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SYSTEMATIC REVIEW AND META-ANALYSIS

Effect of Deep Hypothermic Circulatory Arrest Versus Moderate Hypothermic Circulatory Arrest in Aortic Arch Surgery on Postoperative Renal Function: A Systematic Review and Meta-Analysis

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BACKGROUND: Moderate hypothermic circulatory arrest (MHCA) has been widely used in aortic arch surgery. However, the renal function after MHCA remains controversial. We performed a systematic review and meta-analysis direct comparison of the postoperative renal function of MHCA versus deep hypothermic circulatory arrest (DHCA) in aortic arch surgery.

METHODS AND RESULTS: We searched PubMed, Embase, and the Cochrane Library for postoperative renal function after aortic arch surgery with using MHCA and DHCA, published from inception to January 31, 2020. The primary outcome was renal failure. Secondary outcomes were the need for renal therapy and other major postoperative outcomes. The random-effects model was used for all comparisons to pool the estimates. A total of 14 observational studies with 4142 patients were included. Compared with DHCA, MHCA significantly reduced the incidence of renal failure (odds ratio [OR], 0.76; 95% CI, 0.61–0.94; P=0.011; I^2=0.0%) and the need of renal replacement (OR, 0.68; 95% CI, 0.48–0.97; P=0.034; I^2=0.0%). Subgroup analysis showed that when the hypothermic circulatory arrest time was <30 minutes, the incidence of renal failure in MHCA group was significantly lower than that in DHCA group (OR, 0.73; 95% CI, 0.54–0.99; P=0.040; I^2=1.1%), whereas an insignificant difference between 2 groups when hypothermic circulatory arrest time was >30 minutes (OR, 0.76; 95% CI, 0.51–1.13; P=0.169; I^2=17.3%).

CONCLUSIONS: MHCA compared with DHCA reduces the incidence of renal failure and the need for renal replacement.

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Key Words: aortic arch ■ hypothermia circulatory arrest ■ renal function

Direct aortic arch surgery typically requires a more considerable period of hypothermic circulatory arrest. Although deep hypothermic circulatory arrest (DHCA) is an established classic technique, it is still associated with relatively high short-term mortality and major morbidity, including postoperative neurologic deficit and renal failure.[1] The usage of moderate hypothermic circulatory arrest (MHCA) with selective antegrade cerebral perfusion (SACP) or retrograde cerebral perfusion for adult aortic arch repair has been recognized and popularized since this allows for cerebral perfusion, extends the duration of time for aortic arch reconstruction, and avoids the morbidity of the deeper level of hypothermia. Many studies are focused on the comparison between the neurologic outcomes of MHCA and DHCA and have proved that the infusion

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CLINICAL PERSPECTIVE

What Is New?

- In this meta-analysis and systematic review of 4142 patients undergoing aortic arch surgery, we found that moderate hypothermic circulatory arrest reduced the incidence of renal failure and the need for renal replacement therapy compared with deep hypothermic circulatory arrest.

What Are the Clinical Implications?

- Patients who undergoing aortic arch surgery, implementation of moderate hypothermic circulatory arrest conjunction with selective antegrade cerebral perfusion or retrograde cerebral perfusion is superior to deep hypothermic circulatory arrest, which confers both neuroprotection and renoprotection.

Nonstandard Abbreviations and Acronyms

DHCA deep hypothermic circulatory arrest
MHCA moderate hypothermic circulatory arrest
SACP selective antegrade cerebral perfusion

of brain guaranteed by cerebral perfusion has no significantly different effect on neurological injury between the 2 methods.[2,3]

However, the effect of moderate hypothermia on the visceral organ is unclear.[4] Renal failure in aortic surgery is a devastating complication and significantly affects the length of hospitalization, cost, and mortality.[5] The incidence of renal failure after aortic arch surgery remains as high as 21%.[6–19] Moreover, the appropriate range of temperature which provides the best protection for the kidney from moderate to deep hypothermia during circulatory arrest has not been concluded. Therefore, the purpose of this meta-study is to explore the effect of DHCA and MHCA on renal function after aortic arch surgery.

METHODS

This systematic review and meta-analysis was reported according to the guidelines of the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) group[20] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[21] (Table S1). The study protocol was registered on PROSPERO (https://www.crd.york.ac.uk/prospero/; unique identifier: CRD42020169348). The authors declare that all supporting data are available within the article and its online supplementary files.

Search Strategy

We searched PubMed, Embase, and the Cochrane Library for English articles published from their inception to January 31, 2020, using the following search terms: "aortic or arch and renal failure or kidney injury or dialysis or renal replacement or renal dysfunction or kidney dysfunction and moderate hypothermia or deep hypothermia or hypothermia or MHCA or DHCA" (Table S2). We also searched for ongoing or completed studies on the same topic on ClinicalTrials.gov and reviewed references of the identified studies to identify further relevant studies. All identified articles were systematically assessed using the inclusion and exclusion criteria.

Selection Criteria

The population, intervention, comparator, outcome, and study design approach were used to establish the selection criteria for our meta-analysis. Studies meeting the following criteria were included:

1. Population: The population of interest was the patients undergoing aortic arch surgery (including acute or chronic aortic dissection and aortic aneurysm). Studies targeting children, infants, or newborns were excluded. When the same population was reported in several articles, only the largest study was considered for inclusion.
2. Intervention: MHCA use.
3. Comparator: The MHCA group versus the DHCA group.
4. Outcome: Renal failure, the need for renal replacement.
5. Study design: All observational studies.
6. This temperature category was established by a recent consensus statement issued by thoracic aortic surgeons, the different levels of hypothermia in aortic surgery, which classified profound (≤14°C), deep (14.1–20°C), moderate (20.1–28°C), and mild (>28°C) hypothermia used in arch surgery.[22]

Data Collection and Quality Assessment

Two authors (L.C. and X.G.) independently assessed the selected literature and singled out all observational studies meeting the inclusion criteria. For cases with missing information or when clarification was needed, we contacted the original authors to obtain additional information. Disagreements within the team were resolved through a third reviewer (S.Y.). The 2 authors (Y.J. and L.Y.) independently reviewed all eligible studies. They extracted the following information: first author and year of publication, setting, design, study size, inclusion and exclusion criteria, basic patient characteristics, intervention, control, and outcomes (as mentioned previously). The Newcastle Ottawa Scale was used to assess the methodologic quality of observational studies.[23] A greater overall score indicated a lower risk of bias; a score of ≤5 (of 9) suggested a high risk of bias. The risk of bias also was evaluated independently by 2 authors (L.C. and X.G.).

Outcomes and Definitions

The primary outcome was renal failure, defined as increase serum creatinine to 300% baseline, or an absolute value >4.0 mg/dL or the initiation of renal replacement therapy. The secondary outcomes were the need for the temporary or permanent renal replacement and the major postoperative outcomes, including early mortality, stroke, reoperation for bleeding.

Statistical Analysis

This study used Stata/SE15.1 (StataCorp, College Station, TX) for data analysis. The results were expressed as odds ratios (OR) with a 95% CI. Statistical heterogeneity was evaluated with the Q statistic (P<0.1 was considered indicative of statistically significant heterogeneity) and I^2 test (I^2 >50% denoted a high degree of statistically significant heterogeneity).[24] The random-effects model was used for all comparisons because of the wide range of clinical and methodological variability across the studies. The pooled OR estimates were calculated with the Inverse Variance method. Publication biases were evaluated with the Begg and Egger tests and explored through visual inspection of funnel plots of the outcomes.[25,26] Furthermore, 1-way sensitivity analysis was performed to examine the influence of individual studies on the summary effect estimate, in which the meta-analysis estimates were computed omitting 1 study at a time. Subgroup analyses was conducted to determine whether temporal variation was a potential source of heterogeneity. P<0.05 was considered to be statistically significant.

