Improved Long-Term Survival for Diabetic Patients With Surgical Versus Interventional Revascularization

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Background. **Diabetes is increasing at an alarming rate, affecting nearly 8% of the population. Previous studies have demonstrated a potential benefit for surgical over interventional revascularization in diabetics. However, randomized clinical trials comparing coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) many not accurately reflect current clinical practice. We therefore undertook a prospective registry of coronary revascularization (CR) in diabetic patients with CABG, on-pump and off-pump, and PCI with bare-metal and drug-eluting stents to determine long-term clinical outcomes.**

Methods. **All patients undergoing isolated CR in 8 community hospitals were enrolled. Follow-up was obtained after 5 to 8 years; all mortalities were checked against the Social Security Death Index. The ST-elevation myocardial infarction and salvage patients were excluded. Propensity matching was used to account for differences between PCI and CABG groups. Survival curves were derived using Kaplan-Meier methods, whereas hazard ratios and cumulative hazards were calculated using the Cox proportional hazard model.**

Results. **Of the 3,156 patients in the registry, there were 1,082 diabetics; 334 CABG and 748 PCI. Due to the differences in baseline characteristics between the 2 groups, propensity score matching was used to achieve clinically comparable groups of 240 patients each. In matched patient groups mortality was more common in the PCI group with an odds ratio (OR) of 0.60 (95% confidence interval [CI] 0.39% to 0.93%; $p = 0.023$). Similarly, occurrence of any major cardiac adverse event (MACE) (mortality, non-fatal myocardial infarction, or revascularization) was more frequent in the PCI group with an OR of 0.57 (95% CI 0.31% to 0.70%, $p < 0.001$). Kaplan-Meier event-free survival of matched groups was significantly improved in the CABG versus PCI group ($p = 0.001$).**

Conclusions. **In the current era of on-pump and off-pump CABG surgery and bare-metal and drug-eluting stents, this registry which unselectively records all non-ST elevation myocardial infarction patients undergoing coronary revascularization, diabetic patients benefit from improved long-term survival and reduced MACE with CABG versus PCI. These findings corroborate recent evidence from prospective randomized trials and thus provide clinically relevant validation of their broad applicability to diabetics with extensive coronary artery disease in need of revascularization.**

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Diabetes currently afflicts 25.8 million people in this country, approximately 8.3% of the US population. The prevalence has more than doubled in the past decade [1] and current estimates predict a prevalence rising to between 1 in 5 and 1 in 3 Americans by the year 2050 [2].

The burden of disease associated with diabetes is dramatic; adults with diabetes are 2 to 4 times more likely to have cardiovascular disease than those without it, and at least 65% will die from their cardiovascular disease [3]. The nature of cardiovascular disease in diabetics is clinically challenging because it tends to be extensive and diffuse with multivessel involvement [4, 5]. Perhaps this explains why numerous prospective randomized control trials (PRCT) have demonstrated a benefit for coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) in diabetic patients with multivessel disease [6–10]. Although generally considered to represent the highest level of clinical evidence, PRCTs introduce selection criteria which may yield a study group not representative of the actual treatment population. Between 3% and 8% of patients screened for inclusion in randomized trials comparing CABG versus PCI have actually been enrolled [8, 11–13]. It is therefore essential to corroborate PRCT findings with clinical observation. We therefore examined the diabetic patients with PCI versus CABG in the Coronary Artery Revascularization Evaluation (CARE) registry, a multicenter community-based registry which reflects a "real world" clinical experience, with current strategies, both on-pump and off pump CABG; both bare metal (BMS) and drug eluting stents (DES), for coronary revascularization (CR).

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Material and Methods

As previously published [14, 15], this was a multicenter registry recording data on patients undergoing CR procedures from 8 centers. There were no pre-specified selection criteria and patients were treated according to physician preference. Of the 3,156 patients in the registry, there were 1,082 diabetics; 334 CABG and 748 PCI. Data were collected locally and returned to a central repository where they were entered into a proprietary database, as previously described. The protocol was approved by the Institutional Review Board for North Texas at Medical City Dallas Hospital with a waiver of consent.

Data were collected over a 6-month period from February 1, 2004, until July 31, 2004. All collected data were subjected to quality checks and data validation tests. Follow-up was completed in 2011, when the database was locked. Follow-up included Social Security Death Index (SSDI) validation of all mortalities, hospital and physician inquiries, and letters and telephone calls to the patients. Patients with a diagnosis of ST elevation myocardial infarction (STEMI) or status listed as salvage were deleted from the data set for analysis.

