Acute and 30-day Outcomes in Women After TAVR: Results From the First Women in Transcatheter Aortic Valve Implantation (WIN-TAVI) Real World Registry

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Acute and 30-day Outcomes in Women After TAVR: Results From the First Women in Transcatheter Aortic Valve Implantation (WIN-TAVI) Real World Registry

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ABSTRACT

Background: Although women comprise 50% of patients with symptomatic severe aortic stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR), the optimal treatment strategy remains undetermined.

Objectives: We sought to examine the safety and performance of TAVR using an all-female registry and to further explore the potential impact of female sex-specific characteristics, on clinical outcomes after TAVR.

Methods: WIN-TAVI is a multinational, prospective, observational registry of women undergoing TAVR for AS, conducted without any external funding. The primary endpoint was the Valve Academic Research Consortium (VARC) 2 early safety endpoint at 30-days (composite of mortality, stroke, major vascular complication, life threatening bleeding, stage 2 or 3 acute kidney injury, coronary artery obstruction or repeat procedure for valve-related dysfunction).

Results: Between January 2013-December 2015, 1019 women were enrolled across 19 European and North American centers. The mean patient age was 82.5±6.3 years, mean EuroSCORE I was 17.8±11.7% and mean STS score was 8.3±7.4%. TAVR was performed via transfemoral access in 90.6%, new-generation devices were used in 42.1%. In more than two-thirds cases, an Edwards SAPIEN 23mm or Medtronic CoreValve ≤ 26mm device was implanted. The 30-day VARC-2 composite endpoint occurred in 14.0% with 3.4% all-cause mortality, 1.3% stroke, 7.7% major vascular complications and 4.4% VARC life threatening bleeding. The independent predictors of the primary endpoint were age (OR = 1.04, 95% CI = 1.00-1.08), prior stroke (OR = 2.02, 95% CI = 1.07-3.80), ejection fraction <30% (OR= 2.62, 95 % CI= 1.07-6.40), device

generation (OR= 0.59, 95 % CI= 0.38 – 0.91) and history of pregnancy (adjusted OR= 0.57, 95 % CI= 0.37-0.85).

Conclusions: Women enrolled in this first ever all-female TAVR registry with collection of female-sex specific baseline parameters, were at intermediate-high risk and experienced a 30-day VARC-2 composite safety endpoint of 14.0% with a low incidence of early mortality and stroke. Randomized assessment of TAVR versus surgical aortic valve replacement in intermediate risk women is warranted to determine the optimal strategy.

KEY WORDS: transcatheter aortic valve replacement, first female registry, early outcomes, mortality

CONDENSED ABSTRACT

WIN-TAVI is a multinational, prospective, observational registry of women undergoing transcatheter aortic valve replacement (TAVR) for severe aortic stenosis. Between January 2013-December 2015, 1019 women were enrolled with a mean age of 82.5 ±6.3 years and mean STS score of 8.3±7.4%. TAVR was performed via transfemoral access in 90.6% and new-generation devices were used in 42.1%. The primary endpoint (30-day Valve Academic Research Consortium-2 composite of mortality, stroke, major vascular complication, life threatening bleeding, stage 2/3 acute kidney injury, coronary artery obstruction or repeat procedure for valve-related dysfunction) occurred in 14.0% with 3.4% all-cause mortality and 1.3% stroke

ABBREVIATIONS

TAVR: Transcatheter aortic valve replacement

AVR: Aortic valve replacement

AS: Aortic stenosis

MDCT: Multidetector Computed Tomography

VARC: Valve Academic Research Consortium

BARC: Bleeding Academic Research Consortium

LVEF: Left ventricular ejection fraction

OR: Odds ratio

CI: Confidence interval

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has been clearly demonstrated to be an alternative treatment for severe aortic stenosis (AS) in patients considered at high risk for surgical aortic valve replacement (SAVR) [1, 2]. In the "Placement of AoRTic TraNscathetER valve trial" (PARTNER A), women (n =300; 42.9%) treated with TAVR had lower 12-month mortality compared to men (18.4% vs. 28.0%)[1, 3]. Recently, in the PARTNER 2 cohort A randomized trial, evaluating intermediate-risk patients with severe AS, TAVR was found to be similar to SAVR with respect to the primary end point of 2-year death or disabling stroke (19.3% with TAVR vs. 21.1% with SAVR (HR 0.89; 95% confidence interval , 0.73 to 1.09; P = 0.25; P = 0.001 for non inferiority)[4].

Prior studies have shown that women are better represented in TAVR studies compared with coronary artery disease (CAD) trials, where the inclusion of women has historically been low[3, 5-7]. The reasons for this may be different left ventricular adaptation to AS in women [8, 9] with predominant hypertrophy rather than dilation and preserved systolic function, as well as a low prevalence of concurrent CAD, both of which may delay symptom onset. Consequently women with symptomatic AS are older with a lower body mass index (BMI), characteristics which can influence the therapeutic decision for TAVR[10]. Female sex itself is an independent predictor of survival in older patients undergoing conventional SAVR and therefore has bearing on heart team decision for TAVR rather than SAVR[3, 11]. In addition, the influence of female-specific or female-predominant factors such as frailty, osteoporosis, history of pregnancy and age of menopause on TAVR outcomes is unknown. While frailty and osteoporosis have been linked with poor post-operative recovery[16], osteoporosis and vertebral fractures may also influence cardiac rotation impacting on device positioning and implantation. Lifetime hormonal influences

may have a role in arterial stiffness and diastolic dysfunction, consequently impacting on aortic stenosis [17] and post TAVR outcomes.

Recent data have shown female sex to be independently associated with better recovery of LV systolic function following aortic valve replacement [9, 12, 13] with lower 1-year mortality compared to men undergoing TAVR[14, 15]. Thus, women may be more suited to derive greater benefit from TAVR. Nevertheless, studies have also reported that women undergoing TAVR experience more major vascular and bleeding complications and in a recent meta-analysis women experienced a high 30-day stroke rate[6, 14, 15]. Therefore, the optimal approach to definitive management in women with symptomatic AS is undetermined.

The purpose of this multicenter international registry dedicated to women was to investigate the safety and performance of contemporary TAVR and to further explore the influence of female sex-specific factors which have never previously been investigated but may be relevant in the management of women undergoing TAVR.

METHODS

WIN TAVI (ClinicalTrials.gov Identifier: NCT01819181) is an international, multi-center, prospective, observational registry of women undergoing TAVR at 19 European and North American centers treated with commercially available and approved TAVR devices and delivery systems for the treatment of severe symptomatic AS. The centers were selected based on review of individual site survey responses to determine the total number of TAVR performed at each center (minimum 50) and the planned number of TAVR to be performed in the following year.

All participating sites had institutional approval from the local ethical review board 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 inclusion criteria and provided written informed consent were enrolled in the study. Of note, the study was conducted without any external funding and was driven by the scientific interest and collaboration of the investigators. The protocol and study endpoints were designed by the executive committee and principal investigators of the study.

Eligibility criteria

The main inclusion criteria were: Women with (i) severe AS determined by echocardiography and doppler, defined as: mean gradient >40 mmHg 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 (ii) symptoms of angina, congestive heart failure, New York Heart Association (NYHA) functional class ≥ II, or syncope.

