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FOCUS ON CARDIOVASCULAR OUTCOMES AMONG WOMEN

1-Year Clinical Outcomes in Women After Transcatheter Aortic Valve Replacement

Results From the First WIN-TAVI Registry

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ABSTRACT

OBJECTIVES This study sought to examine the safety and performance of contemporary transcatheter aortic valve replacement (TAVR) in an exclusive all-women TAVR population, and to further investigate the potential impact of female sex-specific characteristics on composite 1-year clinical outcomes.

BACKGROUND Women comprise ≥50% patients undergoing TAVR. Several data have shown the noninferiority of TAVR compared with surgical aortic valve replacement for symptomatic significant aortic stenosis, but no study so far has been specifically powered to detect differences by sex.

METHODS The WIN-TAVI (Women's INternational Transcatheter Aortic Valve Implantation) registry is a multinational, prospective, observational registry of women undergoing TAVR for significant aortic stenosis, across 18 sites in Europe and 1 site in the United States, between January 2013 and December 2015. The primary Valve Academic Research Consortium (VARC)-2 efficacy endpoint was a composite of mortality, stroke, myocardial infarction, hospitalization for valve-related symptoms or heart failure or valve-related dysfunction beyond 30 days. Secondary endpoints included composite 1-year death or stroke. Predictors of 1-year outcomes were determined using Cox regression methods.

RESULTS A total of 1,019 intermediate to high-risk women, with mean age 82.5 ± 6.3 years, mean European System for Cardiac Operative Risk Evaluation (EuroSCORE) I 17.8 ± 11.7% and mean Society of Thoracic Surgeons score 8.3 ± 7.4% were enrolled. TAVR was performed via transfemoral access in 90.6% and new-generation devices were used in 42.1%. The primary VARC-2 efficacy composite endpoint occurred in 111 (10.9%) patients beyond 30 days and in 167 (16.5%) patients at 1 year. The incidence of 1-year death or stroke was 13.9% (n = 141). Death occurred in 127 (12.5%) patients and stroke in 22 (2.2%) patients. Prior coronary revascularization (hazard ratio [HR]: 1.72; 95% confidence interval [CI]: 1.17 to 2.52; p = 0.006) and EuroSCORE I (HR: 1.02; 95% CI: 1.00 to 1.04; p = 0.027) were independent predictors of the VARC-2 efficacy endpoint. Similarly, EuroSCORE I (HR: 1.02; 95% CI: 1.00 to 1.04; p = 0.013), baseline atrial fibrillation (HR: 1.58; 95% CI: 1.07 to 2.33; p = 0.022), and prior percutaneous coronary intervention (HR: 1.50; 95% CI: 1.03 to 2.19; p = 0.035) were independent predictors of 1-year death or stroke. After adjustment, no significant association was observed between history of pregnancy or any sex-specific factors and 1-year TAVR outcomes.

CONCLUSIONS Intermediate to high-risk women enrolled in this first ever all-women contemporary TAVR registry experienced a 1-year VARC-2 composite efficacy endpoint of 16.5%, with a low incidence of 1-year mortality and stroke. Prior revascularization and EuroSCORE I were independent predictors of the VARC-2 efficacy endpoint, whereas EuroSCORE I, baseline atrial fibrillation, and prior percutaneous coronary intervention were independent predictors of the 1-year death or stroke. (J Am Coll Cardiol Intv 2018;11:1-12) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AI = aortic insufficiency

AS = aortic stenosis

CAD = coronary artery disease

CI = confidence interval

DAPT = dual-antiplatelet therapy

EuroSCORE = European System for Cardiac Operative Risk Evaluation

HR = hazard ratio

LVEF = left ventricular ejection fraction

PCI = percutaneous coronary intervention

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

VARC = Valve Academic Research Consortium

Transcatheter aortic valve replacement (TAVR) is now proven to be a suitable alternative treatment to surgical aortic valve replacement (SAVR) for severe aortic stenosis (AS) in both high- or intermediate-risk patients (1–4). In most randomized clinical trials and observational registries evaluating TAVR, women represent ≥50% of the patient population, and despite older age and significantly greater early vascular and bleeding complications, women have consistently shown superior 1-year survival compared with men (5–7). Furthermore, the results of both PARTNER (Placement of AoRTic TraNscathetER valve) trials (PARTNER 1 and PARTNER 2) suggest superiority of TAVR compared with SAVR for women, with lower rates of 2-year death in the PARTNER 1 trial among women undergoing transfemoral TAVR versus SAVR (23.4% vs. 36.9%; p = 0.02) and lower incidence of 2-year death or disabling stroke in the PARTNER 2 trial (16.8% vs. 20.4%; p = 0.05) with transfemoral TAVR versus SAVR attributed to better outcomes in women (3,8).

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Women and men undergoing TAVR have distinct baseline characteristics, which can have a differential impact on post-TAVR and long-term events (7). Compared with men, women have smaller aortic valve annuli, lower origins of coronary arteries, smaller peripheral vessels (9), as well as higher prevalence of osteoporosis (10) and frailty (11), and greater risk of bleeding (5,7). Women also have greater prevalence of coexistent valve disease and heart failure (7). The understanding and appreciation of these risk differences provided an urgent impetus to study women undergoing TAVR in better detail, and to investigate whether female sex-specific characteristics contributed to TAVR outcomes. Indeed, female specific factors such as pregnancy and its complications (12) and age of menopause (13,14) have been suggested to modify future risk for cardiovascular disease, but the role of these parameters in TAVR patients has never hitherto been investigated.

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The aim of this principal report from the WIN-TAVI (Women's INternational Transcatheter Aortic Valve Implantation) registry (15) is to present the 1-year primary Valve Academic Research Consortium (VARC)-2 efficacy endpoint in women undergoing TAVR and to explore for the predictors of the VARC-2 efficacy endpoint and other important composite TAVR outcomes. In addition, we aimed to evaluate whether the observed inverse association between previous history of pregnancy and the 30-day VARC-2 safety endpoint (15) extended to 1-year outcomes.

METHODS

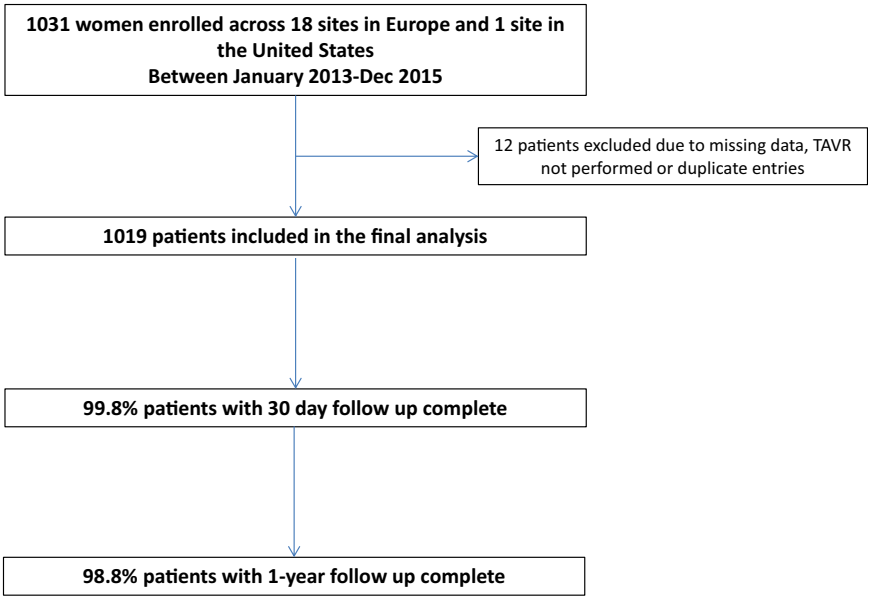
The WIN-TAVI registry (NCT01819181) is an international, multicenter, prospective, observational registry of women undergoing TAVR at 18 European centers and 1 North American center treated with commercially available and approved TAVR devices for the treatment of severe symptomatic AS (15). Participating centers were selected based on review of site survey responses to determine the total number of TAVR procedures performed at each center (minimum of 50) and the planned number of TAVR to be performed in the following year. All sites had institutional approval from the local ethics committee and the study was conducted according to the principles of the Declaration of Helsinki, International Organization for Standardization Guidelines, and Good Clinical Practice Guidelines.

