Supplementary Appendix

This appendix has been prepared by the authors to provide readers additional details and information about the TACT study.

Supplement to Lamas GA, Goertz C, Boineau R, Mark DB. Rozema T, Nahin RL, Lindblad L, Lewis ER, Drisko J, Lee KL. Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: The TACT Randomized Trial.

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Supplementary Appendix

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Sample Size Calculations for TACT and Changes in Sample Size

Original Sample Size Calculations:

As stated in the study protocol, several design factors and research objectives were considered when developing the original sample size estimates for TACT. A first important objective was that there be sufficient patients and a sufficient number of endpoints to provide a high degree of confidence (at least 85% power) for detecting clinically important differences between the randomized arms in the primary endpoint. Second, important secondary endpoints, such as measures of quality-of-life, were also considered. Third, we considered it important for the overall sample to be large enough to permit examination of treatment effects in selected pre-specified subgroups of patients where chelation therapy might be particularly advantageous, or where the question of a treatment benefit from chelation therapy is particularly relevant. Fourth, because the treatment protocol was very intensive (requiring frequent clinic visits for intravenous therapy over an extended period of time), it was likely (despite our best efforts) that some patients would prematurely discontinue therapy (drop-out) and thus not realize the full benefits of the intervention. This likelihood was reflected in the sample size calculations. Finally, the sample size was determined to provide a reasonably robust level of confidence of detecting clinically important therapeutic effects even if our projections of event rates and treatment differences proved to be optimistic.

The assumptions used in the original calculations included the following:

- 20% event rate at 2.5 years in the placebo arm
  (This figure took into account the factorial nature of the study and was based on event rates reported in other studies of similar post-MI patients, as described in the TACT protocol.)
- 25% reduction in the active (chelation) arm (i.e., 15% event rate at 2.5 years)
- Accrual period (length of patient recruitment): 3 years
- Minimum length of follow-up: 1 year
  (Thus, the average duration of follow-up in the trial would be 2-2.5 years.)
- Dropout (non-compliance) rate of 7.2% per year (~22% over three years)
  (Estimated based on a careful review of the previous literature in this area and estimates from the experience of contemporary chelation practitioners)
- Loss to follow-up: 3%
- Equal allocation of patients to the two arms of the trial
- $\alpha = 0.05$
- Power = 0.85

Using the Schoenfeld formulation for calculating sample size for the proportional hazards model (Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics* 1983;39:499-503), appropriately factoring in the non-compliance and loss to follow-up, and

making use the nQuery Advisor sample size software, the resulting total sample size was determined to be **2,372.** This was the target sample size at the beginning of the trial.

Changes to the Study Sample Size:

Enrollment progress in the study was closely monitored by the study leadership as well as in regular reviews of the trial by the NIH-appointed Data and Safety Monitoring Board (DSMB). Patient enrollment proved to be much more challenging than expected, due in part to the heavy demands and time required of patients to undergo the intensive treatment regimen of 40 infusions, each infusion requiring at least 3 hours. It soon became apparent that more than the 3 years originally planned for recruitment would be required to accrue the number of patients originally targeted for the trial. New enrollment projections and timelines were developed, with corresponding statistical power calculations (unconditional power) for those projections.

The first major adjustment to sample size was incorporated in the study protocol dated May 5, 2006 (Protocol Version 4). The sample size was adjusted downward to 1,950 patients, the recruitment period was extended to 4.5 years, and with the other assumptions described above, the power of 85% would be preserved.

Enrollment in the study stayed on target with respect to this modification for a time, but challenges, such as the OHRP inquiry during which all enrollment activity was suspended for several months, slowed progress with patient recruitment, and the study fell short of the enrollment rate required to meet the targets outlined in Protocol Version 4.

In July 2009, continued challenges in the recruitment of patients led the TACT study leadership, completely blinded to all outcome information, to request from the NIH sponsors and the DSMB, a reduction of the total enrollment from 1,950 to 1,700, with follow-up extending through 2011. The investigators projected that this number of patients could realistically be achieved by the 3rd quarter of 2010, allowing at least one full year of follow-up on all patients. With the substantially prolonged enrollment period (approximately 7 years compared to the 3 years originally conceived), the average duration of follow-up for the patients would approach 5 years (instead of the 2-2.5 years originally conceived). This extension in the length of follow-up allowed the unconditional statistical power for the trial to remain at 85%.

Final Note:

It is noteworthy that at the end of the trial after the data were all compiled, the 2.5-year event rate in the placebo arm was 21.6%, slightly higher but remarkably close to the 20% that was projected in planning the trial. Hence the statistical power was not attenuated because of a lower than expected event rate.

Interim Monitoring in TACT and the Final Criterion for Significance

Concerns have been raised about the interpretation of the overall findings in the trial, particularly in view of the relatively large number of interim analyses and the fact that the final p-value fell so close to the required level of significance, and the upper level of the confidence interval for the hazard ratio (0.99) is so close to 1.0.

To ensure the safety of patients enrolled in trials like TACT, it is standard practice in NHLBI-sponsored trials for the DSMB to meet approximately every six months. This frequency of meetings is the pattern that was followed in TACT. With the unknown short and long-term consequences of this therapy, the scrutiny this trial was receiving from outside critics, and the significant investment of public funds that was required to conduct the trial, the DSMB desired a comprehensive report of the accumulating data at these regular meetings. This frequency, combined with the prolonged duration of the trial, explains the number of interim reviews of the data (11). Although many of those reviews were mainly for safety and review of adverse events with no intent of stopping the trial for efficacy, we have nonetheless reported and counted every review in which the DSMB had access to treatment-specific outcome data. The pre-specified statistical plan for the study made provision for interim reviews of the primary outcome data by using the well-established flexible approach involving an alpha-spending function with O'Brien-Fleming type monitoring boundaries as outlined in the study protocol. This particular approach to interim monitoring has been used frequently in clinical trials because the number of analyses and the timing of those analyses do not need to be pre-specified. What is pre-specified is the rate at which the overall alpha is "spent." The O'Brien-Fleming type boundaries are very broad in the early part of the trial so that a rather dramatic result is required to cross an efficacy boundary, and thus very little of the overall alpha is "spent" in the early reviews of the data. With such boundaries, it is highly unlikely that a type I error would be committed early in the trial. As more information accumulates, the height of the boundaries gradually decreases so that at the end of the trial, the final analysis can be performed with a relatively modest adjustment to the overall level of significance chosen for the trial.

