

Current outcomes of off-pump coronary artery bypass grafting: evidence from real world practice

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Abstract: Coronary artery bypass grafting (CABG) can be performed conventionally using cardiopulmonary bypass (CPB) and aortic clamping or on a beating heart (BH) without the use of CPB, the so-called off-pump CABG. Some surgeons, who are proponents of off-pump CABG, preferentially use this technique for the majority of operations, whereas others use it only in certain situations which warrant avoidance of CPB. Ever since the conception of off-pump CABG, the never-ending debate about which technique of CABG is safe and efficacious continues to date. Several randomized controlled trials (RCTs) have been conducted that have either favored on-pump CABG or have failed to show a significant difference in outcomes between the two techniques. However, these RCTs have been fraught with claims that they do not represent the majority of patients undergoing CABG in real world practice. Therefore, assessment of the benefits and drawbacks of each technique through observational and registry studies would be more representative of patients encountered in daily practice. The present review examines various retrospective studies and meta-analyses of observational studies that compare the early and long-term outcomes of off- and on-pump CABG, which assesses their safety and efficacy. Additionally, their outcomes in older patients, females, and those with diabetes mellitus, renal dysfunction, presence of ascending aortic disease, and/or acute coronary syndrome (ACS) have also been discussed separately. The general consensus is that early results of off-pump CABG are comparable to or in some cases better than on-pump CABG. However, on-pump CABG provides a survival benefit in the long term according to a majority of publications in literature.

Keywords: Off-pump coronary artery bypass; real world outcomes

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Introduction

Off-pump surgery has evolved into the most frequently adopted alternative technique to conventional on-pump coronary artery bypass grafting (CABG) in the treatment of patients with coronary artery disease (CAD) over the last two decades. It has even become the procedure of choice for some surgeons, who believe that off-pump CABG is associated with lower occurrence of perioperative complications due to avoidance of cardiopulmonary bypass (CPB) and reduced or lack of manipulation of the ascending aorta. A rise in the number of off-pump CABG procedures in the late nineties and the earlier half of the first decade of the new millennium set off a never-ending debate regarding

the benefits and drawbacks intrinsic to the two techniques of CABG. Several randomized controlled trials (RCTs) were conducted to compare the outcomes of off-pump with on-pump CABG (1-4). Most trials demonstrated no difference in immediate outcomes between the two CABG techniques. Nevertheless, the two major RCTs, the Randomized On/Off Bypass (ROOBY) trial and the Danish On-pump versus Off-pump Randomization Study (DOORS) revealed a significantly higher rate of the primary composite outcome including all-cause mortality, repeat revascularization (RR), or nonfatal myocardial infarction (MI) at 1 year and an inferior graft patency at 6 months following surgery in patients, who underwent off-pump CABG, respectively (2,3). In contrast, other important RCTs such

as the CABG Off- or On-Pump Revascularization Study (CORONARY) and the Surgical Management of Arterial Revascularization Therapies (SMART) trial identified no differences in mortality, stroke, MI, RR and quality of life between off- and on-pump CABG at a follow-up of 1 year (1,5). The latter study also showed similar angiographic patency rates. The power of these RCTs to detect and assess differences in clinically important outcome measures between the two operative techniques has been questionable. In addition, the variations in outcomes and inferences between randomized trials comparing the two CABG techniques have prompted the performance of numerous meta-analyses. Those published more than a decade ago revealed no statistical differences between off- and on-pump CABG with respect to mortality, MI and RR (6,7). However, the more recently published meta-analyses that have included contemporary RCTs have reported variable outcomes (8-12). Such variations in results of meta-analyses were probably due to the heterogeneity in the RCTs included in the analyses, which often had differing methodological quality with varying risks for randomization and blinding, making them prone to outcome reporting bias and systematic and random errors (13). Systematic bias occurs when the participating surgeons are not equally conversant with both, the new and conventional techniques (14). The RCTs comparing off- and on-pump CABG demonstrated diversity in the number, experience, surgical expertise and skills of the participating surgeons, which is one of the most important factors in determining outcomes following off-pump CABG (1,2,4,15). The latter was most evident from the wide range in the rate of conversion of off-pump to on-pump CABG and the lower mean number of distal anastomoses performed using the former technique amongst trials included in the meta-analyses (8). Such trials have often been criticized for the perceived imbalance of experience that favors conventional on-pump CABG. Furthermore, majority of patients enrolled in the RCTs did not represent the typical patients encountered in everyday practice. The vast proportion of them was low-risk patients without left ventricular (LV) dysfunction, in whom the expected postoperative complication rate was small. Moreover, the results of these meta-analyses were also influenced by the outcomes measures that were assessed, viz. mortality, major adverse cardiac and cerebrovascular events (MACCE), stroke, transfusion requirements or renal insufficiency, etc. and variability in the period of follow-up. Although, RCTs and their meta-analyses are considered to provide the highest level of research evidence

in favor or against a therapeutic option, they are also subject to limitations. It is extremely difficult to decipher the stage of development of a particular surgical technique in the institution participating in the trial. Apart from the surgeon, anesthesiologists, assistant surgeons or physicians and intensivists also play an important role in the smooth conduct of an off-pump CABG. Such confounding factors are usually never accounted for in the design of surgical RCTs (16). The results may, therefore, reflect the learning curve of the team as a whole, and not the true therapeutic effect of the surgical procedure.

