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Chelation therapy to treat atherosclerosis, particularly in diabetes: Is it time to reconsider?

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Summary

Reports and case series have suggested a possible beneficial effect of chelation therapy in patients with atherosclerotic disease. Small randomized trials conducted in patients with angina or peripheral artery disease, however, were not sufficiently powered to provide conclusive evidence on clinical outcomes. The Trial to Assess Chelation Therapy (TACT) was the first randomized trial adequately powered to detect the effects of chelation therapy on clinical endpoints. Chelation reduced adverse cardiovascular events in a post myocardial infarction (MI) population. Patients with diabetes demonstrated even greater benefit, with a number needed to treat of 6.5 patients to prevent a cardiac event over 5 years. These results led to the revision of the ACC/AHA guideline recommendations for chelation therapy, changing its classification from class III to class IIb. TACT2, a replicative trial, will assess the effects of chelation therapy on cardiovascular outcomes in diabetic patients with a prior myocardial infarction.

Keywords

myocardial Infarction; diabetes mellitus; secondary prevention; chelation; edetate disodium

1. Introduction

Chelation is a chemical process by which a chelating agent, a molecule with a polydentate, negatively charged pocket, bonds with positively charged ions, leading to their inactivation (as toxicants) and their eventual excretion by renal or biliary mechanisms. Chelation with edetate disodium has been used to treat lead intoxication since the 1940's, but its use for a variety of other diagnoses remained controversial until a recent clinical trial changed conventional medicine's perception of the therapy. We will briefly review the history of chelation therapy for cardiovascular disease, the results of the sole large-scale NIH-funded clinical trial, the hypotheses that might explain its efficacy, and future plans for replicating the trial.

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Declaration of interest

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Chelation therapy for the treatment of cardiovascular disease dates to the 1950s. Probably in an attempt to decalcify diseased coronaries at a primitive time in the history of atherosclerosis treatment [1], Clarke et al treated a small number of patients with severe angina with an edetate disodium (Na_2EDTA) based chelation regimen and found remarkably improved outcomes in 19 out of 20 patients [2]. Other small unblinded studies performed afterwards, also tiny in numbers of patients and length of follow-up by today's standards, had less dramatic and less durable results [3,4]. Based partially on these later studies, conventional practitioners abandoned the practice, supported by traditional medical organizations [5]. In spite of the nearly universal condemnation of chelation by traditional medicine and cardiology, chelation therapy for atherosclerosis did not disappear; and, indeed, flourished.

Alternative medicine practitioners reported excellent results. The reports, however, were of low scientific quality, primarily case reports and case series, and in alternative medicine journals not even perused by conventionally trained cardiologists [6–8]. Yet the practice of edetate disodium chelation for vascular disease did not wither. Despite the opinion of conventional practitioners, edetate disodium-based chelation moved into the realm of alternative medicine, and the practice increased. Patients continued to seek, and practitioners to administer, edetate disodium based chelation.

In spite of, or perhaps because of, nearly universal opprobrium from traditional medicine, chelation practitioners formed various organizations [9,10] which, among other activities, standardized the doses and rate of administration of edetate disodium [11]. These efforts probably succeeded. In the 36 years between 1971 and 2007, a time during which there may have been millions of chelation infusions nationwide, there were only 11 deaths reported to the US Food and Drug Administration related to this drug. In 7 of the 11 deaths, the drug was administered mistakenly due to a prescription or pharmacy error [12]. When infused too quickly, edetate disodium administration can result in hypocalcemia. In response to this, practitioners developed protocols that, when adhered to, make this therapy exceptionally safe [11]. Ultimately an uneasy equipoise developed [13], in which patients and chelation practitioners observed and reported benefit from an “unproven” treatment; and cardiologists criticized the practice as not evidence-based, without the evidence base to do so.

