Towards stroke-free coronary surgery: the role of the anaortic off-pump bypass technique

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Abstract

Coronary artery and cerebrovascular disease represent a major cause of cardiovascular morbidity and mortality worldwide. Despite technological advancements in percutaneous interventions, surgical revascularization remains the preferred strategy in patients with left main or multivessel disease and in those with complex lesions with high SYNTAX score. As a result, an increasing number of older patients with diffuse atherosclerotic extracoronary disease are referred for coronary artery bypass grafting (CABG). Cerebrovascular complications after isolated coronary surgery occurs in 1-5% of patients; the magnitude of injury ranges from overt neurologic lesions with varying degree of permanent disability to "asymptomatic" cerebral events detected by dedicated neuro-imaging, nevertheless associated with significant long term cognitive and functional decline. Thromboembolic events due to manipulation of an atherosclerotic aorta are universally recognized as the leading etiology of early postoperative stroke following CABG. Coronary bypass surgery performed on an arrested heart relies on considerable aortic instrumentation associated with significant atheroembolic risk especially in older patients presenting with diffuse aortic calcifications. Surgical techniques to deal with a calcified ascending aorta during isolated coronary surgery have evolved over the last forty years. Moving away from aggressive aortic debridement or replacement, surgeons have developed strategies aimed to minimize aortic manipulation: from pump-assisted beating heart surgery with the use of composite grafts to complete avoidance of aortic manipulation with "anaortic" off-pump coronary artery bypass grafting, a safe and effective approach in significantly reducing the risk of intraoperative stroke.

1. Introduction

Neurologic injury is a devastating complication of cardiovascular procedures with a tremendous impact on patients in both the short- and long-term. The incidence of neurologic events after isolated coronary artery bypass grafting (CABG) varies from 1% to 5% (1–2), with older age and increased atherosclerotic burden representing important risk factors. Most perioperative strokes after coronary surgery are ischemic in nature with atheroembolic events due to aortic cannulation and cross-clamping playing a major role (3-16). The importance of a versatile approach employing "aortic-no-touch" strategies has been strongly emphasized in a recent Scientific Statement of the American Heart Association (16). Avoiding aortic manipulation with "anaortic" techniques (anaortic off-pump coronary bypass grafting, anOPCAB) significantly reduces the risk of cerebrovascular events (17-26).

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This review will examine how neurologic injury has influenced the current coronary revascularization guidelines, the mechanisms of neurologic injury post-surgery and the evidence related to surgical techniques designed to reduce aortic manipulation and subsequent neurologic risk.

2. Neurologic injury and coronary revascularization strategies

Cardiovascular disease, mostly represented by coronary artery disease (CAD) and stroke, is the major cause of death in the United States (27). The management of CAD, and the choices between medical therapy, percutaneous coronary intervention (PCI) and CABG, remains an intensely debated topic (28,29).

Current evidences support CABG as the optimal revascularization strategy for patients with left main or multivessel disease, high overall complexity disease (high SYNTAX scores) and patients with diabetes or chronic kidney disease (30-34). This is primarily driven by improved intermediate- and long-term survival, reduced myocardial infarction and fewer repeat revascularization procedures. However, in patients with less complex and less diffuse disease, PCI is often considered a better alternative (30,31), because it provides similar survival benefit with less short-term morbidity. Stroke and neurologic injury are an important component of the latter and when used in composite primary endpoints in randomized trials the benefit of CABG is often reduced or offset, leading to the non-inferiority/superiority of PCI with a significant impact on revascularization guidelines.

The higher rate of early stroke is a significant limitation of traditional on-pump CABG compared to PCI and carries a dramatic effect on long term survival (35,36). Evidence from a recent patient-data meta-analysis (35) showed that the long term neurologic benefit of PCI is driven mostly by the significantly higher perioperative stroke risk after CABG, given that the rate between 31 days and 5 years were comparable (PCI 2.2% vs CABG 2.1%, HR 1.05, 95%CI 0.80 - 1.38). Similarly, the SYNTAX trial (37), despite an initial neurologic advantage of PCI at 12-months, showed equivalent stroke rate between PCI and CABG at 5 years (38).

