European Heart Journal (2014) **35**, 2685–2696
doi:10.1093/eurheartj/ehu175

Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes and prognostic markers from a large cohort of patients

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Received 11 August 2013; revised 9 February 2014; accepted 3 April 2014; online publish-ahead-of-print 5 May 2014

Aim The aim of this study was to determine the effects of advanced chronic kidney disease (CKD) on early and late outcomes after transcatheter aortic valve implantation (TAVI), and to evaluate the predictive factors of poorer outcomes in such patients.

Methods and results This was a multicentre study including a total of 2075 consecutive patients who had undergone TAVI. Patients were grouped according the estimated glomerular filtration rate as follows: CKD stage 1-2 ($\geq$60 mL/min/1.73 m^2; $n = 950$), stage 3 (30–59 mL/min/1.73 m^2; $n = 924$), stage 4 (15–29 mL/min/1.73 m^2; $n = 134$) and stage 5 ($<$15 mL/min/1.73 m^2 or dialysis; $n = 67$). Clinical outcomes were evaluated at 30-days and at follow-up (median of 15 [6–29] months) and defined according to the VARC criteria. Advanced CKD (stage 4–5) was an independent predictor of 30-day major/life-threatening bleeding ($P = 0.001$) and mortality ($P = 0.027$), and late overall, cardiovascular and non-cardiovascular mortality ($P < 0.01$ for all). Pre-existing atrial fibrillation (HR: 2.29, 95% CI: 1.47–3.58, $P = 0.001$) and dialysis therapy (HR: 1.86, 95% CI: 1.17–2.97, $P = 0.009$) were the predictors of mortality in advanced CKD patients, with a mortality rate as high as 71% at 1-year follow-up in those patients with these 2 factors. Advanced CKD patients who had survived at 1-year follow-up exhibited both a significant improvement in NYHA class ($P < 0.001$) and no deterioration in valve hemodynamics ($P =$ NS for changes in mean gradient and valve area over time).

Conclusions Advanced CKD was associated with a higher rate of early and late mortality and bleeding events following TAVI, with AF and dialysis therapy determining a higher risk in these patients. The mortality rate of patients with both factors was unacceptably high and this should be taken into account in the clinical decision-making process in this challenging group of patients.

Keywords Chronic kidney disease • Dialysis • Transcatheter aortic valve implantation • Atrial fibrillation

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Introduction

Chronic kidney disease (CKD) is a rapidly growing worldwide public health problem with considerable economic and social repercussions.[1] It is well known that CKD modifies the natural history of cardiovascular diseases, and the presence of CKD has been associated with a much poorer prognosis in patients diagnosed with heart failure, coronary artery or valvular heart disease, and in those undergoing cardiac interventions.[2] The presence of CKD increases the risk of early and late mortality in patients with aortic stenosis undergoing surgical aortic valve replacement (SAVR), and the prognosis can be dismal in those with end-stage kidney disease.[3–7]

Transcatheter aortic valve implantation (TAVI) has been consolidated as a valid alternative to SAVR in those patients considered at high or prohibitive surgical risk.[8] Patients undergoing TAVI nowadays are thus frequently very old and have a high prevalence of non-cardiac comorbidities, including CKD, which accounts for 30–50% of TAVI candidates.[8] Several studies have shown that the presence of CKD is associated with poorer outcomes following TAVI, and early and late mortality rates increase with a greater severity of kidney dysfunction.[8–12] The mortality rate associated with severe CKD has been >30% at 1-year follow-up after TAVI, and this raises doubts about the appropriateness of offering this treatment to patients with aortic stenosis and severe CKD. Indeed, patients with end-stage kidney disease, especially those on dialysis therapy, have been excluded from many TAVI studies[9,11,12] including the PARTNER I and II trials (clinicaltrials.gov. ≠ NCT00530894; clinicaltrial.gov. ≠ NCT01314313) and the pivotal US trial for the CoreValve system (clinicaltrials.gov. ≠ NCT01240902), which may make it even more difficult to draw meaningful conclusions for the clinical decision-making process in such patients. Moreover, no data exist on the factors determining poorer outcomes in patients with advanced CKD undergoing TAVI, and a better knowledge of the prognostic markers among such patients would therefore be of major importance in improving both patient selection and management. Finally, the presence of end stage renal disease has been correlated with enhanced aortic valve calcification and valve disease progression, and cases of very rapid deterioration of surgical aortic bioprostheses have been reported in such patients;[13–15] however, few data exist on the effects of advanced CKD on valve haemodynamics following TAVI. The objectives of this study were therefore (i) to determine the effects of advanced CKD on early and late outcomes, functional status, and valve haemodynamics following TAVI, and (ii) to evaluate the predictive factors of poorer outcomes in patients with advanced CKD undergoing TAVI.

Methods

A total of 2075 consecutive patients who underwent TAVI in nine centres between January 2005 and June 2012 were included. Patients' comorbidities were defined according to the STS risk score definitions. Patient selection, approach and the type of transcatheter valve used during the TAVI procedures were determined by the heart team of each centre. Procedural success and major periprocedural complications were defined according to the VARC-2 criteria.[16]

Evaluation of the renal function

Measurements of creatinine levels were systematically obtained within the week prior to the procedure. Creatinine clearance was determined by the modified diet on renal disease (MDRD) formula [eGFR (mL/min/1.73 m^2) = 186 × SCr − 1.154 × Age − 0.203 × v(1.212 if black) × (0.742 if female)].[17] Patients were classified into four groups on the basis of baseline eGFR: ≥60 mL/min/1.73 m^2 (normal-mild CKD, stage 1–2), 30–59 mL/min/1.73 m^2 (moderate CKD, stage 3), 15–29 mL/min/1.73 m^2 (severe CKD, stage 4), and <15 mL/min/1.73 m^2 or dialysis (kidney failure, stage 5).[17,18] Advanced CKD was defined as CKD stage 4 and 5. The protocol for the prevention of contrast-induced nephropathy was determined at each centre. Serum creatinine values at 48–72 h following the procedure were available in 1951 (94.0%) patients. Acute kidney injury (AKI) was defined as an absolute reduction in kidney function within 72 h according to the modified RIFLE classification.[19] The severity of AKI was defined as stage 1 (increase in serum creatinine of 150–200% or increase of ≥0.3 mg/dL), stage 2 (increase in serum creatinine of 200– 300%), and stage 3 (increase in serum creatinine of ≥300% or serum creatinine of ≥4.0 mg/dL with an acute increase of at least 0.5 mg/dL or new need for renal replacement therapy). Patients with previous dialysis were excluded from the analysis of AKI.

