

Valve-in-valve transcatheter aortic valve implantation after failed surgically implanted aortic bioprosthesis versus native transcatheter aortic valve implantation for aortic stenosis: Data from a nationwide analysis Pierre Deharo, Arnaud Bisson, Julien Herbert, Thibaud Lacour, Christophe Saint Etienne, Nicolas Jaussaud, Alexis Theron, Frederic Collart, Thierry

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Valve-in-valve transcatheter aortic valve implantation after failed surgically implanted aortic bioprosthesis versus native transcatheter aortic valve implantation for aortic stenosis: Data from a nationwide analysis

Abbreviated title: Valve-in-valve versus native TAVI

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Summary

Background. – Valve-in-valve transcatheter aortic valve implantation (TAVI) has emerged as a treatment for aortic bioprosthesis failure in case of prohibitive risk for redo surgery. However, clinical evaluation of valve-in-valve TAVI remains limited by the number of patients analysed. *Aim.* – To evaluate outcomes of valve-in-valve TAVI compared with native aortic valve TAVI at a nationwide level in France.

Methods. – Based on the French administrative hospital discharge database, the study collected information for all consecutive patients treated with TAVI for aortic stenosis or with isolated valve-invalve TAVI for aortic bioprosthesis failure between 2010 and 2019. Propensity score matching was used for the analysis of outcomes.

Results. – A total of 44,218 patients were found in the database. After matching on baseline characteristics, 2749 patients were analysed in each arm. At 30 days, no significant differences were observed regarding the occurrence of major clinical events (composite of cardiovascular mortality, all-cause stroke, myocardial infarction, major or life-threatening bleeding and conversion to open heart surgery) (odds ratio [OR] 0.83, 95% confidence interval [CI] 0.68–1.01; P = 0.32). During follow-up (mean 516 days), the combined endpoint of cardiovascular death, all-cause stroke or rehospitalization for heart failure was not different between the valve-in-valve TAVI and native TAVI groups (RR 1.03, 95% CI 0.94–1.13; P = 1.00).

Conclusion. – We observed that valve-in-valve TAVI was associated with good short- and long-term outcomes. No significant differences were observed compared with native valve TAVI regarding clinical follow-up.

Résumé

Contexte. – L'implantation d'un TAVI (transcatheter aortic valve implantation) valve-in-valve (VIV) est apparue comme une alternative a une nouvelle chirurgie pour le traitement des dégénérescences de bioprothèse aortique. Cependant, l'évaluation clinique de la procédure de VIV TAVI reste limitée par le nombre de patients analysés.

Objectif. – Évaluer les résultats des procédures de VIV TAVI en comparaison au TAVI sur valve aortique native à l'échelle nationale.

Méthodes. - Basée sur la base de données administrative française PMSI, l'étude a collecté des

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informations pour tous les patients consécutifs traités par TAVI pour sténose aortique ou avec un VIV TAVI entre 2010 et 2019. Une analyse avec score de propension a été utilisée pour l'analyse des résultats.

Résultats. – Un total de 44,218 patients ont été identifiés dans la base de données. Après appariement sur les caractéristiques cliniques de base, 2749 patients ont été analysés dans chaque bras. À 30 jours, aucune différence significative n'a été observée en ce qui concerne la survenue d'événements cliniques majeurs (composite de mortalité cardiovasculaire, accident vasculaire cérébral toutes causes, infarctus du myocarde, saignement majeur et conversion chirurgicale) (OR 0,83, IC95 % 0,68–1,01 ; P = 0,32). Au cours du suivi (moyenne 516 jours), le critère d'évaluation combiné de décès cardiovasculaire, AVC toutes causes confondues ou réhospitalisation pour insuffisance cardiaque n'était pas différent entre le VIV TAVI et le groupe TAVI natif (RR 1,03, IC95 % 0,94–1,13 ; P = 1,00).

Conclusion. – Nous avons observé que les procédures de VIV TAVI étaient associées à de bons résultats à court et à long terme. Aucune différence significative n'a été observée par rapport au TAVI pour sténose aortique native concernant le suivi clinique.

KEYWORDS

Valve-in-valve; TAVI; Aortic bioprosthesis

MOTS CLÉS

Valve-in-valve ; TAVI ;

Bioprosthèse aortique

Abbreviations: CCAM, Classification Commune des Actes Medicaux; CI, confidence interval; ICD-10, International Classification of Diseases, Tenth Revision; OR, odds ratio; PMSI, Programme de Médicalisation des Systèmes d'Information; RR, relative risk; SD, standard deviation; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; VIV, valve-in-valve.

