Outcomes of Coronary Artery Bypass Grafting Versus Percutaneous Coronary Intervention With Drug-Eluting Stents for Patients With Multivessel Coronary Artery Disease

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Background—Advances in coronary artery bypass grafting (CABG) surgery and percutaneous coronary intervention (PCI) with drug-eluting stents have dramatically improved results of these procedures. The optimal treatment for patients with multivessel coronary artery disease is uncertain given the lack of prospective, randomized data reflecting current practice. This study represents a “real-world” evaluation of current technology in the treatment of multivessel coronary artery disease.

Methods and Results—A total of 1680 patients undergoing revascularization for multivessel coronary artery disease were identified. Of these, 1080 patients were treated for 2-vessel disease (196 CABG and 884 PCI) and 600 for 3-vessel disease (505 CABG and 95 PCI). One-year mortality, cerebrovascular events, Q-wave myocardial infarction, target vessel failure, and composite major adverse cardiovascular and cerebrovascular events were compared between the CABG and PCI cohorts. Outcomes were adjusted for baseline covariates and reported as hazard ratios. The unadjusted major adverse cardiovascular and cerebrovascular event rate was reduced with CABG for patients with 2-vessel disease (9.7% CABG versus 21.2% PCI; P<0.001) and 3-vessel disease (10.8% CABG versus 28.4% PCI; P<0.001). Adjusted outcomes showed increased major adverse cardiovascular and cerebrovascular event with PCI for patients with 2-vessel (hazard ratio 2.29; 95% CI 1.39 to 3.76; P=0.01) and 3-vessel disease (hazard ratio 2.90; 95% CI 1.76 to 4.78; P<0.001). Adjusted outcomes for the nondiabetic subpopulation demonstrated equivalent major adverse cardiovascular and cerebrovascular event with PCI for 2-vessel (hazard ratio 1.77; 95% CI 0.96 to 3.25; P=0.07) and 3-vessel disease (hazard ratio 1.70; 95% CI 0.77 to 3.61; P=0.19).

Conclusions—Compared with PCI with drug-eluting stents, CABG resulted in improved major adverse cardiovascular and cerebrovascular event in patients with 2- and 3-vessel coronary artery disease, primarily in those with underlying diabetes. Coronary artery bypass surgery may be the preferred revascularization strategy in diabetic patients with multivessel coronary artery disease. (Circulation. 2007;116[suppl I]:I-200–I-206.)

Key Words: multivessel coronary artery disease ■ drug-eluting stent ■ coronary artery bypass grafting

Both coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) represent important and established modalities of mechanical revascularization for patients with coronary artery disease (CAD). These therapies have been shown to relieve symptoms and, in some circumstances, prolong life.1–4

Multiple studies have compared CABG and PCI first with medical therapy alone and then with each other. Whereas hard outcomes (death, myocardial infarction [MI]) between CABG and PCI were generally similar, target vessel failure (TVF) and angina relief were often superior with CABG.5–14 More important, the superiority of CABG was even more apparent in specific high-risk patient subgroups (ie, multivessel disease with left ventricular dysfunction and diabetics). In some individual studies and in a meta-analysis, CABG has demonstrated benefit in death and MI in high-risk patient subsets.15–17

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Although previous studies are certainly relevant, it is important to note that differences in patient demographics, medical therapy, and technological advances limit their applicability to current practice. First, these trials included relatively small numbers of patients with high-risk features such as diabetes, previous CAD, and left ventricular dysfunction. Second, advances in medical therapy not part of standard care at the time of these studies (ie, thienopyridines, statins, and angiotensin-converting enzyme inhibitors) have significantly altered long-term outcomes in patients with CAD.\textsuperscript{18–21} Finally, the comparative trials first compared CABG with balloon angioplasty and then with bare metal stents. In interventional cardiology, the advent of drug-eluting stents (DES) has dramatically reduced restenosis and TVF.\textsuperscript{22,23} Theoretically, this should reduce the combined end points (mortality, MI, and TVF) that often comprise the primary end points of pivotal trials. Using DES, the Arterial Revascularization Therapies Study Part II (ARTS-II) investigators\textsuperscript{24} reported favorable early results, and prospective, randomized trials comparing PCI with DES and CABG in patients with multivessel disease and in diabetics are currently under way.\textsuperscript{25} We evaluated outcomes associated with PCI with DES and CABG in a “real-world” population of patients with multivessel disease at a single high-volume center.

