


# Should EDTA Chelation Therapy be Used Instead of Long-term Clopidogrel plus Aspirin to Treat Patients at Risk from Drug-Eluting Stents?

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Abstract

The recently discovered increased risk of blood clots, leading to myocardial infarction and sudden death beginning six months after medicated stents are implanted in patients following percutaneous transluminal coronary angioplasty (PTCA), has left cardiologists pondering what course of action to take. The purpose of adding implanted medication to a stent is to prevent thrombin accumulation and restenosis. However, these stents may increase, rather than decrease, the risk. Although long-term treatment with clopidogrel bisulfate (Plavix®) plus aspirin for at least 12 months has been suggested as a preventive treatment, there is no evidence from randomized, controlled trials that this treatment is effective for more than six months. Clopidogrel also increases the risk of major bleeding episodes. The author served as the primary investigator for a study that showed cardiovascular patients treated with EDTA chelation therapy had a lower rate of subsequent cardiac events, including myocardial infarction and death, than those treated with cardiac medications, PTCA, or coronary artery bypass graft (CABG). The data also indicated chelation therapy might be effective in preventing thrombosis and cardiac events from stent implantation. There is evidence EDTA chelation therapy might prevent hypercoagulability resulting from the placement of stents, although not specifically medicated stents. Based on the limited data currently available, intravenous EDTA may be safe and effective for treating patients who have implanted medicated stents. Prospective clinical trials are needed, and EDTA should be included in those trials. (*Altern Med Rev* 2007;12(2):152-158)

## Risk of Thrombosis from Medicated Stents

The use of drug-coated (drug-eluting) stents with percutaneous transluminal coronary angioplasty (PTCA) has come into widespread use in recent years. Sirolimus-eluting stents were approved for use in April 2003, and 1.5 million have been implanted worldwide. Paclitaxel-eluting stents were approved in March 2004, and over three million have been implanted worldwide. The purpose of these stents is to reduce restenosis. Medicated stents have become increasingly popular; for example, they account for 90 percent of all stents sold in the United States in recent years. Although this percentage has decreased since reports of unfavorable outcomes began appearing, medicated versions are still being widely used.

An analysis of the Swedish Coronary Angiography and Angioplasty Registry found a promising initial trend, with 13.4 fewer events per 1,000 patients treated during the first six months after the stents were inserted.[1] However, after six months, patients with drug-eluting stents had 12.7 more cardiac events per thousand patients than those with bare metal stents,

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due to an increase in thrombosis at the site of the stent. The risk of death increased by 0.5 percent per year and the risk of myocardial infarction (MI) increased by 0.5-1.0 percent per year. At three years, the adjusted relative risk for death was 1.32 for patients treated with medicated stents compared to patients with non-medicated stents.

Medicated stents have U.S. Food and Drug Administration (FDA) approval for use in patients with single-vessel blockage (no more than two stents per patient) and no other significant medical problems. In September 2006, an FDA panel concluded that patients who have drug-eluting stents have a significantly increased risk for developing blood clots. The report also noted studies indicating a small but significant increased risk for myocardial infarction and stroke.[2] Drug-eluting stent patients had a lesser need for reintervention; however, long-term survival and myocardial infarction-free survival were not improved, compared to patients with bare metal stents.

These risks are of great concern, but an even greater concern, according to the FDA panel, is that at least 60 percent of coated-stent use was off-label, due to the simultaneous insertion of more than two stents and/or the implantation of coated stents in patients with concomitant medical problems, such as myocardial infarction, multivessel disease, and diabetes.[3] For individuals treated for an off-label indication, the drug-eluting stent patients had higher rates of death from cardiovascular causes, more nonfatal myocardial infarctions, and more stent thromboses than bare metal stent patients. One reason for the expanded use of coated stents is that Medicare pays for these off-label, non-FDA-approved indications.

