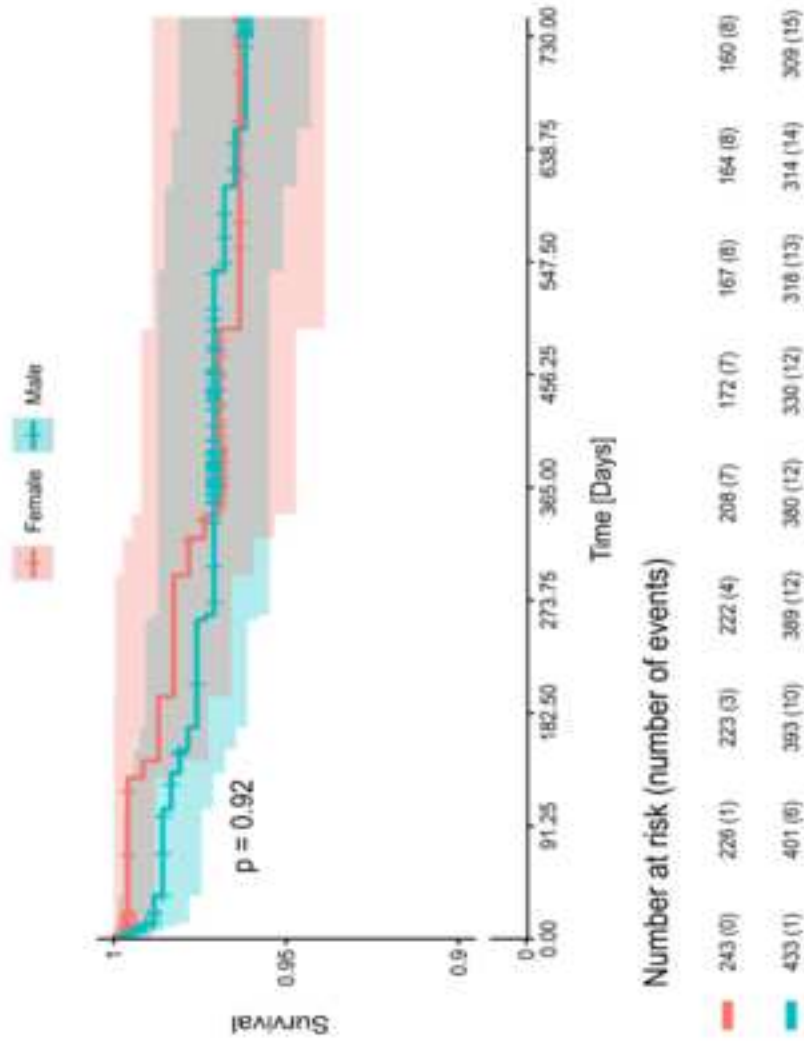


## Sex-related Differences in Patient Outcomes after SAVR

### Summary

In the propensity-score matched cohort of 433 males and 243 females undergoing first-time SAVR ± root replacement/CABG using a bioprosthetic valve, there were no sex-related differences at 2 years post surgery, indicating safety of SAVR and good valve performance in both sexes.

### Survival for all-cause mortality at 2 years



Legend: CABG, coronary artery bypass graft; SAVR, surgical aortic valve replacement

## Sex-related Differences among Patients Undergoing Surgical Aortic Valve Replacement - A Propensity Score Matched Study

Andreas Zierer<sup>1</sup>, MD; Ruggero De Paulis<sup>2</sup>, MD; Farhad Bakhtiary<sup>3</sup>, MD; Ali El-Sayed Ahmad<sup>3</sup>, MD; Martin Andreas<sup>4</sup>, MD; Rüdiger Autschbach<sup>5</sup>, MD; Peter Benedikt<sup>1</sup>, MD; Konrad Binder<sup>6</sup>, MD; Nikolaos Bonaros<sup>7</sup>, MD; Michael Borger<sup>8</sup>, MD; Thierry Bourguignon<sup>9</sup>, MD; Sergio Canovas<sup>10</sup>, MD; Enrico Coscioni<sup>11</sup>, MD; Francois Dagenais<sup>12</sup>, MD; Philippe Demers<sup>13</sup>, MD; Oliver Dewald<sup>14</sup>, MD; Richard Feyrer<sup>14</sup>, MD; Hans-Joachim Geißler<sup>1</sup>, MD; Martin Grabenwöger<sup>16</sup>, MD; Jürg Grünenfelder<sup>17</sup>, MD; Sami Kueri<sup>18</sup>, MD; Ka Yan Lam<sup>19</sup>, MD; Thierry Langanay<sup>20</sup>, MD; Günther Laufer<sup>4</sup>, MD; Wouter van Leeuwen<sup>21</sup>, MD; Rainer Leyh<sup>22</sup>, MD; Andreas Liebold<sup>23</sup>, MD; Giovanni Mariscalco<sup>24</sup>, MD; Parwis Massoudy<sup>25</sup>, MD; Arash Mehdiani<sup>26,38</sup>, MD; Renzo Pessotto<sup>27</sup>, MD; Francesco Pollari<sup>28</sup>, MD; Gianluca Polvani<sup>29</sup>, MD; Alessandro Ricci<sup>2</sup>, MD; Jean-Christian Rousse<sup>30</sup>, MD; Saad Salamate<sup>3</sup>, MD; Matthias Siepe<sup>18, 31</sup>, MD; Pierluigi Stefano<sup>32</sup>, MD; Justus Strauch<sup>33</sup>, MD; Alexis Theron<sup>34</sup>, MD; Andreas Vötsch<sup>35</sup>, MD; Alberto Weber<sup>36</sup>, MD; Olaf Wendler<sup>37</sup>, MD; Matthias Thielmann<sup>38</sup>, MD; Matthias Eden<sup>39</sup>, MD; Beate Botta<sup>40</sup>, PhD; Peter Bramlage<sup>40</sup>, MD; Bart Meuris<sup>41</sup>, MD

