Vitamin E in the Prevention of Cardiovascular Disease- the Importance of Proper Patient Selection

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List of Abbreviations

ASCVD- atherosclerotic cardiovascular disease
BA-FMD- Brachial artery flow-mediated dilatation
CC-IMT- common carotid intima-media thickness
CCS- coronary calcium score
CI- confidence interval
CKD- chronic kidney disease
CV- Cardiovascular
DM- Diabetes Mellitus
ED- endothelial dysfunction
ECG- electrocardiogram
HR- hazard ratio
Hb- Hemoglobin
Hp- Haptoglobin
HRT- hormone replacement therapy
IMT- intima-media thickness
LDL- low-density lipoprotein
MACE- major adverse cardiac events
MI- myocardial infarction
MLD- mean lumen diameter
PUFA- polyunsaturated fatty acids
RCT - Randomized Controlled Trial

RR - relative risk
Abstract

Vitamin E is a naturally occurring fat-soluble antioxidant which has been proposed as a treatment for both primary and secondary protection against cardiovascular (CV) events. Promising data from observational epidemiological studies associating higher vitamin E dietary intake with lower risk of CV events have not been validated in randomized, controlled clinical trials assessing the effect of vitamin E on CV outcomes. While the pendulum of medical opinion has swung to suggest that high dose vitamin E supplements have no place in the treatment and prevention of CV disease, new data is emerging that allows identification of a specific target population for this treatment, namely patients with Diabetes Mellitus and the haptoglobin genotype 2-2. This review details the scientific basis and clinical evidence related to the effect of vitamin E on CV outcomes, and the importance of proper patient selection in gaining therapeutic benefit from this intervention.

Keywords

Vitamin E, cardiovascular outcomes, diabetes mellitus, haptoglobin
Background

Vitamin E is a group of eight lipophilic molecules, four of which are tocopherols and four of which are tocotrienols(1). It is mostly found in nuts and various vegetable oils (2). γ-tocopherol is the most abundant vitamin E in western diet, while α-tocopherol is the most abundant form of vitamin E in plasma, and is most biologically active. In vitro, vitamin E possesses many biological functions, including regulation of cell survival(3-8), enhancement of endothelial function(9-12), and regulation of inflammatory processes(13-27). In vivo it most notable for its antioxidant functions.

Vitamin E is classified as an antioxidant due to its ability to scavenge lipid radicals and terminate oxidative chain reactions(1). It can terminate radical chain reactions by interacting with the lipid peroxyl radical, preventing it from generating a new radical and perpetuating the chain reaction by oxidizing other lipids(1). Following its oxidation, vitamin E can be recycled back to its native unoxidized form by various soluble antioxidants such as vitamin C and ubiquinol. This process prevents the accumulation of vitamin E radicals and their subsequent peroxidation of lipids(28), and is considered by some to be critical for the antioxidant activity of vitamin E(29). It has been suggested that all of the other biological functions of vitamin E are actually a result of its antioxidant activity(30).

Basic research has provided credible mechanisms by which vitamin E might exert CV benefit, including inhibition of oxidation of low-density lipoprotein (LDL) cholesterol in plasma(31). Observational epidemiologic studies suggested that individuals who consumed high amounts of vitamin E through diet or supplements had decreased rates of CV disease(32-35). These observations laid the foundation for additional, more robust clinical research in this field. Thus, several prospective studies were initiated with the aim of assessing the benefit of vitamin E in primary and secondary prevention of CV morbidity and mortality.
Vitamin E in Cardiovascular Protection

Numerous prospective randomized clinical trials assessing the effect of vitamin E supplementation on CV protection have been carried out over the past 15 years. These studies have assessed this intervention in primary and secondary prevention (Table 1).

