

Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine

Rory Collins and Jane Armitage on behalf of the SEARCH Collaborative Group

<u>Financial Disclosure</u>: SEARCH was designed, conducted and analysed by Oxford University independently of the grant source (Merck & Co). No honoraria or consultancy fees accepted.

SEARCH: 2 separate randomized treatment comparisons in 12,064 post-MI patients

More versus less LDL-lowering comparison:

Simvastatin vs Simvastatin 80 mg daily 20mg daily

Homocysteine-lowering comparison:

Folic acid 2mg plus vs Placebo vitamin B12 1mg daily tablets

Mean (SD) duration: 6.7 (1.5) years



SEARCH: Eligibility criteria

Previous myocardial infarction

Men and women

Aged 18 to 80 years

Current use of, or clear indication for, statin

No admission in previous 3 months for MI, unstable angina or coronary revascularisation (and none planned in next 3 months)



AGE and SEX at baseline

| Baseline feature | Number | Percentage | |
|--------------------------|--------|------------|--|
| Age (years) | | | |
| <60 | 3765 | 31% | |
| ≥60 <70 | 4828 | 40% | |
| ≥70 | 3471 | 29% | |
| Mean age 64 years (SD 9) | | | |

Sex

| Male | 10012 | 83% | |
|--------|-------|-----|--|
| Female | 2052 | 17% | |



SEARCH: Vascular outcome definitions

MAJOR CORONARY EVENTS = Non-fatal MI, coronary revascularisation or CHD death

STROKE = Any non-fatal or fatal stroke (including subarachnoid haemorrhage)

REVASCULARISATION = Coronary or non-coronary artery surgery or angioplasty (including amputation)

MAJOR VASCULAR EVENTS = MCE

+ stroke

+ revascularisation



SEARCH: 2 separate randomized treatment comparisons in 12,064 post-MI patients

More versus less LDL-lowering comparison:

Simvastatin vs Simvastatin 80 mg daily 20mg daily

Homocysteine-lowering comparison:

Folic acid 2mg plus vs Placebo vitamin B12 1mg daily tablets

Mean (SD) duration: 6.7 (1.5) years



SEARCH: Baseline LIPID levels after 2 month pre-randomisation run-in on SIMVASTATIN 20mg daily

| | Mean (SD) baseline | | |
|-------------------|--------------------|-----------|--|
| | mmol/l | mg/dl | |
| Total cholesterol | 4.2 (0.7) | 163 (27) | |
| Direct-LDL | 2.5 (0.6) | 97 (23) | |
| HDL | 1.0 (0.4) | 39 (15) | |
| Triglycerides* | 1.9 (1.2) | 168 (106) | |



^{*}Non-fasting

SEARCH: Reduction in LDL CHOLESTEROL with allocation to 80mg versus 20 mg SIMVASTATIN daily

| | Reduction: 20mg – 80mg | | |
|---------|------------------------|-------|---------|
| | mmol/l | mg/dl | percent |
| Month 4 | 0.51 | 20 | 20% |
| Year 1 | 0.39 | 15 | 16% |
| Year 5 | 0.29 | 11 | 12% |
| AVERAGE | 0.35 | 14 | 14% |



SEARCH: Myopathy rates by SIMVASTATIN comparison

Simvastatin allocation (per 1000 person-years)

Years of 80 mg 20 mg follow-up (6031) (6033)

0-1 25 (4.2) 1 (0.2)

2-7 28 (0.8) 2 (0.1)

Total 53

Myopathy: New, unexplained muscle pain or weakness plus CK>10x ULN (7 vs 0 developed rhabdomyolysis)

