Comparison of Survival of Transfemoral Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement for Aortic Stenosis in Low-Risk Patients without Coronary Artery Disease

Marko P.O. Virtanen MD , Juhani Airaksinen MD, PhD , Matti Niemelä MD, PhD , Teemu Laakso MD , Annastiina Husso MD, PhD , Maina P. Jalava MD , Tuomas Tauriainen MD, PhD , Pasi Maaranen MD , Eeva-Maija Kinnunen MD, PhD , Sebastian Dahlbacka MD, PhD , Stefano Rosato MSc , Mikko Savontaus MD, PhD , Tatu Juvonen MD, PhD , Mika Laine MD, PhD , Timo Mäkikallio MD, PhD , Antti Valtola MD, PhD , Peter Raivio MD, PhD , Markku Eskola MD, PhD , Fausto Biancari MD, PhD

PII: S0002-9149(19)31293-7
DOI: https://doi.org/10.1016/j.amjcard.2019.11.002
Reference: AJC 24289

To appear in: *The American Journal of Cardiology*

Received date: 23 September 2019
Revised date: 2 November 2019
Accepted date: 5 November 2019

Please cite this article as: Marko P.O. Virtanen MD , Juhani Airaksinen MD, PhD , Matti Niemelä MD, PhD , Teemu Laakso MD , Annastiina Husso MD, PhD , Maina P. Jalava MD , Tuomas Tauriainen MD, PhD , Pasi Maaranen MD , Eeva-Maija Kinnunen MD, PhD , Sebastian Dahlbacka MD, PhD , Stefano Rosato MSc , Mikko Savontaus MD, PhD , Tatu Juvonen MD, PhD , Mika Laine MD, PhD , Timo Mäkikallio MD, PhD , Antti Valtola MD, PhD , Peter Raivio MD, PhD , Markku Eskola MD, PhD , Fausto Biancari MD, PhD , Comparison of Survival of Transfemoral Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement for Aortic Stenosis in Low-Risk Patients without Coronary Artery Disease, *The American Journal of Cardiology* (2019), doi: https://doi.org/10.1016/j.amjcard.2019.11.002

Comparison of Survival of Transfemoral Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement for Aortic Stenosis in Low-Risk Patients without Coronary Artery Disease

Marko P.O. Virtanen,[a] MD, Juhani Airaksinen,[b] MD, PhD, Matti Niemelä,[c] MD, PhD, Teemu Laakso,[d] MD, Annastiina Husso,[e] MD, PhD, Maina P. Jalava,[b] MD, Tuomas Tauriainen,[f] MD, PhD, Pasi Maaranen,[a] MD, Eeva-Maija Kinnunen,[d] MD, PhD, Sebastian Dahlbacka,[d] MD, PhD, Stefano Rosato,[g] MSc, Mikko Savontaus,[b] MD, PhD, Tatu Juvonen,[d] MD, PhD, Mika Laine,[d] MD, PhD, Timo Mäkikallio,[c] MD, PhD, Antti Valtola,[e] MD, PhD, Peter Raivio,[d] MD, PhD, Markku Eskola,[a] MD, PhD, Fausto Biancari,[b,f] MD, PhD

[a]Heart Hospital, Tampere University Hospital and Faculty of Medicine and Health Technology, University of Tampere, Tampere, Finland;
[b]Heart Center, Turku University Hospital, and Department of Surgery, University of Turku, Turku, Finland;
[c]Department of Internal Medicine, Oulu University Hospital, Oulu, Finland;
[d]Heart Center, Helsinki University Hospital, Helsinki, Finland;
[e]Heart Center, Kuopio University Hospital, Kuopio, Finland;
[f]Department of Surgery, Oulu University Hospital and Research Unit of Surgery, Anesthesia and Intensive Care, Faculty of Medicine, University of Oulu, Oulu, Finland;
[g]National Centre of Global Health, Istituto Superiore di Sanità, Rome, Italy.

