Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 10, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.04.057

Prognostic Value of Chronic Kidney Disease After Transcatheter Aortic Valve Implantation

Masanori Yamamoto, MD, PhD,* Kentaro Hayashida, MD, PhD,† Gauthier Mouillet, MD,* Thomas Hovasse, MD,† Bernard Chevalier, MD,† Atsushi Oguri, MD, PhD,* Yusuke Watanabe, MD,† Jean-Luc Dubois-Randé, MD, PhD,‡§ Marie-Claude Morice, MD,† Thierry Lefèvre, MD,† Emmanuel Teiger, MD, PhD*‡

Créteil and Massy, France

Objectives This study sought to assess the influence of chronic kidney disease (CKD) classification on clinical outcomes in patients undergoing transcatheter aortic valve implantation (TAVI).

Background The prognostic value of impaired renal function according to CKD classification has not been thoroughly investigated in very elderly TAVI cohorts.

Methods Data from 642 consecutive patients who underwent TAVI were prospectively collected. Clinical outcomes were compared in enrolled patients, divided into CKD stage 1+2, CKD stage 3a, CKD stage 3b, and CKD stage 4 on the basis of estimated glomerular filtration rate ≥60, 45 to 59, 30 to 44, and 15 to 29 ml/min/1.73 m^2, respectively.

Results Among the study patients (mean age: 83.5 ± 6.5 years, logistic European System for Cardiac Operative Risk Evaluation score 20.0% [range: 13.6% to 28.8%]), 34% were categorized as CKD stage 1+2 (n = 218), 28.3% as CKD stage 3a (n = 182), 28.2% as CKD stage 3b (n = 181), and 9.5% as CKD stage 4 (n = 61). Thirty-day and cumulative 1-year mortality rates increased significantly across the 4 groups (6.9% vs. 8.8% vs. 13.3% vs. 26.2%, p = 0.002, and 17.2% vs. 23.4% vs. 29.2% vs. 47.8%, p < 0.001, respectively). After adjustment for considerable influential confounders in a Cox multivariate regression model, CKD stage 4 was associated with increased risk for 30-day mortality (hazard ratio: 3.04; 95% confidence interval [CI]: 1.43 to 6.49; p = 0.004), and CKD stages 3b and 4 were related to increased cumulative 1-year mortality (hazard ratios: 1.71 and 2.91; 95% CI: 1.09 to 2.68 and 1.73 to 4.90; p = 0.020 and p < 0.001, respectively) compared with CKD stage 1+2 as the referent.

Conclusions Classification of CKD stages before TAVI allows risk stratification for early and midterm clinical outcomes. TAVI for patients with CKD stage 4 is still considered challenging because of high mortality rates after the procedure. (J Am Coll Cardiol 2013;62:869–77) © 2013 by the American College of Cardiology Foundation

Ten years after its first introduction in the clinical field, transcatheter aortic valve implantation (TAVI) has now become an innovative alternative procedure that enables catheter-based treatment in patients considered high-risk candidates for surgical aortic valve replacement (SAVR) (1–3). Several studies have identified factors associated with poor outcomes after TAVI (4–8). Impaired renal function is widely known to be one of the worst prognostic factors among patients who undergo SAVR (9,10). "Chronic kidney disease" (CKD) is a general term for heterogenous disorders affecting kidney function. Current guidelines provide a classification of CKD stages on the basis of the estimated glomerular filtration rate (eGFR): ≥90 ml/min/1.73 m^2 (stage 1), 60 to 89 ml/min/1.73 m^2 (stage 2), 45 to 59 ml/min/1.73 m^2 (stage 3a), 30 to 44 ml/min/1.73 m^2 (stage 3b), 15 to 29 ml/min/1.73 m^2 (stage 4), and <15 ml/min/1.73 m^2 (stage 5) (11). A recent meta-analysis showed a steep increase in the risk for cardiovascular mortality in a general population in patients with CKD stage 3 and proposed in a consensus report the subdivision of CKD stage 3 into stages 3a and 3b (12,13). Precise pre-screening assessment of

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From the *Department of Interventional Cardiology, AP-HP, Henri Mondor University Hospital, Créteil, France; †Institut Cardiovasculaire Paris Sud, Massy, France; ‡Department of Medical Cardiology AP-HP, Henri Mondor University Hospital, Créteil, France; and the §Université Paris Est, Faculty of Medicine, Créteil, France. Dr. Hayashida is a proctor for transfemoral transcatheter aortic valve implantation for Edwards Lifesciences. Dr. Chevalier is a consultant for Medtronic Inc. Dr. Lefèvre is a proctor for transfemoral transcatheter aortic valve implantation for Edwards Lifesciences and is a consultant for Symetis and Directflow. Dr. Teiger is a proctor for Medtronic Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 18, 2012; revised manuscript received April 10, 2013, accepted April 16, 2013.

