Gender Disparities in Management and Outcomes Following Transcatheter Aortic Valve Implantation With Newer Generation Transcatheter Valves

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The impact of gender on management and early outcomes after transcatheter aortic valve implantation (TAVI) in the setting of newer generation transcatheter heart valves (THVs) is not well known. We evaluated gender-specific differences on clinical management and in-hospital outcomes in adults who underwent TAVI with newer generation THVs. The study population included 298 consecutive patients who underwent TAVI and received a newer generation THV (Sapien 3 [Edwards Lifesciences, Irvine, California] or Corevalve Evolut R or Evolut Pro [Medtronic, Minneapolis, Minnesota]) from December 2015 to June 2018 at an academic tertiary medical center. Of the 298 patients, 154 (52%) were men and 144 (48%) were women. Compared with men, women were older, had lower serum creatinine, higher left ventricular ejection fraction, and lower rates of multiple comorbidities, including previous coronary artery bypass graft surgery, previous myocardial infarction, and atrial fibrillation. Women were noted to have smaller aortic annular area and perimeter and underwent implantation of smaller THVs than men. At the time of discharge, women were more frequently prescribed a P2Y12 inhibitor (primarily clopidogrel) and less frequently prescribed oral anticoagulation (namely warfarin). Hospital length of stay and in-hospital rates of mortality, disabling stroke, and pacemaker were similar in men and women. In conclusion, in this observational prospective study of adults who underwent TAVI with newer generation THVs, while gender-related disparities in clinical presentation and procedural management were observed, no significant difference in clinical outcomes were noted in men and women. Further studies examining gender-related differences in procedural and postprocedural care after TAVI in the contemporary era are warranted to better understand and optimize clinical outcomes in both men and women. **Published by Elsevier Inc. (Am J Cardiol 2019;123:1489−1493)**

Transcatheter aortic valve implantation (TAVI) has become the standard of care to treat patients with severe symptomatic aortic stenosis who are high or prohibitive risk for surgical aortic valve replacement.[1−3] The contemporary era of TAVI has introduced more frequent use of periprocedural conscious sedation, the inclusion of patients of intermediate surgical risk, and newer generation transcatheter heart valves (THVs) with smaller sheath size, less frequent paravalular regurgitation, and ability for valve retrievability (in the case of self-expanding valves). While gender-specific differences in outcomes after TAVI have been reported, disparities in procedural management and outcomes in men and women in the era of newer THVs have not been well studied. With women representing approximately half of the population who underwent TAVI in the United States,[4] it is of high importance to investigate their risk profile, management, and outcomes to provide further optimization of care. Accordingly, we evaluated gender-specific differences in procedural management and clinical outcomes in adults who underwent TAVI with newer generation THVs at an academic tertiary medical center.

Methods

We conducted a prospective cohort study examining differences in outcomes in men and women who underwent TAVI at an academic tertiary medical center. All adults (age ≥18 years) with severe symptomatic aortic stenosis and/or failure of a bioprosthetic valve and who underwent TAVI with a newer generation THV (Sapien 3 valve [Edwards Life Sciences, Irvine, California] or Corevalve Evolut R or Evolut Pro [Medtronic, Minneapolis, Minnesota]) at Stony Brook University Medical Center from December 2015 to June 2018 were included in this study. The demographic and baseline medical history data extracted included age, gender, weight, height, body mass index, previous coronary artery bypass graft surgery

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See page 1492 for disclosure information.

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0002-9149/Published by Elsevier Inc.
https://doi.org/10.1016/j.amjcard.2019.01.048

(CABG), previous myocardial infarction, previous aortic valve replacement, previous balloon aortic valvuloplasty, previous mitral valve surgery, previous pacemaker/defibrillator, atrial fibrillation (AF), chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, previous stroke/transient ischemic attack, carotid disease, peripheral arterial disease, and diabetes mellitus.

Clinical data extracted included echocardiographic data (e.g., aortic valve area and index, left ventricular ejection fraction [LVEF]), gated computed tomography angiography data (e.g., aortic annulus area and perimeter), procedural information (e.g., the use of conscious sedation, transfemoral access, predilatation, transcatheter valve type and size, and postdilatation), and discharge data (e.g., discharge prescriptions for antiplatelet and oral anticoagulants [OAC], discharge location, length of stay [LOS] [admission to discharge, TAVI procedure to discharge], and in-hospital outcomes [all-cause mortality, disabling stroke, and new pacemaker]). This study was approved by our Institutional Review Board. A waiver of consent to use data prospectively was obtained for all patients.

