RESEARCH ARTICLE

Impact of Renal Dysfunction on Mid-Term Outcome after Transcatheter Aortic Valve Implantation: A Systematic Review and Meta-Analysis

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Abstract

Background

There is conflicting evidence regarding the impact of preexisting renal dysfunction (RD) on mid-term outcomes after transcatheter aortic valve implantation (TAVI) in patients with symptomatic aortic stenosis (AS).

Methods and results

Forty-seven articles representing 32,131 patients with AS undergoing a TAVI procedure were included in this systematic review and meta-analysis. Pooled analyses were performed with both univariate and multivariate models, using a fixed or random effects method when appropriate. Compared with patients with normal renal function, mid-term mortality was significantly higher in patients with preexisting RD, as defined by the author (univariate hazard ratio [HR]: 1.69; 95% confidence interval [CI]: 1.50–1.90; multivariate HR: 1.47; 95% CI: 1.17–1.84), baseline estimated glomerular filtration rate (eGFR) (univariate HR: 1.65; 95% CI: 1.47-1.86; multivariate HR: 1.46; 95% CI: 1.24-1.71), and serum creatinine (univariate HR: 1.69; 95% CI: 1.48–1.92; multivariate HR: 1.65; 95% CI: 1.36–1.99). Advanced stage of chronic kidney disease (CKD stage 3-5) was strongly related to bleeding (univariate HR in CKD stage 3: 1.30, 95% CI: 1.13–1.49; in CKD stage 4: 1.30, 95% CI: 1.04–1.62), acute kidney injure (AKI) (univariate HR in CKD stage 3: 1.28, 95% CI: 1.03-1.59; in CKD stage 4: 2.27, 95% CI: 1.74–2.96), stroke (univariate HR in CKD stage 4: 3.37, 95% CI: 1.52–7.46), and mid-term mortality (univariate HR in CKD stage 3: 1.57, 95% CI: 1.26–1.95; in CKD stage 4: 2.77, 95% CI: 2.06–3.72; in CKD stage 5: 2.64, 95% CI: 1.91–3.65) compared with CKD stage 1+2. Patients with CKD stage 4 had a higher incidence of AKI (univariate HR: 1.70, 95% CI: 1.34–2.16) and all-cause death (univariate HR: 1.60, 95% CI: 1.28– 1.99) compared with those with CKD stage 3. A per unit decrease in serum creatinine was also associated with a higher mortality at mid-term follow-up (univariate HR: 1.24, 95% CI: 1.18-1.30; multivariate HR: 1.19, 95% CI: 1.08-1.30).



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Conclusions

Preexisting RD was associated with increased mid-term mortality after TAVI. Patients with CKD stage 4 had significantly higher incidences of peri-procedural complications and a poorer prognosis, a finding that should be factored into the clinical decision-making process regarding these patients.

Introduction

As a rapidly evolving procedure, transcatheter aortic valve implantation (TAVI) has been shown to be a safe and effective alternative to surgical aortic valve replacement (SAVR) in high-risk or inoperable patients with symptomatic aortic stenosis (AS) [1-3]. These aging patients frequently have a high prevalence of chronic renal dysfunction (RD), which portends a poor prognosis in those who undergo SAVR [2-4]. However, the results from studies evaluating the impact of baseline renal function on outcomes after TAVI are conflicting [5-7]. In many TAVI studies, although higher mid-term mortality were observed in patients with RD, these differences were not found to be significant by multivariate analyses [6, 8-10]. In addition, the relationship between varying degrees of RD and mid-term prognosis has also not been elucidated.

Therefore, we conducted a meta-analysis of published studies to clarify the mid-term prognostic value of preexisting RD in patients undergoing TAVI.

Materials and Methods

Search Strategy

The PubMed online database and the Cochrane library were searched for articles published from January 2002 to April 2014. The following search strategy was used: (transcatheter OR percutaneous OR transfemoral OR transapical OR transsubclavian OR transaortic OR transaxillary) AND (aortic valve) AND (implantation OR replacement) AND (risk factor OR risk assessment OR predictor OR kidney disease OR renal insufficiency OR nephropathy OR creatinine OR estimated glomerular filtration rate OR dialysis OR hemodialysis OR hemodialysis). Reference lists of comparable articles were also retrieved to seek potentially relevant citations.

Study Selection

Two reviewers conducted the initial screening of titles and abstracts; full-length reports of identified studies were retrieved; and decisions were then made regarding eligibility according to pre-specified inclusion and exclusion criteria. Studies were included if they (1) reported the predictive value of the pre-procedure renal function or mortality outcomes in patients with RD compared with normal controls; (2) performed follow-ups for at least 6 months; and (3) were human studies and published in English. Studies were excluded if they were (1) abstracts, letters, editorials, or reviews and (2) duplicate publications. Studies with overlapping populations were handled by selecting the study that reported on the largest sample of patients undergoing TAVI, unless they used different definitions of RD or reported results in different analysis models.

Data Extraction

Data were extracted from relevant studies using a pre-specified data collection form that included the first author, journal, year of publication, baseline characteristics, definition of RD, valve type, follow-up duration, and number of complications and deaths. Complications were defined according to the Valve Academic Research Consortium criteria [11], including acute kidney injure (AKI), stroke, all-cause bleeding, and major vascular complications. The outcomes from 6 months to 3 years were defined as mid-term outcomes. The incidence of allcause mid-term mortality was the primary end point. TAVI-related complications were also the end points of interest.

Definitions of RD

RD was defined as a diagnosis of chronic kidney disease (CKD), chronic renal failure, renal insufficiency, decreased estimated glomerular filtration rate (eGFR), or elevated serum creatinine level at baseline. CKD stages were classified according to baseline eGFR as follows [12]: \geq 60 ml/min (normal or mild CKD, stage 1+2), 30–59 ml/min (moderate CKD, stage 3), 15–29 ml/ min (severe CKD, stage 4), and <15 ml/min or dialysis (kidney failure, stage 5). Advanced CKD was defined as CKD stage 3–5.

Statistical Analysis

The hazard ratio (HR) of preexisting RD with regard to mid-term mortality after TAVI was extracted or calculated. The Generic Invers Variance method in the RevMan software, version 5.20 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for synthesis of the effect estimates. Heterogeneity was assessed by the *Q*-statistic and I^2 test. The fixed effects model was selected for the analysis without significant heterogeneity ($I^2 < 50\%$ and a corresponding P > 0.1); otherwise, the random effects model was used to obtain the combined effect estimates. Statistical significance was set at P < 0.05 (two-tailed). Sensitivity analyses were performed using the STATA software version 12.1 (StataCorp, College Station, TX) to test the robustness of the results and the influence of potential effect modifiers. Publication bias was assessed by graphical inspection of funnel plots, Begg's tests, and Egger's tests. The "Trim and Fill method" was applied if there was any evidence of publication bias [13].

The present meta-analysis was conducted and reported according to the recommendation of the MOOSE group [14].

Results

Study Selection

We identified 1096 citations in the initial screening (Fig. 1). After removing duplicates and screening at the abstract level, we retrieved 286 articles for a more detailed evaluation. While 239 studies were subsequently excluded, a total of 47 full-text articles were eligible for this meta-analysis, enrolling a total of 32,131 AS patients with renal function-specific data. No significant limitations were identified for the 47 trials, 3 of which were randomized comparisons [15–17], while others were observational cohort studies [5, 6, 18–56]. Although a few studies had overlapping patient populations, they provided different outcomes according to different definitions of RD, as defined by the author [16, 18, 20, 23, 40, 42, 43], baseline eGFR [10, 27, 49], or serum creatinine [6, 15, 17, 34, 35, 38, 47, 56]. We thus assigned these studies to different ent groups for either univariate or multivariate analysis.







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Study and Patient Characteristics

The baseline features of the included patients are presented in <u>Table 1</u>. Most studies were conducted in the general population, while a few studies performed TAVI in unique patient groups, such as octogenarians and nonagenarians [43], patients at very high risk (with a Euro-SCORE of more than 40%) [42], and patients with chronic lung disease (CLD) [15]. Four studies elucidated the impact of detailed CKD classification on outcomes after TAVI [10, 29, 48, 49]. Patients with end-stage renal disease (ESRD) were included in 14 studies [5, 18, 22–24, 29, 38–41, 43, 47, 53, 55, 56] and were excluded in 7 studies [6, 10, 15–17, 44, 49]. In the remaining

Table 1. Bas	seline cl	haracte	ristics of	f include	d patients.									
Study	_	Male (%)	Age (y)	STS Score	Logistic Euroscore	Hypertension (%)	Diabetes mellitus	Previous CAD (%)	Previous CE (%)	Renal dysfunction, n (%) / l renal function	Baseline	LVEF (%)	Mean AVA (cm ²)	Mean gradient
							(%)			Defined	ESRD		(IIII)	(611111)
Unbehaun <i>et al</i> , 2011 [18]	300	32.3	79.6 ±8.1	19.1 ±15.5	38.5±19.4	N/A	24.0	59.3	32.7	Chronic Renal Failure; Baseline eGFRª = 52.0 ±24.5ml/min/1.73m²	Included	EF<25: 9.3	0.7 ±0.2	48.5±14.9
Tzikas <i>et al</i> , 2011 [<u>19</u>]	63	43	82 (78– 86)	5(3-8)	15(11–19)	57	22	N/A	24	Chronic Renal Disease/ Insufficiency; n = 13(21)	Unclear	49±14	N/A	47±19
Sinning <i>et al</i> , 2012 [20]	146	47.9	80.5 ±6.6	9.8 ±7.3	30.2±18.0	N/A	N/A	61.0	25.3	Chronic Renal Failure; n = 82(56.2)	Unclear	44.5 ±14.5	0.67 ±0.15	38.0 (29.0– 51.0)
Vasa- Nicotera et al, 2012 [21]	122	53.3	81.7 ±6.8	7.3 ±4.3	22.4±13.0	N/A	N/A	62.3	16.4	Chronic Renal Failure; n = 48(39.3)	Unclear	49.9 ±10.9	0.64 ±0.19	44.2±15.8
Wendler et <i>al</i> , 2013 [22]	1387	41.5	80.6 ±7.1	N/A	27.6±16.1	68.9	28.6	55.9	15.2	Renal insufficiency/failure; n = 432(31.2)	18 patients receiving dialysis	EF <30: 5.7	N/A	N/A
Chopard <i>et al</i> , 2014 [23]	3933 ^b	51	82.8 ±7.1	14.1 ±11.7	21.8±14.1	69	26	48	10	Chronic Kidney Disease; n = 336(9)	Included	EF<30: 7.0	N/A	N/A
Muñoz- García et al, 2013 [<u>24</u>]	1220°	45.3	80.7 ±6.3	N/A	17.8±13	79.4	31.2	36.1	1.11	Oliguric Renal Failure; n = 17(1.5)	15 patients receiving dialysis	55.8±14	0.62 ±0.18	51.6±18
Godino <i>et al</i> , 2010 [<u>25</u>]	137	53.3	79.5 ±6.7	7.1 ±4.6	27.4±16.7	N/A	29.2	N/A	22.6	eGFR<60ml/min/1.73m ² ; n = 51(37.2)	Unclear	50.9 ±12.6	N/A	52.3±17.3
Rodés- Cabau <i>et al</i> , 2010 [5]	339	44.8	81±8	9.8 ±6.4	A/A	74.3	23.3	69.0	22.7	eGFR<60ml/min/1.73m ² ; n = 191(56.3); Baseline creatinine = 119±83umol/l	10 patients receiving dialysis	55±14	0.63 ±0.17	46±17
Hayashida <i>et al</i> , 2012 [26]	400	48.5	83.4 ±6.1	7.9 (5.1– 12.3)	22.3(17.1– 30.3)	69.0	23.0	59.3	10.3	eGFR<60ml/min/1.73m ² ; n = 249(63)	Unclear	54.7 ±12.3	0.62 ±0.15	47.8±17.1
Sinning <i>et al</i> , 2012 [<u>27</u>]	152	49.3	80.5 ±6.5	9.8 ±7.3	30.4±18.1	N/A	N/A	61.2	24.3	eGFR ^d <60ml/min/1.73m ² ; n = 87(57.2); Baseline eGFR = 52±21 ml/min/1.73m ²	Unclear	44.2 ±14.5	0.67 ±0.15	38.0 (29.0– 51.0)
Nombela- Franco <i>et al</i> , 2012 [8]	1061	50.7	81±8	6.5 (4.3– 9.7)	N/A	74.5	29.4	64.7	18.1	eGFR<60ml/min/1.73m²; Baseline eGFR = 60.1 ±27.8ml/min/1.73m²	Unclear	EF<40: 22.1	0.66 ±0.19	43±16
Kamaga et <i>a</i> l, 2013 [28]	30	53.3	86±3	N/A	34±12	86.7	20	N/A	16.7	eGFR ^d <60ml/min/1.73m ² ; n = 18(60); Baseline 6GFR = 52±17 ml/min/1.73m ²	Unclear	52±14	N/A	N/A
Dumonteil e <i>t al,</i> 2013 [29]	942	53.8	81.0 ±7.0	N/A	20.9(12.9– 28.9)	69.5	28.5	45.2	15.7	Chronic Kidney Disease: Mild = $329(eGFR^d = 60-$ 89ml/min); Moderate = 399 (eGFR = $30-59ml/min$); Severe = $72(eGFR < 30ml/$ min)	33 patients receiving dialysis	EF <35: 17	N/A	N/A
													ğ	ontinued)