Abbreviations and Acronyms

AKI = acute kidney injury
CI = confidence interval
CKD = chronic kidney disease
eGFR = estimated glomerular filtration rate
EuroSCORE = European System for Cardiac Operative Risk Evaluation
HR = hazard ratio
MDRD = Modification of Diet in Renal Disease
SAVR = surgical aortic valve replacement
TAVI = transcatheter aortic valve implantation

CKD stages may be a valuable tool for predicting the risk for mortality before the procedure. Although some data are available with respect to the relationship between CKD stages and clinical outcomes in the TAVI population, no significant relation between clinical outcomes and the presence of CKD has been observed, and increased mortality rates in patients with advanced CKD are attenuated after adjustment for other influential factors (14,15). The aim of this study was therefore to elucidate the impact of detailed CKD classification on clinical outcomes after TAVI.

Methods

Patient selection. The study population comprised 661 consecutive patients with symptomatic severe aortic stenosis who underwent TAVI procedures at 2 French centers. Patients were selected for TAVI when considered unsuitable or at high risk for SAVR by consensus between individual centers and heart team discussion. Operative risk was calculated using the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) and Society of Thoracic Surgeons predictive risk of mortality score. High surgical risk was defined as a logistic EuroSCORE >20% or a Society of Thoracic Surgeons score >10% and according to the presence of cardiac or noncardiac comorbidities that may constitute contraindications to surgery or increase significantly the surgical risk (16). The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation: eGFR (ml/min/1.73 m^2) = 186 × (serum creatinine)$^{1.154}$ × (age)$^{0.203}$ × (0.742 if female) (17). Patients were classified into 4 groups on the basis of eGFR: ≥60 ml/min/1.73 m^2 (CKD stage 1+2), 45 to 59 ml/min/1.73 m^2 (CKD stage 3a), 30 to 44 ml/min/1.73 m^2 (CKD stage 3b), and 15 to 29 ml/min/1.73 m^2 (CKD stage 4) (11). Nineteen patients receiving regular hemodialysis (CKD stage 5, eGFR <15 ml/min/1.73 m^2) before TAVI were excluded from the initial analysis because of the statistical instability of such a small number of patients. The analysis was performed in the 642 remaining patients. Clinical data, patient characteristics, echocardiographic data, procedural variables, length of hospital stay, and in-hospital and all-cause mortality rates were prospectively examined for each group. Information about the possible occurrence and/or causes of death was obtained from the treating hospital or by telephoning directly the patient or the patient's family. The medical ethics committees at both hospitals approved this study protocol, and written informed consent was obtained from all patients before TAVI.

TAVI procedures. TAVI procedures at the 2 centers have already been described in detail (18–23). Both commercially available valves were used: the balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences, Irvine, California) and the self-expandable Medtronic CoreValve Revalving System (Medtronic Inc., Minneapolis, Minnesota). The prosthesis size was determined from preprocedural echocardiographic and multislice computed tomographic findings (19). The devices were delivered via the femoral, apical, subclavian, transaortic, or transcarotid route. Criteria for selection of the femoral approach were based on the size, calcification, and tortuosity of the aortoiliofemoral arterial tree and the ratio between sheath size and minimal femoral size. The femoral artery was mainly approached percutaneously using a preclosing technique (Proster XL, Abbott Laboratories, Inc., Chicago, Illinois) (20,21,23). The surgical approach was used in instances in which the femoral route was deemed unsuitable, difficult, or high risk. Subclavian and carotid access was obtained by surgical cut-down and closed surgically. The transapical approach was performed through a left anterior minithoracotomy and the transaortic approach via upper limited sternotomy. Edwards devices were implanted using mainly the femoral, apical, or transaortic route. CoreValve devices were implanted using the femoral, subclavian, or carotid route (18–23). Among patients with impaired renal function (eGFR <60 ml/min/1.73 m^2), hydration regimens for reducing the risk for acute kidney injury (AKI) were administered according to previous recommendations (24): isotonic 0.9% saline was started at an infusion rate of 1 ml/kg body weight per hour 12 h before and (continued 12 h) after TAVI. Procedural success and the 30-day combined safety endpoint were evaluated according to the Valve Academic Research Consortium criteria (25). Other procedural complications during TAVI were also assessed on the basis of the Valve Academic Research Consortium classifications.

Statistical analysis. All statistical analyses were performed using SPSS version 19.0 (SPSS, Inc., Chicago, Illinois). Continuous variables are expressed as mean ± SD or as medians, depending on variable distribution. Categorical data are expressed as percents of the total. Comparisons among the 3 age groups were performed using Pearson's bivariate test and chi-square tests for categorical covariates and 1-way analysis of variance for continuous covariates. Prognostic values of baseline renal function in CKD stages 3a, 3b, and 4 compared with CKD stage 1+2 as the referent were assessed using a Cox regression hazard model. A univariate Cox regression analysis was performed to obtain the hazard ratio (HR) for 30-day and 1-year mortality after TAVI. Thereafter, a multivariate analysis was performed using the variables with p values <0.20 in the univariate analysis to examine their independent associations with 30-day and 1-year mortality. The Kaplan-Meier method was used to estimate cumulative mortality rates in the 4 groups. Survival differences in each group were compared using log-rank tests. All statistical tests were 2 sided, and p values <0.05 were considered significant.

