

Current Readings on Outcomes After Off-Pump Coronary Artery Bypass Grafting

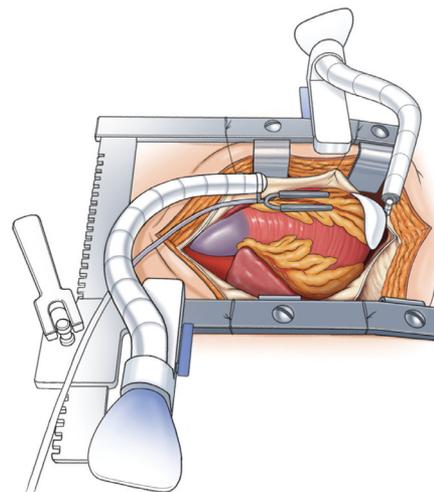


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Off-pump coronary artery bypass grafting (CABG) gained popularity in the 1990s through early 2000s as surgeons sought to mitigate the purported adverse effects of cardiopulmonary bypass and reduce the risk of neurologic events from aortic manipulation. Since then, results of several large randomized controlled trials and meta-analyses have failed to demonstrate an advantage of off-pump CABG over traditional on-pump CABG and have even raised concerns about potential suboptimal outcomes. The modern debate about off- vs on-pump CABG centers around long-term outcomes, the role of surgeon experience, identification of specific patient populations for which off-pump CABG is most appropriate, and identification of novel techniques and technologies to improve long-term outcomes. We review the key findings of 5 contemporary papers that address these issues and provide a current perspective on the status of off-pump CABG.

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Keywords: Coronary artery bypass grafting, On-pump surgery, Off-pump surgery, Outcomes



Off-pump coronary artery bypass grafting with myocardial stabilizer.

Central Message

Off-pump coronary artery bypass grafting (CABG) is appropriate in a specific subset of patients when performed by experienced surgeons to ensure good short- and long-term outcomes. Off-pump CABG with minimal aortic manipulation is a promising strategy.

INTRODUCTION

Coronary artery disease remains the leading cause of death worldwide, and coronary artery bypass grafting (CABG) remains the standard of care for treatment of triple-vessel and left main coronary artery disease with significant atherosclerotic burden.^{1,2}

As the patient population undergoing CABG became older, with increasing comorbidities, solutions were sought to mitigate the purported adverse effects of cardiopulmonary bypass and reduce the risk of neurologic events from aortic manipulation and aortic clamping. Thus, the 1990s saw an increasing interest in off-pump CABG; in the United States, its use peaked in 2002, when it constituted approximately 23% of surgical revascularization procedures.³ Although early studies appeared to show better outcomes, especially for high-risk patients, more recent studies revealed mixed results of off-pump CABG compared with conventional on-pump CABG. This stirred much controversy about the relevance of off-pump CABG,

particularly given its technical challenges, and led to a predictable decline in its use.³

The ROOBY (Randomized On/Off Bypass) trial of 2203 patients at 18 veterans affairs centers showed that at 1 year, those in the off-pump group had worse composite outcomes of mortality and major complications, poorer graft patency, and greater incidence of incomplete revascularization than the on-pump group.⁴ However, off-pump CABG was vindicated in 2 other randomized controlled trials (RCTs)—the CORONARY (CABG Off or On Pump Revascularization) study⁵ and GOPCABE (German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients).⁶ Unlike ROOBY, CORONARY and GOPCABE found no difference in mortality or major complications between on- and off-pump CABG, but did show an increase in very early repeat revascularization.^{5,6} The difference in outcomes between these trials has been largely attributed to differences in the level of experience of surgeons performing off-pump CABG. The median number of off-pump cases performed by surgeons (who in many cases supervised training residents who performed the

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operations) in the ROOBY trial was only 52, a significantly lower threshold than in CORONARY and GOPCABE. Experience is important given the technical nuances and steep learning curve associated with off-pump CABG, and studies have shown a positive volume-outcome relationship in its use.⁷

The modern debate surrounding off- vs on-pump CABG centers around long-term outcomes, the role of surgeon experience, identification of specific patient populations for which off-pump CABG is most appropriate, and identification of novel techniques and technologies to improve patient outcomes. Here, we examine 5 contemporary papers that address these issues and opine on the current status of off-pump CABG.