Categorical variables were presented as percentages and compared with the chi-squared test or Fisher's exact test, if applicable. Continuous variables were presented as means ± standard deviation and compared using student's *t*-test. Multivariable logistic regression was utilized to determine the association between gender and oral anticoagulation at hospital discharge. Predictors for the logistic regression were selected based on previous clinical data and statistical significance in the univariate analysis ($p < 0.1$) and included gender, age, AF, previous aortic valve replacement, previous mitral valve surgery, previous pacemaker/defibrillator and THV size. SPSS version 23.0 (SPSS, Inc. Chicago, Illinois) was used for data analysis and a 2-tailed p value of 0.05 was regarded as statistically significant.

Results

The study population included 298 consecutive patients who underwent TAVI and received a contemporary valve (Sapien 3 [Edwards Lifesciences, Irvine, California] or Corevalve Evolut R or Evolut Pro [Medtronic, Minneapolis, Minnesota]) from December 2015 to June 2018 at an academic tertiary medical center. Of the 298 patients, 154 (52%) were men and 144 (48%) were women. Table 1 highlights the baseline medical history. Compared with their male counterparts, women were older, had lower serum creatinine, and lower rates of previous CABG, previous myocardial infarction, AF, chronic obstructive pulmonary disease, and carotid disease. Women were noted to have smaller aortic valve area (0.70 vs 0.77 cm^2, $p = 0.005$), higher LVEF (59% vs 53%, $p = 0.001$), and smaller aortic annular area and perimeter on gated computed tomography angiography (Figure 1A and B). Table 2 presents the procedural management of men and women who underwent TAVI. Women more often underwent implantation of smaller THVs than men. Of note, there were no men who received a 20-mm THV and no women who received a 34-mm THV. At the time of discharge, women were more frequently prescribed a P2Y12 inhibitor (primarily

Table 1
Baseline

Variable	Men (n = 154)	Women (n = 144)	p value
Age (years)	79 ± 9	81 ± 8	0.020
Weight (kg)	86 ± 16	74 ± 21	<0.001
Height (meters)	1.74 ± 0.07	1.58 ± 0.07	<0.001
Body mass index (kg/m^2)	28.1 ± 5.4	29.0 ± 7.8	0.271
Serum creatinine (mg/dl)	1.5 ± 1.3	1.0 ± 0.4	<0.001
Prior coronary artery bypass grafting	46 (29.9%)	12 (8.3%)	<0.001
Prior myocardial infarction	47 (30.5%)	24 (16.7%)	0.005
Prior aortic valve replacement	7 (4.5%)	6 (4.2%)	0.873
Prior balloon aortic valvuloplasty	5 (3.3%)	4 (2.8%)	1.000
Prior mitral valve surgery	3 (1.9%)	7 (4.9%)	0.206
Prior pacemaker/defibrillator	20 (13.0%)	18 (12.5%)	0.900
Atrial fibrillation	69 (44.8%)	39 (27.1%)	0.001
Chronic obstructive pulmonary disease	40 (26.0%)	22 (15.3%)	0.023
Obstructive sleep apnea	15 (9.7%)	10 (6.9%)	0.384
Prior stroke/transient ischemic attack	22 (14.3%)	24 (16.7%)	0.570
Carotid disease	45 (29.2%)	24 (16.7%)	0.010
Peripheral arterial disease	14 (9.1%)	10 (6.9%)	0.496
Diabetes mellitus	67 (43.5%)	49 (34.3%)	0.103

