HHS Public Access

Chelation therapy to prevent diabetes-associated cardiovascular events

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Abstract

Purpose of review—For over 60 years, chelation therapy with disodium ethylene diamine tetraacetic acid (EDTA, edetate) had been used for the treatment of cardiovascular disease (CVD) despite lack of scientific evidence for efficacy and safety. The Trial to Assess Chelation Therapy (TACT) was developed and received funding from the National Institutes of Health (NIH) to ascertain the safety and efficacy of chelation therapy in patients with CVD.

Recent findings—This pivotal trial demonstrated an improvement in outcomes in postmyocardial infarction (MI) patients. Interestingly, it also showed a particularly large reduction in CVD events and all-cause mortality in the prespecified subgroup of patients with diabetes. The TACT results may support the concept of metal chelation to reduce metal-catalyzed oxidation reactions that promote the formation of advanced glycation end products, a precursor of diabetic atherosclerosis.

Summary—In this review, we summarize the epidemiological and basic evidence linking toxic metal accumulation and diabetes-related CVD, supported by the salutary effects of chelation in TACT. If the ongoing NIH-funded TACT2, in diabetic post-MI patients, proves positive, this unique therapy will enter the armamentarium of endocrinologists and cardiologists seeking to reduce the atherosclerotic risk of their diabetic patients.

Keywords

cardiovascular disease; chelation; diabetes; metals; Trial to Assess Chelation Therapy

INTRODUCTION

In November 2012, we presented the results of the NIH-funded Trial to Assess Chelation Therapy (TACT) at the American Heart Association Scientific Sessions in Anaheim,

California. Metal chelation for atherosclerosis had long been thought to be quackery by traditional cardiologists, yet persisted in clinical use. In spite of the absence of actionable data, a safety and efficacy trial of edetate disodium (disodium ethylene diamine tetra acetic acid, Na$_2$EDTA) chelation in patients following myocardial infarction was funded in 2002 by the NIH, and completed over a decade [1,2].

The results of the primary analysis of TACT were surprising. Instead of debunking a quack therapy, the results of this double-blind, placebo-controlled clinical trial demonstrated benefit of 40 intravenous edetate disodium-based chelation infusions in reducing cardiovascular disease events in a secondary prevention population [1,2] (Fig. 1a). The effect of metal chelation on diabetic patients with cardiovascular disease (CVD, defined as prior myocardial infarction) is the focus of this review.

Of the 1708 post-MI patients studied in TACT, 633 had diabetes [3■■]. Diabetic patients assigned to chelation therapy demonstrated a 41% relative risk reduction in combined cardiovascular events compared with placebo infusions ($P = 0.0002$, 5-year number needed to treat to prevent one event = 6.5) 6.5) (Fig. 1b). There was a 52% relative reduction in the risk of recurrent myocardial infarction ($P = 0.015$; Fig. 1c); and a 43% relative risk reduction in mortality ($P = 0.011$, 5-year number needed to treat to prevent one death = 12; Fig. 1d) [3■■]. This review will touch upon the key role that essential and toxic metals, may play upon the development of vascular complications, particularly in patients with diabetes, the results of a clinical trial of metal chelation, particularly in diabetic patients, and ongoing research.

BRIEF HISTORY OF CHELATION BEFORE THE TRIAL TO ASSESS CHELATION THERAPY

Chelation, etymologically from *chelos,* the Greek word meaning claw, refers to the pincer like manner in which cations are incorporated into an organic molecule referred to as a chelating agent, forming a complex ring structure. The chelate–chelator complex is usually more stable, soluble and resistant to dissociation, allowing for effective removal from tissue and excretion in the urine or in bile [4].

A nearly ideal chelator, edetate is a synthetic amino acid with high affinity for metallic and non-metallic cations. EDTA is water soluble and excreted in the urine, forming strong coordinate bonds with certain ions such as calcium, zinc, cadmium and lead [5]. It was first developed in Germany in the late 1930s for chelation of calcium stains from textiles, and later applied to the treatment of heavy metal poisoning and hypercalcemia. The strong bond of EDTA with calcium led early proponents to hypothesize that it might reduce the calcium burden of atheromatous plaque [6,7].

