Off-pump vs. on-pump CABG: are we any closer to a resolution?

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This editorial refers to ‘Off-pump vs. on-pump coronary artery bypass surgery: an updated meta-analysis and meta-regression of randomized trials’¹, by J. Afilalo et al., on page 1257

Afilalo and colleagues have presented an updated meta-analysis and meta-regression of randomized trials of off-pump vs. on-pump coronary artery bypass grafting (CABG) surgery.¹ Their two major findings are that while there was a reduction in mortality, myocardial infarction, and stroke in the off-pump group, this only reached significance for the latter, and that the effect of off-pump CABG was similar on all clinical outcomes regardless of age, gender, number of grafts, and trial publication date. The two key questions are: (i) Are these conclusions justifiable based on the data presented? (ii) How relevant are the findings to routine clinical practice?

Before answering these questions it is worth addressing (i) the current situation with off-pump CABG and (ii) the appropriateness of the nature and conduct of the meta-analysis and the meta-regression analysis.

Off-pump surgery was initially proposed almost three decades ago² to allow CABG in developing countries without the need for cardiopulmonary bypass that was beyond the economic reality of vast numbers of potential patients. Despite initial scepticism about its technical feasibility, off-pump CABG was gradually adopted by some surgeons in developed countries who believed that the elimination of cardiopulmonary bypass could potentially and substantially eliminate the adverse clinical consequences of extracorporeal circulation. In developed countries this was particularly relevant in a progressively elderly population undergoing cardiac surgery in view of their greater burden of existing co-morbidities and their greater susceptibility to the potentially deleterious consequences of cardiopulmonary bypass. On the other hand, critics maintained that off-pump surgery led to inferior revascularization through a reduction in both the number and quality of bypass grafts and that no study appeared to demonstrate any substantial clinical advantage of the off-pump technique over the ‘gold standard’ conventional technique using cardiopulmonary bypass. These differing views have remained essentially unchanged after 25 years of debate. Off-pump CABG plateaued in Europe and the USA a decade ago, and since then has remained at ~15–20% of all CABG operations. However, it is important to realize that these numbers encompass the practices of a small number of surgeons who do virtually all CABG off pump and the majority who essentially do none using this technique. In contrast to Europe and the USA, in Asian countries off-pump CABG is performed in 60–100% of the whole CABG population.

From a statistical perspective, to determine the overall effect of off-pump surgery the trial data were pooled and a meta-analysis performed using a random effects model. One of the major strengths of the meta-analysis of Afilalo et al.¹ is that by including more recent studies, the pooled sample size is almost three-fold larger than previously published meta-analyses, thereby giving far greater statistical power and narrower confidence intervals (CIs), with a reduced level of uncertainty regarding treatment effects. Secondly, a unique feature of the study is use of meta-regression for the first time that allowed the investigators to examine individual trial characteristics such as mean age, sex, and number of grafts on the effects of off-pump surgery on outcomes.

In summary, the analyses were performed in almost 9000 patients from 59 randomized trials. Post-operative mortality was 1.6% in the off-pump group and 1.9% in the on-pump group [risk ratio (RR) 0.9; 95% CI 0.63–1.3] and for myocardial infarction the respective figures were 3.4% and 3.9% (RR 0.8; 95% CI 0.69–1.13). The most important finding was a one-third reduction in the incidence of stroke from 2.1% in the on-pump group to 1.4% in the off-pump group (RR 0.7; 95% CI 0.49–0.99). For each of these outcomes meta-regression did not identify significant variation in the off-pump vs. on-pump techniques in relation to mean age, proportion of females, trial date, and the number of bypass grafts. This is not the last word, however, as meta-regression based on study-level aggregate data has low power for patient characteristics.³ So we strongly support the authors’ suggestion of a meta-analysis using individual rather than pooled participant data.

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Overall these results are a testament to the excellence of conven-
tional CABG whether done on or off pump. Furthermore, these
results are also consistent with the low incidence of mortality, myo-
cardial infarction, and stroke reported in other contemporary
studies of CABG such as the ART4 and SYNTAX5 trials. What is
less certain from the study of Afilalo et al., however, is how strongly
it can be asserted that, with the possible exception of stroke, there is
no benefit to off-pump surgery on other clinical outcomes in differ-
cent cohorts of patients undergoing CABG.

