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Clinical effects of acute kidney injury after transcatheter aortic valve implantation: a systematic review and meta-analysis

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Abstract

Several observational studies have shown that postoperative acute kidney injury (AKI) may significantly worsen the prognosis of a transcatheter aortic valve implantation (TAVI). The purpose of this systematic review and meta-analysis is to evaluate the recent evidence on the impact of AKI on clinical outcomes following TAVI. A comprehensive search in PubMed, Embase and the Cochrane Library was performed for relevant studies by two independent investigators. We pooled the odds ratio (OR) from individual studies, and performed heterogeneity, quality assessment and publication bias analysis. Forty-three eligible studies comprising 544,112 patients were included. Postoperative AKI not only significantly increased the risk for short-term and long-term all-cause mortality (OR 6.25, 95% CI 5.72–6.83, $P < 0.00001$; OR 3.49, 95% CI 2.78–4.40, $P < 0.00001$, respectively), but also increased the risk for early myocardial infarction (OR 3.98, 95% CI 1.90–8.31, $P = 0.0002$), major and life-threatening bleeding (OR 1.51, 95% CI 1.12–2.03, $P = 0.007$; OR 2.35, 95% CI 1.80–3.06, $P < 0.00001$, respectively), major vascular complications (OR 1.69, 95% CI 1.30–2.18, $P < 0.0001$), need for blood transfusion (OR 2.15, 95% CI 1.89–2.46, $P < 0.00001$) renal replacement therapy (OR 22.36, 95% CI 11.88–42.12, $P = 0.0002$) and cerebrovascular accidents (OR 1.92, 95% CI 1.23–2.98, $P = 0.004$). Acute kidney injury following TAVI is associated with increased postoperative mortality and morbidity. Future efforts are required to determine whether early prevention of post-procedural AKI after TAVI impacts upon clinical outcomes.

Keywords Acute kidney injury · Transcatheter aortic valve implantation · Meta-analysis · Mortality · Morbidity

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Introduction

Increasing evidence has shown that transcatheter aortic valve implantation (TAVI) is used to treat patients with either inoperable aortic stenosis or high risk for surgical aortic valve replacement [1]. Though less invasive, TAVI is associated with varying degrees of complications that may affect outcome. Acute kidney injury (AKI) after TAVI is a common complication, with an incidence ranging from 12 to 57% of the patients undergoing this procedure [2–4].

Currently, the pathophysiologic mechanisms of AKI in the setting of TAVI have not been completely elucidated. Growing evidence has suggested that several factors, such as the amount of contrast medium, perioperative blood transfusion, postoperative severe inflammatory response syndrome and hemodynamic changes after TAVI, might play crucial roles [5–7]. Moreover, the impact of AKI on short-term and long-term postoperative clinical outcomes remains controversial. Previous meta-analysis and reviews conclude that

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Table 1 Study characteristics of observational studies examining postoperative AKI on the clinical outcomes of patients after TAVI

Study	Publication year	Region	Study design	Patients	Access (%)		Valve type (%)		Logistic EuroSCORE (%)[a]	Definition of AKI	Follow-up[a]
					TF	TA	EV	MCV			
Zivkovic	2018	Canada	Retrospective cohort	1993	85.4	NA	NA	NA	7.2 ± 7.3	VARC-2	In-hospital
Nijenhuis	2018	Netherlands	Retrospective cohort	639	58	NA	33	57	NA	VARC-2	2 years
Filho	2018	Brazil	Prospective cohort	794	93.6	NA	24.3	72.9	20.6 ± 14.7	VARC-2	4 years
Zaouter	2017	France	Prospective cohort	62	95	0	NA	NA	18 (8–26)	VARC-2	30 days
Giannini	2017	Italy	Retrospective cohort	397	83	6	60	40	20 (11–31)	RIFLE	643 (390–950) days
Marbach	2017	Canada	Retrospective cohort	195	55.9	NA	59.5	NA	NA	VARC-2	In-hospital
Gupta	2017	America	Retrospective cohort	41,025	NA	NA	NA	NA	NA	AKIN	In-hospital
Arsalan	2016	America	Retrospective cohort	374	69	31	NA	0	NA	VARC-2	3 years
Thongprayoon	2016	America	Retrospective cohort	386	51	44	NA	NA	NA	VARC-2	6 months
Meneguz-Moreno	2016	Brazil	Retrospective cohort	221	76	NA	41.6	36.1	NA	VARC-2	1 year
Giannini	2016	Italy	Retrospective cohort	332	100	0	48	52	NA	VARC	NA
Crowhurst	2016	Australia	Prospective cohort	209	NA	NA	50	41	19.6 (18.1–21.2)	VARC-2	1 year
Dusse	2016	Germany	Prospective cohort	40	NA	85	32.5	NA	NA	VARC-2	30 days
Elmariah	2016	America	Retrospective cohort	44	100	0	100	0	NA	VARC-2	Median 7.8 months
Chatani	2015	Germany	Retrospective cohort	203	98	1	15.8	84.2	24.5 ± 15.0	VARC	2 years
Konigstein	2015	Israel	Prospective cohort	420	100	0	26	73	NA	VARC-2	576 ± 400 days
Munoz-Garcia	2015	Spain	Retrospective cohort	366	89.1	0	0	100	NA	VARC	26.2 ± 17 months
Rosendael	2015	Netherlands	Retrospective cohort	210	41	59	91	9	22.1 ± 13.2	VARC-2	In-hospital
Voigtländer	2015	Germany	Retrospective cohort	540	82.4	9.8	40.9	59.1	24.5 ± 17.9	RIFLE	1 year
Johansson	2014	Sweden	Prospective cohort	64	27	73	100	0	22 ± 12	RIFLE	17 ± 12 months
Barbanti	2014	Italy	Prospective cohort	1157	80	0	0	100	20 (13–31)	VARC	12 (2–24) months
Sinning	2014	Germany	Prospective cohort	132	90.9	0	NA	NA	30.3 ± 18.2	VARC-2	1 year
Généreux	2013	America	Prospective cohort	208	64	36	100	0	NA	VARC	1 year
Saia	2013	Italy	Prospective cohort	102	64.7	23.5	35.3	64.7	22.6 ± 12.4	VARC	1 year
Frerker	2013	Germany	Retrospective cohort	323	100	0	32.2	67.8	24.4 ± 16.6	VARC	30 days
Yamamoto	2013	France	Prospective cohort	415	100	0	48.9	51.1	21.0 (14.4–28.9)	VARC	1 year
Goebel	2013	Germany	Prospective cohort	255	0	100	NA	NA	33.5 ± 18.1	VARC	30 days
Keleş	2013	Turkey	Retrospective cohort	70	92.9	0	NA	NA	21.7	VARC-2	9 (1–17) months
Pilgrim	2012	Switzerland	Prospective cohort	389	79.2	19.5	42.1	57.9	24.3 ± 14.2	VARC	30 days
Alassar	2012	England	Retrospective cohort	79	NA	NA	NA	NA	18.91 ± 12.06	VARC	1 year
Barbash	2012	America	Retrospective cohort	165	70.9	29.1	100	0	NA	VARC	30 days
Gebauer	2012	Germany	Prospective cohort	140	64	36	100	0	24 ± 15	AKIN	Median 309 days
Khawaja	2012	UK	Prospective cohort	248	43.1	41.5	100	0	22.4 ± 13.2	VARC	379 (113–729) days
Kong	2012	Australia	Retrospective cohort	52	78.2	21.2	NA	NA	19.0 (13.0–30.4)	RIFLE	16 (11–23) months
Nuis	2012	Netherlands	Retrospective cohort	995	69.4	27.8	NA	NA	17 (11–30)	VARC	12 (4–23) months
Wessely	2012	Germany	Retrospective cohort	183	100	0	0	100	23.5 ± 11.5	RIFLE	30 days

