Cerebral protection strategies in aortic arch surgery: A network meta-analysis

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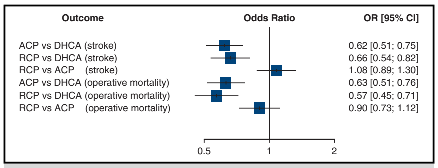
ABSTRACT

Objective: Cerebral protection for aortic arch surgery has been widely studied, but comparisons of all the available strategies have rarely been performed. We performed direct and indirect comparisons of antegrade cerebral perfusion, retrograde cerebral perfusion, and deep hypothermic circulatory arrest in a network meta-analysis.

Methods: After a systematic literature search, studies comparing any combination of antegrade cerebral perfusion, retrograde cerebral perfusion, and deep hypothermic circulatory arrest were included, and a frequentist network meta-analysis was performed using the generic inverse variance method. The primary outcomes were postoperative stroke and operative mortality. Secondary outcomes were postoperative transient neurologic deficits, myocardial infarction, respiratory complications, and renal failure.

Results: A total of 68 studies were included with a total of 26,968 patients. Compared with deep hypothermic circulatory arrest, both antegrade cerebral perfusion and retrograde cerebral perfusion were associated with significantly lower postoperative stroke and operative mortality rates: antegrade cerebral perfusion (odds ratio [OR], 0.62; 95% confidence interval [CI], 0.51-0.75; and OR, 0.63, 95% CI, 0.51-0.76, respectively) and retrograde cerebral perfusion (OR, 0.66; 95% CI, 0.54-0.82; and OR, 0.57; 95% CI, 0.45-0.71, respectively). Antegrade cerebral perfusion and retrograde cerebral perfusion were associated with similar incidence of primary outcomes. No difference among the 3 techniques was found in secondary outcomes. At meta-regression, circulatory arrest duration correlated with the neuroprotective effect of antegrade cerebral perfusion and retrograde cerebral perfusion compared with deep hypothermic circulatory arrest. Unilateral or bilateral antegrade cerebral perfusion and arrest temperature did not influence the results.

Conclusions: Antegrade cerebral perfusion and retrograde cerebral perfusion are associated with better postoperative outcomes compared with deep hypothermic circulatory arrest, and the relative benefit increases with the duration of the circulatory arrest. No differences between antegrade cerebral perfusion and retrograde cerebral perfusion were found for all the explored outcomes. (J Thorac Cardiovasc Surg 2020;159:18-31)



Forest plot comparing the cerebral protection strategies in terms of primary outcomes.

Central Message

ACP and RCP are associated with a lower incidence of postoperative stroke and operative mortality compared with DHCA. No difference between ACP and RCP was shown in terms of postoperative outcomes.

Perspective

The optimal cerebral protection strategy during aortic arch surgery remains controversial. Past meta-analyses have performed only pairwise comparisons of the strategies. This study uses an NMA approach to compare the effect of all 3 cerebral protection strategies on postoperative stroke and operative mortality after aortic arch surgery.

See Commentaries on pages 32 and 34.

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Abbreviations and Acronyms

ACP	= antegrade cerebral perfusion
CI	= confidence interval
DHCA	= deep hypothermic circulatory arrest
MI	= myocardial infarction
NMA	= network meta-analysis
OR	= odds ratio
RCP	= retrograde cerebral perfusion
RCT	= randomized controlled trial

Aortic arch surgery is associated with a non-negligible rate of mortality and neurologic deficits despite advancements in surgical techniques and cerebral monitoring technology.[1-3] Currently, 3 different cerebral protection strategies are available: isolated deep hypothermic circulatory arrest (DHCA), circulatory arrest coupled with retrograde cerebral perfusion (RCP), and circulatory arrest coupled with antegrade cerebral perfusion (ACP). The advantages and disadvantages of these cerebral protection techniques have been extensively studied,[4-11] but consensus on the optimal strategy is still lacking.

Over the past 15 years, 8 meta-analyses have reported pairwise comparisons of DHCA, RCP, and ACP in different combinations.[4-11] However, no meta-analysis has compared all 3 techniques.

Network meta-analyses (NMAs) allow comparisons between more than 2 treatment arms by incorporating direct and indirect evidence (ie, direct intergroup comparisons and comparisons with a common comparator group).[12] NMA is also a powerful technique to reduce heterogeneity and allocation biases, especially when analyzing both randomized controlled trials (RCTs) and observational studies. In the current study, we use the NMA approach to compare the effect of DHCA, ACP, and RCP on postoperative stroke and operative mortality after aortic arch surgery.

MATERIALS AND METHODS

Search Strategy

A medical librarian (M.D.) performed comprehensive searches to identify randomized trials and observational studies comparing ACP, RCP, and DHCA. Searches were run on August 13, 2018, in the following databases: Ovid MEDLINE (ALL; 1946 to August 10, 2018); Ovid EMBASE (1974 to present); and The Cochrane Library (Wiley). The search strategy included the terms "antegrade cerebral perfusion," "retrograde cerebral perfusion," and "hypothermic circulatory arrest." The full search strategy for Ovid MEDLINE is available in Online Data Supplement Table 1.

Study Selection

Searches across the chosen databases retrieved 1789 results. After results were de-duplicated, 2 independent reviewers (I.H. and M.R.) screened a total of 1045 citations. Discrepancies were resolved by the senior author (M.G.). Titles and abstracts were reviewed against predefined inclusion/exclusion criteria. Articles were considered for inclusion if they were written in English, were adjusted or matched observational studies, or were RCTs comparing at least 2 of the 3 cerebral protection strategies (ACP, RCP, and DHCA). Animal studies, case reports, conference presentations, editorials, expert opinions, studies not clearly defining the strategy used or using multiple cerebral protection strategies simultaneously, and studies not defining or reporting postoperative stroke or operative mortality outcomes for the individual cerebral perfusion strategies were excluded.

Full text was pulled for the selected studies for a second round of eligibility screening. Reference lists for articles selected for inclusion in the study were also searched for relevant articles. The full Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram outlining the study selection process is available in Online Data Supplement Figure 1.[13,14] All studies were reviewed by 2 independent investigators (I.H. and M.R.), and disagreements were resolved by the senior author (M.G.). For overlapping studies, the largest series were included.

Two investigators (I.H. and F.M.K.) performed data extraction independently, and the extracted data were verified by a third investigator (M.W.) for accuracy. The following variables were included: study demographics (sample size [preferably matched cohorts], publication year, design, institution, and country) (Table 1), patient demographics (age, sex, comorbidities [hypertension, atherosclerosis/dyslipidemia, peripheral vascular disease, chronic lung disease, diabetes, smoking, previous cerebrovascular accident, and coronary artery disease]) (Online Data Supplement Table 2), and procedural and postoperative factors (procedural status surgery for dissection or aneurysm, total arch or hemiarch replacement, aortic root procedure, bilateral vs unilateral ACP, systemic temperature during circulatory arrest [in degrees Celsius], cardiopulmonary bypass and crossclamp time [in minutes], duration of circulatory arrest [in minutes]) (Table 2).

