The Trial to Assess Chelation Therapy (TACT)
Chelation-Placebo Comparison

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Background

- Disodium ethylene diamine tetra acetic acid (EDTA) binds divalent cations and permits renal excretion

- Clarke- 1956 report of successful treatment of angina

- From 1956 to the present (56 years):
  - Use increased to >100,000 patients in US in 2007 survey
  - Case reports and case series reported benefit
  - Small clinical trials negative for surrogate endpoints
  - Evidence of harm, especially from rapid infusions causing hypocalcemia
TACT timeline

- RFA for efficacy trial released by NCCAM & NHLBI: 04/30/01
- TACT funded as a cooperative agreement: 08/15/02
- IND obtained: 04/23/03
- First patient randomized: 09/10/03
- Patient enrollment
- Patient 1708 enrolled: 10/04/10
- 134th site activated: 08/17/09
- Last patient follow-up: 10/31/11

Date Range:
- 2001-2003
- 2004-2009
- 2010-2011
- 2012
**Design Overview - Factorial Trial**

<table>
<thead>
<tr>
<th>Chelaton + high-dose vitamins</th>
<th>Chelation placebo + high-dose vitamins</th>
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<tbody>
<tr>
<td>Chelation + vitamin placebo</td>
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**Blinding:** double-blind active or placebo infusions were shipped from a central pharmacy to sites.

40 infusions at least 3 hours each; 30 weekly infusions followed by 10 maintenance infusions 2-8 weeks apart.

Eligibility

- Age 50 or older
- MI > 6 months prior
- Creatinine ≤2.0 mg/dL
- No coronary or carotid revascularization within 6 months
- No active heart failure or heart failure hospitalization within 6 months
- Able to tolerate 500cc infusions weekly
- No cigarette smoking within 3 months
- Informed consent
CHELATION INFUSION

- disodium EDTA, 3 grams, adjusted downward based on eGFR,
- ascorbic acid, 7 grams
- magnesium chloride, 2 grams
- potassium chloride, 2 mEq
- sodium bicarbonate, 840 mg
- pantothenic acid, thiamine, pyridoxine,
- procaine, 100 mg
- unfractionated heparin, 2500 U
- sterile water to 500 mL

PLACEBO INFUSION

- normal saline, 1.2% dextrose, 500 mL
Primary Endpoint & Sample Size

- Primary composite endpoint: death, MI, stroke, coronary revascularization, hospitalization for angina

- Original plan was to randomize 2372 patients and follow up a minimum of 1 year - 85% power for detecting a 25% difference.

- In 2009, due to slow enrollment, blinded investigators asked for a reduction of total sample size to 1700, with a compensatory increase in follow-up to maintain same unconditional power. DSMB approved the request.
Data Analysis

- Treatment comparisons as randomized (intent to treat)
- Two sided statistical testing
- Log-rank test using time to first event
- Interim monitoring using alpha-spending function with O’Brien-Fleming monitoring boundaries
- Because of length of study with 11 DSMB reviews to ensure safety, the final level of significance was 0.036
## Baseline Characteristics

1708 patients randomized

<table>
<thead>
<tr>
<th></th>
<th>EDTA Chelation (N=839)</th>
<th>Placebo (N=869)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 (59, 72)</td>
<td>66 (59, 72)</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>30 (27, 34)</td>
<td>30 (27, 34)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Hispanic or non-Caucasian (%)</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Diabetic (%)</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Prior revascularization (%)</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>Statin (%)</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>Beta Blocker (%)</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>85</td>
<td>82</td>
</tr>
<tr>
<td>Aspirin, clopidogrel, or warfarin (%)</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>87</td>
<td>90</td>
</tr>
</tbody>
</table>
Compliance

- Total 55,222 infusions
- 65% completed all 40 infusions; 76% completed at least 30
- 30% discontinued infusions
  - Patient refusal 53%
  - Adverse event 12%
  - To receive open label chelation 11%
  - IV access site problems 10%
  - Other (14%)
- 17% withdrew consent
Side Effects and Safety

