The role of vitamin E in the prevention of coronary events and stroke

Meta-analysis of randomized controlled trials

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the world. Vitamin E as an anti-oxidant vitamin, was suggested to have a role in the prevention of CVD. We did a meta-analysis, using the Cochrane Group Methodology, of all available randomized controlled trials (RCTs) to evaluate the role of vitamin E in the prevention of CVD. Nine studies met inclusion criteria, including 80,645 participants. Vitamin E supplementation was not associated with a reduction in total mortality or total CVD mortality, but it was associated with a small statistically significant reduction in non-fatal myocardial infarction in patients with pre-existing coronary artery disease. Prophylactic use of vitamin E in doses ranging between 50-800 IU was not associated with any increase in the incidence of serious side effects.

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the world.[1] Data from 21 countries showed that the coronary heart disease mortality rate was 189 per 100,000 for men and 45 per 100,000 for women. The non-fatal myocardial infarction (MI) rate was 93 per 100,000 for men and 49 per 100,000 for women.[1] Inexpensive, accessible and safe preventive therapies that decrease the incidence and mortality of CVD are expected to have a great effect on public health.

Oxidative modification of low-density lipoprotein (LDL) is an important step in the development and progression of atherosclerosis.[2-4] Low-density lipoprotein cholesterol is rendered atherogenic by oxidative modifications that allow it to accumulate in artery walls.[4-6] Antioxidant vitamins such as vitamin E inhibit oxidation of LDL and have been shown to slow atherosclerosis.[7-9] Vitamin E (100 IU/d or more) was shown to decrease coronary artery lesion progression, as assessed with angiography.[10] Several epidemiological studies showed that anti-oxidant vitamins, mainly vitamin E, might have a role in the prevention of coronary events.[11-13] Alpha-tocopherol is the most common naturally occurring compound of vitamin E.[14] The recommended dietary allowance of vitamin E is 15 mg daily for adult men and women. Each 1 mg of vitamin E equals to 1.5 IU of natural vitamin E and 2.2 IU of synthetic vitamin E.[14] Vegetable oils, nuts, and green leafy vegetables are the main dietary sources of vitamin E.[14] Vitamin E cost ranges between 0.17-0.31 US $/day.[15]

The primary objective of this review is to assess the role of vitamin E supplements in the prevention of coronary events and stroke in adults.

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Randomized controlled trials (RCTs), in which the outcomes of the intake of vitamin E supplement alone or with other supplements were compared to a control group (placebo or control). Studies of adults of either gender (>18 years) at any given risk of cardiovascular disease (with or without existing cardiovascular disease) were accepted.

Vitamin E alone or with other supplements versus placebo or no intervention. Supplementation may be in a capsule or a tablet form, to be consumed by mouth. At least one of the following outcomes must be reported: total MI, fatal or non-fatal MI, total stroke, ischemic or hemorrhagic stroke, total cardiovascular mortality and total mortality.

The main outcomes were total MI, fatal MI, and non-fatal MI. The secondary outcomes were total stroke, hemorrhagic stroke, ischemic stroke, total mortality and cardiovascular mortality.

Search strategy for identification of studies. The following bibliographic databases were searched to identify the relevant primary studies: The Cochrane Controlled Trials Register (CCTR), MEDLINE, and EMBASE, for articles published between January 1966 and March 2004. The search strategy was conducted using the MeSH terms: "antioxidants" "vitamins", "vitamin E", "alpha-tocopherol", "tocopherol", "cardiovascular-diseases", "coronary disease" "myocardial infarction", "cerebrovascular accident", "prevention", "primary prevention", "secondary prevention m.p." and "randomized controlled trials". These terms were used in various combinations. The Cochrane library, Issue 4, 2002 was searched for relevant articles using the same search strategy.

Additional studies were identified and included where relevant by searching Scisearch, and the bibliographies of review articles and identified trials. No language restrictions were applied.

All identified trials were reviewed independently by 2 reviewers to determine whether trials should be included or excluded. Disagreement was resolved by consensus with provision of arbitration of the third reviewer. All selected studies were published studies.

