Long-Term Outcomes of Conventional Aortic Valve Replacement in High-Risk Patients: Where Do We Stand?

doi: 10.5761/atcs.oa.16-00165

Original Article

Long-Term Outcomes of Conventional Aortic Valve Replacement in High-Risk Patients: Where Do We Stand?

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Purpose: The introduction of transcatheter aortic valves has focused attention on the results of conventional aortic valve surgery in high-risk patients. The aim of the study was to evaluate 5-years outcomes in this category of patients in the current surgical era.
Methods: This is an observational retrospective study of 581 high-risk patients undergoing aortic valve replacement from 2008 to 2013, with a mean logistic EuroSCORE of 26.6% ± 14.6%. Data were prospectively collected in a database of Emilia-Romagna region (Italy).
Results: Overall 30-day mortality was 9.3%. Stroke rate was 1.5%. At 1-, 3-, and 5-years overall mortality was 18.2%, 30.4%, and 42.2%, cardiac death rate was 3.9%, 9.2%, and 12.9%, stroke rate 2.5%, 7.7%, and 10.2%, re-operation occurrence 0.2%, 0.9% and 1.3%, and new pacemaker implantation was 2.3%, 5.1% and 7.8%. At multivariate analysis, urgency, hemodynamic instability, LVEF ≤30%, NYHA III-IV, severe chronic obstructive pulmonary disease (COPD), extra-cardiac arteriopathy, cerebrovascular disease, and creatinine >2.0 mg/dL remained independent predictors of 5-year mortality.
Conclusion: The results of the current study add weight to the evidence that traditional aortic valve replacement can be performed in high-risk patients with satisfactory 5-year mortality and morbidity. Our study may help to improve decision-making in this category of high-risk patients with aortic valve disease.

Keywords: heart valves, aortic stenosis, cardiac surgery

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Introduction

Aortic stenosis (AS) is the most commonly acquired valvular disease in elderly patients in the developed world.[1,2] After the onset of symptoms, patients with severe AS have a poor prognosis with a one-year mortality of 30%–50% with conservative therapy.[3,4] Given current population projections, it is reasonable to expect that the number of patients affected by aortic valve disease will also increase in the coming years.

Surgical aortic valve replacement (SAVR) has become the therapeutic gold standard with well-documented benefits in terms of symptoms relief and survival,[5] also in elderly patients.[6] Recent technological advances in

transcatheter aortic valve replacement (TAVR) proved this new approach as an effective, alternative treatment to conventional SAVR in selected patient populations.[7,8]

An evaluation of outcomes after SAVR in high-risk surgical patients is required in order to identify the best option for each patient population. Recent observational studies have demonstrated that elderly patients or those with depressed left ventricular function or affected by systemic coexisting disorders are at increased risk for operative mortality or morbidity.[5,9–13]

To cast further light on these issues, we conducted this registry study reporting outcomes from a large regional series of high-risk patients undergoing SAVR, with or without associated coronary artery bypass grafting (CABG) from 2008 through 2013 in Emilia Romagna (ER), Italy. The main purpose was to assess 30-day mortality and morbidity, and 5-year outcomes (all-cause mortality, cardiac related death, stroke, re-operation, definitive pacemaker implantation); the second aim was to identify and discuss the potential risk factors for increased early and late mortality.

Materials and Methods

Database and patients selection

ER is an Italian region with about 4 million inhabitants where six hospitals (two public University Hospitals and four private Hospitals) perform cardiac surgery. Since 2002, the Agency for Health and Social Care of ER region has maintained the Registro dell'Emilia Romagna degli Interventi Cardiochirurgici (RERIC)Registry that is a prospective database designed to collect pre-, intra- and postoperative reports from all the patients undergoing cardiac surgery in the ER region. The rationale and methodology of RERIC have been described previously.[14]

The Regional Agency for Health and Social Care is the central core statistical laboratory and is responsible for data quality/completeness control. Information on the occurrence of follow-up outcomes is obtained by linking the RERIC to the ER regional mortality registry, and the regional hospital admission database. RERIC registry is based on current clinical practice, but the requirement for individual patient consent was waived because of the retrospective design of the data analysis and because patients underwent routine surgical care. All data were anonymized and de-identified prior to analysis by the central statistical laboratory of the Regional Agency for Health and Social Care. The protocol of the study is in accordance with the Declaration of Helsinki.

