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Author/s:

Gaudino, M;Angelini, GD;Antoniades, C;Bakaeen, F;Benedetto, U;Calafiore, AM;Franco, AD;Mauro, MD;Fremes, SE;Girardi, LN;Glineur, D;Grau, J;He, GW;Patrono, C;Puskas, JD;Ruel, M;Schwann, TA;Tam, DY;Tatoulis, J;Tranbaugh, R;Vallely, M;Zenati, MA;Mack, M;Taggart, DP

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Off-Pump Coronary Artery Bypass Grafting: 30 Years of Debate

Mario Gaudino, MD; Gianni D. Angelini, MD; Charalambos Antoniades, MD; Faisal Bakaeen, MD; Umberto Benedetto, PhD; Antonio M. Calafiore, MD; Antonino Di Franco, MD; Michele Di Mauro, MD; Stephen E. Fremes, MD; Leonard N. Girardi, MD; David Glineur, MD; Juan Grau, MD; Guo-Wei He, MD; Carlo Patrono, MD; John D. Puskas, MD; Marc Ruel, MD, MPH; Thomas A. Schwann, MD; Derrick Y. Tam, MD; James Tatoulis, MD; Robert Tranbaugh, MD; Michael Vallely, MD; Marco A. Zenati, MD; Michael Mack, MD; David P. Taggart, MD; Arterial Grafting International Consortium (ATLANTIC) Alliance

Off-pump coronary artery bypass surgery (OPCAB) has been performed for >30 years.

The promotion of OPCAB was based on its potential benefits over some of the limitations of traditional on-pump coronary artery bypass surgery (ONCAB) by avoiding the trauma of cardiopulmonary bypass (CPB) and by minimizing aortic manipulation. As such, reductions in early mortality and perioperative neurological events, renal failure, blood product transfusions, and hospital length of stay were expected according to the OPCAB proponents. In contrast, critics of OPCAB remain concerned about incomplete and/or poorer quality coronary revascularization with a potential increase in the need for repeat revascularization and late mortality.

Despite 3 decades of debate, 115 randomized trials, and >60 meta-analyses comparing on- and off-pump coronary artery bypass grafting (CABG), controversy on both the role of and indications for OPCAB remains vigorous.

In this review, we provide a comprehensive update of the evidence for the differences in the biological effects of off- and on-pump surgery and the comparison of the clinical and angiographic results of the 2 techniques. Furthermore, we critically address the relevant technical aspects of OPCAB, the importance of surgeon experience, and the difference in the costs for the 2 procedures.

Search Strategy

The Arterial Grafting International Consortium (ATLANTIC) Alliance is an international writing group on coronary surgery. In January 2018, a comprehensive search to identify studies that evaluated the biological, clinical, angiographic, and economic aspects of OPCAB was performed in the following databases from inception to present: Ovid Medline, Ovid Embase, and the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials [CENTRAL], Cochrane Methodology Register). Search keywords included *myocardial revascularization* in combination with *coronary artery bypass, on pump, off pump, and OPCAB*. Relevant abstracts were reviewed, and the related articles function was used for all included studies. References for all selected studies were cross-checked. The writing group selected the most relevant papers according to both methodological and clinical considerations. Observational series were considered only in the absence of data from randomized controlled trials (RCTs).

From the Department of Cardio-Thoracic Surgery, Weill Cornell Medicine, New York City, NY (M.G., A.D.F., L.N.G., R.T.); Bristol Heart Institute, University of Bristol, United Kingdom (G.D.A., U.B.); University of Oxford, United Kingdom (C.A.); Cleveland Clinic, Cleveland, OH (F.B.); Cardiac Surgery, Pope John Paul II Foundation, Campobasso, Italy (A.M.C.); Cardiovascular Disease Institute, University of L'Aquila, Italy (M.D.M.); Schulich Heart Centre, Sunnybrook Health Science, University of Toronto, Canada (S.E.F., D.Y.T.); Division of Cardiac Surgery, Ottawa Heart Institute, Ottawa, Canada (D.G., J.G.); TEDA International Cardiovascular Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China (G.-W.H.); Department of Pharmacology, Catholic University School of Medicine, Rome, Italy (C.P.); Department of Cardiovascular Surgery, Icahn School of Medicine at Mount Sinai, New York City, NY (J.D.P.); University of Ottawa Heart Institute, Ottawa, Canada (M.R.); University of Toledo College of Medicine, Toledo, OH (T.A.S.); Department of Surgery, University of Melbourne, Parkville, Australia (J.T.); Sydney Medical School, The University of Sydney, Australia (M.V.); Harvard Medical School, Boston, MA (M.A.Z.); The Heart Hospital Baylor Plano, Plano, TX (M.M.); University of Oxford, United Kingdom (D.P.T.).

Correspondence to: Mario Gaudino, MD, Department of Cardiothoracic Surgery, Weill Cornell Medicine, 525 E 68th St, New York, NY 10065. E-mail: mfg9004@med.cornell.edu

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The Technical Evolution of Beating-Heart Coronary Artery Bypass Surgery

The very first direct coronary revascularization procedures in the early 1960s were performed on the beating heart

without CPB.¹ However, the technique was soon abandoned because of developments in extracorporeal circulation and improvement in myocardial protection that made the surgery safer, standardized, and reproducible. In the early 1980s, 2 South American surgeons, Buffolo² and Benetti,³ published their extensive series of OPCAB. Most patients received grafts to the left anterior descending coronary artery (LAD) and the main right coronary artery, but with more limited and difficult grafting of coronary arteries on the posterior and lateral wall. In the mid 1990s, a minimally invasive left internal mammary artery (LIMA)–LAD performed through a small left anterior thoracotomy on the beating heart⁴ was proposed in combination with percutaneous coronary intervention (PCI) for the non-LAD targets.⁵

Innovative technology played a key role in the development of OPCAB by minimizing the motion of the heart during construction of the anastomosis. Initially, stabilization of the target coronary vessel was obtained by stay sutures, but the advent of mechanical stabilizers, by means of pressure or suction pods, transformed the way OPCAB was performed, accompanied by an evident improvement in surgical results.⁶ The critical challenge was the exposure of the lateral and inferior walls. Initially, lifting of the heart and exposure of the targets were achieved with multiple slings⁷ or pericardial stitches, as proposed by Lima and Salerno.⁸ The commercialization of pressure- and vacuum-assisted positioners further changed the field and allowed minimization of hemodynamic changes during exposure. The use of intracoronary shunts rather than snaring of the target native coronary vessel has been shown to significantly reduce intraoperative myocardial dysfunction and hemodynamic instability during OPCAB.⁹

The use of a transit-time flowmeter, high-resolution epicardial ultrasound, or intraoperative fluorescence imaging allowed intraoperative control of the quality of the anastomosis, an issue of particular relevance during the technically more complex OPCAB procedure.¹⁰

For the future of OPCAB, technology will play an increasingly important role with the adoption of hybrid revascularization and robotic assisted OPCAB. The concept of hybrid coronary revascularization (HCR) stems from the hypothesis that the LIMA-LAD graft is superior to coronary stenting of the LAD, whereas contemporary drug-eluting stent-PCI is noninferior to venous bypass grafts used for non-LAD targets. Although still limited to sporadic experiences in dedicated centers, HCR has the potential to combine the advantages of minimally invasive OPCAB with complete coronary revascularization.

The use of robotic assistance during CABG has been associated with superior cosmetic results and reduced postoperative pain but also longer operative times and higher costs.¹¹

Differences in Systemic Inflammatory Reaction and Platelet/Coagulation Activation After On- and Off-Pump CABG

CABG elicits a complex prothrombotic and proinflammatory response that peaks within a time frame spanning from the end of CPB to the early hours thereafter. These molecular changes may persist for days or weeks after CABG.¹² In particular, several studies have described marked and protracted activation of several molecular pathways, reflecting a systemic inflammatory reaction, platelet and coagulation activation, and increased oxidative stress and endothelial dysfunction.¹³ Interestingly, these changes appear to occur after both ONCAB and OPCAB, with a relatively limited number of these pathways (eg, oxidant stress) showing more pronounced activation in the presence of CPB.¹³

Systemic Inflammatory Reaction

Patients undergoing CABG constitute a distinct high-risk group characterized by advanced atherosclerotic disease, low-grade systemic inflammation, and the clustering of several other comorbidities.¹³ The CABG operation per se is a potent triggering factor for cardiovascular events because it elicits major endocrine stress and systemic inflammatory response, which involves the release of acute-phase proteins and sepsis-like symptoms during postoperative recovery.^{14,15} The inflammatory response during CABG may be related, at least in part, to the use of CPB that induces leukocyte and platelet activation, thrombin and plasmin-mediated procoagulant and fibrinolytic effects, and a rapid and sustained multifold increase in the circulating levels of proinflammatory mediators.¹⁶ Myocardial tissue ischemia as a result of aortic cross-clamp, reperfusion injury, plaque rupture and microembolization, and other factors (eg, type of anesthesia) also may play a role in CABG-related inflammation.¹⁷

If and to what extent avoidance of CPB can reduce or even eliminate the systemic inflammatory reaction after surgery is controversial. Studies that evaluated the circulating levels of proinflammatory cytokines (IL-6, -8, and -10) after off- and on-pump- surgery reported contradictory results.^{14,18–22}

The concomitant use of cardiomy suction or non-heparin-bounded CPB circuits in some of the trials is a plausible cause of heterogeneity and may partially explain the contradictory results.

Interestingly, the severity of the inflammatory response to OPCAB might be affected by the type of anesthesia.²³ Inflammation has been proposed to have an important role in determining early postoperative complications (eg, low-output syndrome, myocardial injury, and atrial fibrillation or stroke). Indeed, increased preoperative CRP (C-reactive protein) levels are independently associated with early and late mortality in CABG patients.²⁴ In other studies, preoperative levels of IL-6,

IL-8, and MCP-1 (monocyte chemoattractant protein 1) predict postoperative atrial fibrillation development in CABG patients.²⁵ Gaudino et al²⁶ described a significant correlation between a single-base promoter mutation of the polymorphism of the *IL6* gene, the postoperative level of IL-6, and the development of pulmonary and renal complications and atrial fibrillation after CABG. In RCTs, OPCAB has been associated with significantly lower myocardial injury and increase in inflammatory mediators compared with ONCAB,^{14,15} although early mortality rates did not differ significantly.²⁷ Nevertheless, it must be noted that the results of pharmacological treatment aimed at reducing the postoperative inflammatory reaction after CABG (corticosteroids, statins) have been mixed,^{28,29} so the role of attempts to modulate inflammation in determining postoperative clinical outcome after CABG remains to be determined.