Results

Baseline patient and procedural characteristics. Of the 642 patients included in this study (mean age 83.5 ± 6.5 years, mean logistic EuroSCORE 22.5 ± 12.2%), 34.0% were categorized as CKD stage 1+2 (n = 218), 28.3% as CKD stage 3a (n = 182), 28.2% as CKD stage 3b (n = 181), and 9.5% as CKD stage 4 (n = 61). Variations in baseline characteristics among the 4 study groups resulted in significant differences in the mean logistic EuroSCORE (18.2% [range: 11.1% to 26.6%] vs. 18.4% [range: 12.1% to 26.9%] vs. 22.2% [range: 16.0% to 30.9%] vs. 24.0% [range: 19.1% to 35.0%], p < 0.001) and Society of Thoracic Surgeons score (5.0% [range: 3.6% to 7.7%] vs. 6.0% [range: 4.3% to 10.4%] vs. 8.5% [range: 6.3% to 12.2%] vs. 11.0% [range: 8.7% to 17.7%], p < 0.001) (Table 1). Procedural characteristics are shown in Table 2. The Edwards valve was used in 404 patients (62.9%) and the CoreValve in 238 (37.1%). The transfemoral approach was used in 431 patients (67.1%) and nontransfemoral approaches in 211 (32.9%). Although no significant differences were observed in the type of valve, access site, length of hospital stay, and procedural success rates among the 4 groups, the 30-day mortality rate and 30-day combined safety endpoint significantly increased in parallel with CKD severity in the 4 groups (6.9% vs. 8.8% vs. 13.3% vs. 26.2%, p = 0.002, and 14.7% vs. 17.6% vs. 25.4% vs. 31.1%, p = 0.006, respectively). A trend toward a higher incidence of stroke (1.8% vs. 2.7% vs. 4.4% vs. 8.2%, p = 0.084) and AKI (13.3% vs. 14.3% vs. 19.9% vs. 24.6%, p = 0.083) was observed in parallel with the degree of CKD severity.

Cumulative mortality and baseline renal function. Clinical follow-up was obtained in 100% of patients, with a median follow-up period of 289 days (interquartile range: 84 to 571 days). A total of 177 patients died; of these, 42 patients were in CKD stage 1+2, 40 patients in CKD stage 3a, 56 patients in CKD stage 3b, and 34 patients in CKD stage 4. Kaplan-Meier analysis of cumulative mortality in the 4 groups on the basis of renal function is presented in

