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**Review**

# Vitamin E in the prevention of ischemic heart disease

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**Abstract:**

Ischemic heart disease (IHD) has now assumed a global dimension. It still remains one of the major health problems not only in the advanced countries, but also, is becoming a serious health issue in the developing and the economically weaker countries. Apart from other factors, changing economic scenario, stress and strain in daily life as well as altered dietary habits in the populations appear responsible for the increased incidence of cardiovascular disease (CVD). The treatment modalities, invasive, non-invasive and pharmacological are economically no dearer, even to population of affluent countries. Likewise, treatment costs of serious cardiovascular diseases are becoming difficult to be borne by population of the developing nations. Prevention of IHD would be a better way to protect the population from physical and economic disaster. The current article comprehensively describes the relation between oxidative stress and cardiac disease, explains the direct effect of reactive oxygen species on cardiac function and projects how the use of vitamin E can be of benefit in the prevention of IHD with concluding remarks highlighting the need for inclusion of a fruit and vegetable rich diet and regular exercise to keep the dearer heart active and healthy.

**Key words:**

ischemic heart disease, reactive oxygen species, oxidative stress, vitamin E

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**Abbreviations:** AIDS – aquired immune deficiency syndrome, ATP – adenosine triphosphate, CAD – coronary artery disease, CVD – cardiovascular disease, GPx – glutathione peroxidase, H<sub>2</sub>O<sub>2</sub> – hydrogen peroxide, IHD – ischemic heart disease, I/R – ischemia/reperfusion, LDL – low density lipoprotein, MI – myocardial infarction, PMN – polymorphonuclear neutrophils, PTCA – percutaneous transluminal coronary baloon angioplasty, PUFA – polyunsaturated fatty acid, ROS – reactive oxygen species, SOD – superoxide dismutase.

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**Introduction**

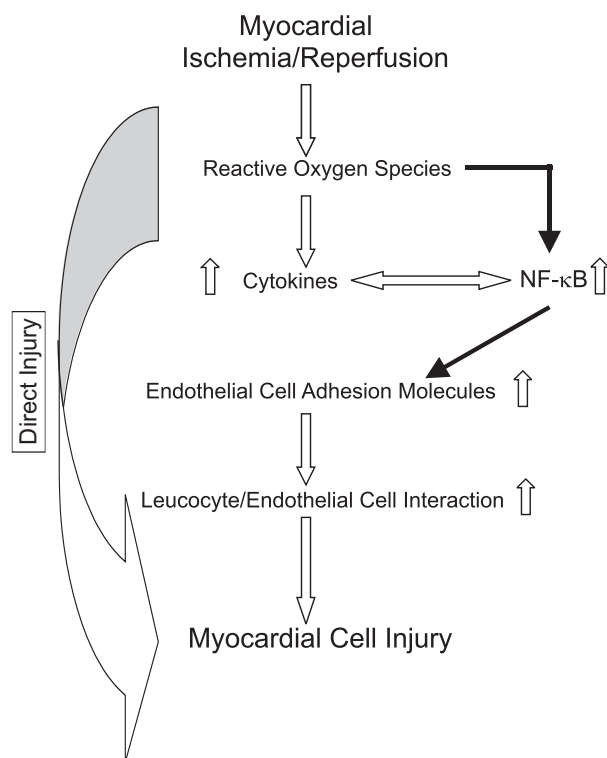
Disability and mortality due to cardiovascular disease (CVD) has now assumed an alarming proportion

around the length and breadth of the globe. Even populations in economically backward and developing nations are no behind the race of getting crippled with CVD when compared with the Western part of the world. Approximately 60 million American citizens have CVD, which accounts for almost half of all deaths in the United States. To present the scintillating scenario, as for example, nearly 14 million Americans have coronary artery disease (CAD), and treatment-related costs for these disease, including emergency room visits, cardiac catheterizations, coronary angioplasties, and bypass surgery, exceed 95 billion US \$ per year [41, 43]. Ischemic heart disease (IHD) resulting from CAD is devastating, with 1.5 million US citizens developing myocardial infarctions that ac-

count for nearly 200,000 deaths every year [41, 43]. Apart from other factors, changing economic scenario, stress and strain in daily life as well as altered dietary habits in the populations of the developing nations appear responsible for the increased incidence of CVD. Because there is a strong causal relationship between elevated serum cholesterol and CAD, it appears likely that acute myocardial infarctions will remain a major biomedical problem of global concern for the foreseeable future. The current article will make an attempt to focus on how oxidative stress is involved in the genesis of IHD and how the natural antioxidant vitamin E could be used as a preventive therapeutic against IHD.

