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Coronary Artery Bypass Grafting With and Without Manipulation of the Ascending Aorta

A Network Meta-Analysis

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ABSTRACT

BACKGROUND Coronary artery bypass grafting (CABG) remains the standard of treatment for 3-vessel and left main coronary disease, but is associated with an increased risk of post-operative stroke compared to percutaneous coronary intervention. It has been suggested that CABG techniques that eliminate cardiopulmonary bypass and reduce aortic manipulation may reduce the incidence of post-operative stroke.

OBJECTIVES A network meta-analysis was performed to compare post-operative outcomes between all CABG techniques, including anaortic off-pump CABG (anOPCABG), off-pump with the clampless Heartstring device (OPCABG-HS), off-pump with a partial clamp (OPCABG-PC), and traditional on-pump CABG with aortic cross-clamping.

METHODS A systematic search of 6 electronic databases was performed to identify all publications reporting the outcomes of the included operations. Studies reporting the primary endpoint, 30-day post-operative stroke rate, were included in a Bayesian network meta-analysis.

RESULTS There were 13 included studies with 37,720 patients. At baseline, anOPCABG patients had higher previous stroke than did the OPCABG-PC (7.4% vs. 6.5%; $p = 0.02$) and CABG (7.4% vs. 3.2%; $p = 0.001$) patients. AnOPCABG was the most effective treatment for decreasing the risk of post-operative stroke (–78% vs. CABG, 95% confidence interval [CI]: 0.14 to 0.33; –66% vs. OPCABG-PC, 95% CI: 0.22 to 0.52; –52% vs. OPCABG-HS, 95% CI: 0.27 to 0.86), mortality (–50% vs. CABG, 95% CI: 0.35 to 0.70; –40% vs. OPCABG-HS, 95% CI: 0.38 to 0.94), renal failure (–53% vs. CABG, 95% CI: 0.31 to 0.68), bleeding complications (–48% vs. OPCABG-HS, 95% CI: 0.31 to 0.87; –36% vs. CABG, 95% CI: 0.42 to 0.95), atrial fibrillation (–34% vs. OPCABG-HS, 95% CI: 0.49 to 0.89; –29% vs. CABG, 95% CI: 0.55 to 0.87; –20% vs. OPCABG-PC, 95% CI: 0.68 to 0.97), and shortening the length of intensive care unit stay (–13.3 h; 95% CI: –19.32 to –7.26; $p < 0.0001$).

CONCLUSIONS Avoidance of aortic manipulation in anOPCABG may decrease the risk of post-operative stroke, especially in patients with higher stroke risk. In addition, the elimination of cardiopulmonary bypass may reduce the risk of short-term mortality, renal failure, atrial fibrillation, bleeding, and length of intensive care unit stay. (J Am Coll Cardiol 2017;69:924–36) © 2017 by the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

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Increasingly elderly and high-risk patients require surgical revascularization for complex coronary artery disease. The SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial demonstrated that coronary artery bypass grafting (CABG) remains the standard of treatment for 3-vessel and left main coronary artery disease (1). These results are also supported by the FREEDOM (Strategies for Multivessel Revascularization in Patients with Diabetes) trial in a population of diabetic patients (2). However, the increased risk of stroke following CABG remains a major disadvantage for surgical revascularization compared with percutaneous coronary intervention. Moreover, the risk of stroke and mortality after CABG is known to increase with age (3).

Aortic "no-touch" or anaortic off-pump CABG (anOPCABG) is a technique of surgical coronary artery revascularization that eliminates all manipulation of the ascending aorta and reliance on cardiopulmonary bypass (CPB) (4). One advantage of anOPCABG may be a reduced risk of neurological injury through avoidance of manipulation of the ascending aorta and disruption of atherosclerotic plaque (5,6). Patients receiving off-pump CABG (OPCABG) without the use of CPB may also benefit from reduced systemic inflammation, end-organ injury, and coagulation disorders (7). These benefits are particularly relevant in high-risk populations, such as elderly patients with a high atherosclerotic burden (3).

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In most centers, OPCABG is performed with an aortic side clamp to achieve proximal aortocoronary anastomosis (i.e., there is manipulation of the ascending aorta). Clampless devices, including the Heartstring system (Maquet Cardiovascular, San Jose, California), have also been developed to enable proximal aortocoronary anastomosis without the use of a side clamp, but still involve a degree of aortic manipulation compared to a true anaortic technique. Thus the present network meta-analysis aimed to evaluate post-operative stroke, mortality, and morbidity following CABG with increasing degrees of aortic manipulation.

METHODS

LITERATURE SEARCH STRATEGY. Following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (8) and the PRISMA Extension for Network Meta-analysis (9), electronic searches were performed by 2 authors (D.F.Z. and M.S.). Details of the literature search strategy are provided in the Online Appendix.

SELECTION CRITERIA. Eligible studies for the present systematic review and network meta-analysis were those published in English that compared anOPCABG, OPCABG using the Heartstring system (OPCABG-HS), OPCABG with partial clamp (OPCABG-PC), or conventional on-pump CABG. Studies that did not contain a comparative group, include stroke as an endpoint, or specify the avoidance of aortic manipulation in OPCABG were excluded. Detailed selection criteria are provided in the Online Appendix.

DATA EXTRACTION AND CRITICAL APPRAISAL. All data were extracted from article texts, tables, and figures. Two investigators (D.F.Z. and M.S.) independently reviewed each included article. Details of study appraisal and quality scoring are provided in the Online Appendix. Discrepancies between the 2 investigators were resolved by discussion and consensus with the senior authors (J.J.E. and M.P.V.).

OUTCOMES. The primary outcome was post-operative stroke in patients receiving anOPCABG compared to OPCABG-PC, OPCABG-HS, or CABG. Secondary outcomes included post-operative mortality, myocardial infarction, renal failure, bleeding, atrial fibrillation, and length of stay in intensive care unit (ICU). The time point for analysis of outcomes was post-operative or 30-day follow-up. Detailed outcome definitions are provided in the Online Appendix.

