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Oral High-Dose Multivitamins and Minerals After Myocardial Infarction

A Randomized Trial

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Background: Whether high-dose multivitamins are effective for secondary prevention of atherosclerotic disease is unknown.

Objective: To assess whether oral multivitamins reduce cardiovascular events and are safe.

Design: Double-blind, placebo-controlled, 2 × 2 factorial, multicenter, randomized trial. (ClinicalTrials.gov: NCT00044213)

Setting: 134 U.S. and Canadian academic and clinical sites.

Patients: 1708 patients aged 50 years or older who had myocardial infarction (MI) at least 6 weeks earlier and had serum creatinine levels of 176.8 μmol/L (2.0 mg/dL) or less.

Intervention: Patients were randomly assigned to an oral, 28-component, high-dose multivitamin and multimineral mixture or placebo.

Measurements: The primary end point was time to total death, recurrent MI, stroke, coronary revascularization, or hospitalization for angina.

Results: The median age was 65 years, and 18% of patients were women. The qualifying MI occurred a median of 4.6 years (interquartile range [IQR], 1.6 to 9.2 years) before enrollment. Median follow-up was 55 months (IQR, 26 to 60 months). Patients received vitamins for a median of 31 months (IQR, 13 to 59 months) in the vitamin group and 35 months (IQR, 13 to 60 months) in the placebo group ($P = 0.65$). Totals of 645 (76%) and 646 (76%) patients in the vitamin and placebo groups, respectively, completed at least 1 year of oral therapy ($P = 0.98$), and 400 (47%) and 426 (50%) patients, respectively, completed at least 3 years ($P = 0.23$). Totals of 394 (46%) and 390 (46%) patients in the vitamin and placebo groups, respectively, discontinued the vitamin regimen ($P = 0.67$), and 17% of patients withdrew from the study. The primary end point occurred in 230 (27%) patients in the vitamin group and 253 (30%) in the placebo group (hazard ratio, 0.89 [95% CI, 0.75 to 1.07]; $P = 0.21$). No evidence suggested harm from vitamin therapy in any category of adverse events.

Limitation: There was considerable nonadherence and withdrawal, limiting the ability to draw firm conclusions (particularly about safety).

Conclusion: High-dose oral multivitamins and multiminerals did not statistically significantly reduce cardiovascular events in patients after MI who received standard medications. However, this conclusion is tempered by the nonadherence rate.

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* TACT Investigators are listed in the **Appendix**, available at www.annals.org.

Patients who maintain a diet rich in a highly complex mix of antioxidants and other micronutrients have lower rates of atherosclerosis (1–3). Clinical trials testing isolated and combination oral micronutrients have not replicated these benefits. Recent meta-analyses noted that only vitamins A, C, and E and the antioxidant mineral selenium have been tested in well-designed trials, with mixed results: High doses of vitamins A and E might increase risk for cancer in selected patients, vitamin C was inactive, and selenium might be beneficial (4, 5). Yet, studies of a few vitamins and minerals do not fully reflect the supplement use of a large segment of the U.S. population, which increasingly favors multivitamin and multimineral supplements.

TACT (Trial to Assess Chelation Therapy), a 2 × 2 factorial trial funded by the National Heart, Lung, and Blood Institute and the National Center for Complementary and Alternative Medicine (6, 7), assessed whether an EDTA-based chelation regimen or an oral high-dose multivitamin and multimineral supplement improved cardiovascular outcomes and was effective for secondary prevention in patients with a history of cardiovascular disease. The chelation results have been published (8). This article compares oral multivitamins and multiminerals with placebo.

Methods

Design

This double-blind, 2 × 2 factorial trial randomly assigned patients to receive oral vitamins and intravenous chelation infusions, oral placebo and intravenous chelation infusions, oral vitamins and placebo intravenous infusions, and oral placebo and placebo intravenous infusions. The design and organizational aspects of TACT have been published (7). 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.

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Supplement

Context

Although high-dose vitamins and minerals are commonly used, whether they reduce cardiovascular events after myocardial infarction (MI) is not known.

Contribution

In this randomized trial, time to recurrent MI, stroke, coronary revascularization, hospitalization for angina, or death did not differ among participants who received daily high-dose multivitamins and minerals or placebo.

Caution

Many patients in the placebo and multivitamin groups withdrew from the trial or did not adhere to treatments during the study, which lasted several years.

Implication

High-dose multivitamins and minerals do not seem to be useful for secondary prevention of cardiovascular events after MI.

