Medicines Adverse Reactions Committee

Meeting date	2/12/2021	Agenda item	3.2.2
Title	**Tocopherol and risk of bleeding**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
<u>General sale</u>		
Ascorbic acid; Cupric oxide; D-alpha Tocoferol; Zinc oxide	Blackmores Macu-Vision Film coated tablet	Blackmores (NZ) Ltd
Ascorbic acid; Biotin; Cocarboxylase; Colecalciferol; Cyanocobalamin; Dexpanthenol; dl-Alpha tocopherol; Folic acid; Nicotinamide; Pyridoxine; Retinol; Riboflavin	Cernevit Powder for injection	Baxter Healthcare Ltd
Ascorbic acid; D-alpha Tocoferol; Folic acid; Garlic oil; Lycopene; Selenomethionine; Zinc sulfate	Menevit Liquid filled capsule	Bayer New Zealand Limited
dl-Alpha tocopherol; Ergocalciferol; Phytomenadione; Retinol	Vitalipid N Adult Emulsion for injection Vitalipid N Infant Emulsion for injection	Fresenius Kabi New Zealand Limited
<u>Pharmacy only</u>		
Ascorbic acid; Biotin; Calcium hydrogen phosphate; Colecalciferol; Copper; Cyanocobalamin; dl-Alpha tocopherol; Ferrous fumarate; Folic acid; Magnesium oxide; Manganese sulfate; Nicotinamide; Pantothenic acid; Potassium iodide; Pyridoxine; Riboflavin; Sod	Elevit Film coated tablet, New formulation	Bayer New Zealand Limited
Ascorbic acid; Biotin; Calcium hydrogen phosphate; Colecalciferol; Copper; Cyanocobalamin; D-alpha Tocoferol; Ferrous fumarate; Folic acid; Magnesium oxide;	Elevit with Iodine Film coated tablet	Bayer New Zealand Limited

Magnesium phosphate; Manganese sulfate; Nicotinamide; Pantothenic acid; Potassium iodide; Pyridoxi These are all medicines with a status of 'Consent given' at 7 October 2021.	
PHARMAC funding	None of the above products are funded.
Previous MARC meetings	Tocopherols have not previously been discussed by the MARC.
International action	None known. This signal was highlighted to Medsafe by a sponsor [redacted]
Prescriber Update	Tocopherols have not been discussed in *Prescriber Update* to date.
Classification	Most tocopherol containing products are General Sale. Elevit is a Pharmacy Only medicine.
Usage data	Number of people who received a dispensing of alpha tocopheryl acetate - Water solubilised soln 156 iu/ml, with calibrated dropper from a pharmacy at least once during the year (includes people who only received a repeat dispensing during the year). • 2015: 4 • 2016: 1 • 2017: 6 • 2018: 2 The product mentioned above is the only product with information in the Ministry's pharmaceutical data web tool. This product was delisted in 2011 because the supplier has withdrawn from the New Zealand market (https://pharmac.govt.nz/assets/form-alphatocopherylacetate-VitaminE-and-Retinol-vitaminA.pdf). There is no funded oral liquid containing vitamin E and until a time when an agreement is made to fund another product, PHARMAC will consider exceptional circumstances applications (https://nzf.org.nz/nzf_5396).
Advice sought	**The Committee is asked to advise:** • whether the evidence supports there being an increased risk of bleeding with tocopherol and if so, is any regulatory action required? • whether this topic requires further communication other than MARC's Remark's in *Prescriber Update*?

Table of Contents

1 PURPOSE

[redacted] advised Medsafe of a signal of tocopherol and intracranial haemorrhage at recommended doses of tocopherol (see section 3.2.1 for more information).

The purpose of this paper is to review the potential safety concern of bleeding with tocopherol.

2 BACKGROUND

2.1 Tocopherol

Tocopherol (vitamin E) is a lipid-soluble antioxidant that reduces the rate of oxidative stress [1]. Tocopherol acts as a radical scavenger, trapping free radicals, and is an important component in the pathogenesis of atherosclerosis [1, 2]. The major role of vitamin E is working as a free radical scavenger to protect polyunsaturated fatty acids from oxidation [3] [4]. Oxidised phospholipids and other lipid peroxidation products allow build-up of plaque in arteries and cause atherogenesis [1]. Vitamin E therefore has a role in inhibiting formation of atherosclerosis [1]. It does this by scavenging reactive oxygen species, modifying vascular endothelium vasodilator responsiveness, reducing platelet aggregation and preserving cell membranes [1]. Deficiency has been connected to cardiovascular events [4].

Tocopherol must be ingested from the diet and cannot be synthesized in the human body [4]. Alpha-tocopherol is the most biologically active form of tocopherol and the form known for its role in human health [4, 5].

Tocopherol's functions depend on the H-atom donating ability, location, and movement within the membrane, as well as the efficiency in the radical recycling by some cytosolic reductants such as ascorbate [2].

2.1.1 Tocopheryl quinone

The main oxidation product of α-tocopherol is tocopheryl quinone [3]. Tocopheryl quinone is conjugated to glucuronate and excreted in bile or further degraded in the kidneys to α-tocopheronic acid before excretion in bile [3]. α-tocopherol has very modest anticlotting activity however in contrast tocopheryl quinone is an anticoagulant [6].

Dowd and Zheng, 1995, looked at the anticoagulant properties of vitamin E. The authors found that vitamin E from all sources inhibited the uptake of $14CO_2$ in the vitamin K-dependent carboxylase assay [6]. They found that purified α-tocopherol showed inhibitory properties only at very high concentrations and by contrast pure vitamin E quinone completely inhibited production of vitamin K oxide [6]. It is thought the low level of inhibitory activity by α-tocopherol might be the result of oxidation to small amounts of vitamin E quinone, inhibiting the vitamin K clotting pathway [6].

2.1.2 Intake recommendations

The New Zealand Formulary (NZF) states the daily requirement of vitamin E is probably around 4 to 10 mg daily [5].

Adequate Intakes (AI) and upper levels (UL) of intake have been published in the Nutrient Reference Values for Australia and New Zealand document and are shown in the table below [3].

Table 1 Adequate intakes (AI) and upper levels (UL) intake of vitamin E in New Zealand

	AI of vitamin E (as α-tocopherol equivalents)	**Upper level of intake of vitamin E (as α-tocopherol equivalents)**
0-6 months	4 mg/day	Not possible to establish. Source of intake should be breast milk, formula and food only.
7-12 months	5 mg/day	

1-3 years	5 mg/day	70 mg/day
4-8 years	6 mg/day	100 mg/day
9-13 years (boys)	9 mg/day	180 mg/day
9-13 years (girls)	8 mg/day	180 mg/day
14-18 years (boys)	10 mg/day	250 mg/day
14-18 years (girls)	8 mg/day	250 mg/day
19-30 years (men)	10 mg/day	300 mg/day
19-30 years (women)	7 mg/day	300 mg/day
31-50 years (men)	10 mg/day	300 mg/day
31-50 years (women)	7 mg/day	300 mg/day
51-70 years (men)	10 mg/day	300 mg/day
51-70 years (women)	7 mg/day	300 mg/day
>70 years (men)	10 mg/day	300 mg/day
>70 years (women)	7 mg/day	300 mg/day
14-18 years (pregnant)	8 mg/day	300 mg/day
19-30 years (pregnant)	7 mg/day	300 mg/day
31-50 years (pregnant)	7 mg/day	300 mg/day
14-18 year (lactating)	12 mg/day	300 mg/day
19-30 years (lactating)	11 mg/day	300 mg/day
31-50 years (lactating)	11 mg/day	300 mg/day

UpToDate, an American electronic clinical research tool, mentions slightly higher limits. The tolerable upper intake level (UL) is 1000 mg/day for any form of alpha-tocopherol (approximately 1500 international units of natural source of 2200 international units of synthetic vitamin E) [4].

