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REVIEW ARTICLE

Impact of Pre-existing Kidney Dysfunction on Outcomes Following Transcatheter Aortic Valve Replacement

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ARTICLE HISTORY

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Abstract: ***Background*:** Pre-existing chronic kidney disease (CKD) portends adverse outcomes following heart valve surgery. However, only limited and conflicting evidence is available on the impact of CKD on outcomes following transcatheter aortic valve replacement (TAVR). The objective of this review was to evaluate the effect of pre-existing CKD on TAVR outcomes.

***Methods*:** We performed a systematic electronic search using the PRISMA statement to identify all randomized controlled trials and observational studies investigating the effect of pre-existing CKD on outcomes following TAVR. 30-day and long-term outcomes were measured comparing patients with Glomerular filtration rate (GFR) ≥60 to those with GFR <60.

***Results*:** Ten studies were analyzed comprising of 8688 patients. Compared to patients with GFR ≥60, those with GFR < 60 had worse 30-day all cause mortality (OR 1.40, 95% CI: 1.13-1.73), cardiovascular mortality (OR 1.66, 95% CI: 1.04-2.67), strokes (OR 1.39, 95% CI: 1.05-1.85), acute kidney injury (OR 1.42, 95% CI: 1.21-1.66) and the risk for dialysis (OR 2.13, 95% CI: 1.07-4.22). There was no difference in device success (p=0.873), major or life threatening bleeds (p = 0.302), major vascular complications (p=0.525), need for pacemaker implantation (p = 0.393) or paravalvular leaks (p = 0.630). All-cause mortality at 1 year was also significantly higher in patients with GFR <60 (OR 1.80, 95% CI: 1.26-2.56).

***Conclusion*:** Pre-existing CKD defined as GFR <60 is a strong predictor of worse short and long-term outcomes following TAVR. Active measures should be taken to mitigate the postprocedure risk in these group of patients.

Keywords: Aortic stenosis, transcatheter aortic valve replacement, chronic kidney disease, replacement, PRISMA, glomerular filtration.

1. INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is a safe and effective treatment for inoperable, intermediate or high-risk patients with severe symptomatic aortic stenosis [1-3], while conservative management is associated with very poor prognosis especially in the presence of comorbidities such as renal failure [4]. The presence of pre-existing chronic kidney disease (CKD) is associated with poor prognosis in patients undergoing surgical aortic valve replacement [5]. However, contemporary TAVR studies [1-3] underrepresented or excluded patients with advanced CKD leading to limited data on outcomes in this patient population. Also, the results of a few studies that evaluated the impact of CKD on TAVR outcomes are conflicting. While some studies showed no impact on outcomes [6-8], others reported worse [9-11] or better outcomes [12, 13]. Additionally, published data from TAVR registries showed conflicting results on the relationship between CKD and mortality [14, 15], while the available meta-analysis on the impact of CKD on TAVR involved a relatively small patient population [16]. This mixed evidence may be due to confounders that affect morbidity and mortality in CKD patients irrespective of the diagnosis and treatment of severe aortic stenosis [17]. Given this contrasting evidence and available recent literature on this topic, there is a rationale to perform a detailed and up to date meta-analysis examining the impact of CKD on TAVR outcomes in a larger patient cohort.

2. METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommended by

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the Cochrane Collaboration was followed in this study (Fig. **1**). A systematic search of Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Web of science, and Scopus was performed to identify potentially relevant articles published from 2002 to 2016. A Boolean search was performed combining the following terms: "Transcatheter aortic valve replacement" OR "transcatheter aortic valve implantation" AND "chronic kidney disease" OR "Renal impairment". No language restriction was applied. We manually scanned the bibliographies of included reports and relevant review articles to Identify additional studies. Only studies that reported data on demographic and procedural characteristics, management, and clinical outcomes of TAVR in relation to glomerular filtration rate (GFR) measurement for CKD were included. We compared TAVR outcomes between subjects with GFR < 60 (CKD group) and those with GFR ≥ 60 (control group). CKD was defined according to the National Kidney Foundation staging. Patients with end-stage kidney disease on hemodialysis were excluded from the analysis. Three authors (II, OO and TB) screened and retrieved reports and excluded irrelevant studies while two other authors participated in the review process when uncertainty arose about eligibility criteria (CE, UNI). Statistical analysis was done using STATA version 14 (StataCorp LLC, College Station, Texas). Comparison between the two groups (GFR ≥ 60 versus < 60) was done using Mantel-Haenszel odds ratio (OR). A forest plot was performed for outcomes of interest while a funnel plot was used to assess publication bias and other reporting biases. We interpreted the asymmetry of funnel plot in conjunction with study characteristics or other contributable factors such as small study effects.

