5-year Outcomes of Transfemoral Transcatheter Aortic Valve Replacement or Surgical Aortic Valve Replacement for Patients at Low- and Intermediate Risk: Final Results from the OBSERVANT Study

Running title: TAVR versus SAVR

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ABBREVIATIONS AND ACRONYMS

AS: Aortic Stenosis

SAVR: Surgical Aortic Valve Replacement

TAVR: Transcatheter Aortic Valve Replacement

MACCE: Major Adverse Cardiac and Cerebrovascular Event

CABG: Coronary Artery Bypass Grafting

PPM: Permanent Pacemaker

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Transcatheter aortic valve replacement (TAVR) has moved from the setting of rigorously controlled clinical trials into real-world clinical practice. The long-term effectiveness of TAVR compared to surgical aortic valve replacement (SAVR) in this population remains poorly investigated.

COMPETENCY IN PATIENT CARE: SAVR was superior to transfemoral TAVR using first-generation devices with respect to rates of death from any cause, MACCE and repeat hospitalization due to cardiac reasons at 5-year among “real-world” patients with AS who were at low or intermediate risk for conventional open-chest surgery.

TRANSLATIONAL OUTLOOK: This study provides evidence on the comparative effectiveness of transfemoral TAVR with early-generation devices compared with SAVR in unselected “real-world” population.
STRUCTURED ABSTRACT

OBJECTIVES. To report the 5-year outcomes of the Italian OBSERVANT (Observational Study of Effectiveness of SAVR–TAVI Procedures for Severe Aortic Stenosis Treatment) study.

BACKGROUND. The OBSERVANT study showed that mortality at 1 year is similar after transfemoral transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) for “real-world” propensity-matched patients with aortic stenosis (AS) at low and intermediate risk.

METHODS. The unadjusted enrolled population (N=7,618) between December 2010 and June 2012 included 5,707 SAVR patients and 1,911 TAVR patients. The propensity score method was applied to select 2 groups with similar baseline characteristics. All outcomes were adjudicated through a linkage with administrative databases. The primary endpoints of this analysis were death from any cause and major adverse cardiac and cerebrovascular events (MACCE) at 5 years.

RESULTS. The matched population had a total of 1,300 patients (650 per group). The propensity score method generated a low and intermediate risk population (mean EuroSCORE 2: 5.1±6.2% vs. 4.9±5.1%, SAVR vs. transfemoral TAVR; p=0.485). At 5 years, the rate of death from any cause was 35.8% in the surgical group and 48.3% in the transcatheter group (hazard ratio [HR]: 1.38; 95% confidence interval [CI]: 1.12 to 1.69; p=0.002). Similarly, TAVR was associated in an increased risk of MACCE as compared with SAVR (42.5% vs. 54.0%, HR: 1.35; 95% CI: 1.11 to 1.63; p=0.003). The cumulative incidence of cerebrovascular events, myocardial infarction, and coronary revascularization was similar in the study groups at 5 years.

CONCLUSIONS. The present results suggest that at 5 years, in a “real-world” population with severe AS and at low and intermediate risk, suggest that SAVR is associated in with lower mortality and MACCE rates than transfemoral TAVR performed using first-generation devices. These data need to be confirmed in randomized trials using new-generation TAVR devices.

Key Words: Aortic stenosis, transcatheter aortic valve implantation, aortic valve replacement, TAVI, intermediate risk.
INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is an alternative to surgical valve replacement (SAVR) in high- and intermediate risk patients with aortic stenosis (AS). The Placement of Aortic Transcatheter Valves (PARTNER) I study showed that 5-year mortality after TAVR was superior to medical therapy and balloon valvuloplasty in patients who could not have surgery\(^1\) and was non-inferior to SAVR in high-risk patients who could undergo surgery.\(^2\) Nevertheless, there is still a paucity of prospective and controlled data reporting on the comparative long-term effectiveness of TAVR versus SAVR in a “real world” setting. The OBSERVANT (Observational Study of Effectiveness of SAVR–TAVI Procedures for Severe Aortic Stenosis Treatment) study showed that mortality at 1 year is similar after TAVR or SAVR for “real-world” propensity-matched patients with AS at low and intermediate surgical risk.\(^3\) This report describes the final 5-year clinical outcomes of this study.