The UL in children ranges from 200 mg/day for 1 to 3 year old children to 600 mg/day for 9 to 13 year olds [4]. The upper limits are based largely on concerns for haemorrhagic effects [4].

2.2 Bleeding

A range of conditions can cause bleeding (haemorrhage): trauma, medical conditions and medicines [7].

Stroke is defined as rapidly developing disturbance of cerebral function, including cerebral infarction, intracerebral haemorrhage and subarachnoid haemorrhage [1]. It is estimated globally that 15.6% of all strokes are haemorrhagic and 84.4% are ischaemic [1]. Intracerebral haemorrhage is the second most common cause of stroke (following ischaemic stroke) but accounts for a disproportionate amount of cerebrovascular morbidity and mortality [8].

The Stroke Foundation of New Zealand estimates over 1000 strokes are experienced each year and are a leading cause of serious adult disability [9]. Stroke is New Zealand's second single biggest killer [9].

Intracranial haemorrhages can be life-threatening [10].

The Stroke Foundation of NZ defines types of haemorrhagic stroke as follows [9]:

- Cerebral haemorrhage: when an artery in the brain ruptures and leaks blood into the brain.
- Subarachnoid haemorrhage: when blood leaks into the surface of the brain.

- Intracranial haemorrhage: when there is bleeding into the brain tissue itself.

2.3 Data sheets

2.3.1 New Zealand

Data sheets are not required in New Zealand for general sale or pharmacy only medicines so not all the tocopherol-containing products listed on the first page have data sheets. The medicines with a data sheet or Consumer Medicine Information (CMI) are listed in the table below.

Table 2 Data sheet wording for the two medicines containing vitamin E which currently have a data sheet in New Zealand.

Product Name (tocopherol dose)	Related information in data sheet or CMI	Indication
Cernevit (data sheet) (Annex 1) 10.20 mg dl-α-tocopherol, corresponding to 11.20IU alpha tocopherol (vitamin E)	Section 4.4 Warnings and precautions for use General monitoring: Clinical status and vitamin levels should be monitored in patients receiving parenteral multivitamins as the only source of vitamins for extended periods of time.	Cernevit is indicated in adults and children over 11 years of age requiring parenteral multi-vitamins supplementation to correct or prevent vitamin deficiencies when oral administration is contraindicated, impossible or insufficient.
Vitalipid (data sheet) (Annex 2) Vitalipid (CMI) 10 ml ampoule contains 9.1 mg (10 IU) dl-alpha-tocopherol (adult) and 6.4 mg (7.0 IU) dl-alpha-tocopherol (infant)	None	Vitalipid N Adult is indicated as a supplement in complete intravenous nutrition to meet the daily requirements of the fat-soluble vitamins A, D_2, E and K_1. Vitalipid N Infant is indicated as a supplement in complete intravenous nutrition to meet the daily requirements of the fat-soluble vitamins A, D_2, E and K_1 in paediatric patients up to 11 years of age.

No information specifically related to bleeding or intracranial haemorrhage was found in the product information.

2.3.2 United Kingdom

There is a published Summary of medicinal Product Characteristics (SmPC) (the UK equivalent to the data sheet) for Cernevit. This contains the same information as listed in the above table for Cernevit.

3 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Loh et al, 2021 (Annex 3) [1]

The authors conducted a systematic literature review with meta-analysis together with trial sequential analysis of randomised controlled trials to evaluate the effect of vitamin E supplementation versus placebo/no vitamin E on the risk reduction of the trial outcome measures: number of total, fatal, non-fatal, haemorrhagic and ischaemic stroke. Meta-analysis was performed using a random-effects model to produce the study risk ratios. The results were pooled if comparable outcome data were available from two or more studies. Risk of bias was evaluated for each included study.

The authors note previous studies on this topic remain inconsistent with differences being found mainly due to the pathological subtypes of stroke, namely ischaemic stroke and haemorrhagic stroke.

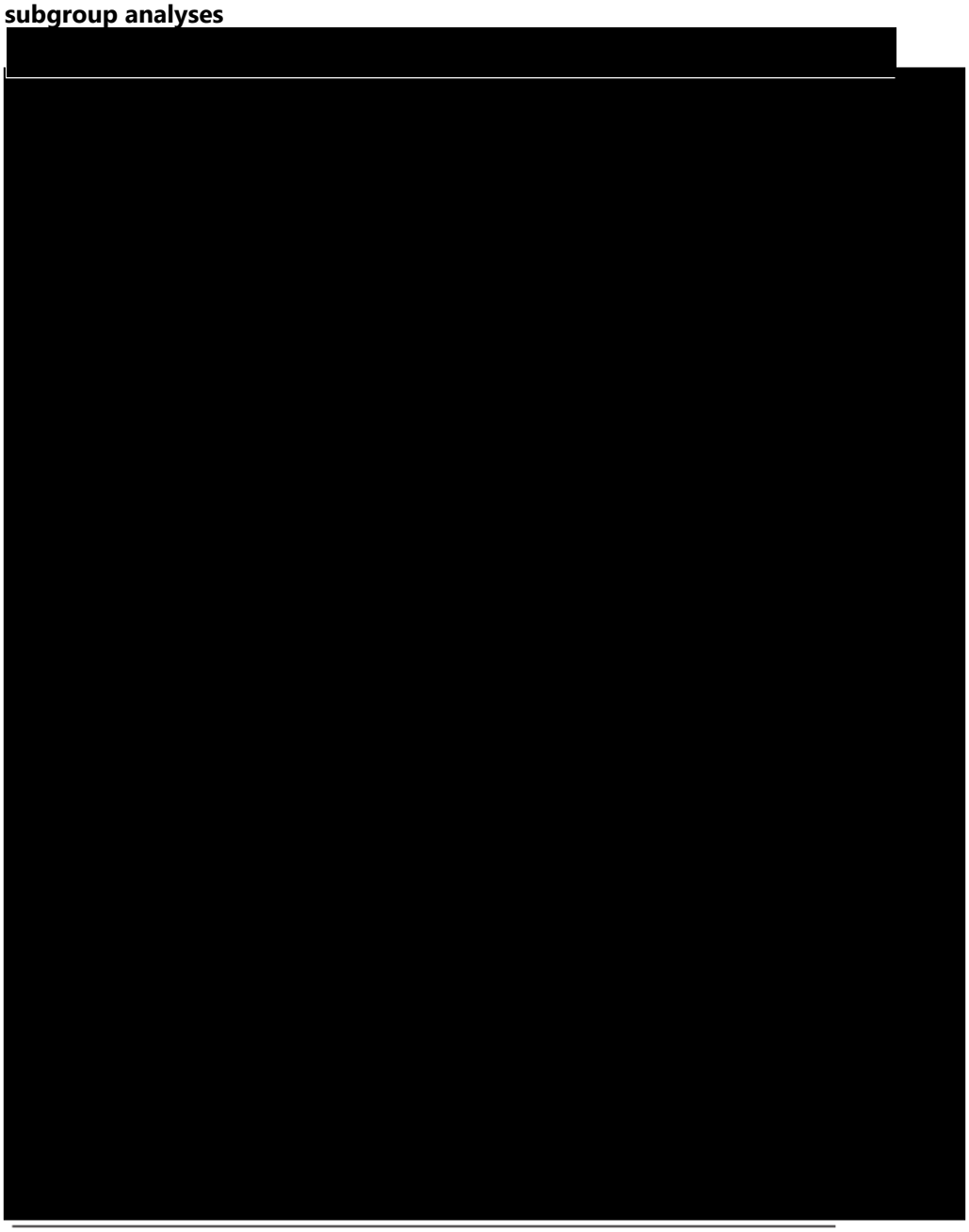
A total of 18 relevant studies were identified using a combination of search terms of tocopherol/ antioxidant and different types of stroke. The studies included 148,016 participants in the analysis (74,000 randomised to vitamin E and 74,016 to control arm). Sample sizes ranged from 100 to 39,876 subjects. Some of the studies are described in more detail further below in section 3.1.

