Coronary Artery Disease

EDTA chelation therapy alone and in combination with oral high-dose multivitamins and minerals for coronary disease: The factorial group results of the Trial to Assess Chelation Therapy

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Background Disodium ethylenediaminetetraacetic acid (EDTA) reduced adverse cardiac outcomes in a factorial trial also testing oral vitamins. This report describes the intent-to-treat comparison of the 4 factorial groups overall and in patients with diabetes.

Methods This was a double-blind, placebo-controlled, 2 × 2 factorial multicenter randomized trial of 1,708 post–myocardial infarction (MI) patients ≥50 years of age and with creatinine ≤2.0 mg/dL randomized to receive 40 EDTA chelation or placebo infusions plus 6 caplets daily of a 28-component multivitamin-multimineral mixture or placebo. The primary end point was a composite of total mortality, MI, stroke, coronary revascularization, or hospitalization for angina.

Results Median age was 65 years, 18% were female, 94% were Caucasian, 37% were diabetic, 83% had prior coronary revascularization, and 73% were on statins. Five-year Kaplan-Meier estimates for the primary end point was 31.9% in the chelation + high-dose vitamin group, 33.7% in the chelation + placebo vitamin group, 36.6% in the placebo infusion + active vitamin group, and 40.2% in the placebo infusions + placebo vitamin group. The reduction in primary end point by double active treatment compared with double placebo was significant (hazard ratio 0.74, 95% CI 0.57-0.95, $P = .016$). In patients with diabetes, the primary end point reduction of double active compared with double placebo was more pronounced (hazard ratio 0.49, 95% CI 0.33-0.75, $P < .001$).

Conclusions In stable post-MI patients on evidence-based medical therapy, the combination of oral high-dose vitamins and chelation therapy compared with double placebo reduced clinically important cardiovascular events to an extent that was both statistically significant and of potential clinical relevance. (Am Heart J 2014;168:37-44.e5.)

Chelation therapy with ethylenediaminetetraacetic acid (EDTA) has long been used to treat atherosclerotic coronary and peripheral artery disease.[1,2] The Trial to Assess Chelation Therapy (TACT)[3] found that this treatment reduced clinical events in post–myocardial infarction (MI) patients, particularly in patients with diabetes.[4] Chelation therapy is often administered in conjunction with a regimen of oral high-dose vitamins and minerals,[5] notwithstanding that the results of clinical trials of lower-dose vitamin therapy have generally been negative.[6,7] Nonetheless, chelation practitioners argued forcefully during the design phase of TACT for the inclusion of an adjunctive high-dose vitamin and mineral regimen. Thus, a 2 × 2 factorial design (intravenous (IV) chelation vs placebo plus oral vitamins vs placebo) was selected to control for the use of vitamins, study the effects of chelation with versus without high-dose vitamins, and thereby eliminate potential confounding due to uncontrolled vitamin use by study participants.[8]

The clinical safety and efficacy of the TACT vitamin regimen have been reported.[9] These analyses demonstrated

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a nonsignificant 11% reduction in the risk of the primary combined end point. The purpose of this paper is to describe the results across the 4 factorial groups in the 1,708 randomized patients and among the 633 with diabetes.

Methods

Overview

TACT, ClinicalTrials.gov identifier NCT00044213, was a double-blind 2 × 2 factorial trial in which patients were randomized to 4 groups:

1. Active IV chelation infusions + active oral vitamins
2. Active IV chelation infusions + placebo oral vitamins
3. Placebo IV chelation infusions + active oral vitamins
4. Placebo IV chelation infusions + placebo oral vitamins

The design and organizational aspects of TACT have been published previously.[8] The National Heart, Lung, and Blood Institute, grant U01 HL92607, and the National Center for Complementary and Alternative Medicine, grant U01 AT001156, provided funding and oversight to support the research and creation of the paper. The institutional review board at each clinical site approved the study, and patients provided written informed consent. A Data and Safety Monitoring Board monitored the study. The authors are solely responsible for the design and conduct of the study, all study analyses, the drafting and editing of the paper, and its final contents.

Study population

Patients were ≥50 years of age and had sustained an MI ≥6 weeks prior to enrollment. Patients were ineligible if they were women of childbearing potential, had a serum creatinine >2.0 mg/dL, or had other exclusion criteria as previously reported.[8] Patients were enrolled at a total of 134 sites in the United States and Canada.

Subgroup with diabetes

The study protocol called for examination of various prespecified subgroups, diabetes among them. Therefore, we also report exploratory analyses of the 4 factorial groups in patients with diabetes.