—The Editors

Setting and Participants

Eligible patients were at least 50 years of age and had sustained myocardial infarction (MI) 6 weeks or more before enrollment. Patients were ineligible if they were women of childbearing age, had a serum creatinine level greater than 176.8 μmol/L (>2.0 mg/dL), or had other exclusion criteria as previously reported (7). Patients were enrolled at 134 sites in the United States and Canada (**Figure 1**).

Randomization and Interventions

Oral vitamins and placebo were prepared by the vitamin manufacturers and shipped to the central pharmacy for distribution to the sites. The active high-dose vitamin treatment was a 28-component mixture to be administered as 3 caplets twice daily throughout the trial, designed to reflect the vitamin regimen commonly used by chelation practitioners (**Table 1**). The placebo caplets contained methylcellulose filler. Intravenous treatment consisted of 40 infusions of disodium EDTA-based chelation therapy or a normal saline placebo (7, 9). The vitamins and infusion therapy were double-blinded. During the infusion phase, all patients received an open-label, oral, low-dose vitamin regimen.

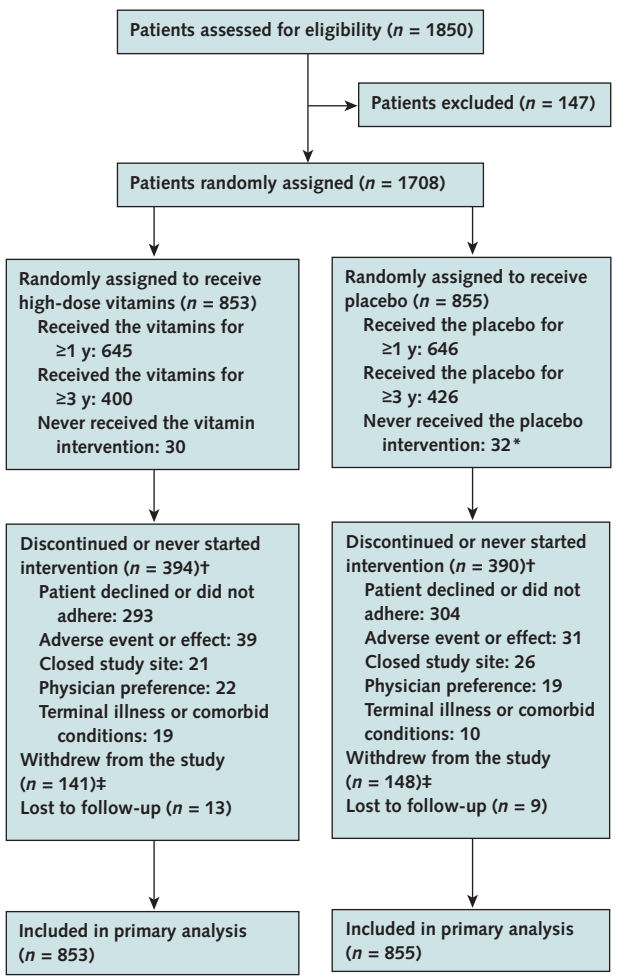
Outcomes and Follow-up

The primary end point was a composite of time to death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina. The composite of time to cardiovascular death, reinfarction, or stroke was a prespecified secondary end point. A blinded independent clinical events committee at Brigham and Women's Hospital, Boston, Massachusetts, adjudicated all nonprocedural components of the primary end point. The Duke Clinical Research Institute, Durham, North Carolina, verified coronary revascularizations from the source medical record.

Patients were seen at baseline and each chelation infusion visit. After 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 or placebo caplets were distributed every 3 to 6 months. Unused pills were returned to the site to assess adherence.

Safety monitoring included periodic physical examinations and laboratory assessments. A blinded medical monitor at the Duke Clinical Research Institute reviewed all

Figure 1. **Study flow diagram.**



* Includes 1 placebo recipient who died before starting the intervention.
† 297 high-dose vitamin recipients and 285 placebo recipients had follow-up after discontinuation and 97 high-dose vitamin recipients and 105 placebo recipients had no follow-up after discontinuation.
‡ 43 met the primary end point before withdrawal (16 in the high-dose vitamin group and 27 in the placebo group). Among the patients who had not had an event before withdrawal, 9 (5 in the high-dose vitamin group and 4 in the placebo group) were found through search of death registries to have died. All of these events were included in the primary end point analysis.

serious adverse events. We prespecified several subgroups for analyses assessing underrepresented populations, subgroups of interest, and high-risk populations (7, 8).

