Non-Antithrombotic Medical Therapy in ACS: Old Agents and New Lines on the Horizon

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Dual Goals for Management of Patients with Ischemic Heart Disease

**Prevent MI and Death (Disease Modification)**

**Improve “Quantity of Life”**

**Reduce Ischemia & Relieve Anginal Symptoms**

**Improve “Quality of Life”**

Boden WE. Medical management of CAD. *Am J Cardiol.* 2008;101:69D-74D.


### “Traditional” Pharmacologic Therapy: 2000

#### Disease-Modifying Therapy
- Aspirin
- Statins
- ACE inhibitors or ARBs
- Beta-blockers Post-MI
- Thienopyridines

#### Symptomatic Treatment for Angina/Ischemia Control
- Beta-blockers w/o MI
- Calcium antagonists
- Nitrates
- Trimetazidines

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Pharmacologic Rx in 2015: A Moving Target—and Improving!

<table>
<thead>
<tr>
<th>Disease-Modifying Therapy</th>
<th>Symptomatic Treatment for Angina/Ischemia Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aspirin</td>
<td>• Beta-blockers w/o MI</td>
</tr>
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<td>• Calcium antagonists</td>
</tr>
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<td>• ACE inhibitors or ARBs</td>
<td>• Nitrates</td>
</tr>
<tr>
<td>• Beta-blocker Post-MI</td>
<td>• Trimetazidine</td>
</tr>
<tr>
<td>• Thienopyridines</td>
<td>• Ranolazine</td>
</tr>
<tr>
<td>• Aldosterone Inhibitors</td>
<td>• Ivabradine &amp; Nicorandil</td>
</tr>
<tr>
<td>• Ezetimibe</td>
<td>• Vorapaxar</td>
</tr>
</tbody>
</table>

2011 ACCF/AHA/AMA-PCPI CAD Measures

• **Symptom Management**: % of Patients aged ≥18 yrs with a diagnosis of CAD seen within a 12-month period & with results of an evaluation of level of activity, AND with an evaluation of presence or absence of anginal symptoms*, with appropriate management of anginal symptoms (evaluation of level of activity & symptoms includes no report of anginal symptoms, OR evaluation of level of activity and symptoms includes report of anginal symptoms, & a plan of care is documented to achieve control of anginal symptoms)

• **Cardiac Rehabilitation Patient Referral from an Outpatient Setting**: All patients evaluated in an outpatient setting who within the previous 12 mos. have experienced AMI, CABG, PCI, cardiac valve surgery, or cardiac transplantation or who have chronic stable angina & have not already participated in an early outpatient CR or secondary prevention program for the qualifying event / diagnosis & should be referred to such a program

* includes assessment of anginal equivalents

CR, cardiac rehabilitation

Treating Angina: Salutary Effects of Exercise Training

• Conditioning increases exercise duration and work capacity. Note that peak heart rate and SBP are unchanged at maximum exertion. The time to onset of angina and ischemic ECG change are prolonged.

[Graph showing changes in SBP, HR, and DBP over time before and after training.]
Effective Drug Classes to Treat Angina in United States 2015

- Nitrates
- Beta-adrenergic blocking drugs
- Calcium Antagonists
- Late $I_{Na}$ inhibitor (ranolazine)
Antianginal Drug Therapy Considerations

- **Beta-adrenergic receptor blockers**: Physical activity figures prominently in angina attack frequency, hypertension, SVT/VT/HF
- **Calcium antagonists**: Hypertension, variant angina
- **Nitrates**: variant angina
- **Late $I_{Na}$ inhibition (ranolazine)**: Bradycardia, low systolic BP, diabetes mellitus
Traditional Anti-Anginal Therapy: Side Effects That May Limit Their Uses

• **Nitrates**: headache, dizziness, flushing, postural hypotension

• **Beta adrenergic receptor blockers**: fatigue, headache, cold extremities, erectile dysfunction, irritable bowel symptoms, bronchospasm

• **Calcium channel antagonists**: peripheral edema, headache, dizziness, flushing, drowsiness

• **Late I Na inhibition**: Nausea, asthenia, constipation, dizziness
Therapeutic Targets:
Late Na\(^+\) Current Inhibitor