Platelet and Coagulation Activation

Activation of the plasmatic and cellular components of the hemostatic system occurs through 2 distinct mechanisms, namely, contact of blood with the surgical wound and contact of blood with the foreign surface of the CPB circuit.³⁰ The former plays a major role in the early activation of the hemostatic system that results in thrombin generation. Besides catalyzing the conversion of fibrinogen to fibrin, thrombin has multiple cellular targets (both in blood [eg, platelets] and the vessel wall) through the interaction with protease-activated receptors.^{30,31} Moreover, there is bidirectional interplay between blood coagulation and inflammation, with activation of the former leading to an inflammatory reaction and vice versa.³⁰ Circulating platelets are activated during CABG by several distinct mechanisms, including thrombin interacting with platelet PAR-1 (protease-activated receptor 1), interaction with fibrinogen bound to the CPB circuit, and contact with foreign surfaces. These activation processes eventually lead to reduced numbers of circulating platelets and perioperative platelet dysfunction.³⁰ Moreover, activated platelets release a broad range of inflammatory mediators, thereby reinforcing the inflammatory reaction.³¹ The increased vascular biosynthesis of the antithrombotic prostanoid prostacyclin (PGI₂) represents a homeostatic response to inflammation and platelet activation.³²

A limited number of studies have compared the effects of ONCAB versus OPCAB on platelet activation and aggregation and failed to demonstrate major differences between them.^{30,33–35} It should be emphasized that these studies relied on measurements of platelet function *ex vivo*, which do not necessarily reflect the extent of platelet activation *in vivo*.³¹

A different and more clinically relevant way of assessing the potential hemostatic/prothrombotic differences related to

ONCAB versus OPCAB is represented by studies of the pharmacodynamic response to antiplatelet drugs in these settings.^{32,33} In a study by Zimmermann et al,³³ the antiplatelet effect of aspirin (100 mg/day started on day 1 after surgery) evaluated at day 5 was largely impaired after CPB but not after CABG without CPB; therefore, increased platelet turnover after CPB appears to contribute to transient aspirin “resistance” because an increased number of new platelets might be competent to form Thromboxane A₂ (TXA₂) within the 24-hour dosing interval.³³ Consistent with this hypothesis, Cavalca et al recently reported impaired aspirin pharmacodynamics early after ONCAB that were associated with significant increases in immature platelets, total platelets, platelet mass, thrombopoietin, IL-6, glyocalicin, leukocytes, and high-sensitivity CRP.³² IL-6 can control inflammation through CRP and modulate megakaryocyte fragmentation, differentiation, and platelet release directly or through thrombopoietin.³² Changes in thrombopoietic indexes were largely reversible 3 months after surgery.³² As shown by 3 independent studies, shortening the dosing interval (ie, twice-daily dosing), but not doubling the dose, safely rescued the impaired antiplatelet effect of low-dose aspirin and prevented platelet activation associated with acute inflammation and enhanced platelet turnover following cardiac surgery.^{32,36,37}

To summarize, at present there is no clear-cut demonstration of a substantial reduction of the postoperative systemic inflammatory reaction and platelet activation after OPCAB. The antiplatelet effect of low-dose aspirin is transiently impaired following ONCAB because of enhanced platelet turnover.

Comparison of Short-Term Clinical Outcomes of On- and Off-Pump CABG

The benefits and risks of OPCAB have been the subject of several large RCTs, observational studies and registries, and >60 meta-analyses. In the largest randomized comparisons (CORONARY [CABG Off or On Pump Revascularization] and ROOBY [Randomized On/Off Bypass] trials), there were no differences in the primary study end point at 30 days.^{27,38} In CORONARY,²⁷ the primary composite outcome of death, nonfatal stroke, or nonfatal myocardial infarction (MI) was similar between OPCAB and ONCAB (9.8% versus 10.3%, $P=0.59$). Similarly in ROOBY, the primary composite outcome of 30-day death or major complications was similar between the 2 arms (7.0% versus 5.6%, $P=0.19$).³⁸ Furthermore, there was no difference in any individual component of these early composite outcomes (Table 1). Consistent with the purported benefits of off-pump surgery, several other perioperative complications (transfusion, reoperation for bleeding, acute kidney injury, and respiratory complications) were reduced in the off-pump patients in CORONARY.

Table 1. Early and Late Outcomes of ONCAB Versus OPCAB

Trial	Median Follow-up	Interventions	Early Outcomes				Late Outcomes				MACCE Definition	
			Mortality	RR	Stroke	MI	Mortality	Stroke	MI	RR		MACCE
CORONARY ³⁹	4.8 y	ONCAB	59/2377 (2.5)	4/2328 (0.2)	27/2377 (1.1)	170/2377 (7.2)	322/2377 (13.5)	66/2377 (2.8)	194/2377 (8.2)	55/2377 (2.3)	560/2377 (23.6)	Death from any cause, nonfatal MI, nonfatal stroke, new renal failure requiring dialysis, RR
		OPCAB	60/2375 (2.5)	16/2330 (0.7)	24/2375 (1.0)	158/2375 (6.7)	346/2375 (14.6)	55/2375 (2.3)	178/2375 (7.5)	66/2375 (2.8)	548/2375 (23.1)	
ROOBY ⁴⁰	5 y	ONCAB	13/1099 (1.2)	8/1099 (0.7)	8/1099 (0.7)	17/1099 (1.8)	131/1099 (11.9)	...	105/1099 (9.6)	131/1099 (11.9)	131/1099 (11.9)	Death from any cause, acute MI, RR
		OPCAB	18/1104 (1.6)	8/1104 (0.7)	14/1104 (1.3)	15/1104 (1.7)	168/1104 (15.2)	...	134/1104 (12.1)	145/1104 (13.1)	145/1104 (13.1)	
GOPCABE ⁴¹	1 y	ONCAB	34/1207 (2.8)	5/1207 (0.4)	32/1207 (2.7)	20/1207 (1.7)	95/1191 (8)	52/1191 (4.4)	28/1191 (2.4)	24/1191 (2.0)	167/1191 (14)	Death from any cause, MI, stroke, RR, new renal failure requiring dialysis
		OPCAB	31/1187 (2.6)	15/1187 (1.3)	26/1187 (2.2)	18/1187 (1.5)	83/1179 (7)	41/1179 (3.5)	25/1179 (2.1)	36/1179 (3.1)	154/1179 (13.1)	

Data are shown as frequency (percentage). CABG indicates coronary artery bypass grafting; CORONARY, CABG Off- or On-Pump Revascularization; GOPCABE, German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients; MACCE, major adverse cardiovascular or cerebral events; MI, myocardial infarction; ONCAB, on-pump coronary artery bypass surgery; OPCAB, off-pump coronary artery bypass surgery; ROOBY, Randomized On/Off Bypass; RR, repeated revascularization.

In GOPCABE (German Off-Pump CABG in Elderly Trial), a German RCT including only patients aged >75 years, there was no significant difference in the primary composite end point of death, stroke, MI, or new renal replacement therapy (7.8% versus 8.2%, $P=0.74$) at 30 days⁴¹ and no differences in the individual components of the composite end point (Table 1). However, there was an increased number of repeat revascularizations with OPCAB (1.3% versus 0.4%, $P=0.04$), a finding also observed in CORONARY (0.7% versus 0.2%, $P=0.01$).

Of note, no reduction in stroke was noted both in hospital and at 1 year (CORONARY: 1.5% versus 1.7%; [hazard ratio (HR): 0.90; 95% confidence interval (CI), 0.57–1.41]; GOPCABE: 3.5% versus 4.4%; $P=0.26$).^{41,42}

At 12 months, the primary composite end point was not different in the OPCAB and ONCAB patients in GOPCABE (13.1% versus 14.0%; $P=0.48$) or in CORONARY (12.1% versus 13.3%; $P=0.24$). In ROOBY, the primary outcome favored on-pump surgery (9.9% versus 7.4%; $P=0.04$), as did death from cardiac causes (2.7% versus 1.3%; $P=0.03$).

In contrast to the randomized trials, large propensity-matched databases have reported superior short-term outcomes with OPCAB, particularly in higher risk patients.

Polomsky and associates, using data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS ACSD) on 876 081 elective isolated CABG operations, found that the odds ratios (ORs) for death and most major complications were significantly lower with OPCAB than with ONCAB.⁴³

A meta-analysis of 35 propensity-matched studies and 123 137 patients found OPCAB to be superior to on-pump surgery for all short-term outcomes including mortality.⁴⁴

To summarize, RCTs have reported similar operative risk for off- and on-pump CABG, whereas single-center studies have reported better outcomes, particularly in high-risk patients.

Comparison of Long-Term Clinical Outcomes of On- and Off-Pump CABG

Conflicting evidence exists on whether off-pump CABG is associated with inferior long-term outcomes. At 5 years, there was no difference in the primary outcome in the CORONARY trial.³⁹ In the ROOBY trial, however, 5-year survival was significantly worse in the off-pump group (15.2% versus 11.9%; $P=0.02$).⁴⁰ Event-free survival was also significantly decreased in the off-pump group (31.0% versus 27.1%; $P=0.05$), along with MI and the need for repeat revascularization (Table 1).

In a single-center observational study of 12 812 patients from Emory University, Atlanta, GA, USA, there was no difference in 10-year mortality between on- and off-pump surgery after propensity score covariate adjustment (HR: 1.00; 95% CI, 0.88–1.14).⁴⁵ Importantly, the authors reported that the key to long-term survival was completeness of revascularization in both on- and off-pump patients. Similarly,

in 942 propensity score-matched patient pairs from a single Italian center, there was no difference in 10-year mortality between on- and off-pump surgery (HR: 1.3; 95% CI, 0.91–1.9).⁴⁶ In a study from the United Kingdom of >13 000 propensity-matched patients followed for 13 years, there was no difference in survival, suggesting that when OPCAB is performed by highly experienced surgeons, there is no adverse effect on survival.⁴⁷

In contrast, a propensity-matched single-institution study from Baylor Research Institute, Dallas, TX, USA showed an elevated risk of late mortality at 10 years with OPCAB (HR: 1.18; 95% CI, 1.02–1.38).⁴⁸ These concerns about late mortality were further explored in a meta-analysis of 42 RCTs and 31 risk-adjusted observational studies that included 1.2 million patients.⁴⁹ OPCAB was associated with a statistically significant 10% relative increase in the probability of mortality at 5 years (95% CI, 5.0–15.0%) that increased to 14% at 10 years in the observational studies (95% CI, 11.0–17.0%). It is important to note, however, that although statistical significance was reached, the clinical relevance of the reported difference remains to be determined (absolute difference: 0.5% at 5 years and 3% at 10 years).

The most recent meta-analysis including only RCTs with ≥4-year outcome and pooling data from 8145 participants reported an OR for long-term mortality of 1.16 for OPCAB (95% CI, 1.02–1.32).⁵⁰

To conclude, long-term data are discordant. Based on the current evidence, the possibility that off-pump surgery results in worse clinical outcomes cannot be excluded.