Assessment of methodological quality. Both reviewers determined the methodological quality of each trial independently and any disagreement was resolved by consensus with provision of arbitration of the third reviewer. The same 2 reviewers assessed the methodological quality of each trial according to the adequacy of allocation concealment, randomization method, the rate of follow up, whether all patients were accounted for in the final analysis, whether patients were analyzed according to the groups to which they were assigned and whether outcome assessment was blinded. Four categories for the allocation concealment are available: A = clearly adequate such as centralized randomization. B = possibly adequate such as stated random, but unable to obtain further details. C = clearly inadequate such as allocation procedure was not adequately concealed. D = not described.

After the independent evaluation, the 2 assessors discussed the results for each study and any discrepancy was resolved by consensus with provision of arbitration of the third reviewer.

Data were independently extracted by the same reviewers and cross-checked. Any discrepancies were discussed by consensus with provision of arbitration of the third reviewer.

Primary measures of interest were the effect of vitamin E supplementation on total MI, fatal and non-fatal MI. Analysis was made for all strokes, ischemic strokes, hemorrhagic strokes, total cardiovascular mortality, and total mortality. Subgroup analysis was made for vitamin E supplement alone, vitamin E with other supplements and for primary prevention and secondary prevention trials.

The Cochrane Statistics Package RevMan, version 4.1 was used. Relative risk (RR) and risk difference (RD) with 95% CI's were reported. If there was a statistically significant RD the number needed to treat (NNT) and number needed to harm (NNH) were calculated. Statistically significant between-study heterogeneity was reported when identified (using $p<0.10$) and we calculated a weighted estimate of the typical treatment effect across trials (RR) using the random effects model.

Details of the included studies are provided in **Table 1**. Nine trials including 80,645 individuals met inclusion criteria. More than 14,000 (18%) of the participants were females. These trials were performed in many countries (Finland, Italy, Canada, China, United Kingdom, United States of America, Denmark, Germany, Ireland, Netherlands, Norway, Spain, Sweden, Switzerland, Israel, and Mexico). The vitamin E dose varied between 50mg/d to 800 mg/d (**Table 1**). Synthetic vitamin E preparations were used in 5 studies.[16-20] Vitamin E of natural sources were used in 3 studies.[21-23] One study did not specify the source of vitamin E.[24] Studies duration ranged between 510 days to 8 years. One study was excluded, as the number of participants in the different intervention groups was not available.[25]

Methodological quality of included studies. The assessment of individual studies is presented in **Table 1**. The lack of placebo in 2 studies precludes blinding of caregivers, but outcome assessment was blinded in these studies.[19,20] All studies were analyzed using the intention to treat principle. In the ATBC trial the drop out rate was high (31.1%), 12.3% had died and 18.8% were alive at the end of the study. Approximately half of those who died had dropped out of the study earlier. The drop out rate varied only slightly across the 4

randomized groups in this study (from 30.1-31.3%).[17]

Table 2 shows the summary of results. 1) Vitamin E alone versus control = there was no statistically significant reduction in all of the outcomes that was available for assessment in studies that used vitamin E alone, (**Table 2**). 2) Vitamin E and other supplements versus control = there was no statistically significant reduction in all of the outcomes that was available for assessment in studies that used vitamin E and other supplements, (**Table 2**). 3) Role of vitamin E in primary prevention = there was no statistically significant reduction in all of the outcomes that was available for assessment in studies that used vitamin E and other supplements (**Table 2**). 4) Role of vitamin E in secondary prevention = there was no statistically significant reduction in all of the outcomes that was available for assessment in studies that used vitamin E for secondary prevention, except for non-fatal MI, (**Table 2**). Three studies (including 3,102 individuals) reported on the role of vitamin E in the secondary prevention of non-fatal MI.[18,22,26] One study showed a statistically significant reduction in the incidence of non-fatal MI in individuals receiving vitamin E supplements (RR 0.32; 95% CI 0.18, 0.58).[22] When all studies were combined there was a significant reduction in the incidence of non-fatal MI (RR 0.51; 95% CI 0.38, 0.70, RD=-0.03, NNT=33). There was statistically

Table 1 - Characteristics of included trials.