From January 2008 through September 2013, data from 5331 aortic valve surgery procedures with or without associated CABG were collected. As already described in other studies[15–17] patients with severe symptomatic aortic valve stenosis and a logistic EuroSCORE ≥15 are generally considered to be at high surgical mortality risk, and are frequently evaluated for transcatheter aortic valve implantation (TAVI) treatment by the transapical or transfemoral approach. Moreover, a risk of death of at least 15% by 30 days after the procedure qualified high-risk patients for the enrolment in the surgical arm of the pivotal PARTNER A trial.[8] Thus the aim of the study was to evaluate outcomes of high-risk patients undergoing SAVR with a logistic EuroSCORE predictive of at least 15% mortality risk after the procedure. We opted to include patients operated during a 5 year period in order to review a contemporary series of consecutive patients, avoiding enrolment periods spanning decades. The study finally included 581 very high-risk patients with logistic EuroSCORE 15% or greater who underwent SAVR with or without CABG. Patients who underwent re-operation cardiac surgery were included. Patients with concomitant mitral or ascending aorta, or carotid pathologies requiring surgery were excluded. Patients not resident in the ER region (95 patients) were included in 30-day outcomes analysis and excluded from the mid- and long-term statistical analysis because of lack of information about their clinical status in the follow-up. The remaining 486 patients were followed through September 2014.

Statistical analysis

Categorical variables were reported as percentage whereas continuous variables were expressed as the mean ± standard deviation (SD). All preoperative and intraoperative characteristics of patients stratified by logistic EuroSCORE, respectively 15% or greater and lower risk, were compared by the Chi-square test, if categorical variables, and by Mann-Whitney U test if continuous variables. P value of 0.05 or lower indicated statistical significance.

Only for regional patients cumulative risk curves for death (taking into account also perioperative deaths), cardiac related death, postoperative stroke, re-operation and pacemaker implantation were estimated at 5 years using Kaplan–Meier method and compared by log-rank test.

Independent variables predictive of 5-year mortality were evaluated with Cox proportional hazards model and the proportional hazard assumption was confirmed using Schoenfeld residuals test.

Table 1 Preoperative Demographics and Risk Factors

Patients variables	No. Pts Log. EuroSCORE <15%	%Log. EuroSCORE <15%	No. Pts Log. EuroSCORE ≥15%	%Log. EuroSCORE ≥15%	P-value
Female	4750	43.3	581	47.8	0.0381
Mean age (± SD)	4750	71.6 (± 10.6)	581	77.5 (± 8)	<.0001
Age ≥80	4750	21.1	581	47.8	<.0001
Biological prostheses	4750	86.9	581	91.6	0.0013
AVR + CABG	4750	24.9	581	31.7	0.0004
Body Mass Index ≥30	4750	24.3	581	16.4	<.0001
Emergency	4750	0	581	5	<.0001
Urgency	4750	9.3	581	28.6	<.0001
Previous PCI	4750	10.9	581	14.1	0.0191
Previous cardiac surgery	4750	4	581	32.2	<.0001
Recent AMI	4750	3.1	581	18.8	<.0001
Congestive heart failure	4750	2.4	581	13.9	<.0001
Unstable angina	4750	1.9	581	14.6	<.0001
Pulmonary hypertension	4750	0.3	581	5	<.0001
Haemodinamic instability	4750	0.1	581	7.9	<.0001
Cardiogenic shock	4750	0.1	581	3.1	<.0001
LVEF ≤30%	4750	1.6	581	12.7	<.0001
LVEF 30%–50%	4750	15.9	581	40.1	<.0001
Mean Log. EuroSCORE (± SD)	4750	5.6 (± 3.3)	581	26.6 (± 14.6)	<.0001
NYHA III-IV	4750	41.6	581	68.3	<.0001
CCS 3-4	4750	4.6	581	18.9	<.0001
Diabetes	4744	19.8	581	27.4	<.0001
Dialysis	4750	0.5	581	1.7	0.0003
Creatinine ≥2 mg/dl	4750	1.2	581	8.4	<.0001
Severe COPD	4750	4	581	12.4	<.0001
Systemic hypertension	4678	74.3	576	79.9	0.0036
Peripheral neurologic dysfunction	4750	0.7	581	7.6	<.0001
Central neurologic dysfunction	4750	0.9	581	9.3	<.0001
Cerebrovascular disease	4750	17.3	581	17.2	0.935
Extra-cardiac arteriopathy	4750	9.4	581	45.1	<.0001
Active infective endocarditis	4750	1.5	581	15.3	<.0001
Active neoplasm	4750	0.7	581	0.7	0.9411