### Oxidative stress and cardiac disease

Coronary artery occlusion resulting from atherosclerotic plaques or vasospasm can result in a reduction in

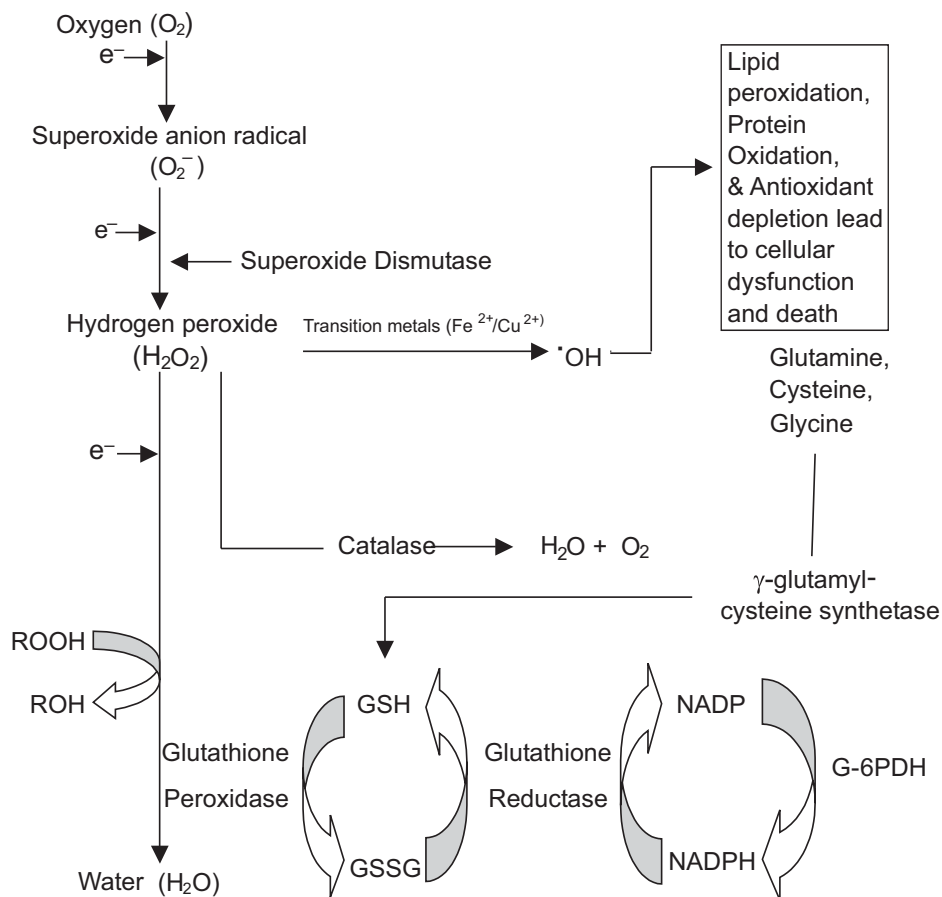


**Fig. 1.** Potential mechanisms of myocardial ischemia/reperfusion injury. Coronary artery occlusion followed by reperfusion results in the production of toxic reactive oxygen species (ROS). ROS can directly induce injury to cardiac myocytes, resulting in myocardial "stunning" and myocardial cell necrosis. In addition, oxygen free radicals can also trigger a series of events that can ultimately lead to myocardial cell injury and necrosis by means of amplification of the inflammatory cascade involving the nuclear transcription factor kappa beta (NF-κB), cytokine production, leucocyte-endothelial cell adhesion molecules, and infiltration of neutrophils

myocardial blood flow that is sufficiently prolonged or severe to produce myocardial injury and necrosis, ultimately leading to diminished (and consequently fatal) cardiac function. The treatment of acute myocardial ischemia involves the use of thrombolytic agents (i.e., tissue plasminogen activator, streptokinase) or percutaneous transluminal coronary balloon angioplasty (PTCA), which effectively restores blood flow to the ischemic myocardium. Although reperfusion of an occluded human coronary artery is known to reduce infarct size, preserve left ventricular function, and reduce overall mortality [7, 25], it is now recognized that the readmission of oxygenated blood into previously ischemic myocardium can initiate a cascade of events that will paradoxically produce additional myocardial cell dysfunction and cell necrosis [17, 30, 51, 57]. This phenomenon termed, "reperfusion injury", can be manifested either as reversible cardiac dysfunction (e.g., myocardial stunning) or irreversible damage (e.g., myocardial infarction).