Assessment of the Quality of Individual Studies and Overall Quality of Evidence

The quality of the included studies was assessed using the Newcastle–Ottawa Scale for observational studies (Online Data Supplement Table 3) and the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (Online Data Supplement Table 4).[15,16]

To assess the overall quality of evidence, we used the Grading of Recommendations, Assessment, Development, and Evaluation approach considering risk of bias, imprecision, inconsistency, indirectness, and publication bias.[17] Confidence (certainty of evidence) was rated as high, moderate, low, or very low[17] (Online Data Supplement Table 5).

Outcomes and Effect Summary

The primary outcomes were postoperative stroke and operative mortality. Secondary outcomes were postoperative transient neurologic deficit, myocardial infarction (MI), respiratory complications, and renal failure. The definition of postoperative stroke and all the other outcomes were those used in the individual studies (Online Data Supplement Table 6 shows details of the individual definitions used).

Pairwise Meta-Analysis

Outcomes were pooled as odds ratio (OR) with 95% confidence intervals (CIs) using the generic inverse variance method[18] for matched (preferentially)/adjusted cohorts. ORs were extracted from the individual studies or calculated on the basis of the number of events. Random effect meta-analysis was performed using "metafor" and "meta" packages,[19,20] and publication bias was assessed by funnel plot and Egger's test. Heterogeneity was reported as low (I^2 = 0%-25%), moderate (I^2 = 26%-50%), or high ($I^2 > 50\%$)[21] (Online Data Supplement Table 7). Leave-1-out analysis for the primary outcome was also performed (Online Data Supplement Figures 2.1-2.6).

Subgroup analysis was used to compare unilateral and bilateral ACP with DHCA and RCP, and to evaluate the effect of circulatory arrest time on the primary outcomes. For this analysis, quartiles of arrest time were

TABLE 1. Summary of included studies

Study/year	Study period	Hospital/country	Country	Type of study*	ACP (n)†	RCP (n)†	DHCA (n)†
Ahn/1997	1986-2004	Seoul National University College of Medicine	Japan	A	12	7	28
Akashi/2000	1989-1999	University School of Medicine	Japan	A	150	55	
Alamanni/1995	1985-1993	University of Milan	Italy	A	16		19
Apaydin/2009	1993-2006	Ege University Medical School	Turkey	A	19	94	48
Apostolakis/2008	1998-2006	School of Medicine, University of Patras	Greece	A	23	25	
Arnaoutakis/2017	-	University of Pennsylvania	United States	A	117	469	
Bavaria/1995	1987-1994	University of Pennsylvania	United States	A		14	24
Bonser/2002	-	Birmingham Queen Elizabeth Medical Centre	United Kingdom	RCT		21	21
Caimmi/1998	1989-1994	Multicenter	Italy	A	3	10	43
Campbell-Lloyd/2010	2000-2008	Princess Alexandra Hospital	Australia	A	31	7	35
Cefarelli/2017	2005-2015	St Antonius Hospital	Netherlands	A	636		155
Coselli/1997	1987-1996	Baylor College of Medicine	United States	A		290	189
Di Eusanio/2003	1995-2001	St Antonius Hospital	Netherlands	A	161		128
Di Mauro/2012	1988-2009	Prince Sultan Cardiac Centre	Saudi Arabia	A	189	198	69
Dong/2002	1985-2000	Beijing Anzhen Hospital	China	A		50	15
Ehrlich/1999	-	University of Vienna	Austria	M		54	55
Forteza/2009	1990-2008	Hospital Universitario 12 de Octubre	Spain	A	23	26	32
Ganapathi/2014	2005-2013	Duke University Medical Center	United States	M	80	80	
Guan/2004	1982-2001	Beijing Anzhen Hospital	China	A		61	17
Hagl/2001	1986-2001	Mount Sinai School of Medicine	United States	A	55	18	83
Halkos/2009	2004-2007	Emory University School of Medicine, Atlanta	United States	A	205		66
Han/2007	2003-2005	Second Military Medical University	China	A	35	43	
Harrington/2004	2001-2003	Queen Elizabeth Hospital	United Kingdom	RCT	20		22
Hata/2018	2006-2017	Nihon University Hospital	Japan	A		57	130
Higgins/2012	1993-2010	University of British Columbia	Canada	A	371	96	132
Immer/2008	-	University Hospital, Switzerland	Switzerland	A	180		387
Kamenskaya/2015	2011-2013	Novosibirsk Research Institute	Russia	RCT	30		31
Kamenskaya/2017	2011-2012	Novosibirsk Research Institute	Russia	RCT	29		29
Kamiya/2007	2000-2005	Hannover Medical School	Germany	M	31		30
Kaneda/2005	1995-2003	Kishiwada City Hospital	Japan	A	51	17	
Kaneko/2014	2002-2012	Brigham and Women's Hospital	United States	A	114	77	276
Kazui/1989	1983-1987	Sapporo Medical College, Japan	Japan	A	11		10
Kitamura/1995	1972-1993	The Heart Institute of Japan	Japan	A	38	24	40
Krahenbuhl/2010	2004-2007	University Hospital Bern	Switzerland	A	280		12
Kruger/2012	2006-2009	Multicenter	Germany	A	1081		355
LeMaire/2001	-	Baylor College of Medicine	United States	P		25	12
Matalanis/2002	1996-2000	University of Melbourne	Australia	A	25	23	14
Milewski/2010	1997-2008	Hospital of University of Pennsylvania	United States	A	94	682	
Misfeld/2012	2003-2009	Universität Leipzig	Germany	A	365	51	220
Mishra/2009	-	All India Institute of Medical Sciences	India	A		52	14

(Continued)

TABLE 1. Continued

Study/year	Study period	Hospital/country	Country	Type of study*	ACP (n)†	RCP (n)†	DHCA (n)†
Moon/2002	1996-2000	Washington University School of Medicine	United States	M		36	36
Müller/2004	1999-2001	University Hospital Frankfurt	Germany	A	30	22	12
Neri/2004	1999-2003	University of Siena	Italy	A	25	19	23
Niinami/2003	1985-2000	The Heart Institute of Japan	Japan	A	11	28	4
Okada/2015	1986-2008	Nagoya University Graduate School of Medicine	Japan	A	145	260	95
Okita/2001	1997-2001	National Cardiovascular Center	Japan	P	30	30	
Okita/2015	2009-2012	Multicenter	Japan	A	7038	1141	
Paramythiotis/2011	1998-2009	University Hospital of Rennes	France	A	13		79
Perreas/2016	2006-2014	Alexandra Hospital	Greece	M	40	40	
Safi/2010	1991-2010	University of Texas Medical School	United States	A		1002	191
Schachner/2004	1980-2002	Medical University Innsbruck	Austria	A	6	25	141
Sinatra/2001	1992-1998	Department of Cardiac Surgery Rome	Italy	A	23	18	44
Stamou/2016	2000-2010	University of Iowa Hospital and Clinics	United States	A	84	55	184
Stevens/2009	1979-2003	Massachusetts General Hospital	United States	A	24	56	
Strauch/2005	1999-2004	Friedrich Schiller University	Germany	A	49		71
Sueda/1992	1987-1992	Hiroshima University School of Medicine	Japan	A	8	6	2
Sundt/2008	1993-2007	Mayo Clinic Rochester	United States	A	74	53	220
Svensson/2001	1996-1999	Lahey Clinic	United States	RCT	10	10	10
Svensson/2015	-	Cleveland Clinic	United States	RCT	61	60	
Tan/2003	1974-1999	Multicenter	Netherlands	A	43		118
Tokuda/2014	2008-2012	Multicenter	Japan	A	2769	1359	
Usui/1999	1990-1996	Nagoya University School of Medicine	Japan	A	91	75	
Vallabhajosyula/2014	2008-2012	University of Pennsylvania	United States	A	75	301	
Wiedemann/2012	1987-2011	Vienna Medical University	Austria	A	91	122	116
Williams/2012	2003-2007	University of Louisville	United States	A	8	29	
Wong/1999	1991-1998	University Hospital Birmingham	United Kingdom	A		96	8
Zierer/2007	1984-2005	Multicenter	United States	A		56	69
Zierer/2005	1999-2003	Johann Wolfgang Goethe University	Germany	A	38	18	

