L-Arginine Therapy, Clopidogrel Therapy, and Ethics

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***Abstract*—The use of L-Arginine therapy for reduction of hypertension and treatment of cardiovascular disease is well-studied with good indication of high efficacy. The use of Clopidogrel bisulfate therapy for treatment of cardiovascular disease and hypertension is independently well-studied with good indication of marginal efficacy, and some indication of adverse effect. This article presents a review of some of the available literature, and raises the question of the medical ethics of continuing studies of Clopidogrel in light of the results of the L-arginine therapy studies.**

I. Introduction

In the treatment of hypertension and other cardiovascular disease, there have been two fundamental approaches: (1) in the first approach the blood condition is altered with the administration of pharmaceuticals so as to inhibit the aggregation of platelets and resultant clotting of blood (so called "blood thinner" pharmaceuticals such as Clopidogrel bisulphate), allowing the blood to more easily flow through restrictions; (2) in the second approach, the blood vessels themselves are altered by either mechanical means (e.g. balloon angioplasty), surgical bypass, or more recently by endothelium treatment with Nitric Oxide (arginine therapy). This article reviews the available literature for both approaches, and strongly suggests that the best approach is the treatment of the endothelium with Nitric Oxide.

II. Arginine Therapy

The use of l-arginine in the treatment of hypertension has a long history. US Patent No. 5217997[1] was issued in 1993 entitled "*Use of L-arginine in the treatment of hypertension and other vascular disorders*". It describes a methodology for treatment of high vascular resistance disorders including hypertension, primary or secondary vasospasm, angina pectoris, cerebral ischemia, and preeclampsia by administration of l-arginine in dose ranges from 1 to 1500 mg daily. In 1998, the Nobel Prize in Physiology or Medicine was awarded to Robert F. Furchgott[2], Luis J. Ignarro and Ferid Murad "*for their discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system*" in which the nitric oxide is derived *in vivo* from l-arginine. Since then, considerable further research and clinical work has revealed the role of both the precursor amino acid l-citruline, and l-arginine, in the cardiovascular system.

L-arginine is a nitric oxide producer and high-potency anti-oxidant that has exceptional power to reverse the buildup of cholesterol in arteries. Newer formulations include the use of l-citruline, which is added to extend the activation of l-arginine in all phases of activity in the nitric oxide pathway. Current l-arginine/l-citruline therapy involves daily administration of between 10,000 to 40,000 mg (10 to 40 g) of both amino acids combined. The preface to Nobel Laureate Dr. Louis Ignarro's recent book "*NO More Heart Disease*"[3] reads: "The nutrients I recommend in *NO More Heart Disease*, including L-arginine, L-citrulline, and a host of heart-healthy foods, are naturally occurring and generally non-toxic at even very high levels. Indeeed, one of the most attractive properties of nitric oxide and its ability to enhance cardiovascular health is that it does not produce the undesirable side effects that are prevalent with pharmaceuticals. This stands to reason, because nitric oxide is produced in your bloodstream—by natural nutrients that are found in abundance in the foods all around you."

Presently, extensive results from medical practices and clinical studies have shown the efficacy of l-arginine/l-citruline therapies, with little or no adverse side effects[4]. This efficacy includes numerous cases of not only the reduction of hypertension, but also removal of plaque and calcium from the endothelial linings to return of near normal conditions. The lessening of post-operative hypertension in children[5] is also being investigated.