Running Title: TAVI and SAVR in low-risk patients

Corresponding Author:
Prof. Fausto Biancari,
Heart Center,
Turku University Hospital,
PO Box 52, 20521 Turku
E-mail: faustobiancari@yahoo.it

Abstract

Increasing data supports transcatheter aortic valve implantation (TAVI) as a valid option over surgical aortic valve replacement (SAVR) in the treatment for severe aortic stenosis (AS) also in patients with low operative risk. However, limited data exists on the outcome of TAVI and SAVR in low-risk patients without coronary artery disease (CAD). The FinnValve registry included data on 6463 patients who underwent TAVI or SAVR with bioprosthesis between 2008 and 2017. Herein, we evaluated the outcome of low operative risk as defined by STS-PROM score<3% and absence of CAD, prior stroke and other relevant comorbidities. Only patients who underwent TAVI with third-generation prostheses and SAVR with Perimount Magna Ease or Trifecta prostheses were included in this analysis. The primary endpoints were 30-day and 3-year all-cause mortality. Overall, 1006 patients (175 TAVI patients and 831 SAVR patients) met the inclusion criteria of this analysis. Propensity score matching resulted in 140 pairs with similar baseline characteristics. Among these matched pairs, 30-day mortality was 2.1% in both TAVI and SAVR cohorts (p=1.00) and 3-year mortality was 17.0% after TAVI and 14.6% after SAVR (p=0.805). Lower rates of bleeding and atrial fibrillation, and shorter hospital stay were observed after TAVI. The need of new permanent pacemaker implantation and the incidence of early stroke did not differ between groups. In conclusion,TAVI using third-generation prostheses achieved similar early and mid-term survival compared to SAVR in low-risk patients without CAD.

Clinical trial registration: ClinicalTrials.gov Identifier: NCT03385915.

Key-words: TAVR; TAVI; transcatheter; aortic valve replacement; low risk.

After the first-in-man transcatheter aortic valve implantation (TAVI) for severe aortic stenosis (AS),[1] this treatment method has proven to be a valid alternative to surgical aortic valve replacement (SAVR) in intermediate- and high-risk AS patients.[2–5] Based on the results of recent trials,[6–8] the indication of TAVI has been expanded to low-risk patients. However, data on the long-term outcomes in these low-risk patients is still limited, particularly in those without coronary artery disease (CAD). Indeed, the prevalence of CAD is higher than 60% in intermediate-risk AS patients, whilst up to 28% of low-risk patients has concomitant CAD.[4–7,9] CAD may negatively affect the outcome after TAVI and SAVR,[10–13] and it may be a major confounding factor in the analysis of the benefits and risks of TAVI and SAVR. Still, only a few studies compared these treatment methods in patients without significant CAD.[14,15] This issue has been investigated in the present nationwide study.

Methods

The FinnValve registry is a nationwide study (ClinicalTrials.gov Identifier: NCT03385915), which includes data on consecutive and unselected patients who underwent TAVI or SAVR for severe AS, between January 2008 and October 2017, at all five Finnish University Hospitals. The study protocol was approved by the Institutional Review Boards of all participating centres. The FinnValve registry included data on patients who underwent primary TAVI or SAVR for AS with or without coronary revascularization. Data was collected retrospectively into a dedicated electronic case report form by physicians and trained research nurses. Data on mortality was obtained from the Finnish Population Register Centre and data on cardiovascular interventions was retrieved from the registry of the Finnish National Institute for Health and Welfare. Follow-up was considered complete for all patients, but for those not residing in Finland whose follow-up was truncated at the time of hospital discharge. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[16]

This analysis included patients with low operative risk (Figure 1), which was defined as a Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) <3% along with the following exclusion criteria: age>85 years, CAD, prior coronary revascularization, prior cardiac surgery, stroke, estimated glomerular filtration rate <30 mL/min/m^2, dialysis, functioning renal transplant, severe frailty, active malignancy, critical preoperative state, acute heart failure within 60 days from the index procedure, porcelain aorta, oxygen therapy, left ventricular ejection fraction ≤30%, severe mitral valve regurgitation, non-transfemoral access for TAVI, and urgent/emergency procedure. The analysis was limited to third-generation TAVI prostheses (Sapien 3, Evolut R, Acurate Neo, Lotus) and SAVR pericardial prostheses (Perimount Magna Ease and Trifecta) in order to avoid any potential bias related to previous generation valve technology. CAD was defined as a stenosis of 50% or more in at least one of the main coronary arteries. Severe frailty was defined as Geriatric Status Scale 2-3 (GCS).[17] Baseline variables were defined according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II criteria.[18]