(%) Defined ESID (m ¹) 37.3 633 19.1 $e6FR-60mimin/1/3m_1^*$, 10 totekar 54 ± 14 n^2 60^2 60^2 20^2 46.3 31.1 8.1 $e6FR-60mimin/1/3m_1^*$, 10 totekar 53.2 0.81 46.3 20.26 46.3 31.2 56.4 NA $e6FR-60mimin/1/3m_1^*$, 10 totekar 55.2 0.87 20.26 46.3 27 65 NA $e6FR-60mimin/1/3m_1^*$, 10 totekar 55.2 0.87 20.26 28.8 51.7 5.9 $e6FR-60mimin/1/3m_1^*$, 10 totekar 55.2 0.75 20.26 41.6 27 65 48.3 72 $0.6FR-60mimin/1/3m_1^*$ 0.76 50.22 41.7 20.26 41.6 72.26 20.24 20.26 20.15 20.26 41.6 20.24 41.6 20.24 41.6 20.24 41.6 20.24 41.6 20.24 41.6 20.24 41.6 20.24 41.6	iontinued) n Male Age 5 (%) (y) 5	d) Male Age (%) (y) 5	Age (y)	0,0,	STS	Logistic Euroscore	Hypertension (%)	Diabetes mellitus	Previous CAD (%)	Previous CE (%)	Renal dysfunction, n (%) / renal function	Baseline	LVEF (%)	Mean AVA	Mean gradient
313 633 181 ceffer-continuin/173m ² , n Unclear 54.4 n= 40.416 341 NA $= 196(60.2)$ $= 196(60.2)$ NA $= 136(60.2)$ NA						2		(%)			Defined	ESRD		(cm ²)	(gHmm)
34.1 NA 8.1 $eGFR-60n/mn/1/3m_7^{*}$, n 143 205 0.66 $4.6.3$ 31.2 56.4 NA $eGFR-60n/mn/1/3m_7^{*}$, n 1730 502 0.66 $4.6.3$ 28.8 51.7 5.9 $6FR-60n/mn/1/3m_7^{*}$, n $106ar$ 553 0.75 502400 28.8 51.7 5.9 $6FR-60n/mn/1/3m_7^{*}$, n $106ar$ 512 0.75 502400 28.4 9.5 $6FR-60n/mn/1/3m_7^{*}$, n $106ar$ 5414 0.72 502400 28.7 65 NA 21633 0.661 0.75 502401 28.4 436 720400 1667 0.75 50240 0.75 502401 28.4 4366 7204000 1623 0.75 0.75 0.75 0.964 4224 28.4 7660000 1633000000 1633000000 $1006ar$ 1632 0.75 0.2424 28.4 76600000000	319 46.1 80±8 6.3 N/A 89.0 (4.1- 8.9)	46.1 80±8 6.3 N/A 89.0 (4.1- 8.9)	80±8 6.3 N/A 89.0 (4.1- 8.9)	6.3 N/A 89.0 (4.1- 8.9)	N/A 89.0	89.0		37.3	63.9	19.1	eGFR<60ml/min/1.73m ² ; n = 192(60.2)	Unclear	54 ± 14	n = 192 (60.2)	40±16
312 64 NA $eGFR-G0N$ minu/1/3m ² , n Undear 52 NA 7.3416 288 517 59 $eGRP+G0N$ minu/1/3m ² , n Undear $F133$ 20.5 50.200 27 65 NA $Continue 1/3m2$, n Undear $F13$ 50.200 20.5 50.200 27 65 NA $Continue 1/3m2$, n 100 54.14 NA 713 28.4 $41(3)$ $Creatine 1/3m2$ $Undear$ 51.2 NA 4163 20.1 NA 76.6 28.4 $000000000000000000000000000000000000$	1318 41.5 81.7 N/A 20.3±13.5 N/A ±6.1	41.5 81.7 N/A 20.3±13.5 N/A ±6.1	81.7 N/A 20.3±13.5 N/A ±6.1	N/A 20.3±13.5 N/A	20.3±13.5 N/A	N/A		34.1	N/A	8.1	eGFR<60ml/min/1.73m ² ; n = 798/1318(60.5)	Unclear	53.5 ±14.7	0.66 ±0.24	46. 3 ±21.8
28.8 51.7 5.9 $c6FR-c6nntion(1, 12nt)^{2}, n = 9(73)$ $c055$ 60.45 $c055$ $c0555$ $c0555$ $c0$	1556 47.6 80.2 7.6 20.5±14 81.4 ±7.6 ±5.3-	47.6 80.2 7.6 20.5±14 81.4 ±7.6 ±5.3-	80.2 7.6 20.5±14 81.4 ±7.6 ±5.3-	7.6 20.5±14 81.4 ±5.3-	20.5±14 81.4	81.4		31.2	56.4	N/A	eGFR<60ml/min/1.73m ² ; n = 882 (56.7)	Unclear	55.2 ±13.9	N/A	47.3±16
27 65 NA Creatinine-106umolt; n= Unclear 64:14 NA NA 264 48.3 7.2 Creatinine-133umolt; n= Unclear 51.2 NA 51.8±17. 264 48.3 7.2 Creatinine-177umolt; n= Unclear 51.3 242.3 30.1 475 NA 7.8 Creatinine-2000molt; n= Unclear 53.1 $0.66.3$ $242.44.4$ 10.4 266.7 $242.44.4$ 10.4 266.7 $242.44.4$ 10.4 $266.6.7$ $263.6.6.7$ $263.6.7.4.6.6.6.7$ $263.6.7.6.6.6.7.6.6.6.6.6.6.6.6.6.6.6.6.6$	118 46.6 82.5 N/A 25.8±15.4 80.5 ±5.87	46.6 82.5 N/A 25.8±15.4 80.5 ±5.87	82.5 N/A 25.8±15.4 80.5 ±5.87	N/A 25.8±15.4 80.5	25.8±15.4 80.5	80.5		28.8	51.7	5.9	eGFR<60ml/min/1.73m ² ; n = 53(44.9); eGFR<30ml/ min/1.73m ² ; n = 9(7.6)	Unclear	EF<30: 5.9	0.75 ±0.15	50.9±20.
264 483 72 Creatinine>133unol; n = Unclear 512 NA 51.841^3 901 NA 14.7 Creatinine>177unol; n = Unclear 53.9 0.7 42.2 90.1 76.6 28.4 Creatinine>177unol; n = Unclear 53.9 0.7 42.2 80.1 76.6 28.4 Creatinine>200unol; n = Unclear 83.1 40.7 $42.341.4$ $812(16.4)$ $812(16.4)$ Unclear 81.4 $82.414.4$ $82.414.4$ $82.414.4$ $82.414.4$ $82.414.4$ $82.41.6$ $82.41.6$ $82.41.6$ $82.41.6$ $82.41.6$ $82.41.6$ $82.41.6$ $82.41.6$ $82.41.6$ $82.41.6$ $82.41.6$ $82.41.6$ 82	116 49 81±8 N/A 21.2±12.3 41	49 81±8 N/A 21.2±12.3 41	81±8 N/A 21.2±12.3 41	N/A 21.2±12.3 41	21.2±12.3 41	41		27	65	N/A	Creatinine>106umol/l; n = 41(35)	Unclear	54±14	N/A	N/A
30.1 N/A 14.7 Creatinine- 177 umol/t n= 53.3 0.7 42.2 N/A 76.6 28.4 Creatinine- 200 umol/t n= Excluded 53.1 0.66 42.3414 22.8 4.76 N/A 56.7 $182(16.4)$ 10.6187 10.7 36.5 22.8 4.76 N/A 57.7 19.3 $Creatinine-200 umol/t, n=$ 10.7687 47.346 10.4 22.8(5.7) 19.3 Creatinine-200 umol/t, n= 10.7687 36.5 33.4 V/A 10.4 Creatinine-200 umol/t, n= 10.7687 36.5 36.4 V/A 10.4 $228(9.4)$ 0.77 36.5 36.4 V/A N/A 2387 116.9 23846 37.9 37.9 24.4 10.4 $228(9.4)$ 0.77 36.5 36.5 23.2 67.9 10.6 23847 34.9 34.9 10.4 10.4 $228(9.4)$	663 44 81.0 ± N/A 23.0±13.7 75.1 7.3	44 81.0 ± N/A 23.0±13.7 75.1 7.3	81.0± N/A 23.0±13.7 75.1 7.3	N/A 23.0±13.7 75.1	23.0±13.7 75.1	75.1		26.4	48.3	7.2	Creatinine>133umol/l; n = 154(23.2)	Unclear	51.2 ±25.5	N/A	51.8±17.
NA 76.6 28.4 Creatinine>200um0/I; n = Excluded 53.1 0.66 4.2.34.1. 22.8 47.6 NA 56.7) 182(16.4) Unclear V/A N/A N/A <t< td=""><td>518 55.1 81.5 8.3 N/A 77.6 ±8.4 ±5.2</td><td>55.1 81.5 8.3 N/A 77.6 ±8.4 ±5.2</td><td>81.5 8.3 N/A 77.6 ±8.4 ±5.2</td><td>8.3 N/A 77.6 ±5.2</td><td>N/A 77.6</td><td>77.6</td><td></td><td>30.1</td><td>N/A</td><td>14.7</td><td>Creatinine>177umol/l; n = 197(38)</td><td>Unclear</td><td>53.9 ±13.9</td><td>0.7 ±0.4</td><td>42.2 ±16.3</td></t<>	518 55.1 81.5 8.3 N/A 77.6 ±8.4 ±5.2	55.1 81.5 8.3 N/A 77.6 ±8.4 ±5.2	81.5 8.3 N/A 77.6 ±8.4 ±5.2	8.3 N/A 77.6 ±5.2	N/A 77.6	77.6		30.1	N/A	14.7	Creatinine>177umol/l; n = 197(38)	Unclear	53.9 ±13.9	0.7 ±0.4	42.2 ±16.3
22.8 47.6 NA Creatinine>200umolit, n = 56(6.7) Unclear NA NA NA NA N/A 61.7 19.3 Creatinine>200umolit, n = 1.5(1.3-1.6)mgd1 Unclear N/A 0.7 36.5 24.4 47.4 10.4 Creatinine>200umolit, n = 1.5(1.3-1.6)mgd1 63 28.6 36.4 24.4 N/A N/A 27.8.16 29(8.9.4) 28(9.4) 36.5 24.4 N/A 28 Renal impairment, n = 9(9) 3 patients 414.6 36.9 23.2 67.9 17.9 Creatinine>200umol/i, n = 9(9) 3 patients 50(1- N/A 47.8416 23.2 67.9 71.9 28(9.4) 286(1-130)umol/i 63 65 55 23.2 67.9 28(81-130)umol/i 16.10 0.7 36.5 55 23.2 57.9 57.9 56 57 0.6 55 55 23.2 57.9 56 57 56 57 55 55	1108 54.4 82.7 11.9 27.2±16.5 N/A ±7.2 ±4.1	54.4 82.7 11.9 27.2±16.5 N/A ±7.2 ±4.1	82.7 11.9 27.2±16.5 N/A ±7.2 ±4.1	11.9 27.2±16.5 N/A ±4.1	27.2±16.5 N/A	N/A		N/A	76.6	28.4	Creatinine>177umol/l; n = 182(16.4)	Excluded	53.1 ±12.8	0.66 ±0.19	42.3±14
NA 61.7 19.3 Creatinine-200umolt; n = $1.5(1.3-1.6)$ mgdi Unclear N/A 0.7 36.5 24.4 47.4 10.4 Creatinine-200umolt; n = 63 52.8 N/A 71.5 34.4 24.4 10.4 Creatinine-200umolt; n = 63 52.8 N/A $47.84.6$ 24.4 10.4 Creatinine-200umolt; n = $9(8)$ 8418618 $51.46.6$ $32.43.64.66.66.67.66.67.66.66.67.66.66.67.66.66.$	870 52.4 81.9 N/A 18.5(11.7- N/A ±7.1 27.9)	52.4 81.9 N/A 18.5(11.7- N/A ±7.1 27.9)	81.9 N/A 18.5(11.7– N/A ±7.1 27.9)	N/A 18.5(11.7– N/A 27.9)	18.5(11.7- N/A 27.9)	N/A		22.8	47.6	N/A	Creatinine>200umol/l; n = 55(6.7)	Unclear	N/A	N/A	N/A
24.4 47.4 10.4 Creatinine-200unol(1, n = 63) 52.8 N/A $47.3+16$ NA N/A 28(9.4) patients ± 14.6 N/A $47.3+16$ NA N/A 28(9.4) $28(9.4)$ $28(9.4)$ $28(9.4)$ $28(9.4)$ 3 patients $50(1 N/A$ $47.3+16$ Su N/A 28 $80(1-)$ $28(1-)30) \text{ unol}(1)$ $29^{\circ 6}$ $61(3)^{\circ 5}$ $55^{\circ 6}$ 32.0 57.2 57.2 27.0 $Chronic Renal Failure, n = 10cluded 16.1 0.7) 0.7) 0.7) 32.0 57.2 27.0 Chronic Renal Failure, n = 10cluded 51.5 0.6 46(3-1) 32.0 57.2 27.0 Chronic Renal Failure, n = 10cluded 51.5 0.6 64(3-1) 32.0 57.2 27.0 Chronic Renal Failure, n = 10cluded 51.5 0.6 46(3-1) 80.1 80.1 80.1 80.1 80.1 80.1 24.1 $	326 44.5 80.6 8.3 22.7(21.2- N/A (79.8- (7.7- 24.2) 81.3) 8.9)	44.5 80.6 8.3 22.7(21.2- N/A (79.8- (7.7- 24.2) 81.3) 8.9)	80.6 8.3 22.7(21.2- N/A (79.8- (7.7- 24.2) 81.3) 8.9)	8.3 22.7(21.2- N/A (7.7- 24.2) 8.9)	22.7(21.2- N/A 24.2)	N/A		N/A	61.7	19.3	Creatinine>200umol/l; n = 29(8.9); Baseline creatinine = 1.5(1.3-1.6)mg/dl	Unclear	N/A	0.7 (0.7– 0.7)	36.5 (34.6– 38.4)
NA NA 28 Renal impairment, n = 9(8) 3 patients 50(11- NA NA NA 23.2 67.9 17.9 Chronic Renal Failure; n = 9(8) ncluded $EF<35$: 0.6 $46(34-3)^{\circ}$ 32.0 57.2 27.0 Chronic Renal Failure; n = 9(8(1-130)umol/) ncluded $E1<-35$: 0.6 $46(34-3)^{\circ}$ 32.0 57.2 27.0 Chronic Renal Failure; n = 9(8(1-130)umol/) ncluded $E1<-35$: 0.6 $46(34-3)^{\circ}$ 32.0 57.2 27.0 Chronic Renal Failure; n = 28(8(1-130)umol/) ncluded $E1<-35$: 0.6 $46(34-3)^{\circ}$ 32.0 57.2 27.0 Chronic Renal Failure; n = 1.3±1.6 mg/di 116.1 0.7	2435 49.8 83±7 N/A N/A 69	49.8 83±7 N/A N/A 69	83±7 N/A N/A 69	N/A N/A 69	N/A 69	69		24.4	47.4	10.4	Creatinine>200umol/l; n = 228(9.4)	63 patients receiving dialysis	52.8 ±14.6	N/A	47.8±16
23.2 67.9 17.9 Chronic Renal Failure; $n = 1$ Included $F < 35$: 0.6 $46(34-1)$ 32.0 57.2 $20(11.9)$; Baseline creatinine $= 98(81-130)umol/l$ 0.7 0.7 55 32.0 57.2 27.0 Chronic Renal Failure; $n = 16.1$ 0.7 0.7 553 32.0 57.2 27.0 Chronic Renal Failure; $n = 16.1$ 21.2 0.6 55.3221 32.0 57.2 27.0 Chronic Renal Failure; $n = 123$ 21.2 0.6 55.3221 24 N/A N/A Chronic Renal Failure; $n = 123$ 116.1 21.2 0.6 55.3221 24 N/A Baseline creatinine = 123 $patients$ $24.0.21$ N/A 28.5 71.5 42.5 53.35 40.21 42.5 0.27 44.17 21.9^4 48.6^4 9.4^4 9.14^4 9.14^4 53.7 0.66 49.14^4 71.9^4 28.1^4 9.4^4 9.14^4 9.14^4 9.14^4 9.14^4 9.14^4	110 46.4 83 N/A 10(2–40) ^e 92 (58– 97) ^e	46.4 83 N/A 10(2–40)° 92 (58– 97)°	83 N/A 10(2–40) ^e 92 (58– 97) ^e	N/A 10(2-40) [€] 92	10(2-40) ^e 92	92		N/A	N/A	28	Renal impairment; n = 9(8)	3 patients receiving dialysis	50(11– 73) ^e	N/A	N/A
3.0 57.2 27.0 Chronic Renal Failure; n = 1.32 6.6 51.2 0.6 55.3221 24 N/A N/A Chronic Renal Failure; n = $1.341.6$ mg/di 11 $EF<30$: 0.67 0.08 55.3421 24 N/A N/A Chronic Renal Failure; n = 123 patients $14:30$ - 40.18 $86:365$ $14:30$ - 40.21 N/A $28:5$ $71:5$ $42:5$ Kidney Failure; Baseline $Unclear 42:16 0.7 44:17 21:9^{1} 48.6^{1} 9.4^{1} Renal Insufficiency; n = 200 41:5 0.2 49:14 21:9^{1} 48.6^{1} 9.4^{1} Renal Insufficiency; n = 200 41:5 0.2 49:14 21:9^{1} 48.6^{1} 9.4^{1} 9:13^{1} $	168 51.8 84 9.1 28.6(17.9– 64.9 (79– (6.3– 41.0) 87) 13.0)	51.8 84 9.1 28.6(17.9- 64.9 (79- (6.3- 41.0) 87) 13.0)	84 9.1 28.6(17.9- 64.9 (79- (6.3- 41.0) 87) 13.0)	9.1 28.6(17.9– 64.9 (6.3– 41.0) 13.0)	28.6(17.9– 64.9 41.0)	64.9		23.2	67.9	17.9	Chronic Renal Failure; n = 20(11.9); Baseline creatinine = 98(81–130)umol/l	Included	EF<35: 16.1	0.6 (0.5– 0.7)	46(34– 55)
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	159 42.7 84.4 11.8 42.3±21.4 89.3 ±5.8 ±3.9	42.7 84.4 11.8 42.3±21.4 89.3 ±5.8 ±3.9	84.4 11.8 42.3±21.4 89.3 ±5.8 ±3.9	11.8 42.3±21.4 89.3 ±3.9	42.3±21.4 89.3	89.3		32.0	57.2	27.0	Chronic Renal Failure; n = 64(40.2); Baseline creatinine = 1.3±1.6 mg/dl	Excluded	51.2 ±15.9	0.6 ±0.18	55.3±21
28.5 71.5 42.5 Kidney Failure; Baseline Unclear 42±16 0.7 44±17 21.9 [†] 48.6 [†] 9.4 [†] Renal Insufficiency; n = 200 41 53.7 0.66 49.1±16. 21.9 [†] 48.6 [†] 9.4 [†] Renal Insufficiency; n = 200 41 53.7 0.66 49.1±16. receiving receiving dialysis	235 49 80±7 6.1 19.1±13.7 56 ±5.5	49 80±7 6.1 19.1±13.7 56 ±5.5	80±7 6.1 19.1±13.7 56 ±5.5	6.1 19.1±13.7 56 ±5.5	19.1±13.7 56	56		24	N/A	N/A	Chronic Renal Failure; Baseline creatinine = 123 ±131umol/l	11 patients receiving dialysis	EF<30: 14; 30− 59: 35	0.67 ±0.21	N/A
21.9 [†] 48.6 [†] 9.4 [†] Renal Insufficiency; n = 200 41 53.7 0.66 49.1±16. (9.13) [†] patients ±13.8 ±0.18 receiving field signals	186 34.4 81±8 23±14 63±16 N/A	34.4 81±8 23±14 63±16 N/A	81±8 23±14 63±16 N/A	23±14 63±16 N/A	63±16 N/A	N/A		28.5	71.5	42.5	Kidney Failure; Baseline creatinine = 1.5±1.0 mg/dl	Unclear	42±16	0.7 ±0.2	44±17
	2254 47.5 86.3 N/A 23.6±16.8 69.9 ^f ±3.5	47.5 86.3 N/A 23.6±16.8 69.9 ^f ±3.5	86.3 N/A 23.6±16.8 69.9 ^f ±3.5	N/A 23.6±16.8 69.9 ^f	23.6±16.8 69.9 ^f	69.9 ^f		21.9 [†]	48.6 [†]	9.4 [†]	Renal Insufficiency; n = 200 (9.13) ^f	41 patients receiving dialysis	53.7 ±13.8	0.66 ±0.18	49.1±16.