The cellular mechanisms involved in the pathogenesis of myocardial ischemia/reperfusion (I/R) injury are complex and involve the interaction of a number of cell types, including coronary endothelial cells, circulating blood cells (e.g., leukocytes, platelets), and cardiac myocytes [26, 27, 29, 30, 57, 58], most of which are capable of generating reactive oxygen species (ROS) (Fig. 1). These ROS have the potential to injure vascular cells and cardiac myocytes directly, and can initiate a series of local chemical reactions and genetic alterations that ultimately result in an amplification of the initial ROS-mediated cardiomyocyte dysfunction and/or cytotoxicity. A key component of the amplification cascade that leads to irreversible tissue damage is the production of factors that promote the recruitment and activation of circulating inflammatory cells.

ROS are molecules with unpaired electrons in their outer orbit. As a consequence, these molecules are very unstable and highly reactive, and they tend to initiate chain reactions that result in irreversible chemical changes in lipids or proteins. These potentially deleterious reactions can result in profound cellular dysfunction and even cytotoxicity (Fig. 2). It is estimated that approximately 5% of the oxygen consumed by normal tissues are transformed into ROS. These basally generated ROS are efficiently detoxified by endogenous enzymatic free radical scavengers, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase [33, 61].



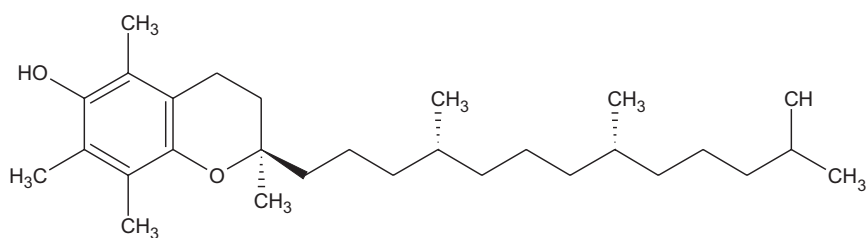
**Fig. 2.** Nearly 5% of the ground state oxygen ( $O_2$ ) utilized by the aerobes is reduced (by one electron reduction at each step) to reactive oxygen species (ROS), some of which are free radicals. Some of the products of  $O_2$  metabolism are shown in this figure. Of the oxygen-based products that are generated, the  $\cdot OH$  is considered to be the most damaging. It is estimated that in excess of 50% of the molecular clutter that accumulates as a consequence of the damage by ROS is due to  $\cdot OH$ . Removal of  $H_2O_2$  from cells is essential in the protection of macromolecules from damage inflicted by the highly toxic  $\cdot OH$ . One means by which steady state concentration of  $H_2O_2$  within the cells are held in check is its enzymatic degradation by glutathione peroxidase and catalase. These enzymes metabolize  $H_2O_2$  to innocuous products. Other enzymes involved in the metabolism of ROS are superoxide dismutase (SOD), glutathione reductase and  $\gamma$ -glutamylcysteine synthetase ( $\gamma$ -GCS). GSH, reduced glutathione; GSSG, oxidized glutathione

However, under conditions associated with excessive production of ROS, such as inflammation or I/R, the flux of ROS generated by tissues can exceed the capacity of endogenous oxidant defense mechanisms to detoxify ROS and prevent deleterious radical-mediated reactions.

#### Direct effects of ROS on cardiac function

ROS have been shown to exert a direct inhibitory effect on myocardial function *in vivo* and *in vitro*. Indeed, exposure of the normal myocardium to ROS-generating system or hydrogen peroxide ( $H_2O_2$ ) alters myocardial function in a fashion that mimics reperfusion injury, including persistent cellular loss of  $K^+$ , depletion of high-energy phosphates, elevated intra-

cellular calcium concentration, loss of systolic force development, a progressive increase in diastolic tension, depressed metabolic function, and arrhythmias [6, 55, 60]. The mechanism underlying the depressed myocardial contractility remains poorly understood. However, membranous components of mitochondria, sarcoplasmic reticulum, and sarcolemma may represent the most critical targets of ROS-mediated myocardial dysfunction. ROS have been shown to impair the function of isolated mitochondria that subsequently results in adenosine (ATP) depletion. Like I/R, exposure of isolated sarcoplasmic reticulum to ROS results in a diminished calcium uptake and depresses  $Ca^{2+}$ ,  $Mg^{2+}$ -ATPase activity. Similarly, ROS have been shown to reduce calcium-stimulated ATPase activity and depress calcium transport in the



**Fig. 3.** The chemical structure of vitamin E ( $\alpha$ -tocopherol), the most important lipid-soluble antioxidant

sarcolemma. Hence, the disturbances in calcium homeostasis that result from ROS interactions with cellular membranes could, at least hypothetically, explain some of the contractile abnormalities associated with I/R.

