Predictors of revascularization method and long-term outcome of percutaneous coronary intervention or repeat coronary bypass surgery in patients with multivessel coronary disease and previous coronary bypass surgery

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Aims The optimal revascularization strategy in patients with symptomatic multivessel coronary artery disease (CAD) and previous coronary artery bypass grafting (CABG) remains unknown.

Methods and results We evaluated all patients with previous CABG undergoing isolated, non-emergency multivessel revascularization between 1 January 1995 and 31 December 2000. The analysis concentrated on the independent predictors of the revascularization method, as well as on long-term mortality and its predictors, after calculating a propensity score for the method of revascularization. There were 2191 patients (1487 with reoperation and 704 with percutaneous coronary intervention, PCI) in the study. The most important factors in choosing reoperation were presence of more diseased or occluded grafts, previous infarction, lower ejection fraction (EF), longer interval from first CABG, and more total occlusions of native arteries, as well as absence of a patent mammary graft. The distribution of the propensity score was skewed towards the two extremes. At 5 years, the unadjusted cumulative survival was 79.5% for CABG and 75.3% for PCI,

\[ P = 0.008. \]

After adjustment for the propensity score for PCI vs. CABG, PCI was associated with a hazard ratio of 1.47 (0.94–2.28),

\[ P = 0.09. \]

The most powerful predictors of mortality were higher age and lower EF.

Conclusion The choice of the revascularization method in patients with previous CABG is dictated mostly by anatomical considerations and less by clinical characteristics. In contrast, clinical characteristics predominantly affect long-term outcome, whereas the method of revascularization has a limited effect. A randomized clinical trial addressing this important segment of the population with ischaemic heart disease is warranted.

Introduction

Randomized clinical trials (RCTs) have compared multivessel percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) as the initial revascularization strategy in patients with multivessel coronary artery disease (CAD).1–6 We reported recently on our experience in over 6000 patients undergoing one of the two procedures at the Cleveland Clinic Foundation between 1995 and 1999.7 While this study reflected more accurately the general population, it excluded patients with previous CABG and thus did not provide guidance with respect to their optimal management when they need repeat multivessel revascularization.

This segment of the CAD population is growing and poses numerous challenges. On one hand, CAD typically progresses in the interval from the first surgery, leaving fewer options for repeat bypass grafting, with lower initial success and diminished durability.8,9 On the other hand, graft attrition and progression of native CAD diminishes the chances for successful PCI.10 The longer the interval from the initial operation, the more difficult it is to intervene on venous bypasses and the less likely it is that the patient will remain free from recurrent ischaemic events.11

Thus, we set out to identify the predictors of the choice of repeat multivessel revascularization in consecutive patients...
with previous CABG and analyse their 5-year survival after the procedure.

Methods
We considered consecutive patients with multivessel CAD and prior CABG revascularized between 1 January 1995 and 31 December 2000. Patients were excluded if they also required valve or aortic surgery, if they were undergoing primary PCI for an acute myocardial infarction (MI), or if they did not have a valid United States Social Security Number. The Cleveland Clinic Institutional Review Board approved research based on ongoing clinical registries of patients undergoing CABG and PCI and waived the requirement for informed consent.

Clinical data
Since early 1970s, clinical and demographic data regarding patients undergoing revascularization have been systematically abstracted and recorded in the cardiovascular information registry, consisting of separate PCI and CABG registries.

Endpoints
The primary endpoint was all-cause mortality. The Social Security Death Index was used to determine timing of death.12–14

In-hospital post-procedural MI was defined as Q-wave MI (QMI, new pathological Q waves) or non-QMI (NQMI, peak CK-MB >30 ng/mL, or ~four times upper limit of normal, PCI cohort only).

