The Effect of Edetate Disodium-based Chelation on Cardiovascular Events in Patients with a Prior Myocardial Infarction and Diabetes – Results of the TACT2 Randomized Trial

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TACT2 Investigators

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I have no conflicts of interest

TACT2: Background

- Lead and cadmium are ubiquitous environmental pollutants and recognized risk factors for atherosclerosis
- Edetate disodium (EDTA) is an avid lead and cadmium chelator, promotes their urinary elimination
- The Trial to Assess Chelation Therapy (TACT, 2003-2012) randomized 1702 patients with a prior MI (633 with diabetes) to placebo or edetate disodium (EDTA) infusions
- Overall cardiovascular events were reduced in the edetate disodium group (HR=0.82, p=0.035)[1] with a marked effect size (HR=0.59, p=0.0002)[2] in patients with concomitant diabetes

1. Lamas G et al. JAMA 2013
2. Escolar E et al. Circ Cardiovasc Qual Outcomes 2014

TACT2: Purpose

The purpose of the Trial to Assess Chelation Therapy 2 (TACT2) was to:

- Efficiently replicate TACT in post MI patients with diabetes
- Measure the effect of repeated edetate disodium infusions on blood lead and urine cadmium

TACT2: Funding and Organization

Funded by the National Institutes of Health

National Center for Complementary and Integrative Health

National Heart Lung and Blood Institute

National Institute for Diabetes Digestive and Kidney Diseases

National Institute of Environmental Health Sciences

Coordinating Centers

Clinical Coordinating Center
Mount Sinai Medical Center
Miami Beach, FL

Data Coordinating Center- Duke Clinical Research Institute (DCRI), Durham, NC

Trace Metals Core and Biorepository Center- Mailman School of Public Health, Columbia University NY, NY

Patient management

Clinical Sites US and Canada (n=88)

DCRI Patient Reported Outcomes (PRO) Call Center

Central Pharmacy to prepare and distribute study drug

TACT2: Design

- Double blind factorial trial of
  - (i) edetate disodium-based infusions and
  - (ii) high dose oral multivitamins and minerals

vs. corresponding placebos

- Randomization was 1:1:1:1

- The present report focuses on edetate disodium vs placebo infusions only

TACT2: Methods

- 1000 post MI patients with diabetes randomly assigned to 40 weekly edetate disodium or placebo infusions and oral low-dose vitamin and mineral supplements

- Follow-up:
  - Planned minimum = 2.5 years
  - Median = 4 years

TACT2: Key Inclusion Criteria

- Age 50 or older, non-childbearing if female
- Prior MI >6 weeks
- Diabetes
- Creatinine ≤ 2.0 mg/dL
- Non-smoker

TACT2: Study Infusions

Active infusions

- edetate disodium up to 3 grams based on renal function
- 7 g of ascorbic acid
- 2 g of magnesium chloride
- Other components as detailed in the design paper *
- Total volume 500mL

Placebo infusions

- 500 mL of normal saline and 1.2% dextrose (2.5 g total).

Infusions administered through peripheral intravenous access over at least 3 hours

*Lamas G et al. Am Heart J 2022

TACT2 Endpoints

- Primary endpoint: composite of time to first occurrence of all-cause mortality, MI, stroke, coronary revascularization, or hospitalization for unstable angina

- The secondary endpoints were:
  - Recurrent events of the primary composite endpoint
  - All-cause mortality
  - Composite of cardiovascular mortality, MI, or stroke

- The metals endpoint was a decrease in body burden of blood lead and urine cadmium

TACT2: Statistical Considerations

- Time from randomization to the first occurrence of any of the primary composite event components using the Cox proportional hazards regression model
- Sample size calculations based on >85% power to detect a 30% reduction in the primary endpoint with an alpha of 0.05.
- The primary analyses are reported for the modified intention-to-treat (mITT) population, which excludes 41 of the 1000 randomized patients who never received any infusions

Selected Baseline Characteristics (mITT Population)

	Total (N=959)
Age-years (median IQR)	67 (60-72)
Female - %	26.9
Non-Hispanic White - %	61.5
Time from qualifying MI to randomization	
Median years (IQR)	5 (2 - 10)
Diabetes Medications - %	
Insulin	46.7
GLP-1a or SGLT-2i	22.2
Other Medications - %	
Aspirin, warfarin, or P2Y12 inhibitor	90.0
Beta-blocker	79.5
Statin	85.9
Hemoglobin A1c, %,Mean ± SD	7.5 ± 1.3
LDL, mg/dL, Mean ± SD	79.6 ± 35.3

