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Acute Kidney Injury following Transcatheter and Surgical Aortic Valve Replacement in Patients with Normal Kidney Function: Results from the FinnValve Registry

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Abstract

Aims: Acute kidney injury (AKI) is a known risk factor for mortality in patients with chronic kidney disease (CKD) undergoing aortic valve replacement. However, the incidence and impact of AKI on patients without CKD after transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) are unknown. The objectives of this study were to compare the incidence of AKI and evaluate its impact on 5-year mortality following TAVR and SAVR in patients without CKD.

Methods and Results: The nationwide FinnValve registry included 4555 consecutive patients without CKD, defined as estimated glomerular filtration rate≥60 ml/min/1.73m^2, who underwent TAVR or SAVR. AKI was defined according to the KDIGO criteria. Propensity-score matching resulted in 672 pairs of patients who underwent TAVR or SAVR without CKD. Patients who underwent SAVR had a significantly higher incidence of AKI in comparison to those who underwent TAVR (unmatched: 16.4% vs. 4.7%, *P* <0.001, multivariable analysis: OR 3.99, 95%CI 2.85-5.70; matched: 20.1% vs. 3.9%, *P*<0.001). At 5 year, patients who developed AKI had significantly increased mortality compared to those without AKI (36.0% vs. 19.1%, log-rank *P* <0.001, multivariable analysis: HR 2.14, 95%CI 1.69-2.67) in the unmatched series. The adjusted hazard

ratios for 5-year mortality were 1.58 (95%CI 1.20-2.08) for AKI grade 1, 3.27 (95%CI 2.09-5.06) for grade 2 and 4.82 (95%CI 2.93-8.04) for grade 3.

Conclusions: In patients without CKD, TAVR was associated with a significantly lower incidence of AKI compared with SAVR. AKI was significantly associated with increased risk of 5-year mortality, correlating with AKI severity.

Clinical Trial Registration: ClinicalTrials.gov, Identifier: NCT03385915.

(URL https://clinicaltrials.gov/ct2/show/NCT03385915)

Keywords: acute kidney injury; aortic stenosis; transcatheter aortic valve replacement; surgical aortic valve replacement

Introduction

Acute kidney injury (AKI) is a common complication in patients undergoing transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR), its incidence ranging from 1% to 56% depending on the study population.[1-5] Patients with pre-procedural CKD who develop AKI have longer hospital stay and higher risk early and late adverse events.[3,6] TAVR has recently become the preferred treatment strategy for severe aortic valve stenosis (AS) in patients at high and intermediate risk with a high prevalence of CKD[3,7,8] and the incidence and clinical impact of AKI have been well documented in patients with CKD.[9,10] During the past few years, the clinical practice has shifted towards treating lower-risk patients without pre-procedural CKD with TAVR.[1] However, no data exist on the occurrence and prognosis of AKI following TAVR in patients without CKD. Accordingly, knowledge of AKI in this subset of patients is essential before we consider expanding the indication for TAVR to lower risk patients with long life expectancy. These issues have been investigated in a nationwide registry.

Methods

Study design and participants

The FinnValve registry (Finnish Registry of Transcatheter and Surgical Aortic Valve Replacement for Aortic Valve Stenosis) is a nationwide registry, which includes retrospectively collected data from consecutive and unselected patients who underwent TAVR or SAVR with a bioprosthesis for AS at all five Finnish university hospitals (Helsinki, Kuopio, Oulu, Tampere and Turku) from January 2008 to October 2017. This study was approved by the Institutional Review Boards of each participating center. During the study period, only these five university hospitals performed both TAVR and SAVR procedures. A small number of TAVR procedures have been performed in three central hospitals during a short period of time during which this procedure was temporarily allowed by the national authorities. Similarly, a small number of SAVR procedures were performed in a central hospital not performing TAVR procedures. Data from patients treated in central hospitals were not collected into this registry, because these procedures were performed outside a heart team environment and this might have introduced bias into the results. The inclusion criteria for the study entry were as follows: 1) age>18 years; 2) primary aortic valve procedure with a bioprosthesis for AS with or without aortic valve regurgitation; 3) TAVR or SAVR with or without associated coronary revascularization. The exclusion criteria were as follows: 1) any prior TAVR or surgical

intervention on the aortic valve; 2) concomitant major procedure on the mitral valve, tricuspid valve and/or ascending aorta; 3) any procedure for isolated aortic valve regurgitation; or 4) acute endocarditis; and 5) SAVR with a mechanical valve prosthesis. The operative risk of the patients was evaluated according to the Society of Thoracic Surgeons (STS-PROM)[11] and the EuroSCORE II[12] risk scoring methods. For the purpose of the current analysis, patients with baseline estimated glomerular filtration rate (eGFR)<60ml/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) equation[13] and dialysis were excluded from this analysis.

Data was retrospectively collected into a dedicated electronical case report form by cardiologists, cardiac surgeons and trained research nurses. Data underwent robust checking of its completeness and quality. Data on mortality was obtained from the national registry Statistics Finland, which is based on death certificates reviewed by local and central authorities. Based on these information, follow-up was considered complete for all patients, but for two patients who were not residing in Finland and for whom follow-up was truncated at hospital discharge.

Definition criteria of baseline risk factors

Baseline variables were defined according to the EuroSCORE II criteria.[12] Stratification of the severity of CKD was performed estimating the glomerular filtration rate using the MDRD equation.[13] CKD was defined as an eGFR <60ml/min/1.73m^2 in accordance with National Kidney

Foundation guidelines.[14] Therefore, non-CKD was defined as eGFR≥60ml/min/1.73m^2. Severe frailty was defined according to the Geriatric Status Scale (GSS) as GSS grades 2-3.[15] Coronary artery disease (CAD) was defined as any stenosis≥50% of the main coronary branches. Recent acute heart failure (AHF) was defined as any new-onset or worsening of symptoms or any signs of heart failure requiring hospital admission and rapid escalation of therapy within 90days prior TAVR or SAVR.

Patient selection

The FinnValve registry includes data from 6463 patients who underwent primary TAVR or SAVR with a bioprosthesis; 2130 (33.0%) patients underwent TAVR and 4333 (67.0%) underwent SAVR. Pertinent to the present analysis, patients with CKD (n= 1807) and those with missing values of serum creatinine (n= 1) were excluded. In 4555 patients (TAVR: n=1215; SAVR: n=3340) without CKD, a propensity score matching model was developed to derive two matched groups for comparative outcome analysis (Figure 1).

Outcome measures

The primary outcome of this study was to elucidate the incidence of post-operative AKI. The secondary outcomes were 5-year all-cause mortality in patients with or without AKI. The early outcomes were defined as peri- and post-procedural outcomes during the hospital stay for the index procedure and 30-day all-cause mortality.

