Impact of TACT on Conventional Cardiovascular Therapy

by L. Terry Chappell, MD

Introduction

After decades of conflict between conventional physicians and alternative doctors who recognized EDTA chelation therapy as an effective treatment for coronary artery disease, the Trial to Assess Chelation Therapy (TACT) was completed in 2012.[1] TACT was published in 2013.[2] The results were statistically significant in a large randomized, double-blind clinical trial. All participants were at least 50 years of age with adequate kidney function and had evidence of a previous myocardial infarction. TACT recommended that all patients receive standard-of-care conventional treatment.

TACT employed a factorial design. This means that more than one type of treatment was tested. Patients were randomly assigned to 40 infusions of disodium EDTA-based chelation treatment or placebo infusions. At the same time, high-dose (orthomolecular) multivitamins and minerals (OMVM) were given to half the patients and oral placebos to the other half.

This design generated four groups:

1. Active chelation + active OMVM
2. Active chelation + placebo OMVM
3. Placebo chelation + active OMVM
4. Placebo chelation + placebo OMVM

Thus, there were four factorial groups with one double placebo section and one double treatment section. During the clinical trial, there were fewer cardiac events over a five-year period in the chelation group and fewer still in those who received both chelation and high-dose vitamins. Diabetic patients had the best results from chelation, but non-diabetic patients had good results as well.

The goal of this paper is to review briefly the multiple articles based on TACT that have been published since the original research was completed. I will summarize what we have learned to date, and explain why I believe there is now sufficient evidence for the wider use of the therapy as an option for preventing and treating cardiovascular disease.

Table 1:
TACT Summary of Results

Post MI ≥ 50 y old, creat ≤ 2.0	Endpoint	Treatment Comparison	Reduction %	P	5-Yr NNT
Overall	Primary	EDTA v Placebo	18%	0.035	18
Overall	Primary	EDTA + oral MVM v Placebo + placebo	26%	0.016	12
Diabetes	Primary	EDTA v Placebo	41%	0.0002	6.5
Diabetes	Death	EDTA v Placebo	43%	0.011	12
Diabetes	Primary	EDTA + oral MVM v Placebo + placebo	51%	<0.001	5.5

MVM= multivitamins and multiminerals; NNT= number needed to treat to prevent an event
Primary endpoint = death, MI, stroke, coronary revascularization, hospitalization for angina

Results of TACT for Treating Cardiovascular Disease

The TACT protocol purposely duplicated the teachings of the two organizations in the US that hold seminars to train physicians to perform chelation therapy safely and effectively: the American College for Advancement in Medicine (ACAM) and the International College of Integrative Medicine (ICIM). TACT was funded by NIH (National Institute of Health) with additional support from NCCAM (the National Center for Complementary and Alternative Medicine). There were 1708 subjects enrolled from Canada and the US, all of whom had a previous MI. After randomization, 30 weekly treatments were followed by 10 more at monthly intervals. No further IV's were administered during the five-year period in which patients were followed. The primary end point was a composite of total mortality, subsequent MI, stroke, coronary revascularization, and hospitalization for angina. In addition to the results published in *JAMA*, the details of the four factorial groups were published in the *American Heart Journal*.[3] The results are summarized in Table 1. The best results were obtained in the group that had both chelation and high-dose vitamins. There was a 26% reduction of cardiac events in the double treatment group compared to double placebo (p=0.016). The number needed to treat to prevent an event (NNT) was 12 for the entire group. It was noted that this was the largest study to date of high-dose vitamin therapy, and the vitamins played a role in clinical improvement when combined with EDTA. No reports of significant adverse effects were found in the study. Gervasio Lamas, a prominent research cardiologist and principal investigator for TACT, published the results of TACT in multiple journals

and presented his findings to faculty at several prominent medical schools.[4-6] With their enthusiastic encouragement, he applied for and received funding for TACT-2, which focuses on diabetic post-MI patients. TACT-2 began enrolling patients in the fall of 2016.

