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1 **Title page**

2

3 **Title:** Comparison of transcatheter to surgical aortic valve implantation in high risk patients: A  
4 nationwide study in France.

5

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38

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43 **Glossary of Abbreviations:**

44

45 AHA/ACC: American Heart Association/American College of cardiology

46 AVR: Aortic valve replacement

47 DRG: Diagnosis-Related-Group

48 ESC: European Society of Cardiology

49 GEE: Generalized Estimating Equations

50 HR: Hazard ratio

51 ICD: International Classification of Diseases

52 PMSI: French Medical Information System

53 PSM: Propensity-score matching

54 RCT: Randomised controlled trial

55 SAVR: Surgical aortic valve replacement

56 TAVI: Transcatheter aortic valve implantation

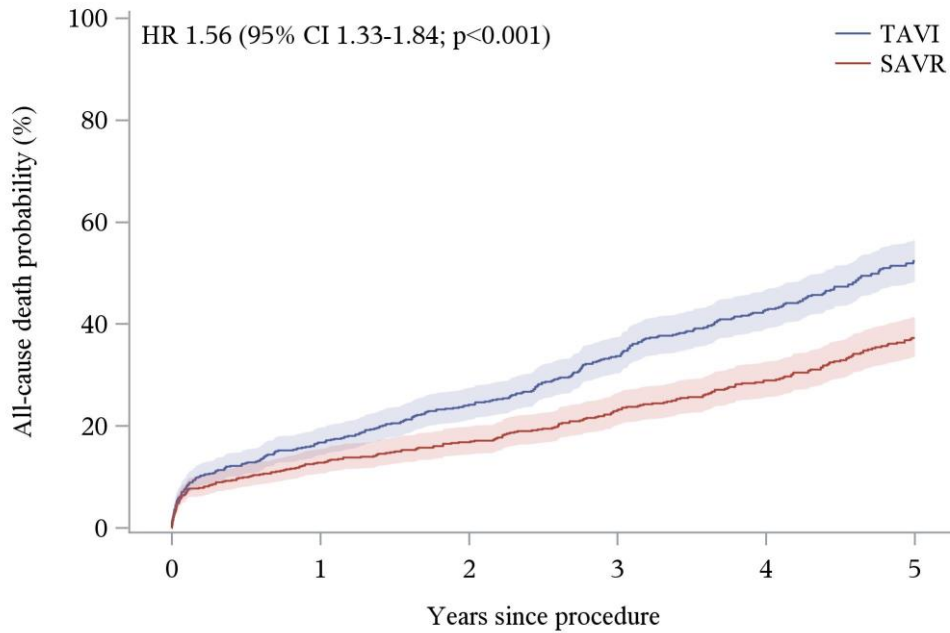
57

58

59 **Central picture**

60

61



	Number at risk					
TAVI	799	587	489	388	304	200
SAVR	799	604	543	456	378	267

62

63 **Legend: Cumulative probability of all-cause in-hospital mortality**

64 Time varying outcome with shaded areas showing 95% confidence intervals based on 1-Kaplan-Meier  
65 estimation of TAVI (transcatheter aortic valve implantation) vs. SAVR (surgical aortic valve replacement); HR =  
66 Hazard ratio.

67

68

69 **Central message**

70 In patients with high-surgical risk, our study using real-world evidence shows TAVI to be  
71 associated with a greater risk of mortality after 1 year which is sustained up to 5 years

72

73 **Perspective statement**

74 The extension of TAVI indications in patients other than those with high or prohibitive-  
75 surgical risk should be cautious until further data, either based on RCTs or real-world  
76 evidence, are made available to inform on the relative long-term effectiveness of TAVI  
77 compared to SAVR.

78

79 **Structured Abstract (241 words)**

80

81 **Objective:** To compare the clinical outcomes and direct costs at 5 years between TAVI or  
82 SAVR using real-world evidence.

83 **Methods:** We performed a nationwide longitudinal study using data from the French Hospital  
84 Information System over 2009-2015. We matched inside hospitals two cohorts of adults who  
85 underwent TAVI or SAVR in 2010 on propensity score based on patients characteristics.  
86 Outcomes analysis included mortality, morbidity, and total costs and with a maximum 60-  
87 month follow-up. Clinical outcomes were compared between cohorts using Hazard Ratios  
88 (HR) estimated from Cox proportional hazards model for all-cause death, and from Fine and  
89 Gray's competing risk model for morbidity.

90 **Results:** Based on a cohort of 1598 patients (799 in each group) from 27 centers, a higher risk  
91 of death was observed after 1 year with TAVI compared to SAVR (16.8% vs. 12.8%  
92 respectively; HR 1.33, 95%CI 1.02-1.72) and was sustained up to 5 years (52.4% vs. 37.2%;  
93 HR 1.56, 95%CI 1.33-1.84). At 5 years, the risk of stroke was increased (HR 1.64, 95%CI  
94 1.07-2.54) as was myocardial infarction (HR 2.30, 95%CI 1.12-4.69) and pacemaker  
95 implantation (HR 2.40, 95%CI 1.81-3.17) after TAVI. The hospitalization costs per patient at  
96 5 years were €69,083 after TAVI and €55,687 after SAVR ( $p < 0.001$ ).