OPCAB in Specific Subsets of Patients

High-Risk Populations

Multiple studies have suggested a benefit of OPCAB in high-risk patient populations. A recent meta-analysis of RCTs demonstrated a significant relationship between the patient risk profile and the benefits from OPCAB, with the most benefit derived from reduced perioperative morbidity.⁵¹

An analysis of the STS ACSD from 1997 to 2007 showed that there were 38% and 55% reductions in the odds of early mortality for patients undergoing off-pump operations in the third- and fourth-highest risk quartiles, respectively.⁵² In contrast, a study of the Australian and New Zealand Society of Cardiac and Thoracic Surgeons database for high-risk patients associated OPCAB with reduced morbidity but showed similar operative mortality as compared to ONCAB.⁵³

Impaired Ventricular Function

As for patients with low ejection fraction (EF), an analysis of the STS ACSD from 2008 to 2011 of 25 667 patients with low

EF (<30%) found that the risks of death, stroke, and major adverse cardiac events (MACE) were lower in the OPCAB group.⁵⁴ These findings were corroborated by analysis of the Japan Adult Cardiovascular Surgery Database in which OPCAB was associated with reduced early morbidity and mortality in patients with EF <30%.⁵⁵ A meta-analysis of observational studies concluded that OPCAB may be associated with lower incidence of early mortality in patients with impaired left ventricular function but noted that the method of handling the conversion-related mortality in each study was uncertain and may have influenced the results. In addition, incomplete revascularization (IR) in the OPCAB group occurred more often and may explain why the early advantage in mortality was not maintained long term.⁵⁶

Advanced Age

Advanced age is a known risk factor in CABG.⁵⁷ In a systematic review of 16 observational studies of CABG in octogenarians (18 685 ONCAB and 8938 OPCAB), in-hospital mortality (pooled OR: 0.64; 95% CI, 0.44–0.93; $P=0.02$), and stroke (pooled OR: 0.61; 95% CI, 0.48–0.76; $P<0.001$) were significantly lower in OPCAB.⁵⁸ However, results from a Danish registry did not show a difference in outcomes between ONCAB and OPCAB in patients aged >70 years.⁵⁹ A propensity matched study of 6943 pairs of octogenarians showed a 30% reduction in the odds of stroke with OPCAB using the Nationwide Inpatient Sample (NIS).⁶⁰ In addition, the largest RCT to date comparing OPCAB and ONCAB in elderly patients (aged ≥ 75 years), reported no significant difference between ONCAB and OPCAB with regard to the composite outcome of death, stroke, MI, repeat revascularization, or new renal replacement therapy within 30 days and 1 year after surgery.⁴¹

Female Sex

Numerous studies report CABG mortality to be higher in women.^{61,62} In fact, according to the STS CABG risk model, female sex is associated with increased risk of operative mortality (OR: 1.31), major complications (OR: 1.18), and increased hospital length of stay (OR: 1.24).⁵⁷ OPCAB, however, may narrow or eliminate this disparity in outcomes between women and men. A large study at an experienced OPCAB US academic center concluded that OPCAB disproportionately benefits women and narrows the sex disparity in outcomes after CABG. Female patients ($n=3248$) and those treated with OPCAB ($n=4492$) were older and had more comorbidities than male patients ($n=8165$) and those treated with ONCAB ($n=6921$), respectively. Women treated with ONCAB had risk-adjusted ORs of 1.60 for death ($P=0.01$) and

1.71 for MACE ($P<0.001$) compared with men who had ONCAB. In contrast, women treated with OPCAB had outcomes similar to men who had either OPCAB or ONCAB. Among women, OPCAB was associated with a significant reduction in death (OR: 0.39; $P=0.001$) and MACE (OR: 0.43; $P<0.001$).⁶³

These findings were replicated at a national level in an STS ACSD study of 63 experienced centers that performed >100 OPCAB cases between 2004 and 2005. Women ($n=11\ 785$) and those treated with OPCAB ($n=16\ 245$) were older and had more comorbidities than men ($n=30\ 662$) and those treated with conventional ONCAB ($n=26\ 202$), respectively. The risk-adjusted ORs for death and major complications were significantly lower with OPCAB than with ONCAB. Among ONCAB cases only, women had a significantly greater adjusted risk of death, prolonged ventilation, and longer hospital length of stay than men; however, among OPCAB cases, women had similar outcomes.⁶⁴ A meta-analysis of observational studies associated OPCAB with reduced perioperative MI but not with reduction of other morbidities or operative mortality.⁶⁵ Of note, women undergoing OPCAB received fewer grafts than those undergoing ONCAB.

OPCAB may have a selective benefit for women. The underlying mechanism is unclear and is unlikely to be related to avoidance of CPB because there is no major sex difference in outcomes associated with valve surgery.⁶⁶ It is interesting, however, that women who undergo OPCAB are more likely to receive an internal mammary artery bypass than those undergoing ONCAB.⁶⁷

Neurological Risk

The possible association of OPCAB with reduced stroke with enhanced benefit in higher risk patients⁶⁷ argues for a potential benefit in patients with a history of atheromatous aorta or cerebrovascular disease. A large single-center study utilizing propensity-matched analysis in patients with atheromatous disease of the ascending aorta associated ONCAB with an increased risk of postoperative stroke (OR: 1.4; $P=0.05$) and operative mortality.⁶⁸ Another study associated OPCAB with reduced stroke and operative mortality in a similar population.⁶⁹ Patients with carotid stenosis may have a potential benefit with OPCAB,⁷⁰ but the evidence is inconclusive, and when it comes to combined CABG and carotid endarterectomy, again, the data are sparse, but both OPCAB and ONCAB may provide equivalent outcomes.⁷¹ In patients with a history of preoperative cerebrovascular events, OPCAB does not appear to confer a risk benefit with regard to postoperative neurological outcome compared with ONCAB.⁷² Of note, postoperative cognitive impairment is similar after on- and off-pump CABG.⁷³

End Organ Failure

The data on the benefit of OPCAB in patients with end-organ failure, including renal failure and cirrhosis, are limited to observational studies and mostly small patient numbers. Despite a higher rate of IR, a propensity-matched analysis associated on-pump with increased operative mortality in patients with advanced chronic kidney disease.⁷⁴ A meta-analysis including 17 studies with 201 889 patients with chronic kidney disease associated OPCAB with lower early mortality (OR: 0.88; 95% CI, 0.82–0.93; $P<0.0001$) and morbidity compared with ONCAB. However, there was no difference regarding long-term survival (HR: 1.08; 95% CI, 0.86–1.36; $P=0.51$).⁷⁵ A large study based on the National Health Research Institute of Taiwan reported similar outcomes of OPCAB and ONCAB in patients on dialysis.⁷⁶ Similar findings were reported by a meta-analysis of 10 retrospective studies.⁷⁷

Cirrhosis substantially increases the operative risk in patients who undergo cardiac surgery. In a national sample of 3 046 709 patients who underwent CABG procedures, of which 744 636 (24.4%) were OPCAB, 6448 patients (0.3%) had cirrhosis. In the overall CABG group, cirrhosis was independently associated with increased mortality (adjusted OR: 6.9; 95% CI, 2.8–17) and morbidity (adjusted OR: 1.6; 95% CI, 1.3–2.0). The OPCAB subgroup analysis revealed that the presence of cirrhosis did not affect mortality or morbidity unless there was severe liver dysfunction. In the ONCAB patients, however, cirrhosis was associated with increased mortality and morbidity regardless of the severity of liver dysfunction.⁷⁸

In summary, the available evidence suggests that OPCAB can be associated with better outcomes in high-risk patients. Elderly patients, patients with low EF, those with high neurological risk, women, and patients with end-organ failure may benefit from off-pump surgery, although the extent of this benefit remains unclear at present.

OPCAB and Graft Patency

The effect of OPCAB on graft patency rate is still controversial. In the angiographic analysis of the ROOBY trial, the 1-year patency rate in the off-pump arm was significantly lower than in the on-pump arm. Follow-up angiography was obtained in 62% of the patients of the initial cohort. Overall patency rate was 82.6% in the off-pump group and 87.8% in the on-pump group ($P<0.001$). At least 1 occluded graft was found in 36.5% of off-pump versus 28.7% of on-pump patients (relative risk: 1.27; 95% CI, 1.09–1.48). Arterial conduits (mainly LIMA to LAD grafts) showed similar patency rates in the 2 groups (92.9% versus 94.8%; $P=0.13$), whereas saphenous vein grafts had a significantly lower patency rate in the off-pump group

(76.6% versus 83.8%; $P<0.001$). Interestingly, however, both arterial and venous conduits had significantly lower perfect patency in the OPCAB group. Grafts to the posterior descending artery had the worse patency when performed off-pump (74.1% versus 82.8%; $P=0.003$).⁷⁹

A smaller single-institution and single-surgeon RCT reported similar angiographic outcomes with the 2 techniques.⁸⁰ A Japanese RCT including 167 consecutive patients found no difference in patency but a numerically higher perfect patency rate in the on-pump group (96% versus 93%; $P=0.09$), particularly for grafts to the right coronary system (99% versus 90%; $P=0.02$).⁸¹ A post hoc analysis of the large angiographic database of the PREVENT (The Project of Ex-vivo Vein Graft Engineering via Transfection) IV study (1920 patients and 4736 grafts) found no difference in the patency rates of the 2 techniques.⁸²

All the meta-analyses report a higher incidence of graft occlusion or failure in the OPCAB arm. A meta-analysis of 12 RCTs pooling together angiographic data from 3894 (OPCAB) and 4137 (ONCAB) grafts reported an increased risk of occlusion of all grafts in the OPCAB group (relative risk: 1.35; 95% CI, 1.16–1.57), mainly due to saphenous vein graft failure (relative risk: 1.41; 95% CI, 1.24–1.60).⁸³ Interestingly, there was no significant difference in graft occlusion between the 2 techniques for internal mammary artery and radial artery grafts.

The most recent meta-analysis pooled angiographic data on 7011 grafts and found an OR of 1.51 for occlusion in the OPCAB arm (95% CI, 1.21–1.88; $P=0.002$).⁸⁴ Differences in surgeons' experience, varying completeness of follow-up, and angiographic definitions are the plausible reasons for the reported discrepancies. In particular, the use of overall patency in some series and perfect patency (ie patency without any irregularity) in others makes the comparison of the different studies difficult.

To summarize, OPCAB seems associated with lower patency and perfect patency rate, although contradictory results have been reported.

Completeness of Revascularization

Completeness of myocardial revascularization is a cornerstone of CABG. In a meta-analysis including aggregated data from 30 389 patients, complete myocardial revascularization had a strong protective effect against long-term mortality (HR: 0.63; 95% CI, 0.53–0.75).⁸⁵

In most published comparative series, the number of grafts per patient in the OPCAB arm is lower than in the pump-assisted group.⁸⁶ A relation with surgeon experience seems to exist, and this has led to concerns that off-pump surgery is achieved at the expense of the completeness of the revascularization, especially when performed by less experienced surgeons.

In fact, despite technological advances, grafting the inferior and posterolateral wall off-pump can be challenging. In the ROOBY trial, the numbers of planned grafts per patient were similar in both groups (3.0 versus 3.0; $P=0.98$), but the number of grafts performed was inferior in the OPCAB arm (2.9 versus 3.0; $P<0.001$).⁴⁰ In the on-pump group, 11.1% of patients received fewer grafts than planned compared with 17.8% in the OPCAB series ($P<0.001$); at 5 years, the respective rates of repeat CABG were 0.5% and 1.4% ($P=0.02$). In the CORONARY trial,⁸⁷ however, which involved more expert off-pump surgeons, the rate of IR was similar in the 2 groups (11.2% OPCAB versus 10% ONCAB; $P=0.05$). Notably, in CORONARY, no differences in repeat revascularization by PCI or CABG were found at 5 years (2.8% versus 2.3% [$P=0.29$] and 0.4% versus 0.2% [$P=0.17$]).