AVR: aortic valve replacement; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; AMI: acute myocardial infarction; LVEF: left ventricular ejection fraction; NYHA: New York Health Association; CCS: Canadian Cardiovascular Society; COPD: chronic obstructive pulmonary disease; SD: standard deviation

Table 2 30-day outcomes

Outcomes	All patients (n = 581)	
Overall 30-day death	54	9.3%
Transient ischemic attack	4	0.7%
Acute myocardial infarction	5	0.9%
Permanent stroke	9	1.5%
Re-exploration for bleeding	37	6.4%
Cardiac tamponade	6	1%
Re-exploration for sternal dehiscence	12	2.1%
Vascular complications	6	1%
Septicemia	11	1.9%
Pneumonia	8	1.4%
Gastrointestinal bleeding or complications	11	1.9%
Postoperative atrial fibrillation	175	30.1%
Complete atrio-ventricular block	51	8.7%
Definitive pacemaker implantation	4	0.7%
Prolonged mechanical ventilation	77	13.3%
Acute renal failure	41	7%
Dialysis	38	6.5%
Multisystem organ failure	19	3.3%

Statistical Analysis Software (SAS) 9.1 software was used to perform all the statistical analysis.

Results

The preoperative characteristics are summarized in **Table 1**. As compared to lower risk patients, those with logistic EuroSCORE 15% or greater were more likely female, with a smaller body mass index, and elderly, with a mean age of 77.5 ± 8 years. As expected, these high-risk patients were more likely to present with symptoms and pre-operative comorbidities such as of New York Health Association (NYHA) III-IV, Canadian Cardiovascular Society (CCS) III-IV, congestive heart failure, urgent surgery, hypertension, diabetes, cerebrovascular disease, previous cardiac surgery procedures, and previous percutaneous coronary interventions.

Bioprosthetic valves were implanted in over 90% of patients in this population. Concomitant CABG was performed in 184 patients (31.7%). As a logistic EuroSCORE, the predicted hospital mortality of our study cohort was 26.6% ± 14.6%.

Thirty-day outcomes are presented in **Table 2**. Overall 30-day mortality was 9.3% (54 pts). In the subgroup of 397 isolated SAVR patients, 30-day mortality was 9.6% (38 pts). In the subgroup of 184 patients who received concomitant CABG 30-day mortality was 8.7% (16 pts). Transient neurologic events (TIA) were uncommon (0.7%), and the rate of permanent stroke was 1.5% (9 pts).