**Methods**

We evaluated 1680 patients with multivessel CAD undergoing revascularization with either CABG or PCI with DES over than an 18-month period for whom 1-year follow-up was available. Patients undergoing PCI for 2-vessel disease were included if both vessels were revascularized within the same hospitalization. Patients with 3-vessel disease were included if all 3 major epicardial vessels were revascularized within 6 weeks of the index procedure. The method of revascularization was at the attending physician’s discretion and often included consultation with cardiac surgical staff. Patients presenting with cardiogenic shock were excluded from analysis, and patients with significant disease of the left main coronary artery and those undergoing associated valvular procedures were also excluded.

Clinical and outcome data were extracted from pre-existing surgical and PCI databases. Patient follow-up was completed via telephone contact or patient visit with experienced personnel. All clinical events were verified and adjudicated by physicians unaware of the study aims.

Patients with PCI received a standard anticoagulation regimen of dual antiplatelet therapy with aspirin (continued indefinitely) and clopidogrel (for ≥6 months) after PCI with DES. Patients undergoing CABG were also encouraged to take aspirin indefinitely and clopidogrel therapy for 3 months after surgery. Optimal medical therapy, including use of statins, was encouraged.

Study end points included cumulative rates of death, Q-wave MI, cerebrovascular event (CVE), and TVF, as well as the composite major adverse cardiovascular and cerebrovascular event (MACCE) rate at 1 year. Q-wave MI was defined as the development of pathological Q waves after the procedure(s). Stent thrombosis was confirmed by angiography in the clinical setting of acute coronary syndrome and was defined as subacute if it occurred in the first 30 days after PCI. CVE was defined as a transient ischemic attack or stroke adjudicated by a neurologist. For CABG patients, TVF was defined as symptomatic graft failure or target territory revascularization; and for the PCI population, TVF was defined as target vessel revascularization or symptomatic occlusion/ restenosis of the target vessel.

The study was approved by the local institutional review board. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Statistical Analysis**

Continuous variables are expressed as mean values (±SD) and compared using the Student t test. Categorical variables are expressed as percentages and compared using the χ² statistic or Fisher exact test. Separate analysis was undertaken for the 2- and 3-vessel disease population. Because of the nonrandomized nature of the study, proportional hazard Cox regression models were used to adjust for baseline covariates (identified after univariate regression analysis) and expressed as hazard ratios (HRs) with 95% CIs. For the 2-vessel population, the outcomes were adjusted for baseline differences in the prevalence of chronic renal insufficiency, peripheral vascular disease, hyperlipidemia, previous CABG, previous PCI, presentation with unstable angina (UA), left ventricular ejection fraction, and involvement of the left anterior descending artery. The 3-vessel disease outcomes were adjusted for baseline differences in the prevalence of chronic renal insufficiency, presentation with UA, left ventricular ejection fraction, and previous CABG and PCI. Statistical analysis was performed using Statistical Analysis Program version 9.1 (SAS Institute). A P value of <0.05 was considered statistically significant. Kaplan–Meier curves were used to illustrate

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>2v CAD (n=196)</th>
<th>P Value</th>
<th>3v CAD (n=505)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ±SD)</td>
<td>65.3 ± 10.7</td>
<td>0.45</td>
<td>64.9 ± 10.7</td>
<td>0.73</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>128 (65.3)</td>
<td>0.93</td>
<td>364 (71.7)</td>
<td>0.10</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>70 (38.7)</td>
<td>0.80</td>
<td>187 (36.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>146 (76.0)</td>
<td>&lt;0.001</td>
<td>381 (76.4)</td>
<td>0.13</td>
</tr>
<tr>
<td>CRI, n (%)</td>
<td>10 (5.1)</td>
<td>0.02</td>
<td>25 (4.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>PVD, n (%)</td>
<td>83 (17.7)</td>
<td>0.03</td>
<td>68 (13.4)</td>
<td>0.51</td>
</tr>
<tr>
<td>Hx of CAD, n (%)</td>
<td>118 (60.2)</td>
<td>0.03</td>
<td>285 (56.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Previous PCI, n (%)</td>
<td>64 (32.7)</td>
<td>0.84</td>
<td>155 (30.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>11 (5.6)</td>
<td>&lt;0.001</td>
<td>23 (4.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>37 (19.1)</td>
<td>0.75</td>
<td>78 (15.7)</td>
<td>0.30</td>
</tr>
<tr>
<td>Unstable angina, n (%)</td>
<td>83 (17.7)</td>
<td>&lt;0.001</td>
<td>97 (19.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%±SD)</td>
<td>50 ± 10</td>
<td>0.003</td>
<td>47 ± 11</td>
<td>0.04</td>
</tr>
<tr>
<td>LAD involved, n (%)</td>
<td>189 (96.4)</td>
<td>&lt;0.001</td>
<td>593 (67.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Baseline characteristics. CRI indicates chronic renal insufficiency; PVD, peripheral vascular disease; LVEF, left ventricular ejection fraction; LAD, left anterior descending artery.
more likely to experience a CVE (2.0% versus 0.1%; \( P=0.005 \)). CABG surgery patients experienced significantly lower rates of TVF (5.6% versus 13.3%; \( P=0.001 \)) and had significantly lower MACCE rates (9.7% versus 21.2%; \( P<0.001 \)). There were 9 cases of subacute thrombosis in the 2-vessel PCI patients and 1 case of late thrombosis, with no significant difference between the diabetic and nondiabetic population.

