



## Review

## Off-pump coronary artery bypass surgery: The long and winding road

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## ABSTRACT

After more than thirty years, a hundred randomized studies and dozens of meta-analyses, there is still controversy on the results and benefits of off-pump coronary artery bypass grafting. The present review summarizes the most relevant evidence, the relation of outcomes with surgeon's and institution's experience, addresses regional variations in popularity of the technique, and the need for structural training.

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## 1. Introduction

More than thirty years have passed since the first reports of off-pump coronary artery bypass (OPCAB) grafting [1]. The primary aim of the technique was to avoid the biological trauma of the cardiopulmonary bypass (CPB) and reduce the extent of aortic manipulation. This, in turn, would be expected to reduce the incidence of neurological events, renal failure, blood products requirements and early mortality. However, OPCAB proved to be more challenging than conventional on-pump coronary artery bypass (ONCAB) grafting and posed questions on haemodynamic instability during exposure of the target coronary, quality of the anastomoses on a beating heart and incomplete revascularization.

A significant part of the surgical community embraced the technique, at time, without enough consideration of the difficulties associated with the learning curve. In the early 2000s, controversies regarding OPCAB and its real clinical benefits started to emerge. This tempered the enthusiasm of surgeons worldwide, with wide geographical differences (Fig. 1); from total embracement to outright refute of the technique [2].

The amount of literature on the subject is somewhat impressive: over thirty years, >100 randomized trials and 60 meta-analyses have compared OPCAB and ONCAB; failing to prove a clear superiority of one technique over the other and often showing conflicting results.

Studies have focused on short- and long-term mortality, completeness of revascularization, angiographic results, biologic effect on platelet

activation/coagulation/inflammatory response, the incidence of neurological events and hospital costs. The lack of a clear demonstrated superiority of either of the two techniques might lead to the assumption that ONCAB and OPCAB are equivalent.

However, a clear picture is emerging, that the results of OPCAB are correlated to both institution and individual surgeon's experience: a dedicated team performing routine OPCAB is more likely to have a lower rate of conversion to ONCAB and achieve complete revascularization.

In the present article, the relevant evidence comparing OPCAB and ONCAB will be reviewed, with a focus on clinical results, subsets of patients and surgeon's experience.

## 2. Evolution of the technique

Coronary artery bypass surgery on the beating heart was first performed in the early 1960s and soon largely abandoned after the spreading use of cardiopulmonary bypass. A few surgeons, mostly in South America, continued performing anastomoses on a beating heart primarily for economic reasons [3]. The number of surgeons performing OPCAB rose steadily in the mid-1990s and early 2000s thanks to the development of devices that made the technique safer and more reproducible: tissue stabilizers, heart positioners and intracoronary shunts. In the USA hardly any OPCAB procedures were performed before 1995; by 1999 > 10% of myocardial revascularizations were performed on a beating heart [4]. In the early 2000s the figure reached 20%–30% and was expected to reach 50% by 2005. The absence of clear evidence of superiority and controversial results, the lack of established training programs, the perception that success with the technique was limited to more proficient surgeons, and a fear of deleterious patient outcomes (especially during the learning curve) [5], led to a steady decline of OPCAB worldwide, although with large regional variations [6].