- Primary prevention

In 1998, Virtamo et al. published the results of a randomized controlled trial (RCT) in which 27,271 Finnish male smokers aged 50 to 69 years with no history of myocardial infarction (MI) were randomly assigned to receive vitamin E (50 mg/day), beta carotene (20 mg/day), both agents, or placebo daily for 5 to 8 years (median, 6.1 years) (36). The end point was the first MI. The incidence of MI decreased 4% among recipients of vitamin E compared with the respective non-recipients, particularly due to a decrease in fatal events. However, the observed effect did not reach statistical significance. In 2001, de Gaetano et al. published the results of the Collaborative Group of the Primary Prevention Project (PPP)(37). In this randomized two-by-two factorial design study, the effect of aspirin (100 mg/day) and vitamin E (300 mg/day) in the prevention of cardiovascular events was assessed in 4,495 people with one or more cardiovascular risk factors. After a mean follow-up of 3.6 years the trial was prematurely stopped on ethical grounds when newly available evidence from other trials on the benefit of aspirin in primary prevention had emerged. Vitamin E treatment had not prevented CV events to a significant degree at the time of study closure. However, a subsequent analysis of outcomes in patients with Diabetes Mellitus (DM) was consistent with the lack of benefit of vitamin E treatment(38). Similar results were obtained from the St. Francis RCT study published in 2005, in which 1,005 asymptomatic men and women aged 50 to 70 years with coronary calcium scores at or above the 80th percentile for age and gender were randomized to atorvastatin (20 mg/d), vitamin C (1 g/d), and vitamin E (1,000 IU/d)(39). All study participants also received aspirin 81 mg daily. Mean duration of treatment was 4.3 years. None of these interventions had an effect on progression of coronary calcium score, or on clinical outcomes. The
authors stipulated that treatment may have reduced cardiovascular events in a subgroup of subjects with very high calcium scores.

Other studies were designed to assess the effect of vitamin E on the progression of atherosclerosis rather than on definitive clinical outcomes. The results of the Vitamin E Atherosclerosis Prevention Study (VEAPS) were presented in 2002(40). Men and women over 40 years old with LDL cholesterol levels above 3.37 mmol/L (130 mg/dL) and no clinical signs or symptoms of CV disease were randomized to vitamin E (400 IU/d) or placebo and followed for an average of 3 years. The primary trial end point was the rate of change in the common carotid artery far-wall intima-media thickness (IMT) assessed by computer image-processed B-mode ultrasonograms. Compared with placebo, vitamin E supplementation significantly reduced circulating oxidized LDL, and reduced LDL oxidative susceptibility. However, vitamin E supplementation did not reduce the progression of IMT. The effect of a treatment strategy consisting of pravastatin, vitamin E, and homocysteine lowering therapy on carotid IMT, endothelial function, and renal function in patients with mild to moderate chronic kidney disease was evaluated in the Anti-Oxidant Therapy in (ATIC) study. Vitamin E supplementation was initiated after 6 months of pravastatin treatment, after which homocysteine-lowering therapy was introduced for another 6 months. Patients were randomized to treatment versus placebo groups and were followed for 18 months. This combined stepwise antioxidant approach yielded a significant decrease in IMT, endothelial dysfunction, and albuminuria, but did not affect renal function(41).

In 2005 the results from the Women Health Study (WHS) were published(42). The trial was designed to test whether vitamin E supplementation decreases the risk of CV disease and cancer among healthy women. 39,876 apparently healthy US women aged at least 45 years were randomly assigned to receive vitamin E (600 IU), aspirin, or placebo, using a two-by-two factorial design, and were followed for an average of 10.1 years. The primary outcomes were a composite end point of first major CV event (nonfatal MI, nonfatal stroke, or CV death) and cancer. During follow-up a non-significant 7% risk reduction (relative risk [RR], 0.93; 95% confidence interval [CI], 0.82-1.05; P = .26) was noted in favor
of the vitamin E treatment. The only statistically significant effect was a 24% reduction (RR, 0.76; 95% CI, 0.59-0.98; P = .03) in CV death. A secondary analysis of these data showed lack of effect of vitamin E to reduce heart failure events in this population(43). Overall the authors concluded that vitamin E treatment did not decrease the number of major CV events, did not affect total mortality, and although there was decreased CV mortality in healthy women, the results did not support recommending vitamin E supplementation for CV disease prevention.