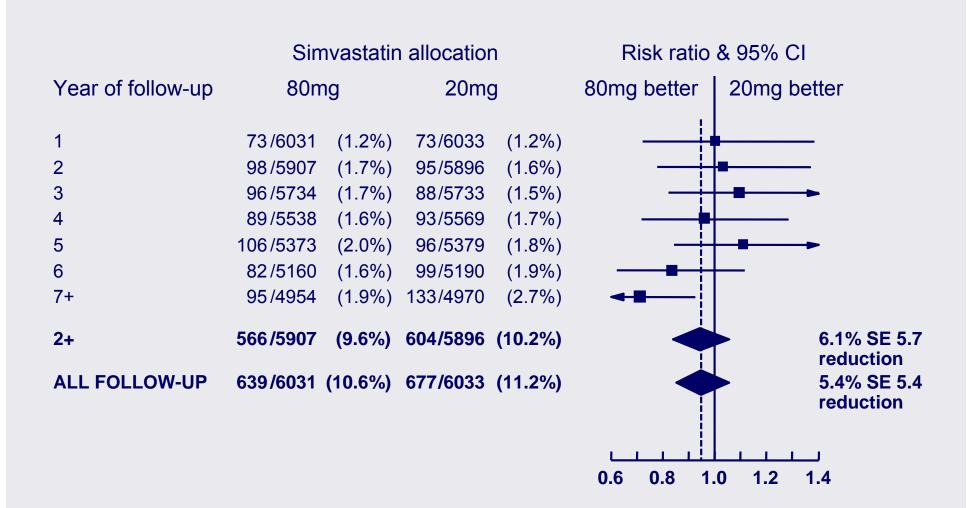


SEARCH: Effects of more vs less STATIN on MORTALITY

| | Simvastati | n allocation | Risk ratio & 95% CI |
|------------------|-------------|--------------|---------------------------|
| Cause of death | 80mg | 20mg | 80mg better 20mg better |
| | (n=6031) | (n=6033) | |
| | , | , | |
| CHD | 447 (7.4%) | 438 (7.3%) | |
| Stroke | 57 (0.9%) | 67 (1.1%) | ■ |
| Other vascular | 53 (0.9%) | 56 (0.9%) | |
| All vascular | 557 (9.2%) | 561 (9.3%) | 0.7% SE 5.9 reduction |
| Neoplastic | 245 (4.1%) | 266 (4.4%) | |
| Respiratory | 74 (1.2%) | 58 (1.0%) | |
| Other medical | 75 (1.2%) | 70 (1.2%) | - ■ |
| Non-medical | 13 (0.2%) | 14 (0.2%) | ← |
| All non-vascular | 407 (6.7%) | 408 (6.8%) | 0.2% SE 7.0 reduction |
| All causes | 964 (16.0%) | 969 (16.1%) | 0.5% SE 4.6 reduction |
| | | | |
| | | | 0.6 0.8 1.0 1.2 1.4 |