Statistical Analysis

We 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 significance level of 0.05. Because of difficulty enrolling patients, the blinded investigators requested, and the data and safety monitoring board and sponsors granted, a reduction in sample size to 1700 coupled with an increase in follow-up to preserve the 85% unconditional power (8).

Secure, Web-based randomization used permuted blocks stratified by clinical site. Treatment groups were compared as randomized (intention-to-treat) using 2-sided significance tests. The log-rank test (10) was used for the statistical comparison of treatment groups with respect to clinical end points. Cumulative event rates were calculated according to the Kaplan–Meier method (11). Hazard ratios with associated CIs were calculated using the Cox proportional hazards model (12). 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 analysis, as well as assignment to treatment or placebo infusions.

Continuous variables are expressed as medians and interquartile ranges (IQRs) unless otherwise specified. Group comparisons of simple proportions were done using the Pearson chi-square test. Final statistical analyses were done using SAS software, versions 8.2 and 9.2 (SAS Institute, Cary, North Carolina).

During the trial, the data and safety monitoring board requested 11 interim analyses of the data. These interim reviews were done primarily to assess the safety and efficacy of the EDTA chelation regimen and used a flexible α-spending function approach with monitoring boundaries similar to the O'Brien–Fleming method (13, 14). The level of significance required for the primary analysis at the completion of the study was 0.036.

Role of the Funding Source

The National Heart, Lung, and Blood Institute and the National Center for Complementary and Alternative Medicine of the National Institutes of Health provided funding and oversight. No companies or commercial entities provided funding or had a role in the execution, interpretation, or decision to submit the manuscript for publication.

RESULTS

Between 10 September 2003 and 4 October 2010, a total of 1708 patients were randomly assigned: 853 to the high-dose vitamin group and 855 to the placebo group.

Table 1. **Vitamin Components**

High-Dose Regimen*	Total Amount for 6 Pills	Daily Value, %
Vitamin A (as fish liver oil and β-carotene)	25 000 IU	500
Vitamin C (as calcium ascorbate, magnesium ascorbate, and potassium ascorbate)	1200 mg	2000
Vitamin D_3 (as cholecalciferol)	100 IU	25
Vitamin E (as *d*-α-tocopheryl succinate and *d*-α-tocopheryl acetate)	400 IU	1333
Vitamin K_1 (as phytonadione)	60 μg	75
Thiamin (vitamin B_1, as thiamin mononitrate)	100 mg	6667
Niacin (as niacinamide and niacin)	200 mg	1000
Vitamin B_6 (as pyridoxine hydrochloride)	50 mg	2500
Folate (as folic acid)	800 μg	200
Vitamin B_{12} (as cyanocobalamin)	100 μg	1667
Biotin	300 μg	100
Pantothenic acid (as *d*-calcium pantothenate)	400 mg	4000
Calcium (as calcium citrate and calcium ascorbate)	500 mg	50
Iodine (from kelp)	150 μg	100
Magnesium (as magnesium aspartate, magnesium ascorbate, and magnesium amino acid chelate)	500 mg	125
Zinc (as zinc amino acid chelate)	20 mg	133
Selenium (as selenium amino acid chelate)	200 μg	286
Copper (as copper amino acid chelate)	2 mg	100
Manganese (as manganese amino acid chelate)	20 mg	400
Chromium (as chromium polynicotinate)	200 μg	167
Molybdenum (as molybdenum amino acid chelate)	150 μg	200
Potassium (as potassium aspartate and potassium ascorbate)	99 mg	3
Choline (as choline bitartrate)	150 mg	–†
Inositol	50 mg	–†
PABA (as paraaminobenzoic acid)	50 mg	–†
Boron (as boron aspartate and boron citrate)	2 mg	–†
Vanadium (as vanadyl sulfate)	39 μg	–†
Citrus bioflavonoids	100 mg	–†

PABA = *p*-aminobenzoic acid.
* Three pills twice daily. Other ingredients were croscarmellose sodium, microcrystalline cellulose, magnesium stearate, hydroxypropyl cellulose, and silicon dioxide.
† Daily value not established.

The last follow-up visit was on 31 October 2011. The median follow-up was 55 months (IQR, 26 to 60 months). The trial ended after the protocol-specified enrollment and follow-up and was not stopped on the basis of interim analyses.