The primary outcomes of this study were 30-day and 3-year all-cause mortality. Secondary early outcomes were stroke, transfusion, reoperation for bleeding, paravalvular regurgitation, new permanent pacemaker implantation (PPI), acute kidney injury (AKI), new dialysis, conversion to cardiac surgery, coronary artery occlusion, aortic dissection/rupture, major vascular complication, atrial fibrillation and postoperative length of stay in the hospital where the index procedure was performed. Late secondary outcomes were repeat operation on the aortic valve prosthesis, prosthetic valve endocarditis, coronary revascularization and new PPI.

VARC-2 criteria[19] were applied for stroke, major vascular complication and perioperative bleeding. Severe bleeding was also defined according to European Coronary Artery Bypass Grafting (E-CABG) bleeding scores 2-3, i.e. transfusion of more than 4 units

of red blood cells and/or reoperation for mediastinal and/or peripheral bleeding.[20] AKI was defined according to the KDIGO criteria.[21]

Statistical analyses were performed using Stata v. 15.1 (StataCorp LLC, Texas, USA) and SPSS v. 25.0 (IBM Corporation, New York, USA) statistical softwares. Continuous variables are reported as means and standard deviations. Categorical variables are summarized as counts and percentages. The Mann-Whitney, Fisher's and Chi-square tests were used for univariate analysis in the unmatched population. A propensity score was estimated using a non-parsimonious logistic regression model including the following covariates: age, gender, body mass index, hemoglobin, estimated glomerular filtration rate, diabetes, pulmonary disease, extracardiac arteriopathy, New York Heart Association class 4 symptoms, left ventricular ejection fraction ≤50%, atrial fibrillation, systolic pulmonary artery pressure, mitral valve regurgitation and prior pacemaker.

One-to-one propensity score matching was performed using the psmatch2 Stata module with a caliper width of 0.01. Standardized differences lower than 0.10 were considered for adequate balance between the study cohorts. The paired t-test, the McNemar test and the Fleiss-Everitt test were used to assess the differences between preoperative variables and the early outcomes in the propensity score matched pairs. Differences in late mortality were evaluated by the Kaplan-Meier method with the log-rank test. Competing risk analysis with the Fine-Gray's test was performed for late non-fatal adverse events because patient's death might have hindered the observation of these events. Statistical significance was set at $p<0.05$.

Results

Of 6463 patients included in the FinnValve registry, 1006 patients (mean age, 73.1±7.0 years; female gender, 53%) fulfilled the inclusion criteria of the current analysis (Figure 1). TAVI

was performed in 175 patients and SAVR in 831 patients. The mean follow-up of this series was 3.7±2.0 years (TAVI cohort, 2.2±0.9 years; SAVR cohort 4.0±2.0 years).

The baseline characteristics of the unmatched cohorts are presented in Table 1. Thirty-day mortality was 1.7% in TAVI and 1.6% in SAVR (p=0.885). Other early outcomes of the unmatched cohorts are presented in Table 2. Three-year all-cause mortality was higher after TAVI (16.6%) compared to SAVR (6.8%) (p=0.003; Table 3).

The propensity score matching resulted in 140 pairs. These cohorts had balanced baseline covariates except for hemoglobin and systolic pulmonary pressure whose standardized differences were slightly over 0.1, without reaching statistically significance in paired tests (Table 1). The mean age of the patients was 76.5±6.8 in the TAVI cohort and 76.9±4.7 in the SAVR cohort (p=0.458). The predicted risk of operative mortality according to EuroSCORE II and STS score was similar between TAVI and SAVR. In the TAVI group, 62% of the patients received a balloon expandable prosthesis, 21% a self-expanding prosthesis and 16% a mechanically expandable prosthesis. In the surgical group, the Perimount Magna Ease bioprosthesis was implanted in 59% of the patients and the Trifecta bioprosthesis in the others.

