Comparison of Graft Patency Between Off-Pump and On-Pump Coronary Artery Bypass Grafting: An Updated Meta-Analysis

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Background. Currently, off-pump coronary artery bypass grafting (OPCAB) and on-pump coronary artery bypass grafting (ONCAB) are 2 well-established therapeutic strategies for patients with coronary artery disease, and debate regarding which strategy provides superior graft patency is ongoing. The current study is a meta-analysis of randomized controlled trials that compared the graft patency between OPCAB and ONCAB.

Methods. Data sources were PubMed, the Cochrane Library, Google Scholar, and ISI Web of Knowledge (1966–2013). We identified studies comparing graft patency after the 2 procedures as the primary intervention for patients with multivessel coronary artery disease and conducted a meta-analysis of randomized controlled trials on graft patency.

Results. A literature search yielded 12 randomized controlled trials, for a total of 3,894 and 4,137 grafts performed during OPCAB and ONCAB procedures, respectively. Meta-analysis of these studies showed an increased risk of occlusion of all grafts (risk ratio [RR], 1.35; 95% confidence interval [CI], 1.16–1.57) and saphenous vein grafts (SVGs) (RR, 1.41; 95% CI, 1.24–1.60) in the OPCAB group, whereas there was no significant difference in graft occlusion of left internal mammary artery (LIMA) (RR, 1.15; 95% CI, 0.83–1.59) and radial artery (RR, 1.37; 95% CI, 0.76–2.47) grafts between OPCAB and ONCAB.

Conclusions. Meta-analysis of currently available randomized controlled trials on graft patency shows that ONCAB reduces the incidence of SVG graft occlusion significantly but does not affect LIMA and radial artery graft patency compared with OPCAB.

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Every year, tens of thousands of patients with coronary artery disease undergo surgical revascularization with cardiopulmonary bypass (on-pump coronary artery bypass [ONCAB]) or without cardiopulmonary bypass (off-pump coronary artery bypass [OPCAB]). The question of which strategy is more safe and effective has been debated by cardiac surgeons since the 2 procedures were introduced. Many prospective randomized or retrospective studies [1–3] are available and focus on the clinical outcomes, including graft patency, of the 2 interventions. However, although meta-analyses have been conducted [4–6], results of graft patency in the literature are still controversial. Previous meta-analyses fail to provide clear-cut conclusions because the numbers of patients and grafts are relatively small; however, since their publication, some large randomized controlled trials and long-term outcomes have been published [7–9]. Therefore, we have conducted a new meta-analysis that includes more recent studies to evaluate the effects of OPCAB and ONCAB on graft patency.

Material and Methods

Search Strategy

We carried out a literature search using PubMed, the Cochrane Library, Google Scholar, and ISI Web of Knowledge of all studies published between 1966 and 2013 comparing graft patency between OPCAB and ONCAB procedures. The last search was through July 2013. Keywords included “off pump,” “off-pump,” “on pump,” “on-pump,” “CABG,” “coronary artery bypass grafting,” “graft patency,” and “randomized controlled trial.” To broaden the search, we used the “related articles” function. We reviewed all abstracts, studies, and citations irrespective of language.

Two reviewers (BZ and JZ) independently extracted the following data from each study: first author, year of publication, trial characteristics, study design, inclusion and exclusion criteria, graft type, timing of graft assessment, and patency rates of bypass grafts.
Inclusion and Exclusion Criteria

To be eligible for inclusion in our meta-analysis, trials had to conform to the following criteria: prospective randomized study comparing OPCAB and ONCAB as primary interventions for multivessel coronary artery disease, graft patency assessed after the operation and data reported in the study regardless of the length of follow-up, and graft patency assessed by computed tomographic angiography (CTA) or coronary angiography (CAG). If the same group reported multiple studies on outcomes of interest at different follow-up points, we extracted patient characteristics from the first study and data for outcomes of interest from the later studies. When 2 studies by the same group reported the same outcomes of interest at similar follow-up points, we adopted either the higher quality or most informative publication.

We excluded studies in which the rates of graft patency were not reported or in which it was impossible to calculate these from the published results.