References for the studies included in this table are available in the Online Data Supplement. *ACP*, Antegrade cerebral perfusion; *RCP*, retrograde cerebral perfusion; *DHCA*, deep hypothermic circulatory arrest. *A: adjusted retrospective study; M: matched retrospective study; P: prospective study; RCT: randomized controlled trial. †Total number of patients matched/adjusted.

calculated, and studies were divided into first, middle 2, and upper quartiles (<24.9, 24.9-39.5, and >39.5 minutes, respectively).

Meta-regression was used to explore the effects of age, sex, prior cerebrovascular events, arrest temperature, duration of circulatory arrest, study year, emergency surgery, aortic dissection, total arch replacement, and aortic root procedure on the OR of the primary outcomes (Table 3). Duration of circulatory arrest and study year were analyzed as continuous and ordinal variables. For the analysis of the arrest temperature as ordinal variable, deep hypothermia was defined as 20°C or less, and moderate hypothermia was defined as 20.1°C to 28°C, as per previous expert consensus.[22] For the analysis of study year as ordinal variable, the middle year of the study period was considered, and studies were then divided in 3 eras (1980-1990, 1991-2000, and 2000-2018). Statistical significance was set at the 2-tailed .05 level, without multiplicity adjustments.

Network Meta-Analysis

The NMA was performed using the generic inverse variance method[19] with the ‘‘netmeta’’ statistical package in R program (version 3.3.3, R Project for Statistical Computing) as described by Rücker and colleagues.[23,24] Random effect meta-analysis was reported, and inconsistency was evaluated with Cochran's Q.[25]

Direct and indirect estimates were assessed for statistically significant differences. A significant difference between direct and indirect estimates was considered as an estimate of inconsistency. Net heat plot was used to assess the source of inconsistency in cases in which inconsistency was found.[25]

Rank scores with probability ranks of different treatment groups were calculated. Ranks closest to 1 indicate the probability that the treatment group leads to the greatest reduction in the relevant adverse outcome. In

TABLE 2. Summary of intraoperative variables of the included studies

Study/year	Type of ACP	Temperature of circulatory arrest (°C)			Cardiopulmonary bypass time (min)			Duration of circulatory arrest (min)		
	ACP	ACP	RCP	DHCA	ACP	RCP	DHCA	ACP	RCP	DHCA
Ahn/1997	Unilateral	NR	NR	NR	179.8 ± 57.2	180.6 ± 30.2	195.4 ± 55	30.8 ± 9.3	36.3 ± 7.1	34.6 ± 17.6
Akashi/2000	Bilateral	NR	NR	NR	244.6	240.5	NR	80.1	29.4	NR
Alamanni/1995	Bilateral	16 ± 2.5	NR	16.5 ± 2	197 ± 78	NR	157 ± 48	47.7 ± 19	NR	47.5 ± 22
Apaydin/2009	Unilateral	NR	NR	NR	251 ± 66	183 ± 41	198 ± 48	NR	NR	NR
Apostolakis/2008	Unilateral	NR	NR	NR	179 ± 28.65	184 ± 33.12	NR	37 ± 14.56 (*ACP)	34 ± 12.88 (*RCP)	NR
Arnaoutakis/2017	Unilateral	NR	NR	NR	178 (140-215)	205 (175-245)	NR	17 (14-20)	22 (19-25)	NR
Bavaria/1995	NR	NR	28-32	28-32	NR	NR	NR	NR	NR	NR
Bonser/2002	NR	NR	15.3	15.3	NR	110.1	96.4	NR	27 (12.3)	32 (9.0
Caimmi/1998	NR	NR	NR	NR	NR	NR	NR	39 ± 13	43 ± 11 38 ± 7	41 ± 8
Campbell-Lloyd/2010	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cefarelli/2017	Bilateral	NR	NR	18	NR	NR	NR	43.3 ± 24.3 (*ACP)	NR	20 ± 7.9
Coselli/1997	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Di Eusanio/2003	Bilateral	NR	NR	NR	198 ± 60	NR	197 ± 54	42 ± 20	NR	29 ± 9
Di Mauro/2012	Unilateral	20	20	20	NR	NR	NR	NR	NR	NR
Dong/2002	NR	NR	NR	NR	NR	219.72 ± 66.42	204.27 ± 56.78	NR	45.5 ± 17.21	35.86 ± 18.81
Ehrlich/1999	NR	NR	17.1	17.8	NR	186 ± 67	169 ± 52	NR	33 ± 19	30 ± 19
Forteza/2009	Unilateral	NR	NR	NR	183 ± 56	183 ± 56	183 ± 56	37 ± 23	37 ± 23	37 ± 23
Ganapathi/2014	Bilateral	14.2	14.5	NR	208 ± 59.8	197.9 ± 40.8	NR	17.7 ± 6.4	17.9 ± 4.3	NR
Guan/2004	NR	NR	NR	NR	NR	NR	NR	NR	NR	35.58 ± 18.81
Hagl/2001	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Halkos/2009	Unilateral	23.2 ± 4.2	NR	19.8 ± 3.8	NR	NR	NR	26.2 ± 12.2	NR	26.0 ± 8.5
Han/2007	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Harrington/2004	NR	24.9	NR	15.3	203 ± 41.8	NR	221 ± 63.7	8 ± 2.9	NR	33 ± 19.4
Hata/2018	NR	NR	29.5 ± 0.87	27.4 ± 0.97	NR	82 ± 12.7	93.3 ± 21.3	NR	10.2± 4.58	18.6 ± 4.24
Higgins/2012	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Immer/2008	Bilateral/ unilateral	NR	NR	NR	NR	NR	NR	21.3	NR	21.3 ± 10.4
Kamenskaya/2015	Unilateral	NR	NR	NR	196.0 (177.0-227.0)	NR	207.0 (194.0-238.0)	38 (30.0-56.0) (ACP)	NR	41 (30-52)
Kamenskaya/2017	Unilateral	NR	NR	NR	213.4 (169.6-224.5)	NR	241.3 (219.2-286.3)	55 (38.0-64.0) ACP	NR	51 (39.0-72.0)
Kamiya/2007	Bilateral	26.0°C ± 1.2°C	NR	26.8 ± 1.3°C	156 ± 57	NR	131 ± 44	NR	NR	NR
Kaneda/2005	Bilateral	30	20	NR	146 ± 55.5 (mild) 217 ± 96.5 (moderate)	300 ± 162	NR	44.29 ± 23.9 mild 61.2 ± 42.9	52.09 ± 18.4	NR
Kaneko/2014	Unilateral	18 (18.0-19.3)	18 (17.8-20)	18 (17.0-19.7)	NR	NR	NR	6 (3-11)	4 (1-14)	21 (15-28)
Kazui/1989	Bilateral	24.3. ± 2.8	NR	16.9 ± 2.7	156 ± 35.8	NR	174 ± 45.0	NR	NR	35.2 ± 3.4
Kitamura/1995	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Krahenbuhl/2010	Bilateral/ unilateral	NR	NR	NR	NR	NR	NR	15.6 ± 7.1	NR	7.3 ± 2.3
Kruger/2012	Bilateral/ unilateral	NR	NR	NR	NR	NR	NR	NR	NR	NR
LeMaire/2001	NR	NR	11.4 ± 2.1	10.8 ± 2.5	NR	125 ± 48	135 ± 20	NR	34 ± 13	35 ± 14
Matalanis/2002	Bilateral	19	NR	NR	247.8 ± 86.4	193.5 ± 34.9	196.0 ± 60.4	11.4 ± 9.6	37.4 ± 19.2	25.2 ± 12.4
Milewski/2010	Bilateral	NR	NR	NR	171.2 ± 50.3	229.9 ± 63.7	NR	30.7 ± 7.5 (ACP)	25 ± 9.7 (RCP)	NR
Misfeld/2012	Bilateral/ unilateral	24	23	22	UACP 208 ± 61 BACP 211 ± 83	205 ± 60	185 ± 65	NR	NR	NR