Treatment

The contents of the preparation and administration of the EDTA and placebo EDTA infusion treatments used in TACT have been described[8] (online Appendix Supplementary Table I). Intravenous treatment consisted of 40 infusions of disodium EDTA-based chelation therapy or a normal saline placebo administered as 30 weekly infusions followed by 10 maintenance infusions 2 to 8 weeks apart. The active oral high-dose vitamin treatment was a 28-component mixture to be taken as 3 caplets twice daily until the end of follow-up.

The components and dosing of the oral vitamins were developed with the assistance of chelation practitioners to reflect their standard practice (online Appendix Supplementary Table II).

Follow-up

Patients were seen at baseline and at each chelation infusion visit. Following the infusion phase, patients were called quarterly, attended annual clinic visits, and were seen at the end of the trial or at the 5-year follow-up, whichever was first. Vitamin/placebo caplets were distributed on a 3- to 6-month basis. Unused pills were returned to the site to assess compliance.

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 key secondary end point. A blinded independent clinical events committee adjudicated all nonprocedural components of the primary end point. The Data Coordinating Center verified the occurrence of coronary revascularizations using patient medical records.

Safety

Safety monitoring included periodic physical examination and laboratory assessments. A masked Medical Monitor at the Data Coordinating Center reviewed all serious adverse events.

Prespecified subgroups

TACT prespecified several subgroups for analyses. The present report restricts itself to an analysis of the factorial groups in patients with diabetes prior to randomization, as previously defined.[4]

Statistical analysis

As previously reported,[3] TACT enrolled 1,708 patients, with a length of follow-up selected to provide 85% power for detecting a 25% relative reduction in the primary end point for each treatment factor, assuming a 2.5-year event rate in the placebo arm of 20% and a significance level of .05.

The TACT statistical analysis plan prespecified that the factorial groups would be analyzed for the overall study to assess any interaction of chelation therapy with oral vitamins. The analysis of the 4 factorial groups in the diabetes subgroup was not pre-specified and, as such, should be considered an exploratory analysis.

Randomization and treatment comparisons have been previously described.[3]The log-rank test[10] was used for the statistical comparison of treatment groups. Cumulative event rates were calculated according to

Table I. Baseline characteristics of patients for all 4 factorial groups

	EDTA chelation and high-dose vitamins (n = 421)	EDTA chelation and placebo vitamins (n = 418)	Placebo infusions and high-dose vitamins (n = 432)	Placebo infusions and placebo vitamins (n = 437)
Demographics				
Age (y)	64.9 (58.8-71.4)	65.2 (59.7-71.6)	65.6 (58.7-72.2)	65.5 (59.2-71.9)
Female	70 (17%)	82 (20%)	77 (18%)	70 (16%)
White	397 (94%)	393 (94%)	400 (93%)	415 (95%)
BMI	29.2 (26.5-33.4)	30.0 (26.6-33.9)	29.7 (25.9-33.4)	29.9 (27.0-33.8)
Blood pressure				
Systolic	130.0 (118.0-140.0)	130.0 (120.0-140.0)	130.0 (119.0-140.0)	130.0 (120.0-140.0)
Diastolic	76.0 (70.0-80.0)	76.0 (70.0-80.0)	76.0 (68.0-82.0)	76.0 (70.0-80.0)
History				
Hypercholesterolemia	337 (81%)	339 (83%)	343 (81%)	351 (82%)
Hypertension	280 (67%)	288 (69%)	294 (68%)	307 (70%)
Former cigarette smoker	236 (56%)	231 (55%)	251 (58%)	237 (54%)
Angina pectoris	226 (54%)	235 (56%)	221 (51%)	244 (56%)
Anterior MI	174 (41%)	163 (39%)	167 (39%)	170 (39%)
Diabetes	159 (38%)	163 (39%)	164 (38%)	147 (34%)
Congestive heart failure	68 (16%)	86 (21%)	69 (16%)	84 (19%)
Peripheral vascular disease	60 (14%)	66 (16%)	65 (15%)	77 (18%)
Stroke	28 (7%)	29 (7%)	28 (6%)	26 (6%)
Time from qualifying MI to randomization (y)*	4.3 (1.7-9.0)	4.3 (1.8-9.3)	4.8 (1.4-10.2)	4.8 (1.6-8.5)
NYHA functional class				
No heart failure or class I	389 (92%)	375 (90%)	397 (92%)	398 (91%)
Coronary revascularization				
Either CABG or PCI	350 (83%)	344 (82%)	355 (82%)	365 (84%)
PCI	238 (57%)	253 (61%)	246 (57%)	270 (62%)
CABG	198 (47%)	186 (44%)	192 (44%)	198 (45%)
Concomitant medications				
Aspirin, warfarin, or clopidogrel	386 (93%)	382 (92%)	395 (91%)	389 (89%)
Aspirin*	365 (87%)	352 (84%)	364 (84%)	346 (79%)
β-Blocker	293 (70%)	318 (76%)	309 (72%)	306 (70%)
Statin	310 (74%)	305 (73%)	319 (74%)	314 (72%)
ACE or ARB	256 (61%)	269 (64%)	273 (63%)	286 (65%)
Clopidogrel	101 (25%)	111 (28%)	99 (24%)	114 (27%)
Warfarin	28 (7%)	45 (11%)	32 (8%)	43 (10%)
Diabetes medication				
Oral hypoglycemic	103 (25%)	88 (22%)	104 (25%)	85 (20%)
Insulin*	25 (6%)	48 (12%)	46 (11%)	41 (10%)
Laboratory examinations				
Total cholesterol (mg/dL)	164.0 (139.0-193.0)	161.5 (141.0-192.0)	163.5 (141.5-194.0)	169.0 (144.0-202.5)
Triglycerides (mg/dL)	138.0 (99.0-203.0)	131.0 (91.0-193.0)	145.0 (101.0-206.0)	147.0 (99.0-210.0)
Glucose (mg/dL)	103.0 (92.0-120.0)	102.5 (92.0-123.0)	102.0 (91.0-124.0)	103.0 (93.0-119.0)
LDL (mg/dL)	88.0 (66.5-113.5)	86.0 (66.0-111.0)	87.5 (66.0-112.5)	93.0 (71.0-122.0)
HDL (mg/dL)	43.0 (36.0-52.0)	43.0 (36.4-52.0)	43.0 (37.0-51.0)	41.0 (36.0-50.0)
Creatinine (mg/dL)	1.1 (0.9-1.2)	1.1 (0.9-1.2)	1.1 (0.9-1.2)	1.1 (0.9-1.2)

