Health care providers' knowledge base and recommendations regarding the use of vitamin E for cardiovascular health

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Health Care Providers’ Knowledge Base and Recommendations Regarding the Use of Vitamin E for Cardiovascular Health

Submitted by

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In partial fulfillment of the requirements for the degree of Master of Science in Biomedical Sciences

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Health Care Providers’ Knowledge Base and Recommendations Regarding the Use of Vitamin E for Cardiovascular Health

Scholarly Project
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Dedications

I would like to thank my husband, Michael Moore, and my parents Audrey and Cheryl Murphy, for their endless love and support throughout PA school.
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Table of Contents

Dedications ........................................................................................................... ii
Acknowledgements .............................................................................................. iii
List of Figures........................................................................................................ v
Literature Review ................................................................................................. 1
Methods ............................................................................................................... 20
Results ............................................................................................................... 21
Discussion ......................................................................................................... 25
References ........................................................................................................ 28
Figures ............................................................................................................. 31
Abstract ........................................................................................................... 38
Figures

Figure 1. Distribution of participants by specialty and type of health care provider .......................................................... 31

Figure 2. Number and distribution of participants by specialty and years of practice................................................................................................................32

Figure 3. The Nurse’s Health Study (1993), an eight year study that involved more than 87,000 female nurses demonstrated that................................. 33

Figure 4. The Heart Protection (2002) demonstrated that vitamin E supplementation..................................................................................................34

Figure 5. Mechanism(s) of action in which vitamin E has been thought to work on the cardiovascular system.................................................................35

Figure 6. Recommendations by specialty..........................................................36

Figure 7. Recommendations by years of practice ..............................................37
Introduction

Cardiovascular disease is the number one killer of both men and women in the United States. Therefore, there is significant interest in researching primary and secondary prevention of cardiovascular disease, and means to decrease its attendant morbidity and mortality. Many studies have indicated that antioxidants such as vitamins A, C, E, and beta-carotene, may help to protect the cells in our bodies from free radicals, and help to prevent cardiovascular disease ("Office of Dietary Supplements", 2004). Free radicals can cause cellular damage, which may contribute to cardiovascular disease ("Office of Dietary Supplements", 2004). Antioxidants have multiple mechanisms of action. However, research has indicated that lipid-soluble antioxidants are likely to be very important in preventing the peroxidation of LDL-cholesterol (Marchioli, 1999). This could be very important in prevention of atherosclerosis. The primary lipid-soluble antioxidant is vitamin E. Epidemiologic and prospective studies have given evidence of an inverse relationship between vitamin E supplementation and cardiovascular disease, specifically coronary artery disease (Diaz, Frei, Vita, & Keaney, 1997).

On August 7, 1997, The New England Journal of Medicine published an article stating, “There is now clear evidence, both epidemiological and from random clinical trials, that vitamin E, at or above a certain daily intake, can dramatically reduce the risk of heart disease.” (Jiang, Christen, Shigenaga, & Ames, 2001). There have been a number of articles supporting this theory including the Nurses Health Study (Stampfer, et al, 1993), the Health Professionals Follow-up Study (Rimm, et al, 1993) the Cambridge Heart Anti-Oxidant Study (CHAOS) (Stephens, et al, 1996), and also the
Iowa Women’s Health Study (Kushi, et al, 1996). However, there has also been much research that speaks against these studies and suggests that vitamin E has no effect on preventing cardiovascular disease. Some randomized clinical trials (“Office of Dietary Supplements”, 2004) have questioned the ability of vitamin E to decrease the incidence of cardiovascular disease and have failed to consistently show the benefits of vitamin E that have been indicated by epidemiologic and prospective studies (Friedrich, 2004).

Vitamin E is a generic term for compounds containing a 6-chromanol ring, an isoprenoid side chain, and the biologic activity of alpha-tocopherol (Beers and Berkow, 2004). There are eight different forms of vitamin E. Vitamin E is a potent antioxidant. Of the 8 isoforms, alpha-tocopherol possesses the greatest antioxidant activity within the human body (“Office of Dietary Supplements”, 2004). Because humans do not synthesize vitamin E, it is primarily acquired through diet. The most prevalent form of vitamin E in the US diet is gamma-tocopherol (Jiang, Christen, Shigenaga, & Ames, 2001). However, plasma levels of gamma-tocopherol have been reported to be 10 times lower than that of alpha-tocopherol (Friedrich, 2004). Vitamin E can be found in a variety of foods, though the main dietary sources are vegetable oils, nuts, and green leafy vegetables. Ester forms of tocoopherol such as alpha-tocopherol acetate and synthetic isomers of alpha-tocopherol are the forms found in vitamin E supplements. The ester forms of tocopherol are more suitable for vitamin E supplements due to less susceptibility to oxidation compared to the free base forms (Chow, 2004).

For men and women over the age of 19, the Recommended Dietary Allowance (RDA) of vitamin E is 15 mg or 22 IU. This recommendation increases with lactation to 19 mg or 28 IU. Recommended Dietary Allowance is defined as the average daily
intake sufficient to meet the nutrient requirements of nearly all (approximately 97%) of healthy people in a particular stage of life and sex (“Office of Dietary Supplements”, 2004).

