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ORIGINAL INVESTIGATIONS

# Long-Term Outcome of PCI Versus CABG in Insulin and Non–Insulin-Treated Diabetic Patients

## Results From the FREEDOM Trial

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## ABSTRACT

**BACKGROUND** The prospective, randomized FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial found coronary artery bypass graft surgery (CABG) was associated with better clinical outcomes than percutaneous coronary intervention (PCI) in patients with diabetes and multivessel disease, managed with or without insulin.

**OBJECTIVES** In this subgroup analysis of the FREEDOM trial, we examined the association of long-term clinical outcomes after revascularization in patients with insulin-treated diabetes mellitus (ITDM) compared with patients not treated with insulin.

**METHODS** A total of 1,850 FREEDOM subjects had an index revascularization procedure performed: 956 underwent PCI with drug-eluting stents (DES), and 894 underwent CABG. A total of 602 patients (32.5%) had ITDM (PCI/DES n = 325, 34%; CABG n = 277, 31%). Subjects were classified according to ITDM versus non-ITDM, with comparison of PCI/DES versus CABG for each group. Interaction analyses were performed for treatment by diabetes mellitus (DM) status alone and for treatment by DM status by coronary lesion complexity. Analyses were performed for the primary outcome composite of death/stroke/myocardial infarction (MI) using all available follow-up data.

**RESULTS** The overall 5-year event rate of death/stroke/MI was significantly higher in ITDM versus non-ITDM patients (28.7% vs. 19.5%, $p < 0.001$), which persisted even after adjustment for multiple baseline factors, angiographic complexity, and revascularization treatment group (death/stroke/MI hazard ratio [HR]: 1.35, 95% confidence interval [CI]: 1.06 to 1.73, $p = 0.014$). With respect to the primary composite endpoint, CABG was superior to PCI/DES in both DM types and the magnitude of treatment effect was similar (interaction $p = 0.40$) for ITDM (PCI vs. CABG HR: 1.21; 95% CI: 0.87 to 1.69) and non-ITDM patients (PCI vs. CABG HR: 1.46; 95% CI 1.10 to 1.94), even after adjusting for the angiographic SYNTAX score level. Based on 5-year event rates, the number needed to treat with CABG versus PCI to prevent 1 event is 12.7 in ITDM and 13.2 in non-ITDM.

**CONCLUSIONS** In patients with diabetes and multivessel coronary artery disease, the rate of major adverse cardiovascular events (death, MI, or stroke) is higher in patients treated with insulin than in those not treated with insulin. Furthermore, we did not detect a significant difference in the magnitude of PCI versus CABG treatment effect for patients treated with insulin and those not treated with insulin. (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes [FREEDOM]; NCT00086450) (J Am Coll Cardiol 2014;64:1189–97) © 2014 by the American College of Cardiology Foundation.