3. RESULTS

Ten studies comprising 8688 patients were included in our meta-analysis. Baseline characteristics of the study population are given in Table **1**. The mean age of the study population was 82±1 years, with 51.5% being female. 82% of the study population had New York Heart Association (NYHA) class III or IV heart failure and the mean left ventricular ejection fraction (EF) was 52 ± 4%. The transfemoral approach was used in 83% of the study population. Device success was achieved in greater than 90% with less than 10% major bleeding or vascular complications in the overall pa-

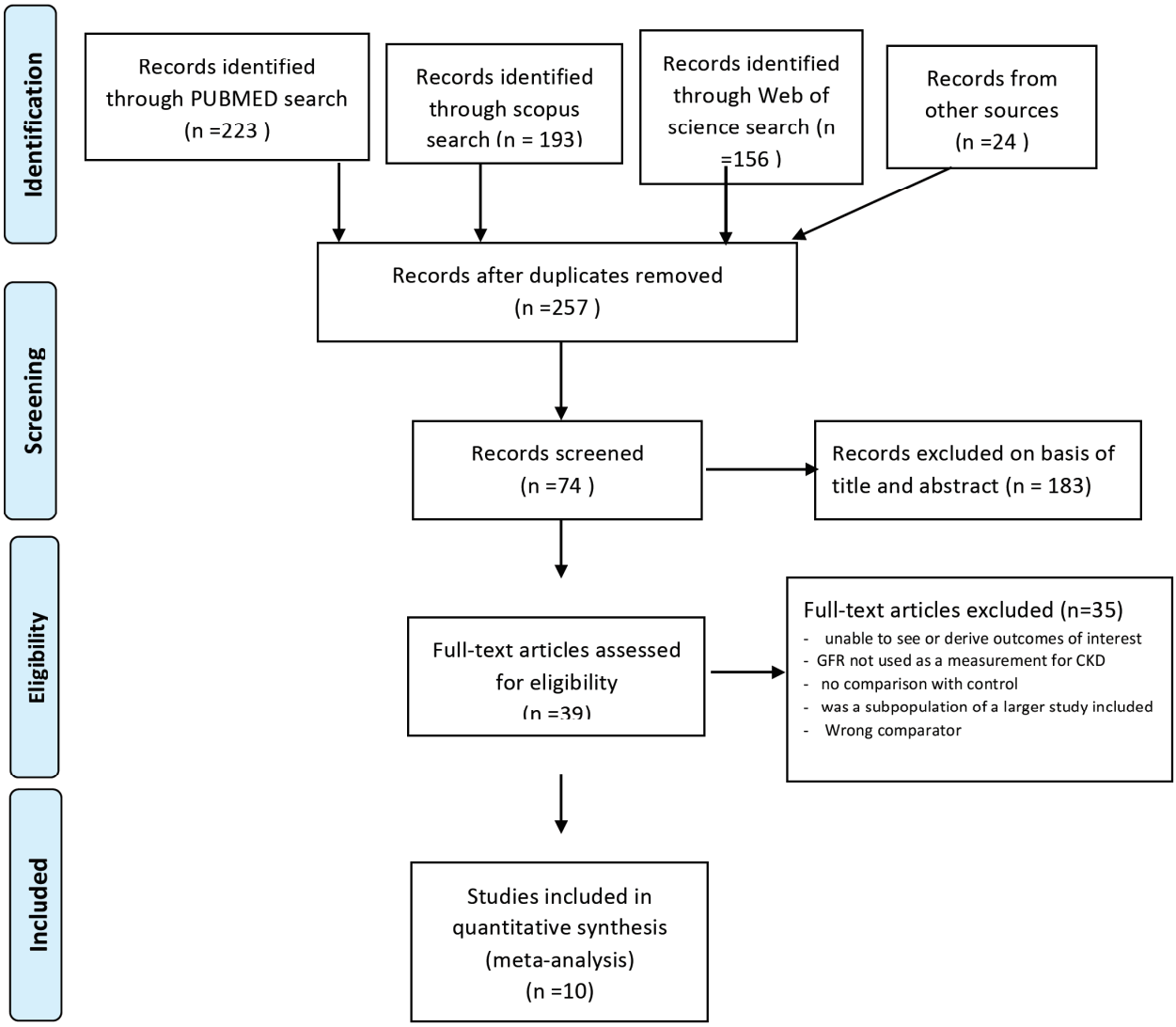

Fig. (1). Prisma flow sheeth.

