Contents

1 Overview of antioxydant

1.1 Included trials

A total of 29 randomized comparisons which enrolled 335810 patients were identified. In all, 1 randomized comparison concerned acetylcysteine , 7 beta carotene , 7 combination , one succinobucol , two vitamin C and 11 vitamin E.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for acetylcysteine, in section **??** (page **??**) for beta carotene, in section **??** (page **??**) for combination, in section **??** (page **??**) for succinobucol , in section **??** (page **??**) for vitamin C and in section **??** (page **??**) for vitamin E.

The average study size was 11579 patients (range 134 to 39876). The first study was published in 1990, and the last study was published in 2008.
A total of 26 trials were double blind and 2 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

1.2 Summary of meta-analysis results

The meta-analysis of the available trials about antioxydant provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

1.2.1 Acetylcysteine

Acetylcysteine was superior to **placebo** in terms of cardiovascular events (RR=0.60, 95% CI 0.38 to 0.95, p=0.0290, 1 trial). However, no significant difference was found on cardiovascular death (RR=1.23, 95% CI 0.51 to 3.00, p=0.6479, 1 trial), all cause death (RR=1.09, 95% CI 0.57 to 2.11, p=0.7897, 1 trial), coronary event (RR=0.70, 95% CI 0.33 to 1.51, p=0.3673, 1 trial)and ischemic stroke (RR=0.31, 95% CI 0.07 to 1.45, p=0.1374, 1 trial).

1.2.2 Beta carotene

No significant difference was found between **beta carotene** and **placebo** in terms of cardiovascular events (RR=0.49, 95% CI 0.07 to 3.36, p=0.4648, 3 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0000)(RR=0.67, 95% CI 0.23 to 1.93, p=0.4600, 6 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0000)(RR=0.64, 95% CI 0.18 to 2.28, p=0.4890, 6 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0000)(RR=0.42, 95% CI 0.07 to 2.60, p=0.3487, 3 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0000)(RR=1.09, 95% CI 0.85 to 1.40, p=0.5088, 1 trial), ischemic stroke (RR=1.12, 95% CI 0.88 to 1.41, p=0.3512, 1 trial), stroke (fatal and non fatal) (RR=0.53, 95% CI 0.07 to 3.97, p=0.5362, 3 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0000)(RR=1.10, 95% CI 0.87 to 1.40, p=0.4136, 1 trial)and haemmorhagic stroke (RR=2.13, 95% CI 0.92 to 4.92, p=0.0780, 1 trial).

1.2.3 Combination

No significant difference was found between **combination** and **placebo** in terms of amputation (RR=0.99, 95% CI 0.42 to 2.37, p=0.9887, 1 trial), cardiovascular events (RR=1.00, 95% CI 0.95 to 1.05, p=0.9635, 4 trials), cardiovascular death (RR=1.12, 95% CI 0.80 to 1.56, p=0.5185, 3 trials), all cause death (RR=1.12, 95% CI 0.87 to 1.44, p=0.3818, 6 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0234)(RR=1.01, 95% CI 0.94 to 1.10, p=0.7319, 2 trials), non fatal MI (RR=0.99, 95% CI 0.87 to 1.12, p=0.8795, 3 trials), stroke (fatal and non fatal) (RR=0.98, 95% CI 0.87 to 1.11, p=0.7966, 2 trials)and non fatal stroke (RR=0.99, 95% CI 0.87 to 1.13, p=0.8548, 2 trials).

1.2.4 Succinobucol

Succinobucol was superior to **placebo** in terms of new-onset diabetes (RR=0.37, 95% CI 0.25 to 0.56, p=0.0000, 1 trial)and cardiovascular death, MI, stroke (RR=0.82, 95% CI 0.69 to 0.98, p=0.0263, 1 trial). But succinobucol increased the risk of new-onset atrial fibrillation (RR=1.92, 95% CI 1.40 to 2.65, p=0.0000, 1 trial). However, no significant difference was found on cardiovascular events (RR=1.00, 95% CI 0.89 to 1.11, p=0.9712, 1 trial).

1.2.5 Vitamin C

Vitamin C was superior to **placebo** in terms of ischemic stroke (RR=0.85, 95% CI 0.73 to 0.99, p=0.0378, 2 trials). However, no significant difference was found on cardiovascular events (RR=1.00, 95% CI 0.92 to 1.08, p=0.9148, 2 trials), cardiovascular death (RR=1.04, 95% CI 0.92 to 1.19, p=0.5107, 2 trials), all cause death (RR=1.05, 95% CI 0.98 to 1.13, p=0.1893, 2 trials), coronary event (RR=1.04, 95% CI 0.83 to 1.32, p=0.7170, 1 trial), non fatal MI (RR=1.09, 95% CI 0.85 to 1.39, p=0.5162, 1 trial), stroke (fatal and non fatal) (RR=0.88, 95% CI 0.76 to 1.01, p=0.0622, 2 trials), non fatal stroke (RR=0.87, 95% CI 0.68 to 1.10, p=0.2335, 1 trial)and haemmorhagic stroke (RR=0.98, 95% CI 0.64 to 1.48, p=0.9074, 2 trials).

1.2.6 Vitamin E

No significant difference was found between **vitamin E** and **control** in terms of cardiovascular events (RR=0.99, 95% CI 0.89 to 1.09, p=0.7865, 2 trials), cardiovascular death (RR=0.94, 95% CI 0.81 to 1.08, p=0.3816, 2 trials), all cause death (RR=0.94, 95% CI 0.84 to 1.05, p=0.2645, 2 trials), coronary event (RR=0.89, 95% CI 0.51 to 1.58, p=0.6972, 1 trial), non fatal MI (RR=1.11, 95% CI 0.93 to 1.32, p=0.2696, 2 trials), ischemic stroke (RR=1.13, 95% CI 0.60 to 2.13, p=0.7106, 1 trial), stroke (fatal and non fatal) (RR=0.93, 95% CI 0.71 to 1.21, p=0.5995, 2 trials), non fatal stroke (RR=1.07, 95% CI 0.62 to 1.83, p=0.8107, 2 trials)and haemmorhagic stroke (RR=4.06, 95% CI 0.18 to 89.97, p=0.3755, 1 trial).

Vitamin E was inferior to **placebo** in terms of haemmorhagic stroke (RR=1.22, 95% CI 1.00 to 1.48, p=0.0477, 5 trials). No significant difference was found on cardiovascular events (RR=0.96, 95% CI 0.89 to 1.04, p=0.3028, 6 trials), cardiovascular death (RR=0.99, 95% CI 0.93 to 1.05, p=0.6852, 6 trials), all cause death (RR=1.03, 95% CI 0.97 to 1.10, p=0.3176, 5 trials), coronary event (RR=0.92, 95% CI 0.73 to 1.16, p=0.4673, 1 trial), non fatal MI (RR=0.75, 95% CI 0.50 to 1.13, p=0.1679, 3 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0008)(RR=0.95, 95% CI 0.84 to 1.06, p=0.3534, 5 trials), stroke (fatal and non fatal) (RR=0.99, 95% CI 0.90 to 1.08, p=0.7566, 5 trials)and non fatal stroke (RR=0.98, 95% CI 0.69 to 1.39, p=0.9188, 2 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0232)

Table 1.1: *Main study characteristics - antioxydant*

Trial	Patients	Treatments	Trial design and method
Acetylcysteine			
Acetylcysteine versus placebo			
Tepel, 2003 [?] n = 64 vs. 70	patients undergoing maintenance hemodialysis for a minimum of 3 months 3 times weekly in anambulatory center	acetylcysteine 600 mg twice daily **versus** placebo	double-blind parallel groups Primary endpoint: cardiovascular event single centre,Germany
Beta carotene			
Beta carotene versus placebo			
ATBC beta carotene, 1994 [?, ?] n = 14560 vs. 14573	male smokers 50 to 69 years of age from southwestern Finland	beta carotene 20mg four times daily **versus** placebo	double-blind factorial plan Primary endpoint: not defined postal survey ,Southwestern Finland
CARET beta carotene, 1996 [?, ?] n = 9420 vs. 8894	smokers, former smokers, and workersexposed to asbestos	combination of30 mg of beta carotene per day and 25,000 IU of retinol(vitamin A) in the form of retinyl palmitate per day **versus** placebo	double-blind parallel groups Primary endpoint: lung cancer multicenter,USA
NSCP (Green) beta carotene, 1999 [?] n = 820 vs. 801	residents of Nambour	beta carotene 30mg four times daily **versus** placebo	double-blind factorial plan Primary endpoint: skin cancer community study,Queensland, Australia
PHS beta carotene, 1996 [?] n = 11036 vs. 1035	male physicians, 40 to 84 years of age with no history of cancer (exceptnonmelanoma skin cancer), myocardial infarction, stroke, or transientcerebral ischemia	beta carotene 50 mg on alternate days **versus** placebo	double-blind factorial plan Primary endpoint: neoplasm except non-melanoma skin cancer USA

continued...

Trial	Patients	Treatments	Trial design and method
SCP beta carotene, 1990 [?] n = 913 vs. 892	age <85 years (most <65 years); previousnon-melanoma skin cancer; 69% male	beta carotene 50mg four times daily **versus** placebo	double-blind parallel groups Primary endpoint: basal cell or squamaous cell skin cancer 4 centres,USA
WACS beta-caroten, 2007 [?, ?, ?] n = 4084 vs. 4087	female health professionals at increased risk (40 years or older with a history of CVD or 3 or more CVD risk factors)	beta carotene (Lurotin) 50 mg every two days **versus** placebo	double blind factorial plan Primary endpoint: MI, stroke, coronary revascularization, CVD death
WHS beta carotene, 1999 [?, ?, ?] n = 19939 vs. 19937	female health professionals, aged 45 years orolder and without a history of cancer (except nonmelanomaskin cancer), coronary heart disease, orcerebrovascular disease	beta carotene 50mg four times daily **versus** placebo	double-blind factorial plan Primary endpoint: not defined USA
Combination			
Combination versus placebo			
POPADAD (antioxydant), 2008 [?] n = 640 vs. 636	patients with diabetes mellitus and asymptomatic peripheral arterial disease	antioxidant capsule containing (alpha-tocopherol 200 mg, ascorbic acid 100 mg, pyridoxine hydrochloride 25 mg, zinc sulphate 10 mg, nicotinamide 10 mg, lecithin 9.4 mg, and sodium selenite 0.8 mg) **versus** placebo	double blind factorial plan Primary endpoint: CV events multicentre,Scotland
HATS, 2001 [?] n = 84 vs. 76	patients with coronary disease, low HDL cholesterol levels and normal LDL cholesterol	antioxidant-therapy (vitamins) **versus** placebo	double-blind factorial plan Primary endpoint: change in coronary stenosis 2 centres,USA, Canada

continued...

Trial	Patients	Treatments	Trial design and method
MVP, 1997 [?] n = 158 vs. 159	patient undergoing angioplasty	multivitamins (30,000 IU of beta carotene, 500 mg of vitamin C, and 700 IU of vitamin E) for four weeks before and six months after angioplasty **versus** placebo	double-blind factorial plan Primary endpoint: extent of restenosis single center,Canada
HPS antioxidant, 2002 [?] n = 10269 vs. 10267	UK adults (aged 4080) with coronary disease, other occlusive arterial disease, or diabetes	antioxidant vitaminsupplementation (600 mg vitamin E, 250 mg vitamin C, and20 mg -carotene daily) **versus** matching placebo	double-blind factorial plan Primary endpoint: coronary events 69 centres,UK
PHS II beta carotene, 2003 [?, ?, ?] n = 2967 vs. 2989	US male physicians enrolled, aged 50 years or older	400 IU of vitamin E every other day and500 mg of vitamin C daily **versus** placebo	double-blind factorial plan Primary endpoint: cardiovascular events
SUVIMAX, 2005 [?, ?, ?] n = 6481 vs. 6536	women aged 35-60 years and men aged 45-60 years	single daily capsule of combination of antioxydants: 120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta carotene, 100 g of selenium, and 20 mg of zinc **versus** matched placebo	double-blind parallel groups Primary endpoint: not defined media campaign,France
WAVE (Waters), 2002 [?] n = 212 vs. 211	postmenopausal women with at least one 15% to 75% coronary stenosis	400 IU of vitamin E twice daily plus 500 mg of vitamin C twice daily **versus** placebo	double-blind factorial plan Primary endpoint: change in minimum lumen diameter 7 centres,US, Canada
Succinobucol			
Succinobucol versus placebo			

continued...

Trial	Patients	Treatments	Trial design and method
ARISE, 2008 [?] n = 3078 vs. 3066	patients with recent (14-365 days) acute coronary syndromes already managed with conventional treatments	succinobucol 300 mg once daily **versus** placebo	double blind parallel groups Primary endpoint: CV death, MI, Stroke, UA, revasc 261 centres,Canada, US, UK, South Africa
Vitamin C			
Vitamin C versus placebo			
PHS II vitamin C, 2008 [?] n = 7329 vs. 7312	US male physicians aged 50 years or older	vitamin C 500mg daily **versus** placebo	double blind factorial plan Primary endpoint: cv death, MI, Stroke postal survey,US
WACS vitamin C, 2007 [?, ?] n = 4087 vs. 4084	female health professionals at increased risk (40 years or older with a history of CVD or 3 or more CVD risk factors)	vitamin C (ascorbic acid) 500 mg/d **versus** placebo	double blind Primary endpoint: MI, stroke, coronary revascularization, CVD death US
Vitamin E			
Vitamin E versus control			
GISSI, 1999 [?] n = 5660 vs. 5664	patients with recent (3 months) myocardialinfarction	vitamin E 300mg/d **versus** no vitamine E	open factorial plan Primary endpoint: death, MI, stroke multicentre,Italy
PPP, 2001 [?] n = 2231 vs. 2264	men and womenaged 50 years or greater, with at least one of the majorrecognised cardiovascular risk factors	vitamin E (300 mg/day) **versus** no vitamin E	open factorial plan Primary endpoint: CV events multicenter,Italy
Vitamin E versus placebo			
CHAOS, 1996 [?] n = 1035 vs. 967	patients with angiographically proven coronary atherosclerosis	vitamin E 400-800UI/d (alpha tocopherol) **versus** identical placebo	double-blind parallel groups Primary endpoint: CV death, MI and non fatal MI alone singlecenter,UK

continued...

Trial	Patients	Treatments	Trial design and method
HOPE, 2000 [?, ?] n = 4761 vs. 4780	women and men 55 years of age or older who were at high risk for cardiovascular events because they had cardiovascular disease or diabetes in addition to one other risk factor.	vitamin E 400IU/d from natural sources **versus** matching placebo	double-blind factorial plan Primary endpoint: CV death, MI, stroke multicenter,Multinational: Canada, USA, Europe, South America
ATBC vitamin E, 1994 [?, ?, ?] n = 14564 vs. 14569	male smokers 50 to 69 years of age from southwestern Finland	vitamin E (alpha-tocopherol) 50mg/d **versus** placebo	double-blind factorial plan Primary endpoint: not defined postal survey ,Southwestern Finland
WACS vitamin E, 2007 [?, ?] n = 4083 vs. 4088	female health professionals at increasedrisk (40 years or older with a history of CVD or 3 or more CVDrisk factors)	vitamin E (600IU every two days) **versus** placebo	double blind factorial plan Primary endpoint: MI, stroke, coronary revascularization, CVD death US
WHS vitamin E, 2005 [?] n = 19937 vs. 19939	apparently healthy US women aged at least 45 years	vitamin E 600 IU every other day (-tocopherol) **versus** placebo	double-blind factorial plan Primary endpoint: major cardiovascular event US
PHS II vitamin E, 2008 [?] n = 7315 vs. 7326	US male physicians aged 50 years or older	vitamin E 400IU every two days **versus** placebo	double blind Primary endpoint: cv death, MI, Stroke postal survey,US
ASAP, 2000 [?, ?, ?] n = 260 vs. 260	smoking and nonsmoking men and postmenopausal women aged 45-69 years with serum cholesterol >= 5.0 mmol/l	d-alpha-tocopherol 91 mg (136 IU) twice daily **versus** placebo	double-blind factorial plan Primary endpoint: carotid artery mean intima-media thickness NA,Finland

continued...

Trial	Patients	Treatments	Trial design and method
AREDS, 2001 [?] n = 2370 vs. 2387	patients with age-related lens opacities and visual acuity loss	daily supplementation of antioxidants (500 mg of vitamin C, 400 IU of vitamin E, and 15 mg of beta carotene) **versus** placebo	double-blind factorial plan Primary endpoint: opacity grades or cataract surgery 11 centres,USA
Linxian, 1993 [?, ?] n = 14792 vs. 14792	apparently healthy Individuals of ages 40-69	beta carotene, vitamin E, and selenium **versus**	

Table 1.2: *Summary of all results for acetylcysteine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
acetylcysteine versus placebo						
cardiovascular events	RR=0.60	0.38;0.95	0.0290	1.0000 (0.00)	1	134
cardiovascular death	RR=1.23	0.51;3.00	0.6479	1.0000 (0.00)	1	134
all cause death	RR=1.09	0.57;2.11	0.7897	1.0000 (0.00)	1	134
coronary event	RR=0.70	0.33;1.51	0.3673	1.0000 (0.00)	1	134
ischemic stroke	RR=0.31	0.07;1.45	0.1374	1.0000 (0.00)	1	134

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 1.3: *Summary of all results for beta carotene*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
beta carotene versus placebo						
cardiovascular events	RR=0.49 [1]	0.07;3.36	0.4648	0.0000 (1.00) †	3	60118
cardiovascular death	RR=0.67 [2]	0.23;1.93	0.4600	0.0000 (0.99) †	6	109186
all cause death	RR=0.64 [3]	0.18;2.28	0.4890	0.0000 (1.00) †	6	81858
coronary event	RR=0.42 [4]	0.07;2.60	0.3487	0.0000 (0.99) †	3	60118
non fatal MI	RR=1.09	0.85;1.40	0.5088	1.0000 (0.00)	1	8171
ischemic stroke	RR=1.12	0.88;1.41	0.3512	1.0000 (0.00)	1	8171
stroke (fatal and non fatal)	RR=0.53 [5]	0.07;3.97	0.5362	0.0000 (1.00) †	3	60118
non fatal stroke	RR=1.10	0.87;1.40	0.4136	1.0000 (0.00)	1	8171
haemmorhagic stroke	RR=2.13	0.92;4.92	0.0780	1.0000 (0.00)	1	8171

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 1.4: *Summary of all results for combination*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
combination versus placebo						
amputation	RR=0.99	0.42;2.37	0.9887	1.0000 (0.00)	1	1276
cardiovascular events	RR=1.00	0.95;1.05	0.9635	0.4433 (0.00)	4	34136
cardiovascular death	RR=1.12	0.80;1.56	0.5185	0.3316 (0.09)	3	21119
all cause death	RR=1.12 [6]	0.87;1.44	0.3818	0.0234 (0.62) †	6	35729
coronary event	RR=1.01	0.94;1.10	0.7319	0.6479 (0.00)	2	20853
non fatal MI	RR=0.99	0.87;1.12	0.8795	0.8897 (0.00)	3	21119
stroke (fatal and non fatal)	RR=0.98	0.87;1.11	0.7966	0.7924 (0.00)	2	20959
non fatal stroke	RR=0.99	0.87;1.13	0.8548	0.9289 (0.00)	2	20696

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.16 95% CI 0.15;0.17
[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.64 95% CI 0.59;0.68
[3] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.23 95% CI 0.22;0.25
[4] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.15 95% CI 0.14;0.17
[5] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.20 95% CI 0.18;0.22
[6] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.05 95% CI 0.99;1.12

Table 1.5: *Summary of all results for succinobucol*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
succinobucol versus placebo						
new-onset diabetes	RR=0.37	0.25;0.56	0.0000	1.0000 (1.00)	1	3873
new-onset atrial fibrillation	RR=1.92	1.40;2.65	0.0000	1.0000 (0.00)	1	5605
cardiovascular events	RR=1.00	0.89;1.11	0.9712	1.0000 (0.00)	1	6144
cardiovascular death, MI, stroke	RR=0.82	0.69;0.98	0.0263	1.0000 (0.00)	1	6144

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 1.6: *Summary of all results for vitamin C*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
vitamin C versus placebo						
cardiovascular events	RR=1.00	0.92;1.08	0.9148	0.7922 (0.00)	2	22812
cardiovascular death	RR=1.04	0.92;1.19	0.5107	0.5631 (0.00)	2	22812
all cause death	RR=1.05	0.98;1.13	0.1893	0.6314 (0.00)	2	22812
coronary event	RR=1.04	0.83;1.32	0.7170	1.0000 (0.00)	1	8171
non fatal MI	RR=1.09	0.85;1.39	0.5162	1.0000 (0.00)	1	8171
ischemic stroke	RR=0.85	0.73;0.99	0.0378	0.7803 (0.00)	2	22812
stroke (fatal and non fatal)	RR=0.88	0.76;1.01	0.0622	0.8616 (0.00)	2	22812
non fatal stroke	RR=0.87	0.68;1.10	0.2335	1.0000 (0.00)	1	8171
haemmorhagic stroke	RR=0.98	0.64;1.48	0.9074	0.7575 (0.00)	2	22812

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 1.7: *Summary of all results for vitamin E*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
vitamin E versus control						
cardiovascular events	RR=0.99	0.89;1.09	0.7865	0.6427 (0.00)	2	15819
cardiovascular death	RR=0.94	0.81;1.08	0.3816	0.7537 (0.00)	2	15819
all cause death	RR=0.94	0.84;1.05	0.2645	0.3897 (0.00)	2	15829
coronary event	RR=0.89	0.51;1.58	0.6972	1.0000 (0.00)	1	4495
non fatal MI	RR=1.11	0.93;1.32	0.2696	0.9197 (0.00)	2	15819
ischemic stroke	RR=1.13	0.60;2.13	0.7106	1.0000 (0.00)	1	4495
stroke (fatal and non fatal)	RR=0.93	0.71;1.21	0.5995	0.3170 (0.00)	2	15829
non fatal stroke	RR=1.07	0.62;1.83	0.8107	0.1321 (0.56)	2	15819
haemmorhagic stroke	RR=4.06	0.18;89.97	0.3755	1.0000 (0.00)	1	4495
vitamin E versus placebo						
cardiovascular events	RR=0.96	0.89;1.04	0.3028	0.0683 (0.51)	6	93072
cardiovascular death	RR=0.99	0.93;1.05	0.6852	0.8458 (0.00)	6	93072
all cause death	RR=1.03	0.97;1.10	0.3176	0.8281 (0.00)	5	30091
coronary event	RR=0.92	0.73;1.16	0.4673	1.0000 (0.00)	1	8171
non fatal MI	RR=0.75 [7]	0.50;1.13	0.1679	0.0008 (0.86) †	3	19714
ischemic stroke	RR=0.95	0.84;1.06	0.3534	0.1159 (0.46)	5	100748
stroke (fatal and non fatal)	RR=0.99	0.90;1.08	0.7566	0.2129 (0.31)	5	101362

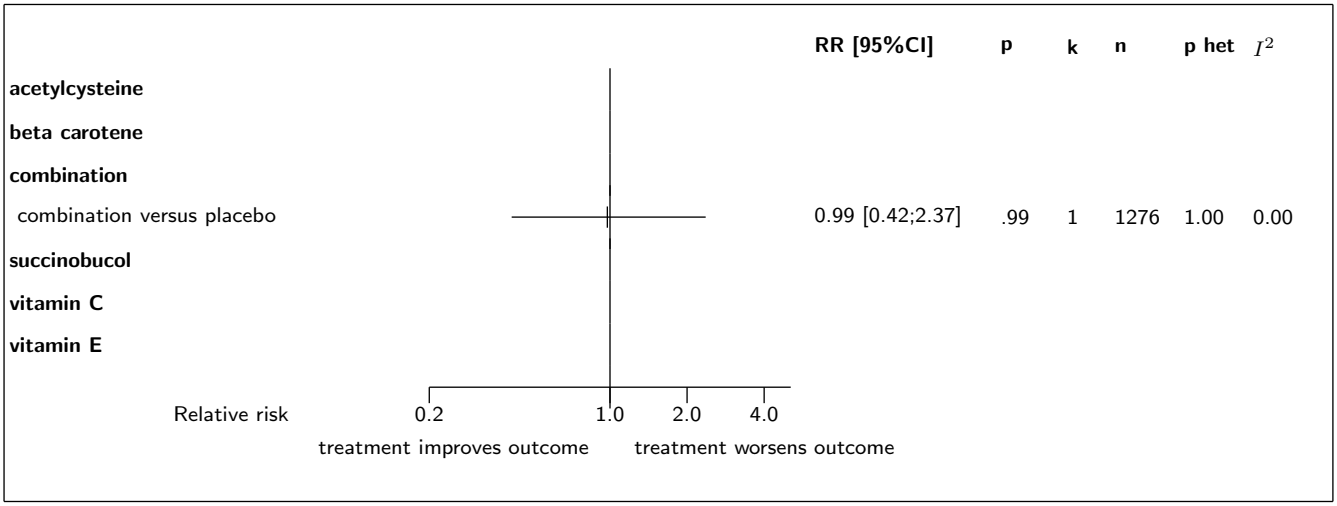
continued...