EDTA Chelation for Diabetic Patients

The authors of TACT noted that 633 out of the 1708 patients in the study had diabetes mellitus. When that subgroup was analyzed, they were found to have even better outcomes than the group as a whole. For diabetics, there were 43% fewer deaths (p=0.011) and 51% fewer primary end points (p=<0.001). The NNT for diabetics was especially impressive at 5.5. These findings were published in *Circulation: Cardiovascular Quality and Outcomes*.[7] The conclusion of the authors was that the findings with diabetic patients were remarkable but that another clinical trial of post-MI, >50 y. o. diabetic patients treated with EDTA chelation and high-dose multivitamins was indicated.[5] If the results are positive with TACT-2, a recommendation to treat all such patients with chelation therapy would evolve.[8]

The Use of Oral High-Dose Vitamins and Minerals in TACT

One TACT objective was to determine whether oral high-dose vitamins and minerals safely reduced cardiovascular events.[9] The 1708 patients in the study were randomized to 853 patients with high-dose vitamins and 855 patients to low-dose vitamins. The authors concluded that there was a slight improvement in the treated group, but it was not statistically significant. The factorial group that had both EDTA chelation and high-dose vitamins did better than the group who received EDTA with placebo-level nutrients. High-dose vitamins by themselves or with EDTA had no unexpected adverse effects.

Chelation Therapy and Heavy Metal Toxicity

Because of cost and perhaps because the study was expected to show negative results, TACT did little to examine potential mechanisms of action of chelation therapy for treating cardiovascular disease. However, practitioners of chelation therapy have taught for many years that EDTA's action of detoxifying the body of heavy metals appears to be the major mechanism of action for the therapy. In preparation for TACT 2, Dr. Lamas studied the role of metal toxicity and other environmental factors in the etiology of cardiovascular disease. He has published several articles and has helped to stimulate a new paradigm in conventional medicine for approaching vascular and other diseases.[10-14] Treating chronic degenerative diseases by reducing the toxic burden in the body might significantly improve outcomes. Environmental factors that interfere with optimal function are gaining acceptance. Toxic metals are at the top of the list.

"Xenobiotic" metals refer to metals that have no specific positive role in the body and might be toxic. The top three hazardous substances listed by the Agency for Toxic Substances are arsenic, lead, and mercury. Significant evidence has linked toxic metals to hypertension, hyperlipidemia, coronary artery disease and peripheral artery disease.[10-14] In particular, lead and cadmium are associated factors for cardiovascular disease. See Table 2. The National Health and Nutrition Examination Survey (NHANES) reported that high blood lead levels were associated with a 25% increased risk for all-cause mortality, a 55% increased risk for cardiovascular disease, and a doubling of mortality from stroke.

Lead contamination comes from soil that was previously plowed by tractors using lead-based gasoline, from soldered pipes, imported food products, and lead-based paints. Dumping lead into the environment began with leaded gasoline shortly after World War II and reached its peak around 1980, when an estimated 600,000 tons of lead were released annually. Even with current environmental restrictions, much of that lead still finds its way into human bodies. It has been suggested that there are no "safe" levels of blood lead; lead stays in the bloodstream for a few weeks. However, that is only part of the story. Only about 1-5% of the total amount of lead in the body is present in the blood at any given moment. It is stored in the bone, brain, and other tissues. The most accurate assessment of the total body burden of lead is a noninvasive x-ray fluorescence of bone. However, that is currently available only in a few research centers.

Unfortunately, it is currently impossible to determine how much of any given metal we have in our body. In order to detect whether an excess body burden of lead, cadmium, and other toxic metals is present, a challenge test should be performed with a single dose of a chelating agent such as EDTA or DMPS to see how much of the metal(s) can be pulled into the urine. Even if toxic metals do not come out with an initial urine challenge, they still might be present in storage and could appear in subsequent challenge tests.

Cadmium is another toxic metal that plays a significant role in stimulating vascular disease.[11] Cadmium is used in rechargeable batteries and during construction. It enters the environment by careless disposal of batteries that lose their activity, through water and atmospheric contamination. Tobacco has important levels of cadmium, helping to put smokers at high risk. Cadmium can be found in fertilizers and many foodstuffs (even in some forms of chocolate). Diabetic patients are particularly sensitive to cadmium and arsenic exposure.