Table 1 (continued)

Study	Publication year	Region	Study design	Patients	Access (%)		Valve type (%)		Logistic EuroSCORE (%)[a]	Definition of AKI	Follow-up[a]
					TF	TA	EV	MCV			
Elhmidi	2011	Germany	Prospective cohort	234	71.5	23.3	23.1	76.9	NA	RIFLE	6 months
Nuis	2011	Netherlands	Prospective cohort	118	NA	NA	0	100	12.3 (9.0–18.4)	VARC	13 (5–24) months
Linden	2011	Germany	Prospective cohort	261	NA	NA	100	0	31.4±15.6	RIFLE	1 year
Bagur	2010	Canada	Prospective cohort	213	52.1	47.9	100	0	29.3±17.5	RIFLE	In-hospital
Sinning	2010	Germany	Prospective cohort	77	100	0	0	100	31.2±17.6	AKIN	283 (49–439) days
Strauch	2010	Germany	Prospective cohort	28	0	100	100	0	19.01 (5.1–77.4)	RIFLE	In-hospital
Aregger	2009	Switzerland	Retrospective cohort	54	79	21	NA	NA	27±16	RIFLE	30 days

VARC Valve Academic Research Consortium, *EV* Edwards valve, *MCV* Medtronic CoreValve, *AKI* acute kidney injure, *TF* trans-femoral, *TA* trans-apical, *RIFLE* Risk, Injury, Failure, Loss and End-stage kidney disease, *AKIN* Acute Kidney Injury Network, *TAVI* transcatheter aortic valve implantation, *NOS* Newcastle–Ottawa Scale, *NA* not available

[a]Data are mean ± standard deviation or median (interquartile range)

postoperative AKI seems to significantly worsen TAVI prognosis [8].

However, these studies included relatively small population sizes and nonconclusive data are available regarding postoperative outcomes such as major vascular complications, need for renal replacement therapy, new pacemaker implantation and cerebrovascular accidents. Therefore, to confirm whether or not AKI patients have more adverse outcomes than non-AKI patients after TAVI, we conducted a meta-analysis of the existing and up-to-date studies to compare the short-term and long-term adverse cardiovascular outcomes between AKI and non-AKI patients after PCI.

Methods

Search strategy

This systematic review and meta-analysis was carried out in accordance with the PRISMA guidelines [9]. An electronic search of the PubMed, Embase and Cochrane Library databases was conducted from inception to May 2018 with no language restrictions. The following key words and medical subject heading terms searched were applied: (transcatheter aortic valve implantation OR transcatheter aortic valve replacement OR TAVI OR TAVR) AND (acute kidney injury OR chronic kidney disease OR renal dysfunction OR renal failure). A manual search of additional articles was carried out using references from comparable articles and published reviews to seek potentially relevant citations.

Study selection

Two independent investigators (M.M and G.WD) performed the initial screening of titles and abstracts. Full-length articles of identified studies were retrieved. Studies were included if they (1) investigated clinical outcomes after TAVI in patients with postoperative AKI; (2) had availability of data of outcomes, or data regarding clinical events from which it could be calculated. Studies were excluded if they were (1) abstracts, letters, conferences, editorials or reviews or (2) duplicate publications. Decisions were made regarding eligibility according to pre-specified selection criteria. Any differing decision was resolved by consensus or discussion with the third investigator (G.YF).

Data extraction and quality assessment

Two main investigators (M.M and G.WD) independently extracted the data and reached a consensus on all items. The following items were extracted from each study if the available: name of the first author, the year of publication, study design, region, number of participants,
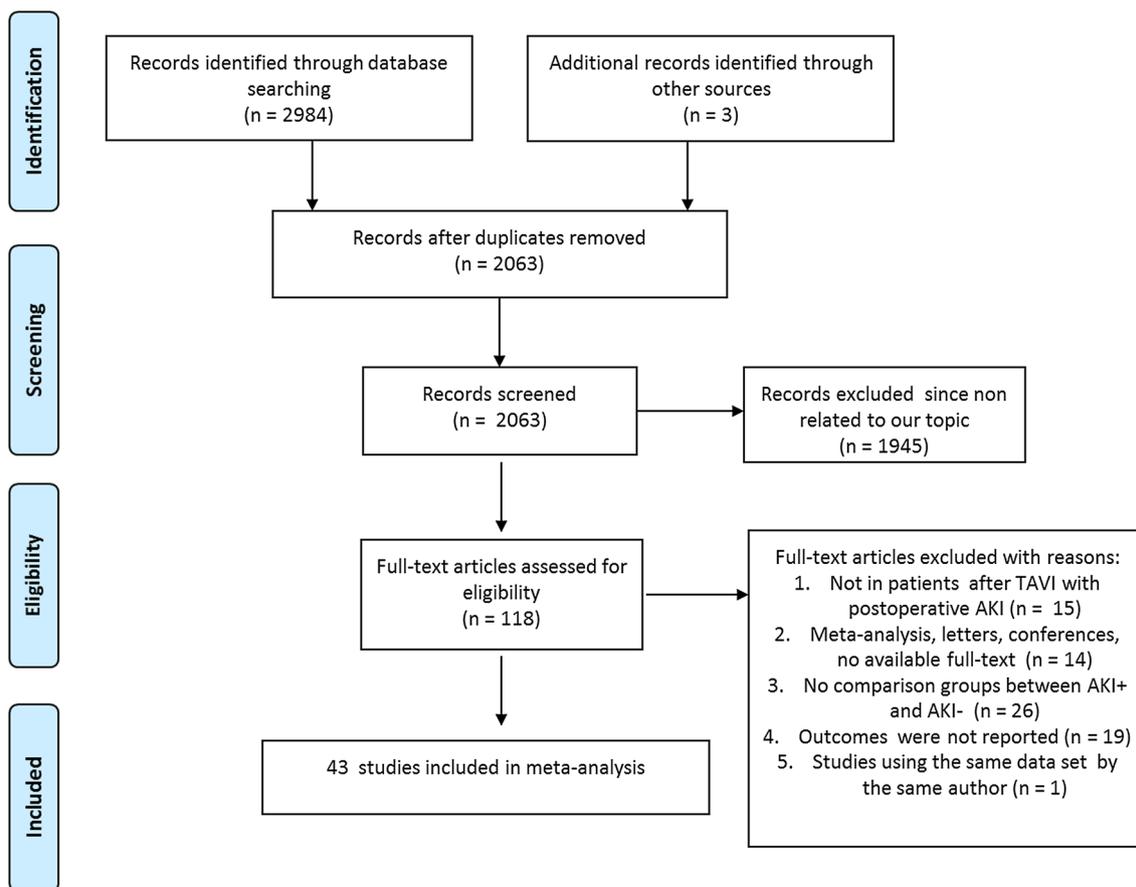
Fig. 1 Flow diagram of literature search and study selection

age of patients, percentage of male participants, valve type, access, logistic EuroSCORE, outcomes of interest, OR and 95% CI and follow-up duration. The primary end points were short-term (in-hospital or 30 days) and long-term (more than 6 months) all-cause mortality. Secondary end points of interest include cerebrovascular accidents (CVA), myocardial infarction, bleeding (major or life threatening), need for red blood cell transfusions, need for postprocedural renal replacement therapy (RRT), need for postprocedural pacemaker implantation, amount of contrast dye administration and in-hospital length of stay. A quality assessment of each selected study was performed by two investigators (G.YF and W.YS) using a nine-item Newcastle–Ottawa Scale (NOS) [10]. A third investigator was consulted for any uncertainty. A total score of ≥ 7 indicated a high-quality study, whereas a total score of < 7 was considered to indicate a low-quality study.