Background

Worldwide, bioprosthetic aortic surgical valves are increasingly favoured over mechanical prostheses. However, bioprosthesis durability is limited over time, with a risk of structural valve degeneration, represented by restenosis or regurgitation or both, within 10–20 years [1-3]. In these patients, according to European Society of Cardiology guidelines, the treatment of choice is a redo surgical aortic valve replacement (SAVR) [4]. However, compared with primary aortic valve replacement, this procedure is associated with higher morbidity and mortality, mostly resulting from the technical aspects of redo surgery, advanced age and associated co-morbidities [5, 6].

Transcatheter aortic valve implantation (TAVI) has emerged as the recommended treatment for severe native aortic stenosis in patients at high surgical risk [4, 7]. Recent data have also shown that TAVI is non-inferior to surgery in low- and intermediate-risk patients [8, 9]. Improvement of this technique has offered an alternative strategy for treating degenerated surgical aortic bioprosthetic valves. Valve-in-valve (VIV) TAVI has proved to be a technically feasible option in most cases, and is associated with reasonable outcomes in these patients. Therefore, the frequency of VIV TAVI procedures has increased in recent years, and is expected to continue to grow.

The French Programme de Médicalisation des Systèmes d'Information (PMSI), a mandatory administrative database, offers a unique opportunity to assess exhaustive and comprehensive data on all consecutive TAVI procedures performed in France. Therefore, based on this large nationwide administrative French database, we aimed to compare long-term outcomes of VIV TAVI versus native aortic valve TAVI.

Methods

Study design

This longitudinal cohort study was based on the national hospitalization database covering hospital care for the entire French population. The data for all patients admitted with aortic stenosis in France from January 2010 to June 2019 were collected from the national administrative PMSI database, which was inspired by the Medicare system in the USA. Through this programme, which was implemented in 2004, medical activity is recorded in a database, computed and rendered anonymous; it includes > 98% of the French population (67 million people) from birth (or immigration) to death (or emigration), even if a person changes occupation or retires. This process allows the determination of

each hospital's budget in the 1546 French healthcare facilities, for both public and private hospitals. Each hospitalization is encoded in a standardized dataset, which includes information about the patient (age and sex), hospital, stay (date of admission, date of discharge and mode of discharge), pathologies and procedures. Medical information collected routinely includes the principal diagnosis and secondary diagnoses. In the PMSI system, identified diagnoses are coded according to the International Classification of Diseases, Tenth Revision (ICD-10). All medical procedures are recorded according to the national nomenclature, Classification Commune des Actes Medicaux (CCAM). The PMSI contains individual pseudoanonymized information on each hospitalization, which is linked to create a longitudinal record of hospital stays and diagnoses for each patient. The reliability of PMSI data has already been assessed, and this database has previously been used to study patients with cardiovascular conditions, including those with aortic stenosis treated with TAVI [10-12].

The study was conducted retrospectively and, as patients were not involved in its conduct, there was no impact on their care. Ethical approval was not required, as all data were anonymized. The French Data Protection Authority granted access to the PMSI data. Procedures for data collection and management were approved by the Commission Nationale de l'Informatique et des Libertés (CNIL), and the independent National Ethical Committee protecting human rights in France, which ensures that all information is kept confidential and anonymous, in compliance with the Declaration of Helsinki (authorization number 1897139).

Study population

From 01 January 2010 to 30 June 2019, 520,662 adults (aged \geq 18 years) were hospitalized with a diagnosis of aortic stenosis (ICD-10 codes I350, I352, I060 and I062) as the principal diagnosis (i.e. the health problem that justified admission to hospital), the related diagnosis (i.e. potential chronic disease or health state during the hospital stay) or a significantly associated diagnosis (i.e. co-morbidity or associated complication). For the analysis of TAVI procedures, we included all adults with a single percutaneous procedure (CCAM code: DBLF001). Patients with TAVI procedures performed using a transapical access were not included in the analysis. A total of 2896 patients were identified as having a history of surgically implanted aortic bioprosthesis needing reintervention with TAVI. Patient information (demographics, co-morbidities, medical history and events during hospitalization or follow-up) was described using data collected in the hospital records. For each hospital stay, combined

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diagnoses at discharge were obtained. Each variable was identified using ICD-10 codes. We also used the Charlson Comorbidity Index and the Claims-based Frailty Indicator to assess patient clinical status [13-15]. The exclusion criterion was age < 18 years.