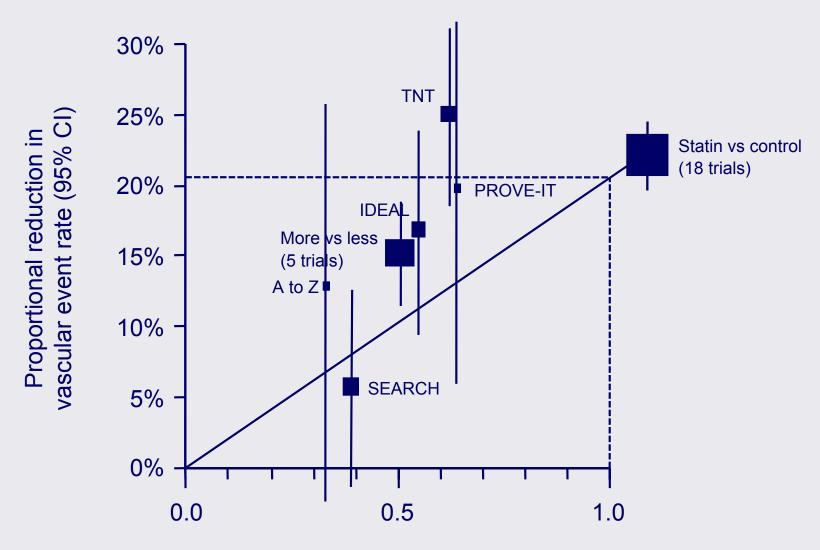
SEARCH

SEARCH: Effects of more vs less STATIN on ANY CANCER by year of follow-up



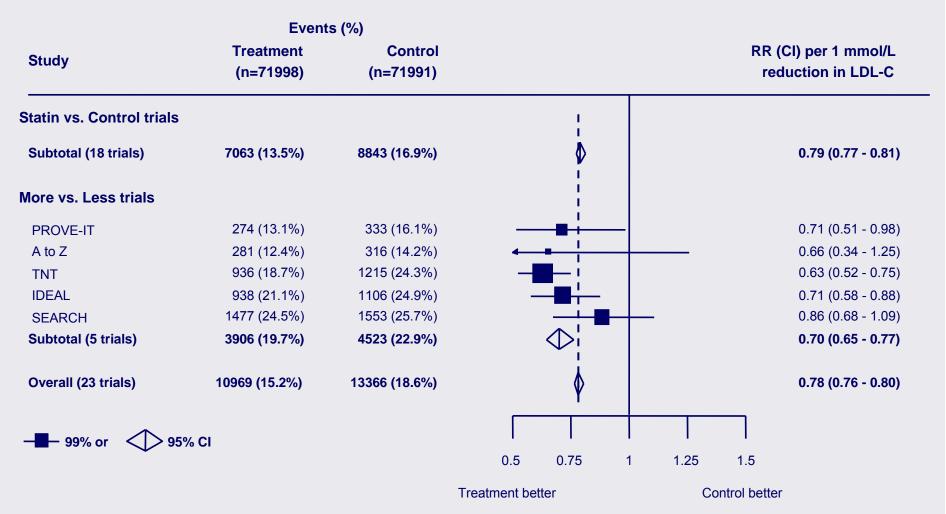


CTT meta-analysis: Proportional reduction in MAJOR VASCULAR EVENTS versus absolute LDL-C reduction



Mean LDL cholesterol difference between treatment groups (mmol/L)

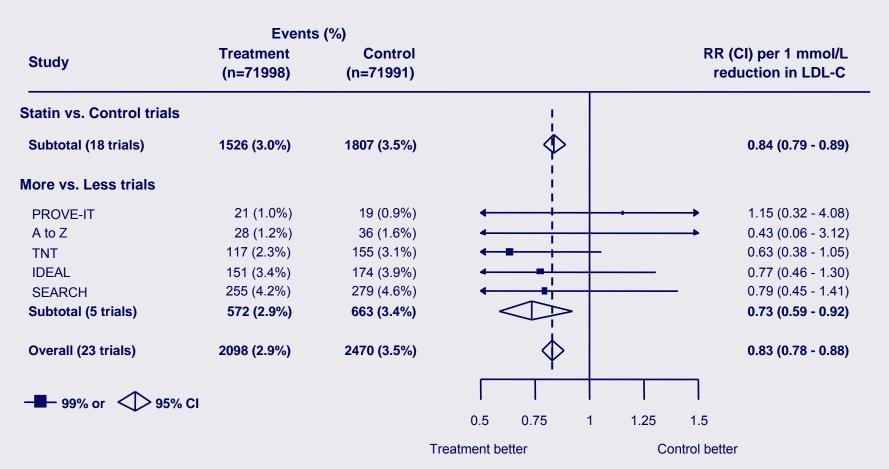
CTT meta-analysis: Effects of STATIN on MAJOR VASCULAR EVENT per mmol/l LDL-C reduction



Heterogeneity within more vs less trials: $\chi_4^2 = 7.34 \text{ (p=0.12)}$

Difference between more vs less and statin vs control trials: $\chi_1^2 = 6.73$ (p=0.01)

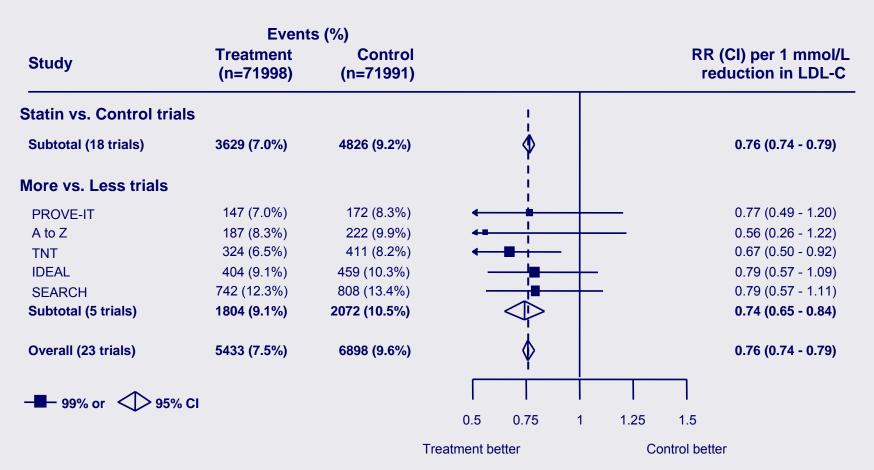
CTT meta-analysis: Effects of STATIN on STROKE per mmol/l LDL-C reduction