III. "Blood Thinner" Therapy

In addition to l-arginine/l-citruline therapy for a variety of cardiovascular diseases, extensive studies involving therapies utilizing "blood thinners" [platelet aggregation inhibitors] such as Clopidogrel Bisulfate[6] have been

[1] US Patent Issued on June 8, 1993; Estimated Patent Expiration Date: April 24, 2012; Abstract: "A method for treating a high vascular resistance disorder in a mammal by administering to a mammalian organism in need of such treatment a sufficient amount of L-arginine or pharmaceutically acceptable salt thereof to treat a high vascular resistance disorder. The L-arginine is typically administered in the range of about 1 mg to 1500 mg per day. High vascular resistance disorders include hypertension, primary or secondary vasospasm, angina pectoris, cerebral ischemia and preeclampsia. Also disclosed is a method for preventing or treating bronchial asthma in a mammal by administering to a mammalian organism in need of such prevention or treatment a sufficient amount of L-arginine to prevent or treat bronchial asthma. [Legal Note: The supposed legal validity of such patent is not endorsed by presentation of this patent abstract. Administration of l-arginine in combination with other chemicals, such as citruline, appears to fall outside of the patent.]

[2] Born 1916, died 2009

[3] *No More Heart Disease : how nitric oxide can prevent—even reverse—heart disease and strokes* / by Louis J. Ignarro © 2005 by Healthwell Ventures; www.stmartins.com

[4] *Journal of Nutrition*137:1650S-1655S, June 2007; Supplement: 6th Amino Acid Assessment Workshop: SESSION 2; The Pharmacodynamics of L-Arginine; Rainer H. Böger: Abstract indicates 3,000 to 8,000 mg/day is safe with no pharmacological side effects, and reports one unsubstantiated study indicating an increased risk of myocardial infarction in persons who had prior history of myocardial infarction. That study was separately criticized by Dr. Louis Ignarro due to lack of control and standard arginine/citruline therapy.

[5] Journal of Thoracic and Cardiovascular Surgery, 2007, vol. 134, no 2, pp. 319-326: "… Using this regimen, plasma arginine, citruline, and nitric oxide metabolite levels were well maintained. Intravenous citruline needs to be studied further as a potential therapy for postoperative pulmonary hypertension."

[6] The second-most-prescribed pharmaceutical in the USA, it is name-branded by Bristol-Meyer-Squibb as PLAVIX, and not yet generically issued in the USA.

repeatedly undertaken in persons having cardiovascular diseases, including peripheral artery disease, pulmonary hypertension, myocardial infarctions, stroke, etc. since it was first approved by the FDA on November 17, 1997 for patient usage. The underlying theory behind this usage is that by preventing aggregation of platelets in regions of blood-flow restriction, clotting of the blood, with resultant dislodged clots, can be lessened.

The CAPRIE[7] study (*Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events*) was a randomized, double-blind trial of 19,185 patients in 304 medical centers comparing PLAVIX (75 mg daily) to aspirin (325 mg daily). The patients randomized had: 1) recent histories of myocardial infarction; 2) recent histories of ischemic stroke; or 3) objectively established peripheral arterial disease. This randomized treatment averaged 1.6 years, to a three-year maximum. The trial's primary outcome was the time to first occurrence of new ischemic stroke (fatal or not), new myocardial infarction (fatal or not), or other vascular death. The event curves for Aspirin and Plavix barely separated, leading to the admonition contained on the pharmaceutical insert: **"**Although *the statistical significance favoring PLAVIX over aspirin was marginal* (P=0.045), and represents the result of a single trial [the CAPRIE study of 19,185 volunteer patients] that has not been replicated, the comparator drug, aspirin, is itself effective (vs. placebo) in reducing cardiovascular events in patients with recent myocardial infarction or stroke. Thus, the difference between PLAVIX and placebo, although not measured directly, is substantial (*sic*). … In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, PLAVIX was not numerically superior to aspirin.**"** (*italics* added for emphasis)

Just how 'substantial' the difference is between PLAVIX and a placebo was measured in the CURE (*Clopidogrel in Unstable angina to prevent Recurrent ischemic Events*) study. The CURE study included 12,562 patients with acute coronary syndrome without ST segment elevation and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischemia. Patients were randomized to receive PLAVIX (300 mg loading dose, 75 mg daily dose) or placebo, and were treated for up to one year. Patients also received aspirin (75-325 mg once daily) and other standard therapies such as heparin. The number of patients experiencing the primary outcome (CV death, MI, or stroke) was 582 *(9.30%) in the PLAVIX-treated group* and 719 *(11.41%) in the placebo-treated group*. Slightly less 'efficacy' was apparent in the co-primary outcome.