IR in the OPCAB group has been correlated with long-term mortality. In a large study in which 5423 on-pump patients were propensity matched with 5423 OPCAB patients, the latter had higher prevalence of IR (6.9% ONCAB versus 13.6% OPCAB; $P<0.001$). Long-term mortality was significantly higher for patients undergoing incomplete OPCAB.⁸⁸

In a recent analysis of >13 000 patients from a single institution, a detrimental effect of IR on survival was demonstrated when at least 1 territory was not revascularized in OPCAB patients. Interestingly, a similar effect was evident only when 2 coronary territories were left ungrafted in the on-pump series; this finding suggests that the pathogenesis and clinical consequences of IR may differ between the 2 techniques.⁸⁹

It must be noted, however, that the interpretation of the literature on the subject is problematic for several reasons. The definition of IR varies markedly among studies, making comparisons between trials very difficult. In addition, IR can be a surrogate marker of a greater burden and complexity of coronary disease and a worse risk profile for the patient. In fact, variables such as reduced EF, advanced age, heart failure, and reoperation have been associated with both IR and survival.⁹⁰ In these situations, it is difficult to determine the effect of IR per se and the role of various preoperative risk factors that are prevalent in the same patients.

In summary, IR is probably an explanation for the worse long-term outcomes of OPCAB and seems to be related to surgeon's experience.

The Role of Surgeon Experience

The individual surgeon's expertise in OPCAB and hospital volume have long been considered important determinants of outcome.⁹¹

RCTs suggesting increased risk with OPCAB have been criticized by those who believe that surgeon experience plays a major role in determining outcomes. In the ROOBY trial, in which OPCAB was associated with increased 5-year mortality

(15.2% in the OPCAB group versus 11.9% in the on-pump group; $P=0.02$), the 53 participating surgeons enrolled an average of only 8 patients per year during the study period and had a high conversion rate to on-pump surgery (12%) and IR (18%).⁴⁰ Moreover, in 60% of the cases, a resident was the primary surgeon. In the GOPCAB study,⁴¹ in which surgeons were required to be established experts with an average of 514 OPCAB procedures (median: 322), no significant differences between OPCAB and on-pump surgery were found. In the CORONARY trial, each procedure was performed by a surgeon who had expertise in the specific type of surgery (>100 cases using the specific technique, off-pump or on-pump) and similar 5-year outcomes with OPCAB and ONCAB were reported.²⁷

Among the observational studies, Lapar et al found a significant surgeon volume–outcome relationship for mortality after OPCAB with a threshold of >50 operations per year.⁹² Glance and colleagues, however, in a registry study from the New York State Database including 36 930 patients and 181 surgeons at 33 hospitals, did not find any association between OPCAB surgeon case volumes and mortality.⁹¹

In a recent post hoc analysis of the ART trial including 1260 and 1700 OPCAB and on-pump patients, respectively,⁹³ OPCAB performed by “sporadic” OPCAB surgeons (1–5 OPCAB procedures) presented a higher rate of conversion (12.9%) and a higher rate of operative mortality (4.8%) compared with ONCAB despite similar distribution of risk factors. OPCAB performed by 3 high-volume OPCAB surgeons (>60) showed a very low conversion rate (1%) and 5-year mortality comparable to ONCAB performed by 95 “on-pump only” surgeons. According to the STS ACS, 84% of participating centers performed <50 off-pump cases per year, 34% of surgeons performed no off-pump operations, and 86% of surgeons performed <20 off-pump cases per year.⁹⁴ A recent analysis of the US NIS⁹⁵ showed that OPCAB performed in low-volume centers and by low-volume surgeons was associated with significantly increased risk-adjusted mortality. In contrast, OPCAB was associated with lower risk adjusted mortality when performed in high-volume hospitals (≥ 164 cases/year) and by high-volume surgeons (≥ 48 cases/year).

To summarize, it seems likely that the unique technical challenges of OPCAB may lead to poorer outcomes during each surgeon's “learning curve.” To minimize the learning curve effect, appropriate patient selection, individualized grafting strategy, peer-to-peer training of the entire team, and graded clinical experience are of paramount importance.

Intraoperative Conversion From Off-Pump to On-Pump

An intraoperative switch from an OPCAB to an ONCAB approach is described as *intraoperative conversion* (IOC).⁹⁶

IOC has been classified as *elective*, in which the change from OPCAB to ONCAB is aimed at the prevention of hemodynamic instability and occurs before the start of any distal coronary anastomosis, and *emergent*, in which the conversion takes place following the onset of hemodynamic instability and typically after the start of the construction of a distal anastomosis.

The reported rate of IOC is quite broad. In a recent analysis of the STS ACSD involving over 196 000 patients, the reported conversion rate was 5.5% of which 50% were elective.⁹⁷

In a meta-analysis including 18 870 patients, IOC occurred in 4.9% of the cases.⁹⁸ In the CORONARY trial, the rate of IOC was 7.9%,⁹⁹ ranging from 0% to 60% among hospitals. The highest rates of IOC were reported before cardiac manipulation (43.5%) and grafting of the LAD (18.3%), whereas IOC before grafting of the lateral and inferior walls was less frequent (9.7% and 3.8%, respectively). In 15.1% of the cases, hemodynamic instability occurring soon after the induction of anesthesia led surgeons to convert before starting surgery.

The most common reason for IOC is hypotension (32.3%), followed by either small size (26.9%) or intramuscular course of target vessels (22.6%), ischemia (17.7%), and arrhythmias (11.3%); less common reasons were hemorrhage, graft occlusion, calcified aorta, and need for concomitant surgery.^{96,99}

Elective IOC is usually well tolerated and associated with no increase in operative mortality.^{96,99,100}

In contrast, emergency IOC is associated with significantly increased mortality risk.⁹⁶ In an analysis based on the STS ACSD, Keeling et al⁹⁷ reported observed to expected mortality of 1.4 for an elective IOC, 1.6 for emergency IOC for visualization reasons, and 2.7 for emergency IOC for hemodynamic instability. In the previously cited meta-analysis, emergency conversion raised the OR of mortality to 6.99 (95% CI, 5.18–9.45).⁹⁸ In addition to the noted increased mortality, IOC is also associated with increased risk of almost all perioperative complications including myocardial ischemic injury, stroke, renal failure, and prolonged ventilation.^{97,100,101} Furthermore, IOC is associated with increased costs¹⁰² as well as hospital readmissions and infectious complications.¹⁰³ Midterm and event-free survival is significantly reduced for patients who undergo IOC.^{64,104}

Identifying patients at high-risk for IOC a priori and avoiding an ill-fated attempt at OPCAB likely constitutes the best strategy to improve OPCAB outcomes. Keeling et al⁹⁷ showed that older age, EF <35%, preoperative need for intra-aortic balloon pump, increasing number of diseased native coronary vessels, history of congestive heart failure, and urgent status of surgery are all independent predictors of IOC. Other identified risk factors for IOC are left main coronary artery disease, intramyocardial course of coronary targets, reoperative procedures, and increasing number of coronary grafts constructed.^{99,100,105}

The rate of IOC declines with increasing OPCAB surgeon and institutional experience.^{100,101}

In summary, IOC occurs in a relatively small percentage of OPCAB cases, although the incidence is related to surgeon experience. Elective IOC is usually a benign event, whereas emergency IOC is associated with significantly worse outcomes.

Comparison of Hospital Costs Between Off- and On-Pump CABG

Controlling costs in health care continues to be a challenge, and CABG, as one of the most frequently performed procedures in the world, remains a visible priority. Indeed, OPCAB was initially embraced as a promising procedure to reduce costs associated with CABG.¹⁰⁶

Despite extensive research and multiple published studies during the past 2 decades, there continues to be debate regarding cost advantages of one versus the other approach.

Table 2 summarizes the most important series comparing the cost of off- and on-pump CABG.

Scott et al,¹¹⁶ in an observational study, found that patients undergoing ONCAB had significantly longer time to extubation, increased blood use, longer intensive care unit and postoperative lengths of stay, and higher in-hospital mortality than patients undergoing OPCAB, which would translate into significantly higher expenses associated with ONCAB. Similarly, in a large propensity-matched registry,¹¹² total costs were higher for ONCAB. Specifically, the operative procedure showed similar costs (roughly \$5000), but other in-hospital costs including surgical devices, intensive care unit, cardiac ward, and blood products were significantly higher in patients undergoing ONCAB. At 1-year follow-up, this difference persisted (\$12 000 for OPCAB versus \$14 000 for ONCAB; $P<0.001$).

In contrast, data from the CORONARY trial showed no difference in costs between the 2 techniques.¹¹⁵ During the index hospitalization, the cost for patients undergoing OPCAB was \$8626 compared with \$8567 for ONCAB, with a nonsignificant difference of \$59. At follow-up, this trend of neutrality continued (\$37 more for OPCAB at 6 months and \$28 less for OPCAB at 1 year). A sensitivity analysis was also performed to evaluate the potential influence of supplies for the 2 surgical strategies. When OPCAB supplies cost \$1000 less than ONCAB supplies, the cost savings with OPCAB were roughly \$1000. However, increasing the cost of off-pump supplies to \$2000 showed a linear increase in the incremental cost up to cost saving of \$1000 for on-pump surgery. Alternatively, the ROOBY trial¹¹⁷ reported significant cost saving with ONCAB (\$56 023 versus \$59 623; $P=0.05$). This finding was also confirmed by a large retrospective study (63 000 patients)¹¹³ in which multivariable regression analysis showed a higher final cost by \$1497 per patient in those

Table 2. Overview of the Series Comparing the Cost of OPCAB and ONCAB

First Author	Year	Study Design	Number of Patients; Cost Benefit	
			Off-Pump	On-Pump
Arom ¹⁰⁷	1999	Retrospective, hospital costs	62; 21% decreased costs	243
Boyd ¹⁰⁸	1999	Retrospective, hospital costs	30; 14% decreased costs	60
Ascione ¹⁰⁹	1999	Prospective, randomized hospital costs	100; 30% decreased costs	100
Nathoe ¹¹⁰ (OCTOPUS trial)	2003	Multicenter, prospective, randomized hospital and 1-year costs	142; hospital: 14% decreased costs, $P<0.01$; 1 year: 12% decreased cumulative costs ($P<0.01$)	139
Puskas ¹¹¹	2004	Prospective, randomized hospital and 1-year costs	100; hospital: 11% decreased costs ($P=0.002$) 1 year: 8% decreased cumulative costs ($P=0.08$)	100
Lamy ¹¹²	2006	Propensity-matched registry	1233; 1-year total costs: 15% decreased ($P<0.001$)	1233
Chu ¹¹³	2009	Data from Nationwide Inpatient Sample 2004	14 389; \$1497 (95% CI, \$779–\$2216) more in overall hospitalization costs in OPCAB than ONCAB	48 658
Shroyer ³⁸ (ROOBY trial)	2009	Multicenter prospective, randomized hospital costs	1104	1099 Hospital: 6% decreased costs ($P=0.05$)
Houliand ¹¹⁴ (DOORS trial)	2013	Multicenter, prospective, randomized hospital and reintervention costs	450; hospital and reinterventions: 7% decreased costs	450
Lamy ¹¹⁵ (CORONARY trial)	2014	Multicenter, prospective, randomized hospital and 1-year costs	2375	2377; hospital: 1% decreased costs ($P=ns$); 1 year: 1% decreased cumulative costs ($P=ns$)
Lamy ³⁹ (CORONARY trial)	2016	Multicenter, prospective, randomized 5-year costs	2375	2377; 5 years: 1% decreased cumulative costs ($P=ns$)