Additional Characteristics (mITT Population)

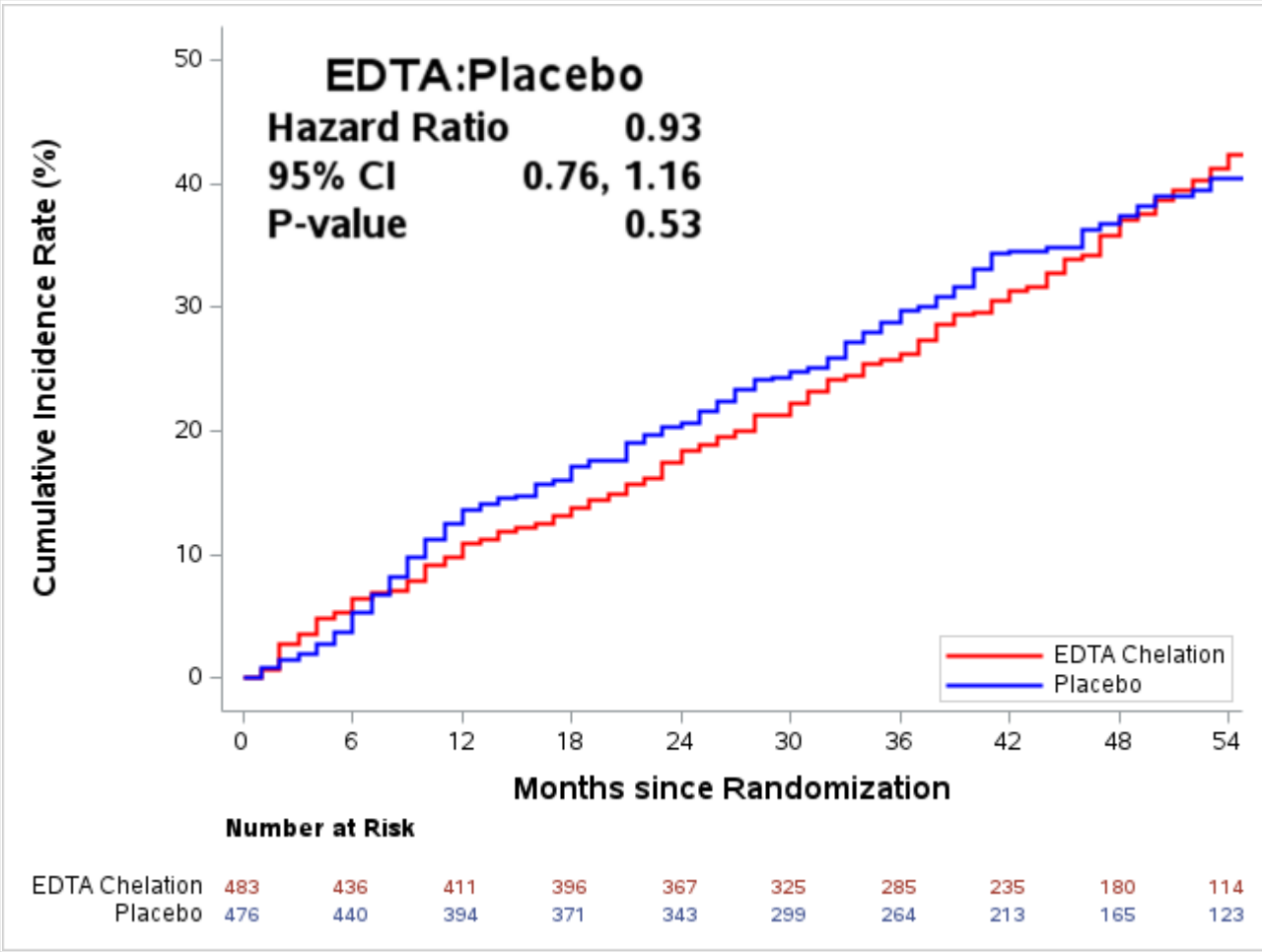
	% Detectable	Median (IQR)
Lead (blood) µg/L	100	9.22 (6.30, 14.00)
Cadmium (urine) µg metal/g Creatinine	97	0.30 (0.18, 0.52)

