The Trial to Assess Chelation Therapy (TACT)

*Connecting Silos of Scientific Information*

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EDTA
Extensive Epidemiological Evidence Showing Adverse CV Effects of Metals

Evidence for harm at low-moderate levels is increasing

Courtesy of Ana Navas-Acien 2013
Metals and CVD: mechanisms

- Increase oxidative stress
- Promote inflammation
- Interfere with calcium signaling
- Affect endothelial function
- Increase blood pressure levels
- Induce renal dysfunction
- Induce epigenetic changes

Courtesy of Ana Navas-Acien 2013
Advanced Glycation End Products (AGEs)

- AGEs are modifications of proteins or lipids that become non-enzymatically glycated and oxidized after contact with aldose sugars.

- The reactive carbonyl group of the sugar reacts with the nucleophilic amino group of the amino acid to form intermediate products known as Schiff base, Amadori, and Maillard products to form AGEs.

- AGEs can arise from glucose and lipids (advanced lipid peroxidation products).

- The degree of “AGE modification” of a molecule is a marker of senescence in vivo (and therefore it may become a target for catabolism).
AGEs may damage cellular structures via a number of mechanisms, including the formation of cross-links between the basement membrane of the extracellular matrix (ECM) and their interaction with RAGEs.
AGEs and diabetic vascular complications

- **AGEs formation are metal-catalyzed oxidation reactions:** Reactive oxygen species (ROS) and free metal ions are key participants in the intermediate reactions (e.g. Maillard reaction) in the formation of AGEs.

- Chelators have been identified as potent inhibitors of cross-linking of proteins by glucose.
Iron and copper are widely recognized as catalytically active metal ions that mediate the production of ROS that initiate autoxidation reactions (oxidation reactions involving oxygen as the oxidizing agent), catalyzing the production of AGEs, advanced lipoxidation end-products (ALEs) and protein oxidation products (PrOPs) in tissues.

AGEs and ALEs bind copper in a catalytically active, pro-oxidant form in tissues.

The chemistry of AGEs forming reactions can be inhibited \textit{in vitro} by chelators, including EDTA.

Frizzell N, Baynes JW. Future Med Chem 5: 1075-1078; 2013
Summary of Background Work

- There is extensive epidemiologic evidence that metal pollutants are associated with cardiovascular disease.
- There is some evidence that this association is strengthened in patients with diabetes.
- Metal catalyzed oxygen chemistry is necessary to produce some of the mediators of complications of diabetes.
- EDTA chelates metals involved in all of the above.
In April 2001, NCCAM and NHLBI released a $30 million RFA for an efficacy trial of EDTA chelation therapy
In August 2012 we unblinded TACT.
Study Organization

- Funding agencies: NCCAM and NHLBI
- Clinical Coordinating Center: Mount Sinai Medical Center, Miami Beach FL
- Data Coordinating Center and EQOL Coordinating Center: Duke Clinical Research Institute
- Clinical Events Committee: Brigham and Women’s Hospital
- Central Pharmacy: Universal Arts, Miami FL
- Vitamins: Douglas Labs, Pittsburgh PA
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.

TACT: High-Dose Oral Treatment

3 caplets twice a day for the duration of the study.

- Vitamin A
- Vitamin C
- Vitamin D₃
- Vitamin E
- Vitamin K
- Thiamin
- Niacin
- Vitamin B₆
- Folate
- Vitamin B₁₂
- Biotin
- Panthothenic Acid

Double-blind active or placebo high dose vitamins were shipped from a central pharmacy to sites.

