Original Article

The Effect of an EDTA-based Chelation Regimen on Patients With Diabetes Mellitus and Prior Myocardial Infarction in the Trial to Assess Chelation Therapy (TACT)

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Background—The Trial to Assess Chelation Therapy (TACT) showed clinical benefit of an EDTA-based infusion regimen in patients aged ≥50 years with prior myocardial infarction. Diabetes mellitus before enrollment was a prespecified subgroup.

Methods and Results—Patients received 40 infusions of EDTA chelation or placebo. A total of 633 (37%) patients had diabetes mellitus (322 EDTA and 311 placebo). EDTA reduced the primary end point (death, reinfarction, stroke, coronary revascularization, or hospitalization for angina; 25% versus 38%; hazard ratio, 0.59; 95% confidence interval [CI], 0.44–0.79; $P<0.001$) over 5 years. The result remained significant after Bonferroni adjustment for multiple subgroups (99.4% CI, 0.39–0.88; adjusted $P=0.002$). All-cause mortality was reduced by EDTA chelation (10% versus 16%; hazard ratio, 0.57; 95% CI, 0.36–0.88; $P=0.011$), as was the secondary end point (cardiovascular death, reinfarction, or stroke; 11% versus 17%; hazard ratio, 0.60; 95% CI, 0.39–0.91; $P=0.017$). However, after adjusting for multiple subgroups, those results were no longer significant. The number needed to treat to reduce 1 primary end point over 5 years was 6.5 (95% CI, 4.4–12.7). There was no reduction in events in non–diabetes mellitus (n=1075; $P=0.877$), resulting in a treatment by diabetes mellitus interaction ($P=0.004$).

Conclusions—Post–myocardial infarction patients with diabetes mellitus aged ≥50 demonstrated a marked reduction in cardiovascular events with EDTA chelation. These findings support efforts to replicate these findings and define the mechanisms of benefit. However, they do not constitute sufficient evidence to indicate the routine use of chelation therapy for all post–myocardial infarction patients with diabetes mellitus.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00044213.

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Key Words: diabetes mellitus ■ myocardial infarction ■ secondary prevention

For >50 years, ethylene diamine tetraacetic acid (EDTA)-based chelation therapy has been used by practitioners to treat complications of atherosclerosis, without a robust evidence base, and with increasing controversy.[1–3] The Trial to Assess Chelation Therapy (TACT), developed in response to a Request for Proposals[4] by the National Center for Complementary and Alternative Medicine and the National Heart, Lung, and Blood Institute, was designed as a pivotal trial of disodium EDTA chelation therapy for patients who had a myocardial infarction (MI). EDTA chelation therapy was found to offer a modest, but significant, reduction in the primary composite cardiovascular end point.[5] As part of the prospective analysis plan,[6] the presence of diabetes mellitus before enrollment was prespecified for subgroup analysis.

Editorial see p 5

Our initial report of TACT included the observation that there was an interaction between EDTA treatment and a

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WHAT IS KNOWN

- EDTA-based chelation infusions have been used for decades to treat atherosclerosis without proof of efficacy.
- The recently-published Trial to Assess Chelation Therapy (TACT) demonstrated a modest improvement in outcomes for patients with post-MI. The prespecified subgroup of patients with self-reported diabetes mellitus showed a particular benefit.

WHAT THE STUDY ADDS

- Patients with diabetes mellitus, when compared with patients without diabetes mellitus, demonstrated a major reduction in the primary end point, and consistent reductions in the individual components of the primary end point.
- This analysis suggests that novel mechanism to treat atherosclerosis in patients with diabetes mellitus may be at play.

self-reported history of diabetes mellitus.[5] EDTA is a potent metal chelator.[7] Therefore, our preliminary observations were consistent with research supporting an important role for metal-catalyzed oxidation reactions in the development of advanced glycation end-products,[8] mediators of complications of diabetes mellitus. The present report provides greater detail on the effect of EDTA-based chelation therapy on patients with diabetes mellitus who have had a prior MI.

Methods

The detailed methodology of TACT has been published.[5] TACT was a double-blind 2X2 factorial trial in which patients (1708) were randomized to receive 40 infusions of disodium EDTA chelation or placebo and additionally to an oral high-dose vitamin and mineral regimen or oral placebo. This report describes the results of EDTA chelation versus placebo in a prespecified subgroup of patients with diabetes mellitus.

Study Population

Patients were aged ≥50 years and had a history of MI ≥6 weeks before enrollment. Major exclusion criteria were women of childbearing potential, a creatinine level >176.8 μmol/L (2.0 mg/dL), platelet count <100 000 per μL, abnormal liver function studies, blood pressure >160/100 mm Hg, past intolerance to the chelation or vitamin components, chelation therapy within 5 years, or revascularization within 6 months. The study enrolled 1708 patients in 134 sites across the United States and Canada (Figure 1). The median duration of follow-up was 55 months. 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.

Diabetes Mellitus Definition

Our prior report demonstrating a significant interaction (P=0.02) of EDTA therapy with the diagnosis of diabetes mellitus was based on patients' self-reported diagnosis of diabetes mellitus, present in 538 (31.5%) cases. The present analyses broadened the definition of diabetes mellitus to be more consistent with current guidelines.[9] Thus, patients included in the present diabetes mellitus subgroup had self-reported diabetes mellitus, were taking oral or insulin treatment for diabetes mellitus, or had a fasting blood glucose of ≥6.99 mmol/L (126 mg/dL) at the time of enrollment in the study. This led to 633 (37.1%) patients with a diagnosis of diabetes mellitus eligible for analysis. The expansion of the diabetes mellitus definition was approved by the TACT Operations Group before performing the resulting analyses. However, results are also provided for the previously defined group of 538 patients (Tables I–III in the Data Supplement).