Vitamin E deficiency is rare (“Office of Dietary Supplements”, 2004). A possible explanation to the low incidence of this particular deficiency is the presence of tocopherol regenerating systems (Chow, 2004). A specific example of a regenerating system involves vitamin C. Since vitamin C is also a potent antioxidant, it also possesses the ability to revert the tocopherol chromanoxy radical back to alpha-tocopherol. A deficiency of vitamin E, though, can have many detrimental effects. Included are mild hemolytic anemia associated with increased erythrocyte hemolysis (Beers and Berkow, 2004) and neurological problems arising from poor nerve conduction (“Office of Dietary Supplements”, 2004). These may present in patients with poor fat absorption possibly resulting from a genetic abnormality called abetalipoproteinemia. Patients with cystic fibrosis, Crohn’s disease, and those who have had part or all of their stomach removed have an increased risk of developing a vitamin E deficiency. Patients with any of these conditions may require vitamin E supplementation (“Office of Dietary Supplements”, 2004). Another group of patients that may also be at risk for vitamin E deficiency are premature/low birth weight infants who may possess the inability to properly absorb fat. This inability can disrupt the making of myelin needed in the central nervous system (Williams, 1997). Vitamin E deficiency may also lead to increased platelet aggregation, which may be associated with mechanisms such as inhibition of protein kinases and membrane stabilization (Asplund, 2002).
Although vitamin E deficiency is rare, a study performed by Maras (2004) showed that only 8.0% of men and 2.4% of women in the United States met the new Estimated Average Requirements (EARs) of vitamin E from food alone. The EAR is the estimated nutrient intake required to maintain a physiological action in half the people in a given age and sex group. It is used when setting goals for the average intake of a population.

**Risks Associated with Vitamin E Supplementation**

A review by Kappus (1992) was performed to establish the safety of vitamin E supplements. In this review, there were not any significant effects of vitamin E on general health, body weight, levels of body proteins, lipid levels, liver or kidney function, thyroid hormones, amount or kinds of blood cells, and bleeding time found over a 4-month period of time. However, long-term safety has not been tested. Some adverse effects of vitamin E that have occasionally been reported are muscle weakness, fatigue, nausea, and diarrhea. These effects may occur in those taking 800-3200 mg of vitamin E per day (Beers and Berkow, 2004). Headache, flatulence, heart palpitations, and fainting have also been reported (Hay, 1998).

Vitamin E can act as an anticoagulant thereby increasing the risk of bleeding abnormalities. The Institute of Medicine has set an upper tolerable intake level at 1,000 mg (“Office of Dietary Supplements”, 2004). A significant increase in risk for fatal/nonfatal intracerebral and subarachnoid hemorrhage was found in subjects taking vitamin E, possibly from its antiplatelet properties. Hay (1998) recommends that people taking anticoagulant medications such as warfarin should avoid high doses of vitamin E.
because of the existent anticoagulant effects of vitamin E. There was also a small study (n=286) published in 1996 that found an increased risk of cardiovascular death in people with abnormally high plasma levels of vitamin E (Asplund, 2002).

**Vitamin E Chemistry**

Vitamin E occurs in eight forms. This includes four tocopherol isomers and 4 tocotrienol isomers. The differing tocopherols are diversified due to the number of methyl groups at the 5- and 7- positions of the chromanol ring. All forms of the vitamin E molecule are potent membrane-soluble chemical entities. They are all also potent antioxidants. The chain-breaking antioxidant activity of the tocopherols is related to their inherent ability to donate electrons to free radicals, such as lipid radicals. A free radical is an atom or molecule, which possesses a free, reactive electron. Gamma-tocopherol, for instance, lacks one of the electron-donating methyl groups on the chromanol ring which alpha-tocopherol contains. This explains why alpha-tocopherol is a slightly more potent inhibitor of lipid peroxidation. Gamma-tocopherol, however, containing the unsubstituted C-5 position, appears to have an increased ability to trap lipophilic electrophiles (lipid soluble ions, molecules, or atoms possessing the ability to donate an electron pair) such as reactive nitrogen oxide species (RNOS). Excess generation of RNOS has been associated with chronic inflammatory diseases including some cardiovascular diseases (Jiang, et al, 2001).

As with many other molecules, vitamin E has a unique mechanism of absorption from the intestines. All isomeric forms of vitamin E are equally absorbed (Munteanu, Zingg, & Azzi, 2004). Unlike other vitamins, such as vitamins A and D, no specific
plasma proteins exist to aide in absorption by transporting vitamin E across the intestinal wall (Kayden and Traber, 1993). Vitamin E must be emulsified and solubilized before it can be absorbed across the epithelial cell lining. This occurs through the process of mechanical forces in the upper gastrointestinal tract. These forces break up lipids into small globules and mix them with bile salts to facilitate solubilization. This allows vitamin E to be transported by passive diffusion across the brush border (Dutta and Dutta, 2003), mainly occurring in the proximal portion (duodenum) of the intestine (Munteanu, et al, 2004). Studies suggest that between 70-90% of vitamin E ingested is absorbed (Dutta and Dutta, 2003) (Kayden and Traber, 2003). However, absorption depends on the amount of vitamin E given and the length of time allowed for absorption. Additionally, vitamin E absorption may differ depending on other dietary lipids present in the gastrointestinal tract. Absorption of vitamin E appears to be enhanced in the presence of medium chain triglycerides. Reduction of vitamin E absorption possibly occurs in the presence of long chain polyunsaturated fatty acids (PUFAs) and retinoic acid. Conversely, some studies have shown that these molecules may actually increase vitamin E absorption (Dutta and Dutta, 2003).