All patients who met the eligibility criteria and provided written informed consent were enrolled in the study. The study was conducted without any external funding and was driven by the scientific interest of the investigators. The protocol and study endpoints were designed by the executive committee and principal investigators of the study (see the Online Appendix).

ELIGIBILITY CRITERIA. The eligibility criteria were indicated in detail in the primary paper (15). In brief, women with: 1) severe AS determined by echocardiography defined as mean gradient >40 mm Hg or peak jet velocity >4.0 m/s and an aortic valve area ≤0.8 cm^2 or aortic valve area index ≤0.5 cm^2/m^2; and 2) symptoms of angina, congestive heart failure, New York Heart Association functional class ≥II, or syncope were considered for enrollment if no exclusions applied.

Additional inclusion criteria were based on high European System for Cardiac Operative Risk Evaluation (EuroSCORE) or presence of other comorbidities (e.g., chronic obstructive lung disease, need for home oxygen, porcelain aorta, previous thoracic

FIGURE 1 Study Flow



TAVR = transcatheter aortic valve replacement.

TABLE 1 Clinical Outcomes During 1-Year Follow-Up

	0-30 Days		0-1 Year	
	n	KM (%)	n	KM (%)
VARC-2 efficacy endpoint*	56	5.6	167	16.5
Secondary endpoints				
All-cause death	40	3.9	127	12.5
Cardiovascular	38	3.7	108	10.8
Noncardiovascular	2	0.2	19	2.0
MI	2	0.2	11	1.1
Stroke	12	1.3	22	2.2
Major vascular complications	81	8.0	83	8.2
VARC life-threatening bleeding	45	4.4	46	4.5
TAV-in-TAV	17	1.7	18	1.8
Acute kidney injury, stage 2 or 3	13	1.3	14	1.4
Other endpoints				
Bleeding				
VARC major	82	8.1	85	8.3
BARC 3 or 5	127	12.5	131	12.9
Arrhythmia				
Any arrhythmia or conduction disturbance	223	21.9	232	22.8
New atrial fibrillation or flutter	31	3.0	37	3.6
Left bundle branch block	103	10.1	103	10.1
PPM implantation	120	11.8	129	12.7
Hospitalizations for heart failure or valve-related symptoms	7	0.7	32	3.2
Composite all-cause death or stroke	49	4.8	141	13.9
Composite all-cause death, MI, or stroke	50	4.9	149	14.7
Composite all-cause death, MI, stroke, or VARC life-threatening bleeding	74	7.3	171	16.9

*Composite of all-cause death, stroke, myocardial infarction, hospitalization for valve-related symptoms or heart failure, or valve-related dysfunction (clinical presentation with valve thrombosis or endocarditis).

BARC = Bleeding Academic Research consortium; KM = Kaplan-Meier; MI = myocardial infarction; PPM = permanent pacemaker; TAV = transcatheter aortic valve; VARC = Valve Academic Research Consortium.

radiotherapy, Childs-Pugh class B and C liver disease) leading to heart team decision for TAVR rather than SAVR. The chief exclusion criteria were untreated clinically significant (>70% obstruction) proximal vessel coronary artery disease (CAD) amenable to revascularization, hemodynamic instability (e.g., requiring inotropic support), active endocarditis or sepsis within 6 months before the study procedure, or use of an investigational device without Conformité Européenne mark.

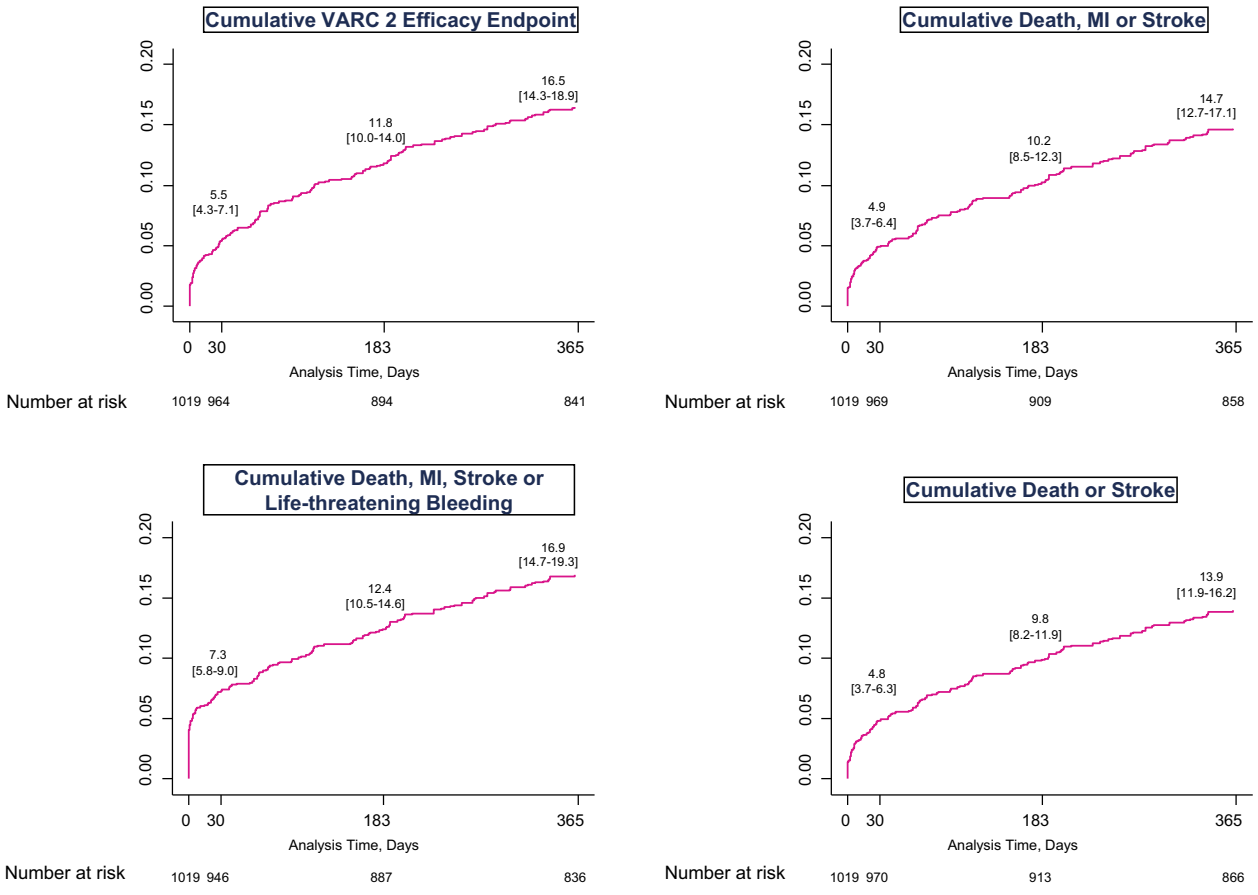
TAVR PROCEDURE AND CLINICAL FOLLOW-UP. Pre-screening included evaluation of medical history and standard of care diagnostic imaging (transthoracic or transesophageal echocardiogram or multidetector computed tomography measurements). We specifically collected information on female sex-related factors including menstrual history, history of pregnancy, pregnancy complications such as gestational hypertension or diabetes, ectopic pregnancy, history of breastfeeding, use of hormone replacement therapy, osteoporosis and use of osteoporosis treatment, gynecological or breast cancer, and gynecological surgery.