Heterogeneity within more vs less trials: $\chi_4^2 = 2.06 \text{ (p=0.73)}$

Difference between more vs less and statin vs control trials: $\chi_1^2 = 1.25$ (p=0.26)

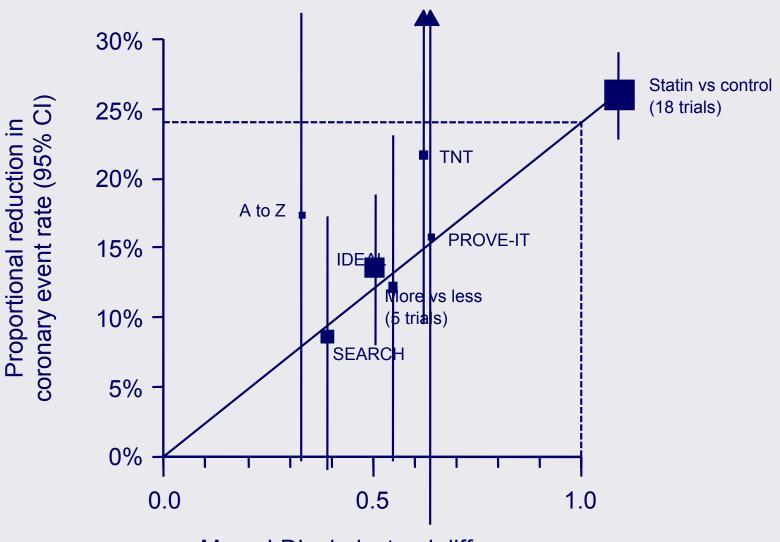
CTT meta-analysis: Effects of STATIN on NON-FATAL MI or CHD DEATH per mmol/I LDL-C reduction



Heterogeneity within more vs less trials: $\chi_4^2 = 2.07$ (p=0.72)

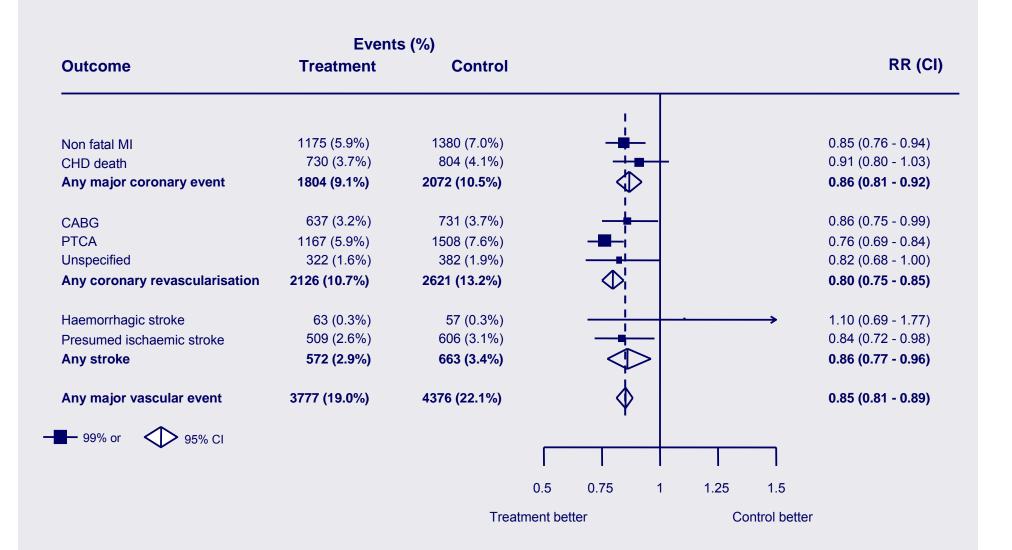
Difference between more vs less and statin vs control trials: $\chi_1^2 = 0.23$ (p=0.63)