METHODS

Study design and patient population

Details of the OBSERVANT study have been previously published.\(^5,6\) Briefly, OBSERVANT (Observational Study of Effectiveness of SAVR–TAVI procedures for severe Aortic stenosis Treatment) is a national observational, prospective, multicenter, cohort study that enrolled consecutive AS patients undergoing TAVI or SAVR at 93 Italian centers (34 cardiology centers and 59 cardiac surgery centers) between December 2010 and June 2012, run by the Italian National Health Institution in cooperation with the Italian Ministry of Health, the National Agency for Regional Health Services, Italian Regions, and Italian scientific societies and federations representing Italian professionals involved in the topic of AS management. Hospitals invited to participate were those where a procedural (SAVR and/or TAVR) treatment could be offered to AS patients. The study protocol complies with the Declaration of Helsinki and it has been approved by the Local Ethics Committee (ASL 2 Melegnano) of the coordinating Institution (Policlinico San Donato). All patients gave an informed consent to the scientific treatment of their data in an anonymous form.
Patients undergoing a transaortic/transapical TAVR and patients reporting porcelain aorta, hostile chest, and those who underwent combined coronary artery bypass grafting or percutaneous coronary intervention have been excluded.

**End points and follow-up**

The primary end points of this analysis were death from any cause, and major adverse cardiac and cerebrovascular events (MACCE) at 5 years. MACCE were defined as the composite of death from any cause, stroke, myocardial infarction, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Prespecified secondary end points included cerebrovascular accidents, acute myocardial infarction, pacemaker implantation, repeat hospitalization due to cardiac reasons and acute heart failure at 5-year.

An administrative follow-up has been set up for each enrolled patient through a record linkage with the National Hospital Discharged Records (HDR) database, for in-hospital events, and with the Tax Registry Information System (TRIS), for information on life status (data provided by Ministry of Health). This approach guaranteed a very low proportion of lost to follow-up.

**Data quality assessment**

Specific quality assessment activities have been arranged to evaluate the reliability of the OBSERVANT database. In particular, independent observers, following specific standard operating procedures (SOPs), monitored the participating hospitals to assess the completeness of the enrolled cohort and to compare the collected data to those reported in the original clinical charts.

**Statistical analysis**

The data are shown stratified by procedure (SAVR/transfemoral TAVR). Continuous variables are presented as mean ± standard deviations and are compared using the Student t test for the descriptive analysis. Categorical variables are presented as counts and percentages and are compared with the chi-square test or Fisher exact test, as appropriate. To overcome possible selection biases, the propensity score method was applied. This approach allowed to select two groups of patients undergoing SAVR and TAVR, respectively, with similar baseline characteristics. The propensity score has been developed using a logistic regression.
and considering the variable “type of intervention” (TAVR vs. AVR) as dependent variable. Adopting a non-parsimonious approach, all measured potential confounders were used in the regression procedure. The propensity score include the following variables: age; sex; previous percutaneous coronary intervention; previous balloon aortic valvuloplasty; previous cardiac surgery; diabetes; chronic obstructive pulmonary disease; smoke; previous myocardial infarction; peripheral arteriopathy; creatinine; critical preoperative state; unstable angina; neurologic dysfunction; pulmonary hypertension (systolic pulmonary arterial pressure >60 mm Hg); chronic liver disease; active neoplastic disease; New York Heart Association (NYHA) class; frailty score (Geriatric Status Scale (16)); left ventricular ejection fraction; coronary artery disease; urgency status; mitral regurgitation. Pairs of TAVR and SAVR patients having the same probability score (nearest neighbor method; caliper = 0.2 * standard deviation of the propensity score logit) have been matched. The Student t-test for paired sample for continuous variables and the McNemar test for dichotomous variables were used to evaluate the balance between the matched groups. Moreover, the standardized differences of baseline variables before and after matching were evaluated to assess the balance in the covariates of the study groups.

