The FREEDOM Trial: CABG Superior to PCI in Diabetic Patients with CAD

Written by ***Rita Buckley***

In the United States alone, ~700,000 patients undergo multivessel coronary revascularization yearly. Of these, 25% have diabetes [Smith SC et al. *Circulation* 2002]. Valentin Fuster, MD, PhD, Mount Sinai School of Medicine, New York, New York, USA, presented results from the Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals with Diabetes [FREEDOM] trial.

According to Dr. Fuster, the FREEDOM trial was the largest prospective study of revascularization strategy in patients with diabetes and multivessel coronary artery disease (CAD) undergoing intensive medical treatment. Its purpose was to compare mortality and major adverse cardiovascular events in diabetic individuals with multivessel CAD randomized to either coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI). The primary outcome measure was a composite of death from any cause, nonfatal myocardial infarction (MI), and nonfatal stroke [Farkouh ME et al. *N Engl J Med* 2012].

FREEDOM was sponsored by the National Heart, Lung, and Blood Institute, and inclusion criteria were a diagnosis of diabetes as defined by the American Diabetes Association guidelines: angiographically confirmed multivessel CAD with severe (>70%) lesions in at least 2 major epicardial vessels, and an indication for revascularization based on symptoms of angina and/or objective evidence of myocardial ischemia. Prior to randomization, all qualifying angiograms were reviewed by a study-related interventionalist and surgeon.

A total of 1900 patients with diabetes and multivessel CAD were enrolled from 2005 through 2010 from 140 international centers, and randomized to undergo either PCI with drug-eluting stents or CABG. Patients were followed for a minimum of 2 years (median among survivors, 3.8 years) and all patients were recommended to be prescribed currently indicated antidiabetic, antihypertensive, and lipid-lowering therapy by their treating physicians [Farkouh ME et al. *N Engl J Med* 2012].

The mean patient age was 63 years, 29% were women, 83% had three-vessel disease, and mean ejection fraction was 66%. As compared with PCI, the primary outcome was significantly reduced with CABG at 5 years (18.7% vs 26.6%; absolute difference, 7.9 percentage points; 95% CI, 3.3 to 12.5; p=0.005). The benefit of CABG was driven by differences in rates of both MI (p<0.001) and death from any cause (p=0.049). Stroke was more frequent in the CABG group, with 5-year rates of 2.4% in the PCI group and 5.2% in the CABG group (p=0.03). There was no statistical interaction between the benefit of CABG on the primary endpoint and Synergy Between PCI with TAXUS and Cardiac Surgery (SYNTAX) score or any other prespecified subgroup.

Dr. Fuster concluded that, in patients with diabetes and multivessel coronary disease, CABG was of significant benefit compared with PCI and it is the preferred method of revascularization in this setting. He noted that FREEDOM was relatively short-term—7 years, with a minimum of 2 years and a median of 3.8—and long-term follow-up would provide a better understanding of the comparative benefit of CABG, specifically on mortality.

Elizabeth A. Magnuson, MD, University of Missouri-Kansas City, Kansas City, Missouri, USA, presented a cost-effectiveness analysis of the FREEDOM trial. While CABG was

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associated with higher initial costs (~$9000) compared with PCI, this cost difference was partially offset by lower costs associated with repeat revascularization and, to a lesser extent, cardiac medications.

At 5 years, CABG improved quality-adjusted life expectancy by ~0.03 years while increasing total costs by ~$3600 per patient. Over a lifetime, CABG was associated with 0.66 quality-adjusted life year (QALY) gained and ~$5400 per patient higher costs yielding an incremental cost-effectiveness ratio of $8132 per QALY gained.

According to Dr. Magnuson, results were robust under various sensitivity analyses regarding the duration of the CABG effect on both survival and costs. Results were also consistent across a wide range of subgroups. Based on these findings, she concluded that CABG provides better long-term clinical outcomes than drug-eluting stent PCI for patients with diabetes and multivessel CAD, and these benefits are achieved at an overall cost that represents an attractive use of societal healthcare resources. The outcomes also provide additional support for existing guidelines that recommend CABG for diabetic patients with multivessel CAD.