RESULTS

Search Results and Study Characteristics

Nine hundred and thirty records were identified through a computerized literature search, among which 397 were duplicates and 407 were excluded after an initial review of titles and abstracts. The remaining 126 publications were reviewed in full-text and assessed against inclusion criteria. Finally, 14 studies were included in our study.[6–12,14–19,27] The search and selection process were depicted in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Figure 1). Descriptions of included studies are presented in Table 1. This study included 4142 patients (1709 of the MHCA group and 2433 of the DHCA group). All of the included studies were observational studies. Four of the 14 included studies were multicenter studies and 5 studies included >500 patients. All of the studies investigated the incidence of renal failure, 10 reported the need for renal replacement.[7,9–11,14,16–19,27] Thirteen reported early mortality,[7–12,14–19,27] all studies reported incidence of stroke,[6–12,14–19,27] and 8 reported incidence of reoperation for bleeding.[8–10,15–17,19,27] Thirteen studies provided the hypothermic circulatory arrest time, including 7 studies[6,7,9,10,12,19,27] with hypothermic circulatory arrest time at <30 minutes and 6 studies[8,11,14,16–18] at >30 minutes.

According to the expert consensus on classifications of hypothermia in circulatory arrest during aortic arch surgery defined that nasopharyngeal temperature of deep hypothermia was 14.1°C to 20°C, moderate hypothermia was 20.1°C to 28°C.[22] The temperature of the MHCA defined in each observational study was summarized respectively in Table 1.

Quality Assessment

The quality assessment of 14 observational studies is shown in Table 2. According to the Newcastle-Ottawa Scale to assess the risk of bias in the observational studies, 14 observational studies scored between 6 and 8, indicating high methodologic quality.

Primary Outcome: Renal Failure

All studies reported on renal failure. The pooled results from the random effect models for renal failure were shown in Figure 2. A total of 4142 patients were included in the analysis. The overall analysis of the 14 observational studies showed that MHCA significantly reduced the incidence of renal failure compared with DHCA (OR, 0.76; 95% CI, 0.61–0.94; P=0.011), with the heterogeneity was observed (I^2=0.0%, P=0.459) (Figure 2).

Secondary Outcomes

Pooled outcomes of the incidence of major postoperative outcomes were presented in Table 3 and Figures S1 through S4. Ten studies investigated the incidence of renal replacement. The need for renal replacement was significantly reduced in the MHCA group compared with DHCA (OR, 0.68; 95% CI, 0.48–0.97; P=0.034), without heterogeneity (I^2=0.0%, P=0.699).

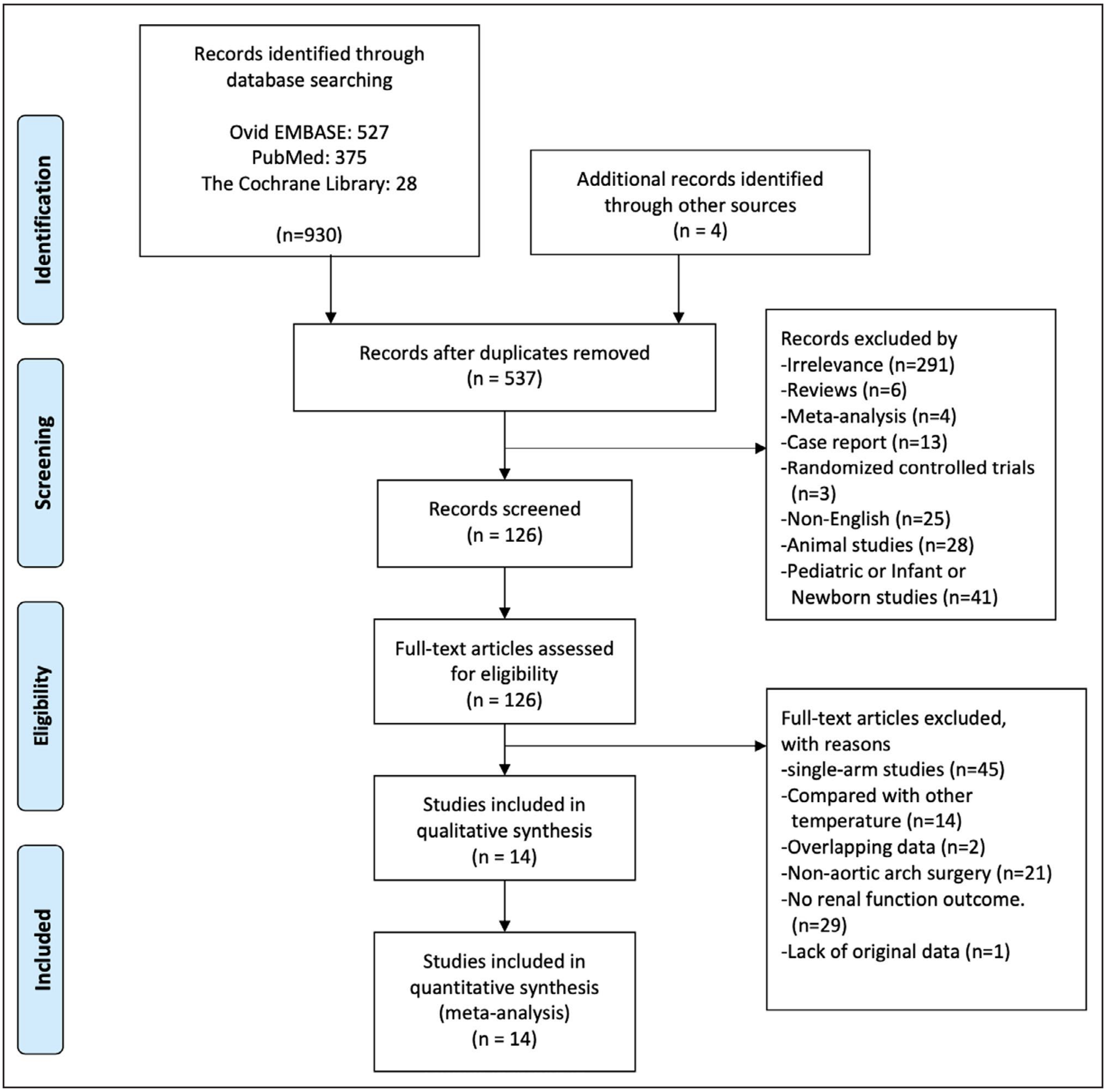

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of selection.

MHCA significantly reduce early mortality compared with DHCA (OR, 0.41; 95% CI, 0.19–0.86, *P*=0.018) with substantial heterogeneity (I^2=79.3%, *P*=0.000), and the random-effects model was applied because heterogeneity was evident among the studies. All studies investigated the incidence of stroke, MHCA was associated with a lower incidence of stroke (OR, 0.52; 95% CI, 0.35–0.78; *P*=0.002) and heterogeneity (I^2=24.8%, *P*=0.194). The incidence of reoperation for bleeding had no significant difference between the MHCA and DHCA group. (OR, 0.84; 95% CI, 0.40–1.76; *P*=0.645) with substantial heterogeneity (I^2=51.4%, *P*=0.055).

