Different impact of sex on baseline characteristics and major periprocedural outcomes of transcatheter and surgical aortic valve interventions: Results of the multicenter Italian OBSERVANT Registry

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Background: Despite the widespread use of transcatheter aortic valve implantation (TAVI), the role of sex on outcome after TAVI or surgical aortic valve replacement (AVR) has been poorly investigated. We investigated the impact of sex on outcome after TAVI or AVR.

Methods: There were 2108 patients undergoing TAVI or AVR who were enrolled in the Italian Observational Multicenter Registry (OBSERVANT). Thirty-day mortality, major periprocedural morbidity, and transprosthetic gradients were stratified by sex according to interventions.

Results: Female AVR patients showed a worse risk profile compared with male AVR patients, given the higher mean age, prevalence of frailty score of 2 or higher, New York Heart Association class of 3 or higher, lower body weight, and preoperative hemoglobin level ($P \leq .02$). Similarly, female TAVI patients had a different risk profile than male TAVI patients, given a higher age and a lower body weight and preoperative hemoglobin level ($P \leq .005$), but with a similar New York Heart Association class, frailty score, EuroSCORE ($P = \text{NS}$), a better left ventricular ejection fraction and a lower prevalence of left ventricular ejection fraction less than 30%, porcelain aorta, renal dysfunction, chronic obstructive pulmonary disease, arteriopathy, and previous cardiovascular surgery or percutaneous coronary intervention ($P \leq .01$). Women showed a smaller aortic annulus than men in both populations ($P < .001$). Female sex was an independent predictor in the AVR population for risk-adjusted 30-day mortality (odds ratio [OR], 2.34; $P = .043$) and transfusions (OR, 1.47; $P = .003$), but not for risk-adjusted acute myocardial infarction, stroke, vascular complications, permanent atrioventricular block ($P = \text{NS}$). Female sex was an independent predictor in the TAVI population for risk-adjusted major vascular complications (OR, 2.92; $P = .018$) and transfusions (OR, 1.93; $P = .003$), but proved protective against moderate to severe postprocedural aortic insufficiency ($P = .018$).

Conclusions: Female sex is a risk factor for mortality after aortic valve replacement, for major vascular complications after TAVI, and for transfusions after both approaches. (J Thorac Cardiovasc Surg 2014;147:1529-39)

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Transcatheter aortic valve implantation (TAVI) has been reported as an effective treatment option for severe aortic stenosis in patients at high risk for current surgical aortic valve replacement (AVR).¹ However, few studies have investigated the impact of sex-related differences on periprocedural outcomes after TAVI, although the role of sex on short- and long-term outcome after cardiac surgery has been addressed extensively and female sex has been shown as a risk factor for perioperative mortality in both the EuroSCORE and Society of Thoracic Surgeons Risk Score.^{2,3} As far as TAVI is concerned, contradictory results have been reached: some investigators have shown improved survival in female patients after TAVI,^{1,4,5} other investigators have found an increased risk for major vascular complications together with a higher rate of blood transfusions.⁶ These studies, however, came from retrospective analyses of single-center experiences.⁴⁻⁶

Abbreviations and Acronyms

AV	= atrioventricular
AVR	= aortic valve replacement
LVEF	= left ventricular ejection fraction
NYHA	= New York Heart Association
OBSERVANT	= Observational Study of Appropriateness, Efficacy, and Effectiveness of AVR-TAVI procedures for the treatment of severe symptomatic aortic stenosis
OR	= odds ratio
PARTNER	= Pivotal Placement of Aortic Transcatheter trial
TAVI	= transcatheter aortic valve implantation

Therefore, the aim of this study was to investigate the role of sex on both clinical presentation and postprocedural outcomes after TAVI and AVR. The analysis was performed from a prospective series of patients enrolled in the Italian National Institute of Health Observational Multicenter Registry (Observational Study of Appropriateness, Efficacy, and Effectiveness of AVR-TAVI procedures for the treatment of severe symptomatic aortic stenosis [OBSERVANT]), a prospective registry aimed at evaluating the efficacy and effectiveness of TAVI versus AVR procedures for the treatment of severe symptomatic aortic stenosis.

