

Moderate and Severe Preoperative Chronic Kidney Disease Worsen Clinical Outcomes After Transcatheter Aortic Valve Implantation Meta-Analysis of 4992 Patients

Giuseppe Gargiulo, MD; Davide Capodanno, MD, PhD; Anna Sannino, MD;
Cinzia Perrino, MD, PhD; Piera Capranzano, MD; Eugenio Stabile, MD;
Bruno Trimarco, MD; Corrado Tamburino, MD, PhD; Giovanni Esposito, MD, PhD

Background—There is a conflicting evidence on safety and efficacy of transcatheter aortic valve implantation in patients with preoperative chronic kidney disease (CKD). Therefore, we conducted a meta-analysis on the impact of CKD on outcomes after transcatheter aortic valve implantation.

Methods and Results—Nine studies including 4992 patients were analyzed. Overall preoperative CKD (stages 3–5) significantly increased early (odds ratio [OR], 1.44; 95% confidence interval [CI], 1.08–1.94 and OR, 1.66; 95% CI, 1.04–2.67) and 1-year (OR, 1.66; 95% CI, 1.23–2.25 and OR, 1.32; 95% CI, 1.06–1.63) all-cause and cardiovascular mortality, respectively. Moderate CKD (stage 3) alone also increased early and 1-year all-cause mortality (OR, 1.43; 95% CI, 1.10–1.85 and OR, 1.41; 95% CI, 1.13–1.74). CKD stages 4 to 5 and 3 compared with stages 1 to 2 increased early stroke (OR, 2.67; 95% CI, 1.53–4.65 and OR, 1.66; 95% CI, 1.09–2.52), acute kidney injury (OR, 2.09; 95% CI, 1.17–3.72 and OR, 1.32; 95% CI, 1.09–1.60) and need for dialysis (OR, 5.92; 95% CI, 2.46–14.27 and OR, 1.55; 95% CI, 0.65–3.70), in the absence of significant differences in contrast medium administration (mean difference, –26.07; 95% CI, –53.00 to 0.85 and mean difference, –0.42; 95% CI, –16.10 to 15.26). Bleeding (life-threatening or major) was nonsignificantly increased in CKD 3 to 5 compared with CKD 1 to 2, but significantly increased in most severe patients (CKD 4–5 versus CKD 1–2: OR, 1.66; 95% CI, 1.13–2.44; CKD 4–5 versus CKD 3: OR, 1.68; 95% CI, 1.27–2.24).

Conclusions—Both moderate and severe preoperative CKD significantly worsen transcatheter aortic valve implantation prognosis. Future studies on risk evaluation, prevention, and postoperative management are needed. (*Circ Cardiovasc Interv.* 2015;8:e002220. DOI: 10.1161/CIRCINTERVENTIONS.114.002220.)

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

Transcatheter aortic valve implantation (TAVI) has emerged as an alternative to surgery therapy for severe aortic stenosis.^{1,2} The detrimental impact of baseline chronic kidney disease (CKD) on worsening the prognosis of patients undergoing surgical aortic valve replacement is well established.^{3,4} Conversely, this remains a debated issue in patients undergoing TAVI.

Mixed evidences are available regarding the relationship between baseline CKD and clinical outcomes in TAVI, and patients with CKD were typically under-represented in TAVI trials. On the other hand, CKD showed to be an independent predictor of mortality at 1-year after TAVI in some registries,^{5–8} but not in others.⁹ The degree of CKD, which exposes to the highest risk is also a matter of debate: recent data suggest that

CKD stage 4 and 5, but not stage 3, are predictors of 30-day and late mortality after TAVI.^{10,11} Finally, cross-sectional studies failed to show a significant impact of CKD on mortality.^{12,13}

On this background, given the contrasting evidence and the latest literature in this field, there is a clinical and scientific rationale to investigate the impact of preoperative CKD on the clinical outcomes of patients undergoing TAVI.

Methods

Study Selection

The study was designed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses requirements. MEDLINE, Cochrane, ISI Web of Science, and SCOPUS databases were searched

Received September 15, 2014; accepted December 30, 2014.

From the Division of Cardiology, Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy (G.G., A.S., C.P., E.S., B.T., G.E.); Division of Cardiology, Ferrarotto Hospital, University of Catania, Catania, Italy (D.C., P.C., C.T.); and Excellence Through Newest Advances (ETNA) Foundation, Catania, Italy (C.T.).

The Data Supplement is available at <http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.114.002220/-/DC1>.

Correspondence to Giovanni Esposito, MD, PhD, Division of Cardiology, Department of Advanced Biomedical Sciences, Federico II University of Naples, Via Pansini 5, 80131 Naples, Italy. E-mail espogiov@unina.it

© 2015 American Heart Association, Inc.

Circ Cardiovasc Interv is available at <http://circinterventions.ahajournals.org>

DOI: 10.1161/CIRCINTERVENTIONS.114.002220

WHAT IS KNOWN

- The detrimental impact of chronic kidney disease (CKD) on prognosis is well-established for surgical aortic valve replacement, but not for those undergoing transcatheter aortic valve implantation.
- Prior studies suggest that severe CKD (stage 4 and 5) is a predictor of early and late mortality in transcatheter aortic valve implantation patients.

WHAT THE STUDY ADDS

- This study observed that patients with stage 3 CKD, in addition to those with severe CKD, experience worse outcomes after transcatheter aortic valve implantation.
- Preoperative CKD (stages 3–5) significantly increases early and 1-year mortality, early stroke, and acute kidney injury including the need for dialysis.
- There is the need for studies on risk stratification, prevention strategies and postoperative management of transcatheter aortic valve implantation patients with CKD.

OR renal failure OR chronic kidney disease OR CKD. Citations were screened at the title and abstract level by 2 independent reviewers, and retrieved as a full text if they reported data on outcomes after TAVI. No language limitations were applied. The full texts and bibliography of all potential articles were also retrieved in detail to look for additional relevant items.

Eligibility Criteria

Studies were included if reporting on outcomes after TAVI in patients with preoperative CKD (defined according to the estimation of glomerular filtration rate), and were excluded if any of the following criteria applied: (1) duplicate publication; (2) lack of data on CKD pre-TAVI; and (3) the outcome of interest was not clearly reported or could not be derived from the published results.

Data Extraction

Two reviewers independently screened the articles for eligibility. The reviewers compared the selected studies and any discrepancy was resolved by consensus.

Study End Points

The primary end point was 1-year all-cause mortality. Secondary end points of interest included: early (≤ 30 days) all-cause mortality, early and 1-year cardiovascular mortality, stroke, bleeding (major or life-threatening), acute kidney injury (AKI), AKI 2 to 3, need for post-procedural dialysis, in-hospital length of stay, and contrast medium administration.

Statistical Analysis

The number of events, participants, means, SDs, and percentages were abstracted. Estimates of effect were calculated with a random-effects model and confirmed by a fixed-effects model and expressed as odds ratio (OR) or mean difference (MD). Statistical significance

for articles published from April 2002 (first-in-human TAVI date) until November 2014. Studies were identified using the major medical subject headings transcatheter aortic valve implantation OR transcatheter aortic valve replacement OR TAVI OR TAVR combined with the following text and keywords: renal function OR renal dysfunction

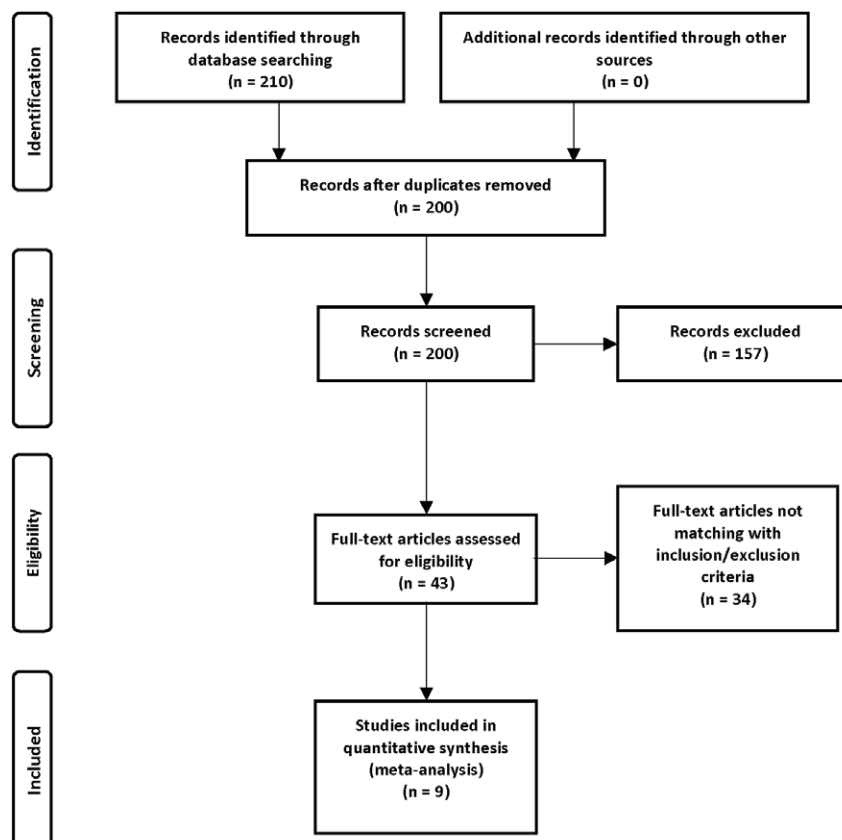


Figure 1. Flow diagram. Studies included in the quantitative synthesis.

was set at $P \leq 0.05$ (2-tailed). Heterogeneity was assessed by Q -statistic and I^2 tests. Significant heterogeneity was considered present for P values < 0.10 or $I^2 > 50\%$. In case of significant heterogeneity, the random-effects model was prioritized over the fixed-effects model and subgroup and sensitivity analyses were performed to explore sources of inconsistency. Meta-regressions were performed to test the influence of baseline characteristics as potential effect modifiers (significance at $P \leq 0.05$). Publication bias was assessed using funnel plots, the Egger test and the Trim and Fill method. All data analyses were performed using the Reviewer Manager Version 5.2 and the Prometa Software Version 2.^{14–16}

Results

Of 210 articles identified by the initial search, 43 were retrieved for more detailed evaluation, and 9 studies were

included in the meta-analysis (Figure 1).^{10–13,17–21} The characteristics of the included studies are reported in Table 1. There was no significant variability in the CKD definitions used across the studies.

All-Cause Mortality

Early all-cause mortality was significantly increased in patients with preoperative CKD stages 3 to 5 compared with stages 1 to 2 (7 studies including 4797 patients; OR, 1.44; 95% confidence interval [CI], 1.08–1.94; $P = 0.01$), in stages 4 to 5 compared with stages 1 to 2 (5 studies; 2300 patients; OR, 2.31; 95% CI, 1.61–3.31; $P < 0.00001$), in stage 3 compared with stages 1 to 2 (5 studies; 3881 patients; OR, 1.43; 95% CI,

Table 1. Baseline Characteristics of Selected Studies Included in Meta-Analysis

	Allende et al ¹⁰	D'Ascenzo et al ¹²	Dumonteil et al ¹⁷	Goebel et al ¹⁸	Nguyen et al ¹⁹	Nuis et al ²¹	Sinning et al ²⁰	Wessely et al ¹³	Yamamoto et al ¹¹
Year	2014	2013	2013	2013	2013	2011	2010	2012	2013
No. of patients	2075	364	942	270	321	118	77	183	642
Age, y	80.5	82.4	81.0	81.6	82.3	82.0	80.8	81.1	83.6
Male, %	49.9	42.0	53.8	44.4	55.8	45.0	48.0	44.8	48.1
BMI, kg/m ²	26.9	NA	26.0	25.9	26.7	26.0	24.8	26.4	25.8
Diabetes mellitus, %	30.1	31.1	28.5	27.6	43.6	23.0	23.0	30.0	22.6
Hypertension, %	78.8	86.6	69.5	96.3	95.0	44.0	94.0	84.2	70.6
Dyslipidemia, %	NA	54.0	NA	NA	90.3	NA	84.0	NA	50.3
Smoke, %	22.8	NA	NA	NA	NA	NA	NA	NA	8.7
Prior stroke/TIA, %	12.6	23.0	15.7	NA	16.2	25.0	26.0	NA	9.9
Prior MI, %	NA	19.4	16.8	NA	NA	25.0	42.0	NA	13.4
Prior CABG, %	24.7	12.6	22.1	NA	37.4	27.0	10.0	NA	15.1
Prior PCI, %	NA	NA	29.4	21.3	NA	25.0	48.0	NA	28.5
CAD, %	58.2	NA	45.2	67.0	NA	NA	65.0	50.8	NA
PAD, %	20.1	23.6	25.3	41.6	34.6	NA	46.0	12.2	28.5
Renal dysfunction,* %	54.2	80.2	53.5	47.8	50.5	53.4	62.0	62.3	66.0
COPD, %	29.8	NA	34.5	21.5	48.9	29.0	26.0	23.9	29.1
Atrial fibrillation, %	30.4	NA	NA	33.1	NA	27.0	NA	33.0	NA
NYHA III/IV, %	82.5	NA	81.3	NA	NA	84.0	NA	NA	80.1
Log Euro score, %	17.6	23.2	20.9	33.5	NA	12.3†	31.2	23.5	19.9
STS score, %	6.5	6.6	NA	14.0	12.1	6.1†	9.3	NA	6.8
AVA, cm ²	0.62	0.63	NA	0.60	NA	0.63	NA	0.69	0.64
Mean aortic gradient, mm Hg	46.0	53.7	NA	47.0	NA	47.0	NA	NA	47.5
Baseline AR moderate–severe, %	NA	NA	NA	NA	NA	32.0	NA	NA	NA
Baseline MR moderate–severe, %	NA	5.0	NA	NA	NA	19.0	NA	NA	NA
EF, %	54.2	52.4	NA	56.0	48.2	51.0	45.3	58.7	50.9
Transapical, %	NA	7.0	9.3	100	NA	NA	0	0	NA
Transfemoral, %	73.7	84.1	74.1	0	NA	NA	100	100	67.1
CoreValve, %	48.1	NA	53.7	0	NA	0	100	100	37.1
Sapien, %	51.9	NA	46.3	96.3	NA	0	0	0	62.9

AR indicates aortic regurgitation; AVA, aortic valve area; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary arterial disease; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MR, mitral regurgitation; NA, not available; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCI, percutaneous coronary interventions; STS, Society of Thoracic Surgeons; and TIA, transient ischemic attack.

*Defined as eGFR < 60 mL/min per 1.72 m².

†Reported as median.

Table 2. Outcomes After Transcatheter Aortic Valve Implantation in Patients With Preoperative CKD 3 to 5 vs CKD 1 to 2

Outcome	Studies	Patients	RE OR [95% CI]	P Value	τ^2	FE OR [95% CI]	P Value	χ^2	I^2 , %	Egger Test	Trim and Fill OR
Death											
Early all-cause	7	4797	1.44 [1.08 to 1.94]	0.01	0.03	1.48 [1.17 to 1.86]	0.0009	7.56	21	0.526	1.44 [1.08 to 1.94]
Early CV	3	1576	1.66 [1.04 to 2.67]	0.03	0.00	1.70 [1.06 to 2.72]	0.003	0.73	0	0.194	1.50 [0.98 to 2.29]
1-year all-cause	6	4421	1.66 [1.23 to 2.25]	0.001	0.07	1.56 [1.35 to 1.81]	<0.00001	13.17	62	0.405	1.52 [1.14 to 2.04]
1-year CV	2	2439	1.32 [1.06 to 1.63]	0.01	0.00	1.32 [1.07 to 1.64]	0.01	0.21	0
Stroke	6	4614	1.86 [1.25 to 2.75]	0.002	0.00	1.87 [1.26 to 2.77]	0.002	0.60	0	0.268	1.75 [1.22 to 2.52]
AKI	6	3937	1.42 [1.20 to 1.68]	<0.0001	0.00	1.43 [1.21 to 1.69]	<0.0001	2.75	0	0.653	1.41 [1.19 to 1.66]
AKI 2–3	6	4396	1.60 [1.08 to 2.36]	0.02	0.09	1.57 [1.22 to 2.03]	0.0006	8.67	42	0.882	1.60 [1.08 to 2.36]
Need for dialysis	6	3840	2.11 [1.15 to 3.90]	0.02	0.03	2.32 [1.32 to 4.09]	0.003	5.26	5	0.328	2.11 [1.15 to 3.90]
Bleeding (major or life-threatening)	3	3381	1.11 [0.91 to 1.35]	0.30	0.00	1.11 [0.91 to 1.35]	0.30	1.64	0	0.966	1.11 [0.91 to 1.35]
Length of stay*	2	963	0.88 [–0.00 to 1.75]	0.05	0.00	0.88 [–0.00 to 1.75]	0.05	0.31	0
Contrast medium*	4	1510	–5.18 [–16.10 to 5.73]	0.35	65.05	–5.16 [–12.59 to 2.27]	0.17	6.34	53	0.970	–5.18 [–16.10 to 5.73]

AKI indicates acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; FE, fixed effects; OR, odds ratio; and RE, random effects.

*The estimation effect is not OR but mean difference.

1.10–1.85; $P=0.008$) and in stages 4 to 5 compared with stage 3 (5 studies; 2507 patients; OR, 1.56; 95% CI, 1.13–2.17; $P=0.007$; Tables 2–5; Figure 2).