In the 3-vessel population, patients undergoing CABG showed similar rates of Q-wave MI (2.0% CABG versus 3.6% PCI; \( P=0.45 \)) and CVE (1.0% CABG versus 1.1% PCI; \( P=1.00 \)) but experienced significantly reduced rates of TVF (5.7% versus 18.8%; \( P<0.001 \)) and mortality (3.1% versus 10.9%; \( P=0.006 \)). Overall MACCE was also significantly reduced for patients undergoing CABG (10.8% versus 28.4%; \( P<0.001 \)). There were no cases of stent thrombosis in the 3-vessel PCI patients.

Figure 3 depicts 1-year outcomes in patients with 2-vessel CAD with diabetes mellitus. The incidence of Q-wave MI was similar between the 2 groups (4.4% PCI versus 0% CABG; \( P=0.14 \)). CVEs occurred with increased frequency in the CABG group (4.3% versus 0.3%; \( P=0.02 \)). The patients undergoing CABG showed reduced mortality (1.4% CABG versus 12.8% PCI; \( P=0.005 \)), TVF (2.9% CABG versus 14.3% PCI; \( P=0.008 \)), and MACCE (8.6% CABG versus 26.6% PCI; \( P=0.001 \)).

Outcomes in diabetic patients with 3-vessel disease are depicted in Figure 4. Patients treated by CABG had reduced MACCE free survival for the 2-vessel and 3-vessel patients including diabetic and nondiabetic populations.

**Results**

Baseline clinical characteristics for the 2- and 3-vessel disease populations are summarized in the Table. A total of 1080 patients were treated for 2-vessel disease (196 CABG and 884 PCI). Of these, 189 patients (96.4%) in the CABG cohort and 593 (67.1%) in the PCI cohort underwent revascularization of the left anterior descending artery (\( P<0.001 \) between groups). In both the 2- and 3-vessel CABG populations, 50% of patients underwent off-pump surgery. More than 98% of patients received ≥1 internal mammary artery, whereas 30% received bilateral mammary arteries, and 25% received exclusively arterial grafts. There was a high prevalence of diabetes mellitus (>55%) in both the PCI and CABG cohorts.

The patients undergoing CABG for 2-vessel disease had a lower prevalence of dyslipidemia (76% versus 86.3%; \( P<0.001 \)), chronic renal insufficiency (5.1% versus 12.8%; \( P=0.002 \)), and peripheral vascular disease (11.7% versus 15.6%; \( P=0.03 \)). In addition, they were more likely to have previous CAD (60.2% versus 51.6%; \( P=0.03 \)) but less likely to have had previous CABG (5.6% versus 15.6%; \( P<0.001 \)). Finally, patients undergoing CABG were less likely to present with UA (13.3% versus 45.9%; \( P<0.001 \)) and had higher average left ventricular ejection fraction (0.50±0.10 versus 0.47±0.14; \( P=0.003 \)).

Six hundred patients were treated for 3-vessel disease (505 CABG and 95 PCI). Those who underwent CABG had a lower prevalence of chronic renal insufficiency (4.9% versus 12.9%; \( P=0.003 \)) and previous CABG (4.5% versus 10.6%; \( P=0.02 \)) and were less likely to present with UA (19.1% versus 35.1%; \( P<0.001 \)). CABG surgery patients in the 3-vessel cohort had slightly lower average left ventricular ejection fraction (0.47±0.11 versus 0.50±0.12; \( P=0.04 \)) and were more likely to have had previous PCI (30.5% versus 16.9%; \( P=0.008 \)).