METHODS**Study Design and Data Collection**

In December 2010, 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 representing the professionals involved in the management of patients with severe aortic stenosis launched OBSERVANT.⁷ Enrollment started in January 2011 and ended in June 2012. However, the present analysis refers to the first 6 months of OBSERVANT data collection. The study protocol was approved by the local ethics committees. All patients enrolled in the database provided informed consent in an anonymous form. A detailed description of the study protocol has been reported previously.⁷

Study Population

On the basis of established criteria, the study included all symptomatic adult patients admitted to hospitals with a diagnosis of severe symptomatic aortic stenosis (defined as an aortic valve area $<1 \text{ cm}^2$, a maximum aortic velocity $>4 \text{ m/s}$, or a mean pressure gradient $>40 \text{ mm Hg}$) and requiring an aortic valve procedure.⁷ Treatment allocation always came from the review of the local multidisciplinary heart team involving cardiologists, surgeons, and anesthesiologists, as per current guidelines.⁸

Because of the observational nature of the registry, there was no standardization of clinical protocols: accordingly, techniques for TAVI and AVR were left to the discretion of each participating center. Each interventional team could choose to implant 1 of the 2 commercially

available valves: the balloon-expandable Edwards Sapien or Sapien XT prosthesis (Edwards Lifesciences, Irvine, Calif) or the self-expandable CoreValve (Medtronic, Minneapolis, Minn). Sapien devices were implanted by either the transfemoral or transapical route, and CoreValve devices were implanted by the transfemoral or transaxillary approach. Antiplatelet regimens and anticoagulation protocols similarly were based on individual institutional policies. Surgery, management of cardiopulmonary bypass, cardioplegic techniques, and anesthetic techniques were all left to each individual center's discretion, although they were based on well-established institutional policies.⁷

End Points and Follow-up Evaluation

Overall hospital mortality was the primary end point of the OBSERVANT study, whereas secondary end points included overall mortality within 12 and 24 months and the incidence of in-hospital major adverse cardiac and cerebrovascular events, as already reported.⁷

For the purpose of this study, differences in preoperative characteristics between women and men in both TAVI and AVR populations were investigated. Hospital mortality was considered the primary end point and was stratified by sex according to interventions. Acute myocardial infarction, stroke, major cardiovascular complications, transfusions, permanent atrioventricular (AV) block, and transprosthetic gradients were secondary end points and similarly stratified by sex according to interventions.⁷ Definitions of end points already have been reported.⁷ End points were adjudicated by 2 independent investigators at each participating center.

Statistical Analysis

All the analyses were performed stratifying by type of intervention and sex.

Continuous variables are presented as mean $\pm$ standard deviations and were compared by the Student *t* test; categorical variables are presented as counts and percentages and were compared by the chi-square test or the Fisher exact test when appropriate. The unadjusted effects of sex on periprocedural outcomes and 30-day mortality were estimated by univariate logistic regression models for dichotomous outcomes and by linear regression models for continuous outcomes. For each considered end point a specific stepwise procedure was used to identify the independent predictors (exclusion probability, 0.10; inclusion probability, 0.20). Sex was used as the determinant, whereas all the measured potential confounders, including variables related to the multicenter nature of the study (ie, volume of cases by center, surgeon experience, management of anesthesiology/surgery/percutaneous procedures), were offered to the model as independent variables. For each considered end point a specific multivariable logistic regression or linear regression model was implemented using age plus the variables selected by the stepwise procedures. Risk-adjusted odds ratio (OR) or exponentiation of the beta coefficient (dependent variable variation in women vs men) and corresponding *P* values are presented for AVR and TAVI separately. Interrelation between independent variables was checked with appropriate tests, and co-linearity was avoided by selecting the most relevant variable (based on statistical and clinical considerations) between 2 co-linear variables.

All the analyses were performed using the statistical package STATA version 11 (Stata Corp, College Station, Tex). A *P* value less than .05 was considered significant.

RESULTS**Population Enrolled and Participating Centers**

A total of 101 centers (60 cardiac surgery units and 41 catheter laboratories) participate in the registry. Between January 2011 and June 2011 the population comprised 2108 patients, 1383 (65.6%) of whom underwent surgical

TABLE 1. Demographics, clinical characteristics, and angiographic and echocardiographic data by sex and type of intervention