Baseline Characteristics

Baseline characteristics were similar between the groups (**Table 2**). Median age was 65 years (IQR, 59 to 72 years), 18% were women, and 6% were nonwhite. The qualifying MI had occurred a median of 4.6 years (IQR, 1.6 to 9.2 years) before enrollment. The study population had a high incidence of diabetes (31%), previous coronary revascularizations (83%), and use of medications recommended by guidelines. Patients had a median fasting low-density lipoprotein cholesterol level of 2.30 mmol/L (89 mg/dL) (IQR, 1.73 to 2.98 mmol/L [67 to 115 mg/dL]).

Table 2. **Baseline Characteristics**

Characteristic	High-Dose Vitamin Group (*n* = 853)	Placebo Group (*n* = 855)
Clinical		
Median age (IQR), *y*	65 (59–72)	65 (60–72)
Women, *n (%)*	147 (17)	152 (18)
White, *n (%)*	797 (93)	808 (95)
Hispanic, *n (%)*	20 (2)	31 (4)
Median BMI (IQR), *kg/m²*	29 (26–33)	30 (27–34)
Median SBP (IQR), *mm Hg*	130 (118–140)	130 (120–140)
Median DBP (IQR), *mm Hg*	76 (70–81)	76 (70–80)
History		
Hypercholesterolemia, *n (%)*	680 (81)	690 (82)
Hypertension, *n (%)*	574 (67)	595 (70)
Former cigarette smoker, *n (%)*	487 (57%)	468 (55)
Angina pectoris, *n (%)*	447 (52)	479 (56)
Anterior MI, *n (%)*	341 (40)	333 (39)
Diabetes, *n (%)*	282 (33)	256 (30)
Congestive heart failure, *n (%)*	137 (16)	170 (20)
Peripheral vascular disease, *n (%)*	125 (15)	143 (17)
Valvular heart disease, *n (%)*	72 (9)	103 (12)
Atrial fibrillation, *n (%)*	80 (10)	115 (14)
Stroke, *n (%)*	56 (7)	55 (6)
Median time from qualifying MI to randomization (IQR), *y*	4.5 (1.6–9.5)	4.6 (1.7–9.0)
CABG or PCI, *n (%)*	705 (83)	709 (83)
PCI, *n (%)*	484 (57)	523 (61)
CABG, *n (%)*	390 (46)	384 (45)
Concomitant medications, *n (%)*		
Aspirin, warfarin, or clopidogrel	781 (92)	771 (90)
Aspirin	729 (85)	698 (82)
β-Blocker	602 (71)	624 (73)
Statin	629 (74)	619 (72)
ACE inhibitor or ARB	529 (62)	555 (65)
Clopidogrel	200 (24)	225 (27)
Warfarin	60 (7)	88 (11)
Oral hypoglycemic diabetes medication	207 (25)	173 (21)
Insulin	71 (9)	89 (11)
Multivitamin	344 (42)	371 (45)
Other vitamins/minerals*	428 (52)	424 (51)
Herbal products	265 (32)	295 (36)
Laboratory examinations		
Median total cholesterol level (IQR)		
mmol/L	4.25 (3.63–4.99)	4.29 (3.68–5.10)
mg/dL	164 (140–193)	166 (142–197)
Median triglyceride level (IQR)		
mmol/L	1.6 (1.1–2.3)	1.6 (1.1–2.3)
mg/dL	141 (99–206)	138 (93–202)
Median glucose level (IQR)		
mmol/L	5.6 (5.1–6.8)	5.7 (5.2–6.7)
mg/dL	102 (92–122)	103 (93–120)
Median LDL cholesterol level (IQR)		
mmol/L	2.28 (1.73–2.93)	2.30 (1.76–3.03)
mg/dL	88 (67–113)	89 (68–117)
Median HDL cholesterol level (IQR)		
mmol/L	1.11 (0.96–1.32)	1.09 (0.93–1.29)
mg/dL	43 (37–51)	42 (36–50)
Median serum creatinine level (IQR)		
μmol/L	84 (79–106)	84 (79–106)
mg/dL	1.1 (0.9–1.2)	1.1 (0.9–1.2)

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; DBP = diastolic blood pressure; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.
* Participants were receiving these agents at baseline/before initiation of the study.

Treatment Adherence

A total of 784 (46%) patients discontinued their regimen during the study (390 [46%] in the placebo group and 394 [46%] in the vitamin group; $P = 0.67$) (**Appendix Figure**, available at www.annals.org). Patients received caplets for a median of 31 months (IQR, 13 to 59 months) in the vitamin group and 35 months (IQR, 13 to 60 months) in the placebo group ($P = 0.65$). A total of 645 (76%) vitamin recipients and 646 (76%) placebo recipients completed at least 1 year of oral therapy ($P = 0.98$), and 400 (47%) and 426 (50%), respectively, completed at least 3 years ($P = 0.23$) (**Table 1** of the **Supplement**, available at www.annals.org).