Once absorbed, some of the vitamin E is taken up by the liver where it is stored in parenchymal cells (Chow, 2004). The vitamin E that is not stored is packed into chylomicrons and subsequently secreted into the lymphatic system where it gains access to the bloodstream. In humans, the major carriers of vitamin E are high density lipoproteins (HDL) and low density lipoproteins (LDL). However, LDL is a more prominent carrier in men and HDL is a more prominent carrier in women (Dutta and Dutta, 2003). Once in the bloodstream, endothelial lipoprotein lipase hydrolyzes the
chylomicrons, releasing part of the vitamin E into the plasma (Munteanu, et al, 2004). Lipoprotein lipase is also expressed in muscle and adipose tissues, which are thought to transport vitamin E in a comparable manner (Dutta and Dutta, 2003).

Plasma levels of vitamin E are found to be the highest in the form of alpha-tocopherol. Subsequent to chylomicron-bound vitamin E distribution to peripheral tissue, resulting chylomicron remnants are taken up by the liver, where alpha-tocopherol is preferentially reincorporated into nascent very-low density lipoproteins (VLDL) by tocopherol transferase. This enables further distribution of alpha-tocopherol throughout the body. This is likely due to the increased affinity of tocopherol transfer protein to bind alpha-tocopherol preferentially over the other isomers (Jiang, et al, 2001). Other vitamin E forms are subject to a cytochrome P450 dependant oxidative degradation to a hydrophilic form and subsequent elimination from the body. As mentioned previously, alpha-tocopherol is also the form of vitamin E that is found in the highest concentrations in the tissues (Kayden and Traber, 1993).

**Vitamin E and the Formation of Atherosclerosis**

Atherosclerosis, characterized by fibro-fatty deposits as plaques protruding or obstructing the vascular lumen, contributes to approximately half of all deaths in the Western world (Schoen and Cotran, 2002). The clinical significance of atherosclerosis lies in the possible onset of conditions such as myocardial infarction, cerebral infarction, aortic aneurysms, peripheral vascular diseases, and other ischemic injuries. Atherosclerosis is exacerbated by risk factors such as high blood pressure and
hypercholesterolemia, leading to an increased propensity for the previously mentioned conditions.

Studies have supported the association of oxidative stress and the formation of atherosclerosis (Chen and Mehta, 2004). Oxidative stress implies the oxidative modification of LDL, a lipoprotein present in atherosclerotic plaques (Kushi, 1996). Many studies suggest that this oxidative modification occurs through reactive oxygen species (ROS). Examples of ROS include hydrogen peroxide, the hypochlorite ion, and the hydroxyl radical. These ROS are constantly being generated by means of normal cellular function (Chen and Mehta, 2004).

The formation of atherosclerotic plaques is initiated when accumulation of LDL into the sub-endothelial space occurs followed by subsequent oxidation of the lipoprotein (Schoen and Cotran, 2002). Oxidized LDL activates endothelial cells within the arterial wall, resulting in the adhesion of leukocytes and monocytes. This also causes the expression of molecules that aid in the adhesion of monocytes and macrophages (Chen and Mehta, 2004). Accumulation of these cells results in further oxidation of LDL causing it to acquire an increasingly negative charge. The negatively charged, oxidized lipids serve as chemoattractants for scavenger receptors on macrophages. Once macrophages recognize the LDL, it is phagocytosed, now forming a foam cell. Because of the buildup of oxidized LDL, macrophages and foam cells become trapped within the vascular wall. This increases the onset of atherosclerosis by causing neighboring cells to release lipids and lysosomal enzymes that supplement the progression (Dutta and Dutta, 2003).
There are other means by which atherosclerosis is thought to be promoted. One mechanism is the proliferation of smooth muscle cells. This occurs as a result of ROS that stimulate expression of fibroblast growth factor (FGF), insulin-like growth factor (IGF), insulin-like growth factor receptor (IGF-R), and epidermal growth factor (EGF). Once these factors are produced, they subsequently increase smooth muscle cell proliferation thereby decreasing the lumen cross-sectional area (Schoen and Cotran, 2002). Another mechanism involves increased adhesion of monocytes to endothelial cells. This may occur through increased concentrations of glucose and/or increased expression of intercellular and vascular adhesion molecules, both of which are significantly increased in the presence of ROS (Chen and Mehta, 2004).

Antioxidant systems are thought to exist in order to help defend against oxidative stress. In addition to vitamin E, vitamin C and beta-carotene are also antioxidants. Each molecule has its own mechanism of combating oxidative stress based upon solubility characteristics. Vitamin E and beta-carotene are lipid soluble, whereas vitamin C is water soluble. Lipid-soluble molecules causing oxidative damage are combated by lipid-soluble antioxidants and water-soluble molecules causing oxidative damage are combated by water-soluble antioxidants. Studies show that lipid-soluble antioxidants are likely to be paramount in the prevention of peroxidation of LDL (Marchioli, 1999). Since vitamin E is a potent lipid-soluble antioxidant, it should theoretically limit the development of atherosclerotic plaques. According to Dutta (2003), vitamin E has been shown to decrease the liberation of pro-inflammatory cytokines and reduce adhesion of monocytes. Furthermore, studies performed in vitro and in vivo revealed that oxidation of LDL is decreased by alpha-tocopherol. Similarly,
another study by Munteanu, et al, (2004) showed that administration of 1200 IU/day of alpha-tocopherol for three months inhibited interleukin-1β, a molecule that promotes adhesion of monocytes to endothelium and cholesterol esterification in macrophages. Vitamin E is also thought to inhibit smooth muscle cell proliferation and platelet aggregation by inhibiting protein kinase C activity (Jiang, et al, 2001) (Munteanu, et al, 2004). Many studies have been dedicated to the theory of the role of vitamin E in the reduction of atherosclerosis and determination of whether or not these actions may aid in prevention of cardiovascular disease.