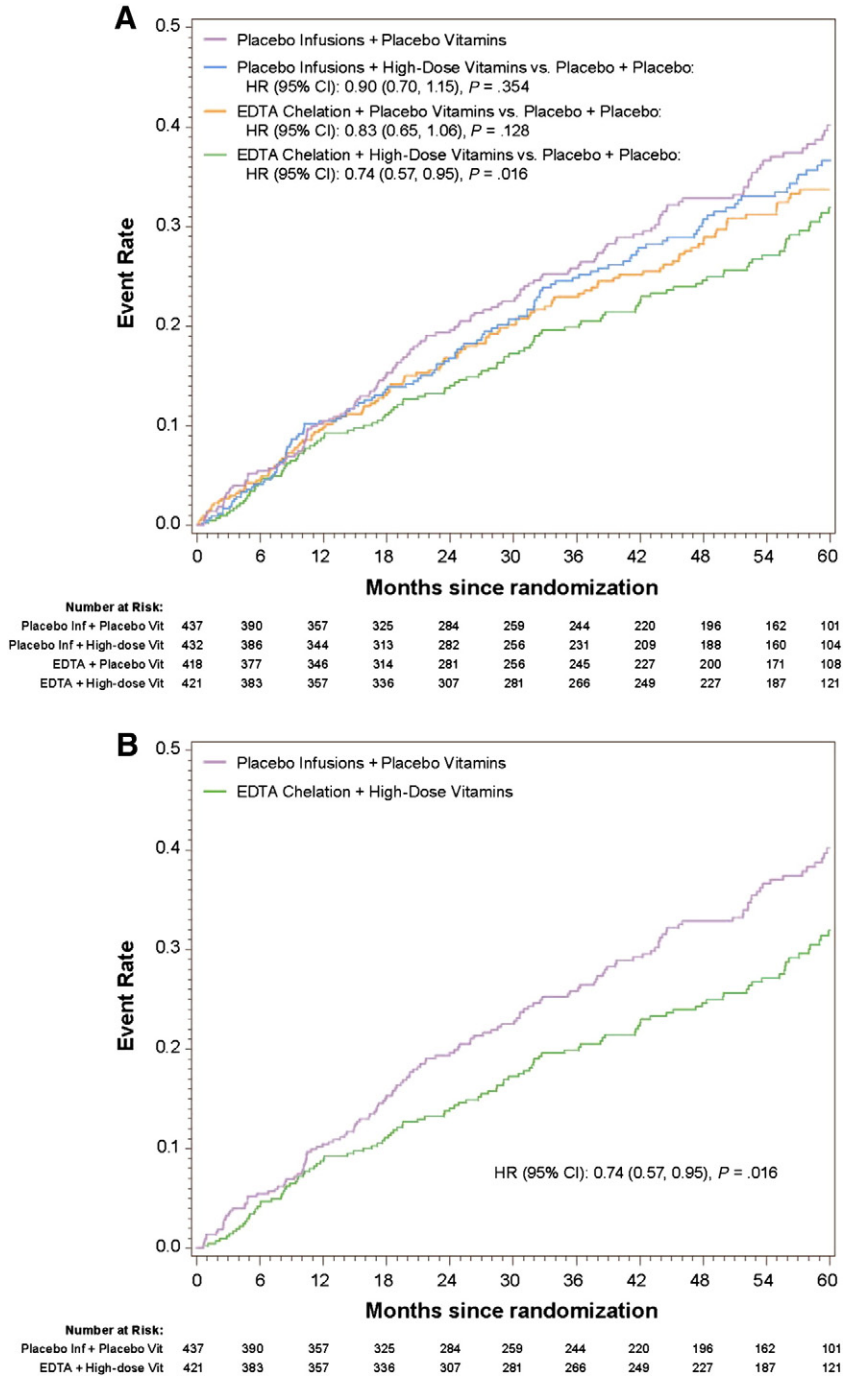
* $P < .05$.