CABG indicates coronary artery bypass grafting; CORONARY, CABG Off- or On-Pump Revascularization; DOORS, Danish On-pump Off-pump Randomization Study; OCTOPUS, A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients trial; ONCAB, on-pump coronary artery bypass surgery; OPCAB, off-pump coronary artery bypass surgery; ROOBY, Randomized On/Off Bypass.

treated by OPCAB ($P<0.001$). Factors influencing the final cost of off-pump surgery were age >65 years, number of grafts, duration of anesthesia, very low EF, and low to medium hospital OPCAB volume.^{115,118} Interestingly, no difference in cost was found in the CORONARY trial¹¹⁸ among the different geographic areas for ONCAB and OPCAB.¹¹⁵

It must be noted that the cost analyses should be extrapolated to individual programs with caution because of the high variability in the cost of devices for different institutions and countries.

To summarize, no clear evidence shows that OPCAB significantly reduces in-hospital costs.

Anaortic, Total Arterial, Off-Pump CABG

The original thesis of OPCAB was that removing the CPB from the procedure would reduce pump-related

inflammation, end-organ injury, and stroke. The vast majority of these procedures were performed using an in situ LIMA to the LAD and ≥ 1 proximal aortocoronary vein grafts placed onto the ascending aorta using a partial-occlusion clamp.

Anaortic OPCAB refers to a distinct off-pump technique with complete avoidance of aortic manipulation. This may prevent dislodgement and embolization of atheromatous plaque in the aorta and reduce the risk of stroke.¹¹⁹ In situ grafts are used including one or both of the internal mammary arteries (and the gastroepiploic, in some cases) to avoid the need for proximal aortocoronary anastomoses and the associated aortic manipulation. Composite grafts are constructed as required including “T” or “Y” grafts or tandem or “I” grafts if an internal mammary artery is extended with a second conduit. Consequently, this technique also has a high percentage of total arterial conduits.

No adequate RCT has compared anaortic OPCAB to ONCAB. However, in a recent network meta-analysis comparing ONCAB, OPCAB with a partial-occlusion clamp, anaortic OPCAB, and OPCAB with a Heartstring “clampless device,” the anaortic technique was found to result in superior short-term outcomes. Anaortic OPCAB resulted in statistically significant reductions in postoperative stroke (−78% versus ONCAB, −66% versus OPCAB with a partial-occlusion clamp; −52% versus OPCAB with a Heartstring device) and early mortality (−50% versus ONCAB; −40% versus OPCAB with a Heartstring device, −20% versus OPCAB with a partial-occlusion clamp), as well as renal failure, bleeding complications, and atrial fibrillation, and shorter length of intensive care unit stay.¹²⁰

The SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) trial remains the most influential study comparing CABG and PCI. The often quoted stroke rate of 2.2% for CABG versus 0.6% for PCI is a significant factor driving patients towards PCI, despite the proven long-term survival benefit and freedom from reintervention with CABG.¹²¹ The CABG group in this trial included both on- and off-pump patients, and the percentage of anaortic patients is not known. Indirect comparisons from the literature show that the anaortic technique compares favorably with PCI (0.4% risk of stroke in the aforementioned network meta-analysis)¹²⁰ and suggests that a formal comparative RCT would be justified.

Minimally Invasive CABG, Total Endoscopic Coronary Artery Bypass, and HCR

The sequelae associated with the median sternotomy can affect postoperative quality of life and recovery. It has been estimated that more than a quarter of patients still have chronic non-cardiac chest pain 1 year after sternotomy, and this does not specifically relate to the harvest of the internal thoracic artery.¹²² The future of surgical coronary revascularization must therefore involve ways to perform effective surgical revascularization without sternotomy.

The development of minimally invasive coronary surgical techniques has been limited by the difficulty in accessing and performing anastomosis in multiple different areas of the heart through a single, small, nonsternotomy incision. Three main options for the performance of CABG without sternotomy are now available (Table 3): (1) minimally invasive CABG, in which all areas of the heart are bypassed via a small left anterolateral thoracotomy, usually without the use of the heart–lung machine¹²³; (2) robotic total endoscopic coronary bypass grafting, in which robotic techniques are used not only for internal mammary artery harvest but also for the performance of all graft anastomoses¹²⁴; and (3) HCR, which combines the performance of a single LIMA–LAD graft via a small anterolateral thoracotomy, with PCI to the other myocardial territories of the heart that require revascularization.¹²⁵

Table 3. Comparison of Nonsternotomy OPCAB Modalities

	MICS CABG	TECAB	HCR
Safety and efficacy	+++	+++	+++
Avoidance of CPB	++	+	+++
Avoidance of invasiveness	++	++	+++
Availability outside of expert centers	+	...	++
Completeness of surgical revascularization	+++	++	+
Ability to perform multiarterial grafting	++	+++	...
Cost containment vs CABG	+++	+	++

CABG indicates coronary artery bypass grafting; CPB, cardiopulmonary bypass; HCR, hybrid coronary revascularization; MICS CABG, minimally invasive coronary artery bypass grafting; OPCAB, off-pump coronary artery bypass surgery; TECAB, total endoscopic coronary artery bypass grafting.

So far, observational data have suggested that these procedures are safe and that patients recover significantly faster than with CABG in the early postoperative period.^{125–127} Furthermore, there may also be benefits related to perioperative morbidity compared with CABG.¹²⁵

No RCT to date has compared minimally invasive techniques with traditional CABG. Two trials are currently under way to evaluate minimally invasive CABG and HCR: the MIST (Minimally Invasive Coronary Surgery Compared to Sternotomy Coronary Artery Bypass Grafting) trial and the National Heart, Lung, and Blood Institute–funded Hybrid Coronary Revascularization Trial. These prospective trials are being undertaken to ascertain, respectively, the amount of recovery benefit that minimally invasive CABG may have over sternotomy CABG and whether HCR is superior to a strategy of multivessel PCI regarding 5-year incidence of major adverse cardiac events. The results of these trials will shed light on the role of nonsternotomy CABG in clinical practice.

Conclusions

More than 30 years after the introduction of OPCAB, its role in coronary surgery remains debated. In the general population, OPCAB has been associated with similar short-term outcomes, at least when performed by experienced surgeons. In the long term, inferior outcomes have been reported with OPCAB. High-risk patients can potentially benefit from OPCAB, and this seems to be particularly relevant for patients at high risk of intraoperative stroke who are operated with the anaortic technique, but this hypothesis has not been adequately tested in randomized studies. The use of minimally invasive and hybrid approaches is promising.