In time, clinical researchers became interested in testing the practice. This led to three small randomized trials to assess the role of chelation therapy in atherosclerotic disease. Two of these trials were carried out in patients with claudication and one in patients with angina [14–16]. The results were negative for these surrogate endpoints, but due to small sample size one could not exclude a small to moderate effect on clinical events. A 2002 Cochrane systematic review [17] agreed with a prior clinical review [13], indicating that existing trial results failed to provide any substantial evidence for or against the use of chelation therapy in patients with cardiovascular diseases. In the face of continuing use of these therapies [18] and the absence of both a clear hypothesis for benefit and definitive evidence to support such use, in 2001 the National Institutes of Health released a Request for Applications (RFA)[19] to carry out a definitive clinical trial of chelation with edetate disodium. Of particular relevance, the RFA required the investigators to work with the leading organization of chelating physicians (American College for Advancement in Medicine [ACAM]), and use

the standard community-based chelation infusion. This turned out to be an infusion consisting primarily of edetate disodium and some additives and will be covered in detail below.

As part of the due diligence in anticipation of the RFA response, the lead investigator visited several chelation practices and contacted leading chelation physicians throughout the US, and worked with ACAM to understand the components of the standard, most prevalent edetate disodium-based solution [11]. It was during these conversations that the ultimate name (and acronym) of the Trial to Assess Chelation Therapy (TACT) suggested itself.

As required by the RFA, the investigators (conventional clinical trialists) formed an alliance with the ACAM-based chelation practitioners that paralleled the uneasy scientific equipoise, yet with one key goal in common. The chelation practitioners were fairly certain the trial would show benefit, but wanted the scientific process to be fair. The clinical trialists felt certain that the study would be negative, likely preventing future patients from undergoing the risk and expense of an ineffective therapy, but took pains to develop a fair scientific process.

At this point, however, it is reasonable to digress and ask if, in light of the extraordinary efficacy and safety of edetate disodium-based chelation demonstrated by TACT and reviewed below, whether traditional scientific literature existed at the time or even subsequently, that would suggest a metal chelator might benefit atherosclerotic patients, particularly diabetic patients. Curiously, this improbable Black Swan event [20] has a long history and robust epidemiological, toxicological, and basic science evidence. Like all Black Swan events, it can be justified in retrospect, but could not be predicted.

2. Edetate disodium as a chelating agent

Munz patented edetate disodium in 1938 [21]. It is an organic molecule with a ring-like polydentate negatively charged pocket able to hold metal ions with up to a +6 valence, but with particular affinity for +2 or +3 ions. Many toxic metals fall within this affinity spectrum, as do calcium and magnesium. Edetate disodium is easily soluble in blood, and is >95% excreted within 24 hours following a single infusion in a patient with normal renal function. Starting in the 1940's the edetates were found to be effective chelators for lead and subsequently for other metals such as cadmium, and were used to treat metal toxicity. The edetate "chemical claw" was known to do one thing in the body: bind metals and facilitate their excretion. Waters and colleagues collected 24-hour urine specimens pre and post administration of edetate disodium based intravenous infusions, much like the infusions given in TACT, to analyze the specimens for the presence of toxic and essential metals and evaluate the physiological effects of edetate administration [22]. Urinary lead and cadmium excretion rose by 3830% and 514%, respectively, over 2 days post edetate disodium infusion. These results lend credibility to the hypothesis that edetate disodium stimulates lead and cadmium excretion from chronic body stores. Whether such an action has any therapeutic value depends, of course, on whether accumulation of higher levels of these metals in the body really has adverse vascular consequences.

