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Is there a long-term survival benefit with on pump coronary artery bypass grafting?

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A simple choice?

Coronary artery bypass grafting (CABG) has become the gold standard of care for the treatment of coronary artery disease involving multiple vessels (1). This involves a choice as to whether to perform the surgery on (with cardiopulmonary bypass, CPB) or off pump (on the beating heart, without CPB). Each technique has its advantages and disadvantages. On pump surgery provides a motionless operative field, but can be associated with a number of complications including myocardial ischemic injury, coagulation disorders, neurocognitive deficits, strokes and a systemic inflammatory response (2). In contrast off pump surgery avoids aortic manipulation and, although more technically demanding (2), has been helped by the invention of stabilizing devices (3). The debate as to which approach is superior has been raging for over 40 years. Indeed, an excellent example of the division in opinion is the conduct of 90% of CABG off pump in India (2) compared to only 20% worldwide (4) and 13% in the US and Canada (5).

Evidence from meta-analyses

By 2012, 86 randomized controlled trials (RCTs) had been completed comparing off *vs.* on pump CABG. This enabled the completion of a Cochrane review on the subject (6). This is one of the largest meta-analyses to date, probably because a range of follow-up times was investigated,

whereas 3 recent meta-analyses, completed in 2016 (7-9), concentrated on short-term outcomes only. The results of the Cochrane review revealed no significant differences in the occurrence of myocardial infarction, re-intervention and renal insufficiency. One analysis, which definitely favoured off-pump was the incidence of atrial fibrillation, where the risk ratio (RR) was 0.78 [95% confidence interval (CI): 0.63–0.96; $I^2=67\%$; $Z=2.29$; $P=0.02$] (6). Off-pump was also favoured if the fixed effect model was used for the stroke analysis ($P=0.04$), although this difference disappeared in the random effects model. Undoubtedly, though the most striking result concerned mortality. The pooled analysis of all RCTs reporting mortality produced an RR of 1.24 (95% CI: 1.01–1.53; $I^2=0\%$; $Z=2.04$; $P=0.04$) favouring on pump (6). In trials that the authors considered to be low risk of bias trial sequential analysis revealed a 30% higher risk of mortality in the off pump group. Further analysis showed the number needed to harm was 67. Subgroup analysis comparing trials with <30 days' follow-up with those with >30 days' follow-up demonstrated that the group responsible for the significant results favouring on pump came from the studies with the longer follow-up. It should be noted though that length of follow-up in the >30 days' subgroup varied widely from 2 months to 5 years (6).

A significant limitation of the Cochrane review was that many of the trials were underpowered. Of the 86 included RCTs, only 25 involved >100 participants and only 2 RCTs

included >500 participants (DOORS and ROOBY) (5,10). This may have contributed to the authors' conclusion that only 10 RCTs were at low risk of bias. Nevertheless, the analysis of the low risk of bias RCTs supported the result concerning mortality (RR 1.35; 95% CI: 1.05–1.7; $I^2=0\%$; $Z=2.51$; $P=0.01$) (6). Other limitations noted by the authors concerned the lack of patients with triple vessel disease and those at high risk. At the time of the Cochrane review the most recent published results they were able to include came from 2011. Since that time, several more RCTs have been published including 2 of the largest to date (CORONARY and GOPCABE) (11,12). These additional RCTs prompted the completion of 3 further meta-analyses in 2016.

The largest meta-analysis to date was conducted by Kowalewski *et al.* (7). This meta-analysis is also unique for its inclusion of meta-regression analysis where the log OR of the Off pump group was plotted against the OR of the control (on pump) group, using the inverse of the log variance as weight. This enabled the authors to investigate the effect of risk. The forest plots revealed no significant difference in the occurrence of mortality or MI, whilst in the case of stroke the off pump group was significantly favoured. The results of the meta-regression suggested that outcomes may be related to the patient's risk profile and that performing surgery off pump may be preferable in high risk patients. It should be noted that this represents only one method for assessing the impact of a patient's risk profile, other parameters such as age, EUROscore, ejection fraction and the presence of pulmonary disease may also be worth investigating. The other 2 meta-analyses published in 2016 produced conflicting results (8,9). The results of Deppe *et al.* (8) concur with those of Kowalewski *et al.* (7) with regard to the significant advantage of off pump with respect to stroke, whereas Dieberg *et al.* (9) found no difference perhaps because they included more studies than Deppe *et al.* (8). Dieberg *et al.* did, however find off pump to be significantly favoured with respect to atrial fibrillation (9).

