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Clinical Impact of Baseline Chronic Kidney Disease in Patients Undergoing Transcatheter or Surgical Aortic Valve Replacement

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ABSTRACT

Objectives: To assess the treatment effect of TAVR versus SAVR on clinical outcomes to 3 years in patients stratified by CKD by retrospectively studying patients randomized to TAVR or SAVR.

Background: The impact of CKD on mid-term outcomes of patients undergoing TAVR versus SAVR is unclear.

Methods: Patients randomized to TAVR or SAVR in the CoreValve US Pivotal High Risk Trial were retrospectively stratified by eGFR: none/mild or moderate/severe CKD. To evaluate the impact of baseline CKD in TAVR patients only, all patients undergoing an attempted TAVR implant in the US Pivotal Trial and CAS were stratified by baseline eGFR into none/mild, moderate, and severe CKD. The primary endpoint was major adverse cardiovascular and renal events (MACRE), a composite of all-cause mortality, myocardial infarction, stroke/TIA, and new requirement of dialysis.

Results: Moderate/severe CKD was present in 62.7% and 60.7% of high-risk patients randomized to TAVR or SAVR, respectively. Baseline characteristics were similar between TAVR and SAVR patients in both CKD subgroups, except for higher rates of diabetes and higher serum creatinine in SAVR patients. Among high-risk patients with moderate/severe CKD, TAVR provided a lower 3-year MACRE rate compared with SAVR: 42.1% vs. 51.0, $p=0.04$. Of 3,733 extreme- and high-risk TAVR patients, 39.9% had none/mild, 53.8% moderate, and 6.4%

severe CKD. Worsening baseline CKD was associated with increased 3-year MACRE rates [none/mild 51.5%, moderate 54.5%, severe 63.1%, $p=0.001$].

Conclusions: TAVR results in lower 3-year MACRE versus SAVR in high-risk patients with moderate/severe CKD. In patients undergoing TAVR, worsening CKD increases mid-term mortality and MACRE. Randomized trials of TAVR vs. SAVR in patients with moderate-severe CKD would help elucidate the best treatment for these complex patients.

Trial Registration:

CoreValve US Pivotal Trial: NCT01240902

CoreValve Continued Access Study: NCT01531374

Keywords: TAVR; SAVR; Renal Disease; Aortic Stenosis

INTRODUCTION

The presence of advanced chronic kidney disease (CKD) significantly worsens the short- and mid-term clinical outcomes of patients undergoing surgical aortic valve replacement (SAVR) for severe aortic stenosis (AS), with operative mortality as high as 21%¹. Transcatheter aortic valve replacement (TAVR) has emerged as a less invasive alternative for patients with severe AS^{2,3}.

The feasibility of TAVR or SAVR in patients with CKD has been shown in observational studies⁴⁻¹⁰. Worsening CKD has been shown to be associated with higher incidence of major bleeding and vascular complications, as well as increased all-cause mortality rates¹¹⁻¹³. The impact of CKD on the mid-term outcomes of patients undergoing TAVR versus SAVR is not known.

The primary aim of this study was to assess the treatment effect of TAVR versus SAVR on the clinical outcomes to 3 years of patients with varying degrees of CKD randomized in the CoreValve US Pivotal High Risk Trial. The secondary aim was to assess the impact of CKD on clinical outcomes to 3 years in all extreme-risk and high-risk patients undergoing TAVR as part of the CoreValve US Pivotal Trial and Continued Access Study (CAS).

METHODS

Study Design

The CoreValve US Pivotal Trial was a prospective, controlled, multicenter clinical trial conducted in patients with severe symptomatic AS and extreme- or high- surgical risk at 45 sites

in the United States. Details of the study design and methodology have been previously published^{14,15}. At each site, the institutional review board approved the study protocol, and all patients provided written informed consent. The present analysis comprises extreme- and high-risk patients from the CoreValve US Pivotal Extreme Risk Trial, Pivotal High Risk Trial, and CAS as further described below.