Table 3 presents the characteristics of the trials. In two trials (PPP and GISSI), vitamin E was compared with no vitamin E while the remaining compared vitamin E to placebo.

Table 3 Characteristics of trials

The effect of vitamin E on total stroke and its subgroup analysis by type of prevention, source of vitamin E, dosage of vitamin E (high if 300 IU or more; low if less than 300 IU) and vitamin E alone (without other pharmacological and/or non-pharmacological intervention) are shown in Table 4.

Table 4 Relative risks of the effects of vitamin E on stroke for the pooled population and its subgroup analyses



No significant differences were found in the prevention of total stroke (RR (relative risk) = 0.98, 95% CI 0.92–1.04, p=0.57), fatal stroke (RR=0.96, 95% CI 0.77–1.20, p=0.73) and non-fatal stroke (RR=0.96, 95% CI 0.88–1.05, p=0.35). Subgroup analyses findings were also insignificant. Vitamin E showed significant risk reduction in ischaemic stroke (RR=0.92, 95% CI 0.85–0.99, p=0.04) but not in haemorrhagic stroke (RR=1.17, 95% CI 0.98–1.39, p=0.08).

The quality of evidence was rated, using GRADE (Grading of Recommendations, Assessment, Development and Evaluations), as high for vitamin E effect on fatal stroke and non-fatal stroke; moderate for total stroke and ischaemic stroke owing to a downgrade for risk of bias as most of the

included studies were ruled out for low risk of bias; and very low for haemorrhagic stroke due to very low number of events and wide confidence intervals.

The authors identified limitations of the analysis, such as: stroke not being the primary outcome in the included trials, low power to detect a change in stroke outcomes, participants may have had different lifestyles or health issues, there were a limited number of studies available for subgroup analysis, studies were mostly done in developed countries and the total sample size for all included studies was insufficient to obtain a meaningful result from meta-analysis.

The authors concluded that the study showed vitamin E supplementation significantly reduced the risk of ischaemic stroke by 8%. The authors consider the mechanism of action for this could be attributed to its antioxidant properties, antiplatelet action and antiatherogenic properties. However, they consider that additional well-designed RCTs are needed to draw any conclusive statement.

In contrast to a meta-analysis performed in 2010 which showed that vitamin E supplementation increased the risk for haemorrhagic stroke by 22% (see section 3.1.3), this study did not detect any significant difference in the risk of haemorrhagic stroke. The authors note this analysis included two additional studies which may be a reason for the difference. The authors consider that even though vitamin E is known for antiplatelet and anticoagulant activities with vitamin K, the conclusion that vitamin E increases the risk of haemorrhagic stroke cannot be established.

3.1.2 Pastori et al, 2013 [10]

The aim of this study was to analyse the relationship between vitamin E and bleeding events in nonvalvular atrial fibrillation (NVAF) patients who were receiving oral anticoagulant therapy (OAT) with warfarin.

566 out of 1012 NVAF patients who were on OAT were identified in this retrospective, single-centre, observational cohort study and followed up for at least 3 months. To be included, analysis of vitamin E had to be done on each patient. One of the exclusion criteria was if a person was taking any antioxidant supplementation.

The study analysed baseline serum cholesterol-adjusted vitamin E (vit E/chol) levels in 566 consecutive patients (59% males, mean age 73.6 years) receiving OAT followed up for a mean time of 22 months. Baseline characteristics can be seen in Table 5.

Table 5 Baseline Characteristics

Mean time in therapeutic INR range (TTR) was 64%. 92 patients (16%) experienced a primary outcome (major or minor bleeding) during follow-up. 4 out of the 19 major bleedings were cerebral haemorrhages (see Table 6 below). The overall incidence rate of any bleeding event was 9.2/100 person-years. Higher vitamin E serum levels were found in patients who experienced bleeding compared to those who did not (5.27±1.93 versus 4.48±1.97 µmol/cholesterol; P<0.001).

Table 6 Bleeding events

[redacted]

A significant increase of bleeding event rate across quartiles was observed (P=0.008; log-rank test) (Figure 1).

Figure 1 Kaplan-Meier estimates of time to main outcome events by vitamin E quartiles

The authors state that the idea that vitamin E possess anticoagulant properties is reinforced by this study as it provides evidence that in NVAF patients on OAT, vitamin E serum levels are predictors of bleeding.

A limitation of this study, according to the authors, is that it was conducted in a single Italian centre and could be hard to extrapolate to other countries with other diets. Additionally, because the clinical relevance of minor bleedings on the management of OAT patients has not yet been established, considering minor bleedings as outcomes should be questionable. Finally, the study has been conducted in a single centre only.