Analogous findings were reported by Gaudino (36): both early and delayed stroke have an extraordinary impact on operative and long-term mortality post isolated CABG (21.3% vs 2.4%, p<0.001 and 10.9% vs 3.4% at 8 years, p<0.001). Meta-regression analysis showed that techniques directed at minimizing aortic manipulation rather than intrinsic patients characteristics had a protective effect on neurologic outcome (β=-0.009 and p=0.01 for off-pump CABG).

Finally, an increasing body of data supports the correlation between evidence of "asymptomatic" brain injury on Diffusion-Weighted Magnetic Resonance Imaging (MRI) and long term neurologic injury (cognitive and functional decline) after both cardiac (39-41) and non-cardiac surgery (42).

3. Mechanism and risk factors of neurologic injury

The spectrum of post-operative neurologic injury can be schematically outlined as:

- intra-operative and early post-operative events – deficit diagnosed on awakening at extubation, mainly related to atheroembolism from aortic manipulation or cerebral hypoperfusion;
- delayed post-operative events – occurring within 30 post-operative days, but after a symptom-free interval following extubation (mainly secondary to atrial fibrillation, low cardiac output states, bleeding and hypoperfusion);
- late events – occurring after the 30-day post-operative period.

Coronary artery bypass performed on an arrested heart relies on aortic cannulation and cross-clamping; both steps represent considerable aortic manipulation associated with significant atheroembolic risk. The mechanisms for this to occur include detachment of atherosclerotic material from the aortic intima as a result of external manipulation (cannulation, aortic cross-clamping and partial occlusion); or internal disruption caused by the "sandblasting" effect of the high-velocity jet of blood exiting the aortic cannula and impacting on the atherosclerotic intima or pedunculated atheroma.

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The role of the "porcelain aorta" (43) (Figure 1) in the pathogenesis of adverse neurologic outcome after isolated CABGs has been postulated for almost four decades (3-6).

Multiple cadaveric studies have documented a high embolic burden to the brain during CPB and aortic manipulation in the presence of ascending aortic atherosclerosis (7,8). This is manifested by specific cerebral microvascular alterations in the form of small capillary and arteriolar dilatation (7). In an autopsy study by Blauth (8) 21.7% of patients who died after cardiac surgery on CPB had evidence of atheroemboli (or abnormalities consistent with atheroemboli) in the brain; severe aortic atherosclerosis and coronary surgery were significantly associated with higher risk of neurologic embolization.

In a multicenter prospective study that enrolled 2,108 patients undergoing elective CABG in 24 U.S. medical institutions, Roach (9) reported an overall incidence of type I cerebral events (coma, stroke or TIA) of 3.1%; moderate to severe aortic atherosclerosis assessed by manual palpation of the ascending aorta was the main risk factor, increasing the rate of postoperative stroke four-fold. Similar findings were reported by Stamou (10) on a series of 16,528 patients who underwent isolated on-pump CABG with an overall stroke rate of 2.0%; atherosclerosis of the ascending aorta and prolonged bypass and cross-clamp time were significantly more frequent in patients with postoperative neurologic complications. Data from Tarakji (1) showed an overall stroke rate of 1.6% in a large series of consecutive isolated CABG performed over a period of 30 years. The main risk factors were older age and variables representing higher atherosclerotic burden like PVD and carotid stenosis. Minimization of aortic manipulation with off-pump or on-pump beating heart techniques provided the lowest risk.

In a review of 6,682 consecutive patients undergoing isolated on-pump CABG performed with single aortic clamp technique and without epiaortic scanning, Borger (11) reported a prevalence of postoperative stroke of 1.5%, associated with a significant increase of in-hospital mortality ($p<0.001$). The atheroembolic etiology of those strokes was supported by radiological and pathological evidence of ischemic lesions in the territory distribution of major cerebral vessels; surgical manipulation (cannulation, cross-clamping, proximal anastomosis) of an atherosclerotic ascending aorta was the most common embolic source.