The Occluded Artery Trial (OAT) added more confusion by challenging the basis of the open artery theory.[4] It looked at 2,166 stable patients with totally occluded arteries several days after an MI and compared those treated with angioplasty plus stent and medications to those treated with medications alone. The patients treated with medications alone did slightly better than those treated with stents, whether the stent was drug-eluting or not. The difference was statistically significant.

The dilemma about when to use medicated stents and how to treat patients who have had them inserted has been so controversial the *New England Journal of Medicine* devoted virtually the entire March 8, 2007, issue to the subject. Unanswered questions remain because, depending on the techniques of analysis, some studies concluded drug-eluting stents impose an increased cardiovascular risk and higher mortality than bare metal stents, while others detect no such increases or even a reverse trend. However, all the studies confirmed the FDA conclusion that stents of any kind can cause thrombosis and that the risk is particularly high with drug-eluting stents used for off-label indications.

## Mechanism and Evidence for the Use of Clopidogrel for Coronary Artery Disease

Clopidogrel inhibits adenosine-induced platelet aggregation. The evidence for its use for cardiovascular disease is primarily based on two randomized, controlled clinical trials. Aspirin inhibits thromboxane A2-induced platelet aggregation. Thus, combining clopidogrel with aspirin results in two slightly different mechanisms of action. The two drugs together are thought to be more effective than either drug alone.

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial,[5] compared aspirin with clopidogrel for an average time of 1.6 years in 19,185 patients with established vascular disease. The incidence of new ischemic strokes was 4.6 percent with clopidogrel and 4.8 percent with aspirin. The incidence of new myocardial infarctions was 2.9 percent with clopidogrel and 3.5 percent with aspirin. The absolute risk was lowered only 0.2 and 0.6 percent, respectively, and the vascular death rates were identical. The relative risks showed a preference for clopidogrel, but based on death rates, the trial did not actually show clopidogrel was superior to aspirin for this broad group of patients.

The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial of 12,562 patients with acute coronary syndrome compared clopidogrel plus aspirin to aspirin alone over a one-year period.[6] Adding clopidogrel lowered the cardiovascular death rate from 5.5 to 5.1 percent, ischemic stroke incidence from 1.4 to 1.2 percent, and MI incidence from 6.6 to 5.2 percent. A small benefit was attributed to combining the two drugs, but this benefit was demonstrated only for patients with the specific vascular problem of acute coronary syndrome (either unstable angina or non-ST elevation myocardial infarction). Importantly, for patients who had acute coronary syndrome, the benefit

**Table 1. EDTA Cardiac Events Study: 220 Patients with Three-year Follow-up**

| | Predicted | Actual |
|---|---|---|
| Myocardial infarctions | 15 | 0 |
| Deaths | 6 | 0 |
| Subsequent angioplasties | 31 | 2 |
| Subsequent CABG | 16 | 6 |

occurred in the first two months after the syndrome was diagnosed. The CURE trial limited stroke analysis to is-1chemic strokes; apparently patients who suffered hemorrhagic strokes were outliers removed from the study.

The CURE study demonstrated clopidogrel had no impact in reducing the number of patients who subsequently needed a coronary artery bypass graft (CABG) or PTCA (with or without stenting). There was no reduction in cardiac deaths for patients with demonstrated vascular disease in general, and for those with acute coronary syndrome the benefit was marginal and limited to the initial two months of therapy.

Eisenstein et al conducted an observational study of patients who received angioplasty and stents at the Duke Heart Center from 2000-2005.[7] They found drug-eluting stent patients who discontinued clopidogrel after six months experienced an increased rate of death and non-fatal MI compared to those treated for 12 months. For patients with bare metal stents there was no such increase. The authors concluded there was a beneficial trend for using clopidogrel for 12 months, but that a randomized clinical trial of sufficient power was needed to provide evidence to determine the optimal length of treatment with clopidogrel. The researchers did not analyze bleeding complications.

The increased risk of blood clots from drug-eluting stents does not begin until six months after insertion. Despite the lack of major clinical benefit and the existence of a significant risk for major bleeding episodes, many cardiologists treat patients who have medicated stents with clopidogrel plus aspirin for at least 12 months, if not indefinitely. Clinical evidence to date does not support this therapy, and there is a significant risk of brain hemorrhage.