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
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
- Signed informed consent
Primary Endpoint & Sample Size

- Primary composite endpoint: death, MI, stroke, coronary revascularization, hospitalization for angina
- 1700 patients with a median followup of about 5 years gave us 85% power for detecting a 25% difference
Data Analysis

- Treatment comparisons as randomized (intent to treat)
- Two sided statistical testing
- Log-rank test using time to first event
- Because of multiple DSMB reviews due to length of study, the final level of significance was 0.036
<table>
<thead>
<tr>
<th>Baseline Characteristics</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>Diabetes (%)</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
- 17% withdrew consent
  - Of these, 18% had an endpoint event before withdrawing consent
  - All had vital status assessed using the national death index
TACT Primary Endpoint Results

Event Rate vs Months since randomization

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

Placebo

Number at risk:
Placebo 869 776 701 638 566 515 475 429 384 322 205
**TACT Primary Endpoint Results**

**EDTA: Placebo**

- HR (95% CI)
  - 0.82 (0.69, 0.99)
- $P = 0.035$

**Number at risk:**
- Placebo: 869, 776, 701, 638, 566, 515, 475, 429, 384, 322, 205
- EDTA chelation: 839, 760, 703, 650, 588, 537, 511, 476, 427, 358, 229

**Event Rate** vs. **Months since randomization**

- Death, MI, stroke, coronary revascularization, hospitalization for angina
### 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>
## Subgroup Results

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Interaction p-value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Subjects</strong></td>
<td>1708</td>
<td></td>
<td>0.82</td>
<td>0.69, 0.99</td>
</tr>
<tr>
<td><strong>High-dose Vitamins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>853</td>
<td>0.94</td>
<td>0.82</td>
<td>0.63, 1.06</td>
</tr>
<tr>
<td>Placebo</td>
<td>855</td>
<td></td>
<td>0.83</td>
<td>0.65, 1.06</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1409</td>
<td>0.58</td>
<td>0.85</td>
<td>0.70, 1.03</td>
</tr>
<tr>
<td>Female</td>
<td>299</td>
<td></td>
<td>0.76</td>
<td>0.48, 1.18</td>
</tr>
<tr>
<td><strong>Anterior MI</strong></td>
<td></td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>674</td>
<td></td>
<td>0.63</td>
<td>0.47, 0.86</td>
</tr>
<tr>
<td>No</td>
<td>1034</td>
<td></td>
<td>0.96</td>
<td>0.77, 1.20</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>538</td>
<td></td>
<td>0.61</td>
<td>0.45, 0.83</td>
</tr>
<tr>
<td>No</td>
<td>1170</td>
<td></td>
<td>0.96</td>
<td>0.77, 1.20</td>
</tr>
<tr>
<td><strong>Statins at baseline</strong></td>
<td></td>
<td>0.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1248</td>
<td></td>
<td>0.85</td>
<td>0.69, 1.05</td>
</tr>
<tr>
<td>No</td>
<td>460</td>
<td></td>
<td>0.77</td>
<td>0.55, 1.07</td>
</tr>
<tr>
<td><strong>CAM site</strong></td>
<td></td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1089</td>
<td></td>
<td>0.89</td>
<td>0.71, 1.12</td>
</tr>
<tr>
<td>No</td>
<td>619</td>
<td></td>
<td>0.72</td>
<td>0.53, 0.97</td>
</tr>
</tbody>
</table>

![Graph showing subgroup results](image)
Conclusion 1

- EDTA-based chelation therapy reduces combined cardiovascular events in post MI patients treated with optimal medical therapy (5-year NNT= 18).
TACT Vitamin
Primary Endpoint Results

**Vitamins: Placebo**

HR (95% CI)  
0.89 (0.75, 1.07)  