Statistical analysis

Meta-analysis and statistical analyses were completed using the RevMan 5.3 (Cochrane Collaboration) and Stata 12.0 (StataCorp). Unadjusted odds ratios (ORs) and adjusted hazard ratio (HR) with 95% CIs were used as the summary statistic for dichotomous outcomes. For continuous outcomes, the summary statistic chosen was the mean difference. Cochrane Chi square test (Q test) and the I^2 statistic were calculated for the detection of heterogeneity, with an I^2 less than 25%, 25 to 50%, and greater than 50% corresponding to low, moderate and high heterogeneity, respectively. If I^2 was $< 50\%$, a fixed effects model was used, while if I^2 was $> 50\%$, a random-effect model (DerSimonian and Laird) was applied. Sensitivity analysis was conducted to investigate the influence of a single study on overall effect estimate and was carried out by sequentially excluding one study at a time. In addition, sensitivity analysis restricted to studies with VARC-2 definition of AKI was carried out to provide a contemporary picture of the incidence and impact of the complication. If substantial heterogeneity was presented

Table 2 Characteristics of patients participating in observational studies examining postoperative AKI on the clinical outcomes of patients after TAVI

Study	Patients (n)		Mean age (years)		Males (%)		HTN (%)		DM (%)		Prior PCI (%)		Prior CABG (%)		Prior MI (%)		Baseline GFR		Contrast medium used (ml)	
	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−
Zivkovic et al.	318	1675	82	82	51	49	87	86	45	34	NA	NA	NA	NA	NA	NA	NA	NA	131.0±73.7	124.2±61.3
Nijenhuis et al.	67	572	82	81	34	43	48	62	18	24	NA	NA	NA	NA	NA	NA	NA	NA	88±39	NA
Filho et al.	143	651	82	81	50	50	80	74	36	31	NA	NA	NA	NA	NA	NA	46.0±22.6	48.9±22.0	175±73	190±116
Zaouter et al.	22	40	80	81	46	35	77	73	23	35	23	28	14	10	18	15	68 (53–79)	63 (50–79)	145 (90–200)	100 (84–120)
Giannini et al. 2017	129	168	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Marbach et al.	60	135	85	NA	45	NA	68	NA	48	NA	NA	NA	18	NA	NA	NA	NA	NA	NA	NA
Gupta et al.	7401	33,624	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Arsalan et al.	144	230	82	82	49	49	NA	NA	44	37	NA	NA	NA	NA	16	25	NA	NA	NA	NA
Thongprayoon et al.	106	280	82	81	58	55	94	89	48	38	58	49	41	44	NA	NA	48±22	58±19	96±57	93±55
Meneguz-Moreno et al.	52	169	83	82	48	46	90	79	42	31	25	25	21	22	21	17	39.59±13.62	48.49±19.60	133.62±74.97	134.88±75.08
Giannini et al. 2016	138	194	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Crowhurst et al.	82	127	82	84	52	46	81	76	39	29	32	32	34	31	12	9	51.1 (47–55)	63.9 (61–67)	NA	NA
Dusse et al.	32	8	81	81	41	38	75	88	31	38	NA	NA	NA	NA	6	25	65.6±15.9	65.0±18.1	102.1±35.8	131.0±44.7
Elmariah et al.	9	35	82	82	56	46	88	83	50	67	25	43	25	23	13	9	46.9±17.0	61.0±17.5	NA	NA
Chatani et al.	39	164	80	80	56	40	80	87	26	27	NA	NA	NA	NA	23	23	NA	NA	289.2±90.8	276.0±80.0
Konigstein et al.	66	354	84	83	38	41	89	87	29	34	44	44	18	17	24	16	56±19	64±18	156±44	145±41
Munoz-Garcia et al.	58	308	80	79	48	40	84	83	29	43	28	28	12	8	12	17	48.3±19.1	49.01±21	NA	NA
Rosendael et al.	51	159	81	81	59	49	88	76	37	26	28	25	35	32	29	21	58±21	70±22	105±68	101±44
Voigtländer et al.	30	510	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Johansson et al.	21	43	79	80	52	39	NA	NA	24	23	33	44	29	30	NA	NA	NA	NA	139±42	126±36
Barbanti et al.	231	926	81	82	40	48	82	81	29	29	27	31	12	17	20	19	27 (19–36)	45 (37–61)	188 (139–235)	180 (130–240)

Table 2 (continued)

Study	Patients (n)		Mean age (years)		Males (%)		HTN (%)		DM (%)		Prior PCI (%)		Prior CABG (%)		Prior MI (%)		Baseline GFR		Contrast medium used (ml)	
	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−
Sinning et al. 2014	30	102	81	81	57	53	43	42	NA	NA	37	40	17	12	40	14	46.9±17.2	52.3±20.1	186 (163–234)	169 (133–192)
Généreux et al.	8	200	84	86	50	51	83	83	38	28	8	80	9	80	NA	NA	52.97±19.21	56.02±21.77	122.61±96.79	103.84±58.53
Saia et al.	42	60	83	84	38	42	88	75	19	25	36	33	19	15	21	33	44.0±21.7	41.1±17.9	111±35	129±31
Frerker et al.	34	289	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Yamamoto et al.	63	352	83	84	52	43	75	74	30	21	30	31	14	NA	14	13	49.3±20.7	57.3±21.9	NA	NA
Goebel et al.	41	214	82	82	56	42	51	56	38	26	22	22	NA	NA	NA	NA	59±23	62±18	87.6±40.0	83.0±31.0
Keleş et al.	5	65	78	78	0	29	100	79	20	28	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Pilgrim et al.	64	325	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Alassar et al.	10	69	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Barbash et al.	24	141	84	85	63	38	92	97	21	34	13	17	38	32	NA	NA	43±18	50±20	98±46	117±88
Gebauer et al.	28	112	79	82	NA	NA	86	75	36	25	NA	NA	32	21	32	22	51±17	57±20	147±71	148±56
Khawaja et al.	89	159	83	82	62	55	67	59	37	15	16	16	28	27	NA	NA	NA	NA	NA	NA
Kong et al.	15	37	84	84	60	65	73	49	40	8	NA	NA	NA	32	NA	NA	56.6±20.0	65.7±14.7	279 (148–380)	216 (142–302)
Nuis et al. 2012	206	789	82	82	50	50	82	76	27	28	31	30	26	27	30	26	NA	NA	158±96	142±97
Wessely et al.	49	134	81	81	49	43	84	84	36	78	45	39	NA	NA	NA	NA	54.7±22.2	54.2±17.2	174.9±67.1	158.0±58.9
Elhmidi et al.	46	188	82	81	33	40	61	71	37	27	NA	NA	NA	NA	NA	NA	NA	NA	144±59	140±62
Nuis et al. 2011	22	96	83	82	50	44	50	44	36	20	27	27	46	21	55	19	54±20	61±18	213±56	196±86
Linden et al.	42	219	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	44.3±15.9	77.4±37.8	NA	NA
Bagur et al.	25	188	84	82	52	46	92	68	28	22	NA	NA	NA	NA	NA	NA	70 (49–80)	57 (43–76)	NA	NA
Sinning et al. 2010	20	57	80	81	60	44	100	91	15	26	55	46	15	9	45	41	38.0 (23.8–48.2)	66.8 (53.3–79.1)	207±70	192±61