STATISTICAL ANALYSIS. In the present network meta-analysis, dichotomous outcome variables were compared with odds ratios (ORs) and 95% confidence intervals (CIs). A hierarchical Bayesian network was used for its greater flexibility, more natural interpretation, and ability to rank treatments according to their comparative effectiveness. It allows for combining of all available comparisons between treatments with the advantage of greater power and precision for rare events (10). Analyses were performed using Bayesian Markov chain Monte Carlo modeling (11). To provide a comparative hierarchy of procedural efficacy and safety, "Rankograms" with surface under the cumulative ranking curve (SUCRA) probabilities were reported. A SUCRA of 90% means that the treatment of interest achieves 90% of effectiveness or safety relative to other interventions. Thus, the larger the SUCRA value, the higher the rank of the treatment, indicating a safer or more effective treatment. All analyses were performed with NetMetaXL 1.6.1 (Canadian Agency for Drugs and

ABBREVIATIONS AND ACRONYMS

anOPCABG = anaortic off-pump coronary artery bypass grafting

CABG = coronary artery bypass grafting

CI = confidence interval

CPB = cardiopulmonary bypass

ICU = intensive care unit

OPCABG = off-pump coronary artery bypass grafting

OPCABG-HS = off-pump coronary artery bypass grafting with Heartstring device

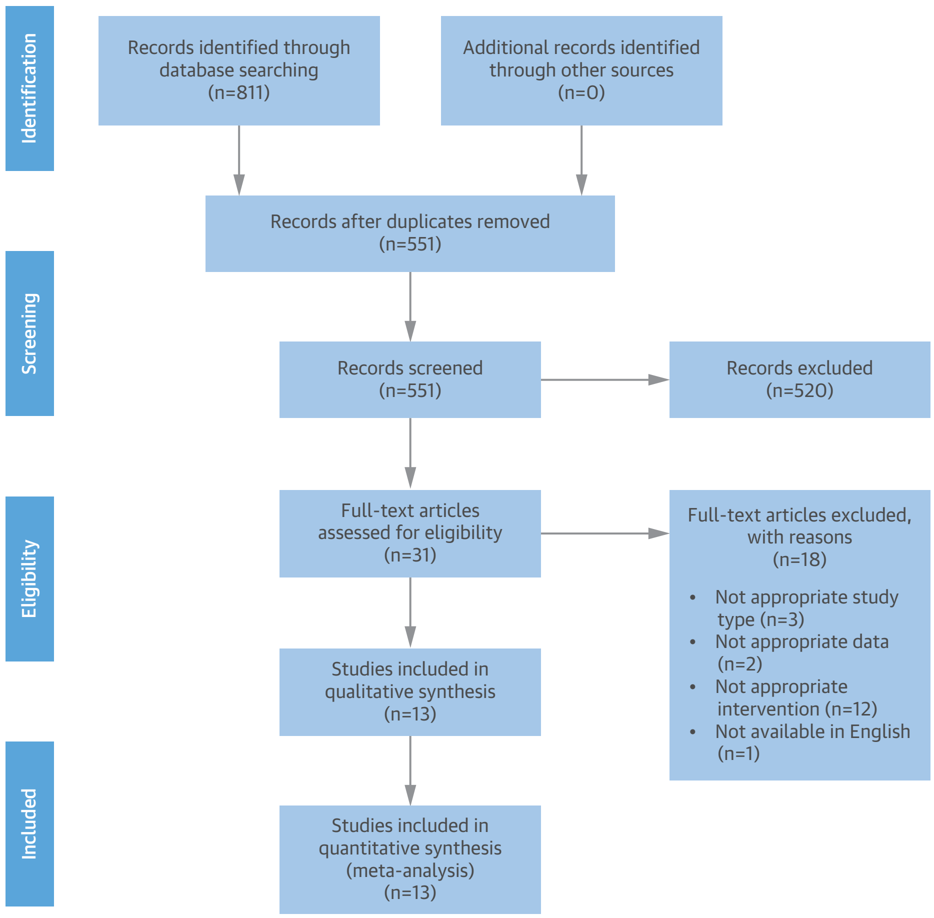
OPCABG-PC = off-pump coronary artery bypass grafting with partial clamp

OR = odds ratio

RR = risk ratio

SUCRA = surface under the cumulative ranking curve

FIGURE 1 PRISMA Flowchart for CABG With and Without Manipulation of the Aorta



Literature search and appraisal for network meta-analysis of coronary artery bypass grafting with and without manipulation of the aorta. CABG = coronary artery bypass grafting; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Technologies in Health, Ottawa, Canada) (12) and WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, United Kingdom). Detailed statistical methods for the Bayesian network, pairwise risk ratio (RR) meta-analysis, and Egger regression asymmetry test are provided in the Online Appendix.

RESULTS

LITERATURE SEARCH. A total of 811 studies were identified through 6 electronic database searches and from other sources including reference lists (**Figure 1**). After exclusion of duplicate or irrelevant references, 31 potentially relevant articles were retrieved. After application of the inclusion and exclusion criteria, 13 relevant articles were included in this study (13-25). A total of 37,720 patients were included for analysis, including 7,098 receiving anOPCABG, 12,512 receiving OPCABG-PC, 2,997 receiving OPCABG-HS, and 15,113 receiving CABG. Study characteristics are summarized in **Table 1**. Study quality assessment is summarized in Online Table 1. Inspection of the funnel plot did not show significant asymmetry to suggest publication bias with stroke and mortality outcomes selected (Online Figure 1). The Egger test for publication bias was not significant with all outcomes selected and demonstrated no small-study effects (anOPCABG vs. CABG, $p = 0.15$; anOPCABG vs. OPCABG-PC, $p = 0.21$). The complete evidence network for all outcomes is shown in **Figure 2**. Stroke definitions across trials are reported in Online Table 2.

PATIENT CHARACTERISTICS. Patients receiving anOPCABG had a significantly higher rate of previous stroke compared to those receiving OPCABG-PC (7.4% vs. 6.5%; $p = 0.02$) and CABG (7.4% vs. 3.2%; $p = 0.001$). There were significantly fewer diseased vessels in anOPCABG compared to CABG (2.6 ± 0.7 vs. 3.2 ± 0.4; $p = 0.002$). Mean European System for Cardiac Operative Risk Evaluation score was less in anOPCABG compared to CABG (4.0 ± 3.2 vs. 4.2 ± 2.4; $p < 0.00001$). Differences were also observed in other patient characteristics (**Table 2**). Additional baseline parameters, including proportion of patients with peripheral vascular disease, diabetes, chronic obstructive pulmonary disease, past myocardial infarction, atrial fibrillation, renal failure, and left-main disease, were similar across all comparison arms.

STROKE. In the network meta-analysis, anOPCABG was associated with a reduction of 78% in the 30-day risk of stroke compared with CABG (OR: 0.22; 95% CI: 0.14 to 0.33), 66% compared with OPCABG-PC (OR: 0.34; 95% CI: 0.22 to 0.52), and 52% compared with OPCABG-HS (OR: 0.48; 95% CI: 0.27 to 0.86) (**Figure 3A**, **Central Illustration**). OPCABG-HS (OR: 0.45; 95% CI: 0.28 to 0.69) and OPCABG-PC (OR: 0.64; 95% CI: 0.48 to 0.83) were associated with a reduction in stroke risk of 55% and 36% compared with CABG, respectively. Comparisons between all other treatments were not significantly different. Heterogeneity was low ($\tau^2 = 0.13$). The league table is shown in **Figure 4A**. Bayesian Markov chain Monte Carlo modeling demonstrated that anOPCABG had the highest probability of having the lowest rate of stroke (SUCRA 99.8%), followed by OPCABG-HS (64.8%), OPCABG-PC (35.4%), and CABG (0.045%) (**Figure 5A**).