**Studies Suggesting Vitamin E is Cardioprotective**

One of the largest initial prospective studies was the Nurses’ Health Study (1980-1988). Over 87,000 female nurses ages 34 to 59 were surveyed regarding their consumption of many different nutrients, including vitamin E supplementation. With a 97 percent complete follow-up over eight years, the number of major coronary disease cases was documented. Short-term periods of less than 2 years of vitamin E supplementation appeared to have an insignificant advantage. However, women who took a multi-vitamin containing vitamin E or a vitamin E supplement for more than two years showed a decrease in major coronary disease cases of about 40 percent versus women who did not take supplements. Vitamin E content in multi-vitamins is approximately 30 IU as compared to 100 IU found in supplements containing only vitamin E. Furthermore, this study exhibits a superiority of vitamin E supplementation to a high vitamin E-containing diet (median of 7.7 IU/day) in decreasing the risk of major
coronary disease. This was true even after the adjustment for coronary risk factors and the intake of other dietary antioxidants (Stampfer, et al, 1993).

A similar prospective study, the Health Professionals Follow-up Study, was conducted in 1986 in nearly 40,000 male health professionals ages 40 to 75. None of these men had been diagnosed with coronary heart disease, diabetes, or hypercholesterolemia. They, too, were questioned about their intake of nutrients and dietary supplements including intake of vitamin C, beta-carotene, and vitamin E. They were also asked questions regarding their medical history. Using fatal coronary disease, nonfatal myocardial infarction, coronary-artery bypass grafting, and percutaneous transluminal coronary angioplasty as end points, a modest decrease in coronary disease was found in men taking at least 100 IU daily of supplemental vitamin E for at least two years. The greatest risk reduction was observed with intakes of 100 to 249 IU daily. The relative risk of coronary disease in men in this study who reported at least 10 years of vitamin E supplementation was 0.65 compared to men who did not take vitamin E supplements. There was no further decrease of risk with doses larger than 249 IU/day. Furthermore, high dietary consumption of vitamin E was also found to decrease the risk of coronary disease for the highest quintile of vitamin E intake compared to the lowest quintile of vitamin E intake. The relative risk was found to be 0.79. This data is consistent with the theory that vitamin E is associated with a decreased risk of coronary disease (Rimm, et al, 1993).

In contrast to the Health Professionals Follow-up Study, the Cambridge Heart Antioxidant Study (CHAOS) studied the effects of alpha-tocopherol on patients with existing coronary heart disease. The endpoints of this study were non-fatal myocardial
infarction alone and a combination of non-fatal myocardial infarction and cardiovascular death. This was a double-blinded, placebo-controlled study with stratified randomization of 2,002 patients that were followed for about 2 years. One-thousand-thirty-five of the patients were assigned either 800 IU or 400 IU alpha-tocopherol (from natural sources) capsules daily. Treatment capsules contained alpha-tocopherol from natural sources. The other 967 patients receive a placebo capsule identical to the alpha-tocopherol capsule. Overall, the alpha-tocopherol group had a significantly decreased risk of subsequent nonfatal myocardial infarction and also a decreased combined endpoint of nonfatal myocardial infarction and cardiovascular death (Vivekananthan, Penn, Sapp, Hsu, & Topol, 2003) after a delay of 200 days compared to the placebo group. The risk of primary endpoint, which was set as a combination of death and nonfatal myocardial infarction was reduced by 47 percent. The trial concluded alpha-tocopherol considerably decreased the incidence of nonfatal myocardial infarction after 1 year of treatment in patients with proven coronary heart disease. The CHAOS study also found that total mortality was slightly higher in the alpha-tocopherol group over the placebo group. However, this increase was not statistically significant (Stephens, et al, 1996).

The Iowa Women’s Health Study was a prospective cohort study of postmenopausal women. A total of 34,486 eligible women were included in the final data. Ineligible women included patients who suffered from angina, heart disease or had previously incurred a myocardial infarction. These women were questioned about their food intake and also their use of supplemental vitamins. This study revealed that there was an inverse relationship in coronary heart disease with the intake of vitamin E
from food. Women with the highest quintile of vitamin E intake from food (≥35.59 IU/day) had a significantly lower risk of coronary heart disease than women in the lowest quintile of vitamin E intake (<5.68 IU/day). The risk of death from coronary heart disease was also inversely correlated with vitamin E intake. Conversely, this association was not observed with the intake of vitamin E supplements in this study (Kushi, et al, 1996).

These supporting studies demonstrate an indirect relationship between vitamin E consumption and cardiovascular events. The majority of studies supporting high intake of dietary vitamin E or the use of vitamin E supplements for cardiovascular benefits have come from observational and cohort studies.

**Studies Suggesting Vitamin E is Not Cardioprotective**

Though the aforementioned studies indicate an indirect relationship between consumption of vitamin E and cardiovascular events, overall results of published trials have been analyzed and the overall results do not indicate significant cardioprotective effects (Clarke and Armitage, 2002). Many randomized clinical trials have been performed to further investigate this relationship. However, these studies raise question to the actual benefits of vitamin E in the prevention of cardiovascular events, suggesting that some of the benefits from observational studies may have been overestimated (Gaziano, 1996).