Table 1 Baseline Patient Characteristics

Variable	CKD Stage 1+2 (n = 218)	CKD Stage 3a (n = 182)	CKD Stage 3b (n = 181)	CKD Stage 4 (n = 61)	p Value
Baseline clinical characteristics					
Age (yrs)	80.6 ± 8.1	84.2 ± 5.0	85.6 ± 4.3	86.1 ± 5.4	<0.001
Men	113 (51.8%)	85 (46.7%)	84 (46.4%)	27 (44.3%)	0.59
BMI (kg/m^2)	27.2 ± 5.0	25.7 ± 4.0	25.0 ± 4.2	23.8 ± 3.9	<0.001
BSA (m^2)	1.80 ± 0.19	1.73 ± 0.17	1.69 ± 0.18	1.70 ± 0.17	<0.001
NYHA classification (III/IV)	166 (76.1%)	143 (78.6%)	152 (84.0%)	53 (86.9%)	0.12
Peripheral artery disease	72 (33.0%)	50 (27.5%)	49 (27.1%)	12 (19.7%)	0.19
Prior MI	29 (13.3%)	23 (12.6%)	26 (14.4%)	8 (13.1%)	0.97
Prior PCI	56 (25.7%)	51 (28.0%)	58 (32.0%)	18 (29.5%)	0.57
Prior CABG	44 (20.2%)	22 (12.1%)	23 (12.7%)	8 (13.1%)	0.083
Prior cardiac surgery	53 (24.3%)	21 (11.5%)	28 (15.5%)	8 (13.1%)	0.005
Prior stroke	21 (9.6%)	17 (9.3%)	18 (9.9%)	7 (11.5%)	0.97
Diabetes mellitus	57 (26.1%)	33 (18.1%)	42 (23.2%)	13 (21.3%)	0.67
Hypertension	155 (71.1%)	122 (67.0%)	129 (71.3%)	47 (70.6%)	0.49
Dyslipidemia	116 (53.2%)	99 (54.4%)	81 (44.8%)	27 (44.3%)	0.17
Smoking	17 (7.8%)	17 (9.3%)	15 (8.3%)	7 (11.5%)	0.82
COPD	65 (29.8%)	49 (26.9%)	54 (29.8%)	19 (31.1%)	0.89
Logistic EuroSCORE (%)	18.2 (11.1–26.6)	18.4 (12.1–26.9)	22.2 (16.0–30.9)	24.0 (19.1–35.0)	<0.001
STS score (%)	5.0 (3.6–7.7)	6.0 (4.3–10.4)	8.5 (6.3–12.2)	11.0 (8.7–17.7)	<0.001
eGFR (ml/min/1.73 m^2)	80.3 ± 19.5	52.5 ± 4.6	38.7 ± 4.0	25.5 ± 4.3	<0.001
Creatinine (mg/dl)	0.92 ± 0.22	1.16 ± 0.23	1.46 ± 0.35	2.10 ± 0.83	<0.001
Echocardiographic data					
LVEF (%)	51.7 ± 14.3	51.9 ± 14.4	50.2 ± 14.2	47.3 ± 14.8	0.12
Aortic annular diameter (mm)	22.1 ± 2.0	21.6 ± 2.4	21.6 ± 2.0	21.6 ± 2.3	0.11
AVA (cm^2)	0.67 ± 0.17	0.64 ± 0.15	0.62 ± 0.17	0.60 ± 0.16	0.002
Mean gradient (mm Hg)	46.4 ± 17.4	47.3 ± 157	48.7 ± 18.5	50.0 ± 19.5	0.43
AR grade (0–4)	0.85 ± 0.70	0.82 ± 0.71	0.85 ± 0.74	0.85 ± 0.78	0.98
MR grade (0–4)	0.93 ± 0.69	0.90 ± 0.72	0.94 ± 0.68	1.12 ± 0.80	0.32
PAP (mm Hg)	47.5 ± 14.0	46.2 ± 14.8	50.0 ± 14.8	51.0 ± 14.7	0.054
Post-TAVI AVA (cm^2)	1.90 ± 0.54	1.87 ± 0.48	1.92 ± 0.54	1.81 ± 0.39	0.87
Post-TAVI mean gradient (mm Hg)	9.0 ± 3.1	8.2 ± 4.6	8.3 ± 2.9	10.1 ± 3.5	0.37

Values are mean ± SD or n (%).

AR = aortic regurgitation; AVA = aortic valve area; BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricle ejection fraction; MI = myocardial infarction; MR = mitral regurgitation; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TAVI = transcatheter aortic valve implantation.

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Table 2 Procedural Patient Characteristics

Variable	CKD Stage 1+2 (n = 218)	CKD Stage 3a (n = 182)	CKD Stage 3b (n = 181)	CKD Stage 4 (n = 61)	p Value
Type of valve					
CoreValve	85 (39.0%)	69 (37.9%)	64 (35.4%)	20 (37.1%)	0.78
Edwards SAPIEN	133 (61.0%)	113 (62.1%)	117 (64.6%)	41 (67.2%)	
Approach route					
Transfemoral	141 (64.7%)	115 (63.2%)	134 (74.0%)	41 (67.2%)	0.12
Nontransfemoral	77 (35.3%)	67 (36.8%)	47 (26.0%)	20 (32.8%)	
Procedural variables					
Procedure time (min)	85.4 ± 36.4	89.1 ± 54.5	87.5 ± 44.4	101.6 ± 52.7	0.23
Fluoroscopy time (min)	18.8 ± 10.4	17.9 ± 9.4	20.3 ± 13.3	20.4 ± 9.5	0.36
Contrast medium volume (ml)	165.2 ± 87.3	152.1 ± 68.5	159.4 ± 64.9	139.6 ± 76.2	0.13
Post-procedural variables					
Length of hospital stay (days)	10.1 ± 6.2	11.3 ± 7.9	11.4 ± 10.5	9.7 ± 6.4	0.24
Procedural success	205 (94.0%)	167 (91.8%)	165 (91.2%)	54 (88.5%)	0.49
30-day mortality	15 (6.9%)	16 (8.8%)	24 (13.3%)	14 (23.0%)	0.002
30-day combined safety endpoint	32 (14.7%)	32 (17.6%)	46 (25.4%)	19 (31.1%)	0.006
Procedural MI	1 (0.5%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0.44
Major stroke	4 (1.8%)	5 (2.7%)	8 (4.4%)	5 (8.2%)	0.084
AKI grade ≥2	29 (13.3%)	26 (14.3%)	36 (19.9%)	15 (24.6%)	0.083
AKI grade 3	2 (0.9%)	2 (1.1%)	3 (1.7%)	3 (4.9%)	0.15
Need for dialysis at discharge	2 (0.9%)	1 (0.5%)	1 (0.6%)	0 (0.0%)	0.87
Major vascular complications	16 (7.3%)	15 (8.2%)	15 (8.3%)	6 (9.8%)	0.93
RBC transfusion	46 (21.1%)	46 (25.3%)	47 (26.0%)	18 (28.5%)	0.48
RBC transfusion ≥4 U	18 (8.3%)	15 (8.2%)	15 (8.3%)	3 (4.9%)	0.84
Pacemaker implantation	19 (8.7%)	24 (13.2%)	19 (10.5%)	4 (6.6%)	0.37
2 valves implanted	5 (2.3%)	6 (3.3%)	6 (3.3%)	0 (0.0%)	0.50
Post-TAVI AR grade ≥2	43 (19.7%)	44 (24.2%)	46 (25.4%)	19 (31.1%)	0.25
Need for any cardiac surgery	4 (1.8%)	6 (3.3%)	5 (2.8%)	4 (6.7%)	0.28
Need for vascular surgery	9 (4.1%)	9 (4.9%)	6 (3.3%)	3 (4.9%)	0.88