Table 1. (Co	ontinuec	<i>4</i>)												
Study	5	Male (%)	Age (y)	STS Score	Logistic Euroscore	Hypertension (%)	Diabetes mellitus	Previous CAD (%)	Previous CE (%)	Renal dysfunction, n (%) / renal function	Baseline	LVEF (%)	Mean AVA ^(cm²)	Mean gradient
							(o/.)			Defined	ESRD		(111)	(6111111)
Saia <i>et al,</i> 2013 [44]	102	39.2	83.7 ±5.3	8.2 ±4.1	22.6±12.4	80.4	22.5	50	4.9	$eGFR^{a} < 30ml/min/1.73m^{2}$; n = 29(28.4)	Excluded	59.9 ±11.6	0.6 ±0.1	46.0±16.7
Conrotto et al, 2014 [45]	511	50.5	N/A	N/A	N/A	91.2	29.4	N/A	14.3	eGFR<30ml/min/1.73m ² ; n = 93(18.2)	Unclear	N/A	N/A	N/A
Sinning <i>et al</i> , 2010 [6]	22	48	80.8 ±6.7	9.3 ±6.1	31.2±17.6	94	23	65	26	eGFP ^d <60ml/min/1.73m ² , n = 48(62.3); Baseline eGFR = 50.6(38.2±63.8)ml/min/ 1.73m ²	Excluded	45.3 ±16.8	N/A	N/A
Tamburino et al, 2012 [46]	218	46.3	80.9 ±5.2	5.5 ±4.3	21.1±14.2	85.3	24.3	N/A	13.8	Creatinine>133umol/l; n = 51(23.4)	Unclear	51.1 ±10.6	0.8 ±0.2	58.2±16.8
Van Belle <i>et al</i> , 2014 [47]	2769	51.1	82.7 ±7.2	N/A	21.5±13.8	20	25.2	47.1	9.5	Creatinine>200umol/l; n = 233(8.4)	Included	N/A	0.68 ±0.18	48.4±16.3
Nguyen <i>et al</i> , 2013 [<u>48]</u>	321	55.8	82.2 ±8.2	12.1 ±7.3	A/A	95.1	43.6	N/A	32.1	Chronic Kidney Disease: Normal/Mild = 159 (eGFR ^d >60ml/min); Moderate = 139(eGFR = 30–59ml/min); Severe = 23 (eGFR<30ml/min);	8 patients receiving dialysis	48.2 ±14.2	NA	NA
Y amamoto <i>et al</i> , 2013 [49]	642	48.1	83.5 ±6.5	N/A	22.9±12.2	70.6	22.6	N/A	8.	Chronic Kidney Disease: Stage1-2 = 218 (eGFR ⁴ ≥60m/min); Stage3a = 182(eGFR = 45- 59m/min); Stage3b = 181 (eGFR = 30-44m/min); Stage4 = 61(eGFR = 15- 29m/min)	Excluded	52.7 ±14.8	0.64 ±0.17	47.6±17.5
D'Ascenzm <i>et al</i> , 2013 [10]	364	42.3	82.4 ±5.3	6.6 ±4.6	23.2±14.1	86.5	31.0	A/A	23.1	Chronic Kidney Disease; Moderate = 219(eGFR ^a = 30–59ml/min); Severe = 73 (eGFR = 15–29ml/min)	Excluded	52.4 ±11.9	0.62 ±0.18	53.2±17.3
Lange <i>et al,</i> 2012 [<u>50]</u>	420	37	80.3 ±7.1	6.1 ±4.1	20.17±13.0	N/A	NA	55	13.2	Baseline Creatinine = 1.20 ±0.56 mg/dl	Unclear	EF >50: 62.4; 35- 50: 22.1; <35: 15.5	A/A	N/A
Houthuizen et al, 2012 [51]	679	47	81 (77– 85)	N/A	16.0(10.0– 25.0)	N/A	23.6	47.0	17.7	Baseline Creatinine = 1.07 (0.85–1.38)mg/dl	Unclear	EF<50: 28.0	0.7 (0.6– 0.8)	4(36–57)
Gotzmann et al, 2012 [52]	198	47	80±6	N/A	22±16	N/A	N/A	52	N/A	Baseline Creatinine = 1.2 ±0.7 mg/dl	Unclear	53±13	0.7 ±0.1	47±13
Codner <i>et al</i> , 2013 [53]	153	37.9	82.1 ±6.0	9.2 ±5.3	22.5±13.2	90.2	29.4	N/A	18.3	Baseline eGFR = 66.7 ±27.3ml/min/1.73m²	3 patients with ESRD	N/A	0.62 ±0.16	50.5±15.4
Sabaté <i>et al</i> , 2013 [54]	1416	46	81±6	N/A	17±11	78	34	N/A	10	Baseline Creatinine = 1.26 ±0.7 mg/dl	Unclear	56±13	0.6 ±0.2	50±15
													ğ	ontinued)

