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Chronic kidney disease is associated with increased mortality and procedural complications in transcatheter aortic valve replacement: a systematic review and meta-analysis

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Abstract

Objective: We performed a systematic review and meta-analysis to explore the association between CKD and mortality and procedural complications in TAVR.

Background: The impact of varying stages of CKD or end-stage renal disease (ESRD) on patients receiving TAVR is not clearly identified.

Methods: We searched the databases of MEDLINE and EMBASE from inception to May 2018. Included studies were published TAVR studies that compared the risk of mortality and procedural complications in CKD patients compared to control patients. Data from each study were combined using the random-effects model.

Results: Twelve studies (42,703 CKD patients and 51,347 controls) were included. Compared with controls, CKD patients had a significantly higher risk of 30-day overall mortality (risk ratio [RR]=1.56, 95% confidence interval [CI]: 1.34-1.80, I^2=60.9), long-term cardiovascular mortality (RR=1.47, 95% CI: 1.20-1.81, I^2=13.2%), and long-term overall mortality (RR=1.66, 95% CI: 1.45-1.91, I^2=80.3), as well as procedural complications including pacemaker requirement (RR=1.20, 95% CI: 1.03-1.39, I^2=56.1%) and bleeding (RR=1.60, 95% CI: 1.26-2.02, I^2=86.0%). Risk of mortality and procedural complications increased with severity of CKD for stages 3, 4, and 5, respectively, in terms of long-term overall mortality (RR=1.28, 1.82, and 2.12), 30-day overall mortality (RR=1.26, 1.89, and 1.93), long-term cardiovascular mortality (RR=1.18, 1.75, and 2.50), and bleeding (RR=1.19, 1.63, and 1.83).

Conclusions: Our meta-analysis demonstrates a significant increased risk of mortality and procedural complications in patients with CKD who underwent TAVR compared to controls.

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Abbreviations

TAVR	transcatheter aortic valve replacement
AS	aortic stenosis
SAVR	surgical aortic valve replacement
CHS	cardiovascular health study
CKD	chronic kidney disease
ESRD	end-stage renal disease

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Introduction

Transcatheter aortic valve replacement (TAVR) is an increasingly common therapeutic procedure for symptomatic, moderate-severe aortic stenosis (AS). In these patients, this intervention is superior to medical therapy alone and has comparable results to the conventional surgical aortic valve replacement (SAVR) (1). TAVR is the treatment of choice for symptomatic AS in inoperable patients or patients with unacceptably high surgical risks (2).

Decreased renal function is associated with worse outcomes in many cardiovascular conditions, such as atherosclerosis, heart failure, pericardial and valvular disease and outcomes of cardiac interventions (3). More than 75% of patients with severe AS may have some degree of renal dysfunction(4, 5). Moreover, chronic kidney disease (CKD) is an

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independent risk factor for mid-term mortality in patients with AS undergoing SAVR and TAVR (6). The impact of varying stages of CKD or end-stage renal disease (ESRD) on patients receiving TAVR is not clearly identified.

We sought to determine the effect of different stages of CKD on both short and long-term overall and cardiovascular mortality in patients who underwent TAVR. Additional outcomes including pacemaker implantation, vascular complications, bleeding and cerebrovascular accident were also evaluated.

Method

Search strategy

Two investigators (JK and PC) independently searched for published studies indexed in MEDLINE and EMBASE databases from inception to May 2018 using a search strategy, described in online supplementary document 1, that included the terms for “chronic kidney disease”, “aortic stenosis”, “transcatheter aortic valve replacement”, “complications”, “vascular complications”, “bleeding”, “pacemaker”, “cardiovascular mortality”, and “mortality”. Only English language publications were included. A manual search for additional pertinent studies and review articles using references from retrieved articles was also completed.

Inclusion criteria

The eligibility criteria included the following:

(1) Cohort study (prospective or retrospective) reporting incident mortality and

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procedural complications, after the TAVR procedure.

(2) Reported relative risk, odds ratio, hazard ratio, incidence ratio, or standardized incidence ratio with 95% confidence intervals (CI), or sufficient raw data for their calculation

(3) Participants without CKD as controls.

Study eligibility was independently determined by two investigators (TR and CK) and differences were resolved by mutual consensus. Newcastle-Ottawa quality assessment scale was used to evaluate each study in three domains: recruitment and selection of the participants, similarity and comparability between the groups, and ascertainment of the outcome of interest among cohort studies (8).

Data extraction

A standardized data collection form was used to obtain the following information from each study: title of study, name of first author, year of study, year of publication, country of origin, number of participants, demographic data of participants, method used to identify cases and controls, method used to diagnose outcomes of interest (mortality and procedural complications), average duration of follow-up, confounders that were adjusted, adjusted effect estimates with 95% CI, and covariates that were adjusted for the multivariable analysis.

To ensure accuracy, all investigators independently performed this data extraction process. Any data discrepancy was resolved by referring back to the original articles.

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Definition of CKD

Chronic kidney disease was previously defined as the presence of kidney damage or decreased kidney function for three or more months, regardless of the cause, which was documented with International Classification of Diseases, Ninth Revision. The definition was introduced by the National Kidney Foundation, Kidney Disease Outcomes Quality Initiative, and modified by the international guideline group Kidney Disease Improving Global Outcomes (9, 10). Chronic kidney disease included in our study were CKD stages 3A to CKD stage 5 or glomerular filtration rate less than 60 ml/min/1.73 m^2. Patients with glomerular filtration rate more than or equal to 60 ml/min/1.73 m^2 were considered as part of the control group.

Outcome definition

Outcomes (overall mortality, cardiovascular mortality, pacemaker requirement, overall bleeding, major bleeding, cerebrovascular accident, major vascular complications, and overall vascular complications) were adjudicated according to Valvular Academic Research Consortium (VARC) criteria (11). Long-term overall mortality was defined as over-all mortality at more than 30 days.

Statistical analysis

We performed a meta-analysis of the included cohort studies using a random-effects model. Studies were excluded if they did not present an outcome in each intervention group

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or did not have enough information required for continuous data comparison. We pooled the point estimates of risk ratio (RR) and rate ratio from each study using the generic inverse-variance method of Der Simonian and Laird (12). The heterogeneity of effect size estimates across these studies was quantified using the I^2 statistic. The I^2 statistic ranges in value from 0 to 100% (I^2<25%, low heterogeneity; I^2=25%–50%, moderate heterogeneity; and I^2>50%, substantial heterogeneity) (13). A sensitivity analysis was performed to assess the influence of the individual studies on the overall results by omitting one study at a time. Publication bias was assessed using funnel plot and Egger's regression test (14) ($p<0.05$ was considered significant). Potential sources of heterogeneity from clinical characteristics were analyzed with subgroup analysis and were compared with meta-regression. All data analyses were performed using Stata SE Statistical Software: Release 14.1, College Station, TX: StataCorp LP, StataCorp 2015.

Sensitivity analysis

We used a sequential exclusion strategy, as described by Patsopoulos and colleagues, to examine whether overall estimates were influenced by the substantial heterogeneity observed (15). In accordance with Cochrane, evidence of publication bias was examined through funnel plots if there were more than 10 available studies. Funnel plot asymmetry was further confirmed with Egger's test. If asymmetry was present, we used the trim-and-fill method to adjust for publication bias.

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Results

Description of included studies

Our search strategy yielded 908 potentially relevant articles (568 articles from EMBASE and 340 articles from MEDLINE). After exclusion of 14 duplicate articles, 894 articles underwent title and abstract review. Seven hundred forty-seven articles were excluded at this stage since they were not cohort studies, did not report the outcome of interest (mortality or compilations) or were not conducted in patients with CKD, leaving 147 articles for full-length article review. One hundred and twenty four of the 147 studies were excluded, as they were descriptive studies without comparators. Two studies were excluded because the same group of authors used the same database. Nine more studies were excluded because of unclear outcome definition. Therefore, 8 retrospective and 4 prospective cohort studies with 42,703 CKD patients and 51,347 controls were included in this meta-analysis. Figure 1 outlines the search and literature review process. Summaries of the included studies and the clinical characteristics are shown in Table 1.

Meta-analysis results

Twelve studies (42,703 CKD patients and 51,347 controls) were included. Compared with controls, CKD patients had a significantly higher risk of 30-day overall mortality (RR=1.56, 95% CI: 1.34-1.80, I^2=60.9) (Figure 2A) and 30-day cardiovascular mortality (RR=1.47, 95% CI: 1.20-1.81, I^2=13.2%) (Figure 2B). CKD patients had a significantly higher risk of long-term cardiovascular mortality (RR=1.44, 95% CI: 1.22-1.70, I^2=36.2%)

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(Figure 3A) and long-term overall mortality (RR=1.66, 95% CI: 1.45-1.91, I^2=80.3) (Figure 3B).

