Chelation Therapy for Cardiovascular Disease: Bringing it Back to the Future

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ABSTRACT

Chelation therapy, a treatment long undervalued by conventional medicine, has been used by alternative medicine practitioners to alleviate various metabolic toxicities. In particular, there has been significant controversy around its use in patients with coronary artery disease. We performed a focused review of the recent National Institute of Health (NIH) trial to investigate the role of chelation therapy in the treatment of patients with coronary artery disease. The study was the first randomized, factorial trial (n=1708) in patients with coronary artery disease, already receiving standard, guideline-approved treatment. Patients were randomized to EDTA chelation therapy with or without oral multivitamin multimineral supplement (OMVM). The trial showed that EDTA chelation reduced the primary endpoint (a composite of total mortality, recurrent myocardial infarction, stroke, coronary revascularization, or hospitalization for angina) by 18% overall (95% confidence interval [CI]: 1–21%). This benefit was increased by addition of OMVM (26% relative reduction; 95% CI: 5–23%), and the effect was most pronounced in patients with diabetes: 51% (95% CI: 25–67%) relative reduction for chelation with, and 41% (95% CI: 21–56%) without OMVM, respectively. Chelation therapy, recently evaluated in the NIH trial of patients with coronary artery disease, has been given a class IIb (may be beneficial) designation by the American College of Cardiology Chronic Ischemic Heart Disease Guidelines. The positive and significant impact of chelation therapy on morbidity and mortality of patients already receiving standard contemporary treatment is pivotal to the advancement of chelation therapy into the mainstream of coronary artery disease treatments.

Keywords: Chelation therapy; Coronary artery disease; Trial to Assess Chelation Therapy (TACT)

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INTRODUCTION

In patients with coronary artery disease (CAD), current pharmacological treatments and interventions may now include chelation therapy. The treatment for stable CAD patients is based on the American College of Cardiology (ACC) guidelines.[1] In most clinical guidelines, risks and benefits of interventions and treatments are assigned by class and level of evidence. All class and level recommendations are typically based on best available clinical evidence (Figure 1). In general, treatments that show the most benefit, usually supported by evidence from large randomized controlled trials (RCTs), are designated class 1. For most alternative and complementary therapies, it is rare to find RCTs fitting such criteria. Chelation therapy, for a long time overshadowed by other treatment modalities for CAD, has recently emerged as an option recognized in the guidelines. A landmark trial of chelation therapy, Trial to Assess Chelation Therapy (TACT) 1 was reported in 2013.[2] The trial showed that chelation therapy was beneficial for patients with prior myocardial infarction (MI), especially for those with diabetes. As a result, the current Chronic Ischemic Heart Disease Guidelines advanced chelation therapy from class 3 (no benefit, possibly to harmful) to class 2b (may be considered), putting it on par with more traditional class 2b CAD treatments.[1] In this article, we will review the history of chelation therapy for CAD, TACT1 trial results, and the impact of clinical strategies that emerged from the trial. A second, pragmatic trial, TACT2, is currently planned to confirm earlier results and lay the foundation for FDA approval of the chelation therapy.

Chelation treatment was first reported to have clinical benefits in symptomatic CAD patients starting in 1956.[3,4] Subsequent clinical investigations of chelation, however, were mixed and academic research in this area stopped in the early 1960s. Alternative medicine practitioners continued to use chelation for prevention of complications of atherosclerosis, yet in academic medicine small studies (with an aggregate of <300 patients) were published showing no benefit from chelation for surrogate endpoints such as time to claudication or angina.[5,6] These studies were too small and of too short duration to exclude a moderate effect on clinical endpoints.[7] Despite recommendations against the practice of chelation by numerous professional medical associations, patients continued to seek, and some practitioners to administer, chelation therapy for a variety of conditions. Because of the lack of proof of benefit and the implausibility of the proposed mechanism of benefit (removal of calcium from complex atherosclerotic plaques), most major mainstream medical