Three patients (2.1%) died in both cohorts at 30 days after the procedure (Table 2). The late all-cause mortality was not different between the TAVI and SAVR cohorts (1-year: 5.0% for both; 2-year: 8.2% vs. 8.7%; 3-year: 17.0% vs. 14.6%, p=0.805, respectively) (Table 3, Figure 2).

Three patients (2.1%) in both cohorts suffered stroke immediately after the procedure. Major vascular complication occurred in 7.9% of TAVI patients and in 0.7% SAVR patients (p=0.006). Similar rates of paravalvular regurgitation were observed in the study cohorts. Atrial fibrillation, bleeding and red blood cell transfusion were more frequent

in the SAVR cohort (Table 2). Patients treated with TAVI had shorter hospital stay compared to the surgical cohort (3.7±3.4 days after TAVI and 7.5±3.4 days after SAVR; p<0.0001). No statistically significant differences were observed in terms of AKI (Table 2). A new PPI was needed immediately after the procedure in 13 patients after TAVI (9.8%) and in eight patients after SAVR (6.1%) (p=0.481). The rate of new PPI was numerically higher in the TAVI cohort compared to the SAVR cohort during follow-up, but the difference did not reach statistical significance (Table 3). Coronary revascularization and repeat aortic valve replacement were rare in these cohorts. No prosthetic valve endocarditis was observed in this series (Table 3).

Discussion

Our study group has previously reported similar results after TAVI and SAVR in patients with low operative risk from the nationwide FinnValve registry.[22] In the present study, we report on updated survival along with prostheses-related adverse events of patients without CAD and other significant comorbidities who underwent isolated TAVI and SAVR. This selected patient population is expected to provide unbiased information on TAVI and SAVR device-related events, because the outcomes of interest are less likely affected by other confounders such as CAD, depressed ventricular function, cerebrovascular disease and renal failure. Indeed, our study cohort is somewhat similar to that of recent randomized controlled trials with low prevalence of atherosclerotic cardiovascular disease.[6,7] Furthermore, the inclusion of patients who received newest generations of TAVI and SAVR prostheses may prevent bias related to less recent valve technology.

The main findings of this study are: 1) 30-day and 3-year survival were similar after TAVI or SAVR; 2) TAVI was associated with shorter hospital stay, lower rates of

bleeding and atrial fibrillation compared to SAVR, but major vascular complications were more frequent after TAVI than after SAVR; 3) no differences in the incidence of early stroke and new PPI was observed between these two treatment strategies; 4) the intermediate-term risk for aortic valve reoperation is very low after TAVI and SAVR.

Thirty-day mortality was similar in the study cohorts (2.1%). This means that, despite its less invasive nature, TAVI was not safer than SAVR in these very low-risk patients. In the propensity score matched cohorts, 3-year survival was 83% after TAVI and 85.4% after SAVR, which demonstrates the clinical efficacy of both treatment methods at intermediate follow-up. Only patients who received most recent TAVI and SAVR prostheses were included in analysis, with low rates paravalvular regurgitation and structural valve deterioration.