Additional inclusion criteria were based on high logistic EuroSCORE or presence of other comorbidities (such as severe airways disease, porcelain aorta, previous thoracic radiotherapy, Childs Pugh class B and C liver disease) leading to multi-disciplinary heart team (interventional cardiologists, cardiothoracic surgeons and cardiac anaesthesiologists) decision for TAVR rather than SAVR.

The exclusion criteria were: Female patients not eligible for TAVR, untreated clinically significant (>70% obstruction) proximal vessel CAD amenable to revascularization, echocardiographic evidence of intra-cardiac mass, thrombus or vegetation, hemodynamic instability (e.g. requiring inotropic support), active endocarditis or sepsis within 6-months prior to the study procedure or use of an investigational device without Conformité Européene mark.

TAVR Procedure and Clinical Follow-Up

Pre-screening included evaluation of medical history and diagnostic imaging performed as per standard of care (transthoracic/transesophageal echocardiogram and/or multidetector computed tomography (MDCT) measurements) at the treating physician's discretion[18]. We also collected information on female specific factors including menstrual history, use of hormone replacement therapy, history of pregnancy, osteoporosis, gynecological or breast cancer.

Procedural selection of access, 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, 12 months and 24 months following TAVR to record clinical status and occurrence of adverse events. Of note, as per the standard of care at the participating sites not all the patients underwent a neurological evaluation after TAVR, unless clinically indicated. All events were reported by the sites in the electronic study database.

The Clinical and Data coordinating center for the study was at the Icahn School of Medicine at Mount Sinai, New York, USA, 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 Event Committee using source documents provided by the sites. The study was endorsed by the Society for Cardiovascular Angiography and Interventions - Women In Innovation (SCAI-WIN) Initiative.

Study endpoints and definitions

Primary endpoint

The primary study endpoint was the Valve Academic Research Consortium (VARC) 2 early safety endpoint at 30-days – a composite of all-cause mortality, all stroke, major vascular

complication, life-threatening bleeding, stage 2 or 3 acute kidney injury (AKI), coronary artery obstruction requiring intervention or repeat procedure for valve-related dysfunction[19].

Secondary Endpoints

Individual safety endpoints included the following: all-cause mortality, cardiovascular mortality, all stroke, myocardial infarction, bleeding (VARC 2 life-threatening or disabling and major bleeding and Bleeding Academic Research Consortium (BARC) bleeding 3 or 5[20], stage 2 or 3 AKI and vascular complications. *Additional TAVR related endpoints* included the following: coronary artery obstruction, surgical conversion, unplanned use of cardiopulmonary bypass, ventricular septal perforation, mitral valve apparatus damage or dysfunction and cardiac tamponade and cardiac arrhythmias or conduction disturbances.

Outcomes beyond 30-days

Both the clinical efficacy endpoint and prosthetic valve performance endpoints will be evaluated beyond 30-days.

Study definitions

History of pregnancy was defined as any history of pregnancy and not pregnancy resulting in a live birth. Frailty was defined as judged by the heart team and use of objective scales was recommended but not mandated. Old-generation devices comprised Edwards SAPIEN XT and Medtronic CoreValve. 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 means and standard deviation or medians and interquartile range and were compared using the student's t-test or

Wilcoxon signed-rank test. Time-to-event curves were represented using Kaplan-Meier methods. Using logistic regression methods, we generated a multivariable model for predictors of the 30-day primary VARC 2 safety endpoint. The following covariates were entered in the model based on prior data or expected impact on the outcome: age, BMI, diabetes, chronic kidney disease, prior coronary revascularization, atrial fibrillation, prior stroke, EuroSCORE I, frailty, left ventricular ejection fraction (LVEF) < 30%, transfemoral vs. non-transfemoral access, new vs. old generation TAVR device, TAVR device > 26mm vs. ≤ 26mm and post-TAVR aortic incompetence (AI) grade 2 or 3. The incremental value of each female-specific characteristic on the 30-day primary endpoint was evaluated adjusted for this model. All analyses were performed using Stata version 14.0 (College Station, Texas) and p values < 0.05 were considered significant.

RESULTS

Study population

From January 2013 to December 2015, 1019 women were enrolled across 19 centers in Europe and North America. Baseline characteristics are shown in **Table 1**. The study population included women with a mean age of 82.5 ± 6.3 years, with mean BMI 26.0 ± 5.5, mean EuroSCORE I 17.8 ± 11.7% and mean STS score 8.3± 7.4%. History of diabetes was present in 264 (26.1%), chronic kidney disease in 306 (30.8%), prior PCI in 233 (22.9%) and prior stroke in 76 (7.5%) of the patients. The most common reasons for TAVR were high surgical risk, age >80 years and frailty as per surgical evaluation; nearly three-quarters (71%) patients had more than 3 high-risk reasons for TAVR (**Figure 1 - A and B**)

The mean aortic annulus diameter was 21.8 ±2.04mm on pre-screening echocardiography and mean LVEF was 55.7 ±10.7%. On MDCT, mean aortic annulus diameter was 22.7 ±2.0mm and mean femoral artery diameter was 7.9 ±3.2mm. Baseline coronary angiography showed no obstructive disease in 62.6%, triple vessel disease in 10.4% and left main disease in 5.7% patients.

Female sex -specific baseline characteristics

A total of 738 (72.4%) patients had a history of pregnancy, only 31 of them reported to have suffered from a pregnancy induced complication, either gestational diabetes or hypertension. History of osteoporosis was reported in 178 (17.5%) women; 56 of them received medications for osteoporosis. Frailty and osteoporosis were noted in 103 (10.1%) of women. History of breast and gynecological cancer were present in 9.3% and 2.3% of patients respectively. The mean age of menopause was 48.8 ±5.1 years.

Discharge information

The mean length of stay in the intensive care unit was 2.9 ± 3.3 days and mean duration of total hospital stay was 11.8 ± 8.0 days. Most (75.3%) of the patients were discharged home. Approximately 89% of patients were discharged on aspirin or $P2Y_{12}$ receptor inhibitor, 50% on dual antiplatelet therapy and 27.1% on an oral anticoagulant.

Procedural characteristics and complications

Table 2 shows the procedural characteristics of the study population. Local anesthesia or conscious sedation was used in 64.2% patients. TAVR was mainly performed via transfemoral access (90%) using a percutaneous approach (87.0%). In 32% of patients the sheath size used was 16 F or smaller. The devices used most often were CoreValve (47.2%) and Edwards SAPIEN (41.7%) New generation devices were used in 42.1% (**Figure 2 - A and B**). In

particular, SAPIEN 3 was used in 229 (22.4%) and Evolute R in 79 (8.1%) of the overall patients. In more than two-thirds of cases, an Edwards SAPIEN 23mm device (68.4% of all Edwards SAPIEN devices) or a Medtronic Core Valve ≤26mm (66.6% of all Medtronic devices) was implanted.

Site reported procedural complications are shown in **Table 3**. Valve embolization occurred in 11 (1.1%) patients. A total of 12 (1.2%) patients had annulus or aortic rupture, whereas 14 (1.4%) patients had ventricular perforation. Procedure-related AV block was reported in 81 (8.1%) cases. **Appendix Table 1** demonstrates the procedural complications by valve type.