The statistical formulation of the O'Brien-Fleming-like cumulative alpha spending function is

$$\alpha(t) = \; 2[\,1 - \phi(z_{\alpha/2}\,/t^{1/2})]$$

where ϕ is the standard normal cumulative distribution function, $z_{\alpha/2}$ is the $\alpha/2$ percentage point of the standard normal distribution, and t represents the information time when the analysis is performed. At the end of the trial (t=1), if the overall level of significance chosen for the trial is 0.05, the value of this expression is simply 0.05, so that all of the alpha is spent.

The table below shows the O'Brien-Fleming type monitoring boundaries for each of the 11 interim reviews of the data, the cumulative alpha spent up to and including the final analysis, and

on the bottom row of the table, the level of significance (0.036) required at the final analysis. As can be seen in the right-hand column, very little alpha was spent for the first 5 or 6 analyses.

Regarding the final alpha level, the results have been checked and the calculations verified by an independent senior-level experienced statistician.

Table A-1. Interim analyses and monitoring boundaries

Interim	Lower Monitoring Boundary	Upper Monitoring Boundary	p-value required for significance	Cumulative alpha
1	-8.0000	8.0000	<0.00001	0.00000
2	-8.0000	8.0000	<0.00001	0.00000
3	-4.3320	4.3320	0.00001	0.00001
4	-3.7166	3.7166	0.00002	0.00021
5	-3.3008	3.3008	0.00096	0.00103
6	-2.9981	2.9981	0.00272	0.00305
7	-2.7656	2.7656	0.00568	0.00668
8	-2.5798	2.5798	0.00989	0.01210
9	-2.4271	2.4271	0.01522	0.01930
10	-2.2986	2.2986	0.02153	0.02815
11	-2.1886	2.1886	0.02863	0.03846
Final	-2.0930	2.0930	0.03635	0.05000

Consent Withdrawals and Loss to Follow-up

As reported in the primary manuscript, there were a total of 289 patients (17%) who, during the course of the trial, withdrew consent for continued follow-up in the study. Of the 289 withdrawals, 115 (40%) were in the EDTA chelation arm, and 174 (60%) were in the placebo arm. A plot of Kaplan-Meier curves depicting the pattern of consent withdrawals in the two randomized arms is presented in Figure A-1, including a statistical assessment of the difference between arms. There were a significantly greater number of placebo patients who withdrew consent compared to the active arm in the trial. The median (IQR) duration of follow-up of the withdrawn patients was 10 (3, 25) months overall, 10 (3, 28) months in the EDTA arm and 10 (3, 23) months in the placebo arm.

In addition to the patients who withdrew consent, at the end of the trial there were 22 patients who, despite concerted efforts, could not be located, and therefore were lost to follow-up (13 in the chelation arm and 9 in the placebo arm). The median (IQR) duration of follow-up of those patients before they became lost was 37 (23, 47) months overall, 37 (33, 47) months in the EDTA chelation arm and 31 (23, 42) months in the placebo arm. With an average of approximately 3 years of follow-up in these patients, the loss of information was less than the loss among patients who withdrew consent.

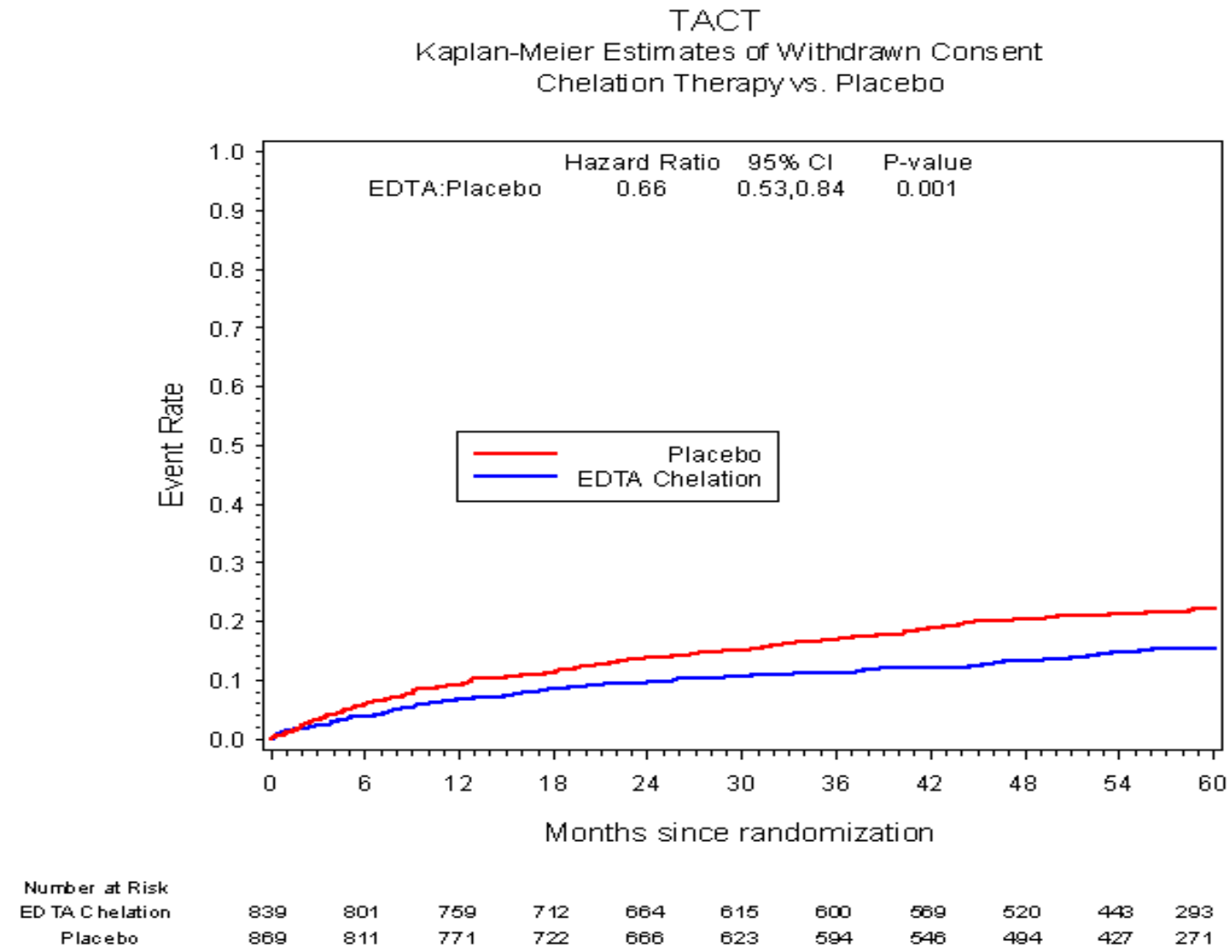
The patients who withdrew consent or were lost to follow-up were included in the analysis with as much follow-up (person-time) as was available until they withdrew consent or were lost to follow-up, at which time the patient became a censored observation. However, not all of these patients were censored observations because a number of them (52 of the 289 patients who withdrew consent and 3 of the 22 patients lost to follow-up) experienced one of the primary events, and those events were all included in the primary treatment comparison. Of the 52 withdrawal patients with an event, 43 withdrew consent later in their follow-up after having experienced one of the primary endpoints. Nine of the 52 withdrew consent prior to experiencing the primary endpoint, but in our search of death registries at the end of the trial, were discovered to have died. The primary analysis was based on all of the outcomes that were known, without any imputation of outcomes in the patients who withdrew consent or were lost to follow-up. However, some sensitivity analyses have been performed to assess the robustness of the results under different assumptions about event rates among the patients who withdrew consent. Those analyses are described in the next section of this supplement.

