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The Trial to Assess Chelation Therapy 2 (TACT2): Rationale and Design

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Abstract

The Trial to Assess Chelation Therapy 2 (TACT2) is an NIH-sponsored, randomized, 2x2 factorial, double masked, placebo-controlled, multicenter clinical trial testing 40 weekly infusions of a multi-component edetate disodium (disodium ethylenediamine tetra-acetic acid, or Na_2EDTA)-based chelation solution and twice daily oral, high-dose multivitamin and mineral supplements in patients with diabetes and a prior myocardial infarction (MI). TACT2 completed enrollment of 1000 subjects in December 2020, and infusions in December 2021. Subjects are being followed for 2.5 to 5 years. The primary endpoint is a composite of the time to first occurrence of all-cause mortality, MI, stroke, coronary revascularization, or hospitalization for unstable angina. The trial is designed to have >85% power to detect a 30% relative reduction in the primary endpoint for each active treatment versus placebo comparison. TACT2 also includes a Trace Metals and Biorepository Core Lab, which will test the novel hypothesis that the prognostic benefits of chelation, if present, are due to removal of lead and cadmium from patients. Most of the design features of TACT2 were chosen to replicate selected features of the first TACT trial, which demonstrated a statistically significant reduction in cardiovascular outcomes in the EDTA chelation arm compared with placebo among patients with a prior MI, with the largest effect in patients with diabetes. Results from TACT2, if concordant with TACT, will provide definitive evidence of the benefit of edetate disodium-based chelation on cardiovascular outcomes, as well as the possible clinical importance of longitudinal changes in toxic metal levels of participants.

Introduction

The Trial to Assess Chelation Therapy 2 (TACT2) is a replicative study of TACT[1], an NIH-sponsored randomized trial of stable post-myocardial infarction (MI) patients carried out between 2002 and 2012. TACT2 focuses on the highest-risk cohort in TACT with the greatest observed effect size (post-MI patients with diabetes) and will test the hypothesis that chelation treatments will result in fewer atherosclerotic vascular events.[2] TACT2 will also determine whether high-dose oral multivitamins and minerals (OMVM) produce a signal of prognostic benefit comparable to that observed in TACT.

The original TACT enrolled 1708 non-smoking post-MI patients who were at least 50 years old and had a serum creatinine of <2.0 mg/dL. Participants were randomly assigned to one of 4 factorial groups. The 2 factors assessed were intravenous chelation versus intravenous placebo and oral high-dose vitamins versus oral placebo. The primary endpoint was time to first component of a composite cardiovascular endpoint (death, recurrent MI, stroke, coronary revascularization, and hospitalization for angina). The primary end point occurred in 222 (26%) chelation-assigned subjects, and 261 (30%) placebo-assigned subjects (hazard ratio [HR], 0.82 [95% CI, 0.69-0.99]; P=0.035)[3]. In 633 participants with diabetes, a pre-specified high-risk subgroup, the corresponding effect size was a 41% relative risk reduction (P=0.0002 for chelation versus placebo; interaction P for diabetes vs no diabetes = 0.004)[2]. These findings led to edetate disodium chelation being classified as a 2B indication in the 2014 ACC/AHA Focused Update of the 2012 Management of Stable Ischemic Heart Disease Guidelines.[4]

Edetate disodium is a potent polydentate chelator, primarily of divalent cations. These include not only calcium and magnesium, but also ubiquitous vasculotoxic pollutant metals such as lead and cadmium [5,6]. A 3-gram infusion of edetate disodium increases urinary excretion of lead by about 4000% and cadmium by about 700% within 12 hours.[6] Edetate disodium is a very safe drug, when used as directed. Published FDA reports show that between 1971 and 2007, a timespan during which hundreds of thousands of doses of edetate disodium likely were used in the community, there were 4 reported deaths clearly associated with edetate disodium.[7] In TACT, after 55,222 placebo or edetate infusions, there were 2 deaths that a masked medical monitor thought might be attributable to the infusion: 1 on active therapy, and 1 on placebo.[3]

The positive primary endpoint findings for chelation in TACT were unexpected and counter to prevailing medical opinion in 2013 regarding the effectiveness of chelation for cardiovascular disease. The impetus to do a second trial came from the desire to ensure that these findings were not simply due to chance, to replicate the findings in a key subgroup (people with diabetes), and to identify, if possible, the mechanistic processes through which the observed benefits of edetate were produced. In addition to the unexpectedness of the TACT results, critiques of the trial noted that a greater proportion of TACT participants assigned to placebo than active infusion (20% vs 13.7%) withdrew consent, which raised concerns regarding the adequacy of masking, and led to speculation about the influence of this unanticipated imbalance on the treatment effect size. Sensitivity analyses, however, suggested the primary trial findings were robust and the greater loss of placebo patients was more likely to produce an underestimate of the effect size rather than an overestimate.[8, 9]

Since pre-trial expectations were that TACT would not find edetate to be effective, the trial did not include a mechanistic aim and no biorepository was established. The diabetes subgroup was prespecified, but a consequential treatment-subgroup interaction was not expected when TACT was designed.