Follow-up

Clinical follow-up was carried out at 30 days, 12 months, and yearly thereafter. The median follow-up was of 15 (5–29) months and no patient was lost to follow-up. All clinical events during the follow-up period were defined according to the VARC-2 criteria.[16] The patients underwent a Doppler echocardiographic examination at baseline before the intervention, at hospital discharge, at 12-month follow-up, and yearly thereafter. The NYHA class was evaluated before the procedure and at each point time during the follow-up period.

Statistical analysis

Continuous variables are presented as mean (standard deviation) or median (25th–75th inter-quartile range) depending on variable distribution. Group comparisons were tested for differences with one-way analysis of variance for continuous variables, and the Pearson's bivariate and χ^2 tests for categorical variables. Comparisons of clinical outcomes between groups were adjusted for baseline differences between groups using a logistic regression analysis that included variables with *P*-value <0.05 in the univariate analysis, and CKD stage 1–2 was the referent for comparison with the other groups. Baseline and procedural variables exhibiting a *P*-value <0.05 in the univariate analysis were included in a logistic regression analysis or in a Cox multivariable analysis to determine the predictive factors of 30-day and cumulative late mortality in the whole population and in the advanced CKD groups. Changes in valve haemodynamics over time between groups were compared using a repeated-measures model with interactions. Further comparisons were performed using the Tukey's technique. Survival curves were presented as Kaplan–Meier curves, and the log-rank test was used for comparison between groups. The results were considered significant with *P*-values <0.05. All analyses were conducted using the SAS statistical package version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Of the 2075 patients who underwent TAVI, 950 patients (45.8%) were classified as CKD stage 1–2, 924 patients (44.5%) as CKD stage 3, 134 patients (6.4%) as CKD stage 4, and 67 patients (3.2%) as CKD stage 5, with 56 patients (2.7%) on regular dialysis therapy. Baseline and procedural characteristics of the study population according to CKD severity are shown in *Table 1*. Patients with CKD stage 5 were younger (*P* = 0.001), and those with advanced

Table 1 Baseline and procedural characteristics of the study population, according chronic kidney disease severity

eGFR (mL/min/1.72 m^2)	CKD stage 1–2	CKD stage 3	Advanced CKD		*P*-value
			Stage 4	Stage 5	
	≥60	<60 to ≥30	<30 to ≥15	<15 or Dialysis	
	n = 950	*n* = 924	*n* = 134	*n* = 67	
Baseline variables					
Age, years	79.4 ± 8.0	81.9 ± 6.2	81.0 ± 7.5	76.9 ± 8.0	0.001
Male sex	537 (56.5)	404 (43.7)	56 (41.8)	39 (58.2)	0.001
Body mass index (kg/m^2)	26.8 ± 5.1	27.0 ± 5.2	27.1 ± 5.6	25.2 ± 4.9	0.048
NYHA class					
I–II	203 (21.4)	138 (14.9)	13 (9.7)	10 (14.9)	0.001
III–IV	747 (78.6)	786 (85.1)	121 (90.3)	57 (85.1)	
Smoker	217 (22.8)	204 (22.1)	39 (29.1)	13 (19.4)	0.242
Diabetes	267 (28.1)	285 (30.8)	53 (39.6)	19 (28.4)	0.069
Hypertension	708 (74.5)	756 (81.6)	114 (85.1)	57 (85.1)	0.001
Coronary artery disease	531 (55.9)	546 (59.1)	88 (65.7)	43 (64.2)	0.092
Prior CABG	241 (25.4)	225 (24.4)	32 (23.9)	14 (20.9)	0.835
Pre-existing atrial fibrillation	265 (27.9)	291 (32.1)	51 (38.1)	23 (34.3)	0.041
Prior stroke	118 (12.4)	115 (12.4)	19 (14.2)	9 (13.4)	0.942
Peripheral vascular disease	171 (18.0)	191 (20.7)	36 (26.9)	19 (28.4)	0.024
Chronic obstructive pulmonary disease	313 (33.0)	252 (27.3)	39 (29.1)	15 (22.4)	0.027
eGFR	81.2 ± 29.0	46.6 ± 8.3	24.6 ± 4.0	10.4 ± 3.6	0.001
STS-PROM score	5.1 (3.5–7.8)	6.7 (4.6–10.0)	11.2 (7.5–16.1)	13.7 (8.2–17.9)	0.001
Logistic euroSCORE	15.2 (9.0–23.2)	19.0 (12.1–28.4)	22.8 (15.4–38.2)	23.1 (14.6–37.6)	0.001
Severely calcified aorta	148 (15.6)	137 (14.8)	17 (12.7)	13 (19.4)	0.619
Echocardiographic variables					
LVEF (%)	55 ± 14	54 ± 14	52 ± 16	50 ± 13	0.009
Mean aortic gradient (mmHg)	47 ± 17	46 ± 17	44 ± 17	44 ± 18	0.201
Aortic valve area (cm^2)	0.63 (0.50–0.80)	0.60 (0.50–0.76)	0.63 (0.50–0.80)	0.60 (0.52–0.80)	0.210
Procedural characteristics					
Approach					
Transfemoral	723 (76.1)	678 (73.4)	87 (64.9)	41 (61.2)	0.003
eNo transfemoral	227 (23.9)	246 (26.6)	47 (35.1)	26 (38.8)	
Prosthesis type					
Balloon-expandable	477 (50.6)	462 (50.7)	77 (57.9)	37 (56.1)	0.361
Self-expandable	465 (49.4)	449 (49.3)	56 (42.1)	29 (43.9)	
Prosthesis size					
20 mm	4 (0.4)	2 (0.2)	0	0	0.001
23 mm	249 (26.2)	319 (34.5)	55 (41.0)	15 (22.4)	
25 mm	2 (0.2)	5 (0.5)	0	0	
26 mm	428 (45.1)	419 (45.3)	65 (48.5)	36 (53.7)	
29 mm	228 (24.0)	155 (16.8)	12 (9.0)	14 (20.9)	
31 mm	31 (3.3)	11 (1.2)	1 (0.7)	1 (1.5)	
Contrast dye (mL)	120 (65–183)	120 (50–175)	62 (25–113)	80 (35–140)	0.001
Device success	769 (80.9)	751 (81.3)	108 (80.6)	54 (80.6)	0.996

Values are expressed as mean (SD), median (IQR), or *n* (%).
eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass graft; CKD, chronic kidney disease; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality; LVEF, left ventricular ejection fraction.