The Physicians Health Study was a randomized, double-blind, placebo-controlled factorial trial of vitamins E (400 IU every other day) and C (500 mg/day), assessing CV outcomes (MI, nonfatal stroke, and CV death) in 14,641 males over the age of 50 years, of which 94.9% were free from CV disease at enrollment. At a follow-up through 8 years none of the interventions had any effect on CV outcomes, but vitamin E was associated with an increased risk of hemorrhagic stroke (hazard ratio [HR], 1.74; 95% CI, 1.04–2.91; P=0.036)(44).

- **Secondary prevention**

In 1992, DeMaio et al. published the results of a RCT aimed at assessing whether vitamin E (1200 IU/d) can prevent restenosis (defined as stenosis ≥ 50%) following percutaneous transluminal coronary angioplasty. Follow-up cardiac catheterization showed that patients receiving vitamin E had a 35.5% restenosis vs. 47.5% restenosis in patients receiving placebo, but this difference did not reach statistical significance(45). The first study to assess robust clinical outcomes associated with vitamin E intervention in the setting of secondary prevention was the Cambridge Heart Antioxidant Study (CHAOS)(46). This RCT investigated the effects of vitamin E (400 IU/day or 800 IU/day) on the risk of CV death and non-fatal MI in patients with overt clinical and angiographic coronary atherosclerosis at recruitment. Overall 1,035 patients received the intervention, and 967 received placebo. In a median follow-up of 510 days the risk of the primary trial endpoint of CV death and non-fatal MI was significantly reduced (relative risk 0.53, p=0.005), with MI being the contributing factor associated with the observed benefit, while excess
CV death rate was noted in the vitamin E treated group. The study was not powered to explain the disparity in treatment effect. Contrary to these findings, the Gruppo Italiano per lo Studio della Sopravvivenza ll'Infartomiocardico(GISSI)-Prevenzione investigators randomly assigned patients surviving recent MI to n-3 polyunsaturated fatty acids (PUFA) (1 g daily, n=2836), vitamin E (300 mg daily, n=2830), both (n=2,830), or none (control, n=2,828) for 3.5 years. The primary combined efficacy endpoint of death, non-fatal MI, and stroke was not affected by vitamin E treatment(47).

In 2000, the results of the Heart and Outcomes Prevention Evaluation (HOPE) study were published(48). In this trial, the investigators enrolled 2,545 women and 6,996 men 55 years of age or older who were at high risk for CV because they had cardiovascular disease or diabetes in addition to one other risk factor. These patients were randomly assigned to treatment groups according to a two-by-two factorial design to receive either vitamin E (400 IU/d) from natural sources or matching placebo, and either an angiotensin-converting- enzyme inhibitor (ramipril) or matching placebo, for a mean of 4.5 years. The combined outcome of CV death, non-fatal MI and stroke, as well as the individual outcomes, did not differ between the groups. The authors conclude that vitamin E had no apparent effect on CV outcomes in this high-risk population. In concurrent publications from the HOPE cohort, lack of vitamin E protection against CV outcomes was noted in patients with DM(49) and mild to moderate chronic kidney injury(50). The HOPE-TOO study(51) was an extension of the original HOPE study, in which patients were randomly assigned to a daily dose of natural source vitamin E (400 IU) or matching placebo, with the main outcome measures being cancer incidence, cancer deaths, and major CV events (MI, stroke, and CV death). Primary outcomes did not differ, while patients in the vitamin E group had a higher risk of heart failure (RR, 1.13; 95% CI, 1.01-1.26; P = .03) and hospitalization for heart failure (RR, 1.21; 95% CI, 1.00-1.47; P = .045).