Values are n (%) or mean ± SD.
AKI = acute kidney injury; RBC = red blood cell; other abbreviations as in Table 1.

Figure 1. Cumulative 1-year and 2-year mortality rates in each individual group were 17.2%, 23.4%, 29.2%, and 47.8%, respectively, and 25.5%, 28.8%, 36.8%, and 68.2%, respectively. The probability of cumulative mortality over the entire follow-up period after TAVI was similar between CKD stage 1+2 and CKD stage 3a ($p = 0.52$). In contrast, the mortality rates of CKD 3b and 4 were significantly higher in comparison with CKD stage 1+2 as the referent ($p = 0.016$ and $p < 0.001$, respectively). The cumulative 30-day (early) and 30-day to 730-day (late) mortality in the 4 groups is also given in Figure 2. Cumulative early and late mortality rates in each individual group were 6.9%, 8.8%, 13.3%, and 23.0%, respectively, and 19.9%, 21.9%, 29.4%, and 58.7%, respectively. A trend toward a higher incidence of late mortality was observed in patients with CKD stage 3b ($p = 0.09$), and a significant increment was observed in patients with CKD stage 4 ($p < 0.001$) compared with CKD stage 1+2.

Prognostic value of baseline renal function after TAVI. The Cox regression analysis for the association between clinical outcomes and CKD classification is shown in Table 3. Predictive factors of overall mortality were assessed using a Cox regression hazard model. CKD stage 3b, CKD stage 4, and logistic EuroSCORE (per 1% increase) were associated with poor prognosis at 30 days. Of these, CKD stage 4 (HR: 3.04; 95% confidence interval [CI]: 1.43 to 6.49; $p = 0.004$) and logistic EuroSCORE (HR: 1.03; 95% CI: 1.00 to 1.05; $p = 0.028$) were independently associated with increased risk for 30-day mortality in the multivariate model. In the univariate analysis, HR for CKD stage 3b, CKD stage 4, New York Heart Association classification (III or IV), prior stroke, chronic obstructive pulmonary disease, left ventricular ejection fraction (per 1% increase), and logistic EuroSCORE were significant predictors of 1-year mortality. The multivariate Cox regression model indicated impaired renal function as CKD stage 3b (HR: 1.71; 95% CI: 1.09 to 2.68; $p = 0.020$), CKD stage 4 (HR: 2.91; 95% CI: 1.73 to 4.90; $p < 0.001$), and logistic EuroSCORE (HR: 1.02; 95% CI: 1.01 to 1.03; $p = 0.009$) as the only independent predictors of 1-year mortality (Table 4).

Discussion

The present study demonstrates that CKD classification provides useful information for predicting early and midterm clinical outcomes in patients undergoing TAVI. Although the 30-day and 1-year outcomes of patients with CKD stage 1+2 and CKD stage 3a (eGFR ≥45 ml/min/1.73 m^2) seemed to be similar, CKD stage 4 (eGFR 15 to 29 ml/min/