Table 2 (continued)

Study	Patients (n)		Mean age (years)		Males (%)		HTN (%)		DM (%)		Prior PCI (%)		Prior CABG (%)		Prior MI (%)		Baseline GFR		Contrast medium used (ml)	
	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−	AKI+	AKI−
Strauch et al.	16	12	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Aregger et al.	15	39	83	83	47	41	93	79	33	13	NA	NA	NA	NA	NA	NA	57±33	58±22	242±101	262±104

AKI acute kidney injury, *GFR* glomerular filtration rate (mL/min/1.73 m²), *CABG* coronary artery bypass graft, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *DM* diabetes mellitus, *HTN* hypertension, *NA* not available

in the meta-analysis, meta-regression for age, gender and baseline estimated glomerular filtration rate (eGFR) and subgroup analyses were performed to identify the potential sources of heterogeneity by study design (retrospective compared with prospective studies), region (studies performed in the European countries compared with studies performed outside of European countries) and number of participants (≤ 200 compared with > 200). Publication bias was assessed by Begg's adjusted rank correlation test and Egger's regression asymmetry test ($P < 0.10$ was considered indicative of statistically significant heterogeneity). $P < 0.05$ was considered statistically significant.

Results

Study selection

A total of 2984 publications were identified through the literature search, with three studies identified through manual searching of reference lists from these articles. After removal of duplicates, a review of the titles and abstracts of 2063 articles was conducted. A total of 118 articles were obtained and read in full. Of these, a further 75 studies were excluded. Methodological details of the search strategy were shown in supplementary appendix Table 1. Ultimately, 43 studies [11–53] that met the inclusion criteria, including 54,412 patients after TAVI with postprocedural AKI, were included (Fig. 1).

Study characteristics and quality assessment

Basic characteristics of the studies are present in Tables 1 and 2. Included studies consisting of 1953 postoperative AKI patients (AKI+) and 7354 non-AKI patients (AKI−) after TAVI were published from 2009 through 2016. 25 out of 36 studies were conducted in European countries (12 in Germany), 5 in America and 6 in other regions. Nineteen studies were prospective cohort studies, and 17 studies were retrospective cohort studies. Mean patient age was around 80 years old. All of the included studies were of high quality (Table 3), with an average NOS score of eight.

All-cause mortality

A total of 35 studies (51,324 patients) report short-term mortality. Patients with AKI experience a significant increase of the short-term all-cause mortality compared to non-AKI patients (OR 6.25, 95% CI 5.72–6.83, $P < 0.00,001$, $I^2 = 24\%$) (Fig. 2). Twenty-seven studies including 8037 patients report long-term mortality. Long-term all-cause

Table 3 Study quality assessment using the Newcastle–Ottawa Scale

First author, year of publication (reference)	Selection				Comparability	Outcome			Total score
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome of interest absent at start of study		Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up	
Zivkovic (2018)	*	*	*	*	* *	*	–	–	7
Nijenhuis (2018)	*	*	*	*	* *	*	*	*	9
Filho (2018)	*	*	*	*	* *	*	*	*	9
Zaouter (2017)	*	*	*	*	* *	*	–	–	7
Giannini (2017)	*	*	*	*	* *	*	*	*	9
Marbach (2017)	*	*	*	*	* *	*	–	–	7
Gupta (2017)	*	*	*	*	* *	*	–	–	8
Arsalan (2016)	*	*	*	*	* *	*	*	–	8
Thongprayoon (2016)	*	*	*	*	* *	*	–	–	7
Meneguz-Moreno (2016)	*	*	*	*	* *	*	*	*	9
Giannini (2016)	*	*	*	*	* *	*	*	*	9
Crowhurst (2016)	*	*	*	*	* *	*	–	–	7
Dusse (2016)	*	*	*	*	* *	*	–	–	7
Elmariah (2016)	*	*	*	*	* *	*	*	*	9
Chatani (2015)	*	*	*	*	* *	*	*	–	8
Konigstein (2015)	*	*	*	*	* *	*	*	*	9
Munoz-Garcia (2015)	*	*	*	*	* *	*	*	*	9
Rosendael (2015)	*	*	*	*	* *	*	–	–	7
Voigtländer (2015)	*	*	*	*	* *	*	*	–	8
Johansson (2014)	*	*	*	*	* *	*	*	*	9
Barbanti (2014)	*	*	*	*	* *	*	*	*	9
Sinning (2014)	*	*	*	*	* *	*	*	*	9
Généreux (2013)	*	*	*	*	* *	*	*	*	9
Saia (2013)	*	*	*	*	* *	*	*	*	9
Frerker (2013)	*	*	*	*	* *	*	–	–	7
Yamamoto (2013)	*	*	*	*	* *	*	*	*	9

Table 3 (continued)

First author, year of publication (reference)	Selection				Comparability	Outcome			Total score
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome of interest absent at start of study		Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up	
Goebel (2013)	*	*	*	*	* *	*	–	–	7
Keleş (2013)	*	*	*	*	* *	*	*	–	8
Pilgrim (2012)	*	*	*	*	* *	*	–	–	7
Alassar (2012)	*	*	*	*	* *	*	*	–	8
Barbash (2012)	*	*	*	*	* *	*	–	–	7
Gebauer (2012)	*	*	*	*	* *	*	–	–	7
Khawaja (2012)	*	*	*	*	* *	*	*	*	9
Kong (2012)	*	*	*	*	* *	*	*	–	8
Nuis (2012)	*	*	*	*	* *	*	*	*	9
Wessely (2012)	*	*	*	*	* *	*	–	–	7
Elhmidi (2011)	*	*	*	*	* *	*	–	–	7
Nuis (2011)	*	*	*	*	* *	*	*	*	9
Linden (2011)	*	*	*	*	* *	*	*	*	9
Bagur (2010)	*	*	*	*	* *	*	–	–	7
Sinning (2010)	*	*	*	*	* *	*	*	*	9
Strauch (2010)	*	*	*	*	* *	*	–	–	7
Aregger (2009)	*	*	*	*	* *	*	–	–	7

Asterisks are the star ratings per the Newcastle–Ottawa Scale. * and ** indicates the highest ratings for these categories

mortality is significantly increased in AKI patients compared to non-AKI patients. The study unadjusted OR is 3.49 (95% CI 2.78–4.40, $P < 0.00,001$, $I^2 = 64\%$) (Fig. 3). Additionally, adjusted long-term HR is 2.82 (95% CI 2.06–3.86, $P < 0.001$, $I^2 = 72\%$) (Fig. 4). Sensitivity analysis suggests that exclusion of any individual study does not significantly change the results. Furthermore, sensitivity analysis restricted to ten studies with VARC-2 definition of AKI confirms the increased short-term and long-term all-cause mortality (OR 7.97, 95% CI 5.78–11.01, $P < 0.00,001$, $I^2 = 37\%$; OR 4.17, 95% CI 2.76–6.31, $P < 0.00001$, $I^2 = 73\%$, respectively) in patients with AKI. Subgroup analysis by study design, region and number of participants does not significantly alter the overall effect estimates. Meta-regression was performed to examine the following potential confounders: age, gender and baseline eGFR. These potential confounders are not able to explain the observed heterogeneity (all $P > 0.05$).