AKI was defined according to the KDIGO classification criteria[16], i.e. stage1 is an increase in serum creatinine≥1.5 times the baseline level or serum creatinine increase ≥26.5 μmol/l, stage2 is an increase in serum creatinine 2.0-2.9 times the baseline, and stage3 is defined as any increase in serum creatinine≥3.0 times the baseline level or serum creatinine increase≥353.65 μmol/l and/or de novo renal replacement therapy during the hospital stay. Definition criteria of the other outcomes are summarized in Supplementary online Table S1.

Statistical analysis

Categorical variables are presented as counts and/or percentages and were compared using the chi-square test. Continuous variables are presented as the mean±standard deviation (SD) or median and interquartile range (25^{th}-75^{th} IQR) were compared using the Student's t-test or the Wilcoxon rank sum test based on their distributions. One-to-one propensity score matching was performed employing the nearest neighbour method and a caliper width of 0.2 of the standard deviation of the logit of the estimated propensity score. Standardized differences lower than 0.10 were considered an acceptable imbalance between the treatment groups. The detailed description of a propensity score matching is shown in Supplementary online Table S2. Early outcomes in the propensity score matched cohorts were evaluated using the t-test for paired samples for continuous variables and the McNemar test for dichotomous variables. These tests were used to evaluate any difference in the adverse events of

propensity score matched pairs. Differences in the long-term survival of unmatched and matched pairs were evaluated by the Kaplan-Meier method with the log-rank test. Covariates including all baseline and procedural characteristics and early outcomes exhibiting a *P* value <0.10 in the univariate analysis were included in a logistic regression analysis or in a multivariate Cox proportional hazard regression to determine the predictive factors of the incidence of AKI, and 5-year all-cause mortality in the unmatched cohort. A $P<0.1$ was set for statistical significance of trend tests and a $P<0.05$ was set for statistical significance for all the other tests. Statistical analysis was performed using JMP version 10.0 (SAS Institute Inc, Cary, NC), and SPSS version 22.0 statistical software (IBM Corporation, New York, USA).

Results

Patient characteristics and early outcomes

A total of 4555 patients without pre-procedural CKD were identified and were the subjects of this analysis. TAVR was performed in 1215 patients and SAVR in 3340 patients (Figure 1). In the unmatched cohort, TAVR patients in comparison to SAVR patients were older, more often female and had a higher predicted risk of operative mortality (Table 1). During the study period, the proportion of SAVR decreased, whereas that of TAVR increased (P_{trend} <0.001) (Supplementary online Figure S1). After propensity score matching, 672 matched pairs of patients with similar baseline characteristics were identified (Table 1 and Supplementary online Figure S2). Patients who underwent TAVR or SAVR without CKD had a similar operative risk (mean STS score of 3.1% vs 3.1%, *P*=0.74 and EuroSCORE II of 4.0% vs 3.9%, *P*=0.82, respectively). The procedural characteristics and early outcomes of patients without CKD who underwent TAVR or SAVR are summarized in Table 2. Among the unmatched and matched series, patient who underwent SAVR had significantly higher bleeding complications according to the E-CABG bleeding grades2-3 and red blood cell transfusion>4 units, and longer length of hospital stay, but fewer major vascular complications and pacemaker implantation, and similar 30-day mortality compared to those who underwent TAVR.

Incidence and predictors of AKI

During the index hospitalization, 13.3%, 4.3% and 1.3% of patients in the unmatched series and 12.0%, 3.7% and 1.0% of those in the matched series developed AKI, AKI grade≥2 and dialysis, respectively (Figure 2). Patients who underwent SAVR had a significantly higher incidence of AKI in comparison to patients who underwent TAVR (unmatched series: AKI: 16.4% vs. 4.7%, P<0.001, AKI grade≥2: 5.2% vs 1.9%, P<0.001 and dialysis: 1.7% vs. 0.2%, P<0.001; matched series: AKI: 20.1% vs 3.9%, P<0.001, AKI grade≥2: 6.1% vs 1.6%, P<0.001 and dialysis: 1.8% vs 0.3%, P=0.026). In the unmatched series, the proportion of AKI in patients who underwent TAVR significantly decreased during the study period (P_{trend} <0.001). In contrast, similar trend was not observed in patients who underwent SAVR (P_{trend} =0.23) (Supplementary online Figure S3).

The results of multivariable analysis performed to identify predictor of AKI in the unmatched series are shown in Table 3. This regression model showed that SAVR (OR:3.99, 95%CI:2.85-5.70) was independently associated with the incidence of AKI. In TAVR cohort, local anesthesia (OR:0.33, 95%CI:0.11-0.96) and transfemoral approach (OR:0.68, 95%CI:0.51-0.88) were significantly associated with fewer incidence of AKI. In the SAVR cohort, the duration of cardiopulmonary bypass (OR:1.09, 95%CI:1.02-1.23) was significantly associated with the incidence of AKI. Throughout these three cohorts, atrial fibrillation and bleeding complications were

independently associated with the incidence of AKI. Other independent predictors are listed in Table 3.

The effect of AKI and its severity on 5-years outcomes

Cumulative 5-year mortality following TAVR or SAVR are displayed in Supplementary online Figure S4. In the unmatched series, 5-year mortality significantly differed between the study groups (TAVR, 40.5% vs SAVR, 18.3%, log-rank $P<0.001$). However, no difference was observed in the matched series between patients who underwent TAVR and SAVR (TAVR, 31.5% vs SAVR, 24.6%, log-rank $P=0.21$).

Cumulative event curves for all-cause mortality between patients with and those without AKI in the unmatched series are displayed in Figure 3. There were significant differences between patients with and those without AKI on all-cause mortality (AKI, 36.0% vs non-AKI, 19.1%, log-rank $P<0.001$) (Figure 3A). Landmark analysis even showed significant different mortality rates from 3 months to 5 years (AKI, 25.8% vs non-AKI, 17.1%, log-rank $P=0.004$). AKI significantly increased all-cause mortality when compared with non-AKI across the subgroups (TAVR cohort: 68.7% vs 38.7%, log-rank $P<0.001$ and SAVR cohort: 36.0% vs 19.1%, respectively) (Figure 3C and D). In multivariable analysis, AKI was significantly associated with increased 5-years mortality (Table 4).

In Kaplan-Meier analysis, higher grades of AKI were associated with an increased 5-year

mortality (Figure 3B). Increasing severity of AKI was associated with incremental risk of 5-year mortality in multivariable analysis. The adjusted HRs for 5-year mortality were 1.58 (95%CI 1.20-2.08) for AKI grade 1, 3.27 (95%CI 2.09-5.06) for AKI grade 2 and 4.82 (95%CI 2.93-8.04) for AKI grade 3 (Figure 4).