In a subset of 20 patients who participated in TACT, the levels of toxic metals were measured at baseline and again after receiving a 3-gram dose of EDTA.[14] After treatment, the largest

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Table 2:
Heavy Metals and Vascular Disease

Sources of Lead and Cadmium: Water, air pollution, tobacco smoke, soil, old paint (lead), discarded batteries (cadmium).

Mechanisms: Oxidative stress, decreased nitric oxide and glutathione, lower heart rate variability, induce epigenetic effects, raise blood pressure, cause kidney malfunction.

Consequences: Atherosclerosis, heart attacks, strokes, peripheral vascular disease.

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increases of metals were with lead (3700%) and cadmium (750%).

The mechanism of metal toxicity is partly understood. There is evidence that lead causes endothelial dysfunction by inhibiting nitrous oxide production and damages cell membranes by creating reactive oxygen species (ROS). Xenobiotic metals can replace essential metals such as zinc, which in turn can inhibit important enzymes and other functions. Complications from diabetes are stimulated by the accumulation of advanced glycation end-products (AGEs), inflammation, and oxidative stress. Toxic metals promote these reactions. More complete discussions of these mechanisms can be found in the articles by Peguero,[10] Solenkova,[13] and Lamas.[15]

Simply speaking, EDTA is infused into the blood carrying magnesium and sodium. It is not metabolized; but if it comes across a toxic metal for which it has greater affinity, EDTA drops the magnesium, surrounds the xenobiotic metal, and transports it safely through the kidneys. There could not be a simpler, more effective way to detoxify the body from dangerous metals, as long as the patient maintains adequate kidney function.

Level of Evidence for Chelation Treating Vascular Disease

In 1956, Clarke was the first to observe that EDTA chelation could improve angina pectoris.[16] Many small case reports and case series followed over the ensuing decades, all of which were underpowered or seriously flawed according to American College of Cardiology/American Heart Association standards. In the mid-1980s, the AMA challenged the minority of physicians who continued to provide the therapy to perform a large clinical trial to show proof of its effectiveness. At that time, because of conventional expert opinion, chelation therapy for vascular disease was classified as Class IIIc ("No additional studies needed. The procedure/treatment should not be performed, since it is not helpful and may be harmful"). It took several tries and a Congressional hearing to provide NIH funding, but TACT was eventually completed in 2012. With TACT added to the body of evidence, the ACC/AHA upgraded chelation therapy to Class IIb ("Additional studies with broad objectives needed; additional registry data would be helpful. *The procedure/ treatment may be considered.*" (Italics added by the author of this article)).

The most frequent ACC/AHA classification for cardiovascular therapies is Class III. Only 41% of procedures reach the level of Class II. According to the ACC website, in 2015, 115,000 percutaneous coronary interventions and 45,000 cardiac catheterizations were done with Class II approval.[15,17,18] Standards of care suggest physicians present all comparable procedures to patients who are considering options of treatments. Chelation therapy is now on par with these common cardiac procedures. EDTA chelation therapy should be one option discussed by physicians under the guideline of patient-centered decision-making.[19]

What We Have Learned from TACT

In the mid-1980s, the AMA challenged the chelation community to provide randomized clinical trial proof that EDTA therapy was effective. Chelation doctors were primarily in private practice, not in research centers; and drug companies had no financial incentive to test EDTA, which is generically available. The chelation community eventually got help from Congress and Dr. Lamas for NIH funding. Dr. Lamas, TACT's chief investigator, had no preconceptions about chelation's effectiveness. TACT has provided exactly the proof that was called for. So far, we have learned the following:

