Effect of Disodium EDTA Chelation Regimen on Cardiovascular Events in Patients With Previous Myocardial Infarction

The TACT Randomized Trial

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Importance Chelation therapy with disodium EDTA has been used for more than 50 years to treat atherosclerosis without proof of efficacy.

Objective To determine if an EDTA-based chelation regimen reduces cardiovascular events.

Design, Setting, and Participants Double-blind, placebo-controlled, 2x2 factorial randomized trial enrolling 1708 patients aged 50 years or older who had experienced a myocardial infarction (MI) at least 6 weeks prior and had serum creatinine levels of 2.0 mg/dL or less. Participants were recruited at 134 US and Canadian sites. Enrollment began in September 2003 and follow-up took place until October 2011 (median, 55 months). Two hundred eighty-nine patients (17% of total; n=115 in the EDTA group and n=174 in the placebo group) withdrew consent during the trial.

Interventions Patients were randomized to receive 40 infusions of a 500-mL chelation solution (3 g of disodium EDTA, 7 g of ascorbate, B vitamins, electrolytes, procaine, and heparin) (n=839) vs placebo (n=869) and an oral vitamin-mineral regimen vs an oral placebo. Infusions were administered weekly for 30 weeks, followed by 10 infusions 2 to 8 weeks apart. Fifteen percent discontinued infusions (n=38 [16%] in the chelation group and n=41 [15%] in the placebo group) because of adverse events.

Main Outcome Measures The prespecified primary end point was a composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina. This report describes the intention-to-treat comparison of EDTA chelation vs placebo. To account for multiple interim analyses, the significance threshold required at the final analysis was $P=.036$.

Results Qualifying previous MIs occurred a median of 4.6 years before enrollment. Median age was 65 years, 18% were female, 9% were nonwhite, and 31% were diabetic. The primary end point occurred in 222 (26%) of the chelation group and 261 (30%) of the placebo group (hazard ratio [HR], 0.82 [95% CI, 0.69-0.99]; $P=.035$). There was no effect on total mortality (chelation: 87 deaths [10%]; placebo, 93 deaths [11%]; HR, 0.93 [95% CI, 0.70-1.25]; $P=.64$), but the study was not powered for this comparison. The effect of EDTA chelation on the components of the primary end point other than death was of similar magnitude as its overall effect (MI: chelation, 6%; placebo, 8%; HR, 0.77 [95% CI, 0.54-1.11]; stroke: chelation, 1.2%; placebo, 1.5%; HR, 0.77 [95% CI, 0.34-1.76]; coronary revascularization: chelation, 15%; placebo, 18%; HR, 0.81 [95% CI, 0.64-1.02]; hospitalization for angina: chelation, 1.6%; placebo, 2.1%; HR, 0.72 [95% CI, 0.35-1.47]). Sensitivity analyses examining the effect of patient dropout and treatment adherence did not alter the results.

Conclusions and Relevance Among stable patients with a history of MI, use of an intravenous chelation regimen with disodium EDTA, compared with placebo, modestly reduced the risk of adverse cardiovascular outcomes, many of which were revascularization procedures. These results provide evidence to guide further research but are not sufficient to support the routine use of chelation therapy for treatment of patients who have had an MI.

Trial Registration clinicaltrials.gov Identifier: NCT00044213

JAMA. 2013;309(12):1241-1250 www.jama.com

TREATMENT OF LEAD TOXICITY with chelation was first reported with EDTA in the early 1950s.[1] Apparent success in reducing metastatic calcium deposits[2] led Clarke et al[3] in 1956 to treat angina patients with EDTA, and others to use chelation for various forms of atherosclerotic disease.[4-6] Chelation therapy evolved to constitute infusions of vitamins and disodium EDTA, a drug that binds divalent and some trivalent cations, including calcium, magnesium, lead, cadmium, zinc, iron, aluminum, and copper, facilitating their urinary excretion.[7,8]

Over the next decades, based on favorable anecdotal and case report experience, chelation practitioners increased their use of EDTA for coronary and peripheral artery disease. The 2007 National Health Statistics Report compared chelation use since 2002 and noted

For editorial comment see pp 1291 and 1293.

Author Video Interview available at www.jama.com.

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A complete list of the TACT Investigators appears in the eAppendix.

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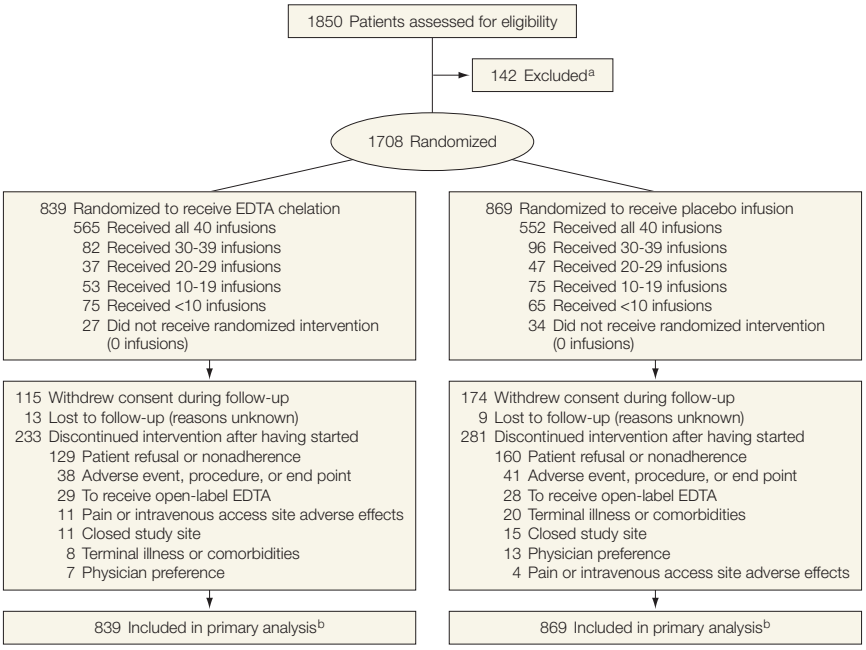
Figure 1. Participant Flow



