Vitamin E and Cardiovascular Disease

Observational Studies

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ABSTRACT: Basic research suggests that oxidative stress may play an important role in many chronic diseases and provides plausible mechanisms by which natural antioxidants such as vitamin E may delay or prevent steps in atherogenesis. Dietary research has shown that those who consume higher amounts of fruits and vegetables have lower rates of heart disease and stroke, raising the possibility that antioxidants are protective. Results from large-scale human observational studies suggest that antioxidant consumption reduces the risk of developing cardiovascular disease (CVD). Both case-control and prospective cohort studies have carefully explored the relationship between vitamin E intake and plasma and tissue vitamin E levels and the risk of CVD. In many, but not all, of these studies vitamin E intake over an extended period was associated with decreased risk of cardiovascular events. Results from studies of blood levels are more limited and less consistent. This presentation summarizes data from the major observational studies. Overall, they support the possibility that vitamin E intake either from food or supplements may reduce risk of CVD; however, these studies have important limitations. For example, uncontrolled confounding can be similar in magnitude to the observed health effects, and antioxidant consumption may be merely a marker for a different cardioprotective factor (such as exercise or diet) that is responsible for these effects. In the search for small to moderate effects, randomized trials may be helpful, although to date, data from large-scale trials have been inconsistent. Several large-scale trials currently under way will help identify the potential benefits of vitamin E in the primary prevention of CVD and other chronic illness. Some are designed to test vitamin E alone as well as in combination with other antioxidant supplements because it is possible that antioxidants may be most effective if taken in particular combinations. Currently, the American Heart Association maintains that there are insufficient efficacy data from completed randomized trials to justify population-wide recommendations for use of vitamin E supplements in disease prevention.

KEYWORDS: antioxidant; cardiovascular disease; vitamin E

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INTRODUCTION

One of the most consistent findings in dietary research is that those who consume higher amounts of fruits and vegetables have lower rates of heart disease and stroke, raising the possibility that antioxidants are protective. The exact mechanism for these apparent protective effects is not entirely clear, although basic research has identified plausible mechanisms by which natural antioxidants may delay or prevent steps in atherogenesis. The oxidation of low-density lipoprotein (LDL) cholesterol is suspected to occur at the initial stages of atherosclerosis, and vitamin E has been shown to inhibit this oxidative reaction.

Many cross-sectional, case-control, and cohort studies have found an association between antioxidant consumption and a reduced risk of developing heart disease, with the strongest data in favor of vitamin E. Conversely, several large-scale, randomized trials of antioxidant supplements have now been completed, but their results are not entirely consistent. In this paper, I will focus on the observational study results, and then briefly put these in the context of the results of the completed large-scale trials as well as review the status of ongoing studies.

BASIC LABORATORY RESEARCH

Oxidative processes may play an important role in the pathogenesis of many chronic diseases, including atherosclerosis, cancer, arthritis, eye disease, and reperfusion injury during myocardial infarction. Data from in vitro and in vivo studies suggest that oxidative damage to LDL promotes several steps in atherogenesis, including endothelial cell damage, foam cell accumulation, and growth and synthesis of autoantibodies. In addition, animal studies suggest that free radicals may directly damage arterial endothelium, promote thrombosis, and interfere with normal vasomotor regulation. Oxidative damage may enhance atherogenesis by a cascade of reactions. Several systems have evolved in aerobic organisms to minimize the damaging effects of uncontrolled oxidation. Mechanisms exist to prevent the formation of unintended free radicals, and oxidative metabolism is carefully compartmentalized with oxygen and its highly reactive species tightly bound to enzymes. Metal ions such as copper and iron are bound to storage or transport proteins to prevent catalytic reactions with oxygen species that could lead to the formation of free radicals. In addition, enzymatic antioxidants (such as superoxide dismutase, catalase, and glutathione peroxidase) and nonenzymatic antioxidants (such as vitamin E) scavenge free radicals, thereby minimizing the damage they can cause once formed. Lastly, there are mechanisms for repairing the damage resulting from unintended oxidative reactions.