Procedural decisions regarding TAVR access, TAVR device type, use of pre- and post-dilation and interventional therapies was at the discretion of the treating physicians. Patient follow-up was conducted by phone contact or clinic visit at 1 month, 6 months, and 12 months after TAVR to record clinical status and occurrence of adverse events. Total planned follow-up is to 24 months. Per standard of care at the participating sites patients underwent neurological evaluation after TAVR, only if clinically indicated.

The clinical and data coordinating center for the study was at the Icahn School of Medicine at Mount Sinai (New York, New York), which was responsible for the monitoring of electronic data entry for accuracy of data, database and data management, and statistical analyses. All events were adjudicated by an independent clinical events committee using source documents provided by the sites. The study was endorsed by the Society for Cardiovascular Angiography and Interventions Women in Innovations initiative.

STUDY ENDPOINTS AND DEFINITIONS. Primary endpoint. The primary study endpoint for the 1-year analysis was the VARC-2 efficacy endpoint beyond

FIGURE 2 **Cumulative Incidence of 1-Year Clinical Outcomes in Women Undergoing TAVR**



Time-to-event curves are represented using Kaplan-Meier curves. *Composite of all-cause death, stroke, myocardial infarction, hospitalization for valve-related symptoms or heart failure or valve-related dysfunction (clinical presentation with valve thrombosis or endocarditis). MI = myocardial infarction; TAVR = transcatheter aortic valve replacement; VARC = Valve Academic Research Consortium.

30 days—a composite of all-cause mortality, all stroke, myocardial infarction, hospitalizations for valve-related symptoms or worsening congestive heart failure or valve-related dysfunction (clinical presentation with valve thrombosis or endocarditis) (16).

Study definitions. Endpoints were adjudicated using the standardized VARC-2 criteria (16).

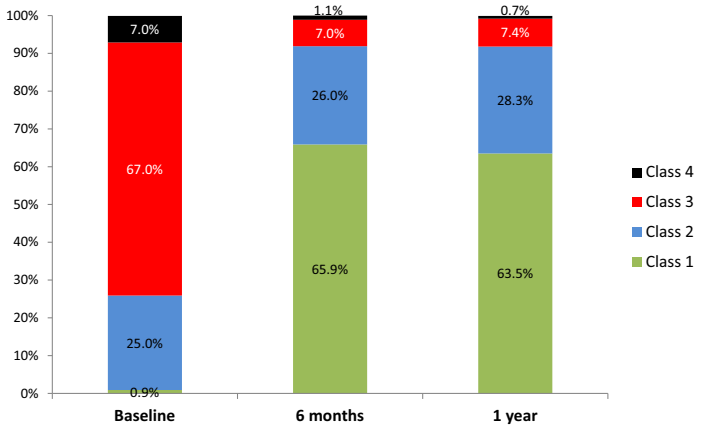
Because echocardiographic examination at 1-year clinical follow-up was not mandatory by study protocol but rather left to local practice, prosthetic valve dysfunction in the patients not undergoing echocardiographic follow-up was evaluated as clinical presentation leading to diagnosis of valve thrombosis or endocarditis.

History of pregnancy was defined as any history of pregnancy and not pregnancy resulting in a live birth. Frailty was subjective as judged by the heart team but the use of objective frailty scales was recommended.

Old-generation devices comprised Edwards SAPIEN XT (Edwards Lifesciences, Irvine, California) and Medtronic CoreValve (Medtronic, Minneapolis, Minnesota). All other prosthesis types are considered new-generation devices.

STATISTICAL APPROACH. Categorical data are presented as frequencies and percentages and were compared using the chi-square or Fisher exact test. Continuous variables are presented as mean ± SD or medians and interquartile range and were compared using the Student *t* test or Wilcoxon signed rank test. Time-to-event curves were constructed using the Kaplan-Meier method and outcomes were compared using the log-rank test. Using Cox regression methods, we generated a multivariable model for

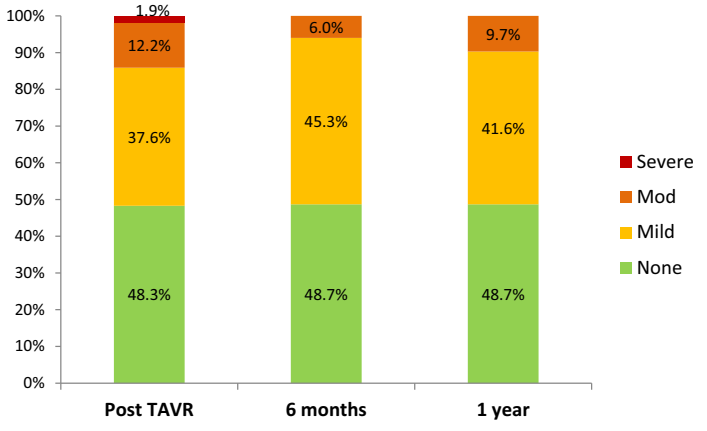
FIGURE 3 Change in NYHA Functional Class Over Time*



Frequencies of patients by NYHA functional class at different time points. *Baseline data available in 855 paents, 6 month data available in 801 paents, 1 year data available in 809 paents. NYHA = New York Heart Association.

predictors of the 1-year composite outcomes. Variables with univariate associations at a significance level of $p < 0.20$ were considered as candidate covariates to generate a multivariable model using stepwise selection (p for entry <0.10, p for exit <0.20). Country was entered as a random effect. All analyses were performed using Stata version 14.0 (StataCorp, College Station, Texas) and p values <0.05 were considered significant.

FIGURE 4 Grades of Paravalvular AI Over Time*



Frequencies of patients by grades of paravalvular AI at different time points. *6 month echo available in 267 paents, 1 year echo available in 351 paents. AI = aortic insufficiency; Mod = moderate; TAVR = transcatheter aortic valve replacement.