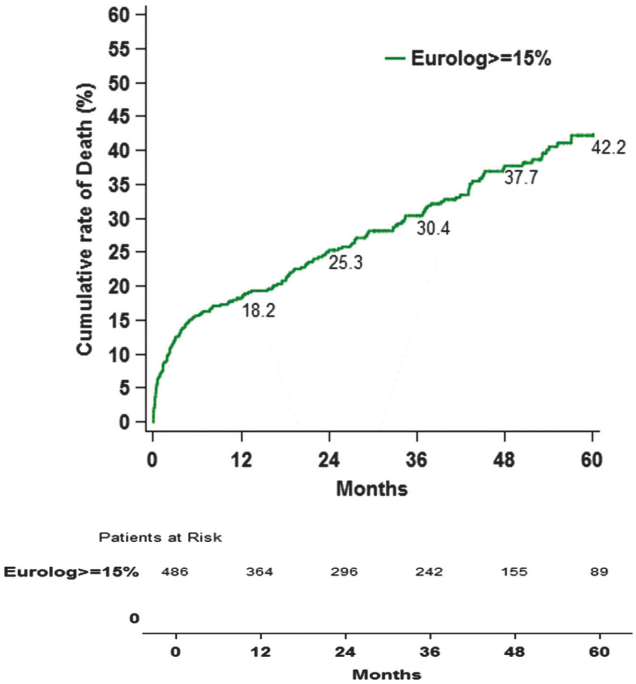

Fig. 1 Kaplan–Meier risk curve: Five years all-cause mortality.

A definitive pacemaker was implanted in four patients (0.7%) during the index hospital admission.

Multivariate analysis revealed urgency (OR 1.9, 95% CI 1.0 to 3.4; p = 0.04), cardiogenic shock (OR 3.8, 95% CI 1.3 to 11.4; p = 0.01), NYHA III-IV (OR 2.3, 95% CI 1.1 to 5.1; p = 0.03), and severe COPD (OR 2.7, 95% CI 1.3 to 5.4; p = 0.006) to be independent predictors of 30-day mortality.