Though RCTs are important research tools, they should not be considered the be- and end-all of research, especially for surgical interventions (17). High-quality observational studies performed using large, multi-institutional datasets, which have been widely adopted in cardiac surgery for quality control and clinical governance (18), to generate risk assessment tools (19,20), and facilitate improved outcomes (21), also provide robust evidence and represent real world practice. Such studies include a larger proportion of the actual patient population, which reduces sampling error, improves external validity (22), and elucidates inferences of causal relationships, if appropriate study designs and statistical modelling techniques are used (23). Additionally, they usually represent current clinical practice as opposed to RCTs that take several years before being published. Such studies are commonly performed by institutions that have achieved a certain level of proficiency and expertise in off-pump surgery and include either all-comers or a particular group of high-risk patients, who would normally be excluded from RCTs. The current review focuses on the results of off-pump CABG in real world practice with respect to safety and efficacy and in certain subsets of patients, in whom off-pump CABG would be expected to provide a substantial benefit.

Safety

Safety is the primary prerequisite for any surgical procedure or technique to be widely accepted as a treatment modality. A procedure should be associated with very few perioperative complications with occurrence rates at least similar to if not fewer than those following the conventional procedure or technique. The commonest perioperative complications that are used as outcome measures to compare on- and off-pump CABG are in-hospital or 30-day mortality, MI, stroke, renal and respiratory insufficiency, blood loss and transfusion requirements.

Several observational studies and outcomes of registry data reporting early results of the two CABG techniques have been published in literature. Some of the earlier reports such as those from the STS National Database between 1998 and 1999 (106,423 patients on-pump CABG; 11,717 patients off-pump CABG) and the New York database between 1997 and 2000 (59,044 on-pump CABG; 9,135 off-pump CABG) demonstrated that patients undergoing off-pump CABG had a lower risk-adjusted mortality, stroke rate, lesser re-exploration for bleeding and shorter postoperative length of stay despite being older with a higher proportion of females and more comorbidities such as chronic obstructive pulmonary disease (COPD), previous strokes and renal failure (24,25). Another large propensity-matched retrospective series involving 11,000 on-pump and 7,200 off-pump CABG patients not only revealed similar results, but also showed that use of CPB predicted overall mortality [odds ratio (OR) 2.08] as well as mortality in re-operations (OR 3.37) (26).

Another study involving the New York State patients from 2001 to 2004 (35,941 on-pump CABG; 13,889 off-pump CABG) by Hannan *et al.* again identified the benefits of off-pump CABG with regards to a significantly lower rate of in-patient mortality (adjusted OR 0.81), stroke (adjusted OR 0.70) and respiratory failure (adjusted OR 0.80) (27). Palmer *et al.* analyzed the CABG arm of the Coronary Artery Revascularization (CARE) study, which included 1,251 patients (654 on-pump CABG; 597 off-pump CABG) (28). On-pump CABG patients had higher risk scores due to a slightly lower ejection fraction (EF), the need for more urgent or emergent operative procedures, or larger number of previous PCI or CABG procedures. Operative mortality was similar between groups, but off-pump patients had significantly lower complication rates such as postoperative atrial fibrillation (AF), respiratory and renal complications and need for transfusions and prolonged ventilation. This study delivered important messages. First, the conversion rate from off- to on-pump CABG was 3.9%, which could be considered slightly high in the hands of experienced off-pump surgeons. However, the converted group of patients had no mortality, MI, stroke or reoperation for bleeding, which shows that the surgeons were experienced enough to identify or preempt the correct time to convert. This ability to anticipate or preempt a problem is one quality every off-pump surgeon should possess. Second, off-pump patients received fewer grafts than on-pump patients (2.9 vs. 3.2). Incomplete revascularization has been one of the commonest and serious concerns raised against

off-pump CABG. The authors, however, demonstrated that the ratio of anastomoses performed to lesions present was the same in both groups, indicating that the difference in the numbers of grafts was a patient selection issue; viz. patients needing fewer bypasses tend to undergo off-pump CABG, and not a result of incomplete revascularization. Third, they also reported the 12-month results revealing no differences in death, MI, or need for RR, which further alleviates the concerns about the quality of grafts or incomplete revascularization with off-pump CABG and further strengthens the belief that off-pump CABG is a safe operation and is at least as good if not better than conventional CABG with respect to short-term outcomes. Li and colleagues evaluated the results of 57,316 isolated CABG surgeries (44,165 on-pump CABG; 13,151 off-pump CABG) performed during the 3-year period between 2003 and 2005 from the California CABG Outcomes Reporting Program (CCORP) database involving 121 reporting hospitals (29). Off-pump CABG patients had more comorbidity, whereas on-pump patients had a poorer cardiac status with more patients suffering from left main or triple vessel disease, lower EF, cardiogenic shock, congestive heart failure, recent MI and a history of previous cardiac surgery. The overall propensity-adjusted operative mortality (PAOMR) was significantly lower in patients undergoing off-pump (2.59%) than on-pump CABG (3.22%) (OR 0.8; $P < 0.0001$). Off-pump CABG had significantly lower PAOMR than on-pump CABG for each quintile (all $P < 0.05$). Furthermore, all subgroup comparisons showed that off-pump CABG had a protective effect on operative mortality compared to on-pump CABG (all *t*-tests, $P < 0.001$). However, in contrast to the previous study, patients requiring conversions (6.2%) had the highest PAOMR compared to both, successful off-pump and on-pump CABGs. Multivariable logistic regression identified female gender, nonwhite, urgent acuity, diabetes, congestive heart failure, prior cardiac surgery, left main disease, ≥ 3 diseased coronary vessels, and moderate mitral insufficiency as the independent predictors of conversion. Their study also found that the probability for the patients with ≥ 3 -vessel disease to be converted to on-pump CABG was 77% higher than for those with < 3 -vessel disease after controlling for other confounders. Considering that most patients with poor cardiac status underwent on-pump CABG, the higher conversion rate and associated mortality observed in this series could be related to the inexperience or learning curve of the surgeons in off-pump CABG. Between 2003 and 2005, the same group further assessed