RESULTS

STUDY POPULATION. From January 2013 to December 2015, 1,019 women were enrolled across 18 centers in Europe and 1 center in North America. One-year follow-up was achieved in 98.8% of eligible patients (Figure 1). The baseline and procedural characteristics have previously been presented in detail (15). The study population included all women with a mean age of 82.5 ± 6.3 years, with mean EuroSCORE I 17.8 ± 11.7% and mean Society of Thoracic Surgeons score 8.3 ± 7.4%. Prevalence of baseline comorbidities included 26.1% patients with diabetes, 30.8% with chronic kidney disease, 22.9% with prior percutaneous coronary intervention (PCI), 20.0% with prior atrial fibrillation (AF), 7.5% with prior stroke, and 9.2% with peripheral arterial disease. The mean left ventricular ejection fraction (LVEF) was 55.7 ± 10.7%. A total of 738 (72.4%) patients had a history of pregnancy; patients without history of pregnancy were more likely to be considered frail on surgical assessment (70.0% vs. 61.3%; p = 0.01) and were more often current smokers (5.4% vs. 2.5%; p = 0.02) or had left main disease ≥50% (8.7% vs. 4.6%; p = 0.06).

The TAVR procedure was conducted under local anesthesia or conscious sedation in 64.2% of patients. TAVR was mainly performed via transfemoral access (90.6%). In 32% of patients the sheath size used was 16-F or smaller. New-generation devices were used in 42.1%.

1-YEAR PRIMARY AND SECONDARY STUDY ENDPOINTS. The clinical outcomes are shown in Table 1 and Figure 2. The primary VARC-2 composite efficacy endpoint beyond 30 days occurred in 111 (10.9%) patients. During 1-year follow-up the VARC-2 efficacy composite occurred in 167 (16.5%) patients. The baseline characteristics in patients with and without 1-year VARC-2 efficacy endpoint are shown in Online Table 1.

One-year death or stroke occurred in 141 (13.9%) patients. Death was reported in 127 (12.5%) patients, of which cardiac death occurred in 108 (10.6%) patients. One-year stroke occurred in 22 (2.2%) patients. Four patients experiencing stroke had baseline AF and 1 patient had new AF post-TAVR. Among patients experiencing stroke, where discharge medications were recorded (n = 18), 8 patients were discharged on an anticoagulant agent (6 on dual therapy with 1 antiplatelet and 1 anticoagulant agent, and 2 on an anticoagulant agent alone), 7 patients were discharged on dual-antiplatelet therapy (DAPT), and 3 patients were discharged on single antiplatelet

therapy. There were 4 hemorrhagic strokes, 2 occurred in patients on dual therapy and 2 occurred in patients where discharge medications were not recorded.

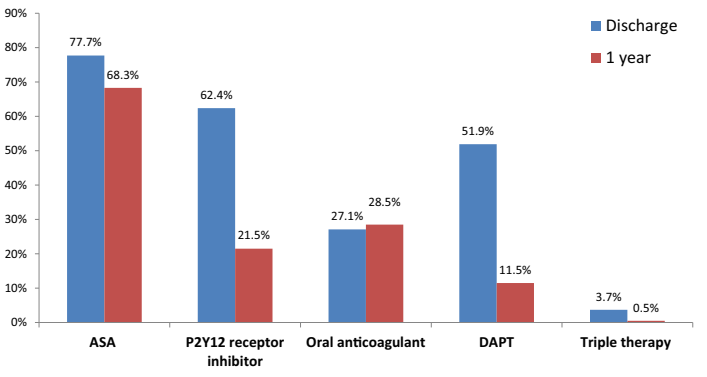
One-year major vascular complications were observed in 83 (8.2%) patients, VARC life-threatening bleeding in 46 (4.5%) patients, and Bleeding Academic Research Consortium 3 or 5 bleeding in 131 (12.9%) patients. TAV-in-TAV implantation occurred in 18 (1.8%) patients, valve thrombosis in 3 (0.3%) patients, and endocarditis in 2 (0.2%) patients. Among patients undergoing echocardiography in follow-up, moderate to severe paravalvular aortic insufficiency (AI) was reported in 9.7% of the patients at 1 year. Any arrhythmia or conduction disturbance was observed in 232 (22.8%) patients after TAVR and new AF in 37 (3.6%) patients, whereas new permanent pacemaker implantation occurred in 129 (12.7%) patients. The incidence of hospitalizations for heart failure or valve-related symptoms during 1-year follow-up occurred in 3.2% of patients. Figure 3 shows the change in New York Heart Association functional class status over time, among survivors.

ECHOCARDIOGRAPHY FOLLOW-UP. At 6 months, echocardiography was available in 275 patients; mean aortic valve gradient was 10.3 ± 5.5 mm Hg, mean peak gradient was 19.2 ± 9.6 mm Hg, mean aortic valve area was 1.79 ± 1.68 cm^2, and LVEF was 57.3 ± 8.8%. At 1 year, echocardiography was available in 373 patients; mean aortic valve gradient was 10.8 ± 5.2 mm Hg, mean peak gradient was 20.2 ± 12.6 mm Hg, mean aortic valve area was 1.50 ± 0.40 cm^2, and LVEF was 57.9 ± 8.7%. The incidence of aortic valve mean gradient >20 mm Hg at 6- or 12-month echocardiography was 4.4%, and the incidence of aortic valve area ≤0.9 cm^2 was 6.0%. This included the 3 patients with valve thrombosis. No patients had severe paravalvular AI. Figure 4 shows the proportion of patients with different grades of paravalvular AI over time.

PHARMACOTHERAPY. Figure 5 shows the frequency of patients on different antithrombotic therapies at discharge and at 1-year follow-up. Although 55.9% patients were discharged on DAPT, only 11.5% remained on DAPT at 1 year. The use of oral anticoagulant agent was similar at discharge (27.1%) and at 1 year (28.5%).

PREDICTORS OF THE 1-YEAR OUTCOMES. On multivariable stepwise Cox regression (Tables 2 to 5), the independent predictors of the 1-year primary VARC-2 efficacy endpoint were prior PCI or coronary

FIGURE 5 Antithrombotic Therapies at Discharge and 1 Year



Frequencies of patients on different antithrombotic therapies at the time of discharge and 1-year after transcatheter aortic valve replacement. ASA = acetylsalicylic acid; DAPT = dual-antiplatelet therapy.

TABLE 2 Predictors of VARC-2 Efficacy Endpoint*

	Univariate Associations		Multivariate Associations	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, yrs	1.02 (0.99–1.05)	0.14		
BMI, kgm^2	0.98 (0.95–1.00)	0.10		
Prior stroke	1.59 (0.97–2.59)	0.064		
Prior PCI or CABG	1.29 (0.93–1.79)	0.13	1.72 (1.17–2.52)	0.006
Prior MI	1.38 (0.87–2.18)	0.17		
Baseline PAD	1.35 (0.85–2.16)	0.21		
Baseline atrial fibrillation	1.37 (0.96–1.96)	0.079		
LVEF <30%	0.84 (0.35–2.05)	0.71		
EuroSCORE I	1.02 (1.01–1.04)	0.004	1.02 (1.00–1.04)	0.027
Baseline renal dysfunction	1.27 (0.92–1.74)	0.14		
Diabetes	0.98 (0.69–1.38)	0.89		
Frailty	0.90 (0.66–1.24)	0.53		
Discharge DAPT	0.76 (0.54–1.07)	0.12	0.70 (0.49–1.01)	0.059
Discharge anticoagulant agent	1.45 (1.01–2.08)	0.043		
Procedure-related variables				
TAVR device generation (new vs. old)	0.87 (0.63–1.20)	0.39		
Access (transfemoral vs. nontransfemoral)	1.01 (0.60–1.69)	0.96		
Device size (>26 mm vs. ≤26 mm)	1.24 (0.86–1.81)	0.25		
Moderate or severe post-TAVR AI	1.16 (0.76–1.78)	0.50		
Female-specific characteristics				
History of pregnancy	0.83 (0.60–1.16)	0.28		
Age of menopause	1.01 (0.98–1.05)	0.50		
History of osteoporosis	0.93 (0.62–1.40)	0.73		

*Composite of all-cause death, stroke, myocardial infarction, hospitalization for valve-related symptoms or heart failure or valve-related dysfunction (clinical presentation with valve thrombosis or endocarditis).