CKD (stage 4 and 5) had more frequently a history of hypertension ($P = 0.001$), atrial fibrillation ($P = 0.041$) and peripheral vascular disease ($P = 0.024$) and lower left ventricular ejection fraction ($P = 0.009$). A parallel increase in risk profile as evaluated by STS and Logistic EuroSCORE was observed with the increasing degree of CKD severity ($P = 0.001$).

Thirty-day and late outcomes

Early (30-day) and late outcomes following TAVI grouped according to CKD severity are shown in *Table 2*. The presence of CKD stage 4 was associated with a higher rate of 30-day stroke ($P = 0.010$) and major/life-threatening bleeding ($P = 0.001$). Patients with advanced CKD (stage 4 and 5) had a trend towards a higher 30-day mortality ($P = 0.089$). Late outcomes showed that advanced CKD groups had a higher rate of all-cause mortality ($P < 0.001$), mainly due to an increase in cardiovascular mortality in the CKD stage 4 group, and non-cardiovascular mortality in the CKD stage 5 group ($P < 0.01$ for all). Non-cardiovascular mortality was secondary mainly to kidney disease progression ($P < 0.001$) and bleeding events ($P = 0.004$). The aetiology of bleeding events according to CKD severity is shown in Supplementary material online, *Table S1*. A total of 12 patients in the advanced CKD group died because of terminal kidney failure, and in 5 of them dialysis therapy was not indicated due to co-morbidities and advanced age. The Kaplan–Meier survival curves according to the severity of CKD are shown in *Figure 1A–C*).

Uni- and multivariable analyses to evaluate the predictors of 30-day major/life-threatening bleeding, 30-day mortality, and cumulative late mortality are shown in Tables 3 and 4. Advanced CKD (stage 4–5) was an independent predictor of 30-day major/life-threatening bleeding (OR: 2.15, 95% CI: 1.49–3.12, $P = 0.001$), 30-day mortality (OR: 1.80, 95% CI: 1.07–3.03, $P = 0.027$) (*Table 3*), and late cumulative mortality (HR: 1.72, 95% CI: 1.33–2.21) (*Table 4*).

Following TAVI, AKI occurred in 348 (18.4%) patients, and was classified as AKI stage 1, 2 and 3 in 274 (14.5%), 42 (2.2%), and 32 (1.7%) patients, respectively. Of the 32 patients with AKI stage 3, 22 required dialysis. No significant differences in the amount of contrast media administered during the procedure were observed between patients with and without AKI [median: 127 cc (IQR 44–186) vs. 117 cc (IQR

Table 2 Thirty-day and late outcomes, according to chronic kidney disease severity

eGFR (mL/min/1.73m^2)	CKD stage 1–2	CKD stage 3	Advanced CKD		*P*-value
			Stage 4	Stage 5	
	≥60 (*n* = 950)	<60 to ≥30 (*n* = 924)	<30 to ≥15 (*n* = 134)	<15 or dialysis (*n* = 67)	
30-day outcomes					
Cerebrovascular events	30 (3.2)	43 (4.7)	10 (7.5)	0	0.021
Stroke	21 (2.2)	33 (3.6)	9 (6.7)	0	0.010
Major or life-threatening bleeding	65 (6.8)	70 (7.6)	22 (16.4)	7 (10.4)	0.001
Major vascular complications	76 (8.1)	79 (8.6)	10 (7.5)	3 (4.5)	0.692
Pacemaker	146 (15.4)	163 (17.7)	17 (12.7)	8 (12.1)	0.261
Aortic regurgitation ≥moderate	112 (12.6)	115 (13.6)	20 (16.7)	7 (11.9)	0.628
AKI[a]	140 (15.8)	169 (19.4)	36 (28.1)	3 (30.0)	0.004
Stage 1	106 (12.0)	139 (15.9)	27 (21.1)	2 (20.0)	0.001
Stage 2	24 (2.7)	18 (2.1)	0	-	
Stage 3	10 (1.1)	12 (1.4)	9 (7.0)	1 (10.0)	
Need for dialysis	3 (0.3)	9 (1.0)	9 (7.0)	1 (10.0)	0.001
Mortality	57 (6.0)	71 (7.7)	14 (10.4)	8 (11.9)	0.082
Length of stay (days)	6 (5–9)	6 (5–10)	7 (5–13)	8 (5–11)	0.055
Late (>30-day) outcomes					
Mortality	191 (21.4)	214 (25.1)	39 (32.5)	26 (44.1)	0.001
Cardiovascular	108 (12.1)	119 (14.0)	24 (20.0)	7 (11.9)	0.053
Non-cardiovascular	83 (9.3)	95 (11.1)	15 (12.5)	19 (32.2)	0.001
Cumulative late outcomes					
Overall mortality	248 (26.1)	284 (30.7)	53 (39.6)	34 (50.7)	0.001
Cardiovascular mortality	165 (17.4)	189 (20.5)	38 (28.4)	15 (22.4)	0.002
Non-cardiovascular mortality	83 (8.7)	95 (10.3)	15 (11.2)	19 (28.4)	0.001
Respiratory	28 (2.9)	24 (2.6)	1 (0.7)	3 (4.5)	0.973
Malignancy	15 (1.6)	20 (2.2)	3 (2.2)	0	0.680
Kidney failure	2 (0.2)	11 (1.2)	5 (3.7)	7 (10.4)	0.001
Bleeding	2 (0.2)	5 (0.5)	2 (1.5)	2 (3.0)	0.004
Non-respiratory sepsis	15 (1.6)	14 (1.5)	1 (0.7)	5 (7.5)	0.034
Other	21 (2.2)	21 (2.3)	3 (2.2)	2 (3.0)	0.551

Values are expressed as *n* (%) or median (IQR).
[a]*n* = 1895 patients (excluding patients with previous dialysis).