Table 1. (C	ontinuec	()												
Study	_	Male (%)	Age (y)	STS Score	Logistic Euroscore	Hypertension (%)	Diabetes mellitus	Previous CAD (%)	Previous CE (%)	Renal dysfunction, n (%) / renal function	Baseline	LVEF (%)	Mean AVA	Mean gradient
							(%)			Defined	ESRD		(cm.)	(6100)
Linke <i>et al,</i> 2014 [55]	1015	49	81.1± 6.4	5.3 (3.6– 7.8)	16.0(10.3– 25.3)	N/A	31.3	57.8	13.1	Baseline Creatinine = 1.25 ±0.75 mg/dl; Creatinine clearance<20ml/min = 148 (14.9) ^g	Included	53.3 ±13.7	0.7 ±0.3	45.6±15.5
Unbehaun <i>et al</i> , 2014 [56]	730	39.9	80.1 (75.3– 84.4)	10.4 (6.1– 17.8)	28.8 (18.9– 48.2)	N/A	29.3	61.2	22.2	Baseline Creatinine Clearance = 53.5(38.9–69.4) ml/min	16 patients receiving dialysis	55.0 (40.0– 60.0)	0.6 (0.6– 0.8)	49.5 (38.0– 57.0)
Kodali <i>et al</i> , 2012 [17]	348	57.8	83.6 ±6.8	11.8 ±3.3	29.3±16.5	N/A	N/A	74.9	29.3	Baseline Creatinine>2mg/dl; n = 38(11.1)	Excluded	52.5 ±13.5	0.7 ±0.2	42.7±14.6
Data are pr operative ris eGFR: estir e. Calculate b. Mid-term c. Data avai d. Calculate e. Data avai f. Data avai g. Data avai	esented sk evalus vid by Cov outcome abble in 2 sented av able in 2 lable in 3	as mear ation; <i>CI</i> ation; <i>CI</i> atroft-Gi ckroft-Gi ss availa 1116 par dificatior s medial 396 pati	h±SD or i AD: coror ault (CG) ault (CG) bble in 35 tients. n (minime ients.	median (nary arter formula. 97 patier in Renal al to max	interquartile raial disease; C ial disease; C Disease (MD range).	ange) as approp E: cerebrovasc RD) formula.	niate. Abbre ular event; f	viation used ESRD: end-s	: STS: Socie stage renal d	ity of Thoracic Surgeons; Euisease; LVEF: left ventricula	IroSCORE:	European : action; AV/	system fo	r cardiac alve area;
doi:10.1371/jo	urnal.pone	.0119817.	t001											

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studies, the number of patients with ESRD was unclear. Procedural characteristics and the main outcomes after TAVI are summarized in <u>Table 2</u>.

Mid-Term Outcomes

Mid-term Mortality according to Different Definitions of RD

Defined by the Author. RD was defined by the author in 12 studies, in which either univariate [18–24] or multivariate [16, 20, 22, 40–43] analysis was performed. These studies enrolled 9769 patients, and the mid-term all-cause mortality rate was 23.6%. Patients with RD had a significantly higher risk for all-cause mortality at the mid-term follow-up (pooled univariate HR: 1.69; 95% CI: 1.50–1.90; pooled multivariate HR: 1.47; 95% CI: 1.17–1.84) compared with patients with normal renal function (Fig. 2). In the univariate model, the results were unchanged when individual studies were omitted or if the study included no more than 100 successful TAVI procedures [19] (pooled univariate HR: 1.67; 95% CI: 1.49–1.88). In the multivariate model, the pooled results also remained stable after removing studies in unique populations, such as patients with a EuroSCORE of more than 40% [42] (pooled multivariate HR: 1.45; 95% CI: 1.13–1.86), octogenarians and nonagenarians [43] (pooled multivariate HR: 1.51; 95% CI: 1.14–1.99), or patients without ESRD [16] (pooled multivariate HR: 1.42; 95% CI: 1.13–1.78).

Defined by eGFR. Thirteen studies that included a total of 6,980 patients defined RD as decreased baseline eGFR [5, 8, 9, 25–32, 44, 45]. The mid-term all-cause mortality rate was 24.5%. In patients with RD, mid-term mortality after TAVI was significantly increased compared with that in patients with normal renal function (pooled univariate HR: 1.65; 95% CI: 1.47–1.86; pooled multivariate HR: 1.46; 95% CI: 1.24–1.71) (Fig. 3). In the univariate analysis, the results remained unchanged after excluding the study with a small sample size [28] (pooled univariate HR: 1.65; 95% CI: 1.47–1.85) or the study that focused on patients with a baseline eGFR less than 30 ml/min/1.73 m² [32] (pooled univariate HR: 1.65; 95% CI: 1.47–1.85). Sensitivity analysis of the multivariate model also confirmed the robustness of the results after deleting 2 studies that reported the impact of severe RD (eGFR<30 ml/min/1.73 m²) on the midterm outcomes [44, 45] (pooled multivariate HR: 1.39; 95% CI: 1.18–1.64).

Defined by Serum Creatinine. We identified 11 studies with mid-term mortality data in patients with elevated serum creatinine [6, 15, 33-39, 46, 47] (Fig. 4). The cumulative all-cause mortality rate of these 9210 patients was 17.2%. The pooled univariate HR suggested that patients with RD had a significantly higher mid-term mortality rate (pooled univariate HR: 1.69; 95% CI: 1.48–1.92) than patients with normal renal function. These results persisted when omitting individual studies or the study that reported outcomes in the CLD subgroup [15] (pooled univariate HR: 1.78; 95% CI: 1.54–2.05). This relationship was also observed in the multivariate model (pooled multivariate HR: 1.65; 95% CI: 1.36–1.99). After removing the relatively small study [6] (pooled multivariate HR: 1.58; 95% CI: 1.30–1.92) or the study that reported outcomes in the CLD subgroup [15] (pooled multivariate HR: 1.58; 95% CI: 1.30–1.92), the pooled results were still unchanged.

Association of Mid-term Outcomes with Varying Degrees of RD

Four studies included a detailed classification of CKD according to the baseline eGFR [10, 29, 48, 49], and an additional 4 studies reported the mid-term mortality of patients on chronic dialysis [5, 22, 24, 38].

Compared with patients with CKD stage 1+2, patients with advanced CKD had significantly higher incidences of all-cause bleeding (univariate HR in CKD stage 3: 1.30, 95% CI: 1.13–1.49; in CKD stage 4: 1.30, 95% CI: 1.04–1.62), post-procedural AKI (univariate HR in CKD stage 3:

Study	Appı (?	roach %)	Valve type (%)	Follow-up	Peri	-procedural co	mplications	i	Death (%)	Cardiovascular death (%)
	TF	ТА			Renal Impairment (%)	Bleeding (%)	MVC (%)	Stroke (%)		
Unbehaun <i>et al</i> , 2011 [18]	N/A	N/A	EV: 100	11.7±8.7mo	N/A	1.3	N/A	N/A	65	N/A
Tzikas <i>et al</i> , 2011 [<u>19</u>]	N/A	N/A	MCV: 100	383d(356-419)	N/A	N/A	N/A	N/A	28.6	N/A
Sinning <i>et al</i> , 2012 [<u>20]</u>	91.8	N/A	MCV: 100	1y	AKI: 23.3	N/A	7.5	5.5	26.7	N/A
Vasa- Nicotera <i>et al,</i> 2012 [<u>21]</u>	97.5	1.7	EV: 20.5; MCV: 79.5	1y	N/A	N/A	N/A	N/A	35.2	N/A
Wendler <i>et al</i> , 2013 [<mark>22</mark>]	N/A	100	EV: 100	2у	Dialysis: 6.7	3.9	2.6	2.5	34.9	N/A
Chopard <i>et al</i> , 2014 [<u>23]</u>	73	18	EV: 66; MCV: 33	1y	AKI: 1.6	11	9.1	3.3	19.1	8.8
Muñoz- García <i>et al</i> , 2013 [<u>24]</u>	91.4	N/A	MCV: 100	238d(50–480)	AKI: 11	N/A	3.9	N/A	10.6	N/A
Godino <i>et al</i> , 2010 [<u>25]</u>	78	11	EV: 57.7; MCV: 42.3	6mo	RRT: 8	N/A	16.8	0.7	13.1	5.1
Rodés-Cabau et al, 2010 [5]	47.8	52.2	EV: 100	8mo(3–14)	Dialysis: 2.6	N/A	13.3	2.4	22.1	N/A
Hayashida <i>et al</i> , 2012 [<u>26]</u>	N/A	N/A	EV: 86.8; MCV: 13.2	279d(101–607)	AKI: 9.0	N/A	8.8	6.5	27.3	N/A
Sinning <i>et al</i> , 2012 [<mark>27</mark>]	92.1	N/A	MCV: 100	1y	AKI: 23.0	9.2	8.6	5.3	27	N/A
Nombela- Franco <i>et al</i> , 2012 [<u>8]</u>	68.4	30.3	EV: 64; MCV: 36	12mo(3–23)	N/A	N/A	2.1	N/A	37.8	N/A
Kamaga <i>et al</i> , 2013 [<u>28]</u>	100	N/A	EV: 100	1y	AKI: 2.5	N/A	3.3	N/A	26.7	N/A
Dumonteil <i>et al</i> , 2013 [29]	84.1	9.3	EV: 46.3; MCV: 53.7	1y	AKI in CKD stage 1+2: 25.7; In CKD stage 3: 23.3; In CKD stage 4: 45.8	CKD stage 1 +2: 42.9; CKD stage 3: 56; CKD stage 4: 52.8; CKD stage 5: 42.4	CKD stage 1+2: 6.1; CKD stage 3: 16.7; CKD stage 4: 11; CKD stage 5: 9.6	CKD stage 1+2: 1.8; CKD stage 3: 3; CKD stage 4: 4.2; CKD stage 5: 6.1	18.8	N/A
Mok <i>et al</i> , 2013 [<u>9]</u>	39.2	N/A	EV: 98.7	12mo(7–25)	N/A	10.7	N/A	3.1	29.5	14.4
Zahn <i>et al</i> , 2013 [<u>30]</u>	88	8.6	EV: 17.9; MCV: 81.5	1y	N/A	N/A	N/A	2.8	21.8	N/A
Urena <i>et al</i> , 2014 [<u>31]</u>	N/A	N/A	N/A	22±17mo	N/A	N/A	N/A	N/A	23.4	16.3
Panico et al, 2012 [<mark>32</mark>]	116	N/A	EV: 69.5; MCV: 30.5	1y	AKI: 28.9	22	5.1	7.6	17.8	N/A
Katsanos <i>et al</i> , 2013 [<u>33]</u>	41	59	EV: 100	25mo(13–45)	N/A	N/A	N/A	N/A	18.1	N/A

Table 2. Procedure features and main outcomes of included studies.

