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EDITORIAL COMMENT

Coronary Revascularization Strategies in Patients With Diabetes and Multivessel Coronary Artery Disease

Has the Final Chapter Been Written?*

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In this issue of the *Journal*, Dangas et al. (1) report on an important subgroup of patients from the FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial, a trial in which patients with type 2 diabetes mellitus (T2DM) and multivessel coronary disease were randomized to revascularization by percutaneous coronary intervention (PCI) using drug-eluting stents versus coronary artery bypass grafting (CABG) (2,3). The present analyses explore the effectiveness of CABG versus PCI on the trial primary outcome among the 602 patients (32.5%) treated with insulin (ITDM) at study entry (325 underwent PCI; 277 underwent CABG), compared with the non-insulin-treated subset (no ITDM).

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Independent of revascularization assignment, in the overall cohort, ITDM had higher risk for the primary composite outcome even after adjustment for clinical demographics, angiographic complexity, and revascularization treatment (adjusted hazard ratio [HR]: 1.35; 95% confidence interval [CI]: 1.06 to 1.73). Qualitatively consistent with the overall trial results, in the ITDM subgroup, the primary event rate was numerically higher with PCI versus CABG, although not statistically significant (HR: 1.21; 95% CI: 0.87 to 1.69). In this context, statistical testing for heterogeneity of treatment effect by insulin-treatment status (i.e., testing for statistical interaction) yielded a p value of >0.05. Thus, no statistically significant interaction by insulin treatment was evident. The investigators concluded that in patients with T2DM and multivessel coronary disease, insulin treatment remains an independent marker of risk; and there was no significant difference in the magnitude of the PCI versus the CABG treatment effect for T2DM patients treated with or without insulin.

Estimating cardiovascular (CV) risk and the effectiveness of CV therapies in T2DM patients is a moving target, with continuous improvements in CV risk and survival over recent decades (4). Yet, there remains an unyielding "incremental risk" for patients with T2DM, even after adjustment for CV risk factors commonly concomitant with T2DM (4,5), with the adjusted risk for major adverse CV events remaining 2- to 4-fold greater in patients with T2DM. This reflects an important gap in understanding the underpinnings of the pathobiological nexus of T2DM and CV disease, and a critically important unmet clinical need.

However, not all of the 29.1 million people with T2DM in the United States have "coronary disease equivalent" risk (4,6). Directly related to duration of T2DM, CV risk increases over time, and quantifying this risk may aid in medical decision making. In this context, the presence of certain high-risk features may inform clinicians on appropriate coronary

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revascularization strategies for patients with T2DM. Among others, age, duration of T2DM, insulin treatment, and complexity of coronary disease are oft-cited high-risk features. There are 2 equally plausible hypotheses related to the treatment effect of CABG relative to T2DM, multivessel disease, and high-risk markers. The first is that CABG versus PCI would have greatest benefit in T2DM patients with higher-risk features, following the principal that the highest-risk patients benefit greatest from effective therapies. An equally compelling hypothesis is that the presence of T2DM requiring insulin treatment represents such a high-risk status in patients with multivessel disease that the competing risk of comorbid conditions could to some degree attenuate the benefit of CABG over PCI. Therefore, CABG versus PCI outcomes could be more comparable in both absolute and relative terms, independent of other proven prognostic factors such as the SYNTAX score, age, or T2DM duration. This is the crux of the importance of the present analyses by Dangas et al. (1).

CONTEXT WITH PRIOR LITERATURE

It is important to place the results of the present FREEDOM substudy into context with prior literature. In general, recent trial data suggest concordance of the benefit of CABG versus PCI in patients with and without T2DM who have multivessel coronary artery disease. The 5-year results from the SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) trial, which randomized patients with multivessel coronary disease to PCI versus CABG and included 296 patients with T2DM, demonstrated that PCI was associated with an increased HR of 2.3 for the composite of death/myocardial infarction (MI)/cerebrovascular accident (CVA)/revascularization (7). Analyzing each component, there was a 2-fold increase in mortality (20.2% vs. 10.1%; $p = 0.027$) and ~3-fold increases in MI (9.2% vs. 3.1%; $p = 0.056$) and repeat revascularization (33.2% vs. 12.5%; $p < 0.001$). Systematic review of CABG versus PCI comparisons included 13 randomized controlled trials and 5 meta-analyses in patients with T2DM and multivessel disease (8), and suggests that CABG is preferred over PCI in appropriate patients with multivessel coronary disease and T2DM. The authors further recommend that the "guidelines be urgently updated to a class I, level A indication." However, this systematic review did not explore heterogeneity of efficacy of CABG versus PCI by high-risk features. Whether the superiority of CABG for patients with T2DM and multivessel disease is independent of T2DM treatment regimens and disease complexity is less clear from the available literature. Both the SYNTAX and FREEDOM investigators have explored these associations by comparing outcomes stratified by insulin treatment, and using the SYNTAX score as a surrogate for coronary disease complexity.

SYNTAX SCORE

Results from the FREEDOM and SYNTAX trials suggest greater treatment benefit of CABG versus PCI with increasing complexity of coronary artery disease (3). In the original FREEDOM report, the HR was numerically lower in the patients with a SYNTAX score of ≤22 versus a score of >22 (1.14 vs. 1.46). The trend was also seen in the present analyses by Dangas et al. (1). Among the non-ITDM patients, the HRs were 1.18, 1.61, and 1.58 favoring CABG with increasing SYNTAX scores of ≤22, 23 to 32, and ≥33, respectively. For patients with ITDM, the HRs were 0.84 (favoring PCI), 1.56, and 1.27 (favoring CABG) with SYNTAX scores of ≤22, 23 to 32, and ≥33, respectively. A similar numerical trend was seen in the 3-year results of the SYNTAX diabetes mellitus (DM) substudy (9). In fact, the point estimate favored PCI in DM patients with SYNTAX scores of <22 in those analyses.

INSULIN TREATMENT

Subgroup analyses of DM patients stratified by insulin treatment have been reported from the SYNTAX trial (9), and now by Dangas et al. (1) from the FREEDOM trial. The substudies from these 2 large-scale, randomized trials are discordant. The SYNTAX analyses suggest a greater magnitude of treatment benefit of CABG versus PCI in the ITDM group, whereas the FREEDOM analyses suggest a numerically decreased effect size. In SYNTAX, there were 182 patients with T2DM treated with insulin and 270 treated with oral agents (9). For patients treated with oral agents, there was an increased estimate of risk for the composite of death/MI/CVA in those randomized to CABG versus PCI (12.0% vs. 7.2%; risk ratio [RR]: 0.6; $p = 0.19$), and a decreased risk estimate in those treated with insulin (8.0% vs. 14.8%; RR: 1.84; $p = 0.16$), though neither analysis achieved statistical difference. The insulin status-by-treatment group interaction term in the SYNTAX analyses was $p = 0.06$. In the FREEDOM substudy, the treatment benefit of CABG versus PCI for the composite of death/MI/CVA was statistically significant in the subgroup of patients treated with oral agents (15.6% vs. 23.2%; RR: 1.46) with qualitatively similar trends observed in the ITDM group (24.3% vs. 32.2%), though analysis of this latter subgroup did not achieve statistical difference (HR: 1.21; 95% CI: 0.87 to 1.69). Notably, in contrast with the