FIVE-YEAR OUTCOMES AFTER ON-PUMP AND OFF-PUMP CORONARY ARTERY BYPASS (ROOBY FOLLOW-UP STUDY)

Shroyer et al extend the original ROOBY study by examining 5-year clinical outcomes of the 2203 patients from the original trial.⁸ Primary outcomes were all-cause mortality and major adverse cardiovascular event (MACE: composite of death, repeat revascularization, and nonfatal myocardial infarction [MI]). Secondary outcomes included death from cardiac causes, repeat revascularization, and nonfatal MI, as well as a composite of these 3.

At 5 years, the off-pump group had higher mortality (15.2% vs 11.9%, $P = 0.02$) and a higher prevalence of MACE (31% vs 27%, $P = 0.046$; Fig. 1). None of the secondary outcomes in the follow-up study met the specified threshold of $P = 0.01$ for statistical significance, and there was no difference in the prevalence of a composite outcome when only cardiac causes of death were included instead of all-cause mortality. Importantly, after removal of patients who crossed over from off-pump to on-pump CABG, there was no difference in 5-year mortality (13.5% vs 11.0%, $P = 0.09$) or MACE (29.1% vs 26.5%, $P = 0.21$) between the 2 groups.

This follow-up study of the first large and well-designed multicenter RCT of on- vs off-pump CABG showed higher all-cause mortality and MACE in the off-pump group 5 years after surgery. Incomplete revascularization is likely the underlying cause of these findings. Surgeon experience may also be a factor. Indeed, after removal of cases in which off-pump CABG was converted to on-pump, there no longer remained a statistically significant difference in all-cause mortality or MACE at 5 years. The role of surgeon experience is corroborated by findings of similar 5-year outcomes between on- and off-pump CABG in the CORONARY⁹ and GOPCABE¹⁰ trials.

ROOBY was confounded by the relatively homogeneous veteran population, limiting extrapolation to the general population and females.

Key Points:

1. Off-pump CABG in a veteran population was associated with higher all-cause mortality (15.2% vs 11.9%, $P = 0.02$) and MACE (31% vs 27%, $P = 0.046$) at 5 years. Outcomes were not statistically significant after removal of off- to on-pump conversions.

2. Surgeon experience may play a role in long-term outcomes after off-pump CABG. The prevalence of conversions from off-pump to on-pump was high (12.4%), and prestudy off-pump case experience was low (median, 50 cases).

FIVE-YEAR OUTCOMES AFTER OFF-PUMP OR ON-PUMP CABG

Lamy et al report the 5-year outcomes of the CORONARY trial, which enrolled 4752 patients from 19 countries between November 2006 and October 2011.⁹ At a mean of 4.8 years after randomization, there was no significant difference in the second coprimary outcome of death, stroke, MI, renal failure, or repeat coronary revascularization between the off- and on-pump groups (23.1% vs 23.6%, hazard ratio [HR] 0.98 [0.87–1.10]; $P = 0.72$), and no differences between groups in the prevalence of individual components of this composite outcome (Table 1). Percutaneous coronary intervention (PCI) due to graft failure matched the occurrence of PCI performed for new lesions. There was also no difference in the mean cost per patient (\$15,107 for off-pump and \$14,992 for on-pump). Both groups experienced a small decline in quality of life at 30 days, but had a sharp increase by the end of the trial; there were no significant differences in these scores between groups at any point in the trial. Both groups experienced similar need for repeat angiography, mostly due to ischemic symptoms or suspected MI. Prevalence of recurrent angina was also similar.

Unlike ROOBY,⁸ this larger and expertise-based multicenter trial found no significant difference between off- and on-pump CABG in patient survival and occurrence of major morbidities at 5 years. These findings are corroborated by the recently reported 5-year results of the GOPCABE trial.¹⁰ However, similar to ROOBY, no significant differences were found in cost between the 2 procedures.¹¹ In addition, CORONARY demonstrated similar effects on quality of life at 5 years between the 2 revascularization strategies.