[7] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.96 95% CI 0.87;1.07

Endpoint	Effect	95% CI	p ass	p het	k	n
non fatal stroke	RR=0.98 [8]	0.69;1.39	0.9188	0.0232 (0.81) †	2	17712
haemmorhagic stroke	RR=1.22	1.00;1.48	0.0477	0.4384 (0.00)	5	100748

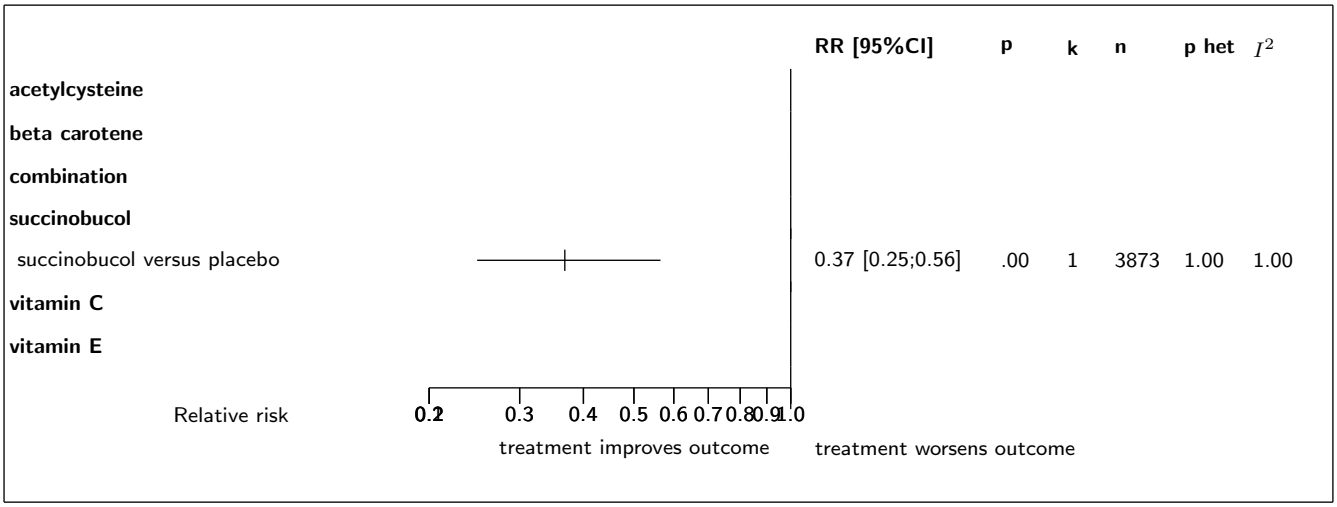
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 1.1: *Forest's plot for amputation*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

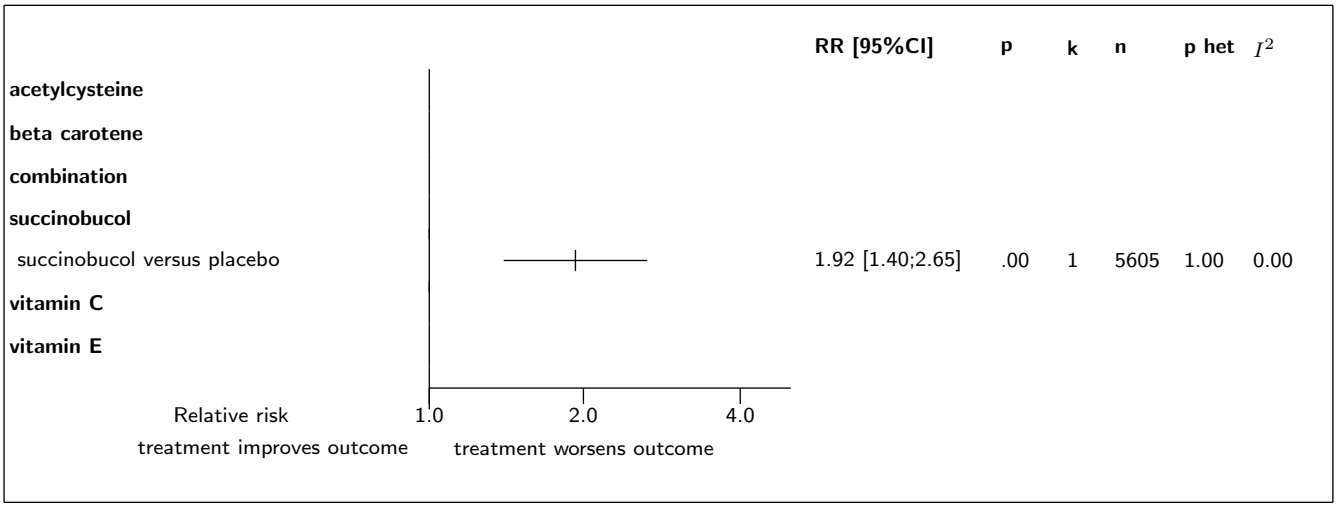
Figure 1.2: *Forest's plot for new-onset diabetes*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

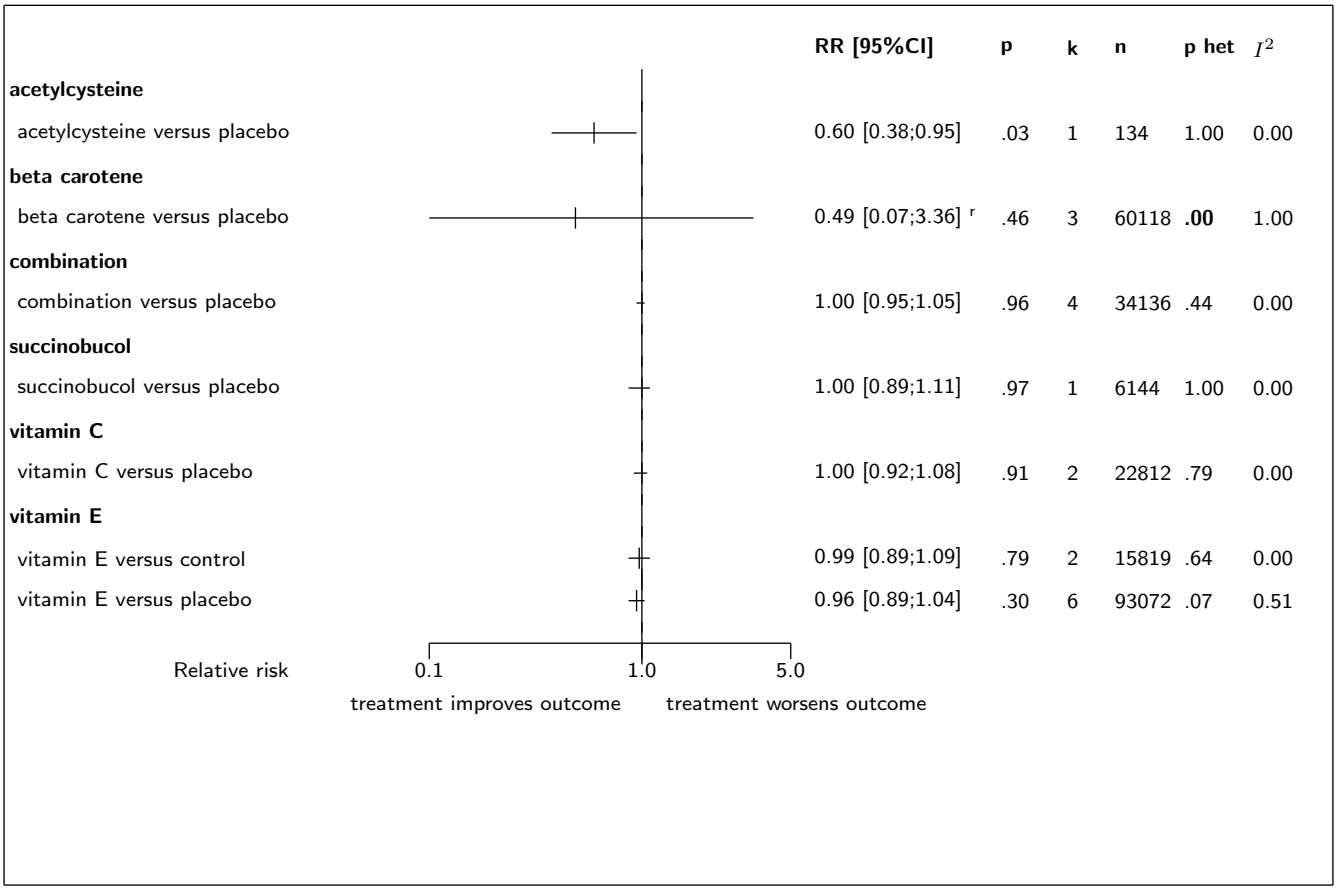
[8] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.01 95% CI 0.87;1.17

Figure 1.3: *Forest's plot for new-onset atrial fibrillation*



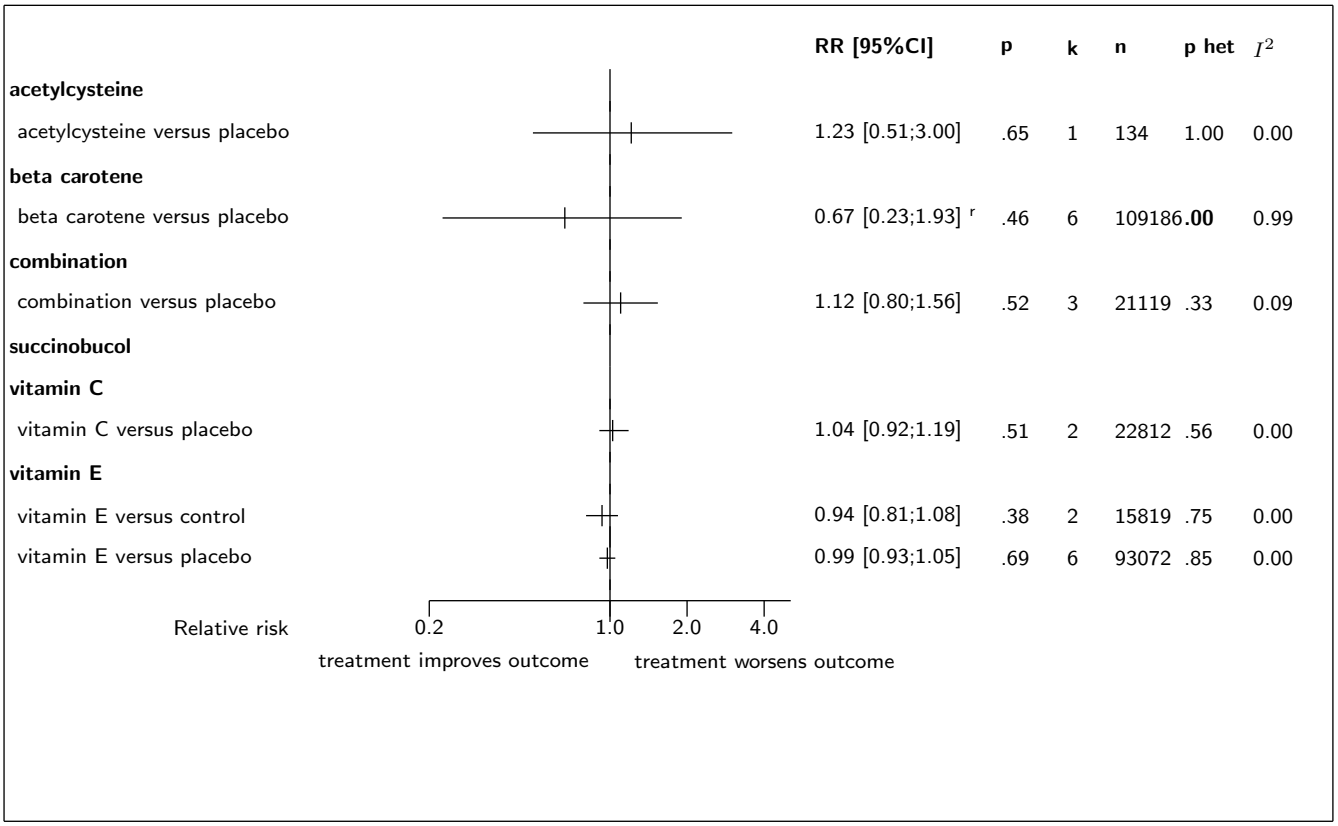
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 1.4: *Forest's plot for cardiovascular events*



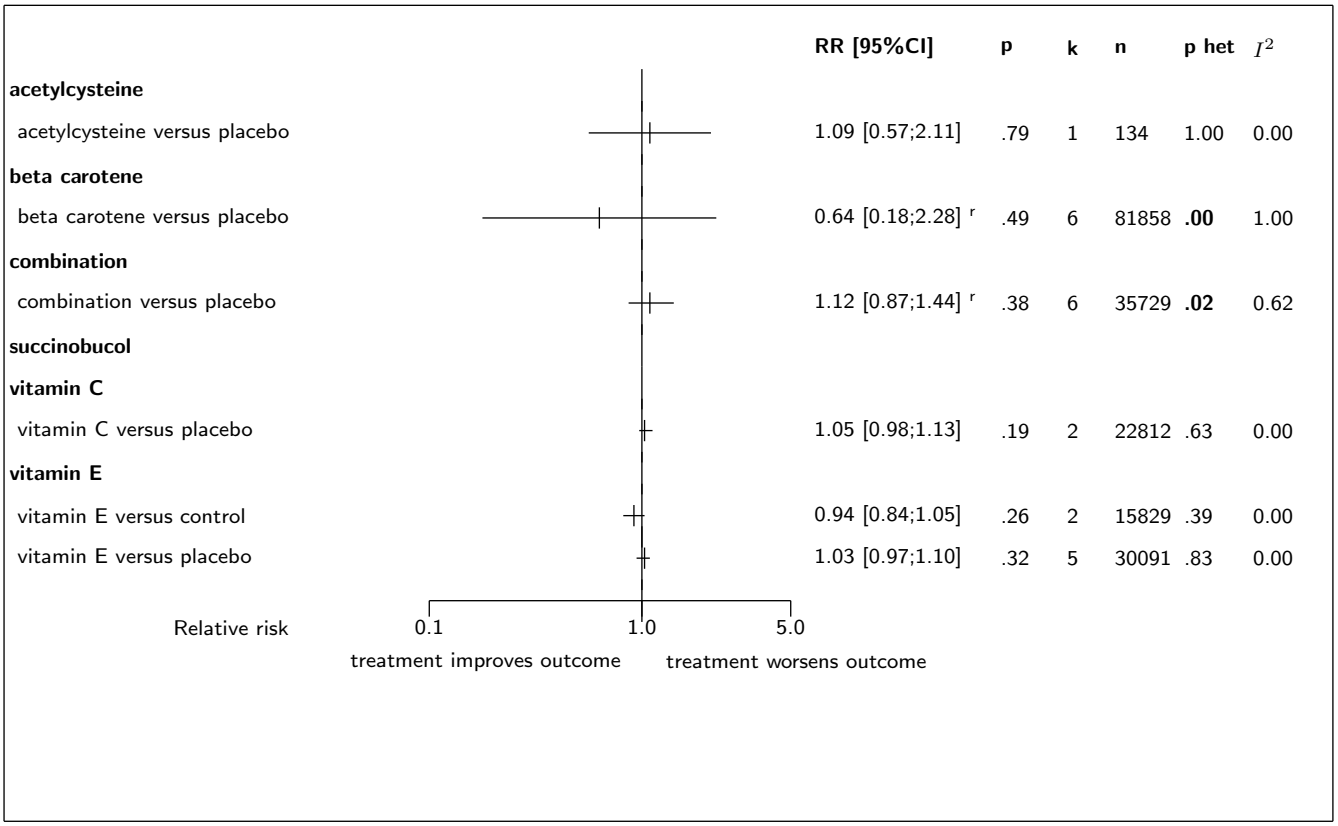
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 1.5: *Forest's plot for cardiovascular death*



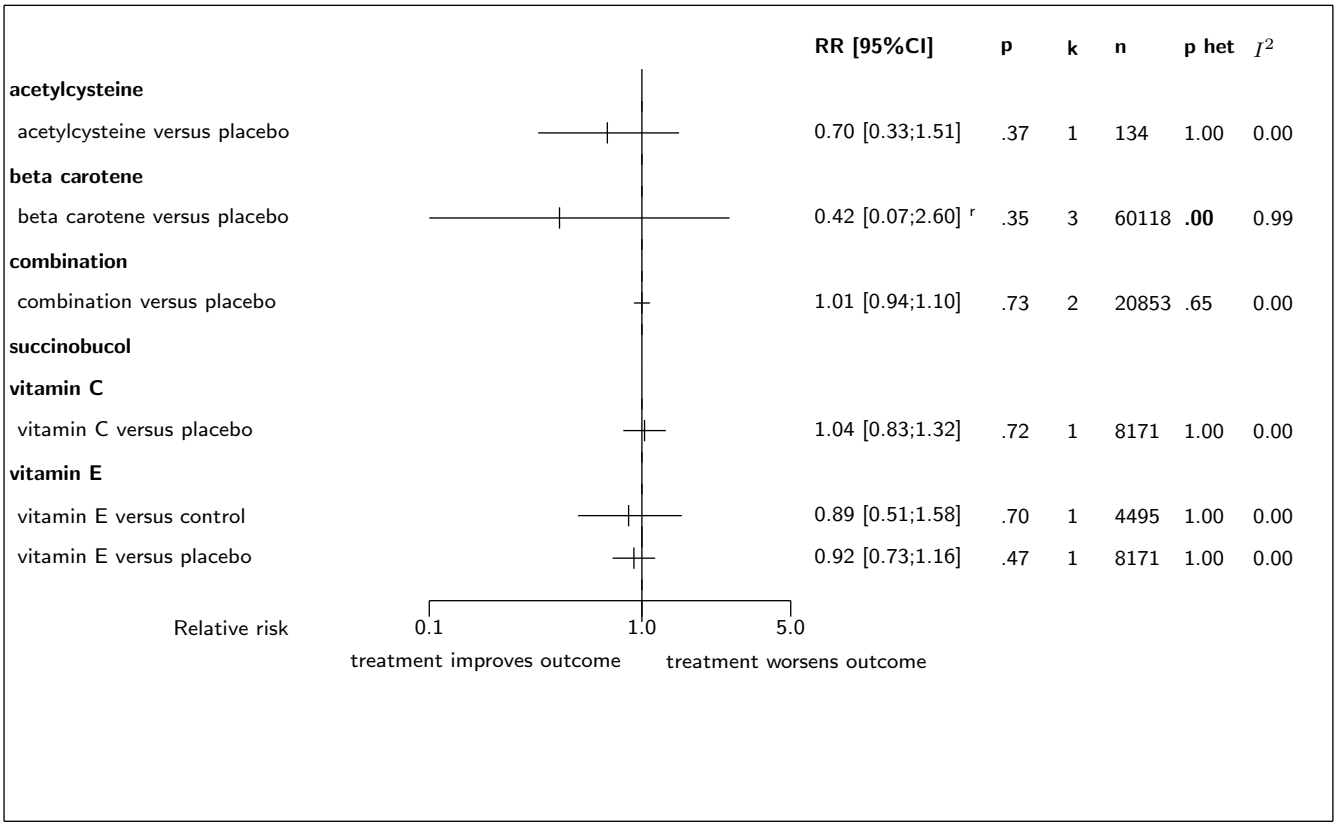
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 1.6: *Forest's plot for all cause death*



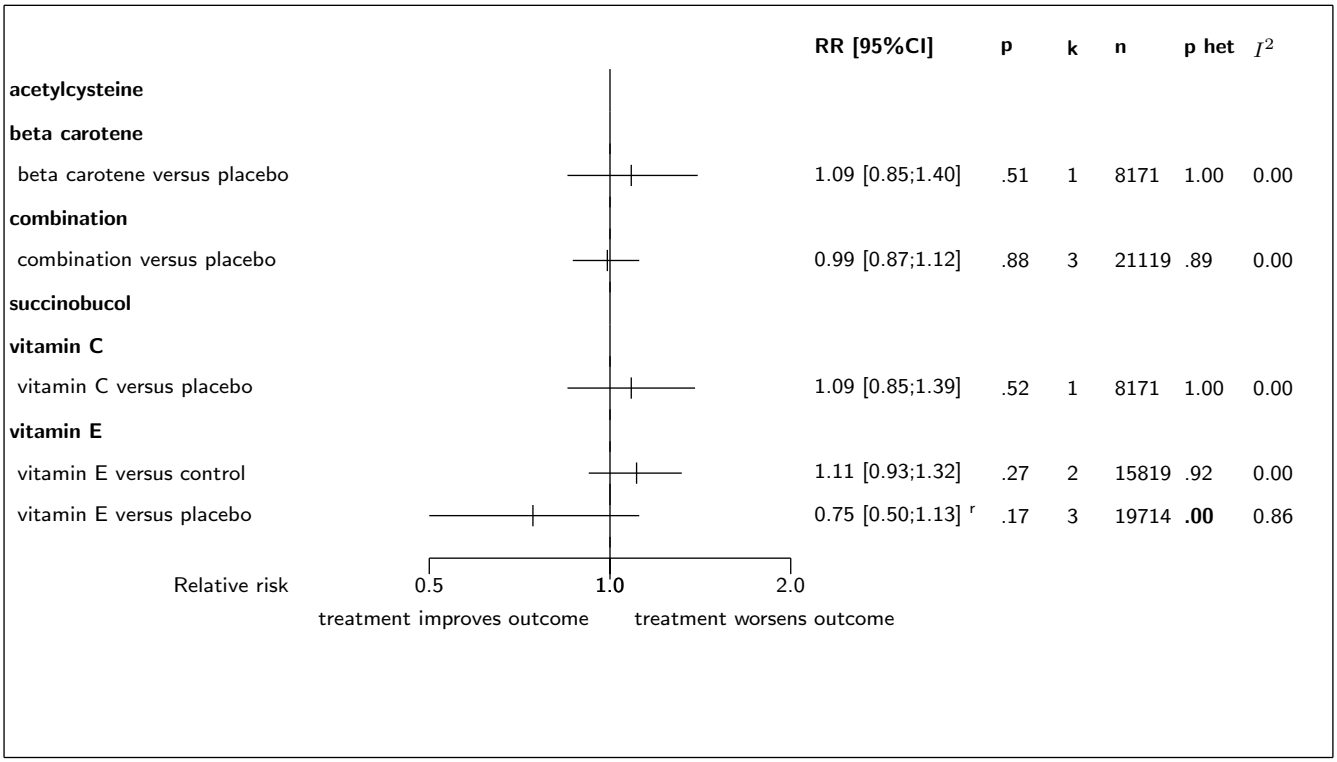
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 1.7: *Forest's plot for coronary event*