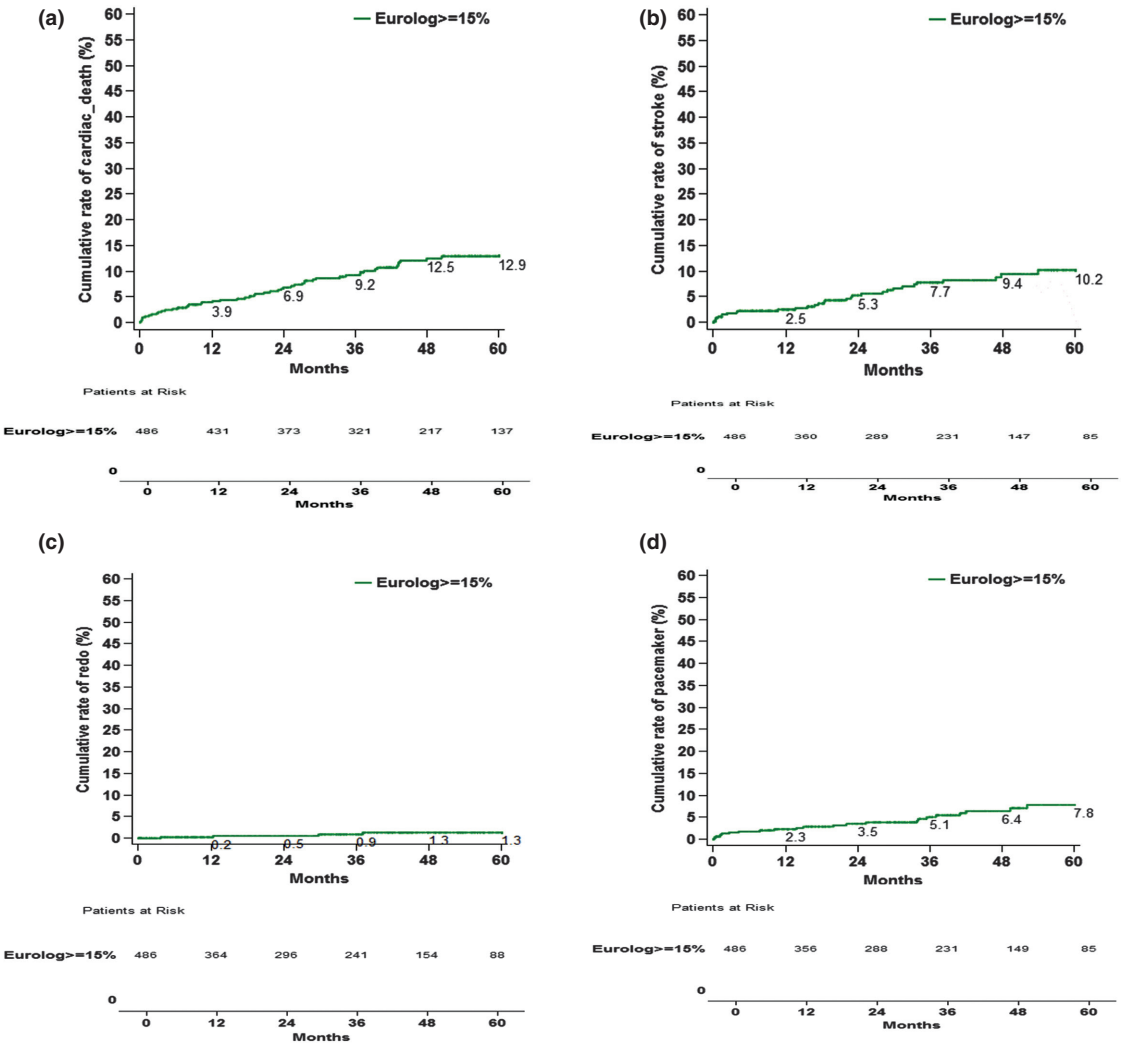

Fig. 2 (**a**) Kaplan–Meier risk curves: Five years cardiac related mortality; (**b**) Kaplan–Meier risk curves: Five years stroke rates; (**c**) Kaplan–Meier risk curves: Five years re-operation rates; (**d**) Kaplan–Meier risk curves: 5 years definitive pacemaker implantation rates.

Survival data at follow-up were obtained for all the 486 patients resident in the ER region (83.6%). Mean follow-up time was 40.8 months. In this high-risk population, overall mortality estimated at 1-, 3-, and 5-years was 18.2%, 30.4%, and 42.2%, respectively (**Fig. 1**). At the same follow-up time intervals (**Fig. 2a–2d**), cardiac death rate was 3.9%, 9.2%, and 12.9%, cumulative rates of stroke resulted 2.5%, 7.7%, and 10.2%, re-operation rates were 0.2%, 0.9% and 1.3%, and finally post-operative pacemaker implantation rates were 2.3%, 5.1% and 7.8% at 1-, 3-, and 5-years, respectively.

As shown by the multivariable Cox proportional hazards model, urgency, hemodynamic instability, LVEF ≤30%, NYHA III-IV, severe COPD, extra-cardiac arteriopathy, cerebrovascular disease, and creatinine levels >2.0 mg/dL remained independent predictors of 5-year mortality (**Table 3**).

Discussion

SAVR is a procedure with a history of more than 50 years of continuous improvement. It is safe and can be performed through a limited thoracotomy or ministernotomy with excellent outcomes and proven long-term durability. Morbidity and mortality rates are low, and hemodynamic performance is good. In a contemporary study of high-risk patients (mean age, 80.4 ± 3.6 years; mean logistic EuroSCORE, 13% ± 7%), the hospital mortality after SAVR was 1.3%,[18] confirming that quality of life is good after SAVR, and the procedure is cost-effective.