55–175), $P = 0.639$]. There was an association between the severity of CKD pre-procedure and the occurrence of AKI and need for dialysis following TAVI ($P = 0.001$ for both), *Table 2*. Patients who suffered AKI had a higher 30-day mortality (14.7 vs. 3.3%, adjusted OR 4.81; 95% CI: 3.18–7.29, $P = 0.001$), cumulative overall mortality (45.7 vs. 24.5%, adjusted HR:1.94; 95% CI:1.60–2.36, $P = 0.001$) and cardiovascular mortality (34.8 vs. 14.7%, adjusted HR:2.37; 95% CI:1.89–2.99, $P = 0.001$), but not non-cardiovascular mortality (10.9 vs. 9.8%, adjusted HR:1.23; 95% CI: 0.85–1.77, $P = 0.276$). Early and late outcomes grouped according to CKD severity based on creatinine values after TAVI are shown in Supplementary material online, *Tables S1* and *S2*.

Valve haemodynamics and functional status changes following transcatheter aortic valve implantation

Echocardiographic data at 1-year follow-up were available in 1038 patients (79% of the patients at risk). Changes in valve haemodynamics following TAVI, according to CKD severity are shown in *Figure 2*. There were no differences in valve haemodynamics (mean transvalvular gradient, valve area) over time across the CKD groups ($P > 0.30$ for both). Changes in functional class following TAVI, according to the severity of CKD are shown in *Figure 3A* and *B*). Similar improvements in NYHA class were observed following TAVI among the different groups of CKD ($P = 0.126$), and no significant differences between groups ($P = 0.693$) were observed at 1-year follow-up.

Prognostic factors in advanced chronic kidney disease patients

The uni- and multivariable analyses evaluating the factors associated with poorer outcomes among patients with advanced CKD (stage 4 and 5) are shown in *Table 5*. In the multivariable analysis, a history of atrial fibrillation (AF) (HR: 2.29, 95% CI: 1.47–3.58, $P = 0.001$), and dialysis therapy (HR: 1.86, 95% CI: 1.17–2.97, $P = 0.009$) determined a higher risk of cumulative late death. Kaplan–Meier survival curves according to the presence of chronic atrial fibrillation, dialysis or both are shown in *Figure 4*. Patients with advanced CKD in dialysis and a history of AF undergoing TAVI had a mortality rate of 70.8% at 1-year follow-up (vs. 20.1% in the absence of these two risk factors; $P < 0.001$) and of 100% at 2-year follow-up (vs. 28.4% in the absence of these two factors, $P < 0.001$).

Discussion

In patients undergoing TAVI, the presence of advanced CKD (stage 4 and 5) was an independent predictor of major/life-threatening bleeding and death within the 30 days after the TAVI procedure. Also, patients with advanced CKD (stage 4 and 5) were at higher risk of mortality after a median follow-up of 15 months, and this was related to an increased risk of overall, cardiovascular and non-cardiovascular mortality, especially secondary to kidney disease progression and bleeding complications. The presence of advanced CKD was not associated with any significant deterioration in valve haemodynamics at 1-year follow-up, and those patients with advanced CKD experienced improvements in functional status similar to those of the rest of the TAVI population. Among advanced CKD patients, the presence of pre-existing AF or dialysis determined a higher risk of death following TAVI. Only ~30% of the patients with both factors (dialysis therapy and pre-existing AF) were alive at 1-year follow-up and none at 2 years.

Advanced chronic kidney disease as a predictor of poorer outcomes

The presence of CKD has been shown to be an important factor of poorer outcomes in patients undergoing TAVI.[8] More recently, some studies have shown that the prognostic value of CKD is associated with its severity, with those patients with severe CKD exhibiting the highest risk of death acutely and at mid-term follow-up.[9–12] Consistent with these data, in the present study advanced CKD (eGFR < 30 mL/min/1.73 m^2 or dialysis) was associated with an increased risk of death at 30-days and after a median follow-up of 15 months following TAVI. Also, advanced CKD led to increased risk of both cardiovascular and non-cardiovascular death.

Chronic kidney disease has been associated with increased cardiovascular mortality through an accelerated progression of coronary artery disease and coronary events, exacerbation of congestive heart failure and an increased risk of sudden death.[2,20,21] Patients with aortic stenosis undergoing TAVI exhibit a high prevalence of coronary artery disease, systolic and diastolic heart failure and conduction disturbances,[8] and the presence of CKD may therefore worsen clinical outcomes by further affecting all these cardiovascular abnormalities. The rate of ~20% of AKI following TAVI and the fact that CKD stage 4 was associated with a higher risk of AKI and CKD progression leading to increase mortality is consistent with previous reports.[22,23] Also, CKD stage 4 and 5 was associated with a higher risk of peri-procedural and follow-up bleeding events. Prior studies have also reported a higher incidence of acute and late life-threatening bleeding events among patients with advanced CKD undergoing TAVI.[10,12] Advanced CKD has been associated with platelet dysfunction and haemostatic abnormalities consistent with a hypercoagulable state leading to a higher risk for haemorrhagic events, especially in those patients on dual antiplatelet or warfarin therapy.[24–27] The difficult equilibrium between thrombotic and haemorrhagic events and the implications for antithrombotic treatment have been well recognized in TAVI patients.[28] The present study showing that the major role of bleeding events in the poorer outcomes of such patients strongly suggests the advisability of avoiding antithrombotic overtreatment and the questionability of using systematic dual antiplatelet therapy in this challenging group.