Statistical analyses
Baseline variables were compared using the Wilcoxon rank sum test or the χ² test as appropriate. Survival was compared with Kaplan–Meier curves15 and multivariable Cox proportional hazards regression,16 confirmed by testing of weighted Schoenfeld residuals.17 Possible non-linear associations between the logarithm of hazard and outcome were tested using restricted cubic splines. A propensity analysis was carried out18,19 using a non-parsimonious logistic regression model for treatment with PCI vs. CABG.20 All the variables listed in Table 1 were included in this model, along with significant interactions. The score was then incorporated into subsequent proportional hazards models as a covariate. We used Cox regression analysis that included PCI, the propensity score, and all the covariates that were included in the derivation of the propensity score. We forced in the model PCI and the propensity score and performed stepwise selection on the other variables. All analyses were performed using the SAS 9.1 system (Cary, North Carolina). Model discrimination was tested by calculation of a c-index for censored data, which corresponds to the area under a receptor–operator curve. This index describes the possibility that for a randomly chosen pair of patients in which one had an event and the other did not, the model correctly found a higher risk in the patient who had an event. For discrimination and calibration, 100 bootstrap resamplings were performed and the resulting 100 models were used for calculating c-indexes and predicted risk.21 Missing values (3.8% overall) were reset to median for continuous variables and the mode for the categorical variables. All statistical tests were two-sided and the significance level was set at 0.05.

Results
During the study period, 2191 patients with previous CABG underwent repeat multivessel revascularization, 1487 with reoperation and 704 with PCI. This cohort represents 5–7% of the procedural volume for each modality during that period. Their baseline characteristics are depicted in Table 1. When compared with re-operated patients, patients selected for PCI were significantly older and more likely to have two vessel-CAD, unstable angina, a patent left internal mammary artery (LIMA) to left anterior descending artery (LAD) and fewer chronic total occlusions. The patients who had PCI were more often women, closer to first CABG, and tended to have a higher left ventricular ejection fraction (EF), although more patients had EF < 30% (assessed visually in contrast ventriculography).

Propensity score for revascularization procedure
Using all the baseline characteristics available, we developed a propensity score for PCI vs. CABG in the study population. The c-statistic was 0.98, indicating that the variables used explained virtually all of the variability in selection of the revascularization procedure and that the patients in the two revascularization groups were very different from each other. The most important predictors of the revascularization method are presented in Table 2. The distribution of propensity scores in the CABG and PCI groups confirmed the extreme differences among the groups. Thus, the number of patients who could be matched by propensity score, to simulate a RCT, was only 105 in each group, rendering a matched group analysis susceptible to bias and uninterpretable.

Revascularization procedure and short-term outcome
There were 3.3 ± 1.1 new distal anastomoses for reoperation patients and 2.9 ± 1.0 vessels treated in PCI patients, \( P < 0.001 \). It resulted in complete revascularization (defined by operator as successful revascularization of all vessels >1.5 mm in diameter, with lesions >50% and not protected by functional graft) in 71% of CABG and 89% of PCI patients, \( P < 0.001 \). More PCIs were performed in the latter portion of the study period. In the PCI cohort, 30% had left main trunk (LMT) intervention, 38% had at least one graft treated and at least one stent was placed in 77%. There was no difference in the outcome of patients undergoing only native artery PCI vs. those with graft PCI (\( P = 0.18 \)).

Within 30 days of revascularization, 2.8% of CABG and 1.7% of PCI patients died, \( P = 0.34 \) (log-rank). The surgical mortality was lower than the nationally reported rate for first CABG.22 Periprocedural Q-wave infarct occurred in 1.4% of CABG and 0.3% of PCI patients, \( P = 0.01 \). In addition, non-Q-wave infarct occurred in 7.7% of PCI patients. Stroke occurred in 1.69 and 0.14%, respectively, \( P < 0.001 \) (Table 3).