tient population (Table **2**). There was a significant increase in the 30-day (OR 1.40, 95% CI 1.13-1.73) and 1-year (OR 1.80, 95% CI 1.26-2.56) all cause mortality in those with baseline GFR < 60 (CKD group) compared to those with GFR ≥ 60 (control group) (Figs. **2** and **3**). All the individual studies reporting 1-year all cause mortality showed significant increase in the CKD group compared to the control group. Early cardiovascular mortality (Fig. **4**) was significantly increased in the CKD group compared with control (OR 1.66, 95% CI 1.04-2.67). One year cardiovascular mortality was excluded from analysis due to the non-specificity and wide range of time frame of follow up to account for this variable. There was no significant difference in early major and life threatening bleeding between the two groups (p = 0.302) (Fig. **5**). Compared to GFR ≥ 60, early stroke rate was increased in patients with GFR < 60 (OR 1.39, 95% CI 1.05-1.85) (Fig. **6**). Also, GFR < 60 was associated with significant increase in early acute kidney injury (OR 1.42, 95% CI 1.21-1.66) (Fig. **7**) and the proportion of people requiring renal replacement therapy (OR 2.13, 95% CI 1.07-4.22) (Fig. **8**). Conversely, there was no significant difference between the two groups in early vascular complication (p=0.525, Fig. **9**), new pacemaker implantation rate (p=0.393, Fig. **10**), device success (p=0.873, Fig. **11**) or paravalvular leak (p=0.630, Fig. **12**).

Table 1. Demographics/Baseline characteristics of the study population.

	Allende *et al.*	D'Ascenzo *et al.*	Dumonteil *et al.*	Ferro *et al.*	Goebel *et al.*	Nguyen *et al.*	Nuis *et al.*	Sinning *et al.*	Wessely *et al.*	Yamamoto *et al.*
Year	2014	2013	2013	2014	2013	2013	2011	2010	2012	2013
Number of Patients	2075	364	942	3696	270	321	118	77	183	642
Age, (mean)	80.5	82.4	81	80.3	81.6	82.3	82	80.8	81.1	83.6
Male, %	49.9	42	53.8	53.5	44.4	55.8	45	48	44.8	48.1
BMI, Kg/m2	26.9	na	26	25.5	25.9	26.7	26	24.8	26.4	25.8
Diabetes Mellitus, %	30.1	31.1	28.5	22.4	27.6	43.6	23	23	30	22.6
Hypertension, %	78.8	86.6	69.5	na	96.3	95	44	94	84.2	70.6
Dyslipidemia, %	na	54	na	na	na	90.3	na	84	na	50.3
Smoke, %	22.8	na	na	2.5	na	na	na	na	na	8.7
Prior stroke/TIA, %	12.6	23	15.7	17.9	na	16.2	25	26	na	9.9
Prior MI, %	na	19.4	16.8	22.5	na	na	25	42	na	13.4
Prior CABG, %	24.7	12.6	22.1	na	na	37.4	27	10	na	15.1
Prior PCI, %	na	na	29.4	na	21.3	na	25	48	na	28.5
CAD, %	58.2	na	45.2	na	67	na	na	65	50.8	na
PAD, %	20.1	23.6	25.3		41.6	34.6	na	46	12.2	28.5
Renal Dysfunction, %	54.2	80.2	53.5	62.4	47.8	50.5	53.4	62	62.3	66
COPD, %	29.8	na	34.5	27	21.5	48.9	29	26	23.9	29.1
Atrial Fibrillation, %	30.4	na	na	24.2	33.1	na	27	na	33	na
NYHA III/IV, %	82.5	na	81.3	83.1	na	na	84	na	na	80.1
Log Euro score, %	17.6	23.2	20.9	18.2	33.5	na	12.3	31.2	23.5	19.9
STS score, %	6.5	6.6	na	na	14	12.1	6.1	9.3	na	6.8
AVA, cm^2	0.62	0.63	na	0.68	0.6	na	0.63	na	0.69	0,64
Mean aortic gradient, mmHg	46	53.7	na	76	47	na	47	na	na	47.5
EF, %	54.2	52.4	na	na	56	48.2	51	45.3	58.7	50.9
Transfemoral,%	73.7	84.2	84	70.1	0	na	na	100	100	67.1
Other approach except transfemoral, %	26.3	15.8	16	29.9	100	na	na	0	0	32.9
Corevalve or similar, %	48.1	na	53.7	na	3.7	na	0	100	100	37.1
Sapien or similar, %	51.9	na	46.3	na	96.3	na	0	0	0	62.9

Na= not available.