Patient Selection

Trial inclusion/exclusion criteria have been previously published^{14,15}. Patients randomized in the US Pivotal High Risk Trial to TAVR or SAVR who received an attempted implant were stratified into none/mild or moderate/severe CKD according to their baseline renal function and their outcomes were evaluated. The Modification of Diet in Renal Disease equation was used to calculate the estimated glomerular filtration (eGFR) from the patient's age, sex, race and baseline serum creatinine. Patients without available baseline renal function data were excluded from this analysis. Patients with end-stage renal disease requiring chronic dialysis or those with an eGFR of ≤ 20 ml/min/1.73m² were excluded from the CoreValve US Pivotal Trial and CAS^{14,15}. Due to the small number of patients with severe CKD precluding meaningful analysis if evaluated separately, they were combined with those with moderate CKD and only 2 groups, none/mild or moderate/severe, were evaluated.

To evaluate the impact of baseline CKD in TAVR patients only, all patients undergoing an attempted TAVR implant in the US Pivotal Trial and CAS were stratified by baseline eGFR

into none/mild (eGFR>60mL/min/1.73m²), moderate (eGFR 30-60mL/min/1.73m²), and severe (eGFR<30mL/min/1.73m²) CKD and their clinical outcomes assessed.

Study Endpoints

The primary endpoint is the composite of major adverse cardiovascular and renal events (MACRE) at 3 years, which included all-cause mortality, any stroke/TIA, myocardial infarction, and new requirement of dialysis. Individual components of MACRE and other clinical endpoints are also reported. Definitions of clinical endpoints are based on the Valve Academic Research Consortium¹⁴⁻¹⁶.

Statistical Analysis

Categorical variables were compared using the Fisher exact test or the chi-square test. Continuous variables are presented as mean ± standard deviation, with a t-test used for comparisons between 2 groups and ANOVA used for comparisons across 3 groups. Kaplan-Meier estimates were used to construct survival and MACRE curves based on all available follow-up data for the time-to-event analysis. Differences in event rates were evaluated using the log-rank test. All testing used a 2-sided α level of 0.05. For the predictors of mortality analysis, variables were selected based on clinical relevance. Cox proportional hazards survival models were used for 1-year mortality univariable and multivariable modeling analysis. Variables for inclusion in the Cox model for 1-year mortality were selected based on clinical relevance (Supplemental Table 1). Multivariable predictors were identified from univariable predictors with $p \leq 0.05$. A stepwise procedure was performed to determine the final model. The significance

level thresholds for entry and exit of independent variables were set at 0.10. Statistical analyses were performed with the use of SAS software, version 9.2 or above (SAS Institute, Cary, NC).

RESULTS

High-Risk Patient Characteristics

Patients randomized as part of the US Pivotal High Risk Trial were stratified according to their CKD (none/mild vs. moderate/severe) to compare the treatment effect of TAVR versus SAVR on clinical outcomes (Figure 1). Among 871 patients enrolled, 797 underwent randomization, with 391 patients among the attempted TAVR group and 359 patients in the attempted SAVR group. Moderate/severe CKD was present in 60.7% of high-risk patients randomized to SAVR and in 62.7% of patients randomized to TAVR. Baseline characteristics were similar between TAVR and SAVR patients in both CKD subgroups, except for higher rates of diabetes and higher serum creatinine in SAVR patients and a higher frequency of hostile mediastinum among TAVR patients in the none/mild CKD group (Table 1).

Clinical Outcomes After TAVR or SAVR

At 3-year follow up, the MACRE rate was lower in TAVR patients compared with SAVR patients in the moderate/severe CKD group (42.1% vs. 51.0%, $p=0.04$) but not in the none/mild CKD group. There were no differences in all-cause mortality, MI or all stroke/TIA or need for new dialysis among groups. AKI was less frequent among TAVR as compared with

SAVR patients in both the none/mild (0.7% vs. 10.7%, $p<0.001$) and moderate/severe (9.6% vs. 18.2%, $p=0.001$) CKD groups. Life-threatening or disabling bleeding was lower among TAVR compared with SAVR patients in both none/mild (15.8% vs. 33.7%, $p<0.001$) and moderate/severe (20.7% vs. 46.4%, $p<0.001$) CKD groups. Major vascular complications and need for new permanent pacemaker were more frequent among TAVR compared with SAVR patients in both CKD groups (Table 2, Figure 2).