Compliance with Infusion Regimen

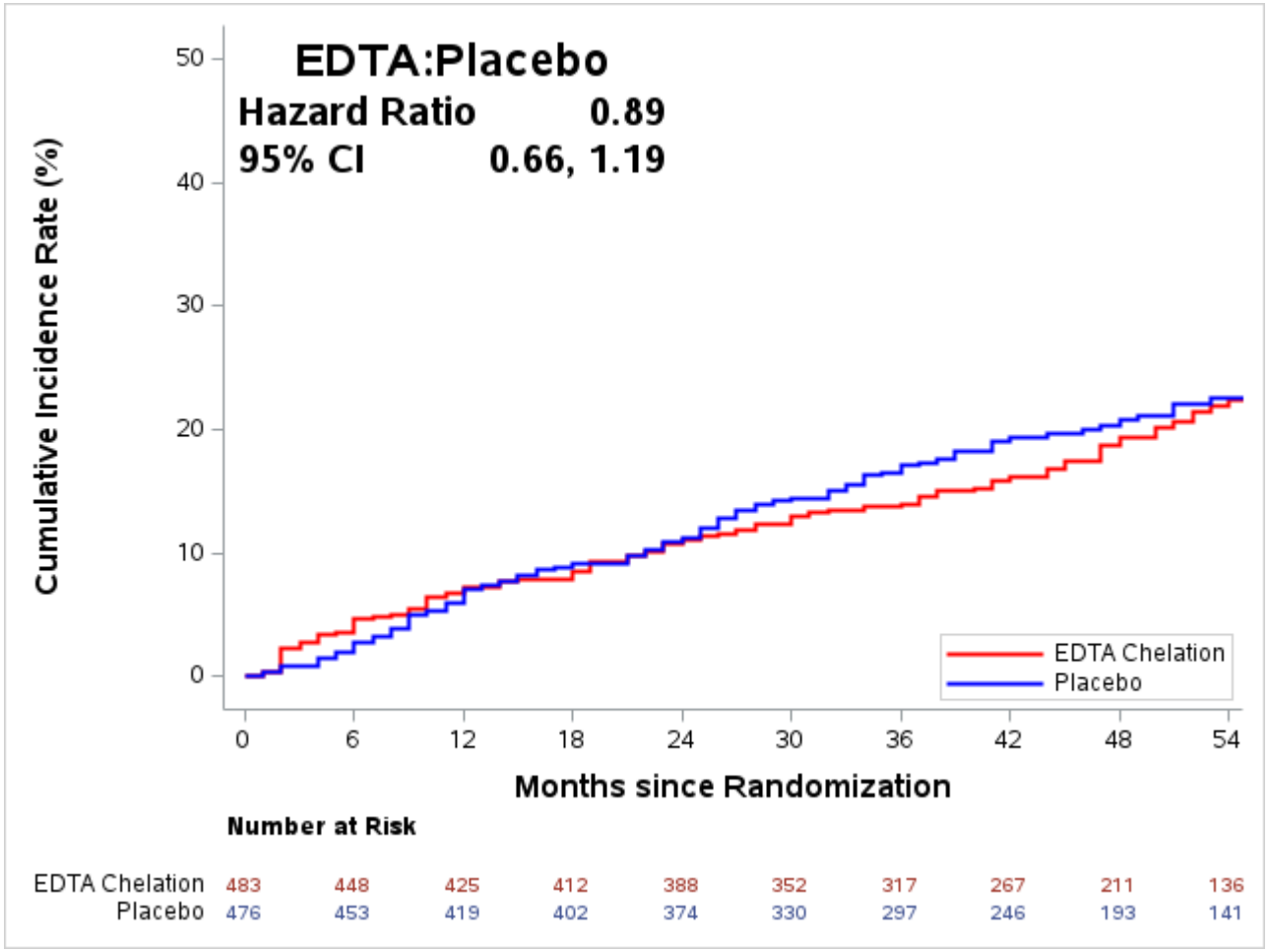
	Total # of infusions 31,615	40 Infusions	20 Infusions
Active	15,787	68%	78%
Placebo	15,828	67%	78%

