A meta-analysis of randomized trials for repeat revascularization following off-pump versus on-pump coronary artery bypass grafting

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Abstract
To determine whether repeat revascularization rates are increased following off-pump coronary artery bypass grafting (CABG), we performed a meta-analysis of randomized controlled trials of off-pump vs on-pump CABG. Databases including MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched through March 2013 using web-based search engines (PubMed, OVID). Studies considered for inclusion met the following criteria: the design was a prospective randomized controlled clinical trial; the study population was patients undergoing CABG; patients were randomly assigned to off-pump vs on-pump CABG and outcomes included repeat revascularization rates at ≥1 year. Our exhaustive search identified 12 prospective randomized controlled trials of off-pump vs on-pump CABG. Pooled analysis demonstrated a statistically significant 38% increase in repeat revascularization rates with off-pump relative to on-pump CABG in the fixed-effects model (odds ratio, 1.38; 95% confidence interval, 1.09–1.76; P = 0.008). In general, exclusion of any single trial from the analysis did not substantively alter the overall result of our analysis. There was no evidence of significant publication bias. The results of our analysis suggest that off-pump CABG may increase repeat revascularization rates by 38% over on-pump CABG.

Keywords: Meta-analysis • Off-pump coronary artery bypass grafting • Randomized controlled trial • Repeat revascularization

INTRODUCTION
Several meta-analyses [1–4] of randomized trials have demonstrated robust evidence of fewer bypass grafts [1] or distal anastomoses [2–4] and lower graft patency [3, 5, 6] in off-pump than in on-pump coronary artery bypass grafting (CABG). Accordingly, it would be expected that repeat revascularization rates may be increased following off-pump compared with on-pump CABG. Previous meta-analyses [4, 7] of randomized trials (including a few trials with ≥1-year follow-up) suggest no significant difference in repeat revascularization rates between off-pump and on-pump CABG. Most recently, two large randomized trials (CABG Off or On Pump Revascularization Study [CORONARY] [see Supplementary material, Reference S1 [E1]] and German Off-pump CABG in Elderly Patients [GOPCABE] study [E2]) have reported repeat revascularization rates at 1 year. Although there was no significant between-group difference (3.1 vs 2.0%; hazard ratio [HR], 1.52; 95% confidence interval [CI], 0.90–2.54; P = 0.11) in the GOPCABE study [E2], a trend towards more 1-year repeat revascularization rates was observed in the off-pump group (1.4 vs 0.8%; HR, 1.66; 95% CI, 0.95–2.89; P = 0.07) in the CORONARY [E1]. To determine whether repeat revascularization rates are increased following off-pump CABG, we performed a meta-analysis of randomized controlled trials of off-pump vs on-pump CABG.

METHODS
To identify all prospective randomized controlled trials of off-pump vs on-pump CABG, databases including MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched through March 2013 using web-based search engines (PubMed, OVID). Keywords included off-pump; and randomized, randomised, randomly or randomization. Studies considered for inclusion met the following criteria: the design was a prospective randomized controlled clinical trial; the study population was patients undergoing CABG; patients were randomly assigned to off-pump vs on-pump CABG and outcomes included repeat revascularization (including both percutaneous coronary intervention and redo CABG) rates at the time of ≥1-year follow-up. For each study, data regarding repeat revascularization in both the off-pump and on-pump CABG groups were used to generate odds ratios (ORs) and 95% CIs. Study-specific estimates were combined using the Mantel-Haenszel method in both fixed-effects and random-effects models. Between-study heterogeneity was analysed by means of standard χ² tests. Where no significant statistical heterogeneity was identified, the fixed-effects estimate was used preferentially as the summary measure. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual trials.
one at a time and recalculating the pooled OR estimates for the remaining studies. Publication bias was assessed graphically using a funnel plot and mathematically using an adjusted rank-correlation and linear regression test. All analyses were conducted using Review Manager version 5.1 (Nordic Cochrane Centre, Copenhagen, Denmark) and Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ, USA).