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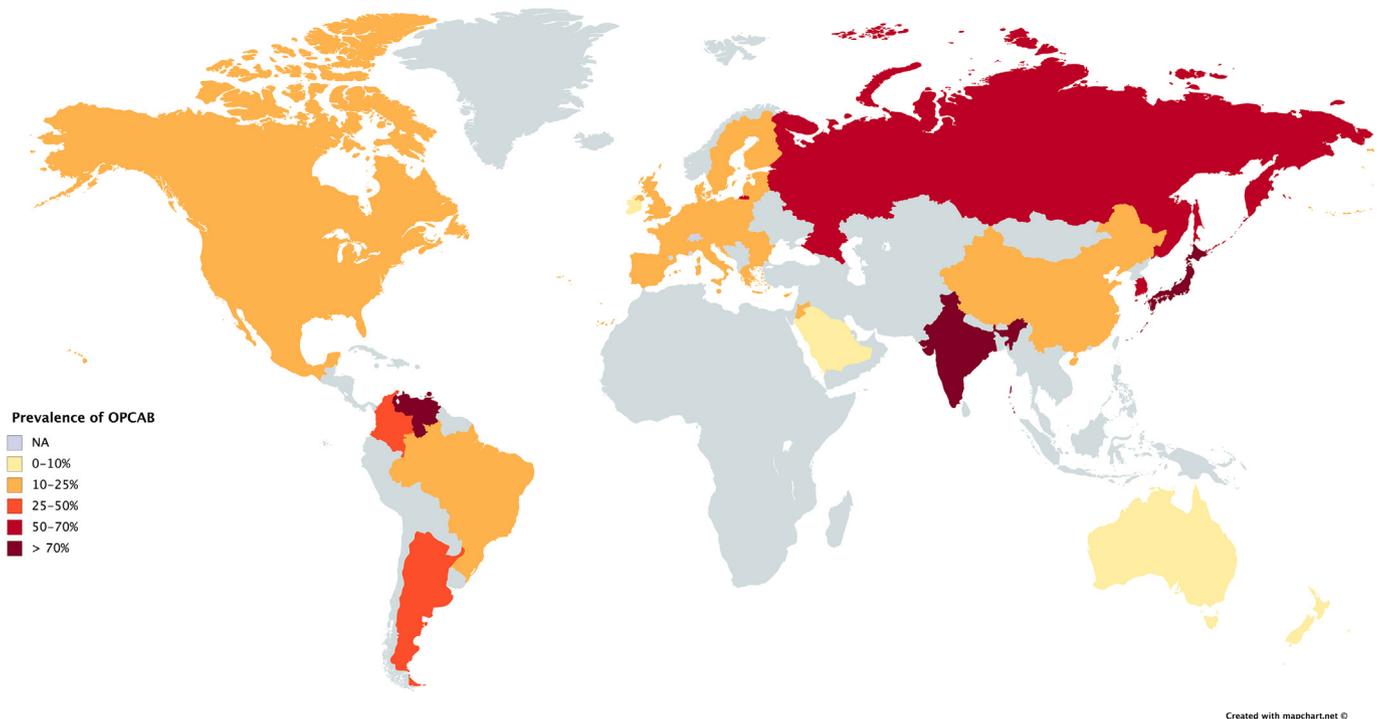


Fig. 1. Estimated prevalence of off-pump coronary artery bypass grafting by geographical region. This information was obtained from published data and personal communications.

### 3. Short-term outcomes

The avoidance of CPB and, whenever possible, aortic clamping with their physiological derangements was the main rationale for the popularisation of OPCAB.

Short-term outcomes following OPCAB compared to ONCAB were reported in both retrospective and randomized clinical studies (RCTs). These were largely single-centre studies from experienced units and surgeons, who had adopted the technique enthusiastically. Despite minor discrepancies, in these studies OPCAB was usually associated with a reduced incidence of early in-hospital complications like stroke, renal and respiratory failure and a reduced requirement for blood products [7,8]. On the other hand, a higher incidence of incomplete revascularization and need for repeat revascularization was observed, with no significant difference in short-term mortality [9]. These preliminary results spurred authors to investigate the comparison of OPCAB vs ONCAB in three large RCTs: the Randomized On/Off Bypass (ROOBY) trial in 2009 ( $n = 1104$  OPCAB vs. 1099 ONCAB) [10], the CABG On or Off Pump Revascularization Study (CORONARY) trial ( $n = 2375$  OPCAB vs. 2377 ONCAB) [11] and the German Off-Pump CABG in Elderly (GOPCABE) trial in ( $n = 1271$  OPCAB vs. 1268 ONCAB) [12], both published in 2013.