Characteristics	AVR (N = 1383) n (%)			TAVI (N = 725) n (%)		
	Men (N = 768)	Women (N = 615)	P value	Men (N = 297)	Women (N = 428)	P value
Age (year)*	70.9 ± 9.9	74.2 ± 8.6	<.001	81.1 ± 6.6	82.4 ± 6.3	.005
Weight (kg)*	80.1 ± 18.7	70.6 ± 17.6	<.001	74.5 ± 17.0	67.6 ± 16.5	<.001
Diabetes	198 (25.8)	148 (24.1)	.920	76 (25.6)	103 (24.1)	.913
Current smoking	255 (33.2)	60 (9.8)	<.001	79 (26.6)	23 (5.4)	<.001
Creatinine level (mg/dL)*	1.2 ± 1.0	0.9 ± 0.6	<.001	1.3 ± 1.0	1.1 ± 0.6	.002
Chronic dialytic treatment	16 (2.1)	8 (1.3)	.777	9 (3.0)	3 (0.7)	.199
Albumin level (mg/dL)*	3.5 ± 1.1	3.5 ± 1.1	.771	3.4 ± 0.9	3.5 ± 0.8	.221
Hemoglobin level (mg/dL)*	13.0 ± 1.8	12.1 ± 1.5	<.001	11.8 ± 1.7	11.4 ± 1.5	.001
Active endocarditis	10 (1.3)	1 (0.2)	.112	0 (0.0)	1 (0.2)	.844
Previous AMI	36 (4.7)	11 (1.8)	.060	7 (2.4)	13 (3.0)	.929
Unstable angina	47 (6.2)	25 (4.1)	.558	17 (5.7)	11 (2.6)	.194
COPD	86 (11.2)	57 (9.3)	.699	107 (36.0)	102 (23.9)	.010
Oxygen dependency	14 (1.8)	4 (0.6)	.379	26 (8.7)	29 (6.8)	.779
Neurologic dysfunction	10 (1.3)	17 (2.8)	.277	29 (9.8)	25 (5.8)	.360
Chronic liver disease	12 (1.6)	10 (1.6)	1.0	14 (4.7)	8 (1.9)	.280
Active neoplastic disease	13 (1.7)	5 (0.8)	.716	14 (4.7)	11 (2.6)	.597
Peripheral arteriopathy	119 (15.5)	56 (9.1)	.001	87 (29.3)	74 (17.3)	.004
Previous cardiac surgery	39 (5.1)	19 (3.1)	.476	74 (24.9)	39 (9.1)	<.001
Previous vascular surgery	19 (2.5)	5 (0.8)	.229	26 (8.7)	11 (2.3)	.007
Porcelain aorta	4 (0.5)	0 (0.0)	.447	29 (9.8)	25 (5.8)	.003
Difficult thoracic approach	1 (0.1)	1 (1.2)	.928	9 (3.0)	13 (3.0)	.954
Frailty score						
2 (partially self-sufficient)	30 (3.9)	37 (6.3)	<.001	48 (16.2)	106 (24.8)	.096
3 (non-self-sufficient)	1 (0.1)	4 (0.6)		3 (1.0)	4 (0.9)	
Previous PCI	76 (9.9)	19 (3.1)	<.001	95 (32.0)	87 (20.4)	.010
Previous aortic balloon plasty	7 (0.9)	3 (0.5)	.813	34 (11.4)	64 (15.0)	.709
Critical preoperative state	26 (3.4)	9 (1.5)	.271	18 (6.1)	18 (4.2)	.813
NYHA class						
III	151 (19.7)	165 (26.9)	.020	129 (43.4)	192 (45.0)	.490
IV	38 (4.9)	29 (4.7)		41 (13.8)	66 (15.5)	
EuroSCORE*	5.9 ± 7.6	6.4 ± 6.4	.238	15.9 ± 16.1	14.6 ± 12.0	.239
EuroSCORE >20	37 (4.8)	19 (3.1)	.016	57 (19.2)	74 (17.3)	.166
Angiographic and echocardiographic findings						
Coronary artery disease						
1 vessel	114 (14.8)	72 (11.7)	<.001	66 (22.2)	75 (18.1)	<.001
2 vessels	81 (10.5)	47 (7.6)		15 (5.1)	22 (5.2)	
3 vessels	79 (10.3)	25 (4.1)		33 (11.1)	13 (3.0)	
Left main	1 (0.1)	0 (0.0)		0 (0.0)	0 (0.0)	
Mitral valve regurgitation						
Mild	351 (45.7)	268 (43.6)	.010	158 (53.2)	207 (48.5)	.508
Moderate	72 (9.4)	96 (15.6)		67 (22.6)	108 (25.3)	
Severe	9 (1.2)	8 (1.3)		6 (2.0)	19 (4.4)	
LVEF (%)*	55.5 ± 10.9	58.1 ± 8.5	<.001	48.2 ± 12.6	53.1 ± 11.4	<.001
LVEF, <30	22 (2.9)	2 (0.3)	.009	29 (9.8)	13 (3.0)	.005
Aortic valve pattern						
Valve area (cm ²)*	0.8 ± 0.3	0.7 ± 0.3	<.001	0.7 ± 0.3	0.6 ± 0.2	<.001
Peak gradient (mm Hg)*	78.8 ± 22.6	87.4 ± 23.8	<.001	79.0 ± 24.5	83.8 ± 21.7	.008
Mean gradient (mm Hg)*	48.5 ± 14.3	54.3 ± 15.8	<.001	48.4 ± 15.3	51.8 ± 14.7	.003
Annulus diameter (cm)*	22.6 ± 2.2	20.9 ± 1.9	<.001	23.0 ± 2.1	21.3 ± 1.8	<.001

AMI, Acute myocardial infarction; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction. *Variables are presented as mean ± standard deviation.