CTT meta-analysis: Proportional reduction in NON-FATAL MI or CHD DEATH versus absolute LDL-C reduction

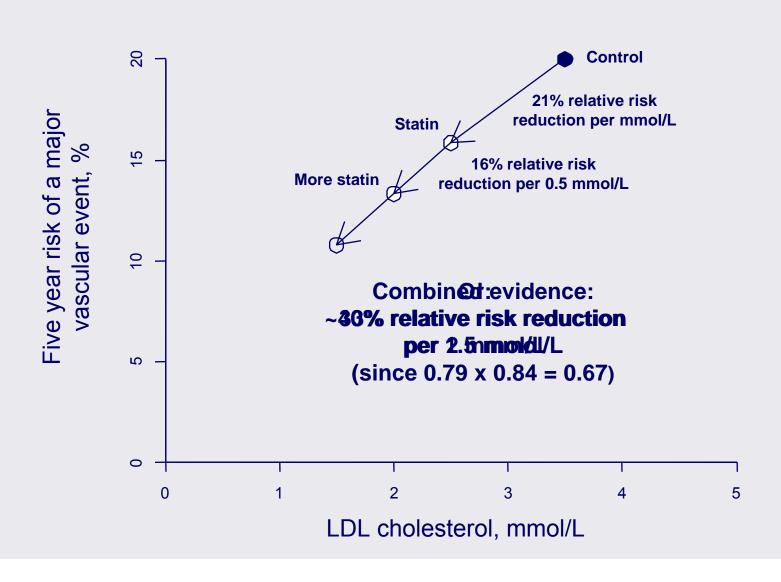


Mean LDL cholesterol difference between treatment groups (mmol/L)

CTT meta-analysis: Effects of MORE vs LESS STATIN (0.5 mmol/l lower LDL-C) on MAJOR VASCULAR EVENTS



Absolute effects on MAJOR VASCULAR EVENTS of lowering LDL cholesterol with STATIN therapy



SEARCH: 2 separate randomized treatment comparisons in 12,064 post-MI patients

More versus less LDL-lowering comparison:

Simvastatin vs Simvastatin 80 mg daily 20mg daily

Homocysteine-lowering comparison:

Folic acid 2mg plus vs Placebo vitamin B12 1mg daily tablets

Mean (SD) duration: 6.7 (1.5) years



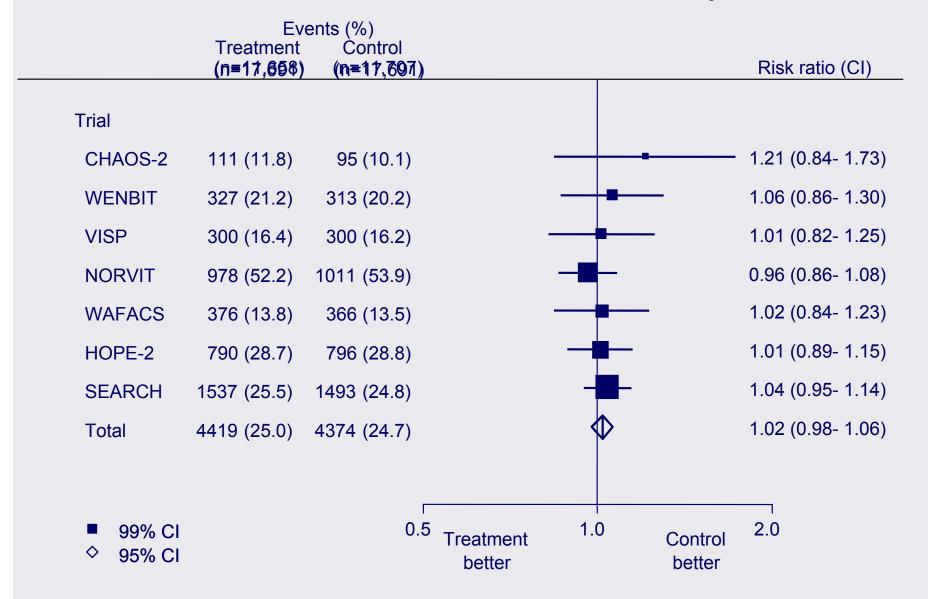
SEARCH: Reduction in HOMOCYSTEINE with allocation to FOLATE/B12 versus placebo