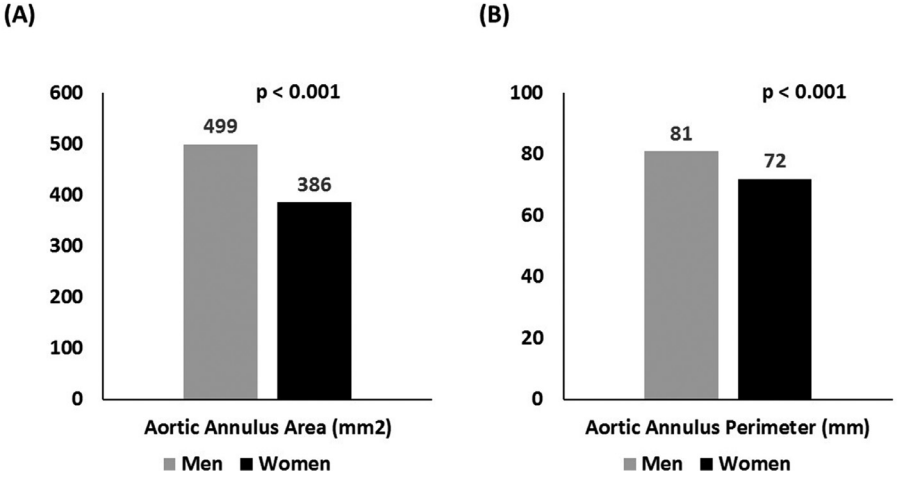

Figure 1. Differences in aortic annulus area (A) and perimeter (B) in men and women who underwent transcatheter aortic valve implantation.

Table 2
Procedural Information

Variable	Men (n = 154)	Women (n = 144)	p value
Conscious sedation	128 (83.1%)	106 (74.1%)	0.058
Transfemoral access	153 (99.4%)	144 (100.0%)	1.000
Predilatation	116 (75.3%)	107 (74.3%)	0.839
Transcatheter valve type			0.655
Edwards Sapien 3	122 (79.2%)	111 (77.1%)	
Medtronic Evolut R/PRO	32 (20.8%)	33 (22.9%)	
Transcatheter valve size (mm)			<0.001
20	0 (0%)	15 (10.4%)	
23	14 (9.1%)	79 (54.9%)	
26	80 (51.9%)	38 (26.4%)	
29	52 (33.8%)	12 (8.3%)	
34	8 (5.2%)	0 (0%)	
Postdilatation	9 (5.8%)	4 (2.8%)	0.260

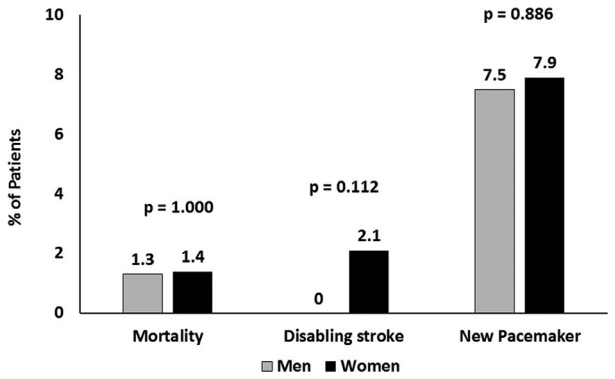

Figure 3. Rates of in-hospital outcomes in men and women who underwent transcatheter aortic valve implantation.

clopidogrel) and less frequently prescribed OAC (namely warfarin; Figure 2). In-hospital outcomes after TAVI are shown in Figure 3. Rates of in-hospital outcomes were similar in men and women. Median LOS in men and women did not differ from admission to discharge (3 vs 3 days, p = 0.336) and procedure to discharge (2 vs 2 days, p = 0.347). Men and women were similarly likely to be discharged to a skilled nursing facility (15% vs 21%, p = 0.305).

In multivariable analysis, female gender was not independently associated with lower rates of OAC (odds ratio [OR] 0.86, 95% confidence interval [CI] 0.38−1.92] at discharge. Predictors of OAC included AF (OR 26.53, 95%CI 12.76−55.14) and previous mitral valve surgery (OR 6.88, 95%CI 1.04−45.63).

Discussion

Several findings are noteworthy in this contemporary observational study of adults who underwent TAVI with newer generation THVs. First, women were older with higher LVEF and fewer co-morbidities. Second, women had smaller aortic annuli and underwent TAVI with smaller THVs. Third, gender disparities in antiplatelet and antithrombotic management after TAVI were observed, specifically, women were more likely to be prescribed clopidogrel and less likely to be prescribed warfarin due to lower rates of AF in women. Finally, no significant gender-specific differences were found in postprocedural outcomes including all-cause mortality, disabling stroke, new pacemaker, and LOS.