- 79 patients discontinued infusions due to AE or side effect.
  - 17 reached an endpoint
  - 11 heart failure
  - 7 other cardiac issue
  - 7 GI problems
  - 5 hematological problems
  - 4 each: neuro-psychiatric, respiratory, general symptoms
  - 20 other reasons

- 4 unexpected severe adverse events possibly or definitely related to study therapy
  - 2 placebo, 1 death
  - 2 chelation, 1 death
TACT: Primary Endpoint Results

Event Rate

Number at Risk
EDTA Chelation
Placebo

Death, MI, stroke, coronary revascularization, hospitalization for angina

Hazard Ratio 95% CI P-value
EDTA:Placebo 0.82 0.69,0.99 0.035
## Components of the Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>EDTA Chelation (N= 839)</th>
<th>Placebo (N= 869)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>222 (26.5%)</td>
<td>261 (30.0%)</td>
<td>0.82 (0.69,0.99)</td>
<td>0.035</td>
</tr>
<tr>
<td>Death</td>
<td>87 (10.4%)</td>
<td>93 (10.7%)</td>
<td>0.93 (0.70, 1.25)</td>
<td>0.642</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>52 (6.2%)</td>
<td>67 (7.7%)</td>
<td>0.77 (0.54, 1.11)</td>
<td>0.168</td>
</tr>
<tr>
<td>Stroke</td>
<td>10 (1.2%)</td>
<td>13 (1.5%)</td>
<td>0.77 (0.34, 1.76)</td>
<td>0.531</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>130 (15.5%)</td>
<td>157 (18.1%)</td>
<td>0.81 (0.64, 1.02)</td>
<td>0.076</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
<td>13 (1.5%)</td>
<td>18 (2.1%)</td>
<td>0.72 (0.35, 1.47)</td>
<td>0.359</td>
</tr>
</tbody>
</table>
### Subgroups analysis

<table>
<thead>
<tr>
<th>Selected Prespecified Subgroup</th>
<th>P for interaction with treatment group assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age&gt;70</td>
<td>0.51</td>
</tr>
<tr>
<td>Gender</td>
<td>0.58</td>
</tr>
<tr>
<td>Race</td>
<td>0.15</td>
</tr>
<tr>
<td>Minority</td>
<td>0.25</td>
</tr>
<tr>
<td>Time from MI to enrollment</td>
<td>0.87</td>
</tr>
<tr>
<td>Chelation site v. conventional</td>
<td>0.28</td>
</tr>
<tr>
<td>Oral vitamins v. placebo</td>
<td>0.94</td>
</tr>
<tr>
<td>MI location</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.02</td>
</tr>
<tr>
<td>Statins at baseline</td>
<td>0.59</td>
</tr>
<tr>
<td>ACE or ARB at baseline</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Predefined Subgroup- Diabetes (31%)

Diabetes

HR: 0.61, 95% CI: (0.45, 0.83)

p-value: 0.002

PLACEBO (102 events)

EDTA CHELATION (67 events)

No Diabetes

HR: 0.96, 95% CI: (0.77, 1.20)

p-value: 0.725

PLACEBO (159 events)

EDTA CHELATION (155 events)
Caveats in Interpretation

- The final adjusted statistical significance meets pre-defined significance, but the upper confidence interval for the hazard ratio of the primary endpoint was 0.99.

- While the relative treatment effect (HR) was similar for all the nonfatal components of the primary endpoint, revascularization was the most common outcome event.

- 17% of patients withdrew consent, resulting in some missing data.
Conclusions

- Study therapy, within the safety net provided by TACT, appears to be safe.

- The 10-component disodium EDTA chelation and ascorbate regimen showed some evidence of a potentially important treatment signal in post-MI patients already on evidence-based therapy.

- However, our findings are unexpected and additional research will be needed to confirm or refute our results and explore possible mechanisms of therapy.

- TACT does not constitute evidence to recommend the clinical application of chelation therapy.