Outcomes

Patients were followed until 30 June 2019 for the occurrence of outcomes. We aimed to evaluate the incidence of all-cause death, cardiovascular death, all-cause stroke, rehospitalization for heart failure, myocardial infarction, major or life-threatening bleeding, new onset of atrial fibrillation and pacemaker implantation. Definitions of relevant events reflected several of those included in the Valve Academic Research Consortium-2 consensus document [16]. To increase validation of our analysis, we also evaluated incidence rates of non-cardiovascular death, cancer and urinary infection as negative control endpoints. The endpoints were evaluated with follow-up starting from the date of either VIV TAVI or native TAVI until the date of each specific outcome or the date of the last news in the absence of outcome. Information on outcomes during follow-up was obtained by analysing the PMSI codes for each patient. All-cause death, heart failure, all-cause stroke, myocardial infarction, major or lifethreatening bleeding, new onset of atrial fibrillation and permanent pacemaker implantations were identified using their respective ICD-10 or procedure codes. Mode of death (cardiovascular or noncardiovascular) was identified based on the main diagnosis during hospitalization resulting in death. Rehospitalization was considered to be the result of heart failure when heart failure was recorded as the first diagnosis. We also evaluated 30-day major clinical events in our analysis, which was a combination of cardiovascular mortality, all-cause stroke, myocardial infarction, major or lifethreatening bleeding and conversion to open heart surgery. A combined endpoint (cardiovascular death, all-cause stroke and rehospitalization for heart failure) was evaluated for long-term follow-up.

Statistical analysis

Qualitative variables are described as frequencies and percentages, and quantitative variables as means ± standard deviations (SDs). Comparisons were made using χ^2 tests for categorical variables and Student's *t* test or the non-parametric Kruskal-Wallis test, as appropriate, for continuous variables.

Owing to the non-randomized nature of the study, and considering significant differences in baseline characteristics and year of implantation, propensity-score matching was used to control for

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potential confounders of the treatment outcome relationship. Propensity scores were calculated using probit regression with treatment (i.e. VIV TAVI or native TAVI) as the dependent variable. The propensity score included all baseline characteristics listed in Table 1. For each patient with VIV TAVI, a propensity score-matched patient with native TAVI was selected (1:1) using the one-to-one nearest neighbour method (with a calliper of 0.01 of the SD of the propensity score on the logit scale) and no replacement. We assessed the distributions of demographic data and co-morbidities in the two cohorts with standardized mean differences, which were calculated as the difference in the means or proportions of a variable divided by a pooled estimate of the SD of that variable. A standardized mean difference of $\leq 5\%$ indicated a negligible difference between the means of the two cohorts.

For the analysis in the matched cohort, we report outcomes at 30 days and during the whole follow-up. A logistic regression model was used for all outcomes at 30 days, and odds ratios (ORs) were reported. The incidence rates (%/year) for each outcome of interest during follow-up was estimated in both groups and compared using incidence rate ratios. The corresponding asymptotic two-sided 95% confidence interval (CI) of the relative risk (RR) was reported. *P* values are reported without and with correction for multiple comparisons using Bonferroni correction. All comparisons with P < 0.05 were considered statistically significant. All analyses were performed using Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA) and STATA version 12.0 (Stata Corp, College Station, TX, USA).

Results

Baseline characteristics

Between 01 January 2010 and 30 June 2019, 44,218 patients were identified in the database, including 2896 patients (6.6%) with VIV TAVI and 41,322 patients with native TAVI (Table 1). In the unmatched population, patients treated with VIV TAVI were older and had a lower Charlson Comorbidity Index and a lower Frailty Index (Table 1); they had experienced acute heart failure, coronary or vascular disease and dilated cardiomyopathy less often than those treated with native TAVI. Patients treated with VIV TAVI also had lower rates of previous pacemaker or defibrillator, chronic kidney disease and chronic lung disease (Table 1).

After propensity score matching, there were 2749 patients in each group. Baseline characteristics in these populations were well matched (Table 2, Fig. A.1 and Fig. A.2).