(Continued)

Table 2. (Continued)

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Study	Appı (roach %)	Valve type (%)	Follow-up	Per	-procedural co	mplications	;	Death (%)	Cardiovascular death (%)
	TF	ТА			Renal Impairment (%)	Bleeding (%)	MVC (%)	Stroke (%)	-	
Tamburino e <i>t al</i> , 2011 [<u>34]</u>	90.3	N/A	MCV: 100	1y	N/A	N/A	1.96	1.2	17.2	N/A
Barbanti <i>et al</i> , 2014 [<u>35</u>]	66.2	33.2	EV: 93.2; MCV: 3.1	2у	N/A	N/A	N/A	N/A	22.8	5.8
Dvir <i>et al</i> , 2014 [<u>15</u>]	N/A	N/A	N/A	1y	N/A	N/A	N/A	N/A	23.4	10.2
Moat <i>et al</i> , 2011 [<u>36]</u>	68.9	N/A	EV: 47.1; MCV: 52.9	1y	N/A	N/A	4	N/A	21.4	N/A
Seiffert <i>et al</i> , 2013 [<u>37]</u>	45.7	52.3	EV: 86.2; MCV: 13.8	1y	AKI: 29.4	7.4	8.6	5.8	29.8	18.7
Luçon et a/, 2014 [<u>38]</u>	74.9	17.5	EV: 67.3; MCV: 32.7	1y	N/A	N/A	1.6	N/A	16.4	10
Heinz <i>et al</i> , 2014 [39]	45	44	N/A	1y	AKI: 55.5	N/A	5	2	27	N/A
Web <i>et al</i> , 2009 [40]	79.2	20.7	EV: 100	221d ^a	AKI: 6.0; Dialysis: 1.8	N/A	6.5	4.2	39.1	N/A
Ben-Dor <i>et al</i> , 2012 [16]	69.1	30.9	EV: 100	399d(167–669)	N/A	N/A	N/A	N/A	30.8	7.5
Nuis <i>et al</i> , 2012 [41]	97	3	MCV: 100	298d(107-688)	AKI: 17	8.9	10.2	4.6	31.1	N/A
Drews <i>et al</i> , 2013 [<u>42]</u>	N/A	100	EV: 100)	2у	N/A	N/A	N/A	N/A	46	N/A
Yamamoto <i>et al</i> , 2014 [<u>43]</u>	79.06	16.42	EV: 68.5; MCV: 31.5	1y	Dialysis: 1.4	1.2	5	2.5	16.9 ^b	N/A
Saia <i>et al</i> , 2013 [<u>44]</u>	64.7	23.5	EV: 35.3; MCV: 64.7	1y	AKI: 41.2	4.9	N/A	2	11.8	N/A
Conrotto <i>et al</i> , 2014 [<u>45]</u>	57.7	23.3	EV: 53.2; MCV: 46.8	400d(178–715)	AKI: 21.1	43.1	7	1.8	20.4	11.9
Sinning <i>et al</i> , 2010 [<u>6]</u>	100	N/A	MCV: 100	1y	AKI: 26	N/A	N/A	N/A	26	N/A
Tamburino <i>et al</i> , 2012 [<u>46]</u>	97.2	1.8	EV: 11; MCV: 89	1y	N/A	5.5	N/A	2.3	12.4	N/A
Van Belle <i>et al</i> , 2014 [<u>47]</u>	75.3	17.2	EV: 11; MCV: 89	306d(178–490)	N/A	N/A	N/A	N/A	11.3	6.3
Nguyen <i>et al,</i> 2013 [<u>48</u>]	62	31	N/A	4 y	Dialysis: 1.9	CKD stage 1 +2: 0.6; CKD stage 3: 1.4; CKD stage 4: 0	N/A	CKD stage 1+2: 1.3; CKD stage 3: 1.4; CKD stage 4: 4.4	N/A	N/A
Yamamoto <i>et al</i> , 2013 [49]	67.1	N/A	EV: 62.9; MCV: 37.1	1y	AKI in CKD stage 1+2: 13.3; in CKD stage 3: 17.1; in CKD stage 4: 15	N/A	CKD stage 1+2: 7.3; CKD stage 3: 8.3; CKD stage 4: 9.8	CKD stage 1+2: 1.8; CKD stage 3: 3.6; CKD stage 4: 8.2	25.2	N/A

(Continued)

Table 2. (Continued)

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Study	App (roach %)	Valve type (%)	Follow-up	Per	i-procedural co	mplications	•	Death (%)	Cardiovascular death (%)
	TF	ТА			Renal Impairment (%)	Bleeding (%)	MVC (%)	Stroke (%)	-	
D'Ascenzm <i>et al</i> , 2013 [10]	69.5	5.8	N/A	450±250d	AKI in CKD stage 1+2: 8; in CKD stage 3: 14; in CKD stage 4: 18	CKD stage 1 +2: 20; CKD stage 3: 22; CKD stage 4: 33	CKD stage 1+2: 10; CKD stage 3: 7; CKD stage 4: 10	CKD stage 1+2: 1.4; CKD stage 3: 2.3; CKD stage 4: 4.1	17.6	10.2
Lange <i>et al</i> , 2012 [<u>50]</u>	61	31	EV: 30.6; MCV: 68.7	6mo	N/A	N/A	18.6	4.5	20	N/A
Houthuizen <i>et al</i> , 2012 [<u>51]</u>	68.2	30.3	EV: 43; MCV: 57	450d ^a	N/A	N/A	N/A	N/A	28.7	N/A
Gotzmann <i>et al,</i> 2012 [<u>52]</u>	N/A	N/A	MCV: 100	535±333d	Dialysis: 2.5	N/A	N/A	2	27.8	16.7
Codner <i>et al</i> , 2013 [<u>53]</u>	73.2	17.6	EV: 40.5; MCV: 59.5	2у	AKI: 5.2	2.6	1.3	3.9	11.8	4.6
Sabaté <i>et al</i> , 2013 [<u>54]</u>	78.7	21.3	EV: 56.9; MCV: 43.1	244d ^c	AKI ^d : 1.0	2.4	3	2.6	15.9	N/A
Linke <i>et al</i> , 2014 [<u>55]</u>	88.4	2.1	MCV: 100	1у	AKI ^d : 6.0	13.8	10.9	3	17.9 ^e	11.7 ^e
Unbehaun <i>et al</i> , 2014 [<u>56]</u>	N/A	100	EV: 100	1.56y(0.40-2.69)	AKI: 18.6; RRT: 3.0	9.7	4	2.3	41.1	N/A
Kodali <i>et al</i> , 2012 [<u>17]</u>	244	104	EV: 100	2у	AKI: 1.2	9.3	11	4.7	33.3	19.3

Data are presented as mean±SD or median (interquartile range) as appropriate. Abbreviation used: TF: trans-femoral; TA: trans-apical; MVC: major vascular complications; EV: Edwards Valve; MCV: Medtronic CoreValve; AKI: acute kidney injure; RRT: renal replacement therapy.

a. Data presented as a median.

b. Data available in 2249 patients.

c. Data presented as a mean.

d. Defined as stage 3 according to the Valve Academic Research Consortium (VARC).

e. Data available in 996 patients.

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1.28, 95% CI: 1.03–1.59; in CKD stage 4: 2.27, 95% CI: 1.74–2.96), and stroke (univariate HR in CKD stage 4: 3.37, 95% CI: 1.52–7.46). Major vascular complications (MVC) were without significant difference according to baseline renal function status (Fig. 5). Compared with CKD stage 3, CKD stage 4 was strongly related to a higher incidence of AKI ((univariate HR: 1.70, 95% CI: 1.34–2.16), however, this difference was not significant when focusing on bleeding or stroke (Fig. 6). Sensitivity analyses were not conducted due to the small number of studies in each groups.

At mid-term follow-up, advanced CKD was significantly related to a poorer prognosis compared with CKD stage 1+2 (pooled univariate HR in CKD stage 3: 1.57, 95% CI: 1.26–1.95; in CKD stage 4: 2.77, 95% CI: 2.06–3.72; in CKD stage 5: 2.64, 95% CI: 1.91–3.65). Moreover, compared with patients with CKD stage 3, mortality was significantly increased in patients with CKD stage 4 (pooled univariate HR: 1.60, 95% CI: 1.28–1.99) (Fig. 7). These results persisted after omitting individual studies in the CKD stage 5 group. Due to the small number of studies, sensitivity analyses were not performed in the other groups.

A total of 9 studies that included 5,266 patients were eligible for the pooled analysis of baseline serum creatinine (for each increase of 1 mg/dl) with respect to mid-term outcomes [18, 37,

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				Hazard Ratio	Hazar	d Ratio		
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixe	d, 95% CI		
Chopard 2014	0.5016	0.0839	50.8%	1.65 [1.40, 1.95]				
Muñoz-García 2013	0.1085	0.67	0.8%	1.11 [0.30, 4.14]		<u> </u>		
Sinning 2012	0.7129	0.3589	2.8%	2.04 [1.01, 4.12]		— —		
Tzikas 2011	0.9675	0.4237	2.0%	2.63 [1.15, 6.04]				
Unbehaun 2011	0.5917	0.277	4.7%	1.81 [1.05, 3.11]		 		
Vasa-Nicotera 2012	0.8047	0.4106	2.1%	2.24 [1.00, 5.00]		<u>├</u>		
Wendler 2013	0.5008	0.0986	36.8%	1.65 [1.36, 2.00]		-		
Total (95% CI)			100.0%	1.69 [1.50, 1.90]		•		
Heterogeneity: Chi ² = 2	.41, df = 6 (P = 0.88)); I² = 0%				1 1	<u> </u>	100
Test for overall effect: Z	= 8.76 (P < 0.0000)	1)			Patients without RD	Patients	with F	RD

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D				Hazard Ratio	Haza	rd Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Rand	om, 95% Cl	
Ben-Dor 2012	0.8511	0.395	6.5%	2.34 [1.08, 5.08]			
Drews 2013	0.4972	0.2436	12.4%	1.64 [1.02, 2.65]			
Nuis 2012	0.1687	0.0583	26.1%	1.18 [1.06, 1.33]		•	
Sinning 2012	-0.4586	0.434	5.6%	0.63 [0.27, 1.48]		+	
Web 2009	1.2483	0.3433	8.0%	3.48 [1.78, 6.83]			
Wendler 2013	0.3864	0.0999	23.1%	1.47 [1.21, 1.79]		+	
Yamamoto 2014	0.3282	0.1573	18.3%	1.39 [1.02, 1.89]		-	
Total (95% CI)			100.0%	1.47 [1.17, 1.84]		•	
Heterogeneity: Tau ² =	0.05; Chi ² = 18.46, d	if = 6 (P =	= 0.005); I	²= 67%		1 10	100
Test for overall effect:	Z = 3.34 (P = 0.0008)			Patients without RD	Patients with R	D

Fig 2. Forest plots of mid-term mortality associated with RD. A, Pooled univariate hazard ratio of patients without RD compared with patients with RD. B, Pooled multivariate hazard ratio of patients without RD compared with patients with RD. RD, renal dysfunction; CI, confidence interval; Fixed, fixed-effects model; Random, Random-effects model; IV, Generic Inverse Variance method.