Primary and Secondary Study Endpoints

Follow-up at 30-days was completed in 99.8% of the patients. The clinical outcomes at 30 days are shown in **Table 4** and the **Central Illustration**. The composite safety primary endpoint occurred in 147 patients (14.0%). All cause death occurred in 40 (3.4%) patients, of these 38 (3.3%) were cardiac deaths. Stroke occurred in 13 (1.3%) patients and death or stroke occurred in 50 (4.9%) patients. Major vascular complications were observed in 80 (7.7%), VARC life threatening bleeding in 45 (4.4 %) and BARC 3 or 5 bleeding in 123 (12%) patients. Coronary artery obstruction occurred in 7 (0.7%), TAV-in-TAV in 17 (1.7%) and surgical conversion in 7 (0.7%) of the patients. The incidence of stage 2 or 3 AKI was 1.3%.

Any arrhythmia or conduction disturbance was reported in 21.9% of the patients after TAVR, however new permanent pacemaker (PPM) implantation occurred in 123 (12.1%) patients. AI ≥ grade 2 was reported in 14.1% and ≥ grade 3 in 1.9% on angiography post-TAVR implantation.

Figure 3 shows the prevalence of female specific characteristics and the incidence of the VARC 2 safety endpoint in patients with versus without history of pregnancy (12.7% vs. 18.9%, p =0.013). 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), had left main disease ≥ 50% (8.7% vs. 4.6%, p = 0.06) or severe aortic valve calcification (39.4% vs. 30.7%, p = 0.04).

Predictors of the 30-day Primary Safety Endpoint

The baseline characteristics of women with and without the 30 day primary safety endpoint are shown in **Appendix Table 2**. On univariable analysis, patients with a prior stroke, higher STS score and LVEF <30% had a higher occurrence of the primary safety endpoint. Moreover, patients with a history of pregnancy had a lower occurrence of the primary safety end-point. On multivariable logistic regression (**Table 5**), age (OR = 1.04, 95% CI = 1.00-1.08; p= 0.028), prior stroke (OR = 2.02, 95% CI = 1.07-3.80; p= 0.029), LVEF <30% (OR= 2.62, 95 % CI= 1.07-6.40; p= 0.035) and TAVR device generation (OR= 0.59, 95 % CI= 0.38 – 0.91; p= 0.018) were independent predictors of the 30 day primary safety endpoint. History of pregnancy was an incremental predictor and was associated with lower rate of the 30-day primary safety endpoint (Crude OR= 0.63, 95% CI= 0.43-0.91, p = 0.013; adjusted OR= 0.57, 95 % CI= 0.37-0.85, p= 0.007).

The 30 day clinical outcomes in patients with and without history of pregnancy are shown in **Appendix Table 3**. Women with a history of pregnancy had lower rate of stroke, death or stroke and AKI but no difference in 30-day death, vascular or bleeding complications post-TAVR compared with women without history of pregnancy.

DISCUSSION

The WIN TAVI registry is the first ever all-female single arm study to evaluate the safety and performance of TAVR in women and to further explore the influence of other female sex-specific characteristics that have never been collected in prior TAVR studies. The study received no external funding and was entirely driven by site principal investigators who conducted enrollment, data collection and follow-up. This was made possible by the leadership of primarily female interventional cardiologists, with scientific collaboration from academic centers in Europe and North America.

The main findings of this report are: 1) Nearly three-quarters of women undergoing TAVR for symptomatic aortic stenosis were >80 years of age, almost 90% were considered high-risk and two-thirds were considered frail on surgical assessment; 2) The incidence of the 30-day VARC 2 composite safety endpoint was 14.0%; all-cause mortality occurred in 3.4% and stroke in 1.3%; 3) Although the primary endpoint was driven largely by vascular or bleeding events, the observed rate of these events was lower than previously reported; 4) The independent predictors of the 30-day VARC-2 composite safety endpoint were increasing age, history of prior stroke, LVEF <30% and TAVR device generation; 5) Remote history of pregnancy was found to be associated with lower rate of the 30-day VARC-2 composite endpoint; 6) Only 12.1% patients received a PPM within 30 days.

Prevalence and characteristics of women undergoing TAVR

Despite the high prevalence of significant AS in women, the most-optimal approach for definitive management remains undetermined. Compared with prior TAVR reports from sex-based subgroup analyses, our study population had lower calculated risk scores, identifying a predominantly intermediate-high risk population[5, 6, 15]. While the prevalence of baseline

comorbidities was in keeping with prior studies, the key reasons for TAVR indicated by local heart teams included high surgical risk, age > 80 years and frailty with 3 or more high-risk reasons influencing decision-making in the majority of the patients. This underlines the discrepancy between historical surgical scores and physician assessment of all individual patient comorbidities for selection of the appropriate treatment strategy. With respect to female sex-specific characteristics, most women (72%) had at least one pregnancy in their lifetime. The mean reported age of menopause and prevalence of osteoporosis was consistent with published literature [21]. Conversely, the low prevalence of pregnancy-induced complications and female cancers may be subject to recall bias and under-reporting. Interestingly, only one-fifth of women with osteoporosis in our study were on treatment for it, a factor that may affect future rehabilitation and functional recovery[16].

With respect to procedural characteristics, this analysis represents current TAVR practice including mainly percutaneous transfemoral approach, low use of general anesthesia, 32% use of sheath sizes ≤16F and 42.1% use of new generation devices[22-25].

30-day Clinical Endpoints

Aligned with prior literature, the most frequent events observed in our population were vascular and bleeding complications while the rate of death, stroke and other endpoints was low. However, the observed rate of vascular and bleeding complications in the current study was lower than prior studies, which have reported an incidence upwards of 7-10% [5, 14, 15]. Several factors may have contributed to these results, including the lower risk profile of our population as compared with women prior TAVR reports[5, 6, 15], the use of new-generation devices compatible with smaller sheaths, completely or partially retrievable, the expertise of our operators and centers and prescribed discharge antithrombotic regimens. We selected the study

centers based on the number of TAVR procedures performed prior to study commencement, reflecting that sites were not in an early learning curve. Moreover, we found that 50% of our study population was discharged on dual antiplatelet therapy while 27% of patients were prescribed an oral anticoagulant. While the ideal antithrombotic regimen in TAVR is currently undetermined, discharge therapies may influence both early and long-term bleeding outcomes. Notably, our 30-day incidence of all-cause mortality (3.4%) and stroke (1.3%) were low as compared to the recent meta-analysis by O'Connor et al who reported a mortality rate of 6.5% and a stroke rate of 4.4% [15]. However, this meta-analysis included older TAVR studies and patients with higher EuroSCORE and/or STS score. Conversely, since post-TAVR neurological evaluation was only performed at the clinical discretion of the centers, neurological events may be under-reported in our study. Certainly, a randomized comparison of SAVR versus TAVR in women is needed to establish the optimal approach. In fact, the findings of the current registry underscore the importance and safety of moving to a lower risk population of women with TAVR. Indeed, the potential superiority of transfemoral TAVR over SAVR in the PARTNER 2A trial may have been driven by better outcomes in women[4].

Predictors of 30-day VARC-2 safety endpoint

We observed that the independent predictors of the 30-day VARC 2 composite safety end point were age, prior stroke, LVEF <30% and TAVR device generation. While other studies have shown age to be a predictor of TAVR mortality, LVEF and prior stroke have been shown to be associated with early events in men but not in women [6, 26]. No study has shown TAVR device generation to be a predictor of early outcomes, however this is consistent with the reduction in outcomes shown in these device trials [22-25, 27]. Indeed, as the indication for TAVR continues to expand in intermediate risk patients, the protective influence of new-

generation TAVR devices is encouraging and may be due to the lower incidence of vascular and bleeding complications with smaller sheath sizes, more precise and accurate positioning with retrievable or partially retrievable devices and lower para-valvular leak.