Statistical Analysis

We carried out our meta-analysis in accordance with Cochrane Collaboration recommendations and Quality of Reporting of Meta-analyses guidelines [10]. RRs were used as the common measure across studies; hazard ratios/odds ratios were sometimes considered equivalent to RRs. An RR less than 1 favored the OPCAB group, and the point estimate of the RR was considered statistically significant at the $p = 0.05$ level if the 95% CI did not include the value 1.

We used a random-effects model in which it was assumed that there was variation among studies, and the calculated RR therefore had a more conservative value [11]. The random-effects model is preferred in surgical research, largely because patients undergoing operations at different centers have varying risk profiles and selection criteria for each surgical technique. In this meta-analysis, we considered only randomized controlled trials that presented the highest quality of evidence. All analyses were conducted using Stata 12.0 software for Windows (StataCorp LP, College Station, TX).

We used 3 strategies to assess heterogeneity. First, heterogeneity among studies was evaluated using the Q-statistic. $I^2$ values of less than 25% were considered to have low heterogeneity, those of 25% to 50% were considered to have moderate heterogeneity, and those of greater than 75% were considered to have high heterogeneity. Second, we reanalyzed data using both random- and fixed-effects models or excluding the trials in which the grafts were assessed by CTA. Third, we evaluated publication bias using a funnel plot.

Results

Twelve randomized controlled trials [7–9, 12–20] published between 2003 and 2012 met the inclusion criteria (Fig 1). These studies included a total of 8,031 grafts with different follow-up times, from 21 days to 8 years; 48.5% were in the OPCAB group and 51.5% were in the ONCAB group. Puskas and colleagues [8, 21] and Lingaas and associates [14, 22] published 2 studies each at different follow-up points in the same group of patients; only the studies [8, 14] with a longer follow-up period were finally included in the meta-analysis. Our 2 reviewers had 100% agreement on data extraction. All trials were prospective randomized trials. A few trials used right internal mammary and gastroepiploic artery grafts, but the number was too small to be analyzed.

Table 1 presents the characteristics of the included trials. Table 2 presents the results of sensitivity analysis of the outcomes of interest.
Table 1. Trial Characteristics

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Country</th>
<th>No. Randomized</th>
<th>Crossover, n (%)</th>
<th>Timing of Graft Patency Evaluation</th>
<th>Proportion Undergoing Graft Assessment, n (%)</th>
<th>Methods of Graft Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hattler</td>
<td>2012</td>
<td>United States</td>
<td>2,203</td>
<td>180 (8.2)</td>
<td>12 mo</td>
<td>1,370 (62)</td>
<td>CAG</td>
</tr>
<tr>
<td>Puskas</td>
<td>2011</td>
<td>United States</td>
<td>200</td>
<td>4 (2.0)</td>
<td>7.5 y</td>
<td>57 (29)</td>
<td>CTA</td>
</tr>
<tr>
<td>Sousa</td>
<td>2010</td>
<td>Portugal</td>
<td>150</td>
<td>3 (2.0)</td>
<td>5 wk</td>
<td>141 (94)</td>
<td>CTA</td>
</tr>
<tr>
<td>Moller</td>
<td>2010</td>
<td>Denmark</td>
<td>341</td>
<td>14 (4.1)</td>
<td>12 mo</td>
<td>69 (20)</td>
<td>CAG</td>
</tr>
<tr>
<td>Angelini</td>
<td>2009</td>
<td>United Kingdom</td>
<td>401</td>
<td>2 (0.5)</td>
<td>8 y</td>
<td>199 (50)</td>
<td>CTA</td>
</tr>
<tr>
<td>Lingaas</td>
<td>2006</td>
<td>Norway</td>
<td>120</td>
<td>7 (3.5)</td>
<td>12 mo</td>
<td>109 (91)</td>
<td>CAG</td>
</tr>
<tr>
<td>Al-Ruzzeh</td>
<td>2006</td>
<td>United Kingdom</td>
<td>168</td>
<td>0</td>
<td>3 mo</td>
<td>151 (90)</td>
<td>CAG</td>
</tr>
<tr>
<td>Kobayashi</td>
<td>2005</td>
<td>Japan</td>
<td>167</td>
<td>1 (0.6)</td>
<td>3 wk</td>
<td>167 (100)</td>
<td>CAG</td>
</tr>
<tr>
<td>Widimsky</td>
<td>2005</td>
<td>Czech Republic</td>
<td>400</td>
<td>33 (8.3)</td>
<td>12 mo</td>
<td>255 (64)</td>
<td>CAG</td>
</tr>
<tr>
<td>Khan</td>
<td>2004</td>
<td>United Kingdom</td>
<td>104</td>
<td>2 (1.9)</td>
<td>3 mo</td>
<td>82 (79)</td>
<td>CAG</td>
</tr>
<tr>
<td>Nathoe</td>
<td>2003</td>
<td>Netherlands</td>
<td>281</td>
<td>16 (5.7)</td>
<td>12 mo</td>
<td>70 (25)</td>
<td>CAG</td>
</tr>
<tr>
<td>Muneretto</td>
<td>2003</td>
<td>Italy</td>
<td>176</td>
<td>8 (4.5)</td>
<td>12 mo</td>
<td>118 (67)</td>
<td>CAG</td>
</tr>
</tbody>
</table>