the Kaplan-Meier method.[11] Relative risks were expressed as hazard ratios (HRs) with associated confidence intervals (CIs) and were calculated using the Cox proportional hazards model.[12] Outcomes were compared across the factorial groups, both in the overall population as well as for the population of patients with diabetes. Comparisons of treatment groups with respect to adherence and safety were performed using the χ^2 test. Continuous variables are expressed as medians and interquartile ranges unless otherwise specified. Statistical analyses were performed using SAS software, versions 8.2 and 9.2 (SAS Institute, Cary NC).

Results

Between September 10, 2003, and October 4, 2010, 1,708 patients were randomized: 421 to EDTA chelation infusions + high-dose oral multivitamins, 418 to EDTA chelation infusions + oral placebo, 432 to placebo infusions + high-dose oral multivitamins, and 437 to placebo infusions + oral

Figure 1



A, Kaplan-Meier curves (4 factorial groups, primary end point). **B**, Kaplan-Meier curves placebo/placebo versus active/active (primary end point).

placebo. The median duration of follow-up was 55 months (interquartile range, 26-60) overall. There was no significant difference in length of follow-up across all 4 groups.

Baseline characteristics

Baseline characteristics were similar among the 4 randomized factorial groups (Table I). Patients were 65

Table II. Primary and secondary end point components for all 4 factorial groups

	EDTA chelation and high-dose vitamins (n = 421)	EDTA chelation and placebo vitamins (n = 418)	Placebo infusions and high-dose vitamins (n = 432)	Placebo infusions and placebo vitamins (n = 437)	P*
Primary end point					
All-cause mortality, MI, stroke, coronary revascularization, or hospitalization for angina	108 (26%)	114 (27%)	122 (28%)	139 (32%)	.016
Death	43 (10%)	44 (11%)	44 (10%)	49 (11%)	.490
MI	23 (5%)	29 (7%)	35 (8%)	32 (7%)	.207
Stroke	4 (1%)	6 (1%)	4 (1%)	9 (2%)	.161
Coronary revascularization	60 (14%)	70 (17%)	72 (17%)	85 (19%)	.017
Hospitalization for angina	6 (1%)	7 (2%)	6 (1%)	12 (3%)	.147
Secondary end point					
Cardiovascular death, MI, or stroke	39 (9%)	57 (14%)	55 (13%)	58 (13%)	.045
Cardiovascular death	19 (5%)	31 (7%)	26 (6%)	25 (6%)	.355

Log-rank 1 *df P* values. This is a comparison of the active-active versus placebo-placebo cells only.

(59-72) years old, 18% were female, and 9% were minorities. The qualifying MI had occurred 4.6 (1.6-9.2) years prior to enrollment. There was a high prevalence of diabetes (37%); prior coronary revascularizations (83%); and postinfarct, guideline-recommended medication use of aspirin (84%), β-blocker (72%), and statin (73%).

Factorial treatment comparisons (overall group)

The 5-year Kaplan-Meier event rate estimate for the primary end point was 31.9% in the chelation + high-dose vitamin group, 33.7% in the chelation + placebo vitamin group, 36.6% in the placebo infusion + active vitamin group, and 40.2% in the placebo infusions + placebo vitamin group (Figure 1, *A*; Table II). The primary end point by treatment group occurred in 139 (32%) of the placebo infusion + placebo vitamin group and 108 (26%) of patients in the chelation + high-dose vitamin group (Figure 1, *B*). The groups with one active therapy had an intermediate number of events and were not statistically significantly different from the placebo-placebo group. The comparison of active infusion + active vitamins with placebo infusions + placebo vitamins was significant (HR 0.74, 95% CI 0.57-0.95, $P = .016$). The absolute difference in 5-year Kaplan-Meier estimated event rates between placebo-placebo and active-active groups was 8.3%, and the number needed to treat (NNT) to prevent 1 event over 5 years was 12.