1. Department of Cardiac, Vascular and Thoracic Surgery, Kepler University Hospital Linz, Linz; and Hospital Wels-Grieskirchen, Wels, Austria; email: [andreas.zierer@kepleruniklinikum.at](mailto:andreas.zierer@kepleruniklinikum.at); [peter.benedikt@kepleruniklinikum.at](mailto:peter.benedikt@kepleruniklinikum.at); [hansjoachim.geissler@klinikum-wegr.at](mailto:hansjoachim.geissler@klinikum-wegr.at)
2. Department of Cardiac Surgery, European Hospital, Rome, Italy; email: [depaulis58@gmail.com](mailto:depaulis58@gmail.com); [ric.ale@hotmail.it](mailto:ric.ale@hotmail.it)
3. Department of Cardiac Surgery, University Hospital Bonn, Bonn, Germany; email: [farhad.bakhtiary@ukbonn.de](mailto:farhad.bakhtiary@ukbonn.de); [ali.assayed@gmail.com](mailto:ali.assayed@gmail.com); [saad.salamate@ukbonn.de](mailto:saad.salamate@ukbonn.de)
4. Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria; email: [martin.andreas@meduniwien.ac.at](mailto:martin.andreas@meduniwien.ac.at); [guenther.laufer@meduniwien.ac.at](mailto:guenther.laufer@meduniwien.ac.at)
5. Department of Thoracic and Cardiovascular Surgery, University Hospital RWTH Aachen, Aachen, Germany; email: [rautschbach@ukaachen.de](mailto:rautschbach@ukaachen.de)
6. Department of Cardiac Surgery, University Hospital St. Poelten, St. Poelten, Austria; email: [konrad.binder@stpoelten.lknoe.at](mailto:konrad.binder@stpoelten.lknoe.at)
7. Department of Cardiac Surgery, Medical University of Innsbruck, Innsbruck, Austria; email: [nikolaos.bonaros@i-med.ac.at](mailto:nikolaos.bonaros@i-med.ac.at)
8. Division of Cardiac Surgery, Leipzig Heart Center, Leipzig, Germany; email: [michael.borger@helios-gesundheit.de](mailto:michael.borger@helios-gesundheit.de)
9. Department of Cardiology and Cardiac Surgery, Tours University Hospital, Tours, France; email: [bourguignon@univ-tours.fr](mailto:bourguignon@univ-tours.fr)
10. Cardiovascular Surgery Department, Hospital University Virgen de la Arrixaca, Murcia, Spain; email: [sjcanovas@gmail.com](mailto:sjcanovas@gmail.com)
11. Division of Cardiac Surgery, University Hospital San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy; email: [enrico.coscioni@sangiovannieruggi.it](mailto:enrico.coscioni@sangiovannieruggi.it)
12. Department of Cardiac Surgery, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Quebec City, Québec, Canada; email: [Francois.Dagenais@fmed.ulaval.ca](mailto:Francois.Dagenais@fmed.ulaval.ca)

- 43 13. Department of Surgery, Montreal Heart Institute, University of Montreal, Montreal, Canada;  
44 email: [philippe.demers@icm-mhi.org](mailto:philippe.demers@icm-mhi.org)
- 45 14. Department of Pediatric Cardiac Surgery, University Hospital Erlangen, Erlangen, Germany; email:  
46 [oliver.dewald@uk-erlangen.de](mailto:oliver.dewald@uk-erlangen.de)
- 47 15. Department of Cardiac Surgery, Clinic for Cardiovascular Surgery, Central Military Hospital,  
48 Koblenz, Germany; email: [richardfeyrer@bundeswehr.org](mailto:richardfeyrer@bundeswehr.org)
- 49 16. Department of Cardiovascular Surgery, Clinic Floridsdorf, Vienna, Austria; email:  
50 [martin.grabenwoeger@wienkav.at](mailto:martin.grabenwoeger@wienkav.at)
- 51 17. Department of Cardiac Surgery, Heart Clinic Zurich, Hirslanden Klinik, Zurich, Switzerland; email:  
52 [juerg.gruenenfelder@hirslanden.ch](mailto:juerg.gruenenfelder@hirslanden.ch)
- 53 18. Department of Cardiovascular Surgery, University Heart Center Freiburg Bad Krozingen, Bad  
54 Krozingen, Germany; email: [sami.kueri@universitaets-herzzentrum.de](mailto:sami.kueri@universitaets-herzzentrum.de); [matthias.siepe@insel.ch](mailto:matthias.siepe@insel.ch)
- 55 19. Department of Cardiothoracic Surgery, Catharina Hospital Eindhoven, Eindhoven, Netherlands;  
56 email: [kayan.lam@catharinaziekenhuis.nl](mailto:kayan.lam@catharinaziekenhuis.nl)
- 57 20. Thoracic and Cardiovascular Surgery, Rennes University Hospital Center, Rennes, France; email:  
58 [thierry.langanay@chu-rennes.fr](mailto:thierry.langanay@chu-rennes.fr)
- 59 21. Department of Cardiothoracic Surgery, Erasmus MC University Medical Center, Rotterdam,  
60 Netherlands; mail: [w.j.vanleeuwen@erasmusmc.nl](mailto:w.j.vanleeuwen@erasmusmc.nl)
- 61 22. Department of Thoracic and Cardiovascular Surgery, University of Wuerzburg, Wuerzburg,  
62 Germany; email: [leyh\\_r@ukw.de](mailto:leyh_r@ukw.de)
- 63 23. Department of Cardiac Surgery, University of Ulm Medical Center, Ulm, Germany; email:  
64 [andreas.liebold@uniklinik-ulm.de](mailto:andreas.liebold@uniklinik-ulm.de)
- 65 24. Department of Cardiac Surgery, National Institute for Health Research Leicester Biomedical  
66 Research Centre, Glenfield Hospital, Leicester, United Kingdom; email: [Giovanni.Mariscalco@uhl-](mailto:Giovanni.Mariscalco@uhl-tr.nhs.uk)  
67 [tr.nhs.uk](mailto:tr.nhs.uk)
- 68 25. Department of Cardiac Surgery, Klinikum Passau, Passau, Germany; email:  
69 [parwis.massoudy@klinikum-passau.de](mailto:parwis.massoudy@klinikum-passau.de)
- 70 26. Department of Cardiac Surgery, University Hospital Duesseldorf, Duesseldorf, Germany; email:  
71 [arash.mehdiani@uk-essen.de](mailto:arash.mehdiani@uk-essen.de)
- 72 27. Cardiothoracic Surgery, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; email:  
73 [Renzo.Pessotto@nhslothian.scot.nhs.uk](mailto:Renzo.Pessotto@nhslothian.scot.nhs.uk)
- 74 28. Department of Cardiac Surgery, Klinikum Nürnberg-Paracelsus Medical University, Nuremberg,  
75 Germany; email: [francesco.pollari@klinikum-nuernberg.de](mailto:francesco.pollari@klinikum-nuernberg.de)
- 76 29. Department of Cardiovascular Surgery, Centro Cardiologico Monzino IRCCS, Milan, Italy; email:  
77 [gianluca.polvani@ccfm.it](mailto:gianluca.polvani@ccfm.it)
- 78 30. Service de chirurgie thoracique et cardiovasculaire, CHU Nantes, Nantes, France; email:  
79 [jeanchristian.rousseau@chu-nantes.fr](mailto:jeanchristian.rousseau@chu-nantes.fr)
- 80 31. Department of Cardiac Surgery, University Hospital Bern, University of Bern, Switzerland; email:  
81 [matthias.siepe@insel.ch](mailto:matthias.siepe@insel.ch)