Cerebrovascular accidents

Secondary outcomes are presented in Table 4. Eleven articles (3885 patients) report data regarding cerebrovascular accidents including stroke. AKI patients have a significant increase of stroke compared to non-AKI patients (OR 1.92, 95% CI 1.23–2.98, $P = 0.001$, $I^2 = 28\%$). Sensitivity analysis restricted to six studies with VARC-2 definition of AKI shows patients with AKI to be significantly associated with increased cerebrovascular accidents (OR 2.99, 95% CI 1.63–5.48, $P = 0.0004$, $I^2 = 36\%$).
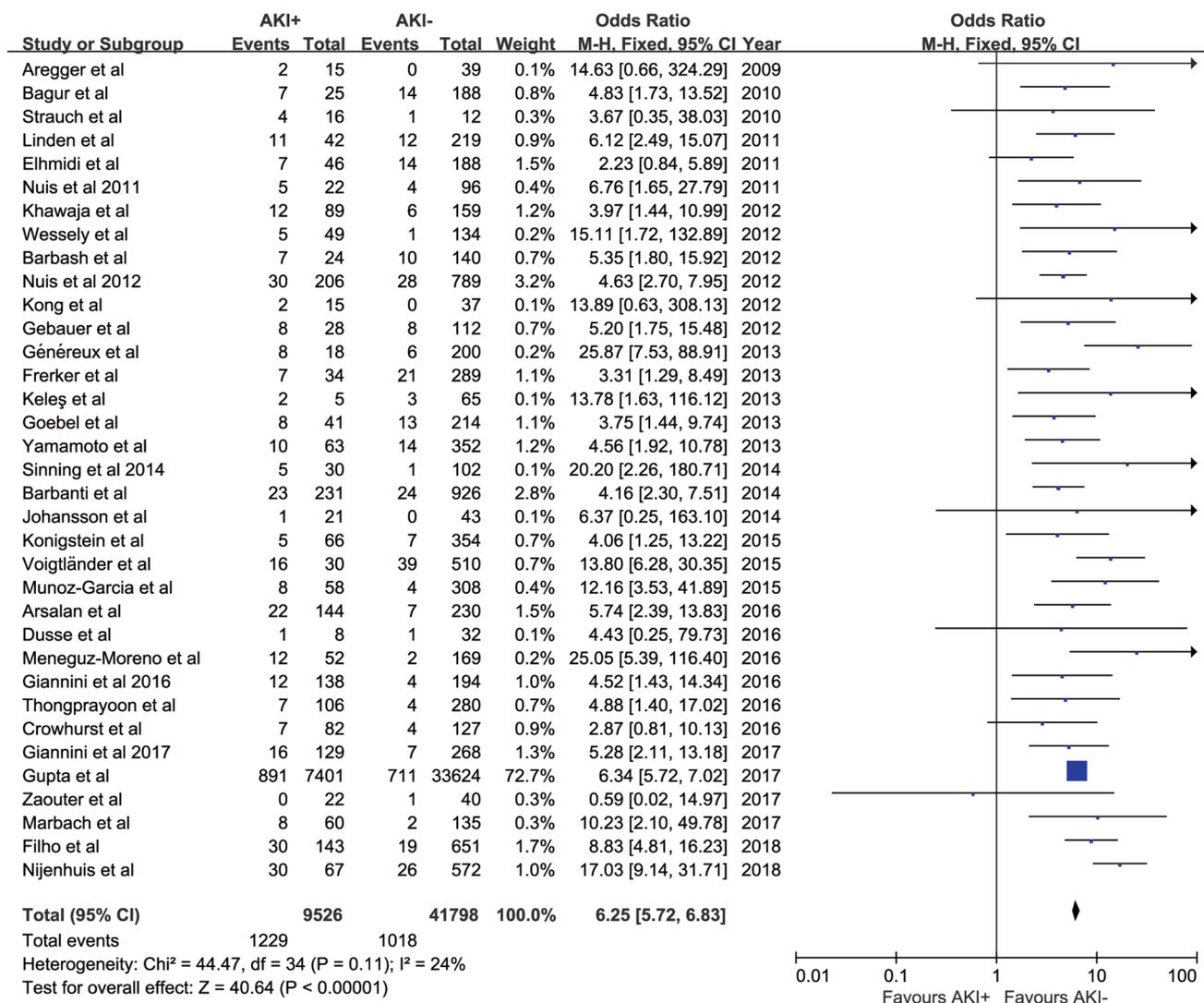
Study or Subgroup	AKI+ Events	Total	AKI- Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year	Odds Ratio M-H, Fixed, 95% CI
Aregger et al	2	15	0	39	0.1%	14.63 [0.66, 324.29]	2009	
Bagur et al	7	25	14	188	0.8%	4.83 [1.73, 13.52]	2010	
Strauch et al	4	16	1	12	0.3%	3.67 [0.35, 38.03]	2010	
Linden et al	11	42	12	219	0.9%	6.12 [2.49, 15.07]	2011	
Elhmidi et al	7	46	14	188	1.5%	2.23 [0.84, 5.89]	2011	
Nuis et al 2011	5	22	4	96	0.4%	6.76 [1.65, 27.79]	2011	
Khawaja et al	12	89	6	159	1.2%	3.97 [1.44, 10.99]	2012	
Wessely et al	5	49	1	134	0.2%	15.11 [1.72, 132.89]	2012	
Barbash et al	7	24	10	140	0.7%	5.35 [1.80, 15.92]	2012	
Nuis et al 2012	30	206	28	789	3.2%	4.63 [2.70, 7.95]	2012	
Kong et al	2	15	0	37	0.1%	13.89 [0.63, 308.13]	2012	
Gebauer et al	8	28	8	112	0.7%	5.20 [1.75, 15.48]	2012	
Généreux et al	8	18	6	200	0.2%	25.87 [7.53, 88.91]	2013	
Frerker et al	7	34	21	289	1.1%	3.31 [1.29, 8.49]	2013	
Keleş et al	2	5	3	65	0.1%	13.78 [1.63, 116.12]	2013	
Goebel et al	8	41	13	214	1.1%	3.75 [1.44, 9.74]	2013	
Yamamoto et al	10	63	14	352	1.2%	4.56 [1.92, 10.78]	2013	
Sinning et al 2014	5	30	1	102	0.1%	20.20 [2.26, 180.71]	2014	
Barbanti et al	23	231	24	926	2.8%	4.16 [2.30, 7.51]	2014	
Johansson et al	1	21	0	43	0.1%	6.37 [0.25, 163.10]	2014	
Konigstein et al	5	66	7	354	0.7%	4.06 [1.25, 13.22]	2015	
Voigtländer et al	16	30	39	510	0.7%	13.80 [6.28, 30.35]	2015	
Munoz-Garcia et al	8	58	4	308	0.4%	12.16 [3.53, 41.89]	2015	
Arsalan et al	22	144	7	230	1.5%	5.74 [2.39, 13.83]	2016	
Dusse et al	1	8	1	32	0.1%	4.43 [0.25, 79.73]	2016	
Meneguz-Moreno et al	12	52	2	169	0.2%	25.05 [5.39, 116.40]	2016	
Giannini et al 2016	12	138	4	194	1.0%	4.52 [1.43, 14.34]	2016	
Thongprayoon et al	7	106	4	280	0.7%	4.88 [1.40, 17.02]	2016	
Crowhurst et al	7	82	4	127	0.9%	2.87 [0.81, 10.13]	2016	
Giannini et al 2017	16	129	7	268	1.3%	5.28 [2.11, 13.18]	2017	
Gupta et al	891	7401	711	33624	72.7%	6.34 [5.72, 7.02]	2017	
Zaouter et al	0	22	1	40	0.3%	0.59 [0.02, 14.97]	2017	
Marbach et al	8	60	2	135	0.3%	10.23 [2.10, 49.78]	2017	
Filho et al	30	143	19	651	1.7%	8.83 [4.81, 16.23]	2018	
Nijenhuis et al	30	67	26	572	1.0%	17.03 [9.14, 31.71]	2018	
Total (95% CI)		**9526**		**41798**	**100.0%**	**6.25 [5.72, 6.83]**		
Total events	1229		1018					