Subgroup Analysis

Thirteen studies provided the time for hypothermic circulatory arrest time. In the subgroup analysis, when hypothermic circulatory arrest time was <30 minutes, the incidence of renal failure significantly reduced in the MHCA group (OR, 0.73; 95% CI, 0.54–0.99; *P*=0.040; I^2=1.1%). While in the hypothermic circulatory arrest time longer than 30 minutes subgroup, there was no significant result (OR, 0.76; 95% CI, 0.51–1.13; *P*=0.169; I^2=17.3%). Overall significance of results was OR, 0.74; 95% CI, 0.59 to 0.92; *P*=0.008; I^2=1.0% (Figure 3).

Table 1. Description of Included Studies

Author, Year	Study Period	Setting	Type of Circulatory Arrest	Sample	Age (y)	Men, n (%)	Duration of CPB (min)	Duration of HCA (min)	Arch Surgery		Arch Replacement Type		Core Temperature of (°C)
									Emergency	Elective	Hemi	Total	
Fang et al, 2019[9]	2013–2016	Single center (China)	MHCA	287	46.1±11.0	224 (78.0)	162.5±44.2	19.7±6.1	NA	NA	0	287	20.1°C–28.0°C
			DHCA	340	47.2±10.1	252 (74.1)	189.3±51.0	22.4±6.8	NA	NA	0	340	14.1°C–20°C
Arnaoutakis et al, 2016[7]	2009–2014	Multicenter (United States)	MHCA	117	61.9±13.4	88 (74.6)	178 (140–215)	17 (14–20)	0	117	117	0	25°C–28°C
			DHCA	496	60.4±13.0	324 (68.8)	205 (175–245)	22 (19–25)	0	496	496	0	<20°C
Leshnower et al, 2015[14]	2004–2014	Single center (United States)	MHCA	206	56±14	138 (67.0)	119±74	39±20	206	0	183	23	>24°C
			DHCA	82	55±14	60 (73.1)	214±73	37±20	82	0	73	9	<24°C
Algarni et al, 2014[6]	1990–2010	Single center (Canada)	MHCA	75	60.6±14.3	54 (72.0)	159±71	25±13	0	75	68	7	22°C–28°C
			DHCA	53	60.5±12.0	40 (75.5)	174±60	29±15	0	53	45	8	<20°C
Tsai et al, 2013[18]	2006–2009	Single center (United States)	MHCA	143	60±15	11 (77.6)	140±46	38±25	13	130	107	36	≥20°C
			DHCA	78	61±14	40 (51.3)	154±62	37±23	14	64	54	24	<20°C
Qian et al, 2013[11]	2007–2012	Single center (China)	MHCA	21	46.9±10.7	17 (81.0)	203.3±61.9	32.1±9.7	21	0	7	14	24°C–25°C
			DHCA	33	44.9±11.7	26 (78.8)	289.5±79.9	44.5±18.4	33	0	7	26	18°C–20°C
Milewski et al, 2010[15]	1997–2008	Multicenter (Italy and United States)	MHCA	94	64.1±11.5	60 (63.8)	171.2±50.3	NA	94	0	NA	NA	26°C
			DHCA	682	59.9±15.3	467 (68.5)	289.5±79.9		682	0	NA	NA	<21°C
Klinkova et al, 2017[8]	NA	Single center (Russia)	MHCA	31	51	22 (71.0)	207.4 (160.2–217.2)	53.0 (38.5–65.4)	0	31	NA	NA	23°C–24°C
			DHCA	37	48	26 (71.0)	249.5 (219.2–287.5)	51.3 (36.7–72.1)	0	37	NA	NA	<18°C
Gong et al, 2016[10]	2014–2015	Single center (China)	MHCA	39	48.6±10.7	30 (76.9)	211±54	28±8	39	0	0	39	20°C–28°C
			DHCA	35	46.7±8.7	24 (68.6)	238±62	29±9	35	0	0	35	<20°C
Stamou et al, 2018[17]	2000–2014	Single center (United States)	MHCA	27	59 (35–83)	22 (81.5)	173 (89–263)	18 (0–46)	27	0	0	27	≥24°C
			DHCA	105	62 (27–86)	72 (68.6)	219 (102–535)	31 (0–146)	105	0	0	105	<24°C
Preventza et al, 2017[16]	2005–2015	Multicenter (United States)	MHCA	438	64 (53–71)	70 (63.9)	Low moderate: 141 (98–189) High moderate: 133 (104–172)	Low moderate: 55 (41–72) High moderate: 49 (37–66)	206	222	191	135	20°C–28°C
			DHCA	116	66 (51–71)	70 (60.3)	137 (107–178)	45 (38–63)	44	72	54	70	14°C–20°C
Halkos et al, 2009[12]	2004–2007	Multicenter (United States)	MHCA	205	57.8±14.1	143 (69.8)	183±64	26±12	65	140	NA	NA	≥20°C
			DHCA	66	54.5±13.9	50 (66.7)	218±75	26±8	40	26	NA	NA	<20°C
Vallabhajosyula et al, 2015[19]	2008–2012	Single center (United States)	MHCA	75	66±11	49 (65.3)	167±49	18±5	0	75	75	0	25°C–28°C
			DHCA	301	60±14	194 (64.5)	222±61	23±8	0	301	301	0	<20°C
Ma et al, 2016[27]	2010–2013	Single center (China)	MHCA	47	46.8±10.8	43(91.5)	218.6±37.1	28.0±6.0	NA	NA	0	47	≥20°C
			DHCA	52	49.5±10.2	41(78.8)	236.3±35.7	31.5±5.7	NA	NA	0	52	<20°C

CPB indicates cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; HCA, hypothermic circulatory arrest time; and MHCA, moderate hypothermic circulatory arrest.

Table 2. Quality Assessment of Observational Studies

Study	Selection				Comparability	Outcome			
	Exposed Cohort	Non-exposed Cohort	Ascertainment of Exposure	Outcome of Interest		Assessment of Outcome	Length of Follow-Up	Adequacy Follow-Up	Total Score
Fang, 2019[9]	*	*	*	*	*	*	*	*	8
Arnaoutakis, 2016[7]	*	*	*	*	*	*	*	*	8
Leshnower, 2015[14]	*	*	*	*	*	*	*	*	8
Algarni, 2014[6]	*	*	*	*	*	*	*	*	8
Tsai, 2013[18]	*	*	*	*	*	*	*	*	8
Qian, 2013[11]	*	*	*	*	*		*	*	7
Milewski, 2010[15]	*	*	*	*			*	*	6
Klinkova, 2017[8]	*	*	*	*		*	*	*	7
Gong, 2016[10]	*	*	*	*	*	*	*	*	8
Stamou, 2018[17]	*	*	*	*	*	*	*	*	8
Preventza, 2017[16]	*	*	*	*	*	*	*	*	8
Halkos, 2009[12]	*	*	*	*	*		*	*	7
Vallabhajosyula, 2015[19]	*	*	*	*		*	*	*	7
Ma, 2015[27]	*	*	*	*	*	*	*	*	8

Risk of bias was assessed using the Newcastle–Ottawa Scale. A higher overall score indicated a lower risk of bias; a score of ≤5 (of 9) suggested a high risk of bias.

Publication Bias and Sensitivity Analyses

The results of publication bias tests are presented in Figure 4 and Table 3. All of the *P* values for the Begg and Egger tests were >0.1, suggesting a low probability of publication bias. We also performed a 1-way sensitivity analysis of outcomes to estimate the effect of each study on operative renal failure. In this analysis, the omission of each study did not make a significant difference (Figure 5), confirming the stability of our results.