- 82 32. Division of Cardiac Surgery, Careggi University Hospital, Florence, Italy; email:  
83 [pierluigi.stefano@unifi.it](mailto:pierluigi.stefano@unifi.it)
- 84 33. Department of Cardiothoracic Surgery, Berufsgenossenschaftliches Universitätsklinikum  
85 Bergmannsheil, Bochum, Nordrhein-Westfalen, Germany; email:  
86 [justus.strauch@bergmannsheil.de](mailto:justus.strauch@bergmannsheil.de)
- 87 34. Cardio-Thoracic Surgery Department, Hospital de la Timone, Marseille, France; email:  
88 [alexis.theron@ap-hm.fr](mailto:alexis.theron@ap-hm.fr)
- 89 35. Department of Cardiovascular and Endovascular Surgery, Paracelsus Medical University,  
90 Salzburg, Austria; email: [a.voetsch@salk.at](mailto:a.voetsch@salk.at)
- 91 36. Department of Cardiovascular Surgery, Heart Center Hirslanden, Zurich, Switzerland; email:  
92 [weber@herzzentrum.ch](mailto:weber@herzzentrum.ch)
- 93 37. Department of Cardiothoracic Surgery, King's College Hospital NHS Foundation Trust, London,  
94 United Kingdom; email: [olaf.wendler@nhs.net](mailto:olaf.wendler@nhs.net)
- 95 38. Department of Thoracic and Cardiovascular Surgery, West-German Heart and Vascular Center,  
96 University Duisburg-Essen, Essen, Germany; email: [matthias.thielmann@uk-essen.de](mailto:matthias.thielmann@uk-essen.de);  
97 [arash.mehdiani@uk-essen.de](mailto:arash.mehdiani@uk-essen.de)
- 98 39. Department of Medicine III: Cardiology, Angiology, and Pneumology, Heidelberg University,  
99 Heidelberg, Germany; email: [matthias.eden@med.uni-heidelberg.de](mailto:matthias.eden@med.uni-heidelberg.de)
- 100 40. Institute for Pharmacology and Preventive Medicine, Cloppenburg, Germany; email:  
101 [beate.botta@ippmed.de](mailto:beate.botta@ippmed.de); [peter.bramlage@ippmed.de](mailto:peter.bramlage@ippmed.de)
- 102 41. Cardiac Surgery, University Hospitals Leuven, Leuven, Belgium; email: [bart.meuris@uzleuven.be](mailto:bart.meuris@uzleuven.be)

103

104 **Correspondence** (for submission)

105 Prof. Dr. Peter Bramlage

106 Institute for Pharmacology and Preventive Medicine

107 Bahnhofstrasse 20, 49661 Cloppenburg, Germany

108 Email: [peter.bramlage@ippmed.de](mailto:peter.bramlage@ippmed.de)

109 Tel.: +49 4471 8503331

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112

113 **Meeting presentation**

114 The included data were presented at EACTS 2023 on 07.10.2023.

115

116 **Word count**

117 4496

118 **Graphical abstract**

119 *Caption: Sex-related Differences in Patient Outcomes at 2 years after SAVR*

120 *Legend: CABG, Coronary artery bypass graft; SAVR, surgical aortic valve replacement.*

121

122 **Trial registration** ClinicalTrials.gov NCT04053088 / - NCT03666741

123 **Highlights:**

124 *Key question*

125 What is the role of sex in clinical presentation and clinical outcomes after SAVR?

126 *Key findings*

127 Despite a worse baseline profile of females, there were no differences in 2-year outcomes after SAVR  
128 between males and females.

129 *Take-home message*

130 SAVR appears similarly effective and safe for males and females as no sex-specific differences were  
131 observed.

132

133 **ABSTRACT**

134 **Objectives:** We investigated the sex-related difference in characteristics and 2-year outcomes after  
135 surgical aortic valve replacement (SAVR) by propensity-score matching (PSM).

136 **Methods:** Data from two prospective registries, INDURE and IMPACT, were merged, resulting in a  
137 total of 933 patients: 735 males and 253 females undergoing first-time SAVR. PSM was performed to  
138 assess the impact of sex on the SAVR outcomes, yielding 433 males and 243 females with comparable  
139 baseline characteristics.

140 **Results:** Females had a lower body mass index (BMI; median 27.1 vs 28.0 kg/m<sup>2</sup>; p=0.008), fewer  
141 bicuspid valves (52% vs 59%; p=0.036), higher EuroSCORE II (mean 2.3 vs 1.8 %; p<0.001) and STS  
142 score (mean 1.6 vs 0.9 %; p<0.001), were more often in NYHA class III/IV (47% vs 30%; p<0.001) and  
143 angina CCS III/IV (8.2% vs 4.4%; p<0.001), but had a lower rate of myocardial infarction (1.9% vs 5.2%;  
144 p=0.028) compared to males. These differences vanished after PSM, except for EuroSCORE II and STS  
145 scores, which were still significantly higher in females. Furthermore, females required smaller valves  
146 (median diameter 23.0 vs 25.0 mm, p<0.001). There were no differences in the length of hospital stay  
147 (median 8 days) or ICU stay (median 24 vs 25 hours) between both sexes. At two years, post-SAVR  
148 outcomes were comparable between males and females, even after PSM.

149 **Conclusions:** Despite females presenting with a significantly higher surgical risk profile, 2-year  
150 outcomes following SAVR were comparable between males and females.

151 **Keywords:** Aortic stenosis; Surgical aortic valve replacement; sex disparities

152	<b>LIST OF ABBREVIATIONS</b>
153	AS – aortic stenosis
154	BMI – body mass index
155	CABG – coronary artery bypass surgery
156	CCS – Canadian Cardiovascular Society
157	MI – myocardial infarction
158	NYHA – New York Heart Association
159	PSM – propensity score matching
160	SAVR – surgical aortic valve replacement
161	STS – Society of Thoracic Surgeons
162	TIA – transient ischaemic attack
163	
164	

## 165 INTRODUCTION

166 Surgical aortic valve replacement (SAVR) has been the gold standard treatment for aortic stenosis (AS)  
167 for decades [1]. However, a precise understanding of specific sex-related differences in baseline  
168 characteristics and post-SAVR long-term outcomes and safety remains debated [2, 3]. Although  
169 women and men share a similar prevalence of AS, SAVR is less often performed in female patients.  
170 Specific anatomical characteristics peculiar to women's hearts, such as smaller valvular size, aortic  
171 annulus/root, and left ventricular outflow tract dimensions, make it technically more complicated and  
172 challenging for SAVR in women [4]. Besides, factors such as advanced age, greater frailty, lower body  
173 size, and the presence of more non-atherosclerotic comorbidities place females in a high-risk  
174 category for SAVR [3, 5, 6].