Aortic calcifications were once again found to increase threefold the risk of post-operative stroke (overall rate 1.4%) in a review of 19,224 patients undergoing isolated on-pump CABG in 31 hospitals in the State of New York by John (12). As for other studies, stroke patients experienced a significantly increased in-hospital mortality (24.8% vs 2.0%, $p<0.001$). Likewise, Rao (14) reported a stroke rate of 1.4% among a series of 3,910 consecutive isolated on-pump CABGs (single clamp technique). Severe coronary artery disease was found to be the most important predictor of stroke, followed by older age, previous TIA/stroke, PVD and diabetes: all those factors clearly represent a surrogate for aortic atherosclerosis. A higher stroke rate of 4.3% was reported by Lynn (15) in a series of 1,000 consecutive on-pump CABGs; extensive aortic calcifications noted by the surgeon was a highly significant risk factor for permanent neurologic deficit (11 strokes in 57 patients with aortic calcification, 19%; $p<0.0001$). Finally, the investigators of the Multicenter Study of Perioperative Ischemia (13) developed a preoperative stroke risk index used to estimate the individual risk of postoperative stroke. Advanced age, PVD and diabetes were strong predictors of atherosclerotic disease of the aorta and cerebral vessels, hence the authors implicated embolization as the likely primary aetiology of major neurologic deficits after CABG.

Early postoperative strokes are more often right-sided compared with delayed strokes that are more uniformly distributed. Data from Boivie and Hedberg (44-46) showed clinical and radiological evidence that right-sided perioperative events were largely preponderant compared to contralateral strokes. Manipulation of a calcified ascending aorta explains the embolic nature of particles tangentially expelled into the brachiocephalic artery.

Grooters (47) looked at the effect of perfusion jets and "sandblasting" from CPB aortic cannulae into the aortic arch. Using transesophageal echo (TEE) they demonstrated that both end-hole and side-holes cannulae generated high velocity jets directed against the aortic wall, potentially responsible for the disruption of friable atherosclerotic plaques. On the other hand, the Dispersion cannula showed a broad wedge-like perfusion pattern with significantly lower exit velocities.

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The effect of aortic clamping has also been extensively investigated. In a cadaveric study from Boivie (48), ten calcified ascending aortas were mounted on a perfusion model, clamped multiple times and finally washed out. The investigators found that a significant amount of particular matter had been released, comprised of both calcified and cellular material (average diameter of 0.63 ± 0.03 mm). Although the majority of the embolic load occurred following the first clamping, subsequent clamps still continued to release particulate matter and therefore this questions multiple-clamp surgical techniques (Figure 2). Barbut (49) looked at the embolic burden detected by transcranial doppler (TCD) during on-pump CABG using a double-clamping technique. The largest number of embolic signals (58%) were noted at aortic cross-clamp or partial-occlusion clamp removal (seven-fold and five-fold higher rates respectively) especially when higher grade of aortic atheroma were present (p<0.05).

Watters (50) detected a significant decrease in TCD embolic signals in patients undergoing off-pump CABG (OPCAB) with partial occlusion clamp, compared to on-pump CABG with double clamping (median embolic signals 79 *vs* 3 respectively). Although this study was non-randomized, the two groups were similar in terms of Parsonnet risk score, number of grafts performed and overall presence of aortic calcification. Finally, in another study involving TCD monitoring during CABG, Taylor (51) showed that a relevant number of embolic events while on CPB were recorded during perfusionist interventions (drugs administration and blood sampling) in the form of small air bubbles.