Key Point:

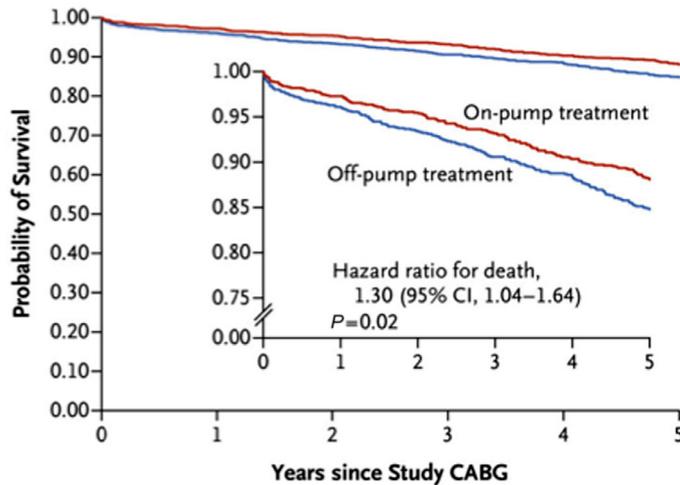
1. Among experienced surgeons, 5-year outcomes did not differ between on- and off-pump CABG.

OFF- VS ON-PUMP CORONARY SURGERY AND THE EFFECT OF FOLLOW-UP LENGTH AND SURGEONS' EXPERIENCE: A META-ANALYSIS

This systematic review provides the most complete and rigorous evaluation of differences in early and late outcomes between off- and on-pump CABG and further explores whether length of follow-up, surgeon experience with off-pump CABG, and the degree of incomplete revascularization affect outcomes.¹²

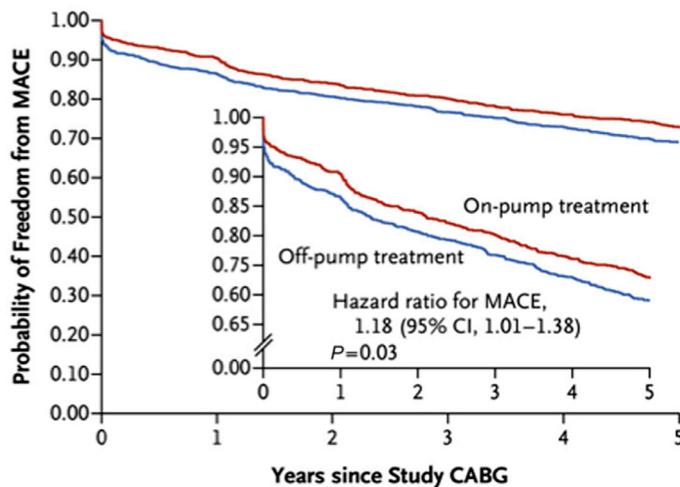
The MEDLINE review included all RCTs up to August 2017 that compared off- and on-pump CABG (Fig. 2). Patients' risk profile, mean follow-up, and operative characteristics (including surgeon experience) were abstracted from the sampled studies. The primary outcome studied was all-cause mortality

A Survival



No. at Risk	0	1	2	3	4	5
On-pump treatment	1099	1069	1049	1024	993	968
Off-pump treatment	1104	1061	1031	1000	976	936

B Freedom from MACE



No. at Risk	0	1	2	3	4	5
On-pump treatment	1099	994	923	881	836	801
Off-pump treatment	1104	955	890	847	805	762

Figure 1. Kaplan-Meier estimates of survival and MACE (composite of death, repeat revascularization, and nonfatal MI at 5 years after surgery). (Adapted with permission from Shroyer et al.⁸)

at the longest reported follow-up. Secondary outcomes were operative mortality, perioperative stroke, perioperative MI, and late repeated revascularization.

Subgroup analyses investigated the effect of length of follow-up (studies with <3 years of follow-up vs studies with ≥3 years), surgeon experience (measured by conversion from off- to on-pump, ≤3% vs >3% but <10%, vs ≥10%), and relative

occurrence of incomplete revascularization on the primary and secondary outcomes.