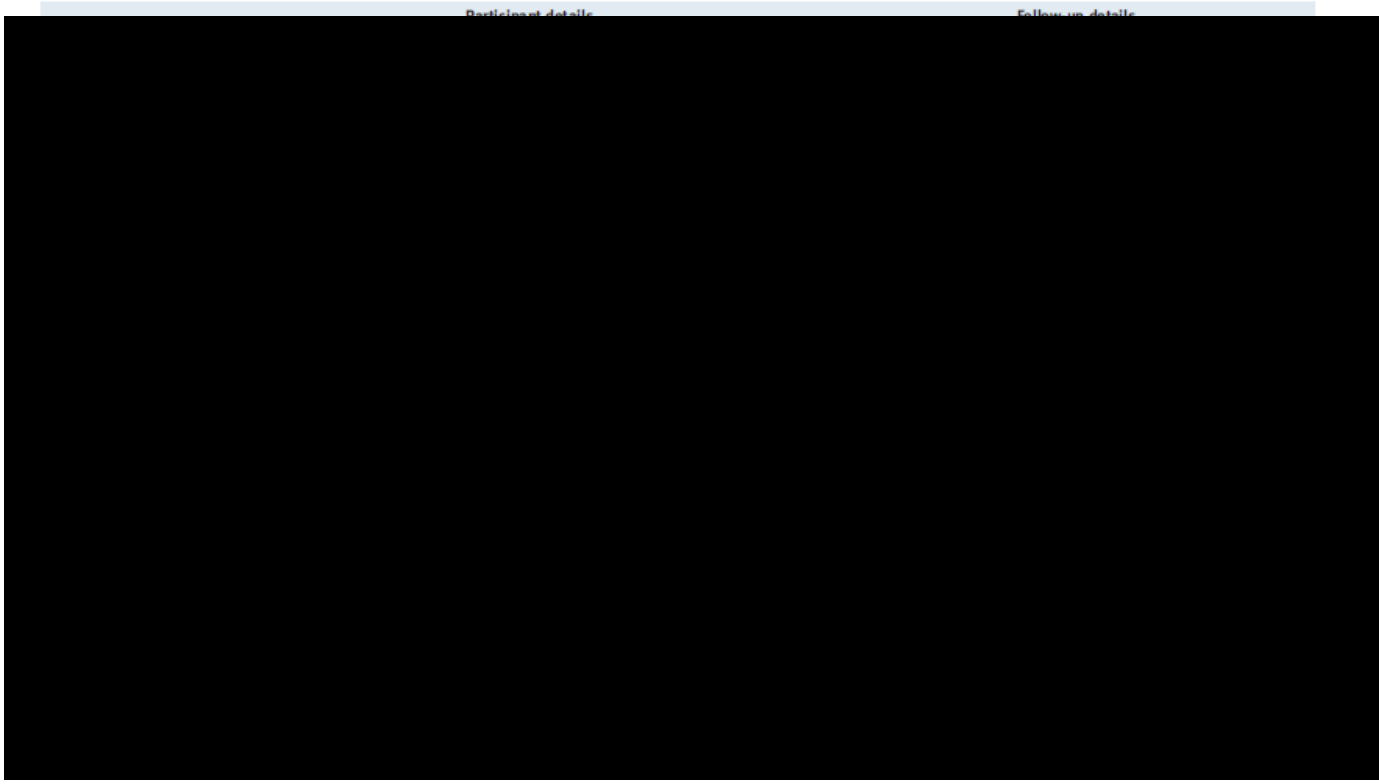
The authors concluded that in this population being treated with warfarin, serum vitamin E predicted haemorrhagic events. Further studies are needed to see if this relationship is maintained with the use of new anticoagulants.

3.1.3 Schurks et al, 2010 [11]

This is a systematic review and meta-analysis of randomised, placebo-controlled trials published until January 2010. Trials with more than one year of follow up investigating the effect of vitamin E on stroke were included.

Nine trials investigating the effect of vitamin E on incident stroke were included, totalling 118765 participants (59357 randomised to vitamin E and 59408 to placebo). 7 out of the 9 trials, provided data for total stroke and none of these individually suggest that vitamin E significantly alters the risk of total stroke. Five trials provided data for haemorrhagic and ischaemic stroke. The characteristics of the trials can be seen in the table below.

Table 7 Characteristics of the nine randomised controlled trials of vitamin E on stroke outcomes



1438 strokes occurred among the 58225 participants randomised to vitamin E and 1475 strokes occurred among the 58342 participants randomised to placebo. Vitamin E had no effect on the risk for total stroke (pooled relative risk 0.98 (95% confidence interval 0.91 to 1.05), P=0.53). In contrast, the risk for haemorrhagic stroke was increased (pooled relative risk 1.22 (1.00 to 1.48), P=0.045). Although results of four trials suggested increases in the relative risks of haemorrhagic stroke among participants receiving vitamin E, only the results from the Physicians' Health Study II reached statistical significance. The risk of ischaemic stroke was reduced (pooled relative risk 0.90 (0.82 to 0.99), P=0.02).

Forest plots for the relative risk of total stroke, haemorrhagic stroke and ischaemic stroke are presented in Figures 2-4 below.

Figure 2 Relative risks of the effect of vitamin E on total stroke for individual trials and for the pooled population

Figure 3 Relative risks of the effect of vitamin E on haemorrhagic stroke for individual trials and for the pooled population

Comment: The Women's Health Study (WHS) 2005 had the lowest relative risk which may be a sign of a gender effect.

Figure 4 Relative risks of the effect of vitamin E on ischaemic stroke for individual trials and for the pooled population

Incidence rates per 1000 were 24.7 for total stroke, 4.4 for haemorrhagic stroke, and 19.4 for ischaemic stroke in patients randomly assigned to vitamin E. For participants randomised to placebo, the incidence rates per 1000 were 25.3, 3.6, and 21.5 respectively. This translates into a risk difference per 1000 treated people of 0.6 fewer total strokes, 0.8 more haemorrhagic strokes, and 2.1 fewer ischaemic strokes. The authors state this means for every 1250 individuals taking vitamin E, one haemorrhagic stroke occurs; whereas one ischaemic stroke is prevented for every 476 individuals treated.

There was little evidence for heterogeneity among studies and results were the same when using a random effects model (pooled relative risk 1.22 (1.00 to 1.48), P=0.048).

The authors identified some limitations of their study, such as only including studies with 'pure' vitamin E and not combinations, considering randomised controlled trials irrespective of blinding and morbidity status of participants to increase the power, including a trial that did not specify the method of analysis and one that separated out haemorrhagic stroke. The authors noted that there is some indication that biological effects may be more complex than observed in the meta-analysis.

The authors also discuss some potential biological mechanisms:

- inhibition of platelet aggregation and adhesion *in vitro*.
- interference with activation of vitamin K dependent clotting factor and exerting an anticoagulant effect (the Women's Health Study saw reduced risk of venous thromboembolism in women randomised to vitamin E).

It is widely agreed that vitamin E has antioxidant properties, and that lipid peroxidation plays a central role in atherogenesis, however it is not known if the vitamin E doses chosen in clinical trials are adequate to prevent lipid peroxidation in humans and if vitamin E plays an important role in preventing lipid peroxidation at all. Novel research shows vitamin E has important functions in the regulation of membrane bound enzymes, cellular trafficking, gene expression and inflammatory responses however the implications of these mechanisms are not well understood yet. The authors state it is also not clear whether bleeding is restricted to the intracranial cavity in vitamin E treatment.