In 1956, Clarke *et al.* [8] described the first use of chelation therapy and showed that 19 out of 20 patients with severe angina had improvement of symptoms and/or electrocardiographic findings after edetate disodium chelation infusions. The beneficial effects reported in this small study were followed by other small case reports and case series that failed to corroborate the efficacy of chelation in treating atherosclerosis. By the 1970s, chelation

therapy had firmly moved into the realm of complementary and alternative medicine (CAM). Clinical trials were eventually performed, but were too small individually or in aggregate to exclude a small-to-moderate beneficial effect [9–13]. Yet over the decades, patients continued to seek and receive chelation from practitioners. Owing to the unsupported use of chelation, the NIH released a Request for Applications (RFAs) in 2001 for a safety and efficacy clinical trial of edetate disodium chelation in cardiovascular disease. The Trial to Assess Chelation Therapy (TACT) was the result. The positive results in patients with diabetes suggest that toxic metals may have a role in the excess atherosclerotic risk of such patients. In order to better understand the TACT results, it is worthwhile; therefore, to consider the epidemiological and mechanistic links between toxic metals and atherosclerosis.

TOXIC METALS AND VASCULAR DISEASE MECHANISMS AND EVIDENCE

Essential metals are crucial in maintaining cellular homeostasis, but excessive exposure may lead to metal-induced toxicity by increasing production of reactive oxygen species (ROS). ROS can overwhelm and deplete the cell's intrinsic antioxidant defenses leading to oxidative stress. Iron and copper are the two best-known metals that have the potential of generating ROS. They are both effectively chelated by the edetates. Other metals, referred to as xenobiotic or toxic metals, have no role in human physiology and, like lead, may be toxic even in dilute concentrations. Some of the most commonly found toxic metals in humans include lead, cadmium, arsenic, and mercury, all of which cause – or at the very least are associated with – CVD.

Diabetes-related macrovascular complications, particularly CVD, have been found to be mediated by advanced glycation end products (AGEs), advanced lipoxygenation end products (ALEs), and protein oxidation products (PrOPs) [14]. AGEs are heterogeneous cross-linked complexes formed by the nonenzymatic glycation and oxidation of aldose sugars with proteins, lipids and nucleic acids [15]. There is also convincing evidence that formation of chemically active, cross-linked aldose sugars requires metal catalyzed oxygen chemistry to produce oxygen and hydroxyl radicals. AGEs have a deleterious effect on the integrity of the vessel walls through several mechanisms, including activation of the receptor for AGE (RAGE) [16]. RAGE activation triggers rapid generation of ROS and a pro-inflammatory signaling cascade with expression of pro-atherogenic adhesion molecules [17]. This interaction between AGE and its receptor perpetuates chronic vascular injury, which may play a role in the progression of diabetic atherosclerosis. These reactions may require metals that donate or accept electrons, in order to create oxygen and hydroxyl-free radicals. There is abundant evidence linking toxic metal accumulation and CVD [18–24]. We restrict our discussion below to lead and cadmium because of their effective chelation by the edetates.

Lead is a toxic metal found in contaminated water, air, food and soil because of its nonbiodegradable nature and continuous use. Human exposure to lead occurs mainly through leaded gasoline still used in piston engine aircraft, lead-containing pipes, smelting of lead and its combustion, lead-based paints and battery recycling (Fig. 2) [25]. Over the past three decades, there has been a dramatic drop in mean lead blood levels in the United

States because of banning lead-based paints and leaded gasoline used by ground vehicles. However, environmental exposure continues, as evident in the recent public health crisis in Flint, Michigan because of lead seepage into drinking water. Lead contamination of drinking water is typically caused by metal corrosion of water pipes, particularly lead service lines. The incidence of elevated blood lead levels after the city of Flint changed its water source to the Flint River increased from 2.4 to 4.9% ($P < 0.05$) [26]. Lead can be inhaled or ingested, and then absorbed into the bloodstream [27]. Once absorbed, lead moves into the red cell compartment, where it is bound by metallothionein-like protein, a thiol-containing protein. Lead has a half-life of about 28–36 days in blood, 1–1.5 months in soft tissue, and about 25–30 years in bone [28–29]. When lead completes its lifespan in blood, it is released and displaces calcium in bone. Bone then acts as an endogenous source of lead, releasing lead back into the bloodstream years after exposure [29]. A single disodium edetate infusion of 3 g will increase lead excretion by nearly 4000% in a few hours [30,31■].