Table 2. Various percentage of outcomes after transcatheter aortic valve replacement comparing Control (GFR≥60) to advanced CKD (GFR <60).

	Allende *et al.*	D'Ascenzo *et al.*	Dumonteil *et al.*	Ferro *et al.*	Goebel *et al.*	Nguyen *et al.*	Nuis *et al.*	Sinning *et al.*	Wessely *et al.*	Yamamoto *et al.*
Early mortality (Control)	6	2.78	5.48	4.75	7.09	3.77	na	na	8.7	6.88
Early mortality (CKD)	8.27	8.56	8.73	6.03	8.53	3.09	na	na	3.51	12.74
1 year mortality (Control)	26.11	9.72	13.24	17.25	na	na	na	10.34	na	17.43
1 year mortality (CKD)	32.98	19.52	23.61	21.31	na	na	na	35.42	na	29.48
Early CV mortality (Control)		2.78	5.02	na	2.84	na	na	na	na	na
Early CV mortality (CKD)		7.53	7.34	na	5.43	na	na	na	na	na
Stroke (Control)	2.21	1.39	1.83	2.59	0.71	1.26	na	na	na	1.84
Stroke (CKD)	3.73	2.74	3.37	2.6	2.33	1.85	na	na	na	4.25
AKI (Control)	14.74	8.33	18.72	na	12.76	na	16.36	na	26.09	13.3
AKI (CKD)	18.49	15.07	26.98	na	20.18	na	20.64	na	27.19	18.16
Need for dialysis (Control)	0.32	na		na	4.97	1.89	na	na	2.9	0.92
Need for dialysis (CKD)	1.69	na		na	10.53	2.16	na	na	6.14	0.47
Bleeding (major or life-threatening) (Control)	6.82	19.44	34.7	na	na	na	na	na	na	na
Bleeding (major or life-threatening) (CKD)	8.8	19.18	34.92	na	na	na	na	na	na	na
Device success (Control)	80.95	na	94.98	95.76	na	na	na	na	na	94.04
Device success (CKD)	81.16	na	93.45	96.53	na	na	na	na	na	91.04
major vascular complication (Control)	8	9.72	9.59	1.94	na	na	na	na	na	7.34
major vascular complication (CKD)	8.18	7.53	11.51	2	na	na	na	na	na	8.49
new pacemaker implantation (Control)	15.37	na	16.44	na	2.13	na	na	na	na	8.72
new pacemaker implantation (CKD)	16.71	na	14.68	na	9.3	na	na	na	na	11.09
Aortic Regurgitation (Control)	11.79	na	18.04	na	na	na	na	na	na	19.73
Aortic Regurgitation (CKD)	12.62	na	15.48	na	na	na	na	na	na	25.71
MI (control)	na	na	0.46	0.65	na	na	na	na	na	0.46
MI (CKD)	na	na	1.39	0.95	na	na	na	na	na	0.47

Na= Not available.

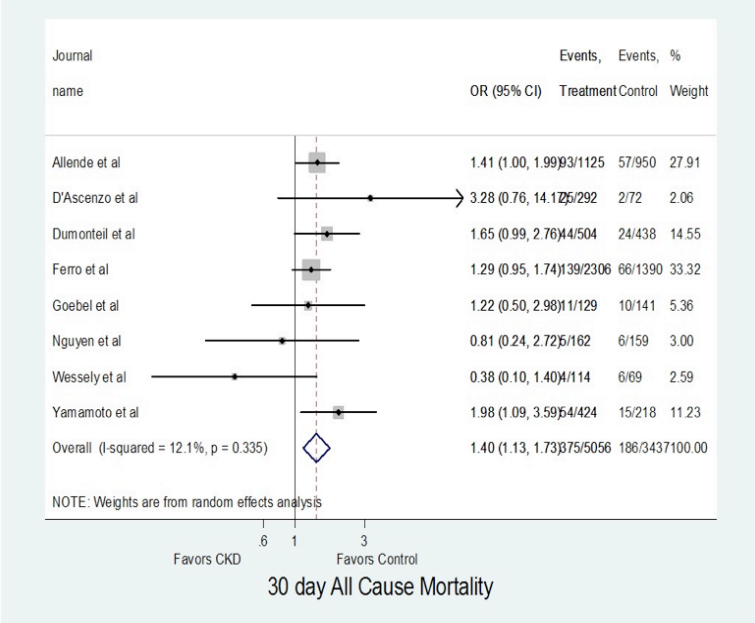

Fig. (2). 30-day all cause mortality.

