A Registry to Evaluate Clinical Outcomes in Patients with Coronary Artery Disease Treated with Nutritional Supplements and EDTA with Magnesium to Reduce Risk Factors that Contribute to Arterial Plaque Production

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I. Background

A. Current Understanding of Plaque Development

Current understanding of arterial plaque development begins with endothelial damage initiated by oxidized low density lipoprotein(LDL) and further developed by such factors as accelerated platelet aggregation, increased thrombin-fibrinogen reaction, elevated antibody formation, high blood pressure, uncontrolled glucose metabolism and calcification of soft tissue resulting from unbalanced calcium/magnesium ratios.

B. Identification of Risk Factors

The major risk factors for myocardial infarction and possible death from coronary artery disease are pre-existing vascular disease of any type, smoking, uncontrolled hypertension, uncontrolled diabetes mellitus, hyperlipidemia, obesity, a sedentary lifestyle, and uncontrolled stress.

Additional laboratory risk factors which have been identified in recent years include positive antibodies for Chlamydia Pneumoniae and Cytomegalovirus, elevated serum levels of Homocysteine, Fibrinogen, Insulin, Lipoprotein (a), Apolipoprotein B, and Ferritin, as well as lowered levels of Antioxidants, Intracellular Magnesium or Potassium, High Density Lipoprotein, Apolipoprotein A1, Brachial Artery Elasticity, and Ejection Fraction.

C. Possible Mechanisms of Action for Magnesium EDTA

The only approved use of EDTA is to bind toxic metal cations, in particular lead. But the ability of EDTA to chelate a variety of metal ions has led to postulations that it might have numerous pharmacologic and biochemical actions in the body. By removing excessive amounts of iron and copper, it may reduce the free-radical oxidation of LDL. It may act as a powerful anti-oxidant by its ability to remove heavy metals. By temporarily lowering serum calcium, it may serve as a potent anti-coagulant and platelet inhibitor, and it may stimulate parathyroid hormone, which in turn could remove metastatic calcium from arterial walls, serve as a vasodilator, and stimulate the activity and release of tissue plasminogen activator (T-PA). EDTA might have additional effects to lower blood pressure, reduce cholesterol, improve glucose metabolism and reduce antibody formation.

In short, EDTA has the potential to modify most of the mechanisms that have been linked to the development of arterial plaque.

D. Nutritional Modification of Risk Factors

Many of the additional laboratory risk factors listed above might be improved by modifying the diet and adding appropriate nutritional supplements. While definitive proof that the use of individual nutritional interventions for identified specific risk factors can result in significant clinical improvement is lacking, the use of multiple safe, inexpensive interventions to try to achieve a comprehensive risk factor reduction is worthy of study to see if improved clinical outcomes can be accomplished. If the

Registry shows a lower death and complication rate with this approach, future clinical trials will need to be designed to determine which are the most important factors.

II. Registry Rationale

A. Use of Registries for Evaluating Outcomes for Cardiovascular Disease

Registries are commonly used to evaluate surgical procedures and medical therapies. The Coronary Artery Surgery Study(CASS) Registry helped to determine the effectiveness and risk of bypass surgery, and the use of angiopasty was justified based on a registry.

B. Risk Factor Modification and the Coronary Artery Disease Registry

The Sponsor and Investigators are convinced that there is ample reason to believe that treatment with EDTA chelation therapy will be an effective therapy for coronary artery disease. The preponderance of the published experience with EDTA suggests that it might improve the ejection fraction, reduce angina pain, and increase exercise capacity in patients with this disease. The Registry will consist of a large, multicenter study with the collection of uniform data. The Registry is designed to answer the question of whether EDTA chelation therapy with or without additional comprehensive risk factor reduction will reduce the aggregate end point of death from cardiovascular disease or the incidence of subsequent myocardial infarction. It will further examine whether the quality of life for treated subjects will be improved. The outcomes of this Registry can then be compared to those of other databases for cardiovascular disease, such as those at Duke University or other medical schools. The Investigators in the Registry will be supervised by several regional Monitors, who will insure that the data collection is accurate and complete.

III. Registry Endpoints

A. Primary Endpoint

Risk factor modification will reduce the incidence of major cardiac events over the follow-up period. Major cardiac events are defined as myocardial infarction with or without death and death from other cardiac and vascular causes including arrhythmia, sudden cardiac death, stroke, and congestive heart failure.