## Mechanism and Evidence for the Use of Intravenous EDTA for Coronary Artery Disease

Many studies affirm the usefulness of intravenous (I.V.) EDTA[8,9] in the treatment of vascular disease, while others report negative conclusions.[10] None of the studies meet the criteria of two National Institutes of Health (NIH) review panels for definitive proof. All have been under-powered and many studies have been uncontrolled, poorly randomized, and selectively reported. The NIH has funded the Trial to Assess Chelation Therapy (TACT), which is in progress at more than 100 centers in the United States and Canada. This randomized, controlled trial is designed to determine whether patients treated with EDTA chelation therapy in addition to standard medications and who have had a previous MI will have fewer cardiac events and deaths than others treated with standard medications alone.

Anticoagulation is a common laboratory use for and known mechanism of EDTA. Studies demonstrate EDTA inhibits platelet aggregation induced by adenosine, epinephrine, and thrombin, while preserving collagen-induced aggregation.[11,12] Thus, EDTA provides good therapeutic effect, with three mechanisms that reduce platelet aggregation, while it maintains a safety factor by not inhibiting collagen-induced aggregation. Clopidogrel inhibits only adenosine-induced aggregation.

EDTA is approved for chelating lead from the body. Recent studies have shown even small amounts of lead can be a major risk for all-cause mortality, cardiovascular mortality, and myocardial infarction.[13] Lead has also been shown to increase free radical activity.[14] Thus, documented mechanisms of action support the use of EDTA for coronary artery disease, whether a stent is also used or not.

The author of this article was the chief investigator for a multicenter, retrospective study of 220 patients with known vascular disease treated from 1992-2001 with I.V. EDTA and followed for three years.[15] The purpose of the study was to compare whether

cardiac events and death rates were reduced compared to what has been reported in the literature for standard therapy (Table 1). Study patients were compared to similar groups of patients reported in the literature treated primarily with PTCA, CABG, or conventional cardiac medications; both surgical groups were also treated with cardiac medications as indicated.

**Table 2. Surgical Procedures Required for Patients Treated Primarily with Angioplasty and Stents with Three-year Follow-up**

| | Control Groups | EDTA Treated (25 patients) |
|---|---|---|
| Percent repeat angioplasties | 22.3% | 4% |
| Percent CABG required | 11.8% | 0% |

Rakesh Shukla of the Center for Biostatistical Services at the University of Cincinnati Medical School performed a meta-analysis on the groups treated with conventional therapies and determined the rate of subsequent cardiac events (MI, CABG, and PTCA) and death together and separately. From the rate of cardiac events and deaths in the meta-analysis, he predicted the 220 patients treated with EDTA chelation therapy should have suffered 15 MIs and six deaths during the three-year follow-up period. There were no MIs and no deaths in the patients treated with EDTA chelation therapy. Furthermore, it was predicted by the meta-analysis that there should have been 16 CABG procedures and 31 PTCAs for the comparable group of 220 patients in the chelation study. There were only six CABG procedures and two PTCAs in the EDTA treatment group.

This article focuses on the groups of patients treated primarily with angioplasty with or without stents. A literature search found seven groups of patients treated primarily with PTCA in a time period similar to the study group. The average number of patients for the PTCA groups was 226. Other characteristics of the PTCA groups were similar to the EDTA group. The average age of the EDTA group was 64 years, while the average age of the PTCA group was 58 years. The chelation group was 72-percent male; the PTCA groups were 82-percent male. Forty-eight percent of the chelation group had never smoked compared to 42 percent of the PTCA groups.

Of the groups treated primarily with PTCA, 7.3 percent had an MI within three years of follow-up, while the incidence of death from any cause was 3.2 percent in the PTCA groups. Of those treated with PTCA, 22.3 percent needed another angioplasty within three years, and 11.8 percent underwent a CABG procedure. Thus, 34.1 percent of patients treated with angioplasty required another surgical procedure within three years. These statistics are comparable to other reports from the literature.