Long-term outcome
Unadjusted survival rates are shown in Figure 1. There were 376 deaths in CABG patients (25.3%) and 196 in PCI patients (27.8%), \( P = 0.008 \). At 1 year, the cumulative survival was 92.8% for CABG and 91.9% for PCI and at 5 years, it was 79.5 and 75.3%, respectively. PCI was associated with a hazard ratio (HR) for death of 1.27 (1.07–1.51). After adjustment for propensity score, the HR was 1.47 (0.94–2.28), \( P = 0.09 \). Adjustment for all clinical and angiographic characteristics of the patients yielded the independent predictors of survival presented in Table 4. The excess
### Table 1  Baseline characteristics according to treatment of multivessel coronary disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PCI (n = 704)</th>
<th>CABG (n = 1487)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years, SD)</td>
<td>66 ± 10</td>
<td>65 ± 9</td>
<td>0.03</td>
</tr>
<tr>
<td>Women</td>
<td>149 (21%)</td>
<td>233 (16%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Months from first CABG (SD)</td>
<td>98 ± 71</td>
<td>141 ± 70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average follow-up for survivors (months, SD)</td>
<td>70 ± 26</td>
<td>81 ± 22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-insulin treated diabetes</td>
<td>152 (22%)</td>
<td>320 (22%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Insulin treated diabetes</td>
<td>85 (12%)</td>
<td>176 (12%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Hypertension</td>
<td>488 (69%)</td>
<td>1087 (77%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>460 (65%)</td>
<td>1028 (70%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>311 (44%)</td>
<td>1182 (80%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m², SD)</td>
<td>29 ± 12</td>
<td>28 ± 5</td>
<td>0.47</td>
</tr>
<tr>
<td>Other clinical data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>4018 (57%)</td>
<td>287 (19%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>500 (71%)</td>
<td>688 (46%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>51 (7%)</td>
<td>287 (19%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>154 (22%)</td>
<td>287 (19%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>27 (4%)</td>
<td>57 (4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Angiographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main stenosis &gt;50%</td>
<td>206 (29%)</td>
<td>426 (29%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Two vessel/Three vessel CAD</td>
<td>121 (17%) /</td>
<td>176 (12%) /</td>
<td>0.0006</td>
</tr>
<tr>
<td>&gt;1 native vessel total occlusion</td>
<td>583 (83%)</td>
<td>1311 (88%)</td>
<td></td>
</tr>
<tr>
<td>Patent LIMA to LAD</td>
<td>481 (68%)</td>
<td>478 (32%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of diseased grafts (SD)</td>
<td>0.4 ± 0.7</td>
<td>1.6 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Occluded grafts (SD)</td>
<td>0.4 ± 0.8</td>
<td>1.3 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>48 ± 14</td>
<td>44 ± 9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ejection fraction ≤30%</td>
<td>114 (17%)</td>
<td>182 (13%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Missing data</td>
<td>18 (3%)</td>
<td>97 (7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Procedural factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days after 1, January 1995a</td>
<td>1291 (657–1758)</td>
<td>942 (498–1499)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*aPresented as median with interquartile range.

### Table 2  Significant predictors of method of revascularization in decreasing order of importance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chi-square</th>
<th>Odds ratioa</th>
<th>Confidence interval (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of diseased grafts (2 vs. 0)b</td>
<td>133</td>
<td>0.01</td>
<td>0.01-0.03</td>
</tr>
<tr>
<td>Number of occluded grafts (2 vs. 0)b</td>
<td>103</td>
<td>0.05</td>
<td>0.03-0.09</td>
</tr>
<tr>
<td>Prior infarct</td>
<td>98</td>
<td>37</td>
<td>18-75</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>82</td>
<td>0.02</td>
<td>0.01-0.04</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>70</td>
<td>0.11</td>
<td>0.06-0.18</td>
</tr>
<tr>
<td>Patent LIMA to LAD</td>
<td>57</td>
<td>6.6</td>
<td>4-11</td>
</tr>
<tr>
<td>EF (50 vs. 40%)b</td>
<td>46</td>
<td>1.3</td>
<td>1.1-1.7</td>
</tr>
<tr>
<td>Years from 1995 (4.4 vs. 1.5)b</td>
<td>40</td>
<td>3.0</td>
<td>1.9-4.6</td>
</tr>
<tr>
<td>Native artery occlusion (2 vs. 1)b</td>
<td>24</td>
<td>0.41</td>
<td>0.229-0.58</td>
</tr>
<tr>
<td>Years from CABG (15 vs. 6)b</td>
<td>23</td>
<td>0.44</td>
<td>0.33-0.63</td>
</tr>
<tr>
<td>Maximum LAD stenosis (100 vs. 80%)b</td>
<td>13</td>
<td>0.73</td>
<td>0.61-0.86</td>
</tr>
<tr>
<td>Maximum LMT stenosis (60 vs. 0%)b</td>
<td>12</td>
<td>0.47</td>
<td>0.31-0.72</td>
</tr>
<tr>
<td>Age (73 vs. 60 years)b</td>
<td>12</td>
<td>1.8</td>
<td>1.3-2.6</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>8</td>
<td>2.0</td>
<td>1.2-3.1</td>
</tr>
<tr>
<td>Number diseased vessels (3 vs. 2)b</td>
<td>5</td>
<td>2.1</td>
<td>1.1-4.1</td>
</tr>
</tbody>
</table>