TAVR Patient Characteristics

To look at TAVR patients in isolation, 3,733 extreme- and high-risk patients who underwent TAVR in the CoreValve US Pivotal Trial and CAS (Supplemental Figure 1) were stratified according to their baseline eGFR: none/mild ($n=1488$, 39.9%), moderate ($n=2007$, 53.8%), or severe ($n=238$, 6.4%) CKD. Baseline clinical and echocardiographic as well as procedural characteristics are presented in Table 3. Patients in the none/mild CKD group were younger, and male sex and hostile mediastinum were more frequent. Patients in the severe CKD group had a higher mean STS-PROM and logistic EuroSCORE, and a higher incidence of comorbidities than patients with none/mild or moderate CKD (Table 3).

Clinical Outcomes: TAVR Patients

Worsening CKD was associated with a higher rate of MACRE at 3 years (Table 4). The difference in MACRE was driven predominantly by an increase in new requirement for dialysis and the all-cause mortality rate in patients with severe CKD. The 3-year MACRE (none/mild

51.5%, moderate 54.5%, severe CKD 63.1%, log-rank $p=0.001$) and all-cause mortality (none/mild 44.1%, moderate 46.1%, severe CKD 56.0%, log-rank $p=0.01$) rates were significantly higher for the severe CKD group (Figure 3). Three-year rates of new requirement of dialysis, cardiovascular mortality, major bleeding, and acute kidney injury continued to be significantly higher in patients with severe CKD (Table 4).

Predictors of 1-Year All-Cause Mortality for TAVR Patients with Moderate/Severe CKD

A Cox regression model was built to identify covariates associated with 1-year all-cause mortality in patients with moderate/severe CKD. Albumin < 3.3 g/dL, male sex, BMI < 21 kg/m², falls in the past 6 months, home oxygen, assisted living residents, baseline moderate/severe baseline mitral regurgitation, peripheral vascular disease, prior stroke/ TIA, moderate/severe baseline tricuspid regurgitation, STS risk score $> 7\%$, and estimated volume of iodinated contrast media used (per 10cc) were found to be predictors of 1-year all-cause mortality. Patients undergoing ilio-femoral access were less likely to die after 1 year (Figure 4).

DISCUSSION

The principal findings of this analysis were: 1) moderate to severe CKD was frequent, being present in over 60% of high or extreme-risk TAVR and high-risk SAVR patients in the present study; 2) in high-risk patients with moderate/severe CKD, TAVR provided better clinical outcomes when compared with SAVR, with a significantly lower 3-year rate of MACRE; 3) in

high- risk patients who underwent TAVR, severe CKD was associated with an increased incidence of the mid-term adverse clinical outcomes, including all-cause mortality and MACRE; 4) several baseline clinical and some procedural features were found to be associated with the 1-year all-cause mortality amongst high- or extreme-risk patients with moderate/severe CKD undergoing TAVR.

Consistent with others, we found a high frequency of moderate/severe CKD among the high- to extreme-risk patients undergoing TAVR and high-risk patients randomized to SAVR ^{11, 17}, which is likely to be multifactorial ^{11, 12, 18-20}. While previous studies ^{11, 12, 21} provided short-term outcomes, the UK TAVI registry ¹⁸ and the present study provide mid-term (3-year) outcomes. Additionally, unlike previous studies, ^{12, 18, 20} our analysis specifically evaluated the impact of CKD on the outcomes of high- and extreme-risk patients undergoing TAVR similar to one prior study from the PARTNER 1 trial ¹¹.