Clinical outcomes at 30 days

In the matched population, all-cause death was reported in 116 (4.2%) patients who had native TAVI and 87 (3.2%) who had VIV TAVI (OR 0.74, 95% CI 0.56–0.98; Table 3). Cardiovascular death (3.6% vs 2.6%; OR 0.70, 95% CI 0.52–0.96), new onset of atrial fibrillation (0.9% vs 1.0%; OR 1.13, 95% CI 0.65–1.96), all-cause stroke (0.5% vs 0.7%, OR 1.29, 95% CI 0.64–2.59), myocardial infarction (0.3% vs 0.2%; OR 0.55, 95% CI 0.19–1.66), major or life-threatening bleeding (3.6% vs 3.4%; OR 0.95, 95% CI 0.71–1.26) and conversion to open heart surgery (0.2% vs 0.1%; OR 0.40, 95% CI 0.08–2.10) were not different between the two groups. Permanent pacemaker implantation (21.8% vs 17.0%; OR 0.73, 95% CI 0.64–0.84) was significantly less frequent after VIV TAVI.

The composite of major clinical events was observed in 8.5% of patients who had native TAVI and 7.1% of patients who had VIV TAVI (OR 0.83, 95% CI 0.68–1.01).

Long-term outcomes

Mean follow-up was 516 ± 543 days, and median follow-up was 349 (interquartile range 24–834) days. In the matched population, all-cause death was recorded in 1232 patients (14.7% in the native TAVI group versus 13.2% in the VIV TAVI group; Table 4 and Fig. 1). The incidences of cardiovascular death (RR 0.96, 95% CI 0.82–1.14; Table 4 and Fig. 2), all-cause stroke (RR 1.24, 95% CI 0.97–1.58; Table 3) rehospitalization for heart failure (RR 1.02, 95% CI 0.92–1.14; Table 4 and Fig. 3) and new onset of atrial fibrillation (RR 1.08 95% CI 0.89–1.31; Table 4 and Fig. 4) were not statistically different between the two groups (Table 4). The combined endpoint (cardiovascular death, all-cause stroke or rehospitalization for heart failure) was not significantly different between the groups (25.4% vs 26.1%; RR 1.03, 95% CI 0.94–1.13; Table 4 and Fig. 5).

For the negative control analysis, there was no statistical difference between patients who had VIV TAVI or native TAVI in terms of the incidence of cancer, urinary infection or non-cardiovascular death (Table 4).

Discussion

In this propensity score-matched analysis, short-term and long-term outcomes following VIV TAVI were not different compared with native aortic valve TAVI. Only pacemaker implantation was reported

less often in case of VIV TAVI. Our study is, to our knowledge, the largest reporting outcomes with these two therapeutic options in this population of unselected patients seen at a nationwide level.

Bioprosthetic aortic valves are increasingly favoured over mechanical devices for the surgical treatment of severe aortic valve disease. This worldwide trend is mainly driven by the possible avoidance of long-life anticoagulant in case of bioprosthesis (when not needed for other reasons) [17]. However, despite improvements in devices, the risk of structural valve degeneration with the current bioprostheses remains one of the main limitations in the long term [1-3]. Because a redo SAVR procedure carries significant risks, VIV TAVI has emerged as a less invasive option in case of failed surgical bioprosthesis. Initial experience has shown acceptable short-term clinical outcomes as well as satisfying echographic data during follow-up [18-23]. New techniques are being developed to overcome challenges associated with the VIV procedure [24], and will need to be evaluated in the near future. With the increase in operator experience and the development of new and improved devices, the procedure is becoming safer, and its use is expanding to new population groups, offering an alternative to redo SAVR.

Our results showed that, in France, patients who underwent VIV TAVI had fewer co-morbidities than patients treated for native aortic valve disease. However, patients in the VIV TAVI group were older, corresponding to a second cardiac intervention. Overall, patients selected for VIV TAVI were at lower risk than those having native TAVI. Moreover, we observed a trend over time, with more VIV TAVI cases in recent years, reflecting the clinical adoption of VIV TAVI at a nationwide level.