CAG = coronary angiography; CTA = computed tomographic angiography.

Table 2. Results of Sensitivity Analysis for Graft Occlusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Graft Occlusion</th>
<th>SVG Occlusion</th>
<th>LIMA Occlusion</th>
<th>Radial Artery Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fixed Effects Model</td>
<td>Random Effects Model</td>
<td>Fixed Effects Model</td>
<td>Random Effects Model</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.38 (1.23–155)</td>
<td>1.35 (1.16–1.57)</td>
<td>1.43 (1.26–1.62)</td>
<td>1.41 (1.24–1.60)</td>
</tr>
<tr>
<td>Heterogeneity (p value)</td>
<td>12.57 (0.322)</td>
<td>2.01 (0.991)</td>
<td>4.86 (0.772)</td>
<td>7.21 (0.302)</td>
</tr>
<tr>
<td>No. of occluded grafts</td>
<td>OPCAB 569 of 3,894</td>
<td>428 of 1,901</td>
<td>72 of 1,274</td>
<td>38 of 314</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.39 (1.23–1.57)</td>
<td>1.35 (1.12–1.63)</td>
<td>1.43 (1.25–1.62)</td>
<td>1.41 (1.24–1.61)</td>
</tr>
<tr>
<td>Heterogeneity (p value)</td>
<td>9.97 (0.267)</td>
<td>0.94 (0.998)</td>
<td>2.06 (0.841)</td>
<td>6.60 (0.086)</td>
</tr>
<tr>
<td>No. of occluded grafts</td>
<td>OPCAB 497 of 3,315</td>
<td>395 of 1,671</td>
<td>56 of 1,056</td>
<td>27 of 258</td>
</tr>
</tbody>
</table>

a $\chi^2$ test.

CAG = coronary angiography; CI = confidence interval; LIMA = left internal mammary artery; ONCAB = on-pump coronary artery bypass; OPCAB = off-pump coronary artery bypass; SVG = saphenous vein graft.
Overall Graft Occlusion

Data for occlusion of all graft types are shown in Fig 2. Twelve groups reported on graft occlusion after either intervention. Meta-analysis of the randomized studies showed a significant difference in the incidence of postoperative graft occlusion between the OPCAB (14.6%) and ONCAB (10.7%) groups (RR, 1.35; 95% CI, 1.16–1.57). After the largest trial (Randomized On/Off Bypass [ROOBY] trial) [7] was excluded, the pooled analyses showed that there was still a 32% increase of postoperative graft occlusion in the OPCAB group over the ONCAB group (RR, 1.32; 95% CI, 1.07–1.64). Nine groups reported on the incidence of graft occlusion assessed by CAG. Among these trials, RR was 1.35 (95% CI, 1.12–1.63), showing that there was a significant difference in the incidence of postoperative graft occlusion between the OPCAB (15.0%) and ONCAB (11.0%) groups. Moreover, 9 trials reported on the incidence of overall graft occlusion after excluding the studies with a proportion of graft patency less than 50%, and 5 trials reported on the incidence of overall graft occlusion in the 12-month follow-up; the results were RR, 1.37, 95% CI, 1.11–1.69 and RR, 1.44; 95% CI, 1.25–1.65, respectively, which were consistent with the previous results.