DISCUSSION

This meta-analysis of the 14 observational studies demonstrated that MHCA significantly reduced postoperative renal failure and the need for renal replacement compared with DHCA for the patient undergoing aortic arch surgery. Moreover, we found that when the hypothermic circulatory arrest time was <30 minutes, the incidence of renal failure in the MHCA group was lower than that in the DHCA group, but when the hypothermic circulatory arrest time was longer than 30 minutes, there was no significant difference in the incidence of renal failure between the 2 groups.

DHCA has been used routinely as a classic technique for aortic arch reconstruction since 1975,[1] based on thatthe deep hypothermia suppressed the cerebral metabolic with a decreased oxygen demand can prolong the time of cerebral ischemia. Recently, the use of MHCA with selective antegrade cerebral perfusion or retrograde cerebral perfusion for adult aortic arch surgery has been recognized and popularized since this guarantees cerebral perfusion thus allowing for extending the duration of time for aortic arch reconstruction and potentially avoiding morbidity of deeper levels of hypothermia and bringing benefits for the patient undergoing aortic arch surgery. However, it is still controversial on whether the moderate degree of hypothermia is the potential risk for visceral organs without selective perfusion, especially the kidney, which is at great risk of experiencing ischemia.[4] Moreover, we have doubted the safety time limitation of renal function with moderate hypothermia.

Previously, many meta-analyses have focused on the comparison of DHCA and MHCA with or without SACP use on neurological complications. Tian and colleagues[28] included 9 studies; 1783 patients who underwent aortic arch surgery found that permanent neurological deficit was significantly lower in the MHCA+SACP group as compared with DHCA. However, no significant difference was observed for the temporary neurological deficit between DHCA and MHCA+SACP. But only 5 studies reported postoperative renal failure, both DHCA and MHCA+SACP groups had comparable outcomes (13.3% versus 12.6%; OR, 1.36; 95% CI, 0.74–2.49; P=0.32; I^2=40%); 4 studies reported reoperation for bleeding was similarly comparable between both groups when reported (10.9% versus 13.3%; OR, 0.85; 95% CI, 0.43–1.69; P=0.65; I^2=62%). Hameed and colleagues[2]

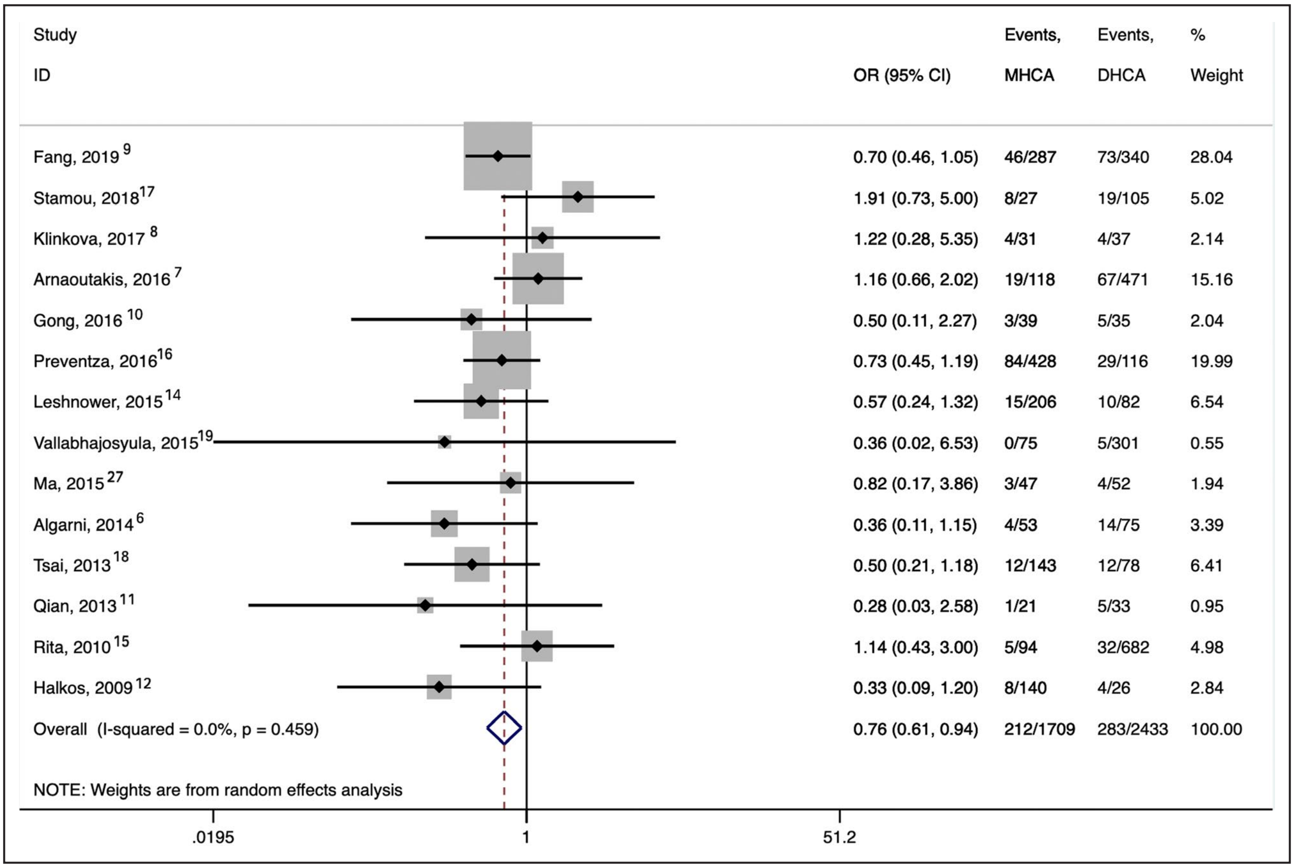

Figure 2. Forest plot of the odds ratio of postoperative renal failure in aortic arch surgery using deep hypothermic circulatory arrest or using moderate hypothermic circulatory arrest.
The overall significance of results (odds ratio, 0.76; 95% CI, 0.61–0.94; *P*=0.011), with the heterogeneity (I^2=0.0%, *P*=0.459). The estimate of the odds ratio of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% CI. On each line, the number of events as a fraction of the total number randomized is shown for both treatment groups. Pooling model using Random (I–V heterogeneity) and the pooled odds ratio estimated by weighting methods. DHCA indicates deep hypothermic circulatory arrest; and MHCA, moderate hypothermic circulatory arrest.

conducted a network meta-analysis and found that the MHCA+SACP did not differ from DHCA in postoperative renal failure and there was also no difference between MHCA+retrograde cerebral perfusion and DHCA. Tian and colleagues[3] conducted another meta-analysis and found that postoperative dialysis was significantly reduced in the warmer target temperatures, but no significant differences in re-exploration for bleeding were found. These findings may indicate that warmer target temperature has little effect on the renal function. Nevertheless, it was noted that renal function outcomes between MHCA and DHCA were infrequently included in previous meta-analyses, thus limiting the evaluation of the authenticity and credibility.

To the best of our knowledge, this study is the first systematic review and meta-analysis to target postoperative renal function of patients undergoing aortic arch surgery using MHCA compared with DHCA. In the present study, we included 14 observational studies with a total of 4142 patients and performed 1-way sensitivity analysis, which may reduce the risk of patient selection bias. Besides, the results of risk assessment of bias showed that our included studies were at a low risk of bias. Hence, the included studies in the present meta-analysis were of satisfactory methodological quality.