AVR, and 725 (34.4%) underwent TAVI. Perioperative data were 100% completed, whereas follow-up data were 95.8% completed for the AVR population and 95.9%

completed for the TAVI cohort. Women represented 59.0% (428 of 725) of the TAVI population and 44.4% (615 of 1383) of the AVR population.

TABLE 2. Procedural characteristics by sex and type of intervention

Characteristics	AVR (N = 1383) n (%)			TAVI (N = 725) n (%)		
	M (N = 768)	F (N = 615)	P value	M (N = 297)	F (N = 428)	P value
Urgency status						
Elective	749 (97.5)	596 (97.1)	.632	286 (96.3)	413 (96.7)	.805
Urgent	10 (1.3)	15 (2.4)		10 (3.4)	10 (2.3)	
Emergent	3 (0.4)	1 (0.2)		1 (0.3)	4 (0.9)	
Associated coronary procedure	214 (27.9)	113 (18.4)	.001	14 (4.7)	24 (5.6)	.841
Approach site						
Femoral	—	—	—	226 (76.1)	335 (78.4)	.858
Iliac	—	—	—	0 (0.0)	0 (0.0)	
Axillary	—	—	—	16 (5.4)	17 (4.0)	
Transapical	—	—	—	54 (18.2)	69 (16.7)	
Type of valve used						
CV	—	—	—	173 (58.2)	200 (46.8)	.032
ELS	—	—	—	124 (41.7)	227 (52.9)	

CV, CoreValve; ELS, Edwards Lifesciences Sapien valve.

Differences in AVR Population According to Sex

Female AVR patients showed different baseline characteristics compared with male AVR patients, such as lower body weight, serum creatinine level, history of smoking, previous percutaneous coronary intervention, peripheral arteriopathy, and prevalence of EuroSCORE greater than 20, but also a higher mean age at intervention, lower baseline hemoglobin level, higher frailty score of 2 to 3, and New York Heart Association (NYHA) class III/IV (Table 1).

Preoperative angiography and/or echocardiography showed a better mean left ventricular ejection fraction (LVEF), a lower prevalence of LVEF less than 30%, a higher prevalence of moderate to severe mitral regurgitation, higher transaortic mean and peak gradients, and lower aortic valve area and annular diameters in women; however, associated coronary artery disease was less frequent (Table 1), which therefore resulted in a less common need for an associated coronary artery bypass graft (Table 2).

Differences in TAVI Population According to Sex

The TAVI population also showed significant differences in baseline characteristics according to sex: in particular, despite a higher mean age at intervention, a lower body weight, and a lower preoperative hemoglobin level, female TAVI patients had a lower history of smoking and chronic obstructive pulmonary disease, serum creatinine level, peripheral arteriopathy, porcelain aorta, previous cardiac and vascular surgery, and previous percutaneous coronary intervention (Table 1). Associated coronary artery disease was similarly less common in women, whereas mean LVEF was higher in view of the lower prevalence of patients with LVEF less than 30% (Table 1). As for AVR populations, female TAVI patients showed a lower aortic valve area, annular diameter, and higher mean and peak gradients

(Table 1). No sex-related differences were found in procedural characteristics, except for a higher use of Edwards prostheses in women (Table 2).

Impact of Female Sex on AVR Outcome

When periprocedural outcomes after AVR were considered, female sex proved to be an independent predictor of risk-adjusted 30-day mortality (OR, 2.34; Table 3), in view of a higher 30-day mortality compared with men undergoing surgery (women, 3.7%; vs men, 2.2%; Table 3). Apart from female sex, concomitant moderate to severe mitral regurgitation independently predicted 30-day mortality (OR, 2.6; $P = .009$). About 55% of women undergoing AVR received transfusions perioperatively, compared with 44.1% of men, with 3.4 ± 3.1 units/patient vs 3.7 ± 3.5 units/patient in men (Table 3). Accordingly, female sex was an independent predictor for risk-adjusted transfusions during the perioperative course (OR, 1.47; Table 3). Preoperative hemoglobin level also significantly affected the perioperative need for transfusions (OR, 0.71; $P = .0001$).

On the other hand, no sex-related differences were recorded in the AVR population in terms of risk-adjusted permanent AV block, major vascular damage, acute myocardial infarction, stroke, and cardiogenic shock. Furthermore, no differences were found between female and male AVR patients in intensive care unit length of stay and hospitalization (Table 3). Finally, higher peak gradients were detected in women after AVR (exponentiation of the beta coefficient, 4.96; Table 3).

