1,289	14	1.15	0.640 to1.889
Total (random effects)	1,289	14	1.27	0.580 to 2.219

Tests for heterogeneity: Cochran Q = 4.575, p = 0.206; I² = 34.4% (95% CI 0.00 to 77.0)
CI, confidence interval

Fig. 2. Proportion meta-analysis of single-arm local studies reporting postoperative (a) stroke and (b) myocardial infarction after isolated or combined aortic valve replacement in low and intermediate risk patients.

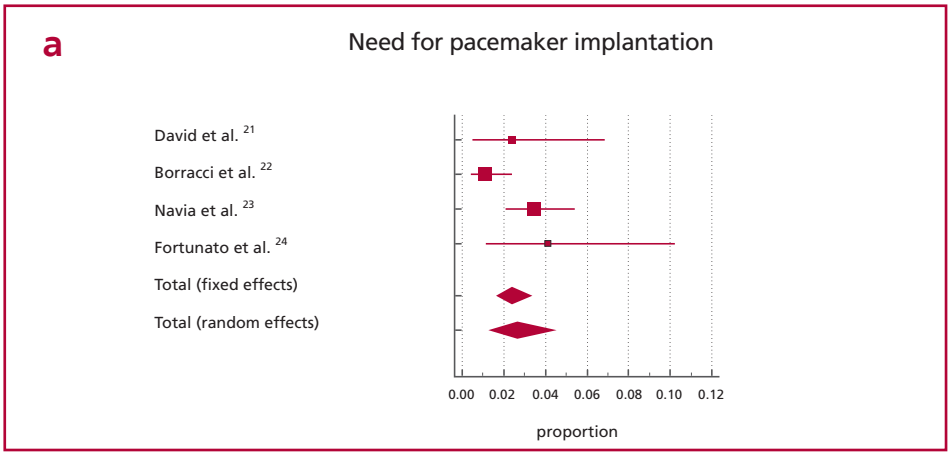


Studies	Sample	Myocardial infarction	Proportion (%)	95% CI
David et al.[21]	125	1	0.80	0.020 to 4.377
Borracci et al.[22]	547	1	0.18	0.005 to 1.014
Navia et al.[23]	520	1	0.19	0.005 to 1.067
Fortunato et al.[24]	97	1	1.03	0.026 to 5.610
Total (fixed effects)	1,289	4	0.40	0.131 to 0.913
Total (random effects)	1,289	4	0.40	0.127 to 0.812

Tests for heterogeneity: Cochran Q = 2.884, p = 0.410; I² = 0.0% (95% CI 0.00 to 86.6)
CI, confidence interval

Fig. 2. Continuation

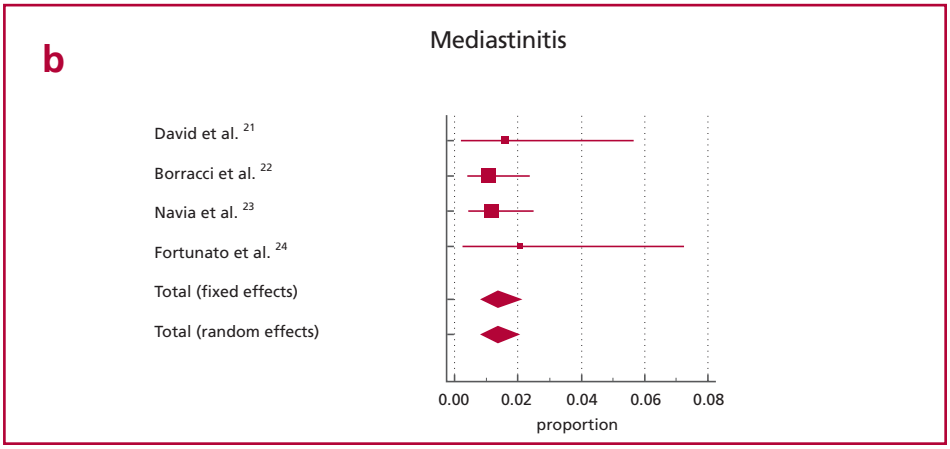
Fig. 3. Proportion meta-analysis of single-arm local studies reporting (a) need for definite pacemaker implantation and (b) mediastinitis or sternal wound infection after isolated or combined aortic valve replacement in low and intermediate risk patients.