In Table A-2, baseline characteristics of the 289 patients who withdrew consent are compared with corresponding characteristics of the patients enrolled in TACT who did not withdraw consent. There are statistically higher percentages of females, anterior MIs, diabetics, and patients with a history of stroke among the patients who withdrew consent, which could translate into a slightly higher risk profile for the consent withdrawal patients. By the same token, diabetes and prior anterior myocardial infarction were markers, in the subgroup analyses, for significant benefit from chelation therapy.

Of key importance, however, is the fact that the baseline characteristics of the patients who withdrew consent are very comparable in the two arms of the trial (Table A-3). That is, the risk profiles of the EDTA patients and the placebo patients who withdrew consent appear to be remarkably similar. Because there were significantly more patients in the placebo arm who withdrew consent compared to the active chelation arm, among the patients where we may possibly be missing primary outcome events because of consent withdrawals, there are likely more such events in the placebo arm than in the active treatment arm (because there were more withdrawals in the placebo arm), which would only accentuate the benefit of chelation therapy.

These observations are relevant in considering imputations of possible outcomes of the patients who withdrew consent or were lost to follow-up as provided in the sensitivity analyses reported in the next section.

Figure A-1



Note: The p-value is based on the log-rank test.

Table A-2. Baseline Characteristics of the Participants Who Did vs. Did Not Withdraw Consent

	Withdrawn Consent (N= 289)	No Withdrawn Consent (N=1419)	P
Demographics			
Age (years)	64 (58, 71)	65 (59, 72)	0.100
Female	63 (22%)	236 (17%)	0.035
Minority (Hispanic or non-Caucasian)	30 (10%)	126 (9%)	0.419
BMI	31 (27, 36)	30 (27, 33)	0.004
History			
Time from qualifying MI to randomization (years)	4.7 (1.6, 9.1)	4.6 (1.7, 9.3)	0.751
Anterior MI	135 (47%)	539 (38%)	0.006
Congestive heart failure	59 (20%)	248 (17%)	0.236
Valvular heart disease	24 (9%)	151 (11%)	0.298
Stroke	27 (9%)	84 (6%)	0.031
Diabetes	110 (38%)	428 (30%)	0.008
Peripheral vascular disease	50 (17%)	218 (15%)	0.390
Hypertension	199 (69%)	970 (68%)	0.868
Hypercholesterolemia	214 (77%)	1156 (83%)	0.026
Atrial fibrillation	33 (12%)	162 (12%)	0.746
Former Cigarette Smoker	166 (57%)	789 (56%)	0.566
Coronary revascularization			
CABG	134 (46%)	640 (45%)	0.694
PCI	179 (62%)	828 (58%)	0.259
Either CABG or PCI	242 (84%)	1172 (83%)	0.639
Presenting Characteristics			
Blood Pressure (mm Hg)			
Systolic	130 (118, 140)	130 (120, 140)	0.221
Diastolic	78 (70, 82)	76 (70, 80)	0.292
NYHA Functional Class			0.671
No heart failure	221 (76%)	1128 (79%)	
Class I	39 (13%)	171 (12%)	
Class II	23 (8%)	99 (7%)	
Class III	6 (2%)	21 (1%)	
Class IV	0	0	

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415 **Table A-2 (continued)**