Impact of Female Sex on TAVI Outcome

When the TAVI population was considered, female sex did not impact risk-adjusted 30-day mortality (Table 3). However, when the 42 deaths recorded in the TAVI population were considered, previous aortic interventions and

TABLE 3. Prevalence of events and risk-adjusted ORs stratified by type of intervention

Outcomes	AVR (N = 1383) n (%)				TAVI (N = 725) n (%)			
	M (N = 768)	F (N = 615)	ORadj		M (N = 297)	F (N = 428)	ORadj	
			(women vs men)	P			(women vs men)	P
30-day mortality	17 (2.2)	23 (3.7)	2.34	.043	20 (6.7)	22 (5.1)	0.93	.855
Residual aortic regurgitation								
None/mild	760 (99.0)	608 (98.9)	1.04	.941	262 (88.2)	398 (93.0)	0.52	.018
Moderate/severe	8 (1.0)	7 (1.1)			35 (11.8)	30 (7.0)		
Permanent AV block	17 (2.2)	16 (2.6)	1.33	.436	51 (17.2)	41 (9.6)	0.61	.050
Major vascular damage	2 (0.3)	0 (0.0)	-		8 (2.7)	25 (5.8)	2.92	.018
AMI	6 (0.8)	2 (0.3)	0.37	.238	3 (1.0)	2 (0.5)	0.79	.818
Stroke	10 (1.3)	10 (1.6)	1.19	.717	3 (1.0)	6 (1.4)	1.97	.417
Transfusions	339 (44.1)	337 (54.9)	1.47	.003	79 (26.6)	150 (35.1)	1.93	.003
Number of units*	3.7 ± 3.5	3.4 ± 3.1	0.97	.908	2.8 ± 2.5	2.5 ± 2.5	0.99	.995
Cardiogenic shock	21 (2.7)	16 (2.6)	1.31	.3495	8 (2.7)	11 (2.6)	1.18	.769
Hospital stay (days)†	7	6	1.83	.549	7	7	0.84	.793
ICU stay (days)†	2	2	1.33	.230	2	2	0.56	.310
Aortic valve pattern								
Peak gradient (mm Hg)*	24.3 ± 10.8	25.8 ± 11.9	4.96	.027	20.1 ± 13.1	20.3 ± 12.8	0.78	.824
Mean gradient (mm Hg)*	13.2 ± 6.7	14.0 ± 7.0	2.29	.054	10.8 ± 7.7	10.8 ± 6.8	1.16	.785

Each end point has been adjusted using factors selected by the stepwise procedures. The variables used to adjust the 30-day mortality ORs were as follows: AVR included the following: age, diabetes, chronic dialytic treatment, previous vascular surgery, frailty score, critical preoperative state, coronary artery disease, pulmonary hypertension; and TAVI included the following: age, creatinine level, unstable angina, previous vascular surgery, critical preoperative state, and LVEF. *ORadj*, Adjusted OR; *AMI*, acute myocardial infarction; *ICU*, intensive care unit; *AV*, atrioventricular. *Variables presented as mean ± standard deviation and exponentiation of the beta coefficient. †Presented as median values and exponentiation of the beta coefficient.

critical preoperative state were independent predictors for risk-adjusted 30-day mortality (OR, 3.7; *P* = .011; and OR, 3.5; *P* = .011, respectively), with only a trend toward statistical significance for risk-adjusted 30-day mortality previous aortic valvuloplasty (OR, 2.13; *P* = .061). Furthermore, the co-existence of moderate to severe mitral regurgitation, in contrast with the AVR population, did not impact 30-day mortality (*P* = .159).

On the other hand, female sex was an independent predictor for major vascular damage (OR, 2.92), which occurred in 5.8% of female compared with 2.7% of TAVI male patients (Table 3). In addition to female sex, preoperative creatinine level greater than 2 mg/dL proved to be an independent predictor of major vascular damage (OR, 3.18; *P* = .031).

As for AVR patients, female sex also significantly impacted the need for periprocedural transfusions (35.1% of female TAVI patients were transfused compared with 26.6% of male TAVI patients; OR, 1.93), with a mean of 2.5 units/patient (Table 3). Major vascular complications indeed were found as the strongest predictors for periprocedural transfusions (OR, 9.7; *P* = .0001), as well as preoperative hemoglobin level (OR, 0.69; *P* = .0001).