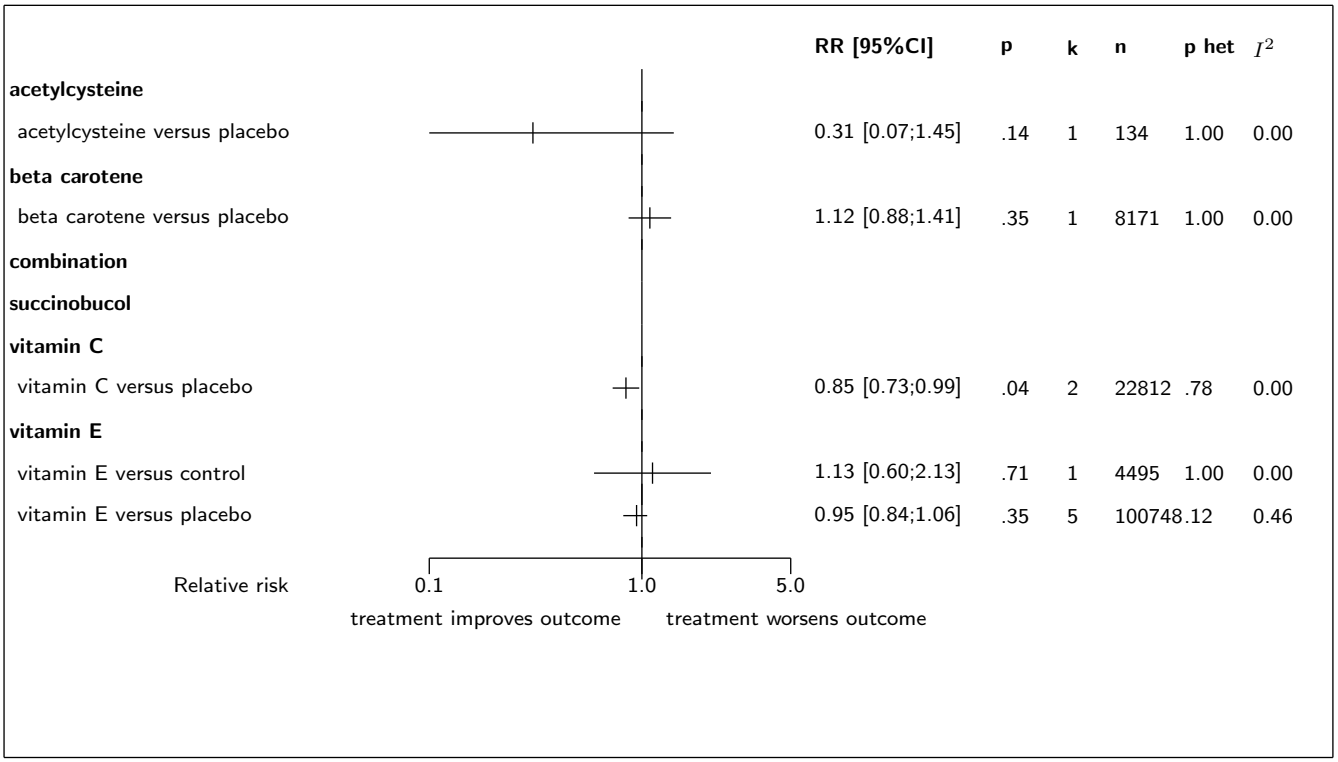
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 1.8: *Forest's plot for non fatal MI*



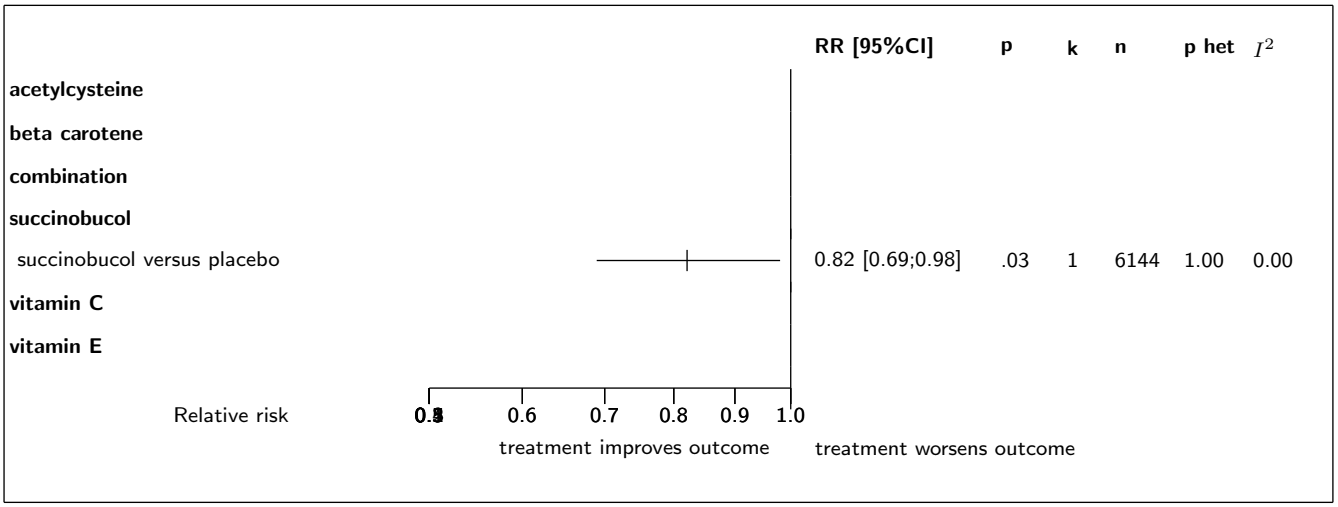
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 1.9: *Forest's plot for ischemic stroke*



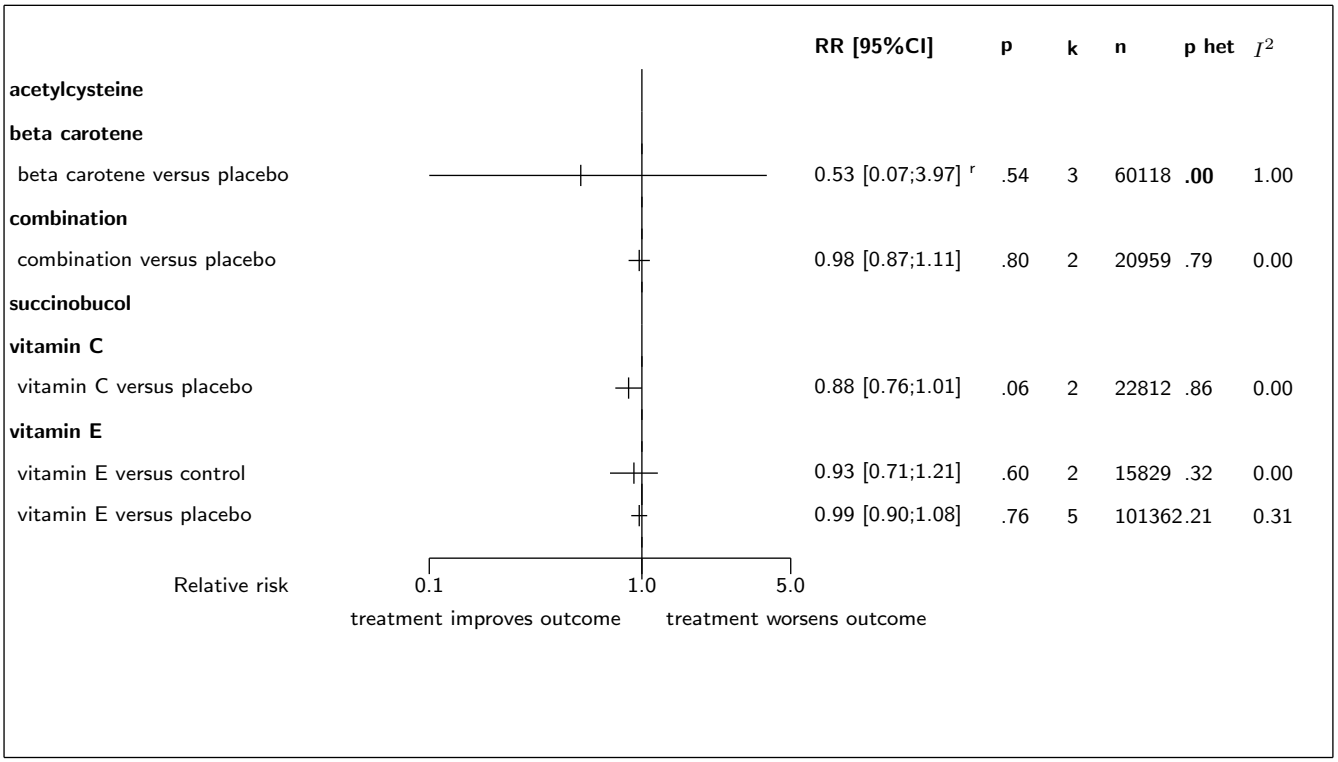
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 1.10: *Forest's plot for cardiovascular death, MI, stroke*



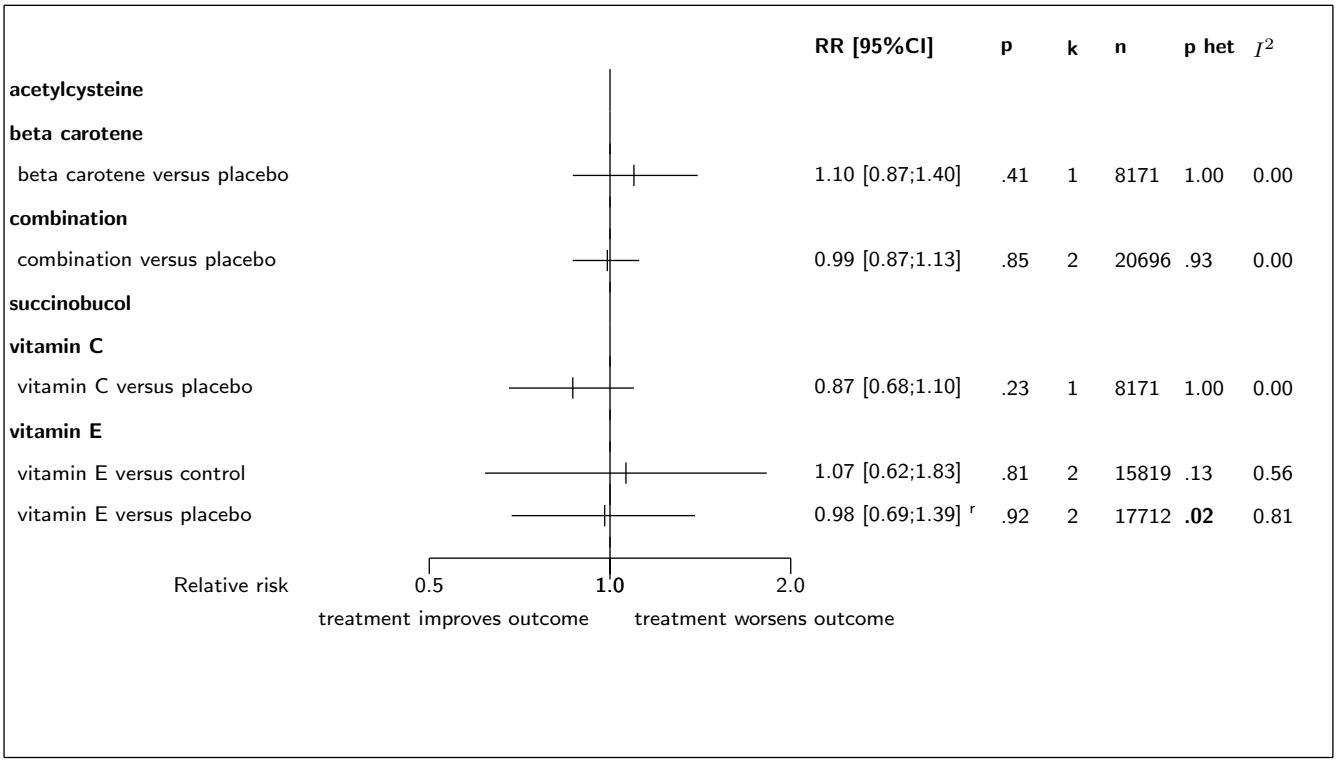
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 1.11: *Forest's plot for stroke (fatal and non fatal)*



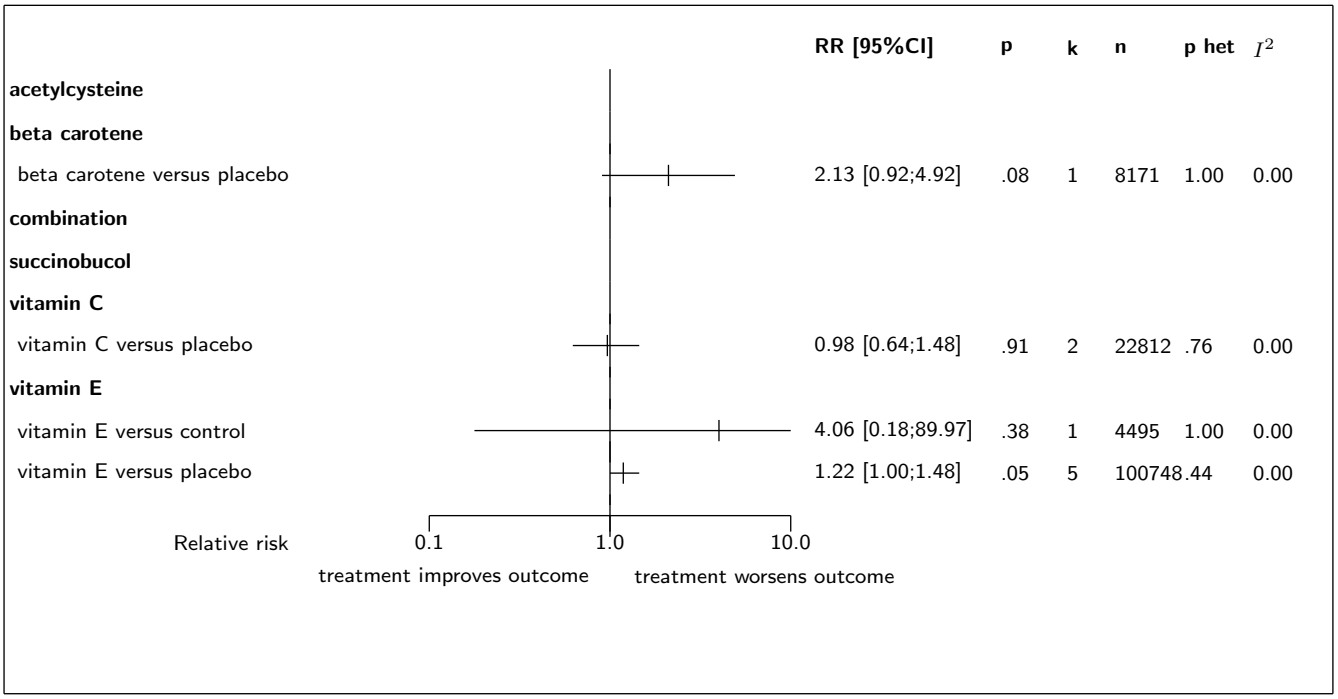
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 1.12: *Forest's plot for non fatal stroke*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 1.13: *Forest's plot for haemmorhagic stroke*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

2 Detailed results for acetylcysteine

2.1 Available trials

Only one trial which randomized 134 patients was identified: it compared acetylcysteine with placebo.
This trial included 134 patients and was published in 2003.
This trial was double blind in design.
It was reported in English language.
Cardiovascular death data was reported in 1 trials; 1 trials reported data on coronary event; 1 trials reported data on cardiovascular events; 1 trials reported data on all cause death; and 1 trials reported data on ischemic stroke.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trial including in this systematic review of randomized trials of acetylcysteine.

Table 2.1: *Treatment description - antioxydant - acetylcysteine*

Trial	Studied treatment	Control treatment
Acetylcysteine versus placebo		
Tepel (2003) [**?**]	acetylcysteine 600 mg twice daily	placebo

Table 2.2: *Descriptions of participants - antioxydant - acetylcysteine*

Trial	Patients	
Acetylcysteine versus placebo		
Tepel (2003) [**?**]	Patients undergoing maintenance hemodialysis for a minimum of 3 months 3 times weekly in anambulatory center	
	Inclusion criteria: not defined	**Exclusion criteria:**

Table 2.3: *Main patients characteristics - antioxydant - acetylcysteine*

Trial	Characteristics
Acetylcysteine versus placebo	
Tepel, 2003 [**?**]	women (%): 43% age (yr): 62 y body mass index: 23

Table 2.4: *Design and methodological quality of trials - antioxydant - acetylcysteine*

Trial	Design	Duration	Centre	Primary endpoint
Acetylcysteine versus placebo				
Tepel, 2003 [**?**] n=134	Parallel groups double-blind confirmatory trial at low risk of bias	14.5 y inclusion period: oct 1999 - sept 2001	Germany single centre	cardiovascular event

2.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Acetylcysteine versus placebo

The single study eligible for this comparison provided data on **cardiovascular events**. The analysis detected a statistically significant difference in favor of acetylcysteine in cardiovascular events, with a RR of 0.60 (95% CI 0.38 to 0.95, p=0.0290).
The single study eligible for this comparison provided data on **cardiovascular death**. No statistically significant difference between the groups was found in cardiovascular death, with a RR of 1.23 (95% CI 0.51 to 3.00, p=0.6479).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 1.09 (95% CI 0.57 to 2.11, p=0.7897).
The single study eligible for this comparison provided data on **coronary event**. No statistically significant difference between the groups was found in coronary event, with a RR of 0.70 (95% CI 0.33 to 1.51, p=0.3673).
The single study eligible for this comparison provided data on **ischemic stroke**. No statistically significant difference between the groups was found in ischemic stroke, with a RR of 0.31 (95% CI 0.07 to 1.45, p=0.1374).

Table 2.5: *Results details - antioxydant - acetylcysteine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
acetylcysteine versus placebo						
cardiovascular events	RR=0.60	[0.38;0.95]	0.0290	1.0000 (I^2=0.00)	1	134
cardiovascular death	RR=1.23	[0.51;3.00]	0.6479	1.0000 (I^2=0.00)	1	134
all cause death	RR=1.09	[0.57;2.11]	0.7897	1.0000 (I^2=0.00)	1	134
coronary event	RR=0.70	[0.33;1.51]	0.3673	1.0000 (I^2=0.00)	1	134
ischemic stroke	RR=0.31	[0.07;1.45]	0.1374	1.0000 (I^2=0.00)	1	134

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 2.1: *Forest's plot for cardiovascular events*

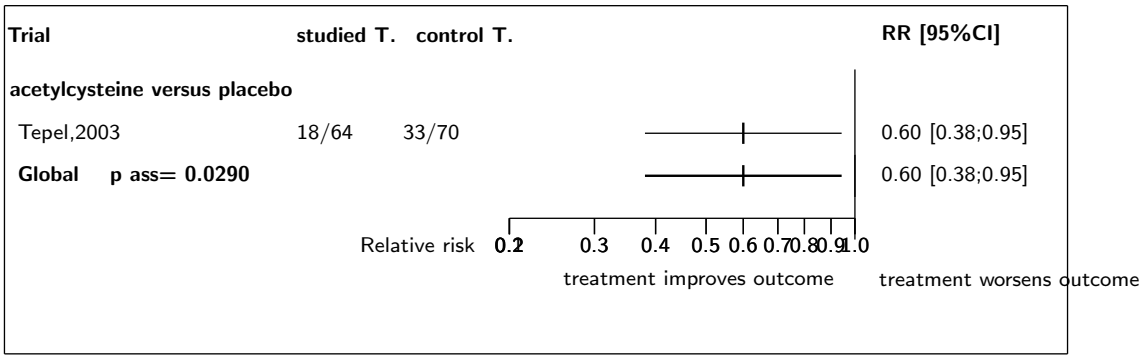


Figure 2.2: *Forest's plot for cardiovascular death*

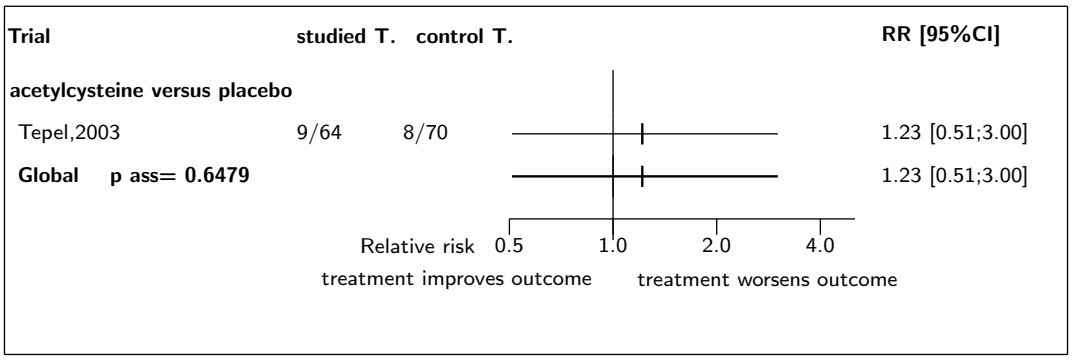


Figure 2.3: *Forest's plot for all cause death*

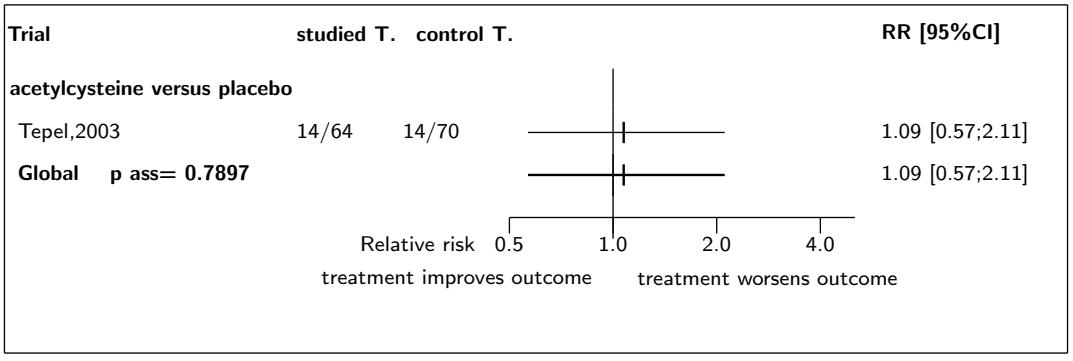


Figure 2.4: *Forest's plot for coronary event*

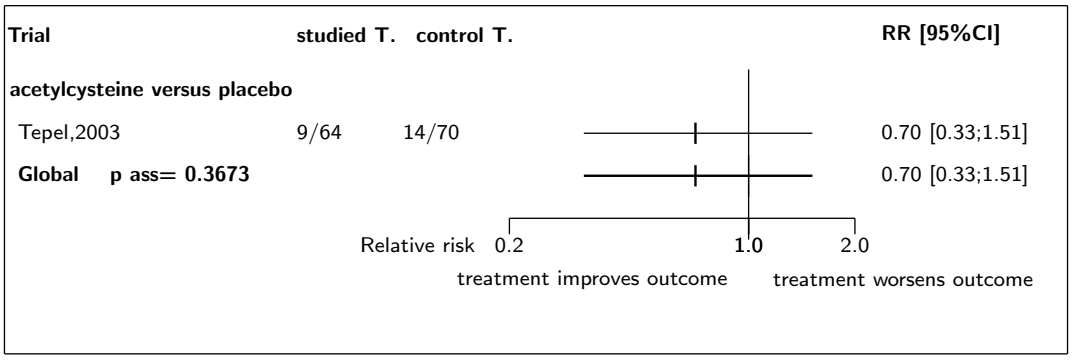
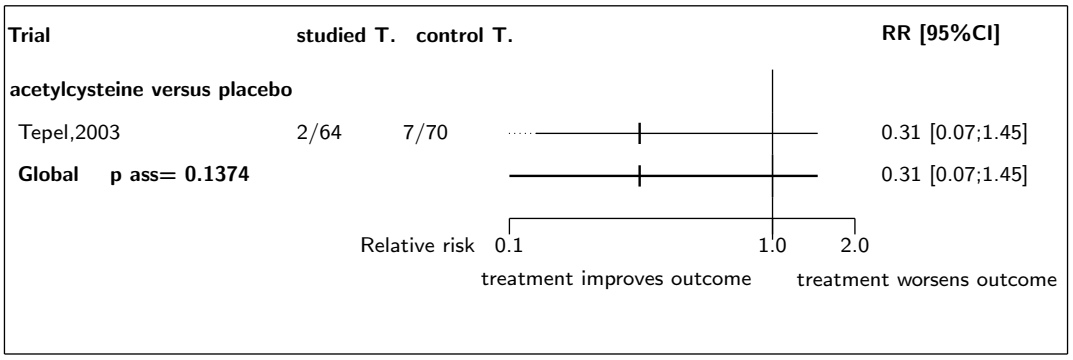


Figure 2.5: *Forest's plot for ischemic stroke*



References

[1] Tepel M, van der Giet M, Statz M, Jankowski J, Zidek W. The antioxidant acetylcysteine reduces cardiovascular events in patients with end-stage renal failure: a randomized, controlled trial. Circulation 2003;107:992-5. [PMID=12600912]

3 Detailed results for beta carotene

3.1 Available trials

A total of 7 RCTs which randomized 110991 patients were identified: all compared beta carotene with placebo.
The average study size was 15855 patients (range 1621 to 39876). The first study was published in 1990, and the last study was published in 2007.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
All cause death data was reported in 5 trials; 5 trials reported data on cardiovascular death; 3 trials reported data on coronary event; 3 trials reported data on stroke (fatal and non fatal); 3 trials reported data on cardiovascular events; 1 trials reported data on haemmorhagic stroke; 1 trials reported data on non fatal stroke; 1 trials reported data on ischemic stroke; and 1 trials reported data on non fatal MI.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of beta carotene.