The principal secondary end point, cardiovascular death, MI, or stroke, occurred in 58 (13%) of the placebo infusions + placebo vitamin group, 57 (14%) of the chelation + placebo vitamin group, 55 (13%) of the placebo infusion + active vitamin group, and 39 (9%) of patients in the chelation + high-dose vitamin group. The comparison of active infusion + active vitamins with placebo infusions + placebo vitamins favored chelation + vitamins (HR 0.66, 95% CI 0.44-0.99, $P = .046$). The groups with one active therapy had an intermediate number of events and were not statistically significantly different from the placebo-placebo group.

Treatment adherence

There were no significant differences in adherence to IV infusions or to oral vitamins between groups (Table III). Consent withdrawal at some point during the trial was reported in 289 patients. A greater frequency of consent withdrawals occurred among patients randomized to placebo infusions.

Safety

Serious adverse events were documented in 55 patients (13%) of the EDTA chelation and high-dose vitamin group, 45 (11%) of the EDTA chelation and placebo vitamin group, 69 (16%) of the placebo infusion and high-dose vitamin group, and 58 (13%) of the placebo infusion and placebo vitamin group ($P = .170$).

Diabetes analyses

In the 633 patients with diabetes, the 5-year Kaplan-Meier event rate estimates for the primary end point was 29.1% in the chelation + high-dose vitamin group, 36.1% in the chelation + placebo vitamin group, 48.1% in the placebo infusion + active vitamin group, and 47.3% in the placebo infusions + placebo vitamin group (Figure 2, *A*). The primary end point by treatment group occurred in 56 (38%) of the placebo infusion + placebo vitamin group and 36 (23%) of patients in the chelation + high-dose vitamin group (HR 0.49, 95% CI 0.33-0.75, $P < .001$, 5-year NNT = 5.5) (Figure 2, *B*). The factorial groups receiving only one active treatment had intermediate treatment benefit not statistically significantly different from double placebo.

Table III. Patient status by all treatment arms

	EDTA chelation and high-dose vitamins (n = 421)	EDTA chelation and placebo vitamins (n = 418)	Placebo infusions and high-dose vitamins (n = 432)	Placebo infusions and placebo vitamins (n = 437)	*P*
Patient status					
Number of infusions	40 (32-40)	40 (31-40)	40 (26-40)	40 (30-40)	.401
Discontinued infusions	114 (27%)	119 (28%)	146 (34%)	135 (31%)	.152
Completed 30 infusions	324 (77%)	323 (77%)	319 (74%)	329 (75%)	.622
Completed 40 infusions	283 (67%)	282 (67%)	267 (62%)	285 (65%)	.275
Discontinued vitamins	185 (44%)	185 (44%)	209 (48%)	205 (47%)	.503
Continued vitamins for at least 1 y	328 (78%)	321 (77%)	317 (73%)	325 (74%)	.384
Continued vitamins for at least 3 y	210 (50%)	216 (52%)	190 (44%)	210 (48%)	.135
Consent withdrawal	50 (12%)	65 (16%)	91 (21%)	83 (19%)	.002

Discussion

TACT was designed as a factorial trial of IV EDTA-based chelation and high-dose oral vitamins to reflect chelation practice in the community and control for confounding. Thus, we performed an analysis of the 4 groups of the factorial treatment allocation. The analyses demonstrated a stepwise gradient in benefit, with highest risk accrued by patients on standard post-MI care, but neither chelation nor vitamins; intermediate risk by patients receiving only one intervention; and lowest risk by patients receiving both chelation and vitamins. When compared with patients receiving placebo only, the HR of patients receiving both the study interventions was 0.74 (95% CI 0.57-0.95, P = .016), with a 5-year NNT for the primary end point of 12. This compares with the 5-year NNT of 16 for statin therapy for secondary prevention.[13] These effects were observed against a background of modern, evidence-based treatments for post-MI patients, including statins in 73% of patients, with a median low-density lipoprotein cholesterol of 89 mg/dL. Moreover, the benefit of combined therapy in patients with diabetes was greater, with a 5-year NNT for the primary end point of 5.5, again with a background of statin therapy in 76% of the diabetic patients.