One-year all-cause mortality (primary end point) was significantly increased in patients with preoperative CKD stages 3 to 5 compared with stages 1 to 2 (6 studies; 4421 patients; OR, 1.66; 95% CI, 1.23–2.25; $P=0.001$), in stages 4 to 5 compared with stages 1 to 2 (5 studies; 2300 patients; OR, 2.56; 95% CI, 1.54–4.24; $P=0.0003$), in stage 3 compared with stages 1 to 2 (5 studies; 3881 patients; OR, 1.41; 95% CI, 1.13–1.74; $P=0.002$) and in stages 4 to 5 compared with stage 3 (5 studies; 2568 patients; OR, 1.69; 95% CI, 1.20–2.38; $P=0.003$; Tables 2–5; Figure 3).

Cardiovascular Mortality

Early cardiovascular mortality was significantly increased in patients with preoperative CKD stages 3 to 5 compared with stages 1 to 2 (3 studies; 1576 patients; OR, 1.66; 95% CI,

1.04–2.67; $P=0.03$), and in stages 4 to 5 compared with stages 1 to 2 (2 studies; 688 patients; OR, 2.24; 95% CI, 1.11–4.52; $P=0.02$), but not significantly in stage 3 compared with stages 1 to 2 (2 studies; 1128 patients; OR, 1.49; 95% CI, 0.87–2.56; $P=0.15$) nor in stages 4 to 5 compared with stage 3 (2 studies; 796 patients; OR, 1.45; 95% CI, 0.80–2.61; $P=0.22$; Tables 2–5; Figure SI in the Data Supplement).

One-year cardiovascular mortality was significantly increased in patients with preoperative CKD stages 3 to 5 compared with stages 1 to 2 (2 studies; 2439 patients; OR, 1.32; 95% CI, 1.06–1.63; $P=0.01$), and in stages 4 to 5 compared with stages 1 to 2 (2 studies; 1296 patients; OR, 1.88; 95% CI, 1.20–2.92; $P=0.005$), but not significantly in stage 3 compared with stages 1 to 2 (2 studies; 2165 patients; OR, 1.22; 95% CI, 0.97–1.53; $P=0.08$) nor in stages 4 to 5 compared with stage 3 (2 studies; 1417 patients; OR, 1.75; 95% CI, 0.96–3.21; $P=0.07$; Tables 2–5; Figure SII in the Data Supplement).

Table 3. Outcomes After Transcatheter Aortic Valve Implantation in Patients With Preoperative CKD 4 to 5 vs CKD 1 to 2

Outcome	Studies	Patients	RE OR [95% CI]	P Value	τ^2	FE OR [95% CI]	P Value	χ^2	I^2 , %	Egger Test	Trim and Fill OR
Death											
Early all-cause	5	2300	2.31 [1.61 to 3.31]	<0.00001	0.00	2.32 [1.63 to 3.31]	<0.00001	3.21	0	0.799	2.31 [1.61 to 3.31]
Early CV	2	688	2.24 [1.11 to 4.52]	0.02	0.00	2.32 [1.16 to 4.62]	0.02	0.48	0
1-year all-cause	5	2300	2.56 [1.54 to 4.24]	0.0003	0.20	2.52 [2.01 to 3.17]	<0.00001	13.00	69	0.716	2.56 [1.54 to 4.24]
1-year CV	2	1296	1.88 [1.20 to 2.92]	0.005	0.03	1.83 [1.31 to 2.56]	0.0004	1.16	14
Stroke	5	2300	2.67 [1.53 to 4.65]	0.0005	0.00	2.67 [1.55 to 4.63]	0.0004	1.17	0	0.265	2.26 [1.38 to 3.68]
AKI	3	1839	2.09 [1.17 to 3.72]	0.01	0.17	1.95 [1.47 to 2.58]	<0.00001	6.43	69	0.785	2.09 [1.17 to 3.72]
AKI 2–3	4	2118	2.59 [1.20 to 5.56]	0.01	0.37	2.67 [1.84 to 3.89]	<0.00001	9.46	68	0.775	2.59 [1.20 to 5.56]
Need for dialysis	4	1757	3.97 [0.72 to 21.79]	0.11	1.42	5.92 [2.46 to 14.27]	<0.0001	5.71	47	0.091	3.97 [0.72 to 21.79]
Bleeding (major or life-threatening)	3	1839	1.66 [1.13 to 2.44]	0.01	0.04	1.63 [1.21 to 2.19]	0.001	3.14	36	0.951	1.66 [1.13 to 2.44]
Length of stay*	2	461	0.83 [–2.06 to 3.71]	0.58	2.83	0.36 [–1.20 to 1.92]	0.65	2.70	63
Contrast medium*	3	606	–26.07 [–53.00 to 0.85]	0.06	477.22	–25.00 [–35.03 to 14.07]	<0.00001	13.10	82	0.845	–26.07 [–53.00 to 0.85]

AKI indicates acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; FE, fixed effects; OR, odds ratio; and RE, random effects.

*The estimation effect is not OR but mean difference.

Table 4. Outcomes After Transcatheter Aortic Valve Implantation in Patients With Preoperative CKD 3 vs CKD 1 to 2

Outcome	Studies	Patients	RE OR [95% CI]	PValue	τ^2	FE OR [95% CI]	PValue	χ^2	I^2 , %	Egger Test	Trim and Fill OR
Death											
Early all-cause	5	3881	1.43 [1.10 to 1.85]	0.008	0.00	1.44 [1.11 to 1.87]	0.005	2.62	0	0.682	1.39 [1.08 to 1.80]
Early CV	2	1128	1.49 [0.87 to 2.56]	0.15	0.00	1.52 [0.89 to 2.60]	0.12	0.59	0
1-year all-cause	5	3881	1.41 [1.13 to 1.74]	0.002	0.02	1.37 [1.18 to 1.60]	<0.0001	5.78	31	0.517	1.37 [1.11 to 1.69]
1-year CV	2	2165	1.22 [0.97 to 1.53]	0.08	0.00	1.22 [0.97 to 1.53]	0.08	0.00	0
Stroke	5	3881	1.66 [1.09 to 2.52]	0.02	0.00	1.67 [1.10 to 2.53]	0.02	0.23	0	0.727	1.66 [1.09 to 2.52]
AKI	3	3002	1.32 [1.09 to 1.60]	0.005	0.00	1.33 [1.09 to 1.61]	0.004	0.48	0	0.113	1.32 [1.09 to 1.60]
AKI 2–3	4	3583	1.27 [0.90 to 1.79]	0.18	0.03	1.27 [0.95 to 1.70]	0.11	3.84	22	0.814	1.27 [0.90 to 1.79]
Need for dialysis	4	3044	1.55 [0.65 to 3.70]	0.32	0.00	1.63 [0.70 to 3.77]	0.26	2.20	0	0.356	1.55 [0.65 to 3.70]
Bleeding (major or life-threatening)	3	3002	0.99 [0.80 to 1.22]	0.93	0.00	0.99 [0.80 to 1.22]	0.93	0.79	0	0.798	0.99 [0.80 to 1.22]
Length of stay*	2	879	0.83 [−0.14 to 1.81]	0.09	0.05	0.84 [−0.09 to 1.76]	0.08	1.11	10
Contrast medium*	3	1170	−0.42 [−16.10 to 15.26]	0.96	134.92	−0.39 [−8.85 to 8.07]	0.93	6.76	70	0.980	−0.42 [−16.10 to 15.26]

AKI indicates acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; FE, fixed effects; OR, odds ratio; and RE, random effects.

*The estimation effect is not OR but mean difference.

Stroke

Early stroke was significantly increased in patients with preoperative CKD stages 3 to 5 compared with stages 1 to 2 (6 studies; 4614 patients; OR, 1.86; 95% CI, 1.25–2.75; $P=0.002$), in stages 4 to 5 compared with stages 1 to 2 (5 studies; 2300 patients; OR, 2.67; 95% CI, 1.53–4.65; $P=0.0005$), in stage 3 compared with stages 1 to 2 (5 studies; 3881 patients; OR, 1.66; 95% CI, 1.09–2.52; $P=0.02$) and in stages 4 to 5 compared with stage 3 (5 studies; 2507 patients; OR, 1.65; 95% CI, 1.01–2.69; $P=0.05$; Tables 2–5; Figure SIII in the Data Supplement).

Acute Kidney Injury

Early AKI was significantly increased in patients with preoperative CKD stages 3 to 5 compared with stages 1 to 2 (6 studies; 3937 patients; OR, 1.42; 95% CI, 1.20–1.68; $P<0.0001$), in stages 4 to 5 compared with stages 1 to 2 (3 studies; 1839 patients; OR, 2.09; 95% CI, 1.17–3.72; $P=0.01$), and in stage

3 compared with stages 1 to 2 (3 studies; 3002 patients; OR, 1.32; 95% CI, 1.09–1.60; $P=0.005$), but not significantly in stages 4 to 5 compared with stage 3 (3 studies; 1921 patients; OR, 1.48; 95% CI, 0.89–2.46; $P=0.13$; Tables 2–5; Figure SIV in the Data Supplement).

AKI Stages 2 to 3

Early AKI 2 to 3 was significantly increased in patients with preoperative CKD stages 3 to 5 compared with stages 1 to 2 (6 studies; 4396 patients; OR, 1.60; 95% CI, 1.08–2.36; $P=0.02$), in stages 4 to 5 compared with stages 1 to 2 (4 studies; 2118 patients; OR, 2.59; 95% CI, 1.20–5.56; $P=0.01$), and in stages 4 to 5 compared with stage 3 (4 studies; 2345 patients; OR, 2.11; 95% CI, 1.341–3.17; $P=0.0003$), but not significantly in stage 3 compared with stages 1 to 2 (4 studies; 3583 patients; OR, 1.27; 95% CI, 0.90–1.79; $P=0.18$; Tables 2–5; Figure SV in the Data Supplement).

Table 5. Outcomes After Transcatheter Aortic Valve Implantation in Patients With Preoperative CKD 4 to 5 vs CKD 3

Outcome	Studies	Patients	RE OR [95% CI]	PValue	τ^2	FE OR [95% CI]	PValue	χ^2	I^2 , %	Egger Test	Trim and Fill OR
Death											
Early all-cause	5	2507	1.56 [1.13 to 2.17]	0.007	0.00	1.55 [1.12 to 2.14]	0.009	2.20	0	0.882	1.56 [1.13 to 2.17]
Early CV	2	796	1.45 [0.80 to 2.61]	0.22	0.00	1.45 [0.80 to 2.61]	0.22	0.00	0
1-year all-cause	5	2568	1.69 [1.20 to 2.38]	0.003	0.07	1.73 [1.40 to 2.15]	<0.00001	7.67	48	0.272	1.69 [1.20 to 2.38]
1-year CV	2	1417	1.75 [0.96 to 3.21]	0.07	0.12	1.55 [1.13 to 2.13]	0.007	2.28	56
Stroke	5	2507	1.65 [1.01 to 2.69]	0.05	0.00	1.62 [0.99 to 2.64]	0.05	1.24	0	0.153	1.43 [0.92 to 2.22]
AKI	3	1921	1.48 [0.89 to 2.46]	0.13	0.13	1.44 [1.10 to 1.88]	0.008	6.21	68	0.899	1.48 [0.89 to 2.46]
AKI 2–3	4	2345	2.11 [1.41 to 3.17]	0.0003	0.03	2.11 [1.47 to 3.02]	<0.0001	3.51	14	0.982	1.67 [0.97 to 2.86]
Need for dialysis	4	2003	4.28 [1.94 to 9.47]	0.0003	0.00	3.97 [1.87 to 8.43]	0.0003	2.18	0	0.231	4.28 [1.94 to 9.47]
Bleeding (major or life-threatening)	3	1921	1.68 [1.27 to 2.24]	0.0003	0.00	1.67 [1.25 to 2.22]	0.0005	1.47	0	0.866	1.39 [1.03 to 1.86]
Length of stay*	2	586	0.08 [−3.81 to 3.98]	0.97	6.23	−0.67 [−2.28 to 0.94]	0.41	4.52	78
Contrast medium*	3	878	−24.67 [−37.89 to 11.45]	0.0003	72.76	−22.82 [−30.55 to 15.10]	<0.00001	4.21	52	0.687	−24.67 [−37.89 to 11.45]

AKI indicates acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; FE, fixed effects; OR, odds ratio; and RE, random effects.

*The estimation effect is not OR but mean difference.

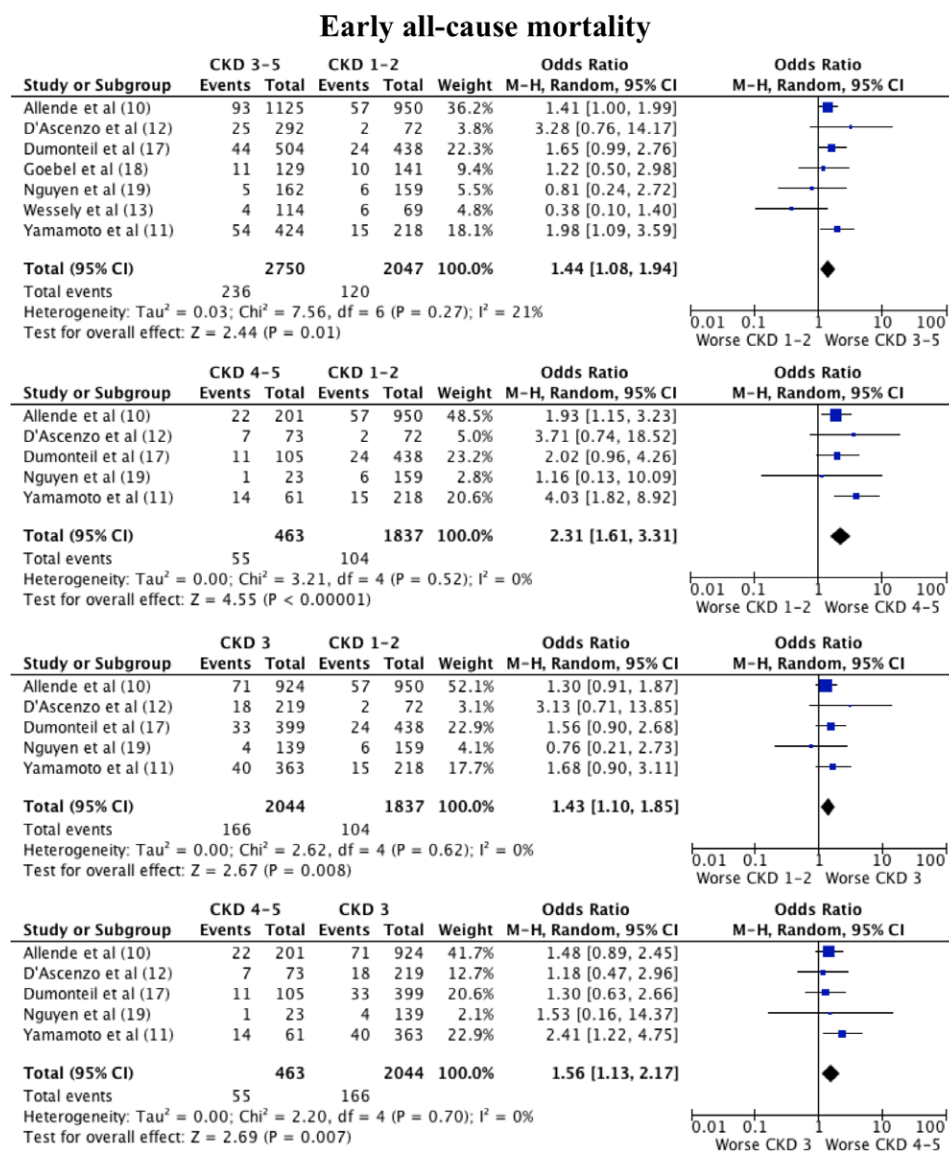


Figure 2. Early all-cause mortality. Early random effects odds ratio and 95% confidence interval (CI) for early all-cause mortality according to chronic kidney disease (CKD) stages. M-H indicates Mantel-Haenszel.

Need for Dialysis

Postoperative need for dialysis was significantly increased in patients with preoperative CKD stages 3 to 5 compared with stages 1 to 2 (6 studies; 3840 patients; OR, 2.11; 95% CI, 1.15–3.90; $P=0.02$), in stages 4 to 5 compared with stages 1 to 2 (4 studies; 1757 patients; fixed effects model OR, 5.92; 95% CI, 2.46–14.27; $P<0.0001$; I^2 , 47%) and in stages 4 to 5 compared with stage 3 (4 studies; 2003 patients; OR, 4.28; 95% CI, 1.94–9.47; $P=0.0003$), but not significantly in stage 3 compared with stages 1 to 2 (4 studies; 3044 patients; OR, 1.55; 95% CI, 0.65–3.70; $P=0.32$; Tables 2–5; Figure SVI in the Data Supplement).

Bleeding

Early bleeding (major or life-threatening) were similar in patients with preoperative CKD stages 3 to 5 compared with stages 1 to 2 (3 studies; 3381 patients; OR, 1.11; 95% CI, 0.91–1.35; $P=0.30$) and in stage 3 compared with stages 1

to 2 (3 studies; 3002 patients; OR, 0.99; 95% CI, 0.80–1.22; $P=0.93$), but significantly increased in stages 4 to 5 compared with stages 1 to 2 (3 studies; 1839 patients; OR, 1.66; 95% CI, 1.13–2.44; $P=0.001$) and to stage 3 (3 studies; 1921 patients; OR, 1.68; 95% CI, 1.27–2.24; $P=0.0003$; Tables 2–5; Figure SVII in the Data Supplement).