Of note, history of pregnancy and the number of prior pregnancies were incremental predictors of the 30-day primary safety endpoint, which remained significant despite adjusting for baseline risks expected to be correlated with adverse early outcomes. We found that patients without history of pregnancy were more frequently active smokers, with significant left main disease or severely calcified aortic valves and were more often considered to be frail on surgical assessment. Furthermore, history of pregnancy was not observed to influence 30-day mortality, vascular or bleeding endpoints but impacted the incidence of 30-day composite death or stroke. This effect of prior pregnancy will need to be confirmed at longer-term follow up, however, this study remains novel for the evaluation of female sex-specific baseline characteristics in the context of TAVR. Additionally, further study on the hormonal influence and effect of pregnancy on cardiovascular outcomes in TAVR is needed.

STUDY LIMITATIONS

This study has several important limitations. First, the study was observational in nature 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 and as such a control arm was not essential by design. Second, since majority of patients in the registry were Caucasian, the results cannot be extrapolated to other populations. However, the patients in this registry had a comparable prevalence of cardiovascular risk factors to multiple other registries and therefore accurately reflect real world practice. Third, our registry included all-comer TAVR patients who were treated with different TAVR valve types per operator discretion,

thus analyses for valve–type are subject to selection bias and will be underpowered to draw reliable conclusions. Fourth, the lack of systematic neurological evaluation after TAVR may have underestimated the true incidence of 30-day stroke. Similarly the low rate of AKI may be related to under-reporting from sites, but is consistent with recent data [4]. Fifth, information on remote female sex-specific characteristics is subject to recall bias.

CONCLUSIONS

Women enrolled in this first ever all-female TAVR registry were at intermediate to high risk compared to women in prior TAVR studies, and experienced a 30-day VARC-2 composite safety endpoint of 14.0%, with a low incidence of early mortality and stroke. Age, prior stroke, LVEF < 30%, TAVR device generation and history of pregnancy were independent predictors of the 30 day composite safety endpoint. Randomized assessment of TAVR versus SAVR in intermediate-risk women with severe AS is warranted to determine the optimal treatment strategy.

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PERSPECTIVES

What is Known?

Women undergoing transcatheter aortic valve replacement (TAVR) have been reported to have more favorable outcomes as compared with their male counterparts, as well as lower 1-year mortality compared to women undergoing surgical aortic valve replacement (SAVR).

What is New?

The WIN TAVI registry is the first ever all-female single arm study to evaluate the safety and performance of TAVR in women and to further explore the influence of other female sex-

specific characteristics that have never been collected in prior TAVR studies. Women enrolled in this registry were at intermediate to high risk compared to women in prior TAVR studies, and experienced a 30-day VARC-2 composite safety endpoint of 14.0%, with a low incidence of early mortality and stroke.

What is Next?

Randomized assessment of TAVR versus SAVR in intermediate-risk women with severe aortic stenosis is warranted to determine the optimal treatment 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**(23): p. 2187-98.
2. Nishimura, RA, Otto, CM, Bonow, RO, et al., *2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol, 2014. **63**(22): p. 2438-88.
3. 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**(15): p. 1522-8.
4. Leon, MB, Smith, CR, Mack, MJ, et al., *Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients.* N Engl J Med, 2016.
5. Hayashida, K, Morice, MC, Chevalier, B, et al., *Sex-related differences in clinical presentation and outcome of transcatheter aortic valve implantation for severe aortic stenosis.* J Am Coll Cardiol, 2012. **59**(6): p. 566-71.
6. Conrotto, F, D'Ascenzo, F, Salizzoni, S, et al., *A gender based analysis of predictors of all cause death after transcatheter aortic valve implantation.* Am J Cardiol, 2014. **114**(8): p. 1269-74.
7. 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**(10): p. 882-6.

8. Aurigemma, GP and Gaasch, WH, *Gender differences in older patients with pressure-overload hypertrophy of the left ventricle.* Cardiology, 1995. **86**(4): p. 310-7.

9. Piro, M, Della Bona, R, Abbate, A, Biasucci, LM and Crea, F, *Sex-related differences in myocardial remodeling.* J Am Coll Cardiol, 2010. **55**(11): p. 1057-65.

10. Landi, F, Onder, G, Gambassi, G, et al., *Body mass index and mortality among hospitalized patients.* Arch Intern Med, 2000. **160**(17): p. 2641-4.

11. Fuchs, C, Mascherbauer, J, Rosenhek, R, et al., *Gender differences in clinical presentation and surgical outcome of aortic stenosis.* Heart, 2010. **96**(7): p. 539-45.

12. Clavel, MA, Webb, JG, Rodes-Cabau, J, et al., *Comparison between transcatheter and surgical prosthetic valve implantation in patients with severe aortic stenosis and reduced left ventricular ejection fraction.* Circulation, 2010. **122**(19): p. 1928-36.

13. Petrov, G, Regitz-Zagrosek, V, Lehmkuhl, E, et al., *Regression of myocardial hypertrophy after aortic valve replacement: faster in women?* Circulation, 2010. **122**(11 Suppl): p. S23-8.

14. 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: p. 377-384.

15. 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**(3): p. 221-8.

16. Oterhals, K, Hanssen, TA, Haaverstad, R, et al., *Factors associated with poor self-reported health status after aortic valve replacement with or without concomitant bypass surgery.* Eur J Cardiothorac Surg, 2014.

17. Coutinho, T, *Arterial stiffness and its clinical implications in women.* Can J Cardiol, 2014. **30**(7): p. 756-64.

18. 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**(8): p. 830-6.

19. 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**(1): p. 6-23.

20. Mehran, R, Rao, SV, Bhatt, DL, et al., *Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium.* Circulation, 2011. **123**(23): p. 2736-47.

21. Looker, AC, Orwoll, ES, Johnston, CC, Jr., et al., *Prevalence of low femoral bone density in older U.S. adults from NHANES III.* J Bone Miner Res, 1997. **12**(11): p. 1761-8.

22. Meredith, IT, Walters, DL, Dumonteil, N, et al., *1-Year Outcomes With the Fully Repositionable and Retrievable Lotus Transcatheter Aortic Replacement Valve in 120 High-Risk Surgical Patients With Severe Aortic Stenosis: Results of the REPRISE II Study.* JACC Cardiovasc Interv, 2016. **9**(4): p. 376-84.

23. Lefevre, T, Colombo, A, Tchetche, D, et al., *Prospective Multicenter Evaluation of the Direct Flow Medical Transcatheter Aortic Valve System: 12-Month Outcomes of the Evaluation of the Direct Flow Medical Percutaneous Aortic Valve 18F System for the*

Treatment of Patients With Severe Aortic Stenosis (DISCOVER) Study. JACC Cardiovasc Interv, 2016. **9**(1): p. 68-75.