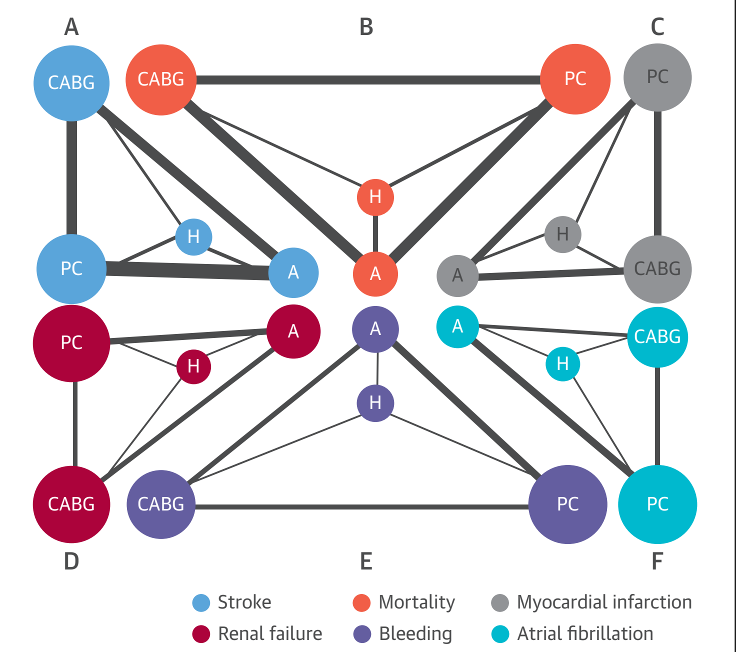
For the purpose of comparison, pairwise meta-analysis was also performed (Online Figures 2 to 5). anOPCABG was associated with a significant reduction in stroke compared with CABG (0.4% vs. 1.8%; RR: 0.3; 95% CI: 0.2 to 0.4; $p < 0.00001$; $I^2 = 0\%$) (Online Figure 2) and OPCABG-PC (0.4% vs. 1.3%; RR: 0.4; 95% CI: 0.3 to 0.6; $p < 0.0001$; $I^2 = 0\%$) (Online Figure 3). OPCABG-HS was associated with a significant reduction in stroke compared with CABG (0.96% vs. 2.2%; RR: 0.4; 95% CI: 0.2 to 0.8; $p = 0.009$; $I^2 = 53\%$) (Online Figure 4). Moderate heterogeneity was present.

MORTALITY. In the network meta-analysis, anOPCABG was associated with a reduction of 50% in the 30-day risk of mortality compared with CABG (OR: 0.50; 95% CI: 0.35 to 0.70) and 40% compared with OPCABG-HS (OR: 0.60; 95% CI: 0.38 to 0.94) (**Figure 3B**). OPCABG-PC was associated with a reduction of 37% in mortality compared with CABG (OR: 0.63; 95% CI: 0.48 to 0.81). Comparisons between all other treatments were not significantly different. Heterogeneity was low ($\tau^2 = 0.12$). The league table is shown in **Figure 4B**. Bayesian Markov chain Monte Carlo modeling demonstrated that anOPCABG had the highest probability of having the lowest rate of mortality (SUCRA 96.3%), followed by OPCABG-PC (67.4%), OPCABG-HS (30.8%), and CABG (5.6%) (**Figure 5B**).

In the pairwise meta-analysis, anOPCABG was associated with a significant reduction in mortality compared with CABG (1.0% vs. 2.2%; RR 0.5; 95% CI: 0.4 to 0.7; $p < 0.0001$; $I^2 = 0\%$) (Online Figure 2).

MYOCARDIAL INFARCTION. No significant differences were found in the network meta-analysis. AnOPCABG was associated with a similar 30-day risk of myocardial infarction compared with CABG (OR: 0.73; 95% CI: 0.44 to 1.18) and OPCABG-PC (OR: 0.86; 95% CI: 0.57 to 1.32) (**Figure 3C**). Comparisons between all other treatments were not significantly

FIGURE 2 Network Diagram for CABG With and Without Manipulation of the Aorta



Comparing **(A)** stroke, **(B)** mortality, **(C)** myocardial infarction, **(D)** renal failure, **(E)** bleeding complications, and **(F)** atrial fibrillation outcomes among coronary artery bypass grafting (CABG) techniques with varying degrees of aortic manipulation. The number of patients in each group is proportional to the size of the circle. The number of direct comparisons is represented by the width of the connecting line. A = anaortic off-pump coronary artery bypass grafting; H = off-pump coronary artery bypass grafting with the Heartstring system; PC = off-pump coronary artery bypass grafting with partial clamp.

TABLE 1 Study Characteristics for Network Meta-Analysis of CABG With and Without Manipulation of the Aorta

First Author (Ref. #)	Year	Study Period	Country	N	anOPCABG	OPCABG-PC	OPCABG-HS	CABG	Study Type
Moss (13)	2015	2002–2013	United States	12,079	1,550 (12.8)	6,449 (53.4)	1,551 (12.8)	2,529 (20.9)	OS, R
Matsuura (25)	2013	1998–2011	Japan	336	264 (78.6)	72 (21.4)	NR	NR	OS, R
Lemma (14)	2012	2006–2010	Italy, Switzerland	411	82 (20.0)	126 (30.7)	NR	203 (40.9)	PRT
Emmert (15)	2011	2004–2009	Switzerland	4,314	271 (6.3)	567 (13.1)	1,365 (31.6)	2,111 (48.9)	OS, R
Misfeld (16)	2010	2002–2007	Australia	3,699	1,346 (36.4)	600 (16.2)	NR	1,753 (47.4)	OS, R
Manabe (17)	2009	2004–2007	Japan	507	185 (36.5)	241 (47.5)	81 (16.0)	NR	OS, R
Izumoto (18)	2009	2000–2002	Japan	191	59 (30.9)	NR	NR	132 (69.1)	OS, R
Lev-Ran (19)	2005	2000–2003	Israel	700	429 (61.3)	271 (38.7)	NR	NR	OS, R
Kapetanakis (20)	2004	1998–2002	United States	7,272	476 (6.5)	2,527 (34.7)	NR	4,269 (58.7)	OS, R
Leacche (21)	2003	1996–2001	Canada	640	84 (13.1)	556 (86.9)	NR	NR	OS, R
Patel (22)	2002	1997–2001	United Kingdom	2,327	597 (25.7)	520 (22.3)	NR	1,210 (52.0)	OS, R
Kim (23)	2002	1998–2001	United States	421	222 (52.7)	123 (29.2)	NR	76 (18.1)	OS, P
Calafiore (24)	2002	1988–2000	Italy	4,823	1,533 (31.8)	460 (9.5)	NR	2,830 (58.7)	OS, R

Values are n (%).

anOPCABG = anaortic off-pump coronary artery bypass grafting; CABG = coronary artery bypass grafting; NR = not reported; OPCABG-HS = off-pump coronary artery bypass grafting with the Heartstring system; OPCABG-PC = off-pump coronary artery bypass grafting with partial clamp; OS = observational study; P = prospective; PRT = prospective randomized trial; R = retrospective.

different. Heterogeneity was moderate ($\tau^2 = 0.21$). The league table is shown in **Figure 4C**. Bayesian Markov chain Monte Carlo modeling demonstrated that OPCAB-HS the highest probability of having the lowest rate of myocardial infarction (SUCRA 72.3%), followed by anOPCABG (71.0%), OPCABG-PC (42.0%), and CABG (14.7%) (**Figure 5C**). No significant differences were detected in the pairwise meta-analysis (Online Figures 2 and 3).