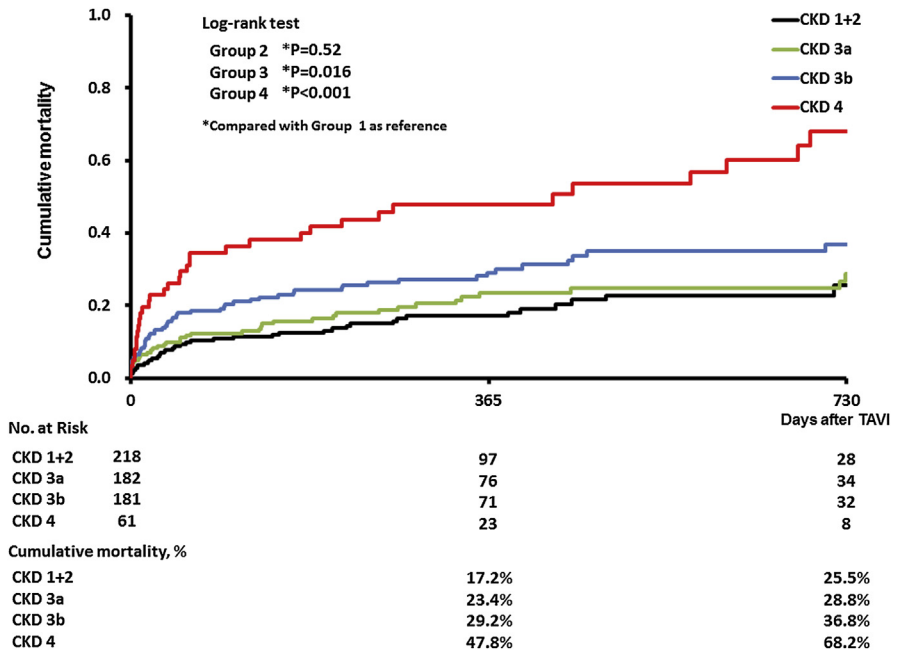


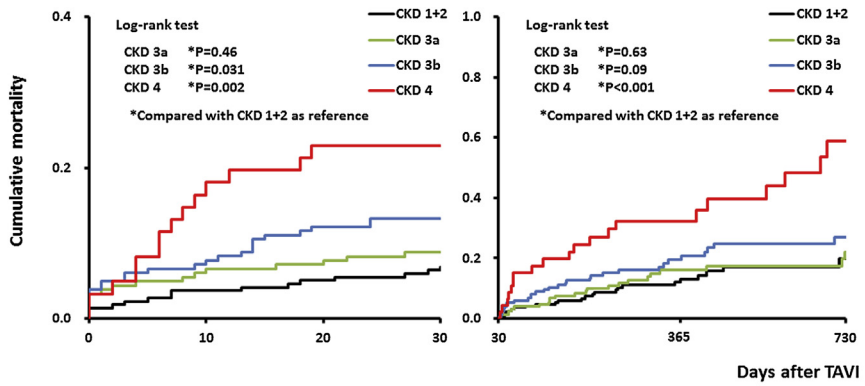
Figure 1 Time-to-Event Curves for Cumulative Mortality

Mortality rate was calculated using Kaplan-Meier methods and compared using the log-rank test according to chronic kidney disease (CKD) classification. TAVI = transcatheter aortic valve implantation.

1.73 m^2) was associated with increased 30-day mortality, and CKD stage 3b (eGFR 30 to 44 ml/min/1.73 m^2) and stage 4 were associated with increased cumulative 1-year mortality without attenuation after adjusting for confounding variables. A trend toward a higher incidence of late (from 30 to 730 days) mortality was also observed in patients with CKD stage 3b ($p = 0.09$), and a significant increment was observed in patients with CKD stage 4 ($p < 0.001$) compared with CKD stage 1+2. In particular, CKD stage 4 was associated with very high 30-day (26.2%) and 1-year (47.8%) mortality rates. The cutoff value of eGFR < 30 ml/min/1.73 m^2 may be considered the threshold for predicting early mortality and eGFR <45 ml/min/1.73 m^2 the threshold for predicting midterm mortality.

Assessment of baseline renal dysfunction is clinically important in patients undergoing TAVI, as it is associated with an increased risk for adverse events (8,26). Whereas previous renal dysfunction criteria were limited given that they were established on an individual basis using mainly serum creatinine values, CKD classification, in contrast, is a global concept that reflects heterogenous disorders affecting kidney function. To date, there have been only a few reports focusing on CKD staging in relation to clinical outcome in TAVI cohorts (14,15). The first report did not reveal any increase in the mortality rate of patients with CKD (eGFR <60 ml/min/1.73 m^2) compared with those without CKD (14). The second report showed a higher incidence of cardiovascular death in patients with advanced CKD (eGFR 30 to 59 and 15 to 29 ml/min/1.73 m^2), although this difference was not found to be significant by multivariate analysis (15). Published guidelines have provided a classification of CKD stages into several categories according to the eGFR (11). A recent meta-analysis revealed a steep rise in the risk for cardiovascular mortality in advanced CKD groups of a general population and suggested that CKD stage 3 (eGFR 30 to 59 ml/min/1.73 m^2) should be divided into stages 3a and 3b using a threshold eGFR of 45 ml/min/1.73 m^2 for each CKD staging assessment (12,13). Consequently, because of the larger number of patients compared with previous reports, our study identified significant prognostic differences on the basis of the subdivided CKD classification. The threshold of eGFR <60 ml/min/1.73 m^2 was considered an indicator of moderate to severe damage in kidney function (11) in patients generally designated as having CKD. However, in high-risk elderly TAVI patients, the present results may suggest that eGFR <45 ml/min/1.73 m^2 as the optimal cutoff value has better predictive accuracy with respect to late adverse clinical outcomes.