The composite endpoint of MACRE is one of the unique features of the present analysis. The MACRE rate was significantly increased with worsening CKD up to 3 years after TAVR and driven by an increase in all-cause mortality and new requirement for dialysis. We also found increased new requirement for dialysis according to CKD. The risk of AKI increased as CKD worsened and likely contributed to the new requirement of dialysis rate. These results are consistent with previous studies which reported only short-term data ¹¹.

As TAVR has emerged as an effective therapy for symptomatic severe AS, the question of offering TAVR rather than SAVR to patients with CKD has become increasingly important.

We found a significantly lower 3-year rate of MACRE with TAVR compared with SAVR in patients with moderate/severe CKD ($p=0.04$). The rates of bleeding (major/life-threatening or disabling) and AKI were consistently higher for SAVR patients. The higher rates of bleeding among SAVR patients may have also resulted in a higher AKI rate. Previous results from the CoreValve High Risk Pivotal Trial demonstrated increased mortality in SAVR patients with AKI, but not TAVR patients with AKI¹³. The increase in bleeding rates in SAVR cases may be related to the platelet dysfunction associated with renal disease, with a further negative impact on platelet function due to cardiopulmonary bypass. These findings suggest worse outcomes with SAVR rather than TAVR in high-risk patients with moderate to severe CKD and are consistent with a retrospective analysis not confined to high- or extreme-risk patients by Nguyen et al.¹⁰.

In patients with moderate/severe CKD, we found baseline clinical features associated with increased disease burden and frailty to be predictors of 1-year all-cause mortality, consistent with previous studies^{11 22 17}. Also consistent with others^{23, 24}, we found multi-valvular involvement including tricuspid regurgitation to be associated with 1-year all-cause mortality, thus, the presence of such multi-valvular pathology should be carefully considered in counseling patients.

We found procedural characteristics to be associated with 1-year all-cause mortality, following TAVR. Consistent with others, we found the volume of iodinated contrast used, especially in patients with baseline renal dysfunction, to be associated with increased risk of acute kidney injury and elevated 1-year mortality highlighting the importance of minimizing

contrast use²⁵⁻²⁷. Consistent with the literature, we found a higher rate of vascular complications and the need for permanent pacemaker placement with TAVR. However, both of these complications will likely continue to decline and may not pose a disadvantage with TAVR rather than a SAVR approach^{28,29}. Also consistent with previous literature¹¹, we found ilio-femoral access to be protective, likely due to the less invasive nature of this approach, and the fact that those undergoing alternative access TAVR often have a higher burden of disease.

There are several limitations to consider. First, the present study was a post-hoc analysis of patients included in the CoreValve US Pivotal Extreme Risk and High Risk Trial and CAS. The number of patients in the severe CKD group was small. The new requirement of dialysis was not a prespecified data collection endpoint, and as such was manually collected and reviewed, and not adjudicated by the Clinical Events Committee. Due to a small sample size in the high-risk cohort with severe CKD, we were only able to perform a 2-group (none/mild and moderate/severe) comparison between TAVR and SAVR, which limits the applicability of our results in patients with severe CKD. Patients with end stage renal disease requiring chronic dialysis or those with an eGFR of ≤ 20 ml/min/1.73m² were excluded from the CoreValve US Pivotal Trial and the CAS; therefore, we were unable to provide outcomes with TAVR or SAVR for this sub-group in the present analysis.

CONCLUSION

In conclusion, TAVR was found to provide a lower 3-year rate of MACRE when compared with SAVR in high-risk patients with moderate/severe CKD suggesting TAVR is the preferred strategy for the treatment of these complex patients. Additionally, in patients undergoing TAVR, worsening CKD increases short- and mid-term all-cause mortality and the incidence of MACRE. Clinical features of increased disease burden, frailty, and procedural characteristics were found to be predictors of 1-year all-cause mortality in patients with moderate/severe CKD, emphasizing the need for a careful risk stratification and choice of procedural approach in such patients.