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50-56] (Fig. 8). The cumulative mortality after TAVI was 24.1%. Each 1 mg/dl increase in serum creatinine significantly raised the mid-term all-cause mortality rate (pooled univariate HR: 1.24, 95% CI: 1.18–1.30; pooled multivariate HR: 1.19, 95% CI: 1.08–1.30). The pooled results remained stable when individual studies in the univariate model were omitted and also persisted in the multivariate analysis after removing the study that excluded patients with ESRD [18] (pooled multivariate HR: 1.24, 95% CI: 1.16–1.32).

The study by Le Ven et al [57] reported a similar finding with regard to baseline eGFR; specifically, each 10 ml/min decrease was found to be associated with a significantly higher risk of all-cause mortality after TAVI (univariate HR: 1.14, 95% CI: 1.07–1.22; multivariate HR: 1.14, 95% CI: 1.07–1.22).

Publication Bias

Although a subtle publication bias was observed in the funnel plot inspection comparing patients with RD (defined as decreased eGFR) with patients with normal renal function in the univariate model, the pooled estimates remained significant after implementing the "Trim and

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				Risk Ratio	Risk Ratio	
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	_
GFR<60						
Dumonteil 2013	0.5783	0.1462	16.4%	1.78 [1.34, 2.37]		
Godino 2010	1.002	0.4458	1.8%	2.72 [1.14, 6.53]		
Hayashida 2012	0.6275	0.2158	7.5%	1.87 [1.23, 2.86]		
Kamaga 2013	1.5404	1.002	0.3%	4.67 [0.65, 33.26]		
Mok 2013	0.47	0.2277	6.8%	1.60 [1.02, 2.50]		
Nombela-Franco 2012	0.41	0.1191	24.7%	1.51 [1.19, 1.90]		
Rodés-Cabau 2010	0.5607	0.2252	6.9%	1.75 [1.13, 2.72]		
Sinning 2012	0.7419	0.3594	2.7%	2.10 [1.04, 4.25]		
Urena 2014	0.1043	0.2271	6.8%	1.11 [0.71, 1.73]	+	
Zahn 2013	0.5224	0.119	24.8%	1.69 [1.34, 2.13]		
Subtotal (95% CI)			98.7%	1.65 [1.47, 1.85]	•	
Heterogeneity: Chi ² = 7.1	7, df = 9 (P = 0.62); I ^z = 0%				
Test for overall effect: Z =	8.39 (P < 0.0000	1)				
GFR<30						
Panico 2012	0.7024	0.5183	1.3%	2.02 [0.73, 5.57]	+	
Total (95% CI)			100.0%	1.65 [1.47, 1.86]	•	
Heterogeneity: Chi2 = 7.3	2, df = 10 (P = 0.7	0); l² = 09	6			
Test for overall effect: Z =	8.49 (P < 0.0000)	1)			Patients without RD Patients with PD	
Test for subaroup differen	nces: Chi² = 0.15.	df = 1 (P	= 0.70), P	² = 0%	Faterits without ND Faterits with ND	

В				Hazard Datia	Uazar	d Datia	
				Hazaru Kauo	Hazai		
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixe	d <u>, 95% Cl</u>	
GFR<60							
Mok 2013	0.1734	0.2778	8.5%	1.19 [0.69, 2.05]	-	-	
Nombela-Franco 2012	0.2423	0.1288	39.5%	1.27 [0.99, 1.64]		F	
Rodés-Cabau 2010	0.8329	0.2614	9.6%	2.30 [1.38, 3.84]			
Zahn 2013	0.3286	0.1379	34.5%	1.39 [1.06, 1.82]		-	
Subtotal (95% CI)			92.2%	1.39 [1.18, 1.64]		•	
Heterogeneity: Chi ² = 4.4	8, df = 3 (P = 0.21); P	²= 33%					
Test for overall effect: Z =	3.91 (P < 0.0001)						
GFR<30							
Conrotto 2014	0.7419	0.3162	6.6%	2.10 [1.13, 3.90]			
Saia 2013	1.748	0.7137	1.3%	5.74 [1.42. 23.26]			
Total (95% CI)			100.0%	1.46 [1.24, 1.71]		•	
Heterogeneity: Chi ² = 9.8	2, df = 5 (P = 0.08); P	²= 49%					400
Test for overall effect: Z =	4.63 (P < 0.00001)				0.01 0.1 Detients without DD	T TU Detiente with	100
Test for subaroup differe	nces: Chi² = 3.67. df	= 1 (P = 1	0.06). I ^z =	72.8%	Fallents without RD	Patients with	RD

Fig 3. Forest plots of mid-term mortality associated with RD. A, Pooled univariate hazard ratio of patients without RD compared with patients with RD. B, Pooled multivariate hazard ratio of patients without RD compared with patients with RD. RD, renal dysfunction; CI, confidence interval; Fixed, fixed-effects model; IV, Generic Inverse Variance method.

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/ \				Hazard Ratio	Hazard Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	_
Creatinine>133umol/I						
Sinning 2010	1.3606	0.4544	4.5%	3.90 [1.60, 9.50]		
Tamburino 2012	0.8171	0.4133	5.5%	2.26 [1.01, 5.09]		
Creatinine>177umol/l						
Barbanti 2014	0.3564	0.2141	20.3%	1.43 [0.94, 2.17]	+	
Dvir 2014	0.3589	0.1831	27.8%	1.43 [1.00, 2.05]	-	
Creatinine>200umol/l						
Moat 2011	0.4402	0.2784	12.0%	1.55 [0.90, 2.68]	+	
Van Belle 2014	0.5617	0.1768	29.8%	1.75 [1.24, 2.48]	-	
Total (95% CI)			100.0%	1.65 [1.36, 1.99]		
Heterogeneity: Chi ² = 9	5.39, df = 5 (P = 0.37	7); l² = 7%	6			
Test for overall effect: J	Z = 5.17 (P < 0.0000	11)			Patients without RD Patients with RD	
Test for subaroup diffe	erences: Chi² = 4.47	. df = 2 (F	P = 0.11).	I² = 55.2%		

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_				Hazard Ratio	Hazard Ratio			
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI			
Creatinine>106umol/								
Katsanos 2013	0.01	0.4477	2.2%	1.01 [0.42. 2.43]				
Creatinine>133umol/	I							
Tamburino 2011	0.5149	0.1709	14.8%	1.67 [1.20, 2.34]	-			
Creatinine>177umol/	I							
Barbanti 2014	0.477	0.1941	11.5%	1.61 [1.10, 2.36]				
Dvir 2014	0.3016	0.1488	19.6%	1.35 [1.01, 1.81]	-			
Heinz 2014	0.9933	0.5276	1.6%	2.70 [0.96, 7.59]				
Subtotal (95% CI)			32.6%	1.49 [1.19, 1.86]	◆			
Heterogeneity: Chi ² = 1	1.86, df = 2 (P = 0.39	3); I² = 0%	6					
Test for overall effect: 2	Z = 3.44 (P = 0.0006	i)						
Creatinine>200umol/	I							
Lucon 2014	0.6635	0.111	35.2%	1.94 [1.56, 2.41]				
Moat 2011	0.5137	0.198	11.1%	1.67 [1.13, 2.46]				
Seiffert 2013	0.6227	0.3244	4.1%	1.86 [0.99, 3.52]				
Subtotal (95% CI)			50.4%	1.87 [1.56, 2.25]	♦			
Heterogeneity: Chi ² =	0.44, df = 2 (P = 0.80	0); I ² = 0%	6					
Test for overall effect:	Z = 6.76 (P < 0.0000	1)						
T-4-140544 00								
Total (95% CI)			100.0%	1.69 [1.48, 1.92]				
Heterogeneity: Chi ² =	6.08, df = 7 (P = 0.53	3); I ² = 0%	6		0.01 0.1 1 10 100			
Test for overall effect:	Z = 7.93 (P < 0.0000	11)			Patients without RD Patients with RD			
Test for subaroup differences: Chi ² = 3.78. df = 3 (P = 0.29). I ² = 20.7%								

Fig 4. Forest plots of mid-term mortality associated with RD. A, Pooled univariate hazard ratio of patients without RD compared with patients with RD. B, Pooled multivariate hazard ratio of patients without RD compared with patients with RD. RD, renal dysfunction; CI, confidence interval; Fixed, fixed-effects model; IV, Generic Inverse Variance method.