**Development of Ischemia**
- Increased oxygen demand
- Tachycardia
- Hypertension
- Preload
- Contractility
- Decreased oxygen supply

**Consequences of Ischemia**
- Na\(^+\) overload
  - Via augmented late-phase Na current
  - Na\(^+\)/Ca\(^{2+}\) Exchange
- Ca\(^{2+}\) overload
  - Electrical instability
  - Myocardial dysfunction
    - Decreased systolic function/
    - Increased diastolic stiffness

**Myocardial Ischemia**

**Ranolazine**
- (reduces late Na\(^+\) current)

**Therapeutic Targets**

- β-blockers
- Nitrates
- Calcium Channel Blockers
Diastolic Relaxation Failure Increases Oxygen Consumption and Reduces Oxygen Supply

Increased myocardial tension during diastole:

- Increases myocardial $O_2$ consumption
- Compresses intramural small vessels
  - reduces myocardial blood flow
- Worsens ischemia and angina
Clinical Development of Ranolazine: Key Comparative Studies

- **Chronic stable angina**
  - Monotherapy
    - MARISA study (n=191)
  - Combination therapy
    - CARISA study (n=823)
    - ERICA study (n=565)

- **Non-ST-elevation acute coronary syndrome**
  - MERLIN-TIMI 36 trial (n=6560)
MERLIN-TIMI 36 Trial: Cardiovascular Death or MI and Recurrent Ischemia

- Primary Endpoint (CVD/MI/Recurrent Ischemia)
  - Hazard Ratio 0.92 (95% CI 0.83-1.02) \( P=0.11 \)

- Cardiovascular Death or MI
  - Hazard Ratio 0.99 (95% CI 0.85-1.15) \( P=0.87 \)

- Recurrent Ischemia
  - Hazard Ratio 0.87 (95% CI 0.76-0.99) \( P=0.03 \)

MERLIN-TIMI 36: Prior Angina Subanalysis

Patients With Antecedent Angina Presenting With ACS

- Hazard Ratio 0.86 (95% CI 0.75-0.97)  
  - P=0.017
- Hazard Ratio 0.78 (95% CI 0.64-0.91)  
  - P=0.002
- Hazard Ratio 0.77 (95% CI 0.64-0.92)  
  - P=0.005
- Hazard Ratio 0.77 (95% CI 0.59-1.00)  
  - P=0.048

Primary outcome: cardiovascular death, MI, or recurrent ischemia.

Percent of Patients With Angina at Baseline vs. 1 Year Post-PCI

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline</th>
<th>One year post-PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYNAMIC</td>
<td>91</td>
<td>26</td>
</tr>
<tr>
<td>ARTS</td>
<td>100</td>
<td>21</td>
</tr>
<tr>
<td>COURAGE</td>
<td>88</td>
<td>34</td>
</tr>
<tr>
<td>SYNTAX</td>
<td>78</td>
<td>28</td>
</tr>
<tr>
<td>BARI 2D*</td>
<td>100</td>
<td>60</td>
</tr>
</tbody>
</table>

*Total N=2364 patients with CAD and Type 2 DM. This analysis includes only the 1434 patients who had classic angina at baseline.

The Ranolazine for Incomplete Vessel Revascularization (RIVER-PCI) Trial

**Background**

- Incomplete revascularization (ICR) following PCI has been associated with a higher rate of recurrent ischemic events.

- Angina is also reported in 20-30% of patients following PCI at 1 year, and is associated with lower QOL.

- In MERLIN, ranolazine reduced the risk of recurrent ischemic events among post-MI patients with a history of prior angina - including those treated with PCI – by up to 30% (HR 0.69; 95% CI 0.51-0.92)*

*Gutierrez et al Clin Cardiol. 2015;38:469–475*
Patients with History of Angina AND Incomplete Revascularization After PCI  
N=2600

1:1 Randomization  
Strata: ACS vs. non-ACS, DM vs. non-DM

Ranolazine 1000 mg BID  
Placebo

Primary Endpoint  
Ischemia-driven revascularization or Ischemia-driven hospitalization

Event driven  
Minimum 1 Year Follow-up

Primary Endpoint

Ischemia-driven revascularization or ischemia-driven hospitalization

![Graph showing the freedom from primary endpoint event percentage over months since randomization for Ranolazine and Placebo. The graph includes the number at risk for each group at various time points.](image)