Discussion

In the present study, we observed the following notable findings: 1) AKI occurred in 12.0% and 13.3% of the patients without CKD following TAVR or SAVR in the unmatched and matched series, respectively; 2) SAVR was independently associated with AKI in comparison to TAVR; 3) the presence of AKI was associated with an increased risk of all-cause mortality at 5 years; and 4) increasing severity of AKI was associated with incremental risk of 5-year mortality. To the best of our knowledge, this is the first comparative analysis of TAVR and SAVR in non-CKD patients to date.

Although several studies have examined the outcomes of AKI in patients with high surgical-risk following TAVR and SAVR, most have included patients with a high rate of CKD, ranging from 3% to 62%.[3,9,17,18] In these high-risk subset of patients, the incidence rates of AKI ranged from 12% to 57% after TAVR, depending on the definition used.[19] On the other hand, among patients with intermediate to low surgical-risk and lower prevalence of CKD, the incidence of AKI after TAVR decreased to less than 5%.[8,20] Our data shows a comparable rate of AKI after TAVR compared to the

previous reports including lower risk patients. As previously reported, patients with CKD undergoing SAVR are at significantly higher risk of AKI and hemodialysis.[5] Gummert JF *et al.* showed that up to 16% of patients with CKD following SAVR required hemodialysis during the post-operative period.[21] In addition to this, we confirmed that SAVR is still associated with a significantly higher risk of AKI compared with TAVR even among patients without CKD. The effects of cardiopulmonary bypass on kidney function after surgical treatment have been well elucidated.[5,22] The effect of cardiopulmonary bypass and severe bleeding requiring blood transfusion could explain the worse kidney function after SAVR in patients without CKD of the present study.

A previous report showed that the occurrence of AKI is associated with higher rates of early and 1-year mortality following TAVR.[17] Among a population at high-risk with 50% of CKD, Elmariah S *et al*. reported of 66.7% in patients with AKI following TAVR, whereas 1-year mortality was 8.6% in patients who did not develop AKI.[23] The current study demonstrated that AKI is still associated with increased mortality following TAVR even in patients without CKD at a relatively low-surgical risk. Moreover, in our study of selected patients without CKD, even patients who developed AKI grade 1 was significantly associated with a worse outcome compared to patients without AKI. The minimally invasive nature of TAVR, the avoidance of cardiopulmonary bypass and the reduce risk of bleeding complications can be considered advantageous in terms of kidney protection.

Several limitations of our analysis should be acknowledged. Firstly, the retrospective nature is the main limitation of this study. Due to the non-randomized design of the study, differences in the incidence of AKI between TAVR and SAVR should be seen as hypothesis generating. Secondly, even though propensity score matching resulted in sufficient balance of baseline characteristics, bias due to unknown or unmeasured confounders cannot be excluded. Thirdly, we do not have data on renal function after discharge and we cannot estimate the rate of late dialysis. Fourthly, we were unable to determine whether the serum creatinine level returned to baseline before patients were discharged from hospital. Finally, the predictors of AKI in TAVR cohort should be interpreted cautiously, because no information on contrast volume administered during TAVR procedures were available for this analysis.

In conclusion, in this nationwide registry, AKI was less frequent after TAVR in comparison to SAVR among patients without CKD. AKI significantly increased the risk of 5-year mortality after either TAVR or SAVR (Take-home figure) and increasing severity of AKI was associated with incremental risk of late mortality.

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Figure legends

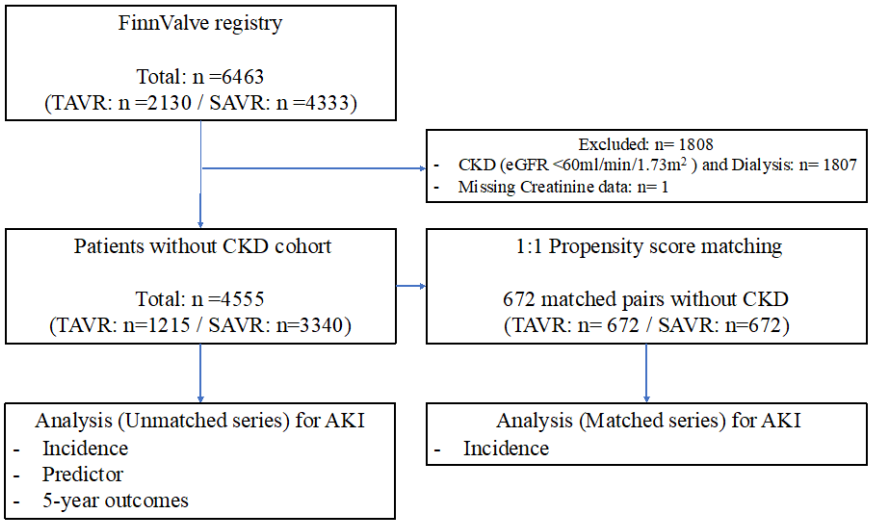


Figure 1. Study flowchart

Flow chart showing patient disposition to arrive at study for present analysis.

AKI=acute kidney injury; CKD=chronic kidney disease; SAVR=surgical aortic valve replacement; TAVR=transcatheter aortic valve replacement.

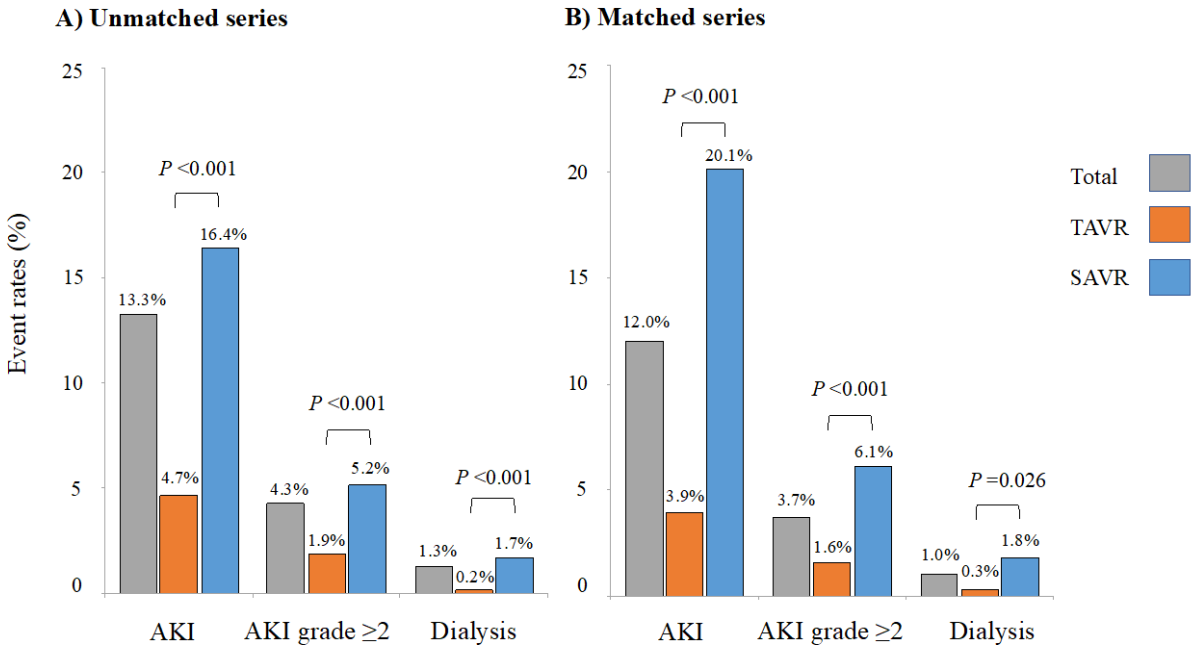
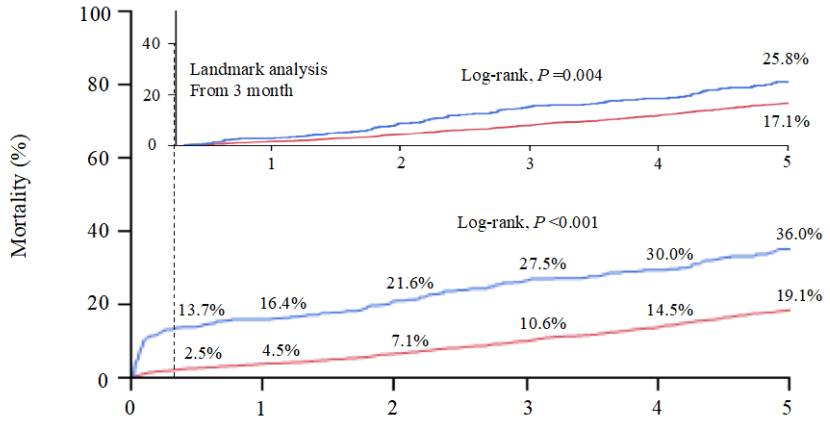