Short-term outcomes (i.e. at 30 days) showed that compared with native TAVI, VIV TAVI was associated with no significant differences in terms of clinical outcomes. Only the need for pacemaker implantation was higher after native TAVI. The rates of events after VIV TAVI are consistent with those seen in registries of selected patients with VIV procedures [18-23]. The short-term mortality rates in the large PARTNER 2 VIV registry, STS/ACC registry and TVT registry were 2.7%, 2.9% and 7.6%, respectively, at 30 days. On the other hand, Tuzcu et al. evaluated VIV TAVI versus native TAVI from the TVT (transcatheter valve therapy) registry, and observed lower 30-day and 1-year mortality rates in 1150 patients who had VIV TAVI compared with in 2259 patients who had native valve TAVI [21]. Overall, in our cohort, the rates of 30-day all-cause and cardiovascular mortality tended to be reported as being lower in the VIV TAVI cohort.

The need for permanent pacemaker implantation is one of the relative Achilles' heels of the TAVI

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procedure. Recent French data showed a rate of new pacemaker implantation of 20–25% after native aortic valve TAVI [11]. Because the surgical bioprosthesis structure protects the conduction system (if not previously injured), VIV procedures may carry a lower risk of mechanical lesions during TAVI [25, 26]. Even if lower than in native aortic valve TAVI, our data showed higher pacemaker implantation rates following VIV TAVI than those reported in most of the registries [18, 19, 21, 27]. Our analysis offers an exhaustive evaluation of unselected patients and their outcomes. Therefore, these high real-life rates of pacemaker implantation after VIV TAVI provide new and robust insights, which may need to be further evaluated in other healthcare systems.

Lower risk of cerebral ischaemic events on magnetic resonance imaging has been reported after VIV TAVI compared with native aortic valve TAVI [28]. The perprocedural risk of stroke associated with TAVI is mainly related to embolization of either aortofemoral or aortic valve material (usually heavily calcified foreign tissue in case of VIV procedure). Despite numerically higher rates, we did not observe significantly higher 30-day or long-term incidences of stroke after VIV TAVI.

Long-term follow-up showed reassuring data, with no differences between the two treatments for a mean follow-up of 516 days. Mostly, rehospitalization for heart failure was not higher in case of VIV TAVI. Despite higher rates of patient prosthesis mismatch, previous data [18, 19, 22] showed stability of haemodynamic variables over time after VIV TAVI, and this could explain these results. However, longer follow-up and larger cohorts are required to further evaluate these strategies. Indeed, the risk of structural valve degeneration may be accelerated after VIV TAVI.

Study limitations

We acknowledge that our work has several limitations. One main limitation is inherent to the retrospective observational nature of the study and its potential biases. Further, the study was based on administrative data, with limitations inherent to such methodology. The PMSI database contains diagnoses coded using ICD-10, which are obtained at hospital discharge and are the physician's responsibility. Data were not systematically checked externally, and this could have caused information bias. However, the large scale of the database is likely to partly compensate for this bias, and, as coding of complications is linked to reimbursement and is regularly controlled, it is expected to be of good quality. We only included in-hospital events, and were not able to analyse data for out-of-hospital deaths.

Our large population of patients admitted for either native or VIV TAVI probably represents a heterogeneous group of patients admitted with various kinds of illnesses and severities, which may have affected prognoses. Further, the non-randomized design of the analysis carries a risk of residual confounding factors. Definite conclusions for comparisons between groups may not be fully appropriate, even though multivariable matching was done, as this cannot fully eradicate the possible confounding variables between these groups. We were also unable to calculate surgical risk scores, such as the EuroSCORE or the Society of Thoracic Surgeons score, although these only aim to evaluate the short-term risk of in-hospital death after cardiac surgery. Therefore, the Charlson Comorbidity Index and the Frailty Index were used as risk predictors of all-cause death over a longer term.

Our analysis was restricted to the variables present in the database, which meant that characteristics such as mean gradient, valve area and paravalvular leak, and postprocedural echocardiography data were not available for analysis. Moreover, it was not possible to analyse the type and size of the surgical prosthesis previously implanted. It is known that VIV TAVI procedural issues (such as valve fracture) and complications related to VIV TAVI (such as risk of coronary occlusion) can be dependent on the type of surgical prosthesis previously implanted.

Conclusions

This analysis included the largest propensity-matched comparison of VIV TAVI versus native aortic valve TAVI. At 30 days and long term, VIV TAVI was not associated with significant differences in terms of clinical outcome occurrence compared with native TAVI. However, pacemaker implantations were less frequent after VIV TAVI.