With regard to long-term outcomes, hazard ratios (HRs) for death from any cause, MACCE at 5 year, and time-to-event curves were calculated using Cox proportional hazard models, taking into account pairing of data. For the purpose of this analysis, problems related to the linkage keys resulted in 25 pairs of TAVR and SAVR patients that did not link with the administrative databases and were definitively lost to follow-up. Nevertheless, for the survival analysis, they were considered censored at the time of discharge after being hospitalized for the procedure. Moreover, when a patient of a pair is lost to follow up and the matched patient is still alive (or free from the considered event), the time of observation of both patients is truncated at the time of the last observation of the lost patient to maintain the comparability between the two groups. Cumulative incidence functions of stroke, acute myocardial infarction, repeat hospitalization for acute heart failure, and repeat hospitalization for cardiac reasons were estimated using a competing risk regression by the method of Fine and Gray. This method employs a semiparametric regression for survival data in the presence of competing risk, positing a model for the sub-hazard function of a failure event of primary interest. In these analyses, death has been considered a competing event because patients under

6 Second draft MB Sept 2018 Confidential
observation might have died, making it impossible for the event of interest to occur. All statistical analyses were performed using the STATA statistical package version 13 (StataCorp LLC, 4905 Lakeway Drive, College Station, Texas 77845-4512, USA) and SAS version 9.4 (SAS Institute Inc., 100 SAS Campus Drive, Cary, NC 27513-2414, USA).

RESULTS

A total of 7,618 consecutive patients with severe AS who underwent SAVR (n=5,707) or TAVR (n=1,911) were enrolled in the OBSERVANT study. For the purposes of this study only patients who underwent transfemoral TAVR were included (n=1,564; 81.8%).

From the entire cohort, 650 pairs of patients undergoing SAVR and transfemoral TAVR with similar baseline demographic and clinical characteristics were obtained using the propensity score method (Tables 1 and 2). The mean EuroSCORE 2 was 5.1±6.2% for the SAVR group and 4.9±5.1% for the TAVR group (p=0.485). Among TAVR group, the 18-Fr self-expanding CoreValve ReValving System® (CRS) (Medtronic Inc., MN, USA) and the Edwards SAPIEN XT (Edwards Lifesciences, Irvine, California) valves were implanted in 358 (55.1%) and 274 (44.9%) patients, respectively. After the procedure, TAVR yielded a slightly lower mean post-procedural aortic valve gradient than SAVR (13.6±6.7 mmHg vs. 10.3±5.6 mmHg; p<0.001). On the other hand, TAVR was associated with a higher incidence of paravalvular regurgitation, with a higher rate of aortic regurgitation (grade 2 or more) compared with SAVR (2.0% vs. 9.8%; p<0.001).

In the Central Illustration, the time-to-event curves for death from any cause (Central Illustration, Panel A) and MACCE (Central Illustration, Panel B) are shown: TAVR was associated with an increased risk of 5-year mortality as compared with SAVR, (Hazard Ratio [HR]: 1.38, 95% confidence interval [CI], 1.12-1.69; p=0.002) (Central Illustration, Panel A). Similarly, TAVR was associated with an increased risk of MACCE as compared with SAVR, (HR: 1.35, 95%CI 1.11-1.63; p=0.003) (Central Illustration, Panel B). The excess risk of TAVR vs. SAVR, as assessed by competing risk regression approach, was not statistically significant for acute myocardial infarction (HR: 0.95, 95%CI 0.53-1.71; p=0.873), (Figure 1, Panel A) cerebrovascular events (HR: 1.22, 95%CI 0.82-1.82; p=0.318) (Figure 1, Panel B), re-do aortic valve procedures (HR: 0.29, 95%CI 0.60-
1.39; p=0.121) (Figure 2, Panel B), re-hospitalization due to cardiac reasons (HR: 1.12, 95%CI 0.94-1.33; p=0.208) (Figure 1, Panel D), and due to acute heart failure (HR: 1.19, 95%CI 0.98-1.43; p=0.073) (Figure 1, Panel C). On the contrary, permanent pacemaker implantation rate was significantly higher in the TAVR group (HR: 2.72, 95%CI 2.00-3.71; p<0.001) (Figure 2, Panel A).