3. Metal toxicants and cardiovascular disease

Epidemiologists have reported for many years the relationship between metal toxicants and various manifestations of cardiovascular disease. For this review we will principally discuss lead and cadmium, 2 toxic metals listed in the top 10 environmental chemicals of concern by the Agency for Toxic Substances and Disease Registry of the Department of Health and Human Services of the US [23]. These metals are not the only cardiovascular toxicants. Strong evidence links arsenic and mercury to cardiovascular disease, while weaker evidence links others such as antimony and tungsten [24,25]. Thus, metal toxicants should be considered an emerging risk factor for atherosclerotic disease, and the evidence reviewed below will support this proposal. We chose lead and cadmium for discussion because their renal excretion is most efficiently enhanced by edetate disodium. The TACT edetate disodium-based solution also chelates aluminum and nickel, 2 additional metals that have no role in the human body [26]. Other essential metal ions such as those present in metalloproteinases, zinc, for instance, may also be chelated and possibly account for the anti-atherosclerotic properties described here [27]. Thus, the focus on lead and cadmium constitutes a hypothesis based on the best existing epidemiologic and basic evidence, but by no means should be considered the final word.

Lead has been a ubiquitous human toxicant since ancient times [28]. In the 20th century, lead production and hence environmental and atmospheric contamination increased precipitously starting in the 1940's with increased numbers of automobiles and the use of tetraethyl lead as an octane booster [29]. The release of lead into the atmosphere reached approximately 200,000 tons each year, more than at any other time in human history, until the US Environmental Protection Agency finally eliminated the use of leaded gasoline for internal combustion, road-driven vehicles in 1980 [30]. This initiated a fall in blood lead levels of over 80%, from 14.6 µg/dL in 1976 [31] to 2.8 µg/dL in 1988–1991 [32]. Still, anyone who was alive during those years has a much greater lead burden than did humans at other times in history. At present, lead body burden is 2 orders of magnitude greater than it was in pre-industrial humans. Unfortunately, lead exposure remains an active public health problem, as is seen by the ongoing disaster with lead poisoning from corroded water pipes in the US city of Flint, Michigan [33]. Other environmental sources include smoking, industrial sources, batteries, toys, soil, and even artificial turf [34].

There is no efficient excretory mechanism for lead. Ingested and inhaled lead enters red blood cells and has a half-life in blood of about 36 days [35]. Subsequently, lead enters its chronic tissue storage cavity, bone, where it can have a half-life of several decades, leeching out slowly over time maintaining a low, but important internal dose for the unsuspecting individual [36]. In patients that do not have acute lead exposure and toxicity, blood lead represents <5% of total body lead burden [37].

Basic research has revealed that lead impairs endothelial function [38], promotes oxidative stress [39], impairs calcium signaling [40], promotes inflammation [41], and even leads to epigenetic modifications [42]. With regards to clinical manifestations, there are robust epidemiologic studies, mostly based on blood lead levels in NHANES, that link lead to hypertension, stroke, myocardial infarction, peripheral artery disease and ischemic heart

disease death [43–45]. Of particular note, all these epidemiologic observations took place during the decades of rapid fall in blood lead levels during and after the reduction and elimination of leaded gasoline. This is important because it has reinforced the conclusion that even at blood levels that would once have been considered low, those patients in the higher ranges of blood lead still have demonstrably higher cardiovascular risk. Thus, it is perhaps, in retrospect, not surprising that a treatment that enhances the excretion of lead from its chronic tissue stores would reduce cardiovascular risk.

Cadmium has a production and release history similar to that of lead. Starting in the mid to late 1940's into the end of the 20th century, cadmium production increased as a result of industrial use as a plastic stabilizer, production of rechargeable nickel-cadmium batteries, and metal coatings. Fortunately, the rate of global cadmium production has flat lined in recent decades [46]. Like lead, because of industrial use, cadmium also contaminates soil and can also act as an atmospheric pollutant in industrial areas. Because of soil contamination, cadmium can enter the food supply [47]. It has particular affinity for some root vegetables and green leafy vegetables [48]. The latter are particularly interesting because they include tobacco plants. Cadmium has, indeed, been linked to peripheral artery disease [49]. The kinetics of ingested cadmium are similar to those of lead, although the long-term storage is in visceral organs and nervous system, not bone. Like lead, however, there is no natural excretory mechanism, so that it has an extremely long half-life, of about 19.4 years (creatinine adjusted)[50]. Because about 50% of cadmium is stored in the kidneys, urine cadmium can be used as an estimate of total body burden [51].