Studies	Sample	Pacemaker	Proportion (%)	95% CI
David et al.[21]	125	3	2.40	0.498 to 6.854
Borracci et al.[22]	547	6	1.10	0.404 to 2.372
Navia et al.[23]	520	18	3.46	2.064 to 5.416
Fortunato et al.[24]	97	4	4.12	1.135 to 10.22
Total (fixed effects)	1,289	31	2.39	1.628 to 3.377
Total (random effects)	1,289	31	2.65	1.241 to 4.561

Tests for heterogeneity: Cochran Q = 8.631, p = 0.035; I^2 = 65.2% (95% CI 0.00 to 88.2)
CI, confidence interval

Fig. 3. Continuation



Studies	Sample	Mediastinitis	Proportion (%)	95% CI
David et al.[21]	125	2	1.60	0.194 to 5.660
Borracci et al.[22]	547	6	1.10	0.404 to 2.372
Navia et al.[23]	520	6	1.15	0.425 to 2.494
Fortunato et al.[24]	97	2	2.06	0.251 to 7.250
Total (fixed effects)	1,289	16	1.37	0.806 to 2.158
Total (random effects)	1,289	16	1.37	0.805 to 2.069

Tests for heterogeneity: Cochran Q = 1.1878, p = 0.756; I^2 = 0.0% (95% CI 0.00 to 67.4)
CI, confidence interval

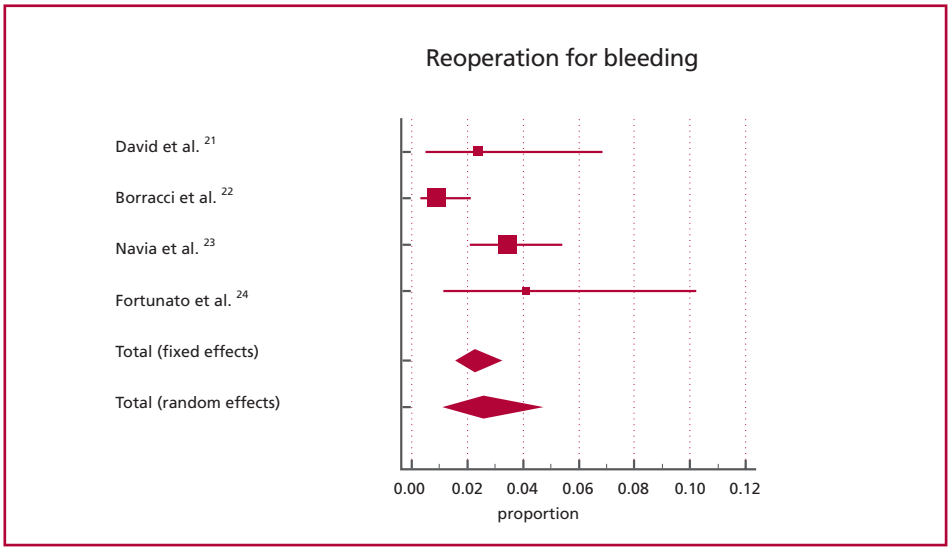


Fig. 4. Proportion meta-analysis of single-arm local studies reporting reoperation for bleeding after isolated or combined aortic valve replacement in low and intermediate risk patients.

Studies	Sample	Reoperation for bleeding	Proportion (%)	95% CI
David et al.[21]	125	3	2.40	0.498 to 6.854
Borracci et al.[22]	547	5	0.91	0.297 to 2.120
Navia et al.[23]	520	18	3.46	2.064 to 5.416
Fortunato et al.[24]	97	4	4.12	1.135 to 10.22
Total (fixed effects)	1,289	30	2.28	1.535 to 3.246
Total (random effects)	1,289	30	2.59	1.090 to 4.713

Tests for heterogeneity: Cochran Q = 10.51, p = 0.015; I^2 = 71.5% (95% CI 18.7 to 90.0)
CI, confidence interval

Table 2. Comparison of the current study results with 30-day outcomes of major randomized trials and registries including surgical aortic valve replacement in intermediate and low risk patients.

Intermediate risk:

Endpoint	Current study	PARTNER 2A[5]	SURTAVI[25]
Mean STS score	5.1%	5.8%	4.5%
All-cause death	6.1%	4.1%	1.7%
Stroke	1.7%	6.1%	5.6%
Myocardial infarction	0.2%	1.9%	1.0%
Permanent pacemaker	2.4%	6.9%	6.6%
Mediastinitis	1.5%	ND	ND
Redo for bleeding	3.4%	ND	ND

Low risk:

Endpoint	Current study	NOTION[26]	GARY[27]	OBSERVANT[28]	PARTNER 3[31]	EVOLUT[32]
Mean STS score	1.5%	3.1%	1.8%	2.5%	1.9%	1.9%
All-cause death	2.7%	3.7%	2.7%	2.9%	1.1%	1.3%
Stroke	0.9%	3.0%	ND	1.1%	2.4%	3.4%
Myocardial infarction	0.4%	6.0%	ND	ND	1.3%	1.3%
Permanent pacemaker	2.6%	1.6%	ND	2.6%	4.0%	6.1%
Mediastinitis	1.1%	ND	ND	ND	ND	ND
Redo for bleeding	2.2%	ND	ND	ND	ND	ND

ND, no data available

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