The 1-year clinical outcomes for the overall 2- and 3-vessel coronary disease populations are summarized in Figures 1 and 2. In the 2-vessel population, mortality was higher with PCI (2.6% CABG versus 8.1% PCI; \( P=0.006 \)). Patients undergoing CABG had similar rates of Q-wave MI (0.5% CABG versus 2.7% PCI; \( P=0.10 \)) but were significantly
mortality (3.2% CABG versus 18.4% PCI; \(P=0.002\)) and TVF (4.8% CABG versus 25% PCI; \(P<0.001\)). The rates of Q-wave MI (1.6% CABG versus 6.3% PCI; \(P=0.16\)) and CVE (1.1% CABG versus 0% PCI; \(P=1.00\)) were similar between groups. Combined MACCE rates (10.7% CABG versus 41.0% PCI; \(P<0.001\)) were significantly lower in the CABG group.

Unadjusted outcomes in patients without diabetes mellitus treated for 2-vessel CAD showed reduced TVF and MACCE with CABG (6.3% CABG versus 12.9% PCI; \(P=0.04\) and 10.3% CABG versus 18.5% PCI, respectively) but showed no difference in mortality (3.2% CABG versus 5.7% PCI; \(P=0.25\)). Patients without diabetes treated for 3-vessel CAD showed a similar reduction in unadjusted TVF (6.2% CABG versus 15.4% PCI; \(P=0.04\)) and a trend toward a reduction in MACCE (10.9% CABG versus 20% PCI; \(P=0.06\)) but no reduction in mortality with CABG (3.1% CABG versus 5.7% PCI; \(P=0.40\)).

With outcomes adjusted for significant differences in baseline variables (Figures 5 and 6), the combined MACCE was higher for PCI in both the overall 2-vessel (HR 3.52; 95% CI 1.48 to 8.43; \(P<0.001\)) and the 3-vessel (HR 4.82; 95% CI 2.39 to 9.72; \(P<0.001\)) cohorts. The adjusted risk of mortality was increased in the 2-vessel (HR 9.19; 95% CI 1.21 to 69.7; \(P=0.03\)) and 3-vessel diabetic cohorts treated with PCI (HR 6.90; 95% CI 2.18 to 21.8; \(P<0.001\)).

In the nondiabetic population, there was no difference in adjusted MACCE for 2-vessel patients (HR 1.77, 95% CI 0.96 to 3.25; \(P=0.07\)) and patients with 3-vessel CAD treated with PCI (HR 1.70, 95% CI 0.77 to 3.61; \(P=0.19\)). There was no increased mortality risk seen with PCI in the nondiabetic patients with 2- or 3-vessel CAD (HR 1.73; 95% CI 0.56 to 5.34; \(P=0.34\) and HR 1.89; 95% CI 0.40 to 8.92; \(P=0.43\), respectively).

Figures 7 and 8 illustrate the adjusted Kaplan–Meier MACCE-free and mortality-free survival curves for the entire 2-vessel and 3-vessel cohorts and the diabetic and nondiabetic subpopulations.

**Discussion**

The primary findings of this study show that although nondiabetic patients with 2- or 3-vessel CAD experience...
similar mortality and MACCE with CABG and PCI, diabetic patients with either 2- or 3-vessel disease experience significantly lower 1-year MACCE for CABG compared with PCI. As shown in the Table, a significant mortality and MACCE advantage for CABG over PCI was seen in the overall population with 2- and 3-vessel CAD; however, after adjustment for baseline variables, this advantage remained significant only in the diabetic populations.

Our findings confirm and extend those shown in previous literature, but important differences must be noted. Although many studies of patients with multivessel disease demonstrated similar outcomes, the number of patients with 3-vessel disease or with diabetes was relatively small. This point is particularly relevant in the Bypass Angioplasty Revascularization Investigation (BARI) study, which was the largest of the comparative studies between balloon angioplasty and CABG and enrolled the largest number of diabetic patients. In this study, investigators demonstrated a significant increase in major adverse cardiac events (MACE) (death, MI, revascularization) for patients with 3-vessel disease and a significant increase in mortality for patients with diabetes treated with balloon angioplasty versus CABG. Similar findings for overall MACE were seen in the ARTS Study, which compared bare metal stents with CABG in patients with multivessel CAD. Yet in ARTS, the benefit of CABG was almost entirely driven by revascularization at both 1-year and 5-year follow-up. Patients with diabetes represent a particularly difficult subset for both CABG and PCI. With regard to CABG, patients with diabetes are subject to increased short- and long-term mortality as well as a higher risk of revascularization procedures. Potential factors contributing to the increased risk include comorbid illness, small, diffusely diseased target vessels, progression of native CAD, hyperglycemic endothelial dysfunction, and systemic inflammation.