the impact of intraoperative conversion to on-pump CABG in 22,389 patients from the CCORP [5,125 (22.9%) off-pump CABG, 595 (11.6%) conversions to on-pump CABG, 17,264 (77.1%) on-pump CABG] on the 30-day readmission rates in hospital survivors (30). Patients undergoing intraoperative conversion to on-pump CABG had a significant effect on readmission (adjusted OR 1.3; $P < 0.0001$), whereas those undergoing successful off- or on-pump CABG did not have higher readmission rates. Interestingly, they found surgeon's off-pump CABG volume (each additional five operations) as an independent predictor of intraoperative conversion (OR 0.9; $P < 0.0001$). Another large non-randomized trial comparing the two CABG techniques included 186,458 patients (120,594 on-pump CABG; 65,864 off-pump CABG) from the STS database that were operated by surgeons having an experience of at least 150 off-pump and 150 on-pump cases over a 3-year period (31). The differences in preoperative profiles of patients in the two groups were similar to those of previous studies. The results favored off-pump surgery due to a significant reduction in operative mortality, overall adverse cardiac events, permanent stroke, dialysis, reoperation, prolonged ventilation, sternal wound infection, renal failure, and prolonged length of stay not only for all patients, but also across all coronary anatomic subsets. One of the more contemporary publications supporting the short-term benefits of off-pump surgery included two studies comparing the two CABG techniques (32). The first study was a single institution report involving 1,030 consecutive patients undergoing isolated on- or off-pump CABG, which used stratification method by propensity scores to demonstrate that off-pump surgery was associated with significantly reduced ventilation time ($P < 0.001$), intensive care unit (ICU) stay ($P < 0.001$), and operative mortality ($P = 0.022$). The second study, which analyzed 2,955 propensity matched pairs of patients from the Japanese National Database undergoing isolated CABG between 2008 and 2010 revealed that off-pump CABG was associated with reduced rates of 30-day ($P = 0.05$) and hospital mortality ($P = 0.05$), bleeding ($P = 0.004$), dialysis ($P = 0.005$), prolonged ICU stay ($P < 0.001$), ventilation ($P < 0.001$) and gastrointestinal bleeding ($P < 0.001$). Another recent report by Lushaj *et al.* analyzed a total of 252 consecutive patients undergoing off-pump ($n = 170$) and on-pump CABG ($n = 82$) at a Veterans Affairs Medical Center over a 5 years period from 2007 to 2012 (33). The two unique features of this study were that all consecutive patients that underwent off- or on-pump CABG were assigned to a surgeon who exclusively

performed off- or on-pump CABG, respectively and higher risk patients (EF $< 45\%$, chronic smokers, cerebrovascular disease) preferentially underwent off-pump revascularization. The former prerequisite was evident from the absence of conversions to on-pump CABG and the equal number of grafts performed by both techniques. Although, no difference was observed in 30-day mortality, off-pump patients had significantly lower occurrence of 30-day composite of mortality and morbidity, chiefly driven by higher rates of stroke and mechanical device implantations in on-pump patients. The Emory group conducted a retrospective cohort study totaling 14,766 consecutive patients undergoing off-pump (7,083; 48.0%) and on-pump CABG (7,683; 52.0%) (34). On dividing the patients into quartiles based on their predicted risk of mortality (PROM), they found no difference in observed mortality between the two CABG techniques in the lower risk quartiles, but off-pump surgery was favorable in higher risk quartiles, with the most significant benefit in the highest risk quartile (OR 0.45; $P < 0.0001$). Moreover, logistic regression analysis favored off-pump CABG by revealing a significant interaction between technique of surgery and PROM ($P < 0.005$). They also included surgeon identity into the model and showed that its effect did not reduce the apparent benefit associated with off-pump surgery. This confirms that avoiding CPB would be most advantageous in patients who are at the highest risk of developing complications following its use. The last two studies and suggestions by several authors imply that high-risk patients and certain patient characteristics such as old age, female sex, peripheral vascular disease or aortic atherosclerosis, renal failure, and severe COPD would benefit the most from off-pump surgery (28,35-39).

High risk profile

Patients with a high-risk profile are frequently excluded from RCTs, which may be the most likely cause of lack of results favoring off-pump CABG in RCTs. Such patients are usually the ones who are highly susceptible to the complications of CPB, which is why off-pump CABG would be expected to serve these patients better than on-pump CABG. A recent meta-analysis of 100 RCTs performed by Kowalewski *et al.* revealed a significant 28% reduction in the odds of cerebral stroke following off-pump CABG ($P = 0.009$) (12). Additionally, a significant relationship between patient risk profile and benefits from off-pump surgery was found in terms of all-cause mortality