24. Manoharan, G, Walton, AS, Brecker, SJ, et al., *Treatment of Symptomatic Severe Aortic Stenosis With a Novel Resheathable Supra-Annular Self-Expanding Transcatheter Aortic Valve System.* JACC Cardiovasc Interv, 2015. **8**(10): p. 1359-67.
25. Thourani, VH, Kodali, S, Makkar, RR, et al., *Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis.* Lancet, 2016.
26. Holmes, DR, Jr., Brennan, JM, Rumsfeld, JS, et al., *Clinical outcomes at 1 year following transcatheter aortic valve replacement.* JAMA, 2015. **313**(10): p. 1019-28.
27. Meredith Am, IT, Walters, DL, Dumonteil, N, et al., *Transcatheter aortic valve replacement for severe symptomatic aortic stenosis using a repositionable valve system: 30-day primary endpoint results from the REPRISE II study.* J Am Coll Cardiol, 2014. **64**(13): p. 1339-48.

FIGURE LEGEND

FIGURE 1A: Frequency of individual high-risk reasons for TAVR

FIGURE 1B: Distribution of number of high-risk reasons for TAVR

FIGURE 2A: Frequency of valve type by device-generation

FIGURE 2B: Frequency of valve type implanted

CENTRAL ILLUSTRATION: Cumulative incidence of 30-day clinical outcomes in women undergoing TAVR

FIGURE 3: Prevalence of female-specific characteristics and effect of pregnancy history on Primary VARC 2 Safety Endpoint

TABLE LEGEND

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APPENDIX °: List of participating centers, local principal investigators and co-investigators

TABLE 1: Baseline characteristics

	N = 1019
Age, mean (SD)	82.5 ± 6.3
Caucasian race	976 (95.8)
Body mass index, mean (SD)	26.0 ± 5.5
Hypertension	819 (81.7)
Diabetes Mellitus	264 (26.1)
Current Smoker	33 (3.3)
Prior myocardial infarction	98 (9.6)
Prior PCI	233 (22.9)
• PCI within 30 days of TAVR	58 (24.9)
Prior CABG	63 (6.2)
Prior Other Cardiac Surgery	117 (11.6)
Prior Aortic Valve Procedure	68 (6.8)
• Prior TAVR	4 (5.9)
Atrial fibrillation on baseline electrocardiography	200 (19.6)
Prior stroke	76 (7.5)
Chronic kidney disease	306 (30.8)
EuroSCORE I	
• Median (IQR)	14.4 (10.1-21.8)
• Mean (SD)	17.8 ± 11.7
Society of Thoracic Surgeons' score	
• Median (IQR)	6.0 (4.1-9.7)
• Mean (SD)	8.3 ± 7.4
Permanent Pacemaker	88 (8.6)
Key Reasons for TAVR	
High surgical risk	906 (89.5)
Age > 80 years	759 (74.7)
SAVR Rejected Due to Frailty	637 (63.6)
Pulmonary Hypertension	309 (30.8)
Renal Failure or on dialysis	274 (28.0)
Left ventricular Ejection Fraction < 50%	283 (27.8)
• Left ventricular Ejection Fraction < 30%	35 (3.5)
Chronic Obstructive Pulmonary Disease	187 (18.5)
Porcelain aorta	63 (6.3)
Previous Thoracic Radiotherapy	65 (6.4)
Active Cancer	36 (3.6)
Echocardiography	
Aortic Annulus diameter (mm), mean (SD)	21.8 ±2.04
Peak AV Gradient (mmHg), mean (SD)	77.9 ±23.6
Mean AV Gradient (mmHg), mean (SD)	49.2 ±15.9
Effective Orifice AV area (cm^2), mean (SD)	0.65 ±0.21
Left Ventricular Mass (g/m^2), mean (SD)	184.3 ±61.1
Pulmonary Artery Pressure (mmHg), mean (SD)	43.7 ±13.7
LV Ejection Fraction (%), mean (SD)	55.7 ±10.7
Aortic Incompetence	
• None or Mild	761 (81.0)
• Moderate	157 (16.7)
• Severe	21 (2.2)
Multidetector computed tomography	
Aortic Annulus diameter (mm), mean (SD)	22.7 ±2.0
Aortic Valve calcification	

• None	63 (8.0)
• Mild	76 (9.7)
• Moderate	385 (49.2)
• Severe	259 (33.1)
Femoral artery diameter (mm), mean (SD)	7.9 ±3.2
Subclavian artery diameter (mm), mean (SD)	8.1 ±1.9
Angiography	
Number of Diseased Vessels	
• 0	443 (62.6)
• 1	130 (18.4)
• 2	61 (8.6)
• 3	74 (10.4)
Left Main disease ≥ 50%	35 (5.7)
Female specific characteristics	
History of Pregnancy	738 (72.4)
Pregnancy induced complications (Diabetes or hypertension)	31 (4.5)
Age of menopause, years, mean (SD)	48.8 ± 5.1
History of gynecological cancer	23 (2.3)
History of gynecological surgery	181 (18.3)
History of breast cancer	87 (9.3)
History of osteoporosis	178 (17.5)
Frailty and osteoporosis	103 (10.1)
Baseline laboratory values	
Hemoglobin, g/dl, mean (SD)	11.8 ± 1.6
Serum creatinine, mg/dl, mean (SD)	1.1 ± 0.5
Serum albumin, g/dl, mean (SD)	3.9 ± 0.5
Baseline medications	
Acetylsalicylic Acid	598 (60.2)
$P2Y_{12}$ receptor inhibitor	260 (26.3)
Oral Anticoagulant	223 (22.6)
Treatment for osteoporosis among those with history of osteoporosis	56 (21.8)
Discharge medications	
Acetylsalicylic Acid	711 (77.7)
P2Y12 Receptor Inhibitors	573 (62.4)
Aspirin or $P2Y_{12}$ receptor inhibitor	823 (89.0)
Aspirin and $P2Y_{12}$ receptor inhibitor	480 (51.9)
Oral Anticoagulant	248 (27.1)
Aspirin and Oral Anticoagulant	109 (11.8)
$P2Y_{12}$ receptor inhibitor and Oral Anticoagulant	92 (9.9)
Discharge information	
Total hospital length of stay, days, Mean (SD)	11.8 ± 8.0
ICU length of stay, days, Mean (SD)	2.9 ± 3.3
Discharge Disposition	
• Home	618 (75.3)
• Outside hospital	40 (4.9)
• Rehabilitation unit	153 (18.6)
• Other	10 (1.2)

Values are presented as n (%) unless indicated otherwise.
PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; TAVR, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; AV, aortic valve; ICU, intensive care unit.

TABLE 2: Procedural characteristics

	N = 1019
Anesthesia type	
• Local	359 (36.9)
• Conscious sedation	267 (27.5)
• General	321 (33.1)
• Combination	24 (2.5)
Concomitant PCI	26 (2.6)
Access site	
• Transfemoral	923 (90.6)
• Trans-subclavian	26 (2.6)
• Transpical	26 (2.6)
• Transaortic	44 (4.3)
Access technique	
• Surgical cut-down	133 (13.0)
• Percutaneous	886 (87.0)
Sheath size	
• 14 French	162 (16.0)
• 16 French	165 (16.3)
• 18 French	596 (58.7)
• 19 French	23 (2.3)
• 20 French	17 (1.7)
• 22 French	6 (0.6)
• 24 French	12 (1.2)
• Other	34 (3.3)
BAV	703 (69.6)
• Rapid pacing during BAV	675 (96.0)
Device type	
• Edwards SAPIEN XT	184 (18.8)
• Edwards SAPIEN 3	224 (22.9)
• Medtronic CoreValve	382 (39.1)
• Medtronic Evolut R	79 (8.1)
• Portico	8 (0.8)
• Direct Flow	34 (3.5)
• Lotus	61 (6.2)
• Symetis Acurate Neo	6 (0.6)
Prosthesis size	
• 23 mm	412 (40.6)
• 25 mm	41 (4.0)
• 26 mm	374 (36.8)
• 27 mm	15 (1.5)
• 29 mm	162 (15.9)
• 31 mm	5 (0.5)
• other	7 (0.7)
Pacing during valve deployment	627 (64.3)
Post-dilation	149 (14.8)
Post-TAVR AI severity	
• 0	473 (48.3)
• 1	368 (37.6)
• 2	119 (12.2)
• 3	19 (1.9)
Closure device use	
• Prostar	454 (48.4)
• Proglide	373 (39.8)
• Other	111 (11.8)
Contrast Volume (ml), Mean (SD)	153.7 ± 77.8

