REPORT

Impact of chronic kidney disease in 29 893 patients undergoing transcatheter or surgical aortic valve replacement from the German Aortic Valve Registry

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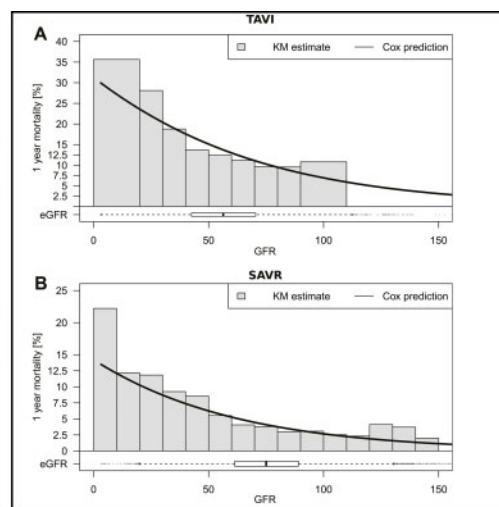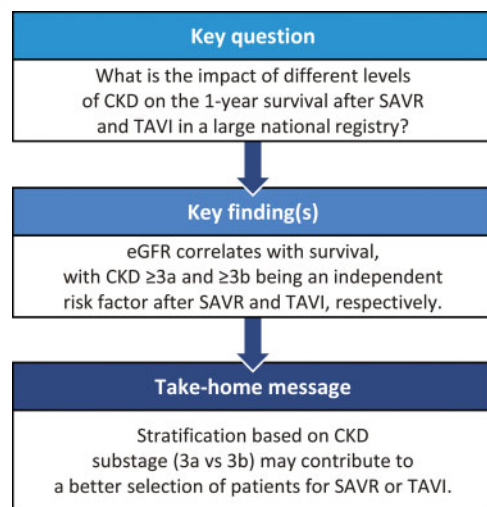
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Presented at the ESC Congress 2020, August 2020 (virtual meeting).
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Abstract

OBJECTIVES: Chronic kidney disease (CKD) is a key risk factor in patients undergoing transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR). We analysed the impact of estimated glomerular filtration rate (eGFR) and CKD stages on their mid-term survival.

METHODS: Data from 29 893 patients enrolled in the German Aortic Valve registry from January 2011 to December 2015 receiving TAVI (n = 12 834) or SAVR (n = 17 059) at 88 sites were included. The impact of renal impairment, as measured by eGFR and CKD stages, was investigated. The primary end-point was 1-year cumulative all-cause mortality.

RESULTS: Higher CKD stages were significantly associated to lower in-hospital, 30-day- and 1-year survival rates. Both TAVI- and SAVR-treated patients in CKD 3a, 3b, 4 and 5 stages showed significant and gradually increasing HR values for 1-year all-cause mortality. The same trend persisted in multivariable analysis, although HR values for CKD 3a and 5 did not reach significance in TAVI patients, whereas CKD 4 + 5 did not reach statistical significance in SAVR. Likewise, eGFR as a continuous variable was a significant predictor for 1-year mortality, with the best cut-off points being 47.4 ml/min/1.73 m^2 for TAVI and 59.8 ml/min/1.73 m^2 for SAVR. Significant 8.6% and 9.0% increases in 1-year mortality were observed for every 5-ml reduction in eGFR for TAVI and SAVR, respectively.

CONCLUSIONS: CKD $\geq$3b and CKD $\geq$3a are the independent major risk factors for mortality in patients undergoing TAVI and SAVR, respectively. In the overall population of patients with severe aortic stenosis, an appropriate stratification based on CKD substage may contribute to a better selection of patients suitable for such therapies.

Keywords: Transcatheter aortic valve implantation • Surgical aortic valve replacement • Aortic stenosis • Chronic kidney disease • Mortality

ABBREVIATIONS

CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
GARY	German Aortic Valve registry
HR	Hazard ratio
ROC	Receiver operating curve
SAVR	Surgical aortic valve replacement
TA	Transapical
TAVI	Transcatheter aortic valve implantation
TIA	Transient ischaemic attack
TV	Transvascular

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is the treatment of choice for patients with severe aortic stenosis and a high surgical risk [1]. Furthermore, recent studies have suggested that patients with intermediate and low risk can also benefit from its use [2]. Several risk factors have been shown to have an impact on clinical outcomes after surgical aortic valve replacement (SAVR) and TAVI [3], and a number of them, including age, frailty and non-cardiac co-morbidities, such as impaired renal function, have been considered by heart teams when selecting patients for the different treatment strategies [4].

Chronic kidney disease (CKD) is a well-recognized risk factor for adverse clinical outcomes in patients with heart failure and coronary or valve diseases [5], as well as in those undergoing interventional or surgical cardiac procedures, such as coronary artery bypass grafting [6], and percutaneous coronary intervention [7]. Whereas in pre-TAVI era a clear-cut association was shown in patients undergoing SAVR [8], the relationship between various CKD stages and outcomes after TAVI is still unclear. Earlier studies reported an influence of pre-operative renal disease on outcomes after SAVR [8]; however, data are still limited on the impact of moderate renal dysfunction after the recent improvements in surgical technique and resources and in an era in which TAVI has been established as a widely used alternative for many patients.

Large registries are essential to confirm findings from clinical trials in a real-world setting. A large European registry has previously investigated the impact of renal dysfunction on TAVI results in the UK [9]. With Germany being the country with the highest number of TAVI procedures performed in Europe [10], the German Aortic Valve Registry (GARY) provides clinical data from one of the largest cohorts of patients undergoing TAVI or SAVR.

We used GARY data to analyse the impact of estimated glomerular filtration rate (eGFR) and various CKD stages, on short- and mid-term outcomes in patients undergoing TAVI and SAVR throughout a 5-year period.

PATIENTS AND METHODS

The German Aortic Valve Registry

This registry has been previously described in detail [11]. From January 2011 to December 2015, all consecutive patients from the vast majority of hospitals performing TAVI and SAVR procedures in Germany (n = 88) were enrolled; the only exclusion criterion was patient's refusal to participate. The registry study was approved by the institutional review board/ethics committee of all participating centres and written informed consent was provided by all patients prior to the intervention.

Data were collected from all hospitals and sent to the BQS Institute for Quality and Patient Safety, an independent research institute for quality control, which also collects follow-up data. The GARY registry receives financial support in the form of unrestricted grants by medical device companies, the German Heart Foundation, the DGK and the DGTHG, none of which have access to the data or any influence on its publications (https://www.aortenklappenregister.de).

Measures of renal function

The eGFR was calculated using the Modification of Diet in Renal Disease equation [12]. Patients were classified into 5 groups

defined by their eGFR (ml/min/1.73 m^2): CKD 1 + 2 ($\geq$60), CKD 3a (45–59), CKD 3b (30–44), CKD 4 (15–29) and CKD 5 (<15). Use of such categories (in particular, assessing 3a and 3b as separate substages) has been previously suggested when evaluating renal function in cardiovascular diseases [13]. For SAVR, CKD stage 4 and CKD 5 were grouped in 1 category due to the limited number of patients in these categories.

Study population

The study population included all patients with severe aortic stenosis undergoing transvascular (TV) or transapical (TA) TAVI, and SAVR. Patients with outlier and/or missing values for key variables such as age and creatinine were excluded, as well as those with a combined therapy (SAVR and coronary artery bypass grafting). Other exclusion criteria are reported in Supplementary Material, Table S1. Patients who were on dialysis prior to the intervention were excluded from the current analysis and will be reported separately since outcomes in this specific group of patients may be significantly influenced by the renal replacement therapy itself and not just by their severe renal dysfunction. Baseline and procedural parameters were assessed.

Outcomes

The primary end-point in our analysis was 1-year cumulative all-cause mortality across CKD stages and its association to eGFR as a continuous variable in patients treated with TAVI and SAVR. Causes of death were also assessed. Secondary end-points included in-hospital and 30-day mortality, and post-procedural complications, including stroke, transient ischaemic attack (TIA), myocardial infarction, new onset of atrial fibrillation, permanent pacemaker implantation, transfusion needs ($\geq$2 red blood cell units), vascular complications, new-onset dialysis (temporary versus chronic), aortic regurgitation (grade $\geq$2), postintervention stay in ICU (days) and postintervention length of hospitalization (days). Further complications at 1 year were also collected.

To describe the renal function status of patients being treated with TAVI or SAVR in our population and its potential drift with the growing use of TAVI interventions in a larger number of patients over the years, the CKD stage proportions in 2011 (a year in which TAVI had not yet achieved the good clinical results found from 2012 onwards [14]) were compared with those in the later years.