Table 3.1: *Treatment description - antioxydant - beta carotene*

Trial	Studied treatment	Control treatment
Beta carotene versus placebo		
ATBC beta carotene (1994) [?, ?] [a]	beta carotene 20mg four times daily	placebo
CARET beta carotene (1996) [?, ?]	combination of30 mg of beta carotene per day and 25,000 IU of retinol(vitamin A) in the form of retinyl palmitate per day	placebo
NSCP (Green) beta carotene (1999) [?] [c]	beta carotene 30mg four times daily	placebo
PHS beta carotene (1996) [?] [d]	beta carotene 50 mg on alternate days	placebo
SCP beta carotene (1990) [?]	beta carotene 50mg four times daily	placebo
WACS beta-caroten (2007) [?, ?, ?] [f]	beta carotene (Lurotin) 50 mg every two days	placebo
WHS beta carotene (1999) [?, ?, ?] [g]	beta carotene 50mg four times daily	placebo

a) factorial design of four regimens: alpha-tocopherol (50 mg per day) alone, beta carotene (20 mg per day) alone, both alpha-tocopherol and beta carotene, or placebo c) factorial design of sunscreen and betacarotene d) factorial design that tested aspirinand beta carotene f) 2x2x2 factorial design testing the effects of ascorbic acid (500 mg/d), vitaminE (600 IU every other day), and beta carotene (50 mgevery other day) g) factorial edsign testing aspirin, vitamin E, and b-carotene

Table 3.2: *Descriptions of participants - antioxydant - beta carotene*

Trial	Patients	
Beta carotene versus placebo		
ATBC beta carotene (1994) [?, ?]	Male smokers 50 to 69 years of age from southwestern Finland	
	Inclusion criteria: smokers (five or more cigarettes per day at entry); 50 to 69 years old	**Exclusion criteria:** history of cancer or serious disease; supplements of vitamin E, vitamin A, or beta carotene in excess of predefined doses; anticoagulant agents
CARET beta carotene (1996) [?, ?]	Smokers, former smokers, and workersexposed to asbestos	
	Inclusion criteria:	**Exclusion criteria:** none
NSCP (Green) beta carotene (1999) [?]	Residents of Nambour	
PHS beta carotene (1996) [?]	Male physicians, 40 to 84 years of age with no history of cancer (exceptnonmelanoma skin cancer), myocardial infarction, stroke, or transientcerebral ischemia	
SCP beta carotene (1990) [?]	Age <85 years (most <65 years); previousnon-melanoma skin cancer; 69% male	
	Inclusion criteria: less than 85 years; could not become pregnant; none of the medical conditions: xeroderma pigmentosum, basal cell nevus, active nonskin cancer, known exposure to arsenic; any other medical problem that would limit the ability to participate in the planned 5 years of study	**Exclusion criteria:**
WACS beta-caroten (2007) [?, ?, ?]	Female health professionals at increased risk (40 years or older with a history of CVD or 3 or more CVD risk factors)	
	Inclusion criteria: women, aged 40 and over, at high risk, with a history of coronary artery disease, carotid endarterectomy, peripheral artery surgery, or three or more coronary heart disease risk factors	**Exclusion criteria:** self-reported history of cancer (excluding nonmelanoma skin cancer) within the past 10 years; any serious non-CVD illness; currently using warfarin sodium or other anticoagulants
WHS beta carotene (1999) [?, ?, ?]	Female health professionals, aged 45 years orolder and without a history of cancer (except nonmelanomaskin cancer), coronary heart disease, orcerebrovascular disease	

Table 3.3: *Main patients characteristics - antioxydant - beta carotene*

Trial	Characteristics
Beta carotene versus placebo	
ATBC beta carotene, 1994 [?, ?]	women (%): 0% age (yr): 57.1y body mass index: 26
CARET beta carotene, 1996 [?, ?]	women (%): 34% age (yr): 58y body mass index: NA
NSCP (Green) beta carotene, 1999 [?]	women (%): 56% age (yr): 48y body mass index: NA
PHS beta carotene, 1996 [?]	women (%): 0%
SCP beta carotene, 1990 [?]	women (%): 30% age (yr): 49% >= 65 years
WACS beta-caroten, 2007 [?, ?, ?]	women (%): 100% age (yr): 60.6 y body mass index: 30.3
WHS beta carotene, 1999 [?, ?, ?]	women (%): 100%

Table 3.4: *Design and methodological quality of trials - antioxydant - beta carotene*

Trial	Design	Duration	Centre	Primary endpoint
Beta carotene versus placebo				
ATBC beta carotene, 1994 [?, ?] n=29133	Factorial plan double-blind exploratory trial	6.1 median (range 5-8y) inclusion period: 1985-1988	Southwestern Finland postal survey	not defined
CARET beta carotene, 1996 [?, ?] n=18314	Parallel groups double-blind confirmatory trial at low risk of bias	4 y inclusion period: 1985-1991	USA multicenter	lung cancer
NSCP (Green) beta carotene, 1999 [?] n=1621	Factorial plan double-blind confirmatory trial at low risk of bias	4.5 y inclusion period: 1992	Queensland, Australia community study	skin cancer
PHS beta carotene, 1996 [?] n=12071	Factorial plan double-blind confirmatory trial at low risk of bias	12 y inclusion period: 1982 - dec 1995	USA	neoplasm except nonmelanoma skin cancer
SCP beta carotene, 1990 [?] n=1805	Parallel groups double-blind	4.02 years inclusion period: feb 1983 -	USA 4 centres	basal cell or squamaous cell skin cancer

continued...

Trial	Design	Duration	Centre	Primary endpoint
WACS beta-caroten, 2007 [?, ?, ?] n=8171	Factorial plan double blind confirmatory trial at low risk of bias	9.4 years inclusion period: jun 1995-oct 1996		MI, stroke, coronary revascularization, CVD death
WHS beta carotene, 1999 [?, ?, ?] n=39876	Factorial plan double-blind confirmatory trial at low risk of bias	2.1y (range 0 - 2.72y) inclusion period: apr 1993	USA	not defined

3.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Beta carotene versus placebo

A total of 3 of the 7 studies eligible for this comparison provided data on **cardiovascular events**. When pooled together, there was no statistically significant difference between the groups in cardiovascular events, with a RR of 0.49 (95% CI 0.07 to 3.36, p=0.4648). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0000, I^2 = 1.00%).

A total of 6 of the 7 studies eligible for this comparison provided data on **cardiovascular death**. When pooled together, there was no statistically significant difference between the groups in cardiovascular death, with a RR of 0.67 (95% CI 0.23 to 1.93, p=0.4600). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0000, I^2 = 0.99%).

A total of 6 of the 7 studies eligible for this comparison provided data on **all cause death**. When pooled together, there was no statistically significant difference between the groups in all cause death, with a RR of 0.64 (95% CI 0.18 to 2.28, p=0.4890). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0000, I^2 = 1.00%).

A total of 3 of the 7 studies eligible for this comparison provided data on **coronary event**. When pooled together, there was no statistically significant difference between the groups in coronary event, with a RR of 0.42 (95% CI 0.07 to 2.60, p=0.3487). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0000, I^2 = 0.99%).

Only one of the 7 studies eligible for this comparison provided data on **non fatal MI**. No statistically significant difference between the groups was found in non fatal MI, with a RR of 1.09 (95% CI 0.85 to 1.40, p=0.5088).

Only one of the 7 studies eligible for this comparison provided data on **ischemic stroke**. No statistically significant difference between the groups was found in ischemic stroke, with a RR of 1.12 (95% CI 0.88 to 1.41, p=0.3512).

A total of 3 of the 7 studies eligible for this comparison provided data on **stroke (fatal and non fatal)**. When pooled together, there was no statistically significant difference between the groups in stroke (fatal and non fatal), with a RR of 0.53 (95% CI 0.07 to 3.97, p=0.5362). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0000, I^2 = 1.00%).

Only one of the 7 studies eligible for this comparison provided data on **non fatal stroke**. No statistically significant difference between the groups was found in non fatal stroke, with a RR of 1.10 (95% CI 0.87 to 1.40, p=0.4136).
Only one of the 7 studies eligible for this comparison provided data on **haemmorhagic stroke**. No statistically significant difference between the groups was found in haemmorhagic stroke, with a RR of 2.13 (95% CI 0.92 to 4.92, p=0.0780).

Table 3.5: *Results details - antioxydant - beta carotene*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
beta carotene versus placebo						
cardiovascular events	RR=0.49	[0.07;3.36]	0.4648	0.0000 (I^2=1.00)	3	60118
cardiovascular death	RR=0.67	[0.23;1.93]	0.4600	0.0000 (I^2=0.99)	6	109186
all cause death	RR=0.64	[0.18;2.28]	0.4890	0.0000 (I^2=1.00)	6	81858
coronary event	RR=0.42	[0.07;2.60]	0.3487	0.0000 (I^2=0.99)	3	60118
non fatal MI	RR=1.09	[0.85;1.40]	0.5088	1.0000 (I^2=0.00)	1	8171
ischemic stroke	RR=1.12	[0.88;1.41]	0.3512	1.0000 (I^2=0.00)	1	8171
stroke (fatal and non fatal)	RR=0.53	[0.07;3.97]	0.5362	0.0000 (I^2=1.00)	3	60118
non fatal stroke	RR=1.10	[0.87;1.40]	0.4136	1.0000 (I^2=0.00)	1	8171
haemmorhagic stroke	RR=2.13	[0.92;4.92]	0.0780	1.0000 (I^2=0.00)	1	8171

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 3.1: *Forest's plot for cardiovascular events*

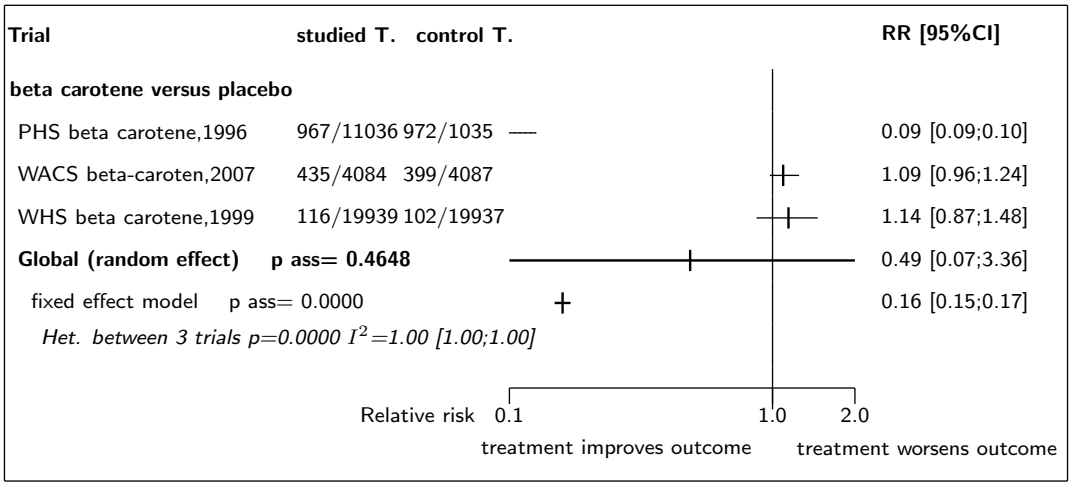


Figure 3.2: *Forest's plot for cardiovascular death*

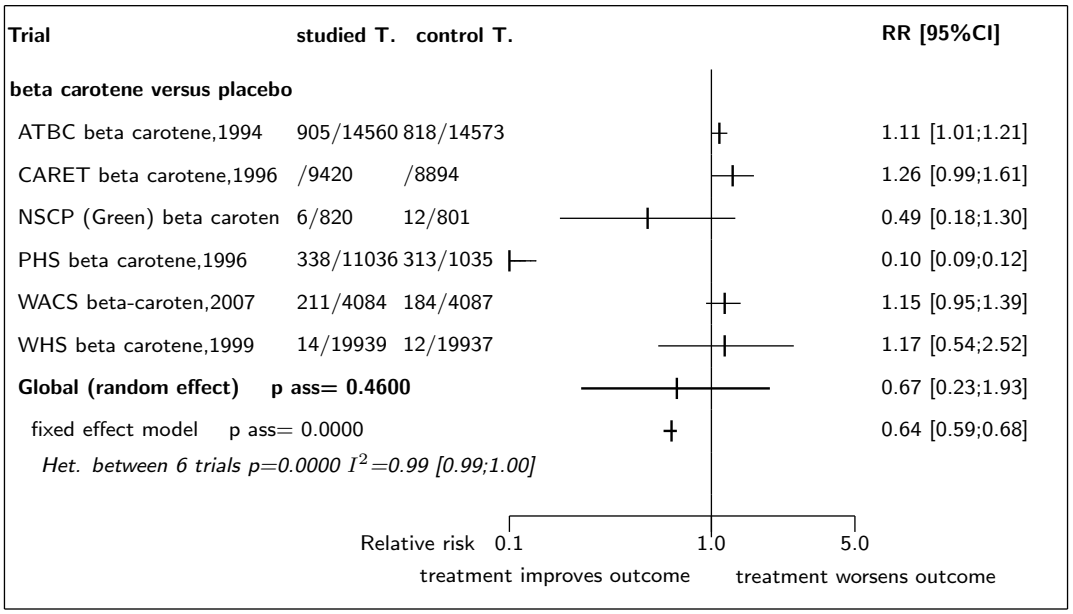


Figure 3.3: *Forest's plot for all cause death*

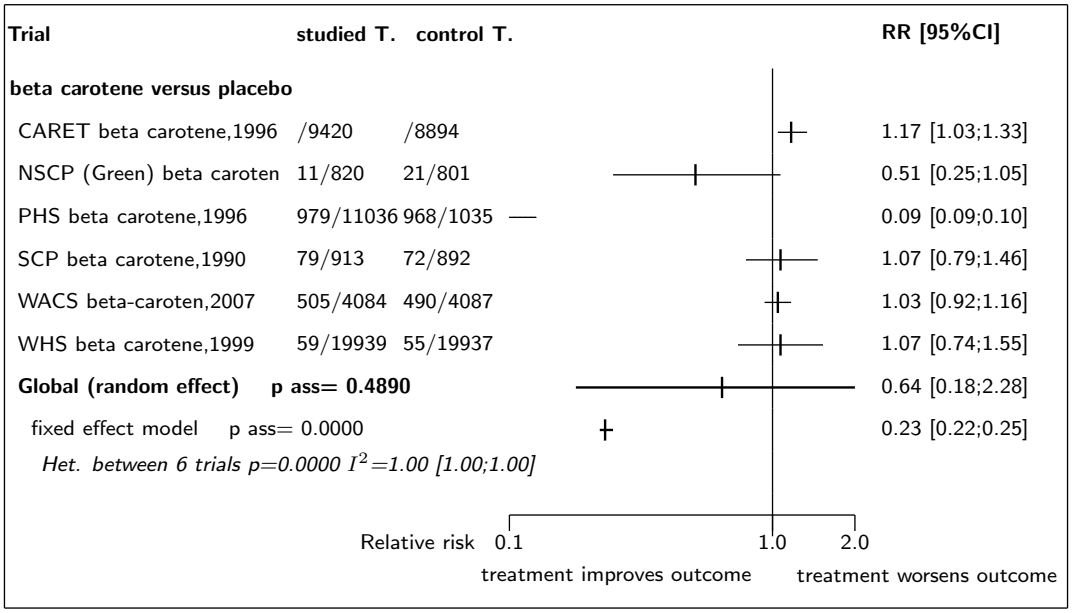


Figure 3.4: *Forest's plot for coronary event*

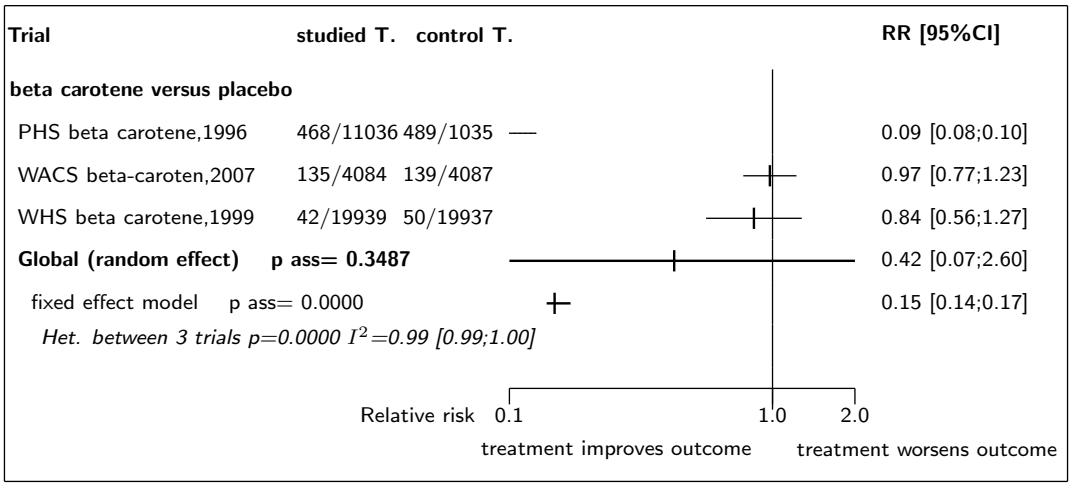


Figure 3.5: *Forest's plot for non fatal MI*

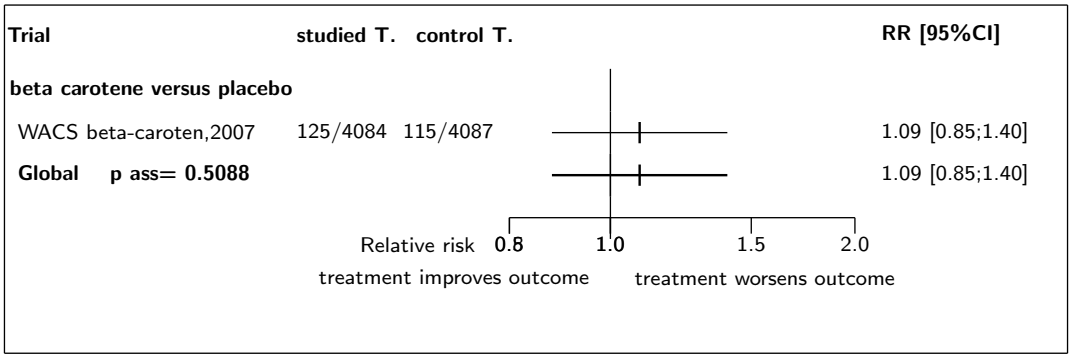


Figure 3.6: *Forest's plot for ischemic stroke*

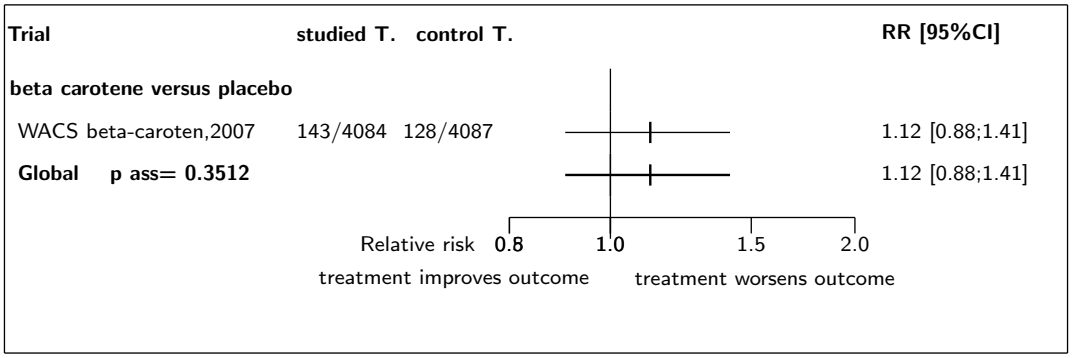


Figure 3.7: *Forest's plot for stroke (fatal and non fatal)*

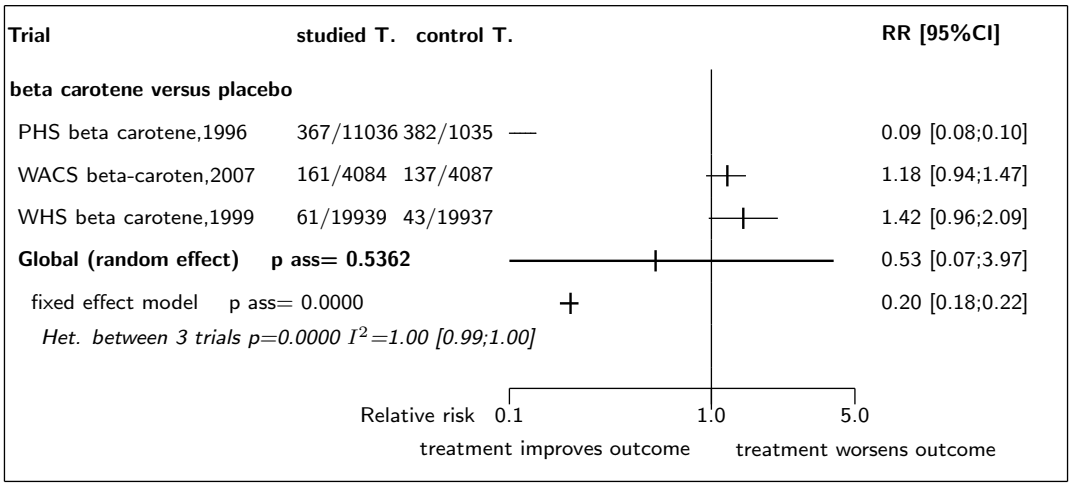


Figure 3.8: *Forest's plot for non fatal stroke*

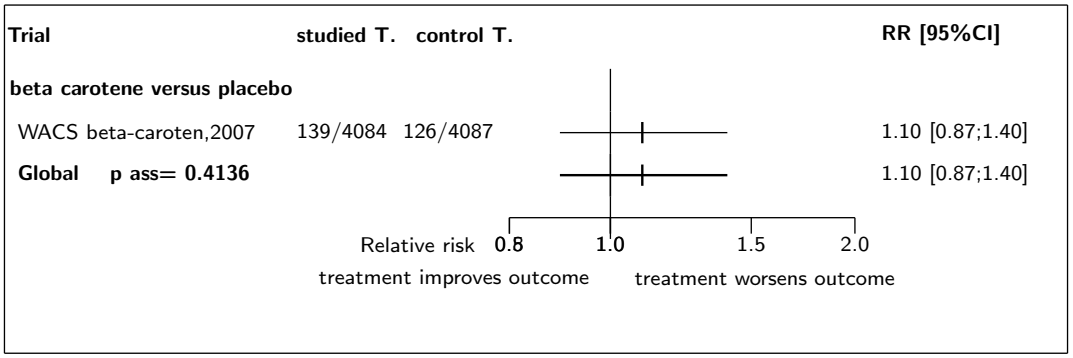
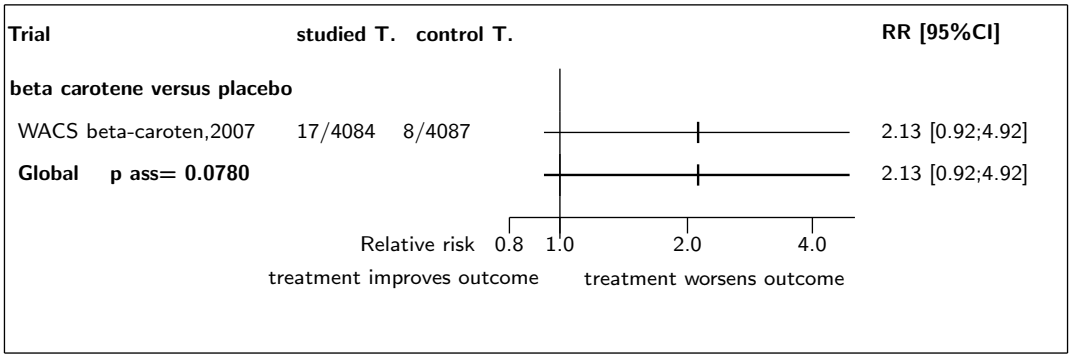


Figure 3.9: *Forest's plot for haemmorhagic stroke*



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4 Detailed results for combination

4.1 Available trials

A total of 7 RCTs which randomized 41685 patients were identified: all compared combination with placebo.
The average study size was 5955 patients (range 160 to 20536). The first study was published in 1997, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
All cause death data was reported in 6 trials; 4 trials reported data on cardiovascular events; 3 trials reported data on cardiovascular death; 3 trials reported data on non fatal MI; 2 trials reported data on coronary event; 2 trials reported data on non fatal stroke; 2 trials reported data on stroke (fatal and non fatal); and 1 trials reported data on amputation.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of combination.

