The TACT Trial: Provocative Results for High-Dose Vitamins and Chelation Therapy

Written by **Rita Buckley**

According to the results of the multivitamin arm of the Trial to Assess Chelation Therapy [TACT; NCT00044213], presented by Gervasio A. Lamas, MD, Mount Sinai Medical Center, Miami Beach, Florida, USA, high-dose vitamins alone do not improve outcomes for postmyocardial infarction (MI) patients.

TACT was a randomized, double-blind, placebo-controlled, 2x2 factorial clinical trial testing the clinical impact of 40 infusions of a multi-component Na_2EDTA-chelation solution and/or high-dose multivitamin and mineral supplement in patients with acute MI. The TACT trial had 4 treatment arms: placebo infusions/placebo vitamins; placebo infusions/high-dose vitamins; EDTA chelation/placebo vitamins; and EDTA chelation/high-dose vitamins. It involved 1708 post-MI patients at least 50 years of age. Approximately a third of the patient population was diabetic. The trial was designed to have >85% power to detect a 25% relative reduction in the primary endpoint for each treatment factor [Lamas GA et al. *Am Heart J* 2012]. The primary endpoint was a composite of time to first occurrence of death, MI, stroke, coronary revascularization, or hospitalization for angina.

The TACT multivitamin primary endpoint results were not significant (Table 1). Use of statins at baseline was the only predefined subgroup that interacted with the oral vitamin therapy, suggesting that patients who self-selected to not take statins (27% of the total) might have a better response to active oral vitamins (p for interaction=0.01). Dr. Lamas cautioned that these subgroup results are hypothesis generating only.

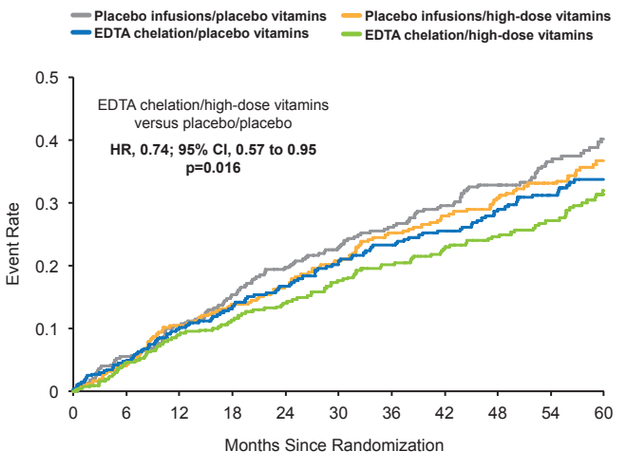
Table 1. Components of the Primary Endpoint

	High-Dose Vitamins (n=853)	Placebo (n=855)	HR (95% CI)	p Value
Primary endpoint	230 (27%)	253 (30%)	0.89 (0.75, 1.07)	0.212
Death	87 (10%)	93 (11%)	0.93 (0.69, 1.24)	0.614
MI	58 (7%)	61 (7%)	0.95 (0.66, 1.36)	0.786
Stroke	8 (1%)	15 (2%)	0.53 (0.22, 1.25)	0.139
Coronary revascularization	132 (15%)	155 (18%)	0.84 (0.66, 1.05)	0.131
Hospitalization for Angina	12 (1%)	19 (2%)	0.72 (0.35, 1.47)	0.359

MI=myocardial infarction.

When the 4 treatment groups were compared, a statistically significant difference of clinically interesting magnitude emerged between placebo infusion/placebo vitamins and active/active therapies (HR, 0.74; 95% CI, 0.57 to 0.95; p=0.016; Figure 1).

Figure 1. TACT Primary Endpoint in the Study's 4 Treatment Arms



EDTA=ethylenediaminetetraacetic acid.

Dr. Lamas noted that despite the evident benefit, the findings are insufficient to recommend the routine use of chelation therapy and high-dose vitamins in post-MI patients. He also reported that the study results do not support the use of high-dose vitamin and mineral therapy as an adjunct to optimal evidence-based medical therapy in patients with prior MI.

Limitations of the trial included constrained power to assess individual components of the composite endpoint; a high vitamin noncompliance rate; many subjects were lost to follow-up and withdrew consent; and potential confounding by oral vitamins and minerals. The hypothesis of proposed benefit of high-dose vitamin therapy was also unclear, which limited interpretation.

Earlier randomized, controlled trials of specific supplements failed to demonstrate a consistent or significant effect of any single or combination of vitamins on incidence of death from cardiovascular disease [Morris CD, Carson S. *Ann Intern Med* 2003]. Dr. Lamas concluded that the results of the study do not support the use of high-dose vitamin and mineral therapy as an adjunct to optimal evidence-based medical therapy in patients with acute MI but should serve as an impetus for further research.

Cangrelor Offers Protective Benefits in PCI Patients

Written by **Phil Vinall**

Cangrelor, an intravenous, potent, direct-acting adenosine diphosphate (ADP) receptor antagonist, significantly reduced the composite endpoint of

death, myocardial infarction (MI), ischemia-driven revascularization, and stent thrombosis in patients undergoing percutaneous coronary intervention (PCI) with no excess in severe bleeding compared with clopidogrel loading at the time of PCI.

The Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention [CHAMPION PHOENIX; Bhatt DL et al. *N Engl J Med* 2013] followed 2 prior studies of cangrelor, CHAMPION PLATFORM [Bhatt DL et al. *N Engl J Med* 2009] and CHAMPION PCI [Harrington RE et al. *N Engl J Med* 2009], 2 large Phase 3 trials that had been stopped early when an interim analysis concluded that the trials were unlikely to show that cangrelor was superior to clopidogrel. Deepak L. Bhatt, MD, MPH, Harvard Medical School, Boston, Massachusetts, USA, presented the results of the CHAMPION PHOENIX study in a late-breaking clinical trial.

Cangrelor is a rapidly acting (half-life of 3 to 6 minutes), reversible and intravenous ADP receptor antagonist that permits return to normal platelet function within one hour after discontinuation. These characteristics have spurred interest in its use in the setting of PCI. The CHAMPION PHOENIX trial was a randomized, double-blind, double-dummy, superiority study conducted globally at 153 sites in 12 countries [Bhatt DL et al. *N Engl J Med* 2013]. The primary efficacy endpoint was the composite of death, MI, ischemia-driven revascularization, and stent thrombosis at 48 hours. Secondary endpoints included the incidence of stent thrombosis at 48 hours, and efficacy endpoints were examined at 30 days. The primary safety endpoint was GUSTO severe bleeding at 48 hours.

Patients with stable angina, non-ST-elevation acute coronary syndrome or ST-elevation MI (STEMI; n=10,900) requiring PCI who were included in the study. Eligible patients could not have received pretreatment with a P2Y12 inhibitor prior to angiography or at any time within 7 days prior to randomization. Once suitability for PCI was confirmed by either angiography or STEMI diagnosis, patients were randomly assigned to 2 arms: Group A received a cangrelor bolus and infusion (30 µg/kg, 4 µg/kg/min) and placebo clopidogrel for the duration of the procedure with a minimum duration of 2 hours and a maximum duration of 4 hours, then clopidogrel 600 mg after the end of the infusion; Group B received placebo bolus and infusion along with active clopidogrel with the loading dose chosen by the investigator (300 or 600 mg) [Bhatt DL et al. *N Engl J Med* 2013].

The study population had a median age of 64 years, were mostly male (72%), the majority were enrolled with stable angina (56%), and most (74%) received a 600-mg loading dose of clopidogrel [Bhatt DL et al. *N Engl J Med* 2013]. Treatment with cangrelor significantly reduced the primary endpoint compared with clopidogrel (4.7% vs 5.9%; OR, 0.78; 95% CI, 0.66 to 0.93; p=0.005).

There was no difference with respect to mortality or for ischemia-driven revascularization, but MI was significantly less frequent with cangrelor (3.8% vs 4.7%; OR, 0.80; 95% CI, 0.67 to 0.97; p=0.02). Subgroup analyses showed consistency of benefit with no significant heterogeneity, with the exception of patients with peripheral artery disease (n=832; p for interaction=0.003) in whom cangrelor appeared to have a nominally more robust benefit. Efficacy results were similar when extended out to 30 days. There were no significant excess in GUSTO severe bleeding (0.16% vs 0.11%; OR, 1.5; 95% CI, 0.53 to 4.22; p=0.44) or transfusions (p=0.16); however, there was more ACUITY major bleeding (4.3 vs 2.5; OR, 1.72; 95% CI, 1.39 to 2.13; p<0.001) with cangrelor compared with clopidogrel. Transient dyspnea occurred more frequently in the cangrelor group (1.2% vs 0.3%; p<0.001).

Limitations of this study include the use of a 300-mg clopidogrel loading dose in 1405 patients in the comparator arm (although results were consistent after adjustment for loading dose), the use of clopidogrel as the comparator instead of the more rapidly acting and potent later generation agents prasugrel and ticagrelor, and the exclusion of patients who were pretreated with clopidogrel prior to angiography. No economic analyses have been presented to-date, and this will remain an important consideration should cangrelor become available for clinical use.

Although patients pretreated with ADP receptor blockers were excluded, the findings support a strategy where treatment with potent anti-platelet therapy may not be necessary prior to delineation of coronary anatomy, which may be beneficial for patients subsequently determined to need urgent surgery. In addition, this intravenous therapy presents an option for patients unable to take oral medications. Dr. Bhatt concluded that intravenous cangrelor might offer an attractive option across the full spectrum of PCI, including stable angina, non-STEMI, and STEMI.

BNP Screening, Targeted Care Reduce Heart Failure in At-Risk Patients

Written by Wayne Kuznar

Structured screening for heart failure (HF) using measurement of B-type natriuretic peptide (BNP) followed by targeted collaborative care was effective at preventing left ventricular dysfunction (LVD) and HF in a community setting.