The data supporting chronic adverse cardiovascular health effects of cadmium exposure again stem from multiple NHANES analyses, [52,53] and analyses of the Strong Heart Study [54]. These are 2 very different populations, which speaks to the broad applicability of the findings. NHANES is a scientifically selected population sample that reflects the US population, [55,56] while the Strong Heart Study is a longitudinal study of various Native American tribes [57]. In both studies, higher urine cadmium levels were associated with atherosclerosis, particularly peripheral artery disease and cardiovascular death, even when controlling for tobacco use. In the Strong Heart Study, the highest quartile of urinary cadmium, when compared with the lowest, had a 48% greater cardiovascular disease incidence, and a 87% greater risk of cardiovascular death [54]. In addition, the relationship between cadmium and cardiovascular events was more evident in patients with diabetes – a subject we will touch upon later [54]. A recent systematic review names cadmium as an emerging coronary risk factor [58].

With regards to mechanisms of action, cadmium may increase oxidative stress, thereby promoting atherosclerosis. Cadmium, as a transition metal, can replace copper and iron in thiol groups, leading to increased intracellular oxidative stress [59,60]. In experimental models, cadmium leads to increased endothelial permeability and ultimately cell death. Like lead, cadmium can also lead to epigenetic modifications, recently reported in the RASAL1 and KLOTHO genes, [61,62] which are involved in longevity and vascular calcification.

4. Diabetes, metals, and chelators

Diabetic patients exist in a heightened oxidative state. Trace mineral nutrients such as iron and copper can act as oxidant stressors in the body [63], as can toxic metals such as lead. There is longstanding scientific literature that emphasizes that metal-catalyzed oxygen chemistry is critical for the production of oxygen free radicals. Oxygen free radicals are most directly involved in the formation of advanced glycation end products (AGEs), advanced lipoyxygenation end products (ALEs), and protein oxidation products (PrOPs)[63]. These are complex chemical modifications to naturally-occurring molecules. These cross-linked molecules are very long-lasting, and are thought to account for some of the complications of diabetes. Once denatured by these crosslinks with oxidized aldose sugars, they are identified by different scavenger receptors, including the receptor for advanced glycation end products (RAGE)[63]. These scavenger receptors may trigger inflammatory cascades that amplify tissue damage. There are more than 30 types of cross-linked, denatured compounds that have been identified in patients [63]. They slowly increase with age, but increase much more rapidly in diabetic patients [63].

Curiously, some of the most successful anti-diabetes medications have *in vitro* metal-chelating properties which can be shown using a standard assay for chelators that involves the rate of metal catalyzed auto-oxidation of ascorbic acid [63].

In the absence of metals, ascorbate's half-life is greater than 1 year in solution, but the addition of 1μM of copper leads to a half-life of less than 30 minutes. Chelation activity tests like these have shown that some ACE inhibitors, angiotensin receptor blockers, thiazides and hydralazine chelate aqueous copper and prevent the oxidation of ascorbate [63]. So, in fact, successful current therapies for complications of diabetes may employ metal chelation (demonstrated *in vitro*). Still, it important to note that while the above experiments were well-described and carried out by recognized scientists, our comments relating these experiments to the benefits observed in diabetic patients are speculative in nature, and by no means can be viewed as conclusive. They do serve, however, to emphasize the double-edged nature of metals, even essential metals, in biological systems. Moreover, these epidemiological and basic science findings also emphasize that although each metal toxicant has idiosyncratic mechanisms of toxicity, all appear to alter the intracellular oxidant balance adversely.