Thus the results of these meta-analyses so far conducted are contradictory, concentrate largely on short-term outcomes and include many small (<100 participants) studies. It is worth mentioning two further meta-analyses in this section, because they attempted to investigate longer-term outcomes, although longer-term in these cases means either 1-year of follow-up or anything over 6 months. One of these studies used inclusion criteria, which excluded participants with a mean age <60 years (13). As a consequence,

only 4 so-called long term studies were included [GOPCABE (1-year) (12); DOORS (6-months) (10); CORONARY (1-year) (14) and Møller (3-year) (15)] and significant RCTs including Angelini *et al.* (4) were missed. In this small comparison there were no differences in the incidences of stroke, MI and mortality (13). In contrast, the meta-analysis investigating 1-year outcomes significantly favoured the on pump group with regard to mortality (16), which correlates with the results of the Cochrane review (6).

Can the large clinical trials provide clarity? Short-term outcomes

Confused? The evidence from the meta-analyses is contradictory and plagued by underpowered RCTs. There are only 4 multicentre RCTs investigating on *vs.* off pump CABG, which included >500 participants. These are CORONARY (11), DOORS (10), GOPCABE (12) and ROOBY (17) (Table 1). At 30 days after surgery all of these RCTs showed an insignificant difference between the on and off pump groups for mortality and stroke. CORONARY (11), DOORS (10) and GOPCABE (12) showed no difference in the incidence of MI and CORONARY (11), GOPCABE (12) and ROOBY (17) showed no difference in new onset renal failure. At this early time point the most worrying aspect concerned the completeness of revascularization, because compared to the on pump group repeat revascularization was significantly greater in the off pump group in CORONARY (11) and DOORS (10) and the number of grafts performed *vs.* those planned in the off pump group was significantly lower in ROOBY (17). In summary at this early time point there were no differences in hard clinical outcomes, although there was a question about the completeness of the revascularization in the off pump group.

Mid-term outcomes

The RCT with the shortest follow-up was DOORS (10), which only investigated mortality at 6 months, finding no difference between the groups. The other three studies reported 1-year outcomes. CORONARY (11) continued to investigate a composite composed of death, MI, stroke and new renal failure requiring dialysis for which there was no difference between the two groups. Although there had been the initial difference at 30 days in the rate of repeat revascularisation, it would be stretching the point too far to say there was still a trend towards an

Table 1 Characteristics of the largest multicentre RCTs investigating on versus off pump CABG

Study	N: On (Off)	Age: On (Off)	Male %: On (Off)	All outcome measures	Timing of measurements
CORONARY 2012; Canada	2,377 [2,375]	67.5±6.9 (67.6±6.7)	82 [80]	Atrial fibrillation; MI; mortality; need for blood transfusion; new renal failure; reoperation for bleeding; respiratory complications; revascularisation; stroke	30 days; 1 year; 5 years
DOORS <i>et al.</i> 2012; Denmark	450 [450]	75 [75]	78 [76]	Hospital stay; ICU stay; MI; mortality; quality of life; stroke	30 days; 6 months
GOPCABE 2013; Germany	1,207 [1,187]	78.4±2.9 (78.6±3.0)	68 [69]	Hospital stay; ICU stay; MI; mortality; new renal-replacement therapy; repeat revascularisation; stroke; ventilation time	30 days; 1 year
ROOBY 2009; USA	1,099 [1,104]	62.5±8.5 (63±8.5)	99 [99]	Cardiac arrest; coma; hospital stay; ICU stay; mediastinitis; mortality; new mechanical support; renal failure; reoperation; stroke; tracheostomy; ventilation time	30 days; 1 year; 5 years

RCT, randomized controlled trial; CABG, coronary artery bypass grafting; ICU, intensive care unit; MI, myocardial infarction.

increased rate of repeat revascularization in the off pump group, as the P value was 0.07. These results are very similar to the GOPCABE group (12), who also found no differences in the rate of death, MI, stroke and new renal replacement therapy. In GOPCABE's case there was no uncertainty, there was definitely no difference in the rate of repeat revascularization between the groups. There was also no difference in repeat revascularization rate at 1-year in the ROOBY RCT (17). However, in contrast to the foregoing discussion, there was a significant difference in the 1-year composite (death, nonfatal MI and repeat revascularization) in the ROOBY RCT. Here the on pump appeared to be favoured with the underlying reason possibly due to a significantly lower number of deaths from cardiac causes (2.7% off pump; 1.3% on pump; $P=0.03$), although there was no significant difference in the Kaplan Meier curves (17). Also noteworthy from the 1-year follow-up of the ROOBY RCT is the significantly lower rate of graft patency in the off pump group. This was especially marked for saphenous vein grafts and when the left internal thoracic was grafted to the left anterior descending artery (17).