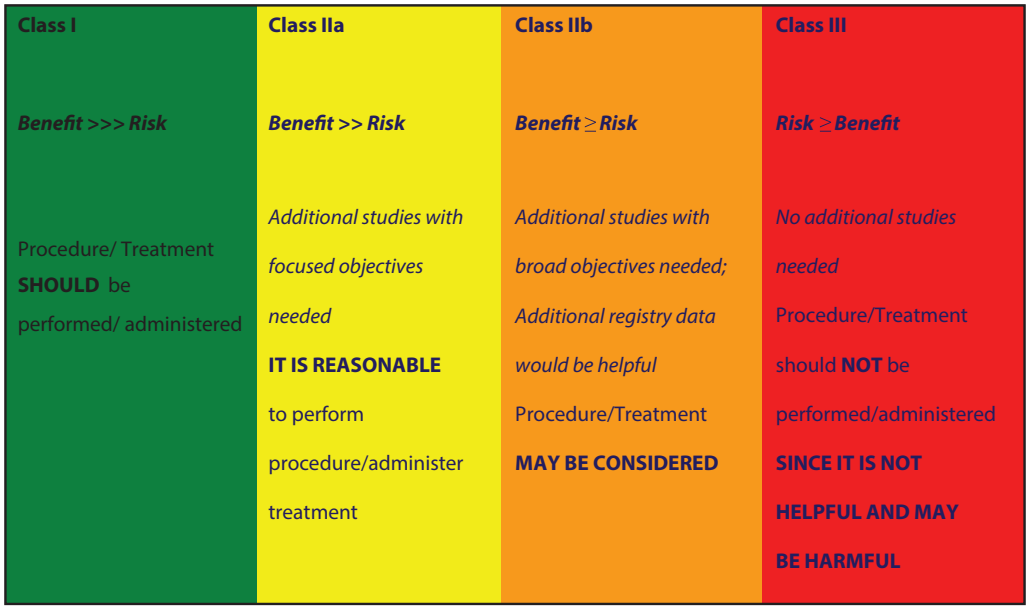

Figure 1: ACC/AHA classification (www.acc.org).

organizations during the 1980s to 1990s made policy statements against chelation.[8–10]

The 1980s and 1990s were marked by a remarkable growth in cardiology, including landmark trials that formed the basis of current cardiovascular diagnosis and treatment. Development of reperfusion strategies, including primary angioplasty and stenting for acute MI, and pivotal trials of pharmacological therapies, such as aspirin, lytic agents, b-blockers and statin medications, pushed alternative modalities out of sight.[11] Rapid growth in technology ushered in advances in myocardial perfusion imaging, and spearheaded development of devices (such as defibrillators and intra-arterial catheters) and drug-eluting stents for management of CAD. The era of intensive and invasive treatments also heralded an establishment of large, randomized double-blind trials as the gold standard for evidence-based investigations, with ACC and American Heart Association (AHA) guidelines based on the outcomes of these trials. In the complementary and alternative realm, a lifestyle approach consisting of low fat, low cholesterol diet and yoga, demonstrated a positive impact on established heart disease, and eventually was approved by Medicare after nearly 25 years.

In recent decades, evidence emerged of the class effect of statin drugs on new-onset diabetes, at a rate of 1 patient among 200 treated, and concerns continue about their impact on short-term memory.[12,13] The re-evaluation of the diet and cholesterol treatment guidelines led to more uncertainty in treatment of CAD.[14,15] Specifically, despite proven benefits of medical and interventional therapies for advanced heart disease, including decreases in morbidity, and all-cause as well cardiac mortality, there has been no impact on the prevalence of cardiovascular risk factors.[16] The burden of metabolic syndrome and diabetes, obesity, and hypertension is considerable.[17] It continues to drive chronic illness, and adversely affects outcomes while increasing health care expenses.[18] CAD remains the number one killer in both men and women in the USA, and many other developed countries.[19] Attention is now turning toward preventive strategies, many of them based on functional, alternative, and complementary therapies. Thus, the opportunities are arising to include such therapies in mainstream cardiac care.