REFERENCES

1. Herzog CA, Ma JZ and Collins AJ. Long-term survival of dialysis patients in the United States with prosthetic heart valves: should ACC/AHA practice guidelines on valve selection be modified? *Circulation*. 2002;105:1336-41.
2. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG and PARTNER 1 Trial Investigators. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477-84.
3. Deeb GM, Reardon MJ, Chetcuti S, Patel HJ, Grossman PM, Yakubov SJ, Kleiman NS, Coselli JS, Gleason TG, Lee JS, Hermiller JB, Jr., Heiser J, Merhi W, Zorn GL, 3rd, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Maini B, Mumtaz M, Conte J, Resar J, Aharonian V, Pfeffer T, Oh JK, Qiao H, Adams DH, Popma JJ and CoreValve US Clinical Investigators. 3-Year Outcomes in High-Risk Patients Who Underwent Surgical or Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol*. 2016;67:2565-74.
4. O'Hair DP, Bajwa TK, Chetcuti SJ, Deeb GM, Stoler RC, Hebler RF, Maini B, Mumtaz M, Kleiman NS, Reardon MJ, Li S, Adams DH, Watson DR, Yakubov SJ, Popma JJ and

Petrossian G. One-Year Outcomes of Transcatheter Aortic Valve Replacement in Patients With End-Stage Renal Disease. *Ann Thorac Surg.* 2017;103:1392-1398.

5. Allende R, Webb JG, Munoz-Garcia AJ, de Jaegere P, Tamburino C, Dager AE, Cheema A, Serra V, Amat-Santos I, Velianou JL, Barbanti M, Dvir D, Alonso-Briaies JH, Nuis RJ, Faqiri E, Imme S, Benitez LM, Cucalon AM, Al Lawati H, Garcia Del Blanco B, Lopez J, Natarajan MK, Delarochelliere R, Urena M, Ribeiro HB, Dumont E, Nombela-Franco L and Rodes-Cabau J. Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes and prognostic markers from a large cohort of patients. *Eur Heart J.* 2014;35:2685-96.

6. Conrotto F, Salizzoni S, Andreis A, D'Ascenzo F, D'Onofrio A, Agrifoglio M, Chieffo A, Colombo A, Rapetto F, Santini F, Tarantini G, Gabbieri D, Savini C, Imme S, Ribichini F, Valsecchi O, Aiello M, Lixi G, Iadanza A, Pompei E, Stolcova M, Ornaghi D, Minati A, Cassese M, Martinelli GL, Sbarra P, Agostinelli A, Audo A, Pieroni A, Fiorilli R, Gerosa G, Rinaldi M and Gaita F. Transcatheter Aortic Valve Implantation in Patients With Advanced Chronic Kidney Disease. *Am J Cardiol.* 2017;119:1438-1442.

7. D'Errigo P, Moretti C, D'Ascenzo F, Rosato S, Biancari F, Barbanti M, Santini F, Ranucci M, Miceli A, Tamburino C, Onorati F, Santoro G, Grossi C, Fusco D, Seccareccia F and Group OR. Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement for Severe Aortic Stenosis in Patients With Chronic Kidney Disease Stages 3b to 5. *Ann Thorac Surg.* 2016;102:540-7.