Table 4.1: *Treatment description - antioxydant - combination*

Trial	Studied treatment	Control treatment
Combination versus placebo		
POPADAD (antioxydant) (2008) [?] [a]	antioxidant capsule containing (alpha-tocopherol 200 mg, ascorbic acid 100 mg, pyridoxine hydrochloride 25 mg, zinc sulphate 10 mg, nicotinamide 10 mg, lecithin 9.4 mg, and sodium selenite 0.8 mg)	placebo
HATS (2001) [?] [b]	antioxidant-therapy (vitamins) antioxidants given twice daily for a total daily dose of800 IU of vitamin E (as d-alpha-tocopherol), 1000 mg of vitaminC, 25 mg of natural beta carotene, and 100 g of selenium	placebo
MVP (1997) [?] [c]	multivitamins (30,000 IU of beta carotene, 500 mg of vitamin C, and 700 IU of vitamin E) for four weeks before and six months after angioplasty	placebo
HPS antioxidant (2002) [?] [d]	antioxidant vitaminsupplementation (600 mg vitamin E, 250 mg vitamin C, and20 mg -carotene daily)	matching placebo
PHS II beta carotene (2003) [?, ?, ?] [e]	400 IU of vitamin E every other day and500 mg of vitamin C daily	placebo
SUVIMAX (2005) [?, ?, ?]	single daily capsule of combination of antioxydants: 120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta carotene, 100 g of selenium, and 20 mg of zinc	matched placebo
WAVE (Waters) (2002) [?] [g]	400 IU of vitamin E twice daily plus 500 mg of vitamin C twice daily	placebo

continued...

Trial	Studied treatment	Control treatment
a) factorial design of aspirin plus antioxidant compared withaspirin alone, antioxidant alone, and placebo. b) factorial design with simvastatin + niacin c) factorial design: probucol and multivitamins d) factorial design with cholesterol lowering therapy e) factorial design with : beta-caroten, vit E and ascorbic acid, multivitamin g) factorial design of 0.625 mg/d of conjugated equine estrogen (plus 2.5 mg/d of medroxyprogesteroneacetate for women who had not had a hysterectomy)		

Table 4.2: *Descriptions of participants - antioxydant - combination*

Trial	Patients	
Combination versus placebo		
POPADAD (antioxydant) (2008) [?]	Patients with diabetes mellitus and asymptomatic peripheral arterial disease	
	Inclusion criteria: adults of either sex, aged 40 or more, with type 1 or type 2 diabetes who were determined as having asymptomatic peripheral arterial disease as detected by a lower than normal ankle brachial pressure index (<=0.99)	**Exclusion criteria:** evidence of symptomatic cardiovascular disease; aspirin or antioxidant therapy on a regular basis; peptic ulceration, severe dyspepsia, a bleeding disorder, or intolerance to aspirin; suspected serious physical illness (such as cancer), which might have been expected to curtail life expectancy; psychiatric illness; congenital heart disease; unable to give informed consent
HATS (2001) [?]	Patients with coronary disease, low HDL cholesterol levels and normal LDL cholesterol	
	Inclusion criteria: men (younger than 63 years of age) and women (younger than 70 years of age) with clinical coronary disease (defined as previous myocardial infarction, coronary interventions, or confirmed angina) and with at least three stenoses of at least 30 percent of the luminal diameter or one stenosis of at least 50 percent; low levelsof HDL cholesterol (35 mg per deciliter [0.91 mmol per liter]or lower in men and 40 mg per deciliter [1.03 mmol per liter] inwomen), LDL cholesterol levels of 145 mg per deciliter (3.75 mmolper liter) or lower, and triglyceride levels below 400 mg per deciliter(4.52 mmol per liter)	**Exclusion criteria:**
MVP (1997) [?]	Patient undergoing angioplasty	
	Inclusion criteria: scheduled to undergo standard balloon angioplasty on at least one native coronary artery and had at least one target lesion with stenosis of 50 percent or more of the luminal diameter as measured by calipers on the angiogram	**Exclusion criteria:** unable to participate in the pretreatment evaluation or unable to return for follow-up; myocardial infarction within the previous seven days; scheduled to undergo stenting or atherectomy; prior angioplasty for another lesion in the preceding six months; treatement for a restenotic lesion; angioplasty of a bypass graft or of a bypassed native vessel with a patent graft
HPS antioxidant (2002) [?]	UK adults (aged 4080) with coronary disease, other occlusive arterial disease, or diabetes	
	Inclusion criteria: men and women; aged about 40 years to 80 years; non-fasting blood total cholesterol concentrations of at least 35 mmol/L; substantial 5-year risk of death from coronary heart disease because of a past medical history of coronary heart disease, of other occlusive arterial disease, of diabetes mellitus, or of treated hypertension alone	**Exclusion criteria:** life-threatening conditions, such as chronic liver disease, severe renal disease, severe heart failure, severe chronic airways disease, or diagnosed cancer (other than non-melanoma skin cancer); high-dose vitamin E supplements

continued...

Trial	Patients	
PHS II beta carotene (2003) [?, ?, ?] [e]	US male physicians enrolled, aged 50 years or older	
SUVIMAX (2005) [?, ?, ?]	Women aged 35-60 years and men aged 45-60 years **Inclusion criteria:**	**Exclusion criteria:** disease likely tohinder active participation or threatened 5-year survival; previous regularsupplementation with any of the vitamins or minerals in thesupplement provided; extreme beliefs or behaviorregarding diet
WAVE (Waters) (2002) [?]	Postmenopausal women with at least one 15% to 75% coronary stenosis	

e) 7641 men from the PHS agreed to participate in the PHSII and, beginning in August 1997, were randomized to PHSII study treatments. Treatment assignment to beta carotene or placebo was retained from the PHS (although participants may have stopped taking beta carotene during the 18-month interval between studies), and the men were newly randomized to receive vitamin E, ascorbic acid, multivitamin, or placebo.

Table 4.3: *Main patients characteristics - antioxydant - combination*

Trial	Characteristics
Combination versus placebo	
POPADAD (antioxydant), 2008 [?]	
HATS, 2001 [?]	women (%): 13% age (yr): 53 y
MVP, 1997 [?]	
HPS antioxidant, 2002 [?]	
PHS II beta carotene, 2003 [?, ?, ?]	
SUVIMAX, 2005 [?, ?, ?]	women (%): 61% age (yr): male: 51.3, female: 46.6 body mass index: 24.05
WAVE (Waters), 2002 [?]	women (%): 100% age (yr): 65 y body mass index: 31

Table 4.4: *Design and methodological quality of trials - antioxydant - combination*

Trial	Design	Duration	Centre	Primary endpoint
Combination versus placebo				
POPADAD (antioxydant), 2008 [?] [(a)] n=1276	Factorial plan double blind confirmatory trial at low risk of bias		Scotland multicentre	CV events

continued...

Trial	Design	Duration	Centre	Primary endpoint
HATS, 2001 [?] n=160	Factorial plan double-blind exploratory trial	inclusion period: jan 1995 - jan 1997	USA, Canada 2 centres	change in coronary stenosis
MVP, 1997 [?] n=317	Factorial plan double-blind exploratory trial	6 montsh inclusion period: NS	Canada single center	extent of restenosis
HPS antioxidant, 2002 [?] n=20536	Factorial plan double-blind confirmatory trial at low risk of bias	jul 1994 - may 1997 inclusion period: jul 1994 - may 1997	UK 69 centres	coronary events
PHS II beta carotene, 2003 [?, ?, ?] n=5956	Factorial plan double-blind confirmatory trial at low risk of bias	8 years inclusion period: jul 1997 -		cardiovascular events
SUVIMAX, 2005 [?, ?, ?] n=13017	Parallel groups double-blind exploratory trial	7.5 years inclusion period: Mar 1994 - Jul 1994	France media campaign	not defined
WAVE (Waters), 2002 [?] n=423	Factorial plan double-blind exploratory trial	2.8 years inclusion period: jul 1997 - jan 2002	US, Canada 7 centres	change in minimum lumen diameter

a) two hierarchical compositeprimary end points of death from coronary heart disease orstroke, non-fatal myocardial infarction or stroke, oramputation above the ankle for critical limb ischaemia;and death from coronary heart disease or stroke

4.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Combination versus placebo

Only one of the 7 studies eligible for this comparison provided data on **amputation**. There was no statistically significant difference in amputation between combination and placebo, with a RR of 0.99 (95%CI 0.42 to 2.37, p=0.9887) in favour of combination. In other words, amputation was slightly lower in the combination group , but this was not statistically significant.
A total of 4 of the 7 studies eligible for this comparison provided data on **cardiovascular events**. When pooled together, there was no statistically significant difference between the groups in cardiovascular events, with a RR of 1.00 (95% CI 0.95 to 1.05, p=0.9635). No heterogeneity was detected (p = 0.4433, $I^2 = 0.00\%$).
A total of 3 of the 7 studies eligible for this comparison provided data on **cardiovascular death**. When pooled together, there was no statistically significant difference between the groups in cardiovascular death, with a RR of 1.12 (95% CI 0.80 to 1.56, p=0.5185). No heterogeneity was detected (p = 0.3316, $I^2 = 0.09\%$).
A total of 6 of the 7 studies eligible for this comparison provided data on **all cause death**. When pooled together, there was no statistically significant difference between the groups in all cause death, with a RR of 1.12 (95% CI 0.87 to 1.44, p=0.3818). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0234, $I^2 = 0.62\%$).
A total of 2 of the 7 studies eligible for this comparison provided data on **coronary event**. When pooled together, there was no statistically significant difference between the groups in

coronary event, with a RR of 1.01 (95% CI 0.94 to 1.10, p=0.7319). No heterogeneity was detected (p = 0.6479, I^2 = 0.00%).
A total of 3 of the 7 studies eligible for this comparison provided data on **non fatal MI**. When pooled together, there was no statistically significant difference between the groups in non fatal MI, with a RR of 0.99 (95% CI 0.87 to 1.12, p=0.8795). No heterogeneity was detected (p = 0.8897, I^2 = 0.00%).
A total of 2 of the 7 studies eligible for this comparison provided data on **stroke (fatal and non fatal)**. When pooled together, there was no statistically significant difference between the groups in stroke (fatal and non fatal), with a RR of 0.98 (95% CI 0.87 to 1.11, p=0.7966). No heterogeneity was detected (p = 0.7924, I^2 = 0.00%).
A total of 2 of the 7 studies eligible for this comparison provided data on **non fatal stroke**. When pooled together, there was no statistically significant difference between the groups in non fatal stroke, with a RR of 0.99 (95% CI 0.87 to 1.13, p=0.8548). No heterogeneity was detected (p = 0.9289, I^2 = 0.00%).

Table 4.5: *Results details - antioxydant - combination*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
combination versus placebo						
amputation	RR=0.99	[0.42;2.37]	0.9887	1.0000 (I^2=0.00)	1	1276
cardiovascular events	RR=1.00	[0.95;1.05]	0.9635	0.4433 (I^2=0.00)	4	34136
cardiovascular death	RR=1.12	[0.80;1.56]	0.5185	0.3316 (I^2=0.09)	3	21119
all cause death	RR=1.12	[0.87;1.44]	0.3818	0.0234 (I^2=0.62)	6	35729
coronary event	RR=1.01	[0.94;1.10]	0.7319	0.6479 (I^2=0.00)	2	20853
non fatal MI	RR=0.99	[0.87;1.12]	0.8795	0.8897 (I^2=0.00)	3	21119
stroke (fatal and non fatal)	RR=0.98	[0.87;1.11]	0.7966	0.7924 (I^2=0.00)	2	20959
non fatal stroke	RR=0.99	[0.87;1.13]	0.8548	0.9289 (I^2=0.00)	2	20696

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 4.1: *Forest's plot for amputation*

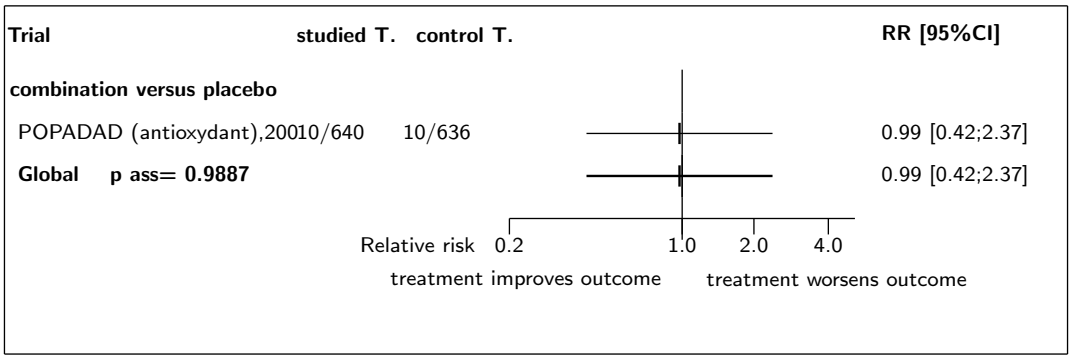


Figure 4.2: *Forest's plot for cardiovascular events*

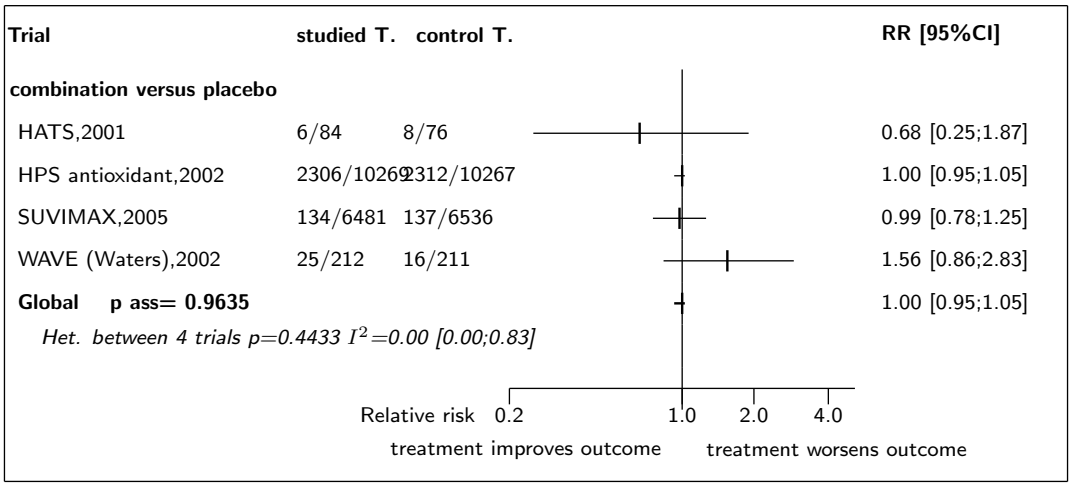


Figure 4.3: *Forest's plot for cardiovascular death*

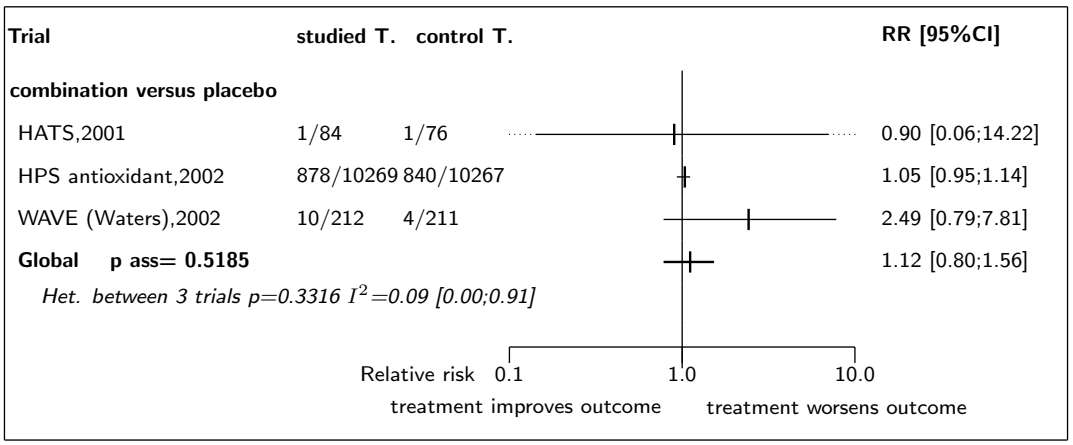


Figure 4.4: *Forest's plot for all cause death*

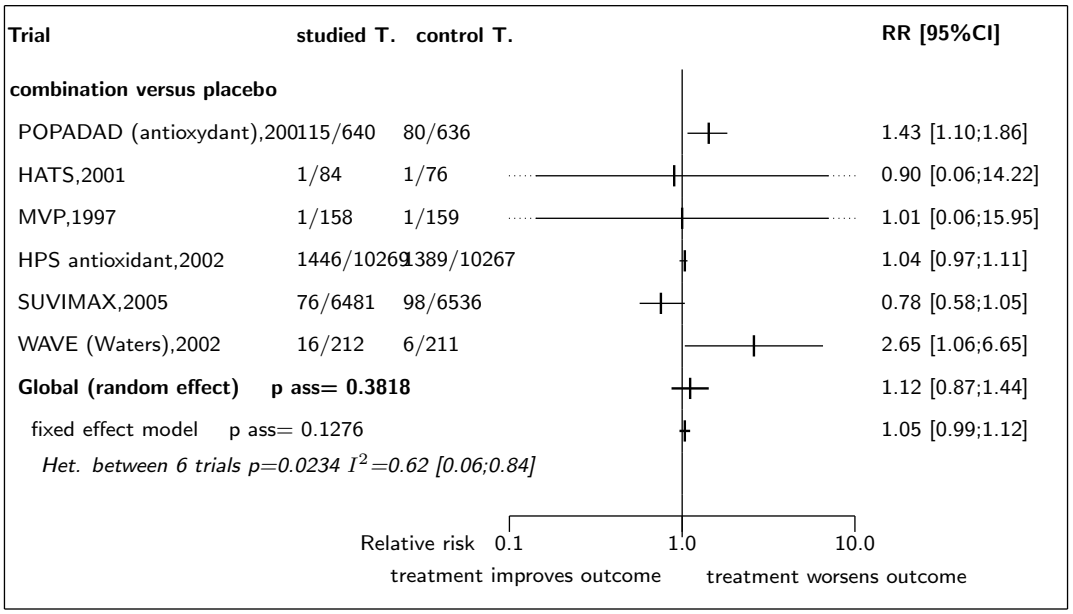


Figure 4.5: *Forest's plot for coronary event*

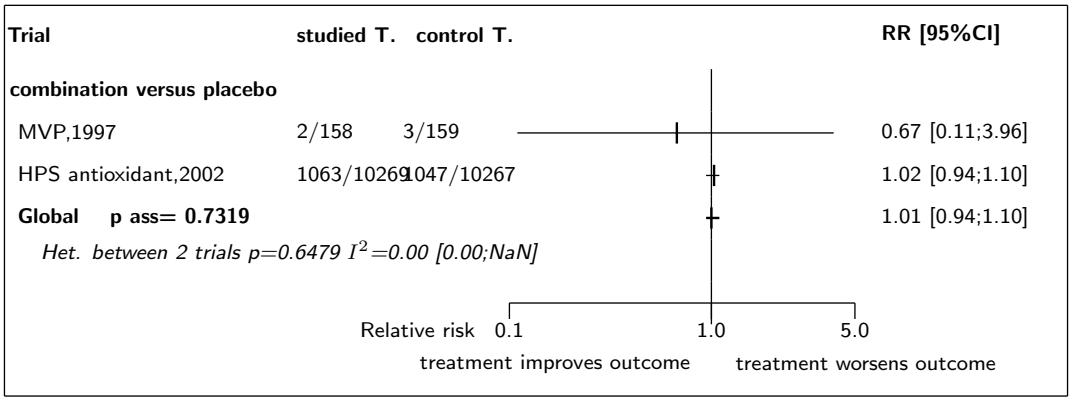


Figure 4.6: *Forest's plot for non fatal MI*

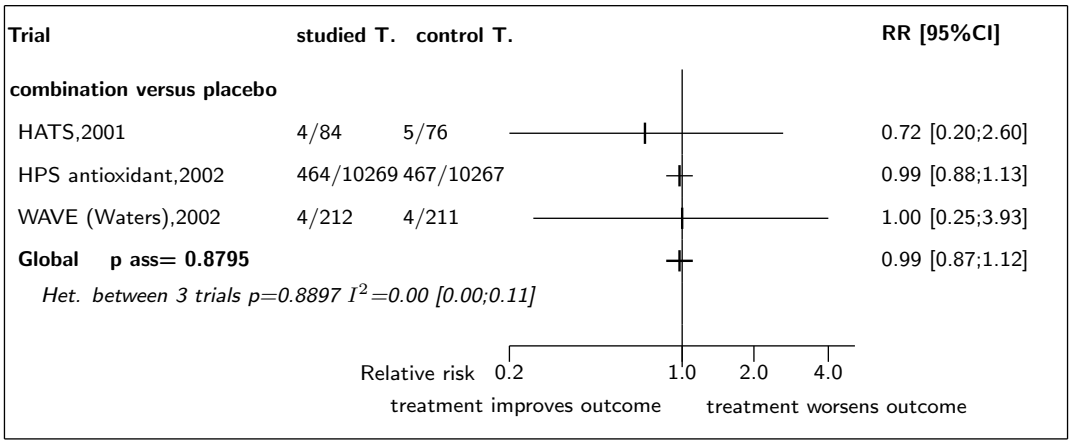


Figure 4.7: *Forest's plot for stroke (fatal and non fatal)*

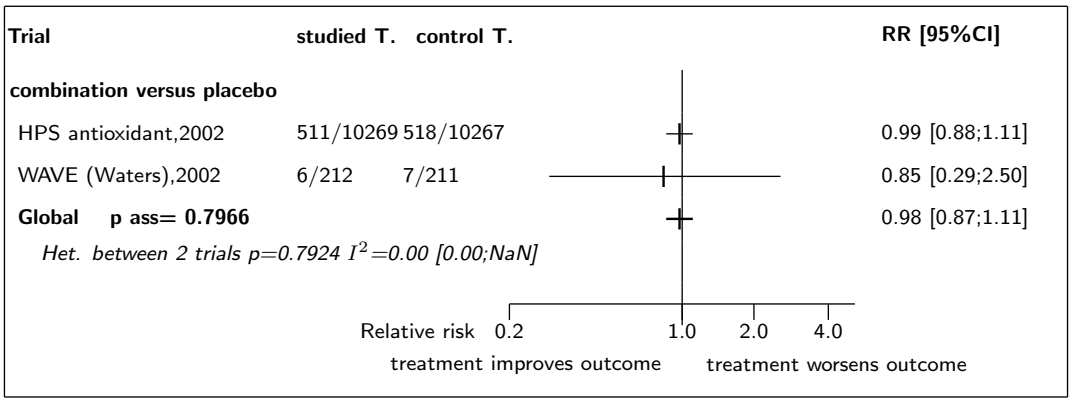
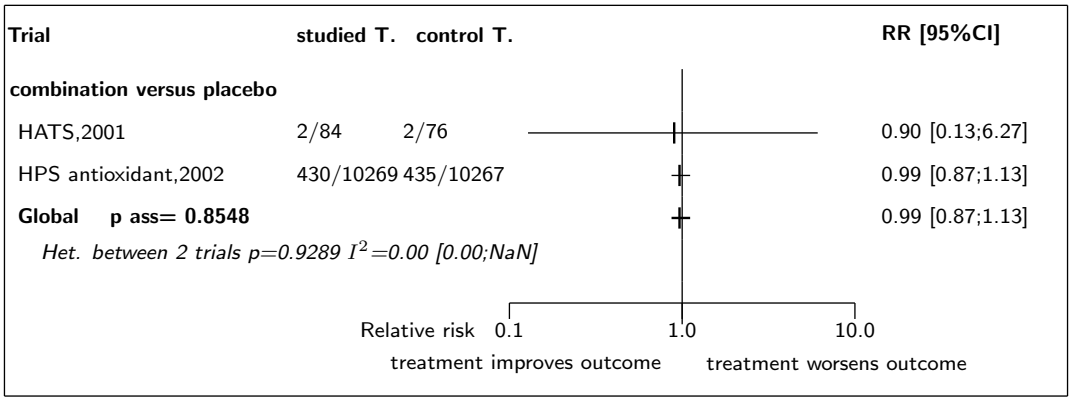


Figure 4.8: *Forest's plot for non fatal stroke*



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5 Detailed results for succinobucol

5.1 Available trials

Only one trial which randomized 6144 patients was identified: it compared succinobucol with placebo.
This trial included 6144 patients and was published in 2008.
This trial was double blind in design.
It was reported in English language.
Cardiovascular events data was reported in 1 trials; 1 trials reported data on new-onset diabetes; 1 trials reported data on cardiovascular death, MI, stroke; and 1 trials reported data on new-onset atrial fibrillation.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trial including in this systematic review of randomized trials of succinobucol .