Length of Stay

In-hospital length of stay was significantly longer in patients with preoperative CKD stages 3 to 5 compared with stages 1 to 2 (2 studies; 963 patients; MD, 0.88; 95% CI, –0.00 to 1.75; $P=0.05$), but not in stages 4 to 5 compared with stages 1 to 2 (2 studies; 461 patients; MD, 0.83; 95% CI, –2.06 to 3.71; $P=0.58$), nor in stage 3 compared with stages 1 to 2 (2 studies; 879 patients; MD, 0.83; 95% CI, –0.14 to 1.81; $P=0.09$), nor in stages 4 to 5 compared with stage 3 (2 studies; 586 patients; MD, 0.08; 95% CI, –3.81 to 3.98; $P=0.97$; Tables 2–5; Figure SVIII in the Data Supplement).

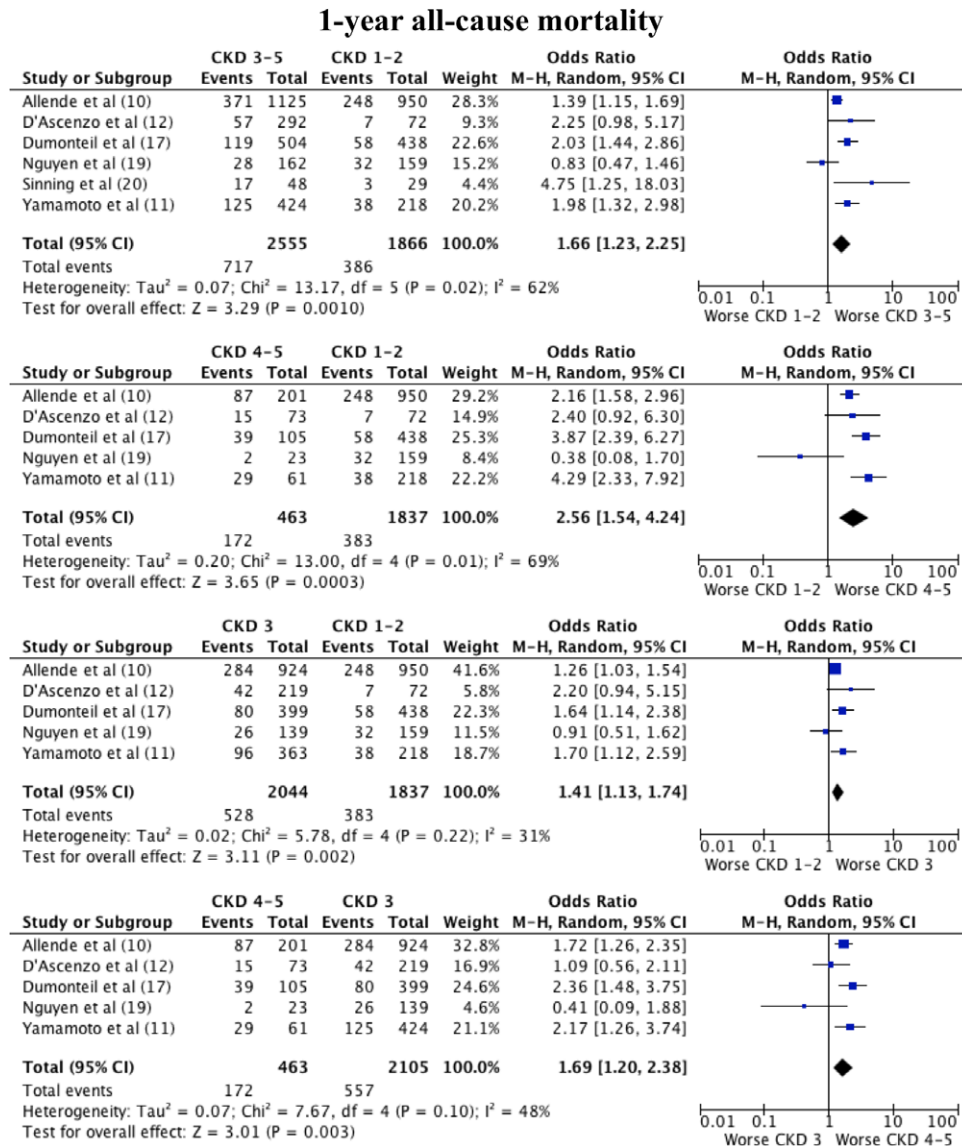


Figure 3. One-year all-cause mortality. Early random effects odds ratio and 95% confidence interval (CI) for 1-year all-cause mortality according to chronic kidney disease (CKD) stages. M-H indicates Mantel-Haenszel.

Contrast Medium Administration

Procedural contrast medium administration was similar in patients with preoperative CKD stages 3 to 5 compared with stages 1 to 2 (4 studies; 1510 patients; MD, -5.18 ; 95% CI, -16.10 to 5.73 ; $P=0.35$) in stages 4 to 5 compared with stages 1 to 2 (3 studies; 606 patients; MD, -26.07 ; 95% CI, -53.00 to 0.85 ; $P=0.06$) and in stage 3 compared with stages 1 to 2 (3 studies; 1170 patients; MD, -0.42 ; 95% CI, -16.10 to 15.26 ; $P=0.96$), but significantly reduced in stages 4 to 5 compared with stage 3 (3 studies; 878 patients; MD, -24.67 ; 95% CI, -37.89 to 11.45 ; $P=0.0003$; Tables 2–5; Figure SIX in the Data Supplement).

Meta-Regression and Sensitivity Analysis

The primary end point of 1-year all-cause mortality was influenced by the following baseline characteristics: prior coronary artery bypass graft (CKD 3–5 versus 1–2, $P=0.012$; CKD 3 versus 1–2, $P=0.021$), prior myocardial infarction (CKD 3–5

versus 1–2, $P=0.030$), prior percutaneous coronary intervention (CKD 3–5 versus 1–2, $P=0.035$), logEuroSCORE (CKD 3–5 versus 1–2, $P=0.005$; CKD 3 versus 1–2, $P=0.033$), diabetes mellitus (CKD 4–5 versus 1–2, $P=0.019$) and hypertension (CKD 4–5 versus 1–2, $P=0.050$; CKD 4–5 versus 3, $P=0.014$).

The significant increase of 1-year all-cause mortality was confirmed for CKD 3 to 5 versus CKD 1 to 2, CKD 4 to 5 versus CKD 1 to 2 and CKD 3 versus 1 to 2 comparisons when meta-analyses were repeated removing 1 study at the time (Tables I–III in the Data Supplement). Additional sensitivity analyses are reported in Tables I–IV in the Data Supplement.

Publication Bias

The funnel plots (Figures SX–SXVIII in the Data Supplement) and Egger test (Tables 2–5) did not suggest any significant publication bias for all the analyses performed. The Trim and Fill analysis (Tables 2–5) did not change the significance

of all the end points with the exception of early cardiovascular mortality for the comparison between CKD 3 to 5 and CKD 1 to 2 (2 of 3 studies trimmed; OR, 1.50; 95% CI, 0.98–2.29; $P=0.06$; Table 2), and stroke (2 of 5 studies trimmed; OR, 1.43; 95% CI, 0.92–2.22; $P=0.10$; Table 5) and AKI 2 to 3 (1 of 4 studies trimmed; OR, 1.67; 95% CI, 0.97–2.86; $P=0.06$; Table 5) for the comparison between CKD 4 to 5 and CKD 3, which lost the statistical significance while maintaining similarly sized directional estimate effects.

Discussion

This meta-analysis, including 4992 patients treated with TAVI, adds to the current knowledge with the following considerations: (1) CKD (stages 3–5) is associated with significant increases of early and 1-year all-cause and cardiovascular mortality, early stroke, AKI, AKI 2 to 3, need for dialysis, and length of stay in the absence of differences in contrast medium administration; (2) compared with lower degree of CKD, worse renal impairment (ie, 4–5 versus 1–2; 4–5 versus 3; 3 versus 1–2) is associated with increased all-cause and cardiovascular mortality, stroke, AKI, AKI 2 to 3, need for dialysis and bleeding; and (3) CKD stage 3 significantly impacts on all-cause mortality, stroke, and AKI. These data in aggregate suggest that not only patients with severe CKD may experience worse outcomes after TAVI but also those with a moderate degree of renal impairment.

Preprocedural CKD has emerged as predictor of worse outcome after TAVI. In particular, the higher risk of mortality has been suggested in patients with more severe CKD.^{10–12,17,20} However, recent data showed that advanced CKD (stages 4–5), but not moderate CKD (stage 3), was a predictor of early and late mortality.^{10,11} In contrast, other studies did not find a significant relationship between CKD and worse outcomes.^{8,9,12,13} Consistent with this background, in the present study, we pooled the available evidence on this issue confirming the negative prognostic impact of advanced CKD, but also demonstrating for the first time that CKD stage 3 is associated with a significant increase of early and late mortality. Frequently, patients with CKD, particularly those at an advanced stage of disease, have more cardiovascular risk factors and experience increased cardiovascular mortality.^{10,22} Given that severe aortic stenosis is per se also associated with other cardiac diseases negatively impacting on prognosis (coronary arterial disease, heart failure and arrhythmias), the presence of CKD may be responsible for an additional risk of cardiovascular mortality. In our study, all-cause mortality in patients with CKD was significantly increased and was related to increased cardiovascular mortality as well as a higher risk of stroke, bleeding (CKD 4–5), AKI (particularly severe AKI 2–3) and the need for postprocedural dialysis.

Few studies provided data on length of hospitalization, which in the pooled analysis resulted significantly longer in patients with CKD compared with those without. On the other hand, no significant differences in length of hospital stay emerged in the comparisons across CKD subgroups, which may reflect the small amount of data available and, possibly, a power issue.

Importantly, the increase of adverse outcomes associated with the presence of preoperative CKD, including AKI, AKI 2 to 3

and dialysis, was not potentially justified from differences in the contrast medium administration across different subgroups. Indeed, the absence of difference in contrast medium administration corroborates the result of the present meta-analysis. This was further reinforced by the observed persistence of increased 1-year all-cause mortality with more advanced stages of CKD (relative to stage 1–2) in multiple sensitivity analyses.

Altogether, these results could be of particular interest adding new insights into the concerns emerged on performing TAVI in patients with severe CKD,^{10,17} also given that these patients were excluded from pivotal randomized trials.^{1,2} However, other data demonstrate that these patients may still benefit from the TAVI procedure because of improvement in functional status (New York Heart Association class) and absence of valve hemodynamic anomalies.¹⁰ Further studies are needed to address this issue by better risk stratification facilitating the proper decision-making for such challenging patients. On the other hand, it should also be considered that some data report an improvement in renal function after TAVI suggesting that, although associated with increased mortality, TAVI might not be precluded to all patients with preoperative CKD.^{12,23–25}

The results of this meta-analysis are affected by limitations and differences of the original included studies themselves. All meta-analyses share limitations related to differences in study design, end point definitions and publication bias. Patient-level data from TAVI studies prospectively reporting on CKD could be of added value to confirm our finding and further elucidate this topic. Because of incomplete/unequal reporting of data, not all the studies were available for pooled analyses of certain outcomes, which could lead to a potential publication bias. Finally, a longer follow-up (>1 year) is not available to date for the majority of the included studies.

Conclusions

Moderate and severe preoperative CKD significantly worsen the early and the late prognosis of patients undergoing TAVI. The results of the present meta-analysis should be considered hypothesis-generating for future studies on risk evaluation, prevention strategies and postoperative management.

Disclosures

None.

References

- Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597–1607. doi: 10.1056/NEJMoa1008232.
- Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187–2198. doi: 10.1056/NEJMoa1103510.
- Dunning J, Gao H, Chambers J, Moat N, Murphy G, Pagano D, Ray S, Roxburgh J, Bridgewater B. Aortic valve surgery: marked increases in volume and significant decreases in mechanical valve use—an analysis of 41,227 patients over 5 years from the society for cardiothoracic surgery

- in Great Britain and Ireland national database. *J Thorac Cardiovasc Surg*. 2011;142:776.e3–782.e3.
4. Mehta RH, Honeycutt E, Patel UD, Lopes RD, Shaw LK, Glower DD, Harrington RA, Califf RM, Sketch MH Jr. Impact of recovery of renal function on long-term mortality after coronary artery bypass grafting. *Am J Cardiol*. 2010;106:1728–1734. doi: 10.1016/j.amjcard.2010.07.045.
 5. Thomas M, Schymik G, Walther T, Himbert D, Lefèvre T, Treede H, Eggebrecht H, Rubino P, Colombo A, Lange R, Schwarz RR, Wendler O. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation*. 2011;124:425–433. doi: 10.1161/CIRCULATIONAHA.110.001545.
 6. Zahn R, Gerckens U, Linke A, Sievert H, Kahlert P, Hambrecht R, Sack S, Abdel-Wahab M, Hoffmann E, Schiele R, Schneider S, Senges J; German Transcatheter Aortic Valve Interventions-Registry Investigators. Predictors of one-year mortality after transcatheter aortic valve implantation for severe symptomatic aortic stenosis. *Am J Cardiol*. 2013;112:272–279. doi: 10.1016/j.amjcard.2013.03.024.
 7. Rodés-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Martucci G, DeVarennes B, Chisholm R, Peterson MD, Lichtenstein SV, Nietlispach F, Doyle D, DeLarochellière R, Teoh K, Chu V, Dancea A, Lachapelle K, Cheema A, Latter D, Horlick E. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J Am Coll Cardiol*. 2010;55:1080–1090. doi: 10.1016/j.jacc.2009.12.014.
 8. Tamburino C, Capodanno D, Ramondo A, Petronio AS, Etori F, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, Antoniucci D, Napolitano M, De Carlo M, Fiorina C, Ussia GP. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation*. 2011;123:299–308. doi: 10.1161/CIRCULATIONAHA.110.946533.
 9. Moat NE, Ludman P, de Belder MA, Bridgewater B, Cunningham AD, Young CP, Thomas M, Kovac J, Spyt T, MacCarthy PA, Wendler O, Hildick-Smith D, Davies SW, Trivedi U, Blackman DJ, Levy RD, Brecker SJ, Baumbach A, Daniel T, Gray H, Mullen MJ. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J Am Coll Cardiol*. 2011;58:2130–2138. doi: 10.1016/j.jacc.2011.08.050.
 10. Allende R, Webb JG, Munoz-Garcia AJ, de Jaegere P, Tamburino C, Dager AE, Cheema A, Serra V, Amat-Santos I, Velianou JL, Barbanti M, Dvir D, Alonso-Briales JH, Nuis RJ, Faqiri E, Imme S, Benitez LM, Cucalon AM, Al Lawati H, Garcia del Blanco B, Lopez J, Natarajan MK, DeLarochellière R, Urena M, Ribeiro HB, Dumont E, Nombela-Franco L, Rodés-Cabau J. Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes and prognostic markers from a large cohort of patients. *Eur Heart J*. 2014;35:2685–2696. doi: 10.1093/eurheartj/ehu175.
 11. Yamamoto M, Hayashida K, Mouillet G, Hovasse T, Chevalier B, Oguri A, Watanabe Y, Dubois-Randé JL, Morice MC, Lefèvre T, Teiger E. Prognostic value of chronic kidney disease after transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2013;62:869–877. doi: 10.1016/j.jacc.2013.04.057.
 12. D'Ascenzo F, Moretti C, Salizzoni S, Bollati M, D'Amico M, Ballocca F, Giordana F, Barbanti M, Ussia GP, Brambilla N, Bedogni F, Biondi Zoccai G, Tamburino C, Gaita F, Sheiban I. 30 days and midterm outcomes of patients undergoing percutaneous replacement of aortic valve according to their renal function: a multicenter study. *Int J Cardiol*. 2013;167:1514–1518. doi: 10.1016/j.ijcard.2012.04.161.
 13. Wessely M, Rau S, Lange P, Kehl K, Renz V, Schönermarck U, Steinbeck G, Fischereder M, Boekstegers P. Chronic kidney disease is not associated with a higher risk for mortality or acute kidney injury in transcatheter aortic valve implantation. *Nephrol Dial Transplant*. 2012;27:3502–3508. doi: 10.1093/ndt/gfs102.
 14. Sannino A, Gargiulo G, Schiattarella GG, Brevetti L, Perrino C, Stabile E, Losi MA, Toscano E, Giugliano G, Scudiero F, Chiacchio E, Trimarco B, Esposito G. Increased mortality after transcatheter aortic valve implantation (TAVI) in patients with severe aortic stenosis and low ejection fraction: a meta-analysis of 6898 patients. *Int J Cardiol*. 2014;176:32–39. doi: 10.1016/j.ijcard.2014.06.017.
 15. Sannino A, Losi MA, Schiattarella GG, Gargiulo G, Perrino C, Stabile E, Toscano E, Giugliano G, Brevetti L, Franzona A, Cirillo P, Imbriaco M, Trimarco B, Esposito G. Meta-analysis of mortality outcomes and mitral regurgitation evolution in 4,839 patients having transcatheter aortic valve implantation for severe aortic stenosis. *Am J Cardiol*. 2014;114:875–882. doi: 10.1016/j.amjcard.2014.06.022.
 16. Stabile E, Sannino A, Schiattarella GG, Gargiulo G, Toscano E, Brevetti L, Scudiero F, Giugliano G, Perrino C, Trimarco B, Esposito G. Cerebral embolic lesions detected with diffusion-weighted magnetic resonance imaging following carotid artery stenting: a meta-analysis of 8 studies comparing filter cerebral protection and proximal balloon occlusion. *JACC Cardiovasc Interv*. 2014;7:1177–1183. doi: 10.1016/j.jcin.2014.05.019.
 17. Dumonteil N, van der Boon RM, Tchetché D, Chieffo A, Van Mieghem NM, Marcheix B, Buchanan GL, Vahdat O, Serruys PW, Fajadet J, Colombo A, de Jaegere PP, Carrié D. Impact of preoperative chronic kidney disease on short- and long-term outcomes after transcatheter aortic valve implantation: a Pooled-Rotterdam-Milano-Toulouse In Collaboration Plus (PRAGMATIC-Plus) initiative substudy. *Am Heart J*. 2013;165:752–760. doi: 10.1016/j.ahj.2012.12.013.
 18. Goebel N, Baumbach H, Ahad S, Voehringer M, Hill S, Albert M, Franke UF. Transcatheter aortic valve replacement: does kidney function affect outcome? *Ann Thorac Surg*. 2013;96:507–512. doi: 10.1016/j.athoracsurg.2013.04.035.
 19. Nguyen TC, Babaliaros VC, Razavi SA, Kilgo PD, Guyton RA, Devireddy CM, Shults CC, Mavromatis K, Kanitkar M, Block P, Lerakis S, Thourani VH. Impact of varying degrees of renal dysfunction on transcatheter and surgical aortic valve replacement. *J Thorac Cardiovasc Surg*. 2013;146:1399–1406, discussion 13406–13407. doi: 10.1016/j.jtcvs.2013.07.065.
 20. Sinning JM, Ghanem A, Steinhäuser H, Adenauer V, Hammerstingl C, Nickenig G, Werner N. Renal function as predictor of mortality in patients after percutaneous transcatheter aortic valve implantation. *JACC Cardiovasc Interv*. 2010;3:1141–1149. doi: 10.1016/j.jcin.2010.09.009.
 21. Nuis RJ, Van Mieghem NM, Tzikas A, Piazza N, Otten AM, Cheng J, van Domburg RT, Betjes M, Serruys PW, de Jaegere PP. Frequency, determinants, and prognostic effects of acute kidney injury and red blood cell transfusion in patients undergoing transcatheter aortic valve implantation. *Catheter Cardiovasc Interv*. 2011;77:881–889. doi: 10.1002/ccd.22874.
 22. Kahn MR, Robbins MJ, Kim MC, Fuster V. Management of cardiovascular disease in patients with kidney disease. *Nat Rev Cardiol*. 2013;10:261–273. doi: 10.1038/nrcardio.2013.15.
 23. Bagur R, Webb JG, Nietlispach F, Dumont E, De Larochellière R, Doyle D, Masson JB, Gutiérrez MJ, Clavel MA, Bertrand OF, Pibarot P, Rodés-Cabau J. Acute kidney injury following transcatheter aortic valve implantation: predictive factors, prognostic value, and comparison with surgical aortic valve replacement. *Eur Heart J*. 2010;31:865–874. doi: 10.1093/eurheartj/ehp552.
 24. Elhmidi Y, Bleiziffer S, Piazza N, Hutter A, Opitz A, Hettich I, Kornek M, Ruge H, Brockmann G, Mazzitelli D, Lange R. Incidence and predictors of acute kidney injury in patients undergoing transcatheter aortic valve implantation. *Am Heart J*. 2011;161:735–739. doi: 10.1016/j.ahj.2011.01.009.
 25. Saia F, Ciuca C, Taglieri N, Marrozzini C, Savini C, Bordoni B, Dall'Ara G, Moretti C, Pilato E, Martin-Suárez S, Petridis FD, Di Bartolomeo R, Branzi A, Marzocchi A. Acute kidney injury following transcatheter aortic valve implantation: incidence, predictors and clinical outcome. *Int J Cardiol*. 2013;168:1034–1040. doi: 10.1016/j.ijcard.2012.10.029.