RESULTS

Our exhaustive search identified 12 prospective randomized controlled trials of off-pump vs on-pump CABG [E1–E12] (Table 1). In total, our meta-analysis included data on 11,594 patients randomized to off-pump or on-pump CABG. Pooled analysis demonstrated a statistically significant 38% increase in repeat revascularization rates with off-pump relative to on-pump CABG in the fixed-effects model (OR, 1.39; 95% CI, 1.04–1.84; P-value for effect = 0.02; P-value for heterogeneity = 0.87). Secondly, we excluded the GOPCABE study [E2], the second-highest-weight (20.0%) and second-largest (2370 patients) trial; or the CORONARY [E1], the third-highest-weight (17.1%) and largest (4752 patients) trial. Without the GOPCABE study or the CORONARY, there was still a statistically significant benefit for on-pump CABG in pooled analysis of the remaining 11 trials (fixed-effects OR for excluding the GOPCABE study, 1.34; 95% CI, 1.03–1.76; P-value for effect = 0.03; P-value for heterogeneity = 0.89; fixed-effects OR for excluding the CORONARY, 1.32; 95% CI, 1.02–1.73; P-value for effect = 0.04; P-value for heterogeneity = 0.91). In general, exclusion of any single trial from the analysis did not substantively alter the overall result of our analysis. To assess publication bias, we generated a funnel plot of the logarithm of effect size vs the standard error for each trial (data not shown). There was no evidence of significant publication bias (P = 0.76 and 0.34 by the adjusted rank-correlation and linear regression test, respectively).

DISCUSSION

The results of our analysis suggest that off-pump CABG may increase repeat revascularization rates by 38% over on-pump CABG, which was robust in sensitivity analyses, even eliminating each of higher-weight or larger trials. No individual trial (even higher-

Table 1: Trial characteristics and patient profiles

<table>
<thead>
<tr>
<th>Trial</th>
<th>Inclusion criteria</th>
<th>Follow-up</th>
<th>Patient profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBS 2011 [E3]</td>
<td>Isolated first-time CABG, elective or subacute operation, ≥54 years, 3-vessel disease, ≥2 additive EuroSCORE</td>
<td>Median 3.7 years (range 1.8–5.8)</td>
<td>339 75.9 64.3 18.0</td>
</tr>
<tr>
<td>BHACAS 1 and 2 2009 [E4]</td>
<td>Exclusion criteria: ≥30% LVEF, recent myocardial infarction within 1 month; history of supraventricular arrhythmia; previous CABG, renal or respiratory impairment; previous stroke, transient ischemic attack or coagulopathy</td>
<td>75.5 ± 20.6 vs 76.7 ± 19.3 months</td>
<td>401 62.2 82.0 23.7</td>
</tr>
<tr>
<td>CORONARY 2013 [E1]</td>
<td>Isolated CABG, ≥1 risk factors in ≥70 years, ≥2 risk factors in 60–69 years; ≥2 risk factors in 55–59 years</td>
<td>1 year</td>
<td>4752 67.5 80.9 47.0</td>
</tr>
<tr>
<td>GOPCABE 2013 [E2]</td>
<td>Isolated first-time CABG, ≥75 years</td>
<td>1 year</td>
<td>2370 79.3 69.2 14.4</td>
</tr>
<tr>
<td>Karolak 2007 [E5]</td>
<td>Exclusion criteria: emergency procedure, concomitant major cardiac procedures, &lt;30% ejection fraction, reoperation</td>
<td>Median 3.8 (IQR 3.4–4.4) years</td>
<td>300 63.0 80.6 32.8</td>
</tr>
<tr>
<td>Lingaas 2006 [E6]</td>
<td>Stable angina pectoris, moderate or good left ventricular function</td>
<td>1 year</td>
<td>120 65 78.3 16.7</td>
</tr>
<tr>
<td>MASS III 2010 [E7]</td>
<td>Isolated first-time CABG, proximal &gt;70% multiple vessel disease, stable angina, preserved left ventricular function</td>
<td>5 years</td>
<td>308 60 79 28</td>
</tr>
<tr>
<td>Muneretto 2003 [E8]</td>
<td>Isolated total arterial CABG with composite grafts on elective basis</td>
<td>15 ± 12 months</td>
<td>176 67 60.8 40.9</td>
</tr>
<tr>
<td>Octopus 2007 [E9]</td>
<td>Isolated first-time CABG</td>
<td>62 ± 3 months</td>
<td>281 61.3 68.3 12.8</td>
</tr>
<tr>
<td>PROMISS 2010 [E10]</td>
<td>First-time CABG, 30–90 days, multiple vessel disease</td>
<td>Mean 498 (range 242–1164) days</td>
<td>147 65.3 83.7 36.1</td>
</tr>
<tr>
<td>ROOBY 2009 [E11]</td>
<td>Urgent or elective CABG only</td>
<td>1 year</td>
<td>2203 62.8 99.4 43.6</td>
</tr>
<tr>
<td>SMART 2004 [E12]</td>
<td>Isolated primary elective CABG</td>
<td>1 year</td>
<td>197 62.4 77.2 33.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>11,594</td>
<td>68.5 80.8 35.5</td>
</tr>
</tbody>
</table>

