Integrative Cardiac Revitalization: Bypass Surgery, Angioplasty, and Chelation. Benefits, Risks, and Limitations

This review is dedicated to my grandfather Richard Kidd. The first words I remember from him were "Prevention better than cure." I can think of no other maxim more applicable to the maintenance of cardiovascular health.

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Abstract

Coronary artery disease (CAD) is still the main cause of premature death in the industrialized world. The revascularization modalities, bypass surgery and angioplasty, when successful provide restored blood flow to the myocardium. Bypass remains the most proven means for managing more severe cases of CAD, namely triple vessel disease with or without complications, while angioplasty works best for cases of single or double vessel disease with minimal complications. Both types of intervention partially relieve angina as they clear arterial blockage. Both save lives to an extent greater than medication alone. However, both are limited to being palliative since they fail to treat the underlying atherosclerotic occlusive process.

EDTA chelation therapy appears to achieve revitalization of the myocardium, and is a viable alternative or adjunct to revascularization. Fish oils are now proven to help revitalize vessel wall endothelia and to partially reverse atherosclerotic damage. Being safe and having proven benefits, chelation therapy and fish oils can be integrated together with nutrients, lifestyle-dietary revision, exercise, and medications as necessary, into a cardiovascular revitalization strategy. Cardiovascular revitalization would be highly cost-effective and procedurally compatible with the revascularization modalities, while extending beyond revascularization to halt atherosclerotic progression, restore cardiac functionality, extend survival, and improve quality of life.

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Introduction

Coronary artery disease (CAD) and the heart dysfunction it causes continues to be the greatest cause of premature death in industrialized countries. It kills more men than does prostate cancer, and more women than does breast cancer. The introduction of revascularization modalities, namely coronary artery bypass surgery ("bypass") in 1969,[1] and percutaneous transluminal coronary angioplasty ("angioplasty") in 1977,[2] ushered in a new era of medical

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management of CAD. By restoring blood flow to damaged myocardium, revascularization offers symptomatic cardiac patients the possibility of salvaging and perhaps revitalizing heart muscle debilitated by hypoxic/ischemic damage. Cardiac recovery with revitalized function means expanded opportunity for freedom from symptoms. This review examines the current state of bypass and angioplasty in CAD management, along with the emergent chelation modality. These modalities for cardiac revitalization can be rationally integrated with medication, lifestyle-dietary revision, and appropriate exercise regimens to slow or reverse CAD and extend survival with higher quality of life.

Coronary Artery Bypass Grafting (CABG, "bypass")

Bypass surgery has been a viable modality in CAD management for close to three decades, and its lifesaving potential is virtually taken for granted. Improvement of cardiac function following bypass has been unequivocally demonstrated. For patients with severe CAD, including left main descending artery disease, bypass is lifesaving. Patients with the most severe and involved coronary disease and poor left ventricular function stand to benefit from successful bypass. However, the long-term (greater than five year) outcome following bypass is far less optimistic than could be inferred from its short-term lifesaving benefits.

The goal of bypass is to restore blood circulation to the myocardial muscle fibers, by replacing occluded coronary arteries with vessels grafted in from other areas. Mammary artery grafts are increasingly being favored over saphenous vein grafts. Revascularization achieved using bypass can benefit angina or ischemia, and help protect the functioning heart muscle against further infarction. Bypass offers hope that zones of the myocardium that are hypofunctional but still viable will become re-activated to get into rhythm with zones that remain functional. Yet with all its technological allure, bypass is still only palliative because it does not affect the underlying pathological processes that generate coronary vessel occlusion in the first place. Thus, "successful" bypass surgery fails to carry any guarantee that the remaining coronary vessels or the newly placed vessels will not subsequently become occluded, thereby necessitating re-operation. In recent years re-operative bypass has become increasingly more common.[3]

Judged by prevailing criteria, bypass is regarded as relatively safe, with an "acceptable" perioperative mortality. Mortality from bypass procedures, as carried out by competent practitioners in adequately prepared institutions, is about five percent.[4] But postoperative survival subsequent to the complex procedures of bypass can be complicated by adverse events that result in considerable and long-lasting morbidity.