175 Several studies indicated that women undergoing SAVR experience worse short-term outcomes,  
176 including higher in-hospital and 30-day mortality, vascular complications, blood transfusion and  
177 increased length of hospital stay [2, 7] compared to men [2, 3, 6, 8]. Although a comparable long-  
178 term survival after SAVR was observed among both sexes [8, 9], extensive research is imperative to  
179 elucidate the male-female differences in the baseline characteristics and clinical outcomes to  
180 optimize the treatment for aortic valve diseases.

## 181 PATIENTS AND METHODS

182 In the present analysis, we combined data from two prospective, observational, multicentre registries  
183 - INDURE and IMPACT [10, 11], to study the sex-related difference in SAVR outcomes. We aimed to  
184 report 2-year follow-up data of male and female patients undergoing SAVR by propensity score  
185 matching (PSM).

## 186 Ethics statement

187 The study was approved by the institutional review board/ethics committee at each participating  
188 centre (**Supplementary Table 1**). A written informed consent was obtained from every patient before  
189 enrolment.



## 190 **Patient population**

191 Adult patients over 18 years of age undergoing SAVR and receiving Edwards INSPIRIS RESILIA  
192 bioprosthesis were enrolled in the registries. In addition, patients undergoing a planned native valve  
193 replacement with or without combined aortic root replacement and/or coronary artery bypass  
194 surgery (CABG) based on the pre-procedural evaluation were included. Exclusion criteria included  
195 prior myocarditis within three months before SAVR and a double valve procedure (replacement and  
196 repair). Additionally, when valve implantation was not possible as per device instruction for use,  
197 individuals with a life expectancy <12 months and pregnant patients at the time of the surgery were  
198 excluded.

## 199 **Objectives**

200 The primary objective of the analysis was to compare baseline and procedural characteristics of male  
201 and female patients undergoing SAVR.

202 The secondary objective was to compare the sex-related difference in post-SAVR clinical outcomes  
203 defined by Valve Academic Research Consortium-2 [12] at 2-year follow-up, which includes incidence  
204 of all-cause mortality, prosthetic endocarditis, thromboembolic events (stroke /transient ischaemic  
205 attack [TIA]), life-threatening valve-related bleeding, repeated procedure requirement and  
206 permanent pacemaker implantation (PPI).

## 207 **Statistical analysis**

208 Data were analyzed using descriptive statistics, with categorical variables presented as absolute  
209 values and frequencies (%) and the continuous variables presented as means (standard deviation  
210 [SD]) and/or median (interquartile range [IQR]). The percentages were calculated based on the  
211 number of patients with valid data per parameter, i.e. excluding patients with missing information.

212 Comparisons were performed using a t-test or Mann-Whitney U-test for continuous variables,  
213 depending on distribution, and a Fisher's exact or Chi-square test for categorical variables. Propensity  
214 scores (PS) were calculated using a Generalized Linear Model to assess the sex-specific effects (male

215 vs. female). The following covariates were selected to calculate the PS: body mass index (BMI), valve  
216 morphology, New York Heart Association (NYHA) III/IV, Canadian Cardiovascular Society (CCS) angina  
217 III/IV, diabetes mellitus, hypertension, left ventricular ejection fraction (LVEF), mean transvalvular  
218 pressure gradient, previous percutaneous intervention, pacemaker, chronic obstructive pulmonary  
219 disease (COPD), dialysis, aortic valve regurgitation (moderate/severe), myocardial infarction (MI),  
220 TIA/stroke, peripheral arterial disease, and coronary artery disease. The 1:2 ratio matching was  
221 performed using nearest neighbour matching with a caliper width equal to 0.2 times the standard  
222 deviation of the PS logit. Post-matching, standardized mean differences were analyzed for all  
223 covariates included in the PS calculation. The mean differences for all covariates post-matching were  
224 within a desirable threshold ( $\pm 0.1$ ), indicating adequate balance. Statistical analyses were performed  
225 using R version 4.3 (<https://www.R-project.org/>).

226

## 227 **RESULTS**

228 A total of 993 patients, 735 males and 253 females, who underwent SAVR using INSPIRIS RESILIA  
229 between 2019 and 2021 were included in the entire cohort. To assess the impact of sex on SAVR  
230 outcomes, a PSM cohort was created, resulting in a total of 676 matched pairs of 433 males and 243  
231 females (**Figure 1**).

### 232 **Patient characteristics**

233 In the entire cohort, female patients had a lower BMI (median 27.1 [IQR 23.4-31.0] vs 28.0 kg/m<sup>2</sup>  
234 [IQR 25.2-31.0];  $p=0.008$ ) and were less likely to have bicuspid valves (52% vs 59%;  $p=0.036$ )  
235 compared to male patients (**Table 1**). Additionally, females exhibited a higher prevalence of  
236 advanced NYHA class III/IV symptoms (47% vs 30%;  $p<0.001$ ) and angina CCS class III/IV symptoms  
237 (8.2% vs 4.4%;  $p=0.019$ ), indicating a higher symptomatic burden at baseline. However, after PSM,  
238 the differences were not significant in any cases.

239 Compared to males, female patients in both cohorts exhibited significantly higher surgical risk with  
240 higher EuroSCORE II ( $2.3\pm 3.1\%$  vs  $1.8\pm 2.0\%$ ;  $p<0.001$ ) and Society of Thoracic Surgeons (STS) score  
241 ( $1.6\pm 2.2\%$  vs  $0.90\pm 2.5\%$ ;  $p<0.001$ ). Notably, these differences persisted after PSM (EuroSCORE II:  
242  $2.4\pm 3.0\%$  vs  $1.6\pm 1.7\%$  in;  $p<0.001$  and STS score:  $1.7\pm 2.0\%$  vs  $1.0\pm 2.3\%$ ;  $p<0.001$ ). In the entire  
243 cohort, females had a lower history of MI ( $1.9\%$  vs  $5.2\%$ ;  $p=0.028$ ) than males.

244 In baseline echocardiography, females exhibited a lower prevalence of moderate to severe aortic  
245 valve regurgitation ( $27\%$  vs  $35\%$ ;  $p=0.015$ ), along with better LVEF ( $60\pm 10\%$  vs  $58\pm 10\%$ ;  $p<0.001$ ) and  
246 slightly higher mean transvalvular pressure gradient ( $46\pm 21$  vs  $43\pm 20$  mmHg;  $p=0.249$ ) compared to  
247 males. This trend did not persist after PSM.

#### 248 **Procedural characteristics**

249 In our study, both females and males had distinct AS aetiology ( $p=0.047$ ), primarily showing  
250 congenital AS ( $51.6\%$  in females vs  $59.8\%$  in males) followed by degenerative AS ( $44.6\%$  vs  $37.1\%$ )  
251 **(Supplementary Table 2)**.