	Clamp time			Type of surgery						
Type of HCA	ACP	RCP	DHCA	Emergent/ urgent surgery %	Elective surgery %	Aortic aneurysm %	Aortic Dissection %	Total arch %	Hemiarch %	Aortic root surgery %
NR	76.3 (19.9)	88.6 (26.2)	82.3 (28.5)	NR	NR	NR	100.0	4.3	34.0	NR
NR	140.1	NR	NR	NR	NR	100.0	NR	35.1	55.6	NR
NR	133 ± 28	NR	106 ± 45	NR	NR	NR	NR	45.7	42.9	5.7
deep	NR	NR	NR	NR	NR	NR	NR	22.4	NR	NR
NR	NR	NR	NR	100.0	NR	NR	100.0	31.3	68.8	NR
moderate for ACP, deep for RCP	135 (98-164)	154 (121-192)	NR	NR	100.0	100.0	NR	NR	100.0	36.2
moderate	NR	NR	NR	NR	NR	NR	60.5	NR	NR	NR
NR	NR	NR	NR	NR	NR	69.0	19.0	NR	NR	NR
moderate for ACP, deep for RCP	NR	NR	NR	82.1	NR	NR	78.6	14.3	75.0	NR
NR	NR	NR	NR	NR	NR	NR	100.0	19.2	86.3	43.8
deep	NR	NR	NR	NR	100.0	94.1	NR	5.6	71.2	52.3
NR	NR	NR	NR	NR	NR	52.0	20.7	NR	NR	NR
deep	NR	NR	NR	NR	NR	NR	42.2	NR	55.4	27.7
NR	NR	NR	NR	NR	NR	NR	52.4	18.0	82.0	15.4
deep	NR	141.44 ± 48.92	82.47 ± 32.17	NR	NR	NR	NR	NR	NR	NR
deep	NR	111± 50	107± 40	NR	NR	33.0	67.0	NR	NR	NR
deep	113	113	113	100.0	NR	NR	100.0	16.0	32.1	NR
NR	129.2± 34.4	131 ± 44.2	NR	NR	NR	88.1	11.9	NR	100.0	NR
deep	NR	NR	NR	NR	NR	625.6	NR	5.1	16.7	246.2
NR	NR	NR	NR	26.3	73.7	NR	NR	57.7	NR	NR
NR	139.1 ± 58.2	NR	128.9 ± 52.3	38.7	61.3	NR	38.7	3.3	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	145± 42	NR	152± 53.7	NR	NR	76.2	14.3	47.6	NR	NR
moderate	NR	NR	NR	100.0	NR	NR	100.0	NR	100.0	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
deep	NR	NR	NR	50.8	NR	NR	43.6	17.8	NR	NR
NR	114.2 (97-126)	NR	115.5 (98-135)	NR	NR	NR	NR	NR	NR	NR
deep	144.7 (118-196)	NR	132.4 (110-185)	NR	NR	NR	100.0	NR	NR	NR
moderate	9.4 ± 0.8	NR	7.5 ± 1.8	4.9	NR	86.9	6.6	NR	100.0	NR
mild /moderate	NR	NR	NR	61.8	NR	NR	73.5	27.9	10.3	5.9
NR	157 (113-186)	143 (104-192)	127 (94-172)	NR	NR	87.6	12.4	NR	100.0	NR
NR	NR	NR	NR	33.3	NR	23.8	23.8	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	100.0	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	16.4	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	100.0	NR	NR	NR
NR	NR	NR	NR	13.5	NR	NR	NR	29.7	67.6	NR
deep	NR	NR	NR	37.1	NR	NR	NR	21.0	51.6	24.2
NR	121.3 ± 35.6	163.8 ± 59.7	NR	NR	100.0	NR	NR	NR	100.0	NR
deep	NR	NR	NR	34.4	NR	59.0	36.8	9.1	71.4	9.9

(Continued)

TABLE 2. Continued

Study/year	Type of ACP	Temperature of circulatory arrest (°C)			Cardiopulmonary bypass time (min)			Duration of circulatory arrest (min)		
	ACP	ACP	RCP	DHCA	ACP	RCP	DHCA	ACP	RCP	DHCA
Mishra/2009	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Moon/2002	NR	NR	19.2 ± 3.2	19.5 ± 2.3	NR	202 ± 43	201 ± 77	NR	40 ± 15	29 ± 14
Müller/2004	Unilateral	22 ± 2	20 ± 2	20 ± 2	201 ± 108	195 ± 75	188 ± 64	25 ± 18	23 ± 11	23 ± 13
Neri/2004	NR	20.9	20.9	19.3	164 ± 32.2	172.4 ± 47.9	132.1 ± 39.7	30.2 ± 6.3 (TCPT)	22.8 ± 7.0 (TCPT)	23.6 ± 7.0 (TCPT)
Niinami/2003	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Okada/2015	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Okita/2001	Unilateral	NR	NR	NR	NR	NR	NR	119 6 ± 45.2 (*ACP)	44.3 6 13.9 (*RCP)	NR
Okita/2015	NR	24.2 ± 3.2	21.2 ± 3.7	NR	240 ± 84	237 ± 81	NR	NR	NR	NR
Paramythiotis/2011	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Perreas/2016	NR	23.2	17-20	NR	NR	NR	NR	29 (24-42)	22.5 (17-37)	NR
Safi/2010	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Schachner/2004	Unilateral	NR	NR	NR	NR	NR	NR	NR	30 (15-79) (Median)	32 (11-71) (Median)
Sinatra/2001	Unilateral	NR	NR	NR	249.2 ± 94.1	219.4 ± 77.4	209.8 ± 88.7	88.8 ± 54.3	56 ± 25.2	50.8 ± 31.9
Stamou/2016	Unilateral	19	17	19	227 (112-430)	207 (102-454)	196 (52-588)	31 (0-73)	36 (4-61)	17 (0-146)
Stevens/2009	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Strauch/2005	Unilateral	20.1 ± 2.5	NR	20.6 ± 2.6	192 ± 50	NR	202 ± 55	21 ± 6	NR	28 ± 12
Sueda/1992	NR	NR	NR	NR	275 ± 187	302 ± 138	NR	NR	NR	NR
Sundt/2008	Unilateral	NR	NR	NR	188 ± 62	176 ± 65	141 ± 54	41 ± 28	33 ± 13	27 ± 14
Svensson/2001	NR	NR	NR	NR	NR	NR	NR	41.4	41.4	41.4
Svensson/2015	Bilateral	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tan/2003	NR	NR	NR	NR	189 ± 65	NR	189 ± 65	NR	NR	36
Tokuda/2014	NR	NR	NR	NR	NR	NR	NR	115.9 ± 37.6	102.1 ± 38.3	NR
Usui/1999	Unilateral	21.6	18.7	NR	297 ± 99	269 ± 112	NR	103 ± 56	54 ± 24	NR
Vallabhajosyula/2014	Unilateral	NR	NR	NR	167 ± 49	222 ± 61	NR	18 ± 5	23 ± 8	NR
Wiedemann/2012	Bilateral/ unilateral	NR	NR	NR	161 (101-303)	198 (121-404)	177 (101-355)	30 (14-92)	30 (14-88)	36 (12-88)
Williams/2012	Unilateral	17	19	NR	190 ± 43	188 ± 58	NR	34 (11)	34 (11)	NR
Wong/1999	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zierer/2007	NR		19 ± 3	17 ± 3	NR	194 ± 65	202 ± 72	NR	39 ± 15	36 ± 15
Zierer/2005	Unilateral	21.1	20.8	NR	120 ± 50	176 ± 34	NR	23 ± 9 (*ACP)	29 ± 13 (*RCP)	NR