AI = aortic insufficiency; BMI = body mass index; CI = confidence interval; DAPT = dual-antiplatelet therapy; EuroSCORE = European System for Cardiac Operative Risk Evaluation; HR = hazard ratio; LVEF = left ventricular ejection fraction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; TAVR = transcatheter aortic valve replacement; other abbreviations as in Table 1.

TABLE 3 Predictors of 1-Year Death or Stroke

	Univariate Associations		Multivariate Associations	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, yrs	1.03 (1.00–1.06)	0.031	1.03 (0.99–1.06)	0.126
BMI, kgm^2	0.97 (0.94–1.00)	0.11		
Prior stroke	1.54 (0.90–2.64)	0.11		
Prior PCI or CABG	1.38 (0.96–1.99)	0.082	1.50 (1.03–2.19)	0.035
Prior MI	1.41 (0.86–2.31)	0.17		
Baseline PAD	1.56 (0.96–2.52)	0.073		
Baseline atrial fibrillation	1.64 (1.13–2.37)	0.10	1.58 (1.07–2.33)	0.022
LVEF <30%	1.02 (0.42–2.49)	0.97		
EuroSCORE I	1.03 (1.01–1.05)	<0.001	1.02 (1.00–1.04)	0.013
Baseline renal dysfunction	1.30 (0.92–1.83)	0.14		
Diabetes	0.88 (0.60–1.30)	0.53		
Frailty	0.88 (0.62–1.23)	0.44		
Discharge DAPT	0.77 (0.52–1.13)	0.18		
Discharge anticoagulant	1.54 (1.03–2.29)	0.034		
Procedure-related variables				
TAVR device generation (new vs. old)	0.88 (0.62–1.24)	0.46		
Access (transfemoral vs. nontransfemoral)	1.06 (0.61–1.83)	0.85		
Device size (>26 mm vs. ≤26 mm)	1.32 (0.88–1.96)	0.18		
Moderate or severe post-TAVR AI	1.09 (0.68–1.75)	0.73		
Female-specific characteristics				
History of pregnancy	0.71 (0.50–1.00)	0.050	0.73 (0.50–1.06)	0.097
Age of menopause	1.02 (0.98–1.06)	0.32		
History of osteoporosis	0.91 (0.58–1.43)	0.69		

Abbreviations as in Tables 1 and 2.

bypass surgery (hazard ratio [HR]: 1.72; 95% confidence interval [CI]: 1.17 to 2.52; p = 0.006) and EuroSCORE I (per unit increase, HR: 1.02; 95% CI: 1.00 to 1.04; p = 0.027), whereas a borderline association was observed with DAPT use (HR: 0.70; 95% CI: 0.49 to 1.01; p = 0.059). Independent predictors of 1-year death or stroke were EuroSCORE I (per unit increase, HR: 1.02; 95% CI: 1.00 to 1.04; p = 0.013), baseline AF (HR: 1.58; 95% CI: 1.07 to 2.33; p = 0.022), and prior PCI (HR: 1.50; 95% CI: 1.03 to 2.19; p = 0.035).

EFFECT OF PREGNANCY ON 1-YEAR OUTCOMES. The 1-year clinical outcomes in patients with and without history of pregnancy are shown in Table 6. Women with versus without a history of pregnancy had tendency for lower unadjusted 1-year risk of death or stroke (Figure 6) (12.8% vs. 17.3%; unadjusted HR: 0.71; 95% CI: 0.50 to 1.00; p = 0.05), but adjusted risk was attenuated and no longer significant between the 2 groups (HR: 0.73; 95% CI: 0.50 to 1.06; p = 0.097). No meaningfully significant associations were observed between female sex-specific factors and 1-year TAVR outcomes (Online Table 2).

DISCUSSION

The WIN-TAVI registry is the first study to examine the safety and performance of contemporary TAVR in women and to explore the possible influence of female sex-specific characteristics. This unique collaboration was undertaken without external funding support and was made possible by the partnership of participating research teams. The main findings of this principal report are as follows: 1) the VARC-2 efficacy endpoint occurred in 16.5% women at 1 year and in 10.9% women beyond 30 days; 2) the composite of 1-year death or stroke was 13.9%, and all-cause mortality occurred in 12.5% and stroke in 2.2%; 3) EuroSCORE I and prior PCI or coronary artery bypass grafting were independent predictors of the 1-year VARC-2 composite efficacy endpoint whereas a borderline association was observed with DAPT at discharge. The independent predictors of 1-year death or stroke were EuroSCORE I, baseline AF, and prior PCI; and 4) remote history of pregnancy demonstrated a univariate but not multivariate protective association with 1-year death or stroke, and was not associated with the VARC-2 composite efficacy endpoint. No other female sex-specific characteristic showed any association with 1-year composite clinical TAVR outcomes.

Despite greater procedural complications, women demonstrate more favorable 1-year survival following TAVR compared with men, as a function of different baseline risks; lower prevalence of CAD, diabetes, and AF; and higher baseline LVEF (5–8). There is also some evidence that women have faster regression of LV mass after SAVR (17) and significant improvement of LVEF after TAVR compared with men (18), which may account for superior survival. Moreover, women are also observed to have better survival after TAVR versus SAVR, whereas men perform equally well with both operative strategies (3,8,19). Given this background, the WIN-TAVI registry is the first TAVR study to specifically examine women undergoing TAVR, where we have previously demonstrated that the independent predictors of the 30-day VARC-2 safety endpoint in women included age, LVEF <30%, device generation, device size >26 mm, and history of pregnancy (15).

In the current report we show that 1-year incidence of the VARC-2 efficacy endpoint was almost one-half the previously reported rates in prior TAVR studies with primarily older-generation devices. Notably, however, few studies routinely present the VARC-2

endpoint despite the recommendation for such standardization in reporting (16). Although the PRAGMATIC (Pooled Rotterdam-Milan-Toulouse in Collaboration) registry showed 1-year efficacy rates of 25.0% to 32.0% depending on valve type (20), a report by Genereux et al. (21) showed that only 2 of 16 TAVR studies (12.5%) reported the VARC-2 efficacy endpoint, which ranged from 70.2% to 72.0%. Our rate of 1-year death (12.5%) correlated well with other recent studies (22,23) and was in keeping with the results from PARTNER 2 trial (12.3%) in an intermediate-risk population (3). Comparatively, our stroke rate was almost one-half (2.2%) that reported in PARTNER 2 (5.0%) and SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) (5.4%) trials (3,4). The lower stroke rate in our study might be due to the use of new-generation devices, low incidence of new AF (3.6%), and expertise of the operators, but is largely attributable to baseline patient characteristics. Nevertheless, women have been shown to be at higher risk of stroke than men (7,24), potentially as a consequence of smaller aortic valve area and higher baseline gradients (25). At the same time, women are considered more likely to be treated with smaller balloon expandable valves, which have been linked with greater cerebral embolization due to plaque fracture from valvuloplasty (26,27).