Several studies have confirmed that women who underwent TAVI are older with fewer co-morbidities and higher LVEF.[5−21] The smaller aortic annuli and implantation of smaller valves in women that we observed are consistent with findings in the literature.[6−10,12,14−17,19,20] In an analysis of 23,652 patients from the national data of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (STS/ACC TVT) Registry, Chandrasekhar et al[15] noted that compared with men, women more frequently received 23-mm THVs (65% vs 12%) and less frequently received 29-mm (5% vs 13%) and 31-mm THVs (0.7% vs 8%; p <0.0001).

Few studies to date have examined gender-related differences in the management after TAVI with newer THVs. Chandrasekhar et al[15] demonstrated that compared with

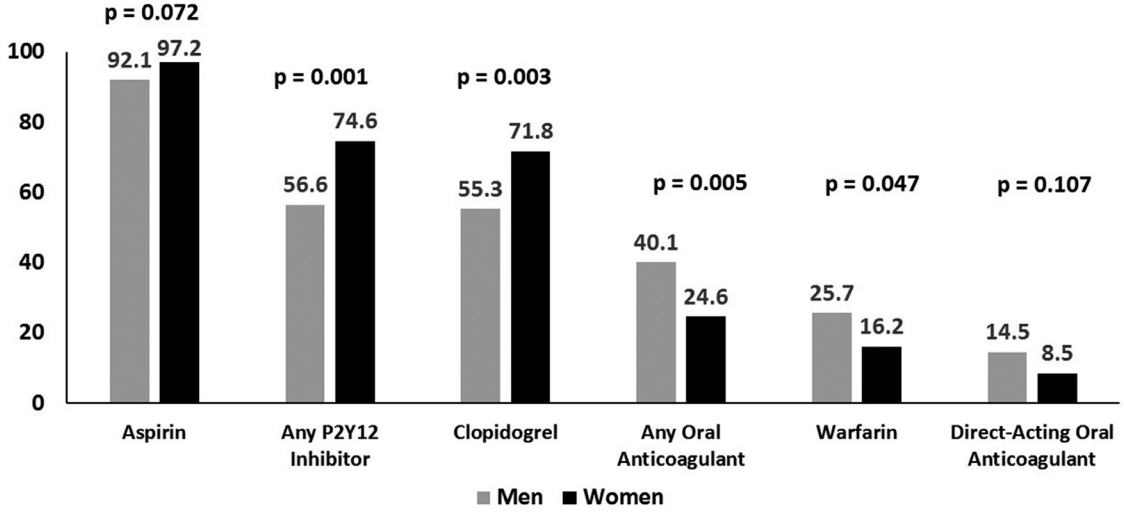

Figure 2. Differences in antiplatelet and anticoagulant medications received upon hospital discharge in men and women.

women, men were more commonly prescribed aspirin (88.7% vs 87.1%, p = 0.0028), P2Y12 inhibitors (63.8% vs 62.0%, p = 0.0205), and dual antiplatelet therapy (57.4% vs 55.1%, p = 0.0001), which was attributed to higher rates of previous CABG in men. Interestingly, no significant differences were found in the use of warfarin (25.0% vs 25.5%, p = 0.4880) or other OAC between men and women despite higher rates of AF in men, although a more frequent use of a P2Y12 inhibitor and oral anticoagulant combination was documented in men (9.1% vs 7.4%, p <0.0001).[15]

Several studies have also documented no differences in post-TAVI outcomes between men and women, including all-cause mortality,[10,12,15,17] stroke,[9–12,15,17,18] and new pacemaker.[9,11,12,17,18] Data from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy registry[15] noted no differences in in-hospital mortality or stroke (adjusted OR 0.93, 95%CI 0.76−1.13), in-hospital mortality (adjusted OR 0.89, 0.71−1.11), or conduction disturbance (adjusted OR 1.08, 95%CI 0.88−1.32). A retrospective study by Gaglia et al[9] reported that female gender was not independently associated with 30-day mortality, but was associated with improved survival at 1 year (hazard ratio 0.57, 95% CI 0.36−0.90). Furthermore, our study did not observe gender-related differences regarding hospital LOS after TAVI, consistent with previous literature.[18,21]

Our study had a number of limitations. First, our findings are based on observational data, which was internally validated, but not centrally adjudicated. Second, the majority of the devices implanted during the study period were balloon-expandable in nature and nearly all cases were transfemoral approach. Third, we did not examine for differences in outcomes according to TAVI time period. Finally, our study was limited to in-hospital outcomes.