To conclude, this meta-analysis found that vitamin E increased the risk for haemorrhagic stroke by 22% and reduced the risk of ischaemic stroke by 10%.

3.1.4 Dereska et al, 2005 [12]

This study aimed to investigate the *in vivo* effect of short-term, moderate dose synthetic dl-alpha-tocopherol acetate supplementation on plate aggregation, coagulation profile and simulated bleeding time in healthy individuals.

42 healthy volunteers (21 male, 21 female, mean age 30.86 years) complied with a two-week abstinence period from the use of anti-platelet agents followed by determination of baseline platelet aggregation properties and coagulation studies using citrated whole blood. 800 IU vitamin E was self-administered for 14 days. After the short-term supplementation, no significant difference was seen in any study parameter. The authors conclude that the effect of vitamin E on platelet aggregation *in vitro* does not appear to be reproducible *in vivo* and therefore perioperative discontinuation of vitamin E may not be necessary.

3.1.5 Hathcock et al, 2005 [13]

This review article looked at the safety of vitamin E across a range of intakes.

Many literature reviews have documented the consistent absence of adverse effects of vitamin E at intakes well above the recommended dietary allowance (RDA).

For example, the Cambridge Heart Antioxidant Study reported no significant adverse effects of vitamin E supplementation (400 or 800 IU/day) over a median follow up of 510 days. The rate of treatment discontinuation due to adverse effects was only 0.55%.

The Heart Outcomes Prevention Evaluation Study investigators concluded that 400 IU/day of vitamin E was well tolerated because the number of adverse effects was not significantly greater in treatment group than placebo over the mean follow-up of 4.5 years.

However, the α-tocopherol, beta-carotene cancer prevention study (ATBC) study raised some caution. 29133 male smokers in Finland (ages 50-69 years) received 50 mg/d (74.5 IU) of vitamin E for 5-8 years. This was associated with a greater risk of death due to haemorrhagic stroke (66 cases (7.8%) in the vitamin group and 44 cases (5.2%) in the control group). The authors of that study concluded that the higher haemorrhagic stroke mortality seen with vitamin E compared to placebo required careful review.

Hathcock et al state a few other reports have suggested that bleeding complications may be associated with vitamin E supplementation. A high intake of vitamin E can influence coagulation in people with drug-induced vitamin K deficiency but most evidence suggests this doesn't occur in patients with adequate amounts of vitamin K.

They refer to a small clinical trial, where proteins induced by vitamin K absence-factor II (an accepted indicator of poor vitamin K status) increased with daily administration of 1000 IU RRR-α-tocopherol. Any clinical significance of this is not clear, however.

Vitamin E may also affect coagulation through its action on platelets. High vitamin E intake inhibits protein kinase C and consequently may limit the ability of platelets to clot.

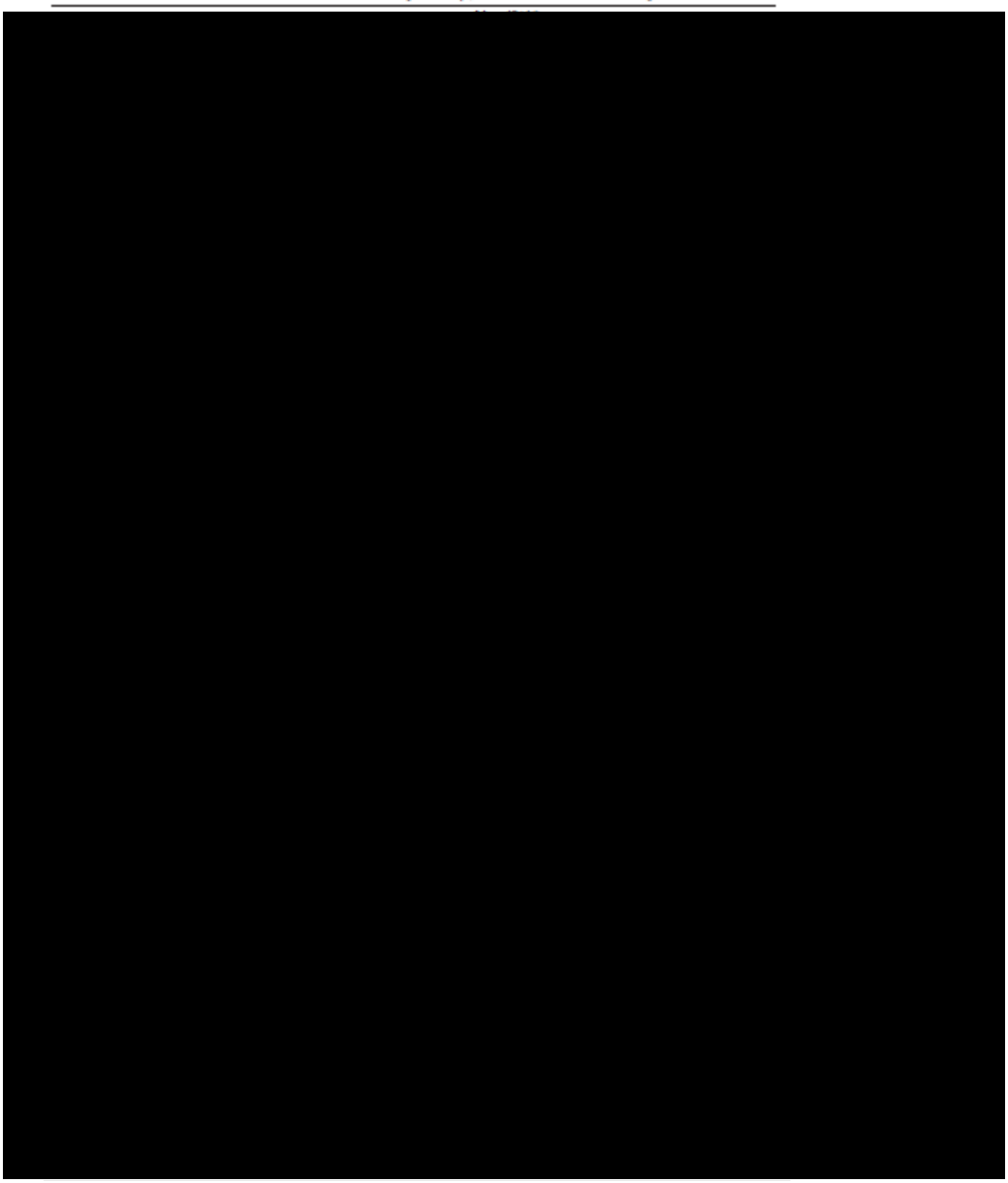
The authors conclude that even the haemorrhage-stroke mortality findings of the ATBC study have not changed initial view that vitamin E intake up to the upper limit is safe. They consider that the fact that adverse effects are rarely reported for vitamin E at amounts higher than the RDA is due to the safety of supplementation up to the UL (see section 2.1.2). It is noted that the upper limit is not intended to apply to the most sensitive persons in sensitive subpopulations but instead to apply to the healthy general population.