Table 3 Predictors for the 5-year mortality risk (Cox proportional hazards model)

	Hazard Ratio	95% CI	P-value
Urgency	1.4	1.0–2.0	0.05
Hemodynamic instability	2.2	1.4–3.5	0.001
LVEF ≤30%	1.6	1.0–2.5	0.04
NYHA III-IV	1.5	1.0–2.2	0.04
Severe COPD	2.1	1.3–3.3	0.001
Extra-cardiac arteriopathy	1.6	1.1–2.2	0.007
Cerebrovascular disease	1.8	1.2–2.9	0.01
Creatinine levels ≥2 mg/dL	2.5	1.5–3.9	0.0002

LVEF: left ventricular ejection fraction; NYHA: New York Health Association; COPD: chronic obstructive pulmonary disease

TAVR has evolved rapidly from an experimental to a routine procedure. Randomized trials have demonstrated that TAVR offers a survival benefit in patients deemed at prohibitive risk for surgery[7] and has early and midterm survival outcomes similar to those of SAVR in a high-risk population.[8] On the basis of these excellent results, recent guidelines recommend that TAVR can be performed in inoperable patients with severe AS.[19] Recently, the PARTNER 2 Investigators found that in intermediate-risk patients with severe symptomatic aortic stenosis, SAVR and TAVR reported similar results with respect to the primary end point of death or disabling stroke for up to 2 years and resulted in a similar degree of improvement of cardiac symptoms.[20] However, before the indications are possibly further extended, the risk-benefit ratio needs to be evaluated particularly because long-term outcomes of TAVR procedures are largely unknown and must be compared to long-term results of SAVR. The aim of the study was to evaluate 5-years outcomes of high-risk SAVR patients, with a logistic EuroSCORE of at least 15%, as reported in the inclusion criteria of other recent publications.[15–17]

In the current study, 30-day mortality and morbidity compared favorably with other reported observational SAVR series.[5,9–13] Interestingly, in our study the uni- and multivariate statistical analyses both showed that preoperative and clinical patient-related factors appear to be major determinants of early survival. This confirms that a delay in surgical intervention in patients with initial deterioration of clinical status with multi-organ failure in fact negatively influences outcomes, not only of SAVR but also of TAVR procedures, as recently reported.[21] Moreover older age, and previous cardiac surgery did not emerge as risk factors for 30-day mortality in our high-risk SAVR population.

Another interesting finding of our study was that concomitant CABG was not a significant risk factor for 30-day mortality and did not worsen 30-day outcomes of our population. Our results do not support the hypothesis reported by other authors that high-risk patients requiring AVR and CABG should be the target of future treatment strategies such as endovascular and/or hybrid procedures.[22,23] The recent American Heart Association (AHA)/American College of Cardiology (ACC) guidelines state that CABG is reasonable in patients undergoing valve repair or replacement with significant CAD (≥70% reduction in luminal diameter in major coronary arteries or ≥50% reduction in luminal diameter in the left main coronary artery). (Class 2A, Level of Evidence: C).[19]

In the current study, overall mortality estimated at 1-, 3-, and 5-years was 18.2%, 30.4%, and 42.2%, and at the same follow-up time intervals cardiac death rate was 3.9%, 9.2%, and 12.9%. As expected, these results were significantly worse than those reported in the subgroup of patients with logistic EuroSCORE <15. Although these results compare well with previously reported midterm survival results in high-risk patients undergoing AVR,[5,9–13] direct comparisons cannot be made because these previous observational studies evaluated elderly patients or those with depressed left ventricular function or affected by systemic coexisting disorders, not further stratified by EuroSCORE. Advancements in preoperative assessment, intraoperative surgical techniques, and intensive postoperative care have contributed to improve in the last years the overall and the cardiac related mortality in this high-risk cohort of patients who underwent SAVR.