Primary Outcome Results

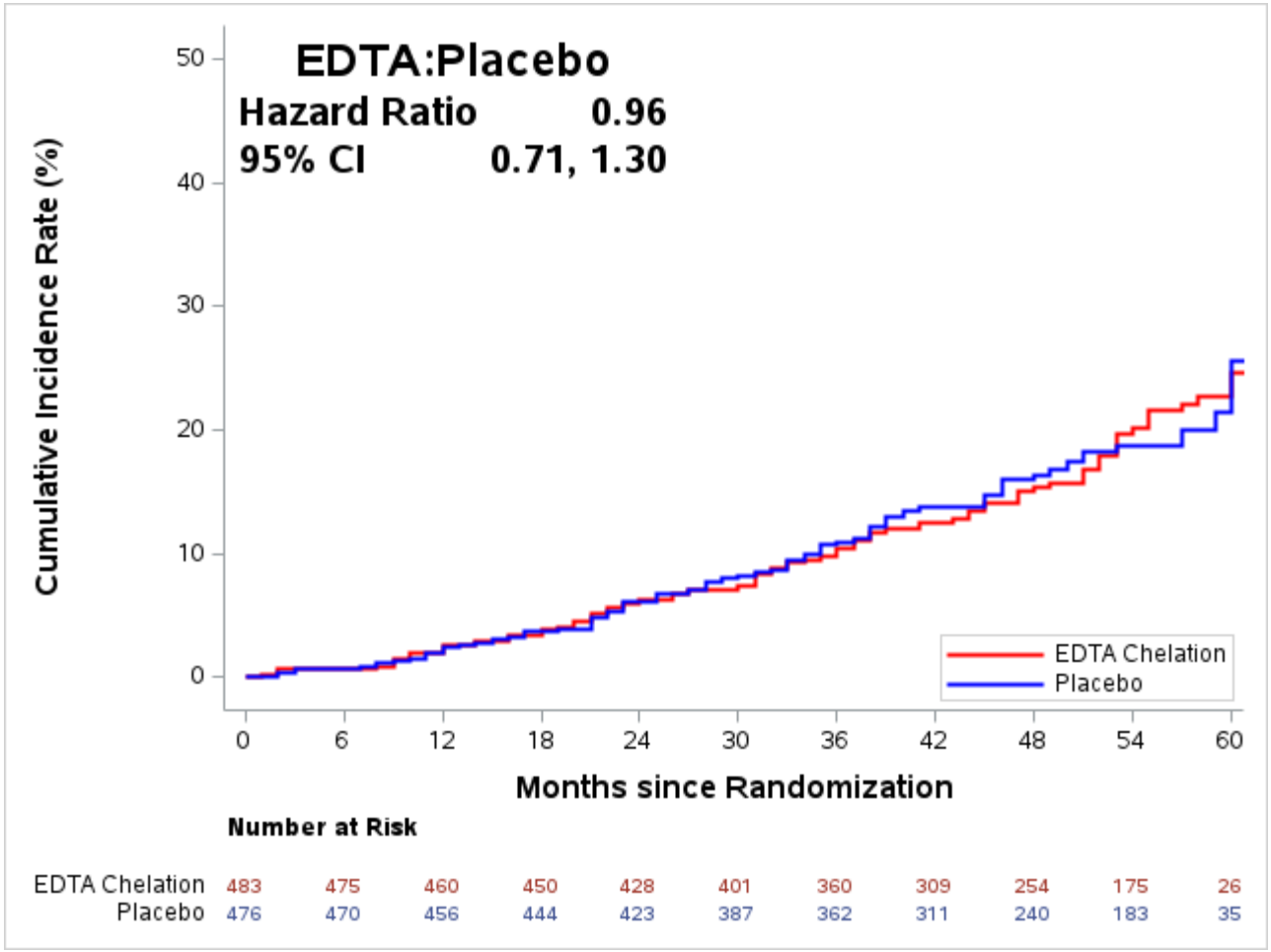
Cumulative Incidence of Time to First Event: Myocardial Infarction, Stroke, Hospitalization for Unstable Angina, Coronary Revascularization, or Death from Any Cause