Treatment

The 10-component 500-mL intravenous solution in TACT consisted of 3 g of disodium EDTA, adjusted downward based on estimated glomerular filtration rate; 7 g of ascorbic acid; 2 g of magnesium chloride; B-vitamins; and other components (Table IV in the online-only Data Supplement). The placebo solution consisted of 500 mL of normal saline and 1.2% dextrose (2.5 g total). The solution was infused for ≥3 hours through a peripheral intravenous line weekly for 30 weeks and then biweekly to bimonthly to complete 40 infusions.

All patients in the trial received a low-dose vitamin and mineral regimen daily while receiving infusions to prevent depletion by the chelation regimen.[6] Evidence-based post-MI therapy was encouraged and monitored by the Coordinating Centers.

Follow-Up

Patients were seen at the baseline visit and at each infusion visit. Once patients completed the infusion phase, they were followed via quarterly telephone calls, annual clinic visits, and a final visit at the 5-year follow-up or at the end of the study whichever came first. Laboratory evaluations included fasting blood glucose levels at baseline and throughout the infusion phase of the trial and fasting lipids at baseline and before infusion 30.

End Points

The primary end point was a composite of death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina. The principal secondary end point consisted of a composite of cardiovascular death, reinfarction, or stroke. All end point events were reviewed and adjudicated by a clinical events committee blinded to the randomized treatment assignment.

Statistical Analysis

Secure Web-based permuted block randomization was stratified by clinical site (diabetes mellitus was not a stratification factor). Baseline characteristics of patients were descriptively summarized using the median and interquartile range for continuous variables and frequencies and percentages for categorical variables. The characteristics of patients with diabetes mellitus were compared with the patients without diabetes mellitus using the Wilcoxon rank-sum test for continuous variables and the conventional χ^2 test for categorical variables. The Wilcoxon test was also used for comparing treatment groups with respect to the change in fasting blood glucose from baseline to the last infusion measurement. The log-rank test was used for comparing diabetes mellitus versus non–diabetes mellitus and the chelation versus placebo treatment arms with respect to the primary and secondary clinical outcomes. Although patients could experience >1 component of the composite primary and secondary end points, each patient was counted only once in treatment comparison of these end points using the time until the occurrence of their first event. All treatment comparisons were performed using 2-sided significance tests and included all patients in the treatment group to which they were randomized (intention to treat). Cumulative event rates were calculated according to the Kaplan–Meier method.[10] Relative risks were expressed as hazard ratios (HRs) with associated confidence intervals (CIs) and were calculated using the Cox proportional hazards model.[11] The Cox model was also used for assessing a treatment by diabetes mellitus interaction. Although nominal P values for treatment comparisons are reported, conservative Bonferroni-adjusted[12] CIs and P values, adjusted for 9 different subgroup factors, are also reported. Consistent with the overall study report[5], statistical significance for comparisons of the primary