[a] Screened patients not randomized because of inclusion/exclusion criteria, unwillingness to participate, or other reasons. Reasons for exclusions were not stored.
[b] All patients were included in the primary "time to event" analysis for the duration of their follow-up, including patients who withdrew consent or were lost to follow-up.

an increase of 68%, from 66 000 to 111 000 adults using chelation therapy,[9] although the indications for therapy were not clearly defined, and the prevalence of use of chelation therapy for cardiovascular disease is unknown.

Three small clinical trials have assessed the effects of chelation on surrogate outcomes, such as walking distance in patients with claudication (2 trials with 185 patients total) and time to exercise-induced ischemia in patients with coronary disease (1 trial with 84 patients). These studies did not find any evidence of treatment efficacy but were underpowered for evaluation of clinical events.[10-12] As a consequence, mainstream medical organizations consider the therapeutic value of chelation for atherosclerotic vascular disease unproven[13] and the use of this therapy potentially dangerous. Disodium EDTA, particularly when infused too rapidly, may cause hypocalcemia and death.[14] The Trial to Assess Chelation Therapy (TACT) was conducted to respond to the public health problem posed by EDTA chelation therapy: large numbers of patients being exposed to undefined risks for unproven benefits.

METHODS

Overview

TACT was a double-blind 2×2 factorial trial: patients were randomized to receive 40 infusions of disodium EDTA chelation or placebo and additionally to an oral high-dose vitamin and mineral regimen or placebo. Details of the study protocol have been published.[15] This report describes the results of the EDTA chelation vs placebo comparison (FIGURE 1).

The National Heart, Lung, and Blood Institute (NHLBI) and the National Center for Complementary and Alternative Medicine (NCCAM) provided sponsorship and oversight. The US Food and Drug Administration (FDA) approved an Investigational New Drug application for disodium EDTA for coronary artery disease. A data and safety monitoring board (DSMB), appointed by NCCAM (the primary institute at the time) and approved by directors of both sponsoring institutes, monitored patient safety, treatment effects, and the conduct of the trial. Institutional review boards approved the final protocol and provided ongoing oversight. All patients provided written informed consent. The Duke Clinical Research Institute (DCRI) performed data management and statistical analyses.

Study Population

Eligible patients were at least 50 years old and had experienced a myocardial infarction (MI) 6 weeks or more prior to enrollment. Patients were ineligible if they were women of childbearing potential, had a serum creatinine level greater than 2.0 mg/dL, platelet count less than 100 000/uL, abnormal liver function studies, blood pressure greater than 160/100 mm Hg, past intolerance to the chelation or vitamin components, chelation therapy within 5 years, coronary or carotid revascularization planned or having taken place within 6 months, cigarette smoking within 3 months, active heart failure or heart failure hospitalization within 6 months, or inability to tolerate 500-mL infusions weekly.[15] Patients were enrolled at 134 sites, of which 81 (60%) were sites in which chelation therapy was already practiced. Race and ethnicity were self-reported and collected as required in federally funded trials.

Treatment

The refrigerated blinded active chelation solution was prepared by a central pharmacy with the ascorbate and EDTA in 2 separate syringes and shipped to arrive at the sites within 48 hours of preparation. Placebo infusions were shipped with identical packaging and 2 separate placebo syringes. Following mixing, the sites were instructed to infuse within 24 hours. The active, 10-component chelation solution was selected to most closely match the standard solution used by chela-

tion practitioners[16] and consisted of up to 3 g of disodium EDTA, adjusted downward based on estimated glomerular filtration rate; 7 g of ascorbic acid; 2 g of magnesium chloride; 100 mg of procaine hydrochloride; 2500 U of unfractionated heparin; 2 mEq of potassium chloride; 840 mg of sodium bicarbonate; 250 mg of pantothenic acid; 100 mg of thiamine; 100 mg of pyridoxine; and sterile water to make up 500 mL of solution. The identical-appearing placebo solution consisted of 500 mL of normal saline and 1.2% dextrose (2.5 g total).

The chelation or placebo infusions were administered through a peripheral intravenous line, weekly for the first 30 infusions, followed by an additional 10 infusions 2 to 8 weeks apart. Infusions were administered over at least 3 hours unless serum calcium corrected for albumin concentration was between 8.0 and 8.5 mg/dL or the patient was unable to tolerate the 3-hour infusion because of heart failure. In those cases, the infusions were administered more slowly. During the infusion phase of the trial, all study patients, including those randomized to placebo infusions, received a daily low-dose vitamin regimen consisting of vitamin B_6, 25 mg; zinc, 25 mg; copper, 2 mg; manganese, 15 mg; and chromium, 50 ug, to prevent potential depletion by the chelation regimen. Investigators were trained in and monitored for the use of evidence-based post-MI therapy.