Study	Duration	Participants	Interventions	Quality
ATBC-Leppala et al 2000[35,37]	6.1 years	29,133 male smokers, 50-69 years of age, without history of stroke.	Vitamin E (50 mg/day), or beta-carotene (20 mg/day), both or placebo.	A
ATBC-Rapola 1997[26]	6.1 years	1,862 men enrolled in the ATBC Prevention Study who had a pervious MI.	Vitamin E (50 mg/day), or beta-carotene (20 mg/day), both or placebo.	A
ATBC-Virtamo 1998[36]	6.1 years	27,271 male smokers enrolled in the ATBC Prevention Study without history of MI.	Vitamin E (50 mg/day), or beta-carotene (20 mg/day), both or placebo.	A
Heart Protection Study[16,38]	5 years	20,536 adults from UK with coronary artery disease, other occlusive arterial disease, or diabetes.	Vitamin E 600 mg/d, vitamin C 250 mg, and beta-carotene 20 mg daily, or matching placebo.	A
CHAOS 1996[22]	510 days	2,002 patients with angiographically proven coronary atherosclerosis.	Vitamin E (800 IU/day for first 546 patients, 400 IU/day for reminder), or matching placebo.	A
GISSI 1999[19]	3.5 years	11,324 Patients with recent (<3 months) MI.	Vitamin E (300 mg daily, n=2830), n=3 PUFA (1g daily, n=2,836), both (n=2,830), or none (control n=2,828).	A
HOPE 2000[23]	4.5 years	9,541 patients at high risk for cardiovascular events.	Vitamin E 400 IU or matching placebo	A
Li et al 1993[18]	6 years	3,318 patients with cytological evidence of esophageal dysplasia.	Daily supplementation with 14 vitamins including vitamin E (60 IU/day) and 12 minerals, or matching placebo.	B
PPP 2001[20]	3.6 years	4,495 patients with one or more of risk factors for cardiovascular disease (mean age 64.4).	Vitamin E (300 mg/day), and No Vitamin E groups, and aspirin (100 mg/day) and No aspirin groups.	A
SPACE 2000[21]	519 days	196 Hemodialysis patients with pre-existing cardiovascular disease aged 40-75	Treatment: Vitamin E 800 IU/day, or matching placebo.	A
Steiner et al 1995[24]	2 years	100 patients with history of TIA, minor stroke, or residual ischemic neurologic deficits.	Aspirin (325 mg/d) and Vitamin E (400 IU/d) or aspirin and matching placebo.	B

ATBC - Alpha-tocopherol Beta-Carotene Cancer, CHAOS - Cambridge Heart Antioxidant Study, GISSI - Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico, HOPE - Heart Outcomes Prevention Evaluation Study, PPP - Primary Prevention Project, SPACE - Antioxidants Of Cardiovascular Disease in Endstage Disease, MI - myocardial infarction, UK - United Kingdom, TIA - transient ischemic attacks, PUFA - n-3 polyunsaturated fatty acids

Table 2 - Summary of results.