97 **Conclusions:** In our study, high-risk patients after TAVI harbor a greater risk of mortality and  
98 morbidity at 5 years compared to SAVR and higher hospitalizations costs. Those results  
99 should encourage to be more cautious before enlarging the indications of TAVI.

100

## 101 **Introduction**

102 More than 15 years after the first-in-man case,<sup>1</sup> transcatheter aortic valve implantation (TAVI)  
103 continues to revolutionize the management of severe aortic stenosis and has become over time  
104 a routinely performed procedure in many cardiac centers worldwide. In early 2014, more than  
105 100,000 had been performed.<sup>2</sup> While the benefit of TAVI was initially demonstrated in  
106 patients ineligible or at high-surgical risk,<sup>3,4</sup> a growing number of studies have evaluated  
107 TAVI in patients with low-to-intermediate risk.<sup>5,6</sup> This has contributed to the currently  
108 observed trend toward enlarged indications of TAVI in patients that would otherwise undergo  
109 surgical aortic valve replacement (SAVR). Several randomised controlled trial (RCTs)  
110 conducted among carefully selected populations have shown promising results on the clinical  
111 effectiveness and safety of TAVI compared to surgery.<sup>4,5,7</sup> Conversely, evidence from real-  
112 world data indicate a better outcome with surgery compared to TAVI.<sup>8</sup> Overall, the largest  
113 reported cohorts have a follow-up limited to one to three years in maximum<sup>9,10</sup> which is  
114 insufficient to provide a long-term view after aortic valve replacement (AVR).  
115 This nationwide study aimed to compare the long-term clinical outcomes and costs between  
116 patients undergoing TAVI and SAVR.

117

## 118 **Material and Methods**

### 119 **Study design and participants**

120 We conducted a propensity-matched cohort study based on the French Medical Information  
121 System (*programme de médicalisation des systèmes d'information [PMSI]*). The PMSI is a  
122 large hospital database with prospectively collected data from all public and private hospitals  
123 in France. The database is routinely implemented for the purpose of care reimbursement  
124 leading to very strong accuracy and exhaustive collection of the data. As a consequence no  
125 patients were lost to follow-up during the considered period. Moreover, the PMSI has a



126 system of coding with strict variable definitions and a subset of records audited on a regular  
127 basis in order to avoid an excessive high rates of coding errors. Inpatient's stays are converted  
128 into one Diagnosis-Related-Group (DRG) based on standard discharge abstracts containing  
129 compulsory information about the patient, primary and secondary diagnoses, using the  
130 International Classification of Diseases (10th revision - ICD-10), as well as procedural codes  
131 associated with the care provided.

132 We selected all adults who underwent TAVI or SAVR in French institutions between 1,  
133 January, 2010 and 31, December, 2010. In order to homogenize study population, we only  
134 selected cases with a main diagnosis of heart failure, rheumatic or nonrheumatic aortic valve  
135 disease (ICD-10 codes I06\*, I35\*, or I50\*). Patients <18 years, having experienced  
136 ambulatory care, or with data inaccuracies were not retained in final cohorts. Within the index  
137 hospitalization stay, we extracted patients' demographics and socioeconomic characteristics,  
138 co-morbidities according to Charlson and/or Elixhauser algorithms<sup>11</sup>, the type and emergency  
139 context of surgical procedure, and length of stay. We subsequently used patient unique  
140 anonymous number in order to link his/her stays in acute and rehabilitation care, allowing the  
141 extraction of hospitalization-related data from 12 months preceding TAVI and SAVR to a  
142 maximum of 60 months thereafter.

143

#### 144 **Outcomes**

145 The primary endpoint was in-hospital mortality from the index hospitalization up to five years  
146 following TAVI or SAVR. Other outcomes included the occurrence of postoperative  
147 admission in intensive ( $\geq 2$  nights) or critical care unit ( $\geq 5$  nights), reoperation, stroke,  
148 myocardial infarction, or pacemaker implantation.

149 Economic evaluation was performed from the hospital perspective based on the total number  
150 of hospitalization stays, days, and costs over 5 years in acute or rehabilitation care. We valued

151 in Euros (€) the in-hospital medical resources consumptions using average expenditures as  
152 observed in the national cost scale for the medicine, surgery, and obstetrics sector.

153

#### 154 **Statistical analysis**

155 To control for the nonrandom assignment of patients to one of the two procedures, we formed  
156 matched pairs of TAVI and SAVR patients using propensity scores. First, propensity scores  
157 were estimated as the predicted probability of a patient undergoing TAVI using a logistic  
158 regression model including the following covariates: sex, age (continuous, with linear,  
159 quadratic and cubic terms), household income (continuous), number of days spent in acute  
160 care hospitalizations the year before the index stay (continuous, with linear, quadratic and  
161 cubic terms), emergency procedure, and a selection of comorbidities (i.e. congestive heart  
162 failure, cardiac arrhythmia, pulmonary circulation disorder, peripheral vascular disease,  
163 hypertension, chronic pulmonary disease, diabetes, renal disease, liver disease, obesity,  
164 myocardial infarction, and cerebrovascular disease). We then matched patients with the  
165 closest propensity score inside hospital to control for confounders at hospital level, using a  
166 greedy 1:1 algorithm without replacement and requiring that the logit of the propensity score  
167 of a patient who underwent TAVI and one who underwent SAVR be within 0.20 standard  
168 deviations of one another. Standardized differences were used to assess the degree of balance  
169 between the matched groups for baseline characteristics. An absolute standardized difference  
170 of  $\leq 0.10$  was chosen to indicate a negligible difference in the mean or prevalence of a variable  
171 between groups. Balance for continuous variables was also assessed with graphical methods  
172 (side-by-side boxplots, empirical cumulative distribution functions, empirical QQ-plots) to  
173 compare the distributions across the two groups. Sensitivity analysis was conducted for the  
174 main outcomes (all-cause death and costs) with 1:1 nearest neighbor matching with  
175 replacement within caliper of 0.20 standard deviation of the logit of the propensity score, with