3.1.6 Lee et al, 2005 [14]

The Women's Health Study by Lee et al investigated whether vitamin E supplementation decreases risks of cardiovascular disease and cancer among healthy women. The study was conducted between

1992 and 2004. 39876 apparently healthy women aged at least 45 years of age were randomly assigned to receive vitamin E or placebo and aspirin or placebo using a 2 x 2 factorial design. 600 IU of vitamin E was administered on alternative days. They were followed up for an average of 10.1 years. Each year, women received calendar packs that contained amber capsules (vitamin E or placebo) and white pills (aspirin or placebo) on alternate days. The baseline characteristics can be seen in the table below.

Table 8 Baseline characteristics of women by group, Women's Health Study



By the end of the trial, 999 major cardiovascular events (253 per 100 000 person-years) had occurred: 482 in the vitamin E group and 517 in the placebo group. This was a nonsignificant 7% risk reduction (relative risk [RR], 0.93; 95% confidence interval [CI], 0.82-1.05; P=.26).

Table 9 Relative risks of cardiovascular disease, cancer and total mortality by group, Women's Health Study

There were no significant effects on the incidences of myocardial infarction (RR, 1.01; 95% CI, 0.82-1.23; P=.96) or stroke (RR, 0.98; 95% CI, 0.82-1.17; P=.82), as well as ischemic or haemorrhagic stroke. For cardiovascular death, there was a significant 24% reduction (RR, 0.76; 95% CI, 0.59-0.98; P=.03).

The study found aspirin was associated with a non-significant 9% reduction in major cardiovascular events. The authors further examined whether random assignment to aspirin modified the effect of vitamin E. No modification of effect was seen.

This study also examined whether vitamin E increased adverse effects due to bleeding because of the potential for vitamin E to inhibit platelet function. There were no differences between reported adverse events in the two groups, except for a small, but significant, increase in the risk of epistaxis (RR, 1.06; 95% CI, 1.01-1.11; P=.02).

The authors concluded that the data does not support recommending vitamin E supplementation for cardiovascular disease prevention in healthy women. No increase in haemorrhagic strokes with vitamin E was seen in this study in contrast to the ATBC trial (see section 3.1.11) which saw a greater number of deaths from these strokes.

3.1.7 Collaborative Group of the Primary Prevention Project, 2001 [15]

The Primary Prevention Project (PPP) is a controlled, centrally randomised, open-label clinical trial designed to test whether chronic treatment with aspirin and vitamin E reduces the frequency of major fatal and non-fatal cardiovascular events, with no clinically relevant safety implications. This study investigated in general practice the efficacy of antiplatelets and antioxidants in primary prevention of cardiovascular events in men and women, aged 50 years or greater, with one or more major cardiovascular risk factors (hypertension, hypercholesterolaemia, diabetes, obesity, family history of premature myocardial infarction, or individuals who were elderly).

Patients were randomly allocated to receive aspirin (one tablet of 100 mg enteric-coated aspirin a day) or no aspirin, and vitamin E (one capsule of 300 mg synthetic alpha-tocopherol a day), or no vitamin E, using a 2x2 factorial design.

The main combined efficacy endpoint was the cumulative rate of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

Between 1994 and 1998, 4495 patients were recruited, 4258 (94.7%) by 315 general practitioners and 237 (5.3%) by 15 hospital hypertension units. Mean age was 64·4 (SD 7.6) years and 2583 (57.7%) of the population were women. Baseline characteristics were well balanced across the groups, except for hypercholesterolaemia and mean cholesterol concentrations which were slightly higher in the aspirin than the no aspirin group.

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 was strictly consistent with the results of the second planned interim analysis. Aspirin lowered the frequency of all the endpoints.

The absence of evidence of effect is consistent for the main combined endpoint, for its components and for the other endpoints apart from the incidence of peripheral-artery disease, which was significantly lower among patients taking vitamin E than controls, with a RRR of 46% (p=0·043).

3.1.8 Leide et al, 1998 [16]

This study was an end-point examination of a random sample of male smokers who had participated in a controlled clinical trial, the ATBC study (see section 3.1.11), for 5.7 years. The objective of this study was to assess the effect of alpha-tocopherol supplementation on gingival bleeding either in combination with acetylsalicylic acid (ASA) or without it.

409 men aged 55-74 years were included. 191 received alpha-tocopherol (50 mg/day), 56 ASA, 30 received both and 132 received neither.

The study found that gingival bleeding was more common in those who received alpha-tocopherol compared with non-receivers among subjects with a high prevalence of dental plaque. However, the subjects with the highest risk of gingival bleeding were those who took both alpha-tocopherol and ASA.

This study concluded that alpha-tocopherol supplementation may increase the risk of clinically important bleedings, particularly when combined with ASA.

3.1.9 Meydani et al, 1998 [17]

A double-blind placebo-controlled trial was performed to assess the effects of 4 months of supplementation with 60, 200, or 800 IU (55, 182, or 727 mg) all-rac-a-tocopherol/d on general health, nutrient status, liver enzyme function, thyroid hormone concentrations, creatinine concentrations, serum autoantibodies, killing of *Candida albicans* by neutrophils, and bleeding time in 88 healthy subjects aged greater than 65 years of age. The participants were free-living, healthy, non-smoking men and women with no known medial illnesses and not taking prescription or dietary supplements.

The authors measured bleeding time before and after supplementation because vitamin E has been shown to decrease eicosanoids involved in platelet aggregation which could lead to changes in blood coagulation. No significant change was seen in bleeding time in either the placebo group or any of the vitamin E supplemented groups (Table 10). The authors consider that bleeding time of subjects taking anticoagulants still needs to be determined as this study was done on elderly who were not regularly taking other anticoagulants.

Table 10 Effect of vitamin E supplementation on bleeding time in healthy elderly

3.1.10 Dowd and Zheng, 1995 [6]

The authors investigated the anticlotting action of vitamin E quinone. When vitamin E is ingested, it is likely a known metabolite of α-tocopherol, vitamin E quinone, will be present at low levels and blood clotting will be inhibited to some degree. Vitamin E quinone is thought to inhibit the vitamin K-dependent carboxylase.

The authors suggest the anticoagulant properties of vitamin E quinone be considered when assessing the effectiveness of vitamin E in reducing the likelihood of ischemic heart attack and ischaemic stroke. Vitamin E quinone could be explored as an alternative treatment and would act directly to inhibit the vitamin K dependent carboxylase in contrast to warfarin which acts by inhibiting the reductase that returns vitamin K oxide to vitamin K.

3.1.11 The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study and related studies

3.1.11.1 The alpha-tocopherol, beta carotene cancer prevention study group, 1994 [18]

This study is a randomised, double-blind, placebo controlled primary-prevention trial investigating whether daily alpha-tocopherol, beta-carotene, or both would reduce the incidence of lung cancer or other cancers.