One category of major adverse events from the bypass procedure is increased formation of emboli. These can lodge in the lung, or reach the brain and cause acute deterioration of cerebral function. All patients on whom bypass is done using bubble oxygenators are said to have cerebral microemboli, and many patients develop early brain swelling.[5] The likelihood of this situation developing during bypass has proven particularly difficult to overcome. Early cognitive defects may occur in 75 percent of bypass patients, and adverse psychological effects are common.[6]

Post-bypass brain damage may afflict as many as 150,000 persons per year in the United States alone.[7] Roach and collaborators[8] evaluated 2,108 bypass patients from 24 U.S. institutions, and found a 6.1-percent occurrence of two types of neurological damage. These were: focal injury, stupor or coma at discharge (Type 1); and deterioration in memory or other intellectual functions, or seizures (Type 2). Death resulted in 21 percent

of the Type 1 patients and 10 percent of the Type 2 patients, as compared with 2 percent of patients with no adverse cerebral effects from surgery. Patients with neurological damage also stayed longer in the hospital and had a higher rate of discharge to facilities for intermediate or long-term care.

Supraventricular arrhythmias (SVA), such as atrial fibrillation or atrial flutter, are associated with hemodynamic deterioration and sometimes lead to stroke. According to a meta-analysis by Andrews and co-researchers,[9] occurrence of SVA following bypass could be as low as 26 percent and as high as 95 percent, depending on how precisely such arrhythmias are measured. Prophylactic beta-adrenoceptor blockers had a protective effect, albeit incomplete, in some patients undergoing bypass.[9]

Other adverse effects following bypass include chest or leg wound discomfort,[10] and the need for blood transfusions. However, the past several years have seen considerable improvements in bypass technique. Increasing use of internal mammary arterial grafts and improvements in surgical techniques have improved the outcome following bypass.

Women have not benefited from the availability of bypass to the same extent as men. For example, Brandup-Wognsen and others[11] examined the clinical course of 2129 men and 402 women in western Sweden for two years following bypass surgery. The females subjected to bypass were found to be older, and more frequently had hypertension, diabetes, congestive heart failure, renal dysfunction and obesity. In a multivariate analysis considering age, history of cardiovascular disease and renal dysfunction, female sex appeared a significant predictor of mortality during the 30 days after bypass was performed ($p<0.05$), but not thereafter. Various postoperative complications—neurological, thoracic, myocardial—and the need for assist devices were also more common in females.

Bypass is a reasonably safe invasive procedure, and is effective as a short-term means of restoring compromised myocardial vascularization, but patients should be reminded bypass is not a long-lasting solution to CAD. To the extent that the bypass "establishment" cultivates the illusion that a bypass operation gives the patient a "new life," an unconditional "fresh start," it must share the responsibility that still too few bypass patients are motivated to change high-risk behavior following surgery. A consensus among cardiologists not biased toward revascularization is that attention to the "secondary prevention" of risk factors (i.e., lifestyle revisions after bypass) will have the most influence on the long-term benefits from surgery. This also recognizes, of course, that the "primary prevention" of risk factors, such as antioxidant insufficiencies, lack of exercise, obesity, abnormal lipoprotein cholesterol and homocysteine levels, should lessen the need for bypass in the first instance.

Patient psychological state is a factor that has large predictive value for outcome following bypass. A 1997 meta-analysis by Duits and collaborators of 17 prospective bypass studies conducted between 1986 and 1996 concluded that individuals who manifest anxiety and depression pre-operatively are likely to have postoperative psychological maladjustment.[12] Denial is also a negative predictor, while optimism, sense of being in control, and adequate social support all tend to improve outcome.

Bates[13] has explored, from an anthropological perspective, the issue of why an expensive, individualistic, and palliative intervention such as bypass came to be so widely used to treat a condition so clearly related to occupational, social, environmental, and lifestyle factors. This review also addressed the issue of why bypass has proliferated in the absence of firm evidence it is an effective long-term mode of treatment

for CAD. After a well-documented critique, Bates asserts, "This review of the literature indicates that CABG [bypass] surgery has not proven effective in many cases in either preventing heart attacks or prolonging life...How can we understand the behavior of physicians and surgeons who ignore the readily available evidence of CABG surgery when they make decisions regarding treatment of many patients with coronary artery disease? The development and continued use of CABG surgery demonstrates how medical and surgical practice in the U.S. is shaped more by socio-cultural, political, and economic forces than by unbiased, value-free, 'scientific' facts or by an overriding concern for the health and welfare of the American public."[13]

Coronary angioplasty (PTCA, "angioplasty")