Follow-up

Study follow-up for clinical events began at randomization. Patients were seen at baseline and at each of the 40 infusion visits. Following the infusion phase, patients were telephoned quarterly, attended annual clinic visits, and were seen at the end of the trial or at the 5-year follow-up, whichever was first. Patient follow-up continued without censoring if a nonfatal end point occurred.

Safety

Safety monitoring included periodic physical examinations and laboratory assessments. These included glucose, calcium, renal function, hepatic function, and hematologic parameters. Patients had body weight assessed prior to infusions to determine whether there was fluid retention. Infusions were delayed until specific abnormal physical or laboratory findings resolved. Rapid infusions were reported electronically to the coordinating centers. A medical monitor at the DCRI who was masked to patient treatment assignment reviewed deaths and unexpected serious adverse events.

End Points

The primary end point was a composite of death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina. The composite of cardiovascular death, reinfarction, or stroke was a prespecified secondary end point. A blinded independent clinical events committee at Brigham and Women's Hospital adjudicated all nonprocedural components of the primary end point. The occurrence of coronary revascularizations was verified from the source medical record by the DCRI.

Prespecified Subgroups

TACT prespecified several subgroups for analyses based on assessing underrepresented populations (women and minorities), elderly persons (aged >70 years), high-risk patients (MI location, diabetes, and metabolic syndrome), and other subgroups of interest (time from index MI to trial enrollment, patients in whom statin therapy was not being used). We also assessed any interaction of the infu-sion therapy with the oral high-dose vi-tamin and mineral component of the factorial trial and with the type of en-rolling site (chelation practice vs not a chelation practice).

Statistical Analysis

TACT originally planned to enroll 2372 patients over 3 years with a minimum follow-up of 1 year. This number provided 85% power for detecting a 25% relative reduction in the primary end point, assuming a 2.5-year event rate in the placebo group of 20% and a level of significance of .05. In July 2009, continued difficulties in recruitment of patients led the blinded investigators to request approval from the DSMB for a reduction of total enrollment to 1700, with a compensatory extension in the length of follow-up to maintain the same level of unconditional statistical power as described above for the original sample of 2372 patients. The DSMB approved the request, and 1708 patients were randomized. The follow-up period for the trial closed October 31, 2011, approximately 1 year after the last patient was enrolled (see eAppendix for additional details; available at http://www.jama.com).

Secure web-based randomization was performed using permuted blocks stratified by clinical site. Time 0 was defined as the time of randomization. Treatment comparisons were performed according to the intention-to-treat principle and included all patients in the group to which they were randomized and all follow-up information that was available on each patient. Patients who withdrew consent or were lost to follow-up were included in the analysis with as much follow-up (person-time) as was available until they withdrew or were lost, including any events that occurred prior to their becoming lost or withdrawing from the study. The log-rank test[17] was used for the statistical comparison of treatment. Although patients could experience more than 1 component of the primary and secondary end points, each patient was counted only once in the analysis using the time until the occurrence of their first event. All treatment comparisons were performed using 2-sided significance tests.

Cumulative event rates were calculated according to the Kaplan-Meier method.[18] Relative risks were expressed as hazard ratios (HRs) with associated 95% confidence intervals and were calculated using the Cox proportional hazards model.[19] The Cox model was also used to assess the consistency of treatment effects by testing for

interactions between treatment and the baseline characteristics prespecified for subgroup analyses as detailed in the previous section. Continuous variables are expressed as medians and interquartile ranges (IQRs) unless otherwise specified. Final statistical analyses were performed using SAS software, versions 8.2 and 9.2 (SAS Institute Inc).

Over the prolonged duration of the trial, the DSMB requested 11 interim analyses of the data. Interim treatment comparisons for the primary end point were monitored with the use of 2-sided symmetric O'Brien-Fleming–like boundaries generated with the Lan-DeMets α spending function approach to group-sequential testing.[20,21] The monitoring boundaries were based on an overall α=.05. Because of the sequential monitoring, the level of significance required for the primary 2-sided analysis at the completion of the study was $P<.036$ (eTable 1).

The primary treatment comparisons were performed without any imputation of outcomes in the patients for whom we did not have complete follow-up because of consent withdrawal or loss to follow-up. However, to assess the robustness of study findings, post hoc sensitivity analyses were performed with imputation of missing outcome data. These analyses incorporated event rate assumptions for withdrawn or lost patients in the placebo group that ranged from 10% to 30%. The differential event rate among withdrawn or lost patients in the chelation group was varied from 10% lower, or slightly favorable to chelation, to 25% higher, or moderately unfavorable to chelation. Using imputed event data among the withdrawn/lost patients combined with the actual follow-up data for all other patients, the treatments were then compared with respect to the primary end point. For each different event rate scenario, multiple replications (500) were performed and the results averaged to obtain the HR and confidence interval.

RESULTS

Between September 10, 2003, and October 4, 2010, 1708 patients were randomized, 839 patients to chelation, and 869 patients to placebo. The last infusion was administered on September 3, 2011, and the last follow-up visit completed on October 31, 2011. The median duration of follow-up was 55 (IQR, 26-60) months overall. Active treatment patients were followed up for 56 (IQR, 28-60) months and placebo patients were followed up for 53 (IQR, 24-60) months. The median time from randomization to first infusion was 8 (IQR, 6-12) days overall (8 [IQR, 6-12] days in the chelation group and 7 [IQR, 6-12] days in the placebo group).