In Table 2 major clinical outcomes at 1-year and 5-year of the propensity score-matched population are reported. At 5-year, the rate of death from any cause was 35.8% in the surgical group as compared with 44.5% in the transcatheter group (p<0.001). In the 1-year analysis, the corresponding rates were 13.6% and 13.8% (p=0.912). Regarding MACCE, the cumulative 5-year incidence was 42.5% and 54.0% in the SAVR and TAVR group, respectively (p<0.001); the corresponding rates were 17.6% and 18.2% (p=0.796) in the 1-year analysis. Similarly, the comparison between SAVR and TAVR groups in terms of re-hospitalization due to acute heart failure showed that the cumulative incidence becomes significantly different only in the 5-year analysis (1-year: 19.7% vs. 19.0%, p=0.722; 5-year: 35.7% vs. 42.5%, p=0.012). On the contrary, the cumulative incidence of cerebrovascular events, myocardial infarction, and coronary revascularization remained similar in the study groups also at 5 years.

**DISCUSSION**

The principal findings of this study based on a “real world” propensity-matched population is that SAVR seems to be superior to transfemoral TAVR with respect to 5-year rates of death from any cause, MACCE, permanent pacemaker implantation, and re-hospitalization for heart failure. The two procedures were associated with similar rates of repeat hospitalization due to cardiac reasons, cerebrovascular events and repeat aortic valve procedures.

Multiple registries have published TAVR outcomes including the Italian CoreValve Registry, the UK TAVI Registry, the GARY Registry in Germany, the FRANCE II Registry, the SOURCE Registry, and the national STS ACC TVT Registry in the USA. Most of them have already reported 5-years outcomes, and a recent systematic review of nearly 14,000 TAVR cases by Chakos et al. reported a cumulative mortality rate at 5 years of 52%. This outcome is seen as an outstanding achievement, given that these registries and trials
encompassed elderly patients deemed inoperable or at very high risk for conventional surgery. However, long-term comparative analyses of TAVR versus SAVR are fundamental to determine the role of TAVR in the treatment of patients with severe AS. To date, the PARTNER I trial is the only study that provided such data in a very high risk population. The study showed that death, stroke, and need for repeat hospital admission are much the same for SAVR and TAVR at 5 years.

However, it must be said that mortality rates reported in both surgical and transcatheter cohorts of the OBSERVANT study were remarkably lower than those observed in the PARTNER trial at 5 years (35.8% vs. 62.4% in SAVR, and 44.5% vs. 67.8% in TAVR), which prevents any comparison with the sole study reporting 5-year outcomes of TAVR versus SAVR.

The final outcomes of the OBSERVANT study showed that SAVR was associated with lower all-cause mortality and MACCE rates compared to transfemoral TAVR, with the curves starting to diverge after 3 years. The higher incidence of MACCE was mainly driven by a higher mortality in the transcatheter group. In fact, the study did not reveal significant differences in terms of stroke, myocardial infarction or need for repeat hospital admission for cardiac reasons at 5 years follow-up. As predictable, patients in the TAVR group had also a higher incidence of pacemaker implantation, but this applied only to the acute post-operative period, with no clues of higher rates of conduction disturbances in the TAVR group throughout the follow-up period. TAVR patients had also an increased risk to be re-hospitalized due to heart failure. This finding is of particular interest because episodes of heart failure are likely related to higher rates of post-procedural moderate or severe paravalvular leak and pacemaker implanted in the TAVR group, and concomitant untreated cardiac pathologies (significant degenerative mitral regurgitation and incomplete coronary revascularization) that might have led to a reduced survival compared with surgery. However, this correlation is only a hypothesis and needs to be confirmed by dedicated analyses.