B. Secondary Endpoints

Risk factor modification will:

1. Reduce the incidence of coronary artery bypass graft surgery;
2. Reduce the incidence of percutaneous transcatheter revascularization;
3. Reduce the incidence of hospitalization for a cardiac reason;
4. Improve the quality of life as measured by the Short Form-36;
5. Improve brachial artery elasticity and ejection fraction.

C. The Two Arms of the Registry

1. Subjects Treated with EDTA with magnesium and Standard Vitamin/Mineral Supplementation

Group A will be treated with EDTA with magnesium with the use of a standard multivitamin and mineral preparation, according to the published ACAM protocol, to reduce the risk factors for coronary artery disease. This group will not be tested for additional risk factors.

2. Subjects Treated with Additional Risk Factor Modification Based on Laboratory Testing

Group B will be treated with the same measures as Group A with the addition of specific nutritional interventions based on abnormal laboratory and other testing for risk factors. Investigators will choose to enter their patients in Group A or Group B for the duration of the Registry. They cannot have some patients in Group A and others in Group B.

D. Monitoring the Integrity of the Data and Safety

Regional Monitors will be appointed to administer and monitor the Registry. The Monitors will assure compliance with all laws, rules and regulations that apply to the Registry. The Monitors will monitor the accuracy and completeness of data collection and the safety of the subjects by reviewing outcomes laboratory data and additional laboratory data required by the published ACAM/ABCT protocol. The outcomes data will then be collected and analyzed by the Central Processing Unit, which will be supervised by the Coordinating Investigator.

E. Qualifications of Investigators

Most Investigators will be required to be certified by the American Board of Chelation Therapy and all will be members of the American College for the Advancement of Medicine or the Great Lakes College of Clinical Medicine. The Coordinating Investigator may appoint a few other Investigators who have passed the written exam and are progressing toward certification and who have outstanding qualifications.

IV. Registry Design

A. Patient Population

Subjects will be recruited and enrolled into the Registry from patients who present to the medical practices of the participating Investigators for treatment of coronary artery disease. They must meet all inclusion criteria and must not have any of the exclusion criteria.

B. Duration

Subjects will be recruited into the Registry over a three year period. The treatment period for each subject will be up to thirty weeks to complete the basic course of therapy and then 24 months of maintenance therapy or until the subject expires. The Registry duration may be extended by the Sponsor and the Coordinating Investigator. The goal of the Registry is to recruit 2000 subjects in Group A and 500 subjects in Group B.

C. Enrollment and Evaluation of Subjects

During Enrollment, Investigators will determine if the subject meets the inclusion criteria and does not meet any exclusion criteria. Each subject will sign a witnessed informed consent and a medical records release form allowing the review and use of their medical records to be used for research purposes. The initial evaluation will include a complete medical history and physical examination and testing as specified in the published protocol. Past medical records will be obtained and reviewed, and the Short Form-36 will be administered. For the patients in Group B, the additional testing to evaluate the presence of risk factors will be obtained. Group A patients will not have any lab results tabulated as part of this Registry.

D. Treatment and Maintenance Visits

At each treatment and maintenance visit, an infusion of EDTA with magnesium will be administered by the staff of the Investigator, according to the published protocol. There will be a minimum of thirty treatments in the basic course of treatment, which will be administered once, twice or three times per week, but never on consecutive days. The basic treatment may be extended if determined necessary by the clinical judgment of the Investigator. After the basic course is completed, treatments will continue at approximately monthly intervals in the maintenance phase for two years. Vital signs and required laboratory monitoring for safety as specified in the published protocol will be obtained by clinical personnel. Questionnaires for both groups and additional laboratory risk factor testing in Group B will be administered and collected at specified intervals. If a subject misses an appointment, he or she will be contacted to determine the reason.

E. Data Analysis and Biostatistics

The Chi-square or t-test statistics (as appropriate) will be used to compare the outcomes of the Registry group with other published data bases.

V. Subject Eligibility

A. Inclusion Criteria

1. Signed informed consent and medical release of records for research purposes.
2. Age >21 years.

3. Documented coronary artery disease as evidenced by one of the following:
   a. >50% narrowing of at least one major coronary artery by angiography. (1255)
   b. Previous documented myocardial infarction, no sooner than two months prior to entering the Registry.
   c. Previous documented coronary bypass surgery or percutaneous transluminal coronary intervention, no sooner than six months prior to entering the Registry. (1255)
   d. Resting electrocardiogram, exercise treadmill testing, stress echocardiogram, or stress radionuclide perfusion scan changes diagnostic for myocardial ischemia.