	Withdrawn Consent (N= 289)	No Withdrawn Consent (N=1419)	P
Concomitant Medications			
Aspirin	235 (81%)	1192 (84%)	0.261
Beta-blocker	204 (71%)	1022 (72%)	0.621
Statin	204 (71%)	1044 (74%)	0.297
ACEI or ARB	182 (63%)	902 (64%)	0.849
Clopidogrel	66 (25%)	359 (26%)	0.612
Warfarin	32 (12%)	116 (8%)	0.064
Aspirin or warfarin	251 (87%)	1251 (88%)	0.625
Aspirin, warfarin or clopidogrel	258 (90%)	1294 (91%)	0.499
Diabetes medication			
Insulin	43 (16%)	117 (9%)	<0.001
Oral hypoglycemic	71 (26%)	309 (23%)	0.205
Multivitamin	116 (43%)	599 (44%)	0.795
Other vitamins/minerals	112 (41%)	740 (53%)	<0.001
Herbal products	80 (30%)	480 (35%)	0.105
Laboratory Examinations			
Glucose (mg/dL)	106 (95, 131)	102 (92, 119)	<0.001
Creatinine (mg/dL)	1.1 (0.9, 1.2)	1.1 (0.9, 1.2)	0.810
Total cholesterol (mg/dL)	165 (144, 206)	164 (141, 193)	0.098
HDL (mg/dL)	41 (35, 49)	43 (37, 51)	0.045
LDL (mg/dL)	91 (66, 123)	88 (67, 113)	0.310
Triglycerides (mg/dL)	160 (109, 216)	137 (95, 200)	0.005

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

Abbreviations used: ACEI= Angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; HDL = High-density lipoprotein; LDL = low-density lipoprotein

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Table A-3. Baseline Characteristics of Participants Who Withdrew Consent by Treatment Group

	EDTA Chelation (N= 115)	Placebo (N= 174)	P
Demographics			
Age (years)	65 (59, 71)	64 (57, 72)	0.285
Female	23 (20%)	40 (23%)	0.547
Minority (Hispanic or non-Caucasian)	11 (10%)	19 (11%)	0.712
BMI	31 (27, 36)	31 (26, 36)	0.478
History			
Time from qualifying MI to randomization (years)	4.3 (1.7, 8.6)	4.9 (1.5, 9.6)	0.900
Anterior MI	50 (43%)	85 (49%)	0.370
Congestive heart failure	31 (27%)	28 (16%)	0.025
Valvular heart disease	8 (7%)	16 (10%)	0.495
Stroke	12 (10%)	15 (9%)	0.604
Diabetes	46 (40%)	64 (37%)	0.581
Peripheral vascular disease	23 (20%)	27 (16%)	0.301
Hypertension	87 (76%)	112 (64%)	0.043
Hypercholesterolemia	85 (77%)	129 (77%)	0.925
Atrial fibrillation	12 (11%)	21 (13%)	0.676
Former cigarette smoker	66 (57%)	100 (57%)	0.989
Coronary revascularization			
CABG	53 (46%)	81 (47%)	0.938
PCI	74 (64%)	105 (60%)	0.493
Either CABG or PCI	98 (85%)	144 (83%)	0.579
Presenting Characteristics			
Blood Pressure (mm Hg)			
Systolic	130 (118, 142)	128 (118, 136)	0.101
Diastolic	79 (70, 82)	76 (66, 81)	0.092

Table A-3 (continued)

	EDTA Chelation (N= 115)	Placebo (N= 174)	P
NYHA Functional Class			0.200
No heart failure	81 (70%)	140 (80%)	
Class I	18 (16%)	21 (12%)	
Class II	13 (11%)	10 (6%)	
Class III	3 (3%)	3 (2%)	
Class IV	0	0	
Concomitant Medications			
Aspirin	95 (83%)	140 (80%)	0.646
Beta-blocker	88 (77%)	116 (67%)	0.072
Statin	79 (69%)	125 (72%)	0.566
ACEI or ARB	71 (62%)	111 (64%)	0.723
Clopidogrel	22 (20%)	44 (28%)	0.184
Warfarin	16 (15%)	16 (10%)	0.201
Aspirin, warfarin or clopidogrel	102 (90%)	156 (90%)	0.980
Diabetes medication			
Insulin	19 (18%)	24 (15%)	0.450
Oral hypoglycemic	26 (24%)	45 (27%)	0.585
Multivitamin	42 (39%)	74 (45%)	0.362
Other vitamins/minerals	40 (38%)	72 (44%)	0.368
Herbal products	34 (32%)	46 (28%)	0.553
Laboratory Examinations			
Glucose (mg/dL)	109 (96, 138)	104 (94, 129)	0.247
Creatinine (mg/dL)	1.1 (0.9, 1.2)	1.0 (0.9, 1.2)	0.513
Total cholesterol (mg/dL)	165 (145, 212)	165 (144, 204)	0.984
HDL (mg/dL)	41 (35, 48)	41 (35, 50)	0.727
LDL (mg/dL)	93 (68, 126)	89 (65, 121)	0.418
Triglycerides (mg/dL)	157 (109, 213)	162 (108, 222)	0.964

For continuous variables, the median, 25th and 75th percentiles are reported.
Abbreviations used: ACEI = Angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; HDL = High-density lipoprotein; LDL = low-density lipoprotein

Sensitivity Analyses with Imputation of Outcomes in Patients Who Withdrew Consent or Were Lost to Follow-up

As a sensitivity analysis, we have assessed how the primary treatment comparison would be affected under a variety of assumptions regarding the occurrence of primary endpoint events among the patients who withdrew consent or were lost to follow-up. In these analyses, we have imputed events only among the consent withdrawal or lost patients who did not have a documented occurrence of one of the primary events prior to the withdrawn consent. This number includes 289-52 = 237 consent withdrawal patients and 22-3 = 19 patients who were lost to follow-up. We performed treatment comparisons where a certain percentage of the withdrawn or lost patients in each arm were assumed to have a primary event. To simplify the calculations, the event was assumed to occur at the censoring time. The different percentages of the withdrawn or lost patients who, in the sensitivity analyses were assumed to have an event are shown in Table A-4, along with the results of the treatment comparison under each assumption. Since only a certain percentage of the patients were assumed to have an event, 500 replications were performed for each scenario using these percentages to randomly select the patients with events, and the results were then averaged to obtain the estimate of treatment effect.