($P < 0.01$), MI ($P < 0.01$), and cerebral stroke ($P < 0.01$). Marui and coworkers compared 1,377 patients undergoing on-pump CABG to 1,091 undergoing off-pump CABG in the Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) Registry by using propensity score-adjusted logistic regression or Cox proportional hazard models following division of all patients into tertiles based on the PROM for each patient (40). Propensity-adjusted 30-day mortality and MI were similar between groups, but the OR for 30-day stroke in on-pump compared with off-pump CABG patients was 8.3 ($P = 0.01$) and that of the composite outcome including death, MI and stroke was 2.7 ($P = 0.03$) in the intermediate risk and 2.6 ($P = 0.01$) in the high-risk tertile. Although, off-pump surgery did not provide mortality benefit, it was associated with a lower risk of stroke in high-risk patients. This could have been related to the sample size and small number of events. Dhurandhar and colleagues reviewed 7,822 high-risk patients in the Australian and New Zealand Society of Cardiac and Thoracic Surgeons' (ANZSCTS) database, who underwent isolated CABG surgery (7,277 on-pump CABG; 545 off-pump CABG). Apart from the higher percentage of older and female patients in the off-pump group, the risk profile of patients undergoing on-pump CABG was worse [higher incidence of MI, triple vessel disease, EF $< 30\%$, and preoperative intra-aortic balloon pump (IABP) insertion]. Similar to the previous study, no significant difference was observed between the on- and off-pump groups in terms of 30-day and 1-year mortality (3.9% vs. 2.4%; 7.4% vs. 5.6%, respectively) (41). The occurrence of major neurological event rates (temporary and permanent) revealed a non-significant higher trend in patients undergoing on-pump CABG. But the beneficial effect of off-pump surgery was most evident by the significantly lower rate of new-onset AF, renal failure and need for blood transfusions.

Aortic atherosclerosis

A severely atherosclerotic ascending aorta is always a cardiac surgeon's nightmare. Even the slightest manipulation of such an aorta could lead to embolization of atheromatous debris resulting in a major stroke, which is arguably one of the most dreaded complications following cardiac surgery. Its incidence ranges from 1% to 2.5% (42,43) and is not only associated with higher mortality (44) but also with reduced long-term survival (45). Therefore, avoiding aortic manipulation would at least reduce, if not eliminate the

occurrence of stroke after cardiac surgery. Fortunately, this is achievable in patients undergoing CABG as opposed to other heart operations, in which use of CPB is mandatory. Off-pump CABG facilitates the surgeons in accomplishing this goal, but only partially, if proximal anastomoses are constructed (46). In order to abstain from aortic manipulation, off-pump CABG has to be performed either with both internal thoracic artery (ITA) grafts *in situ* or composite arterial or arteriovenous Y-grafts (47).

This is probably the indication that warrants off-pump CABG with the so-called aorta "no-touch" technique (48,49). Several studies have shown this technique to be advantageous with regard to the reduction in perioperative stroke. Kapetanakis and associates reported that stroke rate following on-pump CABG was 1.5 times (2.2% vs. 1.6%) that after off-pump CABG with partial aortic clamping and 3 times (2.2% vs. 0.8%) that after no-touch aorta off-pump CABG ($P = 0.01$). Another study found that off-pump CABG was associated with an OR of 7.01 ($P = 0.02$), and on-pump CABG with an OR of 12.33 ($P = 0.0007$) for occurrence of a neurologic event when compared with no-touch aorta operations (49). Kotoh *et al.* revealed partial aortic clamping (OR 11.1; $P = 0.02$) as one of the independent predictors for cerebral infarction (46). Proximal aortic anastomotic devices such as heart string are also associated with a reduced stroke rate. A retrospective Swiss study compared the outcomes in patients undergoing off-pump CABG with partial clamping ($n = 567$) to those with the no-touch aorta technique with either the heart string device ($n = 1,365$) or total arterial composite grafting ($n = 271$). They identified patients operated with heart string device to have significantly lower frequencies of stroke (0.7% vs. 2.3%; $P = 0.04$) and MACCE (6.7% vs. 10.8%; $P = 0.001$) than those undergoing partial aortic clamping, but similar to those who underwent total arterial composite grafting (stroke rate 0.8%; MACCE 7.9%) (50). A recent meta-analysis including two randomized control trials and nine observational studies involving a total of 6,741 patients (4,393 on-pump CABGs and 2,348 off-pump) reported that the incidence rate of postoperative neurologic complications in patients undergoing off-pump CABG was significantly lower (OR 0.56; $P < 0.0001$) than those undergoing on-pump CABG (51). A couple of other meta-analyses detailed elsewhere in the present review and conducted separately by Kowalewski *et al.* and Altarabsheh and colleagues comparing no-touch aorta off-pump with on-pump CABG and all off-pump with on-pump CABGs in octogenarians, respectively further

validate the positive impact of off-pump surgery on the reduction of stroke rates after CABG (12,52).

Age

The elderly are the fastest growing segment of the world population. The World Population Ageing report in 2015 states that the number of people in the world aged ≥ 60 years is projected to reach 1.4 billion by 2030 and 2.1 billion by 2050, a 56 per cent and 100% growth, respectively, than its size in 2015 (53). Correspondingly, the elderly patients presenting with ischemic heart disease for CABG would also be expected to rise in the near future. Patients with advanced age have a smaller physiological reserve, albeit more comorbidity such as diabetes, cerebrovascular disease, COPD, and renal insufficiency, which make them more susceptible to the ill-effects of CPB and thereby more prone to the development of perioperative complications following CABG, particularly stroke and acute renal failure (54,55). Therefore, off-pump CABG has been adopted by several cardiac surgeons as a modality that could reduce the occurrence of perioperative complications, especially those caused by the implementation of CPB (34,56-58). One of the initial reports from the London Health Sciences Centre, Canada, which compared 30 elderly patients undergoing off-pump CABG to 60 elderly patients undergoing on-pump CABG, revealed a significant reduction in low output syndrome and AF and a non-significant trend towards lower postoperative stroke rates in the latter group, which translated into a significant reduction in hospital resource utilization and four times lower prevalence of adverse economic outcomes in off-pump CABG patients (59). A meta-analysis of 14 non-randomized studies comparing the two surgical techniques in a total of 4,921 elderly (>70 years) patients undergoing CABG between 1999 and 2005 demonstrated a lower incidence of postoperative mortality, stroke and AF in patients treated with off-pump CABG, with octogenarians reaping the most benefit. The corresponding reduction in the relative risk was 16%, 44% and 3% (57). A more contemporary report drawn from the real-life registry data of the ANZSCTS database revealed lower, but non-significant trends towards 30-day and 1-year mortality and perioperative stroke, and a significant reduction in postoperative AF and blood transfusions after off-pump CABG, but no differences in new onset acute renal failure between the two CABG techniques. These findings can be explained by an overall smaller number of patients included in this study and