Assessment of Chelation Therapy: The TACT Trial

Written by ***Toni Rizzo***

Disodium ethylene diamine tetra acetic acid (EDTA) binds divalent cations and permits renal excretion. A 1956 study reported improvement of angina with disodium EDTA [Clarke CN et al. *Am J Med Sci* 1956]. By 2007, its use had increased to more than 100,000 patients in the United States. The data for chelation have been mixed with some case reports and case series reporting benefit and other studies suggesting no benefit or even harm, particularly when rapid infusions cause hypocalcemia. Gervasio A. Lamas, MD, Mount Sinai Medical Center, Miami Beach, Florida, USA, reported the results of the Trial to Assess Chelation Therapy [TACT; NCT00044213].

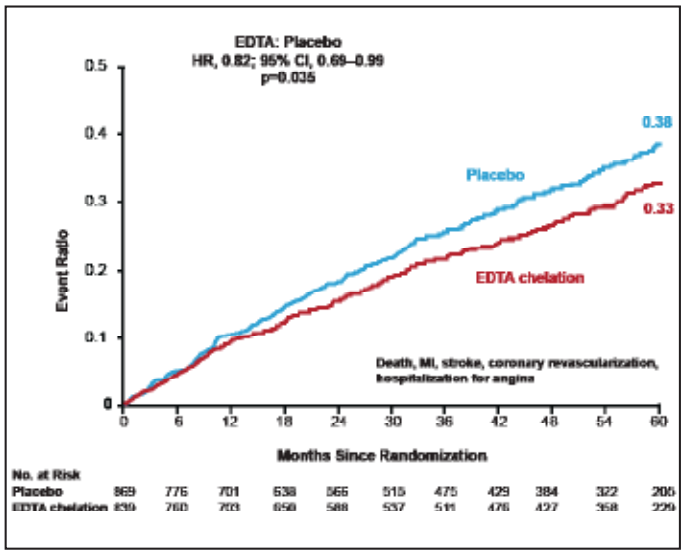
The TACT trial enrolled 1708 patients from 2003 through 2010 [Lamas GA et al. *Am Heart J* 2012]. Patients were eligible if they were aged ≤50 years, had a myocardial infarction (MI) at least 6 months prior to enrollment, and creatinine ≤2.0 mg/dL. They were randomly assigned to chelation therapy or placebo, and high-dose vitamins or placebo in a 2x2 factorial design. The patients were scheduled to receive 40 infusions of at least 3 hours each given as 30 weekly infusions and followed by 10 maintenance infusions 2 to 8 weeks apart. The chelation infusions consisted of 3 g disodium EDTA adjusted downward based on estimated glomerular filtration rate.

The primary endpoint was a composite of death, MI, stroke, coronary revascularization, and hospitalization for angina. Data were analyzed according to the intention-to-treat principle. Because of multiple reviews of the interim data by the Data and Safety Monitoring Board, the final level of statistical significance was p<0.036.

Sixty-five percent of patients received all 40 infusions, and 76% received at least 30 infusions. A total of 79 patients (38 chelation, 41 placebo) discontinued infusions due to adverse events (AEs). Short infusions were administered in 611 instances. Four unexpected severe AEs possibly or definitely related to study therapy occurred—2 in the placebo arm (1 death) and 2 in the chelation arm (1 death).

The primary endpoint event rate was significantly reduced in patients receiving chelation versus placebo (26.5% vs 30.0%; HR, 0.82; 95% CI, 0.69 to 0.99; p=0.035; Figure 1). There was directional consistency among the components of the primary endpoint in favor of chelation versus placebo (Table 1).

Figure 1. Primary Endpoint Results.



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Subgroup analyses suggested that chelation was superior to placebo in patients with anterior MI (HR, 0.63; 95% CI, 0.47 to 0.86; interaction p=0.03) and diabetes (HR, 0.61; 95% CI, 0.45 to 0.83; interaction p=0.02).

Limitations of the TACT trial include the modest statistical significance, with the upper CI of the HR for the primary endpoint of 0.99, missing data (17% of patients withdrew consent), and revascularization being the most common efficacy event.