Valvular and Congenital Heart Disease

Immediate and late outcome of patients aged 80 years and older undergoing isolated aortic valve replacement: A systematic review and meta-analysis of 48 studies

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Objective This study was planned to evaluate the outcome of patients ≥80 years old undergoing isolated conventional aortic valve replacement (AVR).

Methods Systematic review of the literature and meta-analysis of data on octogenarians and nonagenarians who underwent isolated AVR were performed.

Results The literature search yielded 48 observational studies reporting on 13,216 patients ≥80 years old. Pooled proportion of immediate postoperative mortality was 6.7% (95% CI 5.8-7.5, 47 studies, 13,092 patients), and it was 5.8% (95% CI 4.8-6.9) in 18 studies with a mid-date from 2000 to 2006 and 7.5% (95% CI 6.8-8.2) in 30 studies with a mid-date from 1982 to 1999 (P = .004). Pooled proportion of postoperative stroke was 2.4% (95% CI 2.1-2.7, 21 studies, 8,436 patients), that of postoperative dialysis was 2.6% (95% CI 1.6-3.8, 10 studies, 1,945 patients), and that of postoperative implantation of a pacemaker was 4.6% (95% CI 3.6-5.8, 6 studies, 1,470 patients). Pooled survival rates at 1, 3, 5, and 10 years after isolated AVR were 87.6%, 78.7%, 65.4%, and 29.7%, respectively.

Conclusions Immediate postoperative mortality and morbidity after isolated AVR in patients ≥80 years old are rather low. Postoperatively mortality decreased even further in the most recent series. Importantly, isolated AVR in these high-risk patients was associated with good late survival. These findings suggest that advanced age alone cannot be considered as a contraindication to conventional isolated AVR and that any new valve prosthesis implanted in these patients should be durable enough to guarantee the results so far offered by conventional surgery. (Am Heart J 2012;163:477-85.)

In Europe, the number of people ≥80 years old is growing fast (Figure 1) and is projected to almost triple from 21.8 million in 2008 to 61.4 million in 2060.1,2 Data from the United Nations suggest that by 2050, the over-80-year age group is projected to number 379 million worldwide, which is about 5.5 times as many in 2000 when there were 69 million persons aged ≥80 years.3

Because advanced age is associated with aortic valve sclerosis,4,5 this will lead to an increased need of treatment for degenerative aortic valve disease. In 1993, a Finnish study on a random population showed that critical aortic valve stenosis was present in 2.9% of 476 subjects aged 75 to 86 years.6 Because in the near future, the number of very old patients with severe aortic valve stenosis will significantly increase with a clear impact on the burden of its diagnosis and treatment, evaluation of current results are of utmost importance to establish the value of traditional valve surgery. This would provide an estimate of potential benefits and costs associated with the use of transcatheter aortic valve implantation (TAVI) in this growing, high-risk patient population. This issue has been, herein, investigated by systematic review and meta-analysis of studies reporting results after isolated aortic valve replacement (AVR) in patients aged ≥80 years.

Materials and methods

This meta-analysis was performed in accordance with the Cochrane Handbook for Systematic Reviews.7 An English language literature review was performed through PubMed, Scopus, Science Direct, and Cochrane Library up to January...
2011 for any study evaluating the outcome after reoperation for bleeding after coronary artery bypass graft surgery. The words used in the search were as follows: “aortic valve replacement,” “octogenarian,” “nonagenarian,” and “80 years old.” Reference lists of obtained articles were searched as well.

Inclusion criteria
Studies published in English language as full-length article and reporting on the outcome of patients ≥80 years old who underwent isolated AVR were considered for this analysis. Studies including any other associated cardiac surgery procedure and not reporting outcome data on isolated AVR were excluded from this analysis. The language of the articles was defined as reported in PubMed. We did not include in this study unpublished data or data reported only in abstract. We applied the guidelines for Meta-analysis of Observational Studies in Epidemiology.

Data collection and assessment of data quality
One investigator (F.V.) identified the articles potentially dealing with this topic. Two investigators (F.V., F.B.) independently abstracted data from all eligible studies using a standardized Excel file. These authors retrieved data on study design, study period, and mid-date (defined as the middle year of the study period), study size, patient demographics, type of intervention, and 30-day/in-hospital outcome as well as long-term survival. No attempt was made to get missing data from the authors. Any disagreement was solved by consensus by these 2 coauthors.

Outcomes of interest
The main outcome end points of this study were immediate postoperative (defined as any death occurring during in-hospital stay or 30-day postoperative period) and long-term mortality. Secondary outcome end points were stroke, acute renal failure requiring dialysis, the need of pacemaker implantation, and the length of intensive care unit and in-hospital stay. The outcome end points criteria were according to the definition criteria used in the studies.