176 the inclusion of weights in the outcome models (TAVI patients were weighted at 1 and the  
177 weight for a SAVR patient was the number of times it was matched to a TAVI patient).

178

179 Categorical variables were presented using absolute and relative frequencies and continuous  
180 variables were presented using medians and interquartile ranges. Estimates were accompanied  
181 with the corresponding 95% CI and p-values of less than 0.05 were considered to indicate  
182 statistical significance.

183

184 Clinical outcomes were assessed as time-to-event variables, and were evaluated at different  
185 time points  $t$  (1 month, 6 months, then yearly up to 5 years after index procedure). Cumulative  
186 probabilities of events over time were estimated with the non-parametric 1-Kaplan-Meier  
187 estimator for all-cause death, and with the non-parametric Cumulative Incidence Functions  
188 estimator using competing risk of death for postoperative stay in intensive or critical care unit,  
189 reoperation, stroke, myocardial infarction, and pacemaker. To compare the effect of procedure  
190 (TAVI vs. SAVR), Hazard Ratios (HR) were estimated between time 0 and time  $t$ , from Cox  
191 proportional hazards model for all-cause death, and from Fine and Gray's model using  
192 competing risk of death for other clinical outcomes, with robust variance estimator to account  
193 for clustering within matched pairs. A sensitivity analysis was performed for the main clinical  
194 outcome (all-cause death) with a nested frailty model to take into account the two hierarchical  
195 levels of clustering (matched pairs nested within hospitals).

196

197 Health care utilization (number of hospitalization stays, days, and costs) were assessed as  
198 count variables, and were evaluated at different time points  $t$ . The rate of health care  
199 utilization per patient-year was the total number of health care utilization in each procedure  
200 group divided by the total follow-up duration (date of the procedure until the date of death or

201 end of the study period) of all patients in that group between time 0 and time  $t$ . The  
202 consequent rate ratio (RR) comparing TAVI to SAVR was estimated using Generalized  
203 Estimating Equations (GEE) with a log link, a Poisson distribution, and the log of the follow-  
204 up time as an offset. Robust standard errors were estimated using an independent or  
205 exchangeable working correlation structure and clustering on matched-pairs to account for  
206 over dispersion (dependency within matched pairs and within patients experiencing repeated  
207 events). A sensitivity analysis was performed for the main economic outcome (costs) with a  
208 multilevel Poisson regression model to take into account the two hierarchical levels of  
209 clustering (matched pairs nested within hospitals). Mean cumulative numbers of health care  
210 utilization per person at time  $t$  were estimated by multiplying the predicted rate by  $t$ .  
211 Sensitivity analyses were performed with a Negative Binomial distribution for all economic  
212 outcomes and with a Gamma distribution for costs, providing rate ratio estimations.

213

214 Data manipulation and analyses were performed using SAS (version 9.4; SAS Institute Inc.,  
215 Cary, NC) and R (version 3.3.2; R Core Team) softwares.

216

### 217 **Ethics approval:**

218 This study was strictly observational and we used anonymous data retrospectively. Therefore,  
219 in accordance to the French regulation on “non-interventional clinical research”, the written  
220 informed consent from the participants or the authorization from an ethical committee was not  
221 required.

222

223

### 224 **Results**

225

226 **Participants/descriptive data**

227 During Year 2010, 1334 patients underwent TAVI and 6,695 patients underwent SAVR at 27  
228 French hospitals. After applying the selection and matching criteria, 799 pairs of patients were  
229 retained in final analysis (Supplemental 1). Cohorts' baseline characteristics are listed in  
230 Table 1 with negligible difference between those (evolution pre and post-matching is  
231 presented in the Supplemental 2), and distribution of the propensity scores pre and post-  
232 matching are represented in the Supplemental 5.

233

234 **Short-term clinical outcomes**

235 The risk of hospital death from any cause at 30 days, 6 months, and 1 year was respectively  
236 7.5%, 12.7%, and 16.8% in the TAVI group, and 6.6%, 10.0%, and 12.8% in the SAVR  
237 group, and was not different between both groups at 30 days and 6 months (respectively HR  
238 1.15, 95%CI 0.79-1.68; 1.29, 95%CI 0.96-1.73) but was higher after TAVI at 1 year (HR  
239 1.33, 95%CI 1.02-1.72).

