The Trial to Assess Chelation Therapy (TACT)

Chelation-Placebo Comparison

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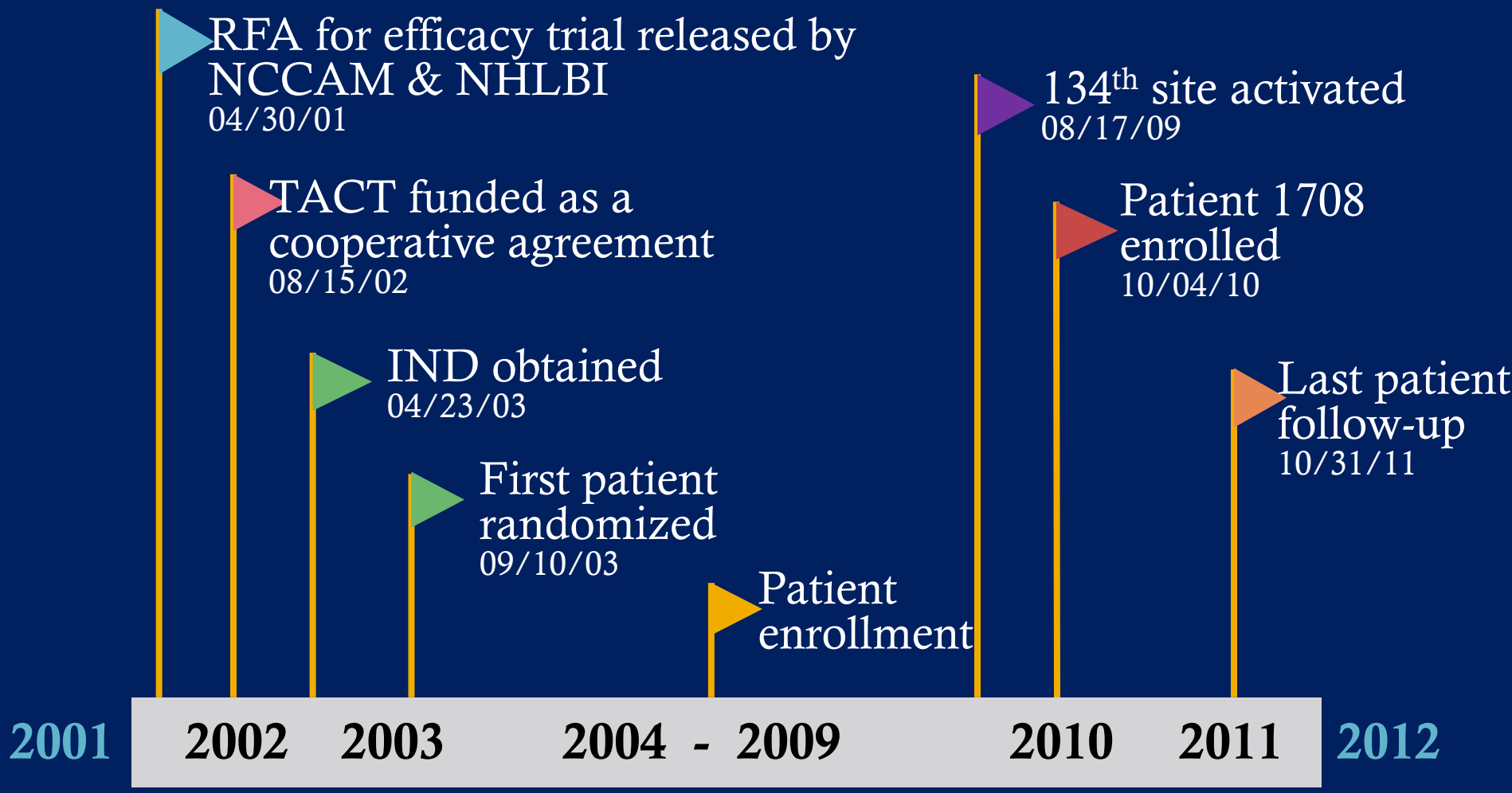
Background

- 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



Design Overview - Factorial Trial

Chelaton + high-dose vitamins	Chelation placebo + high-dose vitamins
Chelation + vitamin placebo	Chelation placebo + vitamin placebo

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.

Lamas GA, Goertz C, Boineau R, et. al. Design of the Trial to Assess Chelation Therapy (TACT). Am Heart J. 2012 Jan;163(1):7-12.