Figure 2. Incidence of acute kidney injury following TAVR and SAVR

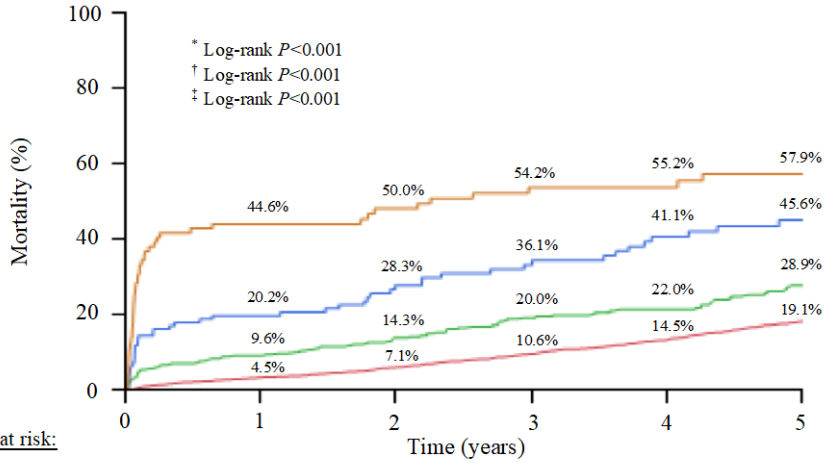
Patients who underwent SAVR had a significantly higher incidence of AKI in comparison to patients who underwent TAVR.

Abbreviations as in Table 1 and Figure 1.



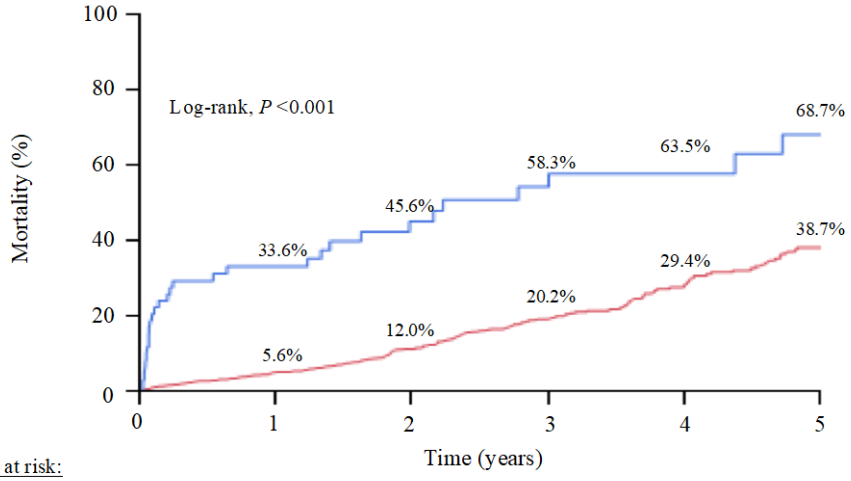
Number at risk:

AKI	606	475	403	319	262	285
Non-AKI	3949	3287	2664	2118	1639	1201



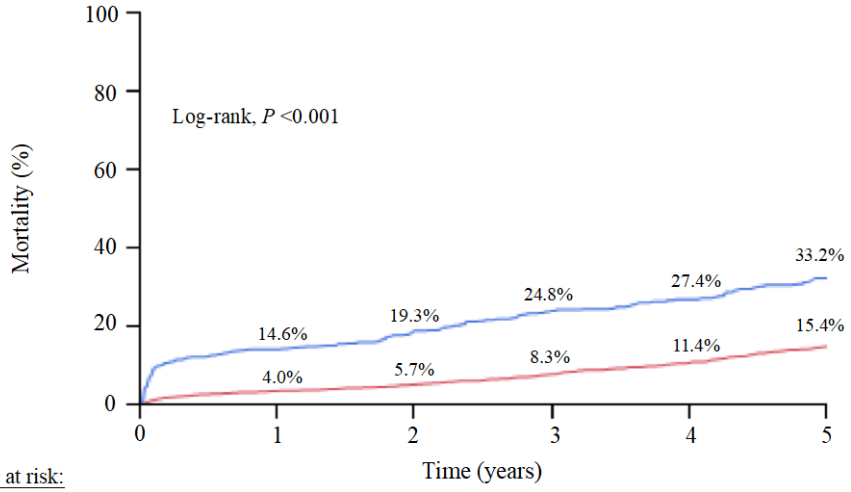
Number at risk:

AKI grade3	83	45	38	31	26	19
AKI grade2	114	85	69	55	45	32
AKI grade1	409	345	296	234	191	134
Non-AKI	3949	3287	2664	2118	1639	1201



Number at risk:

AKI	57	34	20	12	8	6
Non-AKI	1158	808	491	285	163	91



Number at risk:

AKI	549	441	383	307	254	179
Non-AKI	2791	2479	2173	1833	1476	1110

Figure 3. Cumulative event curves for outcomes in patients with or without AKI

(A) Cumulative event curves for all-cause death and landmark analysis from 3 month in total cohort.