252 In the total cohort, minimally invasive surgery (MIS) was more frequent in females ( $46.5\%$  vs  $38.6\%$ ;  
253  $p=0.027$ ) with less concomitant CABG ( $10.9\%$  vs  $16.3\%$ ;  $p=0.034$ ) **(Supplementary Table 2)**. Notably,  
254 these differences disappeared after PSM **(Table 2)**. Females required smaller valves (median  $23.0$  mm  
255 [IQR  $21.0$ - $23.0$ ]) compared to males (median  $25.0$  mm [IQR  $23.0$ - $27.0$ ]), which was significant in both  
256 total and PSM cohorts ( $p<0.001$ ). The majority of female patients received either  $23$  ( $44.4\%$ ) or  $21$   
257 ( $39.9\%$ ) mm valves, while male patients received either  $25$  ( $37.2\%$ ) or  $23$  ( $30.7\%$ ) mm valves. There  
258 were no differences in the the overall procedural time (skin-to-skin) between males and females in  
259 the matched cohort ( $p=0.170$ ). The first implantation attempt was successful in both sexes ( $>99.0\%$ ),  
260 with no intraprocedural mortality.

#### 261 **Discharge characteristics**

262 The overall hospital stay during SAVR was similar between female and male patients in the matched  
263 cohort (median  $8.0$  [IQR  $6.0$ - $10.0$ ] vs  $8.0$  [IQR  $7.0$ - $11.5$ ] days,  $p=0.144$ ; **Table 3**). There was no

264 difference in the LoS in intensive care unit (ICU) and duration of mechanical ventilation in both  
265 groups. A similar proportion of patients were discharged alive (females 99.6% and males 99.3%;  
266 **Supplementary Table 3**). The majority of patients were discharged to home after surgery, followed by  
267 discharge to a rehabilitation unit or another hospital.

### 268 **Clinical outcomes**

269 Both in the entire and PS-matched cohorts, no significant differences were observed in the incidence  
270 of clinical outcomes at 2 years, including endocarditis, thromboembolic events, valve-related  
271 dysfunction, repeated procedure, permanent pacemaker implantation, and valve-related bleeding  
272 between males and females undergoing SAVR ± CABG/root replacement (**Supplementary Table 4**;  
273 **Table 4**) as well as in patients undergoing isolated AVR (**Supplementary Table 5**). The 2-year survival  
274 rate in the PS-matched cohort was 96.2% (95% CI: 94.3–98.1%) in males and 96.3% (95% Confidence  
275 Interval [CI]: 93.9–98.9%) in females (p=0.920); no differences were observed in the total cohort  
276 either (**Figure 2, Supplementary Figure 1**). Although the rate of valve thrombosis at 2 years seemed to  
277 be higher in females (1.3% vs. 0.4% in the PS-matched cohort), the difference did not reach statistical  
278 significance (p=0.093).

279 The majority of patients requiring a repeated procedure at the 2-year follow-up in our study did so  
280 due the presence of the endocarditis; in 1 patient repeated procedure was due to valve thrombosis  
281 while another one had a moderate paravalvular leakage. One patient underwent valve-in-valve  
282 procedure due to AS. Furthermore, all patients reporting a prosthetic valve thrombosis at 2 years in  
283 our study either initiated or changed anticoagulation therapy and had a regression and good  
284 prosthesis function as showed by the decreased mean pressure gradient at the follow-up  
285 echocardiography. For 1 patient, the valve thrombosis was reverted despite the absence of  
286 anticoagulant therapy. Therefore, the presence of the valve thrombosis was mostly subclinical and did  
287 not lead to detrimental clinical consequences after SAVR using a biosprosthetic valve.

288

289

290 **DISCUSSION**

291 Key findings of this propensity-score matched study on 2-year data from INDURE and IMPACT  
292 registries were: 1) Females exhibited higher surgical risk (EuroSCORE II and STS score), had higher  
293 symptomatic burden (NYHA class III/IV and angina CCS III/IV) than males with similar comorbidity  
294 prevalence; 2) Females received smaller valves than males with a median diameter of 23 mm  
295 compared to 25 mm in males; 3) Both male and female patients experienced similar hospital LoS and  
296 ICU stay after SAVR; 4) Patients demonstrated comparable outcomes at 2 years after SAVR, suggesting  
297 that sex-related differences observed at baseline did not impact clinical outcomes.

298 In the overall population (n=993), the proportion of female patients undergoing SAVR from 2019 to  
299 2021 was lower compared to male patients (258 [26.0%] vs 735 [74.0%]). This disparity suggests a  
300 lower incidence of SAVR in females than males, consistent with findings reported in prior literature  
301 [2, 3, 7]. Despite a similar AS prevalence in AS [13], the specific factors contributing to the lower rate  
302 of SAVR in women remain unclear. Several studies have proposed potential explanations, such as the  
303 insidious onset of the disease in females, delayed diagnosis, conservative management, less frequent  
304 referrals to specialists, and fewer diagnostic tests conducted among women [2, 14, 15]. However, it  
305 is important to note that our study did not focus on the male-female disparity in the incidence of  
306 SAVR, the time that elapsed between diagnosis and intervention or the urgency of SAVR, which  
307 represents a limitation of our findings.

308 Several previously published studies [2, 9, 16-18] have investigated sex-related differences in patients  
309 undergoing SAVR. These studies consistently report that females undergoing SAVR tend to be older,  
310 exhibit advanced NYHA symptoms and angina symptoms, and have higher surgical risks compared to  
311 males. Our study aligns with these findings, as females exhibited significantly higher EuroSCORE II and  
312 STS scores in both cohorts ( $p < 0.001$ ), indicating a greater surgical risk profile in females.

313 Nevertheless, there was no significant difference in age between males and females in our study, and

314 they were younger (both sexes) than the population studied earlier [15, 17, 18]. Furthermore, in our  
315 cohort, females showed advanced NYHA class III/IV and angina CCS III/IV symptoms than males  
316 ( $p < 0.001$ ), indicating a heightened cardiac risk and symptomatic burden than male patients and this  
317 trend was consistent with the observations of previous studies [9, 17, 18]. Contrary to the lower  
318 comorbidity prevalence observed among female patients undergoing SAVR in the PARTNER trial [15]  
319 and the study by Tribouilloy et al. [17], our study did not reveal significant differences between males  
320 and females. Nonetheless, our study did note a higher prevalence of previous MI among males,  
321 aligning with the findings of Hernandez-Vaquero et al. [16] and Tribouilloy et al. [17].

322 Notably, a significant difference was observed in implanted valve size between the sexes, with  
323 females being implanted with smaller valves than males (median diameter 23 vs 25 mm;  $p < 0.001$ ).  
324 This is attributed to anatomical differences, with women typically having smaller hearts and aortic  
325 annuli [19] than men. Consequently, the need for smaller aortic bioprosthesis in women has been  
326 recognized in previous research and is associated with increased risk in SAVR [20]. Therefore, it  
327 underscores the importance of selecting valve size based on precise in vivo measurements of the  
328 patient's specific annular dimensions.