Mean (SD) baseline: 13.5 (5) µmol/l

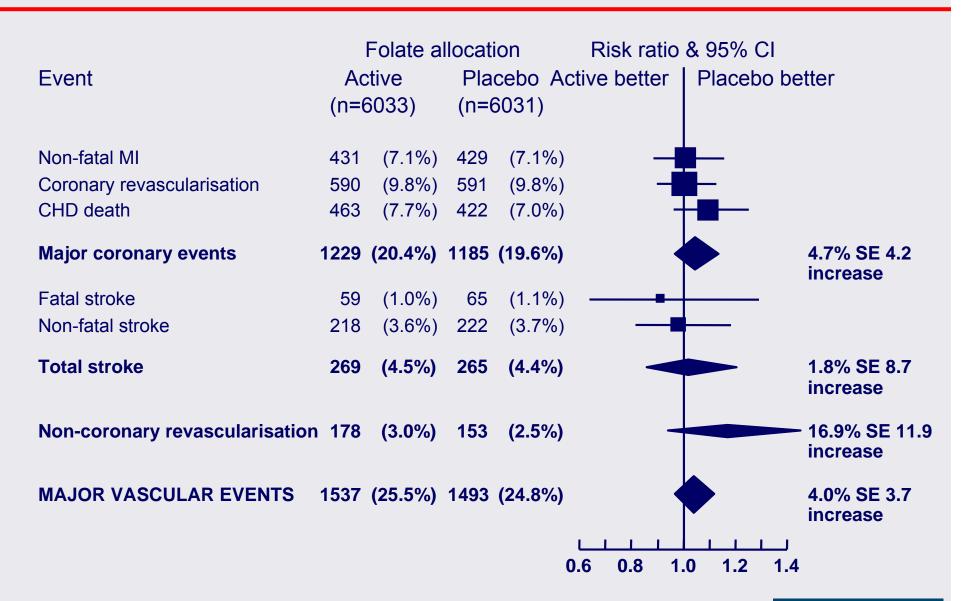
| | Reduction | | |
|---------|-----------|---------|--|
| | µmol/l | percent | |
| Month 4 | 4.2 | 31% | |
| Year 1 | 4.0 | 30% | |
| Year 5 | 3.7 | 27% | |
| AVERAGE | 3.8 | 28% | |
| | | | |