Time to First Event: Myocardial Infarction, Stroke, or Cardiovascular Death

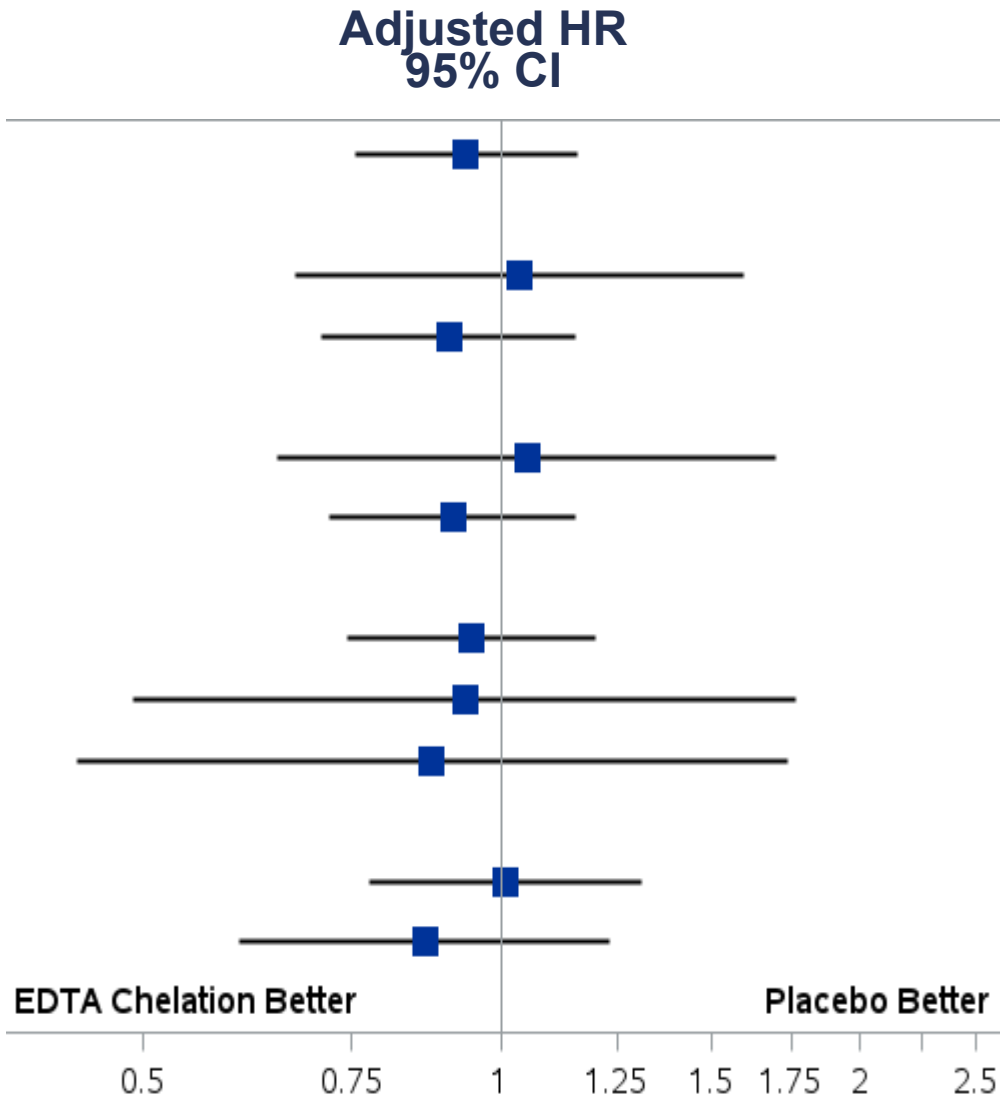


Time to All-Cause Mortality



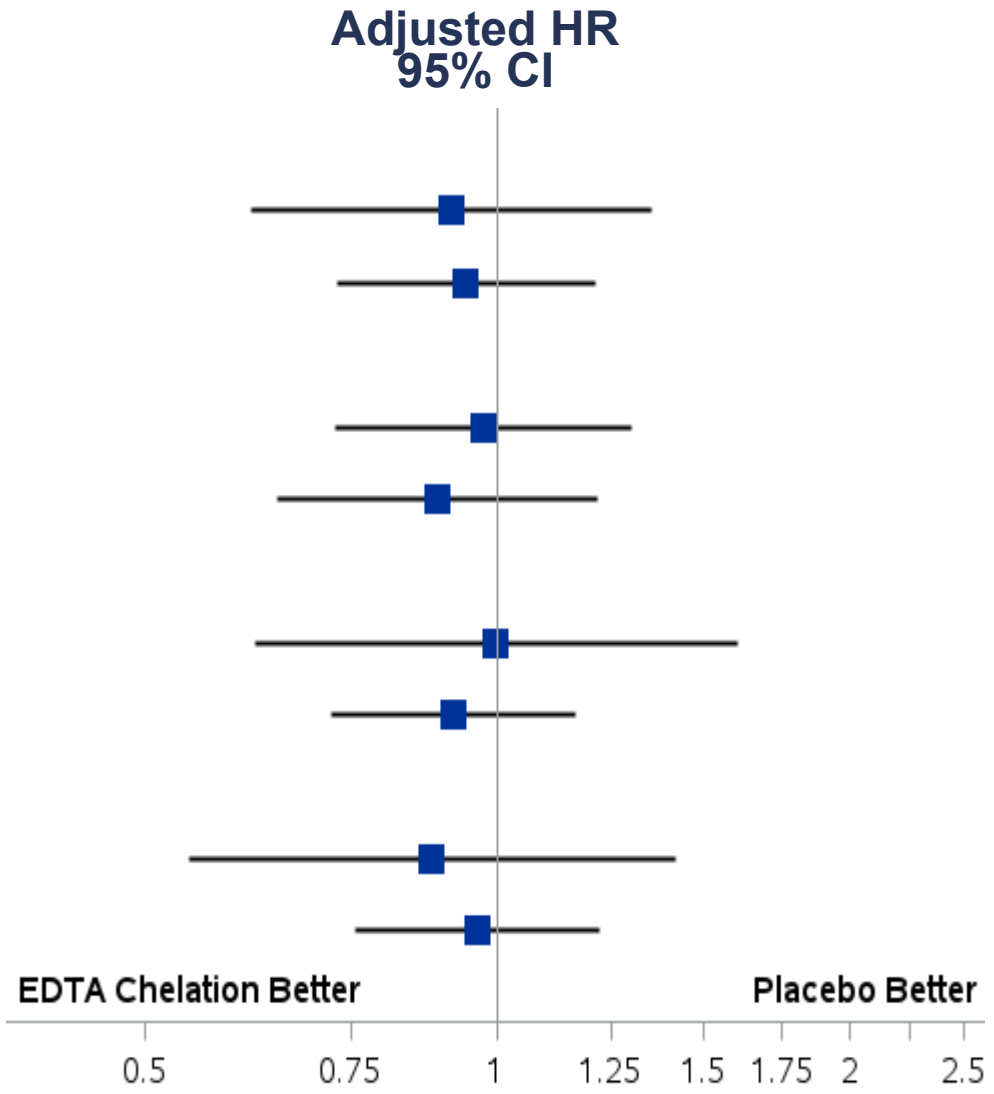
Subgroup Analysis for Primary Endpoint (mITT)

Subject Group	Adjusted Hazard Ratio	95% CI
All Participants	0.93	(0.76, 1.16)
Sex		
Female	1.03	(0.67, 1.59)
Male	0.90	(0.71, 1.16)
Ethnicity		
Hispanic/Latino	1.05	(0.65, 1.70)
Non-Hispanic/Latino	0.91	(0.72, 1.16)
Race		
White	0.94	(0.74, 1.20)
Black	0.93	(0.49, 1.76)
Other	0.88	(0.44, 1.74)
Age		
≤ 70 Years	1.01	(0.77, 1.31)
> 70 Years	0.86	(0.60, 1.23)