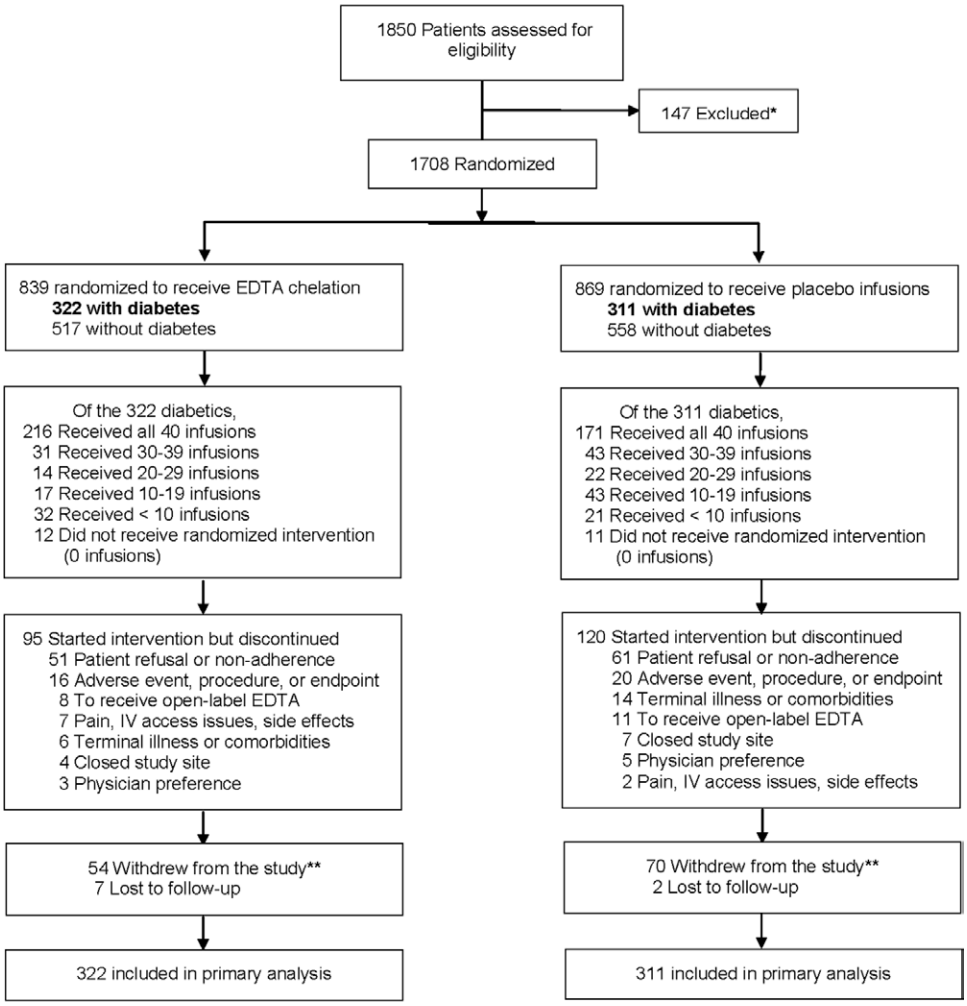

Figure 1. Consort Diagram. *Screened patients not randomized because of inclusion/exclusion criteria, unwillingness to participate, or other reasons. **Among patients who withdrew from the study or were lost to follow-up, 18 met the primary end point before withdrawal or becoming lost. Among the patients who had not experienced an event before withdrawal or becoming lost, 6 were found through search of death registries to have died. All of these events were included in the primary end point analysis. IV indicates intravenous.

end point was defined as $P<0.036$. For other comparisons, significance was defined as $P<0.05$. Number needed to treat with associated CI was calculated using the inverse of the absolute risk reduction in 5-year Kaplan–Meier event rates. Final statistical analyses were performed using SAS software, versions 8.2 and 9.2 (SAS Institute Inc).

Sensitivity Analyses

To assess the robustness of study findings in the face of patients that withdrew consent or were lost to follow-up, post hoc sensitivity analyses were performed with imputation of missing outcome data, as previously published.[6] The event rates among patients that withdrew or were lost to follow-up in each treatment group were varied across a broad spectrum and included scenarios that were markedly unfavorable to chelation. These imputed event rates were combined with the observed event rates to assess the treatment effect and the robustness of the findings in the treatment group comparisons.

Results

A total of 1708 patients were enrolled in TACT, of which 633 (37.1%) had diabetes mellitus according to the expanded definition.

Baseline Characteristics of Patients With and Without Diabetes Mellitus

Compared with patients without diabetes mellitus, fasting blood sugar and body mass index were higher in patients with diabetes mellitus (Table 1). Patients with diabetes mellitus also had a higher prevalence of congestive heart failure, stroke, hypertension, and hypercholesterolemia than patients without diabetes mellitus. There was a particularly high prevalence of peripheral artery disease in patients with diabetes mellitus compared with patients without diabetes mellitus. The proportion of patients who had undergone a coronary revascularization procedure (either coronary artery bypass or percutaneous coronary intervention) was >80% and similar in the 2 groups. Patients with diabetes mellitus were treated more aggressively with blockade of the renin–angiotensin system (73% versus 58%; $P<0.001$) and β-blockers (75% versus 70%; $P=0.012$) than patients without diabetes mellitus. Patients with diabetes mellitus had a lower fasting low-density lipoprotein-cholesterol than patients without diabetes mellitus but lower high-density lipoprotein at study enrollment (Table 1).

Outcome Events by Diabetes Mellitus Status

When compared with patients without diabetes mellitus, patients with diabetes mellitus were more likely to experience the primary end point (197 [31%] versus 286 [27%]; log-rank, $P=0.009$), the secondary end point (87 [14%] versus 122 [11%]; $P=0.057$), and death from any cause (82 [13%] versus 98 [9%]; log-rank, $P=0.003$).

Table 1. Baseline Characteristics of Patients With or Without Diabetes Mellitus

	Diabetes Mellitus (n=633)	Non–Diabetes Mellitus (n=1075)	*P* Value
Demographics			
Age, y	65.4 (59.7, 71.3)	65.2 (58.7, 72.5)	0.784
Women	119 (19%)	180 (17%)	0.280
Minority (Hispanic or non-white)	68 (11%)	88 (8%)	0.077
BMI, kg/m^2	31.8 (28.0, 36.0)	28.8 (25.9, 32.3)	<0.001
History			
Time from qualifying MI to randomization, y*	4.5 (1.5, 9.2)	4.6 (1.8, 9.2)	0.467
Anterior MI	239 (38%)	435 (40%)	0.269
Congestive heart failure	145 (23%)	162 (15%)	<0.001
Valvular heart disease	68 (11%)	107 (10%)	0.570
Stroke	51 (8%)	60 (6%)	0.045
Peripheral vascular disease	136 (22%)	132 (12%)	<0.001
Hypertension	494 (78%)	675 (63%)	<0.001
Hypercholesterolemia	528 (85%)	842 (80%)	0.013
Atrial fibrillation	85 (14%)	110 (11%)	0.041
Former cigarette smoker	354 (56%)	601 (56%)	0.994
Coronary revascularization			
CABG	313 (49%)	461 (43%)	0.008
PCI	353 (56%)	654 (61%)	0.040
Either CABG or PCI	515 (81%)	899 (84%)	0.230
Presenting characteristics			
Blood pressure			
Systolic	130 (120, 140)	130 (118, 140)	0.094
Diastolic	74 (68, 80)	77 (70, 81)	0.001
Concomitant medications			
Aspirin	531 (84%)	896 (83%)	0.772
β-Blocker	477 (75%)	749 (70%)	0.012
Statin	479 (76%)	769 (72%)	0.063
ACEi or ARB	460 (73%)	624 (58%)	<0.001
Clopidogrel	161 (27%)	264 (25%)	0.642
Warfarin	65 (11%)	83 (8%)	0.070
Aspirin, warfarin, or clopidogrel	582 (92%)	970 (91%)	0.202
Diabetes mellitus medication			
Insulin	160 (26%)	0 (0%)	<0.001
Oral hypoglycemic	380 (61%)	0 (0%)	<0.001
Multivitamin	242 (40%)	473 (45%)	0.026
Other vitamins/minerals	292 (47%)	560 (53%)	0.020
Herbal products	190 (31%)	370 (36%)	0.088
Laboratory examinations			
Fasting glucose, mmol/L	7.3 (6, 9)	5.4 (5, 5.8)	<0.001
Creatinine, μmol/L	97.2 (79.6, 114.9)	97.2 (79.6, 106.1)	0.030
Total cholesterol, mmol/L	4.2 (3.6, 5)	4.3 (3.7, 5.1)	0.047
HDL, mmol/L	1.1 (0.9, 1.2)	1.1 (0.9, 1.3)	<0.001
LDL, mmol/L	2.1 (1.6, 2.9)	2.3 (1.8, 3)	<0.001
Triglycerides, mmol/L	1.7 (1.2, 2.6)	1.5 (1, 2.1)	<0.001