The TACT vitamin results also provided additional unexpected findings that called for independent confirmation in a replication trial. The comparison of high-dose oral multivitamins and minerals (OMVM) with oral placebo demonstrated a non-significant benefit favoring OMVM that appeared additive to the beneficial effects of edetate disodium. This trend arose solely from a statistically significant signal of efficacy in the minority of patients not taking a statin at baseline.

To determine whether the findings of TACT could be prospectively reproduced, the investigative team for TACT2 decided it was important to preserve the same factorial design used in TACT. The findings from TACT indicated that the most efficient design for a well-powered replication trial involved enrollment of patients with prior MI and diabetes, use of the same factorial treatment allocation design, and collection of a biorepository to identify potential mechanistic pathways.

METHODS

Design Overview

TACT2, ClinicalTrials.gov identifier NCT02733185, is a randomized, double-masked, placebo-controlled, multicenter, international (USA, Canada), 2x2 factorial trial testing the effectiveness of 40 infusions of a multi-component edetate disodium-based chelation solution compared with placebo, and of an oral, high-dose OMVM supplement compared with placebo. The primary endpoint is a composite of all-cause mortality, MI, stroke, coronary revascularization, and hospitalization for unstable angina. The primary analysis will compare the edetate disodium chelation arm with the intravenous placebo arm. The OMVM vs oral placebo comparison is a secondary endpoint analysis, and therefore TACT2 was not powered/sized for this comparison. A Trace Metals and Biorepository Center has collected and processed urine and blood samples pre and post infusions (infusions 1, 5, 20, 40) for metal analyses and long-term storage of plasma, buffy coat, and urine samples.

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Trial Chronology

Four NIH Institutes / Centers collaboratively funded TACT2 as a UG3/UH3. The UG3 was funded in September 2015 and planned as a start-up phase for finalizing study design, site identification and recruitment, and obtaining regulatory approvals. The TACT2 Research Group (PIs and NIH TACT2 team) finalized the protocol that was submitted and received DSMB approval. The investigators completed the required milestones to transition to UH3 phase and the first patient was randomized in October 2016. The trial concluded enrollment of 1000 patients December 31, 2020. TACT2 infusions were completed by December 31, 2021. The last TACT2 follow-up is expected to take place by June 30, 2023. Database lock and analyses are projected to take 6 months, and TACT2 anticipates reporting results in the 4th quarter of 2023.

Trial Organization

The Clinical Coordinating Center (CCC) is located at Mount Sinai Medical Center, Miami Beach, FL (Gervasio Lamas, PI). The CCC identified, subcontracted, and managed clinical sites, the Central Pharmacy, the TACT2 safety and clinical laboratory, the oral vitamin/placebo manufacturer, and the Clinical Events Committee (CEC).

The Data Coordinating Center (DCC) is located at Duke Clinical Research Institute (DCRI), in Durham, NC and serves as the DCC (Kevin Anstrom and Daniel Mark, co-PIs). The DCC comprises two separate teams, a masked team that has direct contact with investigators, and an unmasked team that has no TACT2-related contact with the masked team, nor with the clinical investigators. The masked DCC team is responsible for the electronic data entry system (Medidata™ Rave), collecting all patient data, clinical site training (with the CCC) and monitoring, adverse event monitoring and reporting, collecting endpoint event data and

communicating with the CEC to adjudicate events. The masked and unmasked statistics teams prepare the DSMB Open report, which provides summary data and can be viewed by the CCC. The unmasked DCC team prepares the DSMB closed report, which is viewed by the DSMB and unmasked NIH statistician only. The CEC is located at Brigham and Women's Hospital, in Boston, MA and serves as the primary review committee of masked endpoints (Eldrin Lewis PI at Stanford University in Palo Alto, CA.)

The Trace Metals and Biorepository Center is located at Columbia University Mailman School of Public Health, New York, NY (Ana Navas-Acien, PI) and is responsible for receiving blood & urine shipped from sites, processing, and storing them, and shipping samples to the Centers for Disease Control and Prevention (CDC) for measurement of metals. Metal levels measured by the CDC include blood lead (together with cadmium, mercury, selenium and manganese) and urinary lead and cadmium (together with barium, beryllium, cobalt, cesium, manganese, molybdenum, lead, platinum, antimony, tin, strontium, thallium, tungsten and uranium). Urinary creatinine is also measured at the CDC in the same sample where metals are measured to correct urinary metal concentrations for urine dilution. Progress and logistics of these activities and any operational problems or difficulties encountered are shared with and coordinated by the Trace Metals and Biorepository Center with the assistance of the CCC and DCC. The masked CDC laboratory reports the blood and urine analyses to the unmasked DCC team.