329 Despite significant differences in baseline characteristics, indicating a high surgical risk among females  
330 in our study, the 2-year outcomes after SAVR revealed comparable outcomes in both sexes. However,  
331 existing literature shows varied findings. For instance, a study by Kulik et al. comparing long-term  
332 outcomes of SAVR over 5.6 years reported a significantly lower reoperation rate in women  
333 (comorbidity-adjusted hazard ratio (HR) 0.4; 95% CI: 0.2 to 0.9) and a higher incidence of late stroke  
334 (HR 1.7; 95% CI: 1.1 to 2.7) compared to men, indicating sex-related differences in long-term SAVR  
335 outcomes exists [21]. Despite these discrepancies, women exhibited better overall long-term survival  
336 than men in their study. Similarly, findings from the Simvastatin Ezetimibe in Aortic Stenosis (SEAS)  
337 study, with a median follow-up of 4 years, revealed that females exhibited lower total mortality and a  
338 reduced rate of ischemic cardiovascular events compared to men, independent of confounding  
339 factors, despite similar AS progression and more severity in females based on echocardiographic

340 indices [22]. On the other hand, another baseline-matched retrospective study reported comparable  
341 long-term survival benefits in females at a 5-year follow-up. However, men faced a higher risk of  
342 bleeding, endocarditis, and early reoperation after SAVR [9]. Thus, collectively, these studies suggest  
343 that female sex does not significantly impact the long-term survival of SAVR when preoperative  
344 characteristics are adjusted between both sexes.

### 345 **Limitations**

346 Our study did not capture data on matching-based postoperative ventricular remodelling and  
347 prosthetic valve performance following surgery, which could elucidate casual factors impacting the  
348 outcome for males and females. Additionally, we did not gather information on the timing of  
349 intervention and the urgency of SAVR. Furthermore, our study lacks data on prosthetic-patient  
350 mismatch, a common complication of cardiac surgery [23].

### 351 **CONCLUSION**

352 Women undergo SAVR less frequently and exhibit a higher risk profile, posing unique challenges for  
353 cardiac surgery. Nevertheless, our analysis reveals that the 2-year clinical outcomes of SAVR are  
354 similar between sexes when baseline characteristics are matched. These findings highlight the  
355 importance of considering sex-related factors in evaluating surgical risk and treatment strategies for  
356 SAVR patients.

357

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#### 371 **AUTHOR'S CONTRIBUTIONS**

372 AZ, RdP, FB, TB, AESA, MB, BB, PBr and BM were involved in the conception, design, data acquisition  
373 and interpretation of the study. PB and BB drafted the manuscript and all other authors revised the  
374 article for important intellectual content. All authors gave approval of the final version and  
375 submission of the manuscript.

#### 376 **AVAILABILITY OF DATA AND MATERIALS**

377 The datasets generated and analyzed during the current study may be available from the  
378 corresponding author upon reasonable request.

#### 379 **ETHICAL APPROVAL/PATIENT CONSENT**

380 The study was approved by the institutional review board/ethics committee at each participating  
381 centre and a written informed consent was obtained from every patient before enrolment.

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387 **Figure Titles/Legends:**

388 **Figure 1:** Study flowchart

389 Legends: CABG, coronary artery bypass graft; PS, propensity score; SAVR, surgical aortic valve  
390 replacement

391 \*Reasons: Not meeting inclusion/exclusion criteria (n=9); Not receiving INSPIRIS Resilia valve (n=10);  
392 Double valve procedure (replacement or repair; n=10), Withdrew from the study (n=2)

393

394 **Figure 2:** Kaplan-Meier survival curve at 2-year all-cause mortality stratified by sex – PS-matched  
395 cohort

396 Legend: PS, propensity score

397

**Table 1:** Patient characteristics

Mean±SD or median (IQR) or n (%)	Full cohort		SMD	95% CI	p-value	PS matched cohort		SMD	95% CI	p-value
	Male, N=735	Female, N=258				Male, N=433	Female, N=243			
Age, years	58.8±9.2	59.8±9.5	-0.11	-0.25, 0.03	0.159	59.0±9.7	59.8±9.5	-0.09	-0.24, 0.07	0.430
Body mass index, kg/m <sup>2</sup>	28.0 (25.2-31.0)	27.1 (23.4-31.0)	0.11	-0.03, 0.25	0.008	27.1 (24.7-30.2)	27.3 (23.5-31.3)	-0.05	-0.20, 0.11	0.601
Valve morphology			0.15	0.01, 0.29	0.036			0.04	-0.12, 0.19	0.647
Bicuspid	434 (59)	133 (52)				236 (55)	128 (53)			
Tricuspid	301 (41)	125 (48)				197 (45)	115 (47)			
NYHA class III/IV	220 (30)	121 (47)	0.36	0.22, 0.50	<0.001	169 (39)	110 (45)	0.13	-0.03, 0.28	0.114
Angina CCS III/IV	32 (4.4)	21 (8.2)	0.16	0.02, 0.30	0.019	22 (5.1)	17 (7.0)	0.08	-0.08, 0.24	0.306
EuroSCORE II, %	1.8±2.0	2.3±3.1	-0.18	-0.32, -0.04	<0.001	1.6±1.7	2.4±3.0	-0.18	-0.32, -0.04	<0.001
STS score, %	0.9±2.5	1.6±2.2	-0.31	-0.46, -0.17	<0.001	1.0±2.3	1.7±2.0	-0.33	-0.48, -0.17	<0.001
Medical history										
Diabetes mellitus	115 (16)	45 (17)	0.05	-0.09, 0.19	0.500	73 (17)	42 (17)	0.01	-0.15, 0.17	0.888
Systemic hypertension	438 (60)	148 (57)	0.05	-0.10, 0.19	0.531	243 (56)	138 (57)	0.01	-0.14, 0.17	0.866
Coronary artery disease	504 (69)	192 (75)	0.14	-0.01, 0.28	0.068	313 (72)	180 (74)	0.04	-0.12, 0.20	0.616
Myocardial infarction	38 (5.2)	5 (1.9)	0.18	0.03, 0.32	0.028	11 (2.5)	5 (2.1)	0.03	-0.12, 0.19	0.692
Peripheral vascular disease	43 (5.9)	11 (4.3)	0.07	-0.07, 0.21	0.334	21 (4.8)	11 (4.5)	0.02	-0.14, 0.17	0.849
TIA/stroke	36 (4.9)	13 (5.0)	0.01	-0.14, 0.15	0.928	19 (4.4)	11 (4.5)	0.01	-0.15, 0.16	0.933
COPD	52 (7.1)	27 (10)	0.12	-0.02, 0.26	0.083	35 (8.1)	22 (9.1)	0.03	-0.12, 0.19	0.663
PPI	13 (1.8)	4 (1.6)	0.02	-0.12, 0.16	1.000	8 (1.8)	4 (1.6)	0.02	-0.14, 0.17	1.000
Previous PCI	78 (11)	19 (7.4)	0.11	-0.03, 0.26	0.131	35 (8.1)	19 (7.8)	0.01	-0.15, 0.17	0.903
Dialysis	8 (1.1)	2 (0.8)	0.03	-0.11, 0.17	1.000	5 (1.2)	2 (0.8)	0.03	-0.12, 0.19	1.000