Antioxidant vitamins represent one of the many nonenzymatic antioxidant defense mechanisms. Vitamin E (of which α-tocopherol is the major component) is among the most abundant and most widely studied natural antioxidants. However, there are hundreds or thousands of other dietary compounds that may function as antioxidants. In vitro data have demonstrated the possible role of these antioxidants in preventing or slowing various steps in atherogenesis by inhibiting the oxidation of LDL or other free radical reactions. These antioxidants have also been shown to prevent experimental atherogenesis in many but not all animal models of atherosclerosis.
OBSERVATIONAL EPIDEMIOLOGY

Basic research provides insight into the mechanisms underlying atherogenesis and helps elucidate potential interventions to modify these effects. But to establish cause and effect, data from complementary methods of population research are needed, including descriptive, analytical, and intervention studies. Each has strengths and weaknesses.

Descriptive studies (case reports, cross-sectional surveys, and cross-cultural analyses) are valuable primarily for their ability to generate hypotheses. However, their design prevents adequate control for potential factors that may confound apparent associations. Observational studies (case-control and prospective cohort studies) give researchers greater control over potential confounders. They are extremely useful in establishing risk attributable to a single factor, particularly when the effect of a given factor is large, as in the case for smoking and lung cancer. But in the search for small-to-moderate effects, the amount of uncontrolled confounding in observational studies may be as large as the probable risk reduction itself. In such cases, randomized trials are essential for confirming causation. Even when causality is not in question, trials help quantify the magnitude of an intervention’s effect. And although logistically difficult and expensive to conduct, randomized trials generally provide the best data on the magnitude of benefit and risk from a given intervention, which is essential for assessing cost efficacy and developing preventive strategies.

Descriptive Epidemiologic Studies

Some of the early data supporting the hypothesis that vitamin E was protective against cardiovascular disease (CVD) came the MONICA (Multinational MONitoring of trends and determinants in CArdiovascular disease) cross-cultural studies; of the 16 populations of men and women that had been analyzed, lipid-standardized α-tocopherol levels were inversely associated ($RR = 0.49; P = .01$) with mortality rates due to ischemic heart disease. In the partial regression analysis, lipid-standardized vitamin E exhibited an even stronger inverse correlation with ischemic heart disease mortality ($RR = 0.69; P < .001$). However, a similar study of four European populations of men between 40 and 49 found a nonsignificant inverse association between vitamin E intake and cardiovascular mortality.

Case–Control Studies

Two separate studies of subsets of the same population of 6,000 Scottish men aged 35 to 54 identified a significant inverse association between plasma antioxidant levels and CVD. Lipid-standardized concentrations of vitamin E in patients with angina (as identified by a questionnaire) were lower than in controls. The first study included 125 men with angina and 430 controls; the vitamin E/cholesterol molar ratio was lower in those with angina than in the controls. The relative risk of angina for those in the lowest versus those in the highest quintile of the vitamin E/cholesterol ratio was 2.2:1. In the second study, 110 men with angina were compared with 394 controls, and Vitamin E was independently and inversely related to the risk of angina after adjusting for age, smoking, blood pressure, lipids, and relative weight.

A large case-control study, the EURAMIC (European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer) study, compared
vitamin E concentrations in adipose tissue samples of 683 people with acute myocardial infarction (MI) and 727 hospital-based controls.\textsuperscript{22} The mean \( \alpha \)-tocopherol concentrations were virtually the same in both groups; low levels were not associated with increased risk of MI. Supplemental vitamin E appeared to be associated with lower risk of MI, a finding consistent with other studies. Adipose levels of \( \beta \)-carotene were also measured, and it appeared to have a protective effect; vitamin E strengthened the inverse association of with MI, which was the greatest at the highest \( \alpha \)-tocopherol concentrations.

**Prospective Cohort Studies**

Although case-control studies are often efficient and less costly than cohort studies, prospective cohort studies are less subject to selection and recall bias because information is collected before disease develops. Many large cohort studies have evaluated the relationship between vitamin E intake and the incidence of coronary disease. These studies are summarized in Table 1.