Table 5.1: *Treatment description - antioxydant - succinobucol*

Trial	Studied treatment	Control treatment
Succinobucol versus placebo		
ARISE (2008) [**?**]	succinobucol 300 mg once daily	placebo

Table 5.2: *Descriptions of participants - antioxydant - succinobucol*

Trial	Patients	
Succinobucol versus placebo		
ARISE (2008) [**?**]	Patients with recent (14-365 days) acute coronary syndromes already managed with conventional treatments	
	Inclusion criteria: men and women (not of childbearing potential);18 years or older and have diabetes; or 60 years or older, or be 55 years or older and at least one of the following risk factors: low HDL cholesterol (<103 mmol/L in men and <130 mmol/L in women); a myocardial infarction before the qualifying event; evidence of additional atherosclerosis in a non-coronary arterial bed (eg, prior stroke, presence of peripheral arterial disease); or prior evidence of heart failure or left ventricular ejection fraction less than 40%	**Exclusion criteria:** recent coronary revascularisation (percutaneous coronary intervention <28 days and coronary artery bypass graft surgery <90 days before randomisation), moderate or severe symptomatic heart failure, systolic blood pressure above 180 mm Hg, serum creatinine of 221 mol/L or greater, concentrations of alanine or aspartate aminotransferases greater than twice the upper limit of normal, use of medications known to increase the QT interval by 15 ms or more, or comorbidity with survival expected to be less than 2 years

Table 5.3: *Main patients characteristics - antioxydant - succinobucol*

Trial	Characteristics
Succinobucol versus placebo	
ARISE, 2008 [**?**]	

Table 5.4: *Design and methodological quality of trials - antioxydant - succinobucol*

Trial	Design	Duration	Centre	Primary endpoint
Succinobucol versus placebo				
ARISE, 2008 [**?**] n=6144	Parallel groups double blind confirmatory trial at low risk of bias	24 mo (range 12-36 mo) inclusion period: jul 2003 - aug 2006	Canada, US, UK, South Africa 261 centres	CV death, MI, Stroke, UA, revasc

5.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Succinobucol versus placebo

The single study eligible for this comparison provided data on **new-onset diabetes**. The analysis detected a statistically significant difference in favor of succinobucol in new-onset diabetes, with a RR of 0.37 (95% CI 0.25 to 0.56, p=0.0000).
The single study eligible for this comparison provided data on **new-onset atrial fibrillation**. The analysis detected a statistically significant difference in favor of placebo in new-onset atrial fibrillation, with a RR of 1.92 (95% CI 1.40 to 2.65, p=0.0000).
The single study eligible for this comparison provided data on **cardiovascular events**. No statistically significant difference between the groups was found in cardiovascular events, with a RR of 1.00 (95% CI 0.89 to 1.11, p=0.9712).
The single study eligible for this comparison provided data on **cardiovascular death, MI, stroke**. The analysis detected a statistically significant difference in favor of succinobucol in cardiovascular death, MI, stroke, with a RR of 0.82 (95% CI 0.69 to 0.98, p=0.0263).

Table 5.5: *Results details - antioxydant - succinobucol*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
succinobucol versus placebo						
new-onset diabetes	RR=0.37	[0.25;0.56]	0.0000	1.0000 (I^2=1.00)	1	3873
new-onset atrial fibrillation	RR=1.92	[1.40;2.65]	0.0000	1.0000 (I^2=0.00)	1	5605
cardiovascular events	RR=1.00	[0.89;1.11]	0.9712	1.0000 (I^2=0.00)	1	6144
cardiovascular death, MI, stroke	RR=0.82	[0.69;0.98]	0.0263	1.0000 (I^2=0.00)	1	6144

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 5.1: *Forest's plot for new-onset diabetes*

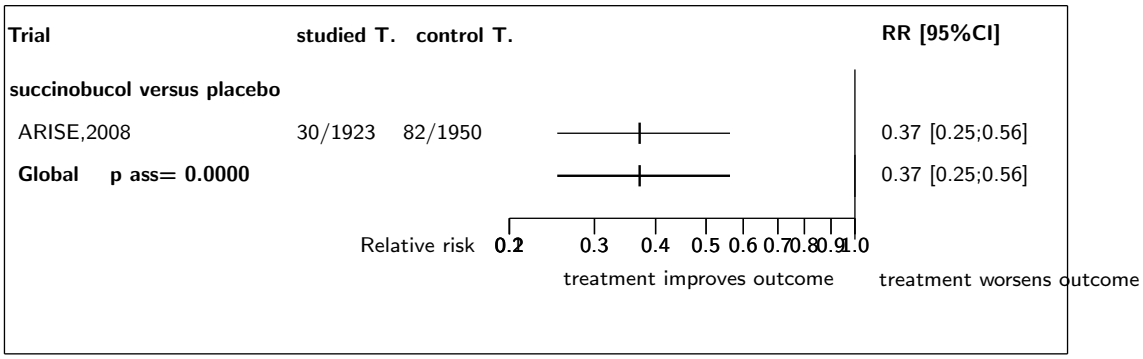


Figure 5.2: *Forest's plot for new-onset atrial fibrillation*

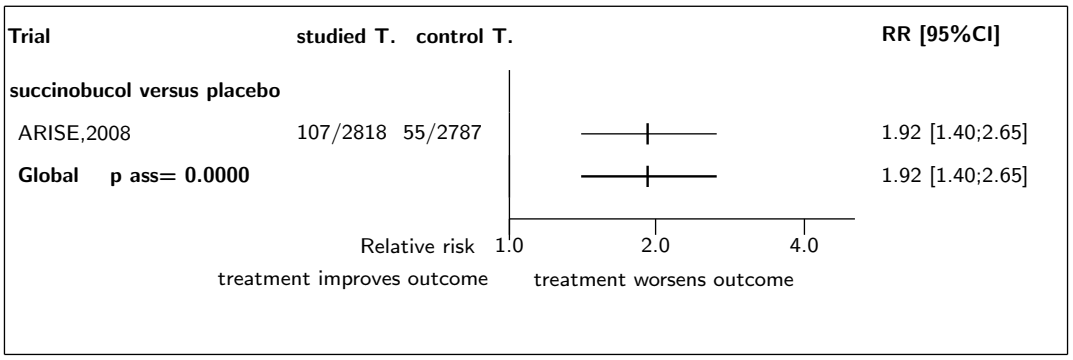


Figure 5.3: *Forest's plot for cardiovascular events*

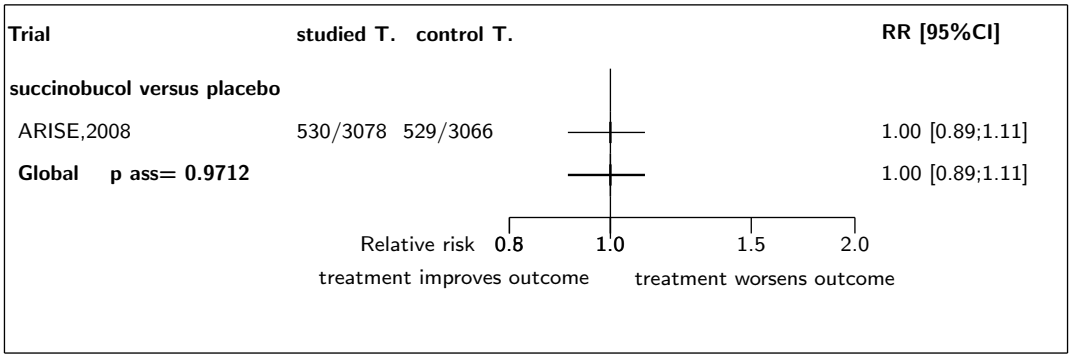
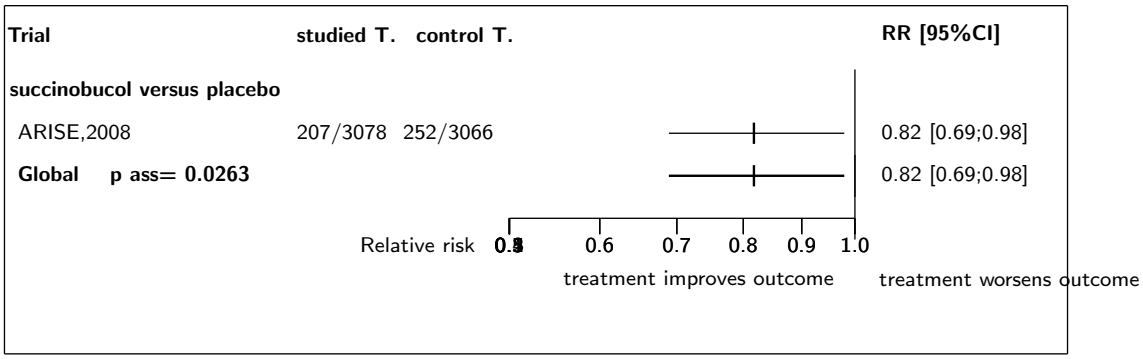


Figure 5.4: *Forest's plot for cardiovascular death, MI, stroke*



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6 Detailed results for vitamin C

6.1 Available trials

A total of 2 RCTs which randomized 22812 patients were identified: all compared vitamin C with placebo.
The average study size was 11406 patients (range 8171 to 14641). The first study was published in 2007, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Cardiovascular death data was reported in 2 trials; 2 trials reported data on ischemic stroke; 2 trials reported data on stroke (fatal and non fatal); 2 trials reported data on all cause death; 2 trials reported data on haemmorhagic stroke; 2 trials reported data on cardiovascular events; 1 trials reported data on coronary event; 1 trials reported data on non fatal stroke; and 1 trials reported data on non fatal MI.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of vitamin C.

Table 6.1: *Treatment description - antioxydant - vitamin C*

Trial	Studied treatment	Control treatment
Vitamin C versus placebo		
PHS II vitamin C (2008) [**?**] [a]	vitamin C 500mg daily	placebo
WACS vitamin C (2007) [**?**, **?**] [b]	vitamin C (ascorbic acid) 500 mg/d	placebo

a) 2x2x2x2factorial trial evaluating vitamin E (400 IUsynthetic alpha-tocopherol), vitaminC(500mg synthetic ascorbic acid), amultivitamin (Centrum Silver daily; Wyeth Pharmaceuticals) and beta carotene (50mg, Lurotin on alternate days) b) 2x2x2 factorial design testing the effects of ascorbic acid (500 mg/d), vitaminE (600 IU every other day), and beta carotene (50 mgevery other day)

Table 6.2: *Descriptions of participants - antioxydant - vitamin C*

Trial	Patients	
Vitamin C versus placebo		
PHS II vitamin C (2008) [**?**]	US male physicians aged 50 years or older	
	Inclusion criteria: men with ahistory of myocardial infarction(MI), stroke, or cancer were eligible	**Exclusion criteria:** historyof cirrhosis; active liver disease; anticoagulants; serious illness that might preclude participation
WACS vitamin C (2007) [**?**, **?**]	Female health professionals at increased risk (40 years or older with a history of CVD or 3 or more CVD risk factors)	
	Inclusion criteria: women, aged 40 and over, at high risk, with a history of coronary artery disease, carotid endarterectomy, peripheral artery surgery, or three or more coronary heart disease risk factors	**Exclusion criteria:** self-reported history of cancer (excluding nonmelanoma skin cancer) within the past 10 years; any serious non-CVD illness; currently using warfarin sodium or other anticoagulants

Table 6.3: *Main patients characteristics - antioxydant - vitamin C*

Trial	Characteristics
Vitamin C versus placebo	
PHS II vitamin C, 2008 [?]	women (%): 0% age (yr): 64.3 y body mass index: 26
WACS vitamin C, 2007 [?, ?]	women (%): 100% age (yr): 60.6 y body mass index: 30.3

Table 6.4: *Design and methodological quality of trials - antioxydant - vitamin C*

Trial	Design	Duration	Centre	Primary endpoint
Vitamin C versus placebo				
PHS II vitamin C, 2008 [?] n=14641	Factorial plan double blind confirmatory trial at low risk of bias	8 years (mean) inclusion period: jul 1997 - jul 2001	US postal survey	Cv death, MI, Stroke
WACS vitamin C, 2007 [?, ?] n=8171	double blind	9.4 years inclusion period: jun 1995 - oct 1996	US	MI, stroke, coronary revascularization, CVD death

6.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Vitamin C versus placebo

All the 2 studies had extractable data about the number of participants with **cardiovascular events**. When pooled together, there was no statistically significant difference between the groups in cardiovascular events, with a RR of 1.00 (95% CI 0.92 to 1.08, p=0.9148). No heterogeneity was detected (p = 0.7922, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **cardiovascular death**. When pooled together, there was no statistically significant difference between the groups in cardiovascular death, with a RR of 1.04 (95% CI 0.92 to 1.19, p=0.5107). No heterogeneity was detected (p = 0.5631, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **all cause death**. When pooled together, there was no statistically significant difference between the groups in all cause death, with a RR of 1.05 (95% CI 0.98 to 1.13, p=0.1893). No heterogeneity was detected (p = 0.6314, I^2 = 0.00%).
Only one of the 2 studies eligible for this comparison provided data on **coronary event**. No statistically significant difference between the groups was found in coronary event, with a RR of 1.04 (95% CI 0.83 to 1.32, p=0.7170).
Only one of the 2 studies eligible for this comparison provided data on **non fatal MI**. No statistically significant difference between the groups was found in non fatal MI, with a RR of 1.09 (95% CI 0.85 to 1.39, p=0.5162).

All the 2 studies had extractable data about the number of participants with **ischemic stroke**. The analysis detected a statistically significant difference in favor of vitamin C in ischemic stroke, with a RR of 0.85 (95% CI 0.73 to 0.99, p=0.0378). No heterogeneity was detected (p = 0.7803, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **stroke (fatal and non fatal)**. When pooled together, there was no statistically significant difference between the groups in stroke (fatal and non fatal), with a RR of 0.88 (95% CI 0.76 to 1.01, p=0.0622). No heterogeneity was detected (p = 0.8616, I^2 = 0.00%).
Only one of the 2 studies eligible for this comparison provided data on **non fatal stroke**. No statistically significant difference between the groups was found in non fatal stroke, with a RR of 0.87 (95% CI 0.68 to 1.10, p=0.2335).
All the 2 studies had extractable data about the number of participants with **haemmorhagic stroke**. When pooled together, there was no statistically significant difference between the groups in haemmorhagic stroke, with a RR of 0.98 (95% CI 0.64 to 1.48, p=0.9074). No heterogeneity was detected (p = 0.7575, I^2 = 0.00%).

Table 6.5: *Results details - antioxydant - vitamin C*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
vitamin C versus placebo						
cardiovascular events	RR=1.00	[0.92;1.08]	0.9148	0.7922 (I^2=0.00)	2	22812
cardiovascular death	RR=1.04	[0.92;1.19]	0.5107	0.5631 (I^2=0.00)	2	22812
all cause death	RR=1.05	[0.98;1.13]	0.1893	0.6314 (I^2=0.00)	2	22812
coronary event	RR=1.04	[0.83;1.32]	0.7170	1.0000 (I^2=0.00)	1	8171
non fatal MI	RR=1.09	[0.85;1.39]	0.5162	1.0000 (I^2=0.00)	1	8171
ischemic stroke	RR=0.85	[0.73;0.99]	0.0378	0.7803 (I^2=0.00)	2	22812
stroke (fatal and non fatal)	RR=0.88	[0.76;1.01]	0.0622	0.8616 (I^2=0.00)	2	22812
non fatal stroke	RR=0.87	[0.68;1.10]	0.2335	1.0000 (I^2=0.00)	1	8171
haemmorhagic stroke	RR=0.98	[0.64;1.48]	0.9074	0.7575 (I^2=0.00)	2	22812

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 6.1: *Forest's plot for cardiovascular events*