Advanced chronic kidney disease and transcatheter aortic valve implantation: identifying those patients at highest risk

The poorer outcomes associated with advanced CKD in patients undergoing TAVI may raise the question of whether or not these high-risk patients do indeed benefit from this procedure, and which patients would be at highest risk for poorer outcome. No data exist to date regarding risk stratification among these patients and, to the best of our knowledge, this is the first study to specifically evaluate the factors associated with poorer outcomes among patients with advanced CKD. Importantly, a history of AF and dialysis therapy were the factors determining worse outcomes in such

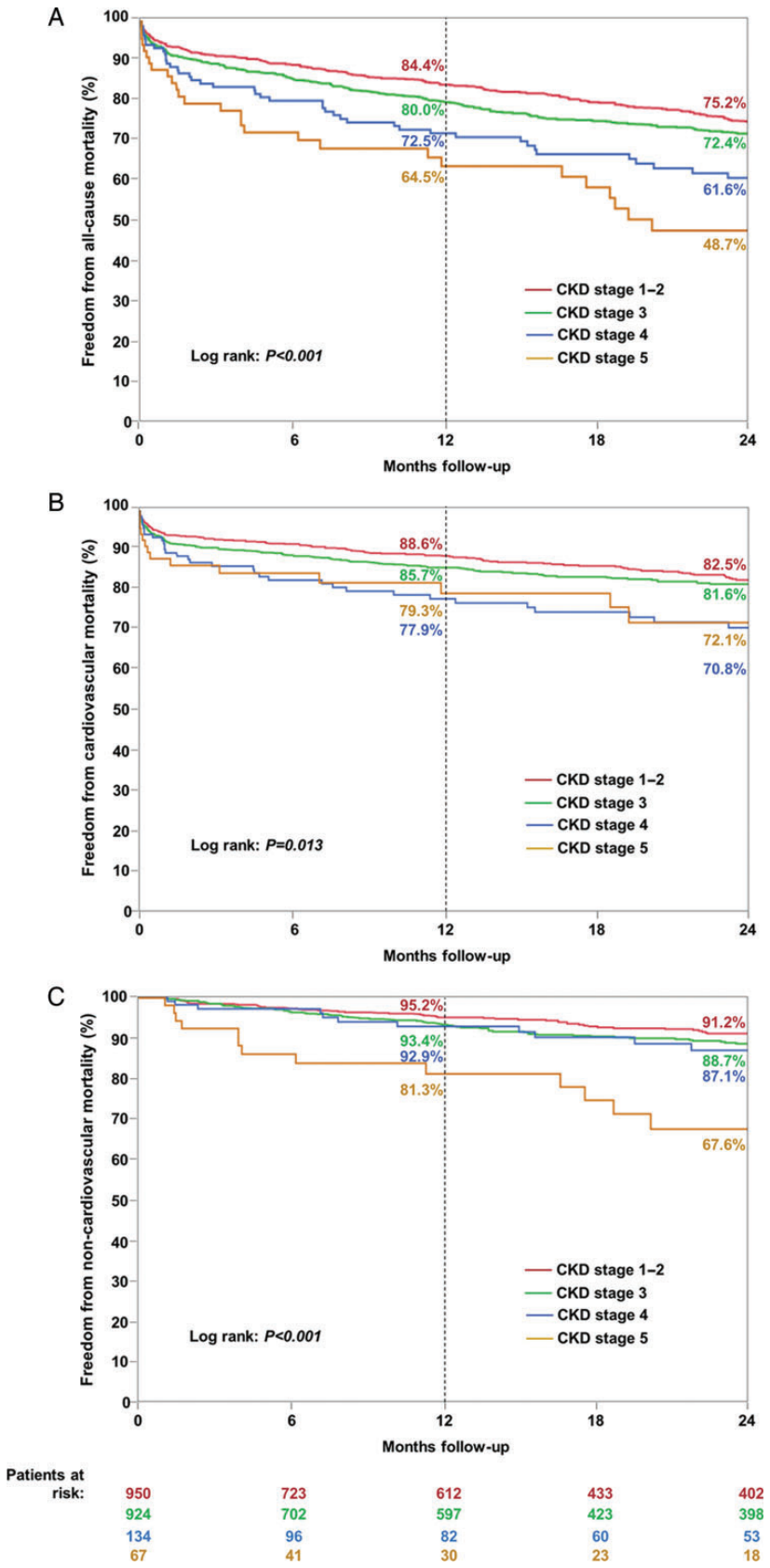

Figure 1 Kaplan–Meier Curves for all-cause mortality (*A*), cardiovascular mortality (*B*), and non-cardiovascular mortality (*C*), according to chronic kidney disease severity.

Table 3 Uni- and multivariable predictors of 30-day mortality ($n = 150$) and 30-day major/life-threatening bleeding ($n = 173$)

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
30-day mortality				
Baseline kidney function				
CKD stage 1–2	1.00		1.00	
CKD stage 3	1.30 (0.91–1.87)	0.149	1.28 (0.89–1.84)	0.179
CKD stage 4	1.83 (0.99–3.38)	0.055	1.71 (0.92–1.84)	0.089
CKD stage 5	2.12 (0.97–4.66)	0.060	1.94 (0.90–4.37)	0.089
Advanced CKD (stage 4–5)	1.93 (1.15–3.23)	0.013	1.80 (1.07–3.03)	0.027
Adjusting factors				
Peripheral vascular disease	1.49 (1.02–2.18)	0.037	1.26 (0.82–1.94)	0.285
Transfemoral approach	0.69 (0.49–0.99)	0.043	0.82 (0.55–1.22)	0.325
30-day major/life-threatening bleeding				
Baseline kidney function				
CKD stage 1–2	1.00	–	1.00	–
CKD stage 3	1.12 (0.79–1.58)	0.539	1.03 (0.72–1.47)	0.873
CKD stage 4	2.67 (1.59–4.51)	0.001	2.39 (1.40–4.08)	0.001
CKD stage 5	1.59 (0.70–3.61)	0.270	1.18 (0.49–2.87)	0.717
Advanced CKD (stage 4–5)	2.30 (1.44–3.66)	0.001	2.15 (1.49–3.12)	0.001
Adjusting factors				
Female sex	1.41 (1.03–1.93)	0.033	1.22 (0.83–1.79)	0.322
Body surface area	0.45 (0.21–0.99)	0.048	0.61 (0.24–1.54)	0.297
Prior CABG	0.66 (0.44–0.98)	0.038	0.59 (0.38–0.92)	0.019
Prior stroke	1.61 (1.07–2.43)	0.022	1.49 (0.96–2.30)	0.075
Peripheral vascular disease	1,90 (1.35–2.68)	0.001	2.15 (1.49–3.12)	0.001

CABG, coronary artery bypass graft.

patients, with those patients with the combination of these two factors exhibiting a dismal prognosis following successful TAVI. On the other hand, patients with advanced CKD and neither of these factors presented similar outcomes to those of the rest of the study population.