Data were summarized and compared using χ^2 statistics for discrete variables and t tests or analysis of variance for continuous data. The propensity matching used 18 preoperative risk parameters and accounted for nesting of patients in hospitals. The scores were put through a 1-to-1 greedy matching algorithm that produced 2 equivalent data sets for PCI and CABG patients with 5+ years of follow-up. Survival curves were derived using Kaplan-Meier methods, whereas hazard ratios and cumulative hazards were calculated using the Cox proportional hazard model. Odds ratios were determined using hierarchic logistic regression (SAS Genmod procedure). All statistical calculations used SAS 9.4 (SAS Institute, Cary, NC).

Results

The initial study collected data on 4,332 patients. After elimination of all STEMI patients, there were 1,082 (334 CABG and 748 PCI) diabetic patients available for follow-up. Length of follow-up was equivalent between groups (mean ± standard deviation: CABG 67.6 ± 25.2 months; PCI 66.2 ± 25.5 months). Bare metal stents were used in 110 patients, DES in 565, and PTCA without stenting in 73; stent types were according to physician preference and contemporary for 2004. On-pump CABG was performed in 172 and off-pump in 162 patients. The internal thoracic artery (ITA) was used in 92.9% of CABG patients, with bilateral ITA grafting in only 5.4% of surgical patients. The PCI patients received 2.19 stents per patient, while CABG patients received 3.17 grafts (distal anastomoses) per patient.

There were numerous differences between the CABG and PCI groups (Table 1). The CABG patients had a higher incidence of previous stroke, recorded arrhythmia, triple vessel disease, urgent status, current smokers, and reduced ejection fraction, while the PCI patients had more frequently undergone a previous intervention (both PCI and CABG) and were more commonly being treated for hyperlipidemia. Because risk factors varied between CABG and PCI groups, which had been selected by physician clinical preference, propensity score matching was used to create 2 equivalent groups of follow-up patients, yielding 240 patients in each group, with no statistically or clinically significant differences between groups except for a slightly higher ejection fraction in the PCI patients (Table 2).

Follow-up data from these groups were analyzed to determine freedom from any major cardiac adverse event (MACE: mortality, non-fatal myocardial infarction, and revascularization). The MACE-free survival was enhanced in the CABG versus PCI groups in both unmatched (Fig 1) and matched patient cohorts (Fig 2). In the unmatched cohorts, patients having CABG initially fared better over the 80 month study period ($p = 0.004$). Matching the patient groups to minimize covariate differences also showed superior MACE-free performance for CABG over PCI ($p = 0.001$). In matched PCI and CABG patients, CABG resulted in a reduction in overall MACE (odds ratio [OR] 0.47; confidence interval [CI] 0.31% to 0.70%; $p < 0.001$), driven both by a reduction in mortality (OR 0.60; CI 0.39% to 0.93%; $p = 0.05$) and a reduction in the need for revascularization (OR 0.32; CI 0.15% to 0.68%; $p = 0.001$) (Table 3). There appeared to be a hierarchy favoring on-pump versus off-pump CABG, with mortality the first event in 23.3% (40 of 172) of on-pump and 30.3% (49 of 169) of off-pump patients, although this difference did not achieve statistical significance in this study ($p = 0.149$).

To determine whether the PCI performance was adversely affected by use of BMS and PTCA alone, we created matched groups of DES and CABG patients, with 202 patients each. Curves of MACE-free survival (Fig 3) again showed a difference between CABG and PCI although a little smaller difference than for the entire cohort of matched patients.

When comparing matched DES (202) with CABG (202) patients, mortality as a first event clearly favored CABG versus PCI (OR 0.58; CI 0.36% to 0.96%; $p = 0.033$), as did overall MACE (OR 0.58; CI 0.37, 0.90; $p = 0.015$) (Table 4). The overall difference in MACE was clearly driven by a difference in mortality, while other events individually had smaller effects. In this study, we found that compared with the nondiabetic patient population, diabetics in general suffered from a higher mortality (OR 1.21; CI 1.02 to 1.43; $p = 0.031$) as well as higher MACE (OR 1.48; CI 1.20 to 1.83; $p < 0.001$).

We created matched groups of 72 insulin dependent diabetics. In this population, there was no difference in overall MACE (OR 1.06; CI 0.51 to 220; $p = 0.875$), with similar MACE-free survival (Fig 4). In the 20 to 60 month period, the curves appear to diverge but longer term approach each other. A matched group of non-insulin dependent diabetics (165 patients in each arm) showed nearly identical MACE-free survival until about 60 months when they start to diverge (Fig 5).