Interestingly, risk of long-term overall mortality increased with severity of CKD for stages 3, 4, and 5, respectively (RR=1.28, 1.82, and 2.12), 30-day overall mortality (RR=1.26, 1.89, and 1.93), and 30-day cardiovascular mortality (RR=1.18, 1.75, and 2.50).

Regarding procedural complications, CKD significantly increased risk of 30-day pacemaker requirement (RR=1.20, 95% CI: 1.03-1.39, I^2=56.1%) (Supplement Figure 1), 30-day overall bleeding (RR=1.60, 95% CI: 1.26-2.02, I^2=86.0%), and 30-day major bleeding (RR=1.40, 95% CI: 1.10-1.78, I^2=88.2%)(Supplement Figure 2). CKD increased the risk of 30-day major vascular complications (RR=1.19, 95% CI: 0.97-1.45, I^2=0.0%) (Supplement Figure 3) as well as 30-day overall vascular complications (RR=1.06, 95% CI: 0.99-1.14, I^2=0.0%)(Supplement Figure 4).

Subgroup analysis of CKD stage 4 increased risk of cerebrovascular accident (RR=1.89, 95% CI: 1.22-2.94, I^2=0.0%) but did not reach statistically significant in overall CKD when compare to control (RR=1.19, 95% CI: 0.95-1.50, I^2=26.9%).

Similar to risk of mortality, risk of 30-day overall bleeding increased with severity of CKD for stages 3, 4, and 5, respectively (RR=1.19, 1.63, and 2.12) (Figure 4A) as well as 30-day major bleeding (RR=1.09, 1.12, and 1.86) (Figure 4B).

Meta-regression was performed in 30-day overall mortality, long-term overall mortality, 30-day pacemaker implantation, and overall bleeding. Stages of CKD were significant sources of heterogeneity for 30-day overall mortality (p=0.024), long-term overall

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mortality (p=0.001), and overall bleeding (p=0.021). As shown in subgroup analysis in Figure 2A, heterogeneity of 30-day overall mortality analysis decreased to 0%, 0%, and 38.4% in CKD stage 3, 4, and 5 subgroups, respectively. Heterogeneity of long-term overall mortality also decreased to 55.8%, 50.2%, and 56.5% in CKD stage 3, 4, and 5 subgroup, respectively (Figure 3B). However, stages of CKD and high-risk preoperative evaluation were not significant sources of heterogeneity of 30-day pacemaker implantation (p=0.246 and p=0.355, respectively). According to sensitivity analysis, no study was found to be a source of heterogeneity in 30-day major bleeding, 30-day overall mortality, and long-term overall mortality.

Quality assessment of included studies

Quality of each study was evaluated by two independent authors (PC, WV). The Newcastle-Ottawa scale (0 to 9) was used to evaluate included studies on 3 domains: selection, comparability, and outcomes. Higher scores represent higher study quality. The score of each study ranged from 7 to 9 which reflected high quality (Supplement Table 1). Intra-study risks of bias of included studies are also described in the supplement Table 2.

Funnel plots of long-term overall mortality, long-term cardiovascular mortality, 30-day overall mortality, and 30-day cardiovascular mortality are shown in Figure 5. Funnel plots were symmetric for long-term cardiovascular mortality and 30-day mortality. However, funnel plots were asymmetric for long-term overall mortality and 30-day cardiovascular mortality. By Egger's test, there was significant publication bias regarding long-term overall

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mortality (p=0.019) and 30-day cardiovascular mortality (p=0.006). Funnel plots for 30-day cerebrovascular accident, 30-day pacemaker implantation, 30-day major bleeding, 30-day overall bleeding, and 30-day vascular complications were symmetric (not shown).

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Discussion

To date, there is limited evidence regarding the association between varying CKD stages and outcomes in patients undergoing TAVR. Our study is the first meta-analysis to address the association between TAVR complications and CKD stages.

Several comorbidities are known to be associated with poor outcomes in patients who receive TAVR. According to the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) Registry, which was conducted in 1,038 patients, CKD was among the strongest independent predictors of 30-day mortality in patients undergoing TAVR (17). A meta-analysis published in 2018 (18) demonstrated an association between advanced CKD, including stages 4 and 5, and higher mortality in high-risk patients undergoing TAVR. However, this study did not demonstrate association between early and advanced stages of CKD and outcomes. Moreover, several studies that were included in that meta-analysis used CKD stage 4, instead of a normal kidney function control, as a control compared to CKD stage 5 (19, 20). Therefore, selection bias of cases and controls was, in our opinion, a major limitation in the previous meta-analysis..

Previous work from Hansen et al. reported significantly increased mortality in stage 3 CKD patients who underwent TAVR (21). However, most studies conducted prior to Hansen et al. (22-27) found this association insignificant. The association between stage 4 or 5 CKD

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and increased mortality was reported as significant in later studies (16, 21, 22, 27, 28). Our meta-analysis demonstrated the association between CKD and 30-day overall mortality, 30-day cardiovascular mortality, long-term cardiovascular mortality, and long-term overall mortality. In meta-regression, stages of CKD also showed to be a significant source of heterogeneity thus confirming the significant correlation between the progression of stages of CKD and 30-day overall mortality, overall bleeding, and long-term overall mortality.

CKD is an established risk factor for stroke (29, 30). Our study showed that CKD stage 4 was associated with increased 30-day cerebrovascular accidents. Nonetheless, the association was not significant in CKD stage 3 and stage 4. Since there were limited number of include studies that reported the incidence of stroke, this could be accountable from underpower of included studies.

Several mechanisms lead to bleeding tendency in CKD patients. Platelet dysfunction progresses as chronic kidney disease advances. The mechanisms are attributed from multifactorial including uremic toxins, anemia, and increased nitric oxide (31). Our study revealed that CKD progression was associated with increased 30-day major bleeding. The association, however, was insignificant in CKD stage 3 and 4. This could be attributed from heterogeneity among studies and underpower.

Limitations

Our meta-analysis is not without limitations. First, included studies were prospective and retrospective cohorts that were observational in nature. Hence, they were subject to

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confounders; however, a randomized-controlled trial would be impractical. Second, certain outcomes reported in the studies varied slightly in their definitions and durations. Random-effect modeling was, therefore, used for the the meta-analysis. Third, the included studies were conducted mostly in Caucasian populations.

Conclusion

Stage of CKD prior to procedure positively correlated with overall bleeding complication, 30-day mortality, and long-term overall mortality in patients undergoing TAVR. The presence of CKD, from early to advanced stages, provides prognostic information that should be taken into account when considering a patient for TAVR.

Figures

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of search strategy and included studies.

Figure 2: Forest plot of 30-day overall mortality (2A) and 30-day cardiovascular mortality (2B) according to stage of CKD.

Figure 3: Forest plot of long-term overall mortality (3) increased and long-term cardiovascular mortality (3) according to stage of CKD.

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Figure 4: Forest plot of 30-day overall bleeding increased with severity of CKD (Figure 4A) as well as 30-day major bleeding (Figure 4B).

Figure 5: Funnel plots of long-term overall mortality (A), long-term cardiovascular mortality (B), 30-day mortality (C), and 30-day cardiovascular mortality (D)

Table

Table 1: Summaries of the included studies and the clinical characteristics

Supplement Table 1: Newcastle-Ottawa quality assessment scale of included studies in meta-analysis

Supplement Table 2: Intra-study risk of bias of included studies in meta-analysis

Supplement document 1: Search keywords

Supplement Figure 1: Forest plot of 30-day 30-day pacemaker requirement with severity of CKD

Supplement Figure 2: Forest plot of 30-day major bleeding with severity of CKD

Supplement Figure 3: Forest plot of 30-day major vascular complications with severity of CKD

Supplement Figure 4: Forest plot of 30-day overall vascular complications with severity of CKD