Heterogeneity: Chi² = 44.47, df = 34 (P = 0.11); I² = 24%
Test for overall effect: Z = 40.64 (P < 0.00001)

0.01 0.1 1 10 100
Favours AKI+ Favours AKI-

Fig. 2 Forest plots for odds ratio of short-term mortality in AKI patients after TAVI

Myocardial infarction

Myocardial infarction after TAVI was reported in six studies. AKI patients suffer a significant increase of myocardial infarction compared to non-AKI patients (OR 3.98, 95% CI 1.90–8.31, $P = 0.0002$; $I^2 = 0\%$). Sensitivity analysis indicates that exclusion of any individual study does not significantly alter the results.

Need for renal replacement therapy and contrast dye volume

Pooled analysis of nine studies conclude that AKI patients have a significant higher risk for the need for postoperative renal replacement therapy compared to non-AKI. The overall OR is 22.36 (95% CI 11.88–42.12, $P = 0.0002$, $I^2 = 0\%$). No difference in contrast media volume is found between

patients with and without AKI after TAVI (mean difference 3.82, 95% CI − 1.34 to 8.98, $P = 0.15$, $I^2 = 69\%$).

Bleeding and need for transfusion

AKI patients experience a significant increase of major bleeding as well as life-threatening bleeding compared to non-AKI patients (OR 1.51, 95% CI 1.12–2.03, $P = 0.007$, $I^2 = 51\%$; OR 2.35, 95% CI 1.80–3.06, $P < 0.00001$, $I^2 = 36\%$, respectively). Sensitivity analysis restricted to six studies with VARC-2 definition of AKI suggests that patients with AKI are significantly associated with increased risk for life-threatening bleeding (OR 2.06, 95% CI 1.20–3.56, $P = 0.009$, $I^2 = 1\%$), but not for major bleeding (OR 1.96, 95% CI 0.82–4.68, $P = 0.13$, $I^2 = 71\%$). In addition, 24 articles (7262 patients) report data regarding blood transfusion. Compared to non-AKI patients, AKI patients have a
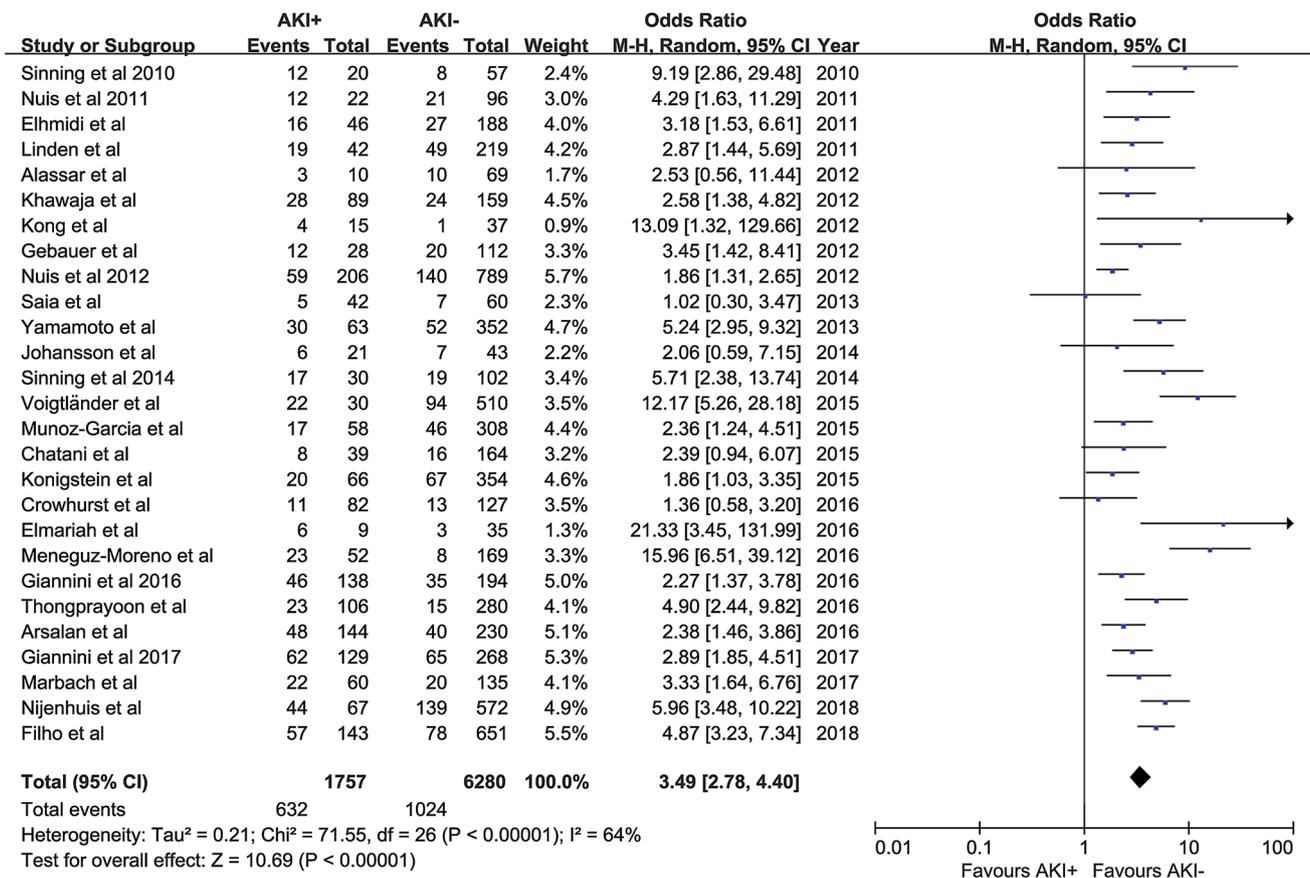
Study or Subgroup	AKI+ Events	AKI+ Total	AKI- Events	AKI- Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Sinning et al 2010	12	20	8	57	2.4%	9.19 [2.86, 29.48]	2010
Nuis et al 2011	12	22	21	96	3.0%	4.29 [1.63, 11.29]	2011
Elhmidi et al	16	46	27	188	4.0%	3.18 [1.53, 6.61]	2011
Linden et al	19	42	49	219	4.2%	2.87 [1.44, 5.69]	2011
Alassar et al	3	10	10	69	1.7%	2.53 [0.56, 11.44]	2012
Khawaja et al	28	89	24	159	4.5%	2.58 [1.38, 4.82]	2012
Kong et al	4	15	1	37	0.9%	13.09 [1.32, 129.66]	2012
Gebauer et al	12	28	20	112	3.3%	3.45 [1.42, 8.41]	2012
Nuis et al 2012	59	206	140	789	5.7%	1.86 [1.31, 2.65]	2012
Saia et al	5	42	7	60	2.3%	1.02 [0.30, 3.47]	2013
Yamamoto et al	30	63	52	352	4.7%	5.24 [2.95, 9.32]	2013
Johansson et al	6	21	7	43	2.2%	2.06 [0.59, 7.15]	2014
Sinning et al 2014	17	30	19	102	3.4%	5.71 [2.38, 13.74]	2014
Voigtländer et al	22	30	94	510	3.5%	12.17 [5.26, 28.18]	2015
Munoz-Garcia et al	17	58	46	308	4.4%	2.36 [1.24, 4.51]	2015
Chatani et al	8	39	16	164	3.2%	2.39 [0.94, 6.07]	2015
Konigstein et al	20	66	67	354	4.6%	1.86 [1.03, 3.35]	2015
Crowhurst et al	11	82	13	127	3.5%	1.36 [0.58, 3.20]	2016
Elmariah et al	6	9	3	35	1.3%	21.33 [3.45, 131.99]	2016
Meneguz-Moreno et al	23	52	8	169	3.3%	15.96 [6.51, 39.12]	2016
Giannini et al 2016	46	138	35	194	5.0%	2.27 [1.37, 3.78]	2016
Thongprayoon et al	23	106	15	280	4.1%	4.90 [2.44, 9.82]	2016
Arsalan et al	48	144	40	230	5.1%	2.38 [1.46, 3.86]	2016
Giannini et al 2017	62	129	65	268	5.3%	2.89 [1.85, 4.51]	2017
Marbach et al	22	60	20	135	4.1%	3.33 [1.64, 6.76]	2017
Nijenhuis et al	44	67	139	572	4.9%	5.96 [3.48, 10.22]	2018
Filho et al	57	143	78	651	5.5%	4.87 [3.23, 7.34]	2018
Total (95% CI)		**1757**		**6280**	**100.0%**	**3.49 [2.78, 4.40]**	
Total events	632		1024				