4. Assessment of the ascending aorta and techniques to reduce aortic manipulation

Recognizing patients with a calcified ascending aorta is essential to preventing neurologic complications. In the era before routine use of perioperative imaging, this diagnosis was made by visual inspection, digital palpation or when the cross-clamp was found to incompletely occlude the aorta (6). These methods have been largely replaced by TEE and epiaortic ultrasound (EAU) (52,53). Katz (54) classified aortic atheroma using intraoperative TEE in five different grades: I= no disease or minimal intimal thickening, II = extensive intimal thickening, III = sessile atheroma < 5mm thick, IV = protruding atheroma [?] 5mm thick, and V = mobile atheroma in the lumen (Figure 3). Katz and Ribakove (54,55) demonstrated how careful aortic assessment by intraoperative TEE guides the operative strategy in terms of cannulation site, choice of aortic cannula and conduct of CPB. Their results showed that the degree of aortic atheroma detected by TEE correlated strongly with perioperative stroke (p=0.001) and that modifications of surgical technique to avoid atheroma had a favorable effect on patients with grade V disease (54).

Although intraoperative TEE is superior to manual palpation in detecting advanced aortic arch atherosclerosis, visualization of the distal ascending aorta can be suboptimal. To overcome these limitations epiaortic ultrasound (EAU) is a preferable intraoperative imaging modality to detect atheroma from the aortic root to the distal ascending aorta and proximal arch (52,56).

Zingone (57) reported a significant reduction in postoperative neurologic complications after the routine introduction of EAU. Pathological findings at EAU guided changes in surgical strategies including the aortic cannulation and cross-clamp sites, the use of DHCA and off-pump techniques. Finally, pre-operative computed tomography (CT) of the chest (with or without contrast) is a valuable tool to fully characterize the degree of aortic atheromatous changes (2018 ESC/EACTS Guidelines Class IIa, Level of Evidence C) (30). Lee (58) reported a significant reduction in the rate of neurologic complications post elective cardiac procedures after the introduction of a pre-operative non contrast CT chest in high risk patients (3.04% pre-CT vs 0.73% post-CT, p=0.05), thanks to ad hoc changes in operative strategy. Similar results were described by Sandner (59): in 435 matched pairs of isolated CABG postoperative stroke was significantly lower in the preoperative CT cohort (0.92% vs 3.22%, p=0.017).

Once severe atheromatous changes of the ascending aorta are detected, a variety of surgical techniques have been employed to minimize the neurologic risk:

- aggressive aortic debridement or replacement under DHCA (55,60,61);
- imaging guided alternative cannulation, cross-clamping and proximal anastomosis sites away from atheroma and use of a modified aortic clamp (62-63);

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- complete avoidance of aortic manipulation ("anaortic" technique).

Early reports by Ribakove (55) described aortic debridement under DHCA via femoral cannulation in patients with grade V atheroma undergoing isolated CABG; alternatively debridement and patch repair of the ascending aorta has been reported by Robicsek (60) and Ott (61) to perform proximal anastomoses. In a series of 500 patients by Wareing (62) epiaortic ultrasound detected moderate to severe atheroma of the ascending aorta in 68 cases. In the majority of patients an alternative site for cannulation and clamping was sufficient to avoid overt neurologic complications; otherwise when clamping wasn't possible hypothermic fibrillation was employed and very occasionally the ascending aorta and proximal hemiarch needed replacement under DHCA (64,65).

A valid alternative to these aggressive strategies is complete avoidance of any aortic manipulation. Over the course of the last four decades "no-touch" techniques have evolved from pump-assisted with peripheral cannulation to totally anaortic off-pump grafting.

Mills and Suma (6,66) were among the first to describe and promote an "aortic no-touch technique" for management of the severely diseased ascending aorta during CABG. Although still utilizing distal arch or peripheral cannulation to accomplish low-flow hypothermic cardiac fibrillatory arrest, the authors successfully introduced the use of T or Y grafts off the internal mammary artery (IMA) or the right gastroepiploic artery to avoid manipulation of the ascending aorta (6). Variations of the "no-touch technique" were described by Holland (67) with the use of the innominate or carotid arteries as proximal inflow for coronary grafts and by Murphy (68) with the idea of a composite left IMA-saphenous vein extension graft to reach a distal marginal branch. Finally, Hendel and Thomson (69) implemented "no-touch" strategies with the adoption of femoral cannulation, fibrillation with venting and core cooling to 25degC and construction of Y-vein-grafts from the left IMA or extension grafts from the right IMA.