In 1999 the results from the Gruppo Italiano per to Studio della Soprawivenza nell'Infarto miocardico (GISSI-Prevenzione Investigators) trial were published. This study was an experimental study designed to look at the benefits of consuming n-3
polyunsaturated fatty acids (PUFA) and vitamin E after myocardial infarction. All patients in this trial had survived myocardial infarctions that occurred less than 3 months prior to the trial. A primary combined endpoint of death, non-fatal MI, and stroke was set for this study. Between October of 1993 and September of 1995, 11,324 patients were followed. Two thousand eight hundred thirty six patients were randomly assigned to take supplements of n-3 PUFA (1 g). Vitamin E was given to 2,830 patients in the form of one capsule of synthetic alpha-tocopherol. Both n-3 PUFA and vitamin E were given to another 2,830 patients. A control group of 2,828 patients without supplements was also followed. At the end of the 3.5 years of study, there was no statistically significant difference found between the patients receiving vitamin E and those taking placebos. There was also no benefit apparent in patients receiving n-3 PUFA plus vitamin E compared to that of n-3 PUFA alone or vitamin E alone. Even when data was further analyzed by a four-way analysis, no benefit was shown in the vitamin E supplement group over controls (GISSI-Prevenzione Investigators, 1999).

The Primary Prevention Project (Collaborative Group of the Primary Prevention Project, 2001) was another study that included investigation of vitamin E supplementation in people with cardiovascular risk. This study was performed in order to explore the efficacy of antiplatelets and antioxidants in primary prevention of cardiovascular events in people with one or more major cardiac risk factors. It sought to determine the benefits of the use of aspirin and vitamin E in the reduction of cardiovascular events. Patients were randomly assigned to receive 100 mg of aspirin or no treatment, and 300 mg synthetic vitamin E or no treatment. As with the GISSI-Prevenzione trial, the primary combined efficacy endpoint was the combination of
cardiovascular death, non-fatal MI, and non-fatal stroke. After 3.6 years, the trial was prematurely stopped on ethical basis that new evidence supporting aspirin in the prevention of cardiovascular death. The results of this study also concluded beneficial results regarding the use of aspirin on the combined endpoint. There was no benefit shown for the use of vitamin E in regard to the primary endpoint. However, there did seem to be a statistically significant decrease \( (p=0.043) \) in the risk of peripheral artery disease with the use of vitamin E (The Primary Prevention Project Study Group, 2001).

Another study performed that did not support the use of vitamin E for cardiovascular benefits was the Heart Protection Study, which included 20,536 UK adults ages 40-80 with coronary disease, other occlusive arterial disease, or diabetes. The subjects were randomly selected to receive supplementation with 600 mg vitamin E, 250 mg vitamin C, and 20 mg β-carotene daily or matching placebo. This study continued for 5 years and was analyzed by a 2 X 2 factorial design. Although the results indicated that antioxidant supplementation was safe, no significant benefits of antioxidant supplementation were observed. This is despite the considerably large increase in plasma levels of all the studied vitamins. The results of the Heart Protection study, “effectively rule out any substantial reductions- or, indeed, increases- in heart attacks, strokes, cancers, or other major adverse events during 5 years of use of these vitamins.” (Heart Protection Collaborative Group, 2002).

The outcomes of the previously mentioned studies do not rule out a mechanistic role of oxidative processes in the pathogenesis of human atherosclerosis. Furthermore, continued research on \textit{in vivo} oxidative mechanisms and enhanced biochemical methods in which to evaluate candidate antioxidant compounds is required. The
discrepancy in the reported clinical data and the hypothesized theoretical benefits could be a result of limited exposure. Perhaps the key to beneficial antioxidant supplementation lies in a lifelong consumption of an antioxidant-rich diet (Kris-Etherton, et al, 2004).

Providers’ Attitudes and Practices Regarding Supplement Usage

Few studies have been conducted regarding the attitudes and practices of physicians and other health care providers on herbs, dietary supplements, and other forms of complementary therapies (those used to supplement conventional treatment) (Kemper, et al, 2003) (Milden and Stokols, 2004). Kemper et al (2003) performed a cross-sectional survey of clinicians including 111 physicians, 30 advanced practice nurses, 46 pharmacists, and 350 dietitians prior to participation in an internet-based educational program about the use of herbs and dietary supplements in the practice of medicine. The clinicians were questioned regarding their knowledge, attitudes, and practices related to herbs and dietary supplements. The survey was divided into four categories: knowledge, confidence, professional practices and personal behavior, and communication practices.

What they found was that registered dietitians were significantly more knowledgeable about this subject than other clinicians. However, even their average score was less than 60 percent. The average knowledge score was 10 out of 20 multiple-choice questions, with a key lack of familiarity regarding adverse effects of herbs and supplements. The average confidence score was 4 out of 10. Confidence scores were obtained from 10 questions that were in the Likert-type format. Each item
was converted to confident or not confident. Strongly agree and agree answers were regarded as confident. Neutral, disagree, and strongly disagree answers were regarded as not confident. The average communication score was 1.4 out of 4 positive responses to statements. The majority of participants (66%) even reported receiving professional training on the subject of herbs and dietary supplements. Additionally, multivitamins were reported as being the most frequently used form of dietary supplements (59%), with vitamin E use being reported at 36%. They also found that clinicians do not routinely discuss herbs and dietary supplements with their patients, nor do they record brands, dosages, or effects of these in the patient’s charts.