Since TV and TA approaches for TAVI are usually employed for different patient profiles [15], we performed a sensitivity analysis specific for each access route. A sensitivity analysis was also performed excluding the year 2011, to remove the impact of a potential learning curve for the transcatheter procedure.

Statistical analysis

All statistical analyses were performed with R software (R Foundation for Statistical Computing, Vienna, Austria) using standard packages (stats, survival, ggplot2) and the survivalROC package version 1.0.3. Continuous variables are presented as mean ± SD or median (min, max), depending on plausibility of a normal distribution. Categorical variables are presented as frequencies and percentages and are compared with chi-squared tests. Differences in quantitative patients' characteristics between groups were analysed using the Wilcoxon–Mann–Whitney U-test or the Kruskal–Wallis test. Kaplan–Meier curves for 1-year cumulative survival were created and a Cox proportional hazard model was developed, using CKD 1 + 2 as the reference category. Cox regression models were used to find independent variables predicting 1-year mortality. In the multivariable analysis, we included all variables with P-values <0.10 found in the univariate analysis as well as some other clinically relevant variables. Multivariable analysis was done as complete case analysis. The proportional hazard assumptions were checked visually and with a score test. A survival receiver operating curve (ROC) was used to assess 1-year mortality prediction based on eGFR as a continuous variable. A cut-off point was also established; statistical significance was based on a P-value of <0.05 in all tests.

RESULTS

Study population

A total of 29 893 patients were included; 12 834 received TAVI and 17 059 SAVR. Most common reasons for exclusion were combined procedures (e.g. CABG plus SAVR), prior valve implantation and patients at very high risk due to previous resuscitation, mechanical ventilation, cardiogenic shock or poor-prognosis co-morbidities (see Supplementary Material, Table S1). A TV approach was used in 10 155 (79.1%) patients, whereas a TA approach was used in 2679 (20.9%). One-year follow-up data were available for all patients. Exclusion criteria are shown in Supplementary Material, Table S1; a total of 49 307 patients were excluded.

The distribution of TAVI patients across CKD stages was: CKD 1 + 2 43.2%, CKD 3a 28.0%, CKD 3b 20.6%, CKD 4 7.6% and CKD 5 0.6%. Overall median eGFR value was 56.4 ml/min/1.73 m^2. For SAVR, the following distribution was found: CKD 1 + 2 77.1%, CKD 3a 16.0%, CKD 3b 5.5% and CKD 4 + 5 1.4%. Overall median eGFR value was 75.0 ml/min/1.73 m^2.

In the first year of the registry, the proportion of TAVI patients in CKD stage 1–2 was 38.5%, whereas in subsequent years, an increased proportion was observed, with values reaching 43.9% (P < 0.001); as a consequence, the proportion of patients in CKD stages 3a–5 showed a reduction in later years. Similarly, after full TAVI introduction, the proportion of SAVR patients in CKD stage 1 + 2 significantly increased every year from 74.2% to 80.0%, while the proportion of patients in CKD 3a–5 was decreasing (P < 0.001).

Baseline clinical and echocardiographic characteristics

The main baseline clinical and echocardiographic characteristics across CKD stages are summarized in Table 1. Age (mean ± SD) of TAVI patients was 82.2 ± 5.5 years, 57.4% were female and Society of Thoracic Surgeons (STS) score (mean ± SD) was 5.0 ± 3.0, which corresponds to an intermediate-risk level. A significant correlation between higher CKD stage and a higher incidence of previous myocardial infarction, cardiac decompensation, arterial vascular disease, insulin-dependent diabetes and severe tricuspid regurgitation was found. Furthermore, higher CKD stages were associated with reduced ejection fraction, low mean transvalvular pressure gradient (Pmean) and higher AKL scores, Euro-Scores and STS scores (all P < 0.001).

As for SAVR patients, more than half of the overall population were men, with an age of 69.7 ± 9.9 years and an overall STS

score of 2.1 ± 1.4. Again, nearly all characteristics became significantly worse with higher CKD stages.

Procedural characteristics

Procedural outcomes are shown in Table 2. Patients received the following transcatheter valve devices from various manufacturers: Sapien™ valves (Edwards Lifesciences Inc., Irvine, CA, USA) in 55.5%; Corevalve™ and Engager™ prostheses (both Medtronic Inc., St. Paul, MN, USA) in 30.6%; Acurate™ prostheses (Symetis Inc., Ecublens, Switzerland) in 6.0%; Direct flow™ prostheses (Direct flow medical, Santa Rosa, CA, USA) in 2.1%; Jenavalve™ prostheses (Jenavalve Inc., Munich, Germany) in 1.4%; Lotus™ prostheses (Boston Scientific, Marlborough, MA, USA) in 1.2%; and Portico™ prostheses (St. Jude Medical Inc., St. Paul, MN, USA) in 1.1%. TA approach, general anaesthesia and urgent procedures were numerically more common in CKD stage 5, while contrast dye amount showed a significant decrease with CKD stage ($P < 0.001$). Patients treated with SAVR received the following devices: Carpentier-Edwards Perimount™ valves (Edwards Lifesciences Inc., Irvine, CA, USA) in 46.6%; St. Jude™ prostheses (St. Jude Medical Inc., St. Paul, MN, USA) in 25.7%; Medtronic's Hancock, Freestyle, Advantage, Open and other prostheses (Medtronic Inc.) in 12.9%; ATS Medical prothesis (ATS Medical Inc., Minneapolis, MN, USA, now also Medtronic Inc.) in 2.3%; Mitroflow and other Sorin Group prostheses (Sorin Group, now part of LivaNova, London, UK) in 9.9%; and Labcor prosthesis (Labcor Inc., Belo Horizonte, Brazil) in 0.5%. Urgent SAVR was more common in CKD 4 + 5 stages ($P = 0.007$).

Mortality and complications

In-hospital, 30-day and 1-year survival rates, causes of mortality and post-procedural complications are shown in Table 3. The overall survival in TAVI patients was 97.3% in-hospital, 96.7% at 30 days and 85.9% at 1 year. All mortality rates were higher in patients with higher CKD stages (all, $P < 0.001$).

Overall, common post-procedural TAVI complications were new-onset atrial fibrillation (22.3%) and permanent pacemaker implantation (16.2%). The need for post-procedural temporary and chronic dialysis increased with CKD stage ($P < 0.001$). ICU stay (mean ± SD) was 2.9 ± 4.5 days and length of hospitalization was 10.7 ± 7.9 days. Both ICU stay and the entire length of hospitalization increased with kidney failure severity (all, $P < 0.001$).

Overall survival in SAVR patients was 98.9% in-hospital, 98.6% at 30 days and 95.7% at 1 year and post-procedural complications are shown in Table 3. All mortality rates increased with CKD stage (all, $P < 0.001$). Cardiovascular causes of death at 1 year were more frequent than non-cardiovascular causes in nearly all CKD categories, but differences were not significant. Post-procedural TIA, atrial fibrillation, renal replacement therapy, mean ICU stay and mean hospital stay increased significantly with renal impairment severity.

Further complications found in a 1-year follow-up period after TAVI and SAVR are shown in Supplementary Material, Table S2.

Main outcome: 1-year cumulative all-cause mortality

Mortality in TAVI patients increased with increasing CKD stage. Kaplan–Meier curves showed an early divergence, which gradually increased all throughout the 1-year period; the higher the CKD stage, the wider the curve's separation from the reference category (CKD 1 + 2) (Fig. 1). The Cox regression univariate analyses for 1-year cumulative all-cause mortality for each CKD stage are shown in Table 4. Taking CKD 1 + 2 as the reference category, CKD 3a, 3b, 4 and 5 showed significant, gradually increasing hazard ratio (HR) values for mortality, as shown in a forest plot (Fig. 2). Multivariable complete case analysis included 9759 patients. Cox multivariable regression analysis was performed using a number of clinically relevant variables and all variables with a P-value of <0.10 in univariate analyses (see Supplementary Material, Table S3). There were no significant deviations from the proportional hazard assumptions (data not shown). HRs for mortality in all higher CKD stages were still above 1 and remained significantly increased in CKD stages 3b and 4. One-year survival was not significantly different in the complete case TAVI subset compared to the TAVI subset with missing cases, and CKD stages were also comparable between the subsets. In a *post hoc* exploratory analysis of combined CKD stages 4 + 5, a multivariable analysis did show a significantly increased mortality (data not shown). Detailed results for multivariable analysis are also found in Supplementary Material, Table S4.