Moderate and Severe Preoperative Chronic Kidney Disease Worsen Clinical Outcomes After Transcatheter Aortic Valve Implantation: Meta-Analysis of 4992 Patients

Giuseppe Gargiulo, Davide Capodanno, Anna Sannino, Cinzia Perrino, Piera Capranzano, Eugenio Stabile, Bruno Trimarco, Corrado Tamburino and Giovanni Esposito

Circ Cardiovasc Interv. 2015;8:

doi: 10.1161/CIRCINTERVENTIONS.114.002220

Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2015 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circinterventions.ahajournals.org/content/8/2/e002220>

Data Supplement (unedited) at:

<http://circinterventions.ahajournals.org/content/suppl/2015/03/09/CIRCINTERVENTIONS.114.002220.DC1>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Cardiovascular Interventions* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation: Cardiovascular Interventions* is online at:
<http://circinterventions.ahajournals.org/subscriptions/>

**MODERATE AND SEVERE PREOPERATIVE CHRONIC KIDNEY DISEASE
WORSEN CLINICAL OUTCOMES AFTER TAVI: A META-ANALYSIS OF 4,992
PATIENTS**

SUPPLEMENTAL MATERIAL

TABLE OF CONTENTS

Page 2. Online Table 1. Sensitivity analysis in patients with CKD 3-5 vs CKD 1-2.
Page 3. Online Table 2. Sensitivity analysis in patients with CKD 4-5 vs CKD 1-2.
Page 4. Online Table 3. Sensitivity analysis in patients with CKD 3 vs CKD 1-2.
Page 5. Online Table 4. Sensitivity analysis in patients with CKD 4-5 vs CKD 3.
Page 6. Online Figure 1. Early cardiovascular mortality according to CKD stages.
Page 7. Online Figure 2. 1-year cardiovascular mortality according to CKD stages.
Page 8. Online Figure 3. Early stroke according to CKD stages.
Page 9. Online Figure 4. Early AKI according to CKD stages.
Page 10. Online Figure 5. Early AKI 2-3 according to CKD stages.
Page 11. Online Figure 6. Early need for dialysis according to CKD stages.
Page 12. Online Figure 7. Early bleeding (life-threatening or major) according to CKD stages.
Page 13. Online Figure 8. In-hospital length of stay according to CKD stages.
Page 14. Online Figure 9. Contrast medium administration according to CKD stages.
Page 15-23. Online Figures 10-18. Funnel plots.
Page 24-25. Supplementary references.

Online Table 1. Sensitivity analysis in patients with preoperative CKD 3-5 versus CKD 1-2

Outcome	Allende et al (1)	D'Ascezo et al (2)	Dumonteil et al (3)	Goebel et al (4)	Nguyen et al (5)	Nuis et al (6)	Sinning et al (7)	Wessely et al (8)	Yamamoto et al (9)
Death									
Early all-cause	1.41 [0.91-2.17]	1.40 [1.04-1.88]	1.36 [0.93-2.01]	1.46 [1.03-2.05]	1.49 [1.10-2.03]	-	-	1.53 [1.20-1.94]	1.34 [0.96-1.87]
Early cv	-	1.56 [0.95-2.58]	2.30 [0.89-5.96]	1.62 [0.97-2.70]	-	-	-	-	-
1-year all-cause	1.80 [1.19-2.71]	1.61 [1.16-2.24]	1.58 [1.09-2.28]	-	1.83 [1.39-2.41]	-	1.58 [1.19-2.11]	-	1.60 [1.11-2.31]
Stroke	2.04 [1.14-3.66]	1.85 [1.24-2.76]	1.85 [1.19-2.88]	1.82 [1.22-2.72]	1.88 [1.26-2.81]	-	-	-	1.79 [1.18-2.73]
AKI	1.55 [1.22-1.97]	1.41 [1.19-1.67]	1.35 [1.11-1.65]	1.40 [1.18-1.66]	-	1.43 [1.20-1.69]	-	1.45 [1.22-1.72]	-
AKI 2-3	1.90 [1.39-2.59]	1.63 [1.07-2.49]	1.30 [0.96-1.76]	1.49 [0.97-2.29]	-	1.62 [1.06-2.49]	-	-	1.67 [0.96-2.92]
Need for dialysis	1.61 [0.82-3.16]	2.06 [1.02-4.17]	-	1.92 [0.80-4.58]	2.39 [1.25-4.60]	-	-	2.01 [0.93-4.30]	2.46 [1.33-4.56]
Bleeding (Major or life-threatening)	1.01 [0.78-1.29]	1.13 [0.88-1.46]	1.21 [0.93-1.66]	-	-	-	-	-	-
Contrast medium*	-	-10.88 [-19.60--2.15]	-	-	-2.65 [-16.44-11.14]	-	-	-4.86 [-19.40-9.68]	-2.70 [-16.95-11.55]

The estimation effect is OR by random effects. *The estimation effect is mean difference by random effects.

Online Table 2. Sensitivity analysis in patients with preoperative CKD 4-5 versus CKD 1-2

Outcome	Allende et al (1)	D'Ascenzo et al (2)	Dumonteil et al (3)	Nguyen et al (5)	Yamamoto et al (9)
Death					
Early all-cause	2.75 [1.65-4.59]	2.25 [1.55-3.27]	2.42 [1.59-3.68]	2.35 [1.63-3.41]	1.99 [1.32-3.00]
1-year all-cause	2.59 [1.29-5.21]	2.54 [1.40-4.60]	2.17 [1.14-4.13]	3.00 [2.04-4.42]	2.19 [1.21-3.9]
Stroke	3.39 [1.57-7.32]	2.65 [1.50-4.69]	2.67 [1.41-5.02]	2.63 [1.49-4.64]	2.37 [1.29-4.36]
AKI	2.90 [1.91-4.40]	2.03 [0.95-4.32]	1.49 [1.03-2.15]	-	-
AKI 2-3	3.39 [1.48-7.78]	2.64 [1.12-6.21]	1.75 [1.07-2.87]	-	2.75 [0.66-8.80]
Need for dialysis	1.49 [0.26-8.60]	3.15 [0.31-31.69]	-	5.84 [0.93-36.78]	6.72 [1.28-35.21]
Bleeding (Major or life-threatening)	1.34 [0.92-1.96]	1.72 [0.99-2.99]	2.04 [1.36-3.04]	-	-
Contrast medium*	-	-38.01 [-59.83--16.18]	-	-13.72 [-33.67-6.23]	-26.37 [-68.51-15.77]

The estimation effect is OR by random effects. *The estimation effect is mean difference by random effects.

Online Table 3. Sensitivity analysis in patients with preoperative CKD 3 versus CKD 1-2

Outcome	Allende et al (1)	D'Ascenzo et al (2)	Dumonteil et al (3)	Nguyen et al (5)	Yamamoto et al (9)
Death					
Early all-cause	1.57 [1.08-2.29]	1.39 [1.07-1.81]	1.39 [1.03-1.87]	1.47 [1.12-1.91]	1.38 [1.03-1.84]
1-year all-cause	1.52 [1.13-2.05]	1.37 [1.10-1.70]	1.35 [1.04-1.76]	1.46 [1.19-1.78]	1.35 [1.05-1.73]
Stroke	1.69 [0.90-3.20]	1.66 [1.09-2.55]	1.66 [1.04-2.66]	1.69 [1.10-2.59]	1.62 [1.03-2.53]
AKI	1.37 [1.00-1.87]	1.30 [1.07-1.59]	1.32 [1.05-1.68]	-	-
AKI 2-3	1.51 [1.05-2.16]	1.29 [0.87-1.91]	1.10 [0.78-1.55]	-	1.23 [0.68-2.22]
Need for dialysis	0.90 [0.28-2.87]	1.59 [0.63-4.03]	-	1.75 [0.62-4.93]	1.96 [0.74-5.16]
Bleeding (Major or life-threatening)	0.93 [0.71-1.20]	1.01 [0.81-1.26]	1.05 [0.77-1.44]	-	-
Contrast medium*	-	-8.51 [-18.97-1.95]	-	2.61 [-21.40-26.62]	4.41 [-17.14-25.95]

The estimation effect is OR by random effects. *The estimation effect is mean difference by random effects.

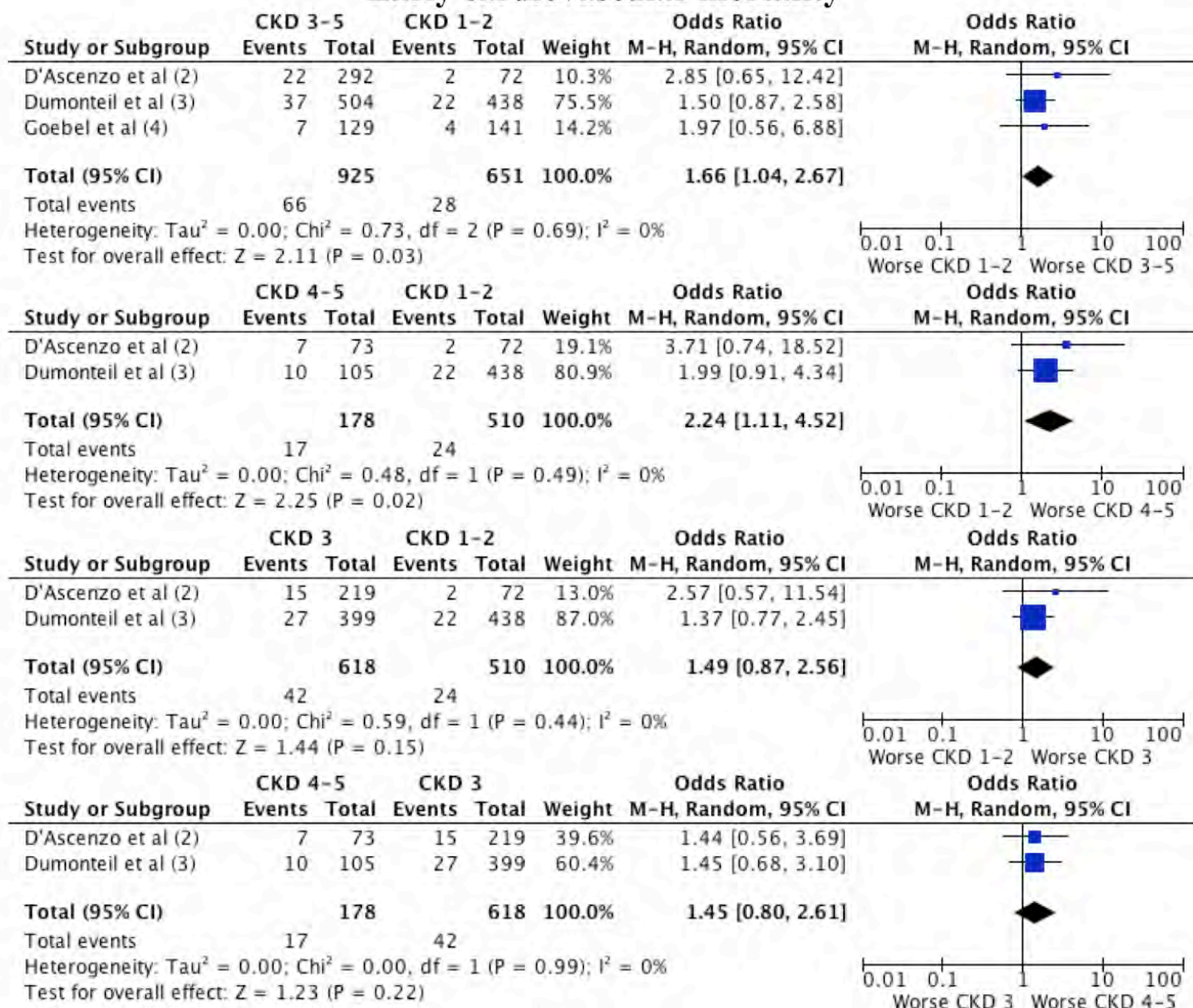
Online Table 4. Sensitivity analysis in patients with preoperative CKD 4-5 versus CKD 3

Outcome	Allende et al (1)	D'Ascenzo et al (2)	Dumonteil et al (3)	Nguyen et al (5)	Yamamoto et al (9)
Death					
Early all-cause	1.63 [1.06-2.50]	1.63 [1.15-2.31]	1.64 [1.14-2.37]	1.57 [1.13-2.18]	1.38 [0.95-2.00]
1-year all-cause	1.58 [0.93-2.70]	1.86 [1.31-2.65]	1.51 [1.00-2.28]	1.82 [1.39-2.38]	1.54 [1.00-2.39]
Stroke	2.00 [1.05-3.83]	1.63 [0.97-2.74]	1.66 [0.95-2.88]	1.61 [0.97-2.65]	1.49 [0.86-2.59]
AKI	1.86 [1.10-3.13]	1.55 [0.74-3.24]	1.13 [0.80-1.58]	-	-
AKI 2-3	2.34 [1.41-3.91]	2.06 [1.27-3.34]	1.63 [1.02-2.61]	-	2.42 [1.47-3.97]
Need for dialysis	2.20 [0.44-10.90]	3.98 [1.63-9.73]	-	4.85 [2.13-11.04]	4.70 [2.07-10.70]
Bleeding (Major or life-threatening)	1.49 [1.04-2.14]	1.68 [1.14-2.47]	1.94 [1.33-2.81]	-	-
Contrast medium*	-	-28.77 [-53.17--4.38]	-	-19.33 [-27.76--10.89]	-28.74 [-49.03--8.45]

The estimation effect is OR by random effects. *The estimation effect is mean difference by random effects.