B. Exclusion Criteria

1. Unwillingness or inability to give informed consent and permission to use medical records for research purposes.
2. Unstable angina within three months of entry into the Registry.
3. Uncorrected left main coronary artery disease exceeding 75%.
4. Hemodynamically significant valvular disease, obstructive hypertrophic cardiomyopathy, or congenital heart disease.
5. Coronary bypass surgery or percutaneous transluminal coronary intervention within six months of entry.
6. Uncontrolled arrhythmias, hypertension, diabetes or other continuing disease.
7. History of stroke or transient ischemic attack within three months.
8. Anemia with a hematocrit of <35%.
9. Clinically significant liver disease
10. Severe renal disease with a serum creatinine >2.5 mg/dl or a 24 hour creatinine clearance of less than 30 mL per minute.
11. Subjects less than 21 years of age.
12. Pregnant or nursing women.
13. Any serious medical, social or psychological condition that in the opinion of the Investigator would likely lead to death or would otherwise disqualify a subject from participation.
14. History of recent drug or alcohol abuse.
15. Sensitivity to EDTA or other ingredient in the treatment solution.

VI. Study Medication, Supplementation and Other Interventions

A. Intravenous Administration of EDTA with Magnesium and Oral Supplementation with Standard Multivitamin and Mineral Preparations

Treatment with these ingredients will be in accordance with the published protocol.

B. Additional Interventions with Specifically Identified Laboratory Risk Factors (Group B only)

1. Positive Chlamydia and/or Cytomegalovirus titres;

   Garlic 350 mg 3 b.i.d.

2. Homocysteine elevation in blood;

   Folic Acid 1 mg, B6 50 mg, B12 1000 mcg 1 b.i.d.

3. Elevated Fibrinogen >350 or Platelet Aggregation (thrombin)>3;

   Vitamin E 400 iu 2-4 q.d.

4. Elevated Lipoprotein (a) >30;

   Vitamin C/Lysine 2-4 gms each q.d.

5. Low intracellular Magnesium and/or Potassium;

   Magnesium/Potassium 100 mg each 1 or 2 b.i.d. (adjust dose if diarrhea occurs)

6. Elevated Cholesterol>200, LDL>130, or Apo B;

   Low fat diet

7. Elevated Triglycerides>170 or Insulin, and low HDL<40;

   Low carbohydrate, moderate fat diet

8. Ejection fraction <50% or Blood Pressure >150/90;

   Coenzyme Q10 200 mg q.d.
   l-Carnitine 250 mg b.i.d.

C. Lifestyle counseling

All subjects will be urged to avoid smoking, to exercise regularly, to eat a prudent diet, and to take measures to cope with stress.

VII. Laboratory Schedule for Group B

Test	Enrollment	30 Tmts.	6 mos.	12 mos.	24 mos.
Chlamydia	x	if abn.			if abn.
CMV	x	if abn.			if abn.
Homocysteine	x	if abn.			if abn.
Insulin	x	if abn.			if abn.
Fibrinogen	x	x	x	x	x
Ferritin	x	x	x	x	x
Antioxidant assay	x	x	x	x	x
Chol/Trig/HDL/LDL	x	x	x	x	x
Lp(a)	x	x			x
Apo A1/Apo B	x	x			x
Platelet Aggreg.	x	x			x
Intracellular Mag/K	x	x			x
Br. artery elasticity	x	x			x
Ejection fraction (by echocardiogram)	x	x			x

All laboratory tests will be sent to Amscot Medical Laboratories, which will manage the data collection. The brachial artery elasticity studies will be done by the CardioVison equipment on site by each investigator. Ejection Fraction measurements by echocardiogram will be arranged by each investigator at a consistent local testing facility. All of these tests apply to Group B only.

VIII. Outcome Measurements for both groups

Investigators will record the incidence of cardiac events for all subjects during the duration of the Registry. The Short Form-36 will be administered at enrollment, at the completion of 30 treatments, at 6 months of maintenance, at 12 months, and at 24 months.

IX. Data Report Forms and Collection of Data

Data report forms will be provided to all investigators and will be completed and copies sent to the Coordinating Investigator within 20 days after each page of the data report forms is completed. This includes the informed consent and the answers to the questionnaires. Laboratory data for Group B subjects will be collected in one computerized data base by the laboratory doing the tests, Amscot Medical Laboratories.

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