It has been demonstrated that MHCA with SACP or retrograde cerebral perfusion is efficient in preventing the incidence of permanent neurologic deficit.[2,3] Moreover, MHCA may be associated with a reduction of in-hospital mortality compared with DHCA.[3] These above results are consistent with the findings of this study. As we know, hypothermia remains the cornerstone of distal organ protection, which can prolong the duration of tissue endurance for ischemia. The protective effects of hypothermia on organ function in the setting of ischemic injury have been previously demonstrated in animal models. Hyperthermia is associated with increased renal injury, whereas hypothermia is protective.[29] The effects of temperature on tissue metabolic rate and related effects on energy and nutrient demand, as well as effects of hypothermia

Table 3. Meta-Analysis for All Secondary Outcomes and Publication Bias

Outcomes	OR (95% CI)	z	*P* Value	I^2 (%)	I^2's *P*	Begg, *P*	Egger, *P*
Renal replacement	0.68 (0.48–0.97)	2.13	0.034	0.0	0.699	0.210	0.420
Early mortality	0.41 (0.19–0.86)	2.37	0.018	79.3	0.000	0.855	0.180
Stroke	0.52 (0.35–0.78)	3.16	0.002	24.8	0.194	0.951	0.831
Reoperation for bleeding	0.84 (0.40–1.76)	0.46	0.645	51.4	0.055	0.133	0.101

OR indicates odds ratio.

on the mediation of reperfusion oxidative injury, are likely mechanisms responsible for this phenomenon. However, in the clinical setting, the benefits of hypothermia remain debated. Recently, urologist Lane and colleagues[30] conducted a study about the comparison of cold and warm ischemia during partial nephrectomy and found that warm ischemia was not the predictor of acute kidney injury. Swaminathan and colleagues[31] randomly assigned 300 patients with coronary artery bypass grafting to examine the effects of warm (35.5°C–36.5°C) versus cold (28°C–30°C) cardiopulmonary bypass management and found no difference between the patient groups in the renal outcome.

These studies indicate that warm temperature is not a risk factor affecting postoperative renal function with the normal renal perfusion. However, for patients

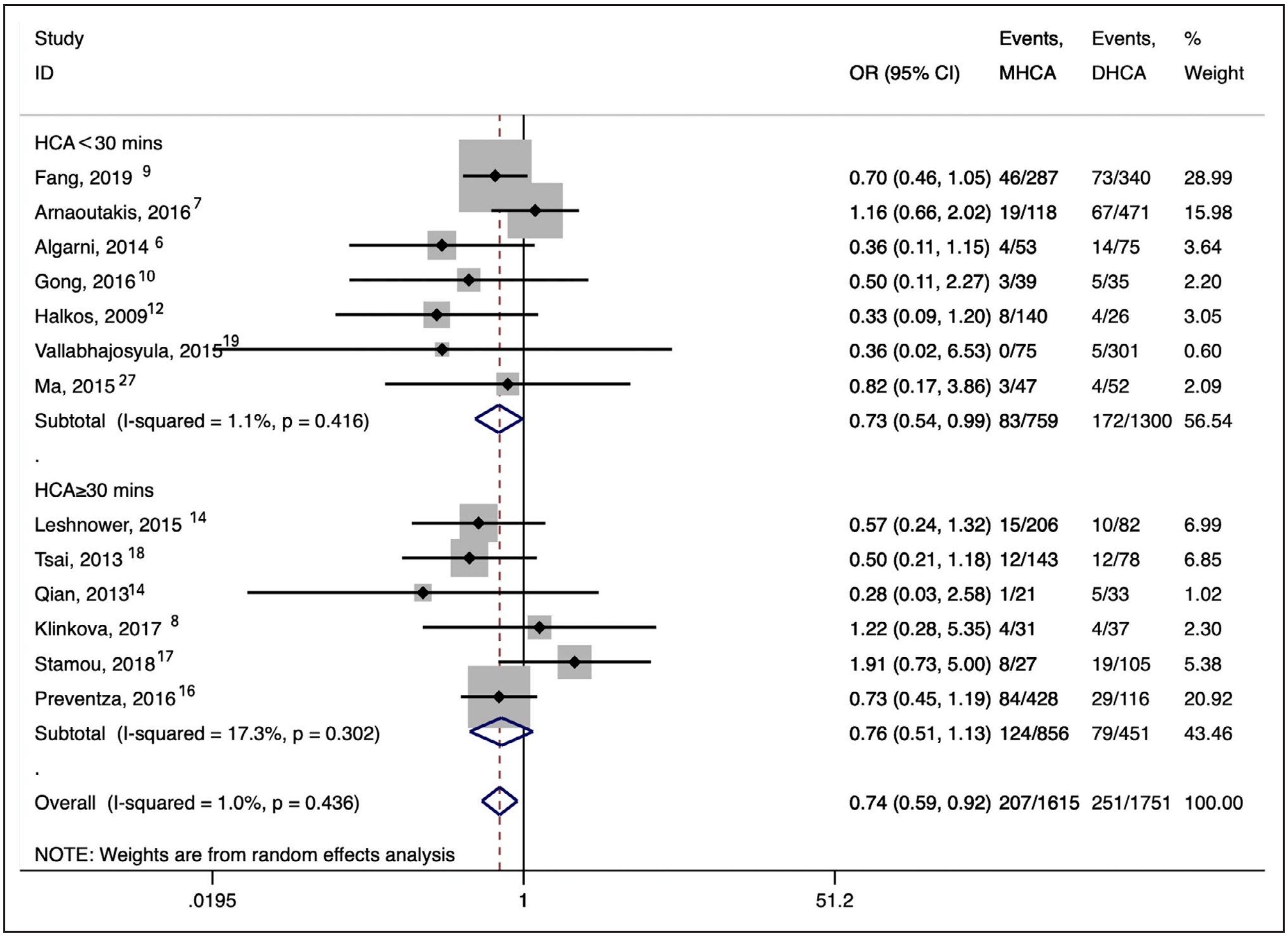

Figure 3. Forest plot shows the odds ratio (OR) of renal failure for studies comparing hypothermic circulatory arrest time <30 minutes and >30 minutes.

For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. Pooling model using Random (I–V heterogeneity). Significance of result in circulatory arrest time <30 minutes (OR, 0.73; 95% CI, 0.54–0.99; *P*=0.040; I^2=1.1%). While circulatory arrest time longer than 30 minutes subgroup has no significantly result (OR, 0.76; 95% CI, 0.51–1.13; *P*=0.169; I^2=17.3%). Overall significance of results (OR, 0.74; 95% CI, 0.59–0.92; *P*=0.008; I^2=1.0%). DHCA indicates deep hypothermic circulatory arrest; and MHCA, moderate hypothermic circulatory arrest.

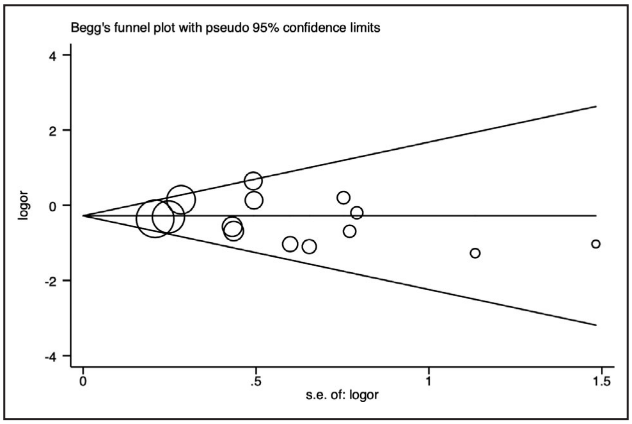

Figure 4. Begg funnel plot for the meta-analysis of renal failure comparing DHCA vs MHCA in all 14 included studies. *P* values for the Begg tests were 0.999. Log of odds ratio comparing renal failure (vertical axis) is presented against the standard error of the log of odds ratios (horizontal axis). The standard error inversely corresponds to study size. Asymmetry of the plot can indicate publication bias. OR indicates odds ratio; and SE, standard error.