One-year survival curves for each CKD stage in SAVR patients are shown in Fig. 1; overall, the pattern of curves divergence was similar to the one observed in TAVI patients. The Cox regression univariable analyses for 1-year cumulative all-cause mortality for each CKD stage when taking CKD 1 + 2 as the reference category are shown in Table 4. HR for mortality increased gradually and significantly with increasing kidney failure severity, as shown in Fig. 2. Supplementary Material, Table S3 shows univariate test results for all risk factors. Those with P-value <0.1 and some other clinically relevant and frequently available variables were included in a multivariable analysis. Multivariable complete case analysis included 11 396 patients. Only minor deviations from the proportional hazard assumptions were observed (data not shown). Mortality in CKD 3a and 3b remained significantly increased in the multivariable analysis, whereas the small group with CKD 4 + 5 did not reach statistical significance. There were only minor differences in the complete case SAVR subset compared to the SAVR subset with missing cases (worse survival in the subset with missing values), but no significant interactions were found between the CKD stages and the selected group with respect to 1-year survival. Detailed results for multivariable analysis including other independent predictors for 1-year all-cause mortality are found in Supplementary Material, Table S4.

Estimated glomerular filtration rate as a predictor for 1-year cumulative all-cause mortality

In TAVI patients, a positive association was found between eGFR and 1-year mortality calculated from Kaplan–Meier estimates, as shown in Fig. 3. The figure displays 1-year mortality in patients with successively higher eGFR values, typically in 10-ml intervals and 20-ml intervals in the boundary regions. In fact, there is a high coincidence with the Cox regression result, predicting the 1-year mortality to increase by 8.6% for every 5-ml reduction in eGFR ($P < 0.001$). A survival ROC analysis at 1-year survival for eGFR as a continuous variable showed an eGFR value of 47.4 ml/min/1.73 m^2 to be the best cut-off point to predict 1-year mortality (Fig. 4). eGFR as a continuous variable was also a

Table 1: Baseline and echocardiographic characteristics in transcatheter aortic valve implantation and surgical aortic valve replacement patients

TAVI	All (n = 12 834)	CKD stages 1/2 (n = 5544)	CKD stage 3a (n = 3592)	CKD stage 3b (n = 2644)	CKD stage 4 (n = 976)	CKD stage 5 (n = 78)	P-value
Age (years), median, min-max	82.5, 36.2-102.0	81.4, 36.2-96.8	83.2, 53.8-102.0	83.7, 48.1-100.1	83.7, 58.6-97.8	82.91, 66.9-93.7	<0.001
Gender (female), n/n (%)	7372/12 834 (57.4)	2815/5544 (50.8)	2211/3592 (61.6)	1658/2644 (62.7)	643/976 (65.9)	45/78 (57.7)	<0.001
BMI (kg/m^2), median, min-max (n = 12 710)	26.57, 14.45-49.56	26.37, 14.67-49.56	26.67, 14.45-48.07	26.78, 15.11-48.85	27.16, 14.87-49.31	27.47, 17.15-39.06	<0.001
Creatinine (mg/dl), median, min-max (n = 12 834)	1.00, 0.20-9.90	0.80, 0.20-1.30	1.10, 0.85-1.50	1.40, 1.10-2.10	2.00, 1.50-3.76	4.00, 2.80-9.90	<0.001
NYHA (III/IV), n/N (%)	10 485/12 834 (81.7)	4357/5544 (78.6)	2943/3592 (81.9)	2252/2644 (85.2)	869/976 (89.0)	64/78 (82.1)	<0.001
Previous MI, n/N (%)	1333/12 823 (10.4)	543/5538 (9.8)	353/3590 (9.8)	309/2641 (11.7)	116/976 (11.9)	12/78 (15.4)	0.014
Previous PCI, n/N (%)	3362/12 834 (26.2)	1371/5544 (24.7)	938/3592 (26.1)	714/2644 (27.0)	314/976 (32.2)	25/78 (32.1)	<0.001
Permanent pacemaker, n/N (%)	1376/12 690 (10.8)	450/5498 (8.2)	402/3548 (11.3)	354/2607 (13.6)	159/959 (16.6)	11/78 (14.1)	<0.001
Arterial vascular disease, n/N (%)	3198/12 825 (24.9)	1238/5540 (22.3)	903/3589 (25.2)	748/2643 (28.3)	282/975 (28.9)	27/78 (34.6)	<0.001
Peripheral arterial vascular disease, n/N (%)	1959/12 824 (15.3)	713/5540 (12.9)	542/3589 (15.1)	501/2642 (19.0)	184/975 (18.9)	19/78 (24.4)	<0.001
Atrial fibrillation, n/N (%)	3506/12 834 (27.3)	1300/5544 (23.4)	989/3592 (27.5)	859/2644 (32.5)	345/976 (35.3)	13/78 (16.7)	<0.001
Mitral regurgitation ≥2°, n/N (%)	2885/12 577 (22.9)	1105/5424 (20.4)	806/3520 (22.9)	665/2600 (25.6)	286/955 (29.9)	23/78 (29.5)	<0.001
EF (%), median, min-max (n = 11 675)	56, 5-85	59, 10-85	56, 5-85	55, 15-84	55, 13-85	55, 20-75	<0.001
Hypertension, n/N (%)	11 435/12 741 (89.7)	4914/5489 (89.5)	3194/3572 (89.4)	2384/2634 (90.5)	868/969 (89.6)	75/77 (97.4)	0.12
Previous cardiac decompensation, n/N (%)	2597/12 463 (20.8)	946/5366 (17.6)	679/3495 (19.4)	667/2577 (25.9)	278/949 (29.3)	27/76 (35.5)	<0.001
AVA (cm^2), median, min-max (n = 11 958)	0.70, 0.10-3.00	0.70, 0.10-3.00	0.70, 0.20-2.40	0.70, 0.20-2.20	0.70, 0.20-2.00	0.70, 0.30-1.00	0.29
Pmean (mmHg), median, min-max	43, 10-100	44, 10-100	43, 10-100	42, 11-99	41, 10-98	40, 15-96	<0.001
Neurological dysfunction (Rankin ≥2), n/N (%)	343/12 168 (2.8)	164/5294 (3.1)	87/3599 (2.6)	59/2686 (2.4)	33/916 (3.6)	0/73 (0.0)	0.081
Lung disease, n/N (%)	2283/12 828 (17.8)	1007/5543 (18.2)	615/3589 (17.1)	460/2643 (17.4)	191/976 (19.6)	10/77 (13.0)	0.27
Pulmonary hypertension >55 mmHg, n/N (%)	2210/12 662 (17.5)	854/5471 (15.6)	602/3539 (17.0)	500/2615 (19.1)	238/960 (24.8)	16/77 (20.8)	<0.001
Insulin-dependent diabetes, n/N (%)	1460/3914 (37.3)	470/1463 (32.1)	379/1070 (35.4)	402/956 (42.1)	193/398 (48.5)	16/27 (59.3)	<0.001
AKL score, median, min-max (n = 12 405)	4.53, 0.41-57.33	3.47, 0.41-34.44	4.70, 0.41-47.56	5.55, 0.41-44.30	7.10, 1.00-49.04	13.68, 2.02-57.33	<0.001
Euro-Score, median, min-max (n = 12 496)	14.24, 1.51-87.96	12.32, 1.51-76.82	14.37, 2.08-77.69	16.09, 1.61-87.96	19.77, 3.28-85.58	27.37, 4.47-64.48	<0.001
STS score, median, min-max (n = 12 792)	4.29, 0.60-43.72	3.35, 0.60-22.11	4.35, 0.85-27.51	5.54, 1.02-26.33	7.57, 1.68-33.87	16.09, 6.08-43.72	<0.001