The effects on ROS-generating systems on myocyte membranes likely reflect the propensity of ROS to interact with protein and lipid components of these membranes [33, 51]. ROS-mediated reactions with proteins can result in the inactivation of key enzymes and ion transporters. Furthermore, the peroxidation of polyunsaturated fatty acid (PUFA) components of the cell membranes to specific ions alters receptor function. Therefore, the combined actions of lipid peroxidation and protein oxidation could well explain the cellular alterations that lead to the depressed cardiac function in conditions associated with excessive production of ROS.

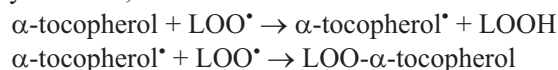
### Role of vitamin E ( $\alpha$ -tocopherol) in the prevention of ischemic heart disease

The chemistry and biology of vitamin E has been the subject of intensive study for more than 50 years [12, 15, 28, 31, 42, 49], and this enormous body of literature demonstrates conclusively that the principal role of vitamin E is to protect the tissue against unwanted, destructive oxidation [8, 11, 45]. Although additional functions of vitamin E have been studied by various investigators [9, 19, 48, 56], the antioxidant function of vitamin E remains the best established. In fact, vitamin E is the most effective lipid-soluble antioxidant present in our cells [8] (Fig. 3).

The most commonly found members of the vitamin E family in humans are the group of tocopherols,  $\alpha$ -tocopherol being the most abundant and the most active isomer in this group. The other group, the tocotrienols are more highly unsaturated, and possibly more potent antioxidants, however, they are present in much smaller quantities.

Once absorbed from the gut, vitamin E is transported to target tissues and cells *via* the lipoproteins (LDL). It is estimated that LDL carries about 50% of circulating vitamin E [8]. Normally, an average of six molecules of  $\alpha$ -tocopherol is present in each LDL particle. Other lipid soluble antioxidants, including  $\gamma$ -tocopherol,  $\beta$ -carotene, and  $\alpha$ -carotene are also found in LDL in much lower quantities compared to  $\alpha$ -tocopherol concentration. The proximity of vitamin E to lipids in LDL explains its unique ability to directly prevent lipid peroxidation within the LDL particle.

Vitamin E functions by donating hydrogen to fatty peroxy radicals, thereby halting lipid peroxidation. This antioxidant can potentially react with two peroxy radicals, as shown below:



The  $\alpha$ -tocopherol radical formed in the first equation assumes a resonance stabilized conformation, enabling the molecule to react with another peroxy radical to form a stable adduct, LOO- $\alpha$ -tocopherol as shown in the second equation.

Experimentally, it has been shown that dietary vitamin E can ameliorate the development of spontaneous atherosclerosis in nutritional models of cardiovascular disease [59]. Atherosclerotic lesions in carotid arteries were induced in a primary model over a period of time by feeding the animals a high cholesterol diet.  $\alpha$ -Tocopherol supplementation was shown to decrease the severity of atherosclerosis and promote the regression of diet-induced atherosclerotic lesions. Studies involving rabbits have also shown that supplementation with vitamin E inhibits oxidative LDL modification. However, it failed to prevent dietary cholesterol-induced atherosclerosis [39].

Vitamin E has been projected to be the most effective antioxidant for reducing lipid peroxidation [20]. An abundance of evidence exists to support this claim. Epidemiological studies have shown that vitamin E is the strongest contributor to the inverse rela-