Echocardiography

AV regurgitation (moderate/severe)	255 (35)	68 (27)	0.18	0.04, 0.32	0.015	128 (30)	66 (27)	0.05	-0.10, 0.21	0.508
LVEF, %	58±10	60±10	-0.28	-0.43, -0.14	<0.001	60±9	60±10	-0.04	-0.20, 0.12	0.464
Mean transvalvular pressure gradient, mmHg	43±20	46±21	-0.16	-0.30, -0.01	0.249	45±18	46±21	-0.05	-0.21, 0.12	0.690

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Legend: AV, aortic valve; CCS, Canadian Cardiovascular Society; EuroSCORE, European System for Cardiac Operative Risk Evaluation; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; PCI, percutaneous intervention; PPI, permanent pacemaker implantation; PS, propensity score; SMD, standard mean difference; STS, Society of Thoracic Surgeons; TIA, transient ischaemic attack

**Table 2:** Procedural details – PS-matched cohort

Mean±SD or median (IQR) or n (%)	Male, N=433	Female, N=243	p-value
Etiology of valve pathology			0.769
Congenital	239 (55.3)	128 (52.7)	
Degenerative	183 (42.4)	106 (43.6)	
Endocarditic	1 (0.2)	1 (0.4)	
Rheumatic	2 (0.5)	2 (0.8)	
None (no aortic stenosis)	7 (1.6)	6 (2.5)	
Isolated AVR	259 (59.8)	149 (61.3)	0.702
MIS	178 (41.1)	114 (46.9)	0.144
Concomitant procedures			
CABG	67 (15.5)	27 (11.1)	0.116
Root replacement	31 (7.2)	11 (4.5)	0.174
Supracoronary tube graft	58 (13.4)	31 (12.8)	0.814
Total operation time (skin-to-skin), min	198.3±62.9 190.0 (155.0, 233.5)	191.1±59.0 184.5 (148.0, 224.0)	0.170
Cross-clamp time, min	75.0±26.8 70.0 (56.0, 92.0)	71.7±26.3 68.0 (54.0, 88.0)	0.111
Cardiopulmonary bypass time, min	103.9±39.3 98.0 (76.0, 126.0)	102.1±38.1 94.0 (77.0, 121.0)	0.542
Final valve size, mm	25.0 (23.0, 25.0) 24.7±2.1	23.0 (21.0, 23.0) 22.3±1.5	<0.001
19	0 (0.0)	8 (3.3)	
21	32 (7.4)	97 (39.9)	
23	133 (30.7)	108 (44.4)	
25	161 (37.2)	27 (11.1)	
27	75 (17.3)	3 (1.2)	
29	32 (7.4)	0 (0.0)	
Implantation details			
1 <sup>st</sup> implantation success	432 (99.8)	242 (99.6)	1.000
2 <sup>nd</sup> implantation with INSPIRIS	1 (0.2)	1 (0.4)	1.000
Resilia			
Paravalvular leak (final)	5 (1.2)	1 (0.4)	0.427
Intraprocedural mortality	0 (0.0)	0 (0.0)	1.000

Legend: CABG; coronary artery bypass graft; IQR, interquartile range; MIS, minimally invasive surgery; PS, propensity score; SD, standard deviation

**Table 3:** Discharge details – PS-matched cohort

Mean±SD or Median (IQR) or n (%)	Male, N=433 <sup>1</sup>	Female, N=243	p-value
Hospital stay, days	9.0±4.5 8.0 (6.0, 10.0)	9.9±6.5 8.0 (7.0, 11.5)	0.144
Discharged alive	428 (99.3)	242 (99.6)	1.000
Discharge to			0.428
Home	257 (59.6)	151 (62.1)	
Other hospital	33 (7.7)	25 (10.3)	
Rehabilitation unit	135 (31.3)	66 (27.2)	
Other	3 (0.7)	0 (0.0)	
Death	3 (0.7)	1 (0.4)	
ICU stay, hours	46.4±54.7 24.0 (21.0, 48.0)	52.0±59.0 25.0 (22.0, 62.0)	0.449
Mechanical ventilation, hours	11.9±39.5 7.0 (4.0, 10.0)	10.1±15.0 7.0 (5.0, 10.0)	0.609

Legends: ICU; intensive care unit; IQR, interquartile range; LoS, length of stay; PS, propensity score; SD, standard deviation

**Table 4:** Two-year clinical outcomes – PS-matched cohort

n (%)	Early ( $\leq 30$ days)		Late (>30 days to 2 year)		Freedom from events at 2 years %(95%CI)		p-value
	Male, N=433	Female, N=243	Male, 732 vy	Female, 400 vy	Male	Female	
All-cause mortality	5 (1.2)	1 (0.4)	10 (1.4)	7 (1.8)	96.2 (94.3, 98.1)	96.3 (93.9, 98.9)	0.920
Cardiovascular-related	5 (1.2)	1 (0.4)	7 (1.0)	3 (0.8)	97.0 (95.4, 98.7)	98.1 (96.3, 100.0)	0.365
Valve-related	2 (0.5)	0 (0)	5 (0.7)	2 (0.5)	98.3 (97.0, 99.6)	98.9 (97.5, 100.0)	0.394
Valve-related - Unknown	1 (0.2)	0 (0)	2 (0.3)	4 (1.0)	99.1 (98.2, 100.0)	98.1 (96.2, 100.0)	0.233
Prosthesis endocarditis	0 (0)	0 (0)	4 (0.5)	2 (0.5)	99.0 (98.0, 100.0)	99.0 (97.5, 100.0)	0.909
Thromboembolic events	11 (2.5)	4 (1.6)	4 (0.5)	4 (1.0)	95.9 (93.8, 97.9)	95.8 (93.0, 98.7)	0.967
Stroke	7 (1.6)	4 (1.6)	0 (0)	1 (0.3)	98.1 (96.7, 99.5)	97.4 (95.2, 99.7)	0.594
Valve thrombosis	0 (0)	0 (0)	3 (0.4)	5 (1.3)	99.7 (99.1, 100.0)	98.0 (96.0, 100.0)	0.093
Valve-related dysfunction	1 (0.2)	0 (0)	3 (0.4)	5 (1.3)	99.5 (98.8, 100.0)	98.6 (97.1, 100.0)	0.196
Repeated procedure	1 (0.2)	0 (0)	0 (0)	3 (0.8)	99.8 (99.3, 100.0)	99.0 (97.5, 100.0)	0.096
Permanent pacemaker	18 (4.2)	9 (3.7)	2 (0.3)	2 (0.5)	95.2 (93.2, 97.3)	95.4 (92.7, 98.1)	0.944
Valve-related bleeding	43 (9.9)	29 (11.9)	2 (0.3)	3 (0.8)	89.5 (86.7, 92.5)	86.6 (82.4, 91.1)	0.282