8. Alqahtani F, Aljohani S, Boobes K, Maor E, Sherieh A, Rihal CS, Holmes DR and Alkhouli M. Outcomes of Transcatheter and Surgical Aortic Valve Replacement in Patients on Maintenance Dialysis. *Am J Med.* 2017 130:1464.e1-1464.e11.
9. Kobrin DM, McCarthy FH, Herrmann HC, Anwaruddin S, Kobrin S, Szeto WY, Bavaria JE, Groeneveld PW and Desai ND. Transcatheter and Surgical Aortic Valve Replacement in Dialysis Patients: A Propensity-Matched Comparison. *Ann Thorac Surg.* 2015;100:1230-6; discussion 1236-7.
10. Nguyen TC, Babaliaros VC, Razavi SA, Kilgo PD, Guyton RA, Devireddy CM, Shults CC, Mavromatis K, Kanitkar M, Block P, Lerakis S and Thourani VH. Impact of varying degrees of renal dysfunction on transcatheter and surgical aortic valve replacement. *J Thorac Cardiovasc Surg.* 2013;146:1399-406; discussion 13406-7.
11. Thourani VH, Forcillo J, Beohar N, Doshi D, Parvataneni R, Ayele GM, Kirtane AJ, Babaliaros V, Kodali S, Devireddy C, Szeto W, Herrmann HC, Makkar R, Ailawadi G, Lim S, Maniar HS, Zajarias A, Suri R, Tuzcu EM, Kapadia S, Svensson L, Condado J, Jensen HA, Mack MJ and Leon MB. Impact of Preoperative Chronic Kidney Disease in 2,531 High-Risk and Inoperable Patients Undergoing Transcatheter Aortic Valve Replacement in the PARTNER Trial. *Ann Thorac Surg.* 2016;102:1172-80.
12. Codner P, Levi A, Gargiulo G, Praz F, Hayashida K, Watanabe Y, Mylotte D, Debry N, Barbanti M, Lefevre T, Modine T, Bosmans J, Windecker S, Barbash I, Sinning JM, Nickenig G, Barsheshet A and Kornowski R. Impact of Renal Dysfunction on Results of Transcatheter Aortic

Valve Replacement Outcomes in a Large Multicenter Cohort. *Am J Cardiol.* 2016;118:1888-1896.

13. Conte JV, Hermiller J, Jr., Resar JR, Deeb GM, Gleason TG, Adams DH, Popma JJ, Yakubov SJ, Watson D, Guo J, Zorn GL, 3rd and Reardon MJ. Complications After Self-expanding Transcatheter or Surgical Aortic Valve Replacement. *Semin Thorac Cardiovasc Surg.* 2017;29:321-330.

14. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, Hermiller J, Jr., Hughes GC, Harrison JK, Coselli J, Diez J, Kafi A, Schreiber T, Gleason TG, Conte J, Buchbinder M, Deeb GM, Carabello B, Serruys PW, Chenoweth S, Oh JK and CoreValve US Clinical Investigators. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol.* 2014;63:1972-81.

15. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Jr., Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK and CoreValve US Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med.* 2014;370:1790-8.

16. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJ, Vahanian A, van Es GA, Vranckx P, Webb JG, Windecker S and Serruys PW. Standardized endpoint

definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *J Am Coll Cardiol*. 2011;57:253-69.

17. Beohar N, Doshi D, Thourani V, Jensen H, Kodali S, Zhang F, Zhang Y, Davidson C, McCarthy P, Mack M, Kapadia S, Leon M and Kirtane A. Association of Transcatheter Aortic Valve Replacement With 30-Day Renal Function and 1-Year Outcomes Among Patients Presenting With Compromised Baseline Renal Function: Experience From the PARTNER 1 Trial and Registry. *JAMA Cardiol*. 2017;2:742-749.

18. Ferro CJ, Chue CD, de Belder MA, Moat N, Wendler O, Trivedi U, Ludman P, Townend JN, Group UTS and National Institute for Cardiovascular Outcomes R. Impact of renal function on survival after transcatheter aortic valve implantation (TAVI): an analysis of the UK TAVI registry. *Heart*. 2015;101:546-52.

19. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P and Vahanian A. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J*. 2003;24:1231-43.

20. Oguri A, Yamamoto M, Mouillet G, Gilard M, Laskar M, Eltchaninoff H, Fajadet J, Iung B, Donzeau-Gouge P, Leprince P, Leguerrier A, Prat A, Lievre M, Chevreul K, Dubois-Rande JL, Teiger E and investigators FR. Impact of chronic kidney disease on the outcomes of transcatheter aortic valve implantation: results from the FRANCE 2 registry. *EuroIntervention*. 2015;10:e1-9.