RENAL FAILURE. In the network meta-analysis, anOPCABG was associated with a reduction of 53% in the 30-day risk of renal failure compared with

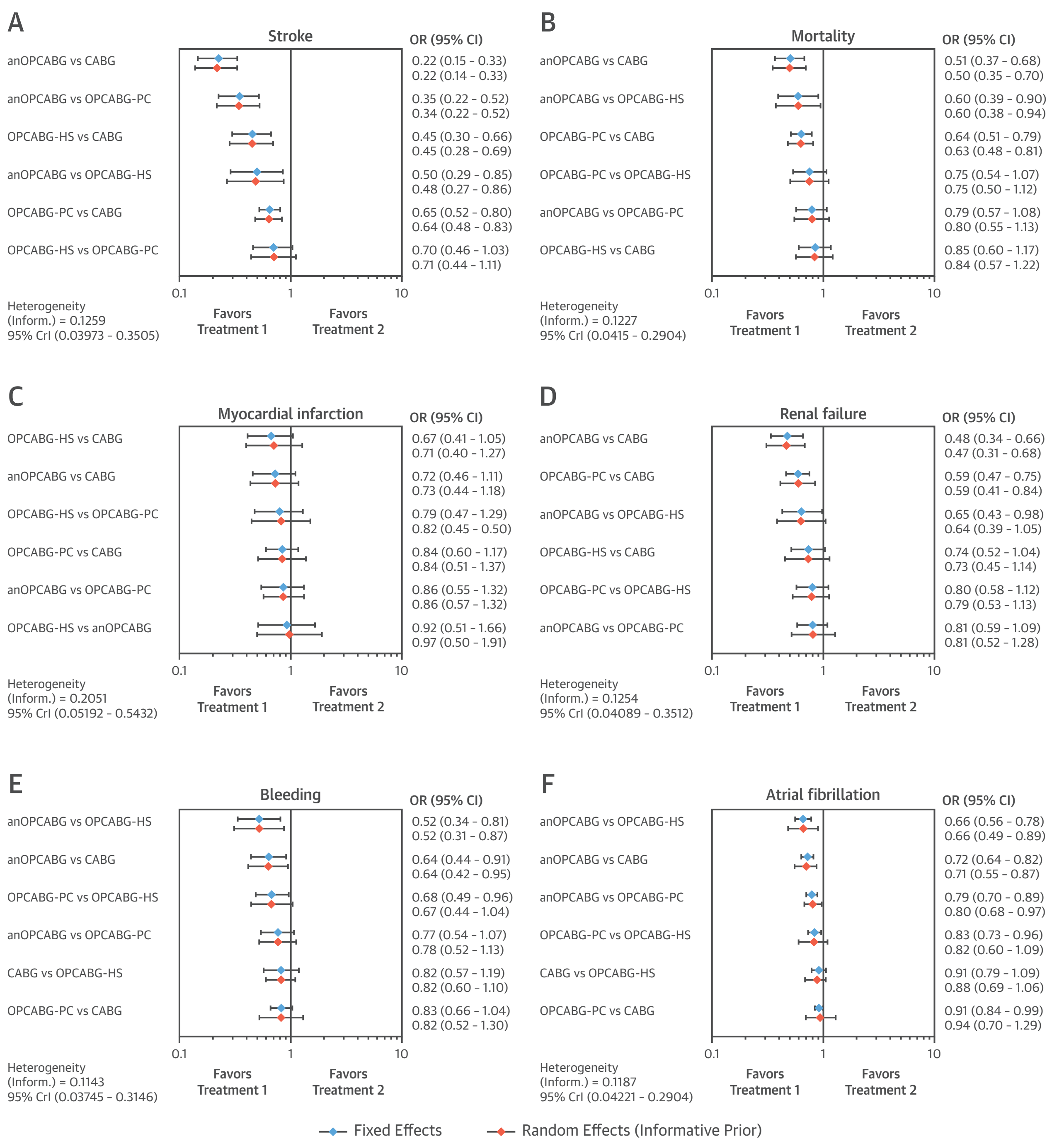
TABLE 2 Baseline Patient Characteristics for Network Meta-Analysis of CABG With and Without Manipulation of the Aorta

					p Value					
	I. anOPCABG	II. OPCABG-PC	III. OPCABG-HS	IV. CABG	I vs. II	I vs. III	I vs. IV	II vs. III	II vs. IV	III vs. IV
Age, yrs	64.5 ± 10.7	64.1 ± 10.6	66.3 ± 10.2	63.6 ± 10.1	0.20	0.03	0.40	<0.00001	0.006	<0.00001
LVEF, %	56.0 ± 13.0	52.6 ± 5.6	53.8 ± 13.4	52.7 ± 13.7	0.06	0.31	0.01	NR	0.93	0.00002
Diseased vessels	2.6 ± 0.7	3.5 ± 0.6	3.2 ± 0.6	3.2 ± 0.4	0.14	0.39	0.002	0.35	0.08	0.32
EuroSCORE	4.0 ± 3.2	4.0 ± 3.3	NR	4.2 ± 2.4	0.40	NR	<0.00001	NR	<0.00001	NR
Male	77.4	72.0	79.7	76.9	0.02	0.52	0.03	0.35	<0.00001	NR
Past stroke	7.4	6.5	14.1	3.2	0.02	0.05	0.001	0.001	0.13	NR
Cerebrovascular disease	14.7	15.5	27.8	12.1	0.75	<0.00001	0.13	0.0002	0.37	NR
Peripheral vascular disease	11.2	13.9	NR	10.5	0.58	NR	0.30	NR	0.24	NR
Diabetes	29.8	36.8	40.4	34.6	0.10	0.06	0.06	0.44	0.14	NR
Hypertension	71.2	76.2	89.8	69.0	0.78	0.0003	0.23	<0.00001	0.20	NR
COPD	8.6	6.0	NR	5.9	0.55	NR	0.53	NR	0.71	NR
Past myocardial infarction	47.7	46.3	NR	44.5	0.45	NR	0.72	NR	0.83	NR
Atrial fibrillation	2.3	2.0	NR	NR	0.68	NR	NR	NR	NR	NR
Dyslipidemia	75.0	80.0	84.8	76.0	0.22	0.90	0.03	0.98	0.05	NR
Heart failure	14.3	17.2	NR	14.5	<0.0001	NR	<0.00001	NR	0.12	NR
Renal failure	5.0	5.5	NR	4.5	0.35	NR	0.98	NR	0.73	NR
LVEF <35%	7.0	10.4	NR	18.8	0.88	NR	0.04	NR	<0.0001	NR
Left-main disease	25.1	19.5	NR	21.1	0.17	NR	0.32	NR	0.20	NR
Triple vessel disease	64.2	75.1	NR	76.7	0.03	NR	0.01	NR	0.61	NR
Previous cardiac operation	4.0	5.6	NR	7.0	0.02	NR	0.007	NR	0.30	NR
Elective operation	70.5	62.6	59.1	65.1	0.59	0.20	0.11	0.01	0.43	0.52

Values are mean ± SD or %.