**Nurses’ Health Study.** The largest of the prospective cohort studies is the Nurses’ Health Study (NHS), an investigation in which the association between vitamin E and CVD was analyzed among more than 87,000 U.S. female nurses between 34 and 59 years old with no history of CVD.\textsuperscript{23} Dietary antioxidant intake and use of antioxidant vitamin supplements were determined using a semi-quantitative food frequency questionnaire administered at baseline; information on vitamin E intake and antioxidant supplements was updated biennially. After 8 years, women in the highest quintile of vitamin E intake had a 34\% lower risk of coronary disease (nonfatal MI and fatal coronary heart disease) compared with those in the lowest quintile (\( P \) for trend < .001). When vitamin E intake was examined separately by source (food or supplements), an inverse association emerged only for supplements. Women who took at least 100 IU of vitamin E supplements per day for more than 2 years experienced reductions of 40\% or more in the risk of coronary disease, after adjustment for age and cardiac risk factors.

**Health Professionals Follow-up Study.** The NHS findings were mirrored in the Health Professionals Follow-up Study (HPFS) of nearly 40,000 U.S. male health professionals aged 40 to 75 who did not have coronary heart disease (CHD), diabetes, or hypercholesterolemia at baseline.\textsuperscript{24} After adjustment for cardiac risk factors, the relative risk of major coronary disease for those in the highest versus the lowest quintile of vitamin E intake was 0.60 (95\% confidence interval (CI), 0.44–0.81; \( P \) for trend = .01). Further analysis revealed that the protective association was strongest for vitamin E consumed in supplements. Men who took at least 100 IU per day for at least 2 years had a multivariate risk of coronary disease of 0.63 (95\% CI, 0.47–0.84) compared with men who did not take vitamin E supplements. A weak association was found for dietary vitamin E intake alone; among men who did not take vitamin supplements, the relative risk comparing the extreme quartiles was 0.79 (95\% CI, 0.54–1.15, \( P \) for trend = .11).

**Iowa Women’s Health Study.** The Iowa Women’s Health Study evaluated the association between antioxidant vitamin intake and CHD mortality over 7 years among 34,486 postmenopausal women with no history of CVD.\textsuperscript{25} In contrast to the NHS and HPFS findings, vitamin E intake from food but not from supplements was strongly associated with a lower risk of CHD mortality. Women in the highest quin-
<table>
<thead>
<tr>
<th>Study</th>
<th>Population and Age (yr)</th>
<th>Exposure</th>
<th>Duration (yr)</th>
<th>Endpoint</th>
<th>Risk Reduction from Vit. E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurses’ Health Study (1993)</td>
<td>87,245 U.S. female nurses, 34–59</td>
<td>Dietary vitamin E &amp; antioxidant supplements</td>
<td>8</td>
<td>Coronary disease (nonfatal MI and fatal CHD)</td>
<td>Yes</td>
</tr>
<tr>
<td>Health Professionals Follow-up (1993)</td>
<td>39,910 U.S. male health professionals, 40–75</td>
<td>Dietary vitamin E and vitamin E supplements</td>
<td>4</td>
<td>Major coronary disease (fatal coronary disease, nonfatal MI, bypass, angioplasty)</td>
<td>Yes</td>
</tr>
<tr>
<td>Iowa Women’s Health Study (1996)</td>
<td>34,486 postmenopausal women, 55–69</td>
<td>Dietary vitamin E and antioxidant supplements</td>
<td>7</td>
<td>CHD mortality</td>
<td>Yes</td>
</tr>
<tr>
<td>Finnish Cohort (1994)</td>
<td>5,133 men, 30–69</td>
<td>Dietary</td>
<td>12–16</td>
<td>CHD mortality</td>
<td>Yes</td>
</tr>
<tr>
<td>French Canadian Men (1996)</td>
<td>2,313 middle-aged men</td>
<td>Vitamin supplements</td>
<td>5</td>
<td>Ischemic heart disease (IHD death, new IHD event, MI, angina)</td>
<td>Yes</td>
</tr>
<tr>
<td>Multiple Risk Factor Intervention (1996)</td>
<td>734 U.S. men, 35–57</td>
<td>Blood samples taken at baseline and frozen for 20 years</td>
<td>20</td>
<td>Nonfatal MI or coronary death</td>
<td>No</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>4,802 Dutch men and women, 55–95</td>
<td>Dietary antioxidants</td>
<td>4</td>
<td>Myocardial infarction</td>
<td>No</td>
</tr>
</tbody>
</table>
tile of dietary vitamin E intake, without any supplementation, had a relative risk of 0.38 compared to those in the lowest quintile \( (P \text{ for trend } = 0.004) \). Controlling for other dietary factors associated with vitamin E intake, such as intake of linoleic acid, folate, and fiber, did not affect the results.