Moderate to severe postprocedural aortic regurgitation was less common in female TAVI patients (7.0%; vs men, 11.8%), thus, resulting in female-sex protection against that complication (OR, 0.52; Table 3). The manufacturer was shown to affect the earlier-mentioned outcome, given the protective effect of the Edwards Lifesciences Sapien valve versus the CoreValve toward postprocedural aortic regurgitation

(OR, 0.61; *P* = .018). However, the type of TAVI prosthesis did not impact 30-day mortality or major vascular complications (OR, 0.60; *P* = .164; and OR, 0.87; *P* = .718 for the Edwards Lifesciences Sapien valve vs the CoreValve, respectively). A permanent AV block was similarly less common in female TAVI patients (9.6% vs 17.2%), thus showing a trend toward significance for female sex as a protective factor against a post-TAVI AV block (*P* = .05; OR, 0.61). Finally, female sex did not impact periprocedural acute myocardial infarction, stroke, cardiogenic shock, length of intensive care unit stay, hospitalization, and transprosthetic gradients after TAVI (Table 3).

DISCUSSION

Several conclusions can be drawn by the present analysis of hospital results after AVR or TAVI in the 2108 patients enrolled in this prospective multicenter registry: (1) female sex is characterized by an overall worse risk profile in the AVR population; (2) female sex carries a different (not necessarily worse) baseline risk profile in TAVI candidates; (3) female sex is still an independent risk factor for mortality after AVR; (4) female sex is not a risk factor for mortality after TAVI but it is an independent predictor for in-hospital major vascular complications; and (5) women need more transfusions regardless of the chosen treatment.

Female-Related Differences in Risk Profiles and Outcome After AVR

Women undergoing AVR in this study showed a significantly worse risk profile than men. These data are not

new, given that female sex is a well-known independent risk factor for surgical mortality in both the EuroSCORE and the Society of Thoracic Surgeons score (www.euroscore.org/euroscore_scoring.htm and <http://209.220.160.181/STSTWebRiskCalc261/>). Although the reasons for these sex-related differences in risk profiles are far from being completely understood, the higher prevalence of comorbid conditions and the older age of women in the majority of the available studies indicated that female sex behaves as a proxy-variable more than individual risk factors.⁹ In addition, the lower body weight and bovine serum albumin level of women, as also found in our AVR cohort from the OBSERVANT registry, and parallel cardiac structures that are smaller than the corresponding counterparts of men, thus suggest more technically demanding interventions.⁹ Furthermore, the lower body mass index of women has been shown to be a risk factor for mortality, morbidity, and bleeding after surgery.⁹ Finally, according to the demonstration that both NYHA and frailty scores impact survival after AVR,^{10,11} and given the higher NYHA and frailty score of our AVR women, it is not surprising that female sex was confirmed as an independent risk factor for mortality in the OBSERVANT registry. Besides such findings, however, we confirmed here that the co-existence of moderate to severe mitral regurgitation also impacted early survival in the surgical cohort, thus fueling the recent highly debated need for concomitant mitral surgery during AVR.¹²

Female sex in AVR patients also proved an independent predictor of intraprocedural/postprocedural transfusions, despite the absence of differences in major vascular complications. The detrimental impact of perioperative transfusions on outcome in the surgical population has been well ascertained.¹³ A recent prospective study on 613 adults undergoing cardiac surgery showed female sex, together with older age, lower preoperative hemoglobin levels, lower body surface area, and higher intraoperative hemodilution, some of which also were prevalent in our female AVR cohort, as independent predictors of postoperative transfusions.¹⁴ Indeed, preoperative hemoglobin level was an independent predictor for transfusions also in our OBSERVANT experience. Finally, it should not be underestimated that aortic valve stenosis is recognized as a hemodynamic condition whose related shear stress favors an acquired von Willebrand syndrome, also affecting platelet function and hemostasis.¹⁵ It can be speculated that a combination of all the earlier mentioned factors might contribute to the higher rate of transfusions observed in women undergoing AVR.

Female-Related Differences in Risk Profiles and Outcome After TAVI

Few studies addressing the role of sex in the TAVI procedure have been published to date. Hayashida et al,⁴

