Coronary Revascularization Strategies in Patients With Diabetes and Multivessel Coronary Artery Disease
Has the Final Chapter Been Written?*

Steven P. Marso, MD, Darren K. McGuire, MD, MHSc

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).

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
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 CAGB relative to T2DM, multivessel disease, and high-risk markers. The first is that CAGB versus PCI would have greatest benefit in T2DM patients with high-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 CAGB over PCI. Therefore, CAGB 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 CAGB 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 CAGB 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 (32.2% vs. 12.5%; p < 0.001). Systematic review of CAGB versus PCI comparisons included 13 randomized controlled trials and 5 meta-analyses in patients with T2DM and multivessel disease (8), and suggests that CAGB 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 CAGB versus PCI by high-risk features. Whether the superiority of CAGB 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 CAGB 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 CAGB 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 CAGB) 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 CAGB 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 CAGB 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 CAGB 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
SYNTAX observations, the effect size was numerically lower in the ITDM group, noting that the insulin status-by-treatment group interaction in the FREEDOM analyses was not significant ($p_{interaction} = 0.40$), statistically excluding heterogeneity of treatment efficacy by insulin treatment status.

The authors’ conclusion that CABG is superior to PCI in “both groups” is not supported by their stratified analyses, given the absence of statistical difference in the ITDM subset, though the results observed in the groups stratified by insulin treatment were qualitatively similar (unlike the SYNTAX ITDM vs. no ITDM comparison). Similarly challenging is the authors’ interpretation of the statistically negative interaction term to demonstrate “similarity.” As opposed to concluding similarity, on the basis of present results, one can only conclude that there is no statistical evidence of heterogeneity of treatment effect, as these analyses are extremely underpowered to rigorously evaluate for interaction. In that light, excepting the rare case of formal statistical testing for equivalence (10), interpretation of comparisons failing to achieve nominal statistical significance should be limited to concluding that no statistical difference is observed, and not that the comparator groups are similar. Thus, in the present study, similarity has not been established by the negative interaction testing, and especially notable is the more than 2-fold differential in the adjusted point estimates of treatment effect–risk differences favoring CABG of 21% in the ITDM contrasted with 46% in the no ITDM group.

Both the SYNTAX and FREEDOM ITDM analyses are limited given the subgroup nature of the analyses and lack of statistical power, both for between-group comparisons within the strata and for interaction testing across the strata. For example, to detect the PCI versus CABG HRs of 1.2 observed in the ITDM subgroup, with 85% power and 2-sided alpha = 0.05, there would need to be approximately 1,200 patients in that subgroup (i.e., double the size of the ITDM cohort in the FREEDOM trial). Given that the conflicting results of these 2 substudies from the SYNTAX and FREEDOM trials cannot both be accurate, the differences must be attributed to either chance or bias. Without additional trials specifically designed to test the hypothesis of heterogeneity of treatment effects of CABG versus PCI by insulin treatment status, it is not possible to resolve the “truth” from the current data. In such a case, the most logical interpretation of the aggregate data is that in the absence of compelling information otherwise, the subsets of patients stratified by insulin use should be expected to derive treatment benefits most comparable to those observed in the overall trial.

**PAST IS PROLOGUE**

With the advent of novel therapies to manage T2DM and CV risk, it has been the longstanding goal to increase the number of patients who can be effectively managed with optimal medical therapy and modern PCI approaches, rather than with CABG. Data from the FREEDOM and SYNTAX trials (8), and a recent systematic review suggest that we are no closer to realizing this goal in 2014 than we were following the 1995 National Heart Lung and Blood Institute BARI Clinical Alert (11). Short of the introduction of new disruptive CABG or PCI therapies, additional trials are not likely to better inform physicians until clinicians and basic scientists can better characterize the phenotype of T2DM and CV risk. The key to closing the gap between the measured efficacy of CABG and PCI will not be with the advent of the “next-generation drug-eluting stent” or even with the introduction of the bioresorbable stent, but rather with the ability to better discern risk in patients with T2DM and with the development of novel medical therapies to mitigate disease progression and the future risk of nonfatal MI. Only then will PCI have a fighting chance of being an effective treatment in patients with T2DM and markers of high risk.

**REPRINT REQUEST AND CORRESPONDENCE:** Dr. Steven P. Marso, University of Texas Southwestern, Department of Internal Medicine, Professional Office Building Office 1, Suite 8.110, 5959 Harry Hines Boulevard, Dallas, Texas 75390-9047. E-mail: Steven.Marso@UTSouthwestern.edu.


KEY WORDS CABG, diabetes mellitus, PCI, revascularization