**Finnish Cohort Study.** Similarly, a 14-year Finnish study also found a significant inverse association between dietary intake of vitamin E and coronary mortality among 5,133 men and women 30 to 69 years of age and initially free of heart disease.\(^{26}\) Among women, those in the highest tertile of vitamin E usage versus those in the lowest had a relative risk of death from heart disease of 0.35 \( (P \text{ for trend } < .01) \). In men, this relative risk was 0.66 \( (P \text{ for trend } = .01) \).

**Study of Middle-Aged French-Canadian Men.** This study assessed the relationship between use of vitamin and mineral supplements in a cohort of 2,313 men from Quebec who provided baseline information on supplement use and risk factors for ischemic heart disease.\(^{27}\) A total of 23% reported taking supplements, with 5.1% of these men receiving vitamin E from supplements. Their progress was followed for 5 years, and, in general, men taking supplements had a statistically significant lower risk of ischemic heart disease and MI. In particular, vitamin E appeared to be more strongly and more consistently associated with a lower incidence of ischemic heart disease events.

**Multiple Risk Factor Intervention Trial.** This nested case-control study consisted of 734 U.S. men age 35–57 at risk for CVD and enrolled in the Multiple Risk Factor Intervention Trial (MRFIT). Blood samples were taken at baseline and frozen for 20 years before being analyzed; there was no association between serum vitamin E levels and risk of nonfatal MI or coronary death.

**Elderly Cohort Studies.** The relationship between vitamin E and CVD has also been examined in two elderly cohorts, the Established Populations for Epidemiologic Studies of the Elderly (EPESE) program, and the Rotterdam Study. EPESE, a National Institute on Aging study of 11,178 U.S. men and women aged 67 to 105 years, found a decreased risk of CHD mortality \( (RR = 0.53; 95\% \text{ CI}, 0.34–0.84) \) and overall mortality \( (RR = 0.66\%; 95\% \text{ CI}, 0.53–0.83) \) among those taking vitamin E supplements (not as part of a multivitamin) over a 9-year period.\(^{28}\)

The Rotterdam Study also assessed an older population, 4,802 Dutch men and women aged 55 to 95 years with no history of MI. However, unlike the EPESE study, it was limited to dietary antioxidants, as determined using the semi-quantitative food frequency questionnaire. After a follow-up period of 4 years, no association between vitamin E intake and myocardial infarction (MI) was observed.\(^{29}\)

**Limitations of Observational Studies**

Observational results suggest that antioxidants may have protective effects, but these studies have important limitations. For example, uncontrolled confounding from unknown or unmeasured confounders can be similar in magnitude to the observed health effects, and antioxidant consumption may be merely a marker for a different cardioprotective factor (such as exercise and diet) that is responsible for the observed health benefits. In addition, intakes of individual dietary antioxidants tend to be highly correlated with each other, making it difficult to determine the specific benefit of a particular antioxidant.
Antioxidant vitamins are commonly used nutritional supplements. Evaluation of the benefits and risks of antioxidants is essential for determining the place of these supplements in clinical medicine. As far back as 1991, the U.S. National Heart, Lung, and Blood Institute’s (NHLBI’s) conference “Antioxidants in the Prevention of Human Atherosclerosis” concluded that data from large-scale randomized trials, which by design can limit the amount of confounding because subjects are randomly assigned to treatment or placebo, were required to test the hypothesis that dietary antioxidants reduce the risk of CVD. Several large-scale randomized trials have now been completed, and more are currently under way.

**COMPLETED RANDOMIZED CLINICAL TRIALS**

**Primary Prevention**

With the completion of the SUplémentation en VItamines et Minéraux AntioXyandants (SU.VI.MAX) study, more detailed data examining the role of antioxidants in reducing CAD should soon be available. The SU.VI.MAX trial evaluated for 8 years the efficacy of a balanced combination of antioxidants (including 30 mg of vitamin E) and minerals in the primary prevention of cancer and CVD in 12,375 French men and women age 35 to 60. The results are slated to be published in the *Archives of Internal Medicine* this year (2004); however, according to information released prior to publication, there was no reduction in CVD risk among those taking the vitamin cocktail.