SAVR	All (n = 17 059)	CKD stages 1/2 (n = 13 149)	CKD stage 3a (n = 2728)	CKD stage 3 b (n = 936)	CKD stages 4/5 (n = 246)		P-value
Age (years), median, min-max	72.2, 18.0-96.0	70.7, 18.0-91.1	75.4, 32.7-96.0	76.6, 49.6-93.8	75.0, 46.4-88.9		<0.001
Gender (female), n/n (%)	7239/17 059 (42.4)	5001/13 149 (38.0)	1552/2728 (56.9)	545/936 (58.2)	141/246 (57.3)		<0.001
BMI (kg/m^2), median, min-max (n = 16 978)	27.76, 12.22-49.94	27.68, 12.96-49.94	28.29, 12.22-49.38	28.65, 16.73-47.38	29.53, 16.42-49.77		<0.001
Creatinine (mg/dl), median, min-max	0.90, 0.10-10.00	0.90, 0.10-1.40	1.10, 0.89-1.82	1.50, 1.14-2.16	2.30, 1.60-10.00		<0.001
NYHA (III/IV), n/N (%)	9894/17 059 (58.0)	7278/13 149 (55.4)	1787/2728 (65.5)	653/936 (69.8)	176/246 (71.5)		<0.001
Previous MI, n/N (%)	572/17 046 (3.4)	399/13 139 (3.0)	104/2725 (3.8)	54/936 (5.8)	15/246 (6.1)		<0.001
Previous PCI, n/N (%)	1323/17 059 (7.8)	932/13 149 (7.1)	245/2728 (9.0)	118/936 (12.6)	28/246 (11.4)		<0.001
Permanent pacemaker, n/N (%)	503/17 016 (3.0)	328/13 127 (2.5)	106/2712 (3.9)	56/932 (6.0)	13/245 (5.3)		<0.001
Arterial vascular disease, n/N (%)	1675/17 040 (9.8)	1165/13 134 (8.9)	323/2725 (11.9)	152/936 (16.2)	35/245 (14.3)		<0.001
Peripheral arterial vascular disease, n/N (%)	664/17 036 (3.9)	449/13 131 (3.4)	145/2725 (5.3)	54/935 (5.8)	16/245 (6.5)		<0.001
Atrial fibrillation, n/N (%)	1232/17 059 (7.2)	774/13 149 (5.9)	271/2728 (9.9)	143/935 (15.3)	44/246 (17.9)		<0.001
Mitral regurgitation ≥2°, n/N (%)	1069/16 430 (6.5)	709/12 651 (5.6)	232/2628 (8.8)	104/910 (11.4)	24/241 (10.0)		<0.001
EF (%), median, min-max (n = 14 700)	60, 5-85	60, 5-85	60, 10-85	60, 15-85	60, 24-81		<0.001
Hypertension, n/N (%)	13 681/16 958 (80.7)	10 313/13 065 (78.9)	2341/2717 (86.2)	818/930 (88.0)	209/246 (85.0)		<0.001
Cardiac decompensation, n/N (%)	924/16 821 (5.5)	610/12 976 (4.7)	213/2686 (7.9)	74/916 (8.1)	27/243 (11.1)		<0.001
AVA (cm^2), median, min-max (n = 14 155)	0.70, 0.10-3.50	0.70, 0.10-3.50	0.70, 0.10-2.50	0.70, 0.30-2.10	0.75, 0.30-2.70		<0.001
Pmean (mmHg), median, min-max (n = 13 805)	48, 10-100	49, 10-100	48, 10-100	46, 11-100	46, 13-93		<0.001
Neurological dysfunction (Rankin ≥2), n/N (%)	168/16 378 (1.0)	116/12 773 (0.9)	30/2637 (1.1)	22/897 (2.5)	0/239 (0.0)		<0.001
Lung disease, n/N (%)	1968/17 053 (11.5)	1466/13 143 (11.2)	328/2728 (12.0)	134/936 (14.3)	40/246 (16.3)		0.002
Pulmonary hypertension >55 mmHg, n/N (%)	690/16 910 (4.1)	456/13 029 (3.5)	140/2708 (5.2)	75/930 (8.1)	19/243 (7.8)		<0.001
Insulin-dependent diabetes, n/N (%)	1308/4055 (32.3)	814/2795 (29.1)	277/784 (35.3)	158/366 (43.2)	59/110 (53.6)		<0.001
AKL score, median, min-max (n = 16 783)	1.35, 0.41-30.90	1.00, 0.41-22.35	1.92, 0.41-26.30	2.07, 0.41-30.90	3.06, 0.54-23.75		<0.001
Euro-Score, median, min-max (n = 16 816)	4.83, 1.51-86.94	4.25, 1.51-85.40	6.32, 1.51-86.94	7.46, 1.51-71.68	8.59, 2.08-61.68		<0.001
STS score, median, min-max (n = 17 043)	1.72, 0.34-26.75	1.50, 0.34-12.49	2.39, 0.65-16.72	3.21, 0.91-16.59	4.92, 1.20-26.75		<0.001

AKL: German Aortic Valve Score; AVA: aortic valve area; BMI: body mass index; CKD: chronic kidney disease; EF: ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; Pmean: mean transvalvular pressure gradient; SAVR: surgical aortic valve replacement; STS: Society of Thoracic Surgeons; TAVI: transcatheter aortic valve implantation.

Table 2: Procedural characteristics in transcatheter aortic valve implantation and surgical aortic valve replacement patients

TAVI	All (n = 12 834)	CKD stages 1/2 (n = 5544)	CKD stage 3a (n = 3592)	CKD stage 3b (n = 2644)	CKD stage 4 (n = 976)	CKD stage 5 (n = 78)	P-value
Urgent, n/N (%)	1235/12 834 (9.6)	484/5544 (8.7)	310/3592 (8.6)	300/2644 (11.3)	125/976 (12.8)	16/78 (20.5)	<0.001
Procedure duration (min), median, min–max (n = 9914)	80, 52–480	79, 52–480	79, 52–390	80, 52–429	80, 52–438	77, 52–179	0.38
Radiation (min), median, min–max (n = 12 664)	12.2, 0–914	12.5, 0–914	12.2, 0–802	12, 0–303	11.5, 0–382	12.05, 0–204	<0.001
Contrast (ml), median, min–max (n = 12 691)	125, 0–1000	126, 0–1000	125, 0–1000	120, 1–1000	115, 1–600	112.5, 1–600	<0.001
General anaesthesia, n/N (%)	7389/12 834 (57.6)	3142/5544 (56.7)	2084/3592 (58.0)	1565/2644 (59.2)	547/976 (56.0)	51/78 (65.4)	0.098
Balloon dilatation, n/N (%)	2002/12 834 (15.6)	827/5544 (14.9)	565/3592 (15.7)	437/2644 (16.5)	161/976 (16.5)	12/78 (15.4)	0.36
Rapid pacing for implant, n/N (%)	8834/12 834 (68.8)	3777/5544 (68.1)	2485/3592 (69.2)	1854/2644 (70.1)	662/976 (67.8)	56/78 (71.8)	0.37
CPB							0.57
With HLM, n/N (%)	127/12 834 (1.0)	44/5544 (0.8)	41/3592 (1.1)	32/2644 (1.2)	10/976 (1.0)	0/78 (0.0)	
Conversion to HLM, n/N (%)	48/12 834 (0.4)	19/5544 (0.3)	12/3592 (0.3)	12/2644 (0.5)	5/976 (0.5)	0/78 (0.0)	0.71
Conversion into surgery, n/N (%)	91/12 834 (0.7)	42/5544 (0.8)	25/3592 (0.7)	15/2644 (0.6)	9/976 (0.9)	0/78 (0.0)	0.83
Pericardial tamponade, n/N (%)	108/12 834 (0.8)	47/5544 (0.8)	32/3592 (0.9)	18/2644 (0.7)	10/976 (1.0)	1/78 (1.3)	
Frailty, n/N (%)	5948/12 834 (46.3)	2448/5544 (44.2)	1721/3592 (47.9)	1292/2644 (48.9)	452/976 (46.3)	35/78 (44.9)	<0.001
Vascular complication, n/N (%)	461/12 834 (3.6)	187/5544 (3.4)	114/3592 (3.2)	116/2644 (4.4)	44/976 (4.5)	0/78 (0.0)	0.013
Post-implant mean gradient							0.084
<10 mmHg, n/N (%)	5015/8437 (59.4)	2198/3760 (58.5)	1391/2357 (59.0)	1032/1696 (60.8)	364/580 (62.8)	30/44 (68.2)	
10–14 mmHg, n/N (%)	2030/8437 (24.1)	904/3760 (24.0)	563/2357 (23.9)	421/1696 (24.8)	133/580 (22.9)	9/44 (20.5)	
>15 mmHg, n/N (%)	1392/8437 (16.5)	658/3760 (17.5)	403/2357 (17.1)	243/1696 (14.3)	83/580 (14.3)	5/44 (11.4)	
Transvascular, n/N (%)	10 155/12 834 (79.1)	4393/5544 (79.2)	2858/3592 (79.6)	2080/2644 (78.7)	764/976 (78.3)	60/78 (76.9)	0.84
Diameter (mm), median, min–max (n = 12 604)	26, 16–32	26, 18–32	26, 18–31	26, 16–31	26, 19–32	26, 23–31	<0.001