References for the studies included in this table are available in the Online Data Supplement. *ACP and *RCP indicate duration of cerebral perfusion. *ACP*, Antegrade cerebral perfusion; *RCP*, retrograde cerebral perfusion; *DHCA*, deep hypothermic circulatory arrest; *NR*, not reported; *TCPT*, total cerebral protection time.

keeping with established methods for NMA,[26] rankings ensure the validity of multiple comparisons without the explicit need for multiple test adjustment or penalization. Statistical significance was considered when the CIs did not cross the line of no effect, with inference threshold at the 2-tailed .05 level, without multiplicity adjustments.

RESULTS

A total of 1070 studies were retrieved, of which 68 met the inclusion criteria and were included in the final NMA (Table 1). Six were multicenter studies; 19 originated from the United States, 13 originated from Japan, 6 originated from Germany, and the remaining originated from other countries. The evidence network is shown in Figure 1.

A total of 26,968 patients were included (ACP = 15,293, RCP = 7511, and DHCA = 4164) from 6 RCTs (n = 354) and 62 observational studies (n = 26,614). Demographics of the included studies are presented in Table 1.

The number of patients in the individual studies ranged from 16 to 8179. The mean age ranged from 48.1 to 71.0 years (48.1-70.5 years in the ACP group, 48.5-71.0 years in the RCP group, and 49.0-68.1 years in the DHCA group). Female sex ranged from 8.0% to 71.4% (8.0%-58.6% in the ACP group, 20.0% to 71.4% in the RCP group, and 17.0% to 60.0% in the DHCA group). The incidence of diabetes was 3.0% to 28.0% (3.0%-28.0% in the ACP group, 2.0%-15.7% in the RCP group, and 3.0% to 13.0% in the DHCA group) (Online Data Supplement Table 2). The assessment of the quality of the individual studies and the evidence is reported in the Online Data Supplement Tables 3 to 5.

	Clamp time			Type of surgery						
Type of HCA	ACP	RCP	DHCA	Emergent/ urgent surgery %	Elective surgery %	Aortic aneurysm %	Aortic Dissection %	Total arch %	Hemiarch %	Aortic root surgery %
NR	NR	NR	NR	NR	NR	100.0	NR	4.5	10.6	57.6
NR	NR	NR	NR	43.1	NR	NR	54.2	20.8	23.6	25.0
deep	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
deep	NR	NR	NR	NR	100.0	73.1	26.9	41.8	58.2	NR
NR	NR	NR	NR	NR	NR	100.0	NR	NR	NR	NR
NR	NR	NR	NR	20.0	80.0	100.0	NR	NR	NR	NR
deep	NR	NR	NR	NR	100.0	NR	NR	100.0	NR	NR
NR	NR	NR	NR	NR	100.0	NR	NR	100.0	NR	NR
NR	NR	NR	NR	47.8	52.2	NR	40.2	NR	NR	NR
moderate for ACP, deep for RCP	NR	NR	NR	66.3	NR	NR	71.3	NR	100.0	NR
NR	NR	NR	NR	23.9	76.1	57.2	42.8	NR	NR	NR
deep	NR	NR	NR	79.7	81.4	NR	NR	NR	NR	NR
NR	NR	NR	NR	100.0	NR	NR	NR	31.8	18.8	24.7
deep	NR	NR	NR	NR	NR	NR	100.0	9.0	59.8	20.4
NR	NR	NR	NR	NR	NR	NR	100.0	6.3	22.5	NR
NR	NR	NR	NR	42.5	57.5	NR	NR	22.5	73.3	NR
NR	118 ± 24	117 ± 76	NR	NR	NR	NR	NR	NR	NR	NR
deep	NR	NR	NR	NR	NR	56.2	35.2	NR	NR	NR
NR	NR	NR	NR	NR	100.0	NR	NR	36.7	56.7	NR
NR	NR	NR	NR	NR	NR	NR	NR	100.0	NR	NR
deep	NR	NR	NR	NR	NR	NR	100.0	5.6	18.6	18.6
NR	NR	NR	NR	97.9	NR	NR	100.0	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	100.0	39.2	NR	NR
NR	128 ± 46	163 ± 57	NR	NR	100.0	NR	NR	NR	100.0	NR
NR	109 (61-179)	114 (62-230)	107 (61-203)	NR	NR	NR	100.0	2.1	NR	1.8
NR	NR	NR	NR	NR	NR	NR	NR	5.4	94.6	43.2
NR	NR	NR	NR	44.2	NR	NR	23.1	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	100.0	NR	45.6	NR
deep	NR	NR	NR	100.0	NR	NR	100.0	NR	NR	NR

Pairwise Meta-Analysis

Detailed results of the pairwise comparisons (ACP vs DHCA, RCP vs DHCA, and ACP vs RCP) are reported in the Online Data Supplement Table 7. Compared with DHCA, ACP and RCP were associated with lower postoperative stroke and operative mortality (OR, 0.69, 95% CI, 0.57-0.82 and OR, 0.66, 95% CI, 0.56-0.78, respectively, for ACP; and OR, 0.62, 95% CI, 0.47-0.83; and OR, 0.51, 95% CI, 0.35-0.73, respectively, for RCP). No differences in primary and secondary outcomes were found between ACP and RCP. Leave-1-out analysis confirmed the solidity of the reported results (Online Data Supplement Figures 2.1-2.6).