- **HR [95%CI] = 0.95 [0.82, 1.10]**
- **p-value = 0.48**

**No. at risk**
- **Ranolazine**
  - 1317
  - 1164
  - 1101
  - 1018
  - 945
  - 891
  - 813
  - 500
  - 266
  - 134
- **Placebo**
  - 1287
  - 1165
  - 1098
  - 1028
  - 960
  - 879
  - 788
  - 461
  - 271
  - 128
  - 45

**Months since randomization**
- 0
- 3
- 6
- 9
- 12
- 15
- 18
- 21
- 24
- 27
- 30

RIVER-PCI QOL Population

Overall Trial Population

(2,604)

1,317 to ranolazine

• 103 questionnaires invalid
• 7 questionnaires not done

1,207 in QOL population

1,287 to placebo

• 97 questionnaires invalid
• 8 questionnaires not done

QOL Population

(2,389)

92%

1,182 in QOL population

78% (1,864) complete data at all time points
SAQ Angina Frequency

<table>
<thead>
<tr>
<th>Study Visit (Months)</th>
<th>Ranolazine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>86.6</td>
<td>69.7</td>
</tr>
<tr>
<td>1</td>
<td>85.8</td>
<td>67.3</td>
</tr>
<tr>
<td>6</td>
<td>88.2</td>
<td>87.7</td>
</tr>
<tr>
<td>12</td>
<td>88.4</td>
<td>88.5</td>
</tr>
</tbody>
</table>

- P = 0.60
- P = 0.62
- P = 0.23
- P = 0.03

Number of Subjects:
- Ranolazine: 1189 1116
- Placebo: 1169 1121
- 1043 1047 979 981
Conclusions

• Despite incomplete revascularization following PCI, there was no reduction in ischemia-driven revascularization, nor was there incremental benefit on angina or QOL measures with the addition of ranolazine in this angiographically-identified population.

• Significant & sustained improvements in angina were observed in both arms following PCI, with most patients having rare or no angina by 1 month.

• Additional research is needed to understand the relationship between incomplete revascularization and ischemia-driven events.
Novel Therapeutic Agents or Interventions

• Infarct Size Reduction
• Chelation Therapy
TIME COURSE OF MYOCARDIAL INFARCTION

% necrosis complete

% potential myocardial salvage

Hours from MI onset
Clinical Trials of MI Reduction

• Many pharmacologic agents that were cardioprotective in animal models failed in clinical trials.
<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Trial Design (Ref. #)</th>
<th>Year</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>LeukoArrest</td>
<td>420 patients randomized to LeukoArrest 0.3 mg/kg, LeukoArrest 1.0 mg/kg, or placebo before reperfusion</td>
<td>2002</td>
<td>No difference in infarct size measured by SPECT No improvement in clinical events</td>
</tr>
<tr>
<td>CD11/CD18 leukocyte integrin receptor inhibitor</td>
<td><strong>ESCAMI</strong> (97) 959 patients randomized to 10-min infusion of eniporide 100 mg, eniporide 150 mg, or placebo before reperfusion</td>
<td>2001</td>
<td>No difference in infarct size measured by mean release of α-hydroxybutyrate dehydrogenase No improvement in clinical outcomes</td>
</tr>
<tr>
<td>Eniporide</td>
<td><strong>CASTEMI</strong> (98) 387 patients randomized to a 48-h infusion of caldaret 57.5 mg, caldaret 172.5 mg, or placebo initiated before reperfusion</td>
<td>2006</td>
<td>No difference in infarct size measured by SPECT No difference in LVEF on day 7 or 30</td>
</tr>
<tr>
<td>Na+/H+ exchange inhibitor</td>
<td><strong>J-WIND-KATP</strong> (58) 545 patients randomized to 0.067-mg/kg bolus followed by 24-h infusion of 1.67 μg/kg/min of nicorandil or placebo</td>
<td>2007</td>
<td>No difference in infarct size measured by CK-MB release</td>
</tr>
<tr>
<td>Caldaret</td>
<td><strong>CREATE-ECLA</strong> (99) 20,201 patients randomized to usual care plus 24-h infusion of GIK or usual care alone</td>
<td>2005</td>
<td>No difference in mortality, cardiac arrest, cardiogenic shock, reinfarction, or heart failure</td>
</tr>
<tr>
<td>Nicorandil</td>
<td><strong>PROTECTION-AMI</strong> (100) Anterior MI cohort: 1,010 patients randomized to 2.5-h infusion of delcaserib 50 mg/h, 150 mg/h, 450 mg/h, or placebo initiated before PCI Inferior MI cohort: 166 patients randomized to 2.5-h infusion of delcaserib 450 mg/h or placebo initiated before PCI</td>
<td>2011</td>
<td>No difference in infarct size measured by CK-MB release or ST-segment resolution in either cohort No difference in clinical outcomes</td>
</tr>
<tr>
<td>K+ channel opener/vasodilator</td>
<td><strong>REVEAL</strong> (101) 222 patients randomized to intravenous epoetin-alfa or placebo within 4 h of repertusion</td>
<td>2011</td>
<td>No difference in infarct size as measured by cardiac MRI at 2 to 6 days or 12 ± 2 weeks Increased infarct size in patients ≥70 yrs who received epoetin-alfa Increased incidence of composite outcome of death, MI, stroke, or stent thrombosis in epoetin-alfa group</td>
</tr>
</tbody>
</table>