Avoiding both aortic manipulation and cardiopulmonary bypass adopting off-pump techniques offer further neurologic protection when intraoperative TEE shows extensive aortic atheroma (70-72). In a large series of consecutive isolated CABGs, Grossi et al (70) selectively performed OPCAB in patients with severe aortic disease detected by intraoperative TEE with a significant reduction of both in-hospital mortality (p=0.08) and perioperative stroke (p=0.01). Using propensity score matching Mishra (71) and Sharony (72) showed significant survival benefit (p<0.001 and p=0.01 respectively) and postoperative stroke reduction (p=0.05 and p=0.03 respectively) when off-pump*vs* on-pump coronary grafting was performed in patients with severe aortic atherosclerosis documented by TEE.

5. From reduction to complete avoidance of aortic manipulations: anaortic OPCAB

Surgical strategies that rely on any type of manipulation of the aorta (including its major branches) *or* on the use of CPB may ultimately fail to meaningly improve the rate of perioperative neurologic injury in patients with severe aortic atherosclerosis. Anaortic OPCAB techniques eliminate aortic handling through the use of Y, T or extension grafts (Figure 4) (73) and have been described as safe and effective in preventing neurologic complications (38). As reflected by Class 1B recommendation in the 2018 ECS/EACTS guidelines (30), solid evidence supports the concept of "aortic no-touch" (17-26, 74-80) in patients with ascending aortic atherosclerosis (Table 1).

In a landmark paper by Calafiore (25) the presence of any aortic manipulation rather than the use of CPB itself was identified as an independent predictor of cerebrovascular accidents, especially in patients with extra-coronary vasculopathy. Similar results were shown by Patel (22), Kim (23), Kapetanakis (24), Vallely (26) and Moss (17): anOPCAB is consistently associated with significant neurologic benefit compared to strategies involving any aortic manipulation either on-pump or off-pump. Finally, Albert (20) reported a postoperative stroke rate as low as 0.49% in a series of 4,485 anOPCABs; although the study wasn't randomized, a significant neurologic advantage of aortic no-touch was found especially for early stroke (0.09% *vs* 0.83%, p<0.0001). When comparing anOPCAB with the CABG arm of the SYNTAX trial a trend for lower stroke rate was found for anOPCAB at 1 year (0.8% *vs* 2.2%; p=0.07) (75); this became significant at 3-years (1.3% *vs* 3.4%; p=0.032) (78). Interestingly when anOPCAB is compared to the PCI arm no

significant differences in terms of neurologic outcome is found at 1 and 3 years (1.3 *vs* 2.0%; p=0.347 and 0.8% *vs* 0.6%l p=NS), showing that surgical technique rather than the revascularization strategy affected the stroke rate. Similar results came from a network meta-analysis by Zhao (79): no difference in 30-day stroke risk when comparing anOPCAB with PCI (OR 0.92, 95% CI 0.47–1.78). The authors concluded that anOPCAB should be considered for reducing stroke risk in patient groups known to benefit most from surgical revascularization compared with PCI.

When looking solely at off-pump CABG performed with or without aortic manipulation, anOPCAB shows superior neurologic outcome both in a single center series (0.2% vs 2.2%, p=0.01) (21) and in two meta-analyses by Misfeld (80) (0.5% *vs* 1.4%; odds ratio, 0.46; 95% confidence interval, 0.29–0.72; I^2=0.8%; p=0.0008) and Pawliszak (18) (0.36% *vs* 1.28%; risk ratio 95% CI: 0.41 (0.27-0.61); p<0.01; I^2=0%).

Finally, a recent large network meta-analysis by Zhao (19) compared post-operative outcomes between all CABG techniques; 13 studies were included with a total of 37,720 patients (Figure 5). AnOPCAB was the most effective treatment for decreasing the risk of post-operative stroke (-78% vs. CABG, 95% CI 0.14 to 0.33; -66% vs. side-clamp OPCAB, 95% CI: 0.22 to 0.52; -52% vs. OPCAB-proximal anastomotic device, 95% CI: 0.27 to 0.86), mortality, renal failure, bleeding complications and atrial fibrillation.