21. Ferro CJ, Chue CD, de Belder MA, Moat N, Wendler O, Trivedi U, Ludman P and Townend JN. Impact of renal function on survival after transcatheter aortic valve implantation (TAVI): an analysis of the UK TAVI registry. *Heart*. 2015;101:546-52.
22. Williams M, Kodali SK, Hahn RT, Humphries KH, Nkomo VT, Cohen DJ, Douglas PS, Mack M, McAndrew TC, Svensson L, Thourani VH, Tuzcu EM, Weissman NJ, Kirtane AJ and Leon MB. Sex-related differences in outcomes after transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis: Insights from the PARTNER Trial (Placement of Aortic Transcatheter Valve). *J Am Coll Cardiol*. 2014;63:1522-8.
23. Lindman BR, Maniar HS, Jaber WA, Lerakis S, Mack MJ, Suri RM, Thourani VH, Babaliaros V, Kereiakes DJ, Whisenant B, Miller DC, Tuzcu EM, Svensson LG, Xu K, Doshi D, Leon MB and Zajarias A. Effect of tricuspid regurgitation and the right heart on survival after transcatheter aortic valve replacement: insights from the Placement of Aortic Transcatheter Valves II inoperable cohort. *Circ Cardiovasc Interv*. 2015;8.
24. Cortes C, Amat-Santos IJ, Nombela-Franco L, Munoz-Garcia AJ, Gutierrez-Ibanes E, De La Torre Hernandez JM, Cordoba-Soriano JG, Jimenez-Quevedo P, Hernandez-Garcia JM, Gonzalez-Mansilla A, Ruano J, Jimenez-Mazuecos J, Castrodeza J, Tobar J, Islas F, Revilla A, Puri R, Puerto A, Gomez I, Rodes-Cabau J and San Roman JA. Mitral Regurgitation After Transcatheter Aortic Valve Replacement: Prognosis, Imaging Predictors, and Potential Management. *JACC Cardiovasc Interv*. 2016;9:1603-14.

25. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB and Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol.* 2004;44:1393-9.
26. Sinning JM, Ghanem A, Steinhauser H, Adenauer V, Hammerstingl C, Nickenig G and Werner N. Renal function as predictor of mortality in patients after percutaneous transcatheter aortic valve implantation. *JACC Cardiovasc Interv.* 2010;3:1141-9.
27. McCullough PA, Wolyn R, Rocher LL, Levin RN and O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med.* 1997;103:368-75.
28. Toggweiler S, Gurvitch R, Leipsic J, Wood DA, Willson AB, Binder RK, Cheung A, Ye J and Webb JG. Percutaneous aortic valve replacement: vascular outcomes with a fully percutaneous procedure. *J Am Coll Cardiol.* 2012;59:113-8.
29. van Rosendael PJ, Delgado V and Bax JJ. Pacemaker implantation rate after transcatheter aortic valve implantation with early and new-generation devices: a systematic review. *Eur Heart J.* 2018;39:2003-2013.

FIGURE LEGENDS

Figure 1. Patient flow diagram for the High-Risk analysis. The "Attempted TAVR" and "Attempted SAVR" cohorts include all patients randomized to TAVR or SAVR who received an attempted implant (also includes intraprocedural deaths or other patients who may not have received an implant).

Figure 2. MACRE and all-cause mortality rates, TAVR vs. SAVR in high-risk patients. MACRE composite outcome in high-risk TAVR (red lines) vs. SAVR (blue lines) patients with none/mild CKD (A) and moderate/severe CKD (B), and all-cause mortality in TAVR (red lines) vs. SAVR (blue lines) for patients with none/mild CKD (C) and moderate/severe CKD (D). Values are KM % [95% CI].

Figure 3. MACRE composite endpoint (A) and all-cause mortality (B) for all TAVR patients up to 3 years post-procedure. Patients were stratified by none/mild (red lines), moderate (blue lines), or severe (black lines) baseline CKD. Values are KM % [95% CI].

Figure 4. Multivariable predictors of 1-year mortality in all TAVR patients with moderate/severe CKD. All TAVR patients with $eGFR \leq 60$ mL/min/1.73m² were included. Variables were selected from univariable predictors with p-value ≤ 0.05 . Stepwise method with thresholds for entry and exit = 0.10.