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

*Median, 25th and 75th percentiles are reported for all continuous variables. To convert to mg/dL, divide by: fasting glucose (0.0555), creatinine (76.26), total cholesterol, HDL and LDL (0.0259), triglycerides (0.0113).

Baseline Characteristics of Patients With Diabetes Mellitus by Infusion Arm

Among patients with diabetes mellitus, 322 were randomized to receive the EDTA chelation-based infusion regimen and 311 received placebo infusions. Baseline characteristics were similar between the treatment groups (Table 2).

Fasting Glucose and Diabetes Mellitus Medications During Follow-Up

There was no EDTA-treatment–based difference in fasting blood glucose from baseline to last infusion requiring a blood draw (chelation glucose change from baseline to last follow-up, 1.0 mg/dL [−29, 24]; placebo, 1.5 mg/dL [−23, 25]; P=0.64). Among patients with diabetes mellitus who completed 30 infusions and had paired medication data on insulin status at the prerandomization visit and at the 30th infusion (n=429), 101 (23.5%) received insulin for diabetes mellitus management at baseline when compared with 100 (23.3%) patients at the 30th infusion. Among the 438 patients with paired data on oral hypoglycemic status, 282 (64.3%) took oral hypoglycemics at baseline when compared with 272 (62.1%) patients at the 30th infusion. These numbers, which reflect minimal changes in medications for diabetes mellitus, were consistent in the 2 treatment arms.

Outcome Events in Patients With Diabetes Mellitus by Infusion Group

The incidence of the primary end point for an extended follow-up of ≈5 years was significantly lower in the EDTA chelation group when compared with placebo (HR, 0.59; 95% CI, 0.44–0.79; P<0.001), with a 15% absolute decrease in the 5-year Kaplan–Meier primary event rate (Figure 2A; Table 3) and a relative reduction of 41%. The result remained significant after Bonferroni adjustment for multiple subgroups (99.4% CI, 0.39–0.88; adjusted P=0.002). The number needed to treat to prevent a single event over 5 years was 6.5 (95% CI, 4.4–12.7). Rates of the secondary end point in patients with diabetes mellitus were also lower for patients randomized to EDTA chelation (HR, 0.60; 95% CI, 0.39–0.91; P=0.017), with a 5.1% absolute decrease in the 5-year Kaplan–Meier event rate and a relative reduction of 40% (Figure 3A). However, this result was not significant after adjusting for multiple subgroups (99.4% CI, 0.32–1.09; adjusted P=0.153). In contrast to the treatment effect observed in patients with diabetes mellitus, patients without diabetes mellitus (n=1075) did not have a treatment effect with regards to the primary end point (HR, 1.02; 95% CI, 0.81–1.28; P=0.877) or the secondary end point (HR, 1.06; 95% CI, 0.74–1.50; Figures 2B and 3B; Table 4). There was a significant interaction between diagnosis of diabetes mellitus and EDTA treatment (P for interaction for the primary end point, 0.0037).

Patients with diabetes mellitus randomized to EDTA chelation had a significant reduction in recurrent MI (HR, 0.48; 95% CI, 0.26–0.88; P=0.015; Figure 4A), in all-cause mortality (HR, 0.57; 95% CI, 0.36–0.88; P=0.011; Figure 4B), and in coronary revascularizations (HR, 0.68; 95% CI, 0.47–0.99; P=0.042). However, after applying the Bonferroni adjustment to these results, they no longer met the criterion for significance. We also analyzed whether patients with diabetes mellitus randomized in chelation sites were more likely to demonstrate a therapeutic benefit of EDTA chelation than patients randomized in conventional sites. The results show the opposite to be the case (Figure I in the Data Supplement).

Treatment Adherence

Among the subgroup with diabetes mellitus, the median number of infusions received was 40 (25, 40); 73% completed 30 infusions; 61% completed 40 infusions; and 34% discontinued study infusions (n=120 [39%] in the placebo group and n=95 [30%] in the chelation group).

Safety

There were 95 serious adverse events (non–end point events) in the population with diabetes mellitus (56 placebo and 39 active). Adverse events attributable to the study medication led 5.7% to withdraw from the trial (20 placebo and 16 active).