Twenty-five of 220 patients in the chelation study group had been treated previously with a PTCA, mostly with stent placement (Table 2). Although this is not a large group, the 25 patients did remarkably well, as only one required a repeat PTCA within the three-year follow-up. None of them had an MI or a CABG procedure, and none of them died. The data from the literature indicate these outcome numbers are less than expected from a group of patients treated primarily with PTCA and followed with conventional cardiac medications.

The chelation study group reported no adverse clinical effects from the intravenous use of EDTA, which was administered according to the published protocol,[15] confirming many reports from the literature that EDTA is a safe treatment when used properly.[9,15] Major bleeding episodes have not been a concern with a properly administered EDTA protocol.

According to the published protocol, EDTA is administered with specified additives intravenously once or twice weekly for 20-30 treatments, each lasting 1.5-3 hours, depending on the dose used. The recommended dose of disodium magnesium EDTA is 50 mg/kg. Some clinicians give a maximum dose of 1.5 g, others 3.0 g; the dose is adjusted based on kidney function. For maintenance, treatments are administered monthly because new platelets are formed approximately every 3.5 weeks; monthly treatments provide continued platelet aggregation inhibition.

## The Case for Using EDTA Chelation Therapy to Prevent Activated Clotting in Patients Treated Previously with Medicated Stents

The mechanism of action of I.V. EDTA arguably fits well as an agent to prevent clotting induced by a medicated stent. It could be theorized its inhibition of adenosine-, epinephrine-, and thrombin-induced platelet aggregation might be more effective than mechanisms that inhibit platelet aggregation more narrowly, as is the case of clopidogrel, which inhibits only adenosine-induced aggregation. Low levels of lead, commonly found in patients, pose a substantial risk for cardiovascular disease. EDTA removes lead from the body. What is needed is clinical data to confirm the assertion that chelation therapy might be a useful treatment.

Although data from a prospective, controlled trial does not exist, the data from the EDTA cardiac events study is discussed above. Twenty-five out of 220 patients treated with EDTA were treated previously with PTCA with or without stent placement. None of these patients had a myocardial infarction or ischemic stroke, and none of them died during the three-year follow-up period. Only one of the 25 patients required a repeat PTCA, and no CABG procedures were performed during the follow-up period, indicating the incidence of cardiac events was apparently significantly reduced by treatment with EDTA from what would be expected in a group of patients with coronary artery disease treated with PTCA and stents.

Table 3 compares the albeit limited data on intravenous EDTA to data supporting the long-term use of clopidogrel plus aspirin to prevent clotting in the presence of medicated stents and the effect of

**Table 3. Thrombosis from Drug-eluting Stents Compared to EDTA**

| | EDTA | Long-term Clopidogrel |
|---|---|---|
| FDA indication | No | No |
| Clinical trials | No | No |
| Platelet inhibition | 3 Mechanisms | 1 Mechanism |
| Risk of major bleeding | Minimal | Yes |
| Preliminary data showing clinical effectiveness | Yes | Yes |

**Table 4. Optimal Treatment for Coronary Artery Disease**

| | Conventional Therapy | Alternative Therapy |
|---|---|---|
| Optimize lifestyle | Yes | Yes |
| ↓ Platelet aggregation | Clopidogrel; Aspirin | EDTA; Fish oils |
| ↓ Lipids | "Statin" drug | Red yeast rice; Niacin; Fish oils |
| ↓ Inflammation | "Statin" drug | Red yeast rice; Fish oils |
| ↓ Arrhythmias | Beta-blocker | Magnesium |
| ↓ Blood pressure | Beta-blocker; ACE inhibitor, Diuretic | Magnesium; Fish oils; Garlic; Medication if necessary |
| Removal of lead | None | EDTA chelation therapy |

clopidogrel in preventing cardiac events for other conditions, the latter of which demonstrated virtually no reduction in death rates. Both therapies are being used off-label in the treatment of coronary artery disease.