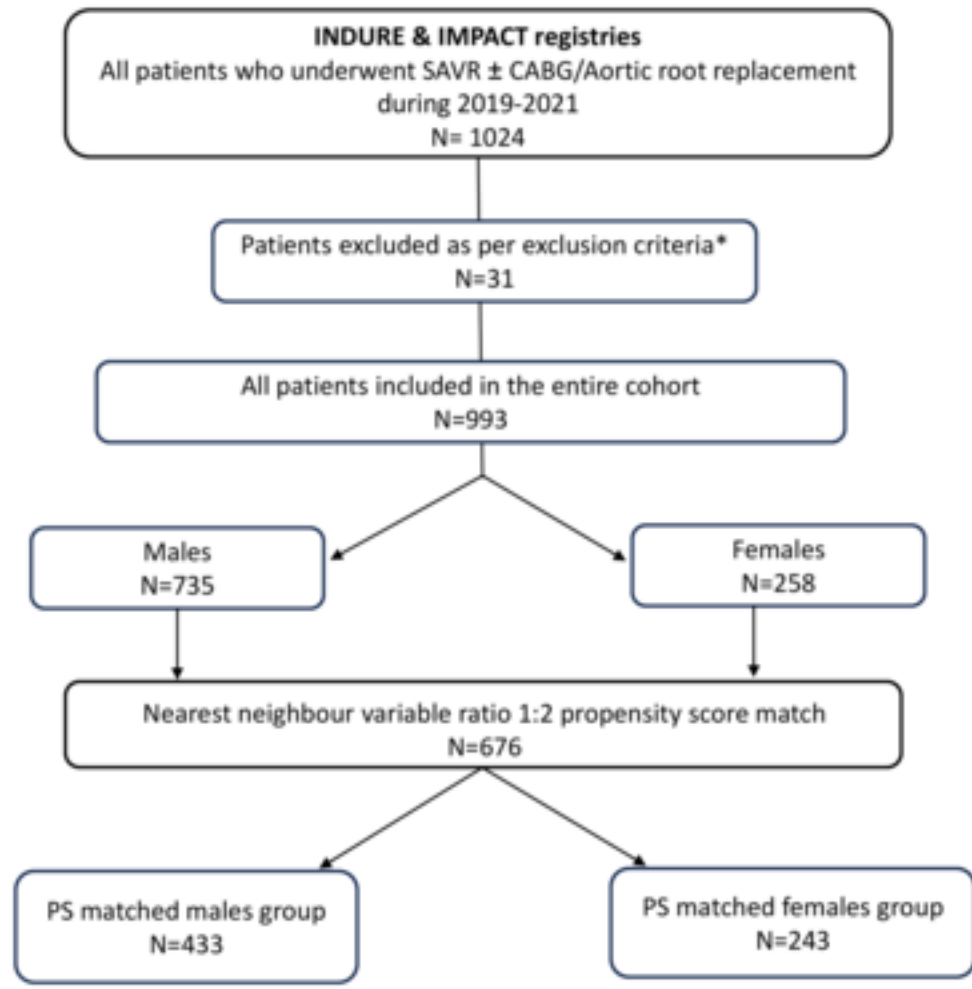
Legends: CI, confidence interval; vy, valve years

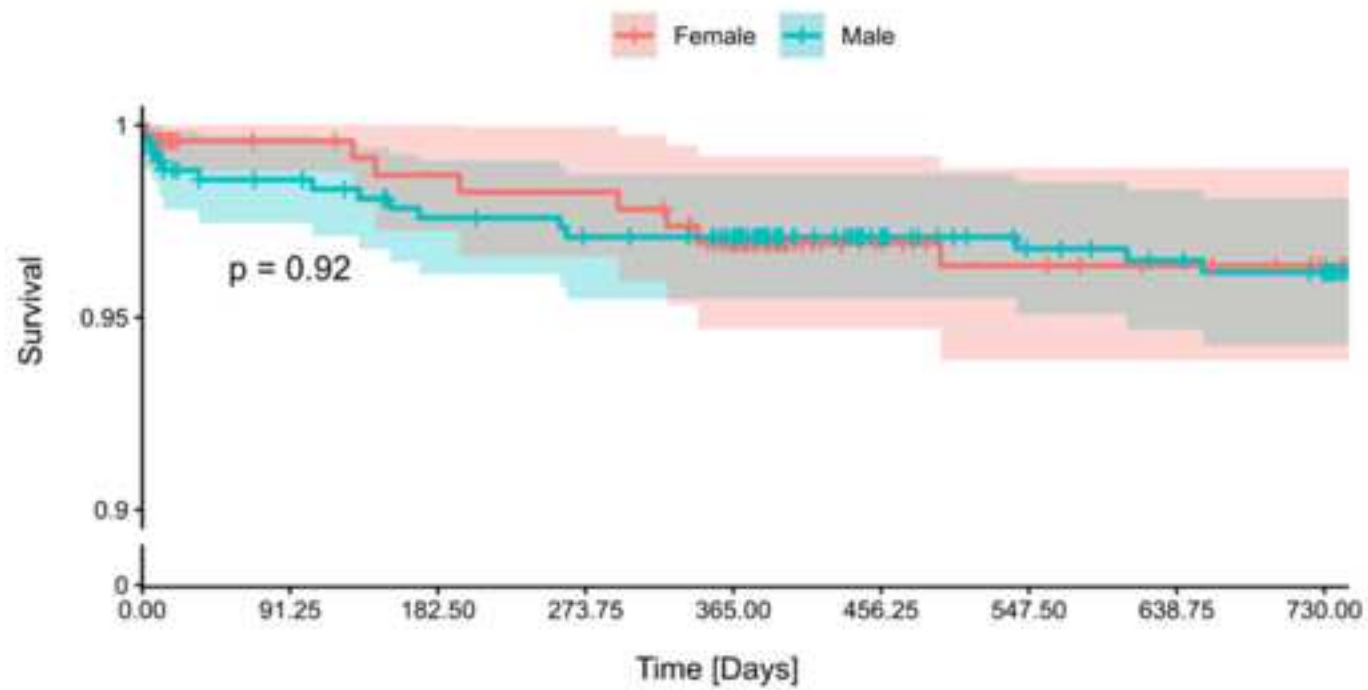
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Number at risk (number of events)

Female	243 (0)	226 (1)	223 (3)	222 (4)	208 (7)	172 (7)	167 (8)	164 (8)	160 (8)
Male	433 (1)	401 (6)	393 (10)	389 (12)	380 (12)	330 (12)	318 (13)	314 (14)	309 (15)