(B) Cumulative event curves according to the AKI grades.

(C, D) Cumulative event curves for all-cause mortality (C) in TAVR cohort and (D) in SAVR cohort.

AKI=acute kidney injury.

*Non-AKI vs AKI grade 1, †AKI grade 1 vs AKI grade 2, and ‡AKI grade 2 vs AKI grade 3.

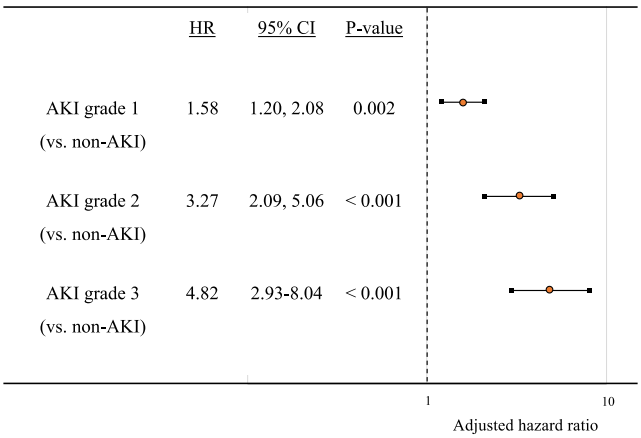
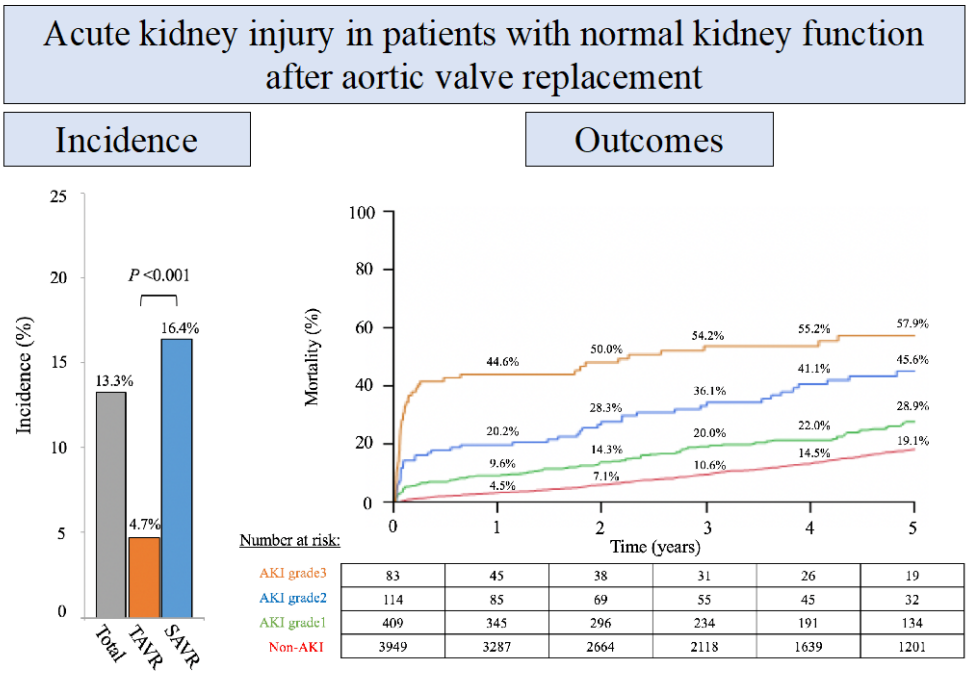


Figure 4. The impact of AKI grades on 5-year mortality

All AKI grades were significantly associated with a higher incidence of mortality. HRs were adjusted by baseline characteristics and early outcomes.

AKI=acute kidney injury; HR=hazard ratio; other abbreviations as in Table 1.



Take-home figure

Illustration showing the incidence and outcomes of acute kidney injury (AKI) in patients with normal kidney function following transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR).

Text tables

Table 1. Baseline characteristics in patients without chronic kidney disease before and after propensity score matching

	Unmatched				Matched			
Variables	TAVR (n=1215)	SAVR (n=3340)	*P* value	Standardized difference	TAVR (n=672)	SAVR (n=672)	*P* value	Standardized difference
Age, y (mean)	80.6±6.8	74.4±6.6	<0.001	0.988	78.5±7.4	78.2±5.5	0.36	0.046
(median)	81.7 (77.4, 85.4)	75.0 (70.3, 79.0)			80.3 (74.3, 83.9)	78.7 (74.6, 82.3)		
Female gender	629(51.8)	1469(44.0)	<0.001	0.157	350(53.6)	354(52.7)	0.74	0.018
Body mass index, kg/m^2	26.8±4.7	27.6±4.7	<0.001	0.170	27.2±5.1	27.4±4.7	0.58	0.040
Diabetes	313(25.8)	851(25.5)	0.85	0.007	172(25.6)	160(23.8)	0.45	0.042
COPD	269(22.1)	493(14.8)	<0.001	0.189	146(21.7)	148(22.0)	0.90	0.007
Atrial fibrillation	451(37.1)	668(20.0)	<0.001	0.386	204(30.4)	214(31.9)	0.56	0.032
Extracardiac arteriopathy	229(18.9)	371(11.1)	<0.001	0.220	100(14.9)	96(14.3)	0.76	0.017
Coronary artery disease	327(26.9)	1493(44.7)	<0.001	0.378	156(23.2)	142(21.1)	0.36	0.051
Previous PMI	208(9.8)	174(4.0)	<0.001	0.230	34(5.1)	40(6.0)	0.47	0.039
Previous cardiac surgery	242(19.9)	78(2.3)	<0.001	0.584	57(8.5)	57(8.5)	1.00	0.000
Previous PCI	250(20.6)	311(9.3)	<0.001	0.328	91(13.5)	95(14.1)	0.75	0.017
Previous MI	156(12.8)	432(12.9)	0.93	0.003	69(10.3)	67(10.0)	0.86	0.009
Previous stroke	138(11.4)	201(6.0)	<0.001	0.192	55(8.2)	57(8.5)	0.84	0.011
Haemoglobin, mg/L	127.2±15.1	133.8±14.3	<0.001	0.449	128.7±15.3	128.2±14.5	0.53	0.034
eGFR, ml/min/1.73m^2	80.8±17.1	83.8±17.1	<0.001	0.175	82.4±18.3	82.4±16.3	0.99	0.000