Epidemiological data from various National Health and Nutrition Examination Surveys (NHANES) support an association between toxic metal exposure and CVD events. The prospective analysis of NHANES III participants showed an increase in all-cause and cardiovascular mortality, with cause specific deaths highest for myocardial infarction and stroke at lead blood levels greater than 0.10 μmol/l [32,33]. Several possible mechanisms have been postulated for the association of lead accumulation and its direct and indirect effect on CVD. In-vivo and in-vitro studies have shown that one mechanism by which chronic lead exposure causes CVD is by increasing production of ROS leading to oxidative stress, limiting nitric oxideavailability and disrupting the nitric oxide signaling cascade [34–37]. Nitric oxide has important cardioprotective roles including regulation of blood pressure and vascular homeostasis such as regulation of vascular dilation, local cell growth and protection of the vessel from injury because of platelet aggregation. Therefore, the impaired synthesis or excessive oxidative degradation of nitric oxide leads to endothelial dysfunction, a starting point for atherosclerosis.

Lead increases protein kinase C (PKC) activity and promotes atherogenicity [38,39]. PKC regulates many functions including cell growth, vascular smooth muscle contraction, blood flow and permeability [39]. Lead additionally promotes inflammation, fibrosis and apoptosis via activation of nuclear factor-κB. Lead also increases the production of endothelin, vasoconstrictor peptides primarily synthesized and secreted by endothelial cells that can raise arterial pressure. Khalil-Manesh *et al.* [40] found that rats exposed to low levels of lead for 1–12 months had a significant rise in arterial pressure and marked increase in plasma endothelin 3 concentrations. These and other proposed mechanisms may explain how lead causes vascular injury in humans. If more than one of these mechanisms is relevant to human diabetes, then lead may act as a risk factor multiplier, perhaps at least partially explaining the effect of lead chelation.

Cadmium is another toxic metal that accumulates in the environment and is associated with atherosclerotic disease. Environmental sources of cadmium include rechargeable batteries, electronics, building construction, jewelry, toys, plastic production, paint pigments and metal coating [41–43]. Tobacco leaves, spinach and root vegetables naturally accumulate and concentrate high levels of cadmium from the soil, dependent on the cadmium content of

fertilizers. Tobacco use, therefore, is one of the single most important sources of cadmium exposure [44]. Cadmium accumulates in both the liver and kidneys, protein bound to metallothionein [45,46]. Because of its slow urinary excretion, cadmium has a half-life up to 38 years [41]. A single disodium edetate infusion of 3 g will increase cadmium excretion by about 700% in a few hours [30,31■].

Similar to lead, there are several mechanisms that have been suggested to explain the role of cadmium in atherosclerosis. In a systematic review, Tellez-Plaza *et al.* [47] found evidence supporting cadmium as a cardiovascular risk factor. Cadmium can indirectly interfere with antioxidant response by binding to metalloproteins, thereby increasing ROS causing lipid peroxidation and cellular injury and DNA damage [48]. The Atherosclerosis Risk Factors in Female Youngsters study examined carotid intima–media thickness in 195 young healthy women and measured serum metal concentrations, including cadmium. They reported an independent association between high cadmium levels and intima–media thickness, exceeding the 90th percentile in distribution, representing early atherosclerotic vessel wall thickening [49]. Cadmium has also been found to raise blood pressure, an established risk factor for cardiovascular disease [50,51]. In a large population study of NHANES III participants between 1988 and 1994, creatinine-corrected urinary cadmium levels in men were associated with an increase in risk of all-cause and cardiovascular mortality, including coronary artery disease-associated mortality [52]. Finally, Tellez-Plaza *et al.* [53■] examined 3348 American Indian adults ages 45–74 years who participated in the Strong Heart Study from 1989 to 1991 and measured urine cadmium levels. Urine cadmium levels were associated with an increased incidence of cardiovascular disease and mortality. The diabetic subgroup in this study showed a stronger, statistically significant association between cadmium and cardiovascular disease endpoints when compared with those without diabetes.