Heterogeneity: Tau² = 0.21; Chi² = 71.55, df = 26 (P < 0.00001); I² = 64%
Test for overall effect: Z = 10.69 (P < 0.00001)

Fig. 3 Forest plots for odds ratio of long-term mortality in AKI patients after TAVI

significant increase in the need for red blood cell transfusion (OR 2.15, 95% CI 1.89–2.46, $P < 0.00001$, $I^2 = 35\%$). Sensitivity analysis restricted to nine studies with VARC-2 definition of AKI also indicates that patients with AKI have a significantly higher risk for blood transfusion requirement compared with non-AKI patients (OR 1.92, 95% CI 1.57–2.34, $P < 0.00001$, $I^2 = 45\%$).

Pacemaker implantation

Six studies enrolling 2183 patients show a non-significant need for postprocedural pacemaker implantation associated with AKI patients (OR 1.05; 95% CI 0.79–1.38, $P = 0.75$, $I^2 = 22\%$).

Major vascular complications

A total of ten studies (3544 patients) report major vascular complications. AKI patients have a significant increase of major vascular complications compared to non-AKI patients

after TAVI (OR 1.69, 95% CI 1.30–2.18, $P < 0.0001$, $I^2 = 17\%$). However, sensitivity analysis restricted to five studies with VARC-2 definition of AKI finds no difference in risk for major vascular complications between the two groups (OR 1.28, 95% CI 0.83–1.99, $P = 0.26$, $I^2 = 26\%$).

Publication bias

Egger's or Begg's test do not reveal significant publication bias in the analysis of short-term mortality (Egger $P = 0.99$ and Begg $P = 0.39$), long-term mortality (Egger $P = 0.12$ and Begg $P = 0.18$) or secondary outcomes.

Discussion

The meta-analysis demonstrates that patients with AKI after TAVI have a significant increase of short- and long-term all-cause mortality. In addition, major and life-threatening bleeding, myocardial infarction, need for transfusion and
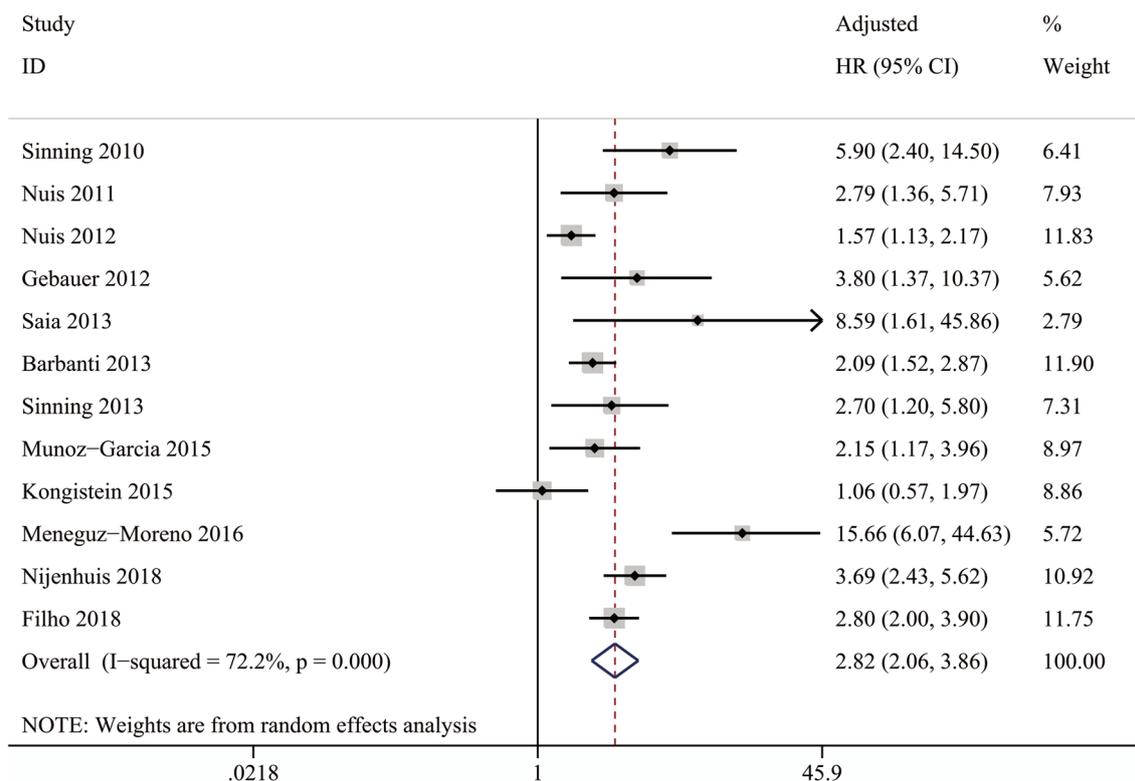
Study ID		Adjusted HR (95% CI)	% Weight
Sinning 2010		5.90 (2.40, 14.50)	6.41
Nuis 2011		2.79 (1.36, 5.71)	7.93
Nuis 2012		1.57 (1.13, 2.17)	11.83
Gebauer 2012		3.80 (1.37, 10.37)	5.62
Saia 2013		8.59 (1.61, 45.86)	2.79
Barbanti 2013		2.09 (1.52, 2.87)	11.90
Sinning 2013		2.70 (1.20, 5.80)	7.31
Munoz−Garcia 2015		2.15 (1.17, 3.96)	8.97
Kongistein 2015		1.06 (0.57, 1.97)	8.86
Meneguz−Moreno 2016		15.66 (6.07, 44.63)	5.72
Nijenhuis 2018		3.69 (2.43, 5.62)	10.92
Filho 2018		2.80 (2.00, 3.90)	11.75
Overall (I−squared = 72.2%, p = 0.000)		2.82 (2.06, 3.86)	100.00

NOTE: Weights are from random effects analysis

.0218   1   45.9

Fig. 4 Forest plots for adjusted hazard ratio of long-term mortality in AKI patients after TAVI

renal replacement therapy, cerebrovascular accidents, major vascular complications, hospital length of stay and contrast medium are all significantly increased in AKI patients. Moreover, the sensitivity analyses performed including only VARC-2 studies does not substantially affect the results.