29133 male smokers (50 to 69 years of age) were randomly assigned to either alpha-tocopherol (50 mg per day), beta-carotene (20 mg per day), both alpha-tocopherol and beta-carotene or placebo.

Men in the cohort averaged 57.2 years of age, smoked an average of 20.4 cigarettes daily and had smoked for an average of 35.9 years.

Alpha-tocopherol had no apparent effect on total mortality. However, more deaths from haemorrhagic stroke were seen among the men who received alpha-tocopherol compared to those who did not.

Figure 5 Deaths and mortality rates (per 10000 person-years), according to cause of death among participants who received alpha-tocopherol supplements and those who did not (upper panel) and among participants who received beta-carotene supplements and those who did not. The cause of death was unknown for four participants.

3.1.11.2 Leppala et al, 1999 [19]

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was a randomised, double-blind, placebo-controlled trial to test the effect of α-tocopherol and β-carotene supplementation on cancer (see section 3.1.11.1).

This study was carried out within the ATBC study. The aim of this study was to evaluate the association of systolic and diastolic blood pressure, serum total and HDL cholesterol, serum a-tocopherol and b-carotene, and cigarette smoking (measured at the beginning of follow-up) with the risks of subarachnoid and intracerebral haemorrhage and cerebral infarction in middle-aged male smokers. Alpha-tocopherol may act as an antioxidant against atherosclerosis and therefore prevent

cerebrovascular diseases, and in addition alpha-tocopherol and its metabolites have antiplatelet and anticlotting actions (but the clinical importance is unknown).

Of the 29133 smokers aged 50 to 69 years who were recruited to the ATBC study from 1985 to 1988, 28519 male smokers without a history of stroke, from southwestern Finland, were included in this study. The median length of follow up was 6 years. From 1985 to 1993, a total of 1057 men suffered from primary stroke: 85 had subarachnoid haemorrhage; 112, intracerebral haemorrhage; 807, cerebral infarction; and 53, unspecified stroke.

Table 12 Participant characteristics at beginning of follow-up by outcome

Table 13 Crude incidence per 10000 person-years and adjusted relative risk (95% CI) of stroke subtypes by serum alpha-tocopherol and beta-carotene at beginning of follow-up

For intracerebral haemorrhage, the adjusted relative risk dropped to approximately 0.5 in all 3 upper serum α-tocopherol quartiles compared with the lowest quartile (<9.8mg/L) (Table 13). Alpha-tocopherol supplementation increased the risk of subarachnoid haemorrhage and decreased the risk of cerebral infarction. The authors concluded that the protective effect of serum alpha-tocopherol on cerebral infarction is consistent with previous studies. The effect of alpha-tocopherol on intracerebral haemorrhage and cerebral infarction could be due to its antioxidant actions in preventing atherosclerosis. Alternatively, the effect could also be mediated by its antiplatelet and anticoagulant actions which would prevent the thrombotic consequences of atherosclerosis.

3.1.11.3 Leppala et al, 2000 [20]

This paper reports on the effects of alpha-tocopherol and beta-carotene on the incidence and mortality from haemorrhagic and ischaemic strokes among the participants of the ATBC study (see section 3.1.11.1).

Baseline characteristics in the supplementation groups were similar (Table 14).

Table 14 Baseline characteristics by supplementation group in a controlled trial of middle-aged male smokers (the ATBC study)

The incidence and mortality of stroke were examined in 28519 male cigarette smokers aged 50 to 69 years without history of stroke who participated in the ATBC Study. The daily supplementation was 50 mg a-tocopherol, 20 mg b-carotene, both or placebo. 1057 men suffered from incident stroke; 85 men had subarachnoid haemorrhage; 112, intracerebral haemorrhage; 807, cerebral infarction; and 53, unspecified stroke. Deaths due to stroke within 3 months numbered 38, 50, 65, and 7, respectively (total 160). a-tocopherol supplementation increased the risk of subarachnoid haemorrhage 50% (95% CI 23% to 132%, P=0.07) but decreased that of cerebral infarction 14% (95% CI 225% to 21%, P=0.03), whereas b-carotene supplementation increased the risk of intracerebral haemorrhage 62% (95% CI 10% to 136%, P=0.01). a-tocopherol supplementation also increased the risk of fatal subarachnoid haemorrhage 181% (95% CI 37% to 479%, P=0.01). The overall net effects of either supplementation on the incidence and mortality from total stroke were nonsignificant (Table 15).

Table 15 Stroke incidence and mortality rates and relative risks (95% CI) by supplementation group in a controlled trial of middle-aged male smokers (the ATBC Study)

The tocopherol dose could be considered low for an antioxidant effect on LDL oxidation. The authors note that the median follow-up of 6 years may be too short considering the long development of atherosclerosis, but they consider it likely long enough for platelet effects of alpha-tocopherol to appear.

The antiplatelet and anticoagulant actions of vitamin E and its metabolites seem plausible explanations for the higher incidence of subarachnoid haemorrhage and the lower incidence of cerebral infarction in a-tocopherol–supplemented men. This explanation is also consistent in the observations of increased fatality of haemorrhagic strokes. The findings are also consistent with a secondary prevention trial report on ischemic stroke in which the combination of vitamin E and aspirin was more effective than aspirin alone.