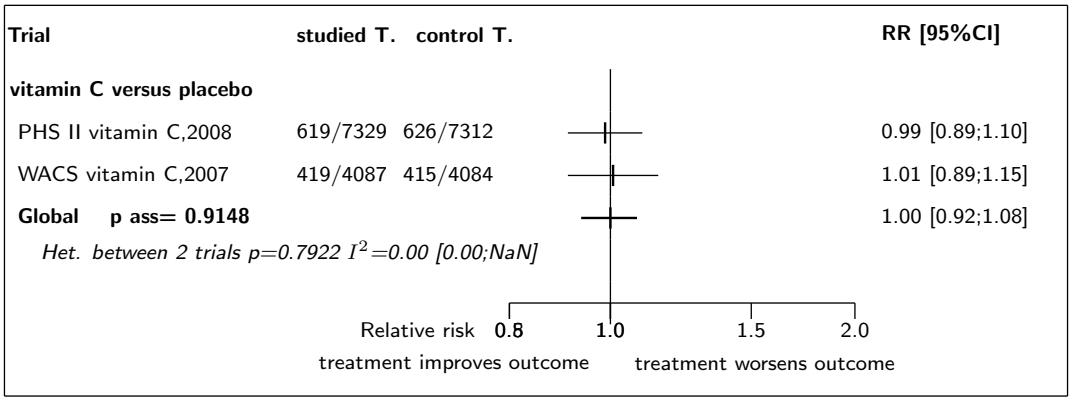


Figure 6.2: *Forest's plot for cardiovascular death*

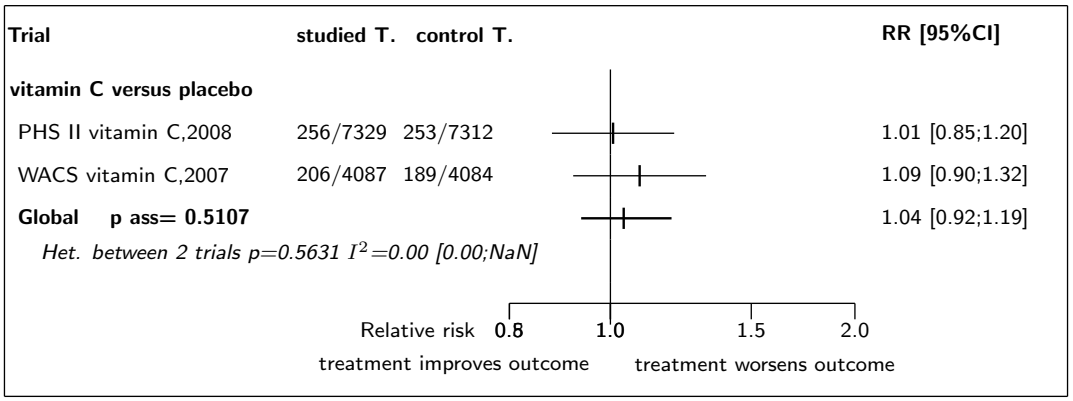


Figure 6.3: *Forest's plot for all cause death*

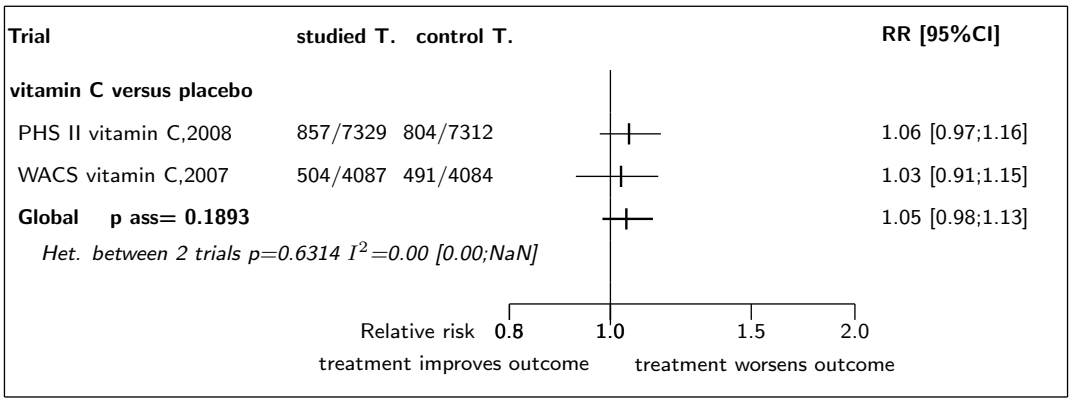


Figure 6.4: *Forest's plot for coronary event*

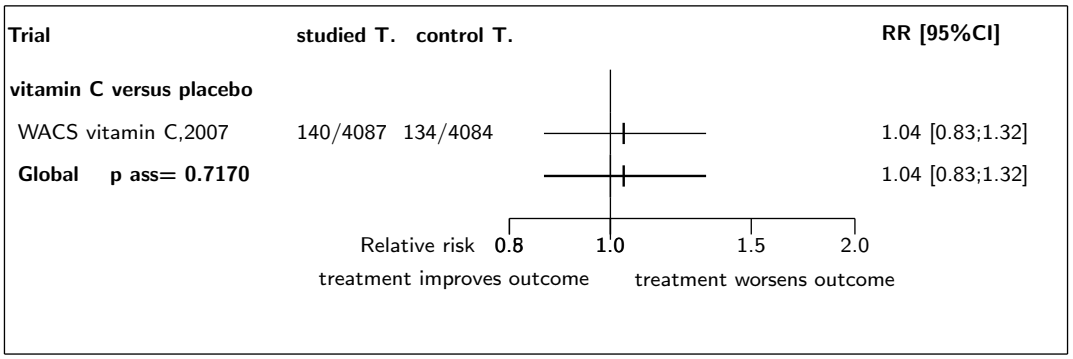


Figure 6.5: *Forest's plot for non fatal MI*

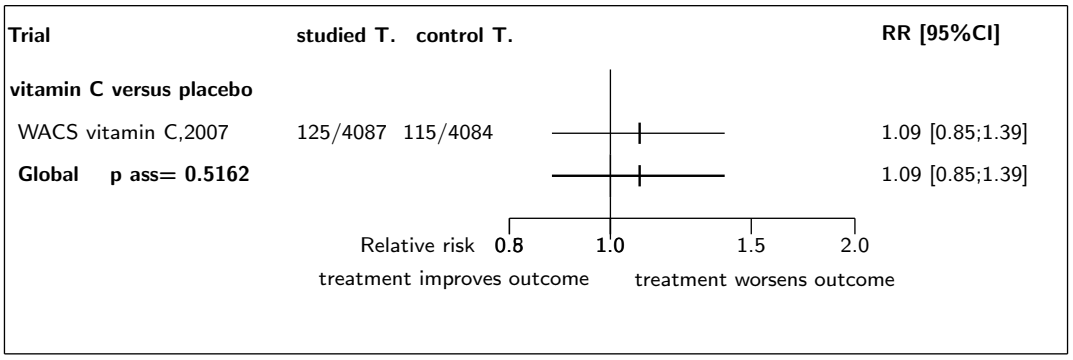


Figure 6.6: *Forest's plot for ischemic stroke*

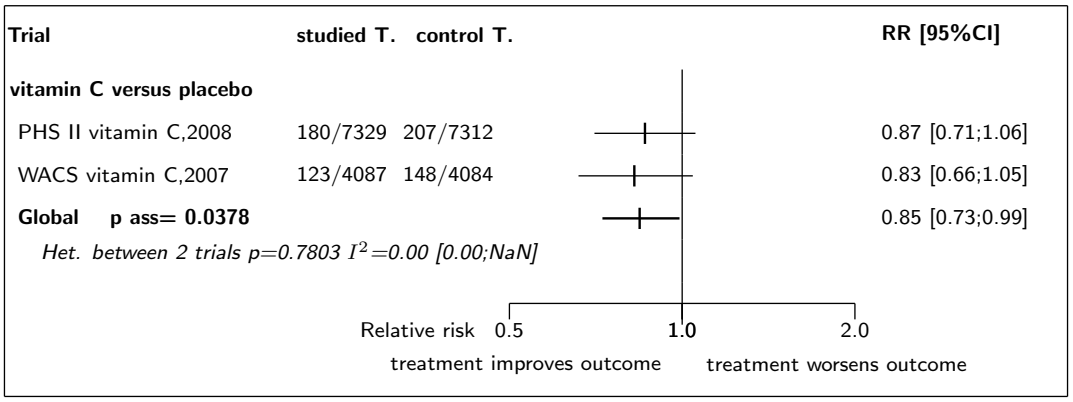


Figure 6.7: *Forest's plot for stroke (fatal and non fatal)*

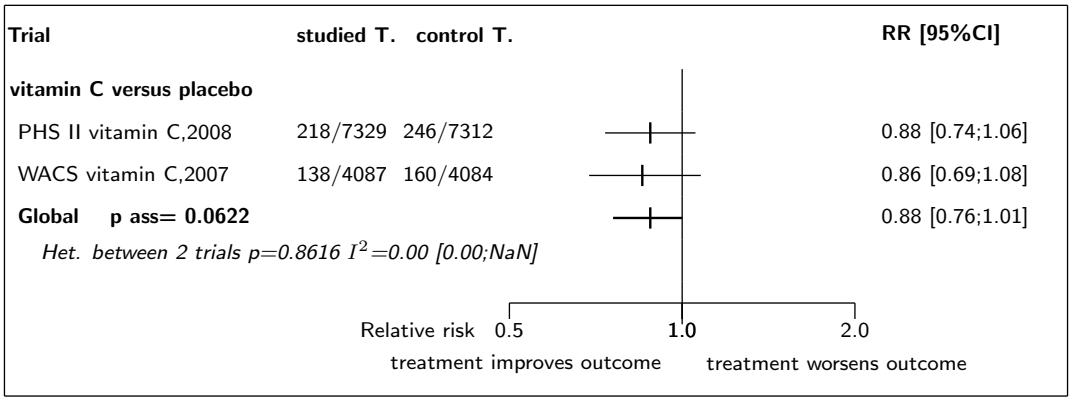


Figure 6.8: *Forest's plot for non fatal stroke*

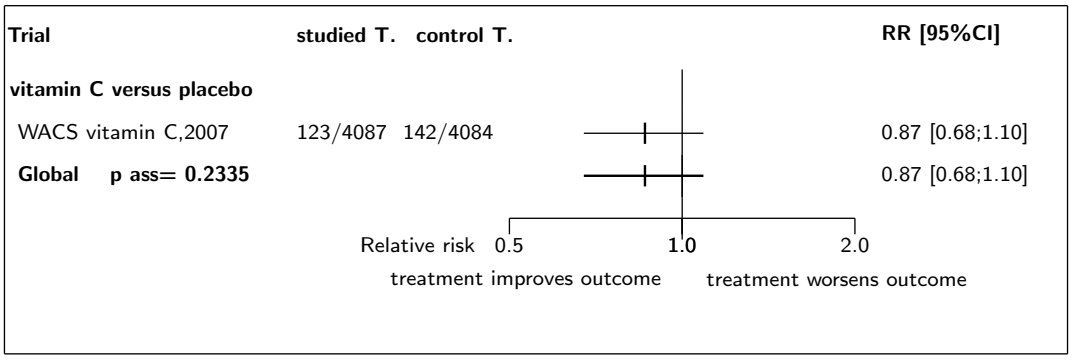
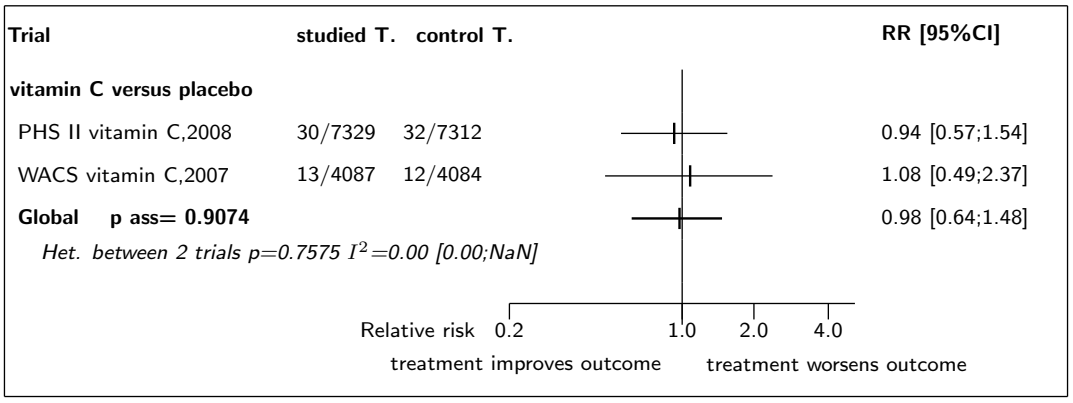


Figure 6.9: *Forest's plot for haemmorhagic stroke*



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7 Detailed results for vitamin E

7.1 Available trials

A total of 11 RCTs which randomized 154044 patients were identified: 2 trials compared vitamin E with control and 9 trials compared vitamin E with placebo.
The average study size was 14004 patients (range 520 to 39876). The first study was published in 1993, and the last study was published in 2008.
A total of 8 trials were double blind and 2 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Cardiovascular events data was reported in 9 trials; 9 trials reported data on cardiovascular death; 7 trials reported data on stroke (fatal and non fatal); 7 trials reported data on haemmorhagic stroke; 7 trials reported data on all cause death; 7 trials reported data on ischemic stroke; 6 trials reported data on non fatal MI; 5 trials reported data on non fatal stroke; and 2 trials reported data on coronary event.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of vitamin E.

Table 7.1: *Treatment description - antioxydant - vitamin E*

Trial	Studied treatment	Control treatment
Vitamin E versus control		
GISSI (1999) [**?**] [a]	vitamin E 300mg/d	no vitamine E
PPP (2001) [**?**] [b]	vitamin E (300 mg/day)	no vitamin E
Vitamin E versus placebo		
CHAOS (1996) [**?**]	vitamin E 400-800UI/d (alpha tocopherol)	identical placebo
HOPE (2000) [**?**, **?**] [b]	vitamin E 400IU/d from natural sources	matching placebo
ATBC vitamin E (1994) [**?**, **?**, **?**] [c]	vitamin E (alpha-tocopherol) 50mg/d	placebo
WACS vitamin E (2007) [**?**, **?**] [d]	vitamin E (600IU every two days)	placebo
WHS vitamin E (2005) [**?**] [e]	vitamin E 600 IU every other day (-tocopherol)	placebo
PHS II vitamin E (2008) [**?**] [f]	vitamin E 400IU every two days	placebo
ASAP (2000) [**?**, **?**, **?**]	d-alpha-tocopherol 91 mg (136 IU) twice daily	placebo
AREDS (2001) [**?**] [h]	daily supplementation of antioxidants (500 mg of vitamin C, 400 IU of vitamin E, and 15 mg of beta carotene)	placebo
Linxian (1993) [**?**, **?**]	beta carotene, vitamin E, and selenium	

continued...

Trial	Studied treatment	Control treatment
a) randomization between 4 treatment: n-3 PUFA (1 g daily), vitamin E (300 mg daily), both or none (control) b) factorial design with aspirin b) factorial design of ramipril and vitamin E c) factorial design of four regimens: alpha-tocopherol (50 mg per day) alone, beta carotene (20 mg per day) alone, both alpha-tocopherol and beta carotene, or placebo d) 2x2x2 factorial design testing the effects of ascorbic acid (500 mg/d), vitaminE (600 IU every other day), and beta carotene (50 mgevery 2day) e) factorial design vitamin E or placebo and aspirin or placebo f) factorial trial evaluating vitamin E (400 IU every 2 days synthetic alpha-tocopherol), vitaminC(500mg synthetic ascorbic acid), a multivitamin (Centrum Silver daily; Wyeth Pharmaceuticals) and beta carotene (50mg, Lurotin on alternate days) h) patients with more than a few small drusen were also randomly assigned to receive tablets with or without zinc (80 mg of zinc as zinc oxide) and copper (2 mg of copper as cupric oxide) as part of the age-related macular degeneration trial		

Table 7.2: *Descriptions of participants - antioxydant - vitamin E*

Trial	Patients	
Vitamin E versus control		
GISSI (1999) [?]	Patients with recent (3 months) myocardialinfarction	
	Inclusion criteria: no age limits	**Exclusion criteria:** contraindications to thedietary supplements (ie, known allergy to n-3 PUFA or -tocopherol, or known congenital defects of coagulation); unfavourable short-term outlook (eg, overt congestive heartfail-ure, cancers, etc)
PPP (2001) [?]	Men and womenaged 50 years or greater, with at least one of the majorrecognised cardiovascular risk factors	
	Inclusion criteria: people with one or more of the following: hypertension, hypercholes-terolaemia, diabetes, obesity, family history of premature myocardial infarction, or individu-als who were elderly: old age (>=65 years); hypertension (SBP >=160 mm Hg or DBP >=95 mm Hg on at least three separate oc-casions); hypercholesterolaemia (total blood cholesterol >=64mmol/L on at least two sep-arate occasions); diabetes mellitus (fasting venous plasma glucose concentration >=78 mmol/L on at least two separate occasions [chronic drug treatment for any of the three latter conditions was also a criterion for in-clusion]); obesity (body mass index >=30 kg/m2); and family history of myocardial in-farction before 55 years of age in at least one parent or sibling	**Exclusion criteria:** treatment with an-tiplatelet drugs (history of vascular events or diseases); chronic use of anti-inflammatory agents or anticoagulants; contraindications to aspirin; diseases with predictable poor short-term prognosis; and predictable psychological or logistical difficulties affecting compliance with the trial requirements
Vitamin E versus placebo		
CHAOS (1996) [?]	Patients with angiographically proven coronary atherosclerosis	
	Inclusion criteria: angiographically proven coronaryatherosclerosis;	**Exclusion criteria:** prior use of vitamin supplements containing vitamin E
HOPE (2000) [?, ?]	Women and men 55 years of age or older who were at high risk for cardiovascular events because they had cardiovascular disease or diabetes in addition to one other risk factor.	
ATBC vitamin E (1994) [?, ?, ?]	Male smokers 50 to 69 years of age from southwestern Finland	
	Inclusion criteria: smokers (five or more cigarettes per day at entry); 50 to 69 years old	**Exclusion criteria:** history of cancer or se-rious disease; supplements of vitamin E, vita-min A, or beta carotene in excess of predefined doses; anticoagulant agents

continued...

Trial	Patients	
WACS vitamin E (2007) [?, ?]	Female health professionals at increasedrisk (40 years or older with a history of CVD or 3 or more CVDrisk factors)	
	Inclusion criteria: women, aged 40 and over, at high risk, with a history of coronary artery disease, carotid endarterectomy, peripheral artery surgery, or three or more coronary heart disease risk factors	**Exclusion criteria:** self-reported history of cancer (excluding nonmelanoma skin cancer) within the past 10 years; any serious non-CVD illness; currently using warfarin sodium or other anticoagulants
WHS vitamin E (2005) [?]	Apparently healthy US women aged at least 45 years	
	Inclusion criteria: age 45 years or older; no previous history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), or other major chronic illnesses; no history of adverse effects from aspirin; no use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) more than once a week, or willingness to forgo their use; no use of anticoagulants or corticosteroids; and no use of individual supplements of vitamin A, E, or beta carotene more than once a week	**Exclusion criteria:**
PHS II vitamin E (2008) [?] [f]	US male physicians aged 50 years or older	
	Inclusion criteria: men with a history of myocardial infarction (MI), stroke, or cancer were eligible	**Exclusion criteria:** history of cirrhosis; active liver disease; anticoagulants; serious illness that might preclude participation
ASAP (2000) [?, ?, ?]	Smoking and nonsmoking men and postmenopausal women aged 45-69 years with serum cholesterol >= 5.0 mmol/l	
	Inclusion criteria: hypercholesterolemiadefined asserum cholesterol >=5.0 mmol/L (193 mg/dL) at screening	**Exclusion criteria:** regular intake of antioxidants, acetosalicylate, or any other drug with antioxidative properties, severe obesity (body mass index >32 kg/m2), type 1 diabetes, uncontrolled hypertension (sitting diastolic blood pressure >105 mm Hg), any condition limiting mobility, or severe disease shortening life expectancy; premenopausal women; oral estrogen therapy
AREDS (2001) [?]	Patients with age-related lens opacities and visual acuity loss	
	Inclusion criteria:	**Exclusion criteria:** illness or disorders (eg, history of cancer with a poor 7-yearprognosis, major cardiovascular or cerebrovascular eventwithin the last year, or hemachromatosis) that would makelong-term follow-up or compliance with the study protocolunlikely or difficult
Linxian (1993) [?, ?]	Apparently healthy Individuals of ages 40-69	

f) 7641 partcipant from PHS I and 7000 new physicians

Table 7.3: *Main patients characteristics - antioxydant - vitamin E*

Trial	Characteristics
Vitamin E versus control	
GISSI, 1999 [?]	women (%): 14.7% age (yr): 59.4 (15.2% >70 y) body mass index: 26.5
PPP, 2001 [?]	women (%): 58% age (yr): 64.4 y (27% >=70y) body mass index: 27.6
Vitamin E versus placebo	
CHAOS, 1996 [?]	women (%): 15.6% age (yr): 61.8y body mass index: 26.5
HOPE, 2000 [?, ?]	women (%): 6.7%
ATBC vitamin E, 1994 [?, ?, ?]	women (%): 0% age (yr): 57.1y body mass index: 26
WACS vitamin E, 2007 [?, ?]	women (%): 100% age (yr): 60.6 y body mass index: 30.3
WHS vitamin E, 2005 [?]	women (%): 100% age (yr): 54.6 y body mass index: 26.04
PHS II vitamin E, 2008 [?]	women (%): 0% age (yr): 64.3 y body mass index: 26
ASAP, 2000 [?, ?, ?]	women (%): 51% age (yr): 59.7 y
AREDS, 2001 [?]	women (%): 55% age (yr): 56 (median)
Linxian, 1993 [?, ?]	women (%): 55%

Table 7.4: *Design and methodological quality of trials - antioxydant - vitamin E*

Trial	Design	Duration	Centre	Primary end-point
Vitamin E versus control				
GISSI, 1999 [?] n=11324	Factorial plan open confirmatory trial at risk of bias	3.5y inclusion period: oct 1983 - sep 1995	Italy multicentre	death, MI, stroke
PPP, 2001 [?] n=4495	Factorial plan open confirmatory trial at risk of bias	3.6y inclusion period: 1994 - 1998	Italy multicenter	CV events
Vitamin E versus placebo				
CHAOS, 1996 [?] [(a)] n=2002	Parallel groups double-blind exploratory trial	1.5y inclusion period: oct 1992 - dec 1994	UK singlecenter	CV death, MI and non fatal MI alone

continued...

Trial	Design	Duration	Centre	Primary endpoint
HOPE, 2000 [?, ?] n=9541	Factorial plan double-blind confirmatory trial at low risk of bias	4.5y	Multinational: Canada, USA, Europe, South America multicenter	CV death, MI, stroke
ATBC vitamin E, 1994 [?, ?, ?] n=29133	Factorial plan double-blind exploratory trial	6.1 median (range 5-8y) inclusion period: 1985-1988	Southwestern Finland postal survey	not defined
WACS vitamin E, 2007 [?, ?] n=8171	Factorial plan double blind confirmatory trial at low risk of bias	9.4 years inclusion period: 1995-1996	US	MI, stroke, coronary revascularization, CVD death
WHS vitamin E, 2005 [?] (e) n=39876	Factorial plan double-blind exploratory trial	10.1 y inclusion period: sept 1992 - may 1995	US	major cardiovascular event
PHS II vitamin E, 2008 [?] n=14641	double blind confirmatory trial at low risk of bias	8 years (mean) inclusion period: jul 1997 - jul 2001	US postal survey	Cv death, MI, Stroke
ASAP, 2000 [?, ?, ?] (g) n=520	Factorial plan double-blind exploratory trial	3 years	Finland NA	carotid artery mean intima-media thickness
AREDS, 2001 [?] n=4757	Factorial plan double-blind exploratory trial	6.3 y inclusion period: nov 1992 - jan 1998	USA 11 centres	opacity grades or cataract surgery
Linxian, 1993 [?, ?] n=29584		5y		

a) 2 primary endpoints but no procedure to control multiplicity e) two primary endpoint specified without method for dealing with multiplicity g) after thedouble-blind 3-year period, the study was continued for another 3years as an open study

7.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Vitamin E versus control

All the 2 studies had extractable data about the number of participants with **cardiovascular events**. When pooled together, there was no statistically significant difference between the groups in cardiovascular events, with a RR of 0.99 (95% CI 0.89 to 1.09, p=0.7865). No heterogeneity was detected (p = 0.6427, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **cardiovascular death**. When pooled together, there was no statistically significant difference between the groups in cardiovascular death, with a RR of 0.94 (95% CI 0.81 to 1.08, p=0.3816). No heterogeneity was detected (p = 0.7537, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **all cause death**. When pooled together, there was no statistically significant difference between the groups in all cause death, with a RR of 0.94 (95% CI 0.84 to 1.05, p=0.2645). No heterogeneity was detected (p = 0.3897, I^2 = 0.00%).

Only one of the 2 studies eligible for this comparison provided data on **coronary event**. No statistically significant difference between the groups was found in coronary event, with a RR of 0.89 (95% CI 0.51 to 1.58, p=0.6972).
All the 2 studies had extractable data about the number of participants with **non fatal MI**. When pooled together, there was no statistically significant difference between the groups in non fatal MI, with a RR of 1.11 (95% CI 0.93 to 1.32, p=0.2696). No heterogeneity was detected (p = 0.9197, I^2 = 0.00%).
Only one of the 2 studies eligible for this comparison provided data on **ischemic stroke**. No statistically significant difference between the groups was found in ischemic stroke, with a RR of 1.13 (95% CI 0.60 to 2.13, p=0.7106).
All the 2 studies had extractable data about the number of participants with **stroke (fatal and non fatal)**. When pooled together, there was no statistically significant difference between the groups in stroke (fatal and non fatal), with a RR of 0.93 (95% CI 0.71 to 1.21, p=0.5995). No heterogeneity was detected (p = 0.3170, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **non fatal stroke**. When pooled together, there was no statistically significant difference between the groups in non fatal stroke, with a RR of 1.07 (95% CI 0.62 to 1.83, p=0.8107). No heterogeneity was detected (p = 0.1321, I^2 = 0.56%).
Only one of the 2 studies eligible for this comparison provided data on **haemmorhagic stroke**. No statistically significant difference between the groups was found in haemmorhagic stroke, with a RR of 4.06 (95% CI 0.18 to 89.97, p=0.3755).

Vitamin E versus placebo

A total of 6 of the 9 studies eligible for this comparison provided data on **cardiovascular events**. When pooled together, there was no statistically significant difference between the groups in cardiovascular events, with a RR of 0.96 (95% CI 0.89 to 1.04, p=0.3028). No heterogeneity was detected (p = 0.0683, I^2 = 0.51%).
A total of 6 of the 9 studies eligible for this comparison provided data on **cardiovascular death**. When pooled together, there was no statistically significant difference between the groups in cardiovascular death, with a RR of 0.99 (95% CI 0.93 to 1.05, p=0.6852). No heterogeneity was detected (p = 0.8458, I^2 = 0.00%).
A total of 5 of the 9 studies eligible for this comparison provided data on **all cause death**. When pooled together, there was no statistically significant difference between the groups in all cause death, with a RR of 1.03 (95% CI 0.97 to 1.10, p=0.3176). No heterogeneity was detected (p = 0.8281, I^2 = 0.00%).
Only one of the 9 studies eligible for this comparison provided data on **coronary event**. No statistically significant difference between the groups was found in coronary event, with a RR of 0.92 (95% CI 0.73 to 1.16, p=0.4673).
A total of 3 of the 9 studies eligible for this comparison provided data on **non fatal MI**. When pooled together, there was no statistically significant difference between the groups in non fatal MI, with a RR of 0.75 (95% CI 0.50 to 1.13, p=0.1679). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0008, I^2 = 0.86%).
A total of 5 of the 9 studies eligible for this comparison provided data on **ischemic stroke**. When pooled together, there was no statistically significant difference between the groups in ischemic stroke, with a RR of 0.95 (95% CI 0.84 to 1.06, p=0.3534). No heterogeneity was detected (p = 0.1159, I^2 = 0.46%).
A total of 5 of the 9 studies eligible for this comparison provided data on **stroke (fatal and non fatal)**. When pooled together, there was no statistically significant difference between the groups in stroke (fatal and non fatal), with a RR of 0.99 (95% CI 0.90 to 1.08, p=0.7566). No heterogeneity was detected (p = 0.2129, I^2 = 0.31%).

A total of 2 of the 9 studies eligible for this comparison provided data on **non fatal stroke**. When pooled together, there was no statistically significant difference between the groups in non fatal stroke, with a RR of 0.98 (95% CI 0.69 to 1.39, p=0.9188). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0232, I^2 = 0.81%).
A total of 5 of the 9 studies eligible for this comparison provided data on **haemmorhagic stroke**. The analysis detected a statistically significant difference in favor of placebo in haemmorhagic stroke, with a RR of 1.22 (95% CI 1.00 to 1.48, p=0.0477). No heterogeneity was detected (p = 0.4384, I^2 = 0.00%).