Notwithstanding the very slight advantage of PLAVIX-plus-aspirin over a Placebo-plus-aspirin, more recent studies have questioned even that 'efficacy'. In the CAPE (*Clopidogrel and Aspirin versus aspirin alone for the Prevention of atherothrombotic Events*) study[8] involving 15,603 randomized patients the authors conclude that there was a **"***suggestion of benefit***"** in patients with symptomatic atherothrombosis and a **"***suggestion of harm***"** in patients with multiple risk factors. Overall, they concluded that *clopidogrel plus aspirin was not significantly more effective than aspirin alone* in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes.

It is with this background of two different approaches [(1) treating the endothelial lining with arginine/nitric oxide to remove plaque, reduce 'hardening' and relax the vessel walls; versus (2) 'thinning' the blood with anti-platelet aggregation agents to ease blood flow though restrictions] to cardiovascular disease that this author addresses this issue and the ethics of treatments surrounding those two modalities.

IV. General Discussion

Cardiovascular disease is the leading cause of death in the "western" world, accounting for approximately 40%[9] of all deaths in the United States. Traditional treatments include the pharmaceutical "blood-thinners" such as clopidogrel bisulphate to ease flow of blood through restrictions without clotting, invasive balloon-catheterization to press plaque build-up against the vessel walls to provide a wider opening for blood-flow, invasive coated-stints to 'prop-open' constrictions in vessels, and by-pass surgeries in which the obstructions are bypassed with vessels obtained from other parts of the body.

During the past two decades, the use of arginine therapy has steadily increased, with exceptionally promising results. Early work involved the use of l-arginine only, but more recent studies involve the use of both l-arginine, and its precursor amino-acid in the body, l-citruline, which allows for a daily oral administration to maintain arginine capacity, rather than oral administration every 4-6 hours as with l-arginine only.

In clinical practice, Dr. Joseph Prendergast[10] has a patient base with nearly 7,000 patients using arginine/citruline therapy. Of those patients, none (0) have required admission

[7] PLAVIX pharmaceutical insert sheet referencing CAPRIE study.

[8] Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events; Bhatt et al.; New England Journal of Medicine, Volume 354:1706-1717, April 20, 2006, No. 16

[9] http://myheartdocs.com/patients.php "Heart disease continues to be the number one killer of adult Americans each year. Heart disease is many times referred to as the "silent killer" because thousands of people die each year of a heart attack even though they never had any signs or symptoms. So, just because you feel fine, doesn't mean you are fine. *Almost 1 out of every 2.4 deaths* are from cardiovascular disease. More than 2600 deaths occur each day from cardiovascular disease, 1 death every 33 seconds. **Cardiovascular disease is the cause of more deaths than the next 7 causes of death combined**. Heart disease is an equal opportunity killer; affecting both sexes, every race, and all ages.

[10] Dr. Joseph Prendergast, Endocrine Metabolic Medical Center, 350 Cambridge Ave., Suite 250, Palo Alto, CA 94306, E-mail: joe@drjoeweb.com, Web site: http://www.endocrinemetabolic.com

to a medical facility for cardiovascular disease, and none have died of myocardial infarction or stroke. This is remarkable in light of the fact that they were admitted to this practice as diabetic patients.

A very recent study concluded earlier this year (2009) at the High Desert Heart Institute[11] with patients drawn from their Congestive Heart Failure Unit (their most desperate patients) showed strong trends in all patients of a lessening of cardiovascular risk. Some individual cases showed dramatic improvement in only 90 days of therapy. One exceptionally dramatic case was of a 60-year-old patient admitted following a myocardial infarction and recurrent ER admissions. The patient had essentially given up hope, had no energy (unable to open a screw-cap on a bottle of water), and refused further hospital admissions (due to the financial cost of repeated hospitalizations whittling away his estate) and was preparing his funeral arrangements[12] in conjunction with his wife. He allowed himself to be admitted to the study only because it would have no financial cost to himself and his prospective widow. Following 90 days of therapy, there have been no ER admissions, his blood-pressure has normalized, he reports he has full energy and feels like he did when he was 40, and credits the arginine/citruline therapy with having saved his life.