To further explain the analyses for the 16 scenarios listed in Table A-4, the placebo event rate listed in the table pertains only to the "imputed patients," that is, to the patients randomly allocated to the placebo arm who were among the 237 consent withdrawal patients and the 19 patients lost to follow-up referenced above. Similarly, the event rate in the EDTA column pertains only to the "imputed patients" in the active chelation arm. The events that are imputed among the patients who withdrew consent or were lost to follow-up were then combined with the event data from all of the other patients (those who did not withdraw consent and were not lost to follow up) to compute a hazard ratio, confidence interval, and p-value. If we postulate, for example, that among the withdrawals or lost to follow-up patients, 20% of the placebo patients and 25% of the EDTA arm patients had events, the patients with events were randomly chosen among the candidates. As explained in the paragraph above, 500 replications were performed for each scenario (each time randomly selecting the patients with events) and the results of those replications averaged to obtain the hazard ratio, confidence interval, and p-value.

The percentage of events among the placebo patients who withdrew consent or were lost to follow-up was varied from 10% to 30% in increments of 10. As reported in Table 2 of the primary manuscript, the percentage of patients in the placebo arm who, during the course of the trial, experienced a primary event was 30%. Although a 30% placebo event rate was included as one of the scenarios in the sensitivity analyses, it is unlikely that the proportion of events among the withdrawn or lost patients would be that high, as these patients had survived and were event-free during the portion of the trial in which they were followed. Hence we also considered several scenarios based on lower percentages of events in the withdrawn or lost patients.

For the chelation arm of the trial, we considered percentages of events among the withdrawn or

lost patients ranging from -10% (i.e., lower by 10% than the percentage in the placebo arm) to 25% higher than the percentage in the placebo arm. The major objective of these sensitivity analyses, of course, was to assess the robustness of the overall trial results in the event that among the patients who withdrew consent or were lost to follow-up, there were more patients in the active arm with events compared to the placebo arm. However, given that (a) the active arm patients had fewer events among all the other patients, and (b) as observed in Table A-2, the patients who withdrew consent had higher percentages with diabetes and an anterior wall MI, we felt it was reasonable to also consider scenarios where the percentage of events for the active arm was slightly lower than for the placebo arm.

Scenario 1, for example, is based on the assumption that 10% of the withdrawn or lost patients in the placebo arm experienced an event, and in the active arm, the percentage was 10% less. Scenarios 2-5 reflect increasingly higher percentages of events in the active arm compared to the placebo arm (up to 25% higher) while maintaining the level at 10% in the placebo arm. Scenarios 6-10 have a similar pattern except the percentage of events in the placebo arm is 20%. In scenarios 11-15, the pattern is again similar except the percentage of events in the placebo arm is 30%. Scenario 16 is an extreme case in which all patients who withdrew consent or were lost to follow-up (in both arms) were assumed to experience an event. We have covered a broad spectrum of possibilities with these scenarios where the withdrawn or lost patients in the active arm were assumed to have a higher rate of events compared to the placebo patients in order to see how extreme the difference would have to be before the treatment comparison would no longer meet the criterion for significance.

To explain the other quantities in Table A-4, the "Relative Increase" is simply the relative change in the percentage of events among the withdrawn or lost patients in the active arm compared to the percentage of events among the withdrawn or lost patients in the placebo arm. The hazard ratio and confidence interval in each case is based on the comparison of EDTA vs. placebo (derived from the Cox model), and the p-value is based on the log-rank test. The expected number of events is simply the number of events projected in each arm for each different scenario.

Based on the other data observed in the trial and because the baseline risk factors of the patients who withdrew consent were very similar in the two arms of the trial, the most plausible scenarios in Table A-4 are those where the percentages of events among the withdrawn or lost patients in the two arms are nearly equal or slightly favor the active arm. However, the comparison of the two arms remains significant at the 0.036 level if the relative increase of events in the active arm is as much as 20% higher than in the placebo arm, and even generally if the percentage of events in the active arm is 25% higher than in the placebo arm. The hazard ratio for all of these scenarios remains in the range of 0.80 to 0.84, the p-values are quite robust, and significance of the treatment effect is maintained, not only for the scenarios for the withdrawn or lost patients that would be considered most plausible, but also for scenarios that are unfavorable to EDTA chelation.

Table A-4. Sensitivity Analyses Imputation scenarios for consent withdrawals and patients lost to follow-up.

Scenario	Percent events Placebo Arm*	Percent events EDTA arm*	Relative Increase	Hazard Ratio**	Lower CI	Upper CI	P-value	EDTA events (expected)	Placebo events (expected)
1	10	9	-10	0.82	0.69	0.97	0.0230	233	277
2	10	10	0	0.82	0.69	0.98	0.0258	234	277
3	10	11	10%	0.82	0.69	0.98	0.0290	235	277
4	10	12	20%	0.83	0.70	0.98	0.0322	235	277
5	10	12.5	25%	0.83	0.70	0.99	0.0362	237	277
6	20	18	-10%	0.81	0.68	0.96	0.0149	242	291
7	20	20	0	0.82	0.69	0.97	0.0189	244	291
8	20	22	10%	0.82	0.69	0.97	0.0238	246	291
9	20	24	20%	0.83	0.70	0.99	0.0330	249	291
10	20	25	25%	0.83	0.71	0.99	0.0368	250	291
11	30	27	-10%	0.80	0.69	0.95	0.0095	252	305
12	30	30	0	0.81	0.69	0.96	0.0137	255	305
13	30	33	10%	0.82	0.70	0.97	0.0216	259	305
14	30	36	20%	0.83	0.71	0.98	0.0297	261	305
15	30	37.5	25%	0.84	0.71	0.99	0.0370	263	305
16	100	100	-	0.79	0.68	0.91	0.0015	331	408

* Imputed event rates in patients who withdrew consent or were lost to follow-up and did not have a primary outcome event prior to censoring

** Hazard ratio calculated by combining the imputed outcomes for patients who withdrew consent or were lost to follow-up with the outcomes of patients who completed the study

Distribution of Infusion Discontinuations by Treatment Arm

Figure A-2 in this section is a Kaplan-Meier plot of infusion discontinuations by treatment arm, showing a somewhat higher degree of discontinuations in the placebo arm after approximately six months into the study.