*aOdds ratio >1 denotes higher likelihood of PCI.

bOdds ratio calculated for 75th vs. 25th percentile for the respective variable in the cohort.
in death associated with PCI remained essentially unchanged in all models. The model had moderate discriminatory ability (c-statistic 0.69) and excellent calibration ability using 100 bootstrap iterations with 400 patients each. There was no evidence of non-proportional hazards (i.e. attributable risk of death was distributed evenly over time, P-value for scaled Schoenfeld residuals for PCI was 0.98). All variables behaved similarly with the exception of presence of native artery total occlusion, which exhibited non-proportional hazard for death (P = 0.004). A test for a non-linear component of the propensity score predicting death was also not significant (P = 0.89), thus there is no non-linear association.23

The two most important predictors of survival, age and EF, were modelled against revascularization method adjusting for confounding variables (continuous variables set to medians and categorical variables set to most common occurrence), as shown in Figures 2 and 3.

### Discussion

This analysis represents, to our knowledge, one of the largest and most contemporary efforts to characterize the outcome of multivessel revascularization in patients with remote CABG, particularly notable because of the absence of a large, dedicated RCT. The population studied is relatively elderly, has moderate systolic dysfunction and a high incidence of diabetes mellitus, hypertension and acute coronary syndromes. All these high-risk characteristics are very distinct from the risk profile of patients enrolled in RCTs. In the context of a single, tertiary-care institution with outstanding surgical results, the following important lessons can be gleaned from the dataset: (1) when patients present with symptomatic multivessel CAD after CABG, the choice of revascularization is dictated mostly by anatomical considerations related to graft function and less by clinical variables; (2) the method of repeat revascularization separates the study population into two distinct groups that are very difficult to compare; (3) short-term outcome after either PCI or reoperation is very favourable; (4) long-term outcome demonstrates a substantial attrition with ~25% of the cohort dead at 5 years; (5) the most significant predictors of long-term longevity are younger age and better systolic function, whereas the method of repeat revascularization plays a minor part in determining outcome, even though there appears to be a slight excess of mortality associated with PCI. This excess in mortality is difficult to interpret in view of the marked differences among the cohorts.

We have reported previously24 on the predictors of choice of repeat revascularization after CABG in 1663 patients treated between 1992 and 1994. More diseased grafts, diabetes, and more jeopardized myocardium tended to predict reoperation rather than PCI. We did not have long-term follow-up to assess the consequences of the decision. Obviously, the current cohort was treated at a time when stenting became ubiquitous and better medical therapy contributed to the better outcome of revascularization procedures.

In an analysis fashioned similarly to this one, we reported on the choice and outcome of multivessel revascularization in 6033 patients without previous CABG.7 The major predictors of choice of CABG were poor EF, LMT stenosis and presence of chronic total occlusions. Clinical factors played a lesser role, similar to the current analysis. In marked contrast to that population (with a similar risk profile to the current cohort), we report here a 5-year mortality nearly twice as high, both in the PCI (25 vs. 16%) and CABG (21 vs. 14%), respectively. This markedly worse outcome emphasizes the significant impact of long-standing CAD, as the current cohort had already had their first CABG in the middle of sixth decade of life.

The sole randomized evaluation of PCI vs. CABG in post-CABG patients was reported by Morrison et al.25 from the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) Trial and Registry. There were 143 patients randomized to PCI (n = 67) or CABG (n = 75), and 618 others in the registry who were preferentially direct to PCI (n = 431) or reoperation (n = 187). The patients were indeed at high risk, with 40% older than 70 years, 33% with diabetes, 15% with EF < 35%, and 15% with recent MI. At 3 years, the survival was ~75%, comparable to the 5-year survival in our cohort. There was no significant advantage of one procedure over the other except in the group (n = 106) in whom the patients chose the procedure and PCI was superior to reoperation (P = 0.001).