The selected trials reported on 20,627 patients relatively well balanced between on- and off-pump CABG. The studies were published from 1995 to 2017, and the sample size ranged from 9 to 2375 patients. At the average weighted follow-up time of 3.7 years, overall mortality was 12.3% in the off-pump

Table 1. Outcomes at 5 Y After Off-Pump and On-Pump CABG. (Adapted With Permission From Lamy et al⁹)

Outcome	Off-Pump Group (N = 2375)	On-Pump Group (N = 2377)	Hazard Ratio (95% CI)	P Value
Second coprimary outcome—no. (%) [*]	548 (23.1)	560 (23.6)	0.98 (0.87–1.10)	0.72
Death	346 (14.6)	322 (13.5)	1.08 (0.93–1.26)	0.30
Myocardial infarction	178 (7.5)	194 (8.2)	0.92 (0.75–1.13)	0.41
Stroke	55 (2.3)	66 (2.8)	0.83 (0.58–1.19)	0.32
New renal failure requiring dialysis	40 (1.7)	45 (1.9)	0.89 (0.58–1.37)	0.60
Repeat revascularization [†]	66 (2.8)	55 (2.3)	1.21 (0.85–1.73)	0.29
PCI	59 (2.5)	52 (2.2)	1.15 (0.79–1.66)	0.48
CABG	9 (0.4)	4 (0.2)	2.27 (0.70–7.38)	0.17
Nonprespecified outcomes—no. (%)				
Cardiovascular death [‡]	237 (10.0)	230 (9.7)	1.04 (0.87–1.24)	0.69
Repeat coronary angiography	125 (5.3)	114 (4.8)	1.11 (0.86–1.43)	0.43
Recurrent angina	41 (1.7)	39 (1.6)	1.05 (0.68–1.63)	0.81
Primary outcome in per-protocol population—no./total no. (%) [§]	487/2148 (22.7)	499/2182 (22.9)	0.99 (0.87–1.12)	0.86

^{*}The second coprimary outcome was a composite of death, nonfatal stroke, nonfatal myocardial infarction, new renal failure requiring dialysis, and repeat revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]).

[†]Some patients had CABG and a PCI.

[‡]All deaths in the first 30 d were considered to be cardiovascular deaths.

[§]The per-protocol population included patients who underwent the randomly assigned procedure (ie, without crossing over to the other procedure).

Long term mortality

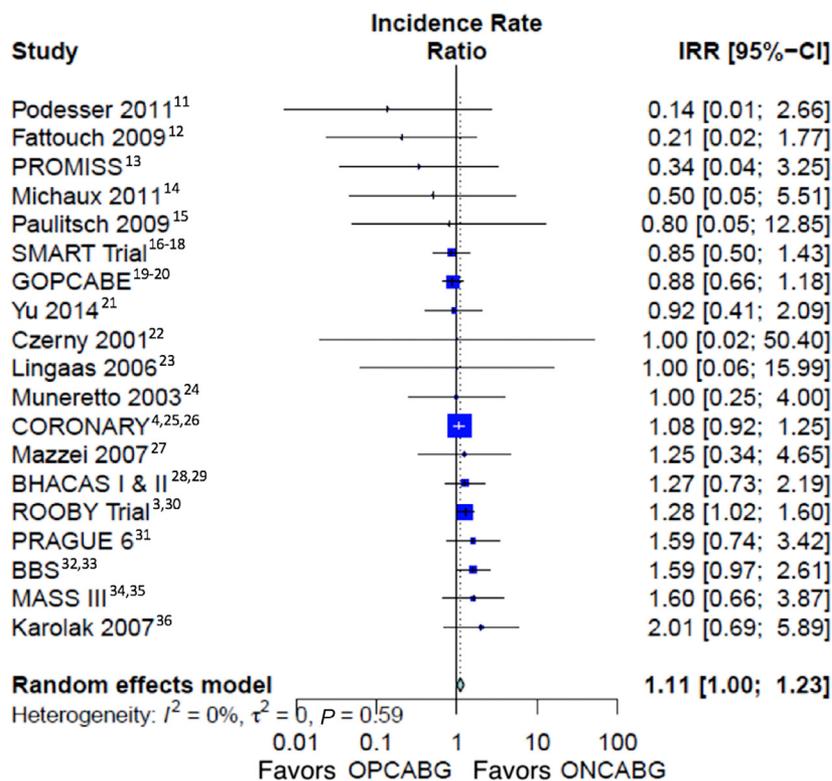


Figure 2. Long-term mortality after off-pump CABG. CI, confidence interval; IRR, incidence rate ratio; ONCABG, on-pump coronary artery bypass grafting; OPCABG, off-pump coronary artery bypass grafting. (Adapted with permission from Gaudino et al.¹²)