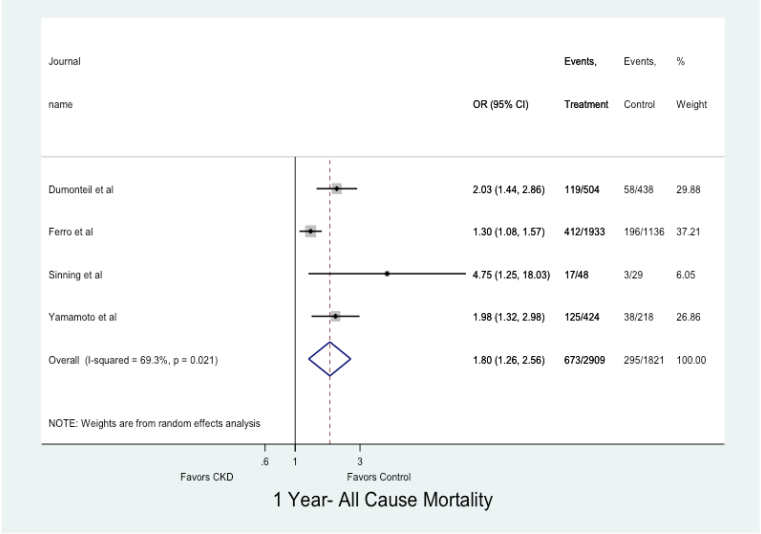

Fig. (3). 1 year all cause mortality.

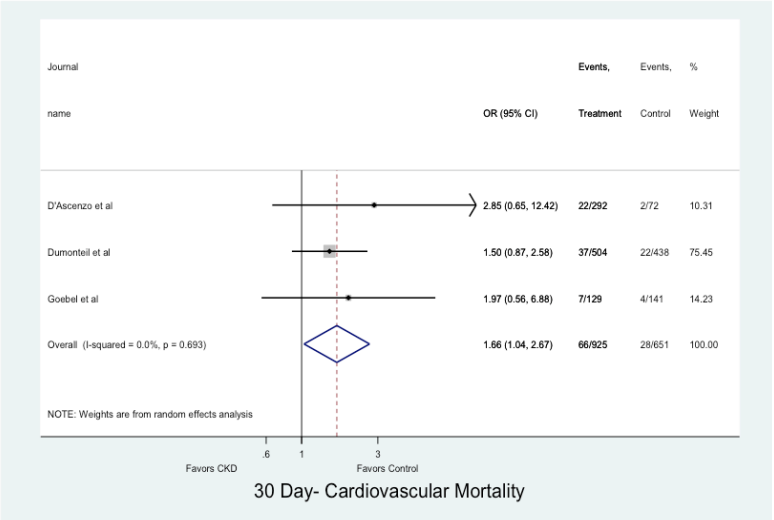

Fig. (4). 30-day cardiovascular mortality.

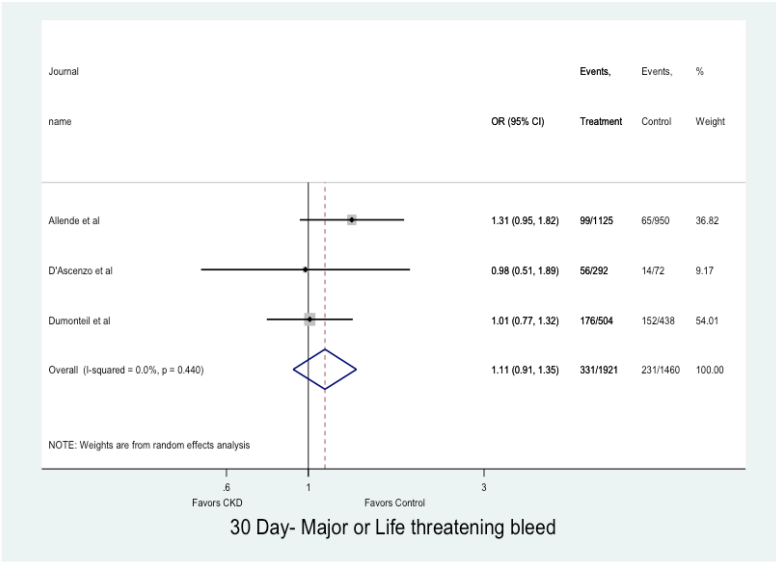

Fig. (5). 30-day major and life threatening bleeding.