With respect to prosthetic valve dysfunction, there were only 3 (0.3%) clinical cases of valve thrombosis and 2 (0.2%) cases of endocarditis reported in the registry. In addition, moderate AI occurred in 9.7% at 1 year, with no patient experiencing severe AI. Despite the very high rate of clinical follow-up (98.8%), we cannot exclude underreporting of prosthetic valve dysfunction in our registry secondary to lack of systematic echocardiographic follow-up. Most elderly TAVR patients tend to follow-up with local general practitioners or referring centers, rather than returning to the tertiary TAVR hospital. Notwithstanding, systematic echocardiographic follow-up is important for documentation of prosthesis function, to inform recommendations for best practice, especially in light of recent reports on leaflet thickening (28). In our subset of patients with echocardiography available at 6 months or 1 year, only 4.4% patients had mean gradient >20 mm Hg and 6.0% patients had area ≤0.9 cm^2. Certainly, the low incidence of clinical valve related dysfunction in this study supports durability of contemporary TAVR valves, noted from the PARTNER trial, with preserved valve hemodynamics up to 5 years (29).

With respect to the low rates of heart failure rehospitalization, although we cannot entirely exclude under reporting from sites, only 3.5% women had LVEF <30% at baseline, which might have influenced readmissions with heart failure. Conversely, in a recent study by Kolte et al. (30), the rate of baseline heart failure was very high (72.6%). Nevertheless, among patients experiencing 30-day hospitalization for any reason in that study, 22.5% were rehospitalized for heart failure, which amounted to 4.0% of the total study population.

TABLE 4 Predictors of 1-Year Death, MI, Stroke, or Life-Threatening Bleeding

	Univariate Associations		Multivariate Associations	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, yrs	1.02 (0.99–1.05)	0.15		
BMI, kg/m^2	0.97 (0.94–1.00)	0.054		
Prior stroke	1.52 (0.93–2.48)	0.092		
Prior PCI or CABG	1.45 (1.04–2.01)	0.027	1.42 (1.00–2.02)	0.049
Prior MI	1.26 (0.79–2.00)	0.34		
Baseline PAD	1.39 (0.88–2.20)	0.16		
Baseline atrial fibrillation	1.36 (0.96–1.93)	0.086		
LVEF <30%	1.23 (0.58–2.62)	0.59		
EuroSCORE I	1.03 (1.01–1.04)	<0.001	1.02 (1.01–1.04)	0.003
Baseline renal dysfunction	1.20 (0.88–1.65)	0.25		
Diabetes	0.81 (0.57–1.16)	0.26		
Frailty	0.97 (0.71–1.33)	0.87		
Discharge DAPT	0.77 (0.55–1.09)	0.14		
Discharge anticoagulant agent	1.36 (0.95–1.94)	0.095		
Procedure-related variables				
TAVR device generation (new vs. old)	0.76 (0.55–1.05)	0.092		
Access (transfemoral vs. nontransfemoral)	1.49 (0.95–2.33)	0.082	1.42 (0.88–2.30)	0.148
Device size (>26 mm vs. ≤26 mm)	1.32 (0.92–1.90)	0.14		
Moderate or severe post-TAVR AI	1.17 (0.77–1.78)	0.46		
Female-specific characteristics				
History of pregnancy	0.82 (0.59–1.14)	0.23		
Age of menopause	1.03 (0.99–1.06)	0.16		
History of osteoporosis	1.05 (0.71–1.56)	0.79		

Abbreviations as in Tables 1 and 2.

PHARMACOTHERAPY POST-TAVR. Recent studies have highlighted the predicament in the optimal prescription of antithrombotic therapy post-TAVR, with occurrence of both embolic episodes and silent cerebral microbleeds (26,31,32). Further, valve leaflet thickening occurring in 13.6% of TAVR patients (28) is amenable to oral anticoagulant therapy, but appears to recur after cessation. One other multicenter registry also observed that valve hemodynamic deterioration was associated with lack of anticoagulation (33). Although 55.9% of our study population was discharged on DAPT, only 11.5% remained on DAPT at 1 year, whereas under one-third of patients were on anticoagulant agents both at discharge and at 1 year. Although this may account for the lower incidence of major bleeding beyond 30 days, conversely we only

TABLE 5 Predictors of 1-Year Death, MI, or Stroke

	Univariate Associations		Multivariate Associations	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, yrs	1.02 (0.99–1.05)	0.13		
BMI, kg/m^2	0.97 (0.94–1.00)	0.094		
Prior stroke	1.56 (0.93–2.62)	0.094		
Prior PCI or CABG	1.36 (0.96–1.94)	0.086	1.43 (0.99–2.07)	0.055
Prior MI	1.41 (0.87–2.28)	0.17		
Baseline PAD	1.45 (0.90–2.35)	0.13		
Baseline atrial fibrillation	1.51 (1.04–2.17)	0.029	1.44 (0.98–2.12)	0.064
LVEF <30%	0.96 (0.39–2.34)	0.93		
EuroSCORE I	1.03 (1.01–1.04)	0.001	1.02 (1.01–1.04)	0.005
Baseline renal dysfunction	1.23 (0.87–1.72)	0.24		
Diabetes	0.89 (0.61–1.29)	0.53		
Frailty	0.88 (0.63–1.22)	0.44		
Discharge DAPT	0.81 (0.56–1.17)	0.26		
Discharge anticoagulant agent	1.43 (0.97–2.11)	0.071		
Procedure-related variables				
TAVR device generation (new vs. old)	0.84 (0.60–1.18)	0.32		
Access (transfemoral vs. nontransfemoral)	1.07 (0.63–1.83)	0.80		
Device size (>26 mm vs. ≤26 mm)	1.28 (0.87–1.89)	0.22		
Moderate or severe post-TAVR AI	1.13 (0.72–1.79)	0.59		
Female specific characteristics				
History of pregnancy	0.77 (0.55–1.09)	0.14		
Age of menopause	1.02 (0.99–1.07)	0.22		
History of osteoporosis	0.99 (0.65–1.52)	0.96		

Abbreviations as in Tables 1 and 2.

observed 3 clinical cases of valve thrombosis in the study.