Long-term outcomes

Perhaps the ultimate test of the efficacy of on or off

pump CABG is patient freedom from cardiovascular events in the long term. This year has witnessed the landmark publication of the 5-year outcomes of the CORONARY (18) and most recently ROOBY (5) trials. The message from the CORONARY (18) trial continued to be no significant differences in the rate of death, MI, stroke, new renal failure requiring dialysis, cost and quality of life. However, in view of the results at 1-year follow-up which began to favour the on pump group, it was of some significance when the 5-year outcomes of the ROOBY RCT (5) became available and the findings if you are an on pump supporter did not disappoint. The primary outcomes investigated were death from any cause and MACE (composite of death from any cause, repeat revascularization or nonfatal MI). Time to event was also recorded. Secondary outcomes included 5-year rate of death from cardiac causes, repeat revascularization, nonfatal MI and the impact of the surgeon's experience. The 5-year rate of death was 15.2% in the off pump group compared to only 11.9% in the on pump group ($P=0.02$) giving rise to a hazard ratio for death in the off pump compared to on pump group of 1.3 (95% CI: 1.04–1.64; $P=0.02$) (5). This translates into a significant 28% higher risk of death from any cause after off pump CABG. There is an interesting symmetry between this and the Cochrane

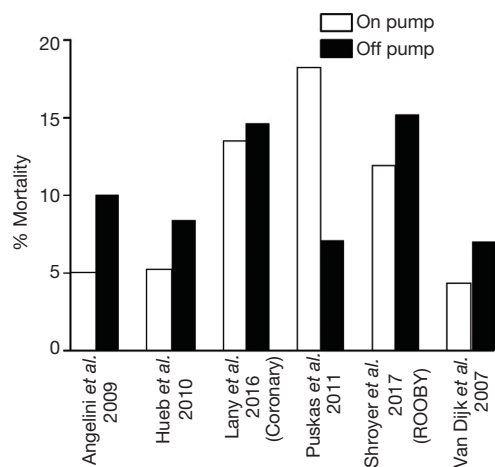


Figure 1 The percentage mortality in the on and off pump groups in studies reporting over 4 years of follow-up. Open bars, on pump; solid bars, off pump.

review (6) with respect to mortality. None of the secondary outcomes showed any significant difference and there was no significant difference based on the surgeon's experience.

Is there a long-term survival benefit with on pump?

The 5-year results from the ROOBY RCT (5) suggested that there was a long-term survival advantage associated with on pump CABG compared to off pump. Is there any other evidence to support this? A total of 6 RCTs have reported over 4 years of outcomes including and in addition to CORONARY (18) and ROOBY (5): Angelini *et al.* (4); Hueb *et al.* (19); Puskas *et al.* (3) and van Dijk *et al.* (20). Figure 1 compares the incidence of mortality in the on and off pump group in each of these studies. In all of these studies bar one (3) the numbers that had died by the follow-up point were larger in the off pump group compared to the on pump group (4,5,18-20). In the exception, Puskas *et al.* (3), although there was a significant difference at the 5 year follow up point, this had disappeared by seven years. Thus far the ROOBY (5) trial is the only trial to report a significant difference in favour of the on pump group at 5 years, though it should be noted that Angelini *et al.* (4) do not state the P value in their study where mortality was double that of the on pump group in the off pump group. The ROOBY (5) trial authors do note that their participants tended to have slightly higher rates of hypertension, peripheral vascular disease and atrial

fibrillation than the CORONARY (11) trial, whilst there were lower rates of urgent status, diabetes and female sex.

Conclusions

Although CABG remains a gold standard choice of treatment for triple vessel coronary artery disease, the opinion as to whether this should be performed off or on pump is divided. Evidence from meta-analyses has been contradictory and overshadowed by the low numbers of participants in many of the trials. Of the four large trials that have been carried out, three have consistently showed no differences in hard clinical outcomes (death, rate of MI, stroke and new renal failure) (10-12). In addition, any early advantages in terms of completeness of revascularization in the on pump group have disappeared by the mid-term follow up. The one exception to this is the ROOBY (5) trial, which has shown at both the mid-term and long-term follow-up points a significant difference favouring on pump with regards to mortality. Perhaps the results of this one, albeit large clinical trial, are insufficient to come to a definitive conclusion; however, they do support the notion that on pump CABG is non-inferior to off pump CABG and may even in certain patients be beneficial. The next question is identifying precisely who those patients are.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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