Our results are balanced with those of previous studies.[8] Randomized trials including low-risk patients and using composite primary outcomes confirmed TAVI as non-inferior treatment over SAVR.[6,7,14] Still there is no clear evidence of a survival benefit of TAVI over SAVR in low-risk populations.[23] Early mortality in our study (30-day: 2.1%, 1-year: 5.0%) was slightly higher than in the PARTNER 3[6] and the Evolut Low Risk Trial[7] (30-day: 0.4-0.5% for TAVI, 1.1-1.3% for SAVR; 1-year: 1.0-2.4% for TAVI, 2.5-3.0% for SAVR), but similar to the results of the NOTION trial[14] (30-day: 2.1% for TAVI, 3.7% for SAVR; 1-year: 4.9% for TAVI, 7.5% for SAVR). Such differences are likely related to different age profiles of the study cohorts. The outcome of low-risk patients (STS score <4%) undergoing isolated aortic valve procedure from the German Aortic Valve Registry (GARY) showed a significantly lower 30-day mortality of patients undergoing TAVI compared to SAVR (1.7% after transvascular TAVI vs. 3.0% after SAVR, p=0.002), whilst 1-year survival was similar with these treatment methods (90.4% after TAVI vs. 91.2% after SAVR, p=0.368).[15] Non-randomized data is also available from the Low Risk Trial, which reported

at 30-day nil mortality after TAVI and 1.7% mortality after SAVR (p=0.079).[24] One-year survival rate was 97% in TAVI cohort.[25] However, the patients in the Low Risk Trial were younger compared to other studies (age 73.6 years, STS 1.8%). The longest follow-up of low-risk patients' outcome is available from the NOTION trial, which demonstrated a 5-year survival of about 72% in the TAVI and SAVR cohorts.[8]

Our results indicate that, despite the low operative risk and the minimally invasive nature of TAVI, these patients are still exposed to a certain risk of early mortality and severe adverse events. Stroke, AKI stage 3, and severe bleeding were not infrequent after TAVI and might have had a negative impact on the longer-term survival after TAVI.[26,27] Importantly, the early outcome of patients who underwent TAVI was affected by a significantly higher rate of major vascular complications, whilst blood transfusion was required frequently after SAVR (Tab. 2). Such differences are due to the different nature of these treatment methods. In fact, the risk of vascular complications at the access site is the Achille's heel of TAVI, even in these low-risk patients. On the contrary, SAVR may increase the risk of exposure to blood products due to significant bleeding from the operative field and to the marked hemodilution occurring during cardiopulmonary bypass. In this study, almost 70% of SAVR patients received blood transfusion, which might be partly explained by a policy of liberal perioperative blood transfusion adopted in our country. Still only 14% of patients required transfusion of more than four units of red blood cell. The risk of stroke after TAVI has remained relatively stable during past years with a rate of 2.0-2.5% as shown in a large database.[28] The present study confirmed that such a risk of stroke exists also in low-risk patients, although previous studies reported on lower stroke rates.[6,7,14]

The risk of PPI was 9.8% after TAVI, which can be considered satisfactory considering that about 60% of TAVI devices were balloon-expandable prostheses.[29] The rate of new PPI after SAVR was 6.1% and remained relatively stable during 3-year follow-up

(9.3%). On the contrary, the rate of new PPI after TAVI increased to 14.6% at 3-years (p=0.082 for TAVI vs. SAVR). Late coronary revascularization was rare in both the study cohorts and prosthetic valve endocarditis was not observed in this series.

The retrospective nature is the main limitation of this study. Secondly, the definition of low operative risk was based on STS score<3% and by excluding patients with significant co-morbidities. Still, it is possible that some patients were incorrectly classified. Third, comparative analysis of the study cohorts is based on propensity score matching and its results are potentially biased by unmeasured confounders. Fourth, the small size and limited follow-up of this series prevent conclusive results on the efficacy and durability of TAVI in this patient population.

In conclusion, TAVI or SAVR with the most recent prostheses achieve similar early and mid-term outcome in low-risk patients without CAD. Potentially life-threatening complications can be expected in very low-risk patients despite the minimally invasive nature of transfemoral TAVI.

Acknowledgments

Disclosure of potential conflicts of interest: Dr. Mikko Savontaus is a proctor for Medtronic, the relationship is significant; Dr. Mika Laine is a proctor for Boston Scientific, the relationship is significant. The other coauthors do not have any conflict of interest related to this study.

Sources of funding and support: This study was not supported by any external funding.

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Legends to figures

Figure 1. Study flow-chart.

