

SEARCH

Study of the Effectiveness of Additional
Reductions in Cholesterol and Homocysteine

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

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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
80 mg daily

vs

Simvastatin
20mg daily

Homocysteine-lowering comparison:

Folic acid 2mg plus
vitamin B12 1mg daily

vs

Placebo
tablets

Mean (SD) duration: 6.7 (1.5) years

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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)

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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

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

| | <u>Mean (SD) baseline</u> | |
|-------------------|---------------------------|-----------|
| | 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

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

| | <u>Reduction: 20mg – 80mg</u> | | |
|----------------|-------------------------------|-----------|------------|
| | 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% |

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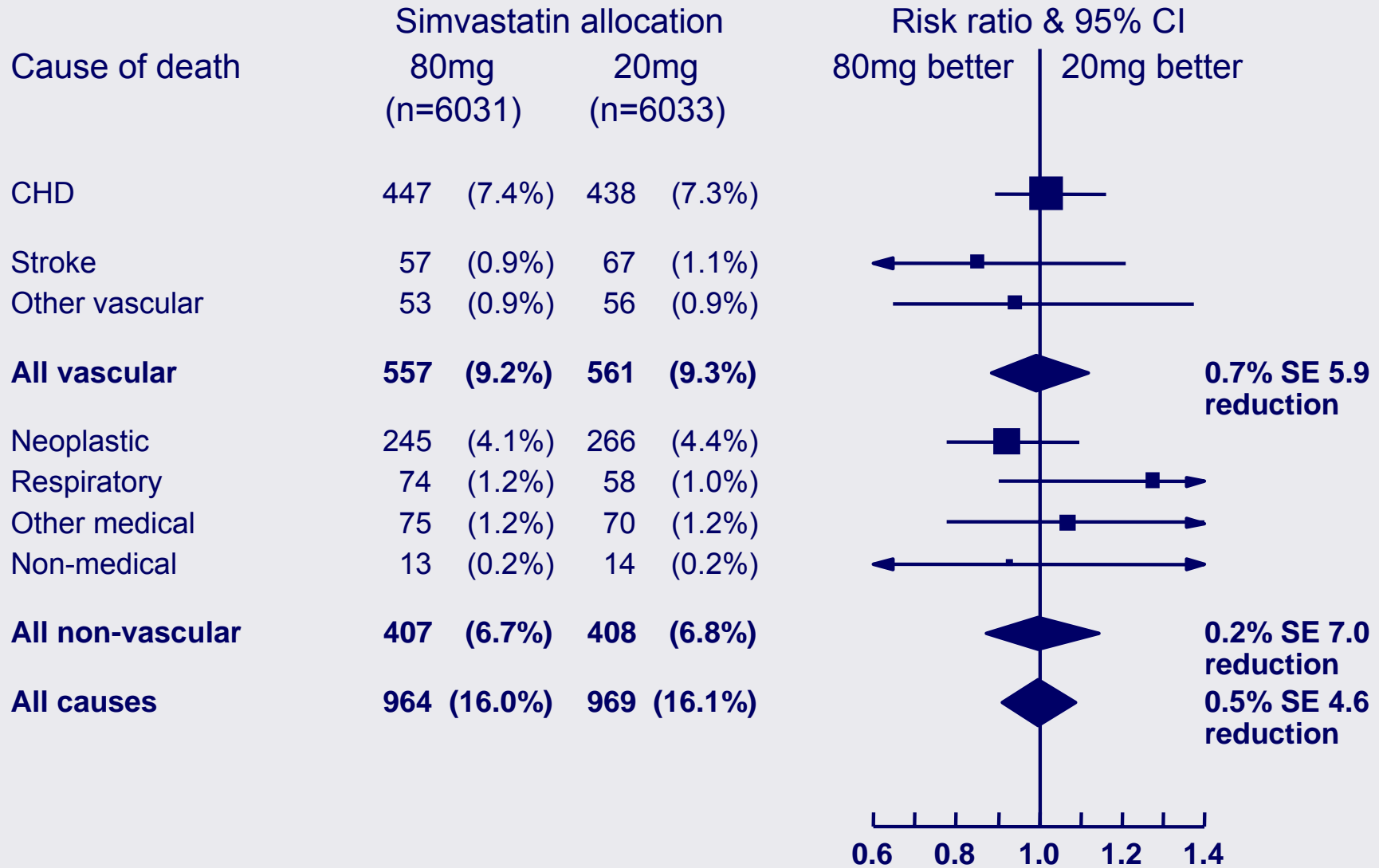
SEARCH: Myopathy rates by SIMVASTATIN comparison

| | Simvastatin allocation (per 1000 person-years) | |
|-----------------------|---|-----------------|
| Years of follow-up | 80 mg (6031) | 20 mg (6033) |
| 0-1 | 25 (4.2) | 1 (0.2) |
| 2-7 | 28 (0.8) | 2 (0.1) |
| Total | 53 | 3 |