Although lung cancer was the primary endpoint of the Alpha-Tocopherol, Beta-Carotene (ATBC) trial, this trial also provided data on antioxidants and heart disease in more than 20,000 male Finnish smokers. After a median treatment period of 6.1 years, supplementation with synthetic vitamin E (50 mg/day) did not reduce the incidence of lung cancer, and there was no clear reduction in risk of death due to ischemic heart disease (\(RR = 0.84; 95\%\, CI, 0.59–1.19\)). However, the risk of developing angina was lower among those taking vitamin E (\(RR = 0.91; 95\%\, CI, 0.83–0.99\)). Initially, it was thought that the lack of convincing beneficial effect may have been due to inadequate dosing of vitamin E or short follow-up time, but post-trial results with 8 more years of follow-up found no effect of \(\alpha\)-tocopherol on total mortality (\(RR = 1.01; 95\%\, CI, 0.96–1.05\)).

Two other primary prevention trials, the Primary Prevention Project (PPP) and the Vitamin E Atherosclerosis Prevention Study (VEAPS), involved larger doses of vitamin E. The PPP was an open-label 2 × 2 factorial trial of 300 mg of synthetic vitamin E and/or 100 mg of low-dose aspirin daily in 4,495 Italian men and women with at least one major risk factor for heart disease. Because of a strong treatment effect for aspirin, the trial was stopped early after a mean follow-up of 3.6 years, but at that time, vitamin E had no effect on reducing the incidence of pre-specified cardiovascular events. It has been suggested that the null findings may have been due to insufficient statistical power.

VEAPS followed the progress of 353 men and women who had LDL cholesterol levels of greater than 130 mg/dL and no clinical symptoms of CVD at baseline for 2 years, 258 of whom continued follow-up for an additional year. The primary endpoint was the rate of change in the common carotid artery far-wall intima-media
thickness; there was no difference in the progression of intima-media thickness in those randomized to 400 IU of vitamin E daily versus those randomized to placebo.

Secondary Prevention

The Cambridge Heart Antioxidant Study (CHAOS) assessed 2,002 patients with coronary artery disease who were randomly assigned to receive vitamin E (either 400 or 800 IU/day) or placebo for a median of 510 days. Those taking vitamin E had a lower risk of nonfatal MI ($RR = 0.23; 95\% \text{ CI}, 0.11–0.47$), but they also had a nonsignificant increase in cardiovascular deaths ($RR = 1.18; 95\% \text{ CI}, 0.62–2.27$). The primary endpoint was combined nonfatal MI and CVD death, and vitamin E reduced this risk ($RR = 0.53; 95\% \text{ CI}, 0.34–0.83$). There is no clear explanation for the striking difference between nonfatal and fatal cardiovascular outcomes; however, because of the relatively small number of participants, the placebo group had more men, lower total cholesterol levels, and lower systolic blood pressures, as well as fewer diabetics.

In the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico (GISSI) Prevention Trial, 11,324 patients with a history of acute MI within the last 3 months were randomized in an open-label design to vitamin E (300 mg daily), n-3 polyunsaturated fatty acids (1 g daily), both, or neither over 3.5 years. The primary analysis included cardiovascular death, nonfatal MI, and nonfatal stroke, and vitamin E did not have an effect on this combined endpoint ($RR = 0.98; 95\% \text{ CI} 0.87–1.10$). However, in contrast to the CHAOS study, vitamin E supplementation did have a statistically significant effect on the secondary endpoint of cardiovascular death ($RR = 0.80; 95\% \text{ CI} 0.65–0.99$).

The Heart Outcomes Prevention Evaluation (HOPE) Study randomized 9,541 participants with CVD or diabetes and at least one other cardiovascular risk factor into a study of 400 IU of vitamin E daily, the angiotensin-converting enzyme inhibitor ramipril, both agents, or neither. The study was stopped early after a mean of 4.5 years because of the beneficial effects of ramipril. Vitamin E had no effect on the primary combined endpoint of MI, stroke, and cardiovascular death ($RR = 1.05; 95\% \text{ CI} 0.95–1.16$), and secondary analysis of various cardiovascular endpoints also failed to show any reduced risk with vitamin E. With high rates of compliance and large doses of vitamin E, this study cast doubt on the clinical usefulness of vitamin E supplementation in patients at relatively high risk for a cardiovascular event.