On subgroup analysis, the use of unilateral or bilateral ACP did not affect the results of the comparison with the 2 other neuroprotective strategies for the incidence of postoperative stroke (the *P* value for the subgroup difference between bilateral ACP and unilateral ACP is .89 for the comparison with RCP and 0.24 for the comparison with DHCA) (Online Data Supplement Figures 3.1 and 3.2). No difference was found between the different circulatory arrest time categories for the ACP versus RCP comparison (*P* for intergroup comparison = .09), whereas in the ACP versus DHCA and RCP versus DHCA comparisons, significant differences in favor of the active perfusion strategy were found for studies with circulatory arrest time above the lower quartile (*P* for subgroup differences = .01 and .003 for ACP vs DHCA and RCP vs DHCA, respectively) (Online Data Supplement Figures 4.1-4.3).

At meta-regression, arrest temperature and arrest time were significant effect modifiers with regard to the incidence of postoperative stroke (Table 3), as follows:

1. The difference in favor of both ACP and RCP compared with DHCA increased with the duration of the arrest (Figure 2).
2. Compared with deep hypothermia (≤20°C), the use of moderate hypothermia (>20°C) in conjunction with cerebral perfusion was associated with better results in the ACP arm in the ACP versus RCP comparison.
3. The duration of arrest was associated with better results in the RCP arm in the ACP versus RCP comparison.

The study period significantly correlated only with the OR for postoperative stroke in the RCP versus ACP comparison, with older studies reporting worse results with RCP. There was no significant correlation among surgical priority, surgery for acute dissection, total arch and root procedure, and primary outcomes (Table 3).

Network Meta-Analysis

Results of the NMA are summarized in Table 4 and Online Data Supplement Table 8. Briefly, both ACP and RCP were associated with lower postoperative stroke (ACP: OR, 0.62, 95% CI, 0.51-0.75; RCP: OR, 0.66, 95% CI, 0.54-0.82) and operative mortality (ACP: OR, 0.63, 95% CI, 0.51-0.76; RCP: 0.57, 95% CI, 0.45-0.71) compared with DHCA; of note, no difference in any outcome was found when comparing ACP versus RCP.

Deep Hypothermic Circulatory Arrest Versus Antegrade Cerebral Perfusion

Compared with DHCA, ACP was associated with lower postoperative stroke and operative mortality (OR, 0.62, 95% CI, 0.51-0.75 and OR, 0.63, 95% CI, 0.51-0.76, respectively). ACP did not differ from DHCA in postoperative transient neurologic deficits, MI, respiratory complications, and renal failure (OR, 1.03, 95% CI, 0.78-1.35; OR, 1.38, 95% CI, 0.56-3.39; OR, 0.89, 95% CI, 0.67-1.18; and OR, 0.87, 95% CI, 0.56-1.35).

Deep Hypothermic Circulatory Arrest Versus Retrograde Cerebral Perfusion

Compared with DHCA, RCP was associated with lower postoperative stroke and operative mortality (OR, 0.66, 95% CI, 0.54-0.82 and OR, 0.57, 95% CI, 0.45-0.71, respectively). There was no difference between RCP and DHCA in postoperative transient neurologic deficits, MI, respiratory complications, or renal failure (OR, 1.27, 95% CI, 0.93-1.74; OR, 0.51, 95% CI, 0.13-2.04; OR, 0.99, 95% CI, 0.72-1.35; and OR, 0.92, 95% CI, 0.55-1.54, respectively).

Antegrade Cerebral Perfusion Versus Retrograde Cerebral Perfusion

There was no difference in any outcomes between ACP and RCP (postoperative stroke: OR, 1.08, 95% CI, 0.89-1.30, operative mortality: OR, 0.90, 95% CI, 0.73-1.12, transient neurologic deficits: OR, 1.24, 95% CI, 0.95-1.62, MI: OR, 0.37, 95% CI, 0.12-1.10, respiratory complications: OR, 1.11, 95% CI, 0.90-1.36, and renal failure: OR, 1.06, 95% CI, 0.70-1.59).

With a focus on rankings, which simultaneously analyze competing interventions, ACP ranked as the best strategy for the prevention of postoperative stroke, and RCP ranked as the best strategy for the reduction of operative mortality (Online Data Supplement Figure 5 and Online Data Supplement Table 9). Heterogeneity/inconsistency estimate, net heat, rank scores, and net split are shown in Online Data Supplement Tables 10 and 11. The level of evidence was high for all comparisons of primary outcomes and moderate for the RCP versus DHCA comparison for stroke (Online Data Supplement Tables 5 and 10).

DISCUSSION

The optimal cerebral protection strategy during aortic arch surgery remains controversial. DHCA has the main advantage of simplicity and does not need any additional cannulation but relies only on hypothermia for neuroprotection. RCP is fast and easy to establish, but its efficacy in reaching the brain parenchyma is debated.[27,28] ACP ensures direct cerebral perfusion at the expense of a more complex cannulation and perfusion setup.

A recent survey shows that most European surgeons use ACP and RCP for emergency cases,[29] whereas in the United States, data from the 2017 Society of Thoracic Surgery Database show that DHCA is the most commonly used method.[30]

In the past, several meta-analyses have compared the different cerebral protection strategies in pairwise comparisons. Takagi and colleagues[8] compared ACP and RCP in a pooled analysis of 19 studies and 15,365 patients, and found no difference in operative mortality and postoperative stroke (OR, 1.07, 95% CI, 0.90-1.26, $P = .46$; and OR, 0.92, 95% CI, 0.79-1.08, $P = .32$, respectively). Guo and associates[7] reported similar findings in a combined analysis of 34 studies (7023 patients).

Tian and colleagues,[4] in a meta-analysis of 28 studies (5522 patients) comparing DHCA and RCP, reported higher operative mortality and stroke rate for DHCA (OR, 1.75, 95% CI, 1.16-2.63, $P = .007$; and OR, 1.50, 95% CI, 1.07-2.10, $P = .02$, respectively). The same group of authors compared DHCA with ACP in a meta-analysis of 9 observational studies (1783 patients) and found a significantly higher risk of stroke in the DHCA arm (OR, 1.8, 95% CI, 1.3-2.5, $P = .0007$), but

TABLE 3. Meta-regression for the primary outcomes in pairwise meta-analyses (antegrade cerebral perfusion, retrograde cerebral perfusion, and deep hypothermic circulatory arrest)