5. Design of TACT

The Trial to Assess Chelation Therapy (TACT) was the first randomized trial to assess clinical outcomes in patients with coronary disease treated with an EDTA based chelation regimen as an adjunct to standard therapy [64]. The design process was unique among trials, in that the study design team had no clinical experience with the treatment (chelation), and the chelation practitioners had no experience in randomized prospective research. The design of the study had to additionally take into account the absence of a clearly developed mechanism, controversies about safety, disagreement among practitioners regarding the content, dosing, and total numbers of infusions, and the confounding effect of high-dose oral multivitamins and minerals administered to all clinical chelation patients by the

practitioners. Moreover, the population to be studied in an outcome-based trial was a post-MI patient population, rather than a primary prevention population, in order to have a sufficient event rate to efficiently reach a robust statistical power. Practical considerations were the rule, as these seemingly insurmountable obstacles were overcome one by one.

The overall population to be studied consisted of patients with a prior MI at least 6 weeks before randomization, who were at least 50 years old, and had a serum creatinine ≤ 2 mg/dL. Major exclusions included recent active smoking, inability to follow the infusion program, and women of childbearing potential.

The concern regarding the high-dose oral multivitamins and multiminerals was managed by developing a factorial trial, randomizing active and placebo infusions, and active and placebo oral therapy, thereby creating 4 randomization groups:

1. Active chelation and active oral vitamins
2. Active chelation and placebo oral vitamins
3. Placebo chelation and active oral vitamins
4. Placebo chelation and placebo oral vitamins

Of the potential comparisons available, we will concentrate on active versus placebo infusions, active versus placebo oral vitamins, and on the key comparison of active-active versus double placebo.

The chelation treatment regimen had been standardized and published by chelation practitioners, [11] and consisted of up to 3 g of disodium EDTA, adjusted downward based on estimated glomerular filtration rate; 7 g of ascorbic acid; 2 g of magnesium chloride; 100 mg of procaine hydrochloride; 2500 U of unfractionated heparin; 2 mEq of potassium chloride; 840 mg of sodium bicarbonate; 250 mg of pantothenic acid; 100 mg of thiamine; 100 mg of pyridoxine; and sterile water to make up 500 mL of solution. The identical appearing placebo solution consisted of 500 mL of normal saline and 1.2% dextrose. The infusion regimen, which consisted of 40 weekly infusions followed by 10 maintenance infusions at 2 week to 2 month intervals.

The oral vitamin treatment regimen consisted of a 28-component high-dose mixture. Placebo pills were identically appearing. A committee of leading chelation practitioners working with study management developed the precise components and doses [65].

The primary endpoint of the trial was composed of death from any cause, recurrent MI, stroke, coronary revascularization, and hospitalization for angina. The principal secondary endpoint was cardiovascular death, MI, or stroke.

Analysis was by intent-to-treat, and we projected that 1700 patients followed for 5 years would have an 85% power to detect a 25% difference. Ultimately 1708 participants were enrolled (839 active chelation, 869 placebo chelation) at 134 sites in North America, with a median follow-up of 55 months. The study protocol pre-specified several subgroups, including diabetic patients [64].

6. Results of TACT

The study met its statistical goals, demonstrating an 18% relative risk reduction in the primary endpoint (Hazard ratio [HR], 95% confidence intervals [95%CI] 0.82, 0.69–0.99, $p=0.035$). The 5-year Kaplan-Meier estimate for the primary endpoint was 38.5% in the placebo group and 32.8% in the chelation group (Figure 1). The number needed to treat (NNT) to prevent an event over 5 years was 18. Visually, despite the discontinuation of chelation infusions after 18 months of treatment, the Kaplan Meier event curves continued to diverge throughout the trial. This suggested a sustained benefit of chelation therapy on cardiovascular risk, perhaps suggestive of the toxic metal hypothesis.