Inotropes	34 (3.5)
Intra-aortic balloon pump support	2 (0.2)
Use of blood products	67 (6.9)

Values are presented as n (%) unless indicated otherwise.
PCI, percutaneous coronary intervention; BAV, balloon aortic valvuloplasty; TAVR, transcatheter aortic valve replacement; AI, aortic incompetence.

TABLE 3: Procedural complications

	N = 1019
Valve embolization	11 (1.1)
Annulus or aortic rupture	12 (1.2)
Pericardiocentesis	13 (1.3)
Ventricular perforation	
• Right ventricle	7 (0.7)
• Left ventricle	7 (0.7)
Complete AV block	81 (8.1)

Values are presented as n (%)

TABLE 4: Clinical outcomes at 30-days

	N = 1019
Primary VARC 2 Safety End-point	147 (14.0)
Secondary Endpoints	
All-cause Death	40 (3.4)
• Cardiovascular	38 (3.3)
• Non-cardiovascular	2 (0.1)
MI	2 (0.2)
Stroke	13 (1.3)
Major Vascular Complications	80 (7.7)
VARC life-threatening Bleeding	45 (4.4)
Coronary obstruction	7 (0.7)
TAV-in-TAV	17 (1.7)
Surgical conversion	7 (0.7)
Acute kidney injury, Stage 2 or 3	13 (1.3)
Other endpoints	
Bleeding	
• VARC major	79 (7.7)
• BARC 3 or 5	123 (12.0)
Arrhythmia	
• Any arrhythmia or conduction disturbance	223 (21.9)
• New atrial fibrillation or flutter	31 (3.0)
• Left bundle branch block	103 (10.1)
• PPM implantation	118 (11.6)
Composite all-cause death or stroke	50 (4.9)
Composite of major vascular complications or VARC life-threatening bleeding	102 (10.0)

Values are presented as n (%)
VARC, Valve Academic Research consortium; TAV, transcatheter aortic valve; BARC, Bleeding Academic Research consortium; PPM, permanent pacemaker.
* Composite of 30-day all-cause death, stroke, myocardial infarction, major vascular complication, VARC life-threatening bleeding, coronary obstruction, re-intervention for valve related dysfunction or stage 2 or 3 acute kidney injury.

TABLE 5A: Multivariate predictors of 30-day Primary VARC 2 Safety End-point

	OR (95% CI)	p-value
Age	1.04 (1.00-1.08)	0.028
Body mass index	1.00 (0.96-1.04)	0.982
Diabetes	0.88 (0.55-1.40)	0.579
Chronic kidney disease	0.94 (0.61-1.45)	0.786
Prior coronary revascularization	1.08 (0.69-1.68)	0.737
Atrial fibrillation	0.96 (0.59-1.56)	0.875
Prior stroke	2.02 (1.07-3.80)	0.029
EuroSCORE I	0.99 (0.97-1.01)	0.265
Frailty	0.93 (0.62-1.39)	0.715
Left ventricular ejection fraction < 30%	2.62 (1.07-6.40)	0.035
Access site – Transfemoral vs. non-transfemoral	1.03 (0.54-1.95)	0.932
Device size (>26mm vs. ≤26mm)	1.54 (0.97-2.45)	0.067
Post-TAVR AI grade 2 or 3	1.05 (0.61-1.82)	0.852
TAVR device generation – New vs. Old	0.59 (0.38 – 0.91)	0.018

TAVR, transcatheter aortic valve replacement; AI, aortic incompetence

TABLE 5B: Effect of female-specific characteristics on 30-day Primary VARC 2 Safety End-point

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Pregnancy	0.63 (0.43-0.91)	0.013	0.57 (0.37-0.85)	0.007
Pregnancy				
0	Ref.		Ref.	
1	0.39 (0.20-0.76)	0.005	0.27 (0.12-0.60)	0.001
2	0.66 (0.41-1.08)	0.097	0.62 (0.36-1.07)	0.086
> 2	0.60 (0.38-0.95)	0.029	0.57 (0.34-0.96)	0.003
Gynecological or breast cancer	1.07 (0.61-1.89)	0.803	1.05 (0.55-1.98)	0.884
Age of menopause	1.02 (0.98-1.06)	0.353	1.02 (0.97-1.07)	0.471
History of osteoporosis	1.20 (0.76-1.88)	0.430	1.18 (0.72-1.95)	0.505

APPENDIX TABLE 1: Valve type in patients with procedural complications

	Patients with events	Valve type		
		Edwards Sapien N = 408	Medtronic CoreValve N = 461	Other N = 109
Valve embolization	11 (1.1)	3 (0.7)	8 (1.7)	0 (0.0)
Annulus or aortic rupture	12 (1.2)	5 (1.2)	4 (0.9)	3 (2.8)
Coronary obstruction	7 (0.7)	3 (0.7)	4 (0.9)	0 (0.0)
Pericardiocentesis	13 (1.3)	5 (1.2)	5 (1.1)	3 (2.8)
Ventricular perforation				
• Right ventricle	7 (0.7)	2 (0.5)	4 (0.9)	1 (0.9)
• Left ventricle	7 (0.7)	1 (0.2)	4 (0.9)	2 (1.8)
Complete AV Block	81 (7.9)	29 (7.1)	42 (9.1)	10 (9.2)
PPM implantation	123 (12.1)	34 (8.3)	70 (15.2)	19 (17.4)
Post-TAVR AI	138 (14.1)	39 (9.6)	94 (20.6)	5 (4.4)

Values are presented as n (%)
AV, atrio-ventricular; PPM, permanent pacemaker; TAVR, transcatheter aortic valve replacement; AI, aortic incompetence

APPENDIX TABLE 2: Baseline characteristics among patients with and without Primary VARC 2 Safety End-point