Likewise, Milden and Stokols (2004) also found that physicians do not feel confident in their ability to discuss complementary and alternative medicine (CAM) with patients. Through their survey-based study, which was sent randomly to 200 California MDs, they found that 61% of physicians “do not feel sufficiently knowledgeable about CAM safety or efficacy”. However, even with 81% of physicians reporting that they would like to know more about CAM, 80% related that they would prefer to only use conventional biomedical treatments.

Besides lack of knowledge regarding the use of dietary supplements for prevention and treatment therapies, lack of research in this area is another possible reason for discouraging clinicians from using these regimens. Mark H. Ebell, M.D. (2005) stated, “Physicians should consider two key factors when weighing new information about treatment: the quality of evidence supporting its use and whether the evidence focuses on patient-oriented outcomes or disease-oriented outcomes.” He also points out that physicians use different levels of evidence when assuming new
treatment practices. For example, some physicians may begin utilizing new treatments when only case series evaluation has been performed. However, other physicians may only integrate a new treatment into their practice after randomized controlled trials have proven its efficacy. Still, others initiate treatments based on laboratory results and their own understanding of physiology and biochemistry.

Vitamin E exemplifies one of the treatments that were initiated by physicians after *in vitro* evidence showed that it prevents oxidation of LDL and platelet adhesion, and subsequently inferred that it may decrease the risk of cardiovascular disease. According to Dr. Ebell, even after randomized controlled trials demonstrated no cardioprotective benefit of vitamin E, “millions of physicians continued to recommend this drug in 20 times the recommended daily allowance to their patients.” In fact, an article released in 2004 from the Journal of the American Dietetic Association states that at least 400 IU of vitamin E is taken by 1 out of 5 adults greater than 55 years of age. They also report that from 1987 to 1992 to 2000, the use of many dietary supplements was increased. The largest increase was in the use of vitamin E supplements, and that females were more likely than males to use vitamin E (Millen, Dodd, and Subar, 2004).

Many physicians continue to prescribe vitamin E supplements to patients for cardiovascular health (Ebell, 2005). In fact, a survey results released in 2001 by the Council for Responsible Nutrition found that out of 300 cardiologists, 75% of them recommend vitamin E to their patients at least some of the time. Thirty-seven percent of the cardiologists stated that they recommend vitamin E “often” or “usually”. The
dose most often recommended was 400 IU daily. Also, 48% of the cardiologists surveyed stated that they themselves take vitamin E supplements.

Conversely, an American Heart Association Science Advisory was released in 2004 stating that current scientific data does not provide substantial evidence to justify everyday utilization of antioxidant supplements, including vitamin E, for the prevention and treatment of cardiovascular disease. The American College of Cardiology/American Heart Association 2002 Guideline Update for the management of patients with chronic stable angina concludes the same recommendation. Furthermore, the “Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women” concludes that antioxidant supplements should not be used to prevent cardiovascular disease, pending the results of ongoing trials. However, the American Heart Association does recommend that further research is needed to solve the question of whether or not the oxidative modification hypothesis is important in the formation of atherosclerosis in humans.

In regard to present day counseling, the American Heart Association recommends physicians to focus on changes in patient diet by increasing food sources high in antioxidants and other cardioprotective nutrients such as fruits, vegetables, whole grains, and nuts instead of supplements to decrease the risk of cardiovascular disease.
Methods

Seventy-two surveys with cover letters were distributed to Medical University of Ohio physicians and residents. Receiving the survey was 16 family medicine physicians and residents, 44 internal medicine physicians and residents, and 12 cardiologists and cardiology fellows. Surveys were delivered by placing them in the individual physician’s mailboxes. Performance sites included; the Center for Heart Sciences, Medical College of Ohio Hospital Building, 3000 Arlington Ave., Toledo, OH, Department of Medicine at the Medical College of Ohio Division of General Internal Medicine, Richard D. Ruppert Health Center, 3120 Glendale Ave., Toledo, OH, and Medical College of Ohio Department of Family Medicine, Garden Lake Building, 1015 Garden Lake Boulevard, Toledo, OH. Eighteen completed surveys were returned via mail in an enclosed self-addressed envelope. The returned surveys included completed surveys from 5 family medicine physicians and residents, 11 internal medicine physicians and residents, and 12 cardiologists.

The survey began by inquiring about demographic information such as the type of health care provider the subject is and how long they have been practicing. The survey also included knowledge-based questions regarding past research and current recommendations regarding the use of vitamin E supplements for cardiovascular health. Also within the survey were questions regarding providers’ personal usage, professional recommendations, and general foundations of knowledge of vitamin E.

There were no foreseeable risks to subjects in this study. Participation was completely voluntary, and subjects could stop completing the survey at any time. We did not guarantee or promise that subjects would receive any benefits from this study.
Results

Section I. Demographics

Seventy-two physicians and resident physicians received the survey. Eighteen surveys (25%) were returned. This included 5 family medicine physicians (27.8%), 3 of which were M.D.’s and 2 of which were D.O.’s. Four surveys were returned by internal medicine residents (22.2%), and 7 by internal medicine physicians (38.9%). All of which were M.D.’s. Two completed surveys were obtained from cardiologists (11.1%). Both of these were form M.D.’s. These demographics can also be viewed in Figure 1.

In regard to years of practice, 1 family practice physician reported 0-5 years of practice. Another reported 11-15 years of practice, and 3 family practice physicians reported >20 years of practice. Of the internal medicine physicians, all reported 0-5 years of practice. Of the cardiologists, 1 reported 6-10 years of practice. The other cardiologist reported >20 years of practice. Figure 2 demonstrates these values.