These observations tend to question the assumption of a substantial equipoise between TAVR and SAVR in terms of mortality, as demonstrated by several rigorous trials (PARTNER 1, CoreValve US, NOTION, PARTNER 2, and SURTAVI) at mid-term follow-up and by the PARTNER 1 at longer term (5-year) follow-up. In addition, we previously showed that mortality at 1 year was much the same with transfemoral TAVR or SAVR for the “real-world” low/intermediate risk population included in OBSERVANT. Therefore, when
reviewing the results of this study, especially mortality, several considerations should be made. First, differently from the above-mentioned trials, the OBSERVANT is an “all-comers” study of all consecutive patients treated with SAVR or TAVR in Italy from December 2010 and June 2012. This means that many patients with unfavorable anatomical and clinical features for TAVR (i.e. bicuspid aortic valve, significant mitral regurgitation, severe coronary artery disease, etc.) were not excluded from the OBSERVANT study. The inclusion of an unselect population likely led to a higher incidence of postprocedural sequela (paravalvular leak, pacemaker implantation) and unsolved cardiac pathologies (above all, incomplete coronary revascularization and untreated degenerative mitral and functional tricuspid regurgitation) that can have had a significant impact on long-term prognosis of TAVR patients. Second, this study enrolled patients during the early months of TAVR adoption in many centers. A learning curve was likely present, which might have affected TAVR outcomes early in the study. Clinical experience leading to better patient selection and overcoming early learning curves has led to better outcomes of TAVR in more recent years. Third, differently from earlier generation TAVR devices used in the OBSERVANT, current transcatheter valve technology incorporated features aimed at facilitating rapid and accurate implantation of the prosthesis and on reducing the risk of vascular injury and paravalvular regurgitation. New transcatheter heart valve prostheses have been now introduced in clinical practice and they have already demonstrated to reduce the majority of TAVR-related periprocedural complications that have a strong impact on mid- and long-term prognosis (especially vascular complications, and paravalvular leak).¹⁹ Therefore, the results of the OBSERVANT study must be examined and discussed bearing in mind the disadvantages of using first-generation prostheses, and the long-term value of TAVR using next-generation prostheses in low and intermediate risk patients should be reassessed in the near future.

**Study limitations**

The present study has some limitations. First, observational studies can lead to less strong conclusions than using an RCT because treatment was not randomly assigned and because of potential residual confounding. In this analysis, we applied a propensity approach that represents a widely used method for analyzing observational data.¹⁵ However, a residual confounding due to unrecorded risk factors cannot be excluded. A specific strength of this study is the use of an administrative follow-up which guarantees an extremely low
percentage of lost to follow-up, the independence of outcomes observation and the possibility of very long-term follow-up analyses in terms of survival, re-hospitalizations and costs related to patients’ management. Second, the lack of a corelab, which centrally assessed echocardiographic parameters, is another important limitation of this study, and it remains unknown whether the valve performance contributed to the main outcome of difference in 5-year all-cause mortality. Finally, this analysis refers to only patients undergoing isolated SAVR and transfemoral TAVR. Whether these results can be applied in patients undergoing concomitant CABG/PCI or TAVR using alternative approaches remains unknown.

CONCLUSIONS

The results of the OBSERVANT study on a propensity-matched cohort of “real-world” patients with severe AS and at low or intermediate surgical risk suggest that, at 5 years, SAVR was associated with lower rates of all-cause mortality and re-hospitalization for heart failure and similar redo aortic valve procedures and re-hospitalization due to cardiac reasons rates compared with transfemoral TAVR using first-generation devices. These findings are potentially important if substantiated by ongoing randomized and observational trials (including the OBSERVANT II) using latest generation transcatheter aortic valves, which will address many of the limitations of the current study.

FUNDING AND ACKNOWLEDGEMENTS

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REFERENCES


9. Ludman PF, Moat N, de Belder MA, et al; UK TAVI Steering Committee and the National Institute for Cardiovascular Outcomes Research. Transcatheter aortic valve implantation in the United Kingdom:


Central Illustration. Time-to-Event Curves for the Primary End Points. Time-to-event curves are shown for death from any cause (Panel A) and MACCE (Panel B). The event rates were calculated with the use of Kaplan–Meier methods and compared with the use of the log-rank test.