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References

- Goetz RH, Rohman M, Haller JD, Dee R, Rosenak SS. Internal mammary-coronary artery anastomosis. A nonsuture method employing tantalum rings. *J Thorac Cardiovasc Surg.* 1961;41:378–386.
- Buffolo E, Andrade JC, Succo J, Leão LE, Gallucci C. Direct myocardial revascularization without cardiopulmonary bypass. *Thorac Cardiovasc Surg.* 1985;33:26–29.
- Benetti FJ, Naselli G, Wood M, Geffner L. Direct myocardial revascularization without extracorporeal circulation. Experience in 700 patients. *Chest.* 1991;100:312–316.
- Calafiore AM, Giammarco GD, Teodori G, Bosco G, D'Annunzio E, Barsotti A, Maddestra N, Paloscia L, Vitolla G, Sciarra A, Fino C, Contini M. Left anterior descending coronary artery grafting via left anterior small thoracotomy without cardiopulmonary bypass. *Ann Thorac Surg.* 1996;61:1658–1665.
- Angelini GD, Wilde P, Salerno TA, Bosco G, Calafiore AM. Integrated left small thoracotomy and angioplasty for multivessel coronary artery revascularisation. *Lancet.* 1996;347:757–758.
- Calafiore AM, Vitolla G, Mazzei V, Teodori G, Di Giammarco G, Iovino T, Iaco A. The LAST operation: techniques and results before and after the stabilization era. *Ann Thorac Surg.* 1998;66:998–1001.
- Calafiore AM, Teodori G, Di Giammarco G, Vitolla G, Maddestra N, Paloscia L, Zimarino M, Mazzei V. Multiple arterial conduits without cardiopulmonary bypass: early angiographic results. *Ann Thorac Surg.* 1999;67:450–456.
- Bergsland J, Karamanoukian HL, Soltoski PR, Salerno TA. "Single suture" for circumflex exposure in off-pump coronary artery bypass grafting. *Ann Thorac Surg.* 1999;68:1428–1430.
- Yeatman M, Caputo M, Narayan P, Ghosh AK, Ascione R, Ryder I, Angelini GD. Intracoronary shunts reduce transient intraoperative myocardial dysfunction during off-pump coronary operations. *Ann Thorac Surg.* 2002;73:1411–1417.
- Ohmes LB, Di Franco A, Di Giammarco G, Rosati CM, Lau C, Girardi LN, Massetti M, Gaudino M. Techniques for intraoperative graft assessment in coronary artery bypass surgery. *J Thorac Dis.* 2017;9:S327–S332.
- Moscarelli M, Harling L, Ashrafian H, Athanasios T, Casula R. Challenges facing totally endoscopic robotic coronary artery bypass grafting. *Int J Med Robot.* 2015;11:18–29.
- Formica F, Mariani S, Broccolo F, Caruso R, Corti F, D'Alessandro S, Amigoni P, Sangalli F, Paolini G. Systemic and myocardial inflammatory response in coronary artery bypass graft surgery with miniaturized extracorporeal circulation: differences with a standard circuit and off-pump technique in a randomized clinical trial. *ASAIO J.* 2013;59:600–606.
- Antoniades C, Demosthenous M, Reilly S, Margaritis M, Zhang M-H, Antonopoulos A, Marinou K, Nahar K, Jayaram R, Tousoulis D, Bakogiannis C, Sayeed R, Triantafyllou C, Koumallos N, Psarros C, Miliou A, Stefanadis C, Channon KM, Casadei B. Myocardial redox state predicts in-hospital clinical outcome after cardiac surgery effects of short-term pre-operative statin treatment. *J Am Coll Cardiol.* 2012;59:60–70.
- Wan IYP, Arifi AA, Wan S, Yip JHY, Sihoe ADL, Thung KH, Wong EMC, Yim APC. Beating heart revascularization with or without cardiopulmonary bypass: evaluation of inflammatory response in a prospective randomized study. *J Thorac Cardiovasc Surg.* 2004;127:1624–1631.
- Czerny M, Baumer H, Kilo J, Lassnigg A, Hamwi A, Vukovich T, Wolner E, Grimm M. Inflammatory response and myocardial injury following coronary artery bypass grafting with or without cardiopulmonary bypass. *Eur J Cardiothorac Surg.* 2000;17:737–742.
- Greilich PE, Brouse CF, Rinder HM, Jessen ME, Rinder CS, Eberhart RC, Whitten CW, Smith BR. Monocyte activation in on-pump versus off-pump coronary artery bypass surgery. *J Cardiothorac Vasc Anesth.* 2008;22:361–368.
- Winterhalter M, Brandl K, Rahe-Meyer N, Osthaus A, Hecker H, Hagl C, Adams HA, Piepenbrock S. Endocrine stress response and inflammatory activation during CABG surgery. A randomized trial comparing remifentanyl infusion to intermittent fentanyl. *Eur J Anaesthesiol.* 2008;25:326–335.
- Nesher N, Frolkis I, Vardi M, Sheinberg N, Bakir I, Caselman F, Pevni D, Ben-Gal Y, Sharony R, Bolotin G, Loberman D, Uretzky G, Weinbroum AA. Higher levels of serum cytokines and myocardial tissue markers during on-pump versus off-pump coronary artery bypass surgery. *J Card Surg.* 2006;21:395–402.
- Ghorbel MT, Cherif M, Mokhtari A, Bruno VD, Caputo M, Angelini GD. Off-pump coronary artery bypass surgery is associated with fewer gene expression changes in the human myocardium in comparison with on-pump surgery. *Physiol Genomics.* 2010;42:67–75.
- Rogers CA, Pike K, Angelini GD, Reeves BC, Glauber M, Ferrarini M, Murphy GJ. An open randomized controlled trial of median sternotomy versus anterolateral left thoracotomy on morbidity and health care resource use in patients having off-pump coronary artery bypass surgery: the Sternotomy Versus Thoracotomy (STET) trial. *J Thorac Cardiovasc Surg.* 2013;146:306–309.
- Meng F, Ma J, Wang W, Lin B. Meta-analysis of interleukin 6, 8, and 10 between off-pump and on-pump coronary artery bypass groups. *Bosn J Basic Med Sci.* 2017;17:85–94.
- Jongman RM, Zijlstra JG, Kok WF, van Harten AE, Mariani MA, Moser J, Struys MMRF, Absalom AR, Molema G, Scheeren TWL, van Meurs M. Off-pump CABG surgery reduces systemic inflammation compared with on-pump surgery but does not change systemic endothelial responses: a prospective randomized study. *Shock.* 2014;42:121–128.
- Bu X, Wang B, Wang Y, Wang Z, Gong C, Qi F, Zhang C. Pathway-related modules involved in the application of sevoflurane or propofol in off-pump coronary artery bypass graft surgery. *Exp Ther Med.* 2017;14:97–106.
- van Straten AHM, Soliman Hamad MA, van Zundert AJ, Martens EJ, Schönberger JPAM, de Wolf AM. Preoperative C-reactive protein levels to predict early and late mortalities after coronary artery bypass surgery: eight years of follow-up. *J Thorac Cardiovasc Surg.* 2009;138:954–958.
- Paschalis A, Tousoulis D, Demosthenous M, Antonopoulos A, Papaioannou S, Miliou A, Koumallos N, Antoniadis C, Stefanadis C. Pre-operative inflammation and post-operative atrial fibrillation in coronary artery bypass surgery. *Int J Cardiol.* 2014;173:327–328.
- Gaudino M, Di Castelnuovo A, Zamparelli R, Andreotti F, Burzotta F, Iacoviello L, Glieda F, Alessandrini F, Nasso G, Donati MB, Maseri A, Schiavello R, Possati G. Genetic control of postoperative systemic inflammatory reaction and pulmonary and renal complications after coronary artery surgery. *J Thorac Cardiovasc Surg.* 2003;126:1107–1112.
- Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes J-C, Novick RJ, Vaijyanath P, Reddy S, Tao L, Olavegeascoechea PA, Arian B, Sulling T-A, Whitlock RP, Ou Y, Ng J, Chrolavicius S, Yusuf S; CORONARY Investigators. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med.* 2012;366:1489–1497.
- Chaney MA. Corticosteroids and cardiopulmonary bypass: a review of clinical investigations. *Chest.* 2002;121:921–931.
- Radaelli A, Loardi C, Cazzaniga M, Balestri G, DeCarlini C, Cerrito MG, Cusa EN, Guerra L, Garducci S, Santo D, Menicanti L, Paolini G, Azzellino A, Lavitrano ML, Mancia G, Ferrari AU. Inflammatory activation during coronary artery surgery and its dose-dependent modulation by statin/ACE-inhibitor combination. *Arterioscler Thromb Vasc Biol.* 2007;27:2750–2755.
- Parolari A, Poggio P, Myasoedova V, Songia P, Pillozzi A, Alamanni F, Tremoli E. Molecular pathways activation in coronary artery bypass surgery: which role for pump avoidance? *J Cardiovasc Med.* 2016;17:54–61.
- Davi G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med.* 2007;357:2482–2494.
- Cavalca V, Rocca B, Veglia F, Petrucci G, Porro B, Myasoedova V, De Cristofaro R, Turnu L, Bonomi A, Songia P, Cavallotti L, Zanolini M, Carnera M, Alamanni F, Parolari A, Patrono C. On-pump cardiac surgery enhances platelet renewal and impairs aspirin pharmacodynamics: effects of improved dosing regimens. *Clin Pharmacol Ther.* 2017;102:849–858.
- Zimmermann N, Kurt M, Wenk A, Winter J, Gams E, Hohfeld T. Is cardiopulmonary bypass a reason for aspirin resistance after coronary artery bypass grafting? *Eur J Cardiothorac Surg.* 2005;27:606–610.
- Bochsen L, Rosengard LB, Nielsen AB, Steinbrüchel DA, Johansson PI. Platelet hyperreactivity in response to on- and off-pump coronary artery bypass grafting. *J Extra Corpor Technol.* 2009;41:15–19.