The most common reason for discontinuation was declining to continue taking the vitamins or placebo (74% in the vitamin group and 78% in the placebo group; $P = 0.24$), but 5.6% and 4.9%, respectively, discontinued because of physician preference ($P = 0.65$), and 9.9% and 7.9%, respectively, discontinued because of adverse events or effects ($P = 0.34$) (**Table 2** of the **Supplement**). Women were more likely to discontinue vitamin therapy than men (**Table 3** of the **Supplement**).

The only difference between groups at baseline among patients who discontinued their regimens was a higher proportion of diabetes and greater use of oral hypoglycemic drugs in the high-dose vitamin group (**Table 4** of the **Supplement**). A total of 289 (17%) patients withdrew from the study (**Figure 1**); these data did not differ by group ($P = 0.69$).

Primary and Secondary Outcomes

The primary end point occurred in 230 (27%) patients in the vitamin group and 253 (30%) in the placebo group. The Kaplan–Meier 5-year event rate estimates were 34.2% (95% CI, 30.5% to 37.9%) for the vitamin group and 37.0% (CI, 33.2% to 40.8%) for the placebo group (hazard ratio, 0.89 [CI, 0.75 to 1.07]; $P = 0.21$) (**Figure 2**, *top*). Treatment comparisons of the individual components of the primary end point were indeterminate because of fewer events for each component (**Table 3**). The composite of cardiovascular death, MI, or stroke occurred in 94 (11%) patients in the vitamin group and 115 (13%) in the placebo group (hazard ratio, 0.82 [CI, 0.62 to 1.07]; $P = 0.142$) (**Figure 2**, *bottom*).

Adverse Events

Serious adverse events occurred in 124 (15%) vitamin recipients and 103 (12%) placebo recipients (difference, 3 percentage points [CI, −0.7 to 5.7 percentage points]) (**Table 5** of the **Supplement**). Adverse events included 12 (1.4%) incident neoplasms in the vitamin group and 11 (1.3%) in the placebo group (difference, 0.1 percentage point [CI, −0.8 to 1.3 percentage points]). No evidence suggested harm from vitamin therapy in any category of adverse events (**Table 6** of the **Supplement**).

Subgroup Analysis

Prespecified tests for treatment interactions (**Figure 3**) indicated no statistically significant interaction ($P = 0.94$) of oral vitamin therapy and EDTA chelation or placebo or between oral vitamin therapy and type of enrolling practice, defined as complementary or alternative medicine or conventional medical practice ($P = 0.39$). Statin therapy at baseline interacted with vitamin therapy (P for interaction = 0.012).

DISCUSSION

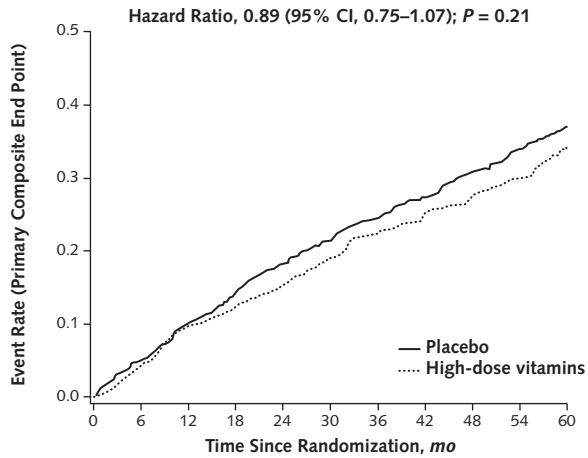
TACT found that a 28-component, high-dose oral multivitamin and multimineral regimen used as secondary prevention in patients who have had MI did not statistically significantly reduce cardiovascular events. The complex mixture seemed safe. However, these conclusions must be interpreted cautiously because of a high rate of withdrawal and nonadherence.