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Author	Country of Origin	Year	Study Design	Setting of Study	Participant Description	Exclusion Criteria	Exposure Group	Total Population	Male (%)	High STS score (%)	Mean age (years)	Outcome Definition	Conclusion by Authors
Allende	Canada	2014	Retrospective cohort study	Hospital based	Consecutive patients who underwent TAVR	Patients with end-stage kidney disease and previous dialysis	CKD stage 1-2 (eGFR≥60 mL/min/1.73 m^2), stage3 (30-59 mL/min/1.73 m^2), stage4 (15-29 mL/min/1.73 m^2) and stage 5 (<15 mL/min/1.73 m^2)	2075	49.9	61.2	80.5	Mortality, stoke, MI, bleeding complications, AKI, vascular complications, conduction disturbances and arrhythmias	Advanced CKD was associated with a higher rate of early and late mortality and bleeding events following TAVR
D'Ascenzo	Italy	2013	Prospective cohort study	Hospital based	All TAVR patients of the institutions	Patients with a clearance less than 15 mL/min/1.73 m^2 or in dialysis	eGFR ≥60 mL/min/1.73 m^2, between 30 and 59 mL/min/1.73 m^2, and between 15 and 29 mL/min/1.73 m^2	364	42.3	100	82.4	Overall mortality, CVS mortality, MI, Stroke, Bleedings, Vascular complications, Pacemaker	Patients with severe chronic renal disease presented higher risk of adverse events.
Codner	Israel	2016	Prospective cohort study	Hospital based	Consecutive patients with severe symptomatic AS who underwent TAVR	Advanced chronic renal dysfunction (CKD stage 4-5)	eGFR: >60 mL/min/1.73 m^2 (group I), 31 to 60 mL/min/1.73 m^2 (group II), ≤30 mL/min/1.73 m^2 (group III), and dialysis (group IV).	1,204	44.7	100	81.5	Major bleeding, major vascular complications, device failure, new permanent pacemaker implantation, inhospital cerebrovascular accident	Advanced CKD and dialysis are associated with increased rates of all-cause and CVS mortality, major and life-threatening bleeding, and vascular complications.
D'errigo	Italy	2015	Prospective cohort study	Hospital based	All consecutive adult patients admitted with a diagnosis of severe AS who require an aortic valve replacement.	Porcelain aorta or hostile chest, undergoing coronary revascularization or intervention on other heart valves, underwent emergency	CKD stages 3b to 5	1,057	63.2	0	79.9	All-cause mortality up to 2 years, stroke, vascular complications, RBC transfusion, AKI	CKD stages 3b to 5 increases the risk of mortality after TAVR and SAVR. The risk of AKI was higher after SAVR.

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						procedures							
Dumontiel	France	2013	Retrospective cohort study	Hospital based	All patients who underwent TAVR	Missing preprocedural serum creatinine, on chronic HD	Normal eGFR (≥90 mL/min), mild (60-89 mL/min), moderate (30-59 mL/min), and severe (<30 mL/min) CKD and those on chronic hemodialysis (HD).	942	53.8	71.6	81.0	1-year survival, 30-day all-cause and CVS mortality, MI, stroke vascular and bleeding complications, AKI, device success, and 30-day combined safety end point	Patients with CKD undergoing TAVR have a higher-risk profile and worse 30-day and 1-year outcomes. Chronic HD and severe preprocedural CKD are independently associated with an increased risk of 1-year mortality after TAVR.
Ferro	UK	2017	Prospective cohort study	Hospital based	All patients not requiring dialysis support before the TAVR procedure	Previously on dialysis	eGFR ≥60 mL/min/1.73 m^2; 45-59 mL/min/1.73 m^2 (CKD stage 3a); 30-44 mL/min/1.73 m^2 (CKD stage 3b); 15-29 mL/min/1.73 m^2 (CKD stage 4); and <15 mL/min/1.73 m^2 (CKD stage 5)	6,464	53.4	75.0	82.9	The incidence of dialysis requirement after TAVR	The patients established on dialysis before TAVR had a >2-fold increased risk of mortality.
Goebel	Germany	2013	Prospective cohort study	Hospital based	All patients underwent transapical transcatheter aortic valve implantation at the center	Patients on chronic hemodialysis	CKD stage 3 and worse, AKI (elevation of creatinine of 0.3 mg/dL or greater, decrease of GFR of greater than 25%, or the need of RRT)	270	44.4	NA	81.6	30-day mortality, cardiac death, stroke, transient neurologic deficit, AKI, RRT, new pacemaker, reoperation	Preoperative CKD does not increase the risk of mortality and AKI after TAVR.
Gupta	USA	2017	Retrospective cohort study	Hospital based	All patients age ≥18 years who underwent TAVR	Patients with ESRD	Patients with CKD were identified using ICD-9-CM codes 35.05 and 35.06	41,025	52.3	NA	81.1	All-cause in-hospital mortality, CVS events, aute MI, stroke, major bleeding, major vascular complications, requirement for pacemaker implantation	Patients with CKD or ESRD have worse in-hospital outcomes after TAVR. AKI is associated with higher in-hospital mortality in patients undergoing TAVR.
Hansen	USA	2017	Retrospective cohort study	Hospital based	Data from the STS/ACC TVT	Patients with GFR	CKD has 5 stages, organized by eGFR (CKD	44,778	51.33	NA	81.96	Death from any cause, new	Increasing CKD stage leads to an increased risk

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					registry from November 2011 through September 2015 on patients undergoing TAVR	measurements >130 ml/min/m^2, currently dialysis dependent, and those that received mitral valve repair or mitral leaflet clip	stage 1 = eGFR >90 ml/min/m^2, stage 2 = GFR 60 to 89 ml/min/m^2, stage 3 = eGFR of 30 to 59 ml/min/m^2, stage 4 = GFR of 15 to 29 ml/min/m^2, stage 5 = eGFR <15 ml/min/m^2). Combined stages 1 and 2 serving as a control group.					requirement of RRT, or a composite of both.	of death and/or RRT. Continuous analysis showed significant differences in outcomes in all levels of CKD when eGFR <60 ml/min/m^2.
Nguyen	USA	2013	Retrospective cohort study	Hospital based	Medical records for all consecutive isolated aortic valve replacements at Emory Healthcare Hospitals	Irretrievable creatinine levels	eGFR > 60 mL/min, eGFR 31 to 60 mL/min, and eGFR ≤ 30 mL/min	1657	38	100	82.2	Transfusion, stroke, AF, pneumonia, New dialysis, worsening renal failure, bleeding, ventilation, ICU, discharge creatinine, length of stay, contrast load	Worsening renal function was associated with increased in-hospital mortality, hospital length of stay, and ICU length of stay in SAVR patients, but not in TAVR patients
Rahman	UK	2015	Retrospective cohort study	Hospital based	Consecutive patients underwent TAVR	Chronic hemodialysis patients	CKD group (eGFR < 60 mL/min/1.73 m^2) and No-CKD group (eGFR > 60 mL/min/1.73 m^2)	118	57	61	81.3	Mortality, MI, vascular complications, overall length of stay	TAVR is safe for patients with CKD. The presence of pre-existing DM and elevated pre-operative serum creatinine appear to confer a greater risk of developing AKI.
Thourani	USA	2016	Retrospective cohort study	Hospital based	Patients enrolled in the PARTNET Trial and continuous access registry and treated with TAVR	Cannot calculate the GFR due to missing data, Post renal transplantation	eGFR > 60 mL/min, GFR 31 to 60 mL/min, and GFR ≤ 30 mL/min	2,531	52.4	100	84.5	Death from any cause, CVS mortality, major bleeding, stroke, new permanent pacemaker, new dialysis, MI, major vascular complications	Preoperative severe renal disease is a significant predictor for all-cause 1-year mortality in TAVR patients.
Wessely	Germany	2012	Retrospective cohort study	Hospital based	Patients with symptomatic high-grade AS	Patients who died within 24 h after TAVR or	Pre-procedural eGFR ≤60 mL/min, equivalent to CKD stage ≥3	199	81.1	100	44.8	Renal function, renal replacement therapy, 30-day	TAVR with the CoreValve prosthesis does not seem to bear an increased risk for

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					undergoing TAVR with the CoreValve prosthesis	patients on chronic HD or in need for pre-interventional RRT						mortality	patients with CKD. For surgical high-risk patients with severe AS, a more consideration for TAVR
Yamamoto	France	2013	Prospective cohort study	Hospital based	Consecutive patients who underwent TAVR	Receiving regular HD before TAVR	CKD stage 1+2, CKD stage 3a, CKD stage 3b, and CKD stage 4 on the basis of eGFR ≥60, 45-59, 30-44, and 15-29 mL/min/1.73 m^2, respectively.	642	48.1	100	83.5	Length of hospital stay, mortality, MI, stroke, AKI, need for dialysis at discharge, vascular complications, transfusion, pacemaker implantation	Classification of CKD stages before TAVR allows risk stratification for early and midterm clinical outcomes. TAVR for patients with CKD stage 4 is still considered challenging because of high mortality rates after the procedure.

Table 1: Summaries of the included studies and the clinical characteristics

ACC: American College of Cardiology, AF: atrial fibrillation, AKI: acute kidney injury, AS: aortic stenosis, CKD: chronic kidney disease, CVS: cardiovascular, eGFR: estimated glomerular filtration rate, ESRD: end stage renal disease, HD: hemodialysis, ICD: international classification of disease, ICU: intensive care unit, MI: myocardial infarction, RRT: renal replacement therapy, SAVR: surgical aortic valve replacement, STS: Society for Thoracic Surgeon, TAVR: transcatheter aortic valve replacement, TVT: transcatheter valve therapy, UK: United Kingdom, USA: United States.