Sensitivity Analyses

As a sensitivity analysis, we assessed the baseline characteristics of the subgroup of patients who withdrew consent (Table V in the Data Supplement). We then assessed how the primary treatment comparison in the subgroup of patients with diabetes mellitus would be affected under a variety of assumptions on the occurrence of primary end point events among the patients who withdrew consent or were lost to follow-up and did not have an end point event before exiting the study (106 consent withdrawals and 9 lost to follow-up; Table VI in the Data Supplement). To assess robustness of the results, these analyses focused on scenarios in which events among withdrawn or lost patients in the active arm were assumed to occur at a higher rate than withdrawn or lost patients in the placebo arm. For all realistic scenarios, the comparison of the 2 arms remained highly significant even if the relative increase of events among patients in the active arm who withdrew or were lost was as much as 100% higher than among withdrawn or lost patients in the placebo arm. The HR for all scenarios was in the range of 0.60 to 0.80, the P values were very robust, and significance of the treatment effect was maintained, even for imputation scenarios that were very unfavorable to the EDTA chelation arm. Finally, we reported the small number of missing values for baseline characteristics in the overall population (Table VII in the Data Supplement) and in the population with diabetes mellitus (Table VIII in the Data Supplement).

Discussion

The present study of EDTA-based chelation therapy in patients with diabetes and a prior MI demonstrates a 41% (P<0.001) relative reduction in the risk of a combined cardiovascular end point; a reduction in risk of the composite of cardiovascular mortality, nonfatal stroke, or nonfatal MI of 40% (P=0.017); a 52% reduction in recurrent MI (P=0.015); and a reduction in death from any cause of 43% (P=0.011). These findings, if replicable, would have an effect on the health of patients with diabetes mellitus. However, we emphasize that these

Table 2. Baseline Characteristics of Patients With Diabetes by Infusion Arm

	EDTA Chelation (N=322)	Placebo (N=311)	*P* Value
Demographics			
Age, y	65.1 (60.3, 71.1)	66.2 (58.8, 71.5)	0.843
Women	55 (17%)	64 (21%)	0.260
Minority (Hispanic or non-white)	31 (10%)	37 (12%)	0.357
BMI, kg/m^2	31.1 (27.9, 35.9)	32.1 (28.4, 36.4)	0.208
History			
Time from qualifying MI to randomization, y*	4.2 (1.6, 8.8)	5.1 (1.4, 9.5)	0.457
Anterior MI	128 (40%)	111 (36%)	0.292
Congestive heart failure	76 (24%)	69 (22%)	0.672
Valvular heart disease	34 11%)	34 (11%)	0.821
Stroke	26 (8%)	25 (8%)	0.987
Peripheral vascular disease	69 (22%)	67 (22%)	0.954
Hypertension	251 (78%)	243 (78%)	0.955
Hypercholesterolemia	273 (86%)	255 (84%)	0.436
Atrial fibrillation	36 (12%)	49 (16%)	0.086
Former cigarette smoker	181 (56%)	173 (56%)	0.882
Coronary revascularization			
CABG	163 (51%)	150 (48%)	0.548
PCI	187 (58%)	166 (53%)	0.234
Either CABG or PCI	271 (84%)	244 (78%)	0.065
Presenting characteristics			
Blood pressure			
Systolic	130 (120, 140)	130 (120, 140)	0.681
Diastolic	74 (68, 80)	74 (68, 80)	0.937
Concomitant medications			
Aspirin	278 (86%)	253 (81%)	0.088
β-blocker	248 (77%)	229 (74%)	0.323
Statin	247 (77%)	232 (75%)	0.536
ACEi or ARB	234 (73%)	226 (73%)	1.000
Clopidogrel	86 (28%)	75 (25%)	0.550
Warfarin	34 (11%)	31 (11%)	0.845
Aspirin, warfarin, or clopidogrel	296 (93%)	286 (92%)	0.909
Diabetes mellitus medication			
Insulin	73 (23%)	87 (29%)	0.114
Oral hypoglycemic	191 (60%)	189 (63%)	0.585
Multivitamin	115 (37%)	127 (43%)	0.112
Other vitamins/minerals	142 (45%)	150 (51%)	0.147
Herbal products	94 (30%)	96 (33%)	0.419
Laboratory examinations			
Fasting glucose, mmol/L	7.1 (5.9, 8.9)	7.4 (6, 9.1)	0.167
Creatinine, μmol/L	88.4 (79.6, 114.9)	97.2 (79.6, 114.9)	0.019
Total cholesterol, mmol/L	4.1 (3.5, 4.9)	4.3 (3.6, 5.2)	0.037
HDL, mmol/L	1.1 (0.9, 1.2)	1.1 (0.9, 1.2)	0.553
LDL, mmol/L	2.1 (1.6, 2.7)	2.2 (1.6, 3)	0.111
Triglycerides, mmol/L	1.7 (1.2, 2.5)	1.8 (1.2, 2.7)	0.299

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

*Median, 25th and 75th percentiles are reported for all continuous variables.