AKI after surgical aortic valve replacement (SAVR) is a frequent complication, with an incidence ranging from 4.1 to 57.7% [54]. TAVI is an alternative to SAVR in higher-risk patients, and will further expand indications to lower-risk patients [55, 56]. AKI is a relevant and frequent complication after TAVI, but less so in TAVI versus SAVR [56]. Similar to AKI following SAVR, the pathogenesis of AKI after TAVR is also multifactorial and is often a combination of the use of nephrotoxic contrast media or medications, hemodynamic instability perioperatively or more specifically during periods of rapid pacing as well as cholesterol atheroembolization to the renal vascular bed from catheter insertion through a calcified aorta [57].

The impact of AKI on long-term mortality remains controversial, with some studies suggesting an increased mortality [11, 13, 18, 20], while others show no differences [15, 23, 27, 33]. Moreover, the impact of AKI on mortality may increase with the aggravating severity of AKI. Crowhurst and colleagues suggest that AKI mortality rates do increase with AKI severity and AKI impacts on mortality only if the patient suffers stage 2 or 3 [15]. Other studies also show

that acute kidney injury, particularly stages 2 and 3, holds a strong negative impact on long-term outcome after TAVI [24, 27]. The study by Chatani et al. [18] reveals that patients with advanced AKI (stages 2 and 3) post-TAVI have a significantly higher mortality at 2 years, whereas patients with AKI stage 1 have a similar long-term outcome to non-AKI patients.

Several studies show similar results with this current meta-analysis. The review includes 13 studies with more than 1900 patients and shows patients developing AKI after TAVI exhibit a two- to sixfold higher mortality rate compared with non-AKI patients, and the 30-day and 1-year mortality rates range from 8.8 to 44.4% and 31.5 to 55.5%, respectively [58]. Another recent meta-analysis investigating the predictors and outcome of AKI after TAVI suggests that even stage 1 AKI exerts detrimental effects on survival within 1 year, and AKI is also independently linked to mortality beyond 3 years [59]. Moreover, the review by Najjar et al. reports that patients who develop AKI after TAVR have a mortality rate of 7.8–29%, which is two to eight times higher than those who do not suffer from AKI, and hospital length of stay is also significantly increased in patients with AKI [57]. A prior meta-analysis by Gargiolo et al. shows mortality, myocardial infarction and blood transfusion are significantly increased in the AKI group, but no statistical difference in stroke, hospitalization and contrast

Table 4 Summary of primary and secondary outcomes in patients after TAVI

| End points | Studies | AKI+ | | AKI− | | Overall effect | | | | Heterogeneity | P |
		Events	Total	Events	Total	MD	OR	95% CI	P value	I²%	
Primary outcomes											
Short-term mortality	35	1229	9526	1018	41,798	NA	6.25	5.72–6.83	< 0.00001	24	0.11
Long-term mortality	27	632	1757	1024	6280	NA	3.49	2.78–4.40	< 0.00001	64	< 0.00001
Secondary outcomes											
Cerebrovascular accident	11	31	723	82	3162	NA	1.92	1.23–2.98	0.004	30	0.16
Myocardial infarction	6	14	471	17	1962	NA	3.98	1.9–8.31	0.0002	0	0.95
Blood transfusion	24	606	1472	1509	5790	NA	2.15	1.89–2.46	< 0.00001	35	0.05
Major bleeding	12	244	945	726	4224	NA	1.51	1.12–2.03	0.007	51	0.02
Life-threatening bleeding	11	99	795	187	3319	NA	2.35	1.80–3.06	< 0.00001	36	0.11
Major vascular complications	10	102	707	242	2837	NA	1.69	1.30–2.18	< 0.0001	17	0.29
Pacemaker implantation	6	80	402	319	1781	NA	1.05	0.79–1.38	0.75	22	0.75
Renal replacement therapy	9	67	409	18	1244	NA	22.36	11.88–42.12	< 0.00001	0	0.54
Hospital stay, day	14	NA	736	NA	2808	4.27	NA	3.03–5.51	< 0.0001	96	< 0.0001
Contrast dye volume	27	NA	1630	NA	6951	3.82	NA	− 1.34 to 8.98	0.15	69	< 0.00001

AKI acute kidney injury, *MD* mean difference, *OR* odds ratio, *CI* confidence interval, *NA* not applicable

medium received between the AKI and non-AKI group after TAVI [8]. However, the present meta-analysis of 36 articles recruiting 9307 patients demonstrates a significant increase of cerebrovascular accidents, hospitalization and volume of contrast dye. AKI after TAVI procedures may be related to several causes such as advanced age, comorbidity, bleeding and anemia, cholesterol embolization due to the manipulation of large catheters in the aorta of patients with a high prevalence of diffuse atherosclerosis, and the complexity and length of the procedure (that requires a higher contrast dose) [53]. In addition, kidney diseases including AKI are associated with impaired primary hemostasis, like platelet malfunctions, which contribute to an increased risk of post-TAVI bleeding and mortality [60, 61]. Patients treated with dual antiplatelet therapy or anticoagulant agents peri-TAVI are at increased risk of major bleeding [62, 63]. Aspirin monotherapy reduces risk of 30 days major vascular complications and bleedings after TAVI, which are confirmed to be independent predictors of 30 days all-cause mortality [63].

Different from other studies, our study has strictly been conducted in patients with AKI after TAVI. Besides, several studies have assessed the impact of AKI on mortality after TAVI, but patients with AKI post-TAVI may have more complications with several co-morbidities, and newly published studies are available; hence, we have conducted a comprehensive meta-analysis regarding postoperative outcomes besides mortality. We find that the baseline eGFR does not have an effect in explaining the observed heterogeneity in the outcomes. This does not mean that baseline eGFR does not impact upon AKI. Indeed, it is well known

from previous evidence that eGFR, even moderate, has an impact on outcomes, including AKI after TAVI.

Limitations

There are several limitations to consider when interpreting the results of the present study. Firstly, the observational studies enrolled in this meta-analysis each have their inherent limitations, such as design bias, selection bias and treatment bias. Although randomized clinical trials are the most persuasive evidence, they recruit few patients and often cannot represent the real-world subjects. Hence, our systematic review and meta-analysis shed light on the clinical outcomes that may be observed in everyday clinical practice. Second, significant between-studies heterogeneity in terms of the effect sizes of several end points are observed in this study and have used a random-effect model for these results. This could be a limitation in this study. While we did perform appropriate statistical analysis including subgroup analysis and meta-regression to assess sources of heterogeneity, the bias caused by the influence of unmeasured confounders could not be eliminated. In addition to that we used summarized published event rates for each study instead of patient-level data, which is subject to confounding and selection bias. An additional caveat is that, as some studies suggest, the incidence of postoperative clinical outcomes may increase with AKI severity, and we could not analyze the impact of different stages of AKI on the prognosis in AKI patients after TAVI because few studies provide related data for calculation.

Conclusions

Acute kidney injury following TAVI is associated with increased postoperative mortality and morbidity. Future efforts are required to determine whether early prevention of post-procedural AKI after TAVI impacts upon clinical outcomes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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