This revascularization modality involves opening the lumen of a partially occluded coronary artery by inflating a balloon at the end of a catheter inserted into the vessel. Success depends on clearing the vessel blockage while preserving the integrity of the vessel wall. Angioplasty is judged to have failed if the involved artery cannot be successfully dilated without the occurrence of a major complication; or if abrupt occlusion occurs and adverse sequelae, including death, myocardial infarct, or emergency surgery follows. "Rescue" angioplasty is sometimes performed when clot-dissolving, thrombolytic drugs have failed to dissolve clotted material that occludes an artery. This procedure is highly controversial. Some physicians believe it is unethical to withhold this option, while others are convinced it is unethical to use it.[14]

For those patients with less severe vessel occlusion and single or double vessel involvement, coronary angioplasty is associated with a mortality rate of about 1 percent and an infarct rate of 2-4 percent.[15] Mortality and complications are markedly higher for angioplasty performed on patients with more severe CAD, such as three-vessel involvement and/or multiple occlusion zones. The primary success rate for angioplasty performed on the former category of patients has increased to well over 90 percent, and emergency bypass made necessary by failed angioplasty has been greatly reduced. For this patient population angioplasty is increasingly preferred over bypass, since bypass has greater perioperative morbidity, somewhat greater cost, and slower recovery time.

A survey of 25 European nations, with a pooled population of 525 million, revealed that angioplasty was performed on more than 183,000 persons in 1993, up 24 percent over 1992.[16] In more than four-fifths of these cases (>80 percent), the procedure was confined to a single coronary vessel. The use of an insert ("stent") to strengthen the vessel wall also is becoming more popular.

The short-term (six months) outcome for angioplasty is limited mainly by the re-stenosis process, which stems from resumption of atherosclerosis-related plaque formation and/or accumulation of thrombus material in the same vessel, sometimes accompanied by ongoing occlusion of other coronary vessels.[16] Re-stenosis occurs in less than six months in 25-55 percent of cases,[17] and is frequently associated with recurrent ischemia. Re-operation (re-dilatation) can be performed with a success rate greater than 95 percent. Often the symptomatic patient with re-stenosis and significant stenosis in other vessels is referred for bypass.

Medium-term (< five years) outcome after angioplasty was surveyed by de Feyter in a population of European patients.[15] Re-dilatation made necessary by re-stenosis was required in 16 percent of patients, and bypass in 10 percent. Among patients exhibiting good patency of the dilated segment over the first year, the six-year survival rate approached 96 percent. Patients whose new coronary

segments developed obstruction were more likely to have adverse events during this period. Like bypass, angioplasty does not effect complete and lasting revascularization of the myocardium.

Because this modality also, like bypass, is only palliative, when more precise criteria are used to judge its success the results are far less remarkable. Thus, when the procedure is successful in restoring the arterial lumen to within 20 percent of its initial diameter when dilated, and the vessel wall is not damaged, the frequency of re-stenosis after nine months (defined as arterial blockage of fifty percent or more) is still 24-27 percent. In a recent survey by Di Luzio and collaborators,[18] among patients who experienced initial "optimal results" from angioplasty, 18.8 percent developed re-stenosis. Of those with initial "sub-optimal" results, more than one-third (37.8 percent) became re-stenosed during this same period. Analysis of the data determined sub-optimal initial dilation, unstable angina, and major wall lesions following angioplasty were major determinants of increased re-stenosis risk.

Angioplasty risks are higher in patients with more anatomically complex lesions; in patients with acute myocardial infarction, myocardial failure, multivessel disease, unstable angina, or previous bypass surgery; and in women and older patients. According to 1990 figures,[19] approximately 3.7 percent of patients having angioplasty require emergency surgery; of these, 39 percent have perioperative infarctions and five percent die.

Bypass Compared with Angioplasty for Specific Conditions

Some reliable evidence is available to facilitate comparisons between bypass and angioplasty in light of their applicability to coronary-centered symptomatologies.

Angina: Both bypass and angioplasty help relieve angina. Pocock and collaborators[20] conducted a meta-analysis of eight randomized trials comparing bypass and angioplasty. The patients included in these trials were predominantly afflicted with double vessel disease, and had a mean left ventricular ejection fraction of greater than 60 percent. Those patients who received bypass had greater relief from angina, more so through the first year.