SVG Occlusion

Results of SVG occlusion are shown in Fig 3. Ten groups reported on SVG occlusion after either intervention. Meta-analysis of the randomized studies showed a significant difference in the incidence of postoperative SVG occlusion between the OPCAB (22.5%) and ONCAB (16.4%) groups (RR, 1.41; 95% CI, 1.24–1.60). After the largest trial (ROOBY trial) [7] was excluded, the pooled analyses showed that there was still a 35% increase of SVG occlusion in the OPCAB group over the ONCAB group (RR, 1.35; 95% CI, 1.10–1.66). Seven groups reported on the incidence of SVG occlusion assessed by CAG. Among these trials, RR was 1.41 (95% CI, 1.24–1.61), showing that there was a significant difference in the incidence of postoperative SVG occlusion between the OPCAB (26.3%) and ONCAB (17.2%) groups.

Left Internal Mammary Artery Graft Occlusion

Results of left internal mammary artery (LIMA) graft occlusion are shown in Fig 4. Nine groups reported on LIMA graft occlusion after either intervention. Meta-analysis of the randomized studies showed no significant difference in the incidence of postoperative LIMA graft occlusion between the OPCAB (5.7%) and ONCAB (5.0%) groups (RR, 1.15; 95% CI, 0.83–1.59). After the largest trial (ROOBY trial) [7] was excluded, the pooled analyses showed that there was no significant difference in LIMA graft occlusion between the OPCAB and ONCAB groups (RR, 1.02; 95% CI, 0.67–1.55). Six groups reported on the incidence of LIMA graft occlusion assessed by CAG. Among these trials, RR was 1.22 (95% CI, 0.84–1.77), revealing no significant difference in the incidence of postoperative graft occlusion between the OPCAB (5.3%) and ONCAB (4.4%) groups.

Radial Artery Graft Occlusion

Results of radial artery graft occlusion are shown in Fig 5. Seven groups reported on radial artery graft occlusion after either intervention. Meta-analysis of the randomized studies showed no significant difference in the incidence of postoperative radial artery graft occlusion between OPCAB (12.1%) and ONCAB (7.4%) groups (RR, 1.37; 95% CI, 0.76–2.47). After the largest trial (ROOBY trial) [7] was excluded, the pooled analyses showed that there was no significant difference in radial artery graft occlusion between the OPCAB and ONCAB groups (RR, 1.67; 95% CI, 0.78–3.60). Four groups reported on the

Fig 2. Forest plot showing results of trials reporting overall graft occlusion between off-pump coronary artery bypass (OPCAB) and on-pump coronary artery bypass (ONCAB). (CI = confidence interval; RR = relative risk.)
incidence of radial artery graft occlusion assessed by CAG. Among these trials, RR was 1.66 (95% CI, 0.56–4.96), showing that there was no significant difference in the incidence of postoperative radial artery graft occlusion between the OPCAB (10.55%) and ONCAB (6.49%) groups.

Publication Bias Assessment
A funnel plot with a proximal standard error between overall graft occlusion values for the OPCAB and ONCAB groups in each study is shown in Fig 6. Rank correlation analysis (Begg’s test) of the funnel plot did not identify any significant graphic or statistical bias (P = 0.451).

Comment
In the present meta-analysis of randomized trials comparing graft patency between OPCAB and ONCAB for patients with multivessel coronary artery disease, there are significantly increased rates (35%) of occlusion of all graft types with OPCAB compared with ONCAB. One popular explanation for this is that in terms of surgical technique, OPCAB is more technically demanding than ONCAB, especially when lateral wall targets are grafted [23]. However, in some randomized controlled trials at a single center and with a single experienced surgeon [8, 12, 15], a significant difference was not seen. This seems to indicate that there would be no significant difference between OPCAB and ONCAB if only experienced surgeons were enrolled in the trials.