The presence of renal failure requiring dialysis is a well-known prognostic factor among CKD patients, especially in those with cardiovascular conditions and in those undergoing cardiac surgery.[2,5–7] Dumonteil *et al.*[10] found an increased risk for mortality among 33 dialysis patients undergoing TAVI, with a mortality rate close to 30% at 1-year follow-up. On the other hand, Rau *et al.*[29] evaluated 10 dialysis patients who underwent TAVI, showing outcomes at 6-month follow-up similar to those of 116 non-dialysis patients. The present study, which included one of the largest series of dialysis patients undergoing TAVI to date, showed a slightly higher mortality at 1-year follow-up among dialysis patients, and a higher increase in mortality after the first year.

In the absence of aortic stenosis, advanced CKD has been associated with a higher incidence of AF, which in turn translates into much higher rates of mortality at mid-term follow-up.[2,30–35] The present study also showed a higher rate of pre-existing AF among TAVI candidates with CKD stage 4, and AF was indeed found to be the most important prognostic factor in this group of patients. The mortality rate in patients with advanced CKD and AF was as high as 41 and 56% at 1- and 2-year follow-up, respectively. In those patients with AF and dialysis, the mortality rate was as high as 71% at 1-year follow-up, and all patients with these two factors had died in <2 years following the TAVI procedure. Pre-existing AF has been recognized as an important prognostic factor in TAVI, and this has been related to an increase in decompensated heart failure, and thrombo-embolic and bleeding events.[36] This study showed that pre-existing AF is the most important prognostic factor in patients with advanced CKD, and this factor identified a group of TAVI candidates with an ominous prognosis when associated with chronic dialysis. These results suggest that elderly patient with aortic stenosis on dialysis therapy and AF should be proposed for TAVI with extreme caution and after thorough evaluation by the heart team. If finally accepted for this procedure, a very close follow-up and probably an adjustment in antithrombotic therapy should be applied in order to reduce bleeding events, which are one of the main drivers of periprocedural and late mortality in these patients. In fact, the use of warfarin in patients with AF and dialysis has been controversial, with some studies showing an excess of major bleeding complications without a clear reduction in thrombo-embolic events in this group of patients.[37,38] The use of single antiplatelet therapy and other therapies such as percutaneous left atrial

Table 4 Uni- and multivariable predictors of late cumulative mortality ($n = 619$)

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Baseline kidney function				
CKD stage 1–2	1.0	—	1.0	—
CKD stage 3	1.16 (0.98–1.38)	0.080	1.07 (0.90–1.28)	0.436
CKD stage 4	1.58 (1.17–2.12)	0.003	1.35 (1.02–1.83)	0.046
CKD stage 5	2.79 (1.95–4.00)	0.001	3.03 (2.08–4.43)	0.001
Advanced CKD stage 4–5	1.90 (1.49–2.43)	0.001	1.72 (1.33–2.21)	0.001
Adjusting factors				
Age, years[a]	1.06 (1.00–1.13)	0.041	1.13 (1.06–1.21)	0.001
Male sex	1.25 (1.07–1.47)	0.006	1.19 (1.00–1.42)	0.055
Body mass index (kg/m^2)[b]	0.98 (0.96–1.00)	0.015	0.99 (0.98–1.01)	0.475
NYHA class III, IV	1.59 (1.25–2.02)	0.001	1.30 (1.02–1.67)	0.037
Smoker	1.20 (1.02–1.46)	0.034	0.96 (0.78–1.17)	0.672
Coronary artery disease	1.42 (1.21–1.68)	0.001	1.25 (1.04–1.49)	0.015
Previous atrial fibrillation	1.75 (1.49–2.05)	0.001	1.63 (1.38–1.93)	0.001
Prior stroke	1.43 (1.16–1.76)	0.001	1.24 (0.99–1.54)	0.058
Peripheral vascular disease	1,68 (1.41–2.01)	0.001	1.26 (1.01–1.56)	0.038
Chronic obstructive pulmonary disease	1.21 (1.03–1.43)	0.024	1.22 (1.02–1.45)	0.029
LVEF (%)[a]	0.95 (0.93–0.98)	0.001	0.99 (0.96–1.02)	0.473
Mean aortic gradient (mmHg)[a]	0.94 (0.91–0.96)	0.001	0.96 (0.94–0.99)	0.004
Approach no TF	1.64 (1.38–1.94)	0.001	1.39 (1.13–1.70)	0.002
Device success	0.80 (0.66–0.97)	0.020	0.66 (0.54–0.80)	0.001

NYHA, New York Heart Association; CABG, coronary artery bypass graft; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; TF, transfemoral.
[a]For each increase of 5 units.
[b]For each decrease of 1 unit.

appendage closure should probably be considered in this high-risk group of patients.

Advanced chronic kidney disease, functional status, and valve haemodynamics

The presence of advanced CKD, and particularly the need for dialysis, has been associated with a more rapid deterioration of valve haemodynamics and the use of biological (vs. mechanical) aortic bioprostheses in this setting has been controversial.[7,13–15] In the present study, the presence of advanced CKD, including patients on dialysis, was not associated with a more rapid deterioration of valve haemodynamics within the months following the procedure. Future studies will be needed to confirm these data at longer term follow-up.