tionship between serum antioxidant concentrations and IHD [16]. An eight-year follow up study involving over 87,000 female nurses has also found that women with the highest intake of vitamin E had a relative risk of CHD 0.66 of that of the group which consumed the least amount of the vitamin, after adjustment for age and smoking [52]. In a dose-response study, 48 healthy nonsmokers were given 0, 60, 200, 400, 800 or 1200 IU of vitamin E per day for eight weeks. LDL susceptibility to oxidation decreased in the men receiving 400 IU or more of vitamin E, but not in those receiving lower levels. No side effects were observed in any of these treatments. The minimum amount of vitamin E needed to inhibit LDL oxidation appeared to be 400 IU [21]. In a study involving over 2300 men, Meyer and coworkers [37] have demonstrated that the subjects who took vitamin supplements had a 70% reduced risk of dying from ischemic heart disease and almost of 50% lower risk of myocardial infarction (MI). The vitamin that appeared to be most protective was vitamin E [37]. Another study has examined the effects of 750 IU of vitamin E supplementation for a period of one year (250 IU three times a day) in diabetic patients. The study revealed a doubling of serum vitamin E level in the first three months which did not increase further and, returned to baseline value. A decrease in lipoprotein peroxidizability was also observed during vitamin E treatment. Since the benefits of the supplement are conferred only while supplementation is continuing it was suggested that life-long supplementation with vitamin E should be considered in patients with type I diabetes [14]. The mortality rate due to CVD in patients with end stage renal disease (who require chronic hemodialysis) is estimated to be 5 to 20 times that of the general population that may be due in part to increased oxidative stress. In SPACE (Secondary Prevention with Antioxidants of Cardiovascular disease in End stage renal disease) trial, the effect of vitamin E (800 IU per day) supplementation (or placebo) on CVD in 200 such patients was studied for a period of about two years. Treatment of the patients with vitamin E was associated with a significant protective effect against cardiovascular death and non-fatal MI (heart attack) [5].

While these studies are encouraging, some studies have shown an effect in men but not in women. Other studies involving patients with existing heart conditions have surprised the investigators by failing to

show a benefit of vitamin E supplementation. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione trial, a secondary prevention trial that enrolled 11,324 Italian patients who had survived an MI within the 3-month period before enrollment [32], failed to show any statistically significant benefit of using vitamin E (300 mg/day of synthetic vitamin) as a cardioprotective dietary supplementation. Similarly, The Heart Outcomes Prevention Evaluation (HOPE) study, a prospective randomized trial showed that ACE-inhibitor Ramipril (10 mg daily) but not vitamin E (400 IU daily) had the ability to significantly reduce the risk of future cardiovascular events in a high-risk population of men and women, including many with diabetes [34, 62, 63]. Additionally, recent clinical studies suggest that vitamin E is also ineffectual in the primary prevention of atherosclerosis [18]. Furthermore, a number of investigators have also demonstrated a positive effect of dietary vitamin E on endothelium and vascular function in animal models of atherosclerosis [35]. Several human clinical trials have also shown an improvement in the surrogate markers of atherosclerosis and vascular function by vitamin E supplementation. However, these findings have been contradicted by several vitamin E supplementation trials for the prevention of secondary cardiovascular events showing null effect. The authors are of the opinion that intervention at a relatively late stage of the disease and the single use of vitamin E rather than in combination with other antioxidants might have contributed to these contradictory findings [35]. Evidence from cell cultures, as well as animal and human clinical and observational studies, strongly supports the contribution of dietary vitamin E to the maintenance of vascular function with other dietary antioxidants, which are found in fruits, vegetables and nuts [35]. Finally, the totality of evidence based on the epidemiologic data, *in vitro* studies and animal models, and the clinical trials appear to support a benefit for  $\alpha$ -tocopherol supplementation in patients with pre-existing CVD [22]. For detailed information on this aspect the reader is referred to a recent article by Pryor [47].

#### **The "correct dose" of vitamin E: primary versus secondary prevention**

Intakes of vitamin E that are used in intervention studies, 100 to 800 IU/day, are virtually impossible to obtain from food. The principal source of vitamin E are

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plant oils that have high contents of fats, food components that are recommended to be only a small part of a well-designed diet. What should be the optimum dose of vitamin E? The answer is not simple. It is likely that protection against different conditions will have different dose-response curves. If so, then, as has already been pointed out [46], different human clinical trials with different endpoints, may find different daily intakes of vitamin E as enough. In fact, a study in rats has shown that different physiological responses have different dose-response curves [1]. In particular, normal weight and growth rates are obtained when the rats are fed 7.5 mg/kg vitamin E. A level of 15 mg/kg was found to be adequate to prevent myopathy. A 50 mg/kg dose was found to be necessary for the prevention of red cell hemolysis. However, lymphocyte response to mitogens, a measure of the immune system response, continues to increase at higher intakes of vitamin E and the optimum level of vitamin E is greater than 50 mg/kg. In fact, the immune system response correlates with plasma vitamin E levels over the enormous range of 0.04 to 18.0  $\mu\text{g/ml}$  [46].