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Disclosure of interest

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Figure legends

Figure 1. Cumulative incidence of all-cause death in patients treated with native transcatheter aortic valve implantation (TAVI) for aortic stenosis versus valve-in-valve TAVI for failure of previous aortic bioprosthesis.

Figure 2. Cumulative incidence of cardiovascular death in patients treated with native transcatheter aortic valve implantation (TAVI) for aortic stenosis versus valve-in-valve TAVI for failure of previous aortic bioprosthesis.

Figure 3. Cumulative incidence of rehospitalization for heart failure in patients treated with native transcatheter aortic valve implantation (TAVI) for aortic stenosis versus valve-in-valve TAVI for failure of previous aortic bioprosthesis.

Figure 4. Cumulative incidence of new-onset atrial fibrillation in patients treated with native transcatheter aortic valve implantation (TAVI) for aortic stenosis versus valve-in-valve TAVI for failure of previous aortic bioprosthesis.

Figure 5. Cumulative incidence of the combined endpoint (cardiovascular death, all-cause stroke, rehospitalization for heart failure) in patients treated with native transcatheter aortic valve implantation (TAVI) for aortic stenosis versus valve-in-valve TAVI for failure of previous aortic bioprosthesis.

	Native TAVI	VIV TAVI	p	SMD ^a (%)
	(<i>n</i> = 41,322)	(<i>n</i> = 2896)		
Age (years)	82.84 ± 6.69	80.43 ± 7.89	< 0.0001	-33.0
Charlson Comorbidity Index	4.2 ± 2.9	4.7 ± 2.9	< 0.0001	16.5
Frailty Index	9.7 ± 9.1	10.5 ± 9.2	< 0.0001	8.0
Male sex	20165 (48.8)	1442 (49.8)	0.3	2.2
Hypertension	33348 (80.7)	2375 (82.0)	0.08	3.4
Diabetes mellitus	12212 (29.6)	841 (29.0)	0.56	-1.1
Heart failure	23015 (55.7)	2126 (73.4)	< 0.0001	37.6
History of pulmonary oedema	2135 (5.2)	240 (8.3)	< 0.0001	12.6
Aortic regurgitation	4656 (11.3)	835 (28.8)	< 0.0001	45.1
Mitral regurgitation	7793 (18.9)	829 (28.6)	< 0.0001	23.0
Previous endocarditis	206 (0.5)	133 (4.6)	< 0.0001	26.2
Dilated cardiomyopathy	6617 (16.0)	599 (20.8)	< 0.0001	12.2
Coronary artery disease	25463 (61.6)	1868 (64.5)	0.002	6.2
Previous myocardial infarction	5878 (14.2)	463 (16.0)	0.01	5.0
Previous PCI	12029 (29.1)	778 (26.9)	0.01	-4.9
Previous CABG	3264 (7.9)	603 (20.8)	< 0.0001	37.6
Vascular disease	15094 (36.5)	1180 (40.7)	< 0.0001	8.7
Atrial fibrillation	18409 (44.6)	1702 (58.8)	< 0.0001	28.7
Previous pacemaker or defibrillator	8361 (20.2)	811 (28.0)	< 0.0001	18.1
Ischaemic stroke	2283 (5.5)	159 (5.5)	0.94	-0.1
Intracranial bleeding	606 (1.5)	59 (2.0)	0.01	4.2
Smoker	3406 (8.2)	337 (11.6)	< 0.0001	11.5
Dyslipidaemia	19320 (46.8)	1563 (54.o)	< 0.0001	14.4
Obesity	10526 (25.5)	829 (28.6)	0.0002	7.2
Alcohol-related diagnosis	1731 (4.2)	168 (5.8)	< 0.0001	7.5

 Table 1
 Baseline characteristics in the overall (unmatched) population.