group vs 11.1% in the on-pump group ($P = 0.05$). Late mortality was higher in the off-pump group in studies with follow-up ≥ 3 years (incidence risk ratio, 1.16; 95% confidence interval [CI] 1.01–1.34) and no different in studies with < 3 years of

follow-up. Among studies with crossover from off- to on-pump $\geq 10\%$, late mortality increased (incidence risk ratio 1.33; 95% CI 1.04–1.62). There was a positive correlation between the proportion of patients who crossed over from off-

Table 2. Long-Term Outcomes Following Off-Pump or On-Pump CABG. (Adapted With Permission From Chikwe et al¹⁴)

	10-Y Cumulative Event Rate % (95% CI)		Adjusted Hazard Ratio (95% CI)
	Off-Pump (n = 6950)	On-Pump (n = 15,295)	
Mortality	33.4 (31.9–34.9)	29.6 (28.7–30.7)	1.11 (1.04–1.18)
Myocardial infarction	7.5 (6.8–8.4)	7.3 (6.8–7.9)	1.10 (0.95–1.26)
Stroke	5.6 (4.9–6.3)	5.7 (5.2–6.2)	0.92 (0.81–1.06)
Repeat revascularization	15.4 (14.4–16.4)	14.0 (13.3–14.7)	1.17 (1.01–1.37)
PCI	14.7 (13.7–15.7)	13.3 (12.7–14.0)	1.18 (1.01–1.39)
CABG	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.96 (0.68–1.38)
New dialysis	4.7 (4.1–5.3)	5.0 (4.6–5.5)	0.88 (0.73–1.06)

CABG, coronary artery bypass grafting; CI, confidence interval; PCI, percutaneous coronary intervention.

Presents unadjusted cumulative event rates among the off-pump and on-pump cohorts, as calculated by Kaplan-Meier analysis (for the outcome of mortality), or competing risk analysis (for the outcomes of myocardial infarction, stroke, repeat revascularization, new renal failure requiring dialysis) with the competing risk of death. Hazard ratios are risk adjusted and were calculated by Cox proportional hazard model, controlling for all patient covariates, with patients clustered within surgeon and hospital. New renal failure requiring dialysis analysis excludes patients with preoperative dialysis requirement (213 off-pump patients and 405 on-pump patients).

to on-pump CABG and the prevalence of incomplete revascularization in the off-pump arm ($P = 0.03$).

This study found that off-pump CABG was not associated with a decrease in operative mortality, but there was a significant increase in mortality risk at later follow-up. Further, it found that a threshold of 10% crossover is associated with lower survival after off-pump CABG. Importantly, there was a strong association between crossovers from off- to on-pump CABG and completeness of revascularization. To put it in simple terms, inexperience, conversion to on-pump CABG, and incompleteness of revascularization go hand in hand and have detrimental long-term consequences after off-pump CABG. These findings are notwithstanding the perioperative detriment of inexperience and conversions that has been well documented.¹³

Key Points:

1. Late mortality is higher after off-pump CABG.
2. Only studies with conversion from off- to on-pump CABG of $\geq 10\%$ were associated with a higher mortality.
3. Surgeon experience and duration of follow-up are important considerations when comparing outcomes between on- and off-pump strategies.