The presence of advanced CKD has been associated with a decrease in functional status and quality of life.[1] However, the present study showed that in those patients who survived the TAVI procedure and were alive at 1-year follow-up, the NYHA class improved significantly in a similar manner to the rest of the study population. This highlights the fact that the procedure was not futile in a significant proportion of patients, and increases the clinical relevance of better identifying those patients with advanced CKD who are likely to survive following a TAVI procedure. However, future studies with more

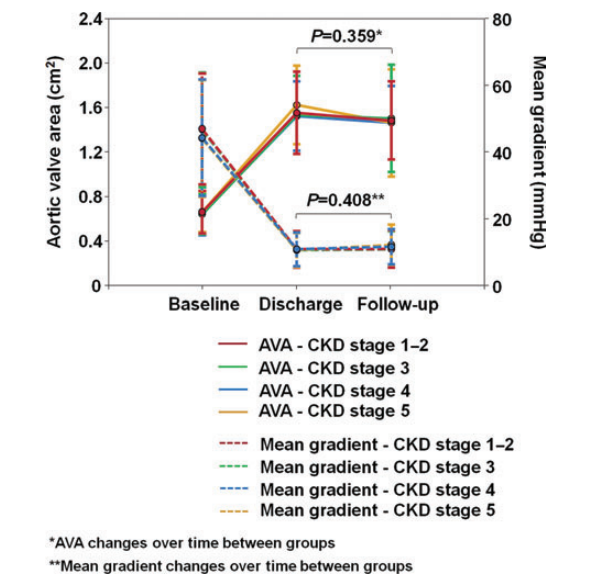

Figure 2 Changes in valve haemodynamics (mean transvalvular gradient, aortic valve area) over time (baseline, hospital discharge, 1-year follow-up), according to chronic kidney disease severity.

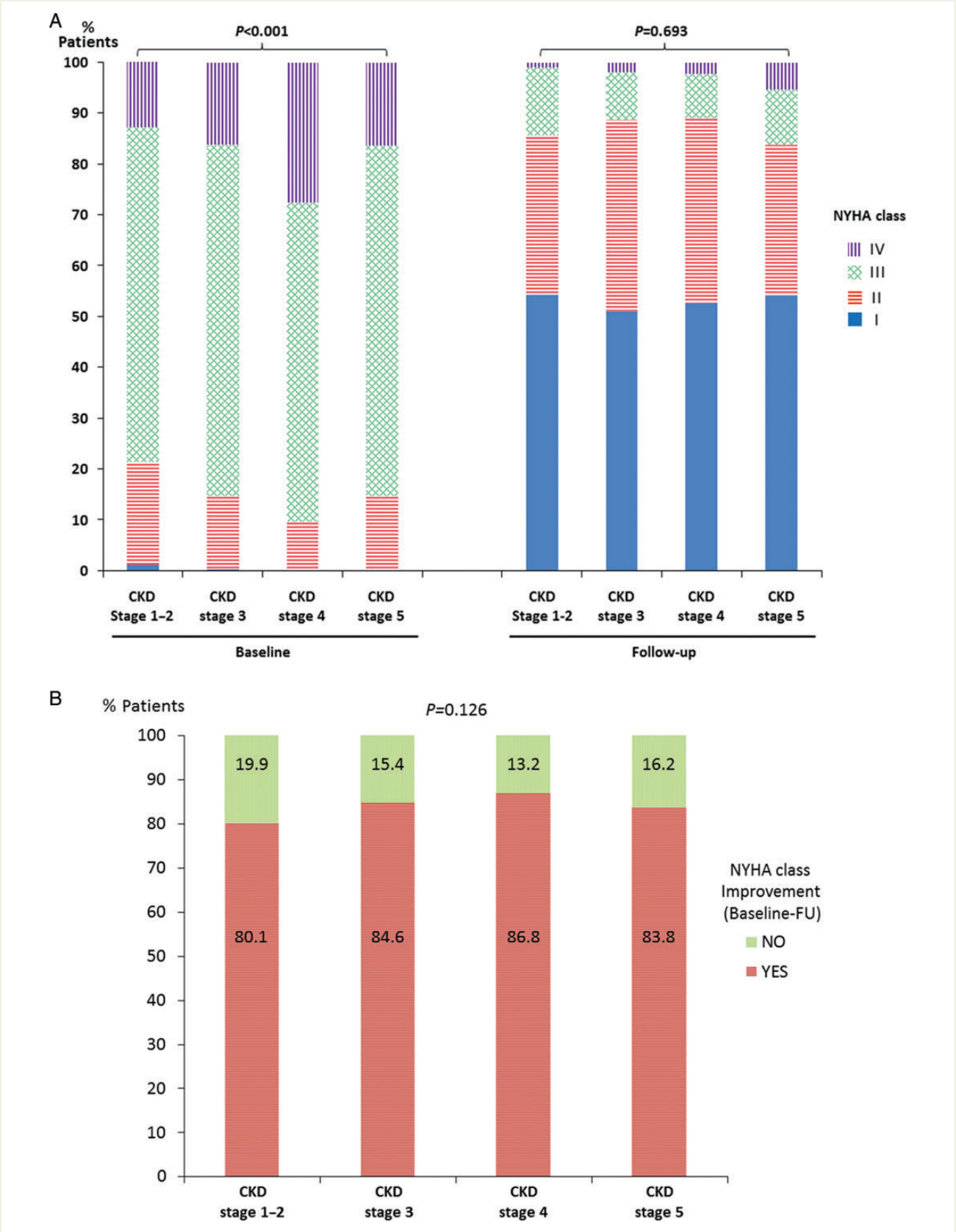

Figure 3 Changes in NYHA class following TAVI (baseline: 1-year follow-up) overall (*A*) or improvement of at least one NYHA class (*B*), according to chronic kidney disease severity. CKD, chronic kidney disease; FU, follow-up.

Table 5 Uni- and multivariable predictors of cumulative overall mortality ($n = 87$) in patients with advanced chronic kidney disease ($n = 201$)