The next key comparison to discuss is the double active factorial group ($n=421$) versus the double placebo group ($n=437$) [66]. Suggesting a beneficial effect of oral high dose vitamin therapy, greater benefit was observed in the active-active group than in the placebo-placebo group, and this benefit exceeded the chelation-placebo comparison (HR, 0.74; 95% CI, 0.57–0.95; $p = 0.016$, Figure 2). The NNT for 5 years to prevent an event was 12; and the Kaplan-Meier 5- year estimate of absolute difference for the primary endpoint between active-active and placebo-placebo was 8.3%.

7. Safety of edetate disodium chelation

Regular physical and laboratory assessments were conducted to ensure subject safety. There were a total of 4 unexpected, severe adverse events. Two of these events occurred in the patients receiving chelation infusions, including 1 death, and two occurred in patients receiving placebo infusions, including 1 death. Heart failure occurred in 57 patients in the chelation group and 71 patients in the placebo group ($P=0.28$). Less than 1% (330 out of 55,222) of infusions were administered too quickly, increasing the risk of hypocalcemia. Hypocalcemia was reported in 52 patients in the chelation group (6.2%) and 30 patients in the placebo group (3.5%) ($P=0.008$). Of the over 27,000 active chelation infusions given in the trial, there was only one that led to symptomatic hypocalcemia which resulted in an emergency department visit.

Potential clinical significance of a new treatment for the vascular complications of diabetes

In 2012 there were 29.1 million diabetic patients in the US, including 27% of people age 65 or older [67]. Of these, 6.4 million had coronary artery disease (CAD) and could potentially be eligible for the therapy to be tested in this application. In addition, diabetes is more prevalent among minorities. Compared with non-Hispanic whites, the risk of diagnosed diabetes is 70% higher among African Americans and 80% higher among Hispanics. Despite medical research advances that have identified effective medical therapy to reduce coronary events in diabetes, 68% of the 223,000 diabetic patients who died in 2012 had heart disease as either the principal or contributing cause. Diabetes consumes a large proportion of national health care budgets. In the US, 1 in 5 health care dollars is spent treating diabetes. The annual expenditure exceeds \$245 billion (B), including \$176B in direct costs and \$69B in indirect costs (disability, work loss, premature mortality). Although we do not yet understand the mechanism of chelation benefit and how it possibly relates to

risk of diabetic patients, one very striking finding from TACT1 was that the chelation strategy diabetic patients had their risk of major adverse cardiovascular events reduced to the level of those patients who did not have diabetes. This finding alone has potentially major public health implications.

8. Clinical effect of edetate disodium on patients with diabetes

The comparison of chelation versus placebo in diabetic patients yielded extraordinary results [68]. Based on a standard definition of diabetes, 37%, or 633 patients met the definition of diabetes and were part of the comparison. We selected diabetes as a subgroup because of enhanced risk in diabetic patients, and not due to any expectation of positive results with chelation therapy.

In fact, diabetic patients had a higher prevalence of congestive heart failure, stroke, peripheral artery disease, hypertension and hypercholesterolemia than non-diabetic patients, meeting our expectations of higher risk.

The primary endpoint event rate was significantly lower in the edetate disodium group, compared with placebo [HR 0.59 (0.44,0.79), $p<0.001$] with a 15% absolute decrease in the 5-year primary event rate (Figure 3) and a relative reduction of 41%. The number needed to treat to prevent a single event was 6.5 patients over 5 years. Rates of the secondary endpoint (cardiovascular death, MI or stroke) in diabetic patients were also lower for patients randomized to edetate disodium, [HR 0.60 (0.39, 0.91), $p=0.017$], with a 5.1% absolute decrease in the 5-year Kaplan-Meier event rates and a relative reduction of 40% (Figure 4). Patients randomized to edetate disodium also had a significant reduction in all-cause mortality (HR 0.57 (0.36, 0.88), $p=0.011$) (Figure 5), in recurrent myocardial infarction (HR 0.48 (0.26,0.88), $p=0.015$), and in coronary revascularizations (HR 0.68 (0.47,0.99), $p=0.042$ (Table 1.)