the inherent bias produced because of off-pump CABG performed in most patients with a high frailty index and aortic calcification (41). Similarly, one of the most recent meta-analysis of 16 retrospective studies published between 2000 and 2013 and comprising 18,000 octogenarians, who underwent off- (n=8,566) and on-pump (n=9,744) CABGs, revealed no differences in early mortality (4.6% and 5.2%; $P=0.6$, respectively), new-onset renal failure ($P=0.99$), AF ($P=0.27$), and MI ($P=0.99$). However, stroke and respiratory failure rates were higher in the on-pump CABG group ($P<0.01$ and $P=0.03$, respectively) (52). Ohira and colleagues stratified 954 patients, who underwent off-pump CABG with at least two distal anastomoses in the left coronary territory, into three groups according to their age at surgery [<65 years (young), 65–74 years (early elderly), and >75 years (late elderly)] (60). In spite of higher rates of diabetes, chronic lung disease, triple vessel and left main disease, moderate mitral regurgitation, lower glomerular filtration rates (GFRs) and higher NYHA classification in the early and late elderly groups, no differences were observed in in-hospital mortality, re-exploration for bleeding, renal failure, perioperative MI, or mediastinitis among the groups. The late elderly group required more frequent transfusions and prolonged ventilation. Additionally, multivariable logistic regression analysis showed that increasing age had only a modest influence on occurrence of all postoperative complications ($P=0.08$).

Gender

Female gender has always been associated with a higher incidence of morbidity and mortality after CABG (61,62), which could be a result of a combination of factors such as smaller conduit and target vessel size, later presentation of disease in women and greater intraoperative technical difficulty that could result in higher number of technical errors and incomplete revascularization. A multicenter, retrospective study reviewed the STS National Cardiac Database for risk factors and clinical outcomes of 42,477 consecutive, nonemergency, isolated, primary off- and on-pump CABG cases performed at 63 North American centers that performed more than 100 of each type of procedure (63). The 11,785 women were significantly older and had more comorbidities and a higher STS PROM than the 30,662 men. Women undergoing off-pump CABG had a significantly lower risk-adjusted risk of death, MI, renal failure, new dialysis, reoperation, prolonged ventilation, and AF and a trend towards reduction in stroke and deep sternal

wound infections. Men showed similar findings to women except for a lack of difference in death between the two CABG techniques. Therefore, no statistically significant interaction was found between gender and surgery type indicating that both men and women benefited significantly from off-pump CABG and that women benefited only modestly more than men. Attaran *et al.* demonstrated no difference in 30-day mortality between female patients undergoing on- and off-pump CABG (0.7% *vs.* 4.8%, $P=0.9$) in a meta-analysis of six observational studies, incorporating 23,313 female patients (13,717 on-pump CABG; $n=9,596$ off-pump CABG) (64). However, occurrence of postoperative MI was significantly greater in female patients undergoing on-pump CABG than those undergoing off-pump CABG (1.9% *vs.* 1.0%, $P=0.0009$), with a non-significant trend towards a higher incidence of neurological dysfunction (2% *vs.* 1%, $P=0.08$), respiratory complications (5.4% *vs.* 2.5%, $P=0.08$), renal dysfunction (3.2% *vs.* 1.9%, $P=0.2$) and renal failure (2.1% *vs.* 0.9%, $P=0.05$).

Diabetes mellitus

The dramatic increase in prevalence and incidence of diabetes mellitus (65) and its frequent association with CAD accounts for its high prevalence (~25%) amongst patients undergoing coronary revascularization (66). Patients with diabetes mellitus tend to have more diffuse multi-vessel CAD, which may often be difficult and at times unsuitable for surgical revascularization. Therefore, performance of off-pump CABG in such patients would be even more demanding than in patients with localized CAD. The Bristol group recently reported one of the largest series ($n=2,450$; 995 propensity matched pairs) with the longest follow-up on the impact of off-pump CABG in diabetic patients with multi-vessel coronary disease (67). Although off-pump CABG was associated with a significantly increased rate of incomplete revascularization (14% *vs.* 7.4%; $P<0.001$) as compared to those undergoing on-pump CABG, no difference was detected in 30-day mortality (2.5% *vs.* 1.9%; $P=0.4$) or the need for renal replacement therapy (4.9% *vs.* 4.3%; $P=0.5$), and more importantly patients had significantly lesser postoperative complications (10.6% *vs.* 14.7%; $P=0.005$) if they underwent off-pump CABG. A 50% relative risk reduction for postoperative CVA (1.2% *vs.* 2.4%; $P=0.04$), need for postoperative IABP (2.6% *vs.* 5.3%; $P=0.002$), and re-exploration for bleeding (2.2% *vs.* 3.9%; $P=0.02$) was observed in patients undergoing