LONG-TERM OUTCOMES AFTER OFF-PUMP VS ON-PUMP CABG BY EXPERIENCED SURGEONS

Chikwe et al performed a retrospective cohort analysis of off- and on-pump CABG data from January 1, 2005, to December 31, 2011, in the New Jersey Open Heart Surgery Registry, a state-mandated registry that captures data from all CABG procedures in the state.¹⁴

Primary analysis included 15,295 patients who underwent on-pump CABG and 6950 who underwent off-pump CABG (Table 2). The study used Kaplan-Meier analysis and Cox proportional hazard models to evaluate a primary endpoint of

all-cause mortality and secondary endpoints of stroke, MI, repeat revascularization, and renal failure requiring dialysis. It excluded patients who had previous cardiac surgery, were hemodynamically unstable, or required emergency intervention. Importantly, patients were included only if their surgeon had performed more than 100 cases of the relevant procedure, and an instrumental variables approach was used to assess outcomes for surgeons who had a preference for one approach vs the other. The study was adjusted for age, sex, race, insurance status, body mass index, comorbidities, ejection fraction, and coronary anatomy.

Off-pump CABG was associated with a higher risk of death at 10 years than on-pump CABG (33.4% vs 29.6%; HR 1.11; $P = 0.002$). This held true in a propensity score-matched analysis after removing excluded observations for lower surgeon experience, and in subgroup analyses of older patients, low ejection fraction, and triple-vessel disease. Off-pump CABG was associated with higher prevalence of incomplete revascularization (15.7% vs 8.8%, $P < 0.001$), which in turn was associated with increased long-term mortality (HR 1.15, $P = 0.006$). Off-pump CABG was also associated with higher prevalence of repeat revascularization at 10 years (15.4% vs 14.0%, $P = 0.048$), but similar occurrence of MI, stroke, and new renal failure requiring dialysis. Analysis accounting for surgeon preference also showed that off-pump CABG was still associated with increased long-term mortality.

Among the plethora of published reports regarding on- vs off-pump CABG, this paper stands out because of the sheer volume of patients from a mandatory registry and quality of the risk-adjusted analysis. In addition to comorbidities, the authors adjusted for surgical approach conversions, surgical experience (>100 on- or off-pump procedures), and surgical preference (use of off- vs on-pump procedures used by surgeons during the year preceding the index operation). The findings will undoubtedly be challenged by off-pump enthusiasts who will point out the inherent biases that cannot be fully adjusted for using administrative databases.