THE TRIAL TO ASSESS CHELATION THERAPY

Coincident with the interest of the diabetes scientific community in metal-catalyzed oxygen chemistry as an important part of the formation of AGEs and complications of diabetes, the cardiology community was in the final phases of planning a metal chelation trial. As noted above, edetate disodium chelation had been used to treat atherosclerotic complications for many years. A literature review in 2000 concluded that there was insufficient evidence for or against the practice [12]. This was followed by a more formal 2002 Cochrane Review again concluding that there was insufficient evidence to decide on the effectiveness of edetate sodium to treat atherosclerotic disease [13]. This conclusion sparked the interest of the NIH to release a RAF for a randomized double-blind, placebo-controlled trial to test the efficacy and safety of chelation therapy in patients with coronary artery disease. The study that resulted, TACT, was widely expected to be negative. During the planning phase, high-dose oral multivitamins and minerals (OMVM) were added in a factorial design, as most chelation practitioners also recommended that patients take large doses of OMVM during intravenous chelation [1]. The four randomized groups in the 2×2 factorial trial included:

1. active chelation and active OMVM

2. active chelation and placebo OMVM

3. placebo chelation and active OMVM

4. placebo chelation and placebo OMVM

Eligible patients had to be at least 50 years of age, have had prior myocardial infarction at least 6 weeks prior to enrollment, and have a serum creatinine level 2.0 mg/dl or less. Enrollment took place between 2003 and 2010. There were 1708 patients enrolled in the clinical trial across 134 sites in the United States and Canada. The blind was broken and analyses were completed, in 2012.

STUDY TREATMENTS

Intravenous chelation regimens developed organically through the years, and although the consistent chelating drug was edetate disodium, other components were often added (Table 1). The TACT infusion regimen included 30 weekly infusions followed by 10 maintenance infusions, the latter 2 weeks to 2 months apart. By 18 months after randomization, over 90% of the infusions had been administered. The randomized OMVM or oral placebo was taken throughout the duration of the trial and consisted of three caplets twice daily, containing 28 individual components (Table 2).

ENDPOINTS AND STATISTICAL POWER

The primary end point was a composite of all-cause mortality, myocardial infarction, stroke, coronary revascularization and hospitalization for angina. The principal secondary end point was cardiovascular mortality, recurrent myocardial infarction and stroke.

OVERALL RESULTS

The intention-to-treat analyses revealed a statistically significant reduction in the primary endpoint (hazard ratio 0.82; 95% CI 0.69–0.99; $P = 0.035$). Although the individual components of the primary endpoint did not reach statistical significance, all but total mortality had point estimates favoring active chelation treatments.

TRIAL TO ASSESS CHELATION THERAPY DIABETES SUBGROUP

Patients with diabetes were defined as those who self-reported diabetes, were receiving pharmacotherapy for diabetes, or had a fasting glucose of at least 126 mg/dl at baseline. Of the 1708 participants enrolled in the study, 633 (37.1%) patients had diabetes mellitus.

BASELINE CHARACTERISTICS

Among the patients with diabetes, 322 were randomized to receive edetate disodium-based infusions and 311 received placebo infusions. There were no significant between-group differences in important baseline characteristics. The median age was 65 years, with 19% women and 11% minorities. The trial encouraged patients to maintain standard, evidence-based treatments for patients with prior MI and diabetes.

Mean fasting blood sugar was 132 mg/dl, and low-density lipoprotein (LDL) cholesterol was 81 mg/dl. Within the diabetic population, 81% had undergone prior coronary revascularization (either percutaneous or surgical). There were 92% of patients on aspirin, clopidogrel or warfarin, and 76% on statins. Treatment of diabetes required insulin in 26%, and oral hypoglycemics in 61%.