off-pump as compared to on-pump CABG. The 5- and 10-year survival was also comparable (82.6% \pm 1.2% and 62.6% \pm 2.0% for off-pump *vs.* 84.3% \pm 1.3% and 64.0% \pm 1.9% for on-pump CABG). Nevertheless, on stratifying the patients according to the completeness of revascularization, the study revealed reduced survival in patients undergoing off-pump CABG with incomplete revascularization versus those undergoing complete revascularization by either technique [hazard ratios (HR) 1.82; $P=0.0002$ for off-pump and HR 1.83; $P<0.0001$ for on-pump]. No differences in survival were observed in patients undergoing complete revascularization by either technique (HR 1.00; $P=0.96$). This study underscores the importance of complete revascularization and validates the benefits of off-pump CABG in high-risk patients, when performed by experienced off-pump surgeons.

LV dysfunction

Patients with LV dysfunction are commonly excluded from RCTs. In the ROOBY trial, only 5.7% of the study population had an EF <35% (2). Similarly, the DOORS trial comprised 5.3% of patients with EF <30% (3). Contrarily, surgeons often encounter patients with severe LV dysfunction in daily practice, because such patients usually have severe multi-vessel disease not amenable to PCI. Off the 55,000 patients undergoing CABG in a study from the New York Statewide database, approximately 15% had an EF <30% (68). A propensity matched analysis involving 256 off-pump and 222 on-pump CABG patients revealed no difference in mortality (2.3% *vs.* 4.1%; $P=0.9$) and MACCE (13.7% *vs.* 17.6%; $P=0.5$) (69). However, off-pump CABG patients demonstrated a lower trend for occurrence of composite of non-cardiac events (12.1% *vs.* 22.1%; $P=0.06$) including renal dysfunction, bleeding and respiratory failure. The rate of complete revascularization was similar (92.2% *vs.* 92.8%; OR 0.75; $P=0.50$). Similarly, several retrospective studies comparing the two CABG techniques have reported no differences at least in in-hospital mortality (36,70,71). This is most likely due to the small number of patients that preclude demonstration of differences in mortality in these studies. Nevertheless, a review of the STS National Database that included 25,667 patients undergoing elective or urgent primary CABG with an echo-documented EF <30% showed that off-pump CABG patients were older ($P<0.0001$), had a higher proportion of women ($P=0.0002$), and had higher rates of preoperative comorbidities, including a lower

estimated GFR ($P<0.0001$), severe chronic lung disease ($P=0.01$), and preoperative arrhythmia ($P<0.0001$) than those undergoing on-pump surgery resulting in a higher PROM (2.1% *vs.* 2.3%, $P<0.0001$) (72). Although the off-pump CABG patients received fewer distal anastomoses (3.5 *vs.* 2.9, $P<0.001$), risk adjusted outcomes such as in-hospital death (OR 0.8; $P=0.045$), stroke (OR 0.7; $P=0.006$), perioperative MI (OR 0.7; $P=0.09$), MACCE (OR 0.7; $P=0.0005$), and prolonged ventilation (OR 0.8; $P<0.0001$) significantly favored off-pump CABG. Moreover, a volume-adjusted analysis (volume of surgery performed per center) further accentuated the benefits of off-pump surgery (in-hospital mortality—0.63, stroke—0.39, major adverse cardiac events—0.54 and prolonged ventilation—0.75). The predominant factors associated with lower in-hospital mortality after off-pump CABG in this report were the lower stroke and other neurologic event rates, transfusion requirements, and incidence of prolonged ventilation.

Renal dysfunction

Several studies in literature have revealed preoperative renal dysfunction to be an independent risk factor for CABG surgery (73–75). However, till date no RCTs comparing the two CABG techniques with a focus on renal dysfunction have been undertaken. Numerous RCTs have compared the results of off- and on-pump CABG, but none of them has stratified preoperative renal function that can range from mild to moderate renal dysfunction to non-dialysis dependent chronic kidney disease to dialysis-dependent end-stage renal disease. Therefore, data and outcomes reported by retrospective studies are the only evidence available at the present time. Mild preoperative renal insufficiency is not associated with worse in-hospital outcomes than those with normal function, at least in those undergoing off-pump CABG. A propensity-matched analysis of 1,236 patients comparing patients with normal ($n=618$) and mildly reduced renal function ($GFR \geq 60$ and <90 mL/min/m²) ($n=618$) undergoing off-pump CABG reported no significant difference in in-hospital outcomes, including stroke, MI, AF, IABP support, respiratory failure, pneumonia, reoperations for bleeding, transfusions, and deep sternal wound infection. Patients with mild preoperative renal insufficiency, however, had slightly higher, but insignificant incidence of acute kidney injury requiring dialysis as compared to patients with normal preoperative renal function (76). At the other end of the spectrum, patients with dialysis-dependent severe

end-stage renal disease usually have diffuse CAD with extensive calcification and small coronary vessels that not only make conducting a perfect anastomosis challenging, particularly during off-pump CABG, but also cause issues related to CPB such as volume overload and coagulopathy in patients undergoing on-pump CABG (77). A meta-analysis of ten retrospective studies including 14,072 patients with ESRD on dialysis (11,310 on-pump CABG; 2,762 off-pump CABG) revealed no differences in early mortality, re-exploration for bleeding, transfusions and AF. Stroke occurred more commonly after on-pump CABG (4.8% *vs.* 2.6%), but the difference was not statistically significant. Off-pump CABG patients were extubated much earlier (RR 0.56; $P=0.003$). While 17.7% off-pump CABG patients needed prolonged ventilation, almost 35% were ventilated for a longer time after conventional surgery probably due to CPB related increase in the inflammatory response, fluid shifts and lung injury. However, the studies included in this meta-analysis were small and prone to procedural and patient selection bias and a high degree of heterogeneity (78).