The Cochrane Collaborative (2002) concluded that there were insufficient data to recommend for or against chelation.[20] The mechanisms of action of ethylenediaminetetraacetic acid (EDTA) chelation are unknown. Environmental health investigations propose that chelation therapy depletes body stores of toxic metals. Such metals, specifically lead and cadmium, are pollutants that accumulate *in vivo* from environmental exposure over decades.[21] Lead and cadmium are both readily chelated by EDTA.[22,23] Cadmium is a highly toxic metal, with long biological half-life in humans (up to 30 years). A by-product of mining and copper, zinc, and lead ore refining, cadmium is also found in such household items as nickel-cadmium batteries, and in plastics (coating stabilizers), and contributes to ambient air pollution.[24] Soil contamination by cadmium leads to bio-concentration in vegetables and grains, leading to exposure through diet and smoking. Lead, previously widely used in house paint, plumbing, and gasoline additives, is implicated in exposure levels that are still two orders of magnitude higher today than prior to the 17th century.[25] Heavy metals such as lead accumulate in the skeleton, and may be slowly released from the bones to produce long-standing ill effects.[26] Post-menopausal women, especially if deficient in vitamin D, experience increased rate of bone turnover, and are at risk of releasing lead into the blood stream. These effects, while not proven, may contribute to the increased incidence of CAD in women after menopause. Additionally, certain patient groups, such as diabetics, are exposed to the effects of advanced glycation products, possibly removed by EDTA chelation.

TRIAL TO ASSESS CHELATION THERAPY (TACT)

TRIAL METHODS

TACT1 was a landmark trial that brought intravenous (IV) EDTA chelation into the mainstream cardiology domain.[27] The trial enrolled patients ≥50 years of age with prior MI and with creatinine ≤2.0 mg/dL. The trial used a 2×2 factorial design with patients randomly assigned to one of four groups:

1. Active IV chelation infusions+active oral multivitamins and multiminerals (OMVM)
2. Active IV chelation infusions+placebo OMVM
3. Placebo IV chelation infusions+active OMVM
4. Placebo IV chelation infusions+placebo OMVM

Patients received standard post-MI pharmacological therapy. Aspirin, clopidogrel, or warfarin was used in 92%, β-blockers in 72%, and statins in 73% of patients. Patients had a median fasting glucose level of 102 mg/dL (131 mg/dL in the diabetic subjects) and a median low-density lipoprotein cholesterol (LDL-C) level of 89 mg/dL. Coronary revascularization had been performed in 83%.

The primary endpoint was a composite of death from any cause (total mortality), recurrent MI, stroke, coronary revascularization, or hospitalization for angina. The composite of cardiovascular death, recurrent MI, or stroke was a pre-specified secondary endpoint. TACT1 enrolled 1708 patients in 134 sites in the USA and Canada, and administered 55,222 infusions of blinded active chelation solution or placebo. The prevalence of diabetes mellitus was approximately 37% in the study cohort.[2,28]

The TACT1 protocol consisted of 40 infusions, with the first 30 delivered weekly, and the maintenance 10 infusions delivered biweekly or bimonthly. The infusions were administered over 3 h, and patients were evaluated for multiple safety end-points, such as hypocalcemia, hypoglycemia, evidence of congestive heart failure, and presence of new fractures. The chelation infusates contained up to 3 g of Na_2EDTA adjusted based on estimated glomerular filtration rate (eGFR), 2 g magnesium chloride, 100 mg procaine hydrochloride, 2500 U heparin, 7 g ascorbate, 2 mEq potassium chloride, 840 mg sodium bicarbonate, 250 mg pantothenic acid, 100 mg thiamine, 100 mg pyridoxine, and sterile water to complete 500 mL. The OMVM consisted of three caplets, twice daily for a total intake of 25,000 IU vitamin A, 1200 mg vitamin C, 100 IU vitamin D3, 400 IU vitamin E, 160 µg vitamin K1, 100 mg thiamin, 200 mg niacin, 50 mg vitamin B6, 800 µg folate, 100 µg vitamin B12, 300 µg biotin, 400 mg pantothenic acid, 500 mg calcium, 150 µg iodine, 500 mg magnesium, 20 mg zinc, 200 µg selenium, 2 mg copper, 20 mg manganese, 200 µg chromium, 150 µg molybdenum, 99 mg potassium, 150 mg choline, 50 mg inositol, 50 mg para-aminobenzoic acid, 2 mg boron, 39 µg vanadium, 100 mg citrus bioflavonoids. Placebo pills consisted of methylcellulose carrier.