Outcomes	N of studies	N of participants	RR (95% CI)
Vitamin E alone versus control			
Total myocardial infarction	4	16234	0.95 (0.86 - 1.06)
Fatal myocardial infarction	3	6693	0.79 (0.46 - 1.37)
Non-fatal myocardial infarction	4	21260	0.91 (0.80 - 1.04)
All stroke	6	34558	1.06 (0.94 - 1.19)
Ischemic stroke	5	28905	1.03 (0.90 - 1.17)
Hemorrhagic stroke	5	28905	1.19 (0.77 - 1.83)
Total cardiovascular disease mortality	6	36460	0.97 (0.89 - 1.06)
Total mortality	6	36460	1.00 (0.94 - 1.06)
Vitamin E and other supplements versus control			
All stroke	2	20223	1.04 (0.89 - 1.21)
Total cardiovascular disease mortality	3	40759	1.02 (0.95 - 1.10)
Total mortality	4	44077	1.03 (0.98 - 1.08)
Role of vitamin E in primary prevention			
Non-fatal myocardial infarction	2	18164	1.04 (0.90 - 1.21)
All stroke	2	18768	1.02 (0.86 - 1.20)
Role of vitamin E in secondary prevention			
Total myocardial infarction	4	12643	0.95 (0.86 - 1.05)
Fatal myocardial infarction	3	3102	1.30 (0.83 - 2.05)
Non-fatal myocardial infarction	3	3102	0.51 (0.38 - 0.70)
All stroke	4	15495	1.10 (0.93 - 1.31)
Ischemic stroke	3	9837	1.11 (0.91 - 1.35)
Hemorrhagic stroke	3	9837	1.44 (0.72 - 2.88)
Total cardiovascular disease mortality	4	17397	0.95 (0.85 - 1.07)
Total mortality	4	17397	0.97 (0.88 -1.05)
Vitamin E 300lU or more versus control			
Total myocardial infarction	4	16234	0.95 (0.86 - 1.06)
Fatal myocardial infarction	3	6693	0.79 (0.46 - 1.37)
Non-fatal myocardial infarction	3	6693	0.52 (0.35 - 0.77)
All stroke	5	19990	1.11 (0.94 - 1.31)
Ischemic stroke	4	14332	1.12 (0.93 -1.36)
Hemorrhagic stroke	4	14332	1.30 (0.69 - 2.47)
Total cardiovascular disease mortality	6	42428	1.01 (0.94 - 1.08)
Total mortality	6	42428	1.01 (0.96 - 1.07)
Vitamin E <300lU versus control			
Total mortality	2	17891	1.01 (0.93 - 1.09)
Synthetic vitamin E versus control			
Non-fatal myocardial infarction	2	19068	0.99 (0.86 - 1.14)
All stroke	2	10153	1.04 (0.73 - 1.48)
Ischemic stroke	2	19068	0.96 (0.80 - 1.15)
Hemorrhagic stroke	2	19068	1.04 (0.6 - 1.83)
Total cardiovascular disease mortality	4	45262	1.0 (0.93 - 1.07)
Total mortality	5	48580	1.01 (0.96 - 1.06)
Natural vitamin E versus control			
Total myocardial infarction	2	9737	1.00 (0.89 - 1.12)
Non-fatal myocardial infarction	2	2198	0.32 (0.19 - 0.56)
All stroke	2	9737	1.16 (0.95 - 1.40)
Ischemic stroke	2	9737	1.14 (0.94 - 1.40)
Hemorrhagic stroke	2	9737	1.31 (0.64 - 2.70)
Total cardiovascular disease mortality	2	9737	1.03 (0.89 - 1.19)
Total mortality	2	9737	1.00 (0.90 - 1.12)
Adverse events			
Hemorrhagic events	2	4595	1.12 (0.58 - 2.16)
Gastrointestinal bleeding	2	4691	1.19 (0.54 - 2.63)