Our study adds to the existing literature on vitamin therapy in 3 ways. First, complementary and alternative medicine practitioners rather than clinical researchers or supplement companies designed the specific components of the oral treatment regimen, leading to a unique high-dose mixture (**Table** 7 of the **Supplement**). Second, an English-language MEDLINE search up to August 2013 showed only 1 other large-scale trial of a multivitamin preparation focusing on cardiovascular outcomes (15) that tested more than 4 components. That trial, the Physicians Health Study II, included only 5.1% ($n = 754$) of patients with self-reported vascular disease. Thus, our multivitamin study, with its multiple high-dose components and enrollment of 1708 patients who have had MI, adds to the knowledge base of multivitamin therapy as secondary prevention. Finally, and most relevant to the complementary and alternative medicine community, the 2 × 2 factorial design permitted the determination that vitamin therapy did not interact with intravenous chelation, an intervention that had a modestly positive effect on cardiovascular outcomes (8).

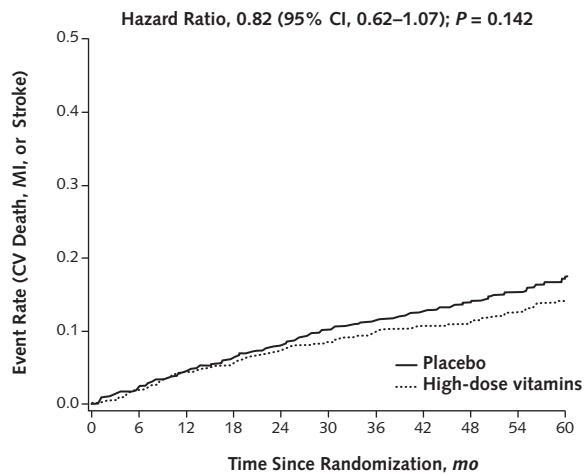
Cardiovascular disease remains the principal cause of death and disability in the United States. Among the interventions used by patients to treat or prevent heart disease are those supported by an evidence base and prescribed by physicians and over-the-counter nutritional supplements, vitamins, and minerals advertised by the vitamin and supplement industry and purchased by many patients. Clinical trials have randomly assigned thousands of patients to trials testing only a few antioxidant vitamins and minerals, typically vitamin C, vitamin E, β-carotene, and selenium, alone or in factorial groups and combinations.

The systematic analyses of trials testing a few vitamins and minerals to prevent cardiovascular disease can be characterized as negative and have suggested that some supplements may be harmful in high doses and for some patients (4, 5, 16). However, the U.S. public has increased its adoption of more complex multivitamin and multimineral supplements to prevent cardiac disease and maintain health (17). The use of multicombination supplements has increased from 30% of the overall supplement market between 1988 and 1994 to 39% between 2003 and 2006. The supplement industry has increased from $4 billion in 1994 to $23.7 billion in 2008 (18, 19). Clinical trials have not kept pace with the use of these multiple-agent supplements.

Figure 2. **Kaplan–Meier estimates of the primary composite end point (*top*) and CV death, MI, or stroke (*bottom*): high-dose vitamins versus placebo.**



Patients at risk, *n*											
Placebo	855	767	703	639	565	515	489	447	396	333	209
High-dose vitamins	853	769	701	649	589	537	497	458	415	347	225



Patients at risk, *n*											
Placebo	855	788	743	689	628	577	558	514	466	403	252
High-dose vitamins	853	783	734	689	631	589	555	522	479	406	273

P values were calculated using the log-rank statistic. CV = cardiovascular; MI = myocardial infarction.

Table 3. **Clinical End Points***

Variable	High-Dose Vitamin Group (*n* = 853)	Placebo Group (*n* = 855)	Hazard Ratio (95% CI)	*P* Value
Primary end point, *n* (%)†	230 (27)	253 (30)	0.89 (0.75–1.07)	0.21
Death	87 (10)	93 (11)	0.93 (0.69–1.24)	0.61
MI	58 (7)	61 (7)	0.95 (0.66–1.36)	0.79
Stroke	8 (1)	15 (2)	0.53 (0.22–1.25)	0.139
Coronary revascularization	132 (15)	155 (18)	0.84 (0.66–1.05)	0.131
Hospitalization for angina	12 (1)	19 (2)	0.63 (0.30–1.29)	0.20
Secondary end point, *n* (%)‡	94 (11)	115 (13)	0.82 (0.62–1.07)	0.142
Cardiovascular death	45 (5)	56 (7)	0.80 (0.54–1.18)	0.26

MI = myocardial infarction.
* The percentages are based on the number of patients having the event at any time during follow-up (not first events) divided by the number of patients randomly assigned.
† The first occurrence of death from any cause, MI, stroke, coronary revascularization, or hospitalization for angina.
‡ The first occurrence of death from a cardiovascular cause, MI, or stroke.