Cole et al.26 reported their experience at a large tertiary centre similar to ours with diabetic patients undergoing PCI (n = 1123) or reoperation (n = 589) ~7 years after initial CABG, between 1985 and 1999. The average age was 64 years and the average EF was 48%. Very few patients had LMT disease. At 5 years, the survival was 62 and 61%, respectively (P = NS), much lower than in our cohort. The

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**Table 3 Procedural details and short-term outcome**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PCI (n = 704)</th>
<th>CABG (n = 1487)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessels treated or distal anastomoses</td>
<td>2.9 ± 1.0</td>
<td>3.3 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete revascularization (%)</td>
<td>89</td>
<td>71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-hospital Q-wave infarct (%)</td>
<td>0.3</td>
<td>1.4</td>
<td>0.01</td>
</tr>
<tr>
<td>In-hospital non-Q-wave infarct (%)</td>
<td>7.7</td>
<td>N/A</td>
<td>−</td>
</tr>
<tr>
<td>In-hospital stroke (%)</td>
<td>0.14</td>
<td>1.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30-day death (%)</td>
<td>1.7</td>
<td>2.8</td>
<td>0.34</td>
</tr>
</tbody>
</table>

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**Figure 1** Unadjusted survival in the PCI and CABG cohort.
major predictors of long-term mortality were higher age and lower EF, as in the current report. Similar results were reported by Stephan et al. The 6-year survival was 74% for PCI and 73% for reoperation (P = 0.32). Age, EF, and diabetes were the main predictors of mortality. In a large cohort of 9600 patients followed for up to 20 years, Sergeant et al. showed that non-risk adjusted survival was superior for CABG in the first 6 years and the curves crossed subsequently.

Our data need to be interpreted cautiously in the context of the inherent limitations of a retrospective analysis. Unlike in most other reports, and although we attempted to use statistical tools to correct for the differences in the characteristics of the two patient groups, we found that they are truly different from each other. The very high c-statistic of the propensity score model and the essential lack of propensity score-matched patients indicate not only that the considered variables account for the choice of revascularization method, but also that this choice creates cohorts of patients with very different risk profiles. In contrast, the mortality multivariable model has only modest discriminatory ability (c-statistic 0.69), such that a considerable variability in death rates cannot be accounted solely by the variables we collect in clinical registries. Furthermore, within this paradigm, the truly important predictors of mortality, such as age and EF, are not amenable to modification. While PCI is statistically associated with some excess mortality, the importance of the choice of revascularization is very small, and equal in weight to achievement of complete revascularization or the overall improvement in survival related to better medical therapies. The interpretation of the excess mortality with PCI is further hampered by the virtual lack of comparable patients, as demonstrated by the distribution of the propensity score and the small number of patients who could be matched. Beyond these considerations, we cannot exclude the fact that some patients may not have been suitable for both procedures and that there was rarely viability data guiding the need for and extent of revascularization. We did not have data on long-term medical therapy (such as anti-platelet and statin therapy), which undoubtedly influenced outcome. Finally, the results are based on a single centre experience, without auditing of data entered in the registries, and may not be applicable to other institutions with worse surgical outcomes.

Conclusion

With these considerations and limitations, we conclude that in the absence of a dedicated, RCT to guide multivessel revascularization in post-CABG patients, clinical practice appears to favour reoperation over PCI for patients at higher risk, with fewer functional grafts, more chronic total occlusions, and lower systolic function, whereas PCI is favoured in those with patent LIMA and amenable anatomy. Long-term mortality is mostly affected by age and EF, while the choice of revascularization has a modest impact. PCI appears to be related to a slight excess in long-term mortality (despite better 30-day outcome) compared with reoperation, an effect markedly attenuated by risk adjustment. The effect of drug-eluting stents, higher success in percutaneous revascularization of chronic total occlusions and improvements in surgical techniques and overall medical care needs to be evaluated prospectively, particularly in high-risk subsets defined by advanced age and systolic dysfunction, before a definitive recommendation can be made for this important segment of the CAD population.

Conflict of interest: none declared.
References


12. Gottlieb SS. Dead is dead—artificial definitions are no substitute. Lancet 1997;349:662–663.