Additional studies assessed the effect of combination vitamin E and vitamin C on CV outcomes. The Women’s Angiographic Vitamin and Estrogen (WAVE) Trial, a randomized, double-blind trial, was designed to determine whether hormone replacement therapy (HRT) or a combination of vitamin E (400
IU/day) plus vitamin C (500mg BID) supplements, alone or in combination, influence the progression of coronary artery disease in 423 postmenopausal women(52). The hazard ratio for death, nonfatal MI, or stroke was 1.5 (95% CI, 0.80-2.9), signifying a trend towards higher risk in vitamin E and C treated patients. In the Heart Protection Study, 20,536 adults (aged 40–80) with coronary disease, other occlusive arterial disease, or diabetes were randomly allocated to receive antioxidant vitamin supplementation (600 mg vitamin E, 250 mg vitamin C, and 20 mg β-carotene daily) versus matching placebo(53). The intervention it did not produce any significant reductions in the 5-year mortality from, or incidence of, any type of vascular disease, cancer, or other major outcome.

Contrary to the above, the Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease (SPACE) study(54), in which hemodialysis patients with CV disease were randomized to vitamin E (800 IU/day) or placebo, showed a beneficial effect for vitamin E. The relative risk for a composite of MI, ischemic stroke, peripheral vascular disease, and unstable angina, at a median of 519 days, was 0.46 (95% CI 0.27-0.78, p=0.014). Death was not affected by the intervention.

In view of the lack of consistent clinical data supporting a beneficial role for vitamin E supplementation in preventing cardiovascular events, the medical community has largely abandoned this avenue of treatment.

**Diabetes, haptoglobin genotype, and vitamin E**

Atherosclerosis is prevalent in diabetics, and over 75% of DM patients die of atheroascular disease(55). The pathogenesis of atherosclerosis in DM is complex. Endothelial dysfunction is the hallmark of the pathological insult inflicted on blood vessels of DM individuals(56, 57). The role of oxidative stress in mediating the development of atherosclerosis has been formulated in the oxidative hypothesis(58), in which the LDL molecule undergoes oxidative modification. Oxidized LDL is not recognized by the LDL receptor but is readily taken up by the CD36 scavenger receptor pathway in macrophages leading to
appreciable cholesterol ester accumulation and foam cell formation(59). Oxidized LDL is pro-
inflammatory, causes inhibition of endothelial nitric oxide synthetase, promotes vasoconstriction and
monocyte adhesion, and promotes platelet aggregation and thrombosis(60). Both oxidative stress and
LDL oxidation are known to be present in patients with DM(59).

Haptoglobin (Hp) is an abundant plasma glycoprotein synthesized by hepatocytes. Two classes of
functional alleles (1 and 2) have been identified, with homozygous (1-1 or 2-2) and heterozygous (2-1)
genotypes possible(61, 62). The frequency of the 3 Hp genotypes in western counties is approximately
16% Hp 1-1, 48% Hp 2-1 and 36% Hp 2-2(61, 62) and is the same in individuals with and without
DM(63). The protein products of the Hp 1 Hp 2 alleles differ in their antioxidant function. Hp is essential
to the clearance of hemoglobin (Hb), and by forming the Hp-Hb complex, Hp prevents oxidative stress on
the vasculature exerted by Hb iron. Studies have shown that Hp 2-2-Hb complexes are cleared less
efficiently than Hp 2-1-Hb and Hp 1-1-Hb complexes(64, 65), particularly in DM individuals(65). Hp-Hb
deficient clearance in Hp 2-2 DM individuals results in increased Hp-Hb binding to Apo A1 on high-
density lipoprotein (HDL), thereby tethering the pro-oxidative heme moiety to HDL(64). HDL in Hp 2-2
DM individuals is deficient in its ability to stimulate the reverse transfer of cholesterol from
macrophages(64). Oxidative modification of the HDL appears to be responsible for these alterations in
HDL function in DM individuals with Hp 2-2(66).