Figure 2. Kaplan-Meier estimate of survival in propensity score matched pairs of low-risk patients with severe aortic stenosis without coronary artery disease who underwent transcatheter (TAVI) or surgical aortic valve replacement (SAVR).

Table 1. Characteristics of unmatched and propensity score matched patients.

Variable	Unmatched cohorts				Propensity score matched cohorts			
	TAVI (n=175)	SAVR (n=831)	Standardized difference	p-value	TAVI (n=140)	SAVR (n=140)	Standardized difference	p-value
Age (years)	77.4±6.4	72.2±6.8	0.790	<0.0001	76.5±6.8	76.9±4.7	0.068	0.458
Women	101 (57.7%)	431 (51.9%)	0.117	0.159	79 (56.4%)	75 (53.6%)	0.057	0.731
Body mass index (kg/m^2)	29±5	28±5	0.151	0.114	29±5	29±5	0.073	0.555
Hemoglobin (mg/L)	130±16	135±13	0.370	<0.0001	130±16	129±14	0.113	0.364
Estimated glomerular filtration rate (ml/min/1.73m^2)	75±21	80±19	0.261	0.001	75±21	74±20	0.038	0.764
Diabetes mellitus	46 (26.3%)	170 (20.5%)	0.138	0.088	35 (25.0%)	37 (26.4%)	0.033	0.883
Pulmonary disease	30 (17.1%)	90 (10.8%)	0.183	0.019	22 (15.7%)	26 (18.6%)	0.076	0.643
Extracardiac arteriopathy	13 (7.4%)	46 (5.5%)	0.077	0.333	11 (7.9%)	10 (7.1%)	0.027	1.000
Ejection fraction ≤50%	29 (16.7%)	88 (10.6%)	0.178	0.023	19 (13.6%)	21 (15.0%)	0.048	0.860
Atrial fibrillation	63 (36.0%)	139 (16.7%)	0.448	<0.0001	47 (33.6%)	46 (32.9%)	0.015	1.000
New York Heart Association Class 4	1 (0.6%)	5 (0.6%)	0.004	1.000	1 (0.7%)	2 (1.4%)	0.069	1.000
Systolic pulmonary artery pressure (mmHg)			0.089	0.519			0.166	0.933
31-55	58 (33.1%)	286 (34.4%)			45 (32.1%)	39 (27.9%)		
>55	9 (5.1%)	28 (3.4%)			6 (4.3%)	11 (7.9%)		
Mitral regurgitation			0.437	<0.0001			0.047	0.944
Mild	54 (33.3%)	174 (21.9%)			46 (32.9%)	43 (30.7%)		
Moderate	14 (8.6%)	15 (1.9%)			7 (5.0%)	7 (5.0%)		
Prior permanent pace-maker	12 (6.9%)	30 (3.6%)	0.146	0.051	7 (5.0%)	8 (5.7%)	0.032	1.000
European System for Cardiac Operative Risk Evaluation II (%)	2.3±1.0	1.6±0.8	0.717	<0.0001	2.1±0.9	2.1±1.1	0.020	0.398
Society of Thoracic Surgeons score (%)	2.1±0.6	1.6±0.6	0.832	<0.0001	2.0±0.6	2.0±0.6	0.089	0.845

TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement. Values are number (%) or mean ± standard deviation.

Table 2. Early outcomes of unmatched and propensity score matched patients.

