Quality of Life Outcomes:
The Trial to Assess Chelation Therapy

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TACT: Background

- Disodium ethylene diamine tetra acetic acid (EDTA) binds divalent cations (e.g., lead, calcium) and permits renal excretion
- Treatment of lead toxicity with EDTA in 1951
- Report of treatment of angina in 1956 by Clarke with ↓ sx

From 1956 to the present:
- Use in atherosclerotic disease expanded
- Evolution of a standardized protocol that included disodium EDTA, ascorbate, B-vitamins, and other components
- Used clinically by chelation practitioners
- Chelation discouraged by traditional professional societies
TACT: Design Overview

1,708 post-MI pts

- Age ≥50
- MI ≥ 6 mos prior to randomization

134 sites (US, CN)

double-blind 2x2 trial

<table>
<thead>
<tr>
<th>Chelation + high-dose vitamins</th>
<th>Chelation placebo + high-dose vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chelation + vitamin placebo</td>
<td>Chelation placebo + vitamin placebo</td>
</tr>
</tbody>
</table>

Mean study follow-up 55 mos

1° endpoint: composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for unstable angina

2° endpoints incl.: quality of life outcomes
**TACT 1° Clinical Endpoint**

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>Months since randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>0.1</td>
<td>6</td>
</tr>
<tr>
<td>0.2</td>
<td>12</td>
</tr>
<tr>
<td>0.3</td>
<td>18</td>
</tr>
<tr>
<td>0.4</td>
<td>24</td>
</tr>
<tr>
<td>0.5</td>
<td>30</td>
</tr>
</tbody>
</table>

**EDTA:Placebo**

- Hazard Ratio: 0.82
- 95% CI: 0.69, 0.99
- P-value: 0.035

**Number at Risk**

<table>
<thead>
<tr>
<th>EDTA Chelation</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>839</td>
<td>869</td>
</tr>
<tr>
<td>760</td>
<td>776</td>
</tr>
<tr>
<td>703</td>
<td>701</td>
</tr>
<tr>
<td>650</td>
<td>638</td>
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<tr>
<td>588</td>
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</tr>
<tr>
<td>537</td>
<td>515</td>
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<tr>
<td>511</td>
<td>475</td>
</tr>
<tr>
<td>476</td>
<td>429</td>
</tr>
<tr>
<td>427</td>
<td>384</td>
</tr>
<tr>
<td>358</td>
<td>322</td>
</tr>
<tr>
<td>229</td>
<td>205</td>
</tr>
</tbody>
</table>

**Event Rate**

- death, MI, stroke, coronary revascularization, hospitalization for angina
TACT Quality of Life Study: Primary Objective

- To determine whether chelation therapy significantly improves physical functioning and psychological well-being in stable CAD patients with a history of MI
TACT QOL Study:
Quality of Life (QOL) Methods Overview

- 911 (53%) of 1708 main TACT pts randomly selected for QOL substudy
- QOL structured interviews at baseline, 6 mos, 12 mos, and 24 mos
- All baseline questionnaires were collected by site coordinators who were trained by DCRI Outcomes Group
- Follow-up interviews were conducted via telephone by DCRI Outcomes Group
- 97% of expected QOL contacts collected
TACT QOL Substudy: Primary QOL Outcome Measures

- **DASI** - cardiac-related functional status.
  - Scores: 0 (worst) to 58 (best), reflect the ability of patients to do physical activities without difficulty or assistance in 12 domains.
  - For an individual pt, a clinically significant change is ≥4 points.

- **MHI-5** - psychological well-being, including both depression and anxiety.
  - Scores: normalized to 50±10.
  - A clinically significant change for an individual patient is approximately ≥ 2.5 points.

- **Other measures**: SAQ (frequency, stability, QOL), SF-36, EQ-5D
TACT QOL: Analysis Methods

- All primary comparisons by intention to treat
- Follow-up QOL comparison p values adjusted for vitamin group and baseline QOL scores
- No adjustment was made in significance levels for multiple comparisons.
<table>
<thead>
<tr>
<th></th>
<th>Chelation (n=451)</th>
<th>Placebo (n=460)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>64 (58 to 71)</td>
<td>65 (58 to 72)</td>
</tr>
<tr>
<td>Female</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>Race, nonwhite</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Current NYHA Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>I</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>II</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>III</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Current CCS Angina Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>79%</td>
<td>79%</td>
</tr>
<tr>
<td>I</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>II</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>III</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>IV</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>32%</td>
<td>35%</td>
</tr>
</tbody>
</table>
TACT QOL Outcomes
DASI

0-58 scale, with higher scores indicating more favorable cardiac physical functioning

0.7 Baseline | 6 months | 12 months | 24 months
---|---|---|---
Chelation | Placebo | Chelation | Placebo | Chelation | Placebo | Chelation | Placebo
24.6 | 23.5 | 29.1 | 27 | 29.4 | 26.3 | 27.1 | 25.1

p=

difference

0.50 | 0.12 | 0.27
1.6 | 0.5
TACT QOL Outcomes
SF-36 MHI-5

Scaled to a norm of 50, SD 10
TACT QOL Outcomes
Seattle Angina Questionnaire – Anginal Frequency

Higher scores = less frequent angina
TACT QOL Outcomes
Seattle Angina Questionnaire – Quality of Life

Higher scores = better quality of life
TACT QOL Outcomes:  
Subgroup Analyses

• None of the prespecified subgroups showed a treatment effect on QOL

• Pts with angina sx at baseline showed a tx effect at 1 year in favor of chelation therapy (4.99 points, p=0.019), but not at other time points or overall

• No tx effect was seen in pts with heart failure sx at baseline
TACT QOL Outcomes: Caveats

- Trial population was largely asymptomatic at baseline (ceiling effect for some measures incl. anginal QOL)

- QOL assessment follow-up was limited to 2 years, 1° clinical outcomes show continued divergence favoring chelation out to 5 years
In a population of stable, predominantly asymptomatic CAD patients with a history of prior MI, the use of EDTA chelation therapy did not produce a consistent sustained improvement in any domain of health-related quality of life.
TACT QOL Outcomes
SF-36 Physical Component Summary

Scaled to a norm of 50, SD 10
TACT QOL Outcomes
SF-36 Mental Component Summary

Scaled to a norm of 50, SD 10
TACT QOL Outcomes
EQ-5D Single Summary Index

Relative desirability of patient’s current health status

Baseline: Chelation 74.9, Placebo 73.9
6 months: Chelation 78.2, Placebo 76.1
12 months: Chelation 81, Placebo 77.7
24 months: Chelation 81.8, Placebo 75.5

p-values:
- Baseline: 0.87
- 6 months: 0.18
- 12 months: 0.002

Difference:
- Baseline: 0.3
- 6 months: 2.1
- 12 months: 5.2

Graph shows the relative desirability of patients' current health status at different time points (Baseline, 6 months, 12 months, 24 months) for Chelation and Placebo groups.
TACT QOL Outcomes: Clinically Significant Improvement in DASI from Baseline

- 6 months: Chelation 46.7%, Placebo 44.0%
- 12 months: Chelation 46.2%, Placebo 42.2%
- 24 months: Chelation 43.5%, Placebo 36.9%

P-values:
- 6 months: 0.44
- 12 months: 0.26
- 24 months: 0.06