6. Conclusion

Adverse neurologic events post coronary revascularization represent a devastating outcome to a small but indeed relevant number of individuals both in the short and long term. Coronary bypass surgery performed on an arrested heart relies on considerable aortic instrumentation associated with significant atheroembolic risk. Surgical techniques aimed at the avoidance of any aortic manipulation are safe and effective and significantly reduce the risk of intraoperative stroke.

Authors contribution:

FR (concept/design/drafting)

MS (drafting/critical revision)

RJB, MFL, JDP, AMC (critical revision)

MPV (critical revision/final approval)

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Figures legend

Figure 1. Sagittal view (A) and 3-D reconstruction (B) of a CT chest showing extensive ascending aortic calcifications in a 71 year-old lady admitted with unstable angina; coronary angiogram showed severe distal left main disease.

Figure 2. Geometric characteristics of calcified particles on the macroscopic scale are demonstrated. Deposits were collected from the ascending aorta following repeated aortic cross-clamping (ACC). A baseline recording prior to clamping is denoted by zero on the horizontal axis. The curve represent embolic load from multiplying the number of particles with particle area produced at ACC 1 to 10. From Boivie et al (48)

Figure 3. Intraoperative TOE showing grade IV (>5mm) and grade 5 (mobile) aortic arch atheroma of a 72 year-old man undergoing combined right carotid endarterectomy and anaortic OPCAB.

Figure 4. Configuration of grafts to achieve complete revascularisation using a left internal mammary artery to left anterior descending artery, and right internal mammary artery-radial artery tandem graft to lateral and inferior walls. From Ramponi et al (73)

Figure 5 Network meta-analysis comparing anOPCAB, OPCAB with proximal anastomotic device, OPCAB with a partial-occlusion clamp, and traditional on-pump CABG with aortic cross-clamping. Taken from Zhao et al (19).

Hosted file

Ramponi_JCS_Table_1.pdf available at https://authorea.com/users/376303/articles/493295-towards-stroke-free-coronary-surgery-the-role-of-the-anaortic-off-pump-bypass-technique

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

A

Stroke

OR (95% CI)

	OR (95% CI)
anOPCABG vs CABG	0.22 (0.15 – 0.33) / 0.22 (0.14 – 0.33)
anOPCABG vs OPCABG-PC	0.35 (0.22 – 0.52) / 0.34 (0.22 – 0.52)
OPCABG-HS vs CABG	0.45 (0.30 – 0.66) / 0.45 (0.28 – 0.69)
anOPCABG vs OPCABG-HS	0.50 (0.29 – 0.85) / 0.48 (0.27 – 0.86)
OPCABG-PC vs CABG	0.65 (0.52 – 0.80) / 0.64 (0.48 – 0.83)
OPCABG-HS vs OPCABG-PC	0.70 (0.46 – 1.03) / 0.71 (0.44 – 1.11)

Heterogeneity
(Inform.) = 0.1259
95% CrI (0.03973 – 0.3505)

0.1   1   10
Favors Treatment 1   Favors Treatment 2

B

Mortality

OR (95% CI)

	OR (95% CI)
anOPCABG vs CABG	0.51 (0.37 – 0.68) / 0.50 (0.35 – 0.70)
anOPCABG vs OPCABG-HS	0.60 (0.39 – 0.90) / 0.60 (0.38 – 0.94)
OPCABG-PC vs CABG	0.64 (0.51 – 0.79) / 0.63 (0.48 – 0.81)
OPCABG-PC vs OPCABG-HS	0.75 (0.54 – 1.07) / 0.75 (0.50 – 1.12)
anOPCABG vs OPCABG-PC	0.79 (0.57 – 1.08) / 0.80 (0.55 – 1.13)
OPCABG-HS vs CABG	0.85 (0.60 – 1.17) / 0.84 (0.57 – 1.22)

Heterogeneity
(Inform.) = 0.1227
95% CrI (0.0415 – 0.2904)

