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].

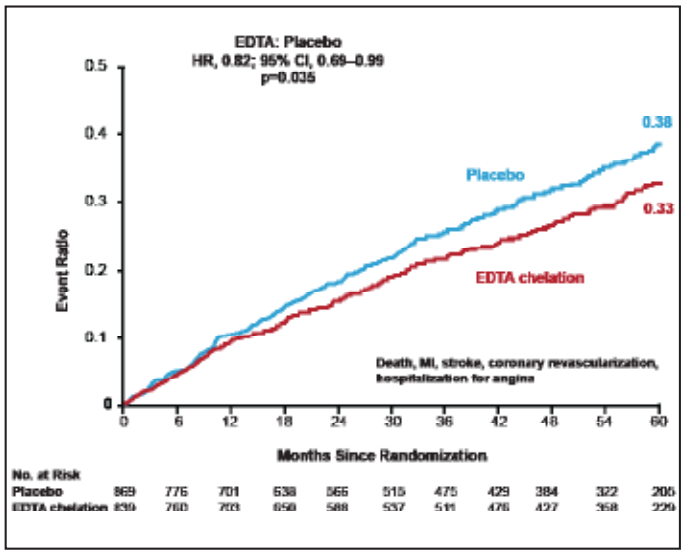
The TACT trial enrolled 1708 patients from 2003 through 2010 [Lamas GA et al. *Am Heart J* 2012]. Patients were eligible if they were aged ≤50 years, had a myocardial infarction (MI) at least 6 months prior to enrollment, and creatinine ≤2.0 mg/dL. They were randomly assigned to chelation therapy or 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.

Table 1. Components of the Primary Endpoint.

Primary Endpoint	EDTA Chelation (%)	Placebo (%)	Hazard Ratio (95% CI)	p Value
Death	10.4	10.7	0.93 (0.70–1.25)	0.642
MI	6.2	7.7	0.77 (0.54–1.11)	0.168
Stroke	1.2	1.5	0.77 (0.34–1.76)	0.531
Coronary revascularization	15.5	18.1	0.81 (0.64–1.02)	0.076
Hospitalization for angina	1.5	2.1	0.72 (0.35–1.47)	0.359

EDTA=ethylene diamine tetra acetic acid; MI=myocardial infarction.

Dr. Lamas concluded that, within the safety net provided by TACT, chelation therapy appears to be safe. The 10-component disodium EDTA chelation and ascorbate regimen demonstrated some evidence of a potentially important treatment signal in post-MI patients already on evidence-based therapy. The TACT trial results are unexpected and additional research is needed to confirm or refute the results and explore possible mechanisms of benefit.

Though the results of the TACT trial are interesting, they should be interpreted with caution as Elliot Antman, MD, Chairman of the AHA Scientific Sessions 2012, Brigham and Women's Hospital, Boston, Massachusetts, USA, pointed out in a formal statement: "As intriguing as the results are, they're unexpected and should not be interpreted as an indication to adopt chelation therapy into clinical practice. Much more information is needed about which elements of the complex infusion mixture might provide benefit; the marked discordance between the observed treatment effect in diabetics versus nondiabetics needs to be understood....TACT raises more questions that must be answered before we are ready to act on the observations that were reported."

OPERA: Omega-3 Fatty Acids Fail to Prevent Postoperative Atrial Fibrillation

Written by ***Rita Buckley***

Postoperative atrial fibrillation (AF) flutter occurs in approximately 1 of 3 patients undergoing cardiac surgery [Hogue CW Jr et al. *Chest* 2005; Mitchell LB et al. *Can J Cardiol* 2011], generating a need for new therapies to prevent it and its associated morbidity and healthcare costs [Mozaffarian D et al. *JAMA* 2012]. Roberto Marchioli, MD, MPH, Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy, reported findings from the Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation trial [OPERA; NCT00970489], which were simultaneously published in the *Journal of the American Medical Association* online [Mozaffarian D et al. *JAMA* 2012].

A few small trials have evaluated whether long-chain n-3 polyunsaturated fatty acids (PUFAs) reduce postoperative AF, with mixed results. The purpose of OPERA, a large multinational, randomized, double-blind, placebo-controlled clinical trial, was to examine whether perioperative intake of n-3 PUFAs would reduce the occurrence of postoperative AF in cardiac surgery patients aged ≥18 years scheduled for cardiac surgery on the following day or later who had sinus rhythm on screening electrocardiogram (ECG).

The primary endpoint was any postoperative AF >30 seconds duration confirmed by rhythm strip or 12-lead ECG. Secondary endpoints were postoperative AF lasting longer than 1 hour resulting in symptoms or treated with cardioversion; postoperative AF, excluding atrial flutter; time to first postoperative AF; number of AF episodes per patient; hospital utilization; and major adverse cardiovascular events, 30-day mortality, bleeding, and other adverse events [Mozaffarian D et al. *JAMA* 2012].

A total of 1516 patients undergoing cardiac surgery in 28 centers in the United States, Italy, and Argentina were randomized to receive fish oil (1 g capsules containing ≥840 mg n-3 PUFAs as ethyl esters) or placebo, with preoperative loading of 10 g over 3 to 5 days (or 8 g over 2 days) followed postoperatively by 2 g/day until hospital discharge or postoperative Day 10, whichever came first.

The average age of enrolled patients was 64 years; 72.2% were men and 51.8% had planned valvular surgery. The primary endpoint occurred in 233 (30.7%) patients assigned to placebo versus 227 (30.0%) assigned to n-3 PUFAs (OR, 0.96; 95% CI, 0.77 to 1.20; p=0.74; Figure 1). None of the secondary endpoints were significantly different between the placebo and fish oil groups, including postoperative AF that was sustained, symptomatic, or treated (231 [30.5%] vs 224 [29.6%]; p=0.70) or number of postoperative AF episodes per patient (1 episode: 156 [20.6%] vs 157 [20.7%]; 2 episodes: 59 [7.8%] vs 49 [6.5%]; or ≥3 episodes: 18 [2.4%] vs 21 [2.8%]; p=0.73).

Other secondary endpoints were not significant: postoperative AF excluding atrial flutter (p=0.87), total number of days with any postoperative AF (p=0.58), and proportion of days free of postoperative AF (p=0.882).