**ABBREVIATIONS AND ACRONYMS**

**BMI** = body mass index

**BUN** = blood urea nitrogen

**CABG** = coronary artery bypass graft surgery

**CI** = confidence interval

**DES** = drug-eluting stent(s)

**DM** = diabetes mellitus

**HR** = hazard ratio

**ITDM** = insulin-treated diabetes mellitus

**ITT** = intention-to-treat

**MI** = myocardial infarction

**MVD** = multivessel coronary disease

**PCI** = percutaneous coronary intervention

The global prevalence of diabetes mellitus (DM) among adults is currently estimated to exceed 6.4% (285 million individuals) and is projected to grow to 7.7% (439 million individuals) by 2030, making diabetes and its complications important public health problems (1). Currently, approximately 26% of the U.S. patients with diabetes are treated with insulin (ITDM) (2), and these patients are known to be at higher risk for complications after coronary reperfusion than both patients with non-ITDM and patients without diabetes (3,4). DM plays an important role in accelerated atherogenesis and atherothrombosis (5), and patients with diabetes are prone to develop multivessel coronary disease (MVD) (6–8). Despite a high technical success rate with MVD stenting, those treated with insulin have a higher rate of coronary artery bypass graft surgery (CABG) or repeat percutaneous coronary intervention (PCI), a higher risk of stent thrombosis, and lower 1-year survival than nondiabetic patients (9,10). Recently, the FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial demonstrated that for patients with diabetes and MVD, CABG is superior to PCI with drug-eluting stents (DES) in that it significantly reduced rates of death and myocardial infarction (MI), albeit with a higher rate of stroke (11). Previous CABG reports had shown that ITDM patients have a particularly elevated risk of in-hospital morbidity and wound infections after CABG, leading to a prolonged length of hospital stay, elevated 30-day mortality, and increased risk of readmission for cardiac causes (12–14).

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The aims of the present study were: 1) to provide a baseline clinical and angiographic description of the ITDM and non-ITDM groups; 2) to examine whether CABG and/or PCI/DES outcomes depend on ITDM status; and 3) to examine the association of ITDM status with the difference between CABG- and PCI/DES-treated patients in the primary composite outcome of death from any cause, nonfatal MI, or nonfatal stroke.

**TABLE 1 Baseline and Procedural Characteristics by ITDM Status**

| | Non-ITDM (n = 1,248) | ITDM (n = 602) | p Value |
|---|---|---|---|
| Age, yrs | 63.2 ± 8.9 | 62.6 ± 9.2 | 0.16 |
| Male | 76.5 | 61.3 | <0.0001 |
| Body mass index, g/m$^2$ | 29.3 ± 5.0 | 30.5 ± 5.9 | <0.0001 |
| Duration of diabetes, yrs | 7.7 ± 7.2 | 15.1 ± 9.9 | <0.0001 |
| Hemoglobin $A_{1c}$, % | 7.5 ± 1.6 | 8.5 ± 1.8 | <0.0001 |
| BUN, mg/dl | 21.0 (15.4–32.0) | 23.1 (16.1–36.0) | 0.02 |
| History of hypertension | (83.2) | 87.5 | 0.02 |
| Peripheral neuropathy | 5.2 | 14.3 | <0.0001 |
| Current smoker | 14.7 | 17.9 | 0.07 |
| Previous MI | 25.8 | 25.6 | 0.92 |
| Previous stroke | 3.1 | 3.8 | 0.44 |
| Congestive heart failure | 24.3 | 32.1 | 0.0004 |
| NYHA functional class I | 75.7 | 67.9 | 0.0004 |
| Number of diseased vessels | | | |
| 2 | 17.7 | 14.8 | 0.13 |
| 3 | 82.3 | 85.2 | |
| Total lesion length, mm | 77.2 ± 33.8 | 79.0 ± 33.0 | 0.26 |
| Any total occlusion in LAD, RCA, or LCx | 23.2 | 23.0 | 0.92 |
| LV ejection fraction | 66.3 ± 11.1 | 65.7 ± 11.9 | 0.34 |
| EuroSCORE | 2.5 ± 2.4<br>1.7 (1.2–3.0) | 2.9 ± 2.4<br>2.1 (1.3–3.0) | <0.0001 |
| SYNTAX score | 26.0 ± 8.6<br>26.0 (19.5–31.0) | 26.4 ± 8.5<br>26.0 (20.0–31.0) | 0.33 |
| Acute coronary syndrome | 28.6 | 35.1 | 0.005 |
| Number of PCI lesions | 3.5 ± 1.4 | 3.5 ± 1.4 | 0.97 |
| Number of CABG grafts | 2.9 ± 0.8 | 3.0 ± 0.8 | 0.05 |

Values are mean ± SD, %, or median (interquartile range).

BUN = blood urea nitrogen; CABG = coronary artery bypass graft surgery; ITDM = insulin-treated diabetes mellitus; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LV = left ventricular; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RCA = right coronary artery.

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