LVEF<51%	310(25.5)	627(18.8)	<0.001	0.162	147(21.9)	147(21.9)	1.00	0.000
NYHA class4	118(9.7)	302(9.0)	0.49	0.024	62(9.2)	63(9.4)	0.93	0.007
Frailty GSS≥2	155(12.8)	72(2.2)	<0.001	0.411	49(7.3)	46(6.9)	0.75	0.016
AHF within 90days	135(11.1)	353(10.6)	0.60	0.016	74(11.0)	76(11.3)	0.86	0.009
Urgent/emergent procedure	79(6.5)	411(12.3)	<0.001	0.200	53(7.9)	53(7.9)	1.00	0.000
Associated PCI or CABG	60(4.9)	1381(41.4)	<0.001	0.960	53(7.9)	45(6.7)	0.40	0.046
STS score, %, (mean)	3.8±2.7	2.6±2.2	<0.001	0.487	3.1±1.9	3.1±2.8	0.74	0.000
(median)	3.1 (2.3, 4.5)	2.1 (1.4, 3.0)			2.8 (2.0, 3.7)	2.4 (1.7, 3.4)		
EuroScore II, % (mean)	5.6±5.7	3.5±4.4	<0.001	0.412	4.0±3.6	3.9±4.3	0.82	0.025
(median)	3.8 (2.4, 6.6)	2.2 (1.4, 3.6)			2.8 (1.9, 4.6)	2.5 (1.8, 4.1)		

Values are expressed as counts and percentages (in parentheses), mean±standard deviation, or median and interquartile range (in parentheses).

AHF=acute heart failure; CABG=coronary artery bypass grafting; COPD=chronic obstructive pulmonary disease; eGFR=estimated glomerular filtration rate; GSS=geriatric status scale; IQR=interquartile range; LVEF=left ventricular ejection fraction; MI=myocardial infarction; NYHA=New York Heart Association; PCI=percutaneous coronary intervention; PMI=pacemaker implantation; SAVR=surgical aortic valve replacement; STS=Society of Thoracic Surgeons; TAVR=transcatheter aortic valve replacement.

Table 2. Procedure characteristics and early outcomes in patients without chronic kidney disease before and after propensity score matching

	Unmatched			Matched		
	TAVR (n=1215)	SAVR (n=3340)	*P* value	TAVR (n=672)	SAVR (n=672)	*P* value
Procedure characteristics						
General anesthesia	356(29.7)	3340(100)	<0.001	174(26.2)	672(100)	<0.001
Noradrenalin at anesthesia induction	255(21.0)	610(18.3)	0.038	127(18.9)	139(20.7)	0.41
Transfemoral approach	1068(87.9)	-		599(89.1)	-	
Pre-balloon dilatation	671(55.2)	-		373(55.5)	-	
Post-balloon dilatation	181(14.9)	-		90(13.4)	-	
Full sternotomy	-	3206(96.4)		-	633(94.5)	
Cardiopulmonary bypass time, min	-	128.6±45.6		-	114.9±41.7	
Early outcomes						
Major vascular complication	104(8.6)	51(1.5)	<0.001	60(8.9)	13(1.9)	<0.001
RBC transfusion>4 units	41(3.4)	634(19.3)	<0.001	23(3.5)	132(20.0)	<0.001
E-CABG bleeding grades2-3*	49(4.1)	722(21.9)	<0.001	26(4.0)	142(21.5)	<0.001
Moderate to severe PVR	45(3.7)	19(0.57)	<0.001	23(3.4)	4(0.60)	<0.001
Stroke	31(2.6)	114(3.4)	0.14	15(2.2)	25(3.7)	0.11
PMI	110(9.1)	127(3.8)	<0.001	64(9.5)	33(4.9)	0.001
Sepsis	7(0.58)	39(1.2)	0.074	4(0.60)	8(1.2)	0.25
Length of hospital stay, days	5.2±4.5	8.0±5.8	<0.001	5.0±4.3	8.2±5.0	<0.001

30-day mortality	31(2.6)	103(3.1)	0.35	17(2.5)	24(3.6)	0.27

Values are expressed as counts and percentages (in parentheses), mean±standard deviation, or median and interquartile range (in parentheses).

E-CABG=The European multicenter study on coronary artery bypass grafting; PMI=pacemaker implantation; PVR= paravalvular regurgitation; RBC=red blood cell; Other abbreviations as in Table 1.

* Brief description of E-CABG bleeding grade 2-3 = transfusion of more than 4 units of red blood cells and/or operation for mediastinal or peripheral bleeding.[24]

Table 3. Multivariable analysis of factors associated with acute kidney injury in patients without pre-procedural chronic kidney disease

Variables	**Multivariable analysis**		
Overall series	OR	(95%CI)	*P* value
SAVR (vs. TAVR)	3.99	2.85, 5.70	<0.001
Female gender	0.68	0.55, 0.84	<0.001
Body mass index	0.93	0.89, 0.99	<0.001
Haemoglobin	0.97	0.93, 0.99	0.041
Atrial fibrillation	1.53	1.23, 1.90	<0.001
AHF within 90days	1.51	1.04, 2.18	0.029
Major vascular complication	1.69	1.01, 2.75	0.05
RBC transfusion>4 units	3.78	2.05, 7.58	<0.001
Moderate to severe PVR	4.01	1.98, 8.11	<0.001
Sepsis	3.09	1.47, 6.31	0.003
TAVR cohort			
Atrial fibrillation	1.91	1.04, 3.54	0.037
Local anesthesia	0.33	0.11, 0.96	0.041
Transfemoral approach	0.68	0.51, 0.88	0.012
E-CABG bleeding grade2-3	18.1	3.48. 94.4	0.001
Moderate to severe PVR	4.64	1.57, 12.0	0.007
SAVR cohort			
Age	1.02	1.01, 1.04	<0.001
Female gender	0.69	0.53, 0.89	0.004
Body mass index	0.92	0.82, 0.99	<0.001
Atrial fibrillation	1.47	1.14, 1.91	0.004
Haemoglobin	0.96	0.92, 0.99	0.038
AHF within 90days	1.62	1.05, 2.49	0.030

NYHA class4	1.80	1.12, 2.89	0.016
Cardiopulmonary bypass time (per 10min)	1.09	1.02, 1.23	<0.001
RBC transfusion>4 units	5.38	2.51, 13.4	<0.001
Sepsis	3.71	1.56, 8.51	0.004

Model contains the following variables; (in total series): all baseline covariates and early outcomes, (in TAVR cohort): all baseline covariates, TAVR specific procedure characteristics and early outcomes, and (in SAVR cohort): all baseline covariates, SAVR specific procedure characteristics and early outcomes.

Abbreviations as in Table 1 and 2.