In effect, the benefit in patients with diabetes was so consistent that the invited editorialist re-examined the data using a Bayesian analysis [69]. This type of analyses reduces significance based on prior data, or much less robustly, on prior expectations in the absence of data [70,71]. Even when a skeptical view point of the TACT diabetes data was used, the Bayesian analysis demonstrated continued statistical significance.

In patients with diabetes, the factorial group analysis comparing active-active therapy with placebo placebo was not pre-specified. Instead, it was an analysis driven by study-derived hypotheses and data. The analyses demonstrated a reduction in the combined primary endpoint, even exceeding the edetate disodium versus placebo comparison (HR=0.49 (0.33, 0.75), $p<0.001$). The NNT to prevent an event over 5 years was 5.5.

9. Diabetes control during follow up

A valid question is whether we had simply improved diabetes management. And of course, we also understand that an improvement in diabetes management has never demonstrated such a magnitude in cardiovascular event reduction. Nevertheless, there was no EDTA-

treatment-based difference in fasting blood glucose from baseline to the last infusion requiring a blood draw ($p=0.64$).

10. Safety and adverse events in diabetes

Ninety-five serious, adverse events were reported in the diabetes sub-group, with 56 occurring in patients receiving placebo infusions and 39 in patients receiving active chelation infusions. Study-drug related adverse events resulted in 5.7% withdrawal from the trial: 20 subjects in the placebo group and 16 in the active chelation group.

11. Expert commentary

The principal observations to be gleaned from TACT are that an edetate disodium-based chelation solution, used for years in the alternative medicine community, reduced recurrent cardiovascular events in a secondary prevention population. This reduction in clinical events was enhanced in diabetic patients, to a point not heretofore seen with glycemic control alone. Therefore TACT yields a strong indication that these benefits are due to alternative, new, mechanisms, that current drug therapies do not address. The researchers hypothesize that the active TACT infusion removed ionic metal catalysts that can promote oxidative stress and catalyze upstream biochemical pathways that may result in conditions conducive to atherosclerotic plaque formation. Moreover, there is a non-significant signal that the high-dose multivitamins and multiminerals used in TACT may also yield a small benefit that is incremental, and may merit future study [72].

The results of TACT have brought edetate disodium chelation therapy from obscurity to the limelight, with clinicians taking special interest in the clinical endpoint results for diabetic patients with cardiovascular disease. While the data demonstrated a significant reduction in adverse cardiovascular events in diabetics, chelation therapy remains in an intellectual purgatory: someplace between vehement derision and cautious acceptance. TACT prompted the medical establishment to seriously reconsider its stance on chelation therapy, yet many cardiologists had trouble accepting the results of TACT due to their decades long aversion to chelation therapy. Most agree that if the endpoint results in diabetics are replicable, TACT and its follow up studies could prove to be paradigm shifting research in the management of cardiac complications in diabetic populations.

12. Five-year view

The 5-year view of chelation for cardiovascular therapy is bright, especially if viewed through the lens of the skepticism through which conventional cardiology viewed the results of TACT. The reception of the TACT results, starting in 2012, was essentially one of disbelief and hostility. However, as the legitimate scientific questions of critics have been distilled from the noise of naysayers and answered, curiosity and positive interest have emerged. Conventional cardiology has largely followed the lead of the carefully completed data analyses, published in top peer-reviewed journals. The most recent Stable Ischemic Heart Disease Guidelines moved chelation from Class 3 to Class 2b [73].

TACT highlighted the need for additional large scale randomized controlled trials powered for clinical endpoint analysis to study the possible benefits of toxic metal chelation with edetate disodium. The TACT data were presented to the US Food and Drug Administration and were received favorably. Nevertheless, the Food and Drug Administration (FDA) encouraged the investigators to carry out another, replicative, clinical trial, preferably in patients with the greatest response to edetate disodium chelation: diabetics. Scientists from the National Institutes of Health have encouraged the investigators to follow the FDA's advice and apply for funding for another study, and this has been done.