Thus, if different responses have different dose-response curves in human as well as in rats, one cannot simply ask, "How much vitamin E is enough?" Instead, one must ask, "How much vitamin E is enough to provide maximum protection against a particular health end-point?" That is, it is possible that optimal protection against one condition, such as a second MI in those who have already proven heart disease, might require a different dose of vitamin E than another condition, such as cancer prevention in a population with normal health, or protection against Alzheimer's disease [40]. Thus, each trial, with different populations and different end-points may find different intakes of vitamin E required for optimum protection.

The problem of varying dose-response curves raises a number of interesting questions. "Will the amount of vitamin E required for the secondary prevention of events in patients with already-proven heart disease differ from the amount necessary for the primary prevention of heart disease in the young and healthy?" Because atherosclerosis begins in the very young [4], it is tempting to speculate about the possible benefits of prolonged vitamin E supplementation, starting in the young, as a tool in the primary prevention of CVD [54]. However, it seems doubtful that this potential benefit could ever be tested in an intervention trial of sufficient length.

### How far is use of vitamin E safe?

There is very substantial consensus among experts that vitamin E is safe at levels up to 800 IU/day and probably safe at levels at least twice that [2, 3, 23, 36]. In a thorough appraisal, Kappus and Diplock [23] have reviewed the tolerance, toxicological considerations, and safety of vitamin E. They conclude that there are no side effects up to 800  $\alpha$ -tocopherol equivalents ( $\alpha$ -TE), equivalent to about 1200 IU. The therapeutic range is given as 200 to 1600  $\alpha$ -TE [23]. Kappus and Diplock state that side effects are only expected to begin at doses of 1000 to 3000 units  $\alpha$ -TE/day (that is, to begin at about 1500 IU/day), and to consist of gastrointestinal complaints, which are, however, generally not severe and which subside rapidly on reducing the dosage or on discontinuing the administration of vitamin E. Therefore, the entire range from the minimal requirement up to a dose of approximately 3,000 mg can be considered as a safe range. There is a risk of adverse effects above intakes of 3,000 mg vitamin E per day. Thus, the levels of vitamin E consumed as a result of supplementation with 400 or even 800 IU/day is well within safe limits. Vitamin E does decrease platelet adhesion and at levels of supplementation above 400 IU/day may increase clotting times [24]. Therefore, it may be prudent for those individuals who take anticoagulants to have periodic monitoring of their clotting times.

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### Concluding remarks

In the post-genomic era, IHD still remains a major health problem of global concern. While active research should continue to strive for the newer techniques (pharmacological and invasive as well as non-invasive) to resolve the crisis of CVD on emergency to save life, attention needs to be focussed on the prevention of the cardiac diseases with the available pharmacological and nutritional tools at our disposal. Inflammatory processes in IHD, produce a high flux of superoxide anion radical, which leads to a cascade of potent oxidants such as the hydroxyl radical, peroxynitrite, and hypochlorite. Therefore, vitamin E might be found to be particularly effective against an inflammatory component of atherosclerotic plaque development, or perhaps more effective in those sub-

jects with higher levels of vascular inflammation. Interestingly, aspirin and vitamin E appear to work synergistically against the risk of CVD [44, 53]. Very recently, Chen et al. [10] have suggested that the reduction of myocardial I/R injury with vitamin E supplementation may be the result of the inhibition of polymorphonuclear neutrophils (PMN) CD 11b expression. According to them, vitamin E may be a promising prophylactic agent for reduction of severity of myocardial I/R injury in patients who have acquired immune deficiency syndrome (AIDS). In the future, it may be possible to identify particular classes of individuals who require vitamin E supplementation more immediately and can be expected to derive greater than usual benefit. However, at present, there is little reason not to supplement the general population, because the side reactions and toxicity of vitamin E, at levels used in the above-mentioned trials, is known to be very low. Finally, in view of the very low risk of supplementation with vitamin E and the difficulty in obtaining more than about 15–30 IU/day from a balanced diet, there is sufficient evidence to recommend modest vitamin E supplementation, as for example, 100 to 400 IU/day as part of a general program of heart-healthy behavior that should include a fruit- and vegetable rich diet and regular exercise, although the usefulness of vitamin E as a dietary supplement or adjunct therapy may be continued to be debated [13, 38, 50].

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