Others have reported epidemiological[14–16] and experimental findings[17–19] that may explain benefits of metal chelation in cardiovascular disease. Lead and cadmium are associated with MI, stroke, hypertension, and death. Mechanisms include individual toxicities for each metal ion, but also a class-specific action on the body's defenses against oxidant stress. EDTA chelates environmental contaminants like lead, cadmium, antimony, tungsten, and many others.[20] In diabetic patients, copper and iron, both chelated by EDTA, are tightly linked to nonenzymatic catalytic oxidation of glucose, leading to the formation of advanced glycation end products. Other metals,[21] also chelated by EDTA, may be involved with these redox reactions in diabetic patients, accounting for yet another mechanism of action for EDTA. The xenobiotic metal hypothesis is particularly appealing because the clinical benefits of chelation persist even after the infusions stop, with continued late separation of event curves.

There are other potential explanations for the observed treatment effect. The chelation solution contains a high dose of vitamin C, an antioxidant vitamin that may help reverse some forms of endothelial dysfunction.[22] Whether repetitive infusions of vitamin C could lead to the persistent effect observed in TACT after infusions stop, however, seems doubtful.

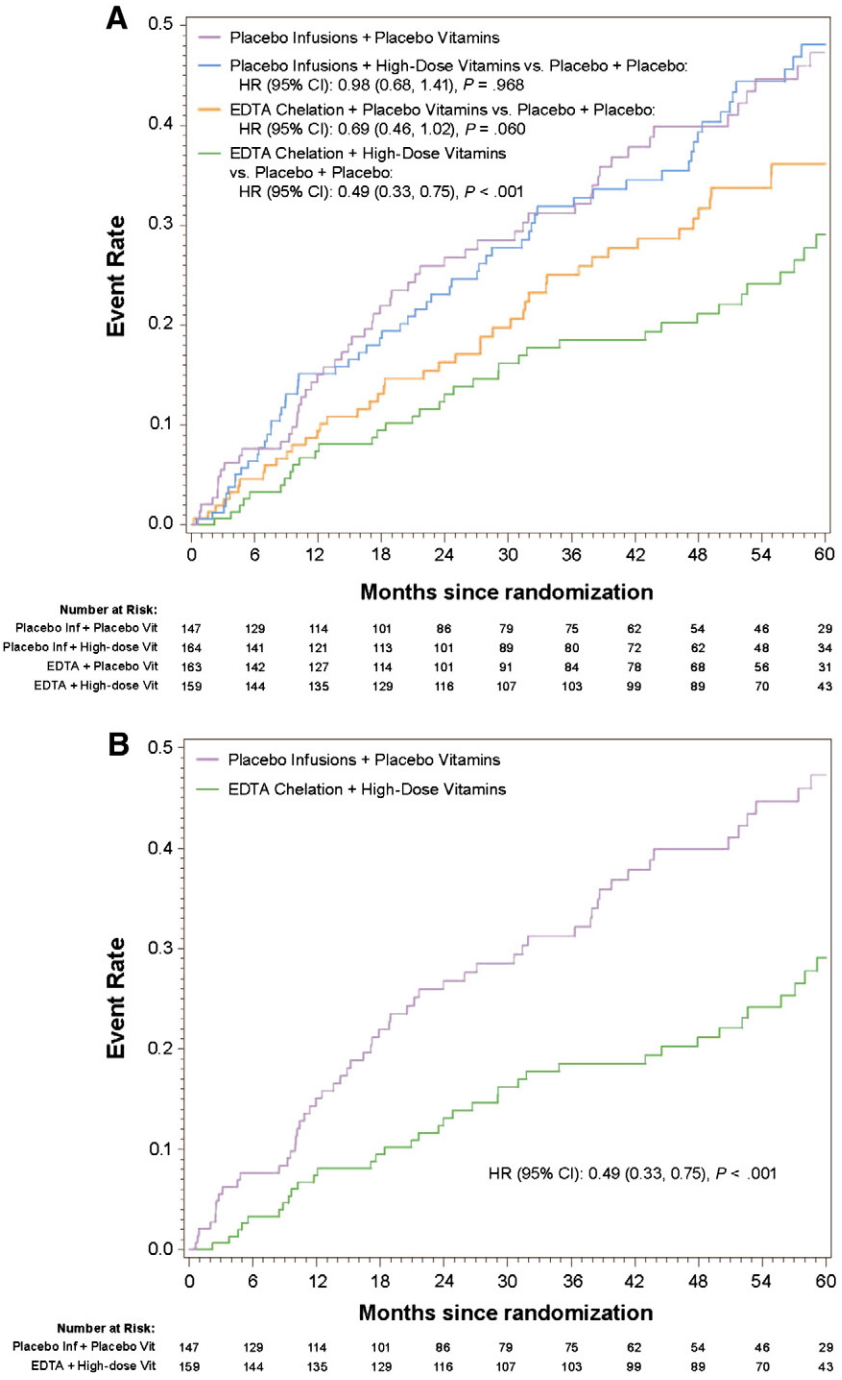
Vitamin therapy has been exhaustively studied in clinical trials as primary prevention for coronary disease. Those trials, which have largely failed to detect any evidence of a treatment benefit, have almost all used one or a small number of single vitamins at modest doses.[7,23] Thus, the lack of benefit of oral vitamins and minerals on cardiovascular events in prior studies should be recognized as pertaining to a different regimen than the high-dose oral multivitamin and mineral regimen used here and a different (primary vs secondary prevention) study population.