TRIAL RESULTS

TACT1 initial analysis evaluated chelation vs. placebo infusions, and OMVM vs. placebo vitamins. The Kaplan–Meier 5-year mortality was 32.8% in the chelation therapy group and 38.5% in the placebo group. The chelation therapy intervention resulted in a relative risk reduction of 18% (HR=0.82; 95% CI=0.69–0.99; *P*=0.035). The 5-year number needed to treat (NNT) to prevent an event was 18. The event rate curves continued to separate after the infusions ended at about 14 months, suggesting a continued effect of the treatment intervention. In the OMVM vs. placebo analysis, the primary endpoint occurred in 230 (27%) patients in the OMVM group and in 253 (30%) in the placebo group (HR=0.89; 95% CI=0.75–1.07; *P*=0.21).

The most significant results of TACT1 emerged upon evaluation of the four factorial groups. The greatest benefit, both absolute and relative, was observed in patients treated with the full chelation strategy (EDTA-based chelation+OMVM) compared with double placebo, demonstrating a relative risk reduction for the primary endpoint of 26% (HR=0.74, 95% CI=0.57–0.95; *P*=0.016). The absolute difference in 5-year Kaplan–Meier estimated event rates was 8.3%, and the NNT to prevent 1 event over 5 years was 12. The factorial analyses suggested an additive benefit of chelation+OMVM over each treatment alone, with no evidence of an interaction.

Diabetes mellitus was pre-specified as a subgroup for analysis in TACT1 and consisted of a total of 633 (37%) patients. Treatment with EDTA infusions reduced the primary endpoint (EDTA chelation vs. placebo, independent of OMVM assignment: 25% vs. 38%; HR=0.59; 95% CI=0.44–0.79; *P*=0.0002). The Kaplan–Meier curves continued to diverge after infusions stopped. There was a 15% absolute decrease in the 5-year Kaplan Meier primary event rate (Figure 2) and a 41% relative reduction in risk. The 5-year NNT was 6.5 (95% CI=4.4–12.7). Rates of the principal secondary endpoint (a composite of cardiovascular death, MI, or stroke) were also lower for diabetic patients randomized to EDTA chelation (HR=0.60; 95% CI=0.39–0.91; *P*=0.017), with a 5.1% absolute reduction in the 5-year Kaplan–Meier event rate and a relative reduction of 40%. There was a reduction in total mortality as well in patients randomized to EDTA chelation (HR=0.57; 95% CI=

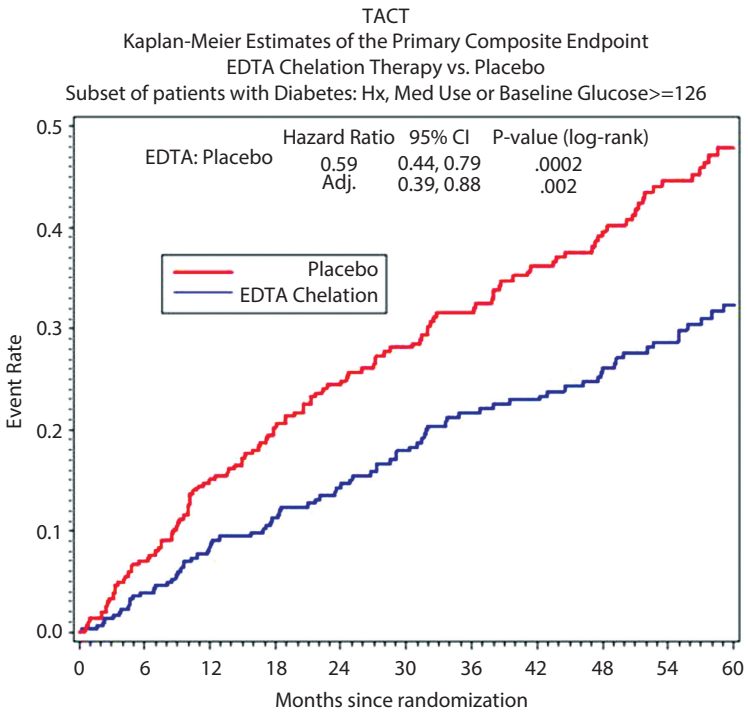

Figure 2: EDTA chelation vs. placebo infusion in patients with diabetes.
(From Escolar E, Lamas GA, Mark, DB, *et al.* The effect of an EDTA-based chelation regimen on patients with diabetes mellitus and prior myocardial infarction in the Trial to Assess Chelation Therapy (TACT). *Circ Cardiovasc Qual Outcomes.* 2014;7(1):15–24.).