![Figure 1. Time-to-Event Curves for Major Clinical Outcomes.](image)

Cumulative incidence of acute myocardial infarction (Panel A), stroke (Panel B), repeat hospitalization for acute heart failure (Panel C), and repeat...
hospitalization for cardiac reasons (Panel D). The event rates were calculated using a competing-risk regression and considering death as a competing event.
Figure 2. Time-to-Event Curves for Valve Related Outcomes. Cumulative incidence of pacemaker implantation (Panel A), and redo aortic valve replacement (Panel B). The event rates were calculated using a competing-risk regression and considering death as a competing event.
### Table 1. Baseline Clinical and Echocardiographic Characteristics

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<th>Clinical Variables</th>
<th>SAVR N=650</th>
<th>TAVR N=650</th>
<th>p-value</th>
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<tr>
<td><strong>Age (years±SD)</strong></td>
<td>80.3±5.1</td>
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<td>Female, n (%)</td>
<td>387 (59.5)</td>
<td>383 (58.9)</td>
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<td>Smoking history, n (%)</td>
<td>71 (11.5)</td>
<td>62 (10.1)</td>
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<td>BMI (kg/m²±SD)</td>
<td>26.9±4.5</td>
<td>26.5±4.8</td>
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<td>Diabetes mellitus, n (%)</td>
<td>165 (25.4)</td>
<td>161 (24.8)</td>
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<td>Creatinine (mg/dL±SD)</td>
<td>1.2±0.8</td>
<td>1.2±0.7</td>
<td>0.823</td>
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<td>3 (0.5)</td>
<td>9 (1.4)</td>
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<td>Albumin (mg/dL±SD)</td>
<td>3.7±0.9</td>
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<td>Hemoglobin (mg/dL±SD)</td>
<td>12.3±1.6</td>
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<td>Previous MI, n (%)</td>
<td>75 (11.5)</td>
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<td>Unstable angina, n (%)</td>
<td>18 (2.8)</td>
<td>21 (3.2)</td>
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<td>COPD, n (%)</td>
<td>141 (21.7)</td>
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<td>Oxygen dependency, n (%)</td>
<td>11 (1.7)</td>
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<td>Neurologic dysfunction*, n (%)</td>
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<td>Chronic liver disease†, n (%)</td>
<td>23 (3.5)</td>
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<td>Active neoplastic disease, n (%)</td>
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<td>Peripheral arteriopathy, n (%)</td>
<td>126 (19.4)</td>
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<td>Pulmonary hypertension, n (%)</td>
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<td>Previous cardiac surgery, n (%)</td>
<td>65 (10.0)</td>
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<td>Frailty score (moderate-severe), n (%)</td>
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<td>NYHA class IV, n (%)</td>
<td>70 (10.8)</td>
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<td>EuroSCORE 2 (%±SD)</td>
<td>5.1±6.2</td>
<td>4.9±5.1</td>
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### Echocardiographic variables

| Left ventricular ejection fraction (%±SD)                | 54.2±11.2        | 53.6±11.4        | 0.349   |
| Left ventricular ejection fractions≤30%, n (%)          | 20 (3.1)         | 16 (2.5)         | 0.499   |
Mitral regurgitation

| Mild, n (%) | 367 (56.5) | 348 (53.5) | 0.753 |
| Moderate, n (%) | 138 (21.2) | 143 (22.0) | 0.097 |
| Severe, n (%) | 14 (2.2) | 16 (2.5) | 0.655 |

Aortic valve pattern

| Aortic Valve area (cm²±SD) | 0.7±0.2 | 0.7±0.3 | 0.097 |
| Peak gradient (mmHg±SD) | 82.1±23.9 | 82.7±22.1 | 0.918 |
| Mean gradient (mmHg±SD) | 51.1±15.9 | 51.0±14.5 | <0.001 |
| Annulus diameter (mm±SD) | 21.3±2.1 | 22.2±2.2 | 0.001 |