While the results of the current analyses of Afilalo et al. are
tirely consistent with previous meta-analyses comparing on-
and off-pump surgery, it is also equally susceptible to the two con-
sistent and predominant reservations regarding previous analyses.
The first is that the operative experience of the surgeons in the
off-pump group is often substantially less than for the on-pump
surgeons, and this criticism has been levelled at two of the most
influential studies in this area. One of the earliest trials reporting
no benefit of off-pump surgery, published in 2004,5 was severely
criticized as the operative experience of the participating surgeons
in the off-pump group was particularly low (<50 patients per
surgeon). Precisely the same criticisms have also been made
against the ROOBY trial7 published 5 years later in the same
journal.

A second and fundamental criticism of all the previous trials is
that they have invariably been conducted in very low risk
patients where demonstration of a significant reduction in mor-
tality from ~1% in elective CABG patients would require
enormous cohorts of patients. Furthermore, there is a consistent
finding from several registries of propensity-matched higher risk
patients of significant reductions in mortality and all components
of major post-operative morbidity in such patients.8–10

For example, this apparent beneficial effect of off-pump coronary
artery bypass has recently been presented again in possibly the
most definitive single study of this issue in > 120 000 propensity-
matched patients, by Kuss and colleagues10 who reported highly
clinically and statistically significant benefits for mortality [odds
ratio (OR) 0.69; 95% CI, 0.60–0.75] and stroke (OR 0.42;
95% CI 0.33–0.54) as well as renal failure, prolonged ventilation
(P < 0.01), inotropic support (P = 0.02), intra-aortic balloon
pump support (P = 0.05), wound infection (P < 0.001), and red
blood cell transfusion (P < 0.0001).

Indeed this discrepancy between the apparent lack of benefit
with off-pump CABG in randomized trials populated by low risk
patients vs. its apparent benefits in higher risk patients enrolled
in registries is analogous to the situation with stents and surgery
for CABG. Earlier randomized trials, largely populated with
patients with low severity coronary artery disease, showed no sur-
vival benefit of CABG over percutaneous coronary intervention
(PCI) while, in contrast, numerous propensity-matched registries,
containing patients with more severe disease and being more
representative therefore of most patients requiring intervention,
reported an important survival benefit of CABG over PCI.11 Of
course the difficulty in interpreting registry data is the potential
for both known and unknown confounding factors. Nevertheless,
it is particularly noteworthy that the SYNTAX trial, which is the
first trial of stents and CABG in a ‘real life’ population with multi-
vessel disease, has confirmed an important survival benefit of
CABG in these patients at 3 years.5 Some resolution of the diver-
gent signals for on- and off-pump CABG may be provided by
the CORONARY trial which is due to complete enrolment
of > 4500 patients in October of this year.12

Another important issue is the relative risk of stoke between the
two techniques. While the analyses of Afilalo et al. shows a
reduction in risk of stroke with off-pump CABG it almost certainly
underestimates the potential to reduce stroke substantially if, in
addition to avoiding extracorporeal circulation, there is complete
avoidance of any aortic manipulation (‘no touch’ aortic technique).
While avoidance of cardiopulmonary bypass means eliminating
the need to place a large bore tube in the aorta and therefore minimize
the risk of causing embolization of atheromatous material to the
head and neck vessels, the attachment of vein grafts to the ascend-
ing aorta involves manipulation with a side biting clamp and its
inherent risk of dislodging diseased material. The use of epiaortic
ultrasound to avoid diseased segments of aorta is a useful inno-
vation, but is still not as reliable as avoiding any aortic manipulation
by, for example, use of composite arterial grafts based on the
internal mammary arteries.

In conclusion, relatively low risk patients can be assured that the
results of surgery are excellent with both on- and off-pump tech-
niques, and in such patients there appears to be no major
reduction in post-operative morbidity, with the possible exception
of stroke. For higher risk patients, the evidence from registry data
seems to send a different signal by consistently reporting significant
clinical benefits in terms of reductions in mortality and all major
complications. At least until the CORONARY trial is reported, this debate is likely to continue.

Conflict of interest: none declared.

References
11. CORONARY TRIAL: NCT00463294

Corrigendum
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Regrettably, on p. 1907, line 14 of the left column, the drug name should read ‘glibenclamide’ and not ‘glimepiride’, so that the sentence reads ‘Furthermore, less progression of the carotid intima-media thickness was reported in patients receiving repaglinide compared with glibenclamide’.

The authors would like to apologize for this error.

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