Variable	Unmatched cohorts			Propensity score matched pairs		
	TAVI (n=175)	SAVR (n=831)	p-value	TAVI (n=140)	SAVR (n=140)	p-value
30-day death	3 (1.7%)	13 (1.6%)	0.885	3 (2.1%)	3 (2.1%)	1.000
Stroke	4 (2.3%)	20 (2.4%)	1.000	3 (2.1%)	3 (2.1%)	1.000
Conversion to cardiac surgery	2 (1.1%)	-	-	2 (1.4%)	-	-
Deep sternal wound infection/mediastinitis	0	11 (1.3%)	0.228	0	2 (1.4%)	0.500
Coronary revascularization	0	6 (0.7%)	0.597	0	1 (0.7%)	1.000
Coronary ostium occlusion	0	3 (0.4%)	1.000	0	1 (0.7%)	1.000
Aortic dissection/rupture	1 (0.1%)	4 (0.5%)	1.000	1 (0.7%)	0	1.000
Major vascular complication	15 (8.6%)	7 (0.7%)	<0.0001	11 (7.9%)	1 (0.7%)	0.006
Red blood cell transfusion	17 (9.9%)	439 (53.9%)	<0.0001	13 (9.6%)	94 (69.1%)	<0.0001
Red blood cell transfusion (units)	0.4±1.7	1.7±2.5	<0.0001	0.4±1.8	2.3±2.7	<0.0001
Red blood cell transfusion >4 units	3 (1.8%)	84 (10.3%)	<0.0001	3 (2.2%)	19 (14.0%)	<0.0001
Resternotomy/thoracotomy for bleeding	2 (1.1%)	65 (7.8%)	<0.0001	2 (1.4%)	11 (7.9%)	0.022
E-CABG bleeding grades 2-3[a]	9 (5.3%)	110 (13.5%)	0.003	7 (5.1%)	23 (16.9%)	0.002
VARC-2 bleeding			<0.0001			<0.0001
Major bleeding	36 (20.8%)	360 (43.3%)		27 (19.6%)	68 (48.6%)	
Life-threatening or disabling	9 (5.2%)	415 (49.9%)		7 (5.1%)	59 (42.1%)	
Acute kidney injury grades 2-3	4 (2.3%)	31 (3.8%)	0.494	4 (2.9%)	7 (5.0%)	0.549
New renal replacement therapy	0	11 (1.3%)	0.228	0	3 (2.1%)	0.250
Paravalvular regurgitation			<0.0001			0.431
Mild	16 (9.1%)	46 (5.5%)		13 (9.3%)	9 (6.4%)	
Moderate	5 (2.9%)	1 (0.1%)		3 (2.1%)	1 (0.7%)	
Severe	0	1 (0.1%)		0	0	
Atrial fibrillation	56 (32.0%)	430 (51.7%)	<0.0001	43 (30.7%)	82 (58.6%)	<0.0001
Permanent pacemaker,[b]	16 (9.8%)	30 (3.7%)	0.001	13 (9.8%)	8 (6.1%)	0.481
Hospital stay (days)	3.8±3.1	7.2±4.3	<0.0001	3.7±3.2	7.5±3.4	<0.0001

TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; E-CABG, European Coronary Artery Bypass Grafting study; VARC, Valve Academic Research Consortium; [a], it includes also intervention for peripheral bleeding; [b], it excludes patients with prior pacemaker implantation. Values are number (%) or mean ± standard deviation.

Table 3. Late outcomes of unmatched and propensity score matched patients.

Variable	Unmatched cohorts TAVI (n=175)	SAVR (n=831)	p-value	Propensity score matched pairs TAVI (n=140)	SAVR (n=140)	p-value
All-cause mortality			0.003			0.805
1-year	4.0%	3.4%		5.0%	5.0%	
2-year	8.6%	4.5%		8.2%	8.7%	
3-year	16.6%	6.8%		17.0%	14.6%	
Coronary revascularization			0.858			0.679
1-year	0.6%	1.1%		0.7%	0.7%	
2-year	0.6%	1.3%		0.7%	0.7%	
3-year	2.6%	1.5%		3.6%	1.7%	
Prosthetic valve endocarditis			-			-
1-year	0	0		0	0	
2-year	0	0		0	0	
3-year	0	0		0	0	
Repeat aortic valve replacement			-			-
1-year	0	0.2%		0	0.8%	
2-year	0	0.6%		0	0.8%	
3-year	0	0.8%		0	0.8%	
New pace-maker implantation			<0.0001			0.082
1-year	13.3%	4.1%		13.8%	6.2%	
2-year	15.4%	5.1%		14.6%	6.2%	
3-year	15.4%	6.0%		14.6%	9.3%	

TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement. P-values are from Kaplan-Meier and competing risk analysis.