Clinical sites

Clinical sites across the US and Canada (n=88) are led by licensed physicians (MD or DO) who meet all NIH, FDA, and Office for Human Research Protections requirements for participation in federally funded clinical studies and have a Federal Wide Assurance number prior to approval as a site. Based on our prior experience with ease of study drug administration and safety of chelation, and markedly increased interest by the cardiology and endocrine communities in the scientific questions posed by TACT2, the Clinical Coordinating Center focused site recruitment activities on conventional medicine sites with prior research experience. Clinical sites that had experience in the first TACT study were invited to participate based on their prior performance in adherence and compliance. This led to a preponderance of "conventional medicine" sites (84%). Following approval as clinical sites, clinical study personnel completed TACT2 investigator and coordinator training directed by the DCC and CCC and the Trace Metals and Biorepository Core Laboratory on-line and in-person. Based on the TACT experience, TACT2 has increased emphasis on adherence to the study infusion and oral regimen, and on managing noncompliant patients to maintain follow-up for endpoints and avoid withdrawal of consent. Sites earned approval from a local (n=19) or central (n=69) Institutional Review Board prior to enrolling patients.

Patient safety oversight and adverse event collection

The NIH, FDA, Health Canada, and local or central IRBs oversee TACT2. An NIH-appointed, independent Data and Safety Monitoring Board (DSMB) meets at least twice each year. The members of the DSMB include experts in clinical trial design and interpretation, bioethics, cardiology, diabetology, pharmacology, biostatistics, and metal

pharmacokinetics and toxicology. At regular meetings, the DSMB reports are prepared by the masked and unmasked DCRI statistics teams. The DSMB reviews unmasked data for safety. Interim analyses at planned pre-specified time points based on the proportion of data available (40%, 60%, and 80% of total expected events) are performed and the DSMB recommends to NIH whether to stop the study for safety, futility, or efficacy. The DSMB, TACT2 leadership, and NIH staff developed the stopping rules as part of the DSMB Charter.

Patient population

Patients were eligible if they were at least 50 years of age, had a history of a myocardial infarction more than 6 weeks prior to enrollment, had diabetes of any type, and had signed the informed consent. Potential participants were ineligible if they had abnormal renal function (defined by serum Cr >2.0 mg/dL), uncontrolled diabetes (defined as a Hb A1c of > 11%), or other exclusions (see Table 1 for full inclusion and exclusion criteria).

Randomization

Randomization was carried out via the TACT2 Medidata™ Rave system, a web-based, electronic data capture system. Patients were randomly assigned in equal proportions to one of the four treatment arms defined by the 2 x 2 factorial design.

Treatment regimens

Patients were randomized to receive 40 weekly infusions of either edetate disodium-based chelation (Table 2) or placebo, with each infusion usually taking 3 to 4 hours in the outpatient setting. A central pharmacy individually prepared and shipped masked chelation/placebo solution to infusion sites. The dose of edetate disodium was based on the estimated creatinine clearance derived from periodically measured serum creatinine levels with a maximum dose of 3 grams per infusion (Appendix 1). The study asked participants to receive weekly infusions, but accommodated unavoidable skipped infusion visits, such as for vacations, illnesses, and sometimes due to the high patient burden of weekly infusions. Sites and participants understood that the expectation was to complete all 40 infusions in 1 year.

Each patient was also randomly assigned to receive either an oral high-dose vitamin and mineral supplement (OMVM), or identical-appearing placebo caplets for up to 5 years. The dosing, components, and excipients of the high-dose oral vitamins were based on the original TACT OMVM (Appendix 2).[10] In addition, during the infusion phase of the trial, all study participants received a daily low-dose regimen of vitamin B6 25 mg, zinc 25 mg, copper 2 mg, manganese 15 mg, and chromium 50 mcg to prevent potential depletion of these micronutrients by the chelation regimen.

Masking

The refrigerated infusion pack shipped to sites contained one ascorbic acid syringe (or ascorbic acid placebo), one syringe with edetate disodium (or placebo), and a bag of active intravenous infusion with all the other components already mixed (or a bag containing only normal saline if the patient was assigned to the placebo arm). Immediately preceding the time of infusion, the Site Coordinator injected the contents of the two syringes into the infusion bag. The placebo OMVM caplets appeared identical to the active therapy.