Ongoing Randomized Clinical Trials

Results from the Women’s Health Study (WHS), which assessed the effect of 600 IU of vitamin E every other day and low-dose aspirin in nearly 40,000 women over a 12-year period, should be available this year (2004). Another primary prevention trial, the Physicians’ Health Study II (PHS II), is evaluating several antioxidants, including 400 IU of vitamin E every other day for 8 years.

The Women’s Antioxidant Cardiovascular Study (WACS), scheduled to end in 2005, and the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which has randomized over 30,000 men, are looking at secondary prevention. In WACS, approximately 8,000 high-risk professionals with preexisting CVD or with several coronary risk factors were randomized to 600 IU of natural vitamin E every
other day or placebo. The main focus of the SELECT trial is prostate cancer, but it will also evaluate any cardiovascular impact associated with taking 400 IU of vitamin E every other day.

SUMMARY AND CONCLUSIONS

Potential biological mechanisms by which vitamin E supplementation may inhibit atherosclerosis have been identified, and, overall, human observational data are compatible with the possibility that vitamin E intake either from food or supplements may reduce the risk of CVD. Many but not all of the prospective cohort studies examining the role of dietary intake of this antioxidant and CVD suggest an inverse association. However, these studies have important limitations, and caution should be exercised when interpreting the data. For example, bias is inherent in the selection of participants. It is possible that the low incidence of heart disease was actually the result of uncontrolled confounding. People who consume large amounts of fruits and vegetables may have more healthy lifestyles, and diets rich in antioxidants are lower in saturated fat and cholesterol and higher in fiber, which could possibly account for the observed health effects.

Clinical trials of vitamin E alone for primary prevention have not generally supported the observational results. The discrepancy between the observational studies could be the result of some of the limitations of the trials with respect to the dose, the duration, and the specific preparations. The ATBC study was restricted to smokers and may have used a subtherapeutic dose, whereas the follow-up time may have been inadequate in the PPP trial, which was stopped early. Secondary prevention trials have tended to show minimal benefit from vitamin E supplementation. The promising findings of the seminal CHAOS trial have generally not been confirmed in subsequent large trials.

No randomized trial has addressed whether antioxidant vitamins from natural food sources are cardioprotective. Dietary vitamin E is a mixture of tocopherols and tocotrienols, whereas vitamin E supplements generally contain only α-tocopherol. It has been suggested that the absence of other tocopherols, particularly γ-tocopherol, may explain some of the disappointing trial results.43–45 Several large-scale trials currently under way will provide additional data to help identify the potential benefits of vitamin E in the primary prevention of CVD as well as other chronic illness. Some of these studies are specifically designed to test the effect of vitamin E alone as well as in combination with other antioxidant supplements because it is possible that antioxidants may be most effective when taken in particular combinations.

At present, according to the American Heart Association (AHA), there is insufficient efficacy data from completed randomized trials to justify establishment of population-wide recommendations regarding the use of vitamin E for disease prevention. Instead, the AHA’s dietary guidelines recommend a balanced diet with an emphasis on antioxidant-rich fruits and vegetables and whole grains. The U.S. Preventive Services Task Force indicates that it is “neither for nor against taking vitamins A, C, or E; multivitamins with folic acid; or combinations of these vitamins for the primary purpose of preventing CVD or cancer.”46 In 2002, the influential Institute of Medicine concurred with this recommendation and concluded that avail-
Gaziano: Vitamin E and Cardiovascular Disease

Able empirical evidence indicates that the relationship between vitamin E supplement use and CHD is “uncertain.”

Even if future clinical trials demonstrate that vitamin E supplementation reduces the risk of CVD, the use of these supplements should be considered an adjunct, not an alternative, to other established cardioprotective measures, such as smoking abstinence, avoidance of obesity, adequate physical activity, and control of high blood pressure and dyslipidemia.

REFERENCES