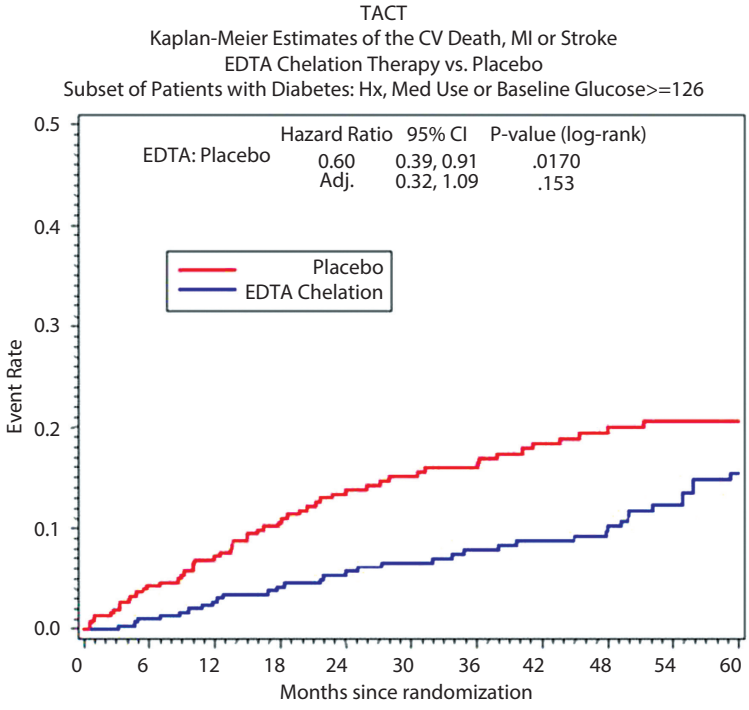

Figure 3: Cardiovascular death, myocardial infarction, or stroke in diabetic subgroup.
(From Escolar E, Lamas GA, Mark, DB, *et al.* The effect of an EDTA-based chelation regimen on patients with diabetes mellitus and prior myocardial infarction in the Trial to Assess Chelation Therapy (TACT). *Circ Cardiovasc Qual Outcomes.* 2014;7(1):15–24.).

Table 1: Effect of OMVM on efficacy.

Patients	Intervention	Relative risk reduction (vs. placebo)	*P*-value	5-year NNT
Overall	Chelation	18%	0.035	18
Overall	OMVM	11%	0.21	–
Overall	Chelation+OMVM	26%	0.016	12
Diabetes	Chelation	41%	<0.001	6.5
Diabetes	OMVM	13%	0.31	–
Diabetes	Chelation+OMVM	51%	<0.001	5.5

0.36–0.88; *P*=0.011; 5-year NNT=12; Figure 3). Consistent with the overall results, there was a significant reduction in recurrent MI (HR=0.48; 95% CI=0.26–0.88; *P*=0.015) and in coronary revascularizations (HR=0.68; 95% CI=0.47–0.99; *P*=0.042).

Similar to the overall study group, the diabetic group analyses comparing chelation+OMVM with double placebo demonstrated the most benefit. The primary endpoint occurred in 56 patients (38%) in the placebo group and 36 (23%) patients in the chelation strategy group, resulting in 51% relative risk reduction (HR=0.49, 95% CI=0.33, 0.75; *P*<0.001, with a 5-year NNT=5.5).

Table 1 shows the summary of the results. The relative reduction in risk is 8% greater when OMVM is utilized in addition to chelation in the overall population and 10% greater in the diabetes population, without any excess of adverse events.

TACT1 demonstrated excellent safety, with no issues related to glycemic control, kidney, liver, hematologic disturbances or heart failure. More hypocalcemia occurred in the full chelation strategy patients, resulting in one patient visiting an emergency room.

CONCLUSION

Chelation therapy, spending several decades in obscurity, has emerged as a potential intervention to benefit patients with prior myocardial infarctions, and especially in those with diabetes. While many questions remain unanswered, the TACT1 trial presents strong evidence in support of the benefits of IV EDTA and OMVM on reducing total mortality and recurrent cardiac events, with the most dramatic results observed in the diabetic patients. The upcoming TACT2 trial will further investigate the benefits of IV chelation in diabetic patients, with the hope to obtain FDA approval for the promising intervention.

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DISCLOSURE OF INTEREST

The author has no financial conflicts of interest to declare.

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