aNot excluded from BHACAS 2.

Peripheral arterial disease, cerebrovascular disease or carotid stenosis of ≥70% of the luminal diameter or renal insufficiency.

Diabetes requiring treatment with an oral hypoglycaemic agent or insulin, the need for urgent revascularization after an acute coronary syndrome, a LVEF of ≥35% or a recent history of smoking (<1 year before randomization).

Insulin-dependent. CABG: coronary artery bypass grafting; IQR: interquartile range.
Figure 1: Meta-analysis of repeat revascularization rates following off-pump vs on-pump CABG using the Mantel-Haenzel method in the fixed-effects model. CI: confidence interval.

SUPPLEMENTARY MATERIAL

Supplementary material is available at ICVTS online.

Conflict of interest: none declared.

REFERENCES


eComment. Stroke rate after surgical myocardial revascularization

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I read with great interest the paper by Takagi et al. in which they tried to answer an important question: Does off-pump coronary artery bypass grafting (CABG) increase the risk of repeat coronary revascularization when compared with on-pump CABG? [1] Data from this meta-analysis confirm that the decreased benefits from on-pump CABG is attributable to the higher incidence of fewer bypass grafts and lower graft patency yielding incomplete and repeat revascularization with this technique. In this valuable meta-analysis, I think that there is yet another topic to be discussed. Proponents of off-pump CABG have claimed that this technique limits the rate of postoperative stroke by avoiding aortic cannulation/decannulation, micro-gaseous and small particulate emboli from the pump circuit and aortic cross-clamping. Off-pump technique does not totally eliminate the necessity for aortic clamping. However, in beating heart operations with no-touch aorta technique, cerebral embolic load is completely reduced by avoiding aortic cross-clamping. Yet, there is still the hazard for neurological insult related to periods of hypotension during manipulation of the heart.

Three large clinical trials have been conducted recently comparing outcomes in cardiac surgery patients using off-pump and on-pump strategy. The Randomized On/Off Bypass (ROOBY) trial [2] is a single-blinded randomized trial involving 2203 patients in 18 Veterans Affairs medical centres. There was no significant difference between off-pump and on-pump CABG in the rate of the 30-day stroke (1.3% vs 0.7%, respectively; P = 0.28). Recently, the results of the Coronary Artery Bypass Surgery Off or On Pump Revascularization Study (CORONARY) [3] has been published. This prospective study involved 4752 patients randomized to either on- or off-pump CABG in 79 centres and 19 countries. The use of off-pump CABG, as compared with on-pump CABG, did not reduce the rate of non-fatal stroke (1.0% vs 1.1%, respectively; P = 0.89) at 30 days or at one year (1.5% vs 1.7%, respectively; P = 0.24). Diegeler et al. reported their results from the German Off-Pump Coronary Artery