240 At 1 year, there was no significant difference in the occurrence of reoperation (1.9% with  
241 TAVI vs. 0.9% with SAVR) or myocardial infarction (0.6% with TAVI vs. 0.1% with  
242 SAVR), but the risk of stroke was higher after TAVI (2.4% vs. 0.9% respectively; HR 2.73,  
243 95%CI 1.14-6.53) as was the risk of new pacemaker implantation (14.5% vs. 4.9%  
244 respectively; HR 3.19, 95%CI 2.23-4.56).

245

246 **Long-term clinical outcomes**

247 The cumulative probabilities and HR of each clinical outcome from 1 to 5 years are presented  
248 in Table 2, accompanied with the cumulative probability curves for death (Central figure) and  
249 for the other clinical outcomes (Supplemental 6).

250 A higher risk of death was observed 2 years after TAVI compared to SAVR (24.2% vs. 16.8%  
251 respectively; HR 1.47, 95%CI 1.17-1.84) and sustained up to 5 years (52.4% vs. 37.3%  
252 respectively; HR 1.56, 95%CI 1.33-1.84).

253 At 5 years, there was a trend toward a higher risk of reoperation after TAVI compared to  
254 SAVR (2.3% vs. 1.1%: HR 2.01, 95%CI 0.90-4.50), while the risk of stroke significantly  
255 increased (6.9% vs. 4.3% respectively; HR 1.64, 95%CI 1.07-2.54), as was myocardial  
256 infarction (3.1% vs. 1.4% respectively; HR 2.30, 95%CI 1.12-4.69), or new pacemaker  
257 implantation (20.4% vs. 9.3% respectively; HR 2.40, 95%CI 1.81-3.17).

258

### 259 **Hospitalization data and cost evaluation**

260 Hospitalization data and cost evaluation up to 5 years after the procedure are presented in  
261 Table 3 and figure 1. At 1 year, the mean cumulative hospitalization costs per patient were  
262 €42,238 after TAVI and €35,128 after SAVR (RR 1.20, 95%CI 1.13-1.28). The increased cost  
263 with TAVI was mainly attributed to the procedure performed during the index stay and was  
264 sustained up to 5 years (€69,083 vs. €55,687 respectively; RR 1.24, 95%CI 1.13-1.36). The  
265 mean cumulative numbers of hospitalization stays and of days of hospitalization per patient  
266 were similar at any time in both groups, except for the mean cumulative number of days of  
267 hospitalization at 1 year which was lower after TAVI (RR 0.86, 95%CI 0.79-0.94).

268

### 269 **Sensitivity analysis for the main outcomes**

270 Matching with replacement resulted in 1089 matched-pairs of TAVI and SAVR and the same  
271 trends for all-cause death and costs, although effects were attenuated and results at 1 year up  
272 to 3 years became non-significant (Supplemental 7).

273 In the cohort matched without replacement, the nested frailty model for all-cause death  
274 resulted in very similar effects (Supplemental 8), whereas the multilevel Poisson regression  
275 for costs did not converge.

276

277

## 278 **Discussion**

### 279 **Principal findings**

280 We have used real-world data from a nationwide database including 100% of the cases during  
281 the considered period to compare the long-term clinical outcomes between TAVI and SAVR  
282 in two propensity score matched cohorts of patients. Our findings showed an increased risk of  
283 death after TAVI at 1 year that increased up to 50% at 5 years. There were also a much higher  
284 risk of stroke, myocardial infarction and pacemaker implantation after TAVI with higher  
285 cumulated costs relating with the index hospitalisation stay.

286

### 287 **Comparison with other studies**

288 The entire TAVI population (n=1274) that we identified from the database was also part of  
289 the *France 2* French registry that enrolled 3195 high-risk patients (mean Logistic Euroscore  
290 21% / 74% with a Logistic Euroscore  $\geq$  20%) between January 2010 and October 2011.<sup>3</sup>

291 While the entire SAVR population had a lower risk compared to the entire TAVI population,  
292 we selected a cohort of patients with much higher risk profile within the entire SAVR  
293 population. Hence, we assume that matching between these populations allowed us to  
294 compare similar cohorts of high-risk patients.

295 Our survival estimates are supported by a longer follow up and larger study sample than  
296 previous publications comparing the two procedures (Table 4). Among RCTs that included  
297 high-risk patients (Logistic Euroscore 18%-29%), there was no significant difference on the

298 risk of death at three years<sup>12</sup> and five years.<sup>13</sup> The results from our study in high-risk patients  
299 contrast greatly with those reported in these two RCTs. While our study outcomes after TAVI  
300 were comparable to those in the US COREVALVE RCT, the survival after SAVR was far  
301 better compared to US COREVALVE. Among the four published propensity-score  
302 matching (PSM) cohort analyses that selected high-risk patients, two studies<sup>10, 14</sup> showed no  
303 difference in mortality after 1 year while two other studies reported a greater mortality with  
304 TAVI from the first year and up to two<sup>15</sup> or four<sup>16</sup> years of follow-up. This increase in  
305 mortality with TAVI compared to SAVR is consistent with our findings and has been recently  
306 emphasized in a meta-analysis of studies that used PSM.<sup>8</sup>

307 The magnitude of the mortality-increase after TAVI compared to SAVR raises the question  
308 on the comparability of TAVI and SAVR cohorts matched using PSM and will be further  
309 discussed. However, we believe that the systematic presence of unidentified confounders  
310 within healthcare databases used across different country settings is unlikely.