Baseline Characteristics

Baseline characteristics were similar between treatment groups (TABLE 1). The median age was 65 (IQR, 59-72) years, 18% were women, 9% were minority, and the median body mass index was 30. The qualifying MI had occurred a median of 4.6 (IQR, 1.6-9.2) years prior to enrollment. The study population had a high prevalence of diabetes (31%), prior coronary revascularizations (83%), and guideline-recommended medication use of aspirin (84%), β-blockers (72%), and statins (73%). Patients had a median fasting glucose level of 102 (IQR, 92-121) mg/dL and a low-density lipoprotein cholesterol (LDL-C) level of 89 (IQR, 67-115) mg/dL.

Treatment Adherence

Patients received a total of 55 222 infusions. The median number of infusions received was 40 (IQR, 30-40); 76% of patients completed at least 30 infusions and 65% completed all 40 infusions, 30% discontinued study infusions (n=233 [28%] in the chelation group and n=281 [32%] in the placebo group), and 5% died or the study ended before infusions could be completed (n=41 [5%] in the chelation group and n=36 [4%] in the placebo group). Fifteen percent discontinued infusions (n=38 [16%] in the chelation group and n=41 [15%] in the placebo group) because of adverse events. The most common reason for discontinuation was patient refusal to continue treatment. There were a total of 289 patients (17% of total; n=115 in the chelation group and n=174 in the placebo group) who, during the course of the trial, withdrew consent for continued follow-up in the study. A plot of Kaplan-Meier curves depicting the pattern of consent withdrawals in the 2 randomized groups is presented in eFigure 1. An additional 22 patients were lost to follow-up (13 in the chelation group and 9 in the placebo group). With an average of approximately 3 years of follow-up in these patients, the loss of information was less than the loss among patients who withdrew consent (see eFigure 2, eFigure 3, eTable 2, and eTable 3 for additional details and analyses).

Outcome Events

The Kaplan-Meier 5-year estimates for the primary end point were 32.8% (95% CI, 29.1%-36.5%) in the chelation group and 38.5% (95% CI, 34.6%-42.3%) in the placebo group (HR, 0.82; 95% CI, 0.69-0.99; $P=.035$) (FIGURE 2). Although treatment comparisons of the components of the primary end point were not individually significant, point estimates for the relative treatment effects (HRs from 0.72 to 0.81) were larger than that for the primary end point for all components except death (HR, 0.93) (TABLE 2). Revascularizations accounted for 45% of primary end point events; nonrevascularization events accounted for the other 55%. The composite of cardiovascular death, nonfatal MI, or nonfatal stroke occurred in 96 chelation patients (11%) and 113 placebo patients (13%) (HR, 0.84; 95% CI, 0.64-1.11; $P=.22$).

Subgroup Analyses

Prespecified tests for treatment by covariate interactions (FIGURE 3) indicated statistically greater benefit in 2 subgroups: patients with prior anterior MI and those with diabetes (FIGURE 4). There was no significant interaction between treatment and

type of enrolling practice (chelation site vs nonchelation, *P*=.28 for interaction) or between the high-dose oral vitamins and chelation therapy in the factorial design (*P*=.94 for interaction) (eTable 4).

Adverse Effects and Safety

Four unexpected severe adverse events occurred that were possibly or definitely attributed to study therapy, 2 in the chelation group (1 death) and 2 in the placebo group (1 death). Heart failure was reported in 57 chelation patients (7%) and 71 placebo patients (8%) (*P*=.28). There were 330 (0.60%) of 55 222 infusions administered at least 30 minutes too rapidly. Hypocalcemia, defined as calcium level less than 8.5 mg/dL prior to an infusion, was reported in 52 chelation patients (6.2%) and 30 placebo patients (3.5%) (*P*=.008). One patient had hypocalcemia associated with muscle cramping that led to an emergency department visit (see eTable 5, eTable 6, and eTable 7 for a complete list of adverse events).

Sensitivity Analyses

In a sensitivity analysis, we assessed how the primary treatment comparison would be affected under a variety of assumptions regarding the occurrence of primary end point events among patients who withdrew consent or were lost to follow-up. The comparison of the 2 groups remained significant at the *P*<.036 level if the relative increase of events among the withdrawn/lost patients in the active group was as much as 20% higher than in the placebo group and even generally if the percentage of events among withdrawn/lost patients in the active group was 25% higher than in the placebo group. The HRs for all of these scenarios remained in the range of 0.80 to 0.84, and the significance of the treatment effect was maintained, not only for the scenarios for the withdrawn or lost patients that would be considered most plausible but also for scenarios

Table 1. Baseline Characteristics[a]