SAVR	All (n = 17 059)	CKD stages 1/2 (n = 13 149)	CKD stage 3a (n = 2728)	CKD stage 3 b (n = 936)	CKD stages 4/5 (n = 246)	P-value
Urgent, n/N (%)	1436/17 059 (8.4)	1079/13 149 (8.2)	228/2728 (8.4)	97/936 (10.4)	32/246 (13.0)	0.007
Procedure duration (min), median, min–max (n = 17 048)	160, 52–574	160, 52–574	155, 63–480	160, 70–467	163.5, 62–480	<0.001
CPB						0.98
With HLM, n/N (%)	17 003/17 059 (99.7)	13 106/13 149 (99.7)	2720/2728 (99.7)	932/936 (99.6)	245/246 (99.6)	
Conversion to HLM, n/N (%)	12/17 059 (0.1)	10/13 149 (0.1)	1/2728 (0.0)	1/936 (0.1)	0/246 (0.0)	
Pericardial tamponade (%)	2/17 059 (0.0)	1/13 149 (0.0)	0/2728 (0.0)	1/936 (0.1)	0/246 (0.0)	0.051
Vascular complication, n/N (%)	43/17 059 (0.3)	28/13 149 (0.2)	7/2728 (0.3)	3/936 (0.3)	5/246 (2.0)	<0.001
Post-implant mean gradient						<0.001
<10 mmHg, n/N (%)	3425/9602 (35.7)	2632/7538 (34.9)	579/1460 (39.7)	167/486 (34.4)	47/118 (39.8)	
10–14 mmHg, n/N (%)	2773/9602 (28.9)	2161/7538 (28.7)	430/1460 (29.5)	155/486 (31.9)	27/118 (22.9)	
>15 mmHg, n/N (%)	3404/9602 (35.5)	2745/7538 (36.4)	451/1460 (30.9)	164/486 (33.7)	44/118 (37.3)	
Diameter (mm), median, min–max (n = 16 996)	23, 16–34	23, 17–34	23, 16–29	23, 18–31	23, 19–29	<0.001

CKD: chronic kidney disease; CPB: cardiopulmonary bypass; HLM: heart-lung machine; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

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Table 3: Survival rates and post-procedural complications in transcatheter aortic valve implantation and surgical aortic valve replacement patients

TAVI	All (n = 12 834)	CKD stages 1/2 (n = 5544)	CKD stage 3a (n = 3592)	CKD stage 3b (n = 2644)	CKD stage 4 (n = 976)	CKD stage 5 (n = 78)	P-value
Stroke, n/N (%)	125/12 657 (1.0)	43/5465 (0.8)	34/3544 (1.0)	34/2609 (1.3)	13/963 (1.3)	1/76 (1.3)	0.18
TIA, n/N (%)	109/12 641 (0.9)	55/5477 (1.0)	25/3535 (0.7)	19/2594 (0.7)	8/958 (0.8)	2/77 (2.6)	0.24
Myocardial infarction, n/N (%)	33/12 834 (0.3)	12/5544 (0.2)	11/3592 (0.3)	6/2644 (0.2)	3/976 (0.3)	1/78 (1.3)	0.40
New-onset atrial fibrillation, n/N (%)	2800/12 567 (22.3)	1051/5461 (19.2)	816/3528 (23.1)	654/2578 (25.4)	271/928 (29.2)	8/72 (11.1)	<0.001
New-onset pacemaker, n/N (%)	1334/8242 (16.2)	579/3861 (15.0)	390/2272 (17.2)	247/1536 (16.1)	105/516 (20.3)	13/57 (22.8)	0.007
Bleeding (≥2 RBC units), n/N (%)	2152/2637 (81.6)	751/921 (81.5)	550/688 (79.9)	538/656 (82.0)	285/336 (84.8)	28/36 (77.8)	0.40
Vascular complication, n/N (%)	943/12 834 (7.3)	423/5544 (7.6)	246/3592 (6.8)	190/2644 (7.2)	75/976 (7.7)	9/78 (11.5)	0.37
New-onset dialysis							<0.001
Temporary, n/N (%)	226/12 834 (1.8)	43/5544 (0.8)	47/3592 (1.3)	62/2644 (2.3)	57/976 (5.8)	17/78 (21.8)	<0.001
Chronic, n/N (%)	28/12 834 (0.2)	5/5544 (0.1)	4/3592 (0.1)	6/2644 (0.2)	8/976 (0.8)	5/78 (6.4)	<0.001
Post-OP stay in ICU (days), median, min–max (n = 12 824)	2.00, 0.00–131.00	2.00, 0.00–131.00	2.00, 0.00–51.00	2.00, 0.00–89.00	2.00, 0.00–59.00	2.00, 0.00–67.00	<0.001
Post-OP hospitalization (days), median, min–max (n = 12 829)	9.00, 0.00–341.00	9.00, 0.00–341.00	9.00, 0.00–209.00	9.00, 0.00–95.00	10.00, 0.00–106.00	11.00, 2.00–67.00	<0.001
Aortic incompetence (≥II), n/N (%)	400/10 713 (3.7)	174/4715 (3.7)	105/2979 (3.5)	85/2169 (3.9)	33/788 (4.2)	3/62 (4.8)	0.27
Survival in-hospital rate (95% CI)	0.973 (0.97, 0.98)	0.981 (0.98, 0.98)	0.976 (0.97, 0.98)	0.967 (0.96, 0.97)	0.939 (0.92, 0.95)	0.882 (0.81, 0.96)	<0.001
Survival at 30-days rate (95% CI)	0.967 (0.96, 0.97)	0.977 (0.97, 0.98)	0.967 (0.96, 0.97)	0.96 (0.95, 0.97)	0.926 (0.91, 0.94)	0.923 (0.87, 0.98)	<0.001
Survival at 1-year rate (95% CI)	0.859 (0.85, 0.87)	0.894 (0.89, 0.9)	0.873 (0.86, 0.88)	0.83 (0.82, 0.84)	0.706 (0.68, 0.74)	0.646 (0.55, 0.76)	<0.001
Causes of 1-year mortality							0.44
Sudden death, n/N (%)	28/809 (3.5)	11/288 (3.8)	4/198 (2.0)	7/194 (3.6)	6/120 (5.0)	0/9 (0.0)	
Cardiovascular, n/N (%)	235/809 (29.0)	75/288 (26.0)	67/198 (33.8)	59/194 (30.4)	33/120 (27.5)	1/9 (11.1)	
Non-cardiovascular, n/N (%)	248/809 (30.7)	99/288 (34.4)	57/198 (28.8)	51/194 (26.3)	39/120 (32.5)	2/9 (22.2)	
Unknown, n/N (%)	298/809 (36.8)	103/288 (35.8)	70/198 (35.4)	77/194 (39.7)	42/120 (35.0)	6/9 (66.7)	