**P = 0.212**

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

Median follow-up 55 months
TACT Primary Endpoint: Factorial Groups

EDTA Chelation/High-dose Vitamins vs. Placebo/Placebo

HR (95% CI): 0.74 (0.57, 0.95)
P = 0.016

8.3%
## Endpoints

<table>
<thead>
<tr>
<th></th>
<th>EDTA Chelation and High-Dose Vitamins (N=421)</th>
<th>Placebo Infusions and Placebo Vitamins (N=437)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>26%</td>
<td>32%</td>
<td>0.74 (0.57, 0.95)</td>
<td>0.016</td>
</tr>
<tr>
<td>CVD, MI or stroke</td>
<td>9%</td>
<td>13%</td>
<td>0.66 (0.44, 0.99)</td>
<td>0.046</td>
</tr>
<tr>
<td>Death</td>
<td>10%</td>
<td>11%</td>
<td>0.87 (0.57, 1.30)</td>
<td>0.481</td>
</tr>
<tr>
<td>Cardiovascular death (CVD)</td>
<td>5%</td>
<td>6%</td>
<td>0.75 (0.41, 1.37)</td>
<td>0.383</td>
</tr>
<tr>
<td>MI</td>
<td>5%</td>
<td>7%</td>
<td>0.71 (0.42, 1.21)</td>
<td>0.230</td>
</tr>
<tr>
<td>Stroke</td>
<td>1%</td>
<td>2%</td>
<td>0.44 (0.13, 1.42)</td>
<td>0.135</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>14%</td>
<td>19%</td>
<td>0.67 (0.48, 0.94)</td>
<td>0.019</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
<td>1%</td>
<td>3%</td>
<td>0.49 (0.18, 1.31)</td>
<td>0.119</td>
</tr>
</tbody>
</table>
Conclusion 2

- High-dose oral vitamins and minerals demonstrate an 11% reduction in cardiovascular events which is not statistically significant, yet this event reduction carries over to the combination of EDTA chelation + oral vitamins.
Conclusion 3

- Compared with OMT + placebo/placebo, OMT + active/active demonstrates an enhanced reduction in clinical events (HR (95% CI): 0.74 (0.57, 0.95), P = 0.016)

- This reduction is of sufficient magnitude to be clinically significant (5-year NNT=12)
Analysis of patients with diabetes at baseline was pre-specified
Primary Endpoint by infusion arm
Diabetes

EDTA Chelation vs. Placebo
HR (95% CI): 0.59 (0.44, 0.79); P = 0.0002
Bonferroni Adjusted: (0.39, 0.88); P = 0.002

RR = 41%
NNT = 6.5 over 5 years CI (4.4, 12.7)

Number at Risk:
<table>
<thead>
<tr>
<th>EDTA Chelation</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>322</td>
<td>311</td>
</tr>
<tr>
<td>286</td>
<td>270</td>
</tr>
<tr>
<td>262</td>
<td>235</td>
</tr>
<tr>
<td>243</td>
<td>214</td>
</tr>
<tr>
<td>217</td>
<td>187</td>
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<tr>
<td>198</td>
<td>168</td>
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<td>187</td>
<td>155</td>
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<td>177</td>
<td>134</td>
</tr>
<tr>
<td>157</td>
<td>116</td>
</tr>
<tr>
<td>126</td>
<td>94</td>
</tr>
<tr>
<td>74</td>
<td>63</td>
</tr>
</tbody>
</table>
Primary Endpoint by infusion arm

Diabetes
EDTA Chelation vs. Placebo
HR (95% CI): 0.59 (0.44, 0.79); P = 0.0002
Adjusted: (0.39, 0.88); P = 0.002

No Diabetes
EDTA Chelation vs. Placebo
HR (95% CI): 1.02 (0.81, 1.28); P = 0.8768
TACT
Kaplan-Meier Estimate of the Primary Composite Endpoint
EDTA Chelation Therapy vs. Placebo
Superimposed Graphs: Subset of Patients with Diabetes & Subset of Patients without Diabetes
EDTA Chelation vs. Placebo