RESULTS OF TRIAL TO ASSESS CHELATION THERAPY IN PATIENTS WITH DIABETES

In spite of the arduous nature of the study therapy, 73% of patients completed 30 infusions, and 61% completed all 40. There was a statistically significant interaction (*P* of interaction of the primary endpoint = 0.004) between edetate disodium therapy effect and the presence of diabetes mellitus at baseline. There was a striking benefit of the edetate disodium infusions in the diabetic patients randomly assigned to receive active infusions compared with placebo with 25% vs. 38% incidence of the primary outcome (hazard ratio 0.59; 95% CI 0.44–0.79; *P* = 0.0002). There was a 15% absolute decrease in the 5-year Kaplan–Meier primary event rate. The number of patients that needed to be treated to prevent a single event over 5 years was 6.5 (Fig. 1b). The prespecified major secondary end point, cardiovascular death, recurrent myocardial infarction or stroke, was also reduced in those randomized to the active chelation treatment, with a 40% relative risk reduction (hazard ratio 0.60; 95% CI 0.39–0.91; *P* = 0.017). Patients with diabetes randomized to EDTA chelation treatment had a reduction in recurrent MI (hazard ratio 0.60; 0.48; 95% CI 0.26–0.88; *P* = 0.015) (Fig. 1c), all-cause mortality (hazard ratio 0.57; 95% CI 0.36–0.88; *P* = 0.011; Fig. 1d), and coronary revascularization (hazard ratio 0.68; 95% CI 0.47–0.99; *P* = 0.042; Table 3). When compared with diabetic patients, the patients without diabetes did not have this treatment effect in primary or secondary event outcomes. In patients with diabetes, the Kaplan–Meier curves continued to separate after infusions were completed, a legacy effect unlike most in cardiology, and perhaps supporting the beneficial effect of toxic metal removal by EDTA.

DISCUSSION

In the United States, 23.3 million people have diabetes mellitus [54]. Another 7.2 million are estimated to have undiagnosed diabetes. Diabetes is a key risk factor for cardiovascular disease with a two-fold to three-fold increased likelihood of vascular death. The cause of this excess cardiovascular morbidity and mortality is not completely clear, but the results of TACT inevitably point to mechanistic speculation. The chelation infusion did not treat hyperglycemia. In TACT, there were no differences in mean fasting blood glucose levels from baseline to the 30th infusion in neither the placebo nor the active chelation groups. There were no differences in pharmacotherapy for diabetes between the treatment groups throughout the study. This evidence suggests that although hyperglycemia, the hallmark of diabetes, is a risk factor for cardiovascular disease, it is clearly not the only modifiable risk factor in diabetic patients.

CONCLUSION

Edetate disodium chelation, far from standard therapy, is currently a Class 2B indication in the Stable Ischemic Heart Disease Guidelines [55]. As such, the results of TACT require replication and mechanistic investigation. With this in mind, NIH (NCCIH, NHLBI, NIDDK, NIEHS) has funded the second Trial to Assess Chelation Therapy, TACT2. TACT2 will have identical inclusion criteria as TACT, with the exception of including only diabetic patients post-MI.

TACT2 is currently enrolling with a target sample size of 1200 post-MI diabetic patients. We welcome potentially interested sites, investigators and patients to contact us for more details, or log on to www.tact2.org.

Acknowledgments

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KEY POINTS

- TACT showed a marked reduction in CVD events and all-cause mortality in the subgroup of patients with diabetes.

- The results may support the concept that metal chelation reduces metal-catalyzed oxidation reactions that promote the formation of advanced glycation end products.