The ROOBY trial enrolled almost exclusively men undergoing elective or urgent CABG at 18 medical centres in the United States. Surgeons could perform OPCAB, regardless of their experience pre-study (the procedures could be performed also by residents). The trial showed no significant difference between OPCAB and ONCAB in terms of the 30-day composite outcome of death or complications (reoperation, new mechanical support, cardiac arrest, coma, stroke, or renal failure) (7.0% and 5.6%, respectively;  $p = 0.19$ ). The study reported a high OPCAB to ONCAB conversion rate (12.4%), which has been attributed to the lack of requirements of OPCAB experience for participating surgeons. Furthermore, the average surgical risk was low, which might have led to underestimate the potential benefits of OPCAB.

The CORONARY trial was a much “improved” version of the ROOBY trial: it enrolled almost twice the number of patient (4752 patients at 79 centres in 19 countries) and assessed the issues of the patient’s

surgical risk and the surgeons’ experience. To be enrolled in the study, patients needed to have one or more risk factors (e.g. diabetes, recent acute coronary syndrome, renal failure, left ventricular ejection fraction <35%, recent history of smoking): younger patients needed to have a higher number of risk factors. Secondly, surgeons were requested to have at least a 2-year experience and 100 OPCAB procedures already performed pre-study. Similarly, to the ROOBY trial, there was no significant difference in the primary endpoint, which was the composite rate of death, nonfatal stroke, non-fatal myocardial infarction, or non-fatal new renal failure requiring dialysis at 30 days. As in previous early trials, a statistically significant reduction in early in-hospital complications was observed.

The GOPCABE study applied the same criteria of the CORONARY trial to a group of older patients: 2539 patients, 75 years of age or older, from 12 German Hospitals. Though the criteria are not clearly specified, it is mentioned that surgeons were required to have a “substantially greater experience with OPCAB than in the ROOBY trial”.

Once again, no difference was observed in the incidence of the composite outcome of death, stroke, myocardial infarction, or new renal-replacement therapy at 30 days. Similarly, to the ROOBY trial, repeat revascularization was more common in the OPCAB arm (1.3% vs. 0.4%; odds ratio, 2.42; 95% CI, 1.03 to 5.72;  $p = 0.04$ ). OPCAB patients required fewer transfusions of packed red cells and were less likely to have received blood products. Operative time, duration of mechanical ventilation, length of ICU, and length of hospital stay were similar in the two groups.

None of the large randomized trials showed significant differences in death or stroke at 30 days, although an increased need for repeat revascularization in the OPCAB group was observed both in ROOBY and GOPCABE. Interestingly, in all these trials OPCAB patients received a smaller number of grafts and a higher incidence of incomplete revascularization was reported. The higher level of expertise required for OPCAB surgeons in the CORONARY and GOPCABE trial was reflected in lower rates of conversion from OPCAB to ONCAB.

A number of meta-analyses have reported conflicting results at 30 days post-surgery: from no differences between the two strategies [13,14], to a significant benefit for OPCAB patients (lower incidence of

MI, cerebrovascular accidents, reoperation for bleeding, renal failure, atrial fibrillation, and wound infections) [15]. A benefit for OPCAB patients in the short-term is also showed by large, single-centre non-randomized studies, particularly in high risk patients [16,17]. This, however, might be the result of a wise matching of patient, technique and surgeon.

#### 4. Long-term outcomes

The consistent higher rate of incomplete revascularization in OPCAB is postulated as the likely explanation for the reported increase mortality at follow-up. [9,18].

In the ROOBY trial, the rate of the 1-year composite outcome of death from any cause, repeat revascularization, or non-fatal myocardial infarction was higher in OPCAB than ONCAB patients (9.9% vs. 7.4%,  $p = 0.04$ ). Graft patency for patients that accepted to undergo follow-up angiograms (1371 patients, 4903 grafts) was also lower in the OPCAB group (82.6% vs. 87.8%,  $p < 0.01$ ). Five-year survival and event-free survival in the OPCAB group was also worse [10].