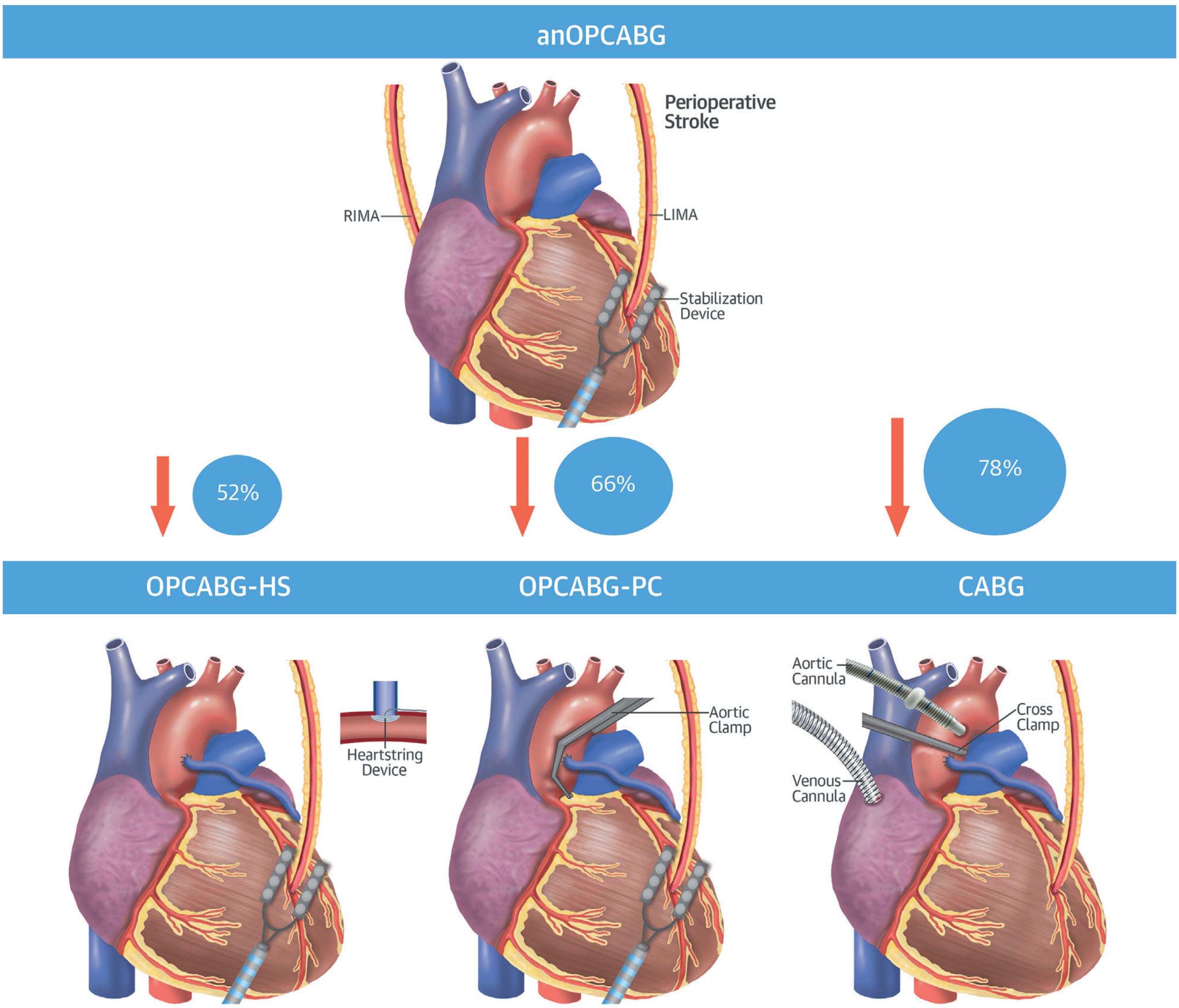
COPD = chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; other abbreviations as in **Table 1**.

FIGURE 3 **Forest Plots for CABG With and Without Manipulation of the Aorta**



Outcomes shown for **(A)** stroke, **(B)** mortality, **(C)** myocardial infarction, **(D)** renal failure, **(E)** bleeding complications, and **(F)** atrial fibrillation following coronary artery bypass grafting (CABG) with and without manipulation of the aorta. anOPCABG = anaortic off-pump coronary artery bypass grafting; CI = confidence interval; CrI = credible interval; Inform. = informative prior; OPCABG-PC = off-pump coronary artery bypass grafting with partial clamp; OPCABG-HS = off-pump coronary artery bypass grafting with the Heartstring system; OR = odds ratio.

CENTRAL ILLUSTRATION Coronary Artery Bypass Grafting With and Without Manipulation of the Ascending Aorta



Zhao, D.F. et al. J Am Coll Cardiol. 2017;69(8):924-36.

Four surgical methods of coronary artery bypass grafting with increasing degrees of aortic manipulation. Percentages pictured represent the relative decrease in risk of perioperative stroke using anOPCABG compared to the other techniques. CABG = coronary artery bypass grafting with cardiopulmonary bypass; anOPCABG = anaortic off-pump coronary artery bypass grafting; LIMA = left internal mammary artery; OPCABG-HS = off-pump coronary artery bypass grafting with the Heartstring system; OPCABG-PC = off-pump coronary artery bypass grafting with partial clamp; RIMA = right internal mammary artery.

CABG (OR: 0.47; 95% CI: 0.31 to 0.68) (Figure 3D). OPCABG-PC was associated with a reduction of 41% in the 30-day risk of renal failure compared with CABG (OR: 0.59; 95% CI: 0.41 to 0.84). Comparisons between all other treatments were not significantly different. Heterogeneity was low ($\tau^2 = 0.13$). The league table is shown in Figure 4D. Bayesian Markov chain Monte Carlo modeling demonstrated that anOPCABG had the highest probability of having the lowest rate of renal failure (SUCRA 95.7%), followed by OPCABG-PC (64.1%), OPCABG-HS (37.5%), and CABG (2.8%) (Figure 5D).