Safety is an important factor in choosing which medication to use. Intravenous disodium magnesium EDTA has been used safely since the modern protocol was established 35 years ago. Clopidogrel carries a significant risk of hemorrhage.

Clopidogrel is often given in a loading dose followed by 75 mg daily. EDTA is usually given intravenously once or twice per week for 20-30 treatments, followed by monthly treatments. The cost of the initial course of treatment is higher with EDTA, but the cost of maintenance treatment with EDTA is probably less than ongoing treatment with clopidogrel. Furthermore, patients receiving monthly I.V. treatments are monitored more closely than those given a three-month prescription for clopidogrel with refills up to one year. At such visits, lifestyle changes can be reinforced, resulting in better compliance, an important consideration given adherence to multiple healthy lifestyle factors might be more important than any therapeutic drug in preventing cardiovascular deaths.[16] An optimal integrative approach to prevention and treatment of coronary artery disease is summarized in Table 4.

## Conclusion

No scientific evidence supports long-term use of clopidogrel in preventing potentially fatal clotting linked to medicated stents. Quite the contrary, there is some indication that the long-term use of clopidogrel might put the patient at risk for a major bleeding episode, especially a hemorrhagic stroke. The benefit of using clopidogrel appears to be limited to the first 60 days after diagnosing acute coronary syndrome, which applies to a minority of patients who have had stents inserted. There is also some evidence that clopidogrel plus aspirin inhibits stent thrombosis during the first 3-6 months after stent placement. The recently detected increased risk of clotting from medicated stents occurs later, at least six months after insertion. Thus, there is no proof via randomized, clinical trials that treating patients with a drug-eluting stent in conjunction with clopidogrel for more than six months is helpful or safe.

Intravenous EDTA has a documented mechanism of action. There is reliable evidence from the literature that it may prevent clotting and subsequent cardiac events, including premature death, in patients who have had PTCA with or without stent placement. The evidence is not conclusive, but it compares favorably to the body of evidence supporting the use of clopidogrel. Neither treatment has an FDA indication for long-term use to prevent complications from the placement of medicated stents. The data in hand, however, appears to indicate that chelation therapy may be an effective component in a comprehensive program to lesson the clotting risk from drug-eluting stents. In addition, any cardiovascular rehabilitation program should include aggressive lifestyle change. While there is some evidence that treatment with clopidogrel might have benefit during the 3-6 months following the placement of a medicated stent, long-term use of clopidogrel has no proven benefit. EDTA appears to be safer than clopidogrel because it is less likely to cause major bleeding episodes.

In a March 8, 2007, *New England Journal of Medicine* article, the FDA called for randomized, controlled trials to determine the best treatment strategies for patients with complex cardiovascular conditions, such as diabetes, acute myocardial infarction, and multivessel coronary artery disease.[17] The FDA emphasized that safety end points such as death and myocardial infarction should be studied, and the duration of therapy with clopidogrel and aspirin needs to be determined. This author proposes treatment with EDTA chelation therapy should also be studied for use in patients treated with medicated stents because of its safety and possible effectiveness. In the article, the FDA did not address the concern that patients with occluded arteries treated with medications alone might have better outcomes than those treated with angioplasty and stents.

The limited data available indicates EDTA may be safer and more effective than clopidogrel in preventing clots, myocardial infarctions, additional surgical procedures, and death as complications from medicated stents placed in coronary arteries, particularly in patients with complex conditions.

EDTA has the additional benefit of removing low levels of lead that add a major risk of cardiovascular disease and increased mortality. EDTA chelation therapy is being examined in the TACT study. Preliminary data from the study cited above, which looked at

the same end points as TACT, indicate EDTA might be effective in preventing cardiac events for patients with known vascular disease. Since the use of angioplasty and stents does not appear to improve outcomes in patients with totally occluded arteries, the addition of EDTA to standard medications may be a promising treatment for coronary artery disease, whether or not drug-eluting stents have been implanted.

## Disclosure

The author has no financial interest in EDTA other than its use for patients in his own office.

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