35. Gielen CLI, Brand A, van Heerde WL, Stijnen T, Klautz RJM, Eikenboom J. Hemostatic alterations during coronary artery bypass grafting. *Thromb Res*. 2016;140:140–146.
36. Ivert T, Dalén M, Ander C, Stålesen R, Näsman P, Lordkipanidzé M, Hjemdahl P. Platelet function one and three months after coronary bypass surgery in relation to once or twice daily dosing of acetylsalicylic acid. *Thromb Res*. 2017;149:64–69.
37. Paikin JS, Hirsh J, Ginsberg JS, Weitz JI, Chan NC, Whitlock RP, Pare G, Eikelboom JW. Once versus twice daily aspirin after coronary bypass surgery: a randomized trial. *J Thromb Haemost*. 2017;15:889–896.
38. Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, Lucke JC, Baltz JH, Novitzky D; Veterans Affairs Randomized On/Off Bypass (ROOBY) Study Group. On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med*. 2009;361:1827–1837.
39. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Straka Z, Piegas LS, Avezum A, Akar AR, Lanas Zanetti F, Jain AR, Noiseux N, Padmanabhan C, Bahamondes J-C, Novick RJ, Tao L, Olavegogeochea PA, Airan B, Sulling T-A, Whitlock RP, Ou Y, Gao P, Pettit S, Yusuf S. Five-year outcomes after off-pump or on-pump coronary-artery bypass grafting. *N Engl J Med*. 2016;375:2359–2368.
40. Shroyer AL, Hattler B, Wagner TH, Collins JF, Baltz JH, Quin JA, Almassi GH, Kozora E, Bakaeen F, Cleveland JC, Bishawi M, Grover FL. Five-year outcomes after on-pump and off-pump coronary-artery bypass. *N Engl J Med*. 2017;377:623–632.
41. Diegeler A, Börgermann J, Kappert U, Breuer M, Böning A, Ursulescu A, Rastan A, Holzhey D, Treede H, Rieß F-C, Veeckmann P, Asfoor A, Reents W, Zacher M, Hilker M; GOPCABE Study Group. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. *N Engl J Med*. 2013;368:1189–1198.
42. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes J-C, Novick RJ, Vijaynath P, Reddy SK, Tao L, Olavegogeochea PA, Airan B, Sulling T-A, Whitlock RP, Ou Y, Pogue J, Chrolavicius S, Yusuf S; CORONARY Investigators. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. *N Engl J Med*. 2013;368:1179–1188.
43. Polomsky M, He X, O'Brien SM, Puskas JD. Outcomes of off-pump versus on-pump coronary artery bypass grafting: impact of preoperative risk. *J Thorac Cardiovasc Surg*. 2013;145:1193–1198.
44. Kuss O, von Salviati B, Börgermann J. Off-pump versus on-pump coronary artery bypass grafting: a systematic review and meta-analysis of propensity score analyses. *J Thorac Cardiovasc Surg*. 2010;140:829–835, 835.e1–13.
45. Lattouf OM, Thourani VH, Kilgo PD, Halkos ME, Baio KT, Myung R, Cooper WA, Guyton RA, Puskas JD. Influence of on-pump versus off-pump techniques and completeness of revascularization on long-term survival after coronary artery bypass. *Ann Thorac Surg*. 2008;86:797–805.
46. Di Mauro M, Gagliardi M, Iacò AL, Contini M, Bivona A, Bosco P, Gallina S, Calafiore AM. Does off-pump coronary surgery reduce postoperative acute renal failure? The importance of preoperative renal function. *Ann Thorac Surg*. 2007;84:1496–1502.
47. Kirmani BH, Holmes MV, Muir AD. Long-term survival and freedom from reintervention after off-pump coronary artery bypass grafting: a propensity-matched study. *Circulation*. 2016;134:1209–1220.
48. Filardo G, Grayburn PA, Hamilton C, Hebler RF, Cooksey WB, Hamman B. Comparing long-term survival between patients undergoing off-pump and on-pump coronary artery bypass graft operations. *Ann Thorac Surg*. 2011;92:571–578.
49. Filardo G, Hamman BL, da Graca B, Sass DM, Machala NJ, Ismail S, Pollock BD, Collinsworth AW, Grayburn PA. Efficacy and effectiveness of on- versus off-pump coronary artery bypass grafting: a meta-analysis of mortality and survival. *J Thorac Cardiovasc Surg*. 2018;155:172–179.
50. Smart NA, Dieberg G, King N. Long-term outcomes of on- versus off-pump coronary artery bypass grafting. *J Am Coll Cardiol*. 2018;71:983–991.
51. Kowalewski M, Pawlitzak W, Malvindi PG, Bokszanski MP, Perlinski D, Raffa GM, Kowalkowska ME, Zaborowska K, Navarese EP, Kolodziejczak M, Kowalewski J, Tarelli G, Taggart DP, Anisimowicz L. Off-pump coronary artery bypass grafting improves short-term outcomes in high-risk patients compared with on-pump coronary artery bypass grafting: meta-analysis. *J Thorac Cardiovasc Surg*. 2016;151:58–60.
52. Puskas JD, Thourani VH, Kilgo P, Cooper W, Vassiliades T, Vega JD, Morris C, Chen E, Schmotzer BJ, Guyton RA, Lattouf OM. Off-pump coronary artery bypass disproportionately benefits high-risk patients. *Ann Thorac Surg*. 2009;88:1142–1147.
53. Dhurandhar V, Saxena A, Parikh R, Vallely MP, Wilson MK, Butcher JK, Black DA, Tran L, Reid CM, Bannon PG. Outcomes of on-pump versus off-pump coronary artery bypass graft surgery in the high risk (AusSCORE > 5). *Heart Lung Circ*. 2015;24:1216–1224.
54. Keeling WB, Williams ML, Slaughter MS, Zhao Y, Puskas JD. Off-pump and on-pump coronary revascularization in patients with low ejection fraction: a report from the Society of Thoracic Surgeons national database. *Ann Thorac Surg*. 2013;96:83–89.
55. Ueki C, Miyata H, Motomura N, Sakaguchi G, Akimoto T, Takamoto S. Off-pump versus on-pump coronary artery bypass grafting in patients with left ventricular dysfunction. *J Thorac Cardiovasc Surg*. 2016;151:1092–1098.
56. Jarral OA, Saso S, Athanasiou T. Off-pump coronary artery bypass in patients with left ventricular dysfunction: a meta-analysis. *Ann Thorac Surg*. 2011;92:1686–1694.
57. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand S-LT, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP; Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1—coronary artery bypass grafting surgery. *Ann Thorac Surg*. 2009;88:S2–S22.
58. Khan H, Uzzaman M, Benedetto U, Butt S, Raja SG. On- or off-pump coronary artery bypass grafting for octogenarians: a meta-analysis of comparative studies involving 27,623 patients. *Int J Surg*. 2017;47:42–51.
59. Houliind K, Kjeldsen BJ, Madsen SN, Rasmussen BS, Holme SJ, Nielsen PH, Mortensen PE; DOORS Study Group. On-pump versus off-pump coronary artery bypass surgery in elderly patients: results from the Danish on-pump versus off-pump randomization study. *Circulation*. 2012;125:2431–2439.
60. Cavallaro P, Itagaki S, Seigerman M, Chikwe J. Operative mortality and stroke after on-pump vs off-pump surgery in high-risk patients: an analysis of 83,914 coronary bypass operations. *Eur J Cardiothorac Surg*. 2014;45:159–164.
61. Edwards FH, Carey JS, Grover FL, Bero JW, Hartz RS. Impact of gender on coronary bypass operative mortality. *Ann Thorac Surg*. 1998;66:125–131.
62. Hannan EL, Bernard HR, Kilburn HC, O'Donnell JF. Gender differences in mortality rates for coronary artery bypass surgery. *Am Heart J*. 1992;123:866–872.
63. Puskas JD, Kilgo PD, Kutner M, Pusca SV, Lattouf O, Guyton RA. Off-pump techniques disproportionately benefit women and narrow the gender disparity in outcomes after coronary artery bypass surgery. *Circulation*. 2007;116:1192–1199.
64. Puskas JD, Edwards FH, Pappas PA, O'Brien S, Peterson ED, Kilgo P, Ferguson TB. Off-pump techniques benefit men and women and narrow the disparity in mortality after coronary bypass grafting. *Ann Thorac Surg*. 2007;84:1447–1456.
65. Attaran S, Harling L, Ashrafian H, Moscarelli M, Casula R, Anderson J, Punjabi P, Athanasiou T. Off-pump versus on-pump revascularization in females: a meta-analysis of observational studies. *Perfusion*. 2014;29:385–396.
66. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand S-LT, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP; Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2—isolated valve surgery. *Ann Thorac Surg*. 2009;88:S23–S42.
67. Edwards FH, Ferraris VA, Shahian DM, Peterson E, Furnary AP, Haan CK, Bridges CR; Society of Thoracic Surgeons. Gender-specific practice guidelines for coronary artery bypass surgery: perioperative management. *Ann Thorac Surg*. 2005;79:2189–2194.
68. Mishra M, Malhotra R, Karlekar A, Mishra Y, Trehan N. Propensity case-matched analysis of off-pump versus on-pump coronary artery bypass grafting in patients with atheromatous aorta. *Ann Thorac Surg*. 2006;82:608–614.
69. Sharyon R, Grossi EA, Saunders PC, Galloway AC, Applebaum R, Ribakove GH, Culliford AT, Kanchuger M, Kronzon I, Colvin SB. Propensity case-matched analysis of off-pump coronary artery bypass grafting in patients with atheromatous aortic disease. *J Thorac Cardiovasc Surg*. 2004;127:406–413.
70. Zembala MO, Filipiak K, Ciesla D, Pacholewicz J, Hrapkowicz T, Knapik P, Przybylski R, Zembala M. Surgical treatment of left main disease and severe carotid stenosis: does the off-pump technique provide a better outcome? *Eur J Cardiothorac Surg*. 2013;43:541–548; discussion 548.
71. Mishra Y, Wasir H, Kohli V, Meharwal ZS, Malhotra R, Mehta Y, Trehan N. Concomitant carotid endarterectomy and coronary bypass surgery: outcome of on-pump and off-pump techniques. *Ann Thorac Surg*. 2004;78:2037–2043.
72. Halkos ME, Puskas JD, Lattouf OM, Kilgo P, Guyton RA, Thourani VH. Impact of preoperative neurologic events on outcomes after coronary artery bypass grafting. *Ann Thorac Surg*. 2008;86:504–510; discussion 510.
73. Kozora E, Kongs S, Collins JF, Hattler B, Baltz J, Hampton M, Grover FL, Novitzky D, Shroyer AL. Cognitive outcomes after on- versus off-pump coronary artery bypass surgery. *Ann Thorac Surg*. 2010;90:1134–1141.
74. Kim HJ, Kim JB, Jung S-H, Choo SJ, Lee JW, Chung CH. Coronary artery bypass grafting in patients with severe chronic kidney disease: a propensity score-weighted analysis on the impact of on-pump versus off-pump strategies. *Eur J Cardiothorac Surg*. 2017;52:937–944.