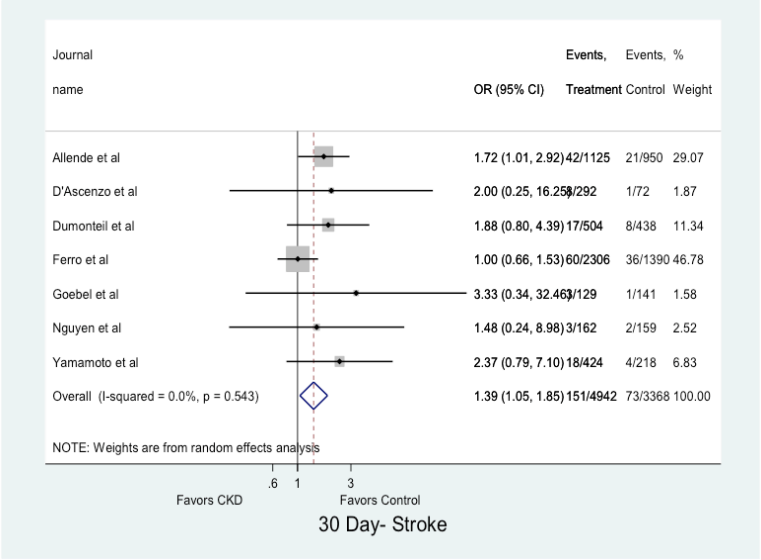

Fig. (6). 30-day stroke rate.

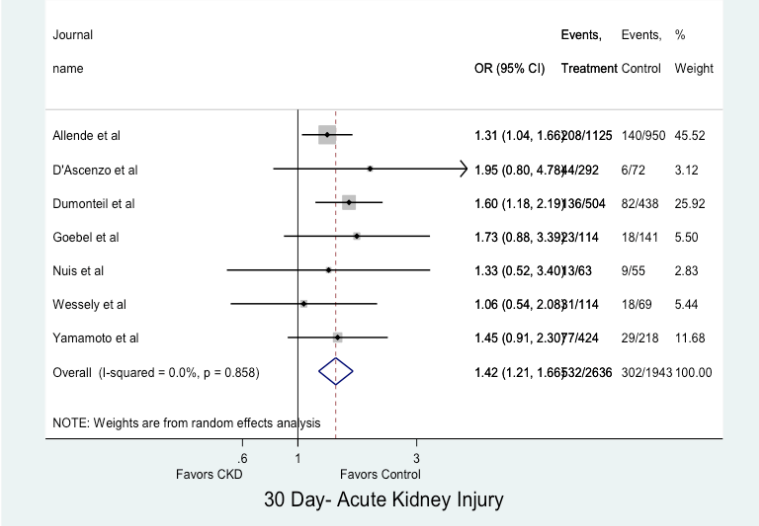

Fig. (7). 30-day acute kidney injury.

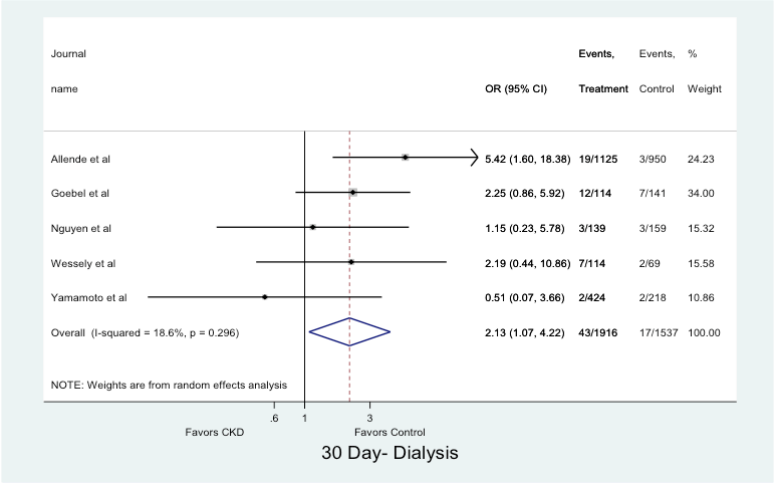

Fig. (8). 30-day need for renal replacement therapy.