BVTT meta-analysis: Effects of FOLATE on MAJOR VASCULAR EVENTS by trial

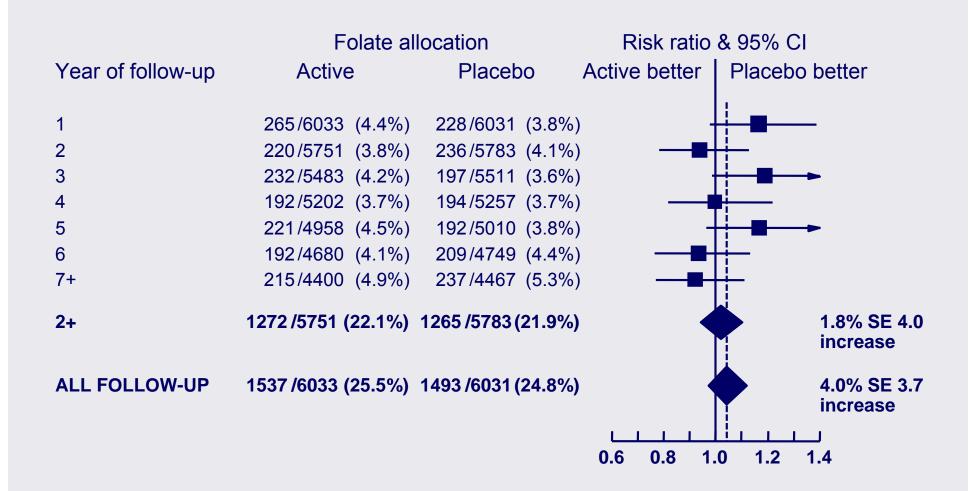


SEARCH: FOLATE/B12 on MAJOR VASCULAR EVENTS



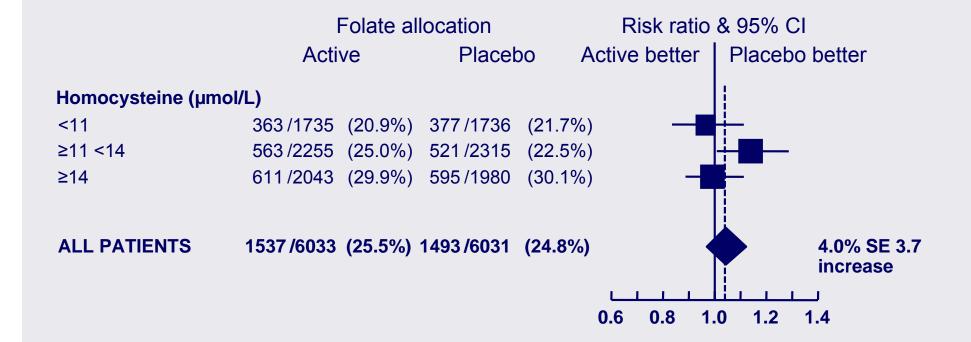


SEARCH: FOLATE/B12 on MAJOR VASCULAR EVENTS by year of follow-up





SEARCH: FOLATE/B12 on MAJOR VASCULAR EVENTS by baseline HOMOCYSTEINE



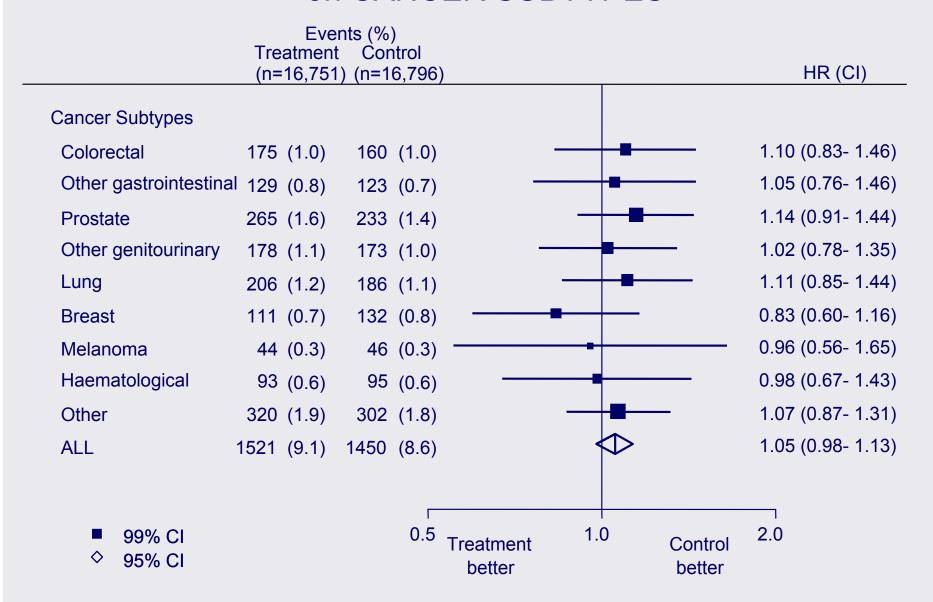


SEARCH: Effects of FOLATE/B12 on MORTALITY

| Cause of death | Folate al Active (n=6033) | location Placebo (n=6031) | Risk ratio & 95% CI Active better Placebo better |
|------------------|---------------------------------|---------------------------------|--|
| CHD | 463 (7.7%) | 422 (7.0%) | ∔ ■ |
| Stroke | 59 (1.0%) | 65 (1.1%) | |
| Other vascular | 51 (0.8%) | | |
| All vascular | 573 (9.5%) | 545 (9.0%) | 5.5% SE 6.1 increase |
| Neoplastic | 260 (4.3%) | 251 (4.2%) | |
| Respiratory | 67 (1.1%) | 65 (1.1%) | |
| Other medical | 67 (1.1%) | 78 (1.3%) | |
| Non-medical | 16 (0.3%) | 11 (0.2%) | - |
| All non-vascular | 410 (6.8%) | 405 (6.7%) | 1.6% SE 7.0 increase |
| All causes | 983 (16.3%) | 950 (15.8%) | 3.8% SE 4.6 increase |
| | | | 0.6 0.8 1.0 1.2 1.4 |

