## How to Avoid a Heart Attack: Putting it all Together

*"Poison is in everything, and no thing is without poison.*

*The dosage makes it either a poison or a remedy."*

—Philipus Aureolus Paracelsus

*"If you don't read the newspaper, you're uninformed.*

*If you do read the newspaper, you're misinformed."*

—Mark Twain

*To the Editor:*

We thank Dr Haffey for his response[1] to our critique[2] of his clinical review article, "How to Avoid a Heart Attack: Putting It All Together," [3] which appeared in the May 2009 supplement to *JAOA—The Journal of the American Osteopathic Association*. Unfortunately, Dr Haffey[1] did not address any of the specific points that we made in our letter.[2] Dosage, the actual substances used, how far along on the age-related continuum we can expect to see reversibility, and the confluence of multiple nutritional factors—each of which may be necessary but not sufficient alone—are all relevant to cardiovascular outcome studies and the specific points that we raised.

Omega-3 fatty acids in the diet have shown considerable power to favorably affect vascular and cardiac outcomes in elderly men with or without high risk for cardiovascular disease (CVD).[4-6] However, large doses of omega-3 fatty acids for short periods may produce adverse results.[7] Of course, there is no shortage of studies in which the use of insignificant amounts of omega-3 fatty acids (eg, 200 mg daily of eicosapentaenoic acid, 500 mg daily of docosahexaenoic acid) led to statistically nonsignificant results.[8] A literature review yielded a study from Japan (where fish intake is much higher than in most other countries) in which further supplementation with 1800 mg daily of eicosapentaenoic acid produced a statistically significant reduction in the number of cardiac events in patients with hypercholesterolemia who were using statins over just a 5-year period.[9]

**Vitamin Supplementation**

A recent study showed that vitamin D, in large annual doses, produced adverse effects that countered the beneficial effects it produced at lower doses.[10] In another recent study, researchers at Boston University Medical Center completed a randomized, blinded controlled clinical trial of vitamin $D_3$ supplementation involving 49 normotensive black youth. The investigators found that 2000 IU daily of vitamin $D_3$ decreased carotid-femoral pulse wave velocity (a measure of arterial stiffness), compared to an increase in carotid-femoral pulse wave velocity in the control group (400 IU daily vitamin $D_3$).[11] Furthermore, evidence from a prospective study of 41,504 individuals indicates that vitamin D deficiency may be associated with prevalent and incident CVD risk factors.[12]

The broad category of CVD has at least 3 age-related common pathways: oxidation, inflammation, and glycation. For the oxidation pathway, the use of antioxidants intuitively makes sense. Although antioxidant supplementation has been shown to reduce oxidative stress and inflammation,[13] should we really expect antioxidants to reverse cellular DNA damage in patients with coronary artery disease?[14]

The Third National Health and Nutrition Examination Survey (NHANES III), covering 1988 to 1994, revealed that 13% of the population in the United States was vitamin C deficient (<11.4 μmol/L), and the 2003-2004 NHANES revealed a prevalence of vitamin C deficiency of 7.1%.[15] Low levels of plasma vitamin C have been associated with progression of atherosclerosis, increased risk of acute myocardial infarction in women,[16] higher levels of low-density lipoprotein cholesterol and triglycerides in a meta-analysis of 13 randomized controlled trials,[17] and a higher rate of stroke among middle-aged men with hypertension.[18] It may seem amazing that vitamin C would disassociate the risk of stroke from the precondition of hypertension. Yet, when one reviews the vitamin C–dependant enzymatic reactions involving connective tissue repair—including blood vessels—this disassociation is not surprising at all.[19]

For water-soluble vitamin C, addition of 500 mg daily to the dietary intake of middle-aged to elderly Americans is probably not enough to produce statistically significant results. Most studies showing benefits of vitamin C have used at least 700 mg daily.[20] However, the bottom of the optimal range may increase with age and may be closer to Linus Pauling's estimate (ie, 2-10 g daily), which was based on the amount of vitamin C necessary to replicate the serum levels of animals that make their own vitamin C. The Linus Pauling Institute recommends vitamin C intake in the range of 200 to 400 mg daily.[21]

Direct arterial infusion of just 1 g of ascorbic acid has been found to improve arterial elasticity immediately in individuals who smoke cigarettes.[22] Single nucleotide polymorphisms that code for L-ascorbic acid cotransporter-1 may impair the access and utilization of vitamin C in a minority of patients.[23]

Pocobelli et al[24] evaluated data from 77,673 men and women, aged 50 to 76 years, who participated in the Vitamins and Lifestyle Study. Questionnaires collected from these participants between 2000 and 2002 provided information on their supplement use over the previous 10 years, and the cohort was followed for 5 years. During the follow-up period, 3577 deaths occurred. Participants whose vitamin C supplementation averaged at least 322 mg daily during the 10-year period had an 11% lower risk of dying during the 5-year follow-up period than did participants who did not use vitamin C. When Pocobelli et al[24] examined participant mortality by cause, multivitamin use of 6 to 7 days per week was associated with a 16% lower risk of death from CVD, and vitamin E use of more than 215 mg daily was associated with a 28% lower risk of death from CVD. Although this was "only" an epidemiologic study, the large numbers of participants and the extended length of time allowed small differences to manifest.