For symptomatic benefit from angina, especially in appropriately selected patients having less severe CAD, angioplasty is less traumatic and is associated with quicker recovery than bypass.[19] For patients with mild angina and no evidence of ischemia, benefits from revascularization are small unless three-vessel disease is present.

Worthy of note is that these randomized trials largely excluded patients who had more severe CAD progression and would have been more suitable for bypass. Excluded were patients with three-vessel disease, highly occluded vessels, and severe manifestations of CAD. This latter group represents the majority of patients referred for revascularization and, had they been included, it is likely bypass would have been found markedly superior over angioplasty for relief of angina at all stages following the procedure.

Unstable angina, defined as chest pain at rest accompanied by reversible ST-segment and T-wave changes on electrocardiography, is not treated by revascularization as successfully as is stable angina.[15] For such patients angioplasty has a lower success rate than bypass.

Single and Double Vessel Coronary Artery Disease: Bypass is applicable to patients covering the entire range of severity of coronary involvement, including those with mild-to-moderate single and double vessel involvement. Angioplasty was originally developed for patients with single-vessel coronary disease, preferably with single atherosclerotic lesions. In these patients angioplasty may well be the better revascularization choice. Given

the availability of well-equipped centers and competent operators, angioplasty prognosis beyond five years is excellent for those patients who initially present with single vessel disease and good left ventricular function.[15] The survival rate for these patients beyond five years exceeds 95 percent, and more than two-thirds experience freedom from major adverse cardiac events.

In Europe, as of 1994, about two-thirds of patients with multivessel disease who were selected for angioplasty had two-vessel disease. Two-thirds of patients recommended for bypass had three-vessel disease.[15] As a ground rule, the prospects for success with angioplasty hinge on the arterial lesions being relatively localized and anatomically simple. When angioplasty cannot achieve complete revascularization, bypass offers longer survival.[19]

Multivessel Coronary Artery Disease: Although angioplasty was initially validated in 1977 by Gruntzig[2] as a treatment for one-vessel disease, subsequent equipment refinements combined with greater operator experience have extended angioplasty to multivessel disease. Currently, almost half of all patients selected for angioplasty have multivessel CAD. Yet complete revascularization can be achieved by angioplasty in only about half of these patients. Dilation of highly occluded vessels is not only hard to achieve by angioplasty, but can be dangerous to the patient as well. The procedural and annual mortality rates are higher for multivessel than for single-vessel disease. The re-stenosis rate is also very high in multivessel disease, and repeat angioplasty must be performed in more than one-third of these patients.

Bypass is well established for its survival benefit to patients with moderate-to-extensive multivessel coronary disease. Several randomized clinical trials have compared bypass against angioplasty for treatment outcome, but sample sizes were not sufficiently large to be definitive. In 1995, Sim and collaborators at Stanford University and the Montreal Heart Institute conducted a meta-analysis of all reported randomized trials which directly compared bypass with angioplasty in multivessel CAD.[21] From an English-language search of the Medline and BIOSIS on-line databases for the years 1985-1995, Sim's group[21] identified five suitable randomized trials. The clinical outcomes of interest were: (1) death, (2) combined death and nonfatal myocardial infarction, (3) freedom from angina, (4) repeat revascularization with bypass, and (5) repeat revascularization with angioplasty. In addition, death and nonfatal myocardial infarction were separately analyzed for in-hospital events and short-term follow-up factors that might have contributed to those outcomes. An odds ratio (OR) was derived as the main summary statistic of increased risk, and p values of <0.05 between ORs were judged significant.

The five trials randomized 2,943 patients, 1,449 to bypass and 1,494 to angioplasty. Patient characteristics were not significantly different between treatment groups. However, the proportion of patients with unstable angina varied widely among the trials. Overall, 15 percent of the patients had one-vessel disease, 57 percent had two-vessel disease, and 28 percent had three-vessel disease. Patients with left main coronary artery disease, recent myocardial infarction (MI), or prior bypass or angioplasty were excluded from the trials. The meta-analysis failed to establish differences with respect to two major clinical outcomes. Thus, at one to three years of follow-up, overall risk of death was lower in bypass patients, but not significantly, while the index of combined risk of death or nonfatal MI was higher, but fell short of statistical significance.