In patients undergoing PCI, diabetes is independently associated with an increased risk of mortality, MI, and TVF. In addition to comorbid disease, small vessel reference diameter, diffuse disease, and systemic inflammation (all shared with the CABG population), the poor results obtained with PCI may specifically be attributable to progression of native CAD proximal to the implanted stents. For instance, on follow-up angiograms performed on 253 patients enrolled in the BARI trial (55 diabetic, 193 nondiabetic), new significant lesions were seen in 22% of the diabetic patients treated with PCI compared with 12% of the nondiabetic patients ($P<0.004$).

The current study furthers the notion that diabetic patients with multivessel disease experience particularly high MACCE and mortality compared with nondiabetic counterparts. In this population, 35.7% of the 1680 patients had underlying diabetes. Although the overall 2- and 3-vessel CABG populations had lower unadjusted MACCE and mortality, it becomes clear after adjustment that the benefit of CABG over PCI is driven almost entirely by the presence of diabetes.

Another important distinction between the current study and previous comparative studies is the PCI technique with which CABG was compared. The Randomized Treatment Intervention of Angina (RITA), Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty versus Coronary Artery Bypass Surgery in Multivessel Disease (ERACI), German Angioplasty Versus Bypass Surgery Investigation (GABI), Emory Angioplasty versus Surgery Trial (EAST), Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI), and BARI trials each compared CABG with balloon angioplasty alone, whereas the ERACI-II, ARTS, Stent or Surgery and Medicine, Angioplasty or Surgery Study (MASS-II) trials compared CABG with PCI with bare metal stents. In contrast to the above trials, the ARTS-II registry (consisting of patients with multivessel disease treated with DES) has reported 1-year results similar to the CABG cohorts in the first ARTS study. The dramatic reduction of TVF and subsequent revascularization seen with DES propounds the possibility that a strategy of PCI with DES conferred at least similar if not beneficial results compared with CABG. This possibility prompted the present study.

As evidenced by our findings, the early results of the unpublished ARTS-II registry cannot be entirely supported. The most likely explanation for the divergent results stems from patient baseline characteristics. Although ARTS-II inclusion criteria were stable angina and de novo coronary disease, and 26% of patients had a history of diabetes, the current study population had much higher proportions of UA (44.6%), previous coronary disease (49.7%), and diabetes (35.3%). These features likely contributed to higher incidences of MACCE in this population than in ARTS-II.

This study has several strengths. The first among them is the nature of the reporting institution and the volume of procedures regarding both CABG and PCI. Another important strength is the diversity of our patient population. With >35% of patients in each cohort presenting with diabetes, a large enough subset exists from which to draw meaningful inferences. Additionally, the socioeconomic and ethnic mix of patients presenting to a tertiary referral center located in an urban area allows for a “real-world” population for study and follow-up.
In this study, the chosen revascularization strategy was at the discretion of the treating physician, often in consultation with cardiac surgeons. This study population represents a nonrandomized, consecutive series and may be subject to a number of potential biases, including differences between groups in the ability to achieve complete revascularization strategy. For instance, the 2-vessel PCI population had a significantly larger proportion of patients presenting with UA, peripheral vascular disease, chronic renal insufficiency, and previous CABG, whereas the 3-vessel PCI population had a significantly larger proportion of patients presenting with UA and previous CABG. Arguably, the treating physician’s judgment may have selected a higher-risk population for PCI for which surgery may not have been considered appropriate or safe. In addition, it is important to recognize that the current study is retrospective in nature and is subject to inherent biases and drawbacks. We eagerly await the results of ongoing randomized trials that will help elucidate the optimal management strategy for patients with multivessel CAD.

In conclusion, based on this study, for diabetic patients with multivessel disease, revascularization by CABG may be preferable to PCI with DES. Although DES use has greatly reduced restenosis and TVF, outcomes associated with these stents in high-risk patient subsets (especially diabetics) are still inferior to CABG. Perhaps even more important, in these subsets, outcomes with both techniques leave considerable room for improvement. Although advances in both cardiac surgery and interventional cardiology hold promise to reduce adverse events, there is no substitute for sound clinical judgment in selecting the appropriate revascularization strategy for patients with multivessel coronary disease.

Disclosures

None.

References

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