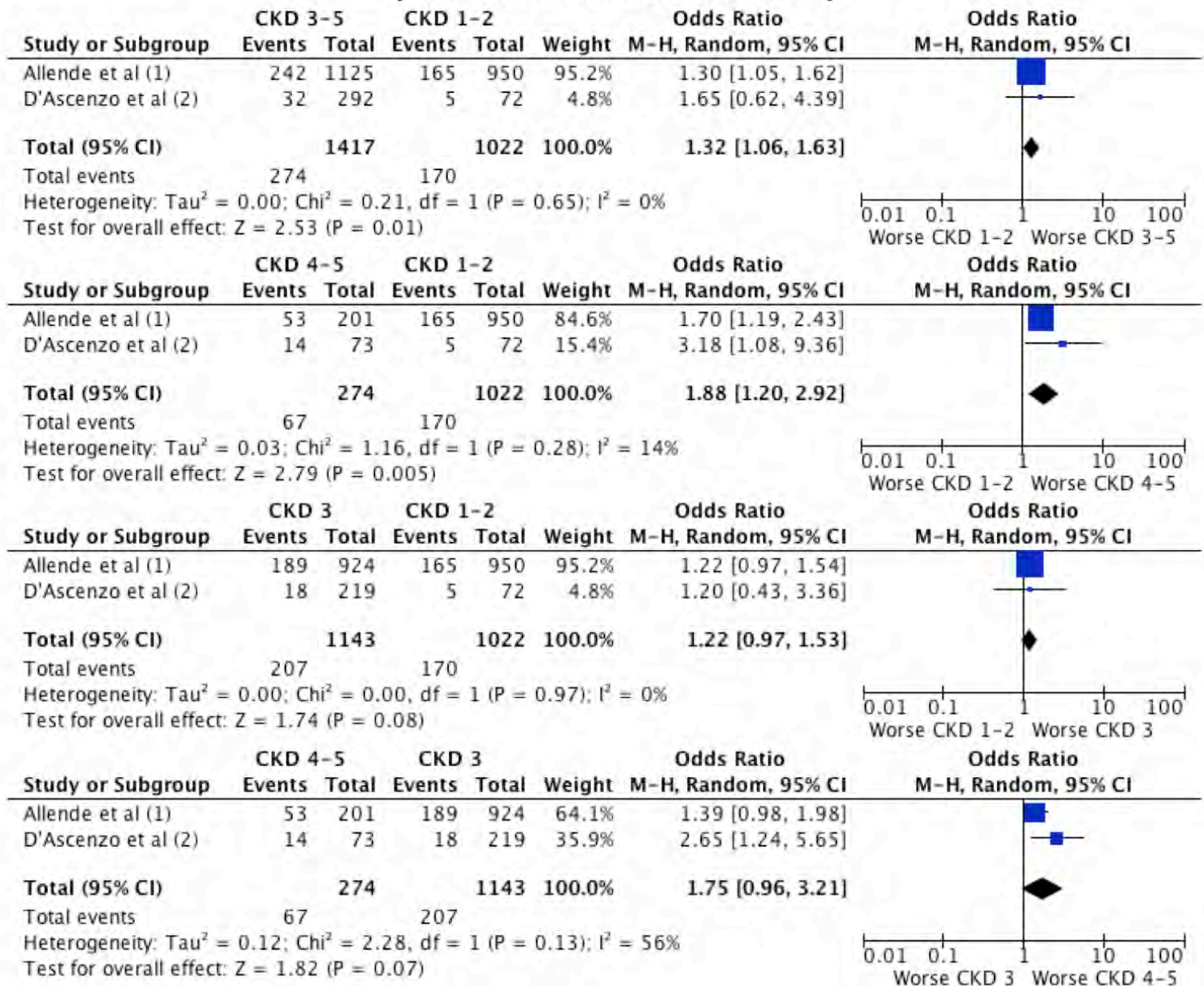
Online Figure 1

Early cardiovascular mortality



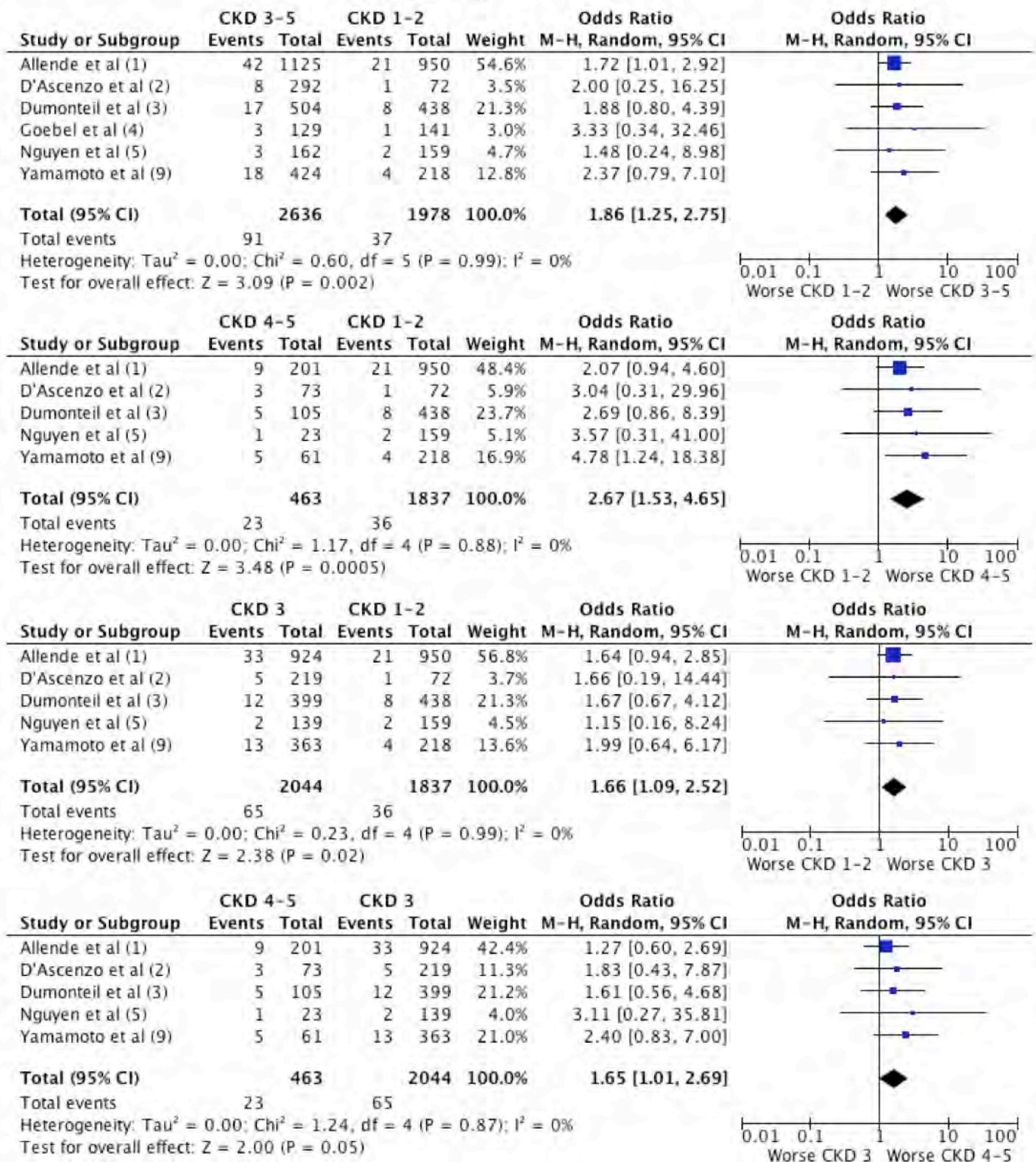
Online Figure 2

1-year cardiovascular mortality



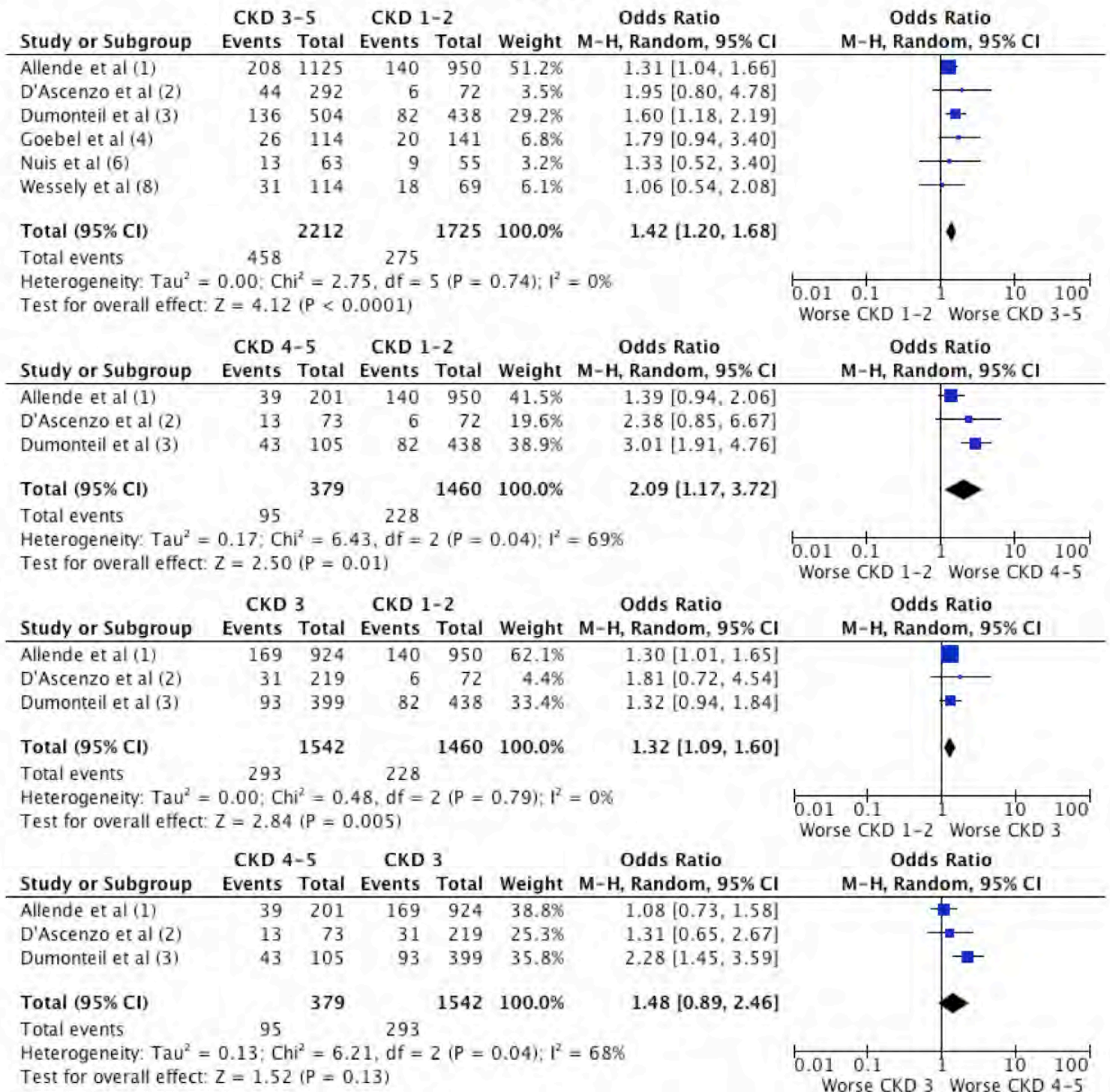
Online Figure 3

Early stroke



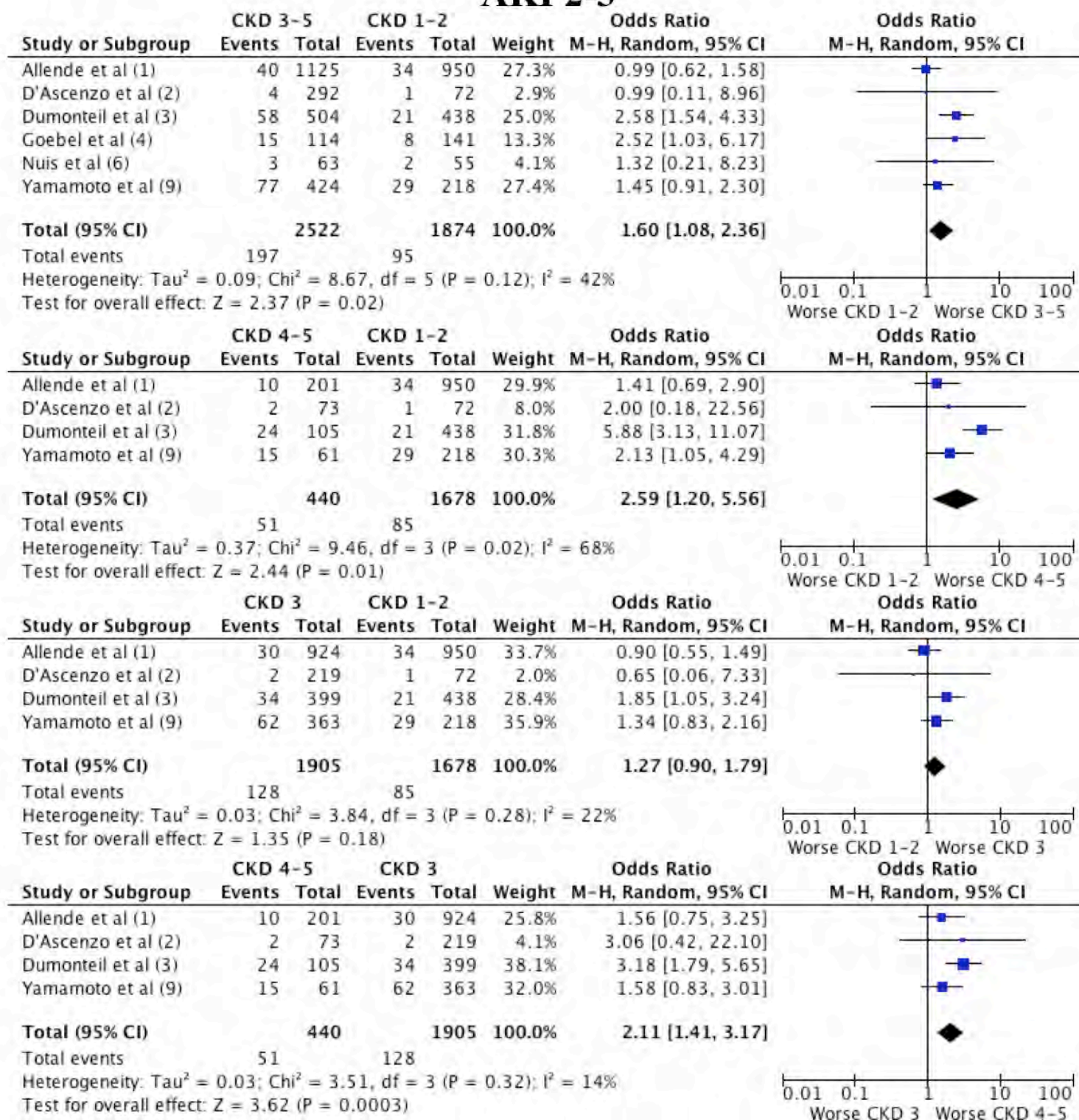
Online Figure 4

AKI



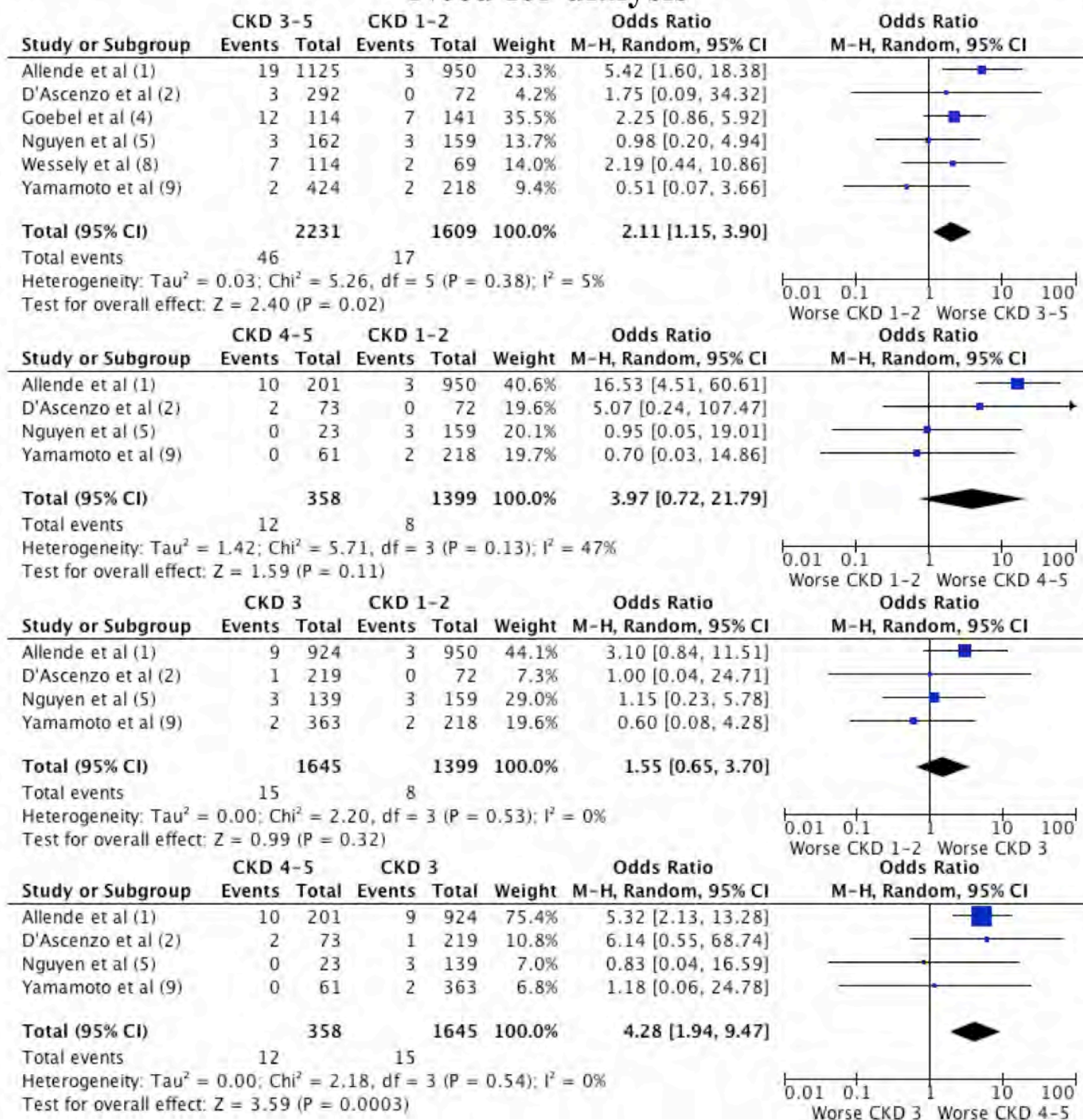