While not all cases in that study are as dramatic, all patients have reported improvements in one or more cardiovascular function markers.

These clinical results with arginine/citruline therapy, while not as extensive in scope as the "blood thinner" studies, appear to have dramatically superior results. As noted earlier, the "blood thinner" studies involving Clopidogrel bisulphate had results no better than using aspirin as a platelet aggregation inhibitor, and marginally better than a placebo. The contraindications for its usage are sufficient for one study group to conclude that its efficacy is highly questionable. Conversely, while not as well-funded as the blood-thinner studies, the arginine/citruline therapy studies seem to indicate exceptionally dramatic results in many cases, with few if any adverse outcomes (myocardial infarction, stroke, etc.). It appears from those studies that the work which resulted in Dr. Ignarro receiving the Nobel Prize was well noted and properly recognized, even if not presently as well-promoted in the literature and advertising media as are the promotions for pharmaceutical "blood thinner" products.

In light of what appears to be a strongly superior modality of treatment – i.e. treating the endothelium with the natural amino acids l-arginine and l-citruline to reduce hypertension and remove plaque, *versus* treating the blood with pharmaceuticals to inhibit platelet aggregation – it appears that an ethical issue arises as to whether further studies of platelet aggregation inhibitors are a medically acceptable course of study, when the alternative treatment with amino acids has been shown to not only reduce blood pressure dramatically, but to remove plaque and concomitant calcification buildup. While some might wish to consider double-blind comparative studies with one group involving patients receiving "blood thinners" and the other group receiving arginine therapy, it appears that the available literature weighs against even such studies on an ethical basis due to the existent strong showing of arginine therapy.

V. Conclusion

Two modalities of attacking the huge cardiovascular disease problem are reviewed by this article. One modality involves utilizing pharmaceutical "blood thinners" (platelet aggregation inhibitors) to ease the flow of blood through restrictions while marginally tending to lessen the clotting of the platelets. This modality is widely publicized in the pharmaceutical literature and on the public print and TV media ("Ask your doctor if Plavix is right for you."). The other modality involves opening of the blood vessels to more extensive blood flow. This includes gross mechanical means for extensive blockages by way of balloon angioplasty, coated-stints, and bypass. An additional method for this second modality has developed, namely the usage of l-arginine/l-citruline therapy which operates directly on the endothelium of even the smallest of vessels, enhancing blood flow to all organs. This emerging therapy garnered the Nobel Prize in medicine in 1999, eleven years ago, for the discovery of how l-arginine is converted into nitric oxide in relaxing the endothelium. It's now time to begin widely implementing that Nobel Prize winning work.

IV. Acknowledgment

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[11] High Desert Heart Institute, 12332 Hesperia Road, Victorville, California, www.heartinstitutehd.com; the referenced study involving 33 high-risk patients from the *Congestive Heart Failure Unit* has a pending publication. ProArgi9 (arginine/citruline plus supplements, as made by one commercial vendor) was involved in a study at the High Desert Heart Institute under the direction of Dr. Siva Arunasalam, M.D. A personal oral report to both authors show trends reported by Dr. Siva as having improved: 1. Blood pressure, including pulmonary artery pressure; 2. Cardiac markers, such as ejection fraction; 3. Cholesterol profiles – markedly; 4. 6-minute walk test; 5. Ankle brachial index; 6. Wound healing. Some individual cases showed dramatic improvement in the 90 days of the study

[12] She participated in a teleconference call, and reported that she had requested her husband do two things before he died – the taxes; and to tell her what music he wanted at his funeral.