Patient follow-up

Data collection by clinical sites—Site personnel collected clinical data, biological samples, outcome events, and adverse events from study screening, and at the time of each infusion through 30 days after the last infusion. The TACT2 site team entered all clinical data through the electronic data capture system. The site investigator documented all adverse events and serious adverse events (SAE) from initiation of study drug through 30 days following the final study infusion. The site investigator assigned initial causality to each SAE using standardized electronic forms.

Data collection by the DCRI Call Center—Starting 6 months after randomization, the DCRI Call Center established contact with study patients. Following the infusion phase, further follow-up takes place by telephone contact every 4 months through the DCRI Call Center. Contact includes assessment of possible endpoints, recording of any interval hospitalizations, and determining compliance with the high dose OMVM regimen. Follow-up will be continued for up to 5 years after randomization, or until the scheduled end of study, whichever is first.

Event adjudication

The DCC Medical Monitor or designee determined which SAEs met the “unexpected” criteria (not labeled in the Investigator’s Brochure) and made an independent assessment of causality. Masked personnel at DCRI also collect patient hospital records based on possible clinical events when indicated by the study site or via calls to the participant by the DCRI Call Center. The site and hospital records are further screened for potential endpoint events by masked medical personnel at the DCC. Records that meet broad criteria for possible endpoint events are referred to the masked CEC at Stanford University (Eldrin Lewis, PI, Palo Alto CA) and Brigham and Women’s Hospital (Boston MA), which is performing 100% clinical event adjudication for the primary endpoint components aside from coronary revascularization (Appendix 4). Coronary revascularizations are part of the primary endpoint, regardless of reason for the procedure. They are verified via document review by the DCC.

Routine medical care of TACT2 participants

All routine medical care for TACT2 participants was provided by their own health care providers. TACT2 encouraged up-to-date, evidence-based medical care for post-MI patients with diabetes, including use of newer cardioprotective anti-diabetes pharmacotherapy. The DCC provided site Pis with report cards that included use of evidence-based medical management and comparison with other sites. The CCC and DCC instructed enrolling sites that did not also provide clinical care for study participants to provide the information to the relevant health care providers. The DSMB reviews patterns of key medication use during its study meetings. Glycemic control and complications of diabetes were monitored throughout the study. Blood glucose was measured at baseline and 2 additional times during the trial. HbA1c and microalbuminuria are measured at baseline prior to the first infusion, and again prior to infusions 20 and 40.

Safety monitoring

Hypocalcemia and renal toxicity are the most serious potential adverse events of edetate disodium. To ensure subject safety, patients with a baseline creatinine >2.0 mg/dL were excluded from the trial. Safety labs were measured by Quest Diagnostics. These included renal function, serum calcium and albumin, liver function studies, and a complete blood count (Table 3), at screening and preceding infusions 5, 10, 20, 30, and 40. Sites were issued an electronic alert, copied to the CCC, when there was a 25% decrease in estimated glomerular filtration rate, with instructions to sites to assess participants for new medications or other clinical changes that might account for a change in renal function. Infusions were paused if there was either a doubling of baseline serum creatinine, or an increase to a level of 2.5 mg/dL or greater. Infusions were resumed when renal function improved.

Patients received infusions over a 3 to 4-hour period. Most patients received a 3-hour infusion. If the serum calcium level, corrected for albumin concentration, was between 8.0 and 8.4 mg/dl, subsequent infusions were extended to 4-hours to minimize potential hypocalcemia. Short infusions, defined as an infusion shorter than 2 hours and 45 minutes with more than 50% of infusion administered, were reported electronically to the site and the DCC. The site was contacted to assess infusion procedures. The DCC reported short infusion occurrences at Study Management meetings, and to the DSMB. Hypoglycemia in patients with diabetes is a potential expected side effect of EDTA chelation. Patients with insulin-treated diabetes were instructed to snack before the infusion, and sites were trained to assess and treat hypoglycemia when necessary.

Additional possible expected side effects included hypotension, mineral and vitamin deficiency syndromes, febrile episodes, and heart failure due to fluid overload. The site team weighed patients prior to all infusions and required a clinical evaluation if the patient gained 3 lbs or more since the last infusion or 5 lbs or more since the baseline visit. If these increases in weight occurred, study personnel evaluated the patient by clinical history and physical exam for potential heart failure. If heart failure was present, sites called the CCC and could be instructed to delay infusions until fluid status normalized.

Infusions were also delayed in patients whose ALT, AST, alkaline phosphatase or bilirubin doubled, or total white blood cell count fell below the normal limit. The development of thrombocytopenia to below 100,000 platelets, or a 50% decrease from baseline led to a delay of infusions until platelet count returned to normal. This could also lead to a decision by the CCC to omit unfractionated heparin from future infusions.