- Intravenous chelation therapy is effective as a secondary prevention therapy to avoid future cardiac events, especially for those at high risk, such as diabetic patients and those with a history of anterior MI's.
- EDTA chelation therapy for cardiovascular disease is a safe therapy.
- TACT provided EDTA treatment for slightly more than one and one-half years but followed patients for five years. The gap between treated patients and placebo patients continued to increase over the five-year period. Physicians with expertise in chelation therapy typically treat their patients with long-term monthly maintenance and add various nutrients to their treatment plans.[20,21] This might explain why most chelation experts report even better outcomes for cardiovascular disease than those from TACT, as well those projected for TACT-2.
- The upgrade of ACC/AHA evidence classification for chelation therapy to IIb puts chelation in the same category as many accepted medical procedures. This should convince regulatory agencies that the therapy is an acceptable treatment.
- Patient-centered decision-making should now require that chelation therapy be included as a choice in discussions with patients by physicians about which therapeutic options are available to treat cardiovascular problems.
- The references listed for this article show impressive support for the therapy. Many of them were published in major medical journals since the original *JAMA* article in 2013. Most of these articles can be viewed in their entirety at the web site, www.tact2.org.
- The contents of this article might be useful in helping patients getting reimbursed from their insurance companies for chelation therapy for the treatment of cardiovascular disease.

Organizations and physicians that have opposed chelation therapy in the past have been slow both to acknowledge that TACT exists and that it constitutes powerful evidence. TACT-2, needed for confirmation, is in progress. However, sufficient evidence is present for chelation to be offered as an option for treating cardiovascular disease. Those who insist that TACT-2 be completed before chelation is accepted

as an option might call for TACT-3 and TACT-4 before the chelation option is fully accepted.

Oral EDTA remains unstudied as a treatment for cardiovascular disease. However, it might prove useful to prevent the absorption of toxic metals from the gut. Ninety to ninety-five percent of oral EDTA is not absorbed. Oral EDTA is also being used to chelate toxic metals from abnormal biofilms that locate in the digestive tract. This can disrupt the biofilms and improve digestion.[22]

Toxic metals, particularly lead and cadmium, are powerful risk factors for cardiovascular and peripheral vascular disease. They might also be important risk factors for cancer, Alzheimer's disease, macular degeneration, autoimmunity, and other conditions. They are removable with intravenous EDTA. Various chelating agents might be required to detect and treat mercury, arsenic, and other xenobiotics.

However, toxic metal activity is not confirmed as the only mechanism of action for chelation therapy. Elevated blood levels of toxic metals should not be required for instituting therapy. Chelation experts insist that a challenge test is needed to detect an elevated body burden of toxic metals. Blood levels are deceptive because toxic metals are stored in the body soon after ingestion. A challenge test with urinary measurement of toxic metals should be performed but should not be the sole determinant for the therapy to be approved for individual patients.

Thus far, with the evidence upgrade, there still has not been a flood of referrals from conventional doctors to chelation experts. Unfortunately, another five years might be required to complete TACT-2. In the interim, lives could be saved and complications prevented if chelation therapy were more widely utilized as an option for treating cardiovascular disease.

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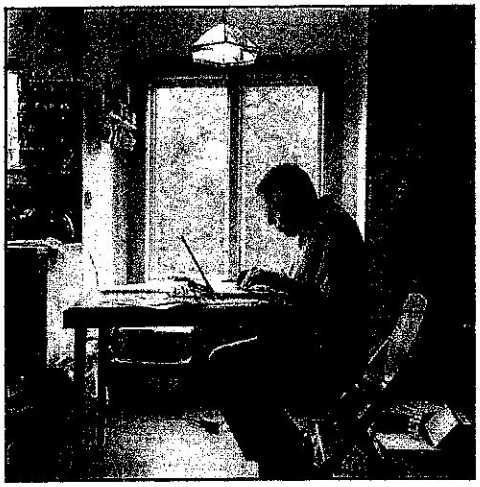

After graduating from the University of Michigan medical school, Dr. Chappell became certified by the American Board of Family Medicine and later by the National Board of Physicians and Surgeons. He is the author of *Questions from the Heart* and has published many articles showing the effectiveness of chelation therapy for vascular disease in the *Townsend Letter* and in other journals. He has run a blog discussing medical news for 10 years. He has served as President of the International College of Integrative Medicine and of the American College of Advancement in Medicine and has frequently lectured for both organizations. Dr. Chappell ran an Institutional Review Board for ICIM in the 1990s. He has provided testimony for six medical boards, one Congressional hearing, the Danish Supreme Court, and the Federal Trade Commission. Twice he served on NIH review committees and later as an investigator for the Trial to Assess Chelation Therapy.