SAVR	All (n = 17 059)	CKD stages 1/2 (n = 13 149)	CKD stage 3a (n = 2728)	CKD stage 3 b (n = 936)	CKD stages 4/5 (n = 246)	P-value
Stroke, n/N (%)	99/16 867 (0.6)	76/13 019 (0.6)	13/2692 (0.5)	10/916 (1.1)	0/240 (0.0)	0.12
TIA, n/N (%)	110/16 878 (0.7)	70/13 013 (0.5)	22/2701 (0.8)	14/920 (1.5)	4/244 (1.6)	<0.001
Myocardial infarction, n/N (%)	68/17 059 (0.4)	47/13 149 (0.4)	12/2728 (0.4)	4/936 (0.4)	5/246 (2.0)	<0.001
New-onset atrial fibrillation, n/N (%)	1433/16 921 (8.5)	936/13 062 (7.2)	313/2697 (11.6)	143/923 (15.5)	41/239 (17.2)	<0.001
New-onset pacemaker, n/N (%)	512/15 291 (3.3)	393/12 012 (3.3)	90/2342 (3.8)	26/746 (3.5)	3/191 (1.6)	0.27
Bleeding (≥2 RBC units), n/N (%)	6041/7074 (85.4)	4177/4916 (85.0)	1184/1401 (84.5)	526/588 (89.5)	154/169 (91.1)	0.003
Vascular complication, n/N (%)	88/17 059 (0.5)	66/13 149 (0.5)	17/2728 (0.6)	4/936 (0.4)	1/246 (0.4)	0.83
New-onset dialysis						<0.001
Temporary, n/N (%)	288/17 059 (1.7)	133/13 149 (1.0)	60/2728 (2.2)	57/936 (6.1)	38/246 (15.4)	<0.001
Chronic, n/N (%)	26/17 059 (0.2)	11/13 149 (0.1)	4/2728 (0.1)	3/936 (0.3)	8/246 (3.3)	
Post-OP stay in ICU (days), median, min–max (n = 17 058)	2.00, 0.00–91.00	2.00, 0.00–91.00	2.00, 0.00–56.00	2.00, 0.00–55.00	3.00, 0.00–78.00	<0.001
Post-OP hospitalization (days), median, min–max (n = 17 056)	10.00, 0.00–309.00	9.00, 0.00–309.00	10.00, 0.00–188.00	11.00, 0.00–68.00	11.00, 0.00–77.00	<0.001
Aortic incompetence (≥II), n/N (%)	45/12 929 (0.3)	33/10 057 (0.3)	10/2022 (0.5)	2/670 (0.3)	0/180 (0.0)	0.23
Survival in-hospital rate (95% CI)	0.989 (0.99, 0.99)	0.991 (0.99, 0.99)	0.985 (0.98, 0.99)	0.981 (0.97, 0.99)	0.947 (0.92, 0.98)	<0.001
Survival at 30-days rate (95% CI)	0.986 (0.98, 0.99)	0.989 (0.99, 0.99)	0.98 (0.97, 0.99)	0.976 (0.97, 0.99)	0.939 (0.91, 0.97)	<0.001
Survival at 1-year rate (95% CI)	0.957 (0.95, 0.96)	0.966 (0.96, 0.97)	0.94 (0.93, 0.95)	0.906 (0.89, 0.92)	0.873 (0.83, 0.92)	<0.001
Causes of 1-year mortality						0.20
Sudden death, n/N (%)	15/318 (4.7)	5/204 (2.5)	6/66 (9.1)	4/43 (9.3)	0/5 (0.0)	
Cardiovascular, n/N (%)	115/318 (36.2)	75/204 (36.8)	22/66 (33.3)	15/43 (34.9)	3/5 (60.0)	
Non-cardiovascular, n/N (%)	94/318 (29.6)	61/204 (29.9)	16/66 (24.3)	15/43 (34.9)	2/5 (40.0)	
Unknown, n/N (%)	94/318 (29.6)	63/204 (30.8)	22/66 (33.3)	9/43 (20.9)	0/5 (0.0)	

CKD: chronic kidney disease; OP: operation; RBC: red blood cell; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation; TIA: transient ischaemic attack.
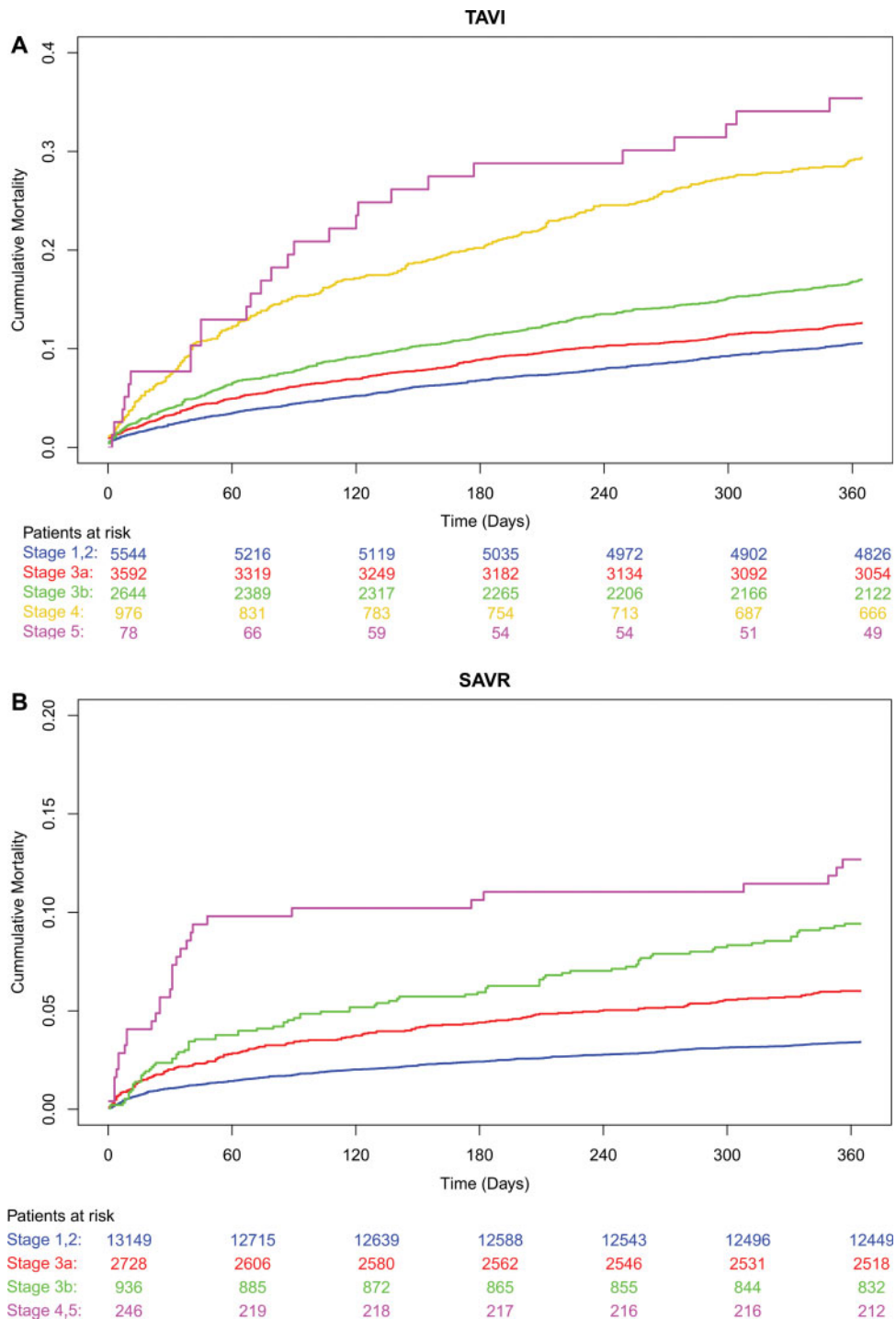
Figure 1: (**A**) Kaplan–Meier curves for 1-year cumulative mortality with patients divided into chronic kidney disease stages 1–2, 3a, 3b, 4 and 5 in transcatheter aortic valve implantation patients. (**B**) Kaplan–Meier curves for 1-year cumulative mortality with patients divided into chronic kidney disease stages 1–2, 3a, 3b and 4–5 in surgical aortic valve replacement patients. Differences were significant in both cases ($P < 0.001$), see Fig. 2 for hazard ratios.

predictor of 1-year mortality in SAVR patients, again consistent with the Cox regression result predicting the mortality to increase in 9.0% for every 5-ml reduction in eGFR (Fig. 3 displaying the association in 10-ml eGFR intervals, $P < 0.001$). The survival ROC curve at 1-year showed an area under the curve of 0.609 (Fig. 4). The best cut-off point was found to be 59.8 ml/min/1.73 m^2, which corresponds to a CKD stage 3a (45–59 ml/min/1.73 m^2).

Sensitivity analyses in patients undergoing transcatheter aortic valve implantation

In a sensitivity analysis, patients who underwent TAVI in 2011 were excluded to remove a potential learning curve effect. The association of CKD stages with 1-year cumulative mortality remained significant and gradually increasing with higher CKD stages. A further sensitivity analysis was performed to assess a potential impact of TV approach; results were highly

Table 4: Univariate and multivariable analyses for 1-year cumulative all-cause mortality for each chronic kidney disease stage in transcatheter aortic valve implantation and surgical aortic valve replacement patients

1 year	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
TAVI				
CKD stage 1 + 2	1 (Ref.)	n.a.	1 (Ref.)	*n.a.*
CKD stage 3a	1.22 (1.077, 1.38)	0.002	1.10 (0.95, 1.27)	0.21
CKD stage 3b	1.67 (1.48, 1.90)	<0.001	1.43 (1.23, 1.67)	<0.001
CKD stage 4	3.14 (2.72, 3.62)	<0.001	2.25 (1.86, 2.72)	<0.001
CKD stage 5	3.95 (2.69, 5.82)	<0.001	1.59 (0.89, 2.84)	0.12
TA CKD stage 1 + 2	1 (Ref.)	n.a.		
TA CKD 3a	1.244 (0.972, 1.593)	0.083		
TA CKD 3b	1.984 (1.566, 2.514)	<0.001		
TA CKD 4	3.361 (2.539, 4.449)	<0.001		
TA CKD 5	3.952 (1.851, 8.438)	<0.001		
SAVR				
CKD stage 1 + 2	1 (Ref.)	n.a.	1 (Ref.)	n.a.
CKD stage 3a	1.79 (1.49, 2.14)	<0.001	1.30 (1.018, 1.65)	0.035
CKD stage 3b	2.83 (2.25, 3.56)	<0.001	1.69 (1.24, 2.31)	<0.001
CKD stage 4 + 5	3.98 (2.77, 5.73)	<0.001	1.21 (0.67, 2.19)	0.53