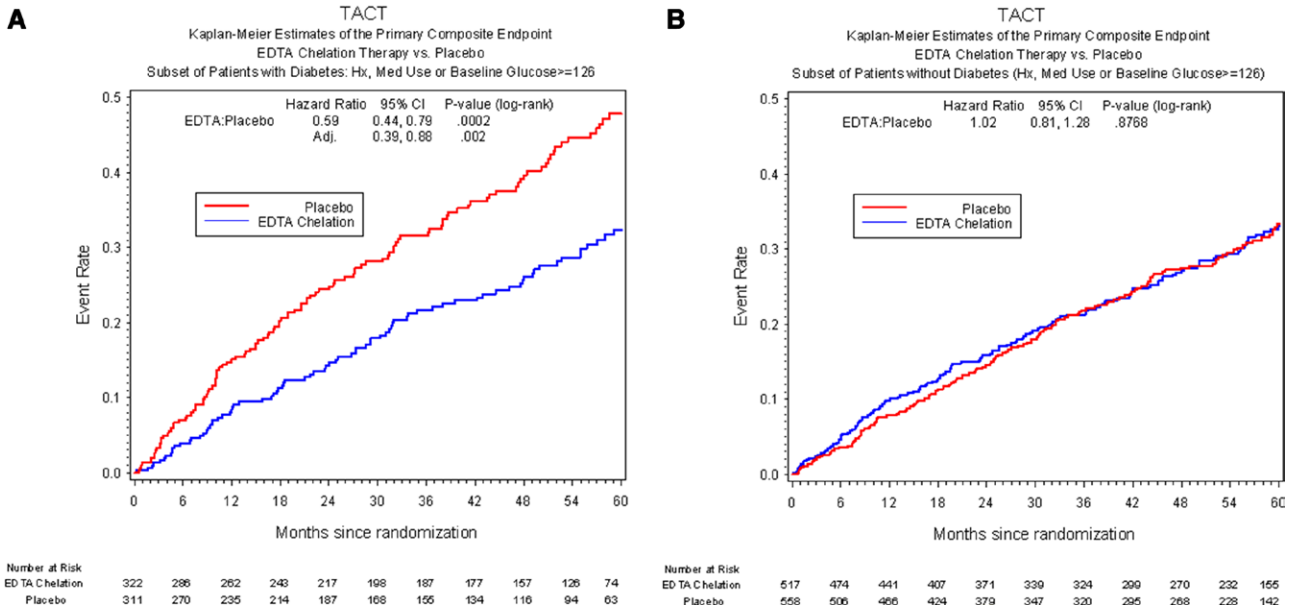

Figure 2. Primary end point in patients with diabetes mellitus (**A**) and without diabetes mellitus (**B**). CI indicates confidence interval; and TACT, Trial to Assess Chelation Therapy.

results are based on a subgroup of the overall trial, albeit prespecified, and, therefore, must be interpreted with caution. Although there was a significant interaction of treatment with diabetes mellitus status, we have provided conservatively adjusted CIs and *P* values to account for the multiplicity of prespecified subgroups. However, even with adjustment, the effect of EDTA chelation therapy in reducing the primary composite end point is highly significant. Although the Bonferroni-adjusted results for the components of the primary end point and for the secondary end point do not meet the nominal criterion for significance, the magnitude of the treatment effect for each major component, including mortality, and for the key secondary end point is remarkably consistent with the primary result.

The US Centers for Disease Control and Prevention report that there are >24 million Americans with diabetes mellitus diagnosed and an estimated 6 million more undiagnosed.[13] Minorities are disproportionately affected adding to their burden of disease.[14] In a meta-analysis of almost a million patients, diabetes mellitus was associated with a 2-fold increased risk of vascular death.[15] Diabetes mellitus increases the risk of mortality and cardiovascular events in patients with established cardiovascular disease.[16] This excess risk was demonstrated within our study as well, with a 27% relative increase in risk of the primary end point when compared with the patients without diabetes mellitus and a 56% relative increase in the risk of death. Moreover, patients with diabetes mellitus were more likely to be obese and were more likely to have a history of congestive heart failure, stroke, peripheral artery disease, hypertension, and hypercholesterolemia than those patients without diabetes mellitus. These differences in risk factors, of course, may explain some of the differences in clinical outcomes overall.

Analyses of prespecified subgroups in TACT suggested that patients with diabetes mellitus accrued particular benefit from

Table 3. Clinical End Points by Infusion Arms for Patients With Diabetes Mellitus

End Point	EDTA Chelation (n=322)	Placebo (n=311)	Hazard Ratio (95% CI)	*P* Value	Adjusted* CI	Adjusted* *P* Value
Primary end point	80 (25%)	117 (38%)	0.59 (0.44–0.79)	<0.001	0.39–0.88	0.002
Death	32 (10%)	50 (16%)	0.57 (0.36–0.88)	0.011	0.30–1.06	0.099
MI	16 (5%)	30 (10%)	0.48 (0.26–0.88)	0.015	0.20–1.13	0.135
Stroke	4 (1%)	3 (1%)	1.19 (0.27–5.30)	0.829	0.14–9.88	…
Coronary revascularization	48 (15%)	62 (20%)	0.68 (0.48–0.99)	0.042	0.40–1.16	0.378
Hospitalization for angina	5 (2%)	6 (2%)	0.72 (0.22–2.36)	0.588	0.13–3.87	…
Secondary end point	35 (11%)	52 (17%)	0.60 (0.39–0.91)	0.017	0.32–1.09	0.153
Cardiovascular death	19 (6%)	27 (9%)	0.63 (0.35–1.13)	0.118	0.27–1.44	…

CI indicates confidence interval; and MI, myocardial infarction.

*Bonferroni adjustment for 9 subgroup factors. CIs are adjusted to a level of 99.4%, and *P* value is 9× the nominal *P* value.