In the pairwise meta-analysis, anOPCABG was associated with a significant reduction in renal failure compared with CABG (1.3% vs. 1.8%; RR 0.5; 95% CI: 0.4 to 0.7; $p < 0.0001$; $I^2 = 0\%$) (Online Figure 2).

FIGURE 4 League Tables for CABG With and Without Manipulation of the Aorta

A Stroke

anOPCABG			
0.48 (0.27 - 0.86)	OPCABG-HS		
0.34 (0.22 - 0.52)	0.71 (0.44 - 1.11)	OPCABG-PC	
0.22 (0.14 - 0.33)	0.45 (0.28 - 0.69)	0.64 (0.48 - 0.83)	CABG

B Mortality

anOPCABG			
0.80 (0.55 - 1.13)	OPCABG-PC		
0.60 (0.38 - 0.94)	0.75 (0.50 - 1.12)	OPCABG-HS	
0.50 (0.35 - 0.70)	0.63 (0.48 - 0.81)	0.84 (0.57 - 1.22)	CABG

C Myocardial infarction

OPCABG-HS			
0.97 (0.50 - 1.91)	anOPCABG		
0.82 (0.45 - 1.50)	0.84 (0.51 - 1.37)	OPCABG-PC	
0.71 (0.40 - 1.27)	0.73 (0.44 - 1.18)	0.86 (0.57 - 1.32)	CABG

D Renal failure

anOPCABG			
0.79 (0.53 - 1.13)	OPCABG-PC		
0.64 (0.39 - 1.05)	0.81 (0.52 - 1.28)	OPCABG-HS	
0.47 (0.31 - 0.68)	0.59 (0.41 - 0.84)	0.73 (0.45 - 1.14)	CABG

E Bleeding

anOPCABG			
0.78 (0.52 - 1.13)	OPCABG-PC		
0.64 (0.42 - 0.95)	0.82 (0.60 - 1.10)	CABG	
0.52 (0.31 - 0.87)	0.67 (0.44 - 1.04)	0.82 (0.52 - 1.30)	OPCABG-HS

F Atrial fibrillation

anOPCABG			
0.80 (0.68 - 0.97)	OPCABG-PC		
0.71 (0.55 - 0.87)	0.88 (0.69 - 1.06)	CABG	
0.66 (0.49 - 0.89)	0.82 (0.60 - 1.09)	0.94 (0.70 - 1.29)	OPCABG-HS

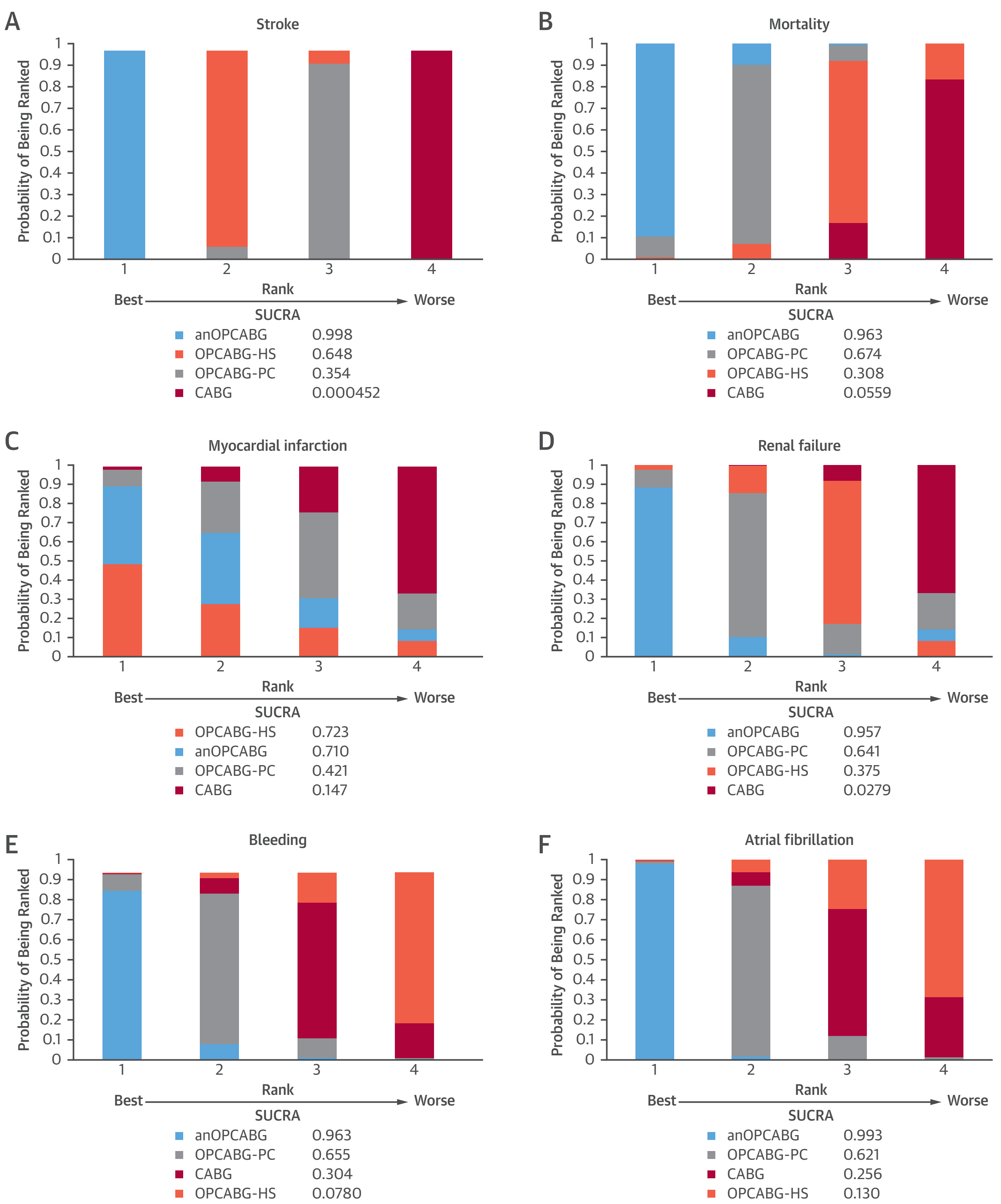
Outcomes shown for **(A)** stroke, **(B)** mortality, **(C)** myocardial infarction, **(D)** renal failure, **(E)** bleeding complications, and **(F)** atrial fibrillation following CABG with and without manipulation of the aorta (OR and 95% CI). OR <1 means the treatment in top left is better. Abbreviations as in Figure 3.