75. Wang Y, Zhu S, Gao P, Zhou J, Zhang Q. Off-pump versus on-pump coronary surgery in patients with chronic kidney disease: a meta-analysis. *Clin Exp Nephrol*. 2018;22:99–109.
76. Chen J-J, Lin L-Y, Yang Y-H, Hwang J-J, Chen P-C, Lin J-L, Chi N-H. On pump versus off pump coronary artery bypass grafting in patients with end-stage renal disease and coronary artery disease—a nation-wide, propensity score matched database analyses. *Int J Cardiol*. 2017;227:529–534.
77. Lim JY, Deo SV, Jung SH, Altarabsheh SE, Erwin PJ, Dillon JJ, Park SJ. Does off-pump coronary artery bypass confer any advantage in patients with end-stage renal failure? A systematic review and meta-analysis. *Heart Lung Circ*. 2015;24:55–61.
78. Gopaldas RR, Chu D, Cornwell LD, Dao TK, Lemaire SA, Coselli JS, Bakaeeen FG. Cirrhosis as a moderator of outcomes in coronary artery bypass grafting and off-pump coronary artery bypass operations: a 12-year population-based study. *Ann Thorac Surg*. 2013;96:1310–1315.
79. Hattler B, Messenger JC, Shroyer AL, Collins JF, Haugen SJ, Garcia JA, Baltz JH, Cleveland JC, Novitzky D, Grover FL. Off-Pump coronary artery bypass surgery is associated with worse arterial and saphenous vein graft patency and less effective revascularization: results from the Veterans Affairs Randomized On/Off Bypass (ROOBY) trial. *Circulation*. 2012;125:2827–2835.
80. Puskas JD, Williams WH, O'Donnell R, Patterson RE, Sigman SR, Smith AS, Baio KT, Kilgo PD, Guyton RA. Off-pump and on-pump coronary artery bypass grafting are associated with similar graft patency, myocardial ischemia, and freedom from reintervention: long-term follow-up of a randomized trial. *Ann Thorac Surg*. 2011;91:1836–1843.
81. Kobayashi J, Tashiro T, Ochi M, Yaku H, Watanabe G, Satoh T, Tagusari O, Nakajima H, Kitamura S; Japanese Off-Pump Coronary Revascularization Investigation (JOCRI) Study Group. Early outcome of a randomized comparison of off-pump and on-pump multiple arterial coronary revascularization. *Circulation*. 2005;112:1338–1343.
82. Magee MJ, Alexander JH, Hafley G, Ferguson TB, Gibson CM, Harrington RA, Peterson ED, Califf RM, Kouchoukos NT, Herbert MA, Mack MJ; PREVENT IV Investigators. Coronary artery bypass graft failure after on-pump and off-pump coronary artery bypass: findings from PREVENT IV. *Ann Thorac Surg*. 2008;85:494–500.
83. Zhang B, Zhou J, Li H, Liu Z, Chen A, Zhao Q. Comparison of graft patency between off-pump and on-pump coronary artery bypass grafting: an updated meta-analysis. *Ann Thorac Surg*. 2014;97:1335–1341.
84. Deppe A-C, Arbash W, Kuhn EW, Slottosch I, Scherner M, Liakopoulos OJ, Choi Y-H, Wahlers T. Current evidence of coronary artery bypass grafting off-pump versus on-pump: a systematic review with meta-analysis of over 16,900 patients investigated in randomized controlled trials†. *Eur J Cardiothorac Surg*. 2016;49:1031–1041; discussion 1041.
85. Takagi H, Watanabe T, Mizuno Y, Kawai N, Umemoto T; ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. A meta-analysis of adjusted risk estimates for survival from observational studies of complete versus incomplete revascularization in patients with multivessel disease undergoing coronary artery bypass grafting. *Interact Cardiovasc Thorac Surg*. 2014;18:679–682.
86. Magee MJ, Hebert E, Herbert MA, Prince SL, Dewey TM, Culica DV, Mack MJ. Fewer grafts performed in off-pump bypass surgery: patient selection or incomplete revascularization? *Ann Thorac Surg*. 2009;87:1113–1118; discussion 1118.
87. Lamy A, Devereaux PJ, Yusuf S. Five-year outcomes after off-pump or on-pump coronary-artery bypass grafting. *N Engl J Med*. 2017;376:894–895.
88. Benedetto U, Caputo M, Patel NN, Fiorentino F, Bryan A, Angelini GD. Long-term survival after off-pump versus on-pump coronary artery bypass graft surgery. Does completeness of revascularization play a role? *Int J Cardiol*. 2017;246:32–36.
89. Benedetto U, Gaudino M, Di Franco A, Caputo M, Ohmes LB, Grau J, Glineur D, Girardi LN, Angelini GD. Incomplete revascularization and long-term survival after coronary artery bypass surgery. *Int J Cardiol*. 2018;254:59–63.
90. Caputo M, Reeves BC, Rajkaruna C, Awair H, Angelini GD. Incomplete revascularization during OPCAB surgery is associated with reduced mid-term event-free survival. *Ann Thorac Surg*. 2005;80:2141–2147.
91. Glance LG, Dick AW, Osler TM, Mukamel DB. The relation between surgeon volume and outcome following off-pump vs on-pump coronary artery bypass graft surgery. *Chest*. 2005;128:829–837.
92. Lapar DJ, Mery CM, Kozower BD, Kern JA, Kron IL, Stukenborg GJ, Ailawadi G. The effect of surgeon volume on mortality for off-pump coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2012;143:854–863.
93. Benedetto U, Altman DG, Gerry S, Gray A, Lees B, Flather M, Taggart DP; Arterial Revascularization Trial Investigators. Off-pump versus on-pump coronary artery bypass grafting: insights from the Arterial Revascularization Trial. *J Thorac Cardiovasc Surg*. 2018;155:1545–1553.e7.
94. Bakaeeen FG, Shroyer ALW, Gammie JS, Sabik JF, Cornwell LD, Coselli JS, Rosengart TK, O'Brien SM, Wallace A, Shahian DM, Grover FL, Puskas JD. Trends in use of off-pump coronary artery bypass grafting: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. *J Thorac Cardiovasc Surg*. 2014;148:856–864.
95. Benedetto U, Lau C, Caputo M, Kim L, Feldman DN, Ohmes LB, Di Franco A, Soletti G, Angelini GD, Girardi LN, Gaudino M. Comparison of outcomes for off-pump versus on-pump coronary artery bypass grafting in low-volume and high-volume centers and by low-volume and high-volume surgeons. *Am J Cardiol*. 2018;121:552–557.
96. Mukherjee D, Ahmed K, Baig K, Patel VM, Darzi A, Athanasiou T. Conversion and safety in off-pump coronary artery bypass: a system failure that needs re-emphasis. *Ann Thorac Surg*. 2011;91:630–639.
97. Keeling B, Thourani V, Aliawadi G, Kim S, Cyr D, Badhwar V, Jacobs JP, Brennan JM, Meza J, Matsouaka R, Halkos ME. Conversion from off-pump coronary artery bypass grafting to on-pump coronary artery bypass grafting. *Ann Thorac Surg*. 2017;104:1267–1274.
98. Mukherjee D, Ashrafian H, Kourliouros A, Ahmed K, Darzi A, Athanasiou T. Intra-operative conversion is a cause of masked mortality in off-pump coronary artery bypass: a meta-analysis. *Eur J Cardiothorac Surg*. 2012;41:291–299.
99. Stevens L-M, Noiseux N, Avezum A, Ayapati DR, Chen X, Lucchese FA, Cacheda H, Parvathaneni S, Ou Y, Lamy A; CORONARY Investigators. Conversion after off-pump coronary artery bypass grafting: the CORONARY trial experience. *Eur J Cardiothorac Surg*. 2017;51:539–546.
100. Edgerton JR, Dewey TM, Magee MJ, Herbert MA, Prince SL, Jones KK, Mack MJ. Conversion in off-pump coronary artery bypass grafting: an analysis of predictors and outcomes. *Ann Thorac Surg*. 2003;76:1138–1143.
101. Reeves BC, Ascione R, Caputo M, Angelini GD. Morbidity and mortality following acute conversion from off-pump to on-pump coronary surgery. *Eur J Cardiothorac Surg*. 2006;29:941–947.
102. Shiga T, Apfel CC, Wajima Z, Ohe Y. Influence of intraoperative conversion from off-pump to on-pump coronary artery bypass grafting on costs and quality of life: a cost-effectiveness analysis. *J Cardiothorac Vasc Anesth*. 2007;21:793–799.
103. Li Z, Amsterdam EA, Danielsen B, Hoegh H, Young JN, Armstrong EJ. Intraoperative conversion from off-pump to on-pump coronary artery bypass is associated with increased 30-day hospital readmission. *Ann Thorac Surg*. 2014;98:16–22.
104. Maroto Castellanos LC, Carnero M, Cobiella FJ, Alswies A, Ayaon A, Reguillo FJ, Garcia M. Off-pump to on-pump emergency conversion: incidence, risk factors, and impact on short- and long-term results. *J Card Surg*. 2015;30:735–745.
105. Chowdhury R, White D, Kilgo P, Puskas JD, Thourani VH, Chen EP, Lattouf OM, Cooper WA, Myung RJ, Guyton RA, Halkos ME. Risk factors for conversion to cardiopulmonary bypass during off-pump coronary artery bypass surgery. *Ann Thorac Surg*. 2012;93:1936–1941; discussion 1942.
106. Mehaffey JH, Hawkins RB, Byler M, Charles EJ, Fonner C, Kron I, Quader M, Speir A, Rich J, Ailawadi G; Virginia Cardiac Services Quality Initiative. Cost of individual complications following coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2018;155:875–882.
107. Arom KV, Emery RW, Flavin TF, Petersen RJ. Cost-effectiveness of minimally invasive coronary artery bypass surgery. *Ann Thorac Surg*. 1999;68:1562–1566.
108. Boyd WD, Desai ND, Del Rizzo DF, Novick RJ, McKenzie FN, Menkis AH. Off-pump surgery decreases postoperative complications and resource utilization in the elderly. *Ann Thorac Surg*. 1999;68:1490–1493.
109. Ascione R, Lloyd CT, Underwood MJ, Lotto AA, Pitsis AA, Angelini GD. Economic outcome of off-pump coronary artery bypass surgery: a prospective randomized study. *Ann Thorac Surg*. 1999;68:2237–2242.
110. Nathoe HM, van Dijk D, Jansen EWL, Suyker WJL, Diephuis JC, van Boven W-J, de la Rivière AB, Borst C, Kalkman CJ, Grobbee DE, Buskens E, de Jaegere PPT; Octopus Study Group. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. *N Engl J Med*. 2003;348:394–402.
111. Puskas JD, Williams WH, Mahoney EM, Huber PR, Block PC, Duke PG, Staples JR, Glas KE, Marshall JJ, Leimbach ME, McCall SA, Petersen RJ, Bailey DE, Weintraub WS, Guyton RA. Off-pump vs conventional coronary artery bypass grafting: early and 1-year graft patency, cost, and quality-of-life outcomes: a randomized trial. *JAMA*. 2004;291:1841–1849.
112. Lamy A, Wang X, Farrokhvar F, Kent R. A cost comparison of off-pump CABG versus on-pump CABG at one-year: the Canadian off-pump CABG registry. *Can J Cardiol*. 2006;22:699–704.
113. Chu D, Bakaeeen FG, Dao TK, LeMaire SA, Coselli JS, Huh J. On-pump versus off-pump coronary artery bypass grafting in a cohort of 63,000 patients. *Ann Thorac Surg*. 2009;87:1820–1827.

114. Houlind K, Kjeldsen BJ, Madsen SN, Rasmussen BS, Holme SJ, Pallesen PA, Mortensen PE, Fenger-Grøn M, Beck SJ, Ehlers LH; DOORS Study Group. OPCAB surgery is cost-effective for elderly patients. *Scand Cardiovasc J*. 2013;47:185–192.
115. Lamy A, Tong W, Devereaux PJ, Gao P, Gafni A, Singh K, Taggart D, Straka Z, Akar AR, Piegas L, Ou Y, Yusuf S. The cost implications of off-pump versus on-pump coronary artery bypass graft surgery at one year. *Ann Thorac Surg*. 2014;98:1620–1625.
116. Scott BH, Seifert FC, Grimson R, Glass PSA. Resource utilization in on- and off-pump coronary artery surgery: factors influencing postoperative length of stay—an experience of 1,746 consecutive patients undergoing fast-track cardiac anesthesia. *J Cardiothorac Vasc Anesth*. 2005;19:26–31.
117. Wagner TH, Hattler B, Bishawi M, Baltz JH, Collins JF, Quin JA, Grover FL, Shroyer ALW; VA #517 Randomized On/Off Bypass (ROOBY) Study Group. On-pump versus off-pump coronary artery bypass surgery: cost-effectiveness analysis alongside a multisite trial. *Ann Thorac Surg*. 2013;96:770–777.
118. Shinjo D, Fushimi K. Preoperative factors affecting cost and length of stay for isolated off-pump coronary artery bypass grafting: hierarchical linear model analysis. *BMJ Open*. 2015;5:e008750.
119. Seco M, Edelman JJB, Van Boxtel B, Forrest P, Byrom MJ, Wilson MK, Fraser J, Bannon PG, Valley MP. Neurologic injury and protection in adult cardiac and aortic surgery. *J Cardiothorac Vasc Anesth*. 2015;29:185–195.
120. Zhao DF, Edelman JJ, Seco M, Bannon PG, Wilson MK, Byrom MJ, Thourani V, Lamy A, Taggart DP, Puskas JD, Valley MP. Coronary artery bypass grafting with and without manipulation of the ascending aorta: a network meta-analysis. *J Am Coll Cardiol*. 2017;69:924–936.
121. Mohr FW, Morice M-C, Kappetein AP, Feldman TE, Stähle E, Colombo A, Mack MJ, Holmes DR, Morel M, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet*. 2013;381:629–638.
122. Meyerson J, Thelin S, Gordh T, Karlsten R. The incidence of chronic post-sternotomy pain after cardiac surgery—a prospective study. *Acta Anaesthesiol Scand*. 2001;45:940–944.
123. McGinn JT, Usman S, Lapierre H, Pothula VR, Mesana TG, Ruel M. Minimally invasive coronary artery bypass grafting: dual-center experience in 450 consecutive patients. *Circulation*. 2009;120:S78–S84.
124. Bonatti J, Schachner T, Bonaros N, Lehr EJ, Zimrin D, Griffith B. Robotically assisted totally endoscopic coronary bypass surgery. *Circulation*. 2011;124:236–244.
125. Puskas JD, Halkos ME, DeRose JJ, Bagiella E, Miller MA, Overbey J, Bonatti J, Srinivas VS, Vesely M, Sutter F, Lynch J, Kirkwood K, Shapiro TA, Boudoulas KD, Crestanello J, Gehrig T, Smith P, Ragosta M, Hoff SJ, Zhao D, Gelijns AC, Szeto WY, Weisz G, Argenziano M, Vassiliades T, Liberman H, Matthai W, Ascheim DD. Hybrid coronary revascularization for the treatment of multivessel coronary artery disease: a multicenter observational study. *J Am Coll Cardiol*. 2016;68:356–365.
126. Bonatti J, Vetrovec G, Riga C, Wazni O, Stadler P. Robotic technology in cardiovascular medicine. *Nat Rev Cardiol*. 2014;11:266–275.
127. Lapierre H, Chan V, Sohmer B, Mesana TG, Ruel M. Minimally invasive coronary artery bypass grafting via a small thoracotomy versus off-pump: a case-matched study. *Eur J Cardiothorac Surg*. 2011;40:804–810.

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