Characteristics	EDTA Chelation (n = 839)	Placebo (n = 869)
Age, median (IQR), y	65 (59-72)	66 (59-72)
Female	152 (18)	147 (17)
Race/ethnicity		
White	790 (94)	815 (94)
Hispanic	22 (3)	29 (3)
Black/African American	29 (3)	31 (4)
Asian	10 (1)	18 (2)
American Indian/Alaska Native	11 (1)	6 (1)
Native Hawaiian or other Pacific Islander	3 (0.4)	3 (0.3)
Body mass index, median (IQR)[b]	30 (27-34)	30 (27-34)
Blood pressure, median (IQR), mm Hg		
Systolic	130 (120-140)	130 (120-140)
Diastolic	76 (70-80)	76 (70-80)
History		
Hypercholesterolemia	676 (82)	694 (81)
Hypertension	568 (68)	601 (69)
Former cigarette smoker	467 (56)	488 (56)
Angina pectoris	461 (55)	465 (54)
Anterior MI	337 (40)	337 (39)
Diabetes	265 (32)	273 (31)
Congestive heart failure	154 (18)	153 (18)
Peripheral vascular disease	126 (15)	142 (16)
Valvular heart disease	92 (11)	83 (10)
Atrial fibrillation	85 (10)	110 (13)
Stroke	57 (7)	54 (6)
Time from qualifying MI to randomization, median (IQR), y	4.3 (1.8-9.1)	4.8 (1.5-9.5)
Current NYHA heart failure class		
No heart failure or class I	764 (91)	795 (91)
Class II	63 (8)	59 (7)
Class III	12 (1)	15 (2)
Coronary revascularizations		
Either CABG or PCI	694 (83)	720 (83)
PCI	491 (59)	516 (59)
CABG	384 (46)	390 (45)
Concomitant medications		
Aspirin, warfarin, or clopidogrel	768 (92)	784 (90)
Aspirin[c]	717 (85)	710 (82)
B-Blocker	611 (73)	615 (71)
Statin	615 (73)	633 (73)
ACE inhibitor or ARB	525 (63)	559 (64)
Clopidogrel	212 (26)	213 (25)
Warfarin	73 (9)	75 (9)
Diabetes medication		
Oral hypoglycemic	191 (24)	189 (23)
Insulin	73 (9)	87 (10)
Multivitamin	356 (44)	359 (43)
Other vitamins/minerals	428 (52)	424 (50)
Herbal products	281 (34)	279 (34)
Laboratory measurements, median (IQR), mg/dL		
Total cholesterol	164 (139-192)	166 (143-198)
Triglycerides	135 (94-199)	147 (99-208)
Glucose	103 (92-121)	102 (92-121)
LDL-C	87 (66-112)	90 (68-117)
HDL-C	43 (36-52)	43 (36-50)
Creatinine[c]	1.06 (0.9-1.2)	1.10 (0.9-1.2)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

SI conversions: To convert total cholesterol, LDL-C, and HDL-C to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0154; to convert glucose to mmol/L, multiply by 0.0167; and to convert creatinine to umol/L, multiply by 88.4.

[a] Data are expressed as No. (%) unless otherwise indicated.

[b] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[c] *P*<.05. There were no other statistically significant differences between groups.

that were unfavorable to EDTA chelation (eTable 8).

COMMENT

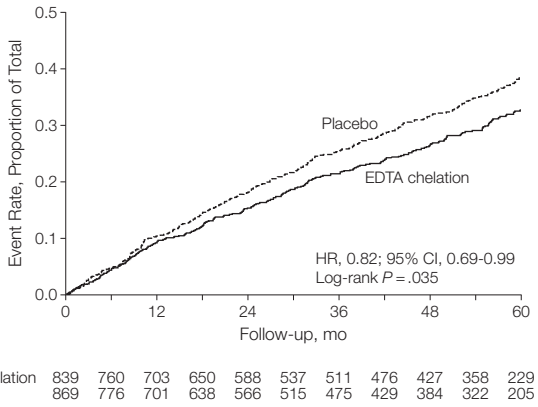
TACT is the first randomized trial, to our knowledge, designed and powered to evaluate the effects of an EDTA-based chelation regimen on clinical outcomes in patients with coronary disease. The trial randomized 1708 patients, administered more than 55 000 double-blind infusions, and accrued more than 6200 patient-years of follow-up experience. These data showed that among patients with a prior MI, a chelation regimen of 40 infusions of disodium EDTA, ascorbate, B vitamins, and other components resulted in a modest reduction in a composite outcome of cardiovascular events. The treatment effect persisted over the 5-year follow-up period without evident attenuation. There was no interaction of infusion therapy with the treatment assignment for the oral vitamin regimen. The study was not designed to ascertain mechanism of action or to identify which of the components of the infusions were responsible for the treatment effect observed.

The effect of EDTA chelation on the nonfatal components of the primary end point was quantitatively consistent with its overall effect. The most frequently occurring component was coronary revascularization. We saw no statistically significant treatment effect on all-cause mortality, but the trial had low statistical power for this evaluation. Likewise, the study was underpowered to detect a difference between groups for the secondary end point of cardiovascular death, MI, or stroke ($P=.22$). These results were observed against the background of modern evidence-based post-MI therapy given to the study patients: 83% had undergone revascularization with either coronary artery bypass grafting or percutaneous intervention, 84% were taking aspirin, 26% were taking clopidogrel, 72% were taking B-adrenergic blockers, and 73% were taking statins, with a median LDL-C level of 89 (IQR, 67-115) mg/dL.

Although the relative reduction in cardiovascular events (18%) was smaller than the effect hypothesized in the study design (25%), no prior effectiveness data were available with which to estimate the effect size. A 25% relative reduction in the event rate is included in the 95% CI around the measured treatment effect (HR, 0.69-0.99). Furthermore, an 18% relative treatment effect is within the range of effects that have been considered clinically important in prior trials, such as the use of clopidogrel for patients with acute coronary syndromes.[22]

Two prespecified subgroups appeared to receive particular benefit of therapy. Patients with diabetes had a reduction in risk (HR, 0.61; 95% CI, 0.45-0.83), and patients with anterior MI, as localized by site investigators, also had a reduction in risk of cardiovascular events (HR, 0.63; 95% CI, 0.47-0.86). Both of these subgroups were prespecified based on representing important high-risk subsets of patients but not because there was any specific biologic reason for suspecting that chelation would be uniquely beneficial for these patients. Whether the partitioning of treatment benefit evident in these subgroups will be replicable should be the subject of future investigation. Thus, at present our understanding of the significance of these subgroup findings is incomplete.