Subgroup analysis by type of graft demonstrated a statistically significant 41% increase in SVG occlusion with OPCAB compared with ONCAB. This result differs from those of LIMA and radial artery grafts, however, for which there was no significant difference in rates of patency between the OPCAB and ONCAB groups,
demonstrating that OPCAB did not affect arterial graft patency when compared with ONCAB. Moreover, exclusion of the largest trial (ROOBY trial) did not substantially alter the results, so the results were very robust.

Based on these findings, the principal cause of decreased rates of graft patency was the increased rate of SVG occlusion in the OPCAB group. In addition to the technical aspects involved, the difference in heparin dose between the OPCAB and ONCAB groups might also have played an important role during the early postoperative months. A single randomized trial has previously shown that the ONCAB group has a higher rate of graft patency than the OPCAB group but that this difference disappeared after the results were adjusted for the total heparin dose [12]. Recent evidence has also demonstrated that the fibrinogen concentration significantly decreases after ONCAB compared with OPCAB and that the grafts in the OPCAB group were therefore at a higher risk of occlusion [24]. Taken together, these findings indicate that the delayed administration of subcutaneous enoxaparin or dual-antiplatelet therapy could reduce the rate of early graft patency in the OPCAB group. Moreover, other aspects, such as the technique of vein harvesting (open or endoscopic), were not available in most studies; thus, these data were not included in the present meta-analysis. Further studies are still needed to add new mechanistic information.

A major limitation of our study is the merging of occlusion percentages at different follow-up times (21 days–8 years). It would be more convincing to perform an analysis using a hazard function; however, the essential data were not available in several trials, so we could not extract survival curve data and calculate hazard ratios. Moreover, the factors influencing vein graft occlusion change over time, and occlusion observed at different time points are likely measuring different technical or biological phenomena. Acute vein failure is most likely attributed to technical failure or thrombosis, whereas late vein failure is likely attributed to atherosclerotic or generalized neointimal hyperplasia [25].

Potential Limitations

Several aspects of the included studies deserve consideration. First, as in other surgical techniques, the effect of the learning curve for OPCAB and ONCAB must be clarified. Some of the trials used a single experienced surgeon, whereas other trials used multiple surgeons, even including surgeons who were at an earlier point on the learning curve [7], which can potentially affect graft patency rates. Second, advances in antiplatelet drugs mean that pharmacologic therapy itself can improve graft patency after either intervention. Recent evidence has shown that dual-antiplatelet therapy after CABG improves early SVG patency and appears to be most beneficial in patients undergoing OPCAB [26]. Third, although the study designs are prospective and randomized, the proportion of patients who underwent clinical evaluation ranged from 20% to 100%, which resulted in an obvious selection bias. Finally, the surgical techniques, surgical strategies, type of anesthesia, and

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Fig 5. Forest plot showing results of trials reporting graft occlusion of radial artery between off-pump coronary artery bypass (OPCAB) and on-pump coronary artery bypass (ONCAB). (CI = confidence interval; RR = relative risk.)

Fig 6. Funnel plot test of all randomized trials for overall graft occlusion between off-pump coronary artery bypass (OPCAB) and on-pump coronary artery bypass (ONCAB). (OR = odds ratio.)
heparin doses differed widely between the 2 groups. All of these factors may increase the degree of clinical heterogeneity. Therefore our results should be interpreted with caution.

Conclusions

Despite the intrinsic limitations of the studies included in this meta-analysis, our findings indicate that ONCAB reduces the incidence of SVG graft occlusion significantly but does not affect LIMA and radial artery graft patency when compared with OPCAB.

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References


INVITED COMMENTARY

Coronary artery bypass grafting (CABG) has existed for nearly 50 years, yet refinements in the operation continue. One modification, coronary artery operations without cardiopulmonary bypass (off-pump CABG), came into popularity >20 years ago, and the relative merits of this technique remain the subject of debate today. For any revascularization strategy to be effective, one overarching tenet must be achieved—the operation must produce a maximal restoration of blood flow to areas of myocardium that do not receive, or are at risk of...