311

312 Although our study did only include high-risk patients, we also examined the published  
313 outcomes after TAVI or SAVR in people with intermediate-risk patients (Table 4) owing to  
314 the increase used of TAVI in this population.

315 Three RCTs that included people with a lower surgical risk reported a similar risk of mortality  
316 but to date the follow-up is limited to a maximum of two-years.<sup>5, 17-19</sup> Two other studies using  
317 PSM in people with similar risk-profile showed a higher risk of death after TAVI at 3 years.<sup>9</sup>  
318 <sup>20</sup>Conversely, Thourani et al.<sup>21</sup> reported a reduced mortality after TAVI at 1 year but these  
319 latter results are however subject to caution given the presence of several major  
320 methodological flaws pertaining to the covariates that were included in the propensity score  
321 model.<sup>22</sup>

322



323 We have observed an increased risk of stroke at five years with TAVI compared to SAVR.  
324 We cannot provide interpretation of these findings based on data pertaining to onset of post-  
325 procedural atrial fibrillation or use of anticoagulation regimen at follow-up. One might  
326 speculate that TAVI patients mostly received dual antiplatelet therapy with clopidogrel and  
327 aspirin while SAVR patients received mostly VKA or just aspirin for three months. However,  
328 in the absence of formal recommendations on anticoagulation management, we believe there  
329 are lots of variations across centers.

330

331 Our study provides further information on hospital resource consumption between TAVI and  
332 SAVR. The cumulative costs were higher after TAVI while there were no differences at 5  
333 years regarding the number of stays or days consumed at hospital. Furthermore, the lower  
334 number of hospitalisations contrasts with the higher total costs at 1 year post-TAVI compared  
335 to SAVR, which can be explained by the cost of TAVI device during the index stay. Although  
336 our study was not designed as a cost-effectiveness evaluation, our results showing a reduced  
337 survival and higher costs with TAVI suggest that TAVI would be dominated by SAVR.

338

### 339 **Limitations**

340 Our study carries several limitations. We identified two cohorts of patients from the French  
341 PMSI database, which is increasingly used in health service research given the exhaustive  
342 collection of medical information at the whole country population.<sup>23,24</sup> To control for the  
343 non-random assignment of patients between TAVI and SAVR procedures, we used  
344 propensity-score-matching-adjustment based on a high number of patient characteristics and  
345 with control for confounders at hospital level. The risk of bias with PSM studies is to omit  
346 some potential confounders that can alter the comparability of populations and therefore  
347 threaten the validity of outcome measures.<sup>25</sup> The PMSI database does not enable to precisely

348 calculate the Euroscore because the clinical variables that are available are not strictly those  
349 listed or are not as accurately defined among the factors that are accounted for in the  
350 Euroscore calculation. Because data granularity did not allow us to accurately describe every  
351 patients profile with respect to the surgical risk, we added the number of hospitalization days  
352 in acute care consumed the year preceding the index stay to account for unmeasured  
353 confounders. Among variables available within the PMSI database, we chose in our  
354 propensity-score based method those with the most clinical relevance to discriminate the  
355 mortality/morbidity risk of populations but also accounting for those with a sufficient degree  
356 of validity. We are aware that the PMSI database variables may also lack of granularity to  
357 account for factors such as patient frailty or the complexity of the procedure.

358 A weakness of large hospital databases is the miscoding of diagnoses during hospital stays  
359 that can underestimate patient's comorbidities.<sup>26</sup> This issue is not specific to a disease area or  
360 to certain type of procedure and is more influenced by a strong coding variability between  
361 healthcare providers and across years. Given this, we matched pairs of patients who  
362 underwent either TAVI or SAVR inside the same hospital and over the same period. Hence,  
363 we believe there is no a priori reason that miscoding would be more prominent in one cohort  
364 than another and would alter their comparability. Another limitation relates to our inability to  
365 capture deaths occurring outside hospital, which means that the mortality rates might be  
366 slightly underestimated. However the rate of death occurring outside hospitals is today  
367 extremely rare and probably negligible. There might also have been an underreporting of  
368 adverse events as suggested by the low incidence of stroke, myocardial infarction, or  
369 permanent pacemaker implantation observed in this study. Again, this issue is not specific to  
370 certain procedure type and we assume that the relative occurrence of these events between  
371 TAVI and SAVI was adequately estimated. Finally, the selected cohorts were treated during  
372 Year 2010, that is seven years ago, and may therefore be less representative of contemporary

373 practices and outcomes related to TAVI in French centers since patients characteristics,  
374 devices, and experience of centers have surely evolved in recent years. However, this choice  
375 enabled to provide the longest ever reported follow-up of TAVI patients based on real-world  
376 data.