Table 4. Multivariable analysis of factors associated with 5-year mortality in patients without pre-procedural chronic kidney disease

Variables	**Multivariable analysis**		
Overall series	HR	(95% CI)	*P* value
TAVR (vs. SAVR)	2.12	1.69, 2.67	<0.001
Age (per 1year)	1.03	1.01, 1.06	<0.001
Female gender	1.28	1.05, 1.57	0.016
Diabetes	1.41	1.15, 1.72	0.001
COPD	1.58	1.27, 1.97	<0.001
Atrial fibrillation	1.27	1.05, 1.55	0.015
AHF within 90days	1.39	1.00, 1.92	0.048
LVEF<51%	1.37	1.09, 1.72	0.007
Major vascular complication	2.61	1.76, 3.84	<0.001
Stroke	2.81	1.90, 4.12	<0.001
AKI	2.14	1.69, 2.67	<0.001
RBC transfusion>4 units	2.92	1.41, 6.87	0.003
TAVR cohort			
Age (per 1year)	1.02	1.01, 10.5	0.006
COPD	2.18	1.46, 3.25	<0.001
LVEF <51%	1.26	1.05, 1.57	<0.001
Transfemoral approach	0.54	0.45, 0.76	<0.001
Major vascular complication	1.82	1.02, 3.18	0.042
AKI	2.80	1.39, 5.56	0.004
RBC transfusion >4 units	3.67	1.45, 7.11	0.017
SAVR cohort			
Age (per 1year)	1.04	1.01, 1.09	<0.001
Diabetes	1.41	1.09, 1.82	0.010
LVEF<51%	1.50	1.17, 2.02	0.008

Cardiopulmonary bypass time (per 10min)	1.01	1.00, 1.02	0.011
Major vascular complication	2.49	1.21, 5.01	0.014
AKI	2.01	1.53, 2.64	<0.001
RBC transfusion>4 units	4.05	1.59, 13.7	0.002

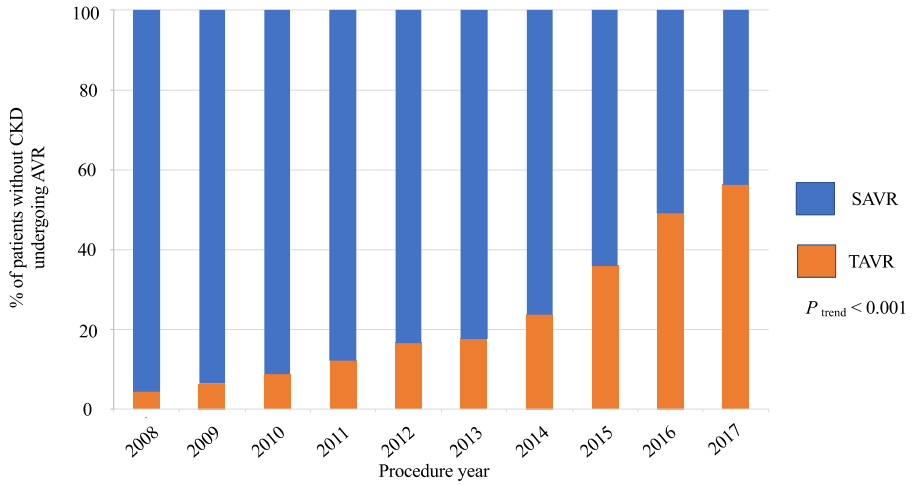
The regression models include the following variables: overall series, all baseline covariates and early outcomes; TAVR cohort, all baseline covariates, TAVR specific procedure characteristics and early outcomes; SAVR cohort, all baseline covariates, SAVR specific procedure characteristics and early outcomes.

Abbreviations as in Table 1 and 2.

Supplementary files

Acute Kidney Injury following Transcatheter and Surgical Aortic Valve Replacement in Patients with Normal Kidney Function; Results from the FinnValve Registry

Noriaki Moriyama and Teemu Laakso et al.



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
All	296	288	351	378	470	525	508	574	630	535
SAVR	283	270	321	332	392	432	387	368	321	234
TAVR	13	18	30	46	78	93	121	206	309	301

Figure S1. Temporal trends in utilization of TAVR and SAVR in patients without chronic kidney disease before matching

TAVR became the predominant modality of AVR in patients without CKD by 2016.

AVR = aortic valve replacement; CKD = chronic kidney disease; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

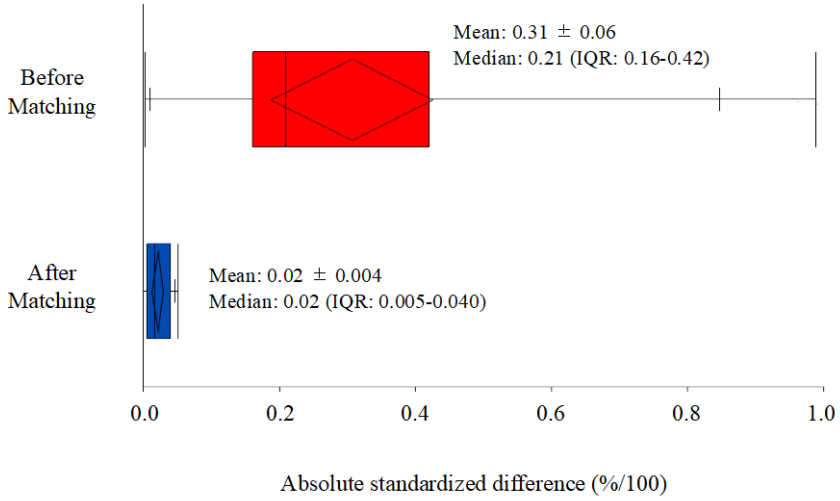


Figure S2. Absolute standardized difference before and after propensity score matching

Standardized mean difference before and after propensity score matching. Standardized mean difference <0.1 indicates effective balance of baseline covariates and thus adequate bias reduction.