All SAEs were reported to the IRBs, DSMB, NIH, and FDA on a regular basis. Deaths and unexpected SAEs were reported in an expedited fashion.

Study endpoints and statistical analyses

Primary Endpoint—The primary objective of TACT2 is to determine if the edetate disodium-based chelation strategy prolongs the time to the first occurrence of the composite TACT2 primary endpoint: all-cause mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for unstable angina compared with the placebo chelation strategy.

The primary endpoint analyses will follow the intent-to-treat (ITT) principle and the treatment effect will be expressed as a hazard ratio and 95% confidence interval estimated using the Cox proportional hazards regression model (Table 4).[11] The treatment effect estimate will be adjusted for age, sex, and baseline use of insulin. In addition, the adjusted model will include indicator variables for the active chelation and active OMVM groups, and an interaction term for active chelation and active OMVM. The interaction term will be dropped if not significant. In this matter, we are following the methods advocated in the Committee for Proprietary Medicinal Products of the European Medicines Agency.[12] That report, which extended recommendations from an International Committee on Harmonization 1998 white paper regarding the analysis of clinical trials, indicated that baseline variables known *a priori* to be strongly associated with the primary outcome should be considered as covariates in the primary analysis in order to improve the precision of the estimation of treatment effect size. In addition to the statistical hypothesis testing, Kaplan-Meier survival estimates will be constructed based on the time from randomization to the first primary event occurrence.

The secondary objectives of TACT2 (Table 4) are to determine:

1. if the edetate disodium-based chelation strategy reduces the overall rate of occurrence of the individual events that comprise the primary endpoint, compared with the placebo infusion strategy, using statistical techniques for multiple events analyses.[13, 14, 15]
2. if the edetate disodium-based chelation strategy increases the time to the first occurrence of a combined secondary endpoint of major adverse cardiovascular events: cardiovascular mortality, recurrent MI, or stroke compared with the placebo chelation strategy.
3. if the edetate disodium-based chelation strategy increases the time to all-cause mortality compared with the placebo chelation strategy.

The analyses for the time-to-first-event secondary endpoints (2 and 3, above) will be like those outlined for the primary endpoint - using the time from randomization through the first occurrence of any component of a specific secondary endpoint (or censoring) as the response variable and controlling for group differences using the Cox proportional hazards regression model.

Secondary Endpoints—The major secondary endpoint analyses proposed in TACT2 have been prespecified for the purpose of confirming an unexpected signal of benefit observed in TACT, or to test novel prespecified mechanistic hypotheses to better understand the benefits of chelation if observed in TACT2. These will include:

1. Analysis of the primary endpoint in patients receiving OMVM compared with oral placebo regardless of the edetate disodium versus placebo treatment group assignment
2. Analysis of the primary endpoint in patients receiving active chelation + active OMVM, compared with placebo chelation + placebo OMVM

3. Analysis of lead and cadmium in blood and urine at baseline and over the infusion period to evaluate:
    a. if the edetate disodium regimen decreases metal internal dose,[16] as represented by blood lead and urine cadmium by comparing body metal levels from baseline to final infusion (lead and cadmium analyzed separately) in the active versus placebo groups.
    b. If the reduction in the primary composite endpoint with edetate disodium therapy relative to placebo increases in participants with higher baseline metal internal dose and with a higher depletion of metal stores over time (lead and cadmium analyzed separately), to identify patients more likely to benefit from edetate disodium treatment,
    c. if the hypothesized reduction of metal levels with edetate disodium (lead and cadmium analyzed separately), mediates the projected clinical benefits EDTA chelation expected in TACT2, using formal mediation analysis.[17]
4. Analysis of markers of diabetes (fasting glucose, Hb A1c, microalbuminuria) between treatment groups of chelation or placebo throughout the infusion regimen
5. Analysis of medical resource use patterns and costs, and estimation of cost effectiveness.

Biorepository for future research

An additional objective of TACT2 is to collect and store blood and urine samples to support future mechanistic research. Samples of blood (plasma and buffy coat) collected pre-infusion, and urine collected pre and post infusion at baseline, infusion 5, infusion 20, and final infusion are stored at −80°C in a secured biorepository at Columbia University's Mailman School of Public Health to ensure their availability for the evaluation of future hypotheses that will be guided by the results of the trial. The samples will be available for mechanistic research and ancillary studies once the primary analyses have been completed and results reported, following the procedures established by the NIH for ancillary research studies in TACT2.

Sample size and statistical power

TACT2 originally planned to enroll 1200 patients over 3 years with a minimum follow-up on the last patient enrolled of 1 year. Enrollment proceeded more slowly than anticipated. Therefore, in mid 2019, based on aggregate event data provided by the masked DCC team, and prior to viewing unmasked data, the DSMB approved a reduction in sample size to 1100 subjects, with a compensatory 1-year increase in minimum follow-up (total 2 years after enrollment) to maintain the total number of events and preserve statistical power. The maximum follow-up of five years was not changed.