Multivariable adjustment for TAVI includes age, gender, BMI, NYHA III/IV versus I/II, previous MI, atrial fibrillation, mitral regurgitation $\geq 2°$, mean EF, hypertension, mean transvalvular pressure gradient (pmean), neurological dysfunction, lung disease, pulmonary hypertension >55 vs $\leq$55 mmHg, arterial vascular disease, peripheral arterial vascular disease, AKL score, Euro-Score, STS score and transapical versus transvascular TAVI. Multivariable adjustment for SAVR includes age, gender, BMI, NYHA III/IV versus I/II, previous MI, previous PCI, mitral regurgitation $\geq 2°$, mean EF, hypertension, mean transvalvular pressure gradient (pmean), aortic valve calcification, neurological dysfunction, lung disease, arterial vascular disease, peripheral arterial vascular disease, AKL score, Euro-Score and STS score. AKL: German Aortic Valve Score; BMI: body mass index; CKD: chronic kidney disease; EF: ejection fraction; MI: myocardial infarction; n.a.: not applicable; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SAVR: surgical aortic valve replacement; STS: Society of Thoracic Surgeons; TA: transapical; TAVI: transcatheter aortic valve implantation.

comparable to those from the whole population. Specifically, when evaluating only patients with the TA approach, HR values for 1-year mortality were also gradually higher with higher CKD stages and achieved statistical significance for CKD stages 3b, 4 and 5 (with a numerical, not significant difference for stage 3a) (see Table 4).

DISCUSSION

To our knowledge, this is, to date, the largest European study on the impact of CKD stages on survival after TAVI, and only second in size to the US registry study worldwide [16]. Our results show that higher CKD stages are significantly associated to higher in-hospital, 30-day and 1-year mortality rates. The need for new-onset dialysis after TAVI increased with CKD stage, as did the length of ICU stay and hospital stay. This could also be related to the higher rate of co-morbidities found in patients with an advanced CKD stage. Similarly, in SAVR patients, higher CKD stages were also significantly associated to higher in-hospital, 30-day and 1-year mortality rates, and to a longer ICU and hospital stay, and a higher new-onset dialysis rate. In addition, atrial fibrillation and TIA were more common in SAVR patients with a higher CKD stage.

Interestingly, in patients undergoing TAVI, there was an annual trend with the proportion of patients in CKD stages 1 + 2 being significantly more frequent in recent years. Similar results were found for SAVR patients. This could reflect the current trend to use TAVI in lower risk patients [1].

As expected, baseline co-morbidities were more common in patients with higher CKD stages. This is in line with recently published data from US administrative databases [17]. Furthermore,

an association of CKD with cardiovascular risk factors has been widely described in previous studies [18].

As opposed to prior results from other investigations [9, 17, 19], our CKD stage 5 population undergoing TAVI was not younger than the rest of patients. This is probably due to the fact that patients on chronic dialysis were not included in this analysis, and such patients are usually younger [20]. TAVI patients in CKD stage 5 underwent more TA procedures, which may be due to a higher prevalence of peripheral arterial vascular disease. Urgent procedures were more frequent as well; similar findings were published from the UK TAVI registry [9]. The lower use of contrast dye in patients with advanced CKD may be influenced by the operators' attempt to lower the risk of contrast-related renal injury as much as possible in such patients.

Several CKD severity classifications have been used to assess the potential association of renal function to TAVI outcomes. In a large analysis based on a US administrative national database including over 40 000 patients, only 3 categories were used (no CKD, CKD or End Stage Renal Disease) [21]. The US STS/ACC TVT Registry used a more detailed classification (CKD stages 1, 2, 3, 4 and 5) [16]. Splitting CKD stage 3 into 3a and 3b subcategories has been recommended for prognosis purposes in cardiovascular diseases [13]. As in the present study, French [19], UK [9] and Italian OBSERVANT [22] TAVI registries have used this classification and found different results in 3a and 3b subgroups. Also, in line with all major registries [9, 16, 19], CKD stages 1 and 2 were combined as a reference category, since they represent patients with an adequate renal function. To date, most studies on SAVR have not used CKD stages to assess renal function or have only used mild–moderate–severe categories [8, 23]. However, a recent study in both TAVI and SAVR patients has already used 5 CKD categories [24].
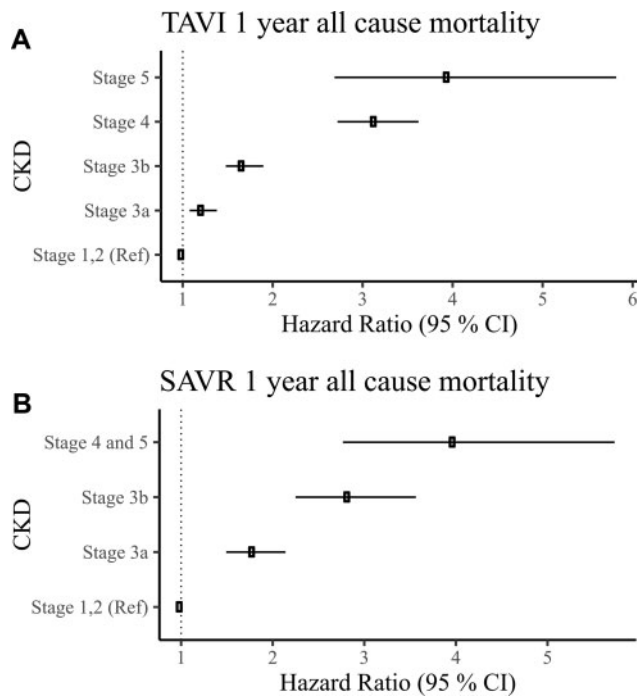
Figure 2: (**A**) Forest plot with hazard ratios with 95% confidence intervals for cumulative 1-year mortality according to chronic kidney disease stages in transcatheter aortic valve implantation patients. (**B**) Forest plot with hazard ratios with 95% confidence intervals for cumulative 1-year mortality according to chronic kidney disease stages in surgical aortic valve replacement patients.

Figure 3: Association between estimated glomerular filtration rate and 1-year cumulative mortality calculated from Kaplan–Meier estimates of the patients with estimated glomerular filtration rate within the respective intervals and compared with Cox regression prediction in these transcatheter aortic valve implantation patients (**A**) and surgical aortic valve replacement patients (**B**).

Whereas initial TAVI studies that included a low number of patients did not find a clear-cut association between CKD and mortality after TAVI [20, 25], such an association was observed in more recent and larger investigations [26]. The association between different CKD stages and survival after TAVI has been a matter of debate, particularly in patients with mild renal function impairment. Whereas Allende *et al.* [27] and the PARTNER trial [28] with a selected population showed only CKD stage 4 and CKD stage 5 to have an impact on short-term and mid-term mortality, the more recent UK (*n* = 3980) [9] and FRANCE (*n* = 2929) [19] registries, as well as a previous small study (*n* = 642) found similar results in CKD stage 3b (30–44 ml/min/1.73 m^2) [29]. However, mortality was not significantly associated to CKD stage 3a. The large US STS/ACC TVT Registry [16] reported data from >40 000 patients; as in our study, dialysis-dependent patients were excluded, which resulted also in a low number of patients in CKD stage 5. Unadjusted 1-year mortality was significantly higher in CKD stage 5, whereas HR after adjustment did not reach statistical significance. The US registry did show an adjusted association of CKD stage 4 and CKD stage 3 with mortality but did not report specific results for stages 3a and 3b separately. Patients with mild renal function impairment (stage 3a) account for a substantial proportion of patients undergoing TAVI, and assessing their risk is certainly important.