*Abbreviations: SAVR, Surgical Aortic Valve Replacement; TAVR, Transcatheter Aortic Valve Replacement; BMI, Body Mass Index; MI, Myocardial Infarction; COPD, Chronic Obstructive Pulmonary Disease; PCI, Percutaneous Coronary Intervention; BAV, Balloon Aortic Valvuloplasty; NYHA, New York Heart Association.*

*Any prior neurological event (cerebrovascular accident [CVA] or transient ischemic attack [TIA])*

†Child-Pugh class B and C
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<th>1 Year</th>
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<th>5 Years</th>
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<tr>
<td>Death from any cause*</td>
<td>82 (13.6)</td>
<td>83 (13.8)</td>
<td>0.912</td>
<td>211 (35.8)</td>
<td>282 (44.5)</td>
<td>&lt;0.001</td>
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<td>Stroke†</td>
<td>29 (4.9)</td>
<td>37 (6.4)</td>
<td>0.243</td>
<td>46 (10.1)</td>
<td>58 (13.2)</td>
<td>0.318</td>
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<tr>
<td>Myocardial Infarction†</td>
<td>18 (3.8)</td>
<td>15 (3.1)</td>
<td>0.442</td>
<td>22 (5.3)</td>
<td>22 (5.0)</td>
<td>0.873</td>
</tr>
<tr>
<td>PCI†</td>
<td>3 (0.6)</td>
<td>10 (1.7)</td>
<td>0.055</td>
<td>5 (1.3)</td>
<td>13 (2.6)</td>
<td>0.087</td>
</tr>
<tr>
<td>MACCE*‡</td>
<td>107 (17.6)</td>
<td>110 (18.2)</td>
<td>0.796</td>
<td>?</td>
<td>?</td>
<td>?</td>
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<tr>
<td>Repeat hospitalization for cardiac reasons†</td>
<td>134 (23.6)</td>
<td>127 (21.9)</td>
<td>0.473</td>
<td>242 (43.0)</td>
<td>265 (48.2)</td>
<td>0.057</td>
</tr>
<tr>
<td>Repeat hospitalization for acute heart failure†</td>
<td>112 (19.7)</td>
<td>110 (19.0)</td>
<td>0.722</td>
<td>200 (35.7)</td>
<td>232 (42.5)</td>
<td>0.012</td>
</tr>
<tr>
<td>Permanent pacemaker‡</td>
<td>43 (7.3)</td>
<td>114 (18.5)</td>
<td>&lt;0.001</td>
<td>52 (10.2)</td>
<td>130 (23.9)</td>
<td>&lt;0.001</td>
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**Abbreviation:** SAVR, Surgical Aortic Valve Replacement; TAVR, Transcatheter Aortic Valve Replacement; MACCE, Major Adverse Cardiac and Cardiovascular Events; PCI, Percutaneous Coronary Intervention.

*Data reported as Kaplan–Meier estimates at the specific time point and do not equal the number of patients with events divided by the total number of patients in each treatment group.

†Data reported as competitive risk estimates at the specific time point and do not equal the number of patients with events divided by the total number of patients in each treatment group.

‡MACCE were defined as the composite of death from any cause, stroke, acute myocardial infarction, PCI and CABG.
APPENDIX

OBSERVANT Research Group,

Fulvia Seccareccia, Paola D’Errigo, Stefano Rosato, Alice Maraschini, Gabriella Badoni,
National Centre for Epidemiology, Surveillance and Health Promotion - ISS; Corrado
Tamburino, Marco Barbanti, SICI-GISE, Gennaro Santoro, FIC, ANMCO; Francesco Santini,
Francesco Onorati, Claudio Grossi, SICCH; Marco Ranucci, Remo Daniel Covello, ITACTA;
Danilo Fusco, Epidemiology Dept. Lazio Region; Rossana De Palma, Emilia Romagna Region;
Salvatore Scondotto, Sicilia Region.