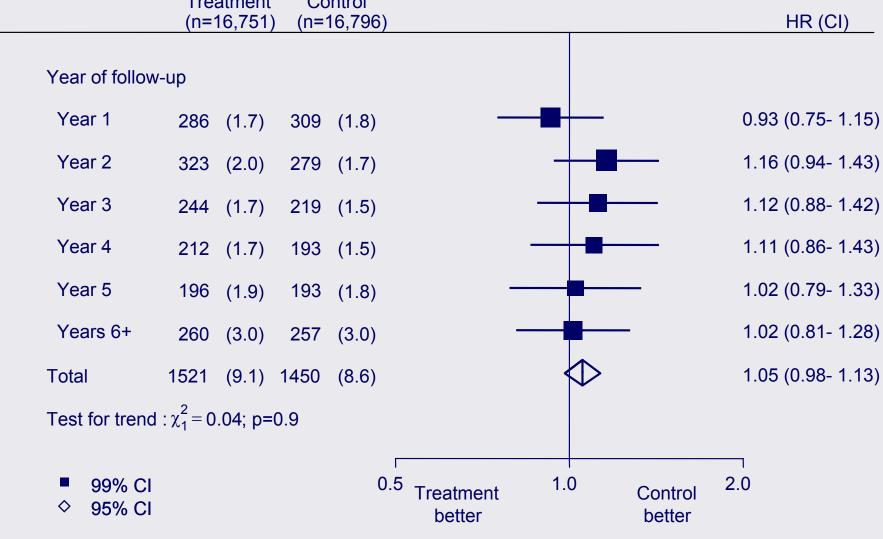


BVTT meta-analysis: Effects of FOLATE on CANCER SUBTYPES



BVTT meta-analysis: Effects of FOLATE on CANCER by year of follow-up

Events (%) Treatment Control



Summary of SEARCH findings in context of meta-analyses of previous trials

More versus less LDL-lowering comparison:

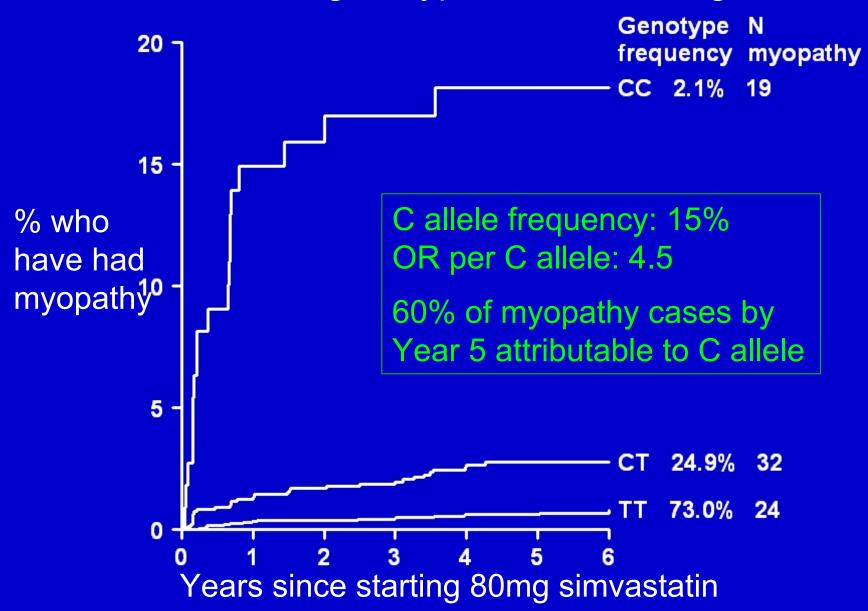
- SEARCH results are consistent with previous trials of statin vs control and of more vs less statin
- Larger reductions in LDL cholesterol with statin therapy produces larger reductions in major vascular events
- No excess of non-vascular outcomes (e.g. cancer)
 when LDL cholesterol is reduced to very low levels

Homocysteine-lowering comparison:

 Lowering homocysteine with folic acid supplementation is safe, but does not reduce the risk of vascular events



SEARCH: Absolute risk of MYOPATHY by rs4149056 genotype in *SLCO1B1* gene



SEARCH: More vs less STATIN on MAJOR VASCULAR EVENTS