Statistical analysis
A meta-analysis of proportions was conducted. Analysis was performed by calculating the number of patient at risk from available survival curves and tables by using a spreadsheet developed by Tierney and collaborators. First, to establish the variance of raw proportions, a Freeman-Tukey transformation was applied. Second, to incorporate heterogeneity (which was anticipated among the included studies), transformed proportions were combined using random effects models. Finally, the pooled estimates were back-transformed. Heterogeneity across studies was evaluated using the Cochran Q test. Thus, the results were presented as pooled proportions (%) with 95% CI. All these
analysis were performed using the freely downloadable software package META for R version 2.13.1.13

Univariate analysis was performed using Mann-Whitney test and Spearman test considering each study’s proportions of immediate postoperative mortality and stroke as dependent variables. These analyses were carried out using PASW statistical software (version 18; IBM SPSS Inc, Chicago, IL). A P value <.05 was considered statistically significant.

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### Results

#### Literature search

The literature search performed on January 2011 yielded 3,364 articles, of which 1,019 were found to be
pertinent with this topic. Forty-eight articles14–61 were found to report data of interest and fulfilled the inclusion criteria of the present study (Figure 2). These studies included 13,216 patients ≥80 years old who underwent primary or redo isolated AVR. Forty-seven studies including 13,092 patients contributed to analysis of immediate postoperative mortality, whereas 28 studies including 3,863 patients contributed to analysis of late survival. Table I summarizes the main characteristics of these studies.

### Immediate postoperative mortality

Pooled proportion of immediate postoperative mortality was 6.7 % (95% CI 5.8-7.5, 47 studies, 13,092 patients), with a significant heterogeneity across studies (P = .0001) (Figure 3). Funnel plot did not show any significant publication bias (Figure 4). Studies with a mid-date from 2000 to 2006 had a pooled proportion of immediate postoperative mortality of 5.8 % (95% CI 4.8-6.9), whereas it was 7.5% (95% CI 6.8-8.2) in studies with a mid-date from 1982 to 1999 (P = .009). Mid-date of studies significantly correlated with postoperative mortality (ρ = −0.307, P = .032 (Figure 5), also when adjusted for the number of patients (P = .044).

Pooled proportion of immediate postoperative mortality was 6.0% (95% CI 4.7-7.4) in audited registries16,26,34,43,55,58 and 7.1% (95% CI 6.3-8.0) in institutional series (P = .176).

Three studies18,33,35 included a variable number of patients operated on through ministernotomy. Their pooled proportion of immediate postoperative mortality was 5.8 % (95% CI 1.6-12.3). Only one study18 included a series of 249 patients who underwent AVR exclusively through ministernotomy and reported a 30-day mortality rate of 3.2%.
Four studies\textsuperscript{16,20,37,44} reported data on primary isolated AVR in 841 patients, and their pooled proportion of immediate postoperative mortality was 4.6% (95% CI 3.3-6.1). Eight studies\textsuperscript{18,31,33,35,36,51,53,55} reported data on 1,981 patients, among whom there were patients with prior cardiac surgery, and the corresponding pooled proportion of immediate postoperative mortality was 6.6% (95% CI 5.0-8.3) (Table I).

Four studies\textsuperscript{16,20,33,36} reported on logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) and the immediate postoperative mortality. The pooled logistic EuroSCORE was 15.0% (95% CI 11.9-18.0), and the pooled proportion of mortality was 6.1% (95% CI 3.5-10.5, predicted-to-observed ratio 2.5).

Other immediate postoperative adverse events
Pooled proportion of postoperative stroke was 2.4% (95% CI 2.0-2.9, \( P \) value for heterogeneity = .215, 21 studies, 8,436 patients) (Figure 6). Eleven studies with a mid-date from 2000 to 2006 had a pooled stroke proportion of 2.3% (95% CI 1.9-2.8), and it was 2.3% (95% CI 1.6-3.2) among 10 studies with a mid-date from 1982 to 1999. Accordingly, mid-date of studies did not correlate with postoperative stroke (\( \rho = 0.275, P = .228 \)).

Pooled proportion of postoperative dialysis was 2.6% (95% CI 1.6-3.8, \( P \) value for heterogeneity = .030, 10 studies, 1,945 patients). Pooled proportion of implantation of pacemaker was 4.7% (95% CI 3.4-6.1, \( P \) value for heterogeneity = .242, 6 studies, 1,470 patients). The mean length of stay in the intensive care unit was 3.5 days (95% CI 2.8-4.3, \( P \) value for heterogeneity = .300, 6 studies, 1,172 patients), and the mean length of in-hospital stay was 13.3 days (95% CI 11.1-15.6, \( P \) value for heterogeneity = .242, 9 studies, 1,172 patients).