Online Figure 5

AKI 2-3



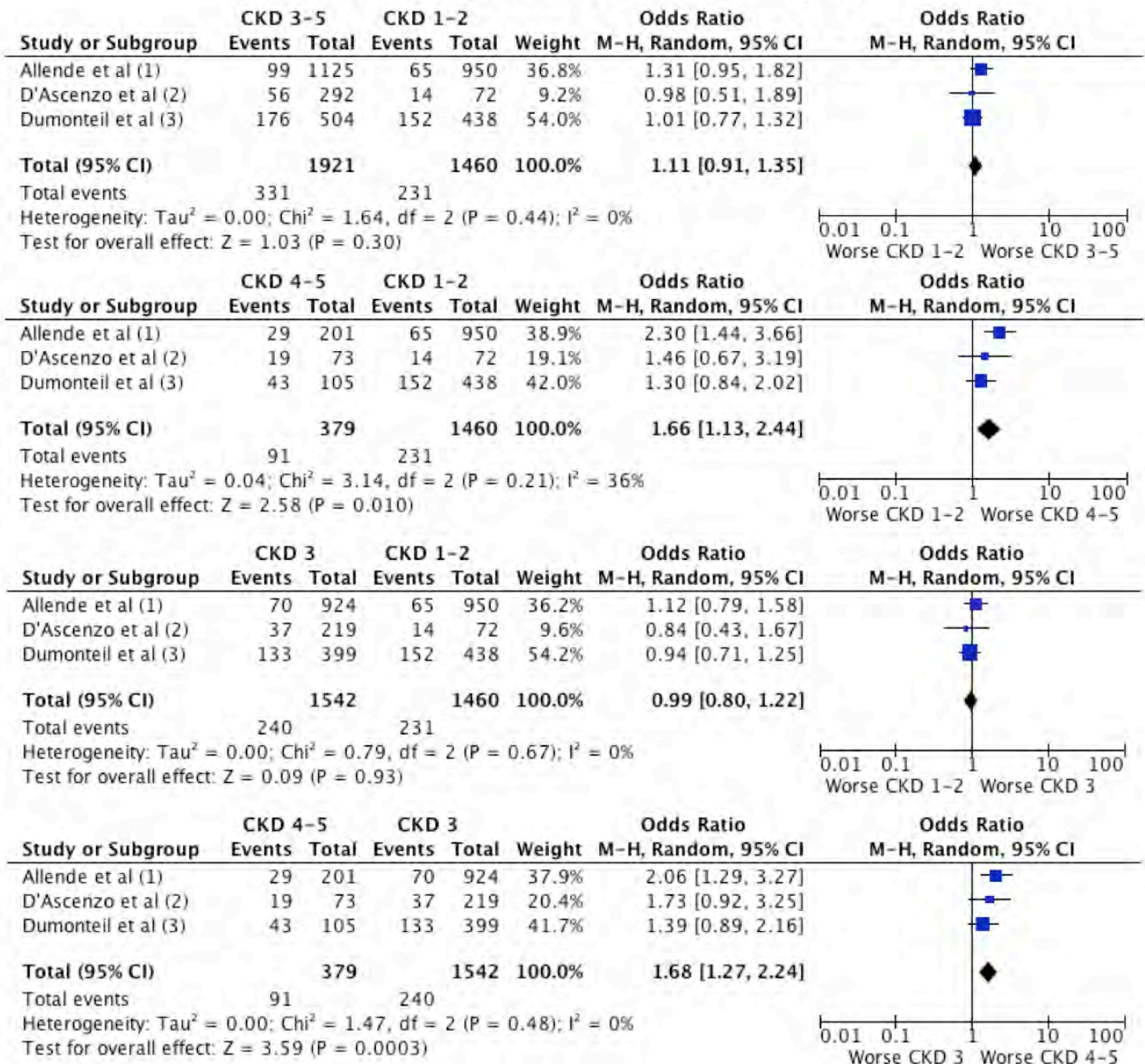
Online Figure 6

Need for dialysis



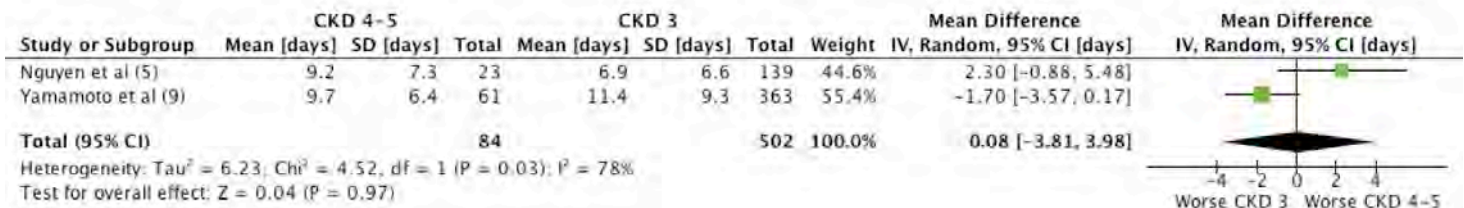
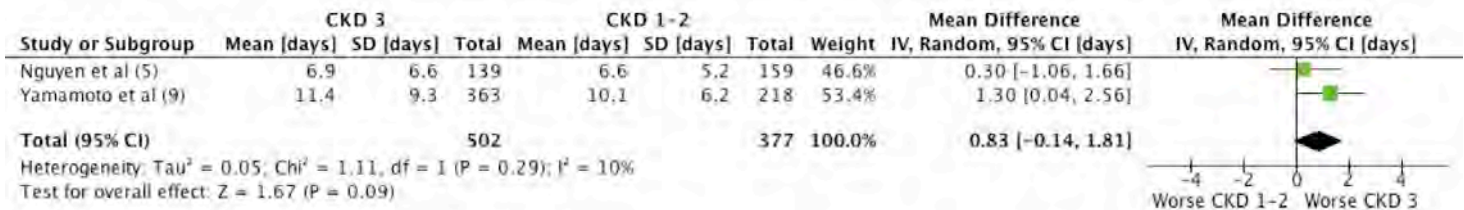
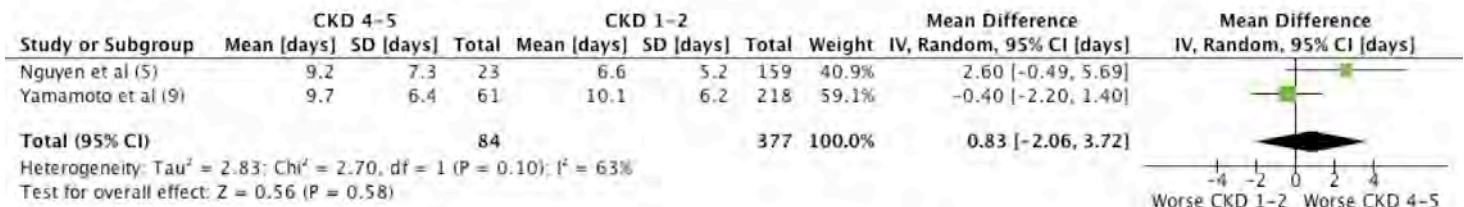
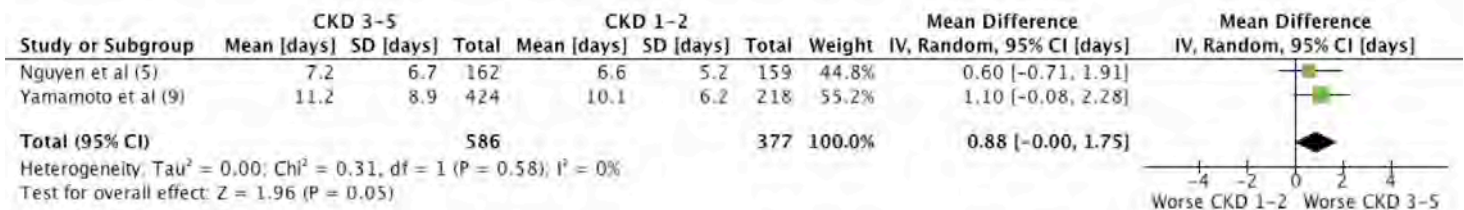
Online Figure 7

Bleeding (life threatening or major)