377

### 378 **Practical implications**

379 The 2017 guidelines from the European Society of Cardiology (ESC)<sup>27</sup> have considered  
380 TAVI in patients who are suitable for SAVR as assessed by the Heart Team but also an  
381 alternative to surgery in people who are at increased surgical risk, the decision being made by  
382 the heart team according to each patient characteristics. Accounting for the results of the  
383 Partner 2 trial,<sup>5</sup> the AHA/ACC recently updated guidelines have extended the indication of  
384 TAVI to intermediate surgical risk depending on patient-specific procedural risks, values, and  
385 preferences.<sup>28</sup> Based on these updated guidelines, the trend toward an enlarged use of TAVI  
386 to lower surgical risk patients is likely to get amplified to a great extent. As previously  
387 emphasized, the results from Partner 2 that suggest the non-inferiority of TAVI and SAVR in  
388 intermediate-risk patients are only available at two years which is notably insufficient to  
389 evaluate the long-term effectiveness of TAVI compared to SAVR for which the outcomes is  
390 demonstrated beyond twenty years. Moreover, the results from Partner 2<sup>5</sup>, along with those of  
391 Partner-high risk<sup>13</sup>, may be not representative of real-world clinical outcomes. Our results  
392 showed an increased risk of mortality for TAVI compared to SAVR using a large nationwide  
393 database providing real-word evidence over a long-term perspective. The implication of our  
394 findings is that the extension of TAVI in patients other than those with high or prohibitive-  
395 surgical risk should be cautious until further data, either based on RCTs or real-world  
396 evidence, are made available to inform on the relative long-term effectiveness of TAVI  
397 compared to SAVR.

398

399

400 **Conclusions**

401 Our study showed that patients after TAVI, compared to those who underwent SAVR, harbor  
402 a greater risk of mortality and morbidity at 5 years, and had higher costs of hospitalizations.

403 These results indicate that more data are needed before considering an enlargement of TAVI

404 indications in people eligible to conventional surgery.

405

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503 **Figure legend:**

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505 **Figure 1: Mean Cumulative costs over time**

506 TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement.

507 Predictions from GEE Poisson regression model.

508

509 **Supplementary material**

510

511 **Supplementary material 1: Study flowchart**

512

513 **Supplementary material 2: Baseline characteristics of patients before and after**  
514 **matching**

515

516 **Supplementary material 3: Cumulative probability of all-cause in-hospital mortality**

517

518 **Supplementary material 4: Mean cumulative costs per person**

519

520 **Supplementary material 5 – Propensity scores distribution before (left) and after (right)**  
521 **matching**

522

523 **Supplementary material 6 – Cumulative incidence curves (cumulative probability of**  
524 **events)**

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526 **Supplementary material 7 - Sensitivity analysis (Matching with replacement)**

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528 **Supplementary material 8 - Sensitivity analysis (Multilevel modelling for the outcomes)**

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**Table 1- Baseline characteristics of patients post-matching**

	<b>TAVI (n=799)</b>	<b>SAVR (n=799)</b>	<b>Standardized differences</b>
Male sex	427 (53.4%)	434 (54.3%)	-0.018
Age, years	81 [76 – 85]	81 [77 – 85]	0.002
Income, euros	19659 [18285 – 21971]	19734 [18395 – 22073]	-0.060
Days of hospitalization in the previous year	11 [4 – 23]	10 [4 – 24]	-0.006
Emergency procedure	13 (1.6%)	13 (1.6%)	0.000
Congestive heart failure	284 (35.5%)	278 (34.8%)	0.016
Cardiac arrhythmias	420 (52.6%)	427 (53.4%)	-0.018
Pulmonary circulation disorders	63 (7.9%)	76 (9.5%)	-0.058
Peripheral vascular disease	90 (11.3%)	93 (11.6%)	-0.012
Hypertension	350 (43.8%)	338 (42.3%)	0.030
Chronic pulmonary disease	89 (11.1%)	88 (11.0%)	0.004
Diabetes	155 (19.4%)	176 (22.0%)	-0.065
Renal disease	122 (15.3%)	119 (14.9%)	0.010
Liver disease	23 (2.9%)	21 (2.6%)	0.015
Obesity	71 (8.9%)	62 (7.8%)	0.041
Myocardial infarction	52 (6.5%)	44 (5.5%)	0.042
Cerebrovascular disease	69 (8.6%)	79 (9.9%)	-0.043

Values are number (%) or median [interquartile range].

TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement.