Figure 1.

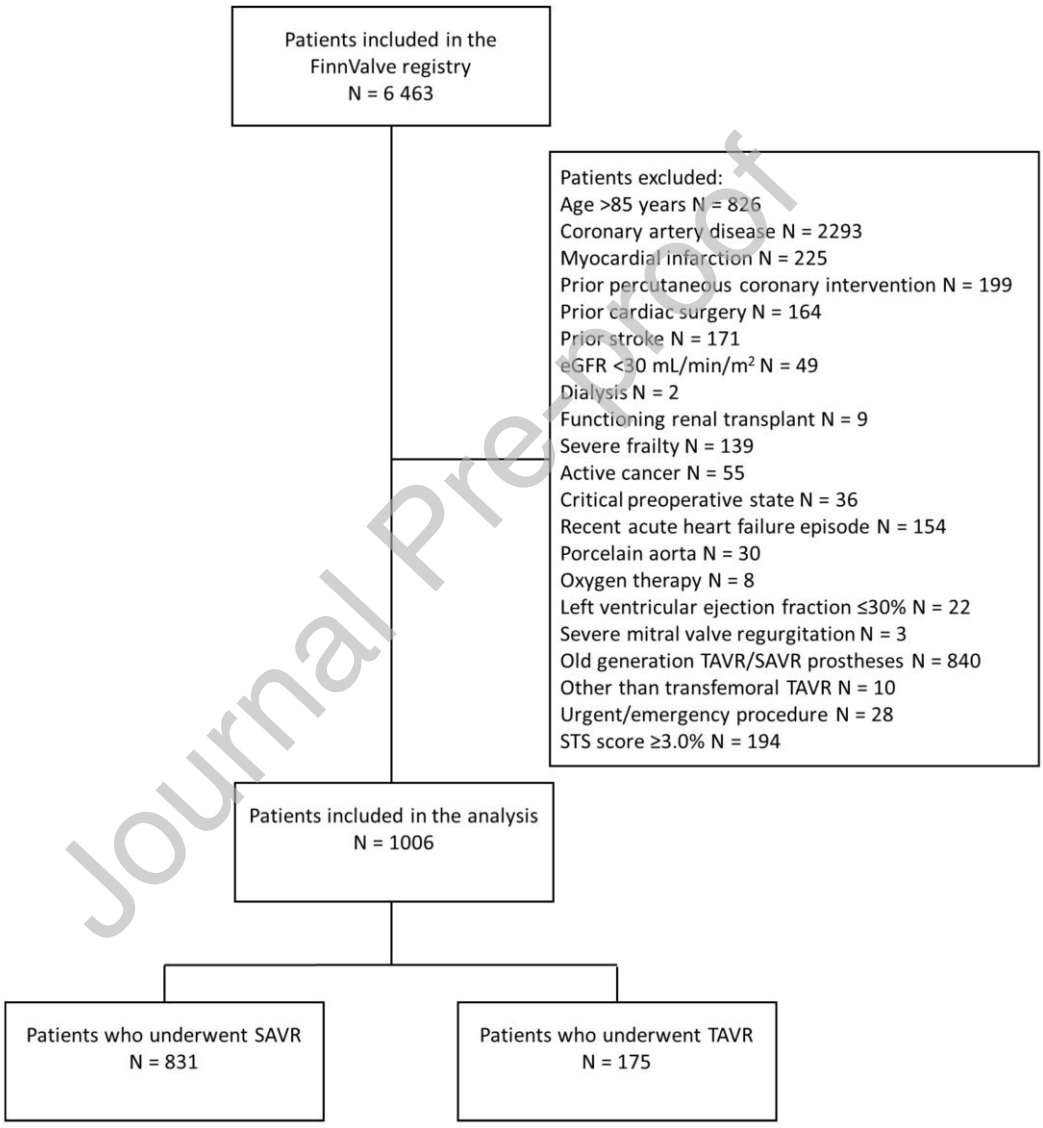

Figure 2.