In the CORONARY trial, no significant difference in the rate of the primary composite was found at 1 year. The difference in the rate of repeat revascularization, which had favoured ONCAB at 30 days, had lost statistical significance at 1 year. No difference was found at 5-year follow-up in the composite outcome of death, stroke, myocardial infarction, renal failure or repeat revascularization. Similar results were reported by our group from the “Beating Heart Against Cardioplegic Arrest” randomized controlled trials (BHACAS 1 and 2) at 8 years follow up [19].

Data from meta-analyses is largely conflicting, having to consider both randomized, prospective non-randomized and retrospective studies [20–22](Table 1). A meticulous analysis would go well beyond the purposes of this review.

OPCAB patients receive a lower number of grafts and are more likely to have incomplete revascularization and a higher need for repeat revascularization. This seems to have an impact on long-term survival, which is generally reported to be lower for OPCAB patients, although the results are controversial. Of note, in reports from OPCAB-expert centres, long-term survival for the two techniques is comparable.

#### 5. Do specific subsets of patients benefit from OPCAB?

Avoiding aortic manipulation and the physiological derangements associated with CPB may become important in specific subsets of patients: those with a high surgical risk, patients with impaired ventricular function, elderly, female subjects, patients at higher risk for stroke and with end-organ failure (Table 1).

In patients with high surgical risk, meta-analyses or RCTs and retrospective analyses have observed reduced perioperative morbidity and mortality [23], especially for those in the third and fourth highest risk quartiles [24]. Similarly, in large retrospective studies, patients with impaired ventricular function undergoing OPCAB have shown a reduced risk of death, stroke, and major adverse cardiovascular events in the short-term [25–27]. Once again, the lack of statistically significant difference on long term has been correlated with the higher incidence of incomplete revascularization.

There seems to be a correlation between age at operation and benefit of OPCAB: although a Danish registry [28] and the GOPCABE study [12] found no difference in outcomes in patients older than, respectively, 70 and 75 years, large propensity matched studies and systematic reviews showed a reduced rate of stroke and in-hospital death for patients older than 80 years [29,30].

In female subjects, OPCAB has been associated with fewer major adverse cardiac events and seemed to benefit women disproportionately, thereby narrowing the gender disparity in clinical outcomes after CABG [31]. This finding remains unexplained, although it is interesting to observe that it has been reported that women who undergo OPCAB are more likely to receive a LIMA to LAD graft as compared to women undergoing ONCAB [32].

Randomized and non-randomized studies have shown that the avoidance of aortic manipulation in OPCAB reduces the neurological risk in the general population of CABG patients. On the other hand, it is not clear whether OPCAB might confer an *additional* benefit in patients who are already at increased neurological risk. Two large single-centre retrospective studies have shown a lower stroke and death rate in OPCAB patients with aortic atheromatous disease assessed by intraoperative transoesophageal echocardiogram [33,34]. In patients with carotid stenosis or history of neurological events, observational