Participating hemodynamic centers

1. Città della Salute e della Scienza - A.O.U. Molinette - San Giovanni Battista di Torino,
   Torino. Marra S., Marra S., D'Amico M.
2. Città della Salute e della Scienza - A.O.U. Molinette - San Giovanni Battista di Torino,
   Torino. Gaita F., Moretti C.
4. A.O. Nazionale Ss. Antonio e Biagio e Cesare Arrigo, Alessandria. Pistis G., Reale M.
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8. I.R.C.C.S. Policlinico San Donato, San Donato M.se (MI). Inglese L., Casilli F.
9. Spedali Civili di Brescia - Università, Brescia. Ettori F., Frontini M.
10. Ospedale Luigi Sacco - A.O. - Polo Universitario, Milano. Antona C., Piccaluga E.
12. A.O. Bolognini Seriate, Seriate (BG). Tespili M., Saino A.
13. Fondazione Poliambulanza Istituto Ospedaliero, Brescia. Leonzi Ornella, Rizzi Andrea
15. A.O. di Padova, Padova. Isabella G., Fracarco C.
20. Maria Cecilia Hospital, Ravenna. Cremonesi A., Colombo F.
22. A.O.U. Senese Le Scotte, Siena. Pierli C., Iadanza A.
24. Ospedale del Cuore Fondazione CNR Regione Toscana G. Monasterio, Massa. Berti S., Mariani M.
25. European Hospital, Roma. Tomai F., Ghini A.
27. Policlinico Gemelli Cardiologia, Roma. Crea F., Giubilato S.
28. Policlinico Umberto I, Roma. Sardella G., Mancone M.
32. A.O.U. Mater Domini, Catanzaro. Indolfi C., Spaccarotella C.
34. A.O.U. "Policlinico - Vittorio Emanuele" - Ospedale Ferrarotto, Catania. Tamburino C., Ussia G.
Participating cardiac surgery centers

1. Villa Maria Pia Hospital Gruppo Villa Maria Cardiochirurgia, Torino. Comoglio C., Dyrda O.
3. Azienda Ospedaliera Universitaria Maggiore della Carità, Novara. Micalizzi E.
4. A.O. S. Croce e Carle, Cuneo. Grossi C., Di Gregorio O.
5. A.O. Nazionale Ss. Antonio e Biagio e Cesare Arrigo, Alessandria. Scoti P., Costa R.
6. Ospedale Mauriziano "Umberto I", Torino. Casabona R., Del Ponte S.
10. Fondazione San Raffaele del Monte Tabor, Milano. Alfieri O., Denti P.
11. I.R.C.C.S. Policlinico San Donato, San Donato M.se (MI). Menicanti L., Agnelli B.
12. IRCCS Multimedica, Milano. Donatelli F.
13. Spedali Civili di Brescia - Università, Brescia. Muneretto C., Frontini M.
14. Spedali Civili di Brescia - Università, Brescia. Rambaldini M., Frontini M.
17. Ospedale Luigi Sacco - A.O. - Polo Universitario, Milano. Antona C., Gelpi G.
22. A.O.U. Santa Maria Della Misericordia di Udine, Udine. Livi U., Pompei E.
23. ICLAS - Istituto Clinico Ligure di Alta Specialità, Rapallo (GE). Coppola R., Gucciardo M.
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50. Azienda Ospedaliera Regionale San Carlo, Potenza. Gaeta R., Di Natale M.
51. S. Anna Hospital, Catanzaro. Cassese M., Antonazzo A.
52. Villa Maria Eleonora Hospital, Palermo. Argano V., Santaniello E.
53. Centro Cuore Morgagni, Pedara (CT). Patanè L., Gentile M., Tribastone S.
55. IS.ME.T.T. (Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione),
         Palermo. Pilato M., Stringi V.
56. A.O. Ospedali Riuniti Papardo - Piemonte, Messina. Patanè F., Salamone G.
58. A.O.U. "Policlinico - Vittorio Emanuele" - Ospedale Ferrarotto, Catania. Mignosa C.,
         Bivona A.
59. A.O. Brotzu, Cagliari. Cirio E.M., Lixi G.