**Table 2- Compared clinical outcomes between TAVI and SAVR cohorts**

Time t	TAVI (n=799)		SAVR (n=799)		HR <sup>b</sup> [CI 95%]	p-value <sup>b</sup>
	N events	% [95% CI] <sup>a</sup>	N events	% [95% CI] <sup>a</sup>		
<b>All-cause death</b>						
At 1 year	127	16.8 [14.3 – 19.6]	97	12.8 [10.6 – 15.4]	1.33 [1.02 – 1.72]	0.033
At 2 years	177	24.2 [21.2 – 27.5]	124	16.8 [14.3 – 19.7]	1.47 [1.17 – 1.84]	0.001
At 3 years	235	33.7 [30.3 – 37.4]	163	23.1 [20.1 – 26.4]	1.52 [1.25 – 1.85]	<0.001
At 4 years	286	42.8 [39.0 – 46.7]	196	29.0 [25.6 – 32.6]	1.58 [1.32 – 1.89]	<0.001
At 5 years	332	52.4 [48.4 – 56.5]	236	37.3 [33.5 – 41.4]	1.56 [1.33 – 1.84]	<0.001
<b>Postoperative stay in ICU/CCU</b>						
At 1 year	296	37.0 [33.7 – 40.4]	537	67.2 [63.8 – 70.3]	0.48 [0.43 – 0.55]	<0.001
At 2 years	313	39.2 [35.8 – 42.5]	540	67.6 [64.2 – 70.7]	0.50 [0.45 – 0.57]	<0.001
At 3 years	326	40.8 [37.4 – 44.2]	548	68.6 [65.2 – 71.7]	0.51 [0.46 – 0.57]	<0.001
At 4 years	334	41.8 [38.4 – 45.2]	550	68.8 [65.5 – 71.9]	0.52 [0.46 – 0.58]	<0.001
At 5 years	340	42.6 [39.1 – 45.9]	556	69.6 [66.3 – 72.6]	0.52 [0.46 – 0.58]	<0.001
<b>Reoperation</b>						
At 1 year	15	1.9 [1.1 – 3.0]	7	0.9 [0.4 – 1.7]	2.15 [0.87 – 5.30]	0.097
At 2 years	16	2.0 [1.2 – 3.2]	7	0.9 [0.4 – 1.7]	2.29 [0.94 – 5.60]	0.069
At 3 years	16	2.0 [1.2 – 3.2]	8	1.0 [0.5 – 1.9]	2.01 [0.85 – 4.71]	0.110
At 4 years	17	2.1 [1.3 – 3.3]	9	1.1 [0.6 – 2.1]	1.90 [0.84 – 4.28]	0.123
At 5 years	18	2.3 [1.4 – 3.5]	9	1.1 [0.6 – 2.1]	2.01 [0.90 – 4.50]	0.090
<b>Stroke</b>						
At 1 year	19	2.4 [1.5 – 3.6]	7	0.9 [0.4 – 1.7]	2.73 [1.14 – 6.53]	0.024
At 2 years	26	3.3 [2.2 – 4.7]	16	2.0 [1.2 – 3.2]	1.64 [0.87 – 3.08]	0.124
At 3 years	40	5.0 [3.6 – 6.7]	23	2.9 [1.9 – 4.2]	1.76 [1.05 – 2.94]	0.031
At 4 years	47	5.9 [4.4 – 7.7]	27	3.4 [2.3 – 4.8]	1.76 [1.10 – 2.84]	0.020
At 5 years	55	6.9 [5.3 – 8.8]	34	4.3 [3.0 – 5.8]	1.64 [1.07 – 2.54]	0.025
<b>Myocardial infarction</b>						
At 1 year	5	0.6 [0.2 – 1.4]	1	0.1 [0.0 – 0.7]	5.01 [0.58 – 42.94]	0.142
At 2 years	13	1.6 [0.9 – 2.7]	4	0.5 [0.2 – 1.2]	3.27 [1.06 – 10.06]	0.039
At 3 years	17	2.1 [1.3 – 3.3]	6	0.8 [0.3 – 1.6]	2.86 [1.12 – 7.27]	0.028
At 4 years	19	2.4 [1.5 – 3.6]	8	1.0 [0.5 – 1.9]	2.39 [1.04 – 5.50]	0.039
At 5 years	25	3.1 [2.1 – 4.5]	11	1.4 [0.7 – 2.4]	2.30 [1.12 – 4.69]	0.023
<b>Pacemaker</b>						
At 1 year	116	14.5 [12.2 – 17.1]	39	4.9 [3.5 – 6.5]	3.19 [2.23 – 4.56]	<0.001

At 2 years	125	15.6 [13.2 – 18.3]	48	6.0 [4.5 – 7.8]	2.80 [2.01 – 3.91]	<0.001
At 3 years	137	17.1 [14.6 – 19.8]	60	7.5 [5.8 – 9.5]	2.47 [1.82 – 3.35]	<0.001
At 4 years	156	19.5 [16.9 – 22.3]	70	8.8 [6.9 – 10.9]	2.42 [1.82 – 3.22]	<0.001
At 5 years	163	20.4 [17.7 – 23.3]	74	9.3 [7.4 – 11.4]	2.40 [1.81 – 3.17]	<0.001

TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement

a Cumulative probability of event [95% CI] at time t from the nonparametric (1 - Kaplan-Meier) estimator for all-cause death; and from the nonparametric Cumulative Incidence Functions estimator using competing risk of death for the other outcomes.

b Hazard Ratios (instantaneous rate of event for TAVI relative to SAVR at any time t) [95% CI] and p-value, estimated between time 0 and time t, from Cox proportional hazards model for all-cause death; and from Fine and Gray's competing risk model for the other outcomes. Matched-pairs design was taken into account with robust variance estimator.