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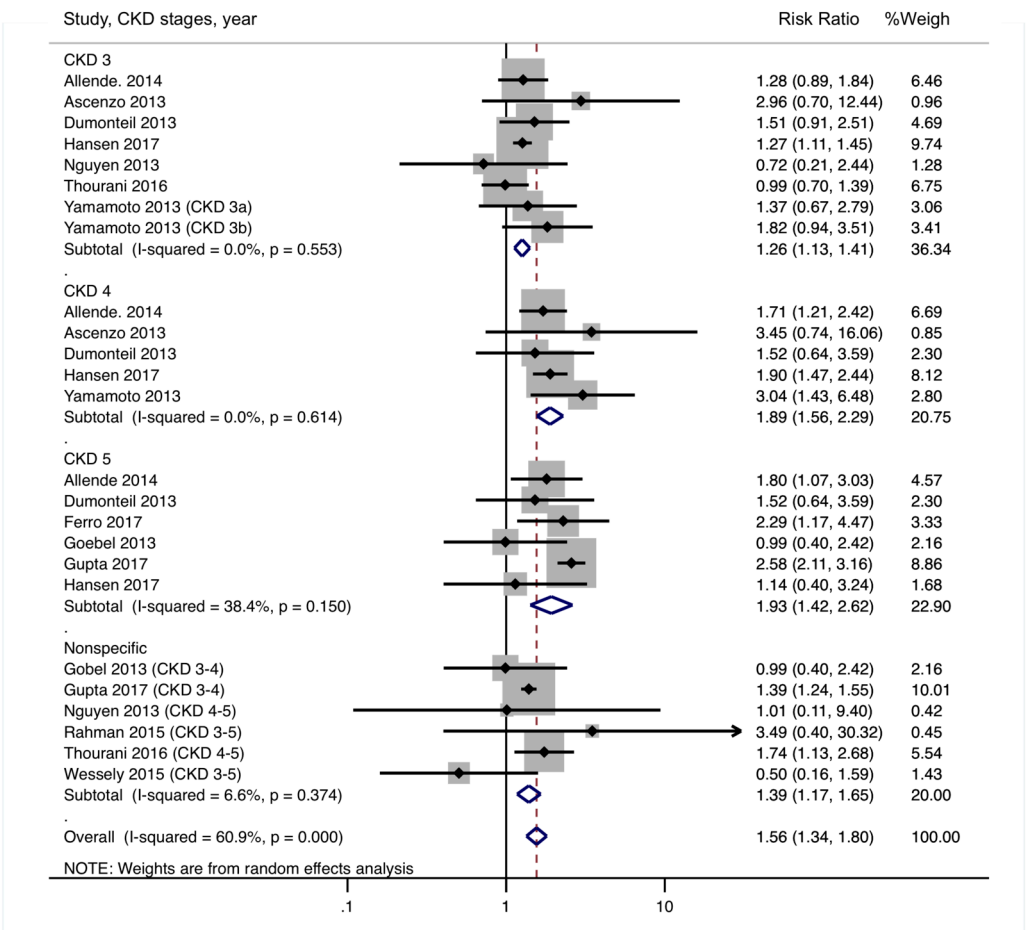

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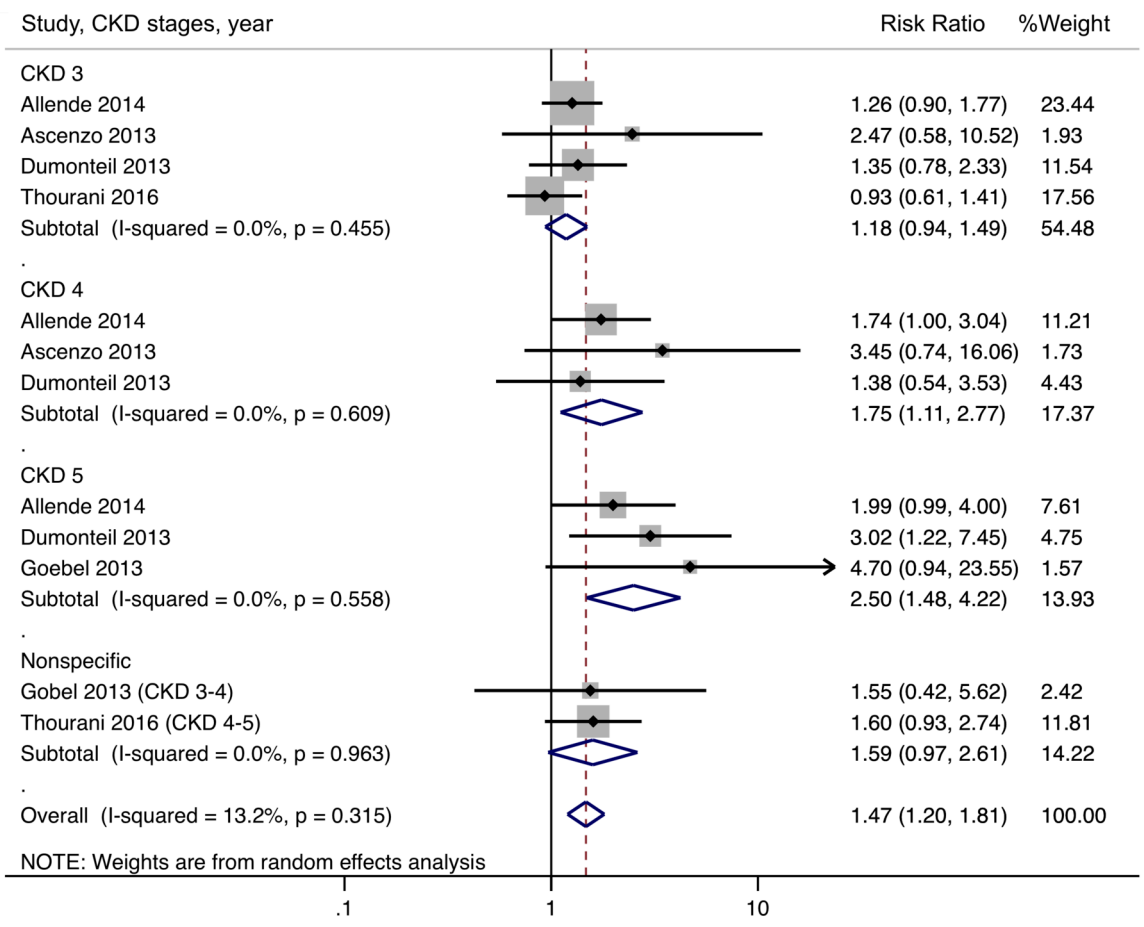

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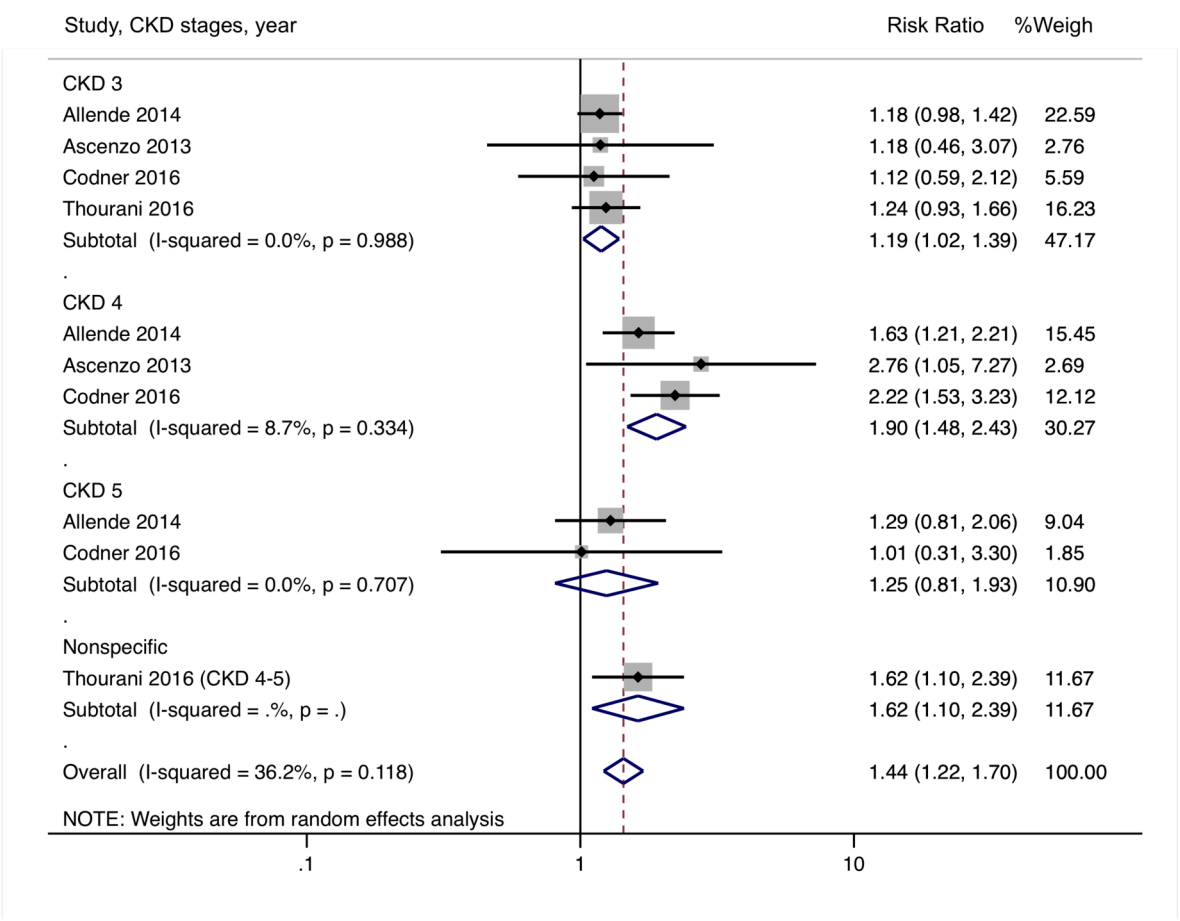