The incremental benefit observed in the vitamin + chelation group calls for a methodological explanation. We reported that there was a nonsignificant 11% reduction in the point estimate of the primary end point with oral vitamin therapy.[9] Our trial was not powered to detect an 11% difference between groups with sufficient precision to exclude the null effect. This small benefit of oral vitamin therapy, although not statistically significant by itself, may explain the incremental reduction in HR, from 0.82^3 to 0.74, we observed when patients receiving both active treatments were compared to the double placebo patients. A similar explanation applies to the large benefit observed in patients with diabetes treated with the double active regimen, compared with the double placebo.

Study caveats

Given the unexpected findings of TACT for practitioners of cardiovascular medicine, establishing the clinical and scientific significance of the TACT findings will require the performance of additional (ie, more than one) high-quality, adequately powered clinical trials, along with relevant laboratory studies to help identify mechanisms of benefit.

Figure 2



A, Kaplan-Meier curves (4 factorial groups, primary end point, diabetes). **B**, Kaplan-Meier curves placebo/placebo versus active/active (primary end point, diabetes).

Noncompliance with randomized treatment likely reduced the power of the study to discern a difference between groups. The compliance issues have been reviewed in detail in prior publications, and the significance of chelation therapy benefit was maintained in conservative sensitivity analyses.[3,4] In addition, all patients had their

death index status checked at the end of the study; and some patients withdrew after having sustained a primary end point, which mitigates some loss of data.

Conclusions

In stable post-MI patients on evidence-based medical therapy, the combination of oral high-dose vitamins and chelation therapy compared with double placebo reduced clinically important cardiovascular events to an extent that was both statistically significant and of potential clinical relevance.

Disclaimer

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Heart, Lung, and Blood Institute; the National Center for Complementary and Alternative Medicine; or the National Institutes of Health.

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Appendix. TACT investigators, leadership, and trial committees

In addition to the authors, the following Investigators and Coordinators participated in the Trial to Assess Chelation Therapy.

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(B) Oral low-dose regimen (taken during infusion phase only)

Supplementary Table I. TACT chelation and placebo solution components (A), and low-dose vitamin regimen (B)

(A) Active infusion

Up to 3 g of disodium EDTA*	
2 g of magnesium chloride	To reduce local discomfort and replace losses
100 mg of procaine HCL	To reduce local discomfort
2500 U of heparin	To reduce local phlebitis
7 g of ascorbate	Antioxidant and to achieve isoosmolarity
2 mEq KCl	To replace losses
840 mg sodium bicarbonate	To act as a buffer and reduce discomfort
250 mg pantothenic acid	For antioxidant properties
100 mg of thiamine	For antioxidant properties
100 mg of pyridoxine	To replace chelation losses
QS with sterile water to 500 mL	
Placebo infusion	
500 mL normal saline and 1.2% dextrose	

*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.

(B) Oral low-dose regimen (taken during infusion phase only)

Taken once daily	Amount	% Daily value
Vitamin B6 (as pyridoxine hydrochloride)	25 mg	1250%
Zinc (as zinc gluconate)	25 mg	167%
Copper (as copper gluconate)	2 mg	100%
Manganese (as manganese gluconate)	15 mg	750%
Chromium (as chromium picolinate)	50 μg	42%

Supplementary Table II. Comparison of TACT vitamins and mineral regimen with Centrum