As reported in 2010, a prospective population-based study, begun in 1994 in the United Kingdom, evaluated plasma levels and oral intake of vitamin C during a 13-year period in 1054 participants older than 65 years in the British National Diet and Nutrition Survey.[25] By September 2008, 74% of the men and 62% of the women had died. The study results showed that increased plasma levels of vitamin C and increased dietary intake of vitamin C were both significantly associated with a reduction in all-cause mortality among participants. The results also revealed that increased dietary intake of vitamins C and E conferred a statistically significant protective effect against cancer.[25]

Another recent prospective population-based study, conducted at the Karolinska Institute in Sweden, examined multivitamin use in 31,671 women with no histories of CVD and 2262 women with histories of CVD between the ages of 49 and 83 years.[26] Use of multivitamins was found to be associated with reduced risk of myocardial infarction—with a multivariable-adjusted hazard ratio of 0.73. In addition, use of multivitamins for at least 5 years was found to be associated with a hazard ratio of 0.59 among women who were initially free from CVD. The authors concluded, "The use of multivitamins was inversely associated with [myocardial infarction], especially long-term use among women with no CVD."[26]

For fat-soluable vitamin E, the use of dl α-tocopherol is clearly inferior to the natural mixture of α-tocopherols, γ-tocopherols, and tocotrienols, because dl α-tocopherol competitively inhibits at least the γ-tocopherols.[27]

The B vitamins may be sufficient to reduce homocysteine levels, but is a homocysteine level of 11 μmol/L really low enough to produce a beneficial effect on endothelial inflammation or already-present atherosIcerosis?[28]

As many as 1 in 10 individuals have a defective thermolabile variant of 5,10-methylenetetrahydrofolate reductase that is associated with mild hyperhomocysteinemia, vascular disease, and neural tube birth defects.[29] These individuals may require 5-methyltetrahydrofolate (5-10 mg daily) or large doses of trimethylglycine or betaine[30] to reduce homocysteine levels to the range of 7 to 8 μmol/L.[31] Folic acid used as part of primary prevention has been shown to reduce the risk of stroke in patients.[32]

Considering the obesity and diabetes mellitus epidemic of the previous 15 years, a rising incidence of glycation is another probable confounding factor. In the management of prediabetes with metformin, it is probably wise to check patients for vitamin $B_{12}$ deficiency on a yearly basis.[33]

**Pharmaceutical Industry Bias**

Crucial to the question of what studies we are to accept as valid is the issue of bias, including bias in the context of the US medical system and specialty bias that might contribute to Dr Haffey's[1] certainty that no published evidence exists to support the use of vitamin supplements to improve cardiovascular health. Considering the existence of such bias, are we really being paranoid in picking apart the evidentiary studies discussed by Dr Haffey[3] and in finding fre-

quent structural deficiencies in the way these studies applied the scientific method?

In the August 2010 *JAOA*, Gary P. MacDonald, DO,[34] summarized the impact of the recent decision by the US Food and Drug Administration (FDA), based on the JUPITER study,[35] to approve use of a particular statin drug for CVD risk reduction in widely expanded populations. Dr MacDonald[34] noted the following:

> There is no doubt that results of JUPITER are significant—both statistically and clinically. However, the manner in which these results were sold to clinicians, the FDA, and the public were deceptive—damaging the credibility of the FDA and AstraZeneca. ... Considering the misguided logic behind the FDA's decision to expand rosuvastatin's use, the question remains: who are the primary beneficiaries of this decision—patients or the pharmaceutical industry?

The FDA did "step up to the plate" with its independent review of the RECORD trial[36] by Marciniak.[37] The independent review provided empirical estimates of the potential bias associated with the open-label design of the industry-influenced RECORD trial,[36] in which investigators were aware of treatment assignment. Among 549 case-report forms in the RECORD trial,[36] the prevalence of such problem cases was higher in the intervention group (16.2%) than in the control group (9.2%).[37]

A September 2009 *New York Times* article reported on a study in *JAMA: The Journal of the American Medical Association* that revealed that of 630 articles published in major medical journals in 2008, 7.8% had ghostwriters.[38] The *JAMA* authors' concern was that "the work of industry-sponsored writers has the potential to introduce bias, affecting treatment decisions by doctors and, ultimately, patient care."[38] Journal authors responding to a survey reported a 10.9% rate of ghostwriting in the *New England Journal of Medicine*, a 7.9% rate in *JAMA*, a 7.6% rate in *PLoS Medicine*, a 4.9% rate in the *Annals of Internal Medicine*, and a 2% rate in *Nature Medicine*.[39] Cynthia E. Dunbar, MD, editor-in-chief of *Blood*, the journal of the American Society of Hematology, reported uncovering 3 ghostwritten manuscripts in which a pharmaceutical company employee should have been listed as an author.[40]