Differences between bypass and angioplasty with respect to other clinical

outcomes were clarified by the meta-analysis. Thus, the bypass patients were significantly more angina-free than were those subjected to angioplasty ($p<0.00001$) and also substantially less likely to undergo either a subsequent bypass or a subsequent angioplasty ($p<0.00001$). In-hospital death rates did not differ significantly (1.4 percent for bypass, 1.2 percent for angioplasty), nor did the measure of combined death plus nonfatal MI (5.7 percent versus 4.4 percent). Sims and collaborators concluded from this meta-analysis[21] that for patients with multivessel CAD bypass is more often indicated. They reported bypass provided better relief of angina and was less likely to lead to a repeat revascularization operation.

In discussing the extensive data made available by their meta-analysis, Sims and collaborators suggested angioplasty might be superior to bypass for two-vessel or milder CAD, whereas bypass was preferred for three-vessel or more severe disease. They called for longer follow-up (beyond five years) to better determine which of these procedures might better lower the risk of death or heart attack. They also cautioned that coronary artery disease tends to reoccur at 5 years or beyond, whether bypass or angioplasty was the initial revascularization intervention.[21, 22] Although repeat operations are an unavoidable feature of revascularization interventions, bypass was less likely to lead to a repeat revascularization operation than angioplasty.

In patients evaluated as unlikely to tolerate surgery because of co-morbidities or the likelihood of complications (including women with more severe CAD, and many elderly patients), angioplasty can be a viable alternative to a risky bypass surgery or ineffectual medication. However, it is important to have adequate surgical backup available to perform emergency surgery in the event angioplasty fails in these patients.[19]

Left Ventricular Dysfunction: Patients with moderate-to-severe left ventricular dysfunction (ejection fraction <35-40 percent of normal) tend to have a poor prognosis in the absence of revascularization. In 1994, Baker and collaborators[23] critically reviewed a number of studies of revascularization for depressed ejection fraction (EF <40) or frank heart failure, conducted between 1966 and 1993. Meta-analysis was not performed because of general heterogeneity in the surgical techniques, the study populations, and study quality. Eight cohort studies were located comparing bypass against standard management involving mostly medications. The investigators assessed each study and concluded patients with moderate-to-severe left ventricular dysfunction and angina had improved survival due to bypass. Bypass also improved physical functioning in these patients.

A similar search strategy on angioplasty yielded a number of case reports and case histories suggesting this revascularization modality can also relieve angina and improve ventricular function. But since the risks associated with angioplasty are not well documented, Baker and colleagues suggested that until documentation becomes available, bypass should be the preferred means of revascularization.

Notwithstanding its better documentation over angioplasty for improving ventricular dysfunction, when performed on patients with low ejection fraction and clinical heart failure, bypass does result in higher mortality and surgical complications. In the Baker trial review, operative mortality ranged from about 5 percent in patients younger than 60 years and having few co-morbid conditions, to 30 percent in patients older than 70 years and experiencing severe ventricular dysfunction with several co-morbid conditions. These patient populations could well have improved post-bypass outcome if pre-operatively loaded with

coenzyme Q10, which is found depleted in dysfunctional myocardium and has been shown to improve postoperative cardiac output.[24,25]

Sudden Cardiac Death: Sudden death from heart attack is the archetypal health nightmare—it strikes quickly and offers no second chance. Each year at least 200,000 people die suddenly from heart attack in the U.S. alone. According to the review by McAlister and Teo,[26] routine prophylactic use of Class 1 anti-arrhythmic agents in survivors of acute myocardial infarction increases the risk of sudden death, as seen from an odds ratio (OR) of 1.13 in 23,486 patients. Beta-blockers decrease the risk of death in this post-infarction patient population (OR 0.81 in 53,521 patients). No benefits were seen with calcium-channel blockers.

McAlister and Teo suggested using aspirin, beta-blockers, lipid-lowering drugs, and angiotensin-converting enzyme (ACE) inhibitors to prevent or minimize ischemic heart muscle damage, and hopefully bring about a decrease in sudden cardiac death.[26] Yet these pharmaceuticals carry substantial risk. The vast majority could be adequately replaced by low-risk orthomolecular and/or phytopharmaceutical oral agents administered under the supervision of competent medical practitioners. As a prostaglandin regulator, aspirin could be augmented or supplanted by fish oils. Inositol hexaniacinate has an excellent benefit-risk profile and could be used in place of the lipid-lowering drugs,[27] most of which deplete coenzyme Q10 from heart muscle and thereby threaten its functionality.[28] The nutrients coenzyme Q10, carnitine and taurine all support cardiac contractility, all are intrinsic to human metabolism, and all are safe for dietary supplementation.