Figure A-3 is a histogram depicting the distribution of the number of infusions received by the patients in each treatment arm. Consistent with Figure A-2, the histogram shows that patients in the placebo arm had slightly fewer infusions than did the patients in the chelation arm, although the treatment arms were comparable with respect to the number of patients who received >35 infusions.

Figure A-2

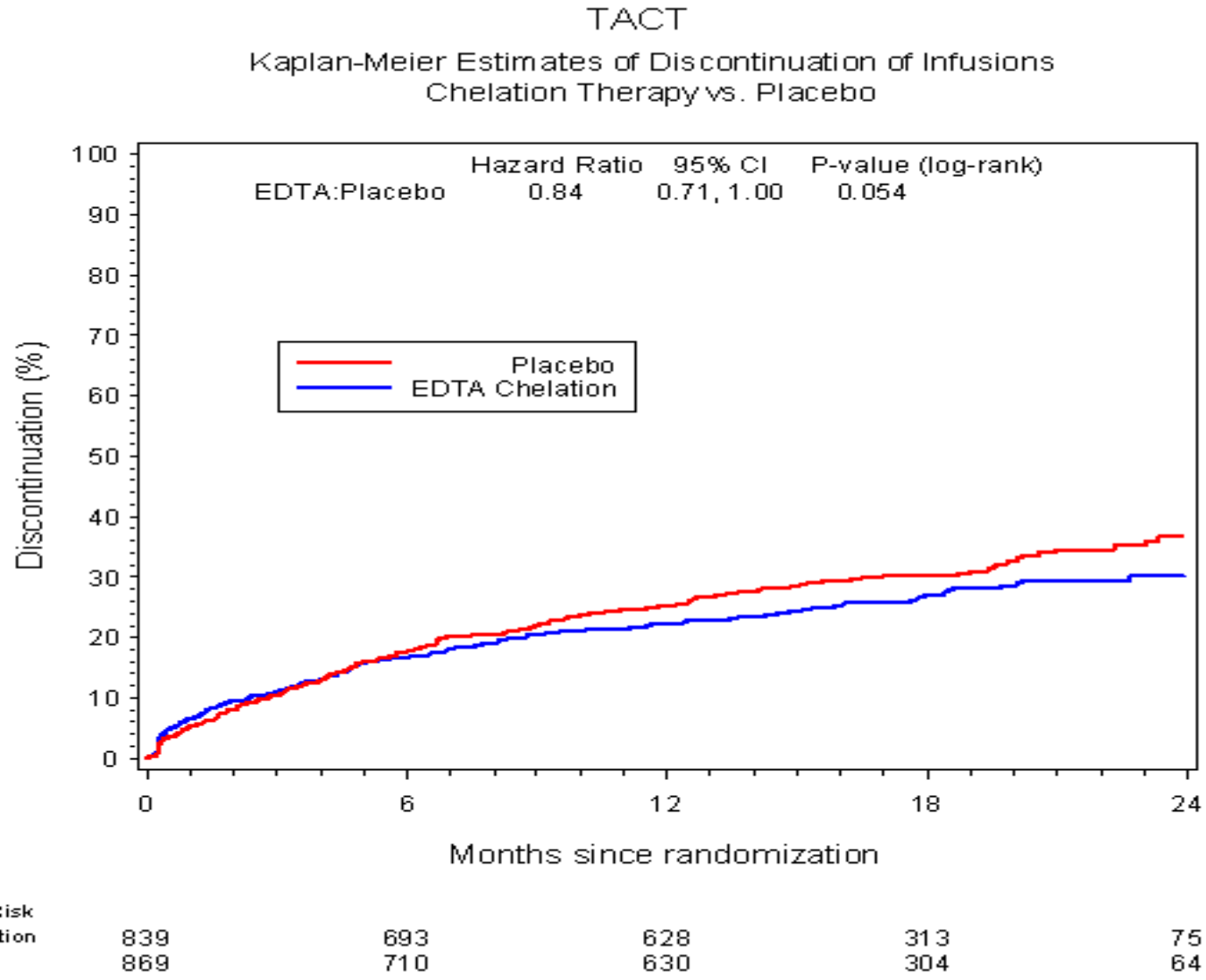
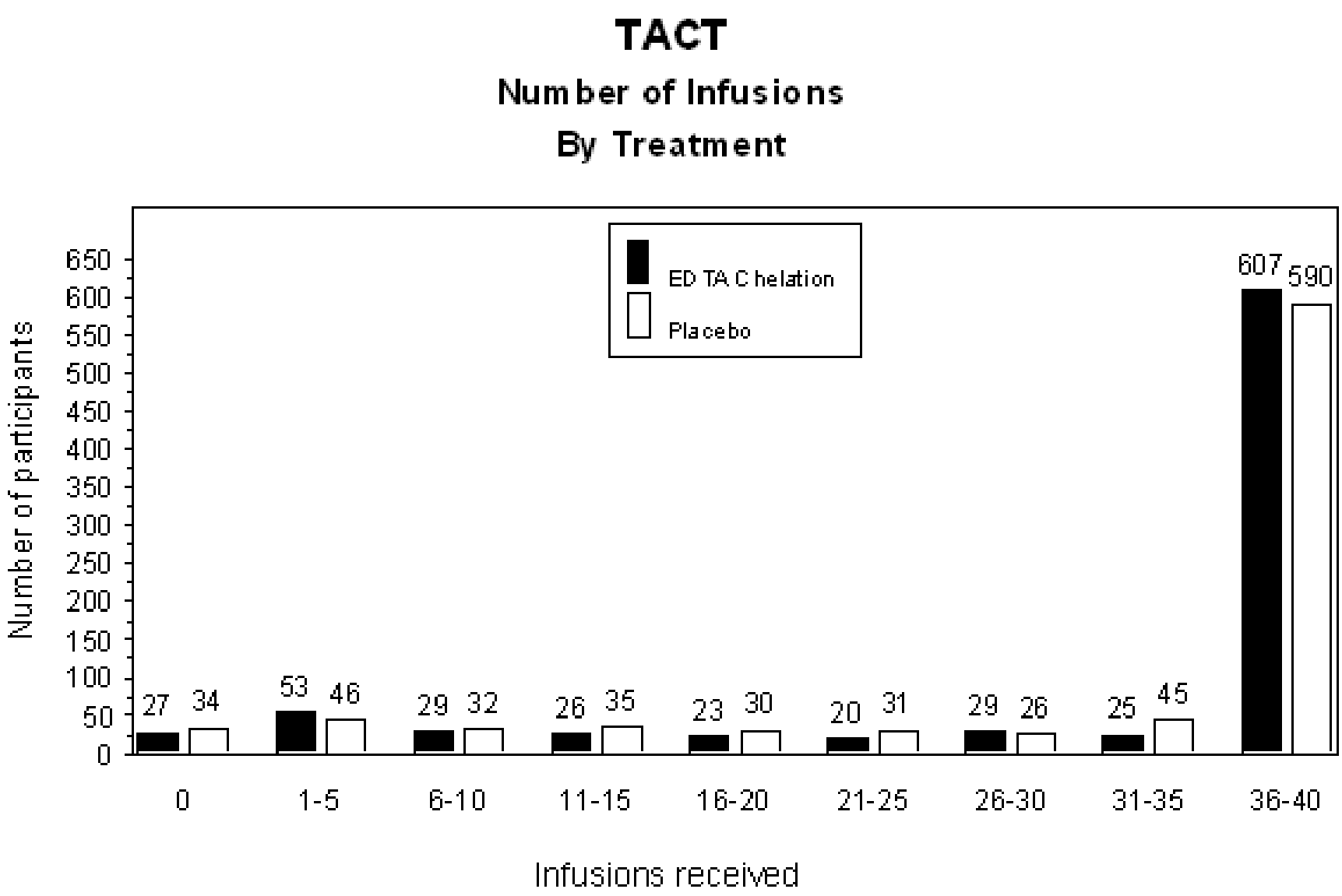