Figure 2. Kaplan-Meier Estimates of the Primary Composite End Point, EDTA Chelation Therapy vs Placebo



HR indicates hazard ratio. The primary end point was a composite of death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina.

Table 2. Clinical End Points[a]

End Points	No. (%) EDTA Chelation (n = 839)	No. (%) Placebo (n = 869)	Hazard Ratio (95% CI)	*P* Value
Primary end point	222 (26)	261 (30)	0.82 (0.69-0.99)	.035
Death	87 (10)	93 (11)	0.93 (0.70-1.25)	.64
Myocardial infarction	52 (6)	67 (8)	0.77 (0.54-1.11)	.17
Stroke	10 (1)	13 (1)	0.77 (0.34-1.76)	.53
Coronary revascularization	130 (15)	157 (18)	0.81 (0.64-1.02)	.08
Hospitalization for angina	13 (2)	18 (2)	0.72 (0.35-1.47)	.36
Secondary end point	96 (11)	113 (13)	0.84 (0.64-1.11)	.22
Cardiovascular death	50 (6)	51 (6)	0.98 (0.67-1.45)	.94

[a] The percentages in each case are based on the number of patients experiencing the event at any time during follow-up (not first events) divided by the number of patients randomized. Primary end point = first occurrence of death from any cause, myocardial infarction, stroke, or hospitalization for unstable angina. Secondary end point = first occurrence of death from a cardiovascular cause, myocardial infarction, or stroke.

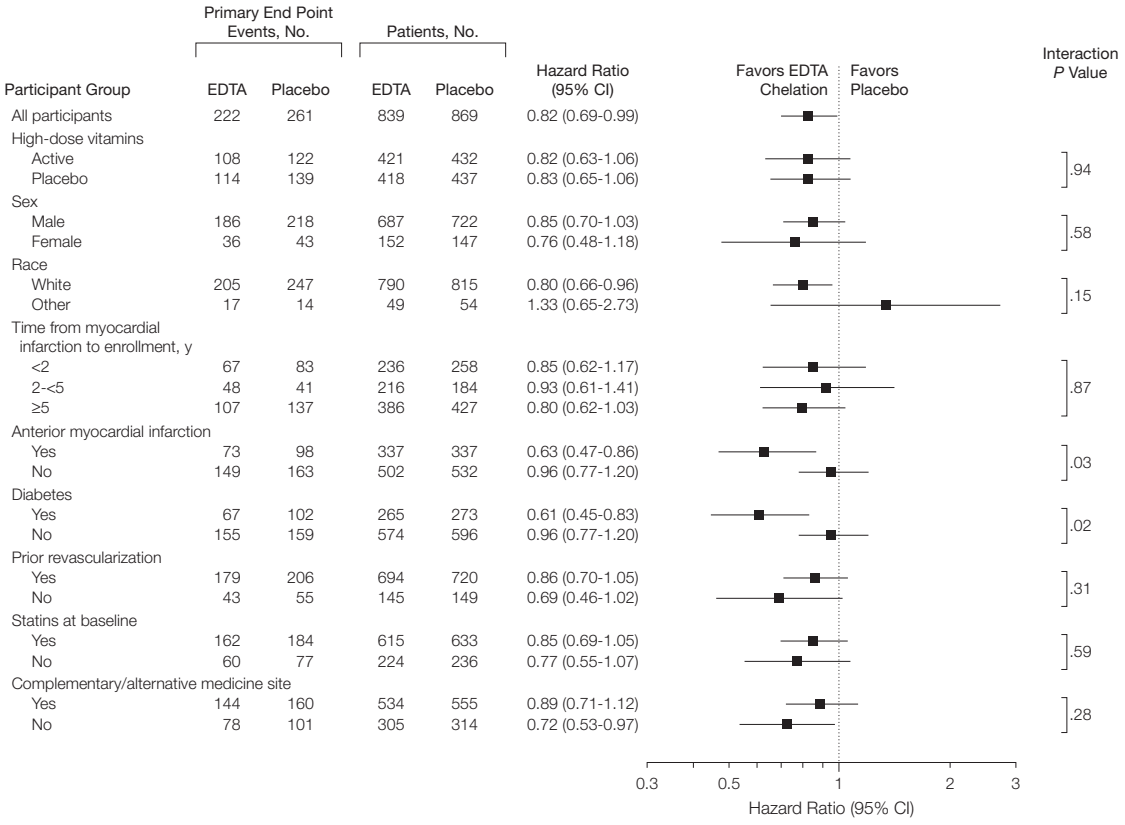
TACT is unique from a historical perspective. Chelation therapy with disodium EDTA has been in use to treat atherosclerotic disease for more than 50 years.[23-26] By 2007, the use of chelation had expanded in the United States to 111 000 adults, exposing this large group of patients to uncertain risks for unproven benefits. However, the prevalence of use of chelation therapy for atherosclerotic disease is not well documented.