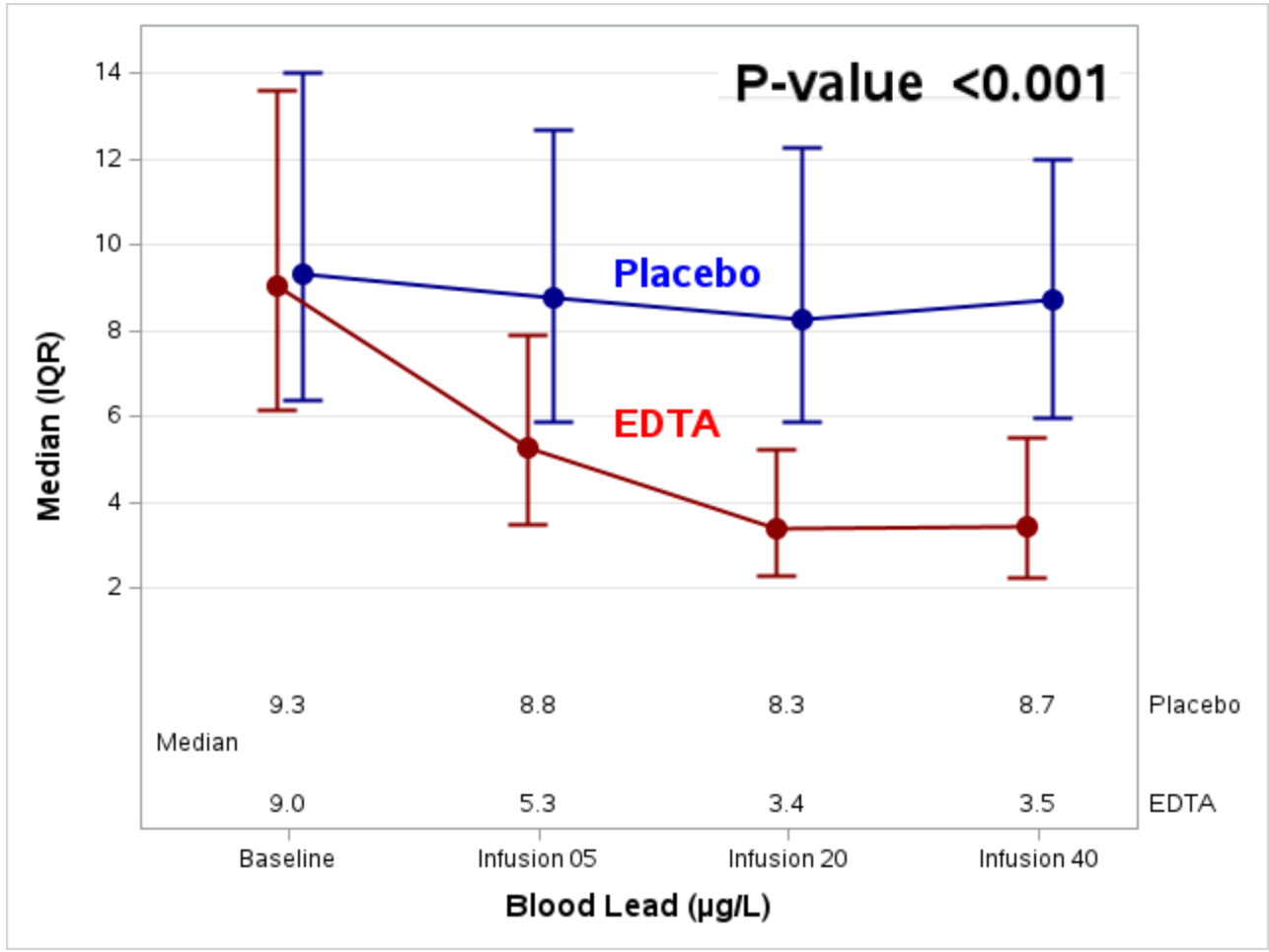


Subgroup Analysis for Primary Endpoint (mITT)

Subject Group	Adjusted Hazard Ratio	95% CI
MI Location		
Anterior MI	0.91	(0.62, 1.36)
Non-anterior MI	0.94	(0.73, 1.21)
Insulin-use at Baseline		
Yes	0.97	(0.73, 1.30)
No	0.89	(0.65, 1.22)
GLP-receptor agonist or SGLT-2 inhibitor at baseline		
Yes	1.00	(0.62, 1.60)
No	0.92	(0.72, 1.16)
Peripheral Artery Disease at baseline		
Yes	0.88	(0.55, 1.42)
No	0.96	(0.76, 1.22)