CK-MB = creatine kinase-MB fraction; GIK = glucose-insulin-potassium; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRI = magnetic resonance imaging; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography.
Adjunctive Agents That *May* Show Promise (in Selected Patient Populations and Under the Right Circumstances)

<table>
<thead>
<tr>
<th>Type of Agent</th>
<th>Study</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>AMISTAD 1 and 2</td>
<td>Reduced Anterior MI infarct size. With early (≤ 3 hours) reperfusion improved clinical outcome (AMISTAD 2).</td>
</tr>
<tr>
<td>Therapeutic Hypothermia</td>
<td>COOL MI</td>
<td>No overall difference in infarct size, clinical events. However patients with anterior AMI cooled &lt; 35°C before PCI had smaller infarcts.</td>
</tr>
<tr>
<td>Hyperoxemic reperfusion</td>
<td>AMIHOT</td>
<td>No overall difference. However, patients with anterior AMI reperfused &lt; 6 hours had greater improvements in function, smaller infarct size, improved ST ↑ resolution.</td>
</tr>
</tbody>
</table>
Interventions to Reduce Reperfusion Injury and/or Reduce Infarct Size

- Most cardiologists agree that the best way to treat acute ST elevation MI in patients is to reperfuse the infarct artery as soon as possible and to keep the artery open.

- In general, RCTs have shown that stenting is better than angioplasty, which is better than thrombolysis.

- Other than agents to keep the artery open (such as antiplatelet agents), statins, anti-remodeling agents (e.g., inhibitors of the renin-angiotensin system [ACEI’s & ARBs], where clinically appropriate), there is no accepted adjunctive drug to further limit myocardial infarct size along with reperfusion.
Excreting Metal Pollutants: Chelation

• **WHAT IS IT:** Intravenous infusions of a drug, called a chelator, that has a pocket with an electrical charge, almost like a baseball mitt with a magnet in it.

• **HOW IT WORKS:** Like a mitt catching a baseball, the chelator captures toxic metals, such as lead or cadmium, and holds onto them. The metals then pass through the body and are excreted in urine.
Environmental pollutants are a modifiable risk factor for coronary disease.

Diabetic patients are an especially vulnerable population.
Lead, Cadmium, and CV Risk

• **Lead** is associated with hypertension, stroke, MI, and mortality. Its principal storage is in bone. Once in bone, the half-life is 30 years.

• **Cadmium** is associated with CAD, cerebrovascular disease, and particularly PAD. Its principal storage is in kidneys, liver, and lung. The half-life is 30 years.
Critical Toxic Metals in the Environment

Lead

Cadmium
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 *(Histone OH-methylation by Cd. EHP 2014)*

*Courtesy of Ana Navas-Acien 2013*
Advanced Glycation End Products (AGEs): Mediators of Complications of Diabetes

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

• AGEs formation are metal-catalyzed oxidation reactions: Reactive oxygen species (ROS) and free metal ions are key participants in the formation of AGEs.
HYPOTHESIS: AGEs and Chelation