undergoing aortic arch surgery, there is no renal perfusion during cardiac arrest. Animal experiments have shown that the effect of moderate hypothermia is poorer than deep hypothermia theoretically, but our statistical results are contrary. We consider that there are 2 factors: First, the duration of cardiac arrest is shorter than the time limit for organ protection at moderate hypothermia. Second, moderate hypothermia reduces the time of cardiopulmonary bypass needed for cooling and rewarming, avoiding pernicious effects caused by deep hypothermia, such as coagulopathy, systematic inflammatory response or organ ischemia reperfusion injury. Cardiopulmonary bypass time is an independent risk factor for postoperative acute kidney injury in cardiac surgery.[32] MHCA avoids the morbidity of deeper levels of hypothermia and reduced cardiopulmonary bypass time may be beneficial for patients. The risks of potential coagulopathy and systemic inflammatory response increased with deeper hypothermia, which accelerates renal tubular injury.[32] In this analysis, we also found that MHCA significantly reduced the need for renal replacement.

Limitations

This study shared the usual limitations of meta-analysis of observational studies. The literature on hypothermia options for aortic arch repairment with the aortic syndrome was significantly limited given the relative lack of high-quality randomized controlled trials, and observational results were likely to be affected by selection bias. Thus, the real impact of deep or moderate hypothermia on renal function in aortic arch surgery had not been defined to date and certainly deserves registry-based studies. For this reason, despite statistical adjustment using a randomized-effects model, the presence of unmeasured

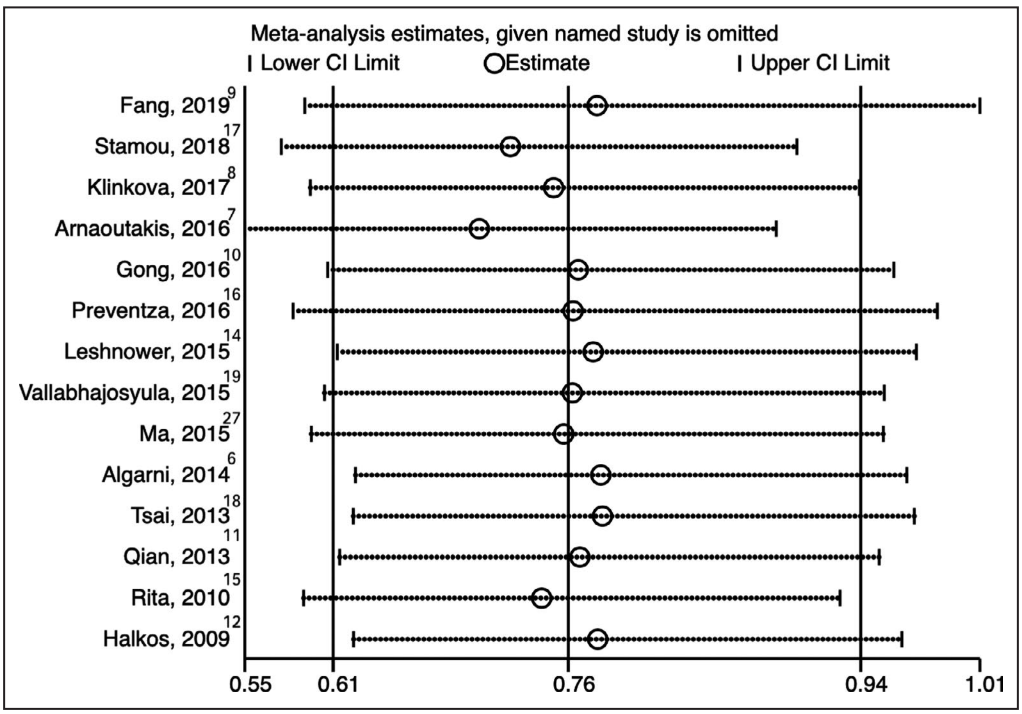

Figure 5. One-way sensitivity analysis of renal failure.
In this analysis, the omission of each study did not make a significant difference, confirming the stability of our results.

confounders and possible treatment allocation bias cannot be excluded. Heterogeneity may exist particularly in terms of definition and diagnosis for renal failure, as well as sample size and surgical expertise. However, the low-to-moderate grade of heterogeneity found across the studies suggests that the importance of these potential biases in this analysis was probably minimal. Further efforts should be made to explore the potential biological mechanism and search for the preventive strategy to decrease the risk of renal failure after aortic arch surgery. Large-scale and long-term randomized controlled trials in various populations are further warranted to show the strength of this association.

CONCLUSIONS

Our study suggests that MHCA compared with DHCA reduces the incidence of renal failure and the need for renal replacement.

ARTICLE INFORMATION

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Cao and Guo contributed to the acquisition of data, analysis, and interpretation of data. Cao contributed to drafting of the article. Jia, Yang, and Wang contributed to screen citations for inclusions and extracting data. Yuan contributed to the conception and design of the study, analysis and interpretation of data, revision of the article, and final approval of the version to be published.

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Disclosures

None.

Supplementary Materials

Tables S1–S2
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Meta-analysis of Observational Studies in Epidemiology (MOOSE) Checklist.

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	Moderate hypothermic circulatory arrest (MHCA) has been widely used in aortic arch surgery. However, the renal function after MHCA remains controversial.
√	Hypothesis statement	MHCA compared with DHCA reduces the incidence of renal failure and the need for renal replacement.
√	Description of study outcomes	Renal failure, the need for renal replacement.
√	Type of exposure or intervention used	MHCA
√	Type of study designs used	All observed studies.
√	Study population	The population of interest was the patients undergoing aortic arch surgery (including acute or chronic aortic dissection, aortic aneurysm).
Reporting of search strategy should include		
√	Qualifications of searchers	The two experienced investigators (L.C. and X.G.) are indicated in the authors list.
√	Search strategy, including time period included in the synthesis and keywords	PubMed, EMBASE and the Cochrane Library were searched for all articles published before January 31, 2020. Using the following search terms: "aortic or arch and renal failure or kidney injury or dialysis or renal replacement or renal dysfunction or kidney dysfunction and moderate hypothermia or deep hypothermia or hypothermia or MHCA or DHCA".
√	Databases and registries searched	PubMed, EMBASE and the Cochrane Library.
√	Search software used, name and version, including special features	We did not employ a search software. Endnote was used to merge retrieved citations.
√	Use of hand searching	We also searched for ongoing or completed studies on the same topic on ClinicalTrials.gov and reviewed references of the identified studies to identify further relevant studies.
√	List of citations located and those excluded, including justifications	Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flowchart of Selection.
√	Method of addressing articles published in languages other than English	Only English language are eligible for inclusion.
√	Method of handling abstracts	We did not include unpublished or abstract only

	and unpublished studies	publications
√	Description of any contact with authors	For cases with missing information or when clarification was needed, we contacted the original authors to obtain additional information.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Studies included in the present meta-analysis according to the following criteria: (1) Population: The population of interest is the patients undergoing aortic arch surgery. (2) Intervention: MHCA use; (3) Control: DHCA use; (4) Outcome: Primary outcome of interest include the incidence of RF. Secondary outcomes of interest include in-hospital mortality, the need for dialysis and possible complications or adverse effects. (5) Study design: All observed studies Exclusion criteria include (1) Studies published as review, case report or abstract; (2) Animal studies; (3) Duplicate publications, when the same population was reported in several articles, only the largest study was considered for inclusion; (4) Studies targeting pediatric or newborns patients are excluded; (5) Studies lacking information about outcomes of interest; (6) Language: Non-English language articles are excluded.
√	Rationale for the selection and coding of data	The following data were extracted: first author and year of publication, setting, design, study size, inclusion and exclusion criteria, basic patient characteristics, intervention, control and outcomes.
√	Assessment of confounding	We conducted subgroup analyses and univariable random-effects meta-regression.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	We used a modified version of the Newcastle Ottawa Scale (NOS) to assess the quality of each study.
√	Assessment of heterogeneity	We used the I^2 and P-value to assess heterogeneity
√	Description of statistical methods in sufficient detail to be replicated	We mentioned type of analysis we used (meta-analysis, subgroup meta-analysis and meta-regression) and type of software we used Stata/SE15.1 (StataCorp, College Station, Tex).
√	Provision of appropriate tables	Table 1. Description of included studies.