**Bias for Interventional Procedures**

Now we turn to a more tacit institutional and specialty bias that exists in the US medical system in favor of interventional procedure-oriented medicine and against primary prevention. Let us consider the radiology department. As early as 1970, John Gofman, MD, PhD, expressed concern in *The Lancet* that the amount of radiation capable of doubling the risk of breast cancer is very low.[41] In 2002, the Life Extension Foundation warned of the dangers of computed tomography (CT) and electron-beam radiation, noting that "a chest CT is equivalent to 400 chest x-rays, or 3.6 years of background radiation."[42] In 2007, Fred Mettler, MD, reported at the annual meeting of the National Council on Radiation Protection and Measurements that patients' radiation exposure had increased more than 750% in the previous 25 years.[43] The use of CT scanning in the United States increased at least 10% per year during that 25-year period, climbing from 3 million scans in 1980 to 60 million scans in 2005.[43] Dr Mettler was quoted as saying, "I don't think radiologists have a clue about how much this has grown."[43]

In 1995, the *American Journal of Roentgenology*, reflecting a different bias, reported that lower doses of radiation were sufficient for good CT image quality.[44] In 2001, editorials in the same journal criticized the excessive use of radiation[45] and asserted that "radiologists have been unaware or indifferent to the high dose of radiation dosage with CT scans."[46]

The American College of Radiology acknowledged in 2007 that the expanded use of medical imaging would result in an increase in cancer cases, although the organization could not quantitate this increase.[47] However, a study by the National Cancer Institute reported that CT scanning performed during 2007 alone would eventually cause 29,000 new cases of cancer and 15,000 deaths.[48] An article published in *JAMA* in 2007 estimated the lifetime increased risk of cancer from a single 64-slice CT coronary angiogram as 1 in 466 for a 60-year-old woman.[49] Radiation from annual full-body CT screening examinations between ages 45 and 75 years has been estimated to result in a lifetime incidence of radiation-induced fatal cancer in 1 of 50 screened individuals.[50] This latter estimate assumes no additional lifetime radiation exposures.

So, do the biases of physicists, radiologists, and the owners of full-body or cardiac calcium-score CT scanners align together in a uniform science-based perspective dedicated to the pursuit of truth—or do their recommendations and conclusions tend to reflect their individual biases?

It is curious that Linus Pauling's shadow[21] should cross this discussion of willful nonengagement regarding the dangers of CT radiation, because Pauling's second Nobel Prize, for peace, was related to his research on the health effects of radiation from atmospheric atomic bomb testing in the 1950s.

**Remember Occam's Razor**

The medical profession today is drowning in data. A necessary survival technique is to preselect the sources of one's information, beginning with attention to the biases of any source. A medical journal will have its own biases, as will each author, specialty, research institution, and funding corporation. Adapting the rule of Occam's razor, the simplest guide is to follow the economic interests of the various parties. If all these biases line up, more or less, along one vector, you are then in a better position to evaluate the usefulness of the reported

"facts" and data.

To evaluate a particular journal article, we should look at the provenance of the article (indicative of its inherent biases and eventual economic impact), the coherency of the scientific method, the biological plausibility of reported results, and the practical usefulness of the results. We all have biases—they are essential parts of who we are. The economic biases of institutions, journals, and authors tend to be stable over time. Thus, conducting a "pre-triage" of reading material is not as daunting as it may seem.

We will leave it to Dr Haffey[1,3] to assess bias in the vascular/cardiology journals, which are more familiar terrain to him than to us. We would expect that he would find a bias for the economic interests of cardiologists, with a preference for interventional procedures over primary prevention.

### Meeting the Challenge

The present letter has focused on primary prevention studies. We plan to present evidence on vitamin/nutritional interventions for secondary CVD prevention in a subsequent letter.

Dr Haffey's challenge[1] to produce studies of sufficient size and clarity to demonstrate the benefits of antioxidant orthomolecular treatment on primary prevention of CVD is a fair one. Part of this challenge is not to spend vast amounts of time and money to produce studies that fail to confirm the biological plausibility of a long trail of epidemiologic studies, prospective cohort studies, and small double-blind studies. Prospective, randomized open trials with blinded endpoint assessment may be the most efficacious type of study for the next decade. Counterintuitive findings in studies must meet and pass higher levels of scrutiny to overcome perceived levels of economic or specialty bias.

The obvious public health problems of cigarette smoking, obesity, and lack of exercise remain to be solved on a societal level. The reduction of trans fatty acids in the food chain is one recent success. It will take time, thought, and considerable amounts of money to meet Dr Haffey's challenge.[1] We hope that will come to pass during our lifetimes.

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Dr Haffey was shown this letter and declined to comment.