BLEEDING. In the network meta-analysis, anOPCABG was associated with a reduction of 48% in the 30-day risk of bleeding complications compared with OPCABG-HS (OR: 0.52; 95% CI: 0.31 to 0.87) and 36% compared with CABG (OR: 0.64; 95% CI: 0.42 to 0.95) (Figure 3E). Comparisons between all other treatments were not significantly different. Heterogeneity was low ($\tau^2 = 0.11$). The league table is shown in Figure 4E. Bayesian Markov chain Monte Carlo modeling demonstrated that anOPCABG had the highest probability of having the lowest rate of bleeding complications (SUCRA 96.3%), followed by OPCABG-PC (65.5%), CABG (30.4%), and OPCABG-HS (7.8%) (Figure 5E).

In the pairwise meta-analysis, anOPCABG was associated with a significant reduction in bleeding complications compared with CABG (1.6% vs. 2.4%; RR 0.7; 95% CI: 0.5 to 0.96; $p = 0.03$; $I^2 = 0\%$) (Online Figure 2).

ATRIAL FIBRILLATION. In the network meta-analysis, anOPCABG was associated with a reduction of 34% in the 30-day risk of atrial fibrillation compared with OPCABG-HS (OR: 0.66; 95% CI: 0.49 to 0.89), 29% compared with CABG (OR: 0.71; 95% CI: 0.55 to 0.87), and 20% compared with OPCABG-PC (OR: 0.80; 95% CI: 0.68 to 0.97) (Figure 3F). Comparisons between all other treatments were not significantly different. Heterogeneity was low ($\tau^2 = 0.12$). The league table is shown in Figure 4F. Bayesian Markov chain Monte Carlo modeling demonstrated that anOPCABG had the highest probability of having

FIGURE 5 **Rankograms for CABG With and Without Manipulation of the Aorta**



Outcomes showing the likelihood of reducing **(A)** stroke, **(B)** mortality, **(C)** myocardial infarction, **(D)** renal failure, **(E)** bleeding complications, and **(F)** atrial fibrillation following coronary artery bypass grafting with and without manipulation of the aorta. SUCRA = surface under the cumulative ranking; other abbreviations as in Figure 3.

the lowest rate of atrial fibrillation (SUCRA 99.3%), followed by OPCABG-PC (62.1%), CABG (25.6%), and OPCABG-HS (13%) (**Figure 5F**).

In the pairwise meta-analysis, anOPCABG was associated with a significant reduction in atrial fibrillation compared with CABG (14.3% vs. 19.9%; RR: 0.7; 95% CI: 0.6 to 0.8; $p < 0.00001$; $I^2 = 0\%$) (Online Figure 2) and OPCABG-PC (17.0% vs. 19.2%; RR: 0.9; 95% CI: 0.7 to 0.98; $p = 0.02$; $I^2 = 32\%$) (Online Figure 3). Moderate heterogeneity was present.

LENGTH OF ICU STAY. In the pairwise meta-analysis, the mean length of ICU stay for anOPCABG was significantly reduced compared with CABG (weighted mean 56.7 ± 82.9 h vs. 71 ± 137.4 h; weighted mean difference (WMD) -13.3 h; 95% CI: -19.32 to -7.26; $p < 0.0001$; $I^2 = 29\%$) (Online Figure 5). Moderate heterogeneity was present.

ADDITIONAL ANALYSES. Results from the Bayesian and pairwise analyses were similar, suggesting model consistency. Sensitivity analyses further confirmed the overall results of this meta-analysis. Excluding 1 study at a time did not demonstrate major changes in direction or magnitude of statistical findings.

A subgroup analysis was performed using only the included on-pump CABG studies specifying single or double-clamp use. Definitions of aortic clamping technique are reported in Online Table 3. Comparison to anOPCABG and OPCABG-PC was possible (there were no such studies that directly compared to OPCABG-HS). The network meta-analysis confirmed anOPCABG as the most effective method for stroke reduction (SUCRA 99.9%). Specifically, anOPCABG was associated with an 81% reduction in the 30-day risk of stroke compared with double-clamp on-pump CABG (OR: 0.19; 95% CI: 0.08 to 0.38), 77% reduction compared with single-clamp on-pump CABG (OR: 0.23; 95% CI: 0.09 to 0.50), and 66% reduction compared with OPCABG-PC (OR: 0.34; 95% CI: 0.15 to 0.71) (Online Figure 6). An additional review of 9 randomized and nonrandomized studies with 5,153 patients was performed comparing the use of single versus double-clamp techniques in on-pump CABG. There was no significant difference in the 30-day risk of stroke between single versus double-clamp on-pump CABG (1.1% vs. 1.7%; RR: 0.7; 95% CI: 0.5 to 1.2; $p = 0.19$; $I^2 = 0\%$) (Online Figure 7). Detailed additional analyses are provided in the Online Appendix.

In addition, a secondary analysis comparing a combination of all off-pump techniques with on-pump CABG was associated with reduced post-operative stroke (0.9% vs. 1.8%; RR: 0.39; 95% CI: 0.27 to 0.57; $p < 0.00001$; $I^2 = 53\%$), mortality (1.2% vs. 2.2%; RR: 0.60; 95% CI: 0.48 to 0.75; $p < 0.00001$; $I^2 = 12\%$), and renal failure (1.7% vs. 1.8%; RR: 0.58; 95% CI: 0.47 to 0.72; $p < 0.00001$; $I^2 = 0\%$) (Online Figure 8).

DISCUSSION

To our knowledge, this is the first network meta-analysis comparing clinical outcomes following CABG with various degrees of aortic manipulation. The results suggest lower rates of post-operative stroke, mortality, and renal failure when manipulation of the ascending aorta is avoided.

Recent randomized controlled trials comparing OPCABG with on-pump CABG in low-risk (ROOBY [Randomized On/Off Bypass] trial) (26), moderate-risk (CORONARY [CABG Off or On Pump Revascularization Study] trial) (27), and high-risk (GOPCABE [Off-Pump versus On-Pump Coronary-Artery Bypass Grafting in Elderly Patients] trial) (28) patients have not found a similar reduction in the rate of post-operative stroke. However, these trials have not reported the degree of aortic manipulation and the proportion of anOPCABG patients is unknown. Given that the majority of surgeons perform OPCABG using a partial clamp it is likely that this was the most frequently used technique. A number of mechanisms may cause stroke or subtle neurological injury after CABG, including embolization of air, debris or clot from the CPB circuit, hypoperfusion or hyper-perfusion, a systemic inflammatory response, or dislodgement of atherosclerotic plaque during manipulation or cross-clamping of the ascending aorta (29). Therefore, elimination of aortic manipulation and CPB may reduce the rate of post-operative stroke.