Eligibility

- Age 50 or older
- MI > 6 months prior
- Creatinine $\leq$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

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

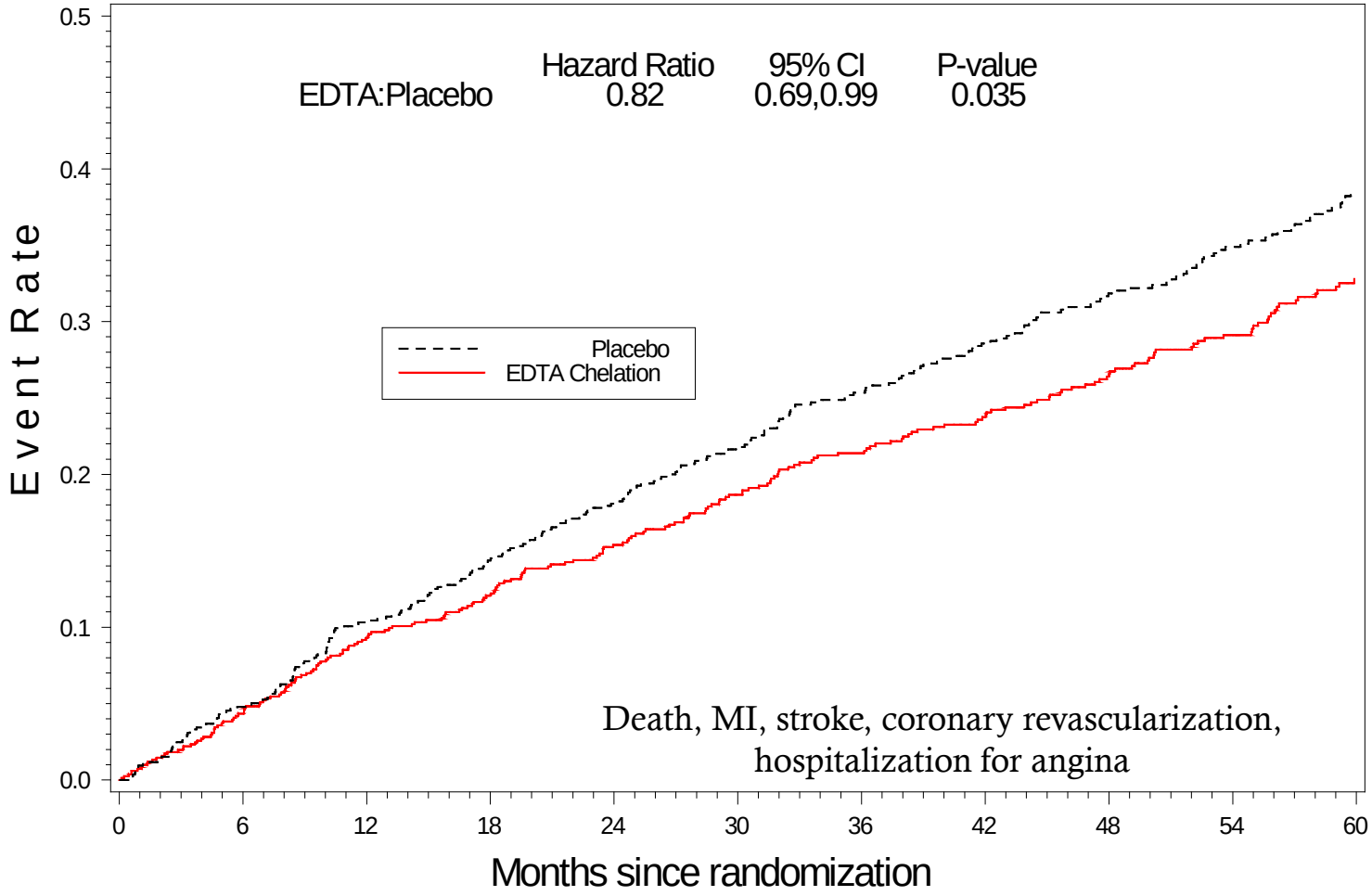
Compliance

- 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



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

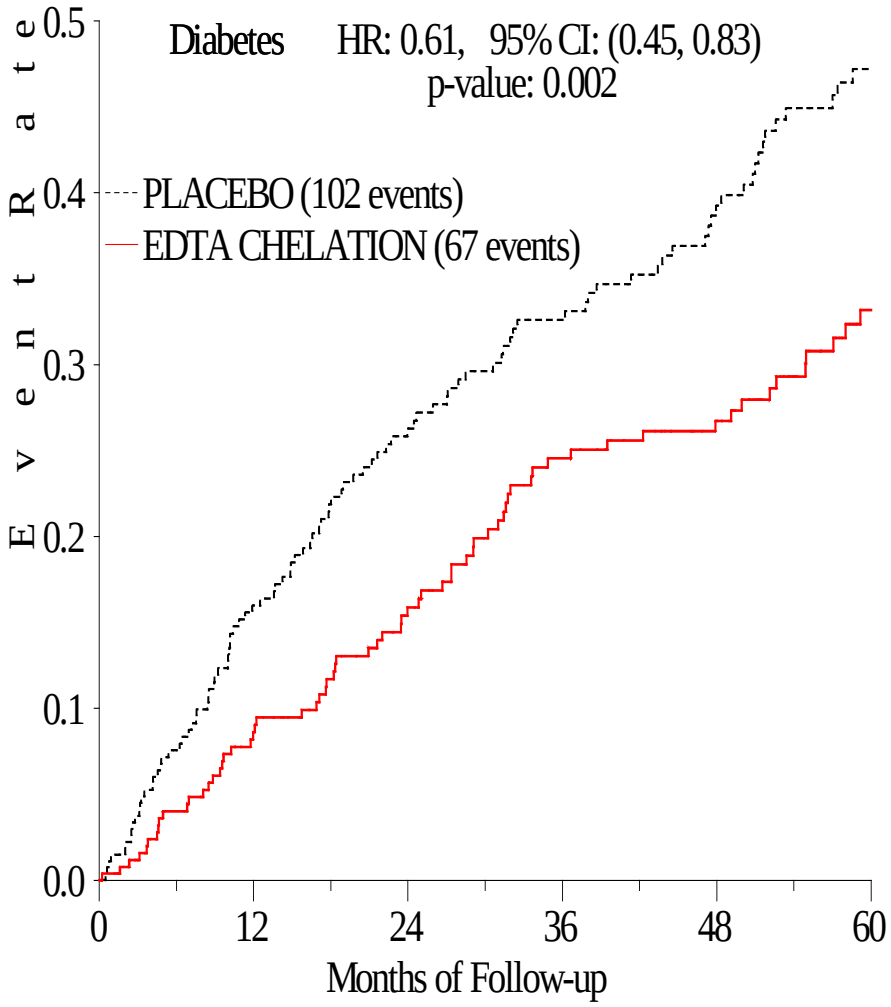
Components of the Primary Endpoint

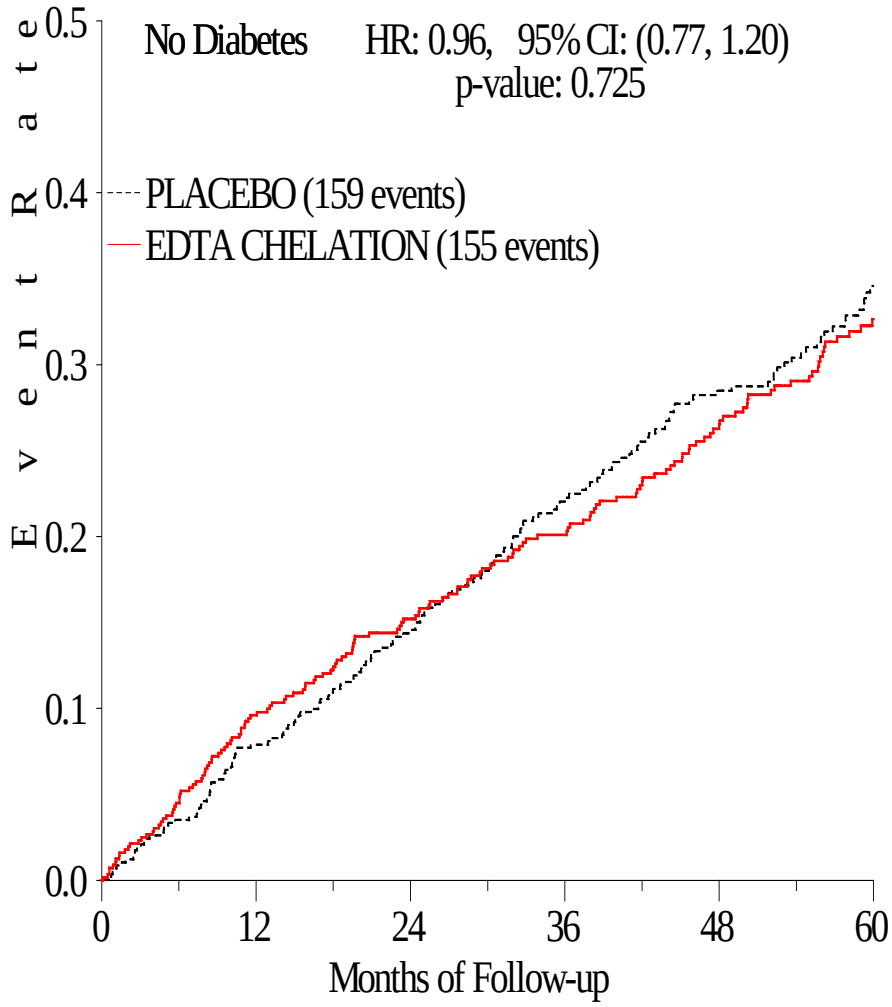
	EDTA Chelation (N= 839)	Placebo (N= 869)	Hazard Ratio (95% CI)	P Value*
Primary Endpoint	222 (26.5%)	261 (30.0%)	0.82 (0.69,0.99)	0.035
Death	87 (10.4%)	93 (10.7%)	0.93 (0.70, 1.25)	0.642
Myocardial Infarction	52 (6.2%)	67 (7.7%)	0.77 (0.54, 1.11)	0.168
Stroke	10 (1.2%)	13 (1.5%)	0.77 (0.34, 1.76)	0.531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

Subgroups analysis

Selected Prespecified Subgroup	P for interaction with treatment group assignment
Age>70	0.51
Gender	0.58
Race	0.15
Minority	0.25
Time from MI to enrollment	0.87
Chelation site v. conventional	0.28
Oral vitamins v. placebo	0.94
MI location	0.03
Diabetes	0.02
Statins at baseline	0.59
ACE or ARB at baseline	0.04

Predefined Subgroup- Diabetes (31%)





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