- TACT2, in diabetic post-MI patients, is currently enrolling patients in an effort to replicate these findings, and define a mechanism of benefit.
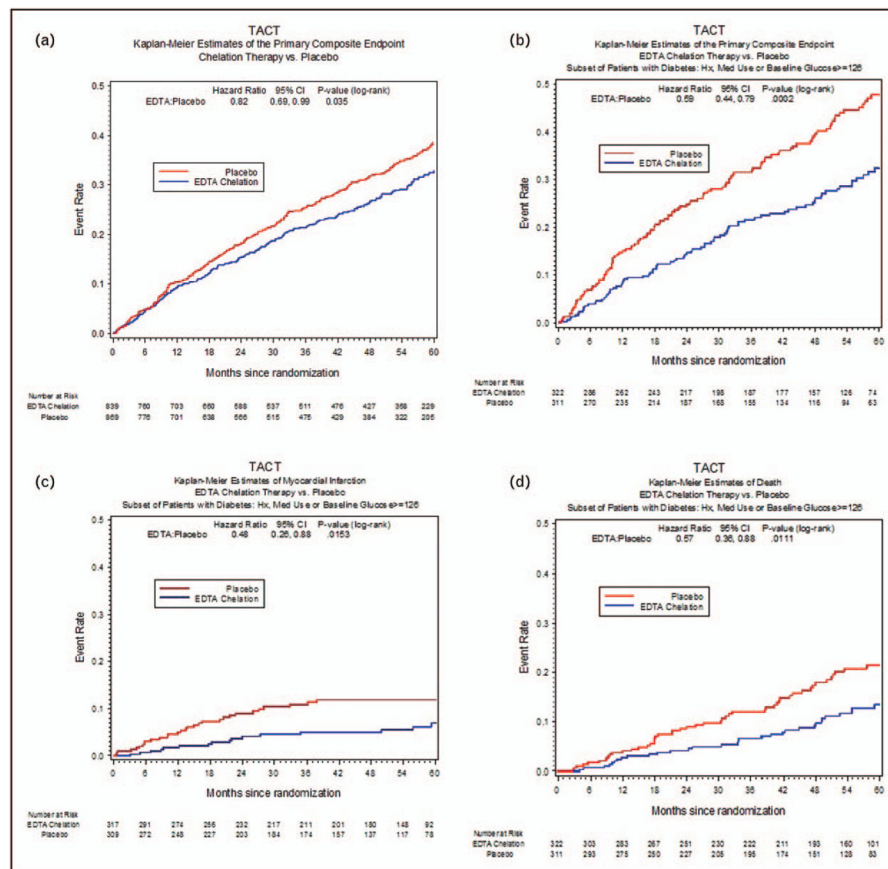
FIGURE 1.

The Trial to Assess Chelation Therapy Kaplan–Meier estimates of the primary composite endpoint: edetate disodium (EDTA) chelation therapy versus placebo (a), primary composite end point: edetate disodium chelation therapy versus placebo, subset of patients with diabetes mellitus (b), myocardial infarction in patients with diabetes mellitus by infusion group (c), mortality in patient with diabetes mellitus by infusion group (d). CI, confidence interval; TACT, Trial to Assess Chelation Therapy.
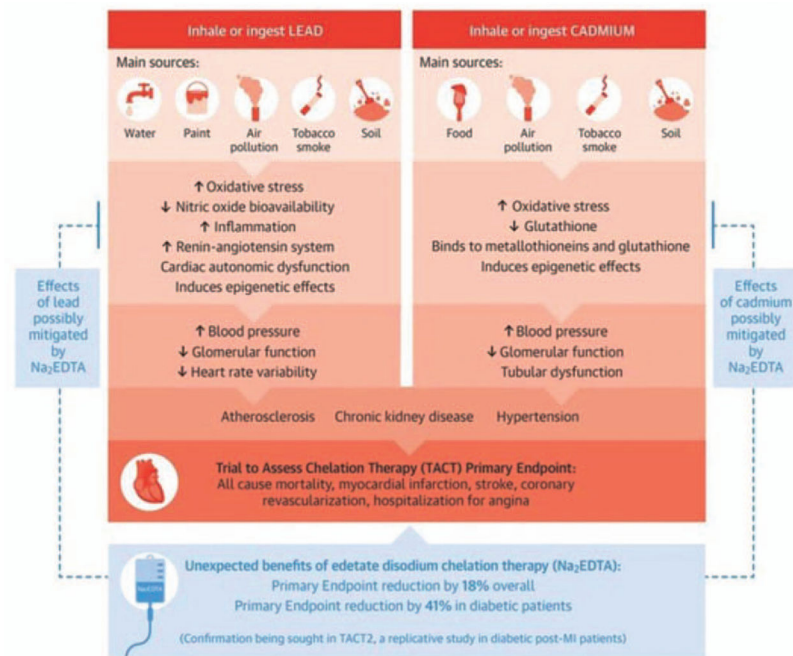
FIGURE 2.
Central illustration. Heavy metals as a risk factor for atherosclerotic cardiovascular disease and the benefits of chelation therapy. Major sources and routes of exposure, mechanisms at the molecular and cellular level, responses at the tissue and organ level, and subclinical and clinical cardiovascular effects on the basis of experimental and epidemiological evidence are shown for lead and cadmium. Arrows denote direction of flow. Na_2EDTA, disodium ethylene diamine tetra acid; NO, nitric oxide; TACT, Trial to Assess Chelation Therapy.