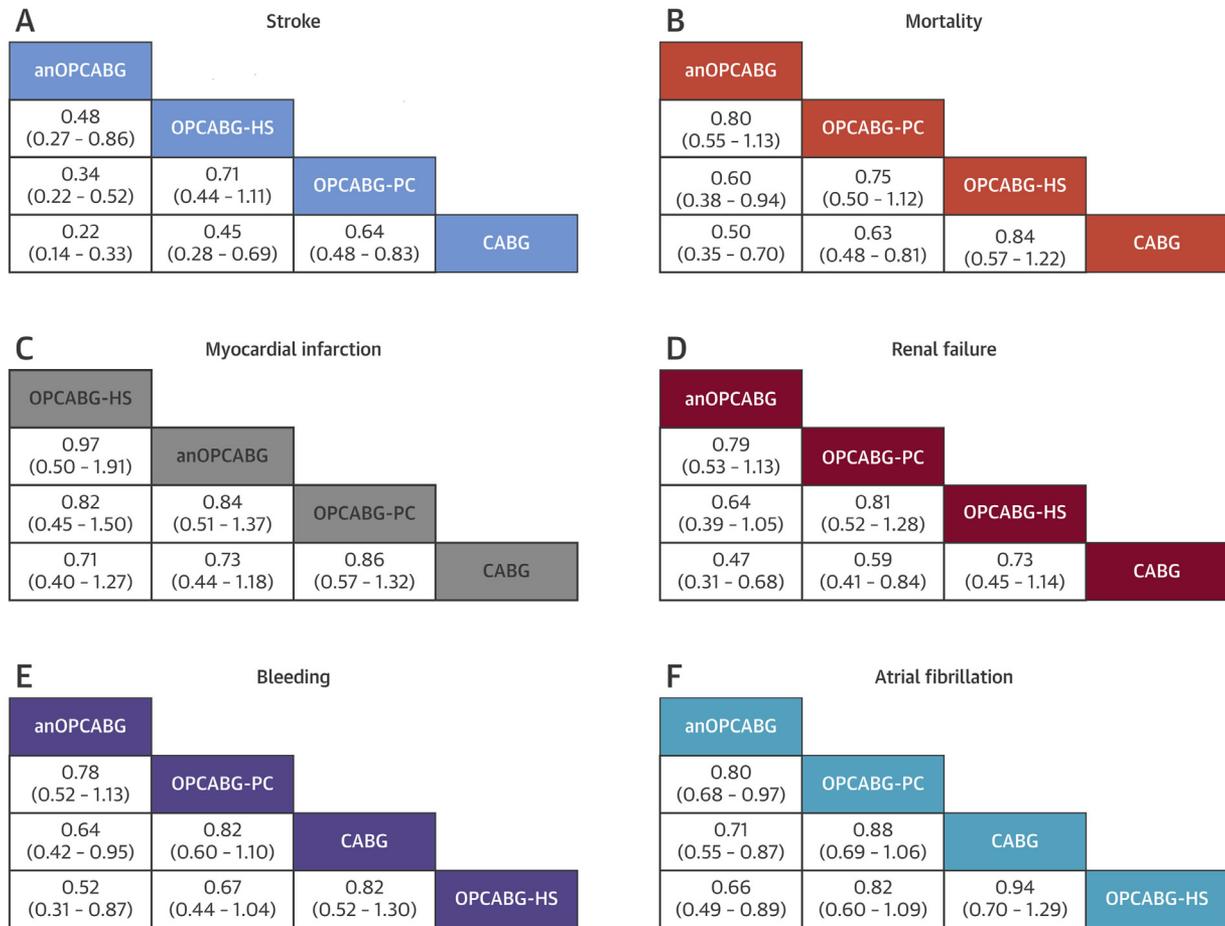


Figure 3. League tables for CABG with and without manipulation of the aorta. Outcomes shown for (A) stroke, (B) mortality, (C) MI, (D) renal failure, (E) bleeding complications, and (F) atrial fibrillation following CABG with and without manipulation of the aorta (OR and 95% CI). OR <1 means that the treatment in top left is better. (Adapted with permission from Zhao et al.¹⁵)

Key Point:

1. At a population level, on-pump CABG may be the most appropriate choice of revascularization for most patients.

CABG WITH AND WITHOUT MANIPULATION OF THE ASCENDING AORTA: A NETWORK META-ANALYSIS

Off-pump CABG is typically performed with an aortic side-clamp to complete proximal anastomoses. As newer devices and techniques have been developed to minimize aortic manipulation, this network meta-analysis evaluated postoperative stroke, mortality, and morbidity after CABG with varying degrees of aortic manipulation.¹⁵

Thirteen relevant studies were included for a total of 37,720 patients; 7098 received anaortic off-pump CABG (anOPCABG), 12,512 received partial-clamp off-pump CABG (pcOPCABG), 2997 received off-pump CABG with the Heartstring device (hsOPCABG), and 15,113 received conventional on-pump CABG. Patients undergoing anOPCABG had more prior strokes than those receiving partial-clamp or conventional

CABG, and had fewer diseased vessels and a slightly lower average EuroSCORE. Otherwise, comorbidities were similar across all comparison groups.

The elegant diagram depiction (Fig. 3) demonstrates that anOPCABG was associated with lower odds of stroke at 30 days than conventional CABG (odds ratio [OR] 0.22, 95% CI 0.14–0.33), pcOPCABG (OR 0.34, 95% CI 0.22–0.52), or hsOPCABG (OR 0.48, 95% CI 0.27–0.86), and hsOPCABG and pcOPCABG were both associated with reduced odds of stroke compared with conventional CABG (OR 0.45, 95% CI 0.28–0.69 and OR 0.64, 95% CI 0.48–0.83, respectively). In addition, anOPCABG was associated with the lowest odds of mortality, renal failure, bleeding, and atrial fibrillation among the evaluated strategies.