TACT
Kaplan-Meier Estimates of Discontinuation of Infusions
Chelation Therapy vs. Placebo
Hazard Ratio 95% CI P-value (log-rank)
EDTA:Placebo 0.84 0.71, 1.00 0.054
Placebo
EDTA Chelation
Discontinuation (%)
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
Months since randomization
Number at Risk
EDTA Chelation 839 693 628 313 75
Placebo 869 710 630 304 64

Figure A-3


TACT
Number of Infusions
By Treatment
ED TA C helation
Placebo
Number of participants
650
600
550
500
450
400
350
300
250
200
150
100
50
0
27 34
53 46
29 32
26 35
23 30
20 31
29 26
25 45
607 590
0
1-5
6-10
11-15
16-20
21-25
26-30
31-35
36-40
Infusions received

Detailed tabulation of treatment discontinuations--Table A-5.

The following table (Table A-5) provides additional detail of infusion discontinuations to supplement the information in the primary manuscript. The table excludes patients who discontinued infusions due to death during the trial, and compares the reasons for discontinuations by treatment group.

Table A-5
Treatment Discontinuations and Side Effects

Reasons for Infusion Discontinuation by Infusion Arm *

	EDTA Chelation (N= 839)	Placebo (N= 869)	All Patients (N=1708)	P-value
Premature discontinuation of treatment (excluding death)				
Study infusions	233 (28%)	281 (32%)	514 (30%)	0.03*
Due to adverse event, procedure or endpoint	38 (16%)	41 (15%)	79 (15%)	0.59**
Patient refusal or noncompliance	129 (55%)	160 (57%)	289 (56%)	0.72**
To receive open-label EDTA	29 (12%)	28 (10%)	57 (11%)	0.37**
Physician preference	7 (3%)	13 (5%)	20 (4%)	0.37***
Pain, IV access or side effects	11 (5%)	4 (1%)	15 (3%)	0.03***
Due to closed site	11 (5%)	15 (5%)	26 (5%)	0.84***
Terminal illness or comorbidities	8 (3%)	20 (7%)	28 (5%)	0.08***

* P-value from Log-Rank Test

** P-value from Chi-Square Test

*** P-value from Fisher's Exact Test

Detailed Tabulations for the Subgroup Analyses

The following table (Table A-6) provides additional detail to supplement the information in the subgroup plot displayed in Figure 2 of the primary manuscript. For each subgroup category, this table provides the number of patients and the number of events for each treatment arm, as well as the hazard ratio and 95% confidence interval for comparing EDTA chelation vs. placebo in each subgroup category.

Table A-6
SUBGROUP ANALYSES COMPARING EDTA CHELATION TO PLACEBO FOR PRIMARY ENDPOINT

	EDTA Chelation		Placebo Infusion			
	# of Patients	# of Events	# of Patients	# of Events	Hazard Ratio	95% CI
All Participants	839	222 (26%)	869	261 (30%)	0.82	0.69, 0.99
High-dose Vitamins						
Active	421	108 (26%)	432	122 (28%)	0.82	0.63, 1.06
Placebo	418	114 (27%)	437	139 (32%)	0.83	0.65, 1.06
Gender						
Male	687	186 (27%)	722	218 (30%)	0.85	0.70, 1.03
Female	152	36 (24%)	147	43 (29%)	0.76	0.48, 1.18
Race						
White	790	205 (26%)	815	247 (30%)	0.80	0.66, 0.96
Other	49	17 (35%)	54	14 (26%)	1.33	0.65, 2.73
Time from MI to enrollment						
< 2 years	236	67 (28%)	258	83 (32%)	0.85	0.62, 1.17
2-5 years	216	48 (22%)	184	41 (22%)	0.93	0.61, 1.41
≥ 5 years	386	107 (28%)	427	137 (32%)	0.80	0.62, 1.03