	and graphics	Table 2. Quality assessment of observational studies. Table 3. Meta-analysis for all secondary outcomes and publication bias. Figure 1 showing literature search flow diagram. Figure 2. Forest plot of the odds ratio (OR) of postoperative renal failure. Figure 3. Begg's funnel plot for the meta-analysis of renal failure. Figure 4. One-way sensitivity analysis of renal failure. Figure 5. Forest plot of subgroup analysis. Supplemental Figure 1-4. Forest plot of secondary outcomes.
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Figure 3 and 4
√	Indication of statistical uncertainty of findings	HR, 95% CI, I^2 and P
Reporting of discussion should include		
√	Quantitative assessment of bias	Two authors (J.Y. and L.Y) independently assess the risk of bias, using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions. The Newcastle-Ottawa Scale (NOS) will be used independently by two authors to evaluate the methodological quality of each included trial. The results of publication bias tests are presented in Figure 3 Begg's funnel plot for the meta-analysis and Table 3.
√	Justification for exclusion	We selected the latest article or the largest sample size if a cohort study was reported in more than one publication.
√	Assessment of quality of included studies	The Newcastle-Ottawa Scale (NOS) will be used independently by two authors to evaluate the methodological quality of each included trial. Table 2. Quality assessment of observational studies.
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Patients who undergoing aortic arch surgery, implementation of moderate hypothermic circulatory arrest with selective antegrade cerebral perfusion or retrograde cerebral perfusion is superior to deep

		hypothermic circulatory arrest not only confers neuroprotection but also renoprotection.
√	Generalization of the conclusions	Our meta-analysis demonstrates MHCA compared with DHCA did reduce the incidence of renal failure and the need for renal replacement.
√	Guidelines for future research	Further efforts should be made to explore the potential biological mechanism and search for the preventive strategy to decrease the risk of RF after aortic arch surgery. Large-scale and long-term randomized controlled trials in various populations are further warranted to show the strength of this association.
√	Disclosure of funding source	None.

Table S2. Ovid MEDLINE search strategy.

No.	Query Results
#4.	#1 AND #2 AND #3
#3.	**Aortic** :ab,ti OR **arch** :ab,ti
#2.	**renal failure** OR **acute kidney injury** OR **dialysis** OR **renal replacement** OR **renal dysfunction** OR **kidney dysfunction**
#1.	'**moderate hypothermia**':ab,ti OR '**deep hypothermia**':ab,ti OR **hypothermic**:ab,ti

Figure S1. Forest plot of renal replacement.

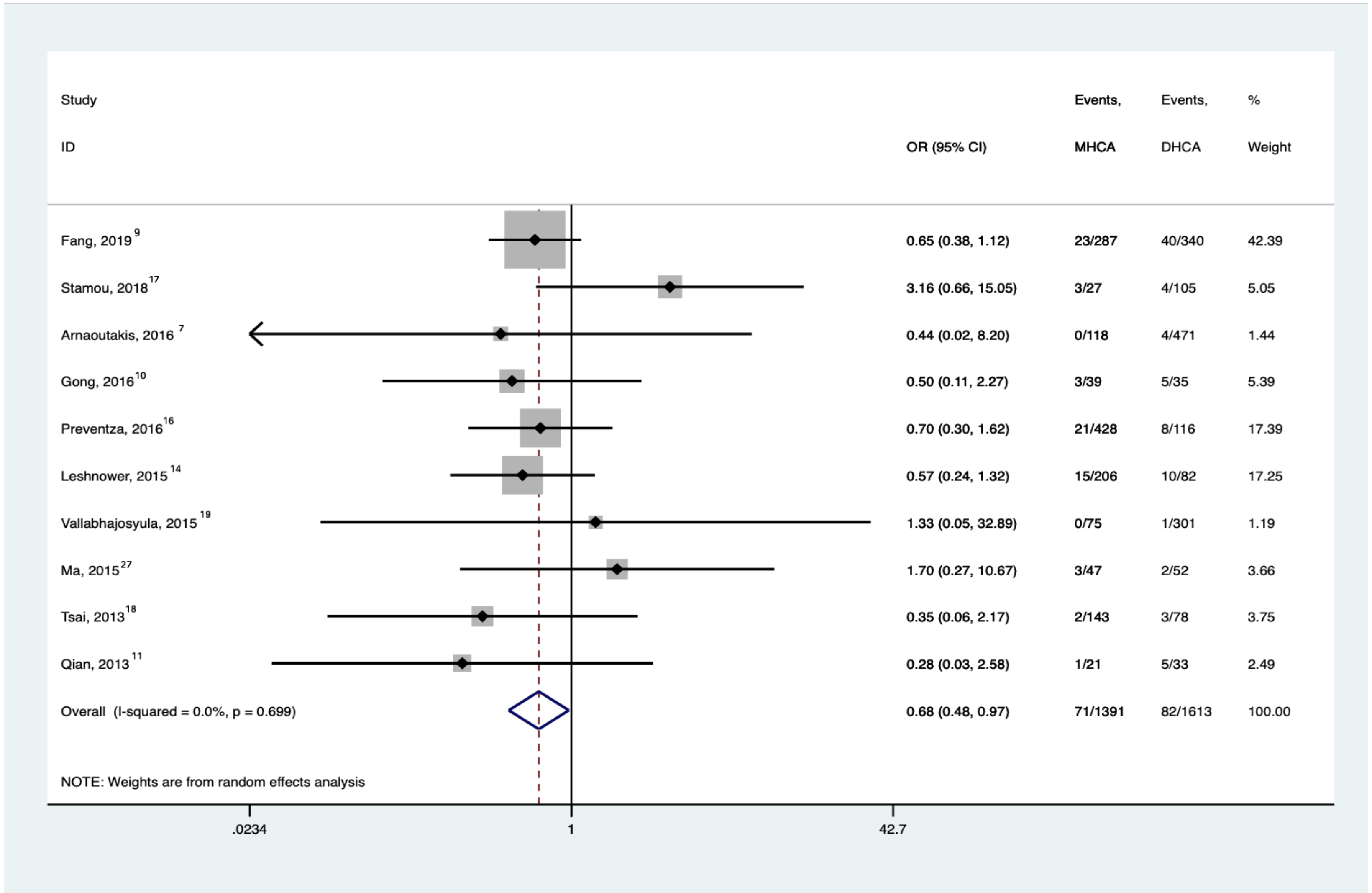

Figure S2. Forest plot of early mortality.