significant between-study heterogeneity for this outcome (p=0.085 for RR). The RR was 0.46 (95% CI 0.25, 0.84) using the random effects model. 5) Post hoc outcomes = there was no statistically significant reduction in all of the outcomes that was available for assessment in studies that used high dose of vitamin E (>300 IU), except for non-fatal MI, (**Table 2**). Three studies reported on the role of high dose vitamin E in the prevention of non-fatal MI.[21-20] There was a statistically significant reduction in the incidence of non-fatal MI (RR 0.52; 95%CI 0.35, 0.77, RD=-0.01, NNT=10). There was statistically significant between study heterogeneity for this outcome (p=0.02). The RR was 0.51 (95%CI 0.21, 1.25) when the random effects model was used. There was no statistically significant reduction in all of the outcomes that was available for assessment in studies that used synthetic vitamin E, (**Table 2**). Natural vitamin E showed a statistically significant reduction of non-fatal MI (RR 0.32; 95% CI 0.19, 0.56, RD=-0.03, NNT=33). There was no statistically significant between-study heterogeneity for this outcome (p=0.93). Vitamin E was well tolerated in all studies, with no significant difference between treatment groups in the incidence of adverse effects. Although few studies detailed the reported adverse effects; there was no statistically significant difference between vitamin E and placebo in the incidence of hemorrhagic events or gastrointestinal bleeding in the combined analysis of studies that reported these adverse events. The methodological quality of the included trials was high. Vitamin E showed a statistically significant reduction in the secondary prevention of non-fatal MI, which was the only statistically significant effect among the prior set outcomes. The NNT to prevent nonfatal MI in patients with pre-existing coronary artery disease was 33. There was statistically significant between-study heterogeneity for this outcome but the effect of vitamin E continued to be statistically significant when we used the random effect model. There was a statistically significant between-study heterogeneity for many outcomes in this analysis which might in part be explained by; variable rates of events in the control groups, differences in the risk for cardiovascular events in the included studies; differences in vitamin E dose (high versus low); differences in vitamin E preparation (synthetic versus natural); differences of the other supplements used with vitamin E; and differences in the characteristics of the different studies populations (including sex ratios, age, and co-morbidities). There were no statistically significant differences for total mortality, and CVD mortality. The results of these outcomes were all centered around a RR of 1.0 with narrow CIs indicating no trends in either direction. Many researchers suggested that high dose of vitamin E (>300 IU daily) should be used to obtain the CVD prevention benefits which was found in observational studies.[27,28] We did a post hoc analysis of high dose vitamin E which showed a statistically significant reduction in non-fatal MI (NNT=10). When the random effect model used to adjust for the between-study heterogeneity there was a statistically non-significant trends of reduction in non-fatal MI. Many researchers suggested that synthetic vitamin E may be less bio-available than natural vitamin E which might affect the role of vitamin E in the prevention of

Table 3 - Characteristics of ongoing studies.

Study	Participants	Interventions	Outcomes
Physicians Health Study II[30]	15,000 US male physicians aged 55 and older with no history of cancer, or cardiovascular disease	Vitamin E or beta-carotene or Vitamin C or a daily multivitamin or placebo in a 2x2x2x2 factorial design.	Total and prostate cancer, CVD, and eye disease
The Supplementation en Vitamins et Mineraux Antioxidant[31]	12,735 French adult men and women 35-60 years old	Vitamin E 30mg, beta-carotene 6000µg; vitamin C 120mg; selenium 100µg; and zinc 20mg or placebo.	Incidence of cancer (all sites) and ischemic heart disease incidence, overall and cause specific mortality.
Women's Atherosclerosis Cardiovascular Study[32]	8,000 female nurses with history of cardiovascular disease	Vitamin E 400IU/d or vitamin C Ig/d, or beta-carotene 20mg/d (2x2x2 factorial design)	MI, stroke, coronary revascularization, and death from cardiovascular disease.
Women's Health Study[33,34]	40,000 postmenopausal US nurses	Vitamin E 600 IU/d beta-carotene 50 mg every other day (3x2 factorial design with aspirin)	MI, stroke, and death from cardiovascular disease.

MI - myocardial infarction, US - United States, CVD - cardiovascular disease

CVD.[27,29] We did a post hoc analysis of natural vitamin E which showed a statistically significant reduction in non-fatal MI (NNT=33), while synthetic vitamin E did not appear to affect the incidence of non-fatal MI.

Limitations. We were not able to carrry out a meta-analysis of the reported adverse events of vitamin E, because few studies detailed these adverse events. However, most studies indicated that there was no statistically significant increase in the incidence of adverse events in the different treatment groups. There was no statistically significant increase in the incidence of hemorrhagic stroke and other hemorrhagic events in studies that reported these outcomes.

In conclusion, vitamin E supplementation results in a 3% absolute reduction in nonfatal MI in patients with pre-existing coronary artery disease but is not associated with a reduction in total mortality or total CVD mortality. Prophylactic use of vitamin E in doses ranging between 50-800 IU was not associated with any serious side effects. The use of vitamin E for the secondary prevention of non-fatal MI at doses ranging between 400-800 IU was shown to be cost-effective and safe. The results of ongoing large RCTs (**Table 3**) are expected to be available in a few years, which will provide a more precise answer about the efficacy of vitamin E especially in the primary prevention of CVD.[30-34] Future RCTs testing the efficacy of vitamin E supplements should use high doses of vitamin E from natural sources.

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