PREDICTORS OF 1-YEAR OUTCOMES. EuroSCORE I is a well-known predictor of procedural mortality with cardiac surgery (34), but its association with outcomes in women undergoing TAVR has not been previously shown. On the other hand, in a meta-analysis O'Connor et al. (5) observed several individual variables that constitute the EuroSCORE to be correlated to greater long-term death. Similarly, coronary revascularization is a well-established risk factor for future cardiovascular outcomes, but interestingly only forms a part of risk calculators for cardiac surgery (34,35), not TAVR (36). Nevertheless, prior PCI serves as a surrogate for CAD and may also be associated with lower LVEF, an important contributor of poorer survival in men compared with women undergoing TAVR. Our findings also support prior association between AF and worse TAVR outcomes (25,37), emphasizing the need to appropriately identify and risk stratify women with AF undergoing TAVR for treatment with oral anticoagulation. Of note, although DAPT use tended to be protective for the efficacy endpoint, it was not protective for 1-year death or stroke.

Interestingly, new generation TAVR devices and access site were only significant predictors of the 30-day safety endpoint but not 1-year outcomes (15). Although transfemoral access is linked with greater procedural vascular complications (38), it is correlated with better longer-term outcomes than nontransfemoral access, especially in women (3,5,8), highlighting the importance of appropriate access site selection. In addition, we must acknowledge the advantages of new-generation devices with smaller sheath sizes for lower vascular event rates and superior valve performance with reduction in paravalvular AI or pacemaker requirement (39). With respect to female sex-specific characteristics, although history of pregnancy was inversely associated with the 30-day safety endpoint, we observed only a weak univariate association with 1-year death or stroke. Given the baseline differences in patients with and without history of pregnancy, pregnancy

TABLE 6 1-Year Clinical Outcomes in Patients With and Without History of Pregnancy

	0–30 Days			0–1 Years		
	History of Pregnancy (n = 738)	No History of Pregnancy (n = 281)	p Value	History of Pregnancy (n = 738)	No History of Pregnancy (n = 281)	p Value
VARC-2 efficacy endpoint*	35 (4.7)	21 (7.5)	0.10	116 (15.8)	51 (18.4)	0.28
Secondary endpoints						
All-cause death	25 (3.4)	15 (5.3)	0.08	84 (11.4)	43 (15.5)	0.075
Stroke	5 (0.7)	7 (2.5)	0.79	12 (1.8)	10 (3.6)	0.054
Composite of death or stroke	29 (3.9)	20 (7.1)	0.14	94 (12.6)	48 (17.3)	0.049
Composite of death, MI, or stroke	30 (4.1)	20 (7.1)	0.12	102 (13.9)	48 (17.3)	0.13
Death, MI, stroke, or VARC life-threatening bleeding	49 (6.6)	26 (9.3)	0.13	119 (16.2)	53 (19.1)	0.25

Values are n (%). *Composite of all-cause death, stroke, myocardial infarction, hospitalization for valve-related symptoms or heart failure, or valve-related dysfunction (clinical presentation with valve thrombosis or endocarditis).

Abbreviations as in Table 1.

may well be a surrogate for other unmeasured confounders (15). Although we found no differences in residence location (home vs. nursing home) at 1 year among patients with or without history of pregnancy, systematic review of social support factors is needed to better understand a possible link. In addition, we did not find any associations between other female specific factors collected in our registry and VARC-2 outcomes at 1 year. Nevertheless, female sex-specific variables are important to understand associations with cardiovascular disease progression and outcomes, as well as to avoid disparities in treatment, as has been highlighted by other authors (40).

STUDY LIMITATIONS. First, this was an observational study without a randomized control arm (men) to provide definitive conclusions with respect to sex differences. However, the main aim of the study was to provide real-world data in women who comprise 50% or more of patients undergoing TAVR; and to examine the effect of female sex-specific characteristics. Patients in this registry had a comparable prevalence of cardiovascular risk factors to multiple other registries and therefore accurately reflect real world practice. The true incidence of stroke may be underestimated due to lack of systematic neurological evaluation after TAVR. In addition, despite the very high rate of clinical follow-up at 1 year in this registry, lack of mandatory echocardiography and electrocardiography at follow-up and the fact that most of the follow-up visits were done with local general practitioners rather than referring centers might have led to underdiagnosis of prosthesis dysfunction and under-reporting of new-onset AF. Information on female sex-specific characteristics are subject to recall bias.

CONCLUSIONS

Intermediate to high-risk women enrolled in this first ever all-women TAVR registry experienced a 1-year VARC-2 composite efficacy endpoint of 16.5%, with a low incidence of 1-year mortality and stroke. EuroSCORE I, baseline AF, and prior PCI were independent predictors of the 1-year death or stroke, and EuroSCORE I and prior PCI or CABG were independent predictors of the VARC-2 efficacy endpoint. After adjustment, no associations were observed between history of pregnancy and 1-year TAVR outcomes.

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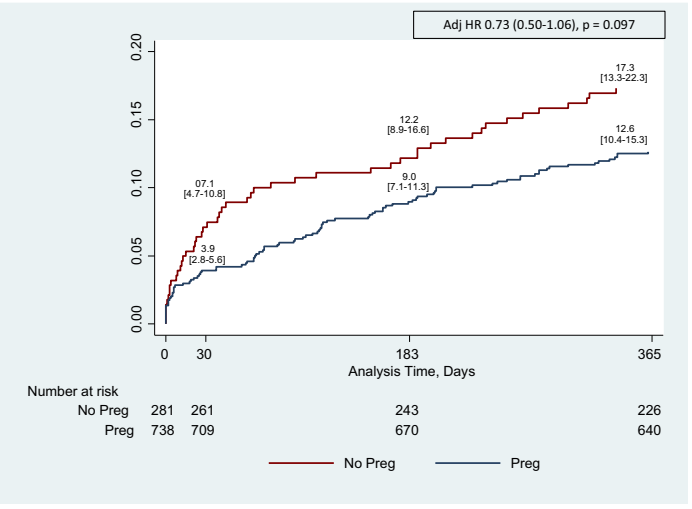
FIGURE 6 Cumulative Incidence of 1-Year Death or Stroke in Women With and Without History of Pregnancy Undergoing TAVR



Time-to-event curves in patients with and without history of pregnancy represented using Kaplan-Meier methods. Adj = adjusted; HR = hazard ratio; Preg = pregnancy; TAVR = transcatheter aortic valve replacement.

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PERSPECTIVES

WHAT IS KNOWN? Women comprise ≥50% patients undergoing TAVR and have superior 1-year survival compared with men. Significant advancements have taken place with respect to experience and skills of TAVR teams, as well as availability of more optimized device iterations.

WHAT IS NEW? The WIN-TAVI registry is the first ever all-women single-arm study to evaluate the 1-year safety and performance of TAVR in women and to further explore the influence of other female sex-specific characteristics that have never hitherto collected in TAVR studies. Intermediate to high-risk women enrolled in this registry experienced a 1-year VARC-2 composite efficacy endpoint of 16.5% and 1-year death or stroke rate of 13.9%.

WHAT IS NEXT? Randomized assessment of TAVR versus SAVR in all-comer women with severe AS is warranted to determine the optimal management strategy.

REFERENCES

1. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.

2. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790–8.

3. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374:1609–20.

4. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med 2017;376:1321–31.

5. O'Connor SA, Morice MC, Gilard M, et al. Revisiting sex equality with transcatheter aortic valve replacement outcomes: a collaborative, patient-level meta-analysis of 11,310 patients. J Am Coll Cardiol 2015;66:221–8.

6. Kodali S, Williams MR, Doshi D, et al. Sex-specific differences at presentation and outcomes among patients undergoing transcatheter aortic valve replacement: a cohort study. Ann Intern Med 2016;164:377–84.