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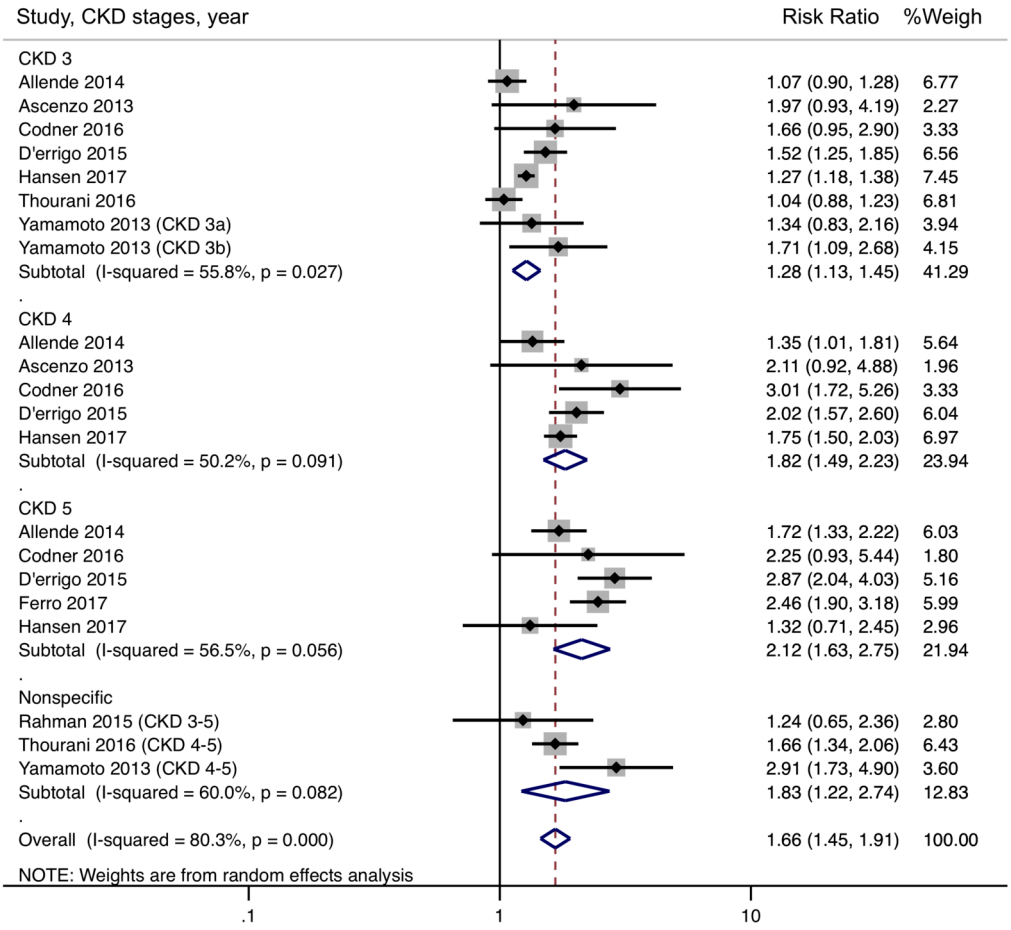

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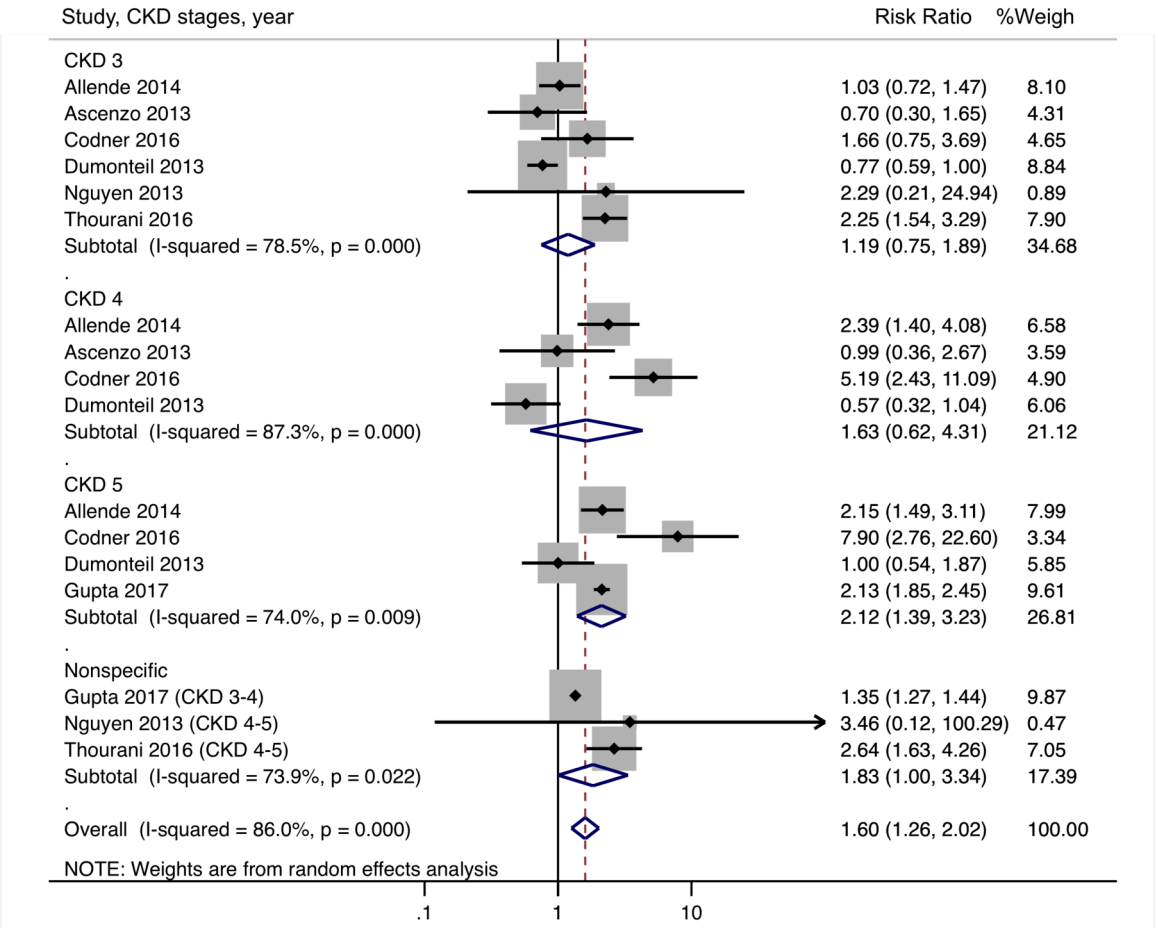