Admittedly, some observations correlate diets rich in varied micronutrients to cardiovascular health and show plausible mechanisms by which complex mixtures of vitamins, minerals, and micronutrients could improve cardiovascular outcomes (1–3). Micronutrients, including vitamin C (20), some bioflavonoids, and others (21), may improve endothelial function. Vitamin E is an antioxidant vitamin and may even repair iron handling within the atherosclerotic plaque, thereby influencing oxidant damage (22). Many other mechanisms have been described that are beyond the scope of this discussion. Moreover, the safety concerns raised by clinical trials with single antioxidant vitamins have not been addressed with complex multivitamin and multimineral mixtures (4, 23, 24). Thus, it is reasonable to expand the reach of vitamin trials and test complex mixtures to elucidate efficacy and safety.

The high-dose vitamins used in TACT showed an 11% relative reduction in the primary composite end point relative to the placebo group that was not statistically significant. This difference was substantially smaller than the trial was powered to measure. Thus, although this trial does not support the routine use of this high-dose oral multivitamin regimen for all patients who have had MI, the reduced statistical power due to a small difference between groups, as well as nonadherence to the study regimen, limits the conclusion of nonefficacy. Future studies of this particular regimen would have to consider a smaller effect size than we estimated, as well as the barriers to adherence that were identified.

We found a significant interaction of vitamin therapy with statin use, reflecting a greater effect of high-dose vitamins in patients not receiving a statin. This finding, which addressed a prespecified subset of patients intolerant to statins or self-selected not to receive statins, should not be interpreted as evidence that vitamin therapy can safely be substituted for statins in patients who have had MI. This finding requires additional mechanistic research and independent replication before the clinical implications can be understood. We also did not replicate the results of Brown and colleagues (25), who observed that a reduction in clinical events associated with simvastatin was attenuated by the concomitant use of vitamins E and C, β-carotene, and selenium.

Despite our conclusions that high-dose oral vitamins and minerals alone do not seem to have a role in the management of patients who have had MI, these persons will probably continue using vitamins for cardiovascular health. It is, therefore, important to comment further on the safety of the TACT vitamins. Despite the doses used (higher in most components than those used by Sesso and associates [15]), serious adverse events and incident cases of cancer did not differ between the groups. However, this conclusion must be tempered by a high rate of discontinuation of the randomly assigned therapy or placebo.

Our study had important limitations. The statistical plan was based on an effect size (25% reduction) that may have been overly optimistic for the oral vitamins. The TACT vitamin regimen, requiring 6 large caplets daily, imposed a barrier to patient adherence.

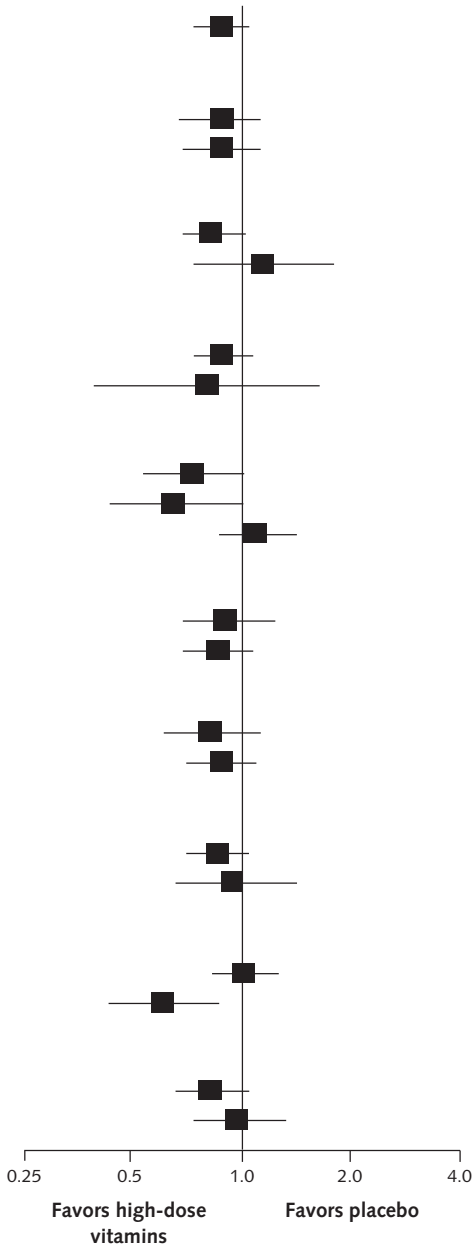
In addition, the patient burden of the chelation component of the factorial trial was high. Combining an oral vitamin regimen with intravenous therapy probably increased the nonadherence rate for the oral therapy reported here. This nonadherence rate reduced the ability to definitively comment about the potential toxicity of such a high-dose vitamin and mineral mixture.