- Clinical studies assessing the risk of cardiovascular complications in diabetics with Hp 2-2
  versus diabetics with Hp non 2-2

One case-control and five prospective longitudinal studies have assessed the association between Hp
genotype and the event rates of stroke, non-fatal MI, CV death, heart failure and mortality, in DM. In the
Strong Heart Study (SHS), a population based longitudinal study in Native Americans, 206 incident cases
and 206 matched controls were analyzed over an interval of six years(66). In a multivariate analyses
controlling for conventional CV risk factors, the Hp genotype was a highly statistically significant,
independent predictor of CV outcomes in DM. The odds ratio (OR) in the SHS study of having CV disease in DM with the Hp-2-2 genotype was 5.0 times greater than in DM individuals with the Hp-1-1 genotype.

In prospective longitudinal trials, 1,829 patients with DM and the Hp 2-2 genotype and 3,135 patients with DM and the Hp 1-1 or Hp 2-1 genotypes, were followed for periods ranging between 30 days and a mean of 18.8 years. Patients enrolled in the Israel Cardiovascular Vitamin E (ICARE) study(67), and a subset of patients from the WHS(68, 69) and HOPE(70, 71) trials, were studied for total mortality, CV mortality, non-fatal MI and stroke. When comparing DM patients with Hp 2-2 to a group of non-2-2 Hp type patients (Hp 1-1 and 2-1), a harmful effect of Hp 2-2 genotype was observed. For CV mortality, the pooled percentage of patients experiencing an event was 3.4% versus 1.2%, for the Hp 2-2 versus the non-2-2 Hp groups, respectively. For stroke, the percentages were 2.8% versus 1.7%, respectively. For non-fatal MI data from a fourth trial were available(72), and the combination of these 4 studies has shown that the percentage of patients experiencing an event in the Hp 2-2 group was 6.29%, versus 3.74% in non-2-2 Hp patients. The ORs for CV mortality, stroke, and non-fatal myocardial infarction all suggest a harmful effect for Hp 2-2 genotype with statistical significance (2.37 (95% CI 1.32 to 4.24), 2.08 (95% CI 1.22 to 3.55), 1.94 (95% CI 1.39 to 2.71), respectively). Combining a total of CV mortality, strokes and non-fatal MIs also shows a striking difference in events of 9.35% versus 5.76% (OR of 2.03 (95% CI 1.46 to 2.81). Total mortality assessed in three trials(72-74) was higher in the Hp 2-2 group (10.54% versus 6.97%, OR 1.53 (95% CI 1.17 to 2.00)). These effects were maintained after adjusting for the duration of follow-up. These effects were maintained after adjusting for the duration of follow-up.

- Controlled clinical studies assessing the effect of vitamin E on rates of CV complications in individuals with diabetes and the Hp 2-2 genotype
In three of these studies (or their subsets) the effect of vitamin E on patients with the Hp2-2 genotype versus patients without the Hp 2-2 genotype was evaluated. The ICARE(67) study was a RCT aimed to evaluate this intervention in DM patients for which the Hp genotype was prospectively collected. Additionally, blood samples from a subset of patients recruited for the WHS (42, 68) and HOPE(48, 69) studies were analyzed for Hp polymorphism, and the outcomes were re-assessed according to the patient’s Hp type. In all of these studies, it was found that Hp 2-2 DM conferred a higher risk for CV mortality without intervention (compared to the non-2-2 Hp cohort), and that intervention with vitamin E significantly decreased this risk. Meta-analysis of the HOPE and ICARE data showed that vitamin E significantly reduces a composite of CV death, MI and stroke in Hp 2-2 diabetes patients (OR 0.58, confidence interval (CI) 0.4-0.86), while having no influence in Hp 1-1 or Hp 2-1 diabetes patients(58). In the WHS cohort, Vitamin E supplementation was associated with an approximately 15% reduction in composite CV outcomes in Hp 2-2 DM individuals, compared to a 20–25% increase in non-Hp 2-2 DM individuals(68).