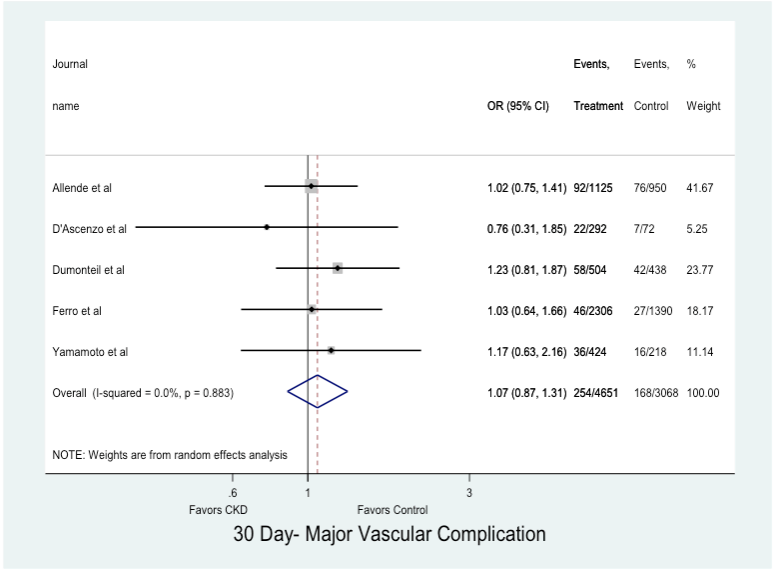

Fig. (9). 30-day vascular complication.

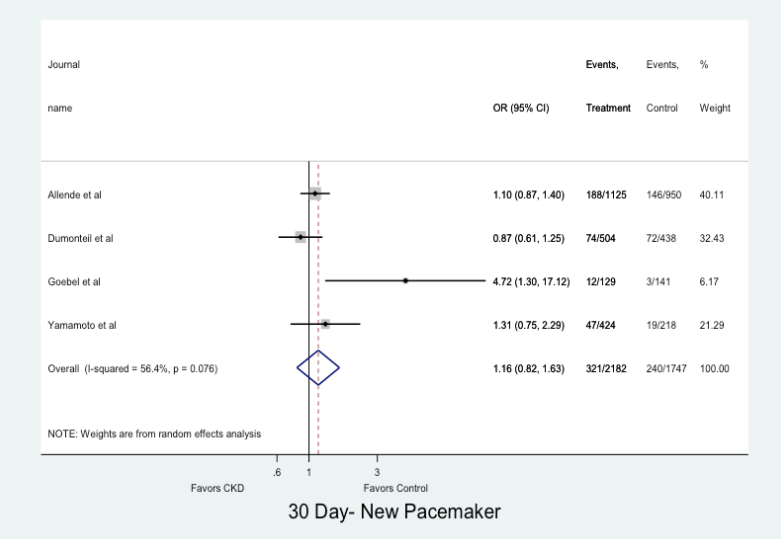

Fig. (10). 30-day new pacemaker insertion.

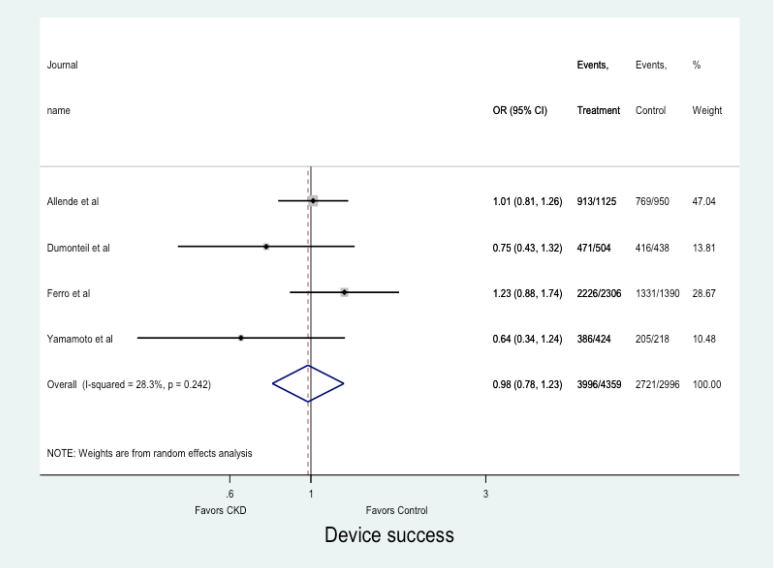

Fig. (11). Device success.