in a single-center French registry, showed an overall better risk profile in women, a finding also confirmed by Humphries et al.⁵ Buchanan et al,⁶ in a single-center Italian experience, similarly showed a higher prevalence of comorbidities in men undergoing TAVI, although women had a worse clinical presentation at hospital admission with a higher NYHA class. Supposedly, the better risk profile of women in the study by Hayashida et al⁴ and Humphries et al⁵ resulted in their lower mortality and the consequent recognition of male sex (rather than female as in the surgical literature) as an independent predictor of mortality in TAVI, thus supporting the protective effect of female sex on 1-year mortality identified by the Pivotal Placement of Aortic Transcatheter (PARTNER) trial cohort A.¹ In our OBSERVANT registry we found a higher prevalence of comorbid conditions in male TAVI patients, but a similar EuroSCORE, NYHA class, and frailty score in men and women. The earlier-mentioned data may help to understand why TAVI seems to reduce the gender disparity seen in the AVR population. Despite the higher prevalence of well-known comorbid conditions affecting outcome detected in male TAVI patients, other unweighted risk factors were present in women, thus balancing the strength of the comorbid conditions, and resulting in similar EuroSCORE, NYHA class, and frailty scores, the latter being the real determinants of early mortality. Indeed, Stortecky et al¹⁶ identified several geriatric proxies, overall assessing the degree of frailty, as better discriminators in the prediction of hospital mortality. Similarly, Munoz-Garcia et al,¹⁷ in a single-center Spanish registry, confirmed the Charlson Index and Karnofsky score as better predictors for hospital mortality than the logistic EuroSCORE. In addition, it must be considered that TAVI procedures do not involve the use of cardiopulmonary bypass, thus removing some of the cardiopulmonary bypass-related risk factors from the risk profile of women undergoing TAVI that already have been proven to preferentially affect women rather than men during AVR (eg, hemodilution).¹⁸ Our findings therefore confirmed the comparable mortality of men and women after TAVI seen by Buchanan et al⁶ in a cohort with a similar risk profile to our population, and also confirm another recent multicenter Italian experience in patients undergoing implantation of CoreValve only that similarly showed comparable baseline comorbidities and similar hospital survival between sexes.¹⁹ However, although it is interesting to note that the type of TAVI prosthesis (Edwards Lifesciences Sapien valve vs CoreValve) did not affect mortality in our experience, determinants of hospital death after TAVI were previous aortic interventions (with a trend also for previous aortic valvuloplasty) and critical preoperative state, the former possibly underscoring the critical role for adequate preoperative planning, and the latter emphasizing the importance of correct indications.

The present study also showed female sex as an independent predictor for major vascular complications. It has been reported that major vascular complications increased the risk for midterm mortality 2-fold.⁴ Another study showed that major and minor vascular complications occur in as high as 10.7% and 11.5%, respectively, of the TAVI population, with rates of life-threatening bleeding, major bleeding, and red blood cell transfusions of 13.9%, 20.9%, and 38.9%, respectively.²⁰ Buchanan et al⁶ reported a trend for women of developing more major vascular complications. Humphries et al⁵ similarly reported a higher incidence of major vascular complications and major/life-threatening bleeds in women. As in our study, in a multicenter European experience Van Mieghem et al²¹ showed female sex as an independent predictor (together with peripheral arterial disease, learning curve, and percutaneous access strategy) for both major vascular complications and life-threatening/disabling bleeding. It is noteworthy that preoperative renal damage (creatinine level > 2 mg/dL) significantly impacted the risk of major vascular complications in OBSERVANT registry that outcome (OR, 3.18), thus suggesting, as in the Van Mieghem et al²¹ study, a pivotal role for severe and calcified atherosclerosis in the genesis of periprocedural vascular complications. As for mortality, it is also worth noting that the type of TAVI prosthesis did not impact vascular complications. Certainly more studies and future analyses are needed to better understand this issue.

Similar to our AVR population, female sex proved to be an independent predictor for transfusions also in our TAVI population, thus confirming previous studies showing a higher transfusion rate in women.⁶ Perioperative transfusions after TAVI affect outcome as in cardiac surgery: a single-center French study showed that transfusions of 4 or more units/patient augment 1-year mortality by 4.66-fold.⁴ Similarly, the recent Pooled Rotterdam-Milano-Toulouse In Collaboration (PRAGMATIC) Plus initiative showed that bleeding was frequent after TAVI and mainly driven by vascular complications, and that red packed cell transfusions were associated with increased 1-year mortality and an increased risk of major stroke and acute kidney injury.²⁰ Although female TAVI patients in our registry had lower preoperative hemoglobin levels than their male counterparts, which also partly explains that result, they, however, had higher major vascular complications. As for the PRAGMATIC Plus study, we confirmed here that major vascular complications were the most important factors impacting the need for transfusions: our data thus underscore the need for multidisciplinary efforts to reduce periprocedural vascular complications.