Primary outcomes	Arm	Variables	Beta* ± SD, P value
Postoperative stroke	ACP vs DHCA	Mean age	0.01 ± 0.04, $P = .91$
		Female %	−0.01 ± 0.01, $P = .29$
		Prior cerebrovascular accident %	0.02 ± 0.02, $P = .30$
		Mean arrest temperature (°C)	0.02 ± 0.07, $P = .80$
		Mean arrest temperature category (°C)	≤20°C −0.08 ± 0.25, $P = .75$
			> 20°C −0.01 ± 0.28, $P = .97$
		Mean circulatory arrest time (min)	**−0.04 ± 0.01, $P = .01$**
		Year	0.01 ± 0.02, $P = .61$
		Era	1980-1990 −0.74 ± 0.65, $P = .25$
			1991-2000 −0.31 ± 0.45, $P = .49$
			2001-2018 −0.19 ± 0.43, $P = .66$
		Emergency surgery %	−0.00 ± 0.01, $P = .89$
		Aortic dissection (acute/chronic %)	−0.00 ± 0.00, $P = .86$
		Total arch replacement %	0.01 ± 0.02, $P = .65$
		Aortic root procedure %	−0.01 ± 0.01, $P = .64$
	RCP vs DHCA	Mean age	0.11 ± 0.06, $P = .09$
		Female %	−0.01 ± 0.01, $P = .33$
		Prior cerebrovascular accident %	−0.02 ± 0.07, $P = .83$
		Mean arrest temperature (°C)	−0.05 ± 0.08, $P = .51$
		Mean arrest temp category (°C)	≤20°C 0.35 ± 0.33, $P = .28$
			> 20°C 0.20 ± 0.51, $P = .69$
		Mean circulatory arrest time (min)	**−0.07 ± 0.02, $P < .01$**
		Year	**0.09 ± 0.03, $P < .001$**
		Era	1980-1990 0.71 ± 1.72, $P = .68$
			1991-2000 0.64 ± 0.51, $P = .21$
			2001-2018 1.39 ± 0.52, $P < .001$
		Emergency surgery %	−0.00 ± 0.01, $P = .72$
		Aortic dissection (acute/chronic %)	0.00 ± 0.01, $P = .81$
		Total arch replacement %	−0.01 ± 0.03, $P = .79$
		Aortic root procedure %	−0.01 ± 0.01, $P = .18$
	ACP vs RCP	Mean age	0.01 ± 0.02, $P = .49$
		Female %	**0.01 ± 0.00, $P = .01$**
		Prior cerebrovascular accident %	0.01 ± 0.03, $P = .70$
		Mean arrest temperature (°C)	0.00 ± 0.05, $P = .94$
		Mean arrest temp category (°C)	≤20°C −0.30 ± 0.26, $P = .25$
			>20°C −0.35 ± 0.14, $P = .01$
		Mean circulatory arrest time (min)	**0.01 ± 0.00, $P = .03$**
		Year	−0.01 ± 0.01, $P = .47$
		Era	1980-1990 2.00 ± 1.61, $P = .21$
			1991-2000 0.48 ± 0.51, $P = .35$
			2001-2018 0.31 ± 0.49, $P = .53$
		Emergency surgery %	0.00 ± 0.01, $P = .59$
		Aortic dissection (acute/chronic %)	−0.00 ± 0.01, $P = .86$
		Total arch replacement %	−0.00 ± 0.00, $P = .98$
		Aortic root procedure %	0.00 ± 0.02, $P = .85$
Operative mortality	ACP vs DHCA	Mean age	0.07 ± 0.04, $P = .07$
		Female %	0.00 ± 0.01, $P = .87$
		Prior cerebrovascular accident %	−0.01 ± 0.02, $P = .76$
		Mean arrest temperature (°C)	0.00 ± 0.08, $P = .97$
		Mean circulatory arrest time (min)	−0.01 ± 0.01, $P = .44$
		Year	−0.01 ± 0.01, $P = .51$
		Era	1980-1990 0.61 ± 0.43, $P = .15$
			1991-2000 0.29 ± 0.36, $P = .42$
			2001-2018 0.22 ± 0.32, $P = .50$
		Emergency surgery %	−0.01 ± 0.01, $P = .35$
		Aortic dissection (acute/chronic %)	0.00 ± 0.00, $P = .77$
		Total arch replacement %	0.01 ± 0.01, $P = .69$
		Aortic root procedure %	−0.00 ± 0.01, $P = .70$

(Continued)

TABLE 3. Continued

Primary outcomes	Arm	Variables	Beta* ± SD, *P* value
	RCP vs DHCA	Mean age	**0.18 ± 0.05, *P* < .001**
		Female %	0.00 ± 0.01, *P* = .71
		Prior cerebrovascular accident %	0.02 ± 0.08, *P* = .77
		Mean arrest temperature (°C)	−0.03 ± 0.09, *P* = .71
		Mean circulatory arrest time (min)	−0.02 ± 0.02, *P* = .42
		Year	0.07 ± 0.03, *P* = .05
		Era	1980-1990 −0.34 ± 1.22, *P* = .78
			1991-2000 0.22 ± 0.65, *P* = .74
			2001-2018 0.35 ± 0.70, *P* = .62
		Emergency surgery %	0.01 ± 0.01, *P* = .64
		Aortic dissection (acute/chronic %)	0.00 ± 0.01, *P* = .67
		Total arch replacement %	0.01 ± 0.02, *P* = .57
		Aortic root procedure %	−0.01 ± 0.00, *P* = .06
	ACP vs RCP	Mean age	−0.02 ± 0.02, *P* = .26
		Female %	0.01 ± 0.01, *P* = .27
		Prior cerebrovascular accident %	−0.03 ± 0.03, *P* = .30
		Mean arrest temperature (°C)	−0.10 ± 0.07, *P* = .17
		Mean circulatory arrest time (min)	0.00 ± 0.00, *P* = .59
		Year	−0.02 ± 0.01, *P* = .25
		Era	1980-1990 1.98 ± 1.44, *P* = .17
			1991-2000 0.51 ± 1.21, *P* = .67
			2001-2018 0.52 ± 1.20, *P* = .67
		Emergency surgery %	−0.01 ± 0.01, *P* = .54
		Aortic dissection (acute/chronic %)	0.00 ± 0.00, *P* = .79
		Total arch replacement %	−0.01 ± 0.00, *P* = .06
		Aortic root procedure %	0.03 ± 0.02, *P* = .09

SD, Standard deviation; *ACP*, antegrade cerebral perfusion; *DHCA*, deep hypothermic circulatory arrest; *RCP*, retrograde cerebral perfusion. *Positive beta implies higher OR with increase in the explored variable, and negative beta implies lower OR with increase in the explored variable.

similar operative mortality (OR, 1.4, 95% CI, 0.9-2.2, *P* = .15).[5]

Angeloni and colleagues[9] showed no difference in operative mortality (8.6% vs 9.2% *P* = .78) and stroke (6.1% vs 6.5%, *P* = .80) between unilateral and bilateral ACP. However, all the quoted meta-analyses were pairwise, and a systematic comparison of all 3 cerebral protection strategies has not been published.

In this setting, the adoption of NMA allows direct and indirect comparisons and can provide a summary of all the

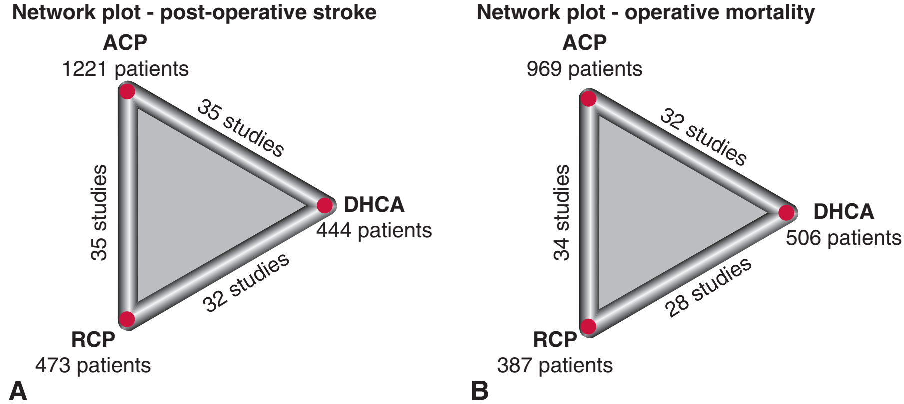

FIGURE 1. Network plots of eligible comparisons among the cerebral perfusion strategies for (A) postoperative stroke and (B) operative mortality. Circles represent each intervention as a node, and lines represent direct comparisons. The sizes of circles are proportional to the number of patients receiving each treatment, and the width of the lines indicate the number of studies comparing each pair of treatments. Compared with DHCA, both ACP and RCP were associated with significantly lower postoperative stroke and operative mortality rates. *ACP*, Antegrade cerebral perfusion; *DHCA*, deep hypothermic circulatory arrest; *RCP*, retrograde cerebral perfusion.