The COVID-19 pandemic, starting in March 2020, adversely impacted both enrollment and follow-up. Enrollment and infusions initially halted and then slowly restarted after a

four-month pause. Despite this unforeseen obstacle, sites succeeded in enrolling 1000 study participants by December 31, 2020.

Based on aggregate event data, the current sample size, and a further DSMB-approved increase of the planned minimum follow-up time by 6 months to 2.5 years minimum, TACT2 projects an adequate aggregate number of events to preserve statistical power. Thus, the statistical plan continues to project >85% power with a two-sided alpha of 0.05 for detecting a 30% relative reduction in the primary endpoint with chelation compared with placebo. In terms of Type I error control, the primary comparison will focus on the active EDTA chelation vs. placebo chelation for the primary endpoint in randomized participants (Appendix 3).

Subgroup analyses

A limited number of pre-specified subgroup analyses of the primary outcome and selected secondary outcomes will test the efficacy of chelation therapy and/or high dose vitamins in different subgroups of the study population. Treatment comparisons will be covariate-adjusted and performed within subgroups defined by:

1. Age >70 years versus younger participants:
2. Sex
3. Race/ethnicity
4. MI location (Anterior MI or not)
5. Known peripheral artery disease at baseline
6. Treatment of diabetes
7. Use of statin therapy at baseline (for OMVM analyses only)

The examination of these pre-specified subgroups will include formal tests of interaction within the Cox regression model, recognizing that such tests are typically underpowered, and thus must be interpreted in the context of consistency and plausibility of treatment effect size patterns across subgroup levels.

Economic Analyses

Economic analyses for TACT2 will include both comparison of resource use patterns and medical costs. Relevant select medical resource use patterns collected on the eCRF will be compared by intention to treat. To compare medical costs between treatment arms, we must: 1) assign costs to all medical resources consumed during the study period; 2) compute mean costs by treatment group (defined by the principle of intention-to-treat); and 3) calculate the difference in mean costs between treatment arms and generate confidence intervals. The cost of US hospital-based care will be estimated by applying hospital-specific, revenue center level cost-to-charge ratios to empirical billing data collected during the study. This approach, which has been used successfully in numerous previous clinical trials,[18,19,20,21,22] takes advantage of the objective, detailed account in hospital bills of services provided to patients, and it recalibrates hospital charges to reflect costs more closely. For the patients without billing data, we will impute costs using a generalized linear model developed using

study data.[23] The cost of stays at non-acute care facilities will be estimated by multiplying the length of stay by the corresponding Medicare reimbursement rate. Costs for physician services will be estimated by mapping major inpatient and outpatient procedures recorded on the case report form to appropriate CPT codes in the Medicare Fee Schedule. We will also assign rounding fees for inpatient stays based on type of unit. The cost of outpatient medications will be estimated based on medication use recorded in the eCRF and unit costs by medication type and class, based on current estimates of acquisition cost.

Our primary comparison of costs will test mean medical costs incurred during the study (index infusion through end of follow-up). Costs will be adjusted for variable study times using the approach of Bang and Tsiatis.[24] Primary statistical comparisons between the two treatment groups will be performed using the intention-to-treat principle. Comparisons will be made using a normal approximation with standard errors estimated using the bootstrap approach. The probability of differences in cost greater than thresholds of policy interest (such as $1000, $2000 or $5000) will be calculated. Differences in cost by treatment group will be interpreted in the context of the trial clinical results, looking for both consistency and plausibility with respect to endpoints as well as measures of resource use.

Cost-Effectiveness Analysis

If the hypothesized improvements in health outcomes with the chelation strategy are found, cost-effectiveness analysis will be performed. This assessment (summarized in the cost-effectiveness ratio) can be interpreted relative to well-understood benchmarks of efficiency in health care and forms a metric of “value for money.”

Our cost-effectiveness analyses will be performed from the US health system perspective. We will estimate costs using empiric resource use patterns and cost weights collected from the TACT2 patient cohort. We will estimate life expectancy using age-based survival models, in which hazard is modeled as function of age rather than time, to maximize our ability to extrapolate survival from patient status at the end of trial follow-up. These survival models will also incorporate clinical and demographic characteristics of patients. Our method for estimating life expectancy has been successfully used in prior clinical trial cost-effectiveness analyses.[18, 19, 25, 26] Quality of life (QOL) adjustments to life expectancy will be applied using preference-weighted EQ-5D scores.[27] If the mortality benefit signal observed in the trial is judged not clinically persuasive, but the trial is still “positive,” the effect on nonfatal Mis and stroke will need to be integrated into the assessment of incremental life expectancy using trial and secondary data sources to derive appropriate hazard weights.