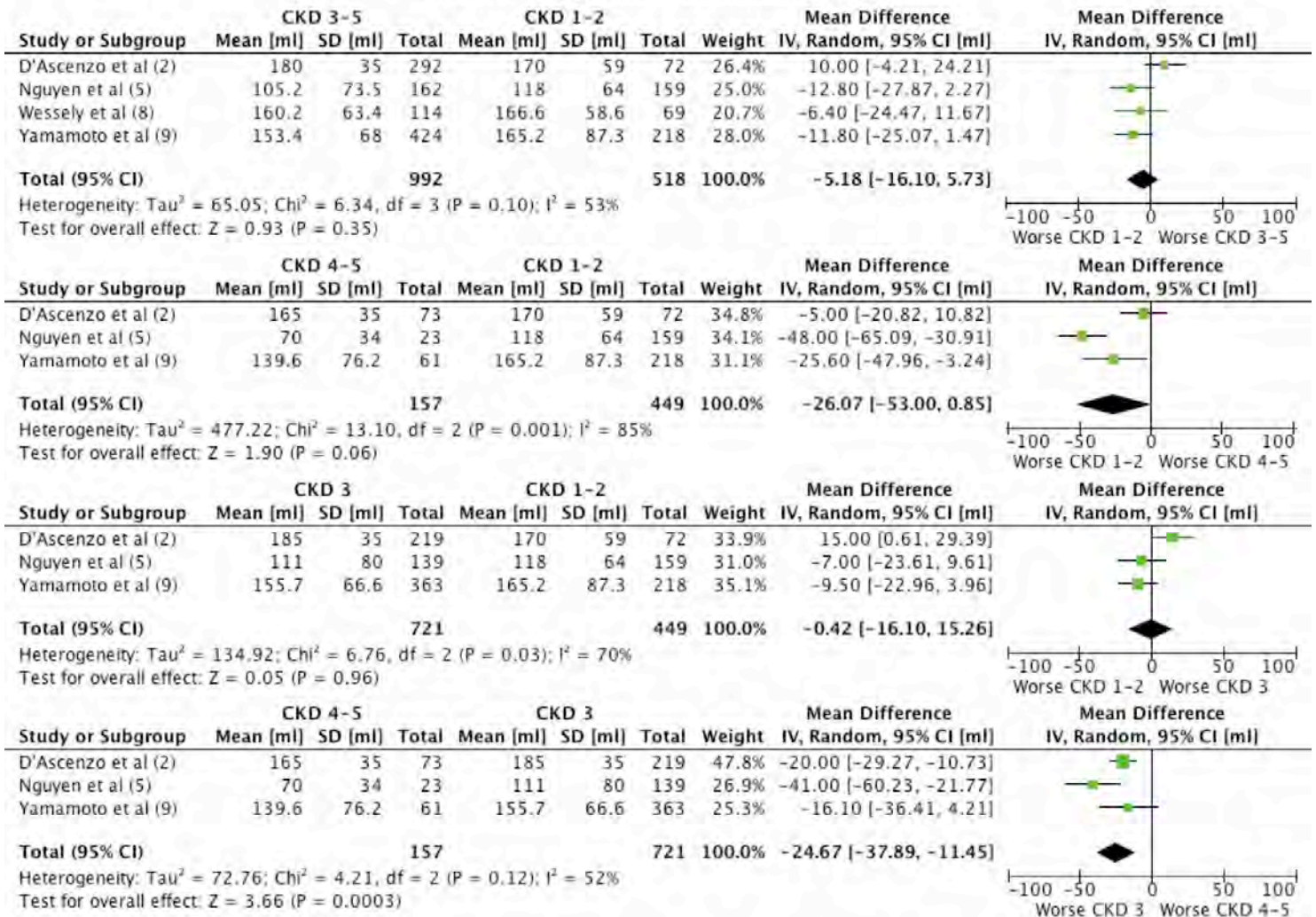
Online Figure 8

In-hospital length of stay



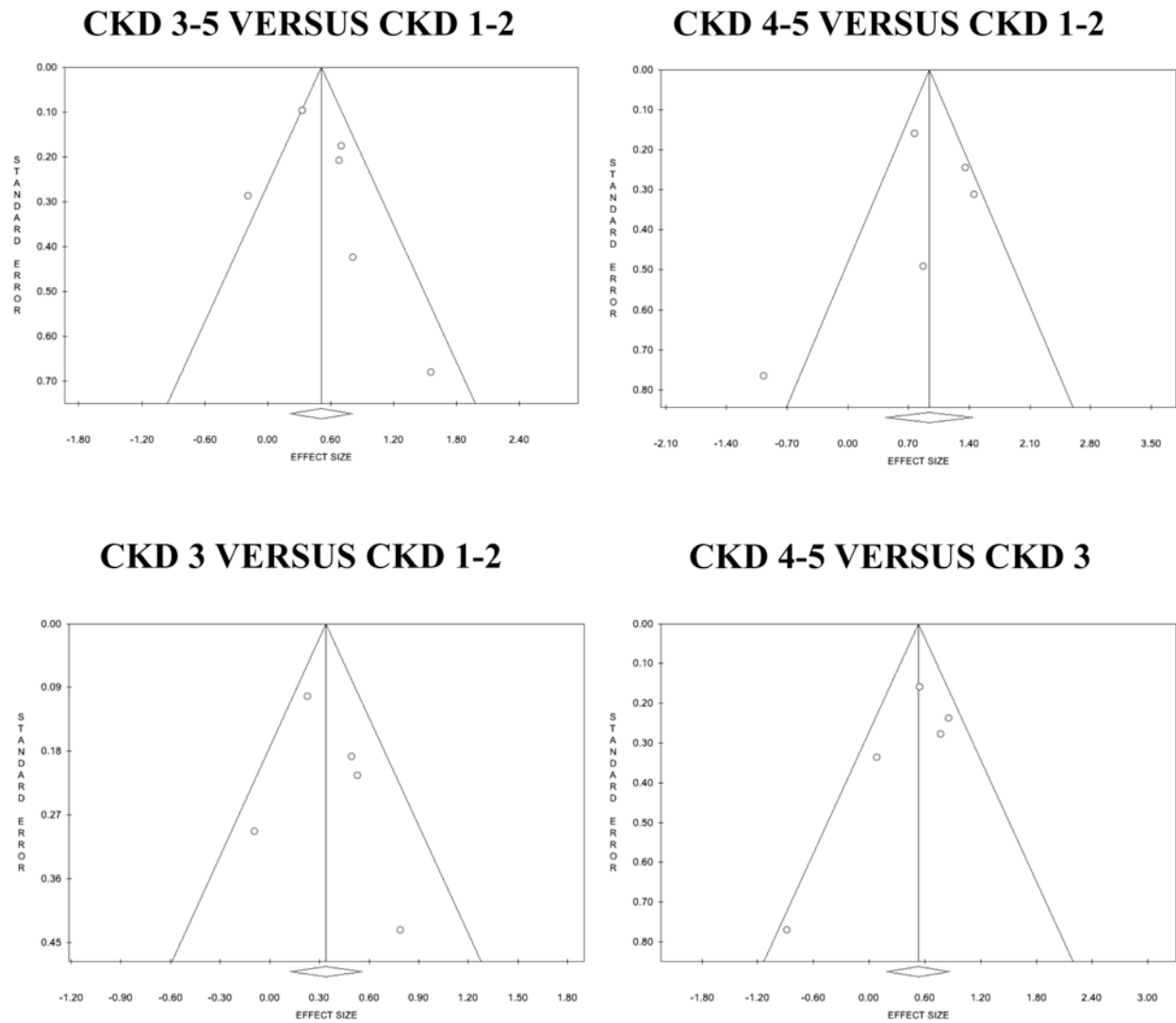
Online Figure 9

Contrast medium administration



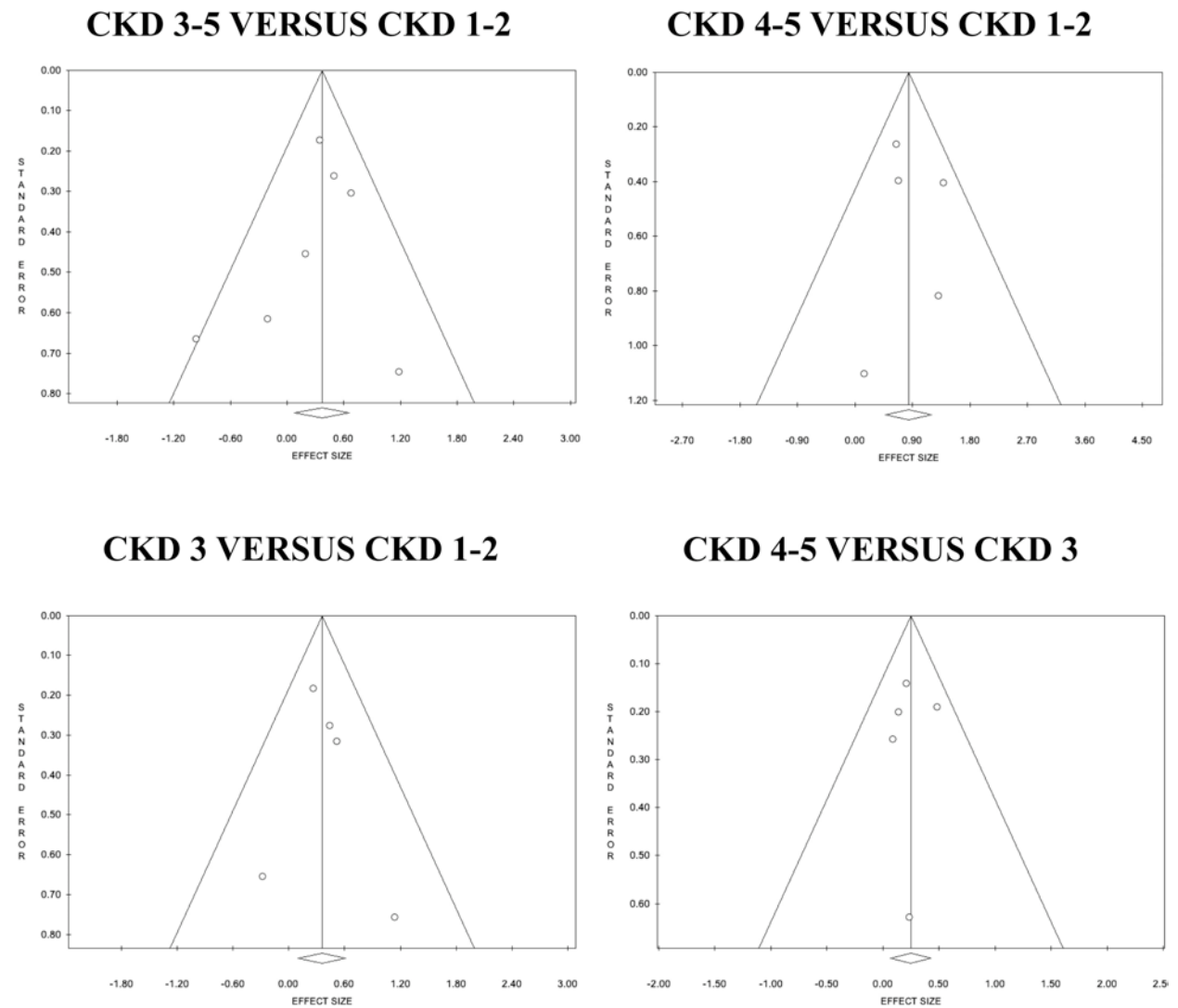
Online Figure 10

1-YEAR ALL-CAUSE MORTALITY



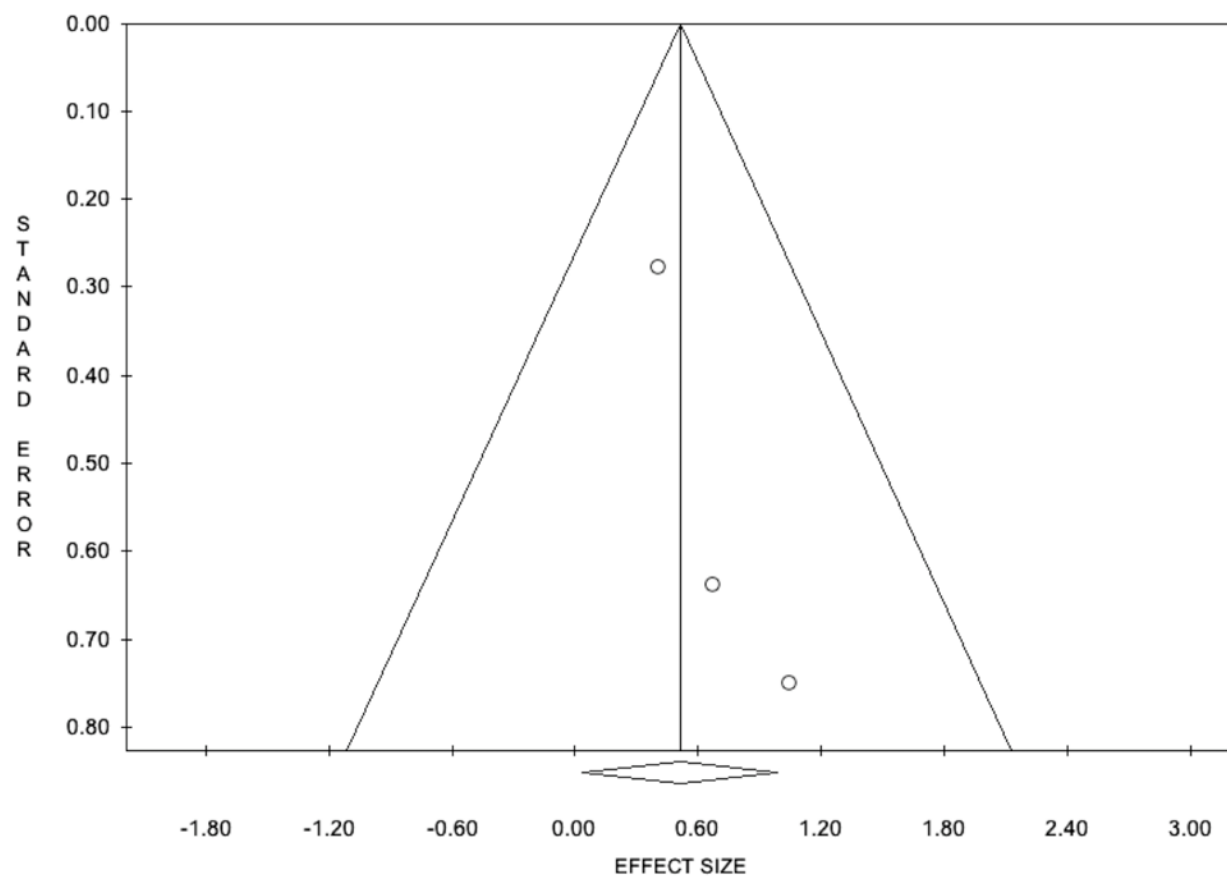
Online Figure 11

EARLY ALL-CAUSE MORTALITY



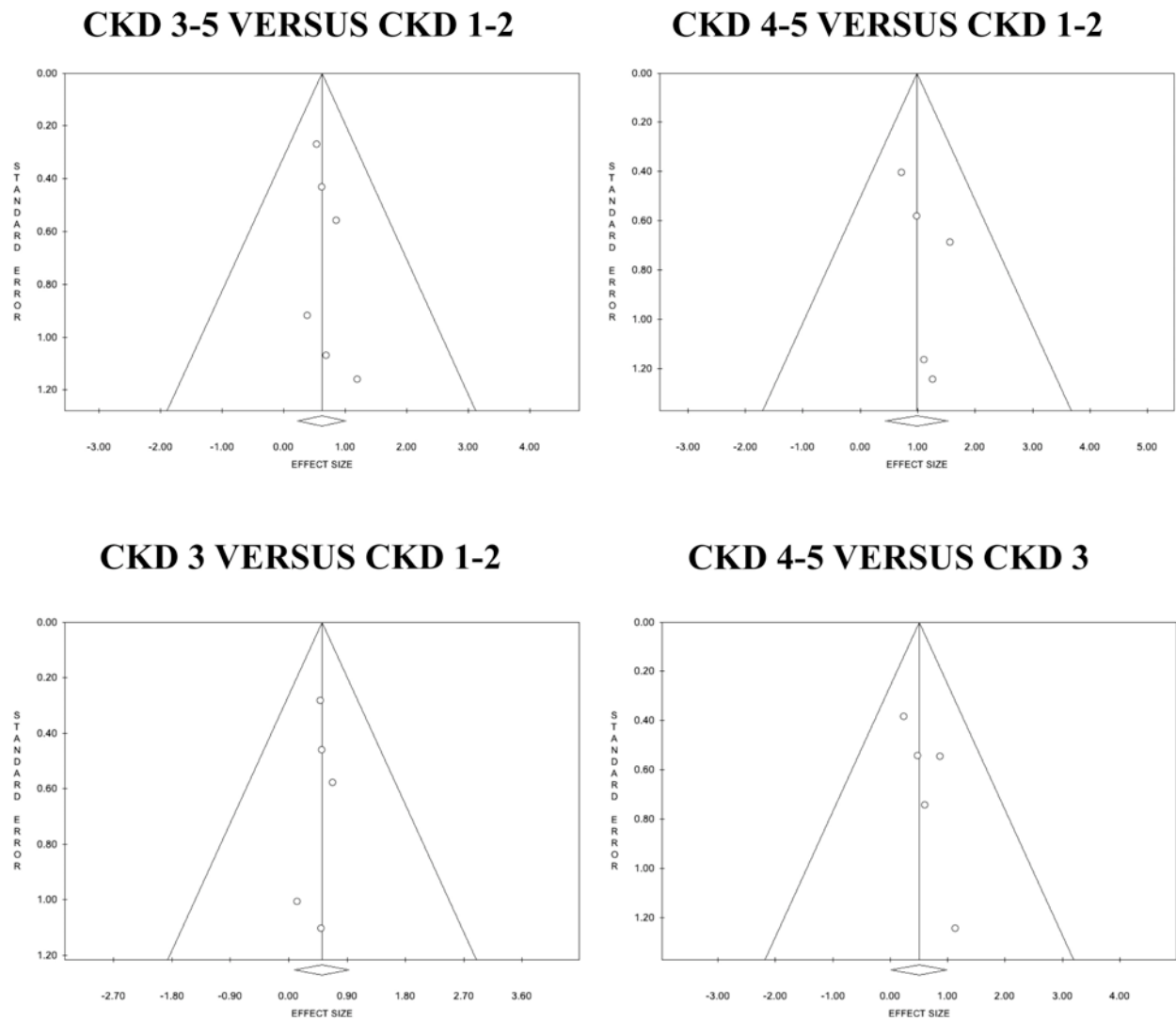
EARLY CARDIOVASCULAR MORTALITY

CKD 3-5 VERSUS CKD 1-2



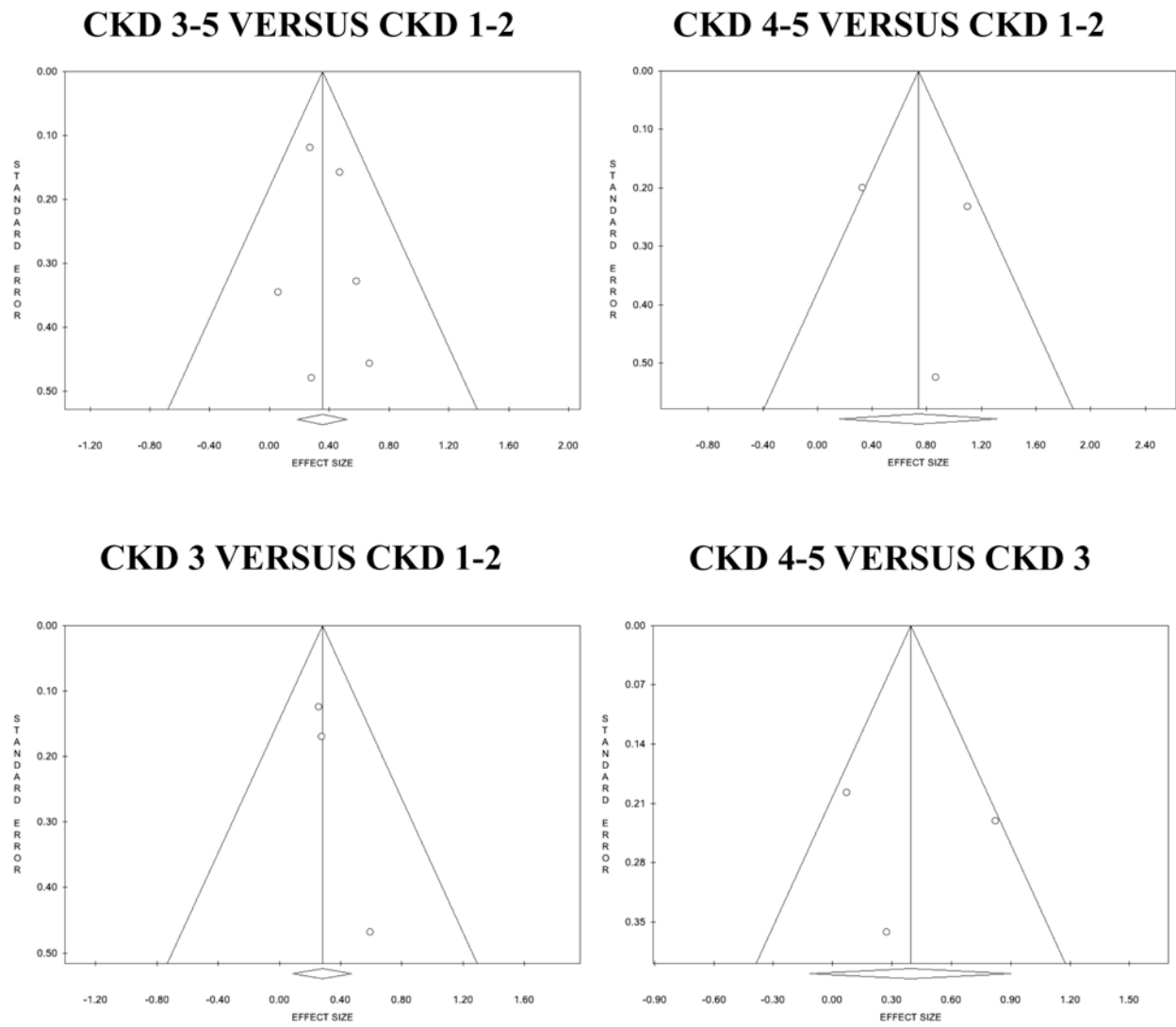
Online Figure 13

EARLY STROKE



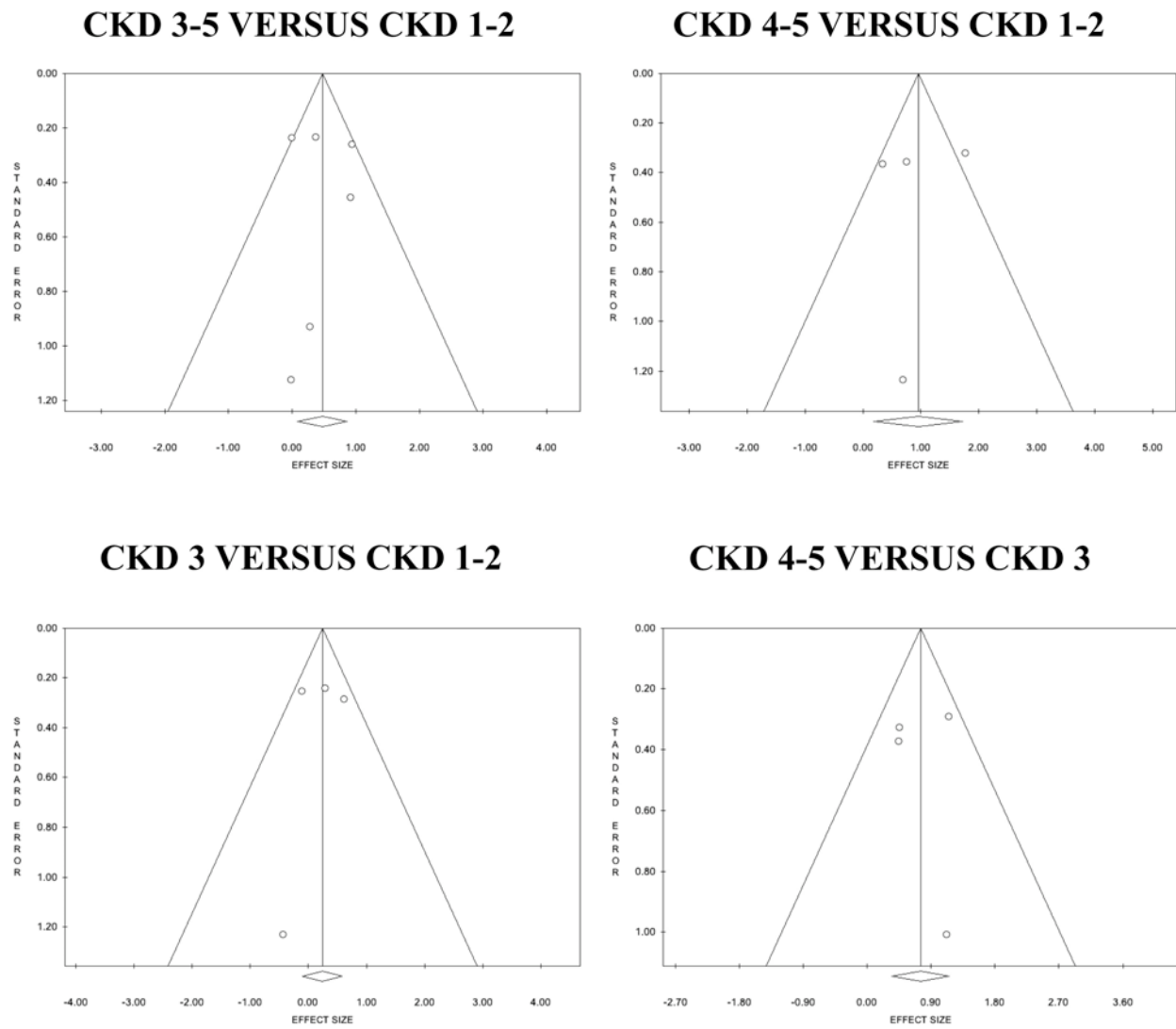
Online Figure 14

EARLY AKI



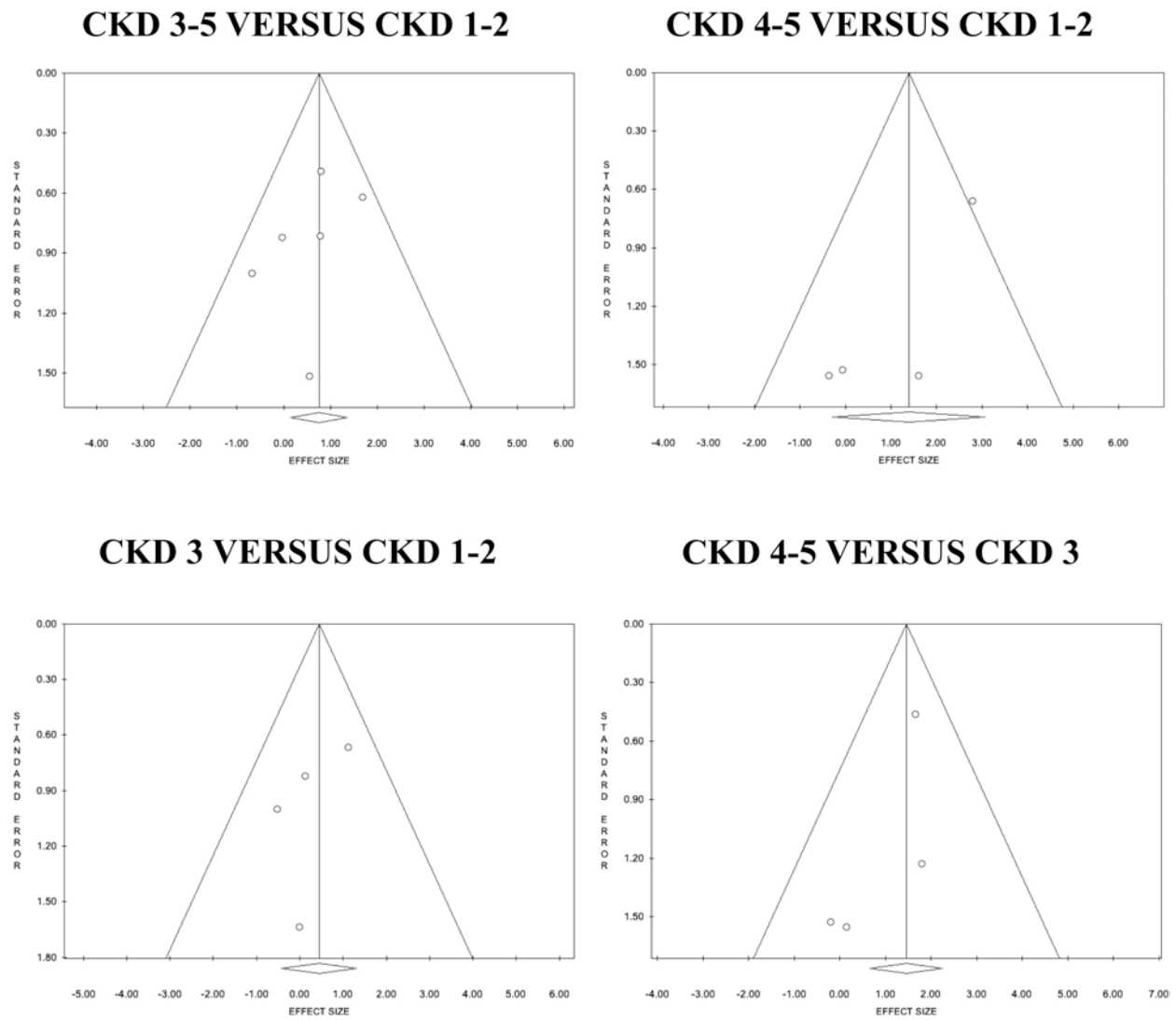
Online Figure 15

EARLY AKI 2-3



Online Figure 16

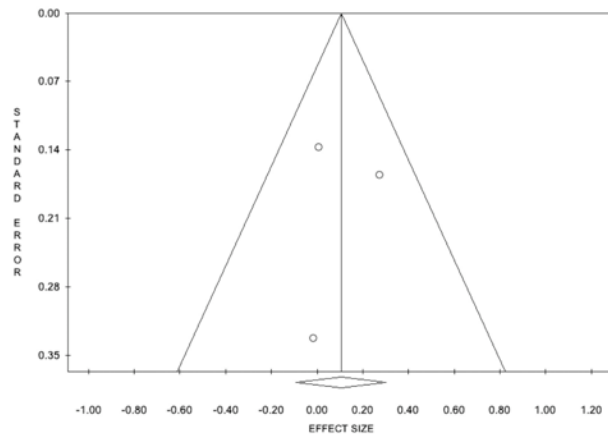
EARLY NEED FOR DIALYSIS



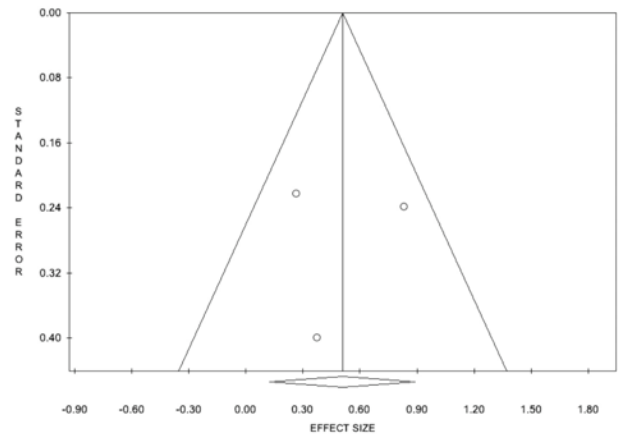
Online Figure 17

EARLY BLEEDING (LIFE-THREATENING OR MAJOR)

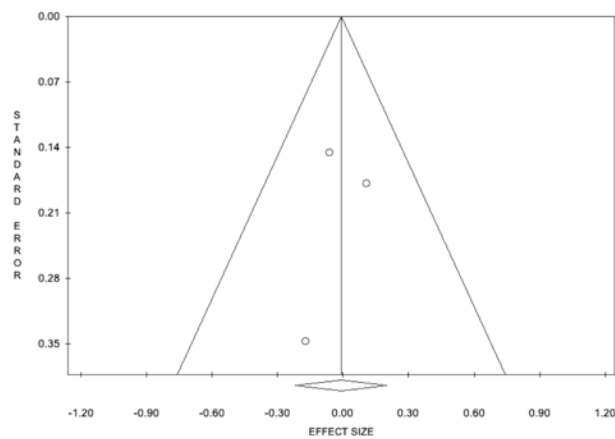
CKD 3-5 VERSUS CKD 1-2



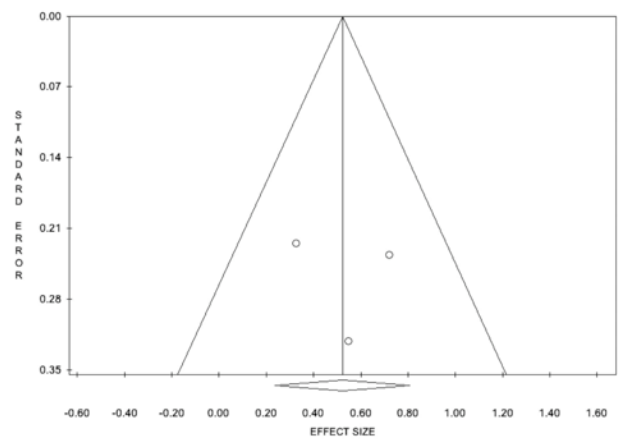
CKD 4-5 VERSUS CKD 1-2



CKD 3 VERSUS CKD 1-2



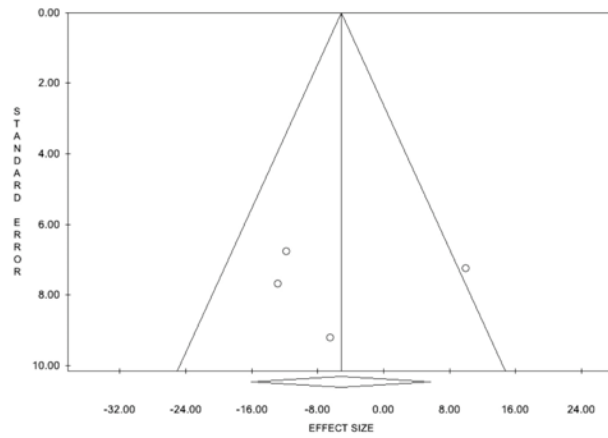
CKD 4-5 VERSUS CKD 3



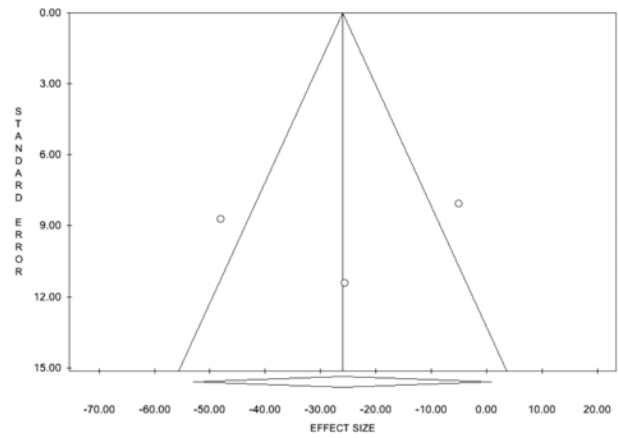
Online Figure 18

CONTRAST MEDIUM ADMINISTRATION

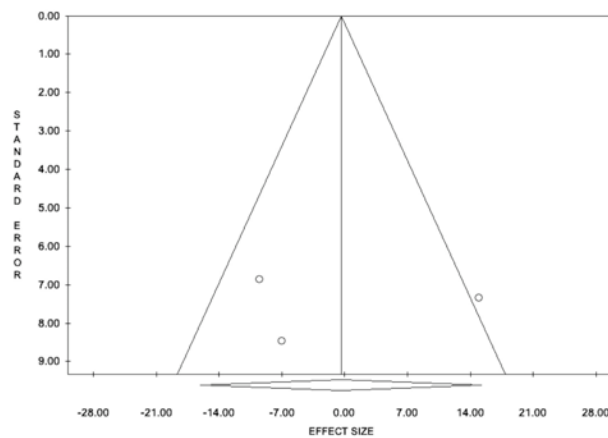
CKD 3-5 VERSUS CKD 1-2



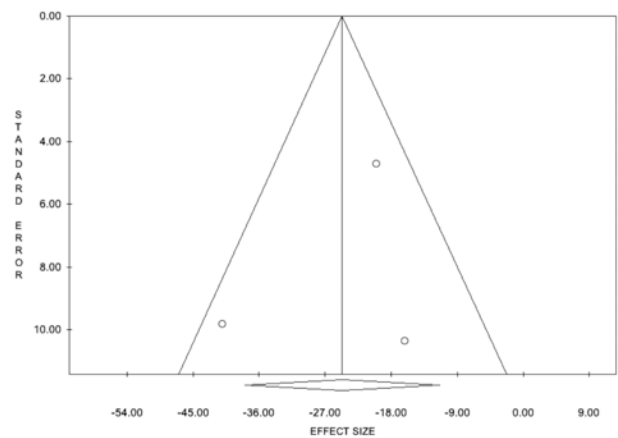
CKD 4-5 VERSUS CKD 1-2



CKD 3 VERSUS CKD 1-2



CKD 4-5 VERSUS CKD 3



Supplementary References

1. Allende R, Webb JG, Munoz-Garcia AJ, de Jaegere P, Tamburino C, Dager AE, Cheema A, Serra V, Amat-Santos I, Velianou JL, Barbanti M, Dvir D, Alonso-Briales JH, Nuis RJ, Faqiri E, Imme S, Benitez LM, Cucalon AM, Al Lawati H, Garcia Del Blanco B, Lopez J, Natarajan MK, Delarochelliere R, Urena M, Ribeiro HB, Dumont E, Nombela-Franco L, Rodes-Cabau J. Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: Insights on clinical outcomes and prognostic markers from a large cohort of patients. *Eur Heart J*. 2014;35:2685-96.
2. D'Ascenzo F, Moretti C, Salizzoni S, Bollati M, D'Amico M, Ballocca F, Giordana F, Barbanti M, Ussia GP, Brambilla N, Bedogni F, Biondi Zoccai G, Tamburino C, Gaita F, Sheiban I. 30 days and midterm outcomes of patients undergoing percutaneous replacement of aortic valve according to their renal function: A multicenter study. *Int J Cardiol*. 2013;167:1514-1518.