Abnormal renal function	7132 (17.3)	625 (21.6)	< 0.0001	11.1
Lung disease	9784 (23.7)	776 (26.8)	0.0001	7.3
Sleep apnoea syndrome	3640 (8.8)	320 (11.0)	< 0.0001	7.5
COPD	6201 (15)	482 (16.6)	0.02	4.5
Liver disease	2018 (4.9)	217 (7.5)	< 0.0001	10.7
Gastro-oesophageal reflux	1412 (3.4)	101 (3.5)	0.84	0.4
Thrombotic microangiopathy	5679 (13.7)	516 (17.8)	< 0.0001	11.0
Inflammatory disease	4184 (10.1)	325 (11.2)	0.06	3.5
Anaemia	11231 (27.2)	1086 (37.5)	< 0.0001	22.3
Previous cancer	7721 (18.7)	564 (19.5)	0.29	1.9
Thrombotic microangiopathy	31 (0.1)	9 (0.3)	< 0.0001	5.4
Balloon-expandable TAVI	25299 (61.2)	1173 (40.5)	< 0.0001	-41.8
Self-expandable TAVI	16023 (38.8)	1723 (59.5)	< 0.0001	41.8
Year of inclusion	2016.1 ± 1.67	2015.47 ± 2.2	< 0.0001	-31.8
Number of TAVRs in the institution	155.54 ± 87.45	157.88 ± 90.35	0.17	2.6
per year				

Data are expressed as mean ± standard deviation or number (%), unless otherwise indicated. CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; PCI: percutaneous coronary intervention; SMD, standardized mean difference; TAVI: transcatheter aortic valve implantation; VIV: valve-in-valve.

^a Native TAVI versus VIV TAVI.

	Native TAVI VIV TAVI		Р	SMDª (%)
	(<i>n</i> = 2749) (<i>n</i> = 2749)			
Age, years	80.59 ± 7.74	80.75 ± 7.63	0.44	2.2
Charlson Comorbidity Index	4.8 ± 2.9	4.6 ± 2.9	0.25	-3.1
Frailty Index	10.6 ± 9.3	10.4 ± 9.2	0.25	-3.2
Male sex	1409 (51.3)	1355 (49.3)	0.15	-3.9
Hypertension	2237 (81.4)	2244 (81.6)	0.81	0.7
Diabetes mellitus	797 (29.0)	798 (29)	0.98	0.1
Heart failure	1986 (72.2)	1988 (72.3)	0.95	0.2
History of pulmonary oedema	211 (7.7)	208 (7.6)	0.88	-0.4
Aortic regurgitation	734 (26.7)	730 (26.6)	0.9	-0.4
Mitral regurgitation	789 (28.7)	755 (27.5)	0.31	-2.9
Previous endocarditis	72 (2.6)	61 (2.2)	0.33	-2.6
Dilated cardiomyopathy	592 (21.6)	560 (20.4)	0.79	0.8
Coronary artery disease	1806 (65.7)	1765 (64.2)	0.25	-3.1
Previous myocardial infarction	486 (17.7)	437 (15.9)	0.08	-5.0
Previous PCI	777 (28.3)	745 (27.1)	0.33	-2.6
Previous CABG	537 (19.5)	533 (19.4)	0.89	-0.4
Vascular disease	1151 (41.9)	1110 (40.4)	0.26	-3.1
Atrial fibrillation	1586 (57.7)	1593 (57.9)	0.85	0.5
Previous pacemaker or	776 (28.2)	754 (27.4)	0.51	-1.9
defibrillator				
Ischaemic stroke	128 (4.7)	142 (5.2)	0.38	2.2
Intracranial bleeding	59 (2.1)	49 (1.8)	0.33	-2.8
Smoker	327 (11.9)	302 (11.0)	0.29	-3.0
Dyslipidaemia	1481 (53.9)	1468 (53.4)	0.73	-0.9
Obesity	755 (27.5)	778 (28.3)	0.49	1.9

Table 2 Baseline characteristics in the matched population.

Alcohol-related diagnosis	170 (6.2)	148 (5.4)	0.2	-3.7
Abnormal renal function	570 (20.7)	580 (21.1)	0.74	0.9
Lung disease	737 (26.8)	740 (26.9)	0.93	0.3
Sleep apnoea syndrome	299 (10.9)	303 (11.0)	0.86	0.5
COPD	463 (16.8)	462 (16.8)	0.97	-0.1
Liver disease	201 (7.3)	192 (7.0)	0.64	-1.4
Gastro-oesophageal reflux	77 (2.8)	94 (3.4)	0.19	3.4
Thrombotic microangiopathy	476 (17.3)	483 (17.6)	0.8	0.7
Inflammatory disease	325 (11.8)	305 (11.1)	0.4	-2.4
Anaemia	1004 (36.5)	1003 (36.5)	0.98	-0.1
Previous cancer	557 (20.3)	531 (19.3)	0.38	-2.4
Thrombotic microangiopathy	9 (0.3)	7 (0.3)	0.62	-1.7
Balloon-expandable TAVI	1179 (42.9)	1147 (41.7)	0.38	-2.4
Self-expandable TAVI	1570 (57.1)	1602 (58.3)	0.38	2.4
Year of inclusion	2015.57 ± 1.82	2015.57 ± 2.12	0.92	-0.3
Number of TAVIs in the institution	157.77 ± 91.48	157.49 ± 90.15	0.91	-0.3
per year				

Data are expressed as mean ± standard deviation or number (%), unless otherwise indicated.

CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; PCI:

percutaneous coronary intervention; SMD, standardized mean difference; TAVI: transcatheter aortic valve implantation; VIV: valve-in-valve.

^a Native TAVI versus VIV TAVI.

 Table 3
 Clinical outcomes at day 30 in the matched cohort.

	Native TAVI	VIV TAVI	OR (95% CI)ª	P (uncorrected)	P (Bonferroni correction)
	(<i>n</i> = 2749)	(<i>n</i> = 2749)			
All-cause death	116 (4.2)	87 (3.2)	0.74 (0.56–0.98)	0.04	0.19
Cardiovascular death	100 (3.6)	71 (2.6)	0.70 (0.52–0.96)	0.02	0.12
All-cause stroke	14 (0.5)	18 (0.7)	1.29 (0.64–2.59)	0.48	1.0
Myocardial infarction	9 (0.3)	5 (0.2)	0.55 (0.19–1.66)	0.29	1.0
Major or life-threatening bleeding	98 (3.6)	93 (3.4)	0.95 (0.71–1.26)	0.71	1.0
Conversion to open heart surgery	5 (0.2)	2 (0.1)	0.40 (0.08–2.10)	0.27	1.0
Major clinical events ^b	233 (8.5)	196 (7.1)	0.83 (0.68–1.01)	0.06	0.32
New-onset atrial fibrillation	24 (0.9)	27 (1.0)	1.13 (0.65–1.96)	0.67	1.0
Permanent pacemaker implantation	600 (21.8)	466 (17.0)	0.73 (0.64–0.84)	< 0.0001	< 0.0001

Data are expressed as number (%) unless otherwise indicated. CI: confidence interval; OR: odds ratio; TAVI: transcatheter aortic valve implantation; VIV:

valve-in-valve.

^a VIV TAVI versus native TAVI

^b Cardiovascular death, all-cause stroke, myocardial infarction, major or life-threatening bleeding or conversion to open heart surgery.

	Native TAVI	VIV TAVI	RR (95% CI) ^b	P (uncorrected)	P (Bonferroni correction)
	(<i>n</i> = 2749)	(<i>n</i> = 2749)			
All-cause death	681 (14.7)	551 (13.2)	0.90 (0.81–1.01)	0.07	0.37
Cardiovascular death	309 (6.6)	267 (6.4)	0.96 (0.82–1.14)	0.67	1.0
All-cause stroke	131 (2.9)	146 (3.6)	1.24 (0.97–1.58)	0.07	0.36
Rehospitalization for heart failure	736 (19.5)	689 (20.0)	1.02 (0.92–1.14)	0.65	1.0
Combined endpoint ^c	933 (25.4)	878 (26.1)	1.03 (0.94–1.13)	0.57	1.0
New-onset atrial fibrillation	211 (4.8)	205 (5.2)	1.08 (0.89–1.31)	0.44	1.0
Negative control analysis					
Non-cardiovascular death	372 (8.0)	284 (6.8)	0.85 (0.73–1.00)	0.05	0.25
Cancer	175 (3.9)	191 (4.8)	1.23 (0.99–1.52)	0.05	0.24
Urinary infection	197 (4.4)	210 (5.3)	1.19 (0.98–1.45)	0.08	0.39

Table 4 Clinical outcomes during the whole follow-up^a in the matched cohort.

Data are expressed as number (%) per year unless otherwise indicated. CI: confidence interval; RR: relative risk; TAVI: transcatheter aortic valve

implantation; VIV: valve-in-valve.

 $^{\rm a}$ Mean 516 \pm 543 days; median 349 (interquartile range 24–834) days.

^b VIV TAVI versus native TAVI.

^cCardiovascular death, all-cause stroke, rehospitalization for heart failure.