**Table 3- Compared health care utilization outcomes between TAVI and SAVR cohorts**

Time t	TAVI (n=799)			SAVR (n=799)			Rate Ratio [95% CI] <sup>a</sup>	p-value <sup>a</sup>
	Total number of health care utilization	Total follow- up (PY)	Mean cumulative number per person <sup>a</sup>	Total number of health care utilization	Total follow-up (PY)	Mean cumulative number per person <sup>a</sup>		
<b>Number of hospitalization stays</b>								
At 1 year	3184	703.61	4.51	3719	724.11	5.10	0.88 [0.72 – 1.09]	0.255
At 2 years	4374	1349.18	6.46	5478	1411.32	7.71	0.84 [0.64 – 1.10]	0.200
At 3 years	5526	1946.03	8.50	7222	2069.87	10.42	0.82 [0.60 – 1.11]	0.192
At 4 years	6843	2480.04	11.02	8641	2689.18	12.81	0.86 [0.61 – 1.20]	0.381
At 5 years	7769	2969.54	13.07	10097	3272.01	15.39	0.85 [0.60 – 1.21]	0.368
<b>Number of days of hospitalization</b>								
At 1 year	35809	703.61	50.04	43040	724.11	58.16	0.86 [0.79 – 0.94]	0.001
At 2 years	45028	1349.18	65.05	51836	1411.32	71.20	0.91 [0.83 – 1.01]	0.071
At 3 years	53527	1946.03	80.36	61474	2069.87	86.17	0.93 [0.84 – 1.03]	0.177
At 4 years	61887	2480.04	97.23	70014	2689.18	100.72	0.97 [0.87 – 1.07]	0.514
At 5 years	68434	2969.54	112.02	79378	3272.01	116.93	0.96 [0.86 – 1.07]	0.432
<b>Costs</b>								
At 1 year	30774212	703.61	42238	26604033	724.11	35128	1.20 [1.13 – 1.28]	<0.001
At 2 years	35123650	1349.18	49330	30183988	1411.32	39917	1.24 [1.15 – 1.33]	<0.001
At 3 years	39051054	1946.03	56102	34014554	2069.87	45031	1.25 [1.15 – 1.35]	<0.001
At 4 years	42295035	2480.04	62992	37295324	2689.18	50107	1.26 [1.15 – 1.37]	<0.001
At 5 years	44889719	2969.54	69083	40860170	3272.01	55687	1.24 [1.13 – 1.36]	<0.001

TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement; PY=Person-year.<sup>a</sup>From GEE Poisson regression model.

**Table 4- Summary of studies identified in our literature search**

Author/study name	Inclusion period	Country	Centers	Sample size	Method of comparison	STS (%)	Logistic Euroscore I (%)	All cause death													
								1 year		2 years		3 years		4 years		5 years					
								TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR				
<b>High-risk patients</b>																					
Partner I <sup>13,29,30</sup>	2007-2009	>USA	25	348/351	RCT	11.8/11.7	29.3/29.2	24.2% p=0.44	26.8%	33.9%	35.0% p=0.78	/	/	67.8%	62.4% p=0.76						
US Corevalve <sup>7,12,31</sup>	2011-2012	USA	45	391/359		7.3/7.5	17.6/18.4	14.2% p=0.04	19.1%	22.2%	28.6% p=0.04	32.9%	39.1% p=0.068	/	/						
Latib et al. <sup>14</sup>	2003-2008 + 2007-2011	Italy	1	111/111	PSM	4.6/4.6	23.2/24.4	6.4% p=0.80	8.1%	/	/	/	/	/	/						
Piazza et al. <sup>10</sup>	2006-2010	3 in EU	3	405/405		/	17.1/17.5	17.5% ** p=0.93	16.5% *	/	/	/	/	/	/						
Johansson et al. <sup>16</sup>	1999-2014	Sweden	1	166/125		/	23/20	19.5% p=0.001	10.4%	/	/	48.2%	27% p=0.001	/	/						
Muneretto et al. <sup>15</sup>	2007-2014	EU	7	204/204		8.2/8.4	19.5/19.2	9.9% p<0.001	3.3%	20.5%	8.7% p<0.001	/	/	/	/						
Our study	2010	France	27 (nationwide)	832/832		/	/	15.7% p=0.326	13.8%	22.8%	17.4% p=0.021	32.5%	22.3% p<0.001	42.0%	29.5% p<0.001	51.5%	36.2% p<0.001				

Intermediate-risk patients															
Notion <sup>17 18</sup>	2009-2013	Denmark	3	145/135	RCT	2.9/3.1	8.4/8.9	4.9% p=0.38	7.5%	8.0% p=0.54	9.8%	/	/	/	
Partner 2 <sup>5</sup>	2011-2013	USA	57	1011/1021		5.8/5.8	/	12.3% p=0.69	12.9%	16.7% p=0.45	18.0%	/	/	/	
Surtavi <sup>19</sup>	2012-2016	USA, Europe, Canada	87	879/867		4.4/4.5	11.9/11.6	6.7% NS	6.8%	12.6% NS	14.0%	/	/	/	
Schymik et al. <sup>9</sup>	2007-2012	Germany	1	216/216	PSM	/	8.7/8.8	11.6% p=0.157*	7.4%	17.1% p=0.157*	9.7%	19.9% p=0.157*	14.3%	/	/
Rosato et al. <sup>20</sup>	2010-2012	Italy	93 (nationwide)	355/355		/	6.3/6.3	11.4% p=0.0075*	7.8%	19.6% p=0.0075*	12.8%	28.0% p=0.0075*	16.6%	/	/
Thourani et al. <sup>21</sup>	2011- 2013 + 2014	USA, Canada	51 + 57	1077/944	PSS	5.2/5.4	/	7.4% p=0.0003	13.0%	/	/	/	/	/	

TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement; RCT = randomized controlled trial; PSM = Propensity-Score Matching; PSS =

Propensity-Score Stratification. \* calculated over the 3 year period \*\* estimated from the number of deaths stated in the manuscript (71 in TAVI, 67 in SAVR)