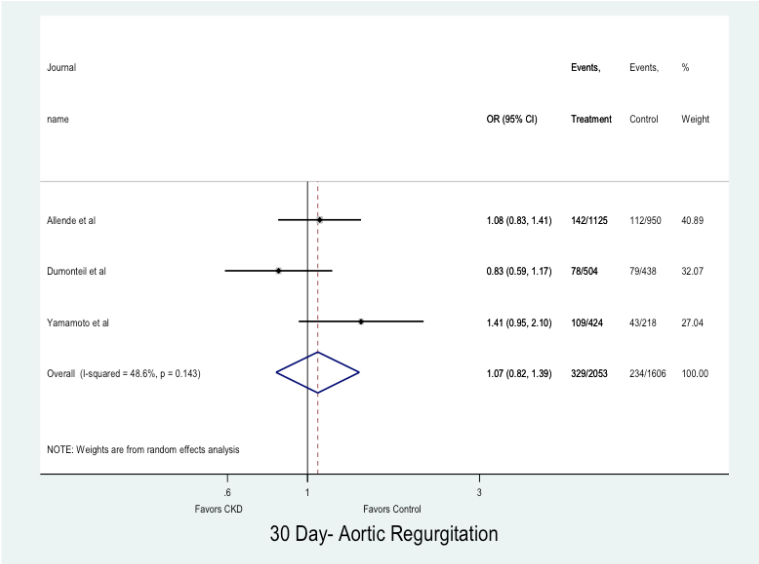

Fig. (12). Paravalvular leak.

4. DISCUSSION

In our study, chronic kidney disease defined by GFR < 60 (NKF CKD stage 3-5) was predictive of increased 30-day and 1 year all-cause mortality, stroke, acute kidney injury, and the need for dialysis compared to GFR ≥ 60 (NKF CKD stage 1,2), and raises some questions regarding the benefits of TAVR in this group of patients. Our findings seem consistent with prior TAVR studies that found CKD to be independently associated with increased mortality and worsening of renal failure [18-20]. This observed outcome could be a confounder as suggested by Sinning *et al*. [11] or a true cause and effect relationship given that other studies have shown late outcomes of TAVR to be primarily determined by co-morbidities unrelated to the aortic valve disease [21-23].

The majority of our study subjects were greater than 80 years and over 80% had NYHA class 3 or 4 heart failure. Although there was no age difference between the control and CKD group, the later had more patients with NYHA class III or IV heart failure. This is significant because prior studies have shown that the regression in left ventricular mass after TAVR, although significant, is incomplete with no accompanying improvement in left ventricular diastolic function [24], leading to poorer prognosis in patients with heart failure undergoing TAVR. In our study, CKD was not predictive of major vascular complications, major bleeding, pacemaker implantation or device success. These findings are in accordance with the study by Sinning *et al.* [11]. Paravalvular leak, which is an independent predictor of 1-year mortality post TAVR [25, 26], was not significantly increased in the CKD group.

TAVR have been shown to be better than the medical management of severe aortic stenosis [1]. Since the medical management of severe aortic stenosis is associated with a poor outcome, and TAVR will continue to be performed in CKD patient, it is worthwhile to actively study this group of

patient in randomized TAVR clinical trials to better understand the efficacy of TAVR in this subpopulation. Long-term data with adequately matched control will shed more light on reliability and durability of the implanted valve prosthesis. On the other hand, not offering TAVR to elderly patients with severe aortic stenosis and co-morbidities including CKD will result in repeat hospitalization, which is associated with a high clinical and financial burden for the patient and is therefore not an appealing alternative [2].

5. Study Limitations

One of the limitations of our study is the exclusion of end stage renal disease patients on hemodialysis in the included studies and the exclusion of data from studies of TAVR that included chronic kidney disease patients but did not report their GFR. Also, not all included studies reported all desired outcomes, leading to the possibility of publication bias when comparing various outcomes. Accurate long-term follow up ($\geq$ 1 year) was not done in some of the included studies therefore limiting the variety of outcomes we reported. Finally, since our study is based on the results of published studies, the possibility of potential publication bias of the included studies cannot be excluded.

CONCLUSION

CKD with GFR <60 is predictive of worse short and long-term outcomes after TAVR. Active measures should be undertaken to study and better understand the factors accounting for these outcomes in order to mitigate them. When TAVR indications are expanded to include low risk patients, the percentage of relatively healthy TAVR population with CKD is expected to increase, thereby potentially improving the overall outcomes data for this group of patients.

LIST OF ABBREVIATIONS

TAVR	=	Transcatheter Aortic Valve Replacement
CKD	=	Chronic Kidney Disease
GFR	=	Glomerular Filtration Rate

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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