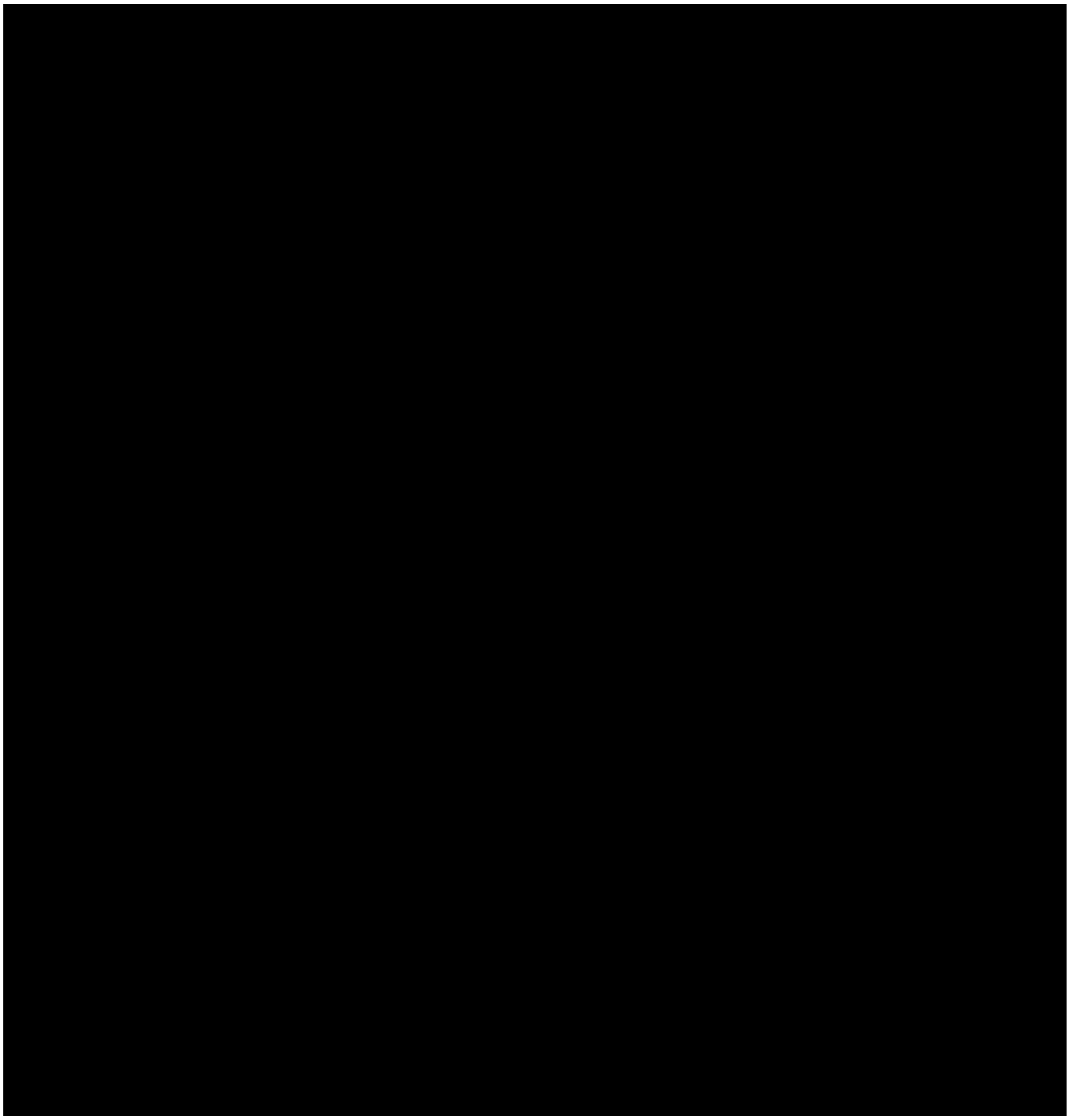


Figure 6 Kaplan-Meier estimates of cumulative frequencies of stroke events among participants who received alpha-tocopherol compared with those who did not in a controlled trial of middle-aged male smokers (the ATBC study). Results of the log-rank test for stroke events are presented. Note that the scales for subarachnoid and intracerebral haemorrhages extend to 0.6%, whereas the scale for cerebral infarction extends to 4.0%

Cumulative frequencies of stroke subtypes are shown in the figure above. The authors conclude a-tocopherol supplementation increases the risk of fatal haemorrhagic strokes but prevents cerebral infarction. The effects may be due to the antiplatelet actions of a-tocopherol.

3.1.11.4 Tornwall et al, 2004 [21]

This study is a 6 year follow up of the alpha tocopherol, beta carotene cancer prevention study (ATBC) (see the ATBC study in section 3.1.11). In this study, 29133 male smokers (50 to 69 years of age) were randomly assigned to either alpha-tocopherol (50 mg per day), beta-carotene (20 mg per day), both alpha-tocopherol and beta-carotene or placebo. The authors of this publication report on the postintervention effects of alpha tocopherol and beta carotene supplementation on stroke and its subtypes.

During this follow-up, 1327 men experienced a stroke: 1087 cerebral infarctions, 148 intracerebral haemorrhages, 64 subarachnoid haemorrhages and 28 unspecified strokes. Rate per 1000 person years of intracerebral haemorrhage varied between 0.83 and 1.46, and for subarachnoid haemorrhage varied between 0.30 and 0.59 in the 4 study groups. Alpha tocopherol supplementation was associated with a post-intervention RR of 1.01 (95% CI, 0.73 to 1.39) for intracerebral haemorrhage and 1.38 (95% CI, 0.84 to 2.26) for subarachnoid haemorrhage (Table 16).

Table 16 Incidence and RR of total stroke and its subtypes during 6-year post-trial follow-up by alpha tocopherol or beta-carotene supplementation

Alpha tocopherol supplementation had no effect on post-trial risk for intracerebral haemorrhage. Of the intracerebral haemorrhages, 84 were fatal. The fatality rate did not differ among those who had been alpha tocopherol recipients compared with nonrecipients (59% versus 54%; P=0.62) or beta carotene recipients compared with nonrecipients (54% versus 60%; P=0.50). There were 31 fatal subarachnoid haemorrhages. The fatality rate of subarachnoid haemorrhages was higher among those who had received alpha tocopherol compared with those who had not (59% versus 33%; P=0.047), whereas beta carotene had no effect (48% versus 48%).

Alpha tocopherol supplementation non-significantly elevated the risk for subarachnoid haemorrhage during trial (RR, 1.50; 95% CI, 0.97 to 2.32) as well as post-trial (RR, 1.38; 95% CI, 0.84 to 2.26). Approximately 60% of subarachnoid haemorrhage cases among the alpha tocopherol supplemented were fatal within 90 days during trial and after trial, whereas only 30% of the cases among the non-supplemented were fatal. The authors considered that some amount of alpha tocopherol might have

been stored in tissues during several years of supplementation, and the release of the stored alpha tocopherol might have maintained the antiplatelet effect for some time after stopping supplementation. Whether alpha tocopherol might have some long-lasting effect on vascular wall at rupture-prone areas is unknown.

[redacted]

3.3 CARM data

Two reports of adverse reactions associated with tocopherol and a bleeding event have been reported to the Centre for Adverse Reactions Monitoring (CARM).

The search does not include reports, if any, to combination medicines including tocopherol.

Report	Date	Gender	Age	Medicine(s)	Reaction(s)
006150	MAR1977	F	52	Tocopheryl acetate	Post-menopausal bleeding Nausea
070874	MAR2006	F	81	Warfarin Tocopherol acetate Felodipine Allopurinol Oxazepam	Drug interaction INR increased

3.4 International cases

[redacted]

4 DISCUSSION AND CONCLUSIONS

A recent meta-analysis concluded that vitamin E supplementation significantly reduced the risk of ischaemic stroke by 8% but did not detect any significant different in the risk reduction of haemorrhagic stroke [1]. This is in contrast to a previous meta-analysis which showed an increased risk of haemorrhagic stroke [11]. The studies do not make consistent conclusions and when statistical significance is seen it is only marginal with relative risks and confidence intervals close to 1.

However, there are biologically plausible mechanisms whereby vitamin E may increase bleeding. In particular, situations where there are high levels of free radicals higher levels of tocopherol quinone are expected. Tocopherol quinone interferes with vitamin K metabolism with the effect of increasing bleeding potential.

5 ADVICE SOUGHT

The Committee is asked to advise:

- whether the evidence supports there being an increased risk of bleeding with tocopherol and if so, is any regulatory action required?
- whether this topic requires further communication other than MARC's Remark's in *Prescriber Update*?

6 ANNEXES

1. Cernevit New Zealand Data Sheet
2. Vitalipid New Zealand Data Sheet
3. Loh et al 2021

7 REFERENCES

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