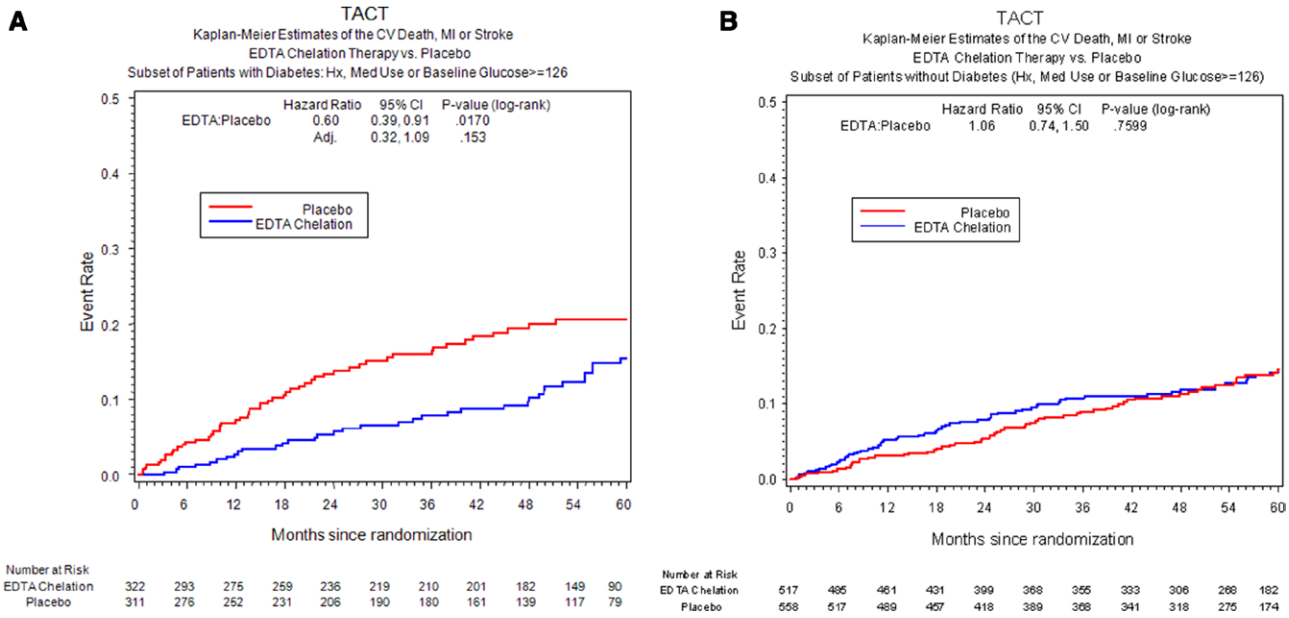

Figure 3. Secondary end point in patients with diabetes mellitus (**A**) and without diabetes mellitus (**B**). CI indicates confidence interval; CV, cardiovascular; MI, myocardial infarction; and TACT, Trial to Assess Chelation Therapy.

EDTA-based infusions.[6] The present work expands on those preliminary observations.

In this study, the EDTA-based chelation regimen markedly improved the clinical outcomes of patients with diabetes mellitus, with a number needed to treat to prevent 1 primary end point event over 5 years of 6.5 (95% CI, 4.4–12.7). Thus, the multicomponent EDTA-based chelation regimen demonstrated a robust reduction in events in this subgroup analysis. This has particular relevance when considering that patients were taking standard, evidence-based medications for patients with post-MI, and patients with diabetes mellitus had a median low-density lipoprotein of 83 mg/dL. We found no improvement in glycemia in the diabetes mellitus subgroup. Other mechanisms must underlie these findings.

The benefits of the multicomponent EDTA-based infusions may be mediated through the chelation of metals, thereby reducing direct end-organ toxicity, as well as toxicity mediated through enhanced metal-catalyzed oxidation. Epidemiological studies support the concept that metals, including lead and cadmium, are linked to cardiovascular risk[17–20] and EDTA chelates both.[21] Clinical trials of patients with advanced chronic kidney disease and chelatable lead, treated with EDTA infusions, have shown preservation of renal function.[22,23] Yet these observations do not explain why there is a significant interaction of chelation treatment with diabetes mellitus status.

However, there are hypotheses on specific effects of metals on patients with diabetes mellitus that have been proposed for >20 years. Complications of diabetes mellitus are at least partially mediated through the accumulation of advanced glycation end products and activation of the receptor of advanced glycation end products,[24] with downstream inflammatory cascades.[25,26] Glycation end-products are created by the nonenzymatic interaction of glucose with proteins, lipids, and nucleic acids.[27] Most advanced glycation end-products require metal-catalyzed oxygen chemistry for their formation. Metals bind to glycation end-products and promote the formation of reactive oxygen species in an autocatalytic reaction. The resultant oxidized end-products accumulate in tissues and promote inflammation and oxidative stress, hallmarks of atherosclerosis. Thus, chelation of metal ions may have particular importance in patients with diabetes mellitus.[28,29] Interestingly, some medications commonly used in diabetes mellitus may also have chelating properties.[30–32]

Table 4. Clinical End Points by Infusion Arms for Patients Without Diabetes Mellitus

End Point	EDTA Chelation (n=517)	Placebo (n=558)	Hazard Ratio (95% CI)	*P* Value
Primary end point	142 (27%)	144 (26%)	1.02 (0.81–1.28)	0.877
Death	55 (11%)	43 (8%)	1.35 (0.90–2.01)	0.137
MI	36 (7%)	37 (7%)	1.03 (0.65–1.64)	0.872
Stroke	6 (1%)	10 (2%)	0.65 (0.24–1.80)	0.406
Coronary revascularization	82 (16%)	95 (17%)	0.90 (0.67–1.21)	0.474
Hospitalization for angina	8 (2%)	12 (2%)	0.71 (0.29–1.74)	0.440
Secondary end point	61 (12%)	61 (11%)	1.06 (0.74–1.50)	0.760
Cardiovascular death	31 (6%)	24 (4%)	1.37 (0.81–2.34)	0.239

CI indicates confidence interval; and MI, myocardial infarction.