The important question is the effect of CABG on patients with chronic kidney disease, who are not dialysis-dependent. Lim *et al.* performed a meta-analysis of nine observational studies and one RCT that included patients with non-dialysis dependent renal dysfunction undergoing CABG (1,850 on-pump CABG; 1,183 off-pump CABG). They found that off-pump CABG was much more beneficial than conventional surgery at preventing development of acute renal failure (OR 0.55; $P=0.01$) and early mortality was lower following off-pump CABG (OR 0.62; $P=0.04$) (79). One of the only retrospective studies to stratify 742,909 patients (584,348 on-pump CABG; 158,561 off-pump CABG) from Society of Thoracic Surgery Database undergoing non-emergent, isolated CABG according to preoperative renal function (as per the GFR) evaluated the effect of the use of CPB during CABG on in-hospital mortality and incident renal replacement therapy. A propensity-weighted analysis demonstrated that off-pump CABG was associated with a reduction in the composite endpoint including in-hospital mortality and renal replacement therapy and that this risk reduction became more pronounced with decrease in preoperative renal function ranging from 0.05 per 100 patients for eGFR >90 mL/min per 1.73 m² to 3.66 per 100 patients for eGFR of 15–29 mL/min per 1.73 m². Individual component endpoints also exhibited the same trend (73).

Acute coronary syndrome (ACS)

The role of off-pump surgery in the setting of ACS is yet to be determined. Patients with evolving ACS represent a heterogeneous group consisting of unstable angina (UA), non-ST-segment elevation MI (NSTEMI) and ST-segment elevation MI (STEMI). A minority of such patients not amenable for PCI, but presenting with refractory symptoms, or hemodynamic instability require urgent or emergent CABG, which is fraught with increased operative mortality (1.6–32%) in comparison to patients undergoing elective CABG for stable angina (80–84). Although a multitude of factors affect the outcomes of such patients, it is speculated that reperfusion injury or no reflow phenomenon following global ischemia due to aortic cross-clamping during conventional on-pump CABG is probably one of the responsible factors that could be modified by performing the operation on a beating heart (BH). Our group has previously shown that BH CABG is associated with better in-hospital and long-term outcomes in patients with ACS (85). Of a total of 638 consecutive patients with ACS undergoing emergency CABG surgery, 240 underwent BH (116 on-pump BH and 124 off-pump CABG) and 398 on-pump arrested-heart CABG. A propensity score adjusted multi-regression analysis revealed significant benefit with regard to less postoperative blood loss, transfusion requirement, inotropic support, shorter ventilation time, lower stroke rate, and shorter ICU stay in patients undergoing BH-CABG. Furthermore, BH-CABG was associated with lower hospital mortality ($P=0.05$), incidence of stroke, inotropic support, acute renal failure, new AF and sternal wound healing complications in patients in cardiogenic shock. Another report on CABG in NSTEMI patients from our group showed that almost 2/3^{ths} of the patients underwent BH-CABG (50.5% off-pump and 16.8% on-pump BH-CABG) (86). In this series, patients undergoing off-pump CABG showed a non-significant trend towards lower re-exploration rates for bleeding and received significantly lesser number of erythrocyte, platelet, or fresh-frozen plasma transfusions compared with those undergoing BH or arrested heart on-pump CABG. In contrast, a recent meta-analysis of eight retrospective studies and one RCT involving a total of 3,001 patients (2,184 on-pump CABG; 817 off-pump CABG) demonstrated that no difference was observed in 30-day or mid-term mortality between the two CABG techniques (OR 0.68, $P=0.1$; OR 1.21, $P=0.6$) (87). Factors that could be held accountable for this lack of difference

could probably be the significantly lower number of grafts per patient ($P<0.00001$), the lower rate of completeness of revascularization ($P=0.0002$) and lower revascularization index ($P<0.00001$). However, re-intervention rates were similar (OR 1.70; $P=0.1$). Although, off-pump CABG may be a safe and comparable alternative to on-pump CABG in clinically stable ACS patients requiring urgent/emergent revascularization, focused RCTs are necessary to prove their definitive benefit. Until then, surgeons should focus on achieving complete revascularization in such patients, a goal that should not be compromised for the purpose of performing the operation off-pump.

Efficacy

The efficacy of CABG is chiefly dependent on the long-term outcomes such as survival and freedom from serious events like MI and RR. Several RCTs that have been conducted to date have reported results only up to 1 year after surgery. However, the major benefits of CABG are most commonly seen in the long term. Therefore, observational studies comparing the two operative techniques and including large patient cohorts to allow for adequate statistical power are the only available evidence providers for comparing the long-term outcomes after off- or on-pump CABG. A single-center case-matched study comparing 2,570 on-pump and 2,333 off-pump CABG cases using inverse-probability-of-treatment weighting revealed that patients undergoing on-pump CABG received a higher number of distal anastomoses than those undergoing off-pump CABG (3.7 ± 1.2 vs. 3.0 ± 1.1 ; $P<0.001$) and demonstrated a similar risk of death at 30 days (OR 0.70; $P=0.3$) and up to 1 year (HR 1.11; $P=0.6$). However, at a median follow-up duration of 6.4 years, overall mortality was significantly higher in patients who underwent off-pump CABG (HR, 1.43; $P<0.0001$) (88). These results are further supported by another retrospective analysis of long-term results of real-world registry data by Nicolini *et al.* (89) and a meta-analysis of 17 observational studies and 5 RCTs involving 104,306 patients, which demonstrated a statistically significant 7% increase in long-term (≥ 5 years) all-cause mortality with off-pump relative to on-pump CABG (HR 1.07; $P=0.0003$) (90). Similar to the previous studies, the index of the completeness of revascularization was reported to be significantly greater with on-pump than with off-pump CABG in six of the eight studies. These studies had two major limitations. The significant difference in the number of distal anastomoses between the two operative techniques and