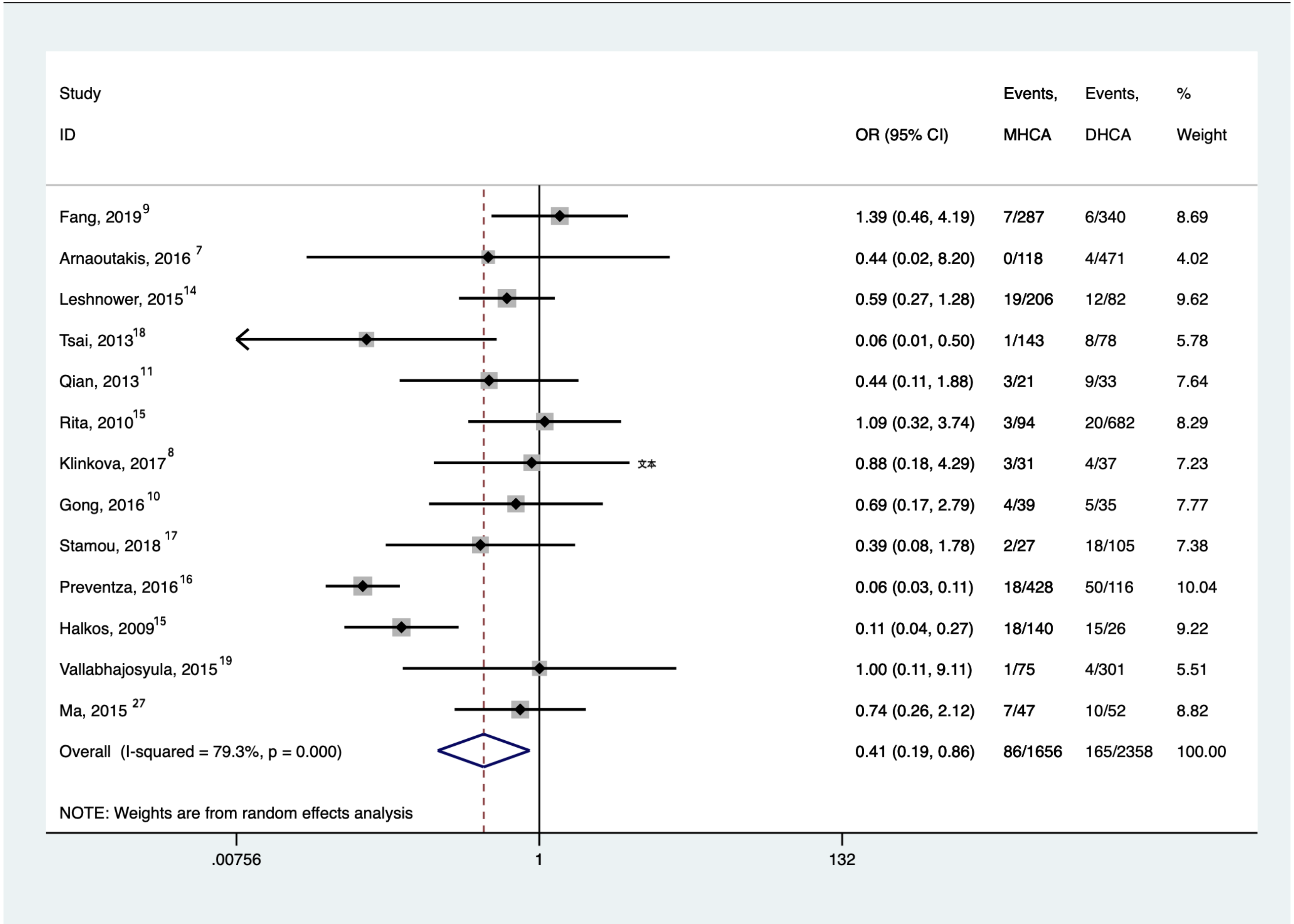

Figure S3. Forest plot of stroke.

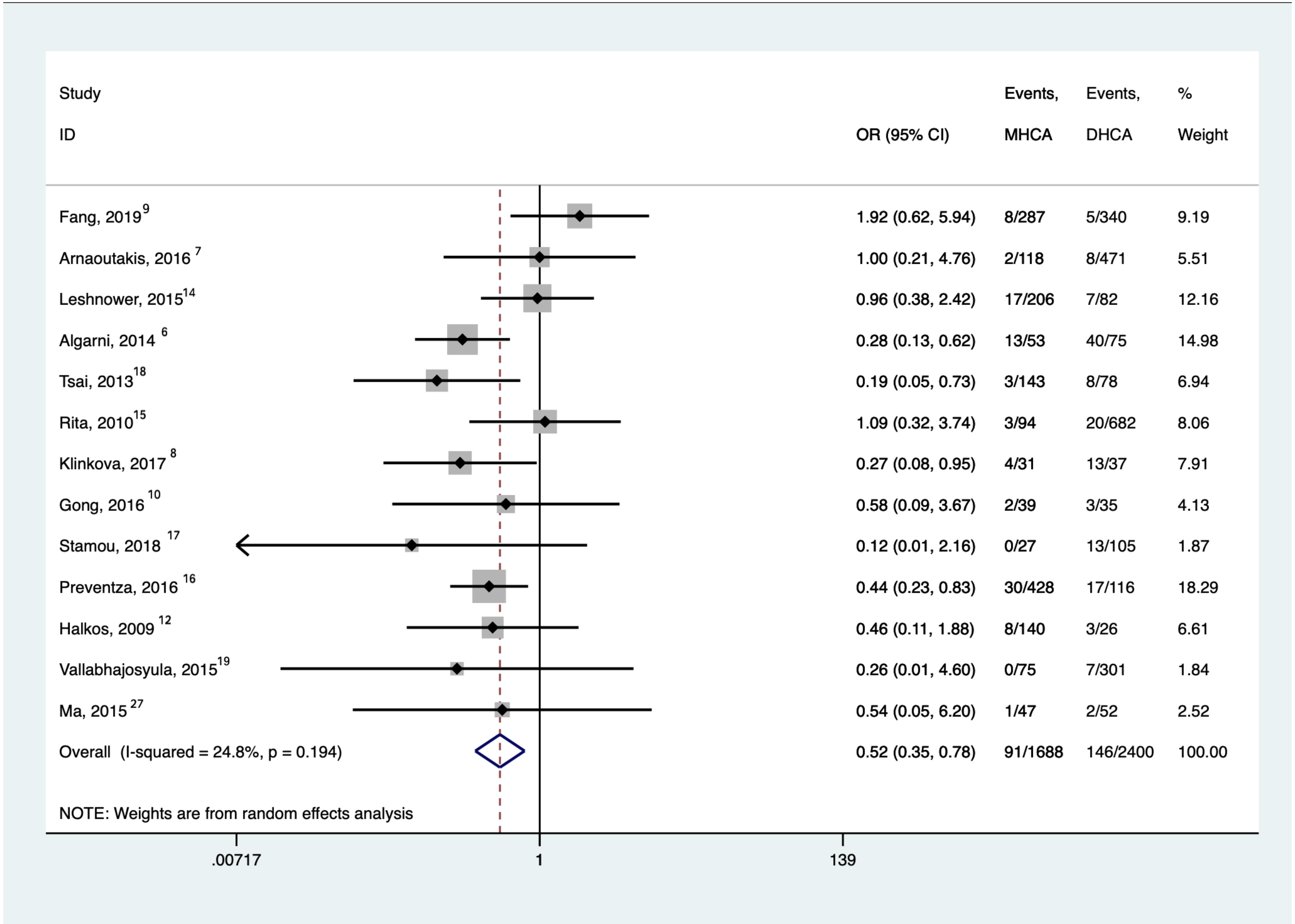

Figure S4. Forest plot of reoperation for bleeding.