HR (95% CI): 0.57 (0.36, 0.88); P = 0.0111

Death by infusion arm - Diabetes
## Endpoints (Diabetes)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>EDTA Chelation (N=322)</th>
<th>Placebo (N=311)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>25%</td>
<td>38%</td>
<td>0.59 (0.44, 0.79)</td>
<td>0.001</td>
</tr>
<tr>
<td>CVD, MI or stroke</td>
<td>11%</td>
<td>17%</td>
<td>0.60 (0.39, 0.91)</td>
<td>0.017</td>
</tr>
<tr>
<td>Death</td>
<td>10%</td>
<td>16%</td>
<td>0.57 (0.36, 0.88)</td>
<td>0.011</td>
</tr>
<tr>
<td>Cardiovascular death (CVD)</td>
<td>6%</td>
<td>9%</td>
<td>0.63 (0.35, 1.13)</td>
<td>0.118</td>
</tr>
<tr>
<td>MI</td>
<td>5%</td>
<td>10%</td>
<td>0.48 (0.26, 0.88)</td>
<td>0.015</td>
</tr>
<tr>
<td>Stroke</td>
<td>1%</td>
<td>1%</td>
<td>1.19 (0.27, 5.30)</td>
<td>0.829</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>15%</td>
<td>20%</td>
<td>0.68 (0.48, 0.99)</td>
<td>0.042</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
<td>2%</td>
<td>2%</td>
<td>0.72 (0.22, 2.36)</td>
<td>0.588</td>
</tr>
</tbody>
</table>
Conclusion 4

- Patients with diabetes demonstrate enhanced efficacy with EDTA chelation. Compared with placebo, EDTA-treated patients demonstrated a 41% reduction in CV endpoints ($p=0.0002$, 5-year NNT = 7), and a 43% reduction in total mortality ($p=0.011$, 5-year NNT=12).

- This reduction is of sufficient magnitude to be clinically significant.
TACT Primary Endpoint in Diabetes: Factorial Groups
TACT Primary Endpoint in Diabetes Subgroup

Event Rate vs. Months since randomization

- Placebo Infusions / Placebo Vitamins
TACT Primary Endpoint in Diabetes Subgroup

Event Rate vs. Months since randomization

- Placebo Infusions / Placebo Vitamins
- Placebo Infusions / High-Dose Vitamins
TACT Primary Endpoint in Diabetes Subgroup

Event Rate vs. Months since randomization

- Placebo Infusions / Placebo Vitamins
- Placebo Infusions / High-Dose Vitamins
- EDTA Chelation / Placebo Vitamins
TACT Primary Endpoint in Diabetes Subgroup

- Placebo Infusions / Placebo Vitamins
- Placebo Infusions / High-Dose Vitamins
- EDTA Chelation / Placebo Vitamins
- EDTA Chelation / High-Dose Vitamins

Event Rate vs. Months since randomization
TACT Primary Endpoint in Diabetes Subgroup

EDTA Chelation/High-dose Vitamins vs. Placebo

HR (95% CI): 0.49 (0.33, 0.75)

P < 0.001
Conclusion 5

- The benefit of vitamin therapy added to EDTA chelation is magnified in the subgroup of patients with diabetes, with a number needed to treat of 6 to prevent 1 primary event over 5 years.

- This effect size is sufficient to put us at a crossroads.
Crossroads

- Do we implement?
- Do we replicate?
- Do we do basic science to understand mechanisms?
What do we have to date?

- There is overall benefit with an unwieldy therapy
- There is a strong clinical signal of extreme benefit in a very high risk subgroup of patients
- We have plausible hypotheses as to the mechanism of action
- Favorable safety data
- An opportunity for real, measurable, patient benefit, especially for diabetic patients
Proposal for the Future

- Focus on this as the potential rise of disruptive pharmacology
- Replicate clinical results in the population with diabetes and vascular disease
- Enroll diabetes + MI, but extend patient eligibility to severe PAD
- Work out mechanisms, particularly the metal – oxidative stress hypothesis
- All this must be done within a clinical trial
References


References


Once again, we will need new sites who can do NIH-level research.

Please stay in touch.

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305-674-2260
Thank you