In conclusion, in this observational study of adults who underwent TAVI with newer generation THVs, gender-related disparities in procedural and postprocedural management were observed, but gender was not associated with differences in clinical outcomes.

Disclosures

The authors have no conflicts of interest to disclose.

1. Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, Bogers AJ, Piazza N, Kappetein AP. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol* 2013;62:1002–1012.
2. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–1607.
3. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739–2791.
4. Mack MJ, Brennan JM, Brindis R, Carroll J, Edwards F, Grover F, Shahian D, Tuzcu EM, Peterson ED, Rumsfeld JS, Hewitt K, Shewan C, Michaels J, Christensen B, Christian A, O'Brien S, Holmes D. Outcomes following transcatheter aortic valve replacement in the United States. *JAMA* 2013;310:2069–2077.
5. Al-Lamee R, Broyd C, Parker J, Davies JE, Mayet J, Sutaria N, Ariff B, Unsworth B, Cousins J, Bicknell C, Anderson J, Malik IS, Chukwuemeka A, Blackman DJ, Moat N, Ludman PF, Francis DP, Mikhail GW. Influence of gender on clinical outcomes following transcatheter aortic valve implantation from the UK transcatheter aortic valve implantation registry and the National Institute for Cardiovascular Outcomes Research. *Am J Cardiol* 2014;113:522–528.
6. Buja P, Napodano M, Tamburino C, Petronio AS, Ettori F, Santoro G, Ussia GP, Klugmann S, Bedogni F, Ramondo A, Maisano F, Marzocchi A, Poli A, Gasparetto V, Antoniucci D, Colombo A, Tarantini G. Comparison of variables in men versus women undergoing transcatheter aortic valve implantation for severe aortic stenosis (from Italian Multicenter CoreValve registry). *Am J Cardiol* 2013;111:88–93.
7. Conrotto F, D'Ascenzo F, Salizzoni S, Presbitero P, Agostoni P, Tamburino C, Tarantini G, Bedogni F, Nijhoff F, Gasparetto V, Napodano M, Ferrante G, Rossi ML, Stella P, Brambilla N, Barbanti M, Giordana F, Grasso C, Biondi Zoccai G, Moretti C, D'Amico M, Rinaldi M, Gaita F, Marra S. A gender based analysis of predictors of all cause death after transcatheter aortic valve implantation. *Am J Cardiol* 2014;114:1269–1274.
8. Forrest JK, Adams DH, Popma JJ, Reardon MJ, Deeb GM, Yakubov SJ, Hermiller JB Jr., Huang J, Skelding KA, Lansky A. Transcatheter aortic valve replacement in women versus men (from the US CoreValve Trials). *Am J Cardiol* 2016;118:396–402.
9. Gaglia MA Jr., Lipinski MJ, Torguson R, Gai J, Ben-Dor I, Bernardo NL, Satler LF, Pichard AD, Waksman R. Comparison in men versus women of co-morbidities, complications, and outcomes after transcatheter aortic valve implantation for severe aortic stenosis. *Am J Cardiol* 2016;118:1692–1697.
10. Asgar A, Chandrasekhar J, Mikhail G, Webb J, Lefevre T, Tamburino C, Hildick-Smith D, Hambrecht R, Van Belle E, Widder J, Dumonteil N, Hink U, Jeger R, Linke A, Deliargyris E, Gao P, Mehran R, Hengstenberg C, Anthopoulos P, Dangas G. Sex-based differences in outcomes with bivalirudin or unfractionated heparin for transcatheter aortic valve replacement: Results from the BRAVO-3 randomized trial. *Catheter Cardiovasc Interv* 2017;89:144–153.
11. Czarnecki A, Qiu F, Koh M, Prasad TJ, Cantor WJ, Cheema AN, Chu MWA, Feindel C, Fremes SE, Kingsbury K, Natarajan MK, Peterson MD, Ruel M, Strauss BH, Wijeysundera HC, Ko DT. Clinical outcomes after trans-catheter aortic valve replacement in men and women in Ontario, Canada. *Catheter Cardiovasc Interv* 2017;90:486–494.
12. Ferrante G, Pagnotta P, Petronio AS, Bedogni F, Brambilla N, Fiorina C, Giannini C, Mennuni M, De Marco F, Klugmann S, Ettori F, Presbitero P. Sex differences in postprocedural aortic regurgitation and mid-term mortality after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2014;84:264–271.
13. Katz M, Carlos Bacelar Nunes Filho A, Caixeta A, Antonio Carvalho L, Sarmento-Leite R, Alves Lemos Neto P, Eduardo Koenig Sao Thiago L, Dias Dourado Oliveira A, Antonio Marino M, Tadeu Tumelero R, Antonio Perin M, Abizaid A, Tarasoutchi F, Sandoli de Brito F Jr. Gender-related differences on short- and long-term outcomes of patients undergoing transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2017;89:429–436.
14. D'Ascenzo F, Gonella A, Moretti C, Omede P, Salizzoni S, La Torre M, Giordana F, Barbanti M, Ussia GP, Brambilla N, Bedogni F, Gaita F, Tamburino C, Sheiban I. Gender differences in patients undergoing TAVI: a multicentre study. *EuroIntervention* 2013;9:367–372.
15. Chandrasekhar J, Dangas G, Yu J, Vemulapalli S, Suchindran S, Vora AN, Baber U, Mehran R. Sex-based differences in outcomes with transcatheter aortic valve therapy: TVT registry from 2011 to 2014. *J Am Coll Cardiol* 2016;68:2733–2744.
16. Erez A, Segev A, Medvedofsky D, Fefer P, Raanani E, Goldenberg I, Guetta V. Factors affecting survival in men versus women following transcatheter aortic valve implantation. *Am J Cardiol* 2014;113:701–705.
17. Stangl V, Baldenhofer G, Knebel F, Zhang K, Sanad W, Spethmann S, Grubitzsch H, Sander M, Wernecke KD, Baumann G, Stangl K, Laule M. Impact of gender on three-month outcome and left ventricular remodeling after transfemoral transcatheter aortic valve implantation. *Am J Cardiol* 2012;110:884–890.
18. Hayashida K, Morice MC, Chevalier B, Hovasse T, Romano M, Garot P, Farge A, Donzeau-Gouge P, Bouvier E, Cormier B, Lefevre T. Sex-related differences in clinical presentation and outcome of transcatheter aortic valve implantation for severe aortic stenosis. *J Am Coll Cardiol* 2012;59:566–571.