Until recently, the standard therapy for heart attack was systemic thrombolysis, involving the use of "clot-busting" drugs initiated as early as possible following myocardial infarction. Results from a recent meta-analysis indicate angioplasty worked significantly better than clot-busting drugs in treating heart attack victims.[29] In summary, this meta-analysis showed in the first 30 days after heart attack the angioplasty patient group had better survival (92.8 percent versus 88.1 percent), and experienced fewer subsequent heart attacks or strokes than did the drug group. The researchers concluded angioplasty patients were one-third less likely to die within the first 30 days, and had a 65-percent lower risk of stroke than those treated with the clot-busters. These findings are concordant with an earlier meta-analysis of 8,496 patients conducted by Michels and Yusuf.[30]

Chelation—Alternative, Adjunctive or Integrative?

Chelation therapy, more formally referred to as EDTA chelation therapy, is a procedure employing intravenous administration of EDTA (ethylene diamine tetra-acetic acid), often along with nutrients, to help manage atherosclerotic vessel diseases and partially revitalize the circulation. EDTA was found to be a chelating agent in the early 1950s, and is excreted from the body intact, mostly in the urine.[31] Modern chelation therapy for circulatory health grew out of the use of EDTA to remove toxic minerals, such as lead, from the body.

Chelation therapy is most effective when employed as part of a comprehensive, individualized program which also includes dietary and lifestyle revision, nutritional supplementation, exercise, stress reduction, and medications when necessary.[32] This integrative chelation management strategy does not depend on surgical revascularization to be successful; rather, chelation might be a viable substitute. It is also likely to enhance outcome following surgery. Chelation has negligible risk,[32] and the materials are affordable and

readily available. Thus, both the benefit-risk profile and the cost-effectiveness of chelation are likely to be superior over bypass and angioplasty.

The word "chelation" comes from the Greek "chele," referring to the claw of a crab or lobster. The chelation concept involves trapping the target ion in a "cage" stabilized by multiple sites of bonding with the chelating agent. EDTA is thought to partially surround, bind with, and tightly grip metal ions, then facilitate their excretion by way of the urine. The EDTA compound used for removal of lead from the body is the calcium-EDTA salt; that used for circulatory revitalization is the disodium-EDTA salt.

The peer-reviewed protocol from Rozema,[32] approved by the American Board of Chelation Therapy and the International Board of Chelation Therapy, involves intravenous infusion of an osmotically standardized EDTA solution over 1.5-3.0 hours. Frequency of treatment is usually once or twice a week; for symptomatic patients a series of 30 or more infusions may be indicated. As documented by Rozema, EDTA chelation therapy benefits all forms of atherosclerotic occlusive arterial disease.

Other disease processes have also been found to benefit from chelation. Scleroderma patients have experienced marked improvement,[31] although lack of benefit was also reported.[33] Rozema claims, "diabetics usually demonstrate great improvement...insulin or oral hypoglycemic medications for glucose control can be reduced or eliminated altogether."[32] Case histories indicate benefit in Alzheimer's disease, multiple sclerosis, rheumatoid arthritis, porphyrias, hypertension, calcinosis universalis and other calcium deposition diseases.[32] Visual function in macular degeneration cases is also often improved.[34]

Rozema has thoroughly documented the pharmacology and safety of EDTA. Gordon and Vance[35] and Halstead[36] earlier reviewed possible mechanisms for its cardiovascular efficacy, yet no distinct mechanism has been established for the cardiotonic benefits from EDTA. Absolute contraindications for EDTA therapy are limited to rare patients exhibiting chemical intolerance to EDTA, patients with acute lead encephalopathy, or patients on renal dialysis. Renal damage is estimated to occur in less than 1 in 30,000 patients, and then only in those with pre-existing kidney hypofunction.[32] EDTA chelation is not yet proven safe for women who are pregnant or might become pregnant.[32]

Olwin and others[37] suggested a rationale for the use of EDTA, magnesium, and heparin in combination to achieve lasting cardiac revitalization. The Rozema EDTA chelation protocol[32] also commented on a number of other substances for suitable co-administration with EDTA, including magnesium (as chloride or sulfate),[38] sodium bicarbonate, local anesthetics, heparin, ascorbic acid (vitamin C), B vitamins, and minerals. A number of chelating agents were reviewed and found to compare negatively with EDTA in respect to safety and benefit. Yet EDTA chelation therapy has yet to receive widespread acceptance by the clinical community.