- Lack of benefit of a combination of Vitamin C and Vitamin E on atherosclerosis in Hp 2-2 diabetic individuals

A potential inconsistency in the hypothesis that vitamin E supplementation provides cardiovascular protection in Hp 2-2 diabetic individuals, is the failure to demonstrate a protective effect of the combination of vitamin C and vitamin E against the angiographic progression of atherosclerosis in WAVE Hp 2-2 participants. In the initial analysis of WAVE(52), change of mean lumen diameter (MLD) from baseline to the concluding angiogram was not affected by a combination of vitamin E plus vitamin C supplements. Retrospective analysis of these data after Hp genotypes were obtained on the entire WAVE cohort demonstrated a significant benefit from the combined treatment with vitamin C and vitamin E on MLD progression in Hp 1-1 and a significant worsening in MLD progression in Hp 2-2 individuals, especially in the setting of diabetes(73). We have proposed that this apparent harmful effect of vitamin C in Hp 2-2 diabetic individuals on angiographic progression of atherosclerosis was due to the
ability of vitamin C to promote redox cycling of the increased non-transferrin bound iron (Hp 2-2-Hg complexes) found in Hp 2-2 diabetic individuals(74). Supporting this hypothesis, divergent effects of α-tocopherol and vitamin C on HDL function have been demonstrated in vitro and in vivo in Hp 2-2 diabetic mice(75). It was shown that vitamin C could not block HDL oxidation by glycosylated Hp 2-2 – Hb complexes in vitro (glycosylated Hb was prepared by a 3-day incubation with glycolaldehyde), nor could it restore the ability of serum from Hp 2-2 diabetic mice to mediate HDL mediated cholesterol efflux from macrophages, whereas α-tocopherol could favorably affect both. Importantly, the addition of vitamin C to α-tocopherol in this study was shown to diminish the protective effect of vitamin E on HDL function. These results emphasize that in assessing the effect of antioxidant supplementation on the risk of vascular diabetes complications, all antioxidants are not equivalent and different outcomes may be obtained with different combinations of antioxidants.

Conclusions

Does vitamin E protect against the development of CV disease? The answer appears to be a resounding no when one provides vitamin E indiscriminately to unselected populations. However, vitamin E has been shown to be cardio-protective in certain patient subgroups under high levels of oxidative stress such as those individuals on hemodialysis (SPACE) or in diabetic individuals with the Hp 2-2 genotype (ICARE). A plausible biological rational has been provided. The adoption of a pharmacogenomic approach to the use of vitamin E appears to identify a subgroup of individuals for whom vitamin E provides significant clinical benefit.
Acknowledgements

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Disclosure

APL is the author of a patent which is owned by his institution that claims that the Hp genotype is predictive of DM complications. He is also a consultant for Haptocure which has licensed this patent from his institution.
References


43. Chae CU, Albert CM, Moorthy MV, Lee IM, Buring JE. Vitamin E supplementation and the risk of heart failure in women. *Circ Heart Fail. 5*:176-82.