- Chelators have been identified as potent inhibitors of cross-linking of proteins by glucose.
- The chemistry of advanced glycation end products (AGEs) forming reactions can be inhibited \textit{in vitro} by chelators, including disodium EDTA.
## TACT Design - Factorial Trial

<table>
<thead>
<tr>
<th>IV Chelation + ORAL high-dose vitamins (active-active)</th>
<th>IV Placebo chelation + ORAL placebo vitamins (placebo-placebo)</th>
</tr>
</thead>
</table>

Treatment Regimen Components

• **Infusion treatments (X40)**
  
  – *Active infusions: Na$_2$EDTA 3 g, ascorbic acid 7 g, electrolytes, B-vitamins, UF heparin (2500U), procaine (total 500 mL)*
  
  – *Placebo infusions (X40): 0.9N NaCl + 6g dextrose (total 500 mL)*
  
  – 55,222 infusions administered

• **Oral treatments throughout course of trial**
  
  – *Active oral vitamins – 28 component MVM*
  
  – *Placebo oral vitamins – methylcellulose carrier*
TACT Eligibility

- Age 50 or older
- MI > 6 weeks prior
- Creatinine < 2.0 mg/dL

Vital stats: $30M; 10 years; 1708 patients in US and Canada; 134 sites; 55,222 infusions

Relevance: 615,000 new MI survivors annually; 196,000 have diabetes
Primary Endpoint

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

Results

EDTA: Placebo

HR (95% CI)
0.82 (0.69, 0.99)

P = 0.035

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

• Number at risk:
  - Placebo 869
  - EDTA chelation 229

Months since randomization

<table>
<thead>
<tr>
<th>Months</th>
<th>Placebo</th>
<th>EDTA chelation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>776</td>
<td>839</td>
</tr>
<tr>
<td>6</td>
<td>701</td>
<td>760</td>
</tr>
<tr>
<td>12</td>
<td>638</td>
<td>703</td>
</tr>
<tr>
<td>18</td>
<td>566</td>
<td>650</td>
</tr>
<tr>
<td>24</td>
<td>515</td>
<td>588</td>
</tr>
<tr>
<td>30</td>
<td>475</td>
<td>537</td>
</tr>
<tr>
<td>36</td>
<td>429</td>
<td>511</td>
</tr>
<tr>
<td>42</td>
<td>384</td>
<td>476</td>
</tr>
<tr>
<td>48</td>
<td>322</td>
<td>427</td>
</tr>
<tr>
<td>54</td>
<td>205</td>
<td>358</td>
</tr>
</tbody>
</table>

Placebo

EDTA Chelation
## 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>All Subjects</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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>674</td>
<td>0.03</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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>538</td>
<td>0.02</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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1248</td>
<td>0.59</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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1089</td>
<td>0.28</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>
Primary Endpoint by Infusion Arm in Diabetics

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:
- EDTA Chelation: 322, 286, 262, 243, 217, 198, 187, 177, 157, 126, 77
TACT Primary Endpoint in Diabetes Subgroup

Event Rate vs. Months since randomization

Placebo Infusions + Oral Placebo Vitamins

EDTA Chelation + Oral High-Dose Vitamins

EDTA Chelation/High-dose Vitamins vs. Placebo

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

P < 0.001
## Endpoints (Diabetes)

<table>
<thead>
<tr>
<th></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>
TACT Trial Conclusion

• Patients with diabetes demonstrated 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).

• CONTEXT: Statin therapy for secondary prevention (DM): 5 year NNT was 15 for major coronary events.
...and Where Does Cardiology Stand on Chelation Today…?


Circulation. published online July 28, 2014;

•2014 FOCUSED GUIDELINE ON STABLE ISCHEMIC HEART DISEASE
Replicative trial of IV chelation + oral vitamins vs double placebo in 1,200 post-MI diabetic patients

Strong mechanistic component with a focus on toxic metals
Summary

• Angina persists for many patients despite medical therapy and/or revascularization

• For all patients with angina, aggressive risk factor modification and optimized medical management must be instituted

• Revascularization is indicated for high-risk patients or patients with persistent symptoms who fail OMT

• β-blockers and CCBs remain first-line agents; however, most patients require multiple medications for symptom control

• Novel agents with new mechanisms may increase treatment options, and are under prospective study