Table 7.5: *Results details - antioxydant - vitamin E*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
vitamin E versus control						
cardiovascular events	RR=0.99	[0.89;1.09]	0.7865	0.6427 (I^2=0.00)	2	15819
cardiovascular death	RR=0.94	[0.81;1.08]	0.3816	0.7537 (I^2=0.00)	2	15819
all cause death	RR=0.94	[0.84;1.05]	0.2645	0.3897 (I^2=0.00)	2	15829
coronary event	RR=0.89	[0.51;1.58]	0.6972	1.0000 (I^2=0.00)	1	4495
non fatal MI	RR=1.11	[0.93;1.32]	0.2696	0.9197 (I^2=0.00)	2	15819
ischemic stroke	RR=1.13	[0.60;2.13]	0.7106	1.0000 (I^2=0.00)	1	4495
stroke (fatal and non fatal)	RR=0.93	[0.71;1.21]	0.5995	0.3170 (I^2=0.00)	2	15829
non fatal stroke	RR=1.07	[0.62;1.83]	0.8107	0.1321 (I^2=0.56)	2	15819
haemmorhagic stroke	RR=4.06	[0.18;89.97]	0.3755	1.0000 (I^2=0.00)	1	4495
vitamin E versus placebo						
cardiovascular events	RR=0.96	[0.89;1.04]	0.3028	0.0683 (I^2=0.51)	6	93072
cardiovascular death	RR=0.99	[0.93;1.05]	0.6852	0.8458 (I^2=0.00)	6	93072
all cause death	RR=1.03	[0.97;1.10]	0.3176	0.8281 (I^2=0.00)	5	30091
coronary event	RR=0.92	[0.73;1.16]	0.4673	1.0000 (I^2=0.00)	1	8171
non fatal MI	RR=0.75	[0.50;1.13]	0.1679	0.0008 (I^2=0.86)	3	19714
ischemic stroke	RR=0.95	[0.84;1.06]	0.3534	0.1159 (I^2=0.46)	5	100748
stroke (fatal and non fatal)	RR=0.99	[0.90;1.08]	0.7566	0.2129 (I^2=0.31)	5	101362
non fatal stroke	RR=0.98	[0.69;1.39]	0.9188	0.0232 (I^2=0.81)	2	17712
haemmorhagic stroke	RR=1.22	[1.00;1.48]	0.0477	0.4384 (I^2=0.00)	5	100748

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 7.1: *Forest's plot for cardiovascular events*

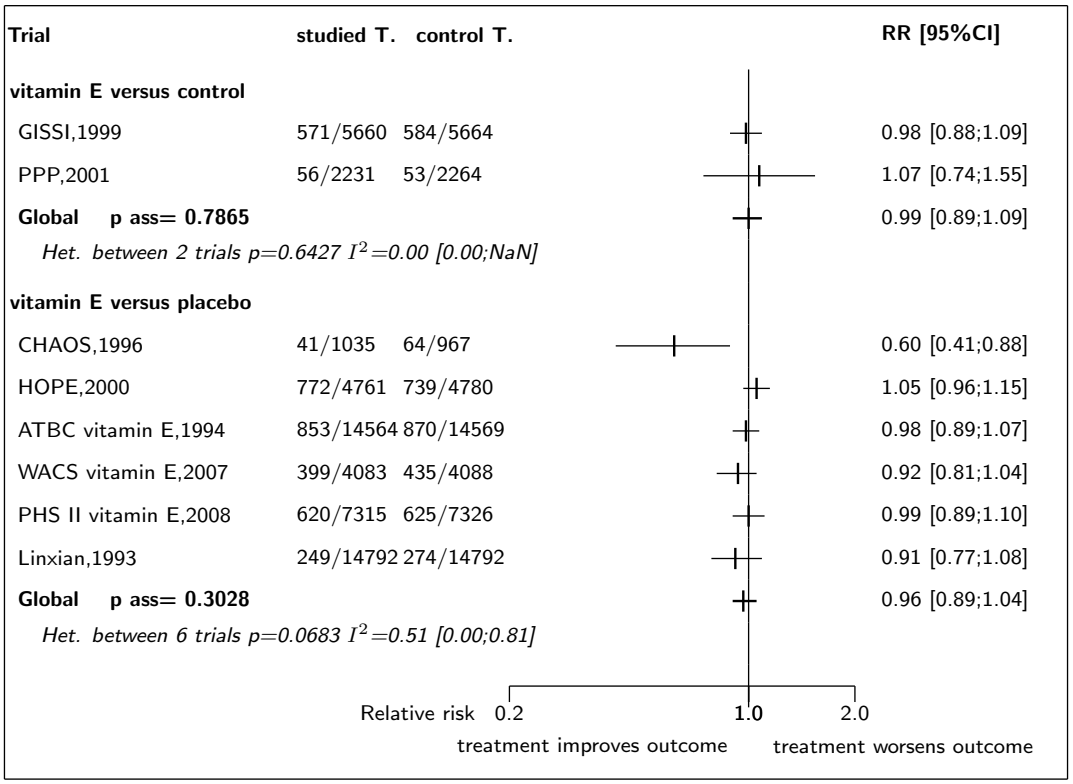


Figure 7.2: *Forest's plot for cardiovascular death*

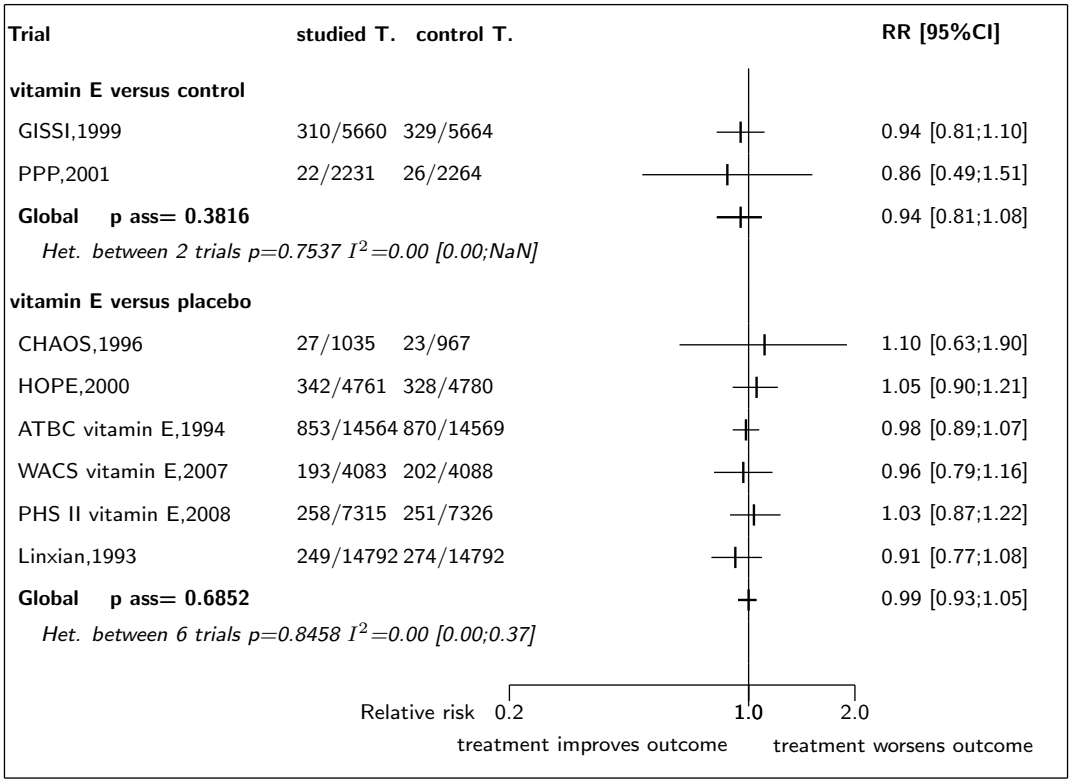


Figure 7.3: *Forest's plot for all cause death*

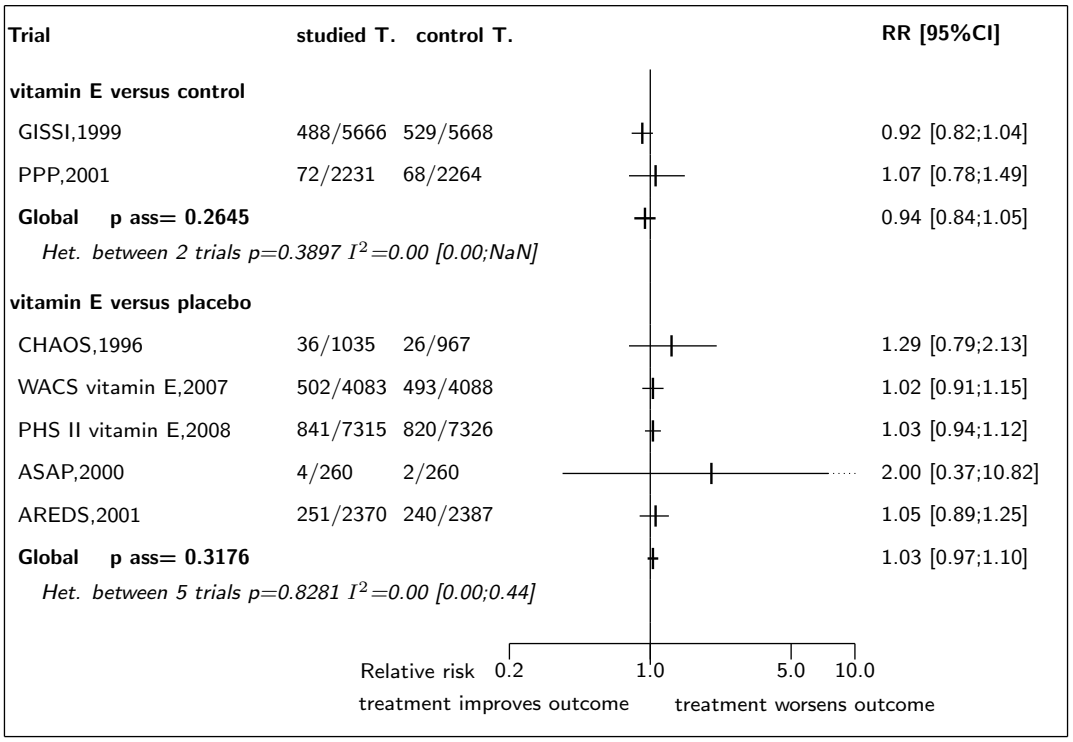


Figure 7.4: *Forest's plot for coronary event*

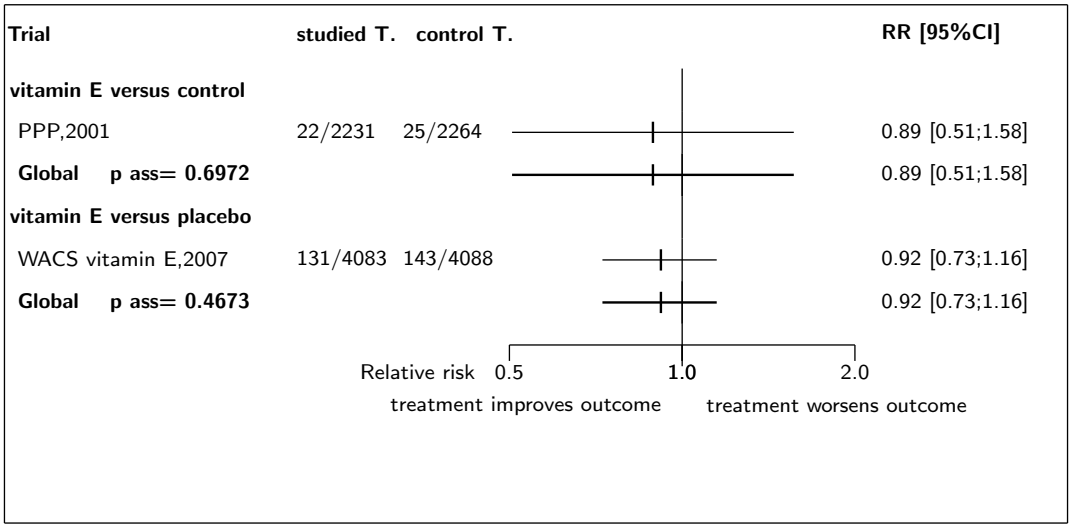


Figure 7.5: *Forest's plot for non fatal MI*

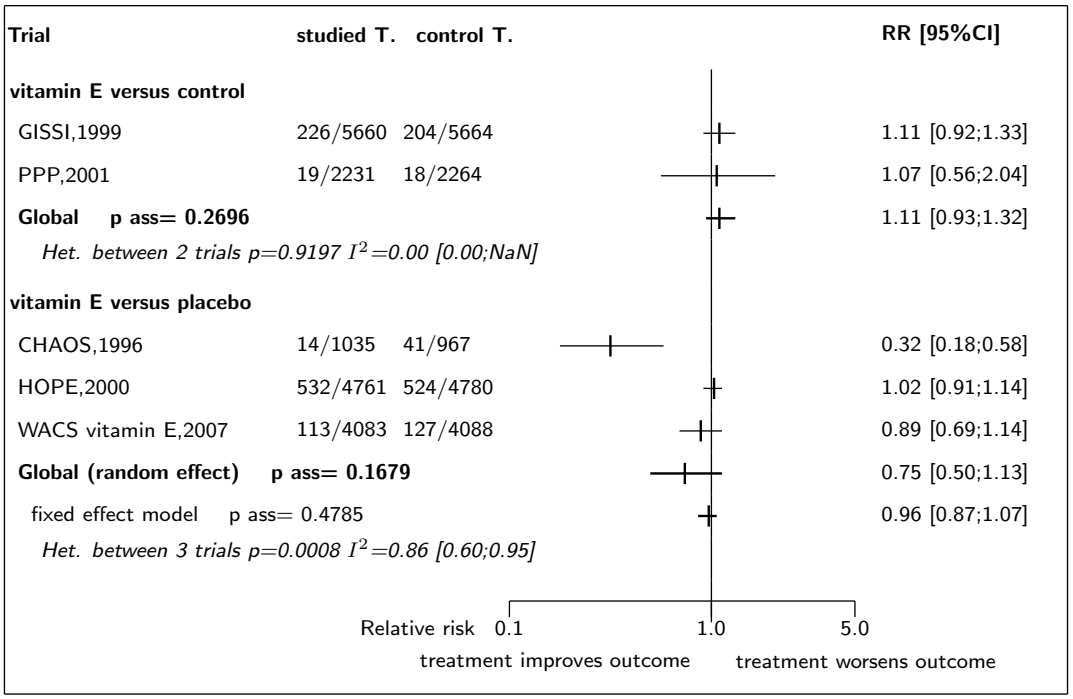


Figure 7.6: *Forest's plot for ischemic stroke*

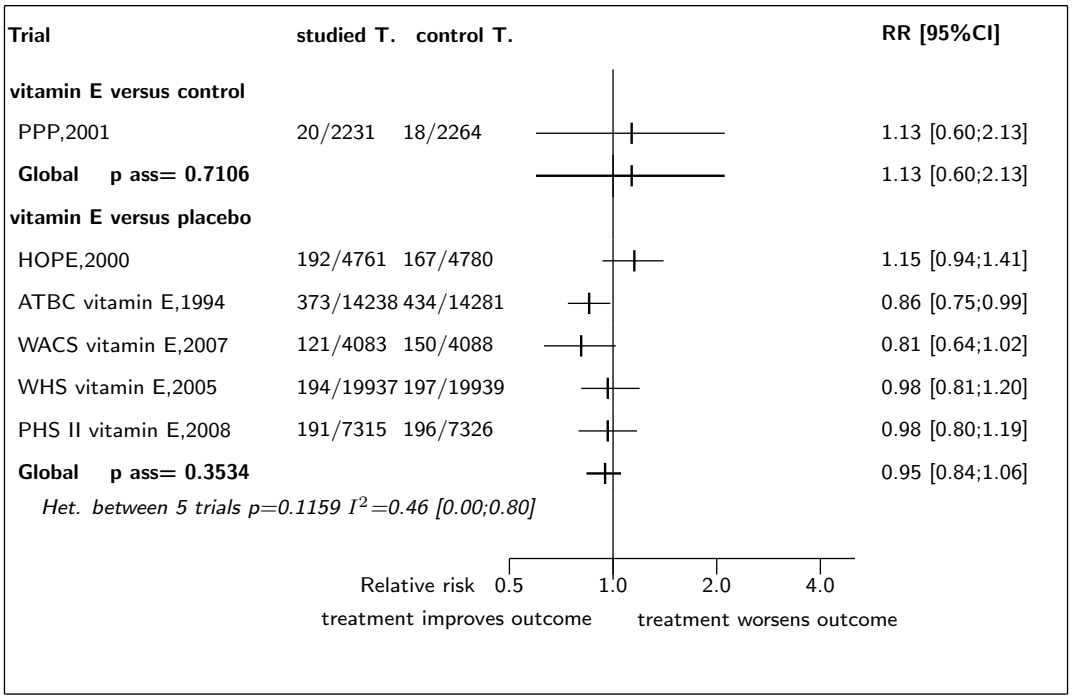


Figure 7.7: *Forest's plot for stroke (fatal and non fatal)*

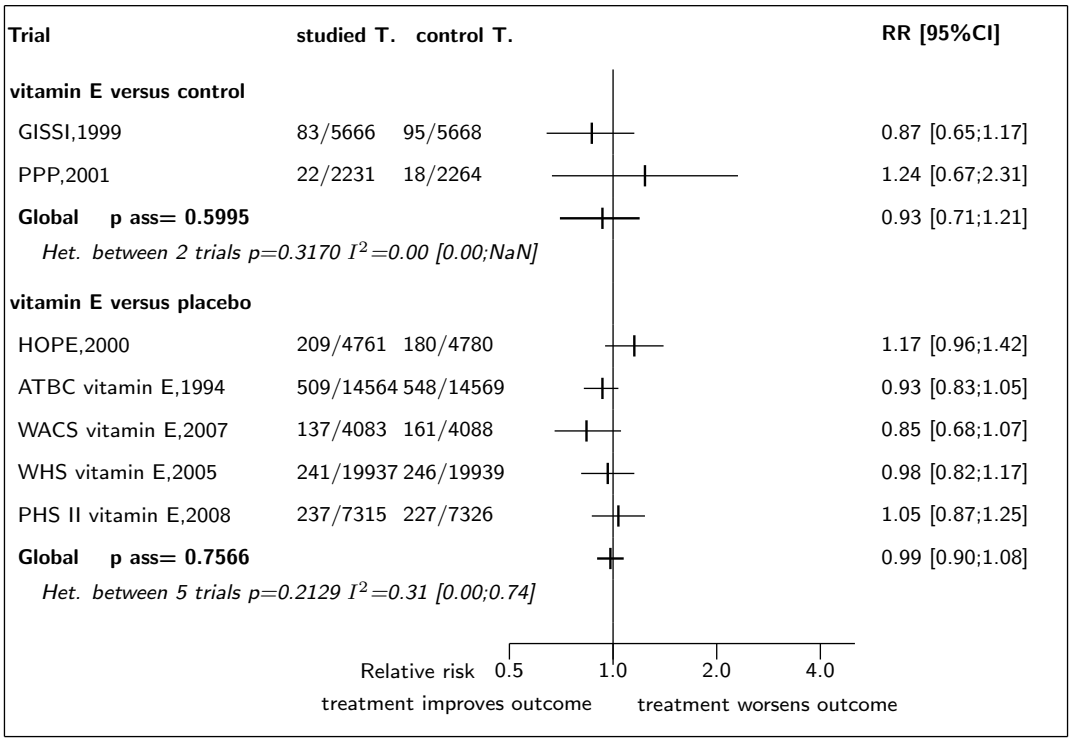


Figure 7.8: *Forest's plot for non fatal stroke*

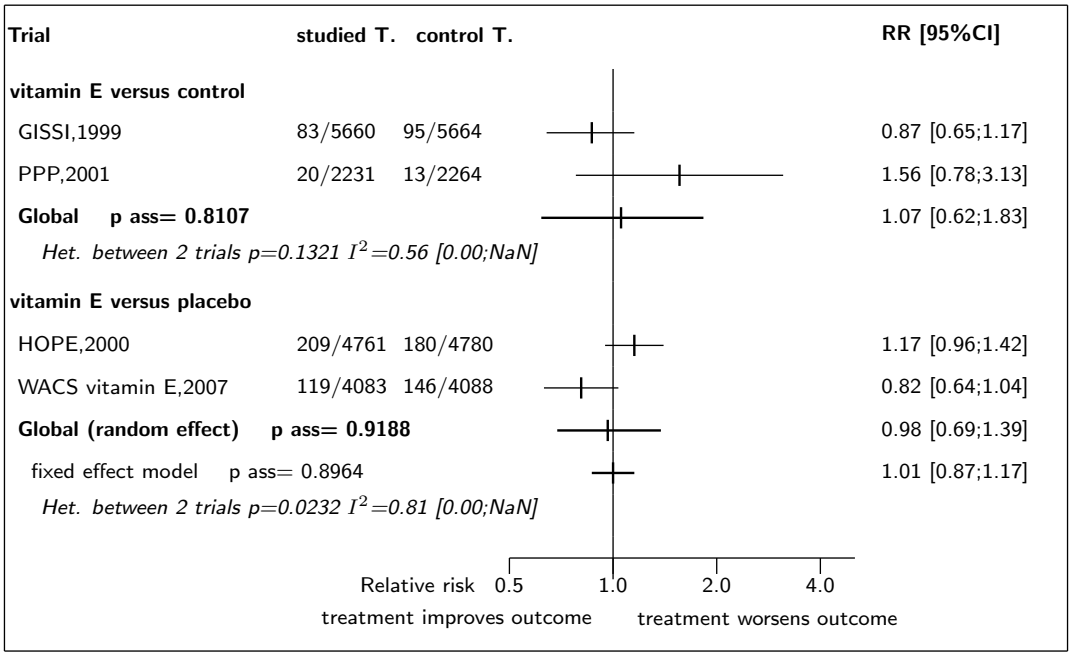
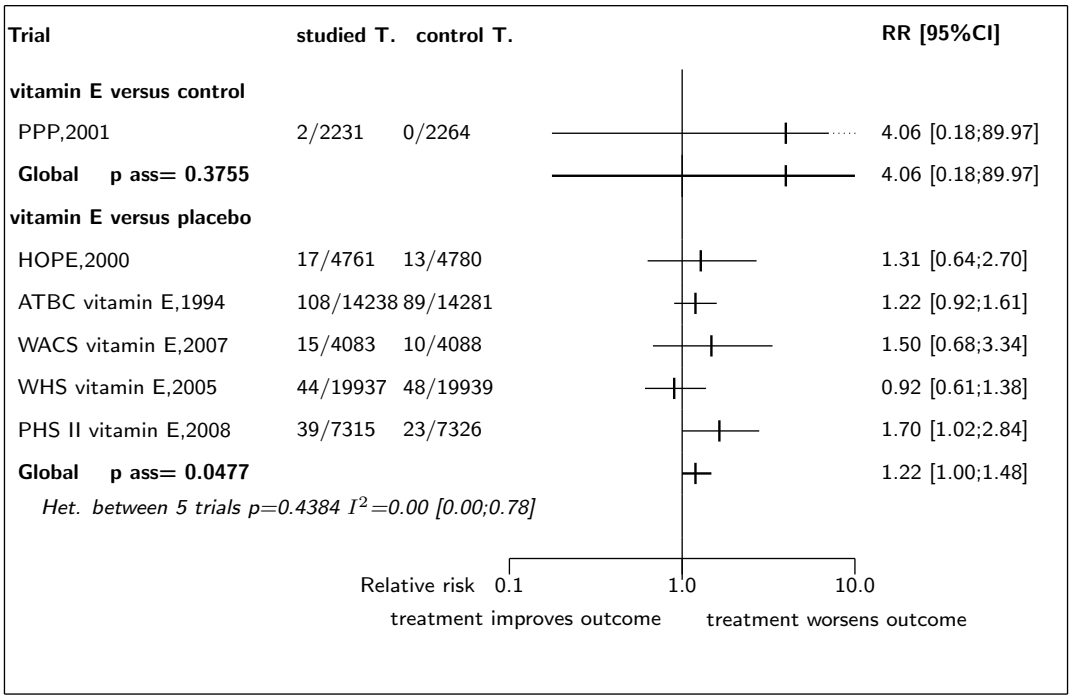


Figure 7.9: *Forest's plot for haemmorhagic stroke*



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8 Global meta-analysis: all antioxydant

8.1 Global meta-analysis: all antioxydant versus control

Table 8.1: *All antioxydantversus control*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.99	0.89;1.09	0.7865	0.6427 (0.00)	2	15819
cardiovascular death	RR=0.94	0.81;1.08	0.3816	0.7537 (0.00)	2	15819
all cause death	RR=0.94	0.84;1.05	0.2645	0.3897 (0.00)	2	15829
coronary event	RR=0.89	0.51;1.58	0.6972	1.0000 (0.00)	1	4495
non fatal MI	RR=1.11	0.93;1.32	0.2696	0.9197 (0.00)	2	15819
ischemic stroke	RR=1.13	0.60;2.13	0.7106	1.0000 (0.00)	1	4495
stroke (fatal and non fatal)	RR=0.93	0.71;1.21	0.5995	0.3170 (0.00)	2	15829
non fatal stroke	RR=1.07	0.62;1.83	0.8107	0.1321 (0.56)	2	15819
haemmorhagic stroke	RR=4.06	0.18;89.97	0.3755	1.0000 (0.00)	1	4495

legend B

8.2 Global meta-analysis: all antioxydant versus placebo

Table 8.2: *All antioxydantversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
amputation	RR=0.99	0.42;2.37	0.9887	1.0000 (0.00)	1	1276
new-onset diabetes	RR=0.37	0.25;0.56	0.0000	1.0000 (1.00)	1	3873
new-onset atrial fibrillation	RR=1.92	1.40;2.65	0.0000	1.0000 (0.00)	1	5605
cardiovascular events	RR=0.82 [1]	0.51;1.33	0.4239	0.0000 (1.00) †	17	216416
cardiovascular death	RR=0.91 [2]	0.66;1.27	0.5948	0.0000 (0.98) †	18	246323
all cause death	RR=0.96 [3]	0.57;1.60	0.8729	0.0000 (1.00) †	20	170624
coronary event	RR=0.65 [4]	0.25;1.69	0.3787	0.0000 (0.99) †	8	97447
non fatal MI	RR=0.96 [5]	0.83;1.10	0.5304	0.0259 (0.56) †	8	57175
ischemic stroke	RR=0.94	0.85;1.03	0.1616	0.1076 (0.39)	9	131865
cardiovascular death, MI, stroke	RR=0.82	0.69;0.98	0.0263	1.0000 (0.00)	1	6144
stroke (fatal and non fatal)	RR=0.82 [6]	0.48;1.39	0.4546	0.0000 (0.99) †	12	205251
non fatal stroke	RR=0.99	0.88;1.11	0.8381	0.2016 (0.31)	6	54750
haemmorhagic stroke	RR=1.20	1.01;1.43	0.0383	0.4707 (0.00)	8	131731

legend B

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.64 95% CI 0.63;0.66
[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.87 95% CI 0.84;0.91
[3] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.59 95% CI 0.57;0.61
[4] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.51 95% CI 0.48;0.54
[5] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.99 95% CI 0.92;1.07
[6] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.68 95% CI 0.64;0.71

9 Ongoing studies

No ongoing trial was identified.

10 Excluded studies

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

Table 10.1: *Excluded studies of antioxydant*

Study	**Exclusion reason**
MASI (2000) [**?**]	purely explicative study
SECURE (2001) [**?**]	substudy of the Heart Outcomes Prevention Evaluation (HOPE) trial