the higher index of completeness of revascularization in on-pump CABG cases was probably due to a higher rate of incomplete revascularization in the off-pump CABG patients considering that the number of patients with single vessel disease did not differ between the two groups. This portrays inexperience of the surgeons in off-pump surgery and the inferior long-term results may be attributed to higher incomplete revascularization rates rather than to the off-pump technique. Therefore, surgeons should perform off-pump surgery only if they are confident of performing the same extent of revascularization as they would by using CPB. This fact is validated by a 15-year follow-up study of 1,412 propensity matched patients, which demonstrated no difference in survival at a mean follow-up of approximately 10 years between patients undergoing on- or off-pump bilateral ITA-saphenous vein grafting and also between on- or off-pump single ITA-saphenous vein graft CABG cases, but revealed a significant survival benefit in favor of patients undergoing bilateral ITA-saphenous vein graft as compared to single ITA-saphenous vein graft CABG (91). This study proved that the use of CPB does not significantly affect the long-term outcomes in patients as long as full revascularization with similar conduits is achieved. Secondly, important outcomes that would directly relate to incomplete revascularization or graft patency issues with off-pump surgery such as cardiac death, MI and RR have not been evaluated in the previous studies. One cannot assume the cause of death to be of cardiac origin in all patients who die at follow-up. Another large observational study consisting of 11,021 patients undergoing isolated CABG (27.2% off-pump CABG) demonstrated that off-pump CABG was not a risk factor for long-term mortality after adjustment (HR 0.96; $P=0.4$), but on-pump CABG was associated with significantly lower hospitalization for subsequent PCI even after adjustment for confounding factors (HR 0.7; $P<0.001$). Off-pump CABG thus carried a 42% higher risk for subsequent PCI than on-pump CABG. The incidence of repeat CABG was similar between groups (92). However, this study had no data available on the completeness and effectiveness of revascularization, patency of grafts or details about RR. Hence, the inferences formulated have to be taken within the context of an observational study.

Chaudhry *et al.* conducted a very large meta-analysis including 5 RCTs, 5 registry-based studies, 10 propensity-matched studies, and 12 other observational studies incorporating 52,783 patients (93). They found similar mid-term survival between on- and off-pump CABG (HR 1.1; $P=0.3$), but a significant trend favoring on-pump CABG in

long-term survival (HR 1.1; $P=0.05$). However, subgroup analysis revealed comparable long-term survival for RCTs, registry-based studies, propensity-matched studies, and observational studies. No differences were recorded in secondary outcomes such as RR events (HR 1.1; $P=0.2$), MI, heart failure, and cerebrovascular accident.

Although most studies have favored on-pump CABG with regard to long-term survival, the afore-mentioned limitations, the heterogeneity in the conduct and statistical analyses of various observational studies, the inclusion of patients with different risk-profiles, the variability in definitions of preoperative parameters and outcomes and inclusion of a few RCTs in meta-analyses pose a major hindrance to the reliable interpretation of the long-term outcomes after off- or on-pump CABG.

Comments

After reviewing the current outcomes of off-pump CABG, one can safely infer that off-pump CABG may serve high-risk patients particularly those with non-dialysis dependent chronic kidney disease, severe aortic disease, LV dysfunction and ACS better than on-pump CABG. Contrarily, on-pump CABG may provide survival benefit in the long term, most likely due to better graft patency and higher index of revascularization. It is also important to remember that the choice of grafts and the configuration used for revascularization have a significant impact on long-term outcomes. A propensity-matched analysis of 5,459 on-pump and 2,133 off-pump CABG cases identified no difference in long-term survival, when the patients were matched for demographic variables. However, when conduit choice was included into the matched analysis, on-pump CABG was associated with significantly improved long-term survival after the 3rd year of surgery ($P=0.0003$) (94).

All this being said and discussed, we as responsible coronary surgeons should not disregard the big picture of restoring normal or near-normal blood flow to all areas of myocardium feasible for the longest conceivable interval of time in our effort to accommodate the patient to the operation rather than tailoring the operation to our patient. Our main focus should be on completeness of revascularization with the best possible conduits and configuration and the most appropriate technique for every individual patient. It is obvious that advancements in modern stabilizers, heart positioning devices, or intracoronary shunts, and the experience of the surgeons would help improve their ability to construct anastomoses,

which are qualitatively similar to those constructed with CPB. Additionally, establishment of guidelines for the performance of off-pump CABG and maintenance of national off-pump CABG registries that include both the early (30-day) and long-term outcomes such as mortality, MI, stroke, graft occlusion, recurrent angina, need for any RR, and re-hospitalization for ACS could further provide real world data on off-pump CABG. Standardization of protocols during and after off-pump CABG would also assist in improving early and late outcomes. Finally, both techniques have their place in surgical revascularization. They should be complementary to each other rather than being competitive and should be regarded as important tools in the armamentarium of the coronary surgeon.

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Footnote

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