AHA 2012 LBT Commentary

Trial to Assess Chelation Therapy (TACT)

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Sunday November 4, 2012
Los Angeles
Disclosure Statement  Paul W. Armstrong MD

Details available @ http://www.vigour.ualberta.ca

- **Research Grants**
  - Boehringer Ingelheim
  - sanofi aventis
  - Merck
  - Astra Zeneca
  - Eli Lilly
  - GlaxoSmithKline
  - Regado Biosciences

- **Consultant**
  - Regado Biosciences

- **Data & Safety Monitoring Boards**
  - Roche
  - Orexigen
  - Lilly
Balancing TACT in Context

Pro
CT is valuable effective & safe
Chappell & Jansen

Con
CT is likely unsafe, certainly ineffective & should be abandoned
Ernst

Alternative Medicine

Traditional Medicine
EDTA chelation therapy meets evidence-based medicine

- According to World Health Organization estimates, ~66,000 US pts Rx chelation in 2002: (↑ to 111,000 in 2007)
- ~$5000 for full course of 40-50 infusions
- Imposes significant patient burden & potential serious side effects
- Challenging 7 yr operations: 2003-11: original plan 36 mo enrollment
- Interim TACT progress 2006: 900 patients enrolled & > 25,000 infusions administered in ~100 US sites
- Trial stopped ~1500 pts Sept 2008: OHRP & FDA investigate ICF process & trial conduct: corrective steps, then re-started June 2009
- Oct 2010 n=1708 vs planned 2372 pts: 85% power to detect 25% RR in primary composite death, MI, stroke, coronary revasc & hospitalization angina
TACT: Primary Endpoint Results

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

Number at Risk
EDTA Chelation 839 760 703 650 588 537 511 476 427 358 229
Placebo 869 776 701 638 566 515 475 429 384 322 205

483 events : intergp diff=39

EDTA:Placebo Hazard Ratio  0.82  95% CI  0.69,0.99  P-value  0.035
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>EDTA</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>222(26%)</td>
<td>261(30%)</td>
<td>0.82(0.69-0.99)</td>
</tr>
<tr>
<td>Death</td>
<td>87(10%)</td>
<td>93(11%)</td>
<td>0.93(0.70-1.25)</td>
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<tr>
<td>Myocardial infarction</td>
<td>52(6%)</td>
<td>67(8%)</td>
<td>0.77(0.54-1.11)</td>
</tr>
<tr>
<td>Stroke</td>
<td>10(1%)</td>
<td>13(1%)</td>
<td>0.77(0.34-1.76)</td>
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<tr>
<td>Coronary revasc.</td>
<td>130(15%)</td>
<td>157(18%)</td>
<td>0.81(0.64-1.02)</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
<td>13(2%)</td>
<td>18(2%)</td>
<td>0.72(0.35-1.47)</td>
</tr>
</tbody>
</table>
Primary Composite  n=1708

Diabetics 31%

483 events : diff =39

Number at Risk
EDTA Chelation  839  760  703  650  588  537  511  476  427  358  229
Placebo  869  776  701  638  566  515  475  429  384  322  205

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

169 events:diff =35

Diabetes  HR:0.61, 95% CI:(0.45,0.83)
p-value:0.002

No Diabetes  HR:0.96, 95% CI:(0.77,1.20)
p-value:0.725
TACT: What We Need to Know

- Power to exclude chance given sample size, 18 vs 25% RR, p value 0.035, wide 95% CI & 11 interim looks
- Rx interaction EDTA & high dose vitamins
- Impact very long window of enrollment & trial interruption
- Adequacy of f/up, compliance, retention & cross over issues
- Comparability & adequacy of background EB Rx
- Change in primary endpoint i.e add coronary revasc & drop CHF (More re safety esp. CHF, renal)
- Mechanism(s) of Rx benefit & logic subgroups esp. ant MI
- Impact on quality life and functional status
Diverse multi component intervention

Absence of clear biologic rationale

Several operational / methodologic issues

High % diabetics who dominate the effect

Coronary revasc principal driver: co-linear with angina hospitalization in composite

Hypothesis generating: not practice changing