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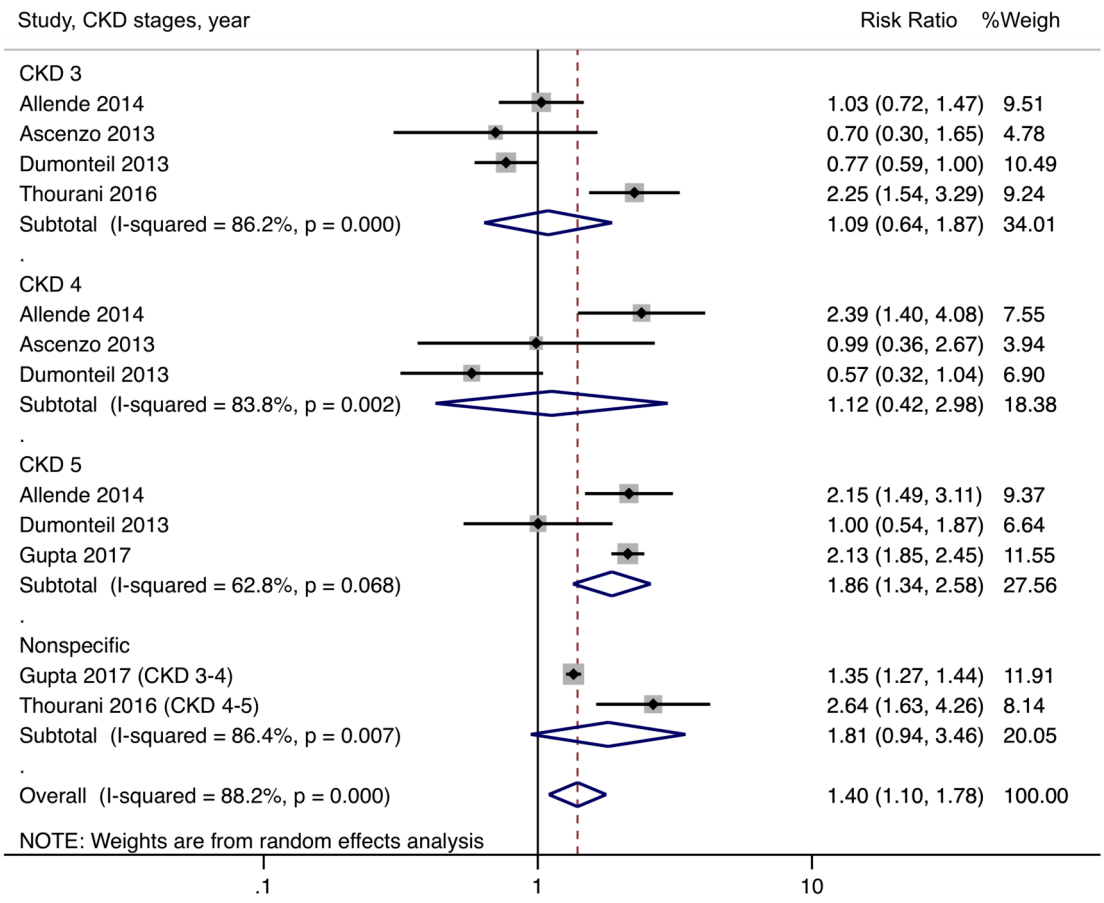

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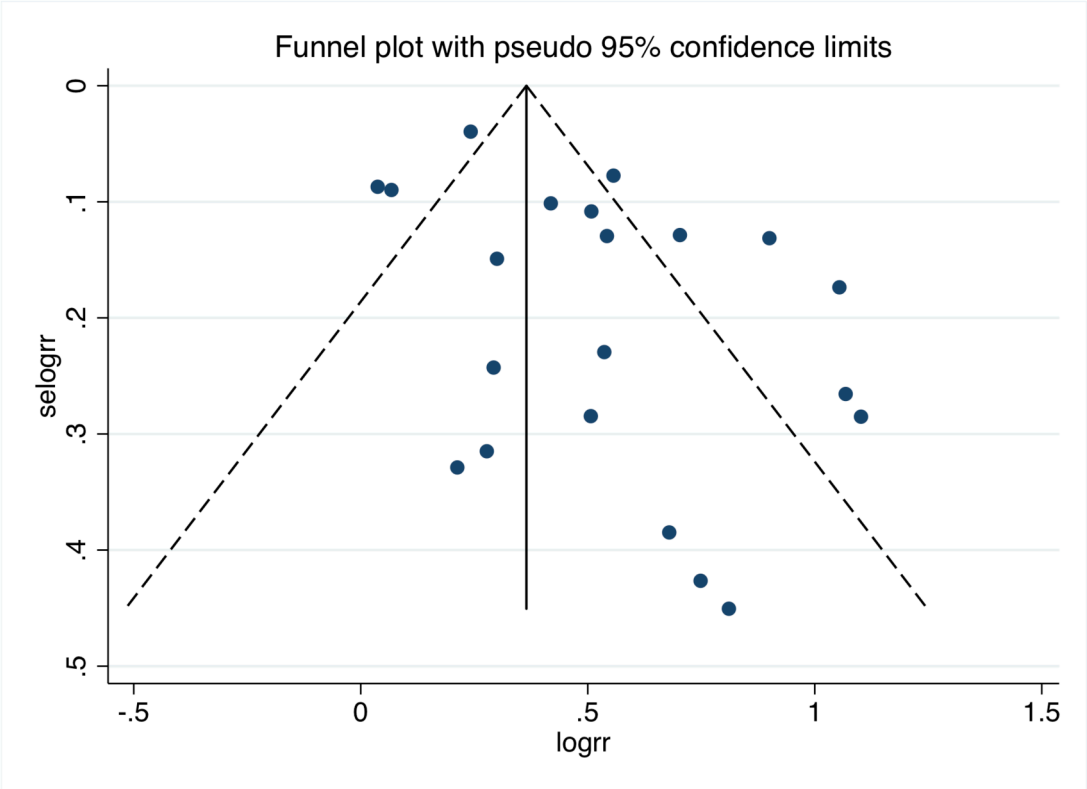
5A



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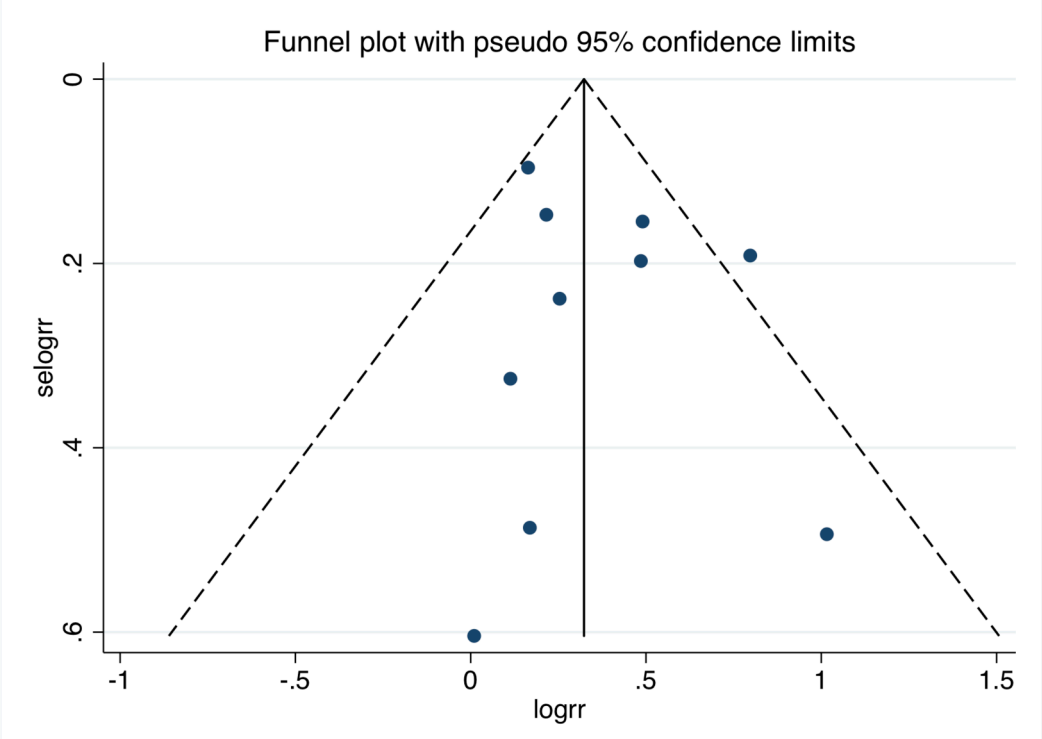