Although it has not been subjected to vast numbers of clinical trials, two meta-analyses suggest EDTA chelation therapy benefits cardiovascular symptoms in more than four out of five patients. In 1993, Chappell and Stahl[39] published an analysis of data on 22,765 patients, compiled from 19 published clinical studies. They found a correlation coefficient of 87 percent between EDTA therapy and improved cardiovascular symptomatology based on objective testing. Subsequently, they obtained unpublished "file drawer" data on 1,241 objectively-sorted patients from 32 clinicians.[40] From this approach they obtained a correlation coefficient of 88 percent, further building the case for cardiovascular benefit from EDTA.

EDTA chelation therapy may eventually be proven a viable alternative to bypass or angioplasty. Danish physicians Hancke and Flytlie[41] reported retrospectively on 470 patients with atherosclerosis. Of 65 patients awaiting bypass surgery and subjected to chelation, the vast majority showed clinical improvement; when chelation was completed only seven still required bypass. Of 27 patients previously scheduled for leg amputation, only three required surgery following courses of chelation therapy. These enticing results from EDTA chelation invite a well-controlled comparison of chelation and revascularization, with the hope of being able to replace surgical revascularization techniques or to use chelation as an adjunct to these interventions.

Fish Oils Improve Outcome Following Revascularization

In a review on atherosclerosis published in a previous issue of this journal,[42] this author stated "dietary fish oil supplements unquestionably can extend the lives of subjects with heart disease." This assertion is supported by findings from nine randomized controlled trials conducted to date on the efficacy of fish oils in preventing re-stenosis following re-vascularization. Gapinski and collaborators,[43] and separately O'Connor's group,[44] conducted meta-analyses of these trials, which included almost one thousand patients. Whereas the earlier meta-analysis by O'Connor's group was more sketchy and drew more cautious conclusions, that of Gapinski's group was conducted in greater detail and concluded, "...we have shown a clear benefit of fish oil supplementation following PTCA in reducing re-stenosis rates at six months...[and] currently there is a rationale for the use of...[fish oil] omega-3 fatty acids after patients have undergone successful PTCA."[43]

In another randomized, controlled study, 610 patients undergoing bypass were divided into a fish oil group and a control group. One year after bypass, those who received fish oils had a significantly lower incidence of re-stenosis.[45]

Some of the findings from controlled trials with fish oils may have been confounded by dose-related paradoxes, most likely related to the high oxidizability of these polyunsaturated oils. The available data are consistent with intakes of 1500 mg total (EPA+DHA) per day being most beneficial;[43] intakes at or above 3000 mg total (EPA+DHA) tended to have adverse effects, particularly on the gastrointestinal and immune systems.[43]

The positive findings from controlled trials with fish oil supplements are consistent with copious data gathered from trials on fish consumption. In one study of 334 patients between 1988 and 1994,[46] an average daily intake of 5.5 grams of omega-3 fish oils per month (equivalent to 1 fish meal per week) was associated with 70-percent less risk of a first heart attack. A large, randomized, controlled trial known as the South Wales Study[47] found that a modest intake of fish (two or three portions per week) significantly reduced the risk of sudden cardiac death in men who had already had one heart attack. Autopsy findings from the Honolulu Heart Program[48] indicate fish consumption may protect the heart muscle by means independent of protection of the larger arteries.

The Honolulu Heart Program is a long-term, prospective epidemiologic study that seeks to analyze risk factors for heart disease and stroke. It has been following an initial cohort of 8,006 Japanese-American men since 1965, and relies heavily on autopsy studies. Burchfiel and his collaborators[48] searched at autopsy for heart muscle lesions in men from this cohort who were free of moderate or severe atherosclerosis in the larger coronary vessels. They found that men who had eaten fish meals twice or more per week were more protected against myocardial lesions. The

investigators suggested heart disease can sometimes be localized in the myocardium distal from the larger vessels, and fish oils could protect the smaller vessels or the myocardium itself. Among the many potential mechanisms, fish oils could down-regulate coagulation mechanisms, promote clot dissolution, or reduce myocardial propensity for arrhythmia.[49,50]