Section II. Knowledge

Of the 18 respondents, only 1 (5.5%) of them answered correctly that the Nurse’s health study showed a decrease risk of coronary disease in women who took vitamin E supplements. Two (11.1%) physicians thought that the Nurse’s Health Study had shown an increased risk of cardiovascular disease with vitamin E supplements. Five (27.8%) physicians responded that the Nurse’s Health Study showed no change in the risk of cardiovascular disease with vitamin E supplements. However, 10 (55.6%) respondents answered that they were not familiar with the Nurse’s Health Study. Figure 3 demonstrates these responses in regard to specialty.
There was better knowledge in regard to the Heart Protection Study. Eleven (61.1%) respondents answered correctly that the Heart Protection Study showed no apparent effect on cardiovascular outcomes. One (5.5%) physician responded that this study showed a reduced risk of having a cardiovascular event. One other physician responded that the Heart Protection Study showed an increase in the risk of having a cardiovascular event. Five (27.8%) physicians thought that the Heart Protection Study showed that vitamin E supplements are not safe for any patient. No physician responded that he or she was unfamiliar with this study. Figure 4 demonstrates these responses in regard to specialty.

When questioned about the mechanism(s) that vitamin E has been thought to work on the cardiovascular system, 5 (27.8%) respondents answered correctly that all of the listed mechanisms were correct. These included inhibition of smooth muscle cell proliferation, decreased oxidation of LDL, inhibition of platelet aggregation, and decreased monocyte adhesion. All other respondents answered that vitamin E acts only by decreasing oxidation of LDL. These responses in regard to specialty are demonstrated in Figure 5.

Fifteen (83.3%) respondents answered correctly that the use vitamin E supplements is still controversial, but their use is relatively safe. The other 3 respondents failed to answer this question.

**Section III. Attitudes and Perceptions**

When asked whether or not they recommend vitamin E supplements to their patients for cardiovascular benefits, only 1 (5.5%) stated that he or she frequently (>70% of patients) recommends it to his or her patients. This physician’s specialty was
internal medicine. Another 1 (5.5%) physician recommends vitamin E occasionally (30-69% of patients). This physician’s specialty was also internal medicine. Four (22.2%) physicians stated that they rarely (<30% of patients) recommend vitamin E to their patients. Two of these respondents were family medicine physicians. One was an internal medicine physician, and the other was a cardiologist. This relates to only 33.3% of physicians in the surveyed specialties recommending vitamin E supplements to their patients. The other 12 (66.7%) physicians responded that they never recommend vitamin E to their patients. Three of these were family medicine physicians. Eight of these were internal medicine physicians, and the other was a cardiologist. Figure 6 demonstrates the differences in recommendation by specialty.

An important question of this research was whether or not the number of years a physician has been practicing affects how often they recommend vitamin E supplements to their patients for cardiovascular benefits. The physicians who answered that they frequently and occasionally recommend vitamin E supplement had both been practicing for 0-5 years. Of the 4 physicians who answered that they rarely recommend vitamin E supplements to their patients, 1 reported 0-5 years of practice, 1 reported 6-10 years of practice, 1 reported 11-15 years of practice, and reported >20 years of practice. Figure 7 demonstrates these differences in vitamin E recommendation and years of practice.

When physicians were asked what dosage of vitamin E they would recommend to their patients, five (27.8%) physicians stated that they would recommend 200 IU daily. Four (22.2%) physicians stated that they recommend 400 IU daily. One (5.5%)
physician stated that he or she recommends a dosage of 100 IU daily, and one stated that he or she recommends a dosage of 1000 IU daily.

None of the respondent physicians stated that they personally take vitamin E supplements for cardiovascular benefits. One physician stated that he or she previously took vitamin E supplements at a dosage of 200 IU daily. “No reason” was given as the reason that he or she no longer takes vitamin E supplements. Sixteen physicians indicated that they have never taken vitamin E supplements for cardiovascular benefits. The remaining physician indicated that he or she is part of the ongoing Physician's Health Study, and did not know whether he or she was taking vitamin E supplements or placebo.

In regard to asking patients if they are taking nonprescription supplements, 4 (22.2%) physicians stated that they ask patients at every visit. Seven (38.9%) physicians stated that they ask patients at most visits. The other 7 physicians stated that they ask patients at some visits.

Physicians were also asked their opinion of who should be taking vitamin E supplements. One (5.5%) physician responded that he or she thinks that patients without evidence of cardiovascular disease should take vitamin E for prevention of cardiovascular disease. One (5.5%) physician responded that patients with a previous cardiovascular event should take vitamin E for prevention of another cardiovascular event. Nine (50%) physicians stated that no patient should take vitamin E supplements. One (5.5%) physician stated that he or she is uncertain who should be taking vitamin E supplements. Four physicians (22.2%) failed to respond to this question.
Discussion

In theory, the antioxidant effects of chemical entities, such as Vitamin E, possess the ability to reduce the risk of detrimental cardiovascular events. The aim of this project focuses on the overall knowledge of vitamin E’s cardioprotective role among health professionals, and their habits of counseling patients on the use of this nutraceutical. It is the responsibility of clinician to keep current on the relevant studies and recommendations concerning the use of antioxidants and other nutraceuticals in regard to health benefits and potential adverse effects or drug interactions. Health professionals should also inform patients of other supplemental approaches and preventative practices that may be beneficial.