Centrum adults			**TACT high-dose regimen**		
Serving size 1 tablet			*Serving size 6 tablets*		
Each tablet contains		% Daily value	Each tablet contains		% Daily value
Vitamin A	3500 IU (29% as β-carotene)	70%	Vitamin A (as fish liver oil and β-carotene)	25,000 IU	500%
Vitamin C	60 mg	100%	Vitamin C (as calcium ascorbate, magnesium ascorbate, and potassium ascorbate)	1200 mg	2000%
Vitamin D	400 IU	100%	Vitamin D_3 (as cholecalciferol)	100 IU	25%
Vitamin E	30 IU	100%	Vitamin E (as D-α tocopheryl succinate and D-α tocopheryl acetate)	400 IU	1333%
Vitamin K	25 µg	31%	Vitamin K_1 (as phytonadione)	60 µg	75%
Thiamin	1.5 mg	100%	Thiamin (vitamin B_1) (as thiamin mononitrate)	100 mg	6667%
Riboflavin	1.7 mg	100%			
Niacin	20 mg	100%	Niacin (as niacinamide and niacin)	200 mg	1000%
Vitamin B6	2 mg	100%	Vitamin B_6 (as pyridoxine hydrochloride)	50 mg	2500%
Folic Acid	400 µg	100%	Folate (as folic acid)	800 µg	200%
Vitamin B12	6 µg	100%	Vitamin B_{12} (as cyanocobalamin)	100 µg	1667%
Biotin	30 µg	10%	Biotin	300 µg	100%
Pantothenic acid	10 mg	100%	Pantothenic acid (as D-calcium pantothenate)	400 mg	4000%
Calcium	200 mg	20%	Calcium (as calcium citrate and calcium ascorbate)	500 mg	50%
Phosphorus	20 mg	2%			
Iodine	150 µg	100%	Iodine (from kelp)	150 µg	100%
Magnesium	50 mg	13%	Magnesium (as magnesium aspartate, ascorbate, and amino acid chelate)	500 mg	125%
Zinc	11 mg	73%	Zinc (as zinc amino acid chelate)	20 mg	133%
Selenium	55 µg	79%	Selenium (as selenium amino acid chelate)	200 µg	286%
Copper	0.5 mg	25%	Copper (as copper amino acid chelate)	2 mg	100%
Manganese	2.3 mg	115%	Manganese (as manganese amino acid chelate)	20 mg	400%
Chromium	35 µg	29%	Chromium (as chromium polynicotinate)	200 µg	167%
Molybdenum	45 µg	60%	Molybdenum (as molybdenum amino acid chelate)	150 µg	200%
Chloride	72 mg	2%			
Potassium	80 mg	2%	Potassium (as potassium aspartate and potassium ascorbate)	99 mg	3%
Boron	75 µg	*	Boron (as boron aspartate and boron citrate)	2 mg	*
Nickel	5 µg	*			
Silicon	2 mg	*			
Tin	10 µg	*			
Vanadium	10 µg	*	Vanadium (as vanadyl sulfate)	39 µg	*
			Citrus bioflavonoids	100 mg	*
			Choline (as choline bitartrate)	150 mg	*
			Inositol	50 mg	*
			Para-amino benzoic acid	50 mg	*
*Daily value not established.			On Centrum, but not on TACT vitamins		

Suggested use: adults—take one tablet daily with food.

Supplementary Table III. Serious adverse events

Events	EDTA chelation and high-dose vitamins (n = 421)	EDTA chelation and placebo vitamins (n = 418)	Placebo infusions and high-dose vitamins (n = 432)	Placebo infusions and placebo vitamins (n = 437)	*P*
Total	55 (13%)	45 (11%)	69 (16%)	58 (13%)	.170
Blood and lymphatic system disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
Cardiac disorders	18 (4%)	15 (4%)	21 (5%)	18 (4%)	.833
Ear and labyrinth disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
Eye disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
Gastrointestinal disorders	8 (2%)	4 (1%)	4 (1%)	8 (2%)	.451
General disorders and administration site conditions	5 (1%)	4 (1%)	8 (2%)	6 (1%)	.708
Hepatobiliary disorders	1 (0%)	2 (0%)	2 (0%)	0 (0%)	.497
Immune system disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
Infections and infestations	9 (2%)	9 (2%)	7 (2%)	9 (2%)	.937
Injury, poisoning, and procedural complications	3 (1%)	4 (1%)	4 (1%)	3 (1%)	.936
Investigations	2 (0%)	1 (0%)	2 (0%)	1 (0%)	.866
Metabolism and nutrition disorders	0 (0%)	2 (0%)	1 (0%)	1 (0%)	.617
Reproductive system and breast disorders					
Musculoskeletal and connective tissue disorders	3 (1%)	0 (0%)	0 (0%)	2 (0%)	.128
Neoplasms	6 (1%)	1 (0%)	1 (0%)	3 (1%)	.140
Nervous system disorders	4 (1%)	4 (1%)	7 (2%)	3 (1%)	.642
Psychiatric disorders	1 (0%)	0 (0%)	2 (0%)	1 (0%)	.808
Renal and urinary disorders	1 (0%)	3 (1%)	5 (1%)	1 (0%)	.281
	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
Respiratory, thoracic, and mediastinal disorders	5 (1%)	7 (2%)	13 (3%)	8 (2%)	0.256
Skin and subcutaneous tissue disorders	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0.744
Surgical and medical procedures	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0.245
Vascular disorders	3 (1%)	1 (0%)	3 (1%)	4 (1%)	0.712