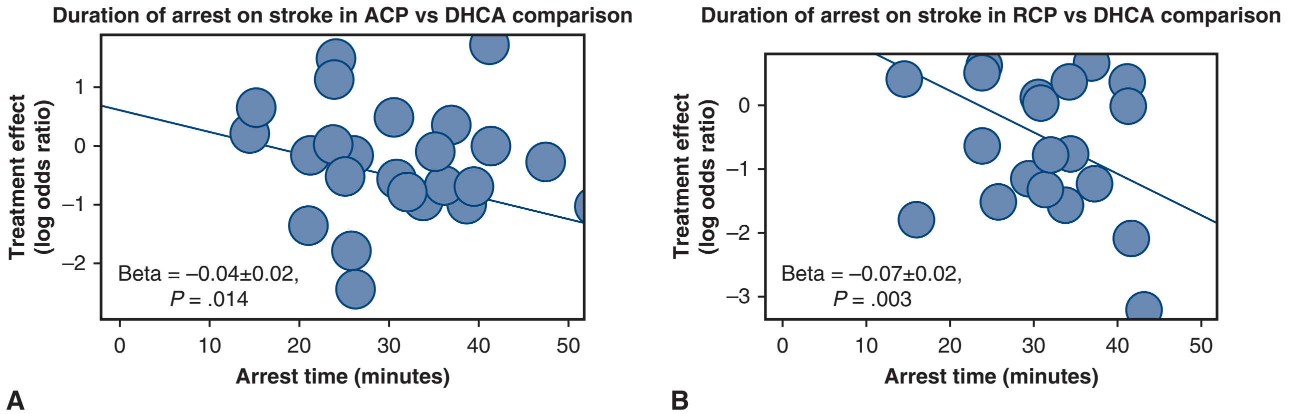

FIGURE 2. Bubble plots with the fitted meta-regression lines depicting the relationship between circulatory arrest time and incidence of postoperative stroke. The negative regression coefficients in (A) ACP versus DHCA (beta $= -0.04 \pm 0.02$, $P = .014$) and (B) RCP versus DHCA (beta $= -0.07 \pm 0.02$, $P = .003$) signify an inverse relationship between OR of postoperative stroke in ACP and RCP (with respect to DHCA) and circulatory arrest time, that is, the difference in incidence of postoperative stroke in favor of both ACP and RCP compared with DHCA increased with the duration of the arrest. *ACP*, Antegrade cerebral perfusion; *DHCA*, deep hypothermic circulatory arrest; *RCP*, retrograde cerebral perfusion.

available evidence. Also, NMAs have been shown to be more effective than pairwise comparisons in minimizing biases, especially when pooling data from randomized and observational series.[12,31]

By using the NMA approach, we have found that both ACP and RCP are associated with significantly lower postoperative stroke and operative mortality rates compared with DHCA. Of note, the difference in favor of both ACP and RCP compared with DHCA increased with the duration of the arrest. Although we used aggregate data, the definition of cutoffs is problematic and must be considered exploratory. Our data suggest that when the arrest time exceeds 25 minutes, the benefits of ACP and RCP over DHCA become significant. We found no difference between ACP and RCP for all the explored outcomes, although at meta-regression, the use of moderate hypothermia was associated with better results in the ACP arm, and the duration of arrest was associated with better results in the RCP arm. Of note, the use of unilateral or bilateral ACP did not affect the results of the comparison with the other neuroprotective strategies.

Our results are in line with those of Englum and associates,[30] who compared all the different combinations of neuroprotection during aortic arch surgery using data of 12,521 patients from the Society of Thoracic Surgeons Database and found that DHCA was associated with the highest risk of the combined end point of operative mortality or neurologic complication.

Study Limitations

This study shares the usual limitations of meta-analyses of observational studies. Despite statistical adjustment and the use of NMA, the presence of unmeasured confounders and possible treatment allocation bias cannot be excluded. Heterogeneity may exist particularly in terms of definition and diagnosis for stroke, 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. In addition, we did not adjust for multiple testing, and thus the risk of spurious significance due to multiplicity should be borne in mind. Indeed, because the established practice in pairwise meta-analyses is not to perform adjustments, readers should make informed judgments on the validity of our quantitative findings based on unadjusted *P* values. Focusing explicitly on our NMA, readers should rely mainly on rankings to summarize multiple comparisons.[26]

CONCLUSIONS

In an NMA of the available evidence, we found both ACP and RCP to be associated with superior neuroprotection compared with DHCA. The benefit associated with the use of these strategies increases with the duration of circulatory arrest and is not influenced by the arrest temperature or the use of unilateral or bilateral ACP. ACP and RCP should be preferred to DHCA, especially in cases of extended circulatory arrest time.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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TABLE 4. League tables summarizing the outcomes of the network meta-analysis (expressed as odds ratio with 95% confidence interval) for different outcomes using random effect model

A. Postoperative stroke		
DHCA		
0.62 (0.51-0.75)	ACP	
0.66 (0.54-0.82)	1.08 (0.89-1.30)	RCP
B. Operative mortality		
DHCA		
0.63 (0.51-0.76)	ACP	
0.57 (0.45-0.71)	0.90 (0.73-1.12)	RCP
C. Postoperative transient neurologic deficits		
DHCA		
1.03 (0.78-1.35)	ACP	
1.27 (0.93-1.74)	1.24 (0.95-1.62)	RCP
D. Postoperative MI		
DHCA		
1.38 (0.56-3.39)	ACP	
0.51 (0.13-2.04)	0.37 (0.12-1.10)	RCP
E. Respiratory complications		
DHCA		
0.89 (0.67-1.18)	ACP	
0.99 (0.72-1.35)	1.11 (0.90-1.36)	RCP
F. Renal failure		
DHCA		
0.87 (0.56-1.35)	ACP	
0.92 (0.55-1.54)	1.06 (0.70-1.59)	RCP

A. Postoperative stroke (interpreted as ACP [OR, 0.62, 95% CI, 0.51-0.75] and RCP [OR, 0.66, 95% CI, 0.54-0.82]) were associated with lower postoperative stroke compared with DHCA; there was no difference between RCP and ACP in terms of postoperative stroke (OR, 1.08, 95% CI, 0.89-1.30); $tau^2 = 0.0425$, $I^2 = 14.1\%$). B. Operative mortality ($tau^2 = 0.0718$, $I^2 = 21.8\%$). C. Postoperative transient neurological deficits ($tau^2 = 0.1112$, $I^2 = 25.0\%$). D. MI ($tau^2 = 0$; $I^2 = 0\%$). E. Respiratory complications ($tau^2 = 0.0392$; $I^2 = 40.8\%$). F. Renal failure ($tau^2 = 0.0759$; $I^2 = 20.0\%$). *DHCA*, Deep hypothermic circulatory arrest; *ACP*, antegrade cerebral perfusion; *RCP*, retrograde cerebral perfusion; *MI*, myocardial infarction.

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