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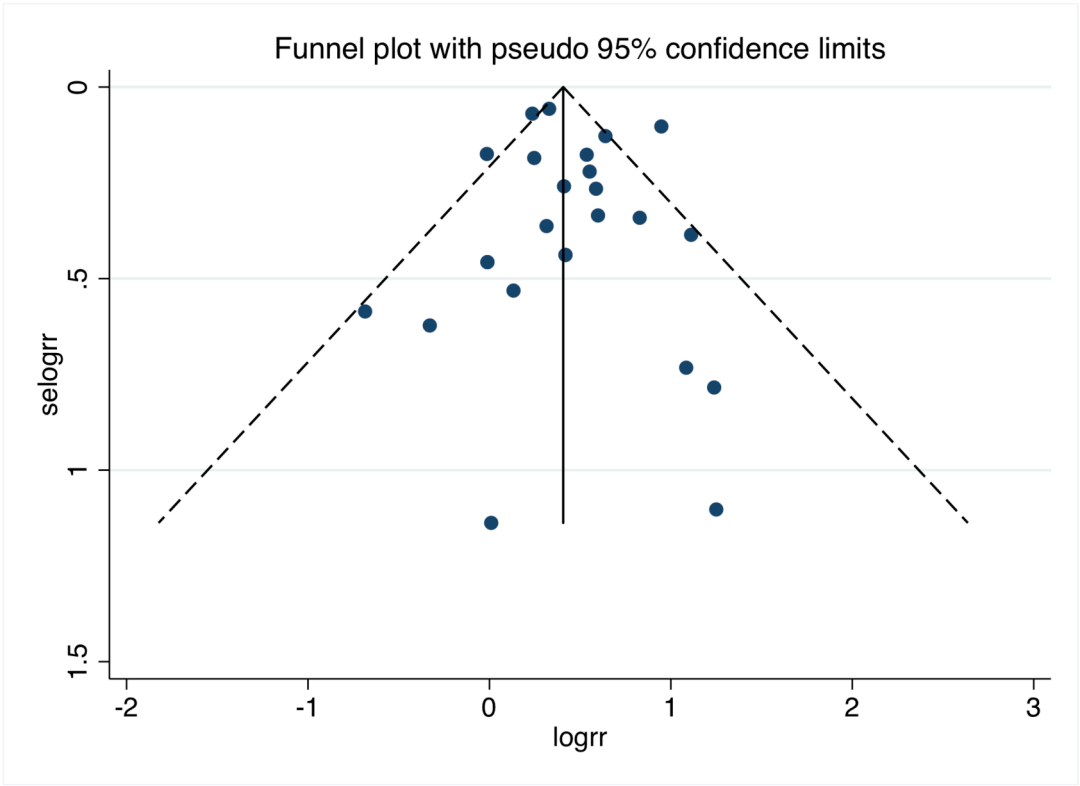

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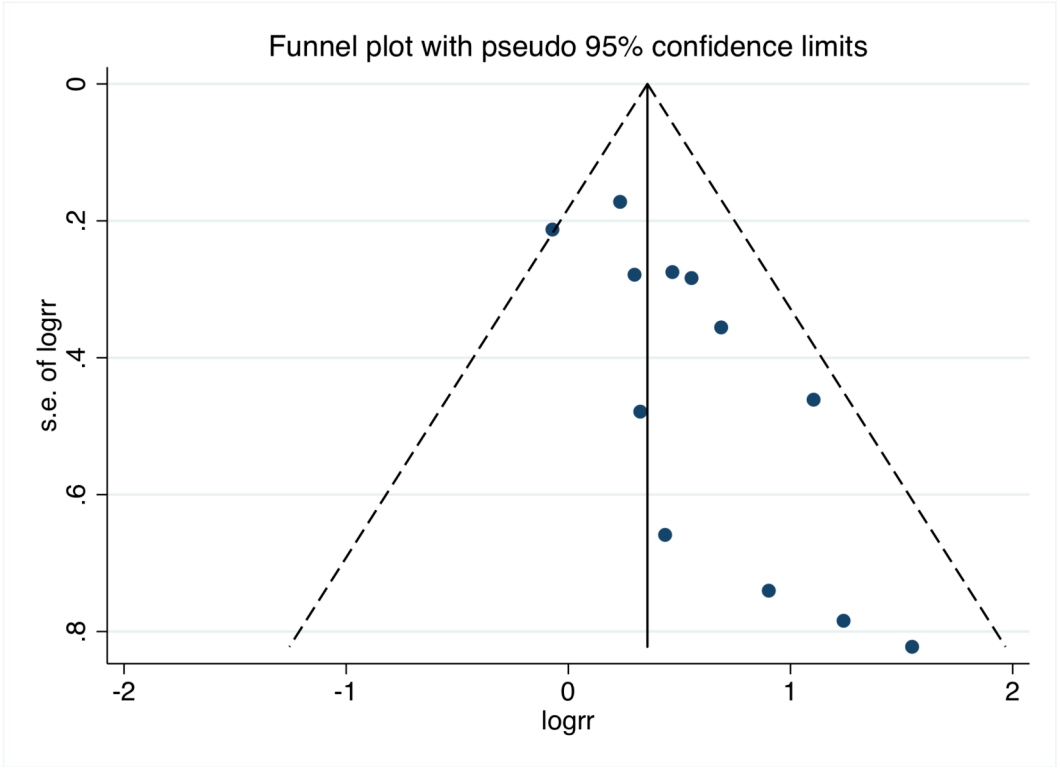

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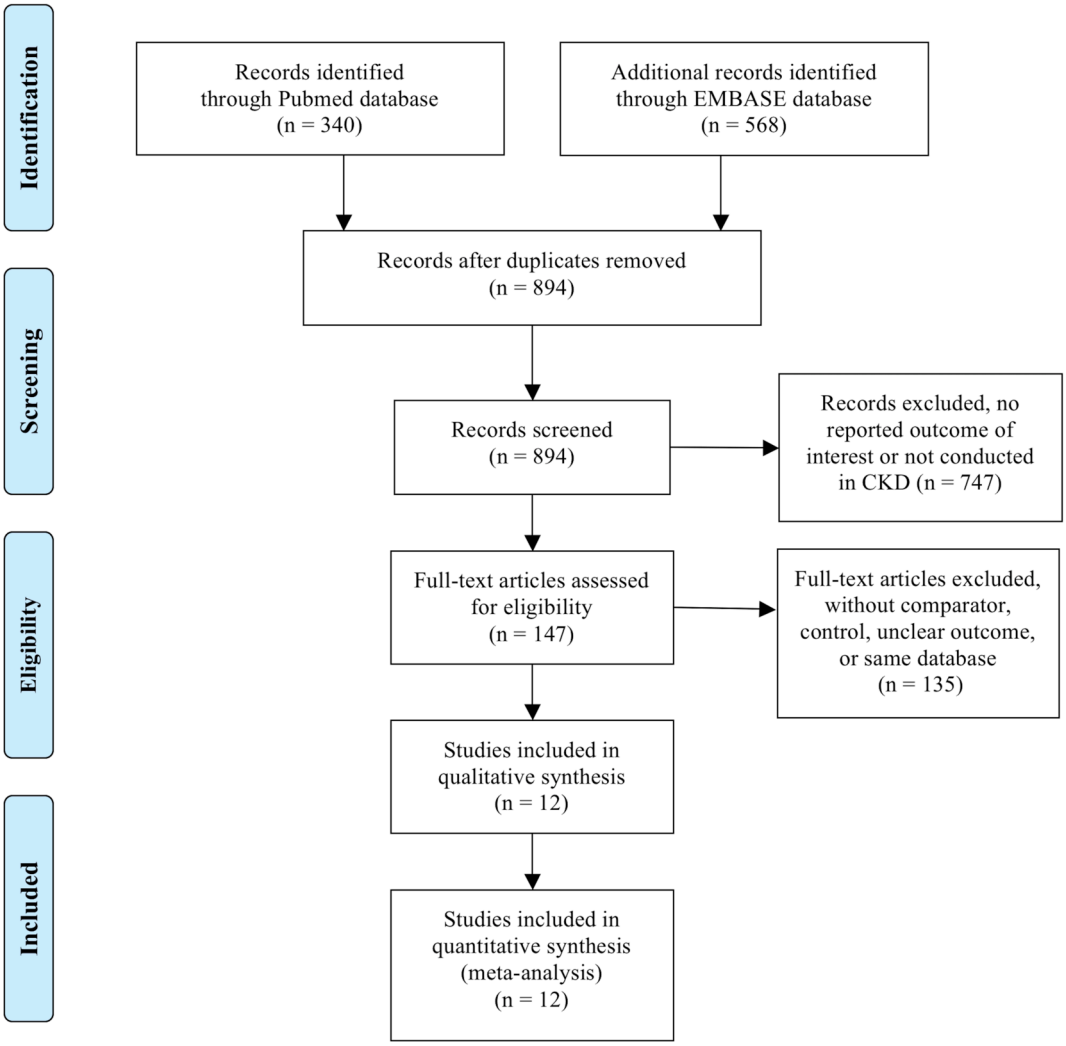