19. Humphries KH, Toggweiler S, Rodes-Cabau J, Nombela-Franco L, Dumont E, Wood DA, Willson AB, Binder RK, Freeman M, Lee MK, Gao M, Izadnegahdar M, Ye J, Cheung A, Webb JG. Sex differences in mortality after transcatheter aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol* 2012;60:882–886.
20. Szerlip M, Gualano S, Holper E, Squiers JJ, White JM, Doshi D, Williams MR, Hahn RT, Webb JG, Svensson LG, Kirtane AJ, Cohen DJ, Douglas PS, Alu MC, Crowley A, Tuzcu EM, Makkar RR, Herrmann HC, Babaliaros V, Thourani VH, Leon MB, Kodali SK, Mack MJ. Sex-specific outcomes of transcatheter aortic valve replacement with the SAPIEN 3 valve: insights from the PARTNER II S3 high-risk and intermediate-risk cohorts. *JACC Cardiovasc Interv* 2018;11:13–20.
21. Buchanan GL, Chieffo A, Montorfano M, Maisano F, Latib A, Godino C, Cioni M, Gullace MA, Franco A, Gerli C, Alfieri O, Colombo A. The role of sex on VARC outcomes following transcatheter aortic valve implantation with both Edwards SAPIEN and Medtronic CoreValve ReValving System(R) devices: the Milan registry. *EuroIntervention* 2011;7:556–563.