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			Patients with RD	Patients without RD		Hazard Ratio	Hazard Batio
Study or Subgroup log	[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
CKD Stage 3							
D'Ascenzo 2013	-0.3503	0.4371	219	72	12.7%	0.70 [0.30, 1.66]	
Dumonteil 2013	0.2792	0.2019	339	438	59.7%	1.32 [0.89, 1.96]	
Yamamoto 2013	0.1187	0.2975	363	218	27.5%	1.13 [0.63, 2.02]	T
Heterogeneity Chi?= 1 72	df= 2/P= 0.4	21-17=09	921	120	100.0%	1.17 [0.60, 1.59]	Ť
Test for overall effect Z = 1	0.99 (P = 0.32)	2), 1 = 0 9	•				
CKD Stage 4							
D'Ascenzo 2013	-0.0138	0.5081	73	72	19.6%	0.99 [0.36, 2.67]	
Dumonteil 2013	0.5293	0.3007	72	438	56.0%	1.70 [0.94, 3.06]	
Yamamoto 2013	0.2928	0.4563	61	218	24.3%	1.34 [0.55, 3.28]	
Subtotal (95% CI)			206	728	100.0%	1.44 [0.93, 2.24]	-
Heterogeneity: Chi* = 0.88	$f_{1} \text{ of } = 2 (P = 0.6)$	4); I* = U%	6				
restion overall ellect. Z =	1.62 (P = 0.10)						
							0.01 0.1 1 10 100
							Faterits without RD Faterits with RD
R							
D			0-1-1-1-00	0-1		line of Deter	United Dates
Study or Subaroup log	[Hazard Datio]	CE.	Patients with KD	Patients without RD	Moight	Hazard Ratio	Hazard Ratio
CKD Stage 3	mazara Radoj	36	Total	Total	weight	IV, FIXed, 55% CI	IV, HXed, 554 CI
D'Ascenzo 2013	0.1197	0 2717	219	72	6.7%	1 13 10 66 1 921	-
Dumonteil 2013	0.2668	0.0731	339	438	92.9%	1.31 [1.13, 1.51]	
Nguyen 2013	0.8276	1.2192	139	159	0.3%	2.29 [0.21, 24.96]	— <u>—</u>
Subtotal (95% CI)			697	669	100.0%	1.30 [1.13, 1.49]	•
Heterogeneity: Chi ² = 0.49	df = 2 (P = 0.78	s); I ² = 0%					
Test for overall effect: Z = 3	8.67 (P = 0.0002)					
010 01000							
CKU Stage 4	0 6262	0.2024	70	20	15.29	1 60 10 06 2 000	
Dumonteil 2013	0.5252	0.2324	73	/2	84.2%	1.09 [0.95, 3.00]	-
Nauven 2013	1 204	1.6118	12	438	0.5%	3.33 [0.14 78 60]	
Subtotal (95% CI)	1.204	1.0110	160	669	100.0%	1.30 [1.04, 1.62]	•
Heterogeneity: Chi ² = 1.35	df = 2 (P = 0.51); I ² = 0%					
Test for overall effect: Z = 2	2.28 (P = 0.02)						
							0.01 0.1 1 10 100
							Patients without RD Patients with RD
0							
C							
			Datients with RD	Patients without RD		Hazard Ratio	Hazard Patio
Study or Subgroup log	[Hazard Ratio]	SE	Total	Total	Weight	IV. Fixed, 95% CI	IV. Fixed, 95% CI
CKD Stage 3	Interest of the second			10101		11111111111111111111111	
D'Ascenzo 2013	0.5298	0.4248	219	72	6.6%	1.70 [0.74, 3.91]	+
Dumonteil 2013	0.2191	0.1348	399	438	65.8%	1.24 [0.96, 1.62]	#
Yamamoto 2013	0.2499	0.208	363	218	27.6%	1.28 [0.85, 1.93]	+
Subtotal (95% CI)			981	728	100.0%	1.28 [1.03, 1.59]	•
Heterogeneity: Chi ² = 0.49	, df = 2 (P = 0.7)	B); I ² = 09	6				
Test for overall effect: Z = 2	2.27 (P = 0.02)						
CKD Stage 4							
D'Acconto 2012	0.7504	0 4640	72	72	0.496	2 1 4 10 96 5 211	
Dumonteil 2013	0.8953	0.4040	73	438	68.9%	2 45 [1 78 3 36]	
Yamamoto 2013	0.6144	0.2831	61	218	22.7%	1.85 [1.06, 3.22]	
Subtotal (95% CI)			206	728	100.0%	2.27 [1.74, 2.96]	•
Heterogeneity: Chi2 = 0.76	, df = 2 (P = 0.6)	B); I ² = 09	6				
Test for overall effect Z = 6	6.09 (P < 0.0000	11)					
							0.01 0.1 1 10 100
							Patients without RD Patients with RD
1000							
П							
D							
Chudu as Cub-	filment Device		Patients with RD	Patients without RD	1110-0-1	Hazard Ratio	Hazard Ratio
Study or Subgroup log	mazard Ratio	SE	Total	Total	weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Diacconto 2013	0.497	1.087	210	70	8.6%	1 64 10 20 12 941	
Dumonteil 2013	0.4927	0.4512	300	A20	49.6%	1.65 [0.68 3 99]	- +
Nauven 2013	0.1344	0.9932	139	159	10.2%	1.14 [0.16 8.01]	
Yamamoto 2013	0.6687	0.5653	363	218	31.6%	1.95 [0.64, 5.91]	+-
Subtotal (95% CI)			1120	887	100.0%	1.67 [0.90, 3.12]	◆
Heterogeneity: Chi# = 0.22	df = 3 (P = 0.97); I ² = 0%					
Test for overall effect: Z = 1	.62 (P = 0.11)						
0110 01 1							
CKD Stage 4							
CKD Stage 4 D'Ascenzo 2013	1.0848	1.1427	73	72	12.6%	2.96 [0.32, 27.78]	
CKD Stage 4 D'Ascenzo 2013 Dumonteil 2013	1.0848	1.1427	73 72	72 438	12.6%	2.96 [0.32, 27.78] 2.28 [0.62, 8.40]	
CKD Stage 4 D'Ascenzo 2013 Dumonteil 2013 Nguyen 2013 Vamamuta 2012	1.0848 0.8247 1.6677	1.1427 0.665 1.1946	73 72 15	72 438 159	12.6% 37.3% 11.6%	2.96 [0.32, 27.78] 2.28 [0.62, 8.40] 5.30 [0.51, 55.10]	
CKD Stage 4 D'Ascenzo 2013 Dumonteil 2013 Nguyen 2013 Yamamoto 2013 Subtotal (95% Ch	1.0848 0.8247 1.6677 1.4968	1.1427 0.665 1.1946 0.655	73 72 15 61	72 438 159 218 897	12.6% 37.3% 11.6% 38.5%	2.96 [0.32, 27.78] 2.28 [0.62, 8.40] 5.30 [0.51, 55.10] 4.47 [1.24, 16.13] 3.37 [1.52, 7.46]	
CKD Stage 4 D'Ascenzo 2013 Dumonteil 2013 Nguyen 2013 Yamamoto 2013 Subtotal (95% CI) Heterogeneity: Chi ^a = 0.69	1.0848 0.8247 1.6677 1.4968 df = 3 (P = 0.95	1.1427 0.665 1.1946 0.655	73 72 15 61 221	72 438 159 218 887	12.6% 37.3% 11.6% 38.5% 100.0%	2.96 [0.32, 27.78] 2.28 [0.62, 8.40] 5.30 [0.51, 55.10] 4.47 [1.24, 16.13] 3.37 [1.52, 7.46]	
CKD Stage 4 D'Ascenzo 2013 Dumonteil 2013 Nguyen 2013 Yamamoto 2013 Subtotal (95% CI) Heterogeneity: Chi ^a = 0.69 Test for overall effect Z = 2	1.0848 0.8247 1.6677 1.4968 , df = 3 (P = 0.88 2.99 (P = 0.003)	1.1427 0.665 1.1946 0.655 I); I ² = 0%	73 72 15 61 221	72 438 159 218 887	12.6% 37.3% 11.6% 38.5% 100.0%	2.96 [0.32, 27.78] 2.28 [0.62, 8.40] 5.30 [0.51, 55.10] 4.47 [1.24, 16.13] 3.37 [1.52, 7.46]	
CKD Stage 4 D'Ascenzo 2013 Dumonteli 2013 Nguyen 2013 Yamamoto 2013 Subtotal (95% Cl) Heterogeneity: Chi ^a = 0.69 Test for overall effect. Z = 2	1.0848 0.8247 1.6677 1.4968 , df = 3 (P = 0.88 2.99 (P = 0.003)	1.1427 0.665 1.1946 0.655 I); I ² = 0%	73 72 15 61 221	72 438 159 218 887	12.6% 37.3% 11.6% 38.5% 100.0%	2.96 [0.32, 27.78] 2.28 [0.62, 8.40] 5.30 [0.51, 55.10] 4.47 [1.24, 16.13] 3.37 [1.52, 7.46]	
CKD Stage 4 D'Ascenzo 2013 Dumonteli 2013 Nguyen 2013 Yamamoto 2013 Subtotal (95% Cl) Heterogeneity: Chi ^a = 0.69 Test for overall effect. Z = 2	1.0848 0.8247 1.6677 1.4968 df= 3 (P = 0.88 2.99 (P = 0.003)	1.1427 0.665 1.1946 0.655 0); I ^a = 0%	73 72 15 61 221	72 438 159 218 887	12.6% 37.3% 11.6% 38.5% 100.0%	2.96 [0.32, 27.78] 2.28 [0.62, 8.40] 5.30 [0.51, 55.10] 4.47 [1.24, 16.13] 3.37 [1.52, 7.46]	

Fig 5. Forest plots of peri-procedural complications associated with RD. A, Pooled univariate hazard ratio of patients without RD compared with patients with RD for all-cause bleeding. B, Pooled univariate hazard ratio of patients without RD compared with patients with RD for major vascular complications. C, Pooled univariate hazard ratio of patients without RD compared with patients with RD for acute kidney injure. D, Pooled univariate hazard ratio of patients without RD compared with patients with RD for stroke. RD, renal dysfunction; CI, confidence interval; Fixed, fixed-effects model; IV, Generic Inverse Variance method.

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A			Datients with CKD Stane A	Patients with CKD Stage 3		Hazard Ratio	Hazard Ratio
Study or Subgroup	Ion[Hazard Ratio]	SE	Total	Total	Weight	IV Fixed 05% CI	IV Fixed 95% CI
Diacconto 2012	0.4055	0.2102	72	210	25.4%	1 50 10 00 2 271	
Dumontoil 2012	0.4033	0.1222	73	213	74 106	1 11 0 97 1 411	-
Nauvon 2012	0.1029	1 6266	12	120	0.6%	1 76 0 00 24 971	
Nguyen 2013	0.5590	1.5200	15	155	0.3%	1.75 [0.08, 54.07]	
Total (95% CI)			160	757	100.0%	1.20 [0.97, 1.48]	•
Heterogeneity: Chi ² =	1.60, df = 2 (P = 0.45	5); I ² = 09	b.				
Test for overall effect:	Z = 1.72 (P = 0.09)						0.01 0.1 1 10 100
							Patients with CKD Stage 3 Patients with CKD Stage 4
в							
D			Patients with CKD Stage 4	Patients with CKD Stage 3		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Tota	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
D'Ascenzo 2013	0.2296	0.3015	73	219	16.4%	1.26 [0.70, 2.27]	
Dumonteil 2013	0.6762	0.157	27	399	60.3%	1.97 [1.45, 2.67]	-
Yamamoto 2013	0.3644	0.2523	61	363	23.3%	1.44 [0.88, 2.36]	
Total (95% CI)			161	981	100.0%	1.70 [1.34, 2.16]	•
Heterogeneity: Chi ² =	2.29, df = 2 (P = 0.3)	2); I ² = 13	1%				
Test for overall effect:	Z = 4.35 (P < 0.0001	1)					U.U1 U.1 1 10 100
							Patients with CKD Stage 3 Patients with CKD Stage 4
С							
Chudu an Cubanau	In office and Detical		Patients with CKD Stage 4	Patients with CKD Stage 3	Mainha	Hazard Ratio	Hazard Ratio
Study of Subgroup	log Hazard Ratio	0 74 77	Total	Total	vveight	IV, FIXed, 95% CI	IV, FIXed, 95% CI
D'Ascenzo 2013	0.5878	0.7177	13	219	21.0%	1.80 [0.44, 7.35]	
Dumonteil 2013	-0.2336	0.6038	12	399	29.6%	0.79 [0.24, 2.59]	-
Nguyen 2013	1.5333	1.1942	15	139	7.6%	4.63 [0.45, 48.13]	
ramamoto 2013	0.828	0.5077	61	363	41.9%	2.29 [0.85, 6.19]	
Total (95% CI)			221	1120	100.0%	1.68 [0.88, 3.19]	◆
Heterogeneity: Chi ² =	2.65, df = 3 (P = 0.45	5); I ² = 09	6				
Test for overall effect:	Z = 1.57 (P = 0.12)						0.01 0.1 1 10 100
							Patients with CKD Stage 3 Patients with CKD Stage 4

Fig 6. Patients with CKD stage 3 versus patients with CKD stage 4 for peri-procedural complications. A, Pooled univariate hazard ratio of CKD stage 3 compared with CKD stage 4 for acute kidney injure. C, Pooled univariate hazard ratio of CKD stage 3 compared with CKD stage 3 compared with CKD stage 3 compared with CKD stage 4 for acute kidney injure. C, Pooled univariate hazard ratio of CKD stage 3 compared with CKD stage 4 for stroke. RD, renal dysfunction; CI, confidence interval; Fixed, fixed-effects model; IV, Generic Inverse Variance method.

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Fill" method. In the rest of the analyses, funnel plots, Begg's test and Egger's test did not provide clear evidence for publication bias (S1-S5 Figs).

Discussion

The present study is the first to conduct pooled analyses (using both univariate and multivariate models) of the mid-term prognostic value of RD after TAVI. Preexisting RD, despite different definitions, was found to be associated with significantly increased mid-term mortality. Although it has been clearly demonstrated that aging patients with symptomatic AS have a high prevalence of RD, only a few TAVI studies have treated RD as a component of the primary study question, and the results have been conflicting [6, 7, 10, 29, 44, 48, 49, 58]. By conducting this meta-analysis, we have clearly shown a correlation between mid-term outcome and baseline renal function, as reflected by either baseline eGFR or serum creatinine.