(continued on next page)

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Table A-6
SUBGROUP ANALYSES COMPARING EDTA CHELATION TO PLACEBO FOR PRIMARY ENDPOINT

	EDTA Chelation		Placebo Infusion			
	# of Patients	# of Events	# of Patients	# of Events	Hazard Ratio	95% CI
All Participants	839	222 (26%)	869	261 (30%)	0.82	0.69, 0.99
High-dose Vitamins						
Active	421	108 (26%)	432	122 (28%)	0.82	0.63, 1.06
Placebo	418	114 (27%)	437	139 (32%)	0.83	0.65, 1.06
Gender						
Male	687	186 (27%)	722	218 (30%)	0.85	0.70, 1.03
Female	152	36 (24%)	147	43 (29%)	0.76	0.48, 1.18
Race						
White	790	205 (26%)	815	247 (30%)	0.80	0.66, 0.96
Other	49	17 (35%)	54	14 (26%)	1.33	0.65, 2.73
Time from MI to enrollment						
< 2 years	236	67 (28%)	258	83 (32%)	0.85	0.62, 1.17
2-5 years	216	48 (22%)	184	41 (22%)	0.93	0.61, 1.41
≥ 5 years	386	107 (28%)	427	137 (32%)	0.80	0.62, 1.03

(continued on next page)

Adverse Events Reported During the Trial

The following tables (Table A-7 and Table A-8) provide additional detail to supplement the information in Table A-5 and in the manuscript. The serious and non-serious adverse events reported in the trial are individually listed, grouped by the system involved (from the MEDRA coding), and compared by infusion group.

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Table A-7
Serious Adverse Events

Events	EDTA Chelation (N=839)	Placebo (N=869)	P-value
Total	100 (12%)	127 (15%)	0.1009
Blood and Lymphatic System Disorders	0 (0%)	0 (0%)	N/A
Cardiac Disorders	33 (4%)	39 (4%)	0.5685
Ear and Labyrinth Disorders	0 (0%)	0 (0%)	N/A
Eye Disorders	0 (0%)	0 (0%)	N/A
Gastrointestinal Disorders	12 (1%)	12 (1%)	0.9309
General Disorders and Administration Site Conditions	9 (1%)	14 (2%)	0.3345
Hepatobiliary Disorders	3 (0%)	2 (0%)	0.6818
Immune System Disorders	0 (0%)	0 (0%)	N/A
Infections and Infestations	18 (2%)	16 (2%)	0.6527
Injury, Poisoning and Procedural Complications	7 (1%)	7 (1%)	0.9474

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Table A-7
Serious Adverse Events

Events	EDTA Chelation (N=839)	Placebo (N=869)	P-value
Investigations	3 (0%)	3 (0%)	1.0000
Metabolism and Nutrition Disorders	2 (0%)	2 (0%)	1.0000
Musculoskeletal and Connective Tissue Disorders	3 (0%)	2 (0%)	0.6818
Neoplasms	7 (1%)	4 (0%)	0.3340
Nervous System Disorders	8 (1%)	10 (1%)	0.6899
Psychiatric Disorders	1 (0%)	3 (0%)	0.6248
Renal and Urinary Disorders	4 (0%)	6 (1%)	0.7536
Reproductive System and Breast Disorders	0 (0%)	0 (0%)	N/A
Respiratory, Thoracic and Mediastinal Disorders	12 (1%)	21 (2%)	0.1388
Skin and Subcutaneous Tissue Disorders	0 (0%)	1 (0%)	1.0000
Surgical and Medical Procedures	1 (0%)	0 (0%)	0.4912
Vascular Disorders	4 (0%)	7 (1%)	0.3958

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Table A-8
Non-Serious Adverse Events by Infusion Arm

Events	EDTA Chelation (N=839)	Placebo (N=869)	P-value
Total	572 (68%)	582 (67%)	0.5955
Blood and Lymphatic System Disorders	48 (6%)	37 (4%)	0.1644
Cardiac Disorders	47 (6%)	54 (6%)	0.5918
Ear and Labyrinth Disorders	2 (0%)	4 (0%)	0.6872
Eye Disorders	9 (1%)	5 (1%)	0.2544
Gastrointestinal Disorders	105 (13%)	124 (14%)	0.2874
General Disorders and Administration Site Conditions	128 (15%)	92 (11%)	0.0040
Hepatobiliary Disorders	2 (0%)	1 (0%)	0.6183
Immune System Disorders	4 (0%)	1 (0%)	0.2102
Infections and Infestations	98 (12%)	117 (13%)	0.2667
Injury, Poisoning and Procedural Complications	28 (3%)	26 (3%)	0.6834

(continued on next page)

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Table A-8
Non-Serious Adverse Events by Infusion Arm

Events	EDTA Chelation (N=839)	Placebo (N=869)	P-value
Investigations	198 (24%)	208 (24%)	0.8704
Metabolism and Nutrition Disorders	249 (30%)	223 (26%)	0.0635
Musculoskeletal and Connective Tissue Disorders	70 (8%)	61 (7%)	0.3041
Neoplasms	4 (0%)	8 (1%)	0.2723
Nervous System Disorders	64 (8%)	51 (6%)	0.1469
Psychiatric Disorders	12 (1%)	16 (2%)	0.5038
Renal and Urinary Disorders	62 (7%)	89 (10%)	0.0379
Reproductive System and Breast Disorders	5 (1%)	9 (1%)	0.3136
Respiratory, Thoracic and Mediastinal Disorders	73 (9%)	81 (9%)	0.6546
Skin and Subcutaneous Tissue Disorders	25 (3%)	19 (2%)	0.3008
Vascular Disorders	38 (5%)	38 (4%)	0.8755

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572