At present, we have received funding from the National Center for Complementary and Integrative Health for a planning year for TACT2. TACT2 will determine if the chelation-based strategy in patients with diabetes and prior MI improves event-free survival and overall survival. An economic analysis will also be completed. If fully funded, TACT2 will test the metal-oxidative stress hypothesis and collect a metal biorepository. We are currently still looking for enrolling sites in what promises to be a landmark trial.

We expect, in 5-years, to be ready to present to the FDA yet again. The 5-year outlook is that we will recognize that environmental metal toxicants are a new, modifiable cardiovascular risk factor, and that simple, safe oral chelators will be developed to take their place in cardiologists' armamentarium (Figure 6).

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Key issues

- We are exposed to toxic environmental metals on a daily basis, and these foreign metal ions are stored in bone, visceral organs, and neural tissue indefinitely
- These ions leach out of the body's stores for the duration of one's life. Epidemiological data from NHANES and the Strong Heart Study has linked increased metal levels to adverse cardiovascular events
- Chelation therapy makes use of chelators, molecules that bind and remove heavy metals, to decrease the physiological metal load
- The Trial to Assess Chelation Therapy (TACT), a 10 year, NIH funded randomized controlled trial, demonstrated a decrease in adverse cardiovascular events in patients treated with edetate disodium chelation therapy
- This decreased incidence was magnified in diabetic patients, a pre-specified subgroup in the TACT trial
- Diabetics exist in a heightened oxidative state, and metal ions have been shown to act as catalysts in the reactions that yield advanced glycation end products (AGES), molecules that activate toxic cytokines and may be responsible for some of the complications of diabetes
- The removal of metal ion catalysts and possible resultant decrease in AGES is one hypothesis for the markedly positive effects of the active TACT infusions in diabetic patients
- Ultimately, further studies are required to confirm the signals of benefit noted in TACT. TACT2 is a replicative study, in diabetics with a history of MI, to establish chelation's effectiveness in mitigating adverse events in high risk diabetic patients
- TACT2 is recruiting clinical sites to carry out this important research

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

Figure 1.
TACT- Kaplan-Meier Estimates of the Primary Composite Endpoint Chelation Therapy vs.
Placebo

Figure 2.
TACT- Kaplan Meier Estimates: placebo/placebo versus active/active (primary end point).

Figure 3.
Primary end point in patients with a history (Hx) of diabetes mellitus.

Figure 4.
Secondary end point in patients with diabetes mellitus.

Figure 5.
Mortality in patients with diabetes mellitus by infusion group.

Figure 6.
Present and Future Treatment of Environmental Metal Toxicants

Table 1

Clinical End Points Infusion Arms for Patients with Diabetes Mellitus

Endpoint	EDTA Chelation (N=322)	Placebo (N=311)	Hazard Ratio (95% CI)	P Value
Primary Endpoint	80 (25%)	117 (38%)	0.59 (0.44–0.79)	<0.001
Death	32 (10%)	50 (16%)	0.57 (0.36–0.88)	0.011
MI	16 (5%)	30 (10%)	0.48 (0.26–0.88)	0.015
Stroke	4(1%)	3 (1%)	1.19 (0.27–5.30)	0.829
Coronary revascularization	48 (15%)	62 (20%)	0.68 (0.48–0.99)	0.042
Hospitalization for angina	5(2%)	6 (2%)	0.72 (0.22–2.36)	0.588
Secondary Endpoint	35 (11%)	52 (17%)	0.60 (0.39–0.91)	0.017
Cardiovascular Death	19(6%)	27(9%)	0.63 (0.35–1.13)	0.118

CI Indicates confidence interval; and MI, myocardial infarction.