To our knowledge, our study (*n* = 12 834) is the largest TAVI prospective registry cohort study reporting survival data in patients with mild renal impairment (CKD stage 3a) compared to patients with eGFR >60 ml/min/1.73 m^2. In univariate analyses, patients in CKD 3a, 3b, 4 and 5 showed significant, gradually increasing HR values for 1-year all-cause mortality when using CKD 1 + 2 as reference. The same trend was observed at multivariable analysis but HR values for CKD 3a and 5 did not reach significance after multivariable adjustment. Similar to the US registry [16], lack of
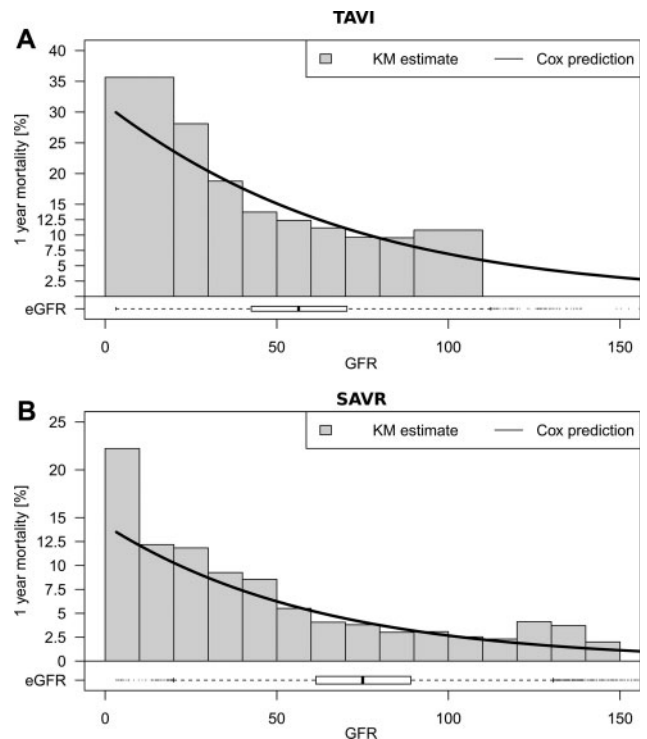
statistical significance for CKD stage 5 after multivariable adjustment can be explained by the relatively low number of patients in this group, due to the exclusion of patients with chronic renal replacement therapy, which account for most patients in stage 5. In fact, our *post hoc* analysis based on combined CKD stages 4 + 5 did show statistical significance also in multivariable analysis.

When compared to patients with CKD stages 1 and 2, in patients with CKD stage 3a, HR for 1-year mortality became non-significant after multivariable adjustment, which suggests that other clinical factors may explain their higher mortality risk. In addition, the positive relationship between eGFR assessed as a continuous variable and 1-year cumulative mortality in our series showed the best cut-off value to be 47 ml/min/1.73 m^2, which is very close to the limit defining CKD stage 3b. A similar value has also been suggested in previous studies (eGFR 45) [19, 29]. For every 5 ml/min/1.73 m^2 reduction in eGFR, 1-year mortality increased in nearly 9% in our population. This effect size is higher than previously reported in the UK registry [9], in which in-hospital mortality increased by 8.2% and cumulative mortality increased by 4.4% for every 10 ml/min/1.73 m^2 reduction [9].

Based on our sensitivity analyses, our conclusions on mortality do not appear to be affected by a potential learning curve in the first year of the registry. Moreover, results were also similar when only considering TAVI performed using a TV or a TA approach.

As expected, after TAVI, overall ICU stay and hospitalization were longer in patients in higher CKD stages; this is in accordance with previous literature [19, 21].

In patients undergoing SAVR, our findings confirm the previously observed association of higher CKD stages to higher mortality rates. The association seems to be clearly present from CKD 3a
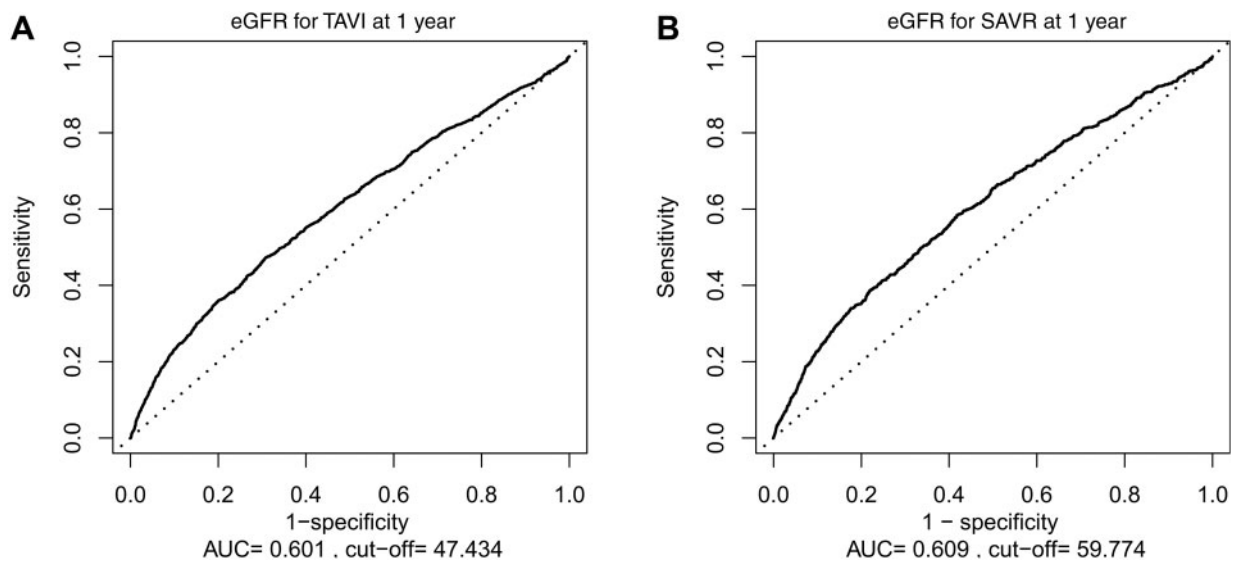
Figure 4: (**A**) Receiver operating curve analysis assessing the prediction of estimated glomerular filtration rate as a continuous variable for 1-year mortality in trans-catheter aortic valve implantation patients. (**B**) Receiver operating curve analysis assessing the prediction of estimated glomerular filtration rate as a continuous variable for 1-year mortality in surgical aortic valve replacement patients.

stage upwards, as previously suggested [23]. Our confirmatory findings have been obtained in an era of increasing TAVI use as an alternative to surgery, with the current SAVR population having a lower risk profile. However, due to the low number of patients, statistical significance was not achieved for CKD 5 after multivariable adjustment. Most deaths were due to cardiovascular reasons. After SAVR, for every 5 ml/min/1.73 m^2 reduction in eGFR, 1-year mortality increased by 9%, which is very similar to the reduction we found in TAVI patients. Complications associated to a high CKD stage were also similar to the ones previously reported in SAVR. Specifically, a more common severe bleeding [23], and a higher new-onset dialysis rate are in line with previous observations [8].

Existing risk scores either do not take renal function into account or only consider 3 CKD categories. The entire recently available evidence on renal function markers, including our present findings, along with other biomarkers having been shown to have prognostic significance in patients undergoing TAVI or SAVR in the last years, will have to be considered when updating existing risk scores for future versions.

Strengths and limitations

This real-world registry includes most consecutive patients having undergone TAVI and SAVR in Germany throughout a 5-year period, based on the participation of the vast majority of hospitals performing such procedures. Thus, it is clearly representative of the whole population of patients undergoing TAVI and SAVR for aortic stenosis. With Germany being the country with the highest number of TAVI procedures performed in Europe [10], the large size of the present study becomes one of its main strengths. Despite a thorough adjustment for many variables, some unrecognized confounders may remain. We report short-term and 1-year results, but a longer follow-up is needed to fully evaluate the impact of renal function on survival in the long-term. Finally, we acknowledge the limitation of having estimated glomerular filtration rates based on serum creatinine.

CONCLUSION

The present study shows that CKD $\geq$3b is a significant independent major risk factor for mortality in patients undergoing TAVI. Similarly, in SAVR, CKD $\geq$3a is also a significant independent risk factor for mortality. Thus, in the general population of patients with severe aortic stenosis, an appropriate stratification based on CKD substage may contribute to a better selection of patients suitable for valve replacement.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

ACKNOWLEDGEMENTS

Funding

and reports consultancy activities for Abbott Vascular, Boston Scientific and Edwards Lifesciences. M.V.-N. is a proctor for Abbott Vascular, Boston Scientific and Medtronic. S.E. reports consultant and speaker honoraria for Edwards Lifesciences and speaker honoraria for Medtronic. C.W.H. serves on the advisory board of Medtronic. T.W. is a proctor and reports consultancy activities for Abbott Vascular, Boston Scientific and Edwards Lifesciences. S.F. is a proctor and reports consultancy activities for Abbott Vascular and Edwards Lifesciences. The remaining authors report no conflicts of interest regarding the content herein.

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Reviewer information

European Journal of Cardio-Thoracic Surgery thanks Rafael Garcia-Fuster, Robert Guidoin, Clarence Pienteu Pingpoh and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

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