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).

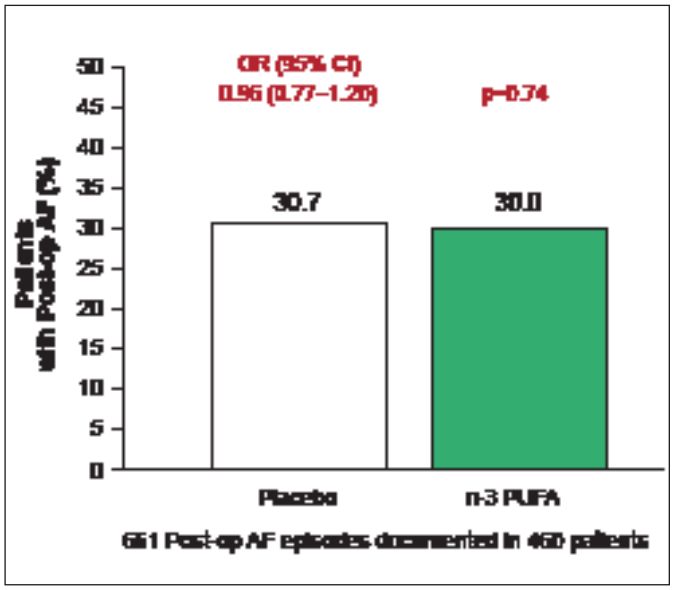
The primary endpoint was any postoperative AF >30 seconds duration confirmed by rhythm strip or 12-lead ECG. Secondary endpoints were postoperative AF lasting longer than 1 hour resulting in symptoms or treated with cardioversion; postoperative AF, excluding atrial flutter; time to first postoperative 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).

Figure 1. OPERA Primary Endpoint: Postoperative AF Episodes.



Reproduced with permission from R Marchioli, MD, MPH, and D Mozaffarian, MD, PhD.

Based on the data, Prof. Marchioli concluded that postoperative AF remains an enigmatic and difficult-to-prevent complication of cardiac surgery. While n-3 PUFA appeared to be safe and well-tolerated with no evidence of increased bleeding, the OPERA trial "provides evidence that perioperative n-3 PUFA does not appreciably reduce postoperative AF in the acute setting of cardiac surgery."

Multivitamins for the Prevention of Cardiovascular Disease in Men

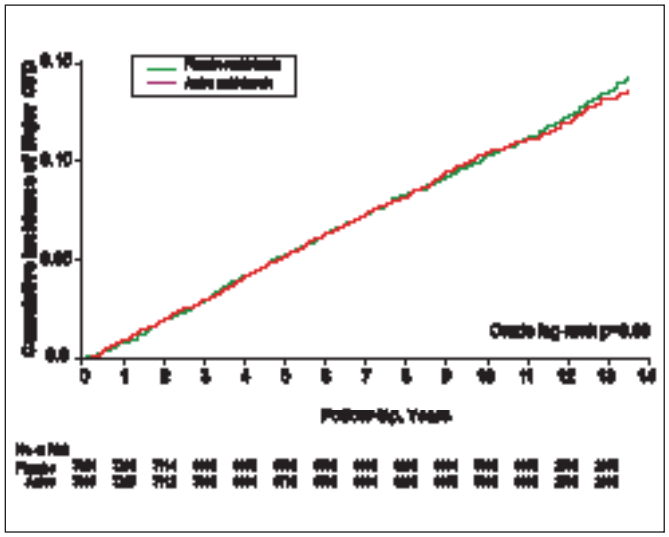
Written by ***Toni Rizzo***

Basic research has suggested that some individual vitamin and mineral components of multivitamins might reduce the risk of cardiovascular disease (CVD). However, no large-scale, long-term randomized trials have tested the effect of multivitamins. Howard D. Sesso, ScD, MPH, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented results from the Physicians' Health Study II (PHS II) on the long-term risks and benefits of multivitamin use in male physicians [Sesso HD et al. *JAMA* 2012].

PHS II was a randomized, double-blind, placebo-controlled, 2x2x2x2 factorial trial testing multivitamin, vitamin E, vitamin C, and beta-carotene. It was conducted by mail in 14,641 male physicians aged ≥50 years. A total of 7641 PHS I participants and 7000 new physicians were randomized to take an active multivitamin or its placebo, as well as for the other vitamin arms. For the multivitamin component, the primary cardiovascular (CV) endpoint was major CV events (nonfatal myocardial infarction [MI], nonfatal stroke, and CV death). The secondary endpoints were total and fatal MI, total and fatal stroke, ischemic and hemorrhagic stroke, CVD mortality, and total mortality. The participants were followed for a mean of 11.2 years, resulting in 164,000 person-years of follow-up.

Multivitamin compliance was 77% at 4 years, 72% at 8 years, and 67% at study end. Baseline characteristics were well balanced between the multivitamin and placebo groups. The cumulative incidence of major CV events at study end was not significantly different between the 2 groups (HR, 1.01; 95% CI, 0.91 to 1.10; crude log-rank p=0.69; Figure 1). Similarly, no significant differences were seen in the incidences of secondary endpoints (Table 1). There was a borderline significant reduction in MI death (27% vs 43%; HR, 0.61; 95% CI, 0.38 to 0.995; p= 0.048) that may have due to chance, given its small case counts.

Figure 1. Major CV Events: Active Versus Placebo Multivitamins During 11.2 Years of Follow-Up.



Notably, the total number of cancers—the other primary endpoint of the multivitamin component of the trial—was modestly but significantly reduced, with 1290 in the multivitamin group versus 1379 in the placebo group (HR, 0.92; 95% CI, 0.86 to 0.998; p=0.04). The total number of incident cancers among participants with a baseline history of cancer was also significantly lower in the multivitamin group (95) versus the placebo group (126; HR, 0.73; 95% CI, 0.56 to 0.96; p=0.02) but was not significantly lower among participants without a baseline history of cancer (1195 vs 1253; HR, 0.94; 95% CI, 0.87 to 1.02; p=0.15).