	No primary safety endpoint N = 872	Primary safety endpoint N = 147	p-value	Standardized differences
Age, mean (SD)	82.4 ± 6.1	83.0 ± 7.2	0.279	-0.091
Body mass index, mean (SD)	26.0 ± 5.4	25.7 ± 5.9	0.475	0.062
Hypertension	705 (82.3)	114 (78.1)	0.228	0.105
Diabetes Mellitus	229 (26.5)	35 (23.8)	0.496	0.061
Prior myocardial infarction	86 (9.9)	12 (8.2)	0.513	0.060
Prior PCI	200 (23.0)	33 (22.4)	0.874	0.014
• PCI within 30 days of TAVR	46 (23.0)	12 (36.4)	0.100	-0.293
Prior CABG	55 (6.3)	8 (5.4)	0.675	0.038
Prior Other Cardiac Surgery	105 (12.2)	12 (8.2)	0.161	0.133
Atrial fibrillation on baseline ECG	172 (20.2)	28 (20.0)	0.964	0.004
Prior stroke	59 (6.8)	17 (11.6)	0.040	-0.167
Chronic kidney disease	265 (31.3)	41 (28.3)	0.474	0.065
Permanent Pacemaker	79 (9.1)	9 (6.1)	0.239	0.111
EuroSCORE I				
• Median (IQR)	14.1 (10.1-22.1)	14.4 (11.4-19.5)	0.686	
• Mean (SD)	17.9 (11.9)	17.4 (10.3)	0.630	0.045
STS score				
• Median (IQR)	5.8 (4.0-9.5)	6.6 (4.7-10.6)	0.064	
• Mean (SD)	8.2 (7.4)	8.4 (5.49)	0.806	-0.026
SAVR Rejected Due to Frailty	544 (63.6)	93 (63.7)	0.986	-0.002
Pulmonary Hypertension	264 (30.8)	45 (30.8)	0.997	-0.000
Renal failure or dialysis	233 (27.9)	41 (28.5)	0.882	-0.013
Left ventricular ejection Fraction				
• <30%	26 (3.0)	9 (6.2)	0.053	-0.152
• 30-50%	214 (24.9)	34 (23.3)	0.679	0.037
Chronic Obstructive Pulmonary Disease	160 (18.5)	27 (18.4)	0.970	0.003
Porcelain aorta	57 (6.7)	6 (4.1)	0.225	0.117
Echocardiography				
Aortic Annulus diameter (mm), mean (SD)	21.8 ±2.0	21.7 ±2.2	0.760	0.040
Peak AV Gradient (mmHg), mean (SD)	78.3 ±23.3	75.6 ±25.1	0.269	0.112
Mean AV Gradient (mmHg), mean (SD)	49.4 ±15.7	48.0 ±17.0	0.330	0.087
Effective Orifice AV area (cm^2), mean (SD)	0.65 ±0.20	0.65 ±0.23	0.837	0.019
Pulmonary Artery Pressure (mmHg), mean (SD)	43.6 ±13.7	44.2 ±13.7	0.679	-0.047
Aortic Incompetence				
• None or Mild	658 (81.8)	103 (76.3)	0.276	0.136
• Moderate	128 (15.9)	29 (21.5)		-0.143
• Severe	18 (2.2)	3 (2.2)		0.001
Multidetector computed tomography				
Aortic Annulus diameter (mm), Mean (SD)	22.7 ±1.9	22.5 ±2.3	0.371	0.095
Aortic Valve calcification				
• None	44 (6.7)	19 (14.6)	0.013	-0.256
• Mild	62 (9.5)	14 (10.8)		-0.042
• Moderate	332 (50.8)	53 (40.8)		0.203
• Severe	215 (32.9)	44 (33.9)		-0.019

Femoral artery diameter (mm), Mean (SD)	7.9 ±3.2	8.1 ±3.7	0.617	-0.055
Angiography				
Number of Diseased Vessels			0.765	
o 0	378 (63.1)	65 (59.6)		0.071
o 1	106 (17.7)	24 (22.0)		-0.108
o 2	52 (8.7)	9 (8.3)		0.015
o 3	63 (10.5)	11 (10.1)		0.014
Left Main Disease ≥ 50%	28 (5.5)	7 (6.9)	0.328	-0.059
Female specific characteristics				
History of pregnancy	644 (73.9)	94 (63.9)	0.013	0.215
History of pregnancy induced complications				
• Gestational Diabetes	10 (1.7)	0 (0.0)	0.617	0.183
• Gestational Hypertension	21 (3.5)	1 (1.2)	0.499	0.148
Mean age of menopause, mean (SD)	48.8 ± 5.1	49.3 ± 5.1	0.353	-0.100
History of gynecological cancer	19 (2.3)	4 (2.9)	0.558	-0.038
History of gynecological surgery	153 (18.1)	28 (19.6)	0.678	-0.037
History of breast cancer	75 (9.5)	12 (8.8)	0.818	0.022
History of osteoporosis	149 (19.2)	29 (22.1)	0.430	-0.073
New generation TAVR device implantation	363 (43.6)	49 (33.8)	0.028	0.202

Values are presented as n (%) unless indicated otherwise.
PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; TAVR, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; AV, aortic valve; ICU, intensive care unit.

APPENDIX TABLE 3: 30-day clinical outcomes in patients with and without history of pregnancy

	Total N = 1019	No history of pregnancy N = 281	History of pregnancy N = 738	p-value	Standardized differences
Primary VARC 2 Safety End-point*	147 (14.0)	53 (18.9)	94 (12.7)	0.013	0.168
Secondary endpoints					
All-cause Death	40 (3.4)	15 (5.3)	25 (3.4)	0.152	0.095
• Cardiovascular	38 (3.3)	14 (5.0)	24 (3.3)	0.193	0.087
• Non-cardiovascular	2 (0.1)	1 (0.4)	1 (0.1)	0.478	0.044
Myocardial infarction	2 (0.2)	0 (0.0)	2 (0.3)	1.000	.
Stroke	13 (1.3)	7 (2.5)	6 (0.8)	0.033	0.132
Major Vascular Complications	80 (7.7)	28 (10.0)	52 (7.0)	0.122	0.105
VARC life-threatening bleeding	45 (4.4)	13 (4.6)	32 (4.3)	0.840	0.014
Coronary obstruction	6 (0.6)	2 (0.7)	4 (0.5)	0.670	0.021
TAV-in-TAV	17 (1.7)	4 (1.4)	13 (1.8)	1.000	-0.027
Surgical conversion	7 (0.7)	2 (0.7)	5 (0.7)	1.000	0.004
Acute kidney injury, Stage 2 or 3	13 (1.3)	7 (2.5)	6 (0.8)	0.033	0.132
Other endpoints					
Bleeding					
• VARC major	79 (7.7)	28 (10.0)	51 (6.9)	0.122	0.110
• BARC 3 or 5	123 (12.0)	40 (14.2)	83 (11.2)	0.191	0.090
Arrhythmia					
• Any arrhythmia or conduction disturbance	203 (21.9)	63 (22.4)	140 (19.0)	0.218	0.085
• New atrial fibrillation or flutter	31 (3.0)	9 (3.2)	22 (3.0)	0.854	0.013
• Left bundle branch block	103 (10.1)	38 (13.5)	65 (8.8)	0.026	0.150
• PPM implantation	118 (11.6)	26 (9.3)	92 (12.5)	0.152	-0.103
Composite of death or all-cause stroke	50 (4.9)	20 (7.1)	30 (4.1)	0.044	0.133
Major vascular complications or VARC life-threatening bleeding	102 (10.0)	34 (12.1)	68 (9.2)	0.170	0.093

Values are presented as n (%)
VARC, Valve Academic Research consortium; TAV, transcatheter aortic valve; BARC, Bleeding Academic Research consortium; PPM, permanent pacemaker.
* Composite of 30-day all-cause death, stroke, myocardial infarction, major vascular complication, VARC life-threatening bleeding, coronary obstruction, re-intervention for valve related dysfunction or stage 2 or 3 acute kidney injury.