0.1   1   10
Favors Treatment 1   Favors Treatment 2

C

Myocardial infarction

OR (95% CI)

	OR (95% CI)
OPCABG-HS vs CABG	0.67 (0.41 – 1.05) / 0.71 (0.40 – 1.27)
anOPCABG vs CABG	0.72 (0.46 – 1.11) / 0.73 (0.44 – 1.18)
OPCABG-HS vs OPCABG-PC	0.79 (0.47 – 1.29) / 0.82 (0.45 – 0.50)
OPCABG-PC vs CABG	0.84 (0.60 – 1.17) / 0.84 (0.51 – 1.37)
anOPCABG vs OPCABG-PC	0.86 (0.55 – 1.32) / 0.86 (0.57 – 1.32)
OPCABG-HS vs anOPCABG	0.92 (0.51 – 1.66) / 0.97 (0.50 – 1.91)

Heterogeneity
(Inform.) = 0.2051
95% CrI (0.05192 – 0.5432)

0.1   1   10
Favors Treatment 1   Favors Treatment 2

D

Renal failure

OR (95% CI)

	OR (95% CI)
anOPCABG vs CABG	0.48 (0.34 – 0.66) / 0.47 (0.31 – 0.68)
OPCABG-PC vs CABG	0.59 (0.47 – 0.75) / 0.59 (0.41 – 0.84)
anOPCABG vs OPCABG-HS	0.65 (0.43 – 0.98) / 0.64 (0.39 – 1.05)
OPCABG-HS vs CABG	0.74 (0.52 – 1.04) / 0.73 (0.45 – 1.14)
OPCABG-PC vs OPCABG-HS	0.80 (0.58 – 1.12) / 0.79 (0.53 – 1.13)
anOPCABG vs OPCABG-PC	0.81 (0.59 – 1.09) / 0.81 (0.52 – 1.28)

Heterogeneity
(Inform.) = 0.1254
95% CrI (0.04089 – 0.3512)

0.1   1   10
Favors Treatment 1   Favors Treatment 2

E

Bleeding

OR (95% CI)

	OR (95% CI)
anOPCABG vs OPCABG-HS	0.52 (0.34 – 0.81) / 0.52 (0.31 – 0.87)
anOPCABG vs CABG	0.64 (0.44 – 0.91) / 0.64 (0.42 – 0.95)
OPCABG-PC vs OPCABG-HS	0.68 (0.49 – 0.96) / 0.67 (0.44 – 1.04)
anOPCABG vs OPCABG-PC	0.77 (0.54 – 1.07) / 0.78 (0.52 – 1.13)
CABG vs OPCABG-HS	0.82 (0.57 – 1.19) / 0.88 (0.60 – 1.10)
OPCABG-PC vs CABG	0.83 (0.66 – 1.04) / 0.82 (0.52 – 1.30)

Heterogeneity
(Inform.) = 0.1143
95% CrI (0.03745 – 0.3146)

0.1   1   10
Favors Treatment 1   Favors Treatment 2

F

Atrial fibrillation

OR (95% CI)

	OR (95% CI)
anOPCABG vs OPCABG-HS	0.66 (0.56 – 0.78) / 0.66 (0.49 – 0.89)
anOPCABG vs CABG	0.72 (0.64 – 0.82) / 0.71 (0.55 – 0.87)
anOPCABG vs OPCABG-PC	0.79 (0.70 – 0.89) / 0.80 (0.68 – 0.97)
OPCABG-PC vs OPCABG-HS	0.83 (0.73 – 0.96) / 0.82 (0.60 – 1.09)
CABG vs OPCABG-HS	0.91 (0.79 – 1.09) / 0.88 (0.69 – 1.06)
OPCABG-PC vs CABG	0.91 (0.84 – 0.99) / 0.94 (0.70 – 1.29)

Heterogeneity
(Inform.) = 0.1187
95% CrI (0.04221 – 0.2904)

0.1   1   10
Favors Treatment 1   Favors Treatment 2

—◆— Fixed Effects   —◆— Random Effects (Informative Prior)

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.

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