7. Chandrasekhar J, Dangas G, Yu J, et al. Sex-based differences in outcomes with transcatheter aortic valve therapy: TVT registry from 2011 to 2014. J Am Coll Cardiol 2016;68:2733–44.

8. Williams M, Kodali SK, Hahn RT, et al. Sex-related differences in outcomes after transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis: Insights from the PARTNER Trial (Placement of Aortic Transcatheter Valve). J Am Coll Cardiol 2014;63:1522–8.

9. Hamdan A, Barbash I, Schwammenthal E, et al. Sex differences in aortic root and vascular anatomy in patients undergoing transcatheter aortic valve implantation: A computed-tomographic study. J Cardiovasc Comput Tomogr 2017;11:87–96.

10. Cawthon PM. Gender differences in osteoporosis and fractures. Clin Orthop Relat Res 2011;469:1900–5.

11. Humphries KH, Toggweiler S, Rodes-Cabau J, et al. Sex differences in mortality after transcatheter aortic valve replacement for severe aortic stenosis. J Am Coll Cardiol 2012;60:882–6.

12. Park K, Wei J, Minissian M, Bairey Merz CN, Pepine CJ. Adverse pregnancy conditions, infertility, and future cardiovascular risk: implications for mother and child. Cardiovasc Drugs Ther 2015;29:391–401.

13. Mondul AM, Rodriguez C, Jacobs EJ, Calle EE. Age at natural menopause and cause-specific mortality. Am J Epidemiol 2005;162:1089–97.

14. Li S, Rosenberg L, Wise LA, et al. Age at natural menopause in relation to all-cause and cause-specific mortality in a follow-up study of US black women. Maturitas 2013;75:246–52.

15. Chieffo A, Petronio AS, Mehilli J, et al. Acute and 30-day outcomes in women after TAVR: results from the WIN-TAVI (Women's INternational Transcatheter Aortic Valve Implantation) real-world registry. J Am Coll Cardiol Intv 2016;9:1589–600.

16. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Thorac Cardiovasc Surg 2013;145:6–23.

17. Petrov G, Regitz-Zagrosek V, Lehmkuhl E, et al. Regression of myocardial hypertrophy after aortic valve replacement: faster in women? Circulation 2010;122:S23–8.

18. Stangl V, Baldenhofer G, Knebel F, et al. Impact of gender on three-month outcome and left ventricular remodeling after transfemoral transcatheter aortic valve implantation. Am J Cardiol 2012;110:884–90.

19. Piazza N, Kalesan B, van Mieghem N, et al. A 3-center comparison of 1-year mortality outcomes between transcatheter aortic valve implantation and surgical aortic valve replacement on the basis of propensity score matching among intermediate-risk surgical patients. J Am Coll Cardiol Intv 2013;6:443–51.

20. Chieffo A, Buchanan GL, Van Mieghem NM, et al. Transcatheter aortic valve implantation with the Edwards SAPIEN versus the Medtronic CoreValve Revalving system devices: a multicenter collaborative study: the PRAGMATIC Plus Initiative (Pooled-RotterdAm-Milano-Toulouse In Collaboration). J Am Coll Cardiol 2013;61:830–6.

21. Genereux P, Head SJ, Van Mieghem NM, et al. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. J Am Coll Cardiol 2012;59:2317–26.

22. Levi A, Landes U, Assali AR, et al. Long-term outcomes of 560 consecutive patients treated with transcatheter aortic valve implantation and propensity score-matched analysis of early- versus new-generation valves. Am J Cardiol 2017;119:1821–31.

23. Herrmann HC, Thourani VH, Kodali SK, et al. One-year clinical outcomes with SAPIEN 3 transcatheter aortic valve replacement in high-risk and inoperable patients with severe aortic stenosis. Circulation 2016;134:130–40.

24. Holmes DR Jr., Brennan JM, Rumsfeld JS, et al. Clinical outcomes at 1 year following transcatheter aortic valve replacement. JAMA 2015;313:1019–28.

25. Kapadia S, Agarwal S, Miller DC, et al. Insights into timing, risk factors, and outcomes of stroke and transient ischemic attack after transcatheter aortic valve replacement in the PARTNER Trial (Placement of Aortic Transcatheter Valves). Circ Cardiovasc Interv 2016;9:e002981.

26. Van Mieghem NM, El Faquir N, Rahhab Z, et al. Incidence and predictors of debris embolizing to the brain during transcatheter aortic valve implantation. J Am Coll Cardiol Intv 2015;8:718–24.

27. Mastoris I, Schoos MM, Dangas GD, Mehran R. Stroke after transcatheter aortic valve replacement: incidence, risk factors, prognosis, and preventive strategies. Clin Cardiol 2014;37:756–64.

28. Chakravarty T, Sondergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet 2017;389:2383–92.

29. Kapadia SR, Leon MB, Makkar RR, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2485–91.

30. Kolte D, Khera S, Sardar MR, et al. Thirty-day readmissions after transcatheter aortic valve replacement in the United States: insights from the Nationwide readmissions database. Circ Cardiovasc Interv 2017;10:e004472.

31. Van Belle E, Hengstenberg C, Lefevre T, et al. Cerebral embolism during transcatheter aortic valve replacement: the BRAVO-3 MRI study. J Am Coll Cardiol 2016;68:589–99.

32. Van Belle E. Silent cerebral microbleeds during TAVR: insight from a prospective study. Presented at: ACC 2017; March 19, 2017; Washington, DC.

33. Del Trigo M, Munoz-Garcia AJ, Wijeysundera HC, et al. Incidence, timing, and predictors of valve hemodynamic deterioration after transcatheter aortic valve replacement: multicenter registry. J Am Coll Cardiol 2016;67:644–55.

34. Nashef SA, Roques F, Michel P, et al. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9–13.

35. Online STS Adult Cardiac Surgery Risk Calculator. 2007. Available at: http://riskcalc.sts.org/stswebriskcalc. Accessed April 2017.

36. Edwards FH, Cohen DJ, O'Brien SM, et al. Development and validation of a risk prediction model for in-hospital mortality after transcatheter aortic valve replacement. JAMA Cardiol 2016;1:46–52.

37. Tarantini G, Mojoli M, Urena M, Vahanian A. Atrial fibrillation in patients undergoing transcatheter aortic valve implantation: epidemiology, timing, predictors, and outcome. Eur Heart J 2017;38:1285–93.

38. Chandrasekhar J, Hibbert B, Ruel M, et al. Transfemoral vs non-transfemoral access for transcatheter aortic valve implantation: a systematic review and meta-analysis. Can J Cardiol 2015;31:1427–38.

39. Chamandi C, Puri R, Rodriguez-Gabella T, Rodes-Cabau J. Latest generation TAVR devices and procedures. Can J Cardiol 2017;33:1082–90.

40. Ouyang P, Wenger NK, Taylor D, et al. Strategies and methods to study female-specific cardiovascular health and disease: a guide for clinical scientists. Biol Sex Differ 2016;7:19.

KEY WORDS female-specific characteristics, first female registry, transcatheter aortic valve replacement, 1-year outcomes

APPENDIX For an expanded Methods section and supplemental tables, please see the online version of this paper.