Sudden cardiac death terminates at least 200,000 lives every year in the United States, accounting for nearly half of all cardiovascular deaths. Very recently, fish intake data were correlated with figures on sudden cardiac death in the large, ongoing Physicians Health Study.[51] This study began in 1982, tracking an initial cohort of 20,551 doctors. The finding was that those who ate "fatty" fish (such as tuna, salmon, mackerel, or shellfish) at least once a week had half the risk of sudden death compared to those who ate fish less than once a month. An accompanying editorial stated, "The existing evidence suggests that consumption of fish once a week will help prevent coronary artery disease and therefore should be a component of a healthy diet. Two fish servings per week...not only may help reduce coronary heart disease mortality but also may favorably influence all-cause mortality." The author also stressed the possibility that constituents of fish other than fish oils could be contributing to the cardiovascular benefits.[52]

Concluding Remarks

For many societies, coronary artery disease is the single most financially costly medical condition. Thus, any improvements in the management of coronary artery disease have great potential consequences to the larger society as well as to individual patients. Overall, angioplasty is preferable for cases of single or double vessel disease without critical left anterior descending artery (LAD) stenosis. For cases with marked LAD involvement and/or multivessel disease, bypass is preferable. Both modalities help relieve angina, particularly the stable form, but only to the extent that complete revascularization is achieved from the procedure.

For the more severe or recalcitrant coronary vessel pathologies, bypass clearly is preferable over angioplasty. Patients with chronic coronary artery occlusion, multiple severe stenoses, severely impaired left ventricular function, or valvular or aneurysmic involvement should have bypass surgery. But even the staunchest advocates of revascularization intervention are likely to concede that these modalities have major liabilities related to their invasiveness, including significant risk of death, high likelihood of coronary re-occlusion necessitating re-operation, and high financial cost.

Whether initial myocardial revascularization is achieved by angioplasty or bypass, re-occlusion of the initially treated vessels or the continued progression of occlusive disease in untreated vessels has the potential to cause life-threatening damage over the long term. If lifestyle and dietary changes can be implemented in advance of vessel re-occlusion and the re-emergence of symptoms, the chances for long-term survival and quality of life are likely to be markedly improved. Individuals unable or unwilling to implement preventive cardiac maintenance are likely to have their options become progressively more limited to invasive cardiac intervention.

Both bypass and angioplasty are invasive procedures necessitated by the need to salvage heart muscle damaged by coronary insufficiency. Both bypass and angioplasty pose significant risk, and both are highly expensive with poor cost-effectiveness. The "clot-busting" enzymes can be useful adjuncts to either of these procedures, but have a very narrow time window of effectiveness (usually in the range of 1-3 hours), past which they can become paradoxically harmful. Clearly this is an

area of medicine that is begging for a new integrative rationale.

One candidate modality around which a new integrative rationale for CAD could be assembled is EDTA chelation therapy. Although stubbornly regarded by mainstream medicine as still less than proven, in the hands of many competent physicians this therapy has been proven to restore circulatory health, particularly when used in conjunction with magnesium, vitamin C, and other nutrients. A cardiovascular revitalization program involving chelation, dietary supplementation, exercise, and lifestyle changes would be minimally invasive and far more cost-effective than the current revascularization strategies. It could be implemented on patients with any degree of morbidity, in parallel with bypass or angioplasty, or in place of these. Such a program would offer benefits far more long-lasting than bypass or angioplasty, which often have to be repeated every few years.

Coronary artery disease and its sequelae kill more women in the United States than does breast cancer. Females often are referred so late in their progression they suffer increased risk of postoperative complications and early death following bypass. Women who decide to go ahead with bypass surgery would be prudent to begin a cardiac revitalization program as early as possible prior to surgery, in order to better cope with the surgery and its aftermath.

Some of the orally bioavailable nutrients indicated for a cardiovascular revitalization program are (1) all the B vitamins, for ubiquitous metabolic support; (2) all the essential minerals, and especially generous intakes of magnesium, potassium, zinc, and selenium; (3) coenzyme Q10, carnitine, and taurine, to directly support myocardial contractility; (4) vitamins C and E, and the carotenoids, as antioxidants; and (5) moderate intakes of the omega-3 essential fatty acids, particularly the longer-chain fish oils EPA and DHA, to help rebuild vascular endothelial integrity.

This is an opportune time for a frank and open debate between cardiac surgeons, cardiology internists, and all progressive physicians, with the aim being to develop safe and effective, truly integrative protocols for the management of coronary artery disease.

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