Table 1

The Trial to Assess Chelation Therapy chelation components

Up to 3 g of disodium EDTA[a]
2 g of magnesium chloride
100 mg of procaine HCl
2500 U of heparin
7 g of ascorbate
2 mEq KCl
840 mg sodium bicarbonate
250 mg pantothenic acid
100 mg of thiamine
100 mg of pyridoxine
Add with sterile water to 500 ml

[a]The maximum dose of EDTA was 3 g for patients who have at least 60 kg of lean body weight and normal kidney function. Reduction in kidney function and/or lower lean body weight led to a reduction in the total EDTA dose infused.

Table 2

High-dose oral contents used in TACT

High-dose regimen (taken twice daily)	Total amount for 6 pills	% RDA
Vitamin A	25 000 IU	500%
Vitamin C	1200 mg	2000%
Vitamin D3	100 IU	25%
Vitamin E	400 IU	1333%
Vitamin K1	60 μg	75%
Thiamin	100 mg	6667%
Niacin	200 mg	1000%
Vitamin B6	50 mg	2500%
Folate	800 μg	200%
Vitamin B12	100 μg	1667%
Biotin	300 μg	100%
Pantothenic acid	400 mg	4000%
Calcium	500 mg	50%
Iodine	150 μg	100%
Magnesium	500 mg	125%
Zinc	20 mg	133%
Selenium	200 μg	286%
Copper	2 mg	100%
Manganese	20 mg	400%
Chromium	200 μg	167%
Molybdenum	150 μg	200%
Potassium	99 mg	3%
Choline	150 mg	[a]
Inositol	50 mg	[a]
PABA (para-aminobenzoic acid)	50 mg	[a]
Boron	2 mg	[a]
Vanadium	39 μg	[a]
Citrus bioflavanoids	100 mg	[a]

RDA, recommended daily allowance.

[a] Recommended daily allowance not established. Other ingredients: croscarmellose sodium, microcrystalline cellulose, magnesium stearate, hydroxypropyl cellulose, and silicon dioxide.

Table 3

Clinical end points by infusion arms for patients with diabetes mellitus in TACT

End point	EDTA chelation (*n* = 322)	Placebo (*n* = 311)	Hazard ratio (95% CI)	*P* value
Primary end point	80 (25%)	117 (38%)	0.59 (0.44–0.79)	< 0.001
Death	32 (10%)	50 (16%)	0.57 (0.36–0.88)	0.011
MI	16 (5o/o)	30 (10%)	0.48 (0.26–0.88)	0.015
Stroke	4 (1o/o)	3 (1%)	1.19 (0.27–5.30)	0.829
Coronary	48 (15%)	62 (20%)	0.68 (0.48–0.99)	0.042
Revascularization				
Hospitalization for angina	5 (2%)	6 (2%)	0.72 (0.22–2.36)	0.588
Secondary end point	35 (11%)	52 (17%)	0.60 (0.39–0.91)	0.017
Cardiovascular death	19 (6%)	27 (9%)	0.63 (0.35–1.13)	0.118

CI, confidence interval; MI, myocardial infarction.