The 30-day and cumulative 1-year mortality rates in the 4 study groups were 6.9%, 8.8%, 13.3%, and 26.2%, respectively, and 17.2%, 23.4%, 29.2%, and 47.8%, respectively. In addition, cumulative 2-year mortality of patients with stage 4 CKD was 68.2%. Cohort B of the pivotal Placement of Transcatheter Aortic Valves study was designed to compare the clinical outcomes of patients considered inoperable for



No. at risk

CKD 1+2	218	203	203	97	28
CKD 3a	182	166	166	76	34
CKD 3b	181	157	157	71	32
CKD 4	61	47	47	23	8

Cumulative mortality, %

CKD 1+2	6.9%	11.3%	19.9%
CKD 3a	8.8%	16.0%	21.9%
CKD 3b	13.3%	18.3%	29.4%
CKD 4	23.0%	32.2%	58.7%

Figure 2 Time-to-Event Curves for Cumulative Early (30-Day) and Late (30-Day to 730-Day) Mortality

Mortality rate was calculated using Kaplan-Meier methods and compared using the log-rank test according to chronic kidney disease (CKD) classification. TAVI = transcatheter aortic valve implantation.

SAVR who were randomized to TAVI versus medical treatment (27). The 30-day and 1-year all-cause death rates were 5.0% and 30.7% in the TAVI group and 2.8% and 50.7% in the medical group (27). The 2-year follow-up results showed a very high mortality rate in the medical group (68.0%) (28). We observed similar 1-year and 2-year death rates in patients with CKD stage 4 after TAVI, but we were unable to extrapolate what would have been the 2-year

Table 3 Cox Regression Analysis for the Association Between 30-Day Cumulative Mortality and Clinical Findings

	Univariate Analysis			Multivariate Analysis		
Variable	HR	95% CI	p Value	HR	95% CI	p Value
Baseline renal function						
CKD stage 1+2 (eGFR >60 ml/min/1.73 m^2)	1.00			1.00		
CKD stage 3a (eGFR 45–60 ml/min/1.73 m^2)	1.30	0.64–2.62	0.47	1.37	0.67–2.78	0.39
CKD stage 3b (eGFR 30–45 ml/min/1.73 m^2)	2.00	1.05–3.81	0.035	1.82	0.94–3.50	0.074
CKD stage 4 (eGFR <30 ml/min/1.73 m^2)	3.63	1.75–7.52	0.001	3.04	1.43–6.49	0.004
Adjusting factors						
Age (per 1-yr increase)	1.01	0.98–1.05	0.49			
Male	1.06	0.66–1.69	0.82			
BSA (per 0.1-m^2 increase)	0.55	0.15–1.93	0.35			
NYHA classification (III/IV)	1.93	0.93–4.04	0.080	1.63	0.77–3.45	0.21
Peripheral artery disease	1.10	0.66–1.83	0.72			
Prior MI	1.53	0.84–2.80	0.17	1.32	0.71–2.44	0.38
Prior cardiac surgery	1.62	0.94–2.80	0.085	1.37	0.76–2.45	0.30
Prior stroke	1.78	0.94–3.40	0.078	1.51	0.78–2.90	0.22
Diabetes mellitus	0.79	0.52–1.21	0.28			
COPD	1.31	0.80–2.14	0.29			
LVEF (per 1% increase)	0.99	0.97–1.01	0.21			
Pulmonary hypertension (>60 mm Hg)	0.81	0.44–1.48	0.49			
Logistic EuroSCORE (per 1% increase)	1.03	1.01–1.05	0.001	1.03	1.00–1.05	0.028
Valve type (CoreValve)	0.68	0.40–1.14	0.14	0.75	0.44–3.45	0.21
Approach route (transfemoral)	0.75	0.47–1.22	0.25			

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

Table 4 Cox Regression Analysis for the Association Between 1-Year Cumulative Mortality and Clinical Findings