In the current study, the satisfactory stroke rates estimated at 1-, 3-, and 5-years were 2.5%, 7.7%, and 10.2%, respectively, although higher than those reported in the subgroup of patients with logistic EuroSCORE <15. In a recent paper reporting basic data from 176 studies on the immediate outcome of after SAVR with or without CABG, stroke rate was 2.1% after isolated SAVR and 3% after

SAVR associated with CABG.[22] Recently the PARTNER IA Trial showed rates of major stroke in SAVR arm at one and five years of 3.2%, and 11.3%, respectively.[24] A meta-analysis of randomized, clinical trials also confirmed a significantly higher incidence of stroke with TAVR compared with SAVR at a mean follow-up of 99 weeks.[25]

Information about the occurrence of valve-related complications in the follow-up (thromboembolism, endocarditis, anticoagulant-related haemorrhage, paravalvular leak) were not collected and analyzed in this study. However, the reoperation rates in our series were very low, at 1-, 3-, and 5-years 0.2%, 0.9% and 1.3%, respectively. Interestingly no significant statistical difference was found between the groups of patients with logistic EuroSCORE <15 and logistic EuroSCORE ≥15. On the basis of our results we can only indirectly infer that prosthetic structural failure requiring surgery or significant paravalvular leak, that remains the Achilles heel of TAVR procedures, occurred very rarely in this series of high-risk SAVR patients.

Postoperative complete atrio-ventricular block occurred in 51 patients (8.7%), but it was transient in most of them. In fact definitive pacemaker implantation was necessary only in four of them. Post-operative pacemaker implantation rates in the follow-up were 2.3%, 5.1% and 7.8% at 1-, 3-, and 5-years respectively, although these results were worse than those reported in the subgroup of patients with logistic EuroSCORE <15. It is well known that the need for pacemaker implantation after aortic valve surgery is related to a consequent well described morbidity. Chronic right ventricular pacing in fact involves negative hemodynamic effects associated with left atrial remodeling, and left ventricular dyssynchrony, resulting in impaired left ventricular function, limited exercise capacity, and progressive left ventricular remodelling, finally leading to heart failure.[26]

Limitations

The current study is retrospective and thus subject to the weaknesses of this type of analysis. Information about any markers of frailty or the occurrence of specific valve-related complications (thromboembolism, endocarditis, anticoagulant-related haemorrhage, paravalvular leakage) was not collected, due to the original design of our regional database, and we were thus unable to analyze the impact of these complications on the 30-day and follow-up results. We had no information about the patients not resident in the ER region and excluded from the 1 and 5-year follow-up analysis because of lack of information about their clinical status in the follow-up. Finally, it is not known how many patients referred for surgery were refused for various reasons in the ER region. Therefore, our real-world registry addresses 5-year outcomes only in the high-risk patients actually undergoing SAVR in these institutions, but not in the larger population of patients potentially suitable for either SAVR or TAVR.

Conclusions

The current study is unique in that we specifically evaluate the results of a large real-world registry reporting the 5-year outcomes of high-risk patients with a mean logistic EuroSCORE of 26.6% ± 14.6%, also providing results on endpoints such as overall death, cardiac death, stroke, repeat hospitalization, and new post-operative pacemaker implantation. The results of the current study add to the increasing weight of evidence that suggests open, traditional SAVR can be performed in high-risk patients with satisfactory 5-year mortality and morbidity. In our study uni- and multivariate statistical analysis showed that preoperative and clinical patient-related factors appear to be major determinants of early and 5-year survival. A delay in surgical intervention in patients with severe AS significantly influences outcomes of SAVR procedures so that candidates suffering from deteriorated clinical status and/or multiorgan failure, experience suboptimal 30-day outcomes.

We hope that those results may be of aid to improve treatment decision-making in high-risk patients with severe aortic valve stenosis.

Acknowledgements

We thank Lois Clegg, English Language Teacher, University of Parma, for her assistance in the revision of the manuscript.

Disclosure Statement

The authors state to have no financial relationship with a biotechnology manufacturer, a pharmaceutical company, or other commercial entity that has an interest in the subject matter or materials discussed in the manuscript.

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