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Baseline variables				
Age, years[a]	1.08 (0.93–1.24)	0.317		
Male sex	1.04 (0.68–1.59)	0.843		
Body mass index (kg/m^2)[b]	0.96 (0.92–1.01)	0.090		
NYHA class III, IV	1.20 (0.60–2.40)	0.601		
Smoker	1.42 (0.90–2.23)	0.127		
Diabetes	0.79 (0.50–1.24)	0.305		
Hypertension	1.06 (0.60–1.85)	0.840		
Coronary artery disease	1.64 (1.03–2.61)	0.039	1.55 (0.97–2.50)	0.069
Prior CABG	1.11 (0.67–1.82)	0.687		
Previous atrial fibrillation	2.18 (1.42–3.33)	0.001	2.29 (1.47–3.58)	0.001
Prior stroke	1.50 (0.87–2.58)	0.146		
Peripheral vascular disease	1.72 (1.09–2.71)	0.019	1.31 (0.82–2.10)	0.265
Previous dialysis	1.70 (1.08–2.67)	0.022	1.86 (1.17–2.97)	0.009
Chronic obstructive pulmonary disease	1.38 (0.87–2.19)	0.175		
Severely calcified aorta	0.96 (0.52–1.77)	0.901		
STS score	1.02 (0.99–1.05)	0.096		
Logistic EuroSCORE	1.01 (0.99–1.02)	0.234		
Echocardiographic variables				
LVEF (%)[a]	1.00 (0.94–1.06)	0.959		
Mean aortic gradient (mmHg)[a]	0.95 (0.89–1.01)	0.112		
Aortic valve area	1.98 (0.71–5.53)	0.189		
Procedural characteristics				
Approach no TF	1.39 (0.90–2.16)	0.139		
Device success	0.92 (0.55–1.55)	0.759		

CABG, coronary artery bypass graft; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; TF, transfemoral.
[a]For each increase by 5 unit.
[b]For each decrease by 1 unit.

objective and reliable functional tests and quality of life data will be needed to further determine the futility of TAVI in patients with advanced CKD.

Study limitations

While the calculation of eGFR values using the MDRD equation has been largely validated and its superiority with respect to simple serum creatinine values for evaluating renal function is well established, its use in elderly patients has some limitations mainly due to the significant decline in muscle mass in this population.[39] Several differences in baseline characteristic were present across the groups. Despite adjustment for differences between groups, this may not control for all confounding factors and some bias in the final results cannot be ruled out. The fact that patients in the CKD stage 5 group were significantly younger than the other groups may be due to a selection bias related to anticipated poorer outcomes in older patients on regular dialysis treatment. Data on administration of contrast media (such as preoperative computed tomography or percutaneous coronary intervention) within the same hospital stay were not available. There was no independent event adjudication committee for this study; and while this might have been less relevant for the outcome of mortality (yes/no), it is a limitation when establishing the causes of death, especially during the follow-up period. While clinical data were prospectively collected in each participating centre, data analyses were performed retrospectively and there was no pre-specified case report form designated for this study. Finally, no data on the type and number of antithrombotic drugs and changes in renal function over time were available.

In conclusion, advanced CKD in patients undergoing TAVI seems to determine a higher risk for early and mid-term cardiovascular and non-cardiovascular mortality. The occurrence of severe bleeding events played an important role in early and late deadly events, and the use of antithrombotic therapy overtreatment, especially dual antiplatelet therapy and/or the combination of warfarin with antiplatelet agents, should probably be re-evaluated in such patients. Among advanced CKD patients, those with either AF or dialysis therapy were

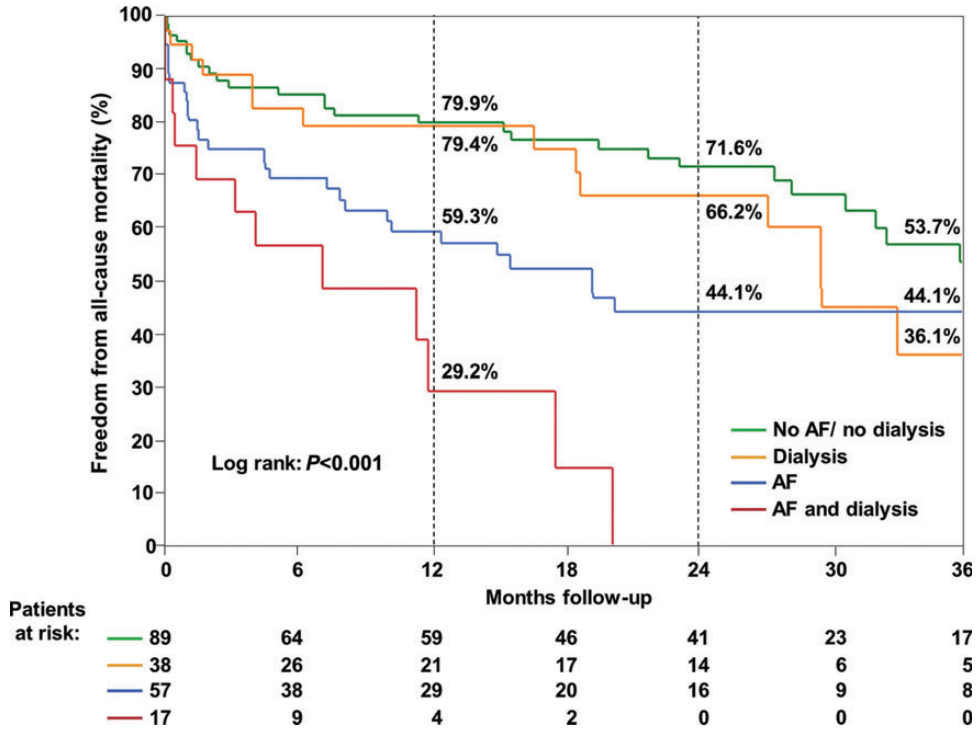

Figure 4 Kaplan–Meier survival curves at 3-year follow-up for all-cause mortality in patients with advanced chronic kidney disease, according to the presence of pre-existing atrial fibrillation and/or dialysis therapy. AF, atrial fibrillation.

at the highest risk, and in particular the combination of these two factors led to an unacceptable mortality rate within the months following the TAVI procedure. These data may help to improve the clinical decision-making process in this challenging group of patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

The authors want to thank Melanie Côté, MSc, from the Quebec Heart & Lung Institute, for her help in the preparation of figures.

Funding

L.N.-F. received funding via a research grant from the Fundación Mutua Madrileña (Spain). H.B.R. is supported by a research PhD grant from 'CNPq, Conselho Nacional de Desenvolvimento Científico e Tecnológico - Brasil'.

Conflict of interest: J.G.W. and J.R.-C. are consultants for Edwards Lifesciences and St-Jude Medical. E.D. and J.L.V. are consultants for Edwards Lifesciences. P.d.J. is consultant for Medtronic. The rest of the authors had no conflict of interest to disclose.

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