The Centers for Disease Control and Prevention have reported deaths from misuse of EDTA chelation. In a June 2008 *Federal Register* notice, the FDA informed the public that edetate disodium was being withdrawn from the market[27] Mainstream medical practitioners in general have been highly skeptical that chelation therapy provides any clinical benefit. The most recent American College of Physicians/American College of Cardiology/American Heart Association guideline for the management of stable ischemic heart disease gives chelation therapy a class III recommendation (not useful/effective and may be harmful).[28] Disodium EDTA remains available through compounding pharmacies. Patients continue seeking out and receiving EDTA chelation therapy, and chelation practitioners continue to recommend this therapy. It is in the context of this half-century controversy that we carried out and now report TACT.

The interpretation of TACT is made more difficult by the absence of supporting research identifying the most plausible mechanism(s) of action. Although TACT was not a mechanistic study, the data obtained do allow some cautious conjectures regarding potential mechanisms meriting future investigation. Two, in particular, can be mentioned. Heavy metal exposure, particularly to lead, has been recognized as a risk for MI and stroke.[29,30] The association of heavy metal pollutants with cardiovascular events extends to antimony, cadmium, cobalt, and tungsten.[31] The continued separation of the Kaplan-Meier curves for chelation and placebo, after the infusions stop in year 2, might lend support to a hypothesis that removal of heavy metals has benefit beyond the active infusion phase.

Endothelial dysfunction is generally accepted as a common pathogenic abnormality in patients with atherosclerotic vascular disease. Improvement in endothelial function is a frequent finding with efficacious cardiovascular therapies. Disodium EDTA

Figure 3. Subgroup Analysis of the Primary Composite End Point, EDTA Chelation Therapy vs Placebo



The primary end point was a composite of death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina.

does not apparently show this effect.[32] The chelation infusions, however, also contained 7 g of ascorbate, a vitamin that improves endothelium-dependent vasodilation.[33,34] Yet clinical trials of oral antioxidant vitamins have been negative.[35,36]

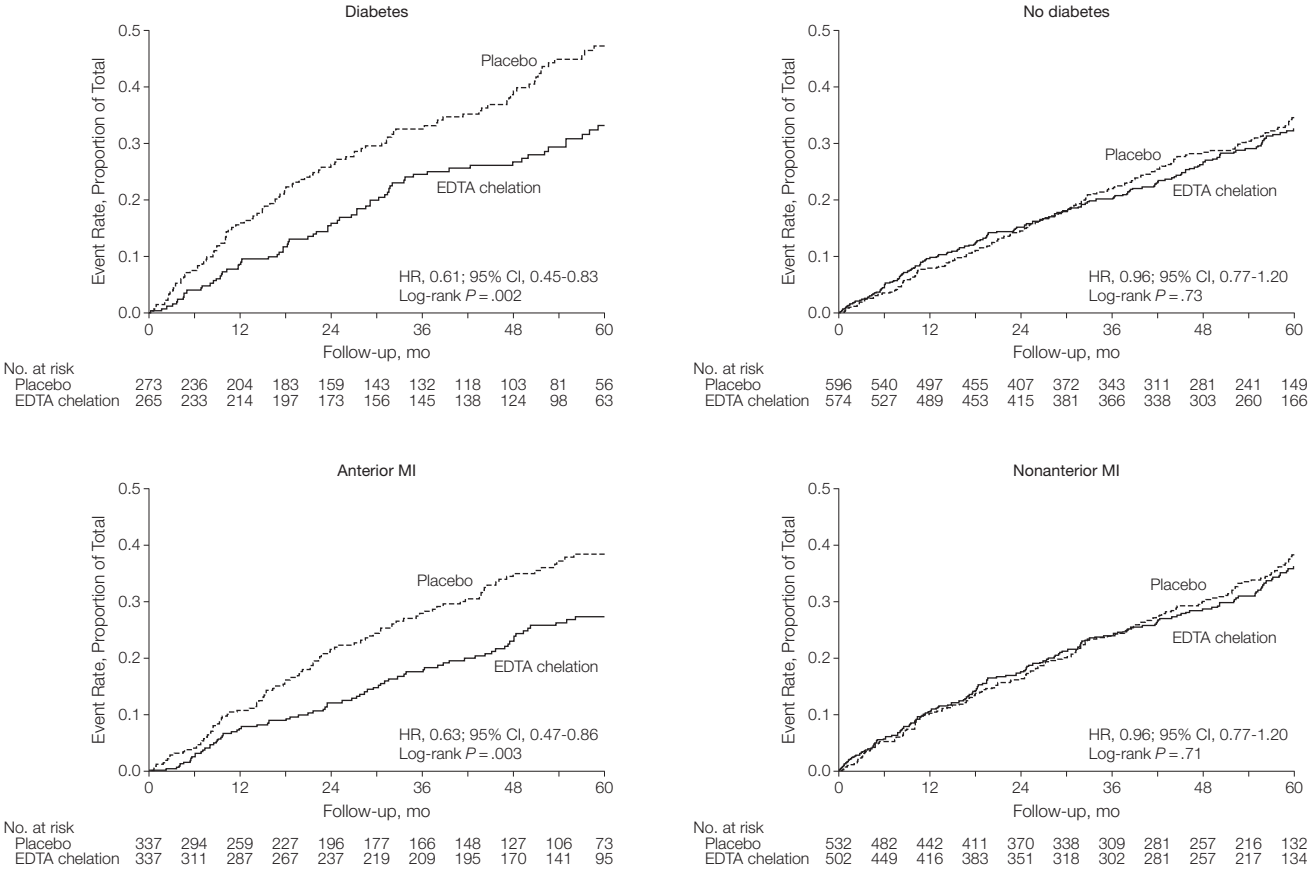
Our use of repetitive intravenous infusions would have led to higher ascorbate blood levels than that of any oral regimen previously studied in cardiovascular clinical trials.[37] Thus, it is possible that improved endothelial function might account for some of the modest benefit observed. Oxidative LDL-C modification facilitated by transition metals is an interesting potential mechanism for the association of atherosclerosis with heavy metals. Transition metals are thought to promote LDL-C oxidation, while antioxidants are thought to retard it.[38] Thus, a combination of EDTA and ascorbate might lead to a beneficial effect on oxidized LDL-C.