The base case cost-effectiveness ratio will be calculated as the difference in estimated mean lifetime costs divided by the difference in mean life expectancy (chelation strategy versus placebo). Uncertainty in the cost-effectiveness estimates related to sampling variation will be quantified using non-parametric bootstrap techniques. We will also perform relevant sensitivity analyses to evaluate the impact on cost effectiveness of changes to assumptions and key parameters that cannot be empirically established.

Discussion

TACT2 has three principal purposes. First and most importantly, the study will demonstrate (test) whether the benefits of EDTA based chelation in the subgroup of post-MI participants with diabetes reported nearly a decade ago in TACT are reproducible[2]. Should TACT2 reduce primary endpoint events, it will be the second NIH-funded randomized clinical trial to support the benefits of EDTA chelation, adding further impetus to the adoption of toxic metal chelation as another routine, guideline-based therapy to reduce cardiovascular events in post-MI patients with diabetes.

Secondly, TACT2 will test the toxic metal hypothesis proposed by our team to explain the TACT results. EDTA, an artificial amino acid first synthesized in the 1930's, is a versatile polydentate chelator with affinity for cations with a +2 valence. Among these cations are lead and cadmium, two ubiquitous divalent toxic metals with robust basic science and epidemiological evidence of adverse effects on the vasculature.[28,29,30]

The third reason is to assess whether the TACT OMVM reduced cardiovascular endpoints in conjunction with EDTA infusion. The overall history of well-designed vitamin trials is nearly uniform in its conclusion that vitamin supplementation does not reduce adverse cardiovascular outcomes. Almost all these studies, however, used low doses of a limited number of vitamins and minerals in a primary prevention setting.[31] In TACT, there was a weak non-significant signal of benefit for OMVM reducing the primary endpoint.[10, 32] The investigators felt it was relevant to confirm or refute the OMVM results of TACT.

One perceived weakness of the initial TACT, when presented in 2012 and published in 2013, was the virtual absence of any underlying accepted hypothesis presented to support the unexpectedly positive results of the trial. In the last two decades since the TACT research program started, evidence supporting 3 key concepts that render TACT2 timely and relevant has grown:

1. environmental pollutants, in particular inhaled pollutants, induce vascular damage and coronary events;[33 34]
2. lead and cadmium, ubiquitous metal pollutants, have prominent cardiovascular toxicity; [35] and
3. edetate disodium efficiently chelates and increases urinary excretion of metal pollutants, such as lead and cadmium.[6]

Some other aspects of TACT2 merit special notice. TACT2 is a secondary prevention trial of CVD in patients with prior MI and diabetes. It has long been known that advanced glycation end products, protein oxidation products, and oxidized lipids, contribute to atherosclerotic events, and metal-catalyzed oxygen chemistry contributes to their formation.[36, 37] Possibly for this and other reasons, patients with diabetes demonstrated the greatest effect size from active chelation in TACT. Thus, in the early planning phase for TACT2, FDA strongly urged the investigative team to restrict a replication trial to post-MI patients with diabetes, as the most efficient path to assessing the reproducibility of TACT and a potential indication for treatment of cardiovascular disease. In fact, a recent systematic review of all known

chelation studies in cardiovascular disease discerned a signal of benefit for chelation in patients with diabetes and peripheral artery disease.[38]

The content of the study infusion also merits discussion. An ideal experiment would have omitted all the components of the active infusion save edetate disodium. The NIH Request for Applications (AT-01-004) through which the original TACT received funding requested that the most prevalent chelation mix in the community be tested. The recommended chelation mix within the practitioner community was the 10-component infusion that TACT tested (Table 2). Once TACT showed positive results, the investigative team committed to replicate the clinical trial with the infusions used in TACT. Thus, TACT2 uses the same complex mix as TACT. It is possible that, if this study is positive, future studies might explore whether the non-EDTA additives influence cardiovascular events.