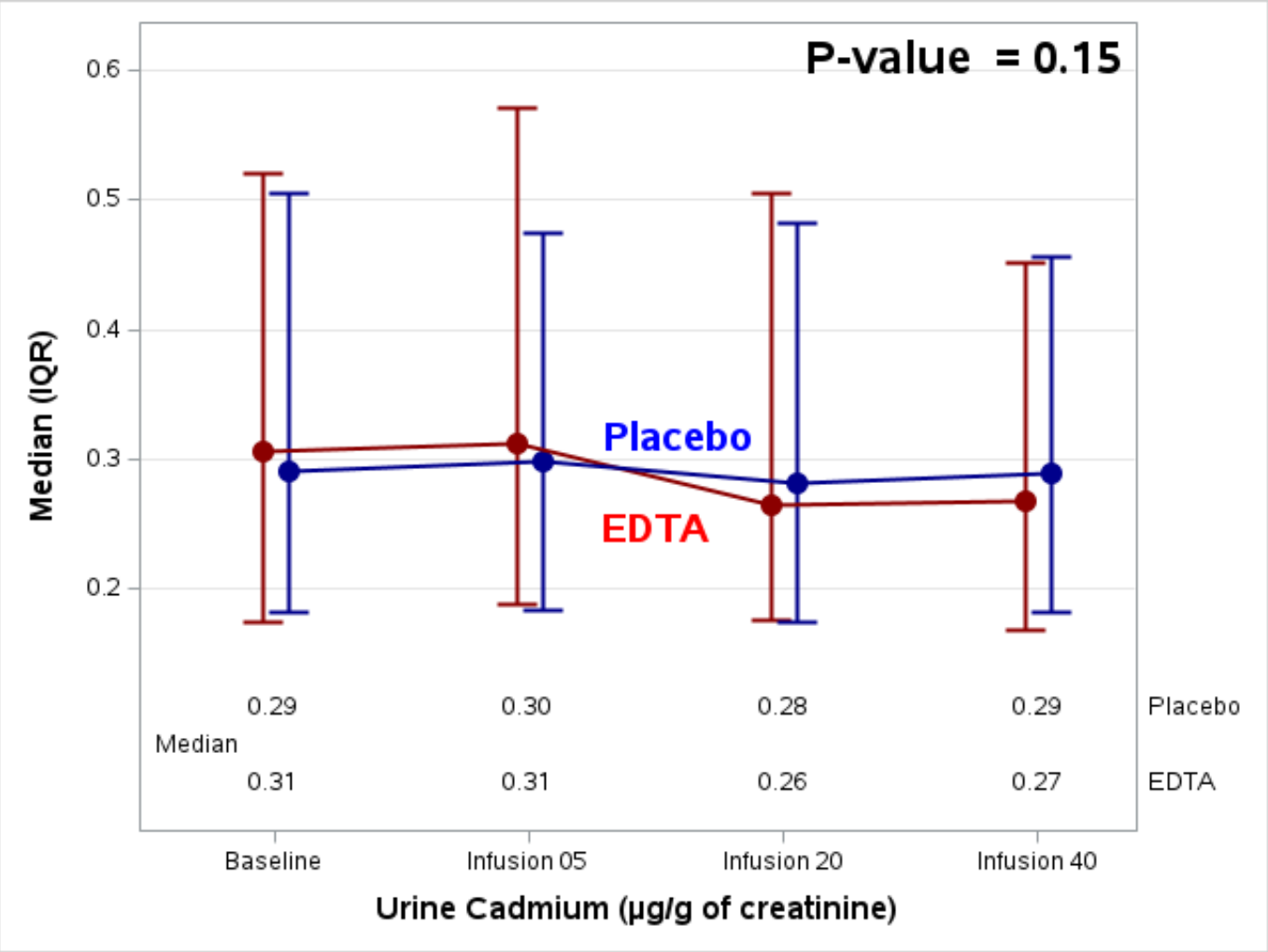


Pre-Infusion Blood Lead (µg/L) Levels at Baseline and during Study



Note: P-value tests the change from baseline to pre-infusion 40 between active and placebo using the Wilcoxon rank sums test.

Pre-Infusion Urine Cadmium (µg/g of creatinine) Levels at Baseline and during Study



Note: P-value tests the change from baseline to pre-infusion 40 between active and placebo using the Wilcoxon rank sums test.

TACT2 Summary

- EDTA chelation produced >60% reduction in blood lead levels
- No safety issues
- EDTA did not result in a significant clinical benefit on primary or secondary endpoints or on all-cause mortality

Why were the results of TACT (2003-2012) and TACT2 (2016-2023) so different?

- NHANES may shed light
  - 2003 to 2010 (TACT) blood lead levels 17 mcg/L
  - 2015 to 2020 (TACT2) blood lead levels 10 mcg/L (41% drop)
  - TACT2 blood lead levels even lower at baseline: 9 mcg/L

- Hypothesis: US blood lead levels have markedly dropped since 2003, possibly reducing the potential therapeutic impact of further lowering blood lead level

Conclusion

- TACT2 does not support the use of edetate disodium (EDTA) chelation for risk reduction in stable post MI patients with diabetes