Nevertheless, the loss of outcomes data is at least partially mitigated because the death status of all patients was checked at the end of the study using the Social Security Death Index and the Canadian death registry. In addition, although more patients withdrew from the study than expected, some did so after having a primary end point. Patients who discontinued vitamins or placebo continued to be followed (unless they withdrew from the study); therefore, we obtained follow-up information for those who discontinued vitamins or placebo but remained in the trial.

In stable patients with a history of MI receiving appropriate, evidence-based medical therapy, use of high-

Figure 3. **Subgroup analyses comparing high-dose vitamins with placebo.**

Participant Group	Patients/Events, *n/N*		Interaction *P* Value	Hazard Ratio (95% CI)
	High-Dose Vitamin Group	Placebo Group		
All participants	853/230	855/253		0.89 (0.75–1.07)
Infusions			0.94	
EDTA	421/108	418/114		0.89 (0.68–1.15)
Placebo	432/122	437/139		0.90 (0.70–1.15)
Sex			0.171	
Men	706/188	703/216		0.84 (0.69–1.03)
Women	147/42	152/37		1.17 (0.75–1.83)
Race			0.58	
White	797/215	808/237		0.90 (0.75–1.09)
Other	56/15	47/16		0.82 (0.40–1.67)
Time from MI to enrollment			0.046	
<2 y	246/67	248/83		0.74 (0.54–1.02)
2–5 y	199/36	201/53		0.67 (0.44–1.02)
≥5 y	408/127	405/117		1.11 (0.87–1.43)
Anterior MI			0.79	
Yes	341/83	333/88		0.93 (0.69–1.26)
No	512/147	522/165		0.88 (0.70–1.09)
Diabetes			0.72	
Yes	282/85	256/84		0.84 (0.62–1.14)
No	571/145	599/169		0.90 (0.72–1.12)
Previous revascularization			0.59	
Yes	705/180	709/205		0.87 (0.71–1.06)
No	148/50	146/48		0.97 (0.66–1.45)
Statins at baseline			0.012	
Yes	629/179	619/167		1.03 (0.84–1.27)
No	224/51	236/86		0.62 (0.44–0.87)
CAM site			0.39	
Yes	544/141	545/163		0.84 (0.67–1.05)
No	309/89	310/90		0.99 (0.74–1.33)



CAM = complementary and alternative medicine; MI = myocardial infarction.

dose oral multivitamins and multiminerals seemed safe but did not statistically significantly reduce cardiovascular events. These conclusions must be interpreted cautiously because of a high rate of nonadherence to the study regimen.

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Note: Dr. Lamas had full access to all of the data in the study and had final responsibility for the decision to submit this article for publication.

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; National Center for Complementary and Alternative Medicine; or National Institutes of Health.

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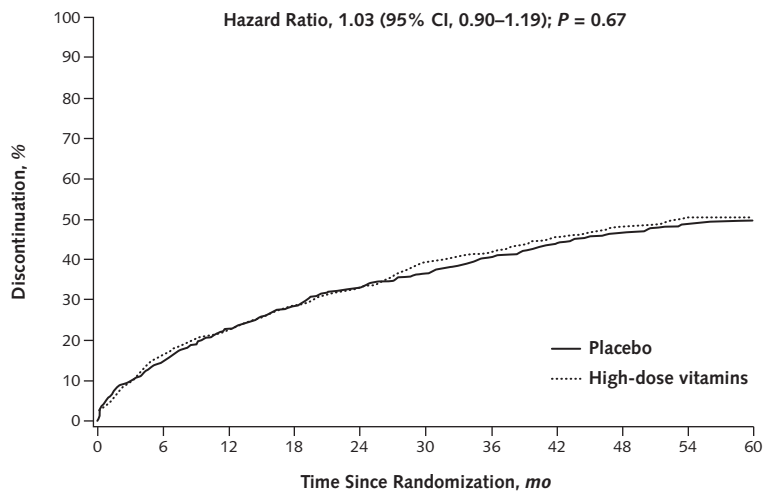
Appendix Figure. **Kaplan–Meier estimates of discontinuation of vitamins: high-dose vitamins versus placebo.**



Patients at risk, *n*											
High-dose vitamins	853	707	645	571	504	433	400	359	320	256	160
Placebo	855	725	646	578	515	463	426	377	332	280	176