This is the first meta-analysis comparing clinical outcomes after CABG with various degrees of aortic manipulation. Large RCTs have not shown a similar reduction in postoperative strokes, but these studies have not accounted for varying levels of aortic manipulation. Given that the majority of surgeons performing off-pump CABG use a partial clamp for proximal anastomoses, this could well obfuscate the benefits of off-pump

CABG for perioperative stroke reduction. Further, use of an aortic technique implies greater use of arterial grafts in revascularization. This is particularly important given the durability and long-term survival advantage afforded by arterial conduits.

This study is susceptible to bias given its nonrandomized structure. Although the off-pump group had a lower average number of diseased vessels and a lower proportion of triple-vessel disease, the results are telling given the improved outcomes despite the higher occurrence of prior stroke in the anaortic and Heartstring off-pump CABG groups.

Key Points:

1. Anaortic off-pump CABG offers an incremental advantage over off-pump CABG.
2. Lack of differentiation for level of aortic manipulation in the existing RCTs evaluating off-pump CABG may contribute to poorer outcomes associated with this technique.

COMMENT

In steering the debate regarding use of on- vs off-pump CABG, 3 important considerations emerge:

1. Off-pump CABG can be beneficial in high-risk subgroups not typically captured in trials.
2. Potential benefits realized in the perioperative period are primarily limited to softer clinical endpoints (eg, perioperative bleeding, atrial fibrillation) and not to mortality and major complications.
3. Surgical experience, skill, and preference are important in strategy (on- vs off-pump) selection and affect short- and long-term outcomes.

The 5-year results from the 3 largest RCTs—ROOBY, CORONARY, and GOPCABE—provide insight into the outcomes of off-pump CABG, ranging across the spectrum of lower to higher risk patients and surgical expertise.^{4–6} The bottom line is that off-pump CABG may be associated with diminished long-term survival, particularly when performed by surgeons who do not qualify as off-pump CABG experts. Concerns about intraoperative conversions and incompleteness of revascularization are well founded.¹² CORONARY and GOPCABE demonstrated a mitigating effect of surgical expertise, with equivalent 5-year outcomes between on- and off-pump CABG, but this assurance was not reproduced by the Chikwe et al large “real-life” study.¹⁴ Surgical expertise, however, is a nebulous variable that is hard to measure. A good off-pump surgeon is likely to be a high-volume off-pump surgeon, not necessarily vice versa.

A meta-analysis of RCTs demonstrated an important relationship between patient risk profile and benefits of off-pump surgery.¹⁶ In addition, an analysis of The Society of Thoracic Surgeons national database from 1997 to 2007 showed significantly lower odds of early mortality for patients undergoing

off-pump operations in the third and fourth highest risk quartiles.¹⁷ Current expert consensus associates off-pump CABG with reduced stroke, atrial fibrillation, and renal failure in the short-term perioperative period, but cautions about suboptimal long-term results.¹⁸ Incomplete revascularization, which has been shown to be a risk factor for long-term mortality,^{18,19} is more prevalent in off-pump cases.

Another important consideration in the differing outcomes between off- and on-pump CABG is the heterogeneity in off-pump techniques. Zhao et al describe outcomes after CABG associated with varying levels of aortic manipulation.¹⁵ While most off-pump CABG surgeons use a partial clamp technique, use of anaortic off-pump CABG is associated with reduced occurrence of postoperative stroke, even among patients with prior stroke, while still avoiding the harmful effects of cardiopulmonary bypass and thus reducing the risk of short-term mortality, renal failure, atrial fibrillation, and bleeding, and shortening the length of ICU stay. Moreover, use of anaortic technique implies greater use of arterial grafts in revascularization; this is significant, because the ROOBY trial has shown that reduced graft patency in off-pump CABG is largely attributable to lower saphenous vein graft patency.⁴

In summary, at a population level, off-pump CABG does not confer its anticipated benefits on the average cardiac surgical patient and may even have deleterious effects on long-term survival. However, it is a viable option for higher risk patients who could benefit from the short-term reduction in morbidity and mortality, particularly in the hands of surgeons who qualify as off-pump experts. Moving forward, off-pump CABG with minimal aortic manipulation, particularly in conjunction with multiarterial grafting, may prove to be the most valuable advancement in off-pump surgery.

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