	Univariate Analysis			Multivariate Analysis		
Variable	HR	95% CI	p Value	HR	95% CI	p Value
Baseline renal function						
CKD stage 1+2 (eGFR >60 ml/min/1.73 m^2)	1.00			1.00		
CKD stage 3a (eGFR 45–60 ml/min/1.73 m^2)	1.35	0.84–2.16	0.22	1.34	0.83–2.15	0.23
CKD stage 3b (eGFR 30–45 ml/min/1.73 m^2)	1.86	1.19–2.89	0.006	1.71	1.09–2.68	0.020
CKD stage 4 (eGFR <30 ml/min/1.73 m^2)	3.54	2.14–5.85	<0.001	2.91	1.73–4.90	<0.001
Adjusting factors						
Age (per 1-yr increase)	1.01	0.98–1.04	0.33			
Male	1.30	0.94–1.81	0.11	1.24	0.88–2.31	0.15
BSA (per 0.1-m^2 increase)	0.86	0.36–2.05	0.74			
NYHA classification (III/IV)	1.63	1.02–2.62	0.042	1.43	0.88–2.31	0.15
Peripheral artery disease	1.22	0.86–1.73	0.26			
Prior MI	1.30	0.82–2.04	0.26			
Prior cardiac surgery	1.16	0.77–1.77	0.48			
Prior stroke	1.72	1.08–2.73	0.022	1.59	0.99–2.55	0.052
Diabetes mellitus	0.79	0.52–1.21	0.28			
COPD	1.49	1.06–2.08	0.021	1.36	0.96–1.91	0.082
LVEF (per 1% increase)	0.99	0.98–0.99	0.025	0.99	0.98–1.01	0.71
Pulmonary hypertension (>60 mm Hg)	1.11	0.77–1.63	0.57			
Logistic EuroSCORE (per 1% increase)	1.03	1.02–1.04	<0.001	1.02	1.01–1.03	0.009
Valve type (CoreValve)	0.81	0.57–1.15	0.23			
Approach route (transfemoral)	0.81	0.58–1.13	0.22			

Abbreviations as in Tables 1 and 3.

mortality rate of these patients if they had been treated medically.

Patients with hemodialysis were excluded from the analysis of this study. Operative mortality rates after SAVR among hemodialysis patients have been reported to be between 10% and 35% and 1-year mortality rates between 20% and 45% (29–32). These results translate into a very poor outcome, which is, nevertheless, comparable with that observed in patients with CKD stage 4 undergoing TAVI. In view of these data, TAVI for dialysis patients may represent a significant challenge, and a large-scale analysis would be warranted to clarify the clinical outcomes of dialysis patients undergoing TAVI.

In the present report, we have highlighted trends toward higher incidence of major stroke and AKI in patients with advanced-stage CKD. When dividing the patients into 2 groups with an eGFR cutoff of 45 ml/min/1.73 m^2, the incidences of major stroke, AKI grade ≥2 and AKI grade 3 complications are significantly higher in the low-eGFR group (2.3% vs. 5.4%, $p = 0.035$, 13.8% vs. 21.1%, $p = 0.015$, and 1% vs. 3.3%, $p = 0.037$, respectively). Both procedural stroke and AKI have been shown to be significant predictors of higher mortality rates after TAVI (8,33–36). The mechanisms of procedural stroke were multifactorial and were triggered by multiple factors, such as cerebral embolism of aortic valve tissue, atherosclerotic debris embolization from the aorta, and ischemic hypoperfusion brain damage during the procedure (33). The occurrence of AKI was also associated with several causes other than baseline renal function (36), which presented as advanced CKD class in our study, but also hypertension or need for red blood cell transfusion (35). In addition, we have shown recently that the amount of contrast media is associated with increased risk for AKI after TAVI (37). Thus, efforts to reduce the contrast media dose during screening and TAVI procedures should be considered, especially in patients with impaired renal function. Although the best solution to prevent these complex complications has not been clearly identified, further therapeutic considerations and device refinements are necessary in these high-risk patients.

Study limitations. We report a prospective multicenter TAVI cohort of a relatively moderate number of patients, which is too limited in size to allow us to define the optimal cutoff value of eGFR and CKD classification. A median follow-up duration of 289 days is insufficient. The calculation of eGFR using the MDRD equation in elderly patients is limited in terms of reliability, as is the Cockcroft-Gault method (38), although these methods proved superior to serum creatinine for estimating renal function. We should consider the fact that eGFR defined using the MDRD formula in the elderly is affected by the considerable decline in muscle mass with age, as well as by drugs and diet. Even if several formulas are commonly used as surrogates of the patients' glomerular filtration rates across all ages, few participants age >80 years have been enrolled in the studies that evaluated the reliability of these formulas. The serial change in renal function is clinically important especially in the group of impaired renal function after TAVI. However, these informative data were not available in our study. The direct causes of death may be difficult to determine in

a cohort of elderly patients and were, consequently, not always clearly identified in this study.

Conclusions

The results of our study suggest that CKD classification could be a useful tool for potential risk stratification before TAVI. Indeed, dividing TAVI candidates into CKD categories may be clinically important for risk assessment with a view to ensuring optimal TAVI management in patients with advanced-stage CKD.

Acknowledgment
The authors thank Catherine Dupic for her assistance in the preparation of this report.

Reprint requests and correspondence: Dr. Emmanuel Teiger, Department of Interventional Cardiology, Assistance Publique–Hôpitaux de Paris, Henri Mondor University Hospital, 51 Avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France. E-mail: emmanuel.teiger@hmn.aphp.fr OR Dr. Thierry Lefèvre, Institut Cardiovasculaire Paris Sud, 6 Avenue du Noyer Lambert, 91300 Massy, France. E-mail: t.lefevre@angio-icps.com.

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Key Words: chronic kidney disease ■ prognosis ■ transcatheter aortic valve implantation.