Although previous pairwise meta-analyses have demonstrated reduced stroke following anOPCABG (5,30,31), the present network meta-analysis included all possible comparisons between anOPCABG, OPCABG-PC, OPCABG-HS, and traditional on-pump CABG in a Bayesian network. By ranking treatments according to their comparative effectiveness for reducing stroke rate, the model demonstrated that anOPCABG was the superior CABG technique (SUCRA 99.8%), followed by OPCABG-HS, then OPCABG-PC, and finally on-pump CABG (**Figure 5A**). This is despite the anOPCABG and OPCABG-HS patient groups having higher rates of previous stroke and known cerebrovascular disease compared with those who underwent on-pump CABG (**Table 2**). In addition, studies that utilized epiaortic ultrasonography found that a larger proportion of anOPCABG patients had severe atherosclerotic disease in the ascending aorta (>5 mm thickness) (13,17). We have performed an additional subgroup network analysis evaluating the effect of single and double-clamp techniques in CABG patients—anOPCABG compared favorably to both techniques. A pairwise analysis of randomized and nonrandomized studies comparing single versus double-clamp techniques in CABG suggested a trend to a lower rate of stroke that did not achieve statistical significance (1.1% vs. 1.7%; $p = 0.19$). The relationship between increasing amounts of aortic manipulation and increasing risk of stroke adds weight to the hypothesis that there is the potential for disruption of atherosclerotic plaque with ascending aorta manipulation.

The reduced rate of stroke in the anOPCABG group compared with the OPCABG-PC group (**Figures 3 and 4**) may explain the inability of the randomized trials to detect a difference in stroke between OPCABG and on-pump CABG. Indeed, the rate of stroke reported in anOPCABG patients in this meta-analysis (0.4%) was favorable compared to OPCABG outcomes in the ROOBY (1.3%) (26), CORONARY (1.5%) (27), and GOPCABE (2.2%) trials (28), and with percutaneous coronary intervention in the SYNTAX trial (0.6%) (1). Patients included in the ROOBY and CORONARY trials were of similar age and rate of pre-operative stroke compared with anOPCABG patients in this analysis; other characteristics differed. Patients in the GOPCABE trial were older and had a slightly higher rate of pre-operative incidence of stroke. The impact of post-operative dual antiplatelet therapy in reducing stroke could not be analyzed in the present dataset but deserves further investigation.

AnOPCABG was associated with a lower risk of post-operative mortality (SUCRA 96.3%), renal failure (SUCRA 95.7%), bleeding complications (SUCRA 96.3%), atrial fibrillation (SUCRA 99.3%), and length of ICU stay (**Figures 3 to 5**, Online Figure 5). The likely mechanism of these findings is multifactorial. Multiorgan damage and coagulopathy may result from the systemic inflammatory response associated with CPB (7). Renal and end-organ injury may be caused by relative hypoperfusion on CPB, and by distal embolization of atherosclerotic plaque, air, or debris from the CPB circuit and cross-clamp (29). Reduced post-operative renal failure and bleeding in OPCABG was also reported in the CORONARY trial (27). Post-operative atrial fibrillation may also be decreased by reduced systemic inflammation, myocardial ischemia, avoidance of cardioplegia, and other mechanisms. In turn, this may contribute to the reduced risk of peri-operative stroke by preventing the formation of thrombi in the left atrium. Because stroke is associated with increased mortality (32), anOPCABG may further reduce mortality through this mechanism. However, these results are not supported by the randomized ROOBY (26) and GOPCABE (28) trials.

There were no significant differences between any of the techniques in post-operative myocardial infarction (**Figures 3 to 5**), where OPCABG-HS and anOPCABG were closely matched for the superior technique in this regard (SUCRA 72.3% and 71.0%, respectively). Complete revascularization with multiple inflows through the use of bilateral internal mammary arteries and/or composite/tandem grafts is possible with anOPCABG and has been described in detail (4,33). The use of bilateral internal mammary arteries is also associated with improved long-term survival (34,35). Should the surgeon wish to perform a proximal aortocoronary anastomosis, the Heartstring system is associated with a lower rate of stroke and may be preferable to OPCABG-PC. Other novel aortocoronary devices, such as the automated PAS-Port system, may also be considered (36,37).

STUDY LIMITATIONS. There are no randomized controlled trials comparing anOPCABG with the other CABG techniques and thus the results are susceptible to selection bias, as demonstrated by the differences in baseline characteristics. The present analysis reported only short-term outcomes and additional studies with long-term data are needed to evaluate repeat revascularization. Compared to patients receiving on-pump CABG, anOPCABG patients had fewer average number of diseased vessels and a lower proportion of triple vessel disease at baseline. Nonetheless, complete revascularization was reported in 4 of the included studies the using the anaortic technique (16,21–23). OPCABG patients had a lower European System for Cardiac Operative Risk Evaluation score and lower proportion with left ventricular ejection fraction <35% compared to on-pump CABG. Such bias is difficult to eliminate without a well-designed randomized trial.

Unadjusted summary estimates were used for meta-analysis and confounders could not be ruled out. However, the network meta-analysis offers greater power and precision for rare events while controlling for publication bias and small-study effects. The network model was tested for consistency and heterogeneity. There was a moderate amount of heterogeneity in some outcomes, and these results should be interpreted with caution. Nonetheless, this is the largest and most comprehensive meta-analysis currently available in the literature with 37,720 patients, and provides a high quality of evidence regarding the degree of aortic manipulation in CABG.

CONCLUSIONS

This network meta-analysis of all available studies found that the risk of post-operative stroke, mortality, renal failure, atrial fibrillation, bleeding, and length of ICU stay was the lowest using an anOPCABG technique, where manipulation and clamping of the ascending aorta is completely avoided. The superiority of the anOPCABG technique over OPCABG-PC and OPCABG-HS techniques may explain why the large randomized studies, which have eliminated CPB but not aortic manipulation, have failed to show a benefit in neurological outcomes between OPCABG and on-pump CABG. The use of bilateral internal mammary arteries or composite grafts should be used to achieve complete coronary revascularization whilst maintaining an anaortic technique. Further randomized studies utilizing a true anaortic technique are still needed to confirm these results.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Dislodgement and embolism of atheromatous material from the ascending aorta during cross-clamping and related manipulations during CABG increases the risk of stroke, and techniques that avoid manipulation of the ascending aorta are associated with lower risk of post-operative stroke. Concurrently, avoidance of CPB (anOPCABG) reduces short-term mortality, renal failure, atrial fibrillation, bleeding, and length of ICU stay after CABG.

TRANSLATIONAL OUTLOOK 1: Randomized trials are needed to better evaluate the relative efficacy, safety, and long-term outcomes associated with anOPCABG compared to conventional and hybrid procedures and the mechanisms responsible for these effects.

TRANSLATIONAL OUTLOOK 2: Well-designed randomized controlled trials are needed to better evaluate the efficacy of anOPCABG for stroke reduction and its long-term outcomes.

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KEY WORDS aorta, cardiopulmonary bypass, coronary artery bypass grafting, no-touch, off-pump, stroke

APPENDIX For expanded Methods, Results, and References sections as well as supplemental figures and tables, please see the online version of this article.