Finally, this clinical trial offers substantial advantages over observational epidemiology designs by directly measuring the impact of repeated chelation treatment on metal levels in study participants and the relationship of such to clinical events. No other clinical trial has done this to date. Moreover, maintaining additional samples, including DNA, will allow follow-up projects to understand the biochemistry and cellular biology (or underlying mechanisms) of metal chelation in disease etiology, as well as potential mitigation strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Inclusion and Exclusion Criteria

INCLUSION CRITERIA (all must be present)		**EXCLUSION CRITERIA (none may be present)**	
1	Men or postmenopausal women age ≥ 50 years	**1**	Baseline serum creatinine >2.0 mg/dL.
2	History of diabetes, defined as medical record evidence or patient report of currently using insulin or oral hypoglycemic agents, or with a history of fasting blood glucose measurement of 126 mg/dL or higher, or a history of HbA1c of 6.5% or higher.	**2**	HbA_1C>11%.
3	History of myocardial infarction based on the Universal Definition of MI.	**3**	Myocardial infarction within 6 weeks of randomization.
a.	When information about the MI hospitalization is available, all MI types except Type 2 qualify for study entry.	**4**	Allergy to any study drug
b.	When information about the MI hospitalization is not available, a wall motion abnormality on imaging or a perfusion defect on scan that corresponds to a coronary distribution, whether or not accompanied by pathological Q waves in the appropriate distribution, will qualify the patient for study entry. This criterion requires CCC case review.	**5**	Coronary or peripheral arterial revascularization within 6 months.
		6	Planned revascularization
		7	Heart failure hospitalization within 6 months
		8	Poor or no venous access
		9	a. Prior intravenous chelation therapy consisting of > 1 infusion within 5 years b. Oral chelation therapy within 2 years.
		10	Prior participation in TACT.
		11	Baseline platelet count <100,000.
		12	Cigarette smoking within the last 3 months.
		13	ALT or AST > 2.0 times the upper limit of normal.
		14	Wilson’s disease, hemochromatosis, or parathyroid disease.
		15	Medical condition that will limit patient survival over the duration of the trial.
		16	Any factor that suggests that the potential participant will not be able to adhere to the protocol.
		17	Women of child-bearing potential

Table 2.

Edetate disodium Chelation Infusion Contents

Additives
• Up to 3 g of Na_2EDTA
• 2 g of magnesium chloride
• 100 mg of procaine HCL
• 2500 U of unfractionated heparin
• 7 g of ascorbic acid
• 2 mEq KCl
• 100 mg of thiamine
• 250 mg pantothenic acid
• 100 mg of pyridoxine
• 840 mg sodium bicarbonate
• QS with sterile water to 500 mL

The dose of EDTA changes based on estimated GFR; the maximum dose is 3 grams.

Table 3.

Scheduled Labs

Laboratory Tests	**Screening**	**Inf 1**	**Inf 5**	**Inf 10**	**Inf 20**	**Inf 30**	**Inf 40**
Creatinine	X		X	X	X	X	X
Calcium	X		X	X	X	X	X
Albumin	X		X	X	X	X	X
Glucose	X				X		X
HbA1c	X				X		X
Microalbumin	X				X		X
CBC/plt	X				X		
Liver Function	X						
Lipids	X						X
Metals (pre/post infusion) [+]							
Cadmium (urine) [#]		X	X		X		X
Lead (blood) [*]		X	X		X		X

[*] Blood metals are only measured pre-infusion.

[+] Post-infusion refers 3 hours after the start of an infusion.

[#] While blood lead pre-infusion and urine cadmium pre and post-infusion are the key metal measurements for the Trace Metals and Biorepository Core Lab, a suite of urine toxic metals will also be measured, as stated earlier.

Table 4.

Key Clinical Study Objectives and Estimands.

Question of Interest	Objective Description / Study Population	Endpoint	Intercurrent Events	Population Summary
Does chelation reduce ischemic events for patients with a history of MI and diabetes?	Primary Objective of the Study / All Randomized Participants	Time to randomization to death, stroke, MI, coronary revascularization, or hospitalization for unstable angina. All endpoint components except coronary revascularization are determined by the CEC.	All other intercurrent events will be ignored in these analyses. Supplemental analyses will censor deaths due to COVID-19 infection.	Hazard ratio estimate based on a Cox proportional hazards model. Values below 1.0 suggest benefit from chelation.
Does chelation reduce hard ischemic events for patients with a history of MI and diabetes?	Key Secondary Objective of the Study / All Randomized Participants	Time from randomization to death, stroke, or MI.	All other intercurrent events will be ignored in these analyses.	Hazard ratio estimate based on a Cox proportional hazards model. Values below 1.0 suggest benefit from chelation.
Does chelation reduce the death rate for patients with a history of MI and diabetes?	Key Secondary Objective of the Study / All Randomized Participants	Time from randomization to death.	All other intercurrent events will be ignored in these analyses.	Hazard ratio estimate based on a Cox proportional hazards model. Values below 1.0 suggest benefit from chelation.
Is chelation therapy safe to apply in a high-risk CAD population?	Key Secondary Objective of the Study / All Randomized Participants receiving at least one infusion of study drug	Total number of SAE and percentage of patients experiencing at least 1 SAE.	Some patients may decide to not take study drug after randomization and will be excluded from these analyses.	