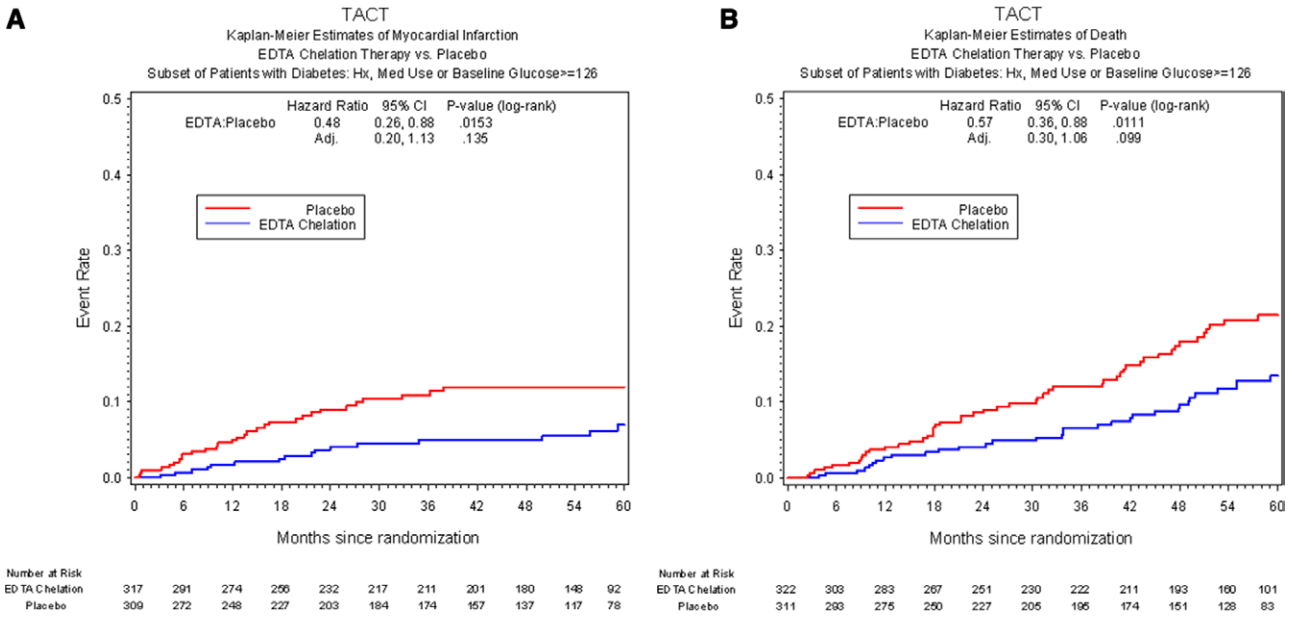

Figure 4. Myocardial infarction (**A**) and mortality (**B**) in patients with diabetes mellitus by infusion group.

The benefits reported here for EDTA chelation potentially support a mechanism linking metal ions to oxidative stress and vascular complications, particularly in patients with diabetes mellitus and certainly merit further study. Of particular, albeit inferential importance is the continued separation of event curves late in the trial, long after infusions have stopped, suggesting that removal of toxic xenobiotic metals may have long-term benefit in these patients.

There remain important limitations of these analyses. First and foremost, although this subgroup analysis was prespecified, subgroup findings, regardless of how robust they appear, must be considered hypothesis generating, rather than conclusive or definitive and must be replicated. Likewise, *P* values, although nominally significant, must also be interpreted cautiously, particularly as there were multiple subgroups analyzed. Adjusted *P* values, using the conservative Bonferroni correction, have been displayed for comparison. An unexpectedly high number of patients withdrew consent, including a slightly higher percentage among patients with diabetes mellitus compared with patients without diabetes mellitus, somewhat limiting the events that could be accrued and attributed during follow-up. Given that more placebo patients than chelation patients withdrew consent, however, the bias is conservative. That is, the effect of active treatment is likely underestimated by the analyses presented. We performed sensitivity analyses of patients that withdrew consent, making adverse assumptions as to their outcomes in the active therapy arm, and found that the findings reported here remain robust. Finally, although there are plausible hypotheses on the effects of this therapy, we do not have measurements of the levels of metals, glycation end-products, or oxidative stress to corroborate or refute our hypotheses. Therefore, future studies should be planned and include bioassay assessment of potential pathways to clarify the mechanisms of benefit.

Conclusions

Patients with post-MI diabetes mellitus aged ≥50 years on evidence-based medications demonstrated a marked reduction in cardiovascular events, including total mortality in the unadjusted analyses, with EDTA-based chelation therapy. These findings support the initiation of clinical trials in patients with diabetes mellitus and vascular disease to replicate these findings and define the mechanisms of benefit. However, they do not constitute sufficient evidence to indicate the routine use of chelation therapy for all patients with post-MI diabetes mellitus.

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Disclosures

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 ties were severed as of September 10, 2003. The other authors report no conflicts.

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