Study Limitations

This study has several limitations. First, the necessity of using a composite end point as the primary outcome event in a clinical trial creates some unavoidable uncertainties about the actual treatment benefit because study power is insufficient to show an effect on any individual end point and the components are not all considered of equal clinical importance. In TACT, coronary revascularizations were the most frequently observed end point events. Revascularization events are considered "softer" because of the necessary element of physician decision making involved in the event, but such events are nonetheless commonly used in composite end points in cardiovascular trials. In TACT, the revascularization events were verified by staff masked to patient treatment assignment. The consistency of relative treatment effect on all individual nonfatal components of the primary end point provides some reassurance that the observed chelation benefits were not seen only because of some extratherapeutic effect on revascularization decisions.

Second, an unusually high number of patients in TACT withdrew con-

Figure 4. Kaplan-Meier Estimates of the Primary Composite End Point for the Diabetes and Anterior MI Subgroups, EDTA Chelation Therapy vs Placebo



HR indicates hazard ratio; MI, myocardial infarction. The primary end point was a composite of death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina.

sent, leading to some lost data. However, all patients had, with appropriate institutional review board approval to do so, their National Death Index status checked at the end of the study, and some patients withdrew after having a primary end point event. Post hoc sensitivity analyses with imputations for missing data, included in eTable 8, are consistent with our prespecified analyses.

Third, unblinding is a possible explanation for the observation that placebo patients were more likely to discontinue therapy, withdraw consent, or be lost to follow-up than chelation patients. Widespread unblinding of study patients is unlikely, however. There is no evidence from a review of adverse effects that patients perceived a difference between a saline infusion and a chelation infusion. Blinding of coordinators was maintained by the techniques developed to reproduce the viscosity and mask the color of the vitamin C syringes. In addition, there was no heterogeneity in the effect of chelation therapy based on whether a patient was enrolled and followed up at a chelation site or a conventional cardiology site. The imputations performed (eTable 8) support a modest benefit of chelation therapy.

Fourth, the study was initiated without a well-established hypothesis for the mechanism(s) of benefit, and this limits our ability to understand and use the results.

Fifth, the 40-infusion chelation regimen tested in TACT is not easy for patients to receive (each infusion takes about 3 hours and the first 30 infusions are administered at weekly intervals).

Finally, one trial, no matter how large or well conducted, cannot answer all the questions needed to transform a novel hypothesis into a clinical treatment that merits guideline endorsement. Moreover, as the first trial of a chelation regimen in this patient population, the possibility that the results represent chance findings must be considered, especially in light of the narrow difference between the significance level calculated and that prespecified for the analysis. Accordingly, the results of this study should be viewed as an important but single step on the long path toward better understanding the pathophysiologic and therapeutic implications of chelation therapy but do not provide evidence to support its routine use in clinical practice.

CONCLUSION

In stable patients with a history of MI, the use of an intravenous chelation regimen with disodium EDTA, compared with placebo, modestly reduced the risk of a composite of adverse cardiovascular outcomes, many of which were revascularization procedures. These results provide evidence to guide further research but are not sufficient to support the routine use of chelation therapy for treatment of patients who have had an MI.

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Statistical analysis: Lamas, Lindblad, Lee.
Obtained funding: Lamas, Boineau, Mark, Lee.
Administrative, technical, or material support: Lamas, Boineau, Mark, Rozema, Nahin, Lewis, Drisko, Lee.
Study supervision: Lamas, Boineau, Mark, Nahin, Lewis, Lee.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Lamas reports that from 2000 to 2003 he served as a consultant to OmniComm, the electronic data capture company used in the trial. No funds were received and all relationships were severed as of September 10, 2003. No other disclosures were reported.
Funding/Support: The NCCAM (grant U01AT001156) and the NHLBI (grant U01HL092607) provided sole support for this study.
Role of the Sponsor: Robin Boineau, MD, NHLBI, Richard Nahin, PhD, NCCAM, Mario Stylianou, PhD, NHLBI, and Yves Rosenberg, MD, NHLBI, respectively, were involved as part of the NIH Cooperative Agreement process, in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
Disclaimer: The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the NHLBI, the NCCAM, or the National Institutes of Health.
Online-Only Material: The Author Video Interview, eAppendix, 3 eFigures, and 8 eTables are available at http://www.jama.com.
Additional Contributions: We gratefully acknowledge the scientific contributions and support of Yves Rosenberg, MD, and Mario Stylianou, PhD, NHLBI; the organizational skills of Ana Mon, MPH, clinical coordinating center at Mt Sinai Medical Center; Alyssa Cotler, NCCAM, Susan Dambrauskas (formerly NHLBI), and Vivian Thompson, DCRI, for their competent professional assistance; and the Florida Heart Research Institute for supporting the pilot study. The above mentioned contributors received no compensation for their work other than their usual salary.

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