Late survival
Pooled proportions of late survival are summarized in Figure 7. Data are characterized by significant heterogeneity at all intervals. Pooled survival rates at 1, 3, 5, and 10 years were 87.6%, 78.7%, 65.4%, and 29.7%. Studies with a mid-date after 1999 and those with an earlier mid-date had similar pooled 5-year survival (65.4% [95% CI 58.3-71.8%] vs 65.2% [95% CI 62.3-73.3%]).

Discussion
The present results suggest that isolated AVR in patients \( \geq 80 \) years old is associated with a rather low postoperative mortality rate. This seems to have also markedly decreased during the last years as a result of remarkable advances in perioperative management.\textsuperscript{16,58} Even lower were the rates of postoperative stroke, need of dialysis, and, surprisingly, need of pacemaker implantation. The pooled length of stay in the intensive care unit and in-hospital were, however, rather long, and this tells us that recovery after isolated AVR is often slow and complicated in the very old patients, but such a high price is paid back by excellent late survival (Figure 7). We do not have data about the intrinsic durability of aortic valve prosthesis
and its possibly related late adverse events in these patients, but we assume that it might not differ from those of younger patients.

“What experience and history teach is this, that people and government never have learned anything from history, or acted on principles deduced from it”: these words by Hegel are valuable also in our daily clinical practice, where experience and developments of several decades are often not taken into account in favor of new, often less invasive, treatment methods without enough data on their efficacy and durability. In an era of enthusiasm toward emerging minimally invasive technology in the management of cardiovascular disease, the present study may be considered as a historical report of the results of an old treatment method in high-risk patients with a short-life expectancy. However, looking at these data, we got an unexpected picture of this old surgical procedure. Considering that, herein, the pooled survival rates at 5 and 10 year were 65% and 30%, respectively, cardiologists and surgeons must be aware that a large number of patients have a long expectancy of life despite their advance age and, therefore, would require a durable procedure. The recent large study by Elbardissi and colleagues,18 who reported 30-day and 5- and 10-year survival rates of 70%, 77%, and 56%, after isolated AVR through ministernotomy in patients ≥ 80 years old, provides important insights into the excellent benefits associated with conventional aortic valve surgery. Other recent series also reported 5-year survival rates of more than 70%, which confirm that survival after conventional aortic valve surgery in patients ≥ 80 years old may approach that after coronary artery bypass surgery.62

Transcatheter aortic valve implantation is referred as particularly suitable in the very old patients, and its use is rapidly spreading. However, there are not much data on the outcome after TAVI in patients ≥ 80 years old. The series by Bekeredjian and colleagues is, so far, the only one including only patients ≥ 80 years old undergoing TAVI. The authors reported on 87 patients whose 30-day mortality was 6.9%, but no data either on postoperative complications or on late outcome were reported. With regard to postoperative complications, some studies considering patients with a mean age of more than 80 years reported an incidence of postoperative stroke ranging from 0.6% to 7% after TAVI, whereas, herein, the pooled rate of stroke after isolated AVR in patients ≥ 80 years old was 2.4%. Pooled analysis of 6 studies showed a rate of permanent pacemaker implantation after isolated AVR of 4.6%, whereas its implantation has been reported in up to one third of patients undergoing TAVI.67 This complication has significant clinical and economical implications and must be considered as an important outcome end point in this setting.

The present results are of economical importance as isolated AVR in the very old patients who are fit for
surgery can be associated with significantly reduced costs compared with TAVI. In fact, at our institution, the costs of AVR average 19,000 euros, whereas TAVI approaches 30,000 euros. Despite such costs may significantly change during the next future, at this stage, even if TAVI can be considered noninferior to AVR, its associated incremental costs along with the lack of data about its durability may pose a contraindication to TAVI in patients fit for surgery.

Four studies reported on logistic EuroSCORE, and this prevented us to use this score in sensitivity analysis. These results confirmed that EuroSCORE markedly overestimates the operative risk. Recent refinements of the original EuroSCORE are expected to enhance its predictive accuracy also in patients undergoing AVR and become a valid parameter for risk adjustment analysis.

The present findings must be viewed in light of a preoperative selection bias, which certainly contributed to such excellent results. These patients are “self-selected” by their preoperative status because not infrequently octogenarians and nonagenarians with aortic valve disease are left untreated because of prohibitive operative risk and poor life expectancy. Therefore, the present results are representative only for the very old patients who are fit for surgery.

In conclusion, isolated AVR can be performed with a low risk of major complications in patients ≥80 years old. Importantly, pooled analysis of late results indicates that late survival in the very old patients undergoing isolated AVR can be surprisingly good and suggest that any new valve prosthesis implanted in these high-risk patients should be durable enough to guarantee the results so far offered by conventional surgery.

**Disclosures**

None of the authors have any conflicts of interest. This study was not financially supported.

**References**