The physicians that participated in this study were not very knowledgeable regarding the Nurse’s health study or the Heart Protection Study, 2 major studies that have been conducted in the conquest to determine the cardioprotective role of vitamin E supplementation. Out of 18 physicians, only 1 of them correctly answered that the Nurse’s Health Study demonstrated a cardioprotective role of vitamin E. Eleven of the 18 physicians answered correctly that the Heart Protection Study showed no apparent effect on cardiovascular outcomes. Of course there have been many other studies conducted, and it is virtually impossible for physicians to be aware of every study that is published. What is more important though, was that 15 of the 18 physicians correctly indicated that the role of vitamin E in cardiovascular health is still controversial.

Within the population of respondent physicians, only 33.3% replied that they ever recommend vitamin E supplements to their patients. This leaves 66.7% of physicians who never recommend this nutraceutical to patients for possible cardioprotective
benefits. Of the cardiologists in this study, one indicated that he or she rarely recommends vitamin E to his or her patients, and the other indicated that he or she never recommends vitamin E to his or her patients. This is in great contrast to the study conducted in 2001 by the Council for Responsible Nutrition, which found 75% of cardiologists recommending vitamin E to their patients at least some of the time.

When asked their opinion regarding who should take vitamin E supplements, 50% of respondents replied that no patients should take vitamin E supplements. This relates fairly well to the fact that 66.7% of the respondents do not recommend vitamin E to their patients. However, 1 physician wrote in that he or she was uncertain who should take vitamin E supplements, and another 4 physicians failed to respond to this question, which may indicate that they too are uncertain who should be taking vitamin E supplements. This would correlate to 27.8% of respondent physicians who are not sure who should be taking vitamin E supplements. Therefore, more physician education is needed in this area. According to a study performed by Milden and Stokols (2004), 61% of physicians do not feel they are knowledgeable enough in the use of complementary and alternative medicine. This would include vitamin E. The question could be raised as to whether physicians are not prescribing vitamin E supplement because of lack of knowledge, or lack of scientific proof and a current recommendation to support such use.

The most commonly recommended dose of vitamin E in this survey was 200 IU/daily, followed by 400 IU/daily. The most commonly recommended dose of vitamin E by cardiologists in the 2001 survey conducted by the Council for Responsible Nutrition was 400 IU/daily. Thirteen percent of the cardiologists recommended 800 IU/daily.
Furthermore, Dr. William A. Pryor, “an expert in the field of antioxidant research” recommends a dose of 100-400 IU daily in a 2000 article of *Free Radical Biology & Medicine*. These doses are deemed as safe, and the minor side effects of vitamin E do not generally occur until over 800 IU or more daily (Council for Responsible Nutrition, 2001).

There were some limitations to this study. When asking about the current recommendations regarding vitamin E and its cardioprotective role, the survey did not include the option of the current recommendation from the American Heart Association, which states, “at this time, the scientific data do not justify the use of antioxidant vitamin supplements for the CVD (cardiovascular disease) risk reduction” (Kris-Etherton, et al. 2004). Including this statement into the answers of the survey options would be beneficial in more precisely determining whether or not physicians are actually up to date with current recommendations.

Another limitation to the study was that the population sample was too small. The population of cardiologists was too small to compare the results of this study to the one conducted by the Council for Responsible Nutrition. Therefore, this study could be reproduced using a larger sample population in order to more accurately compare these results and obtain more accurate results over all physicians.
References


Figure 1. Distribution of participants by specialty and type of health care provider.
Figure 2. Number and distribution of participants by specialty and years of practice.

How long have you been practicing in this area?

- 0-5 years
- 6-10 years
- 11-15 years
- > 20 years

Medical specialty

- Family
- Internal Med
- Cardiology

Number of participants

12
10
8
6
4
2
0
Figure 3. The Nurse’s Health Study (1993), an eight year study that involved more than 87,000 female nurses demonstrated that
Figure 4. The Heart Protection (2002) demonstrated that vitamin E supplementation provider unfamiliar with study has no apparent effect on cardiovascular outcomes significantly increases the risk of cardiovascular event significantly reduces risk of cardiovascular event provider unfamiliar with study significantly reduces risk of cardiovascular event

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Figure 5. Mechanism(s) of action in which vitamin E has been thought to work on the cardiovascular system
Figure 6. Recommendations by specialty

How often do you recommend a patient to begin taking

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Figure 7. Recommendations by years of practice

How long have you been practicing in this area?
- 0-5 years
- 6-10 years
- 11-15 years
- > 20 years

How often do you recommend a patient to begin taking
Abstract

Objective: To determine physician’s knowledge and recommendations regarding use of vitamin E supplements for cardiovascular benefits. Method: Delivered surveys to mailboxes of MUO physicians in family medicine, internal medicine, and cardiology. Results: 25% of the 72 surveys were returned. 5.5% of respondents answered correctly that the Nurse’s health study showed a decrease risk of coronary disease in women taking vitamin E supplements. 61.1% of respondents answered correctly that the Heart Protection Study showed no effect on cardiovascular outcomes. 83.3% of respondents answered correctly vitamin E supplements are controversial, but their use is relatively safe. 33.3% of respondents recommend vitamin E supplements to their patients. The most commonly recommend doses were 200 and 400 IU/daily. Conclusion: Although respondents were not very knowledgeable regarding studies in this survey, they were knowledgeable about the current recommendations. Their recommended doses were consistent with doses identified in similar studies and doses that minimize potential adverse effects.