Despite finding a lower body weight and lower annular diameter in female TAVI patients, as already reported by both Hayashida et al⁴ and Buchanan et al,⁶ we also

confirmed a similar hemodynamic profile of TAVI prostheses in women and men in terms of comparable peak and mean gradients after risk adjustment (Table 3). On the other hand, female sex was a protective factor in the TAVI population against moderate to severe aortic regurgitation, and also showed a protective trend against the need for a permanent pacemaker. Unbehaun et al²² already reported male sex as a predictor of post-TAVI paravalvular leakage, underscoring the direct relation between sex, annular dimensions, and paravalvular leakage after TAVI, and further showing the beneficial effect of oversizing of TAVI in women to reduce the risk of postprocedural regurgitation. The protective effect of the Edwards Life-sciences Sapien valve against postprocedural moderate to severe aortic regurgitation, as found in the OBSERVANT registry, also was noteworthy. This finding already has been suggested in the literature,²² and was addressed specifically by Nombela-Franco²³ in a recent study comparing the hemodynamic performances of self-expandable versus balloon-expandable TAVI prostheses.

When the postprocedural need for a permanent pacemaker was considered, our findings confirmed previous literature studies showing fewer pacemaker implantations in women,¹⁹ which possibly also was related to the lower rate of CoreValve implantations in our female TAVI patients.²⁴

Finally, we reported a lower rate of early stroke in both AVR and TAVI patients compared, for example, with that reported in the PARTNER A trial, although we did not show sex-related differences for stroke in both populations as in the PARTNER A trial.²⁵ OBSERVANT was an observational registry mirroring the real world practice of all-comers in current Italian practice, whereas the PARTNER Trial was a prospective randomized study aimed at the direct comparison between the 2 procedures.²⁵ Indeed, our results also agree with a recent meta-analysis on more than 10,000 published patients, reporting a stroke incidence of 1% to 3% in the first 30 postoperative days.²⁶ Furthermore, other published nonrandomized studies specifically focused on the role of sex reported a stroke incidence comparable with OBSERVANT results.^{4,6} Moreover, literature data showed the importance of preoperative peripheral arteriopathy, porcelain aorta, and history of stroke (whose prevalence was relatively low in the OBSERVANT population) in favoring postprocedural cerebrovascular events.²⁷ However, the present study was not targeted for perioperative stroke, although future investigations are needed to better assess the prognostic factors and the impact on outcome of this life-threatening complication.

In conclusion, our prospective multicenter registry confirms that female sex is still a risk factor for hospital mortality after AVR, for in-hospital major vascular complications after TAVI, and for transfusions during

hospitalization after both approaches. Outcome data reflect to some extent the different baseline risk profile of women in the 2 populations. Tremendous efforts should be made by surgeons, cardiologists, and anesthesiologists in the near future to significantly decrease major periprocedural complications and transfusion rates. The different hemodynamic behavior of AVR and TAVI in female patients early after the procedure, together with their impact on ventricular remodeling and on mid- to long-term follow-up evaluation, deserves future investigations.

Study Limitations

Evaluating the impact of a specific treatment by using a registry can lead to incorrect conclusions because of the influence of unassessed confounding variables. In this study, treatment was not assigned randomly but was assigned after the evaluation of a multidisciplinary local heart team, as suggested by current guidelines,⁸ although this policy still might have generated an unavoidable risk for bias regarding treatment selection. No standardized protocols for cardiopulmonary bypass and anesthetic techniques were used.⁷ No specific recommendation or protocols exist on perioperative transfusions,⁷ therefore, our results showing a different transfusion rate between male and female patients might have been biased by other variables that were not included. However, details on preoperative stratification, treatment allocation, techniques used (surgery or TAVI, transfemoral vs nontransfemoral routes, choice of surgical and percutaneous valves, and so forth), definition of outcome variables, postprocedural medical management, data management, quality control of registry, and so forth, all have been detailed previously.⁷ On the other hand, results coming from registries are considered the real-world mirror of current practice. These strengths and limitations stem from the observational nature of the OBSERVANT study, which is a mirror of the current Italian clinical practice. For any observational study/registry, no standardization is planned a priori by definition; similarly, for any observational study, no quality measurement between centers at different volumes, historical results, skills, and so forth were considered as end points, although they were considered in the multivariate analyses. Furthermore, all end points were risk adjusted for all the collected variables by means of univariate and multivariate models; again, uncollected variables, as for any study of this type, potentially may have affected the results of these models.

Another important limitation was that outcomes were not defined according to the Valve Academic Research Consortium. This mainly was because the data collection began before the publication of the Valve Academic Research Consortium criteria. Another reason was that those definitions were designed specifically to define complications after TAVI, therefore they may be misleading

to illustrate complications after AVR, likely resulting in their overestimation. The incompleteness of enrollment at the time of this writing may have limited the conclusions. Finally, the study was not targeted to compare women undergoing AVR with those undergoing TAVI; therefore, no comparison between the 2 procedures are provided here. However, the results of this study, as well as the absence in the current literature of comparisons between AVR and TAVI in female patients, emphasize the urgent need for outcome results after TAVI and AVR in this particular subset of patients.

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APPENDIX 1

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