APPENDIX°: List of participating centers, local principal investigators and co-investigators in chronological order of number of patients enrolled in the study

stcox age BMI ohrf_diab ohrf_kidney pr_pci_cabg afib ohrf_stroke euro_score1 kr_savr kr_lv_30 acc_site aortic_valve26 postAI gen , strata(country)

Ludwig-Maximilians-University of Munich, Munich, Germany, Julinda Mehilli, MD and David Jochheim, MD

San Raffaele Scientific Institute, Milan, Italy, Alaide Chieffo, MD, Antonio Colombo MD and Susanna Benincasa, MD

AOUP Cisanello, University Hospital, Pisa Italy, Anna Sonia Petronio, MD and Cristina Giannini, MD

Institut Hospitalier Jacques Cartier Ramsay Générale de Santé, Massy, France, Thierry Lefevre, MD and Marie Claude Morice, MD

Istituto Clinico Humanitas, Milan, Italy, Patrizia Presbitero, MD and Marco Luciano Rossi, MD

University of Catania, Catania, Italy, Piera Capranzano, MD and Corrado Tamburino, MD

Clinique Pasteur, Toulouse, France, Didier Tchetche, MD, Adele Pierri, MD and Caterina Cavazza, MD

Azienda Ospedaliera Universitaria Senese, Policlinico Le Scotte, Siena, Italy, Alessandro Iadanza, MD and Carlo Pierli MD

Policlinico “Umberto I”, “Sapienza” University of Rome, Rome, Italy, Gennaro Sardella, MD and Mauro Pennacchi, MD

Ersamus Medical Center, Thoraxcenter, Rotterdam, the Netherlands, Nicholas van Mieghem, MD, PhD and Peter de Jaegere, MD

Mauriziano Hospital, Turin, Italy, Emanuel Meliga, MD, Mauro De Benedictis, MD and Catia De Rosa, MD

Rangueil University Hospital, Toulouse, France, Nicolas Dumonteil, MD and Didier Carrie, MD

University of Padova, Padova, Italy, Chiara Fraccaro, MD, PhD and Giuseppe Tarantini, MD, PhD

Centro Cardiologico Monzino, Milan, Italy, Daniela Trabattoni, MD and Antonio Bartorelli, MD

Imperial College Healthcare NHS Trust, Hammersmith Hospital, London , United Kingdom, Ghada W Mikhail, MD and Iqbal Malik, MD.

Mount Sinai Hospital, New York, US, Samin Sharma, MD and Roxana Mehran, MD

Hospital Universitario Miguel Servet, Zaragoza, Spain, Maria C Ferrer and Isabel Calvo Cebollero, MD

Contilia Heart and Vascular Centre, Elisabeth Krankenhaus Essen, Germany, Christoph K. Naber, MD, and Alexander Wolf, MD

Radboud University Medical Centre, Nijmegen, the Netherlands, Peter Kievit, MD and Michel Verkroost MD

FIGURE 1A: Frequency of individual high-risk reasons for TAVR

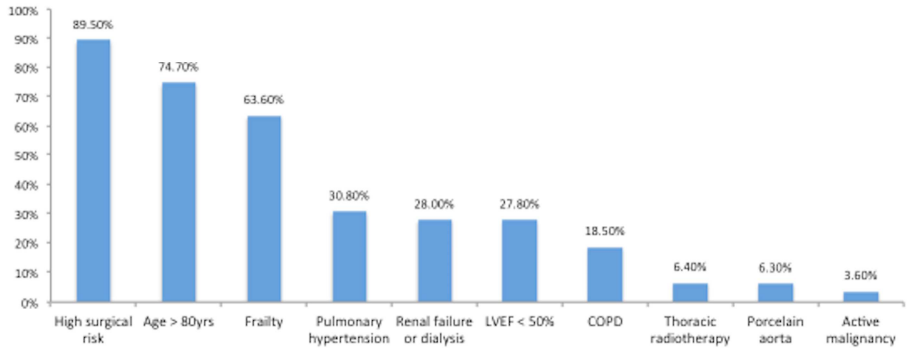


FIGURE 1B: Distribution of number of high-risk reasons for TAVR

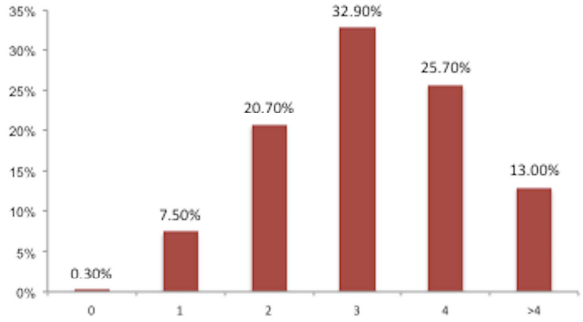


FIGURE 2A: Frequency of valve type by device-generation

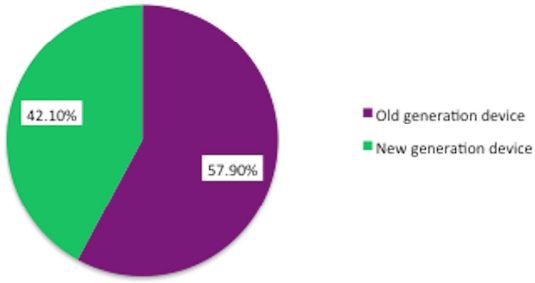


FIGURE 2B: Frequency of valve type implanted

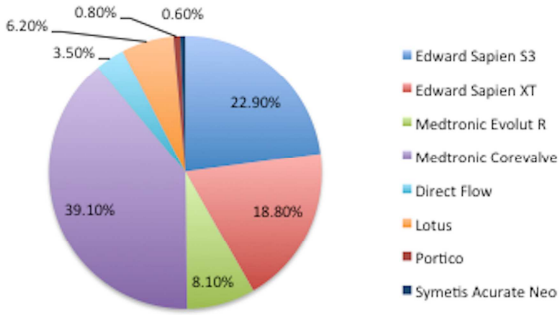
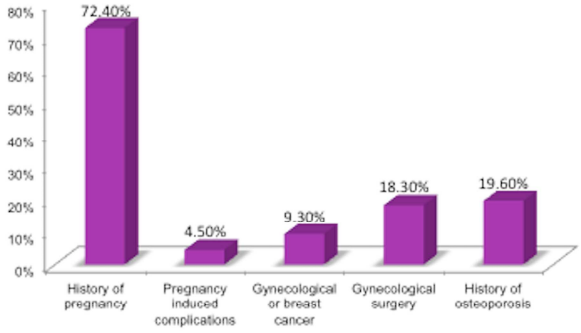
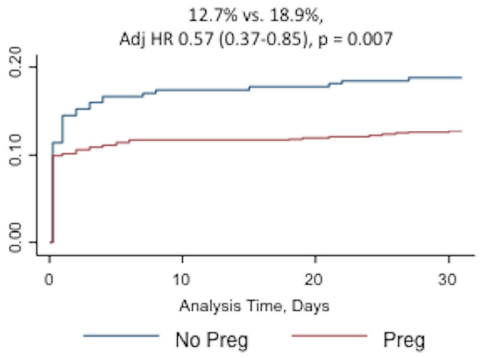


Figure 3: Prevalence of female-specific characteristics and effect of pregnancy history on Primary VARC 2 Safety End-point

Prevalence of female-specific characteristics



Cumulative incidence of 30 day VARC 2 Primary Safety End-point in patients with and without history of pregnancy



CENTRAL ILLUSTRATION: Cumulative incidence of 30-day clinical outcomes in women undergoing TAVR