Varying degrees of RD, as classified by advanced stages of CKD, were associated with significantly higher incidences of bleeding, AKI, and mid-term mortality after TAVI. Post-procedural stroke occurred more frequently in patients with CKD stage 4 compared with CKD 1+2. These findings were in line with previous TAVI studies focusing on the peri-procedural complications [8, 44, 59]. However, differences about the incidence of MVC were not significant in our study. At mid-term follow-up, patients with CKD stage 4 were noted to have a poorer prognosis compared with patients with CKD stage 3. This graded association was further confirmed when considering baseline serum creatinine (for each 1 mg/mL decrease), which was also strongly related to increased mid-term mortality. In previous studies, advanced stages of



Λ

A			CKD	No-CKD		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV. Random, 95% (CI IV. Random, 95% CI
CKD Stage3							
D'Ascenzo 2013	0.6794	0.385	219	72	8.4%	1.97 [0.93, 4.2]	[c
Dumonteil 2013	0.4148	0.158	399	438	50.1%	1.51 [1.11, 2.0]	õ] 🗖
Yamamoto 2013	0.4435	0.1735	363	218	41.5%	1.56 [1.11, 2.1	3] 🕂 🕂
Subtotal (95% CI)			981	728	100.0%	1.57 [1.26, 1.9	5]
Heterogeneity: Tau ² = I	0.00; Chi ² = 0.41, df	= 2 (P = 1	0.82); P	²=0%			
Test for overall effect: 2	Z = 4.02 (P < 0.0001))					
CKD Stage 4							
D'Accenzo 2012	0 7492	0.4265	70	72	12.5%	2 1 1 10 0 2 1 9	21
Dumonteil 2013	0.7403	0.4203	73	438	53.1%	2.57 [0.52, 4.0	5) 7)
Vamamoto 2013	1 2636	0.2007	61	218	34.5%	3.54 [2.14, 5.8]	51 -
Subtotal (95% CI)	1.2000	0.2000	206	728	100.0%	2.77 [2.06, 3.72	21 •
Heterogeneity: Tau ² = 1	0.00: Chi ² = 1.53. df	= 2 (P = 1	0.47): P	²= 0%			*
Test for overall effect: 2	Z = 6.77 (P < 0.0000	1)					
CKD Stage 5							
Dumonteil 2013	1 2333	0 2265	33	438	23.4%	3 43 12 20 5 3	51
Lucon 2014	0.7922	0.2200	63	2207	28.4%	2 21 [1 56 3 1/	41 -
Muñoz-García 2013	1 4864	0.2897	15	1099	18.3%	4 42 [2 51 7 8]	
Rodés-Cabau 2010	0.6577	0.5197	10	148	8.1%	1.93 [0.70, 5.3]	51
Wendler 2013	0.6156	0.2416	18	955	22.1%	1.85 [1.15, 2.9]	
Subtotal (95% CI)			139	4847	100.0%	2.64 [1.91, 3.65	5] 🔶
Heterogeneity: Tau ² = 1	0.06; Chi ² = 8.00, df	= 4 (P = 0	0.09); P	²= 50%			
Test for overall effect: 2	Z = 5.90 (P < 0.0000	1)					
							0.01 0.1 1 10 100
							Patients without RD Patients with RD
Р							
Б							
Chudu an Cultura I	a office and Dotion	Cł	CD Stag	Je 3 CKD	Stage 4	Hazard R	Atio Hazard Ratio
Study of Subgroup 1		3E 2697		262	<u>10tâl</u>	17.5% 1.07.00.6	95% CI IV, FIXED, 95% CI
Diascenzo 2013 Dumontoil 2012	0.009 0	1042		202	72	22.6% 1.66.(1.17	, i.orj 1.o. 401 –

D'Ascenzo 2013	0.069	0.2687	363	61	17.5%	1.07 [0.63, 1.81]			—		
Dumonteil 2013	0.5083	0.1943	399	72	33.5%	1.66 [1.14, 2.43]			-		
Yamamoto 2013	0.5865	0.1605	219	73	49.0%	1.80 [1.31, 2.46]			-		
Total (95% CI)			981	206	100.0%	1.60 [1.28, 1.99]			•		
Heterogeneity: Chi ² = 2.79, d	f = 2 (P = 0.25)	5); I ² = 28%					0.01	0.1	1	10	100
lest for overall effect: Z = 4.1	8 (P < 0.0001)					(CKD Stage	3 CK	D Stage	4

Fig 7. Patients with advanced stages of CKD versus patients with CKD 1+2 for mid-term mortality. A, Pooled univariate hazard ratio of advanced stages of CKD compared with CKD stage 1+2 for all-cause mid-term mortality. B, Pooled multivariate hazard ratio of advanced stages of CKD compared with CKD stage 1+2 for all-cause mid-term mortality. CI, confidence interval; Random, Random-effects model; Fixed, fixed-effects model; IV, Generic Inverse Variance method.

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CKD have been shown to be independent risk factors in patients undergoing TAVI [10, 29, 49]. However, no stepwise increased adverse events was observed in patients with more severe CKD [10, 29]. By pooling estimate effects from these individual studies, we found that patients with CKD stage 4 had significantly higher incidence of AKI and mortality rates compared with those with CKD stage 3. Because patients with ESRD have been excluded from many TAVI studies, only sparse data exist on the prognostic value of CKD stage 5 [29, 60]. In the present study, pre-procedural chronic dialysis was also shown to be a strong risk factor for mid-term mortality after TAVI.

The presence of RD is an important factor contributing to poorer outcomes in patients undergoing TAVI. This phenomenon can be explained by several aspects. (1) Patients with RD

A							
<i>,</i> , ,				Hazard Ratio	Hazar	d Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixe	d, 95% CI	
Codner 2013	0.4725	0.2152	1.3%	1.60 [1.05, 2.45]			
Gotzmann 2012	0.2974	0.1087	5.1%	1.35 [1.09, 1.67]		-	
Houthuizen 2012	0.2581	0.0472	27.2%	1.29 [1.18, 1.42]		-	
Lange 2012	0.283	0.1526	2.6%	1.33 [0.98, 1.79]		-	
Linke 2014	0.2213	0.0551	19.9%	1.25 [1.12, 1.39]		-	
Sabaté 2013	0.1744	0.0641	14.7%	1.19 [1.05, 1.35]		-	
Seiffert 2013	0.0954	0.0751	10.7%	1.10 [0.95, 1.27]		+	
Unbehaun 2014	0.1885	0.0573	18.4%	1.21 [1.08, 1.35]		-	
Total (95% CI)			100.0%	1.24 [1.18, 1.30]		•	
Heterogeneity: Chi ² =	6.20, df = 7 (P = 0.52	2); I² = 0%	6			1 10	100
Test for overall effect:	Z = 8.68 (P < 0.0000	11)			Patients without RD	Patients with	RD

В					
				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Codner 2013	0.4383	0.2185	3.8%	1.55 [1.01, 2.38]	
Houthuizen 2012	0.2689	0.0467	20.5%	1.31 [1.19, 1.43]	-
Kodali 2012	0.0611	0.0312	23.1%	1.06 [1.00, 1.13]	•
Lange 2012	-0.1778	0.2838	2.4%	0.84 [0.48, 1.46]	
Linke 2014	0.1376	0.0753	15.4%	1.15 [0.99, 1.33]	
Sabaté 2013	0.1697	0.0666	16.9%	1.18 [1.04, 1.35]	•
Unbehaun 2014	0.2151	0.0611	17.9%	1.24 [1.10, 1.40]	-
Total (95% CI)			100.0%	1 10 [1 08 1 30]	•
Hotorogonoity Tou? -	0.01.068-10.02	₩ C /D -	- 0.0043-1	1.19[1.00, 1.30] z = cox	
Telefogenelly. Tau" =	0.01, 0111 = 18.82, 0	л — 0 (F -	- 0.004), 1	- 00%	0.01 0.1 1 10 100
lest for overall effect:	Z = 3.66 (P = 0.0002	9			Patients without RD Patients with RD

Fig 8. Forest plots of mid-term mortality associated with RD. A, Pooled univariate hazard ratio of patients without RD compared with patients with RD for all-cause mid-term mortality. B, Pooled multivariate hazard ratio of patients without RD compared with patients with RD for all-cause mid-term mortality. B, Pooled multivariate hazard ratio of patients without RD compared with patients with RD for all-cause mid-term mortality. RD, renal dysfunction; CI, confidence interval; Fixed, fixed-effects model; Random, Random-effects model; IV, Generic Inverse Variance method.

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were older, were frailer, and presented with a significantly higher Logistic Euroscore in previous studies [10, 29, 49]. In view of these data, RD may serve as a marker of unbalanced baseline risk profiles. Patients with RD frequently have a higher burden of severe morbidities, which may adversely affect their survival after TAVI. (2) RD modifies the natural history of AS, presumably through a pathophysiological mechanism that promotes calcium deposition on aortic leaflets, thereby worsening aortic stenosis and reducing cardiac output [61]. Severe AS with decreased flow to important organs is responsible for the onset of severe complications, which subsequently increase the mortality after TAVI [8, 48, 62]. RD was also found to be associated with disorders of primary hemostasis, in particular platelet malfunctions [63], which played an important role in the occurrence of peri-procedural bleeding and subsequently increased mortality [59]. (3) It is well known that one of the advantages of TAVI is the avoidance of cardiopulmonary bypass, which is one of the most important risk factors for post-procedural AKI [64]. However, the incidence of contrast-induced nephropathy (CIN) could conceivably increase as a result of the extensive use of contrast medium and multiple injections [65, 66]. Although few studies have identified a significant association between contrast agents and AKI in the general population [67, 68], when focusing on patients with RD, the incidence of CIN was found to be

significantly enhanced. Among patients with CKD, the occurrence of CIN was strongly associated with a higher 60-day mortality [69], indicating that the nephrotoxic mechanisms of CIN were one of the major issues contributing to the mid-term mortality in such patients.

In patients with more severe kidney failure, a higher Logistic Euroscore and lower ejection fraction were more frequent [10, 29]. Moreover, the incidence of post-procedural renal impairment was also significantly higher in patients with more severe RD, despite using a smaller dose of contrast medium [29]. These results could explain the graded association between the severity of RD and the stepwise increase in mortality after TAVI.

In view of these data, RD appears to be not only a marker of illness severity, but it also represents a risk factor for mid-term prognosis. Therefore, rigorous risk assessment, preventive therapies for bleeding and stroke, and timely detection of AKI would be crucial interventions that would improve the mid-term mortality after TAVI. Our study revealed higher incidence of peri-procedural complications and poorer outcomes in patients with CKD stage 4. However, this result also raises questions regarding whether these high-risk patients actually benefit from a TAVI procedure and which patients are at the highest risk of mid-term mortality.

Limitations

Several limitations exist in our study. (1) Because the present meta-analysis was based only on published studies, the possibility of potential publication bias cannot be completely ruled out. (2) Although careful screening was conducted, the possibility of overlapping study populations could result in similar estimates. (3) Our meta-analysis was not conducted at the patient level, and only 5 studies treated RD as the primary study question. Even though the renal function-specific baseline characteristics were not available, the effects of comorbidities could not be assessed. (4) The adjusted prognostic value of different degrees of RD on the mid-term mortality after TAVI was not assessed due to the scarcity of study data. (5) Most included studies calculated eGFR using the MDRD equation, which is affected by the considerable decline in muscle mass with age, severe cardiovascular disease, drugs, and diet, making it difficult to reflect the actual renal clearance in the cohort of elderly patients.

Conclusions

Preexisting RD, despite different definitions, was associated with significantly increased midterm mortality after TAVI. Varying degrees of RD were strongly associated with a stepwise increase in mid-term mortality rates. Given that patients with CKD stage 4 had a higher incidence of peri-procedural complications and a poorer prognosis, TAVI in such patients may present a significant challenge.

Supporting Information

S1 Checklist. (DOC)

S1 Fig. Funnel plots of comparison between RD (defined by the author) and normal renal function for mid-term mortality. A, Comparison in univariable model (Begg's test: P = 0.23; Egger's test: P = 0.208; Trim and Fill Analysis not performed). B, Comparison in multivariable model. (Begg's test: P = 0.548; Egger's test: P = 0.215; Trim and Fill Analysis not performed). (TIF)

S2 Fig. Funnel plots of comparison between RD (defined as decreased eGFR) and normal renal function for mid-term mortality. A, Comparison in univariable model. (Begg's test: P = 0.119; Egger's test: P = 0.129; Trim and Fill Analysis not performed). B, Comparison in

multivariable model. (Begg's test: P = 0.133; Egger's test: P = 0.06; Trim and Fill Analysis: Pooled estimate = 0.306, P<0.001). (TIF)

S3 Fig. Funnel plots of comparison between RD (defined as increased Serum creatinine) and normal renal function for mid-term mortality. A, Comparison in univariable model. (Begg's test: P = 0.711; Egger's test: P = 0.711; Trim and Fill Analysis not performed). B, Comparison in multivariable model. (Begg's test: P = 0.133; Egger's test: P = 0.086; Trim and Fill Analysis: Pooled estimate = 0.436, P<0.001). (TIF)

S4 Fig. Funnel plots of comparison between CKD stage 5 and CKD stage 1+2 for mid-term mortality. Begg's test: P = 0.806; Egger's test: P = 0.841; Trim and Fill Analysis not performed. (TIF)

S5 Fig. Funnel plots for the impact of baseline serum creatinine (for each increase of 1 mg/ dl) on the mid-term mortality. A, Preformed in univariable model. (Begg's test: P = 0.902; Egger's test: P = 0.430; Trim and Fill Analysis not performed). B, Preformed in multivariable model. (Begg's test: P = 0.764; Egger's test: P = 0.507; Trim and Fill Analysis not performed). (TIF)

Author Contributions

Conceived and designed the experiments: CC MC DJH. Performed the experiments: CC ZGZ YBL YP QTM HC QL XLL WL CZ. Analyzed the data: CC ZGZ. Contributed reagents/materials/analysis tools: CC ZGZ. Wrote the paper: CC.

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