Table 1: Prospective Studies Assessing Vitamin E for Cardiovascular Protection.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>Follow-up [years]</th>
<th>Specific patient characteristics</th>
<th>Number of patients</th>
<th>Clinical outcomes</th>
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<tbody>
<tr>
<td></td>
<td><strong>Studies assessing vitamin E for primary prevention</strong></td>
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<td></td>
<td><em>(Results are given in relative measures (95% CI) or absolute numbers (p-value))</em></td>
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<tr>
<td>Virtamo et al.(36)</td>
<td>α-tocopherol (50 mg/d), beta carotene (20 mg/d), both, or placebo</td>
<td>6.1</td>
<td>Male, smokers</td>
<td>27,271</td>
<td>First MI and CV death:</td>
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<td>- RR 0.98 (0.87-1.10)</td>
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<tr>
<td>PPP(37)</td>
<td>Aspirin (100 mg/day) and α-tocopherol (300 mg/day) (2X2 design)</td>
<td>3.6</td>
<td>Over 1 CV risk factor</td>
<td>4,495</td>
<td>CV death, MI, stroke:</td>
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<td>- RR 1.07 (0.74–1.56)</td>
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<tr>
<td>St. Francis(39)</td>
<td>Atorvastatin (20 mg/day) plus vitamin C (1 g/day) plus α-tocopherol (1,000 IU/day) vs. placebo</td>
<td>4.3</td>
<td>CCS≥ 80th percentile</td>
<td>1,005</td>
<td>ASCVD event rate:</td>
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<td>- 6.9% vs. 9.9% (p=0.08)</td>
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<tr>
<td>VEAPS(40)</td>
<td>DL-α-tocopherol (400 IU/d) or placebo</td>
<td>3</td>
<td>LDL &gt; 3.37 mmol/L</td>
<td>353</td>
<td>CC-IMT change from baseline:</td>
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<td></td>
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<td></td>
<td>- 0.0023±0.0007 vs. 0.0040±0.0007 (p=0.08)</td>
</tr>
<tr>
<td>ATIC(41)</td>
<td>α-tocopherol, pravastatin, and homocysteine-lowering therapy, consecutively introduced.</td>
<td>1.5</td>
<td>CKD</td>
<td>93</td>
<td>CC-IMT, ED, renal function,albuminuria:</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>- CC-IMT: 0.68 to 0.63mm vs. 0.65 to 0.71mm (p&lt;0.001)</td>
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<td>- BA-FMD: 4.66% to 7.56% vs. 6.21% to 4.73%(p&lt;0.001)</td>
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<td>- eGFR: 32 to 35 mL/min/1.73m² vs.</td>
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<tr>
<td>Study</td>
<td>Treatment</td>
<td>Duration</td>
<td>Gender</td>
<td>Participants</td>
<td>Outcomes</td>
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<tr>
<td>WHS(42,43)</td>
<td>α-tocopherol (600 IU), aspirin, or placebo</td>
<td>10.1</td>
<td>Women</td>
<td>39,876</td>
<td>CV death, MI, stroke: RR 0.93 (0.82-1.05)</td>
</tr>
<tr>
<td>PHS II(44)</td>
<td>α-tocopherol (400 IU every other day), vitamin C or placebo</td>
<td>8</td>
<td>Men</td>
<td>14,641</td>
<td>CV death, MI, stroke: HR 1.01 (0.90–1.13)</td>
</tr>
</tbody>
</table>

Studies assessing vitamin E for secondary prevention
(Results are given in relative measures (95% CI) or absolute numbers (p-value))

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Duration</th>
<th>Gender</th>
<th>Participants</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeMaio et al.(45)</td>
<td>DL-α-tocopherol (1200 IU/d) or placebo</td>
<td>0.33</td>
<td>-</td>
<td>100</td>
<td>Restenosis: 34.6% vs. 50% (p = 0.06)</td>
</tr>
<tr>
<td>CHAOS(46)</td>
<td>DL-α-tocopherol (400 IU/d or 800 IU/d) or placebo</td>
<td>1.4</td>
<td>-</td>
<td>2,002</td>
<td>CV death and non-fatal MI: RR 0.53 (0.34-0.83)</td>
</tr>
<tr>
<td>GISSI-Prevenzione(47)</td>
<td>PUFA (1 g/day), DL-α-tocopherol (300 mg/day), both or none</td>
<td>3.5</td>
<td>-</td>
<td>5,658</td>
<td>Death, MI, and stroke: RR 0.95 (0.86–1.05)</td>
</tr>
<tr>
<td>HOPE(48)</td>
<td>α-tocopherol (400 IU/day), ACE inhibitor or placebo (2X2 design)</td>
<td>4.5</td>
<td>-</td>
<td>9,541</td>
<td>CV death, MI and stroke:</td>
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<tr>
<td>Study</td>
<td>Intervention</td>
<td>Duration</td>
<td>Participants</td>
<td>Outcomes</td>
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<tr>
<td>WAVE(52)</td>
<td>Vitamin E (400 IU/day) plus vitamin C (500mg BID), HRT, or placebo (2X2 design)</td>
<td>4</td>
<td>Post-menopausal women 423</td>
<td>Death, MI, stroke: HR, 1.5 (0.80-2.9)</td>
<td></td>
</tr>
<tr>
<td>Heart Protection Study (53)</td>
<td>DL-(\alpha)-tocopherol (600 mg/day), vitamin C (250 mg/day), and (\beta)-carotene (20 mg/day) or placebo.</td>
<td>5</td>
<td>-</td>
<td>CV death, MI, stroke, revascularization: RR 1.00 (0.94–1.06) Cancer: RR 0.98 (0.89–1.08)</td>
<td></td>
</tr>
<tr>
<td>SPACE (54)</td>
<td>(\alpha)-tocopherol (800 IU/day) or placebo</td>
<td>1.4</td>
<td>Hemodialysis 196</td>
<td>MI, ischemic stroke, peripheral vascular disease, and unstable angina: RR 0.46 (0.27-0.78)</td>
<td></td>
</tr>
</tbody>
</table>