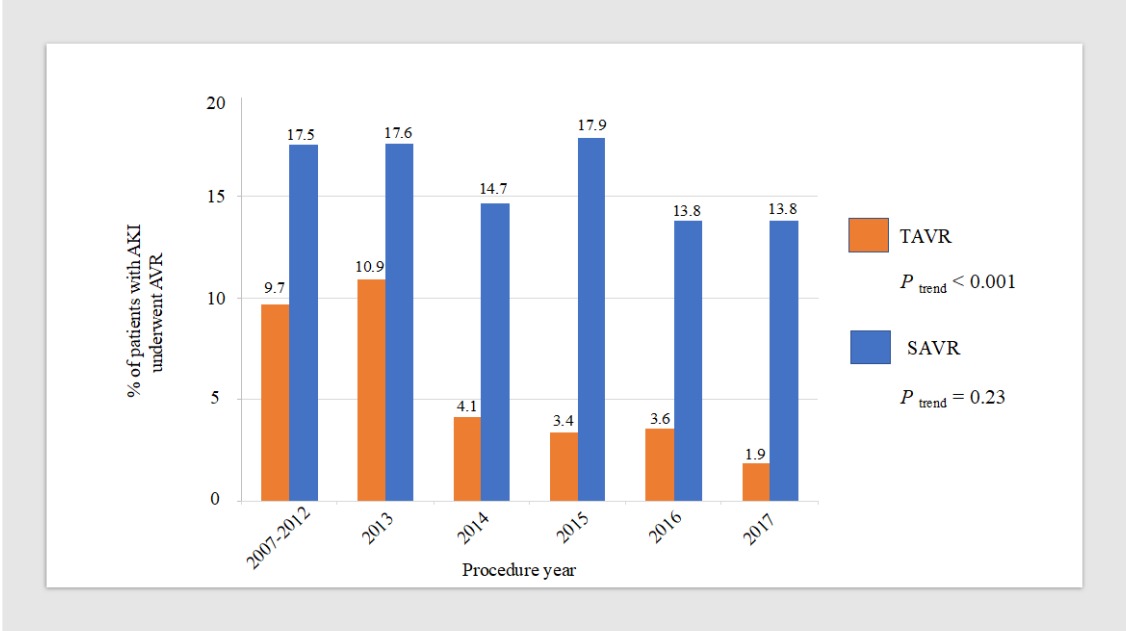
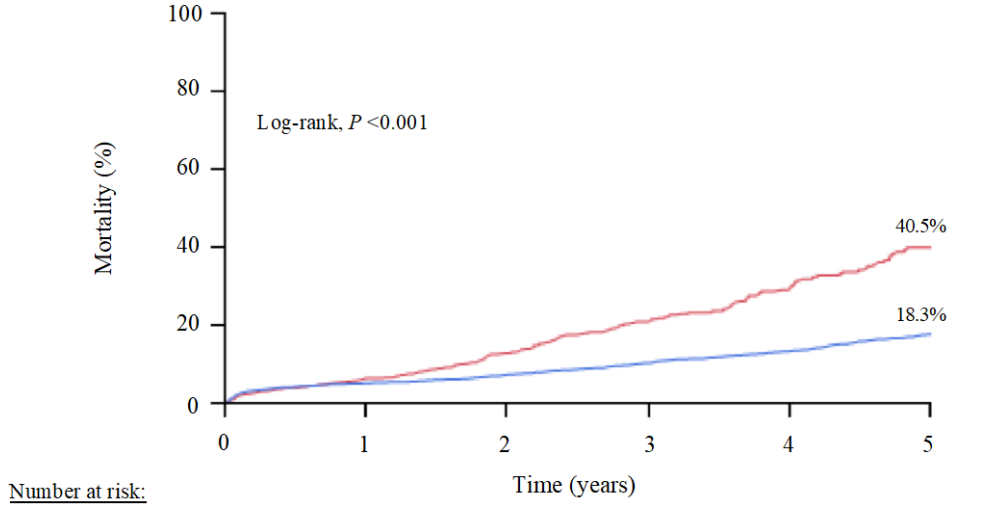


Figure S3. Temporal trends of the incidence of AKI in patients without chronic kidney injury before propensity score matching.

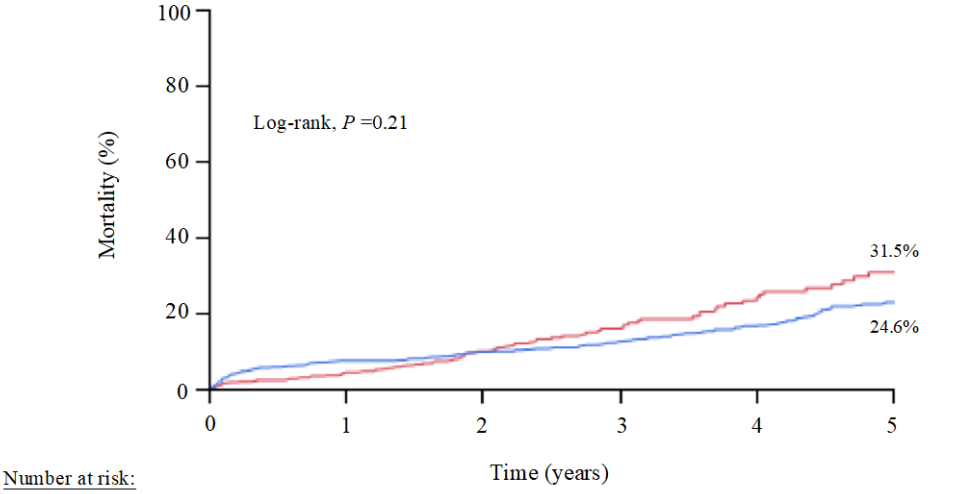
The proportion of AKI in patients who underwent TAVR significantly decreased during the study period. Since the number of TAVR population was small between 2007 and 2012, the incidence of AKI was reported in total during the period.

AKI = acute kidney injury; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.



Number at risk:

TAVR	1215	842	511	297	171	97
SAVR	3340	2920	2556	2140	1730	1289



Number at risk:

TAVR	672	457	273	163	95	54
SAVR	672	574	514	442	359	257

Figure S4. Cumulative event curves for all-cause mortality following TAVR or SAVR

(A) Kaplan-Meier analysis in the unmatched cohort and (B) in the matched cohort.

AKI = acute kidney injury; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

Table S1. Definitions of secondary outcomes

Stroke	Stroke was defined according to Valvular Academic Research Consortium-2 (VARC-2) criteria as any focal or global neurological deficit lasting ≥24 hours; or <24 h if available neuroimaging documents of a new haemorrhage or infarct; or the neurological deficit resulting in death.[25]
Major vascular complications	Major vascular complications were defined according to VARC-2 criteria as any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, new apical aneurysm/pseudo-aneurysm, or access site or access-related vascular injury leading to death, life-threatening or major bleeding, visceral ischaemia, neurological impairment, or distal embolization from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage, or the use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischaemia or neurological impairment, or any new ipsilateral lower extremity ischaemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram, or surgery for access site-related nerve injury, or permanent access site-related nerve injury.[25]
Major bleeding	Major bleeding was defined as E-CABG bleeding grades 2-3, i.e. transfusion of more than 4 units of red blood cells and/or resternotomy for excessive bleeding.[24] In this study, the VARC-2 definition of major and life-threatening bleeding was not applied because, contrary to patients undergoing TAVR, a significant decrease of haemoglobin level is observed in most of patients undergoing SAVR and this does not always reflect a condition of major perioperative blood loss.
Paravalvular regurgitation	Paravalvular regurgitation was defined according to the VARC-2 criteria and was graded by local physicians before discharge.[25]

Table S2. A propensity score matching

A propensity score was estimated using a non-parsimonious logistic regression model including covariates as follows: Age, gender, body mass index, diabetes, chronic obstructive pulmonary disease, atrial fibrillation, extracardiac arteriopathy, CAD, previous pacemaker implantation (PMI), previous cardiac surgery, previous percutaneous coronary intervention (PCI), previous myocardial infarction, previous stroke, haemoglobin, eGFR, left ventricular ejection fraction (LVEF) <51%, NYHA class 4, Frailty GSS ≥2, AHF within 90days, urgent or emergent status, associated PCI or CABG, STS score and EuroSCORE II.