Figure 1 Search methodology and selection process

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Author	Country of Origin	Year	Study Design	Setting of Study	Participant Description	Exclusion Criteria	Exposure Group	Total Population	Male (%)	High STS score (%)	Mean age (years)	Outcome Definition	Conclusion by Authors
Allende	Canada	2014	Retrospective cohort study	Hospital based	Consecutive patients who underwent TAVR	Patients with end-stage kidney disease and previous dialysis	CKD stage 1-2 (eGFR≥60 mL/min/1.73 m^2), stage3 (30-59 mL/min/1.73 m^2), stage4 (15-29 mL/min/1.73 m^2) and stage 5 (<15 mL/min/1.73 m^2)	2075	49.9	61.2	80.5	Mortality, stoke, MI, bleeding complications, AKI, vascular complications, conduction disturbances and arrhythmias	Advanced CKD was associated with a higher rate of early and late mortality and bleeding events following TAVR
D'Ascenzo	Italy	2013	Prospective cohort study	Hospital based	All TAVR patients of the institutions	Patients with a clearance less than 15 mL/min/1.73 m^2 or in dialysis	eGFR ≥60 mL/min/1.73 m^2, between 30 and 59 mL/min/1.73 m^2, and between 15 and 29 mL/min/1.73 m^2	364	42.3	100	82.4	Overall mortality, CVS mortality, MI, Stroke, Bleedings, Vascular complications, Pacemaker	Patients with severe chronic renal disease presented higher risk of adverse events.
Codner	Israel	2016	Prospective cohort study	Hospital based	Consecutive patients with severe symptomatic AS who underwent TAVR	Advanced chronic renal dysfunction (CKD stage 4-5)	eGFR: >60 mL/min/1.73 m^2 (group I), 31 to 60 mL/min/1.73 m^2 (group II), ≤30 mL/min/1.73 m^2 (group III), and dialysis (group IV).	1,204	44.7	100	81.5	Major bleeding, major vascular complications, device failure, new permanent pacemaker implantation, inhospital cerebrovascular accident	Advanced CKD and dialysis are associated with increased rates of all-cause and CVS mortality, major and life-threatening bleeding, and vascular complications.
D'errigo	Italy	2015	Prospective cohort study	Hospital based	All consecutive adult patients admitted with a diagnosis of severe AS who require an aortic valve replacement.	Porcelain aorta or hostile chest, undergoing coronary revascularization or intervention on other heart valves, underwent emergency procedures	CKD stages 3b to 5	1,057	63.2	0	79.9	All-cause mortality up to 2 years, stroke, vascular complications, RBC transfusion, AKI	CKD stages 3b to 5 increases the risk of mortality after TAVR and SAVR. The risk of AKI was higher after SAVR.
Dumontiel	France	2013	Retrospective cohort study	Hospital based	All patients who underwent TAVR	Missing preprocedural serum creatinine, on chronic HD	Normal eGFR (≥90 mL/min), mild (60-89 mL/min), moderate (30-59 mL/min), and severe (<30 mL/min) CKD and those on chronic hemodialysis (HD).	942	53.8	71.6	81.0	1-year survival, 30-day all-cause and CVS mortality, MI, stroke vascular and bleeding complications, AKI, device success, and 30-day combined	Patients with CKD undergoing TAVR have a higher-risk profile and worse 30-day and 1-year outcomes. Chronic HD and severe preprocedural CKD are independently associated with an

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												safety end point	increased risk of 1-year mortality after TAVR.
Ferro	UK	2017	Prospective cohort study	Hospital based	All patients not requiring dialysis support before the TAVR procedure	Previously on dialysis	eGFR ≥60 mL/min/1.73 m^2; 45-59 mL/min/1.73 m^2 (CKD stage 3a); 30-44 mL/min/1.73 m^2 (CKD stage 3b); 15-29 mL/min/1.73 m^2 (CKD stage 4); and <15 mL/min/1.73 m^2 (CKD stage 5)	6,464	53.4	75.0	82.9	The incidence of dialysis requirement after TAVR	The patients established on dialysis before TAVR had a >2-fold increased risk of mortality.
Goebel	Germany	2013	Prospective cohort study	Hospital based	All patients underwent transapical transcatheter aortic valve implantation at the center	Patients on chronic hemodialysis	CKD stage 3 and worse, AKI (elevation of creatinine of 0.3 mg/dL or greater, decrease of GFR of greater than 25%, or the need of RRT)	270	44.4	NA	81.6	30-day mortality, cardiac death, stroke, transient neurologic deficit, AKI, RRT, new pacemaker, reoperation	Preoperative CKD does not increase the risk of mortality and AKI after TAVR.
Gupta	USA	2017	Retrospective cohort study	Hospital based	All patients age ≥18 years who underwent TAVR	Patients with ESRD	Patients with CKD were identified using ICD-9-CM codes 35.05 and 35.06	41,025	52.3	NA	81.1	All-cause in-hospital mortality, CVS events, aute MI, stroke, major bleeding, major vascular complications, requirement for pacemaker implantation	Patients with CKD or ESRD have worse in-hospital outcomes after TAVR. AKI is associated with higher in-hospital mortality in patients undergoing TAVR.
Hansen	USA	2017	Retrospective cohort study	Hospital based	Data from the STS/ACC TVT registry from November 2011 through September 2015 on patients undergoing TAVR	Patients with GFR measurements >130 ml/min/m^2, currently dialysis dependent, and those that received mitral valve repair or mitral leaflet clip	CKD has 5 stages, organized by eGFR (CKD stage 1 = eGFR >90 ml/min/m^2, stage 2 = GFR 60 to 89 ml/min/m^2, stage 3 = eGFR of 30 to 59 ml/min/m^2, stage 4 = GFR of 15 to 29 ml/min/m^2, stage 5 = eGFR <15 ml/min/m^2). Combined stages 1 and 2 serving as a control group.	44,778	51.33	NA	81.96	Death from any cause, new requirement of RRT, or a composite of both.	Increasing CKD stage leads to an increased risk of death and/or RRT. Continuous analysis showed significant differences in outcomes in all levels of CKD when eGFR <60 ml/min/m^2.
Nguyen	USA	2013	Retrospective cohort study	Hospital based	Medical records for all consecutive isolated aortic valve replacements at Emory	Irretrievable creatinine levels	eGFR > 60 mL/min, eGFR 31 to 60 mL/min, and eGFR ≤ 30 mL/min	1657	38	100	82.2	Transfusion, stroke, AF, pneumonia, New dialysis, worsening renal failure, bleeding, ventilation, ICU, discharge creatinine,	Worsening renal function was associated with increased in-hospital mortality, hospital length of stay, and ICU length of stay in SAVR patients, but not in TAVR patients

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					Healthcare Hospitals							length of stay, contrast load	
Rahman	UK	2015	Retrospective cohort study	Hospital based	Consecutive patients underwent TAVR	Chronic hemodialysis patients	CKD group (eGFR < 60 mL/min/1.73 m^2) and No-CKD group (eGFR > 60 mL/min/1.73 m^2)	118	57	61	81.3	Mortality, MI, vascular complications, overall length of stay	TAVR is safe for patients with CKD. The presence of pre-existing DM and elevated pre-operative serum creatinine appear to confer a greater risk of developing AKI.
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Wessely	Germany	2012	Retrospective cohort study	Hospital based	Patients with symptomatic high-grade AS undergoing TAVR with the CoreValve prosthesis	Patients who died within 24 h after TAVR or patients on chronic HD or in need for pre-interventional RRT	Pre-procedural eGFR ≤60 mL/min, equivalent to CKD stage ≥3	199	81.1	100	44.8	Renal function, renal replacement therapy, 30-day mortality	TAVR with the CoreValve prosthesis does not seem to bear an increased risk for patients with CKD. For surgical high-risk patients with severe AS, a more consideration for TAVR
Yamamoto	France	2013	Prospective cohort study	Hospital based	Consecutive patients who underwent TAVR	Receiving regular HD before TAVR	CKD stage 1+2, CKD stage 3a, CKD stage 3b, and CKD stage 4 on the basis of eGFR ≥60, 45-59, 30-44, and 15-29 mL/min/1.73 m^2, respectively.	642	48.1	100	83.5	Length of hospital stay, mortality, MI, stroke, AKI, need for dialysis at discharge, vascular complications, transfusion, pacemaker implantation	Classification of CKD stages before TAVR allows risk stratification for early and midterm clinical outcomes. TAVR for patients with CKD stage 4 is still considered challenging because of high mortality rates after the procedure.

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