3. Dumonteil N, van der Boon RM, Tchetché D, Chieffo A, Van Mieghem NM, Marcheix B, Buchanan GL, Vahdat O, Serruys PW, Fajadet J, Colombo A, de Jaegere PP, Carrie D. Impact of preoperative chronic kidney disease on short- and long-term outcomes after transcatheter aortic valve implantation: A pooled-rotterdam-milano-toulouse in collaboration plus (pragmatic-plus) initiative substudy. *Am Heart J*. 2013;165:752-760.
4. Goebel N, Baumbach H, Ahad S, Voehringer M, Hill S, Albert M, Franke UF. Transcatheter aortic valve replacement: Does kidney function affect outcome? *Ann Thorac Surg*. 2013;96:507-512.
5. Nguyen TC, Babaliaros VC, Razavi SA, Kilgo PD, Guyton RA, Devireddy CM, Shults CC, Mavromatis K, Kanitkar M, Block P, Lerakis S, Thourani VH. Impact of varying

degrees of renal dysfunction on transcatheter and surgical aortic valve replacement. *J Thorac Cardiovasc Surg.* 2013;146:1399-1406; discussion 13406-13407.

6. Nuis RJ, Van Mieghem NM, Tzikas A, Piazza N, Otten AM, Cheng J, van Domburg RT, Betjes M, Serruys PW, de Jaegere PP. Frequency, determinants, and prognostic effects of acute kidney injury and red blood cell transfusion in patients undergoing transcatheter aortic valve implantation. *Catheter Cardiovasc Interv.* 2011;77:881-889.
7. Sinning JM, Ghanem A, Steinhauser H, Adenauer V, Hammerstingl C, Nickenig G, Werner N. Renal function as predictor of mortality in patients after percutaneous transcatheter aortic valve implantation. *JACC. Cardiovasc Interv.* 2010;3:1141-1149.
8. Wessely M, Rau S, Lange P, Kehl K, Renz V, Schonermarck U, Steinbeck G, Fischereder M, Boekstegers P. Chronic kidney disease is not associated with a higher risk for mortality or acute kidney injury in transcatheter aortic valve implantation. *Nephrol Dial Transpl.* 2012;27:3502-3508.
9. Yamamoto M, Hayashida K, Mouillet G, Hovasse T, Chevalier B, Oguri A, Watanabe Y, Dubois-Rande JL, Morice MC, Lefevre T, Teiger E. Prognostic value of chronic kidney disease after transcatheter aortic valve implantation. *J Am Coll Cardiol.* 2013;62:869-877.