**Longitudinal studies assessing CV outcomes according to Hp phenotype in patients with DM**

(Results are given in relative measures (95% CI) or percentages (\(p\)-value))

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Participants</th>
<th>CV events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Heart Study(66)</td>
<td>6</td>
<td>Native Americans 412</td>
<td>OR Hp 2-2 vs. 1-1: 5.08 (2.37–10.89) OR Hp 2-2 vs. 2-1: 3.26 (1.67–6.37)</td>
</tr>
<tr>
<td>Burbea et al.(71)</td>
<td>3</td>
<td>Hemodialysis 392</td>
<td>3 years survival rate: Hp 2-2 45.1% vs. Hp non 2-2 50% ((p&lt;0.003))</td>
</tr>
<tr>
<td>Costacou et al.(76)</td>
<td>18</td>
<td>CV disease free, type 1 453</td>
<td>Angina, ischemic ECG, MI, angiographic</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Population</td>
<td>Event / Time</td>
<td>Outcome</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------</td>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>Roguinet al. (70)</td>
<td>-</td>
<td>1</td>
<td>Post PTCA</td>
</tr>
<tr>
<td>Suleiman et al. (72)</td>
<td>-</td>
<td>30 days</td>
<td>Acute MI</td>
</tr>
</tbody>
</table>

### Longitudinal studies assessing CV outcomes according to Hp phenotype with and without vitamin E treatment

(Results are given in relative measures (95% CI))

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Women</th>
<th>CV death, MI, stroke:</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHS study data (42, 68)</td>
<td>α-tocopherol (600 IU), aspirin, or placebo</td>
<td>10.1</td>
<td>Women</td>
<td>721</td>
<td>OR in Hp 2-2 0.87 (0.49, 1.53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR in Hp non 2-2 1.33 (0.75, 2.37)</td>
</tr>
<tr>
<td>ICARE (67)</td>
<td>D-α-tocopherol (400 IU/day) or placebo</td>
<td>1.5</td>
<td>-</td>
<td>2,967</td>
<td>CV death, MI, stroke:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR in Hp 2-2 0.46 (0.25, 0.85)</td>
</tr>
<tr>
<td>HOPE study data (48, 69)</td>
<td>Vitamin E (400 IU/day), ACE inhibitor or placebo (2X2 design)</td>
<td>4.5</td>
<td>-</td>
<td>530</td>
<td>CV death, MI, stroke:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR in Hp 2-2 0.69 (0.42, 1.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR in non-Hp 2-2 1.02 (0.69, 1.62)</td>
</tr>
</tbody>
</table>
ASCVD- atherosclerotic cardiovascular disease (events includes coronary death, non-fatal MI, coronary revascularization procedures, non-hemorrhagic stroke, and peripheral revascularization procedures), BA-FMD: Brachial artery flow-mediated dilatation, CC-IMT- common carotid intima-media thickness, CCS- coronary calcium score, CKD- chronic kidney disease, CV- cardiovascular, DM- diabetes mellitus, ED- endothelial dysfunction, ECG- electrocardiogram, HR- hazard ratio, HRT- hormone replacement therapy, LDL- low-density lipoprotein, MACE- major adverse cardiac events, MI- myocardial infarction, MLD- mean lumen diameter, OR- odds ratio, RR- relative risk