**Table 1**  
Selection of meta-analyses comparing OPCAB and ONCAB.

| Authors  | N of patients         | Type of studies   | Findings   |
|--|-----------------------|---|--|
| Parolari 2003 [13]                               | 1090                  | RCTs  | OPCAB patients showed a (not statistically significant) reduction in the risk of death, stroke and myocardial infarction   |
| Reston 2003 [15]<br>Kuss 2010 [17]               | 46,621<br>123,137     | RCTs and observational studies<br>Propensity-score matched analyses             | OPCAB appears to reduce length of hospital stay, operative morbidity, and operative mortality<br>OPCAB reduces mortality, stroke, renal failure, red blood cell transfusion, wound infection, prolonged ventilation, inotropic support, and intra-aortic balloon pump support<br>30% reduction in the occurrence of post-operative stroke with OPCAB. No significant difference in mortality or myocardial infarction. |
| Afilalo 2012 [14]                                | 8961                  | RCTs  | OPCAB was associated with a significant reduction in the rate of stroke. In high risk patients, there seem to be also a benefit in terms of all-cause mortality and myocardial infarction.   |
| Kowalewski 2016 [23]                             | 19,192                | RCTs  | At 10 years, OPCAB is associated with an increase in all-cause mortality   |
| Takagi 2017 [20]<br>Filardo 2018 [21]            | 82,316<br>1.2 million | Propensity-score matched analyses<br>RCTs and propensity-score matched analyses | Evidence from RCTs showed no differences between the techniques, whereas rigorously adjusted observational studies (with >1.1 million patients) and the combined analysis indicated that OPCAB offers lower short-term mortality but poorer long-term survival.  |
| Smart 2018 [22]                                  | 8145                  | RCTs and observational studies  | OPCAB appears to reduce long-term survival   |
| Specific subsets of patients<br>Jarral 2001 [27] | 7759                  | Observational studies   | In patients with <b>impaired left ventricular function</b> , OPCAB may be associated with lower incidence of early mortality. The early advantage in mortality was not continued to the late term.   |
| Lim 2015 [40]<br>Khan 2017 [30]                  | 14,072<br>27,623      | Retrospective studies<br>Retrospective studies                                  | OPCAB doesn't seem to confer any additional benefit in <b>dialysis-dependent patients</b><br>In <b>octogenarians</b> , OPCAB is associated with lower in-hospital mortality, stroke rate and length of hospital stay.  |
| Wang 2018 [38]                                   | 201,889               | RCTs, observational prospective and retrospective studies                       | In patients with <b>chronic kidney disease</b> , OPCAB offers a significantly lower early mortality, decreased risk of atrial fibrillation, cerebrovascular accident, blood transfusion, pneumonia, prolonged ventilation, and shorter hospital stays. Long-term survival and rate of myocardial infarction are similar.   |

RCTs: randomized controlled trials. OPCAB: off-pump coronary artery bypass.

studies failed to find any statistically significant difference in the rate of postoperative stroke between OPCAB and OBCAB [35,36].

In patients with renal failure, small observational studies and meta-analyses have shown a reduction of short-term mortality, reduced need for prolonged ventilation and reduced sternal infection rate in OPCAB patients, despite a higher rate of incomplete revascularization [37,38]. Interestingly, large national databases have shown similar outcomes for OPCAB and ONCAB in patients on chronic dialysis [39,40].

Whereas liver cirrhosis has been shown to be independently associated with increased mortality in CABG patients regardless of the level of liver dysfunction, in OPCAB patients it seems to affect mortality or morbidity only if the liver dysfunction is very severe [41].

High risk patients seem to benefit from OPCAB, at least in the short term. On the long term, the results tend to be equal, once again presumably to a higher rate of incomplete revascularization.

## 6. Learning curve for OPCAB

OPCAB is technically more demanding than conventional ONCAB and requires a longer learning curve. It requires a team effort: a good understanding between the surgeon and anaesthetist is essential, particularly when it comes to a series of technical aspects that involve heart positioning, myocardial protection during the construction of the anastomosis and maintenance of proper haemodynamic status. There is overwhelming evidence that surgeon's and institution's experience are determinant factors in OPCAB outcome. Unexperienced of "sporadic" OPCAB surgeons will have a higher rate of intraoperative conversion to ONCAB and a higher rate of incomplete revascularization. The correlation between experience and conversion to ONCAB is important, since conversion has been correlated with increased risk of perioperative complications such as myocardial ischemic injury, stroke, renal failure, prolonged mechanical ventilation, increased readmissions, infectious complications and increased hospital cost and mortality [42–44]. Similarly, mid-term survival and event-free survival appear to be significantly reduced for patients who underwent intraoperative conversion [45].

The reported rates of conversion vary significantly: if the STS database reports, over 196,000 patients, conversion rate was 5.5% (of which 50% were elective) [42], the two largest RCTs showed a rate of conversion to ONCAB of 7.9% (in CORONARY) and 12.5% (in ROOBY). Lower conversion rates are reported by experienced surgeons in dedicated centres [10,11,43,46,47].

Surgeon's and institution's experience influence also the rate of incomplete revascularization, which in turn is believed to affect long-term mortality. Poorer outcomes might be expected at the beginning of the learning curve, if the team (surgeon, anaesthetist) is not adequately mentored. 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.

## 7. Regional variations

There are wide regional variations in the diffusion of OPCAB (Fig. 1). Currently, in the US and Europe OPCAB is provided roughly to 25% of CABG patients. It is surprising how, after 30 years of OPCAB, most of the national cardiothoracic societies still do not include the technique in the trainees' curriculum, nor have they recognised the need for established training programs. In the United Kingdom, the fear of deleterious patient outcomes (individual surgeons' results are made available to the public) may also account for the lack of enthusiasm in taking up OPCAB.

In Japan and India, on the other hand, OPCAB is the most common strategy for surgical myocardial revascularization [48]. Although the evidence regarding cost differences are inconclusive, Indian surgeons have reported that the diffusion of OPCAB in their country is mostly driven by

economic considerations [49]: many Indian citizens must pay for their treatment in absence of government funded healthcare. CABG is often offered as a package, with almost all hospitals putting a limit on the cost of medicines and consumables allowed. The cost of oxygenator, tubing and cannulae needed for ONCAB would therefore be billed to the patient. On the other hand, in OPCAB the stabilizer can be reused after sterilization and the price is divided among several patients. Given to this and to a shorter ICU stay, it is reported that an OPCAB patient will generally pay a lower price for a CABG procedure [49]. In Japan, OPCAB is slightly less common than in India but still prevails over ONCAB. In this case, the phenomenon does not seem to be driven by economic consideration and is perhaps harder to explain, although Japanese surgeons have traditionally embraced the most advanced modes of myocardial revascularization, and the adoption of OPCAB seems coherent with this philosophy. It is worth mentioning that, in 2012, the then 78-year-old emperor of Japan Akihito underwent a successful OPCAB procedure [50].

## 8. Conclusions

Conventional ONCAB is one of the most commonly performed surgical procedures in the world, with excellent results in terms of mortality and morbidity. The purpose of OPCAB is to spare the patients the biological trauma of cardiopulmonary bypass and, in some cases (when clampless devices or *anaortic* strategies are employed), unnecessary aortic manipulation. Large randomized trials have shown that OPCAB is safe and offers short-term rates of mortality and stroke like ONCAB. Postoperative bleeding, atrial fibrillation and time on mechanical ventilation are generally reduced in OPCAB. However, this is often achieved at the expense of a reduced average number of grafts and higher rate of incomplete myocardial revascularization, which might explain the worse long-term outcomes showed by some studies. Long-term results seem comparable when OPCAB is performed by experienced surgeons at experienced centres. There are groups of patients in whom the avoidance of cardiopulmonary bypass and aortic manipulation reduce short-term morbidity and mortality: elderly and high risk of neurological events patients, female patients and, more in general, patients with high surgical risk.

OPCAB requires dedication, infrastructure, and expertise to achieve proficiency and good results. This in turn raises the question: can OPCAB simply be introduced into routine clinical practice, or should it be a specialized technique? The evidence seems to suggest the latter: OPCAB is an important tool if it is performed in selected patients, by experienced surgeons and teams. The establishment of a dedicate OPCAB team in each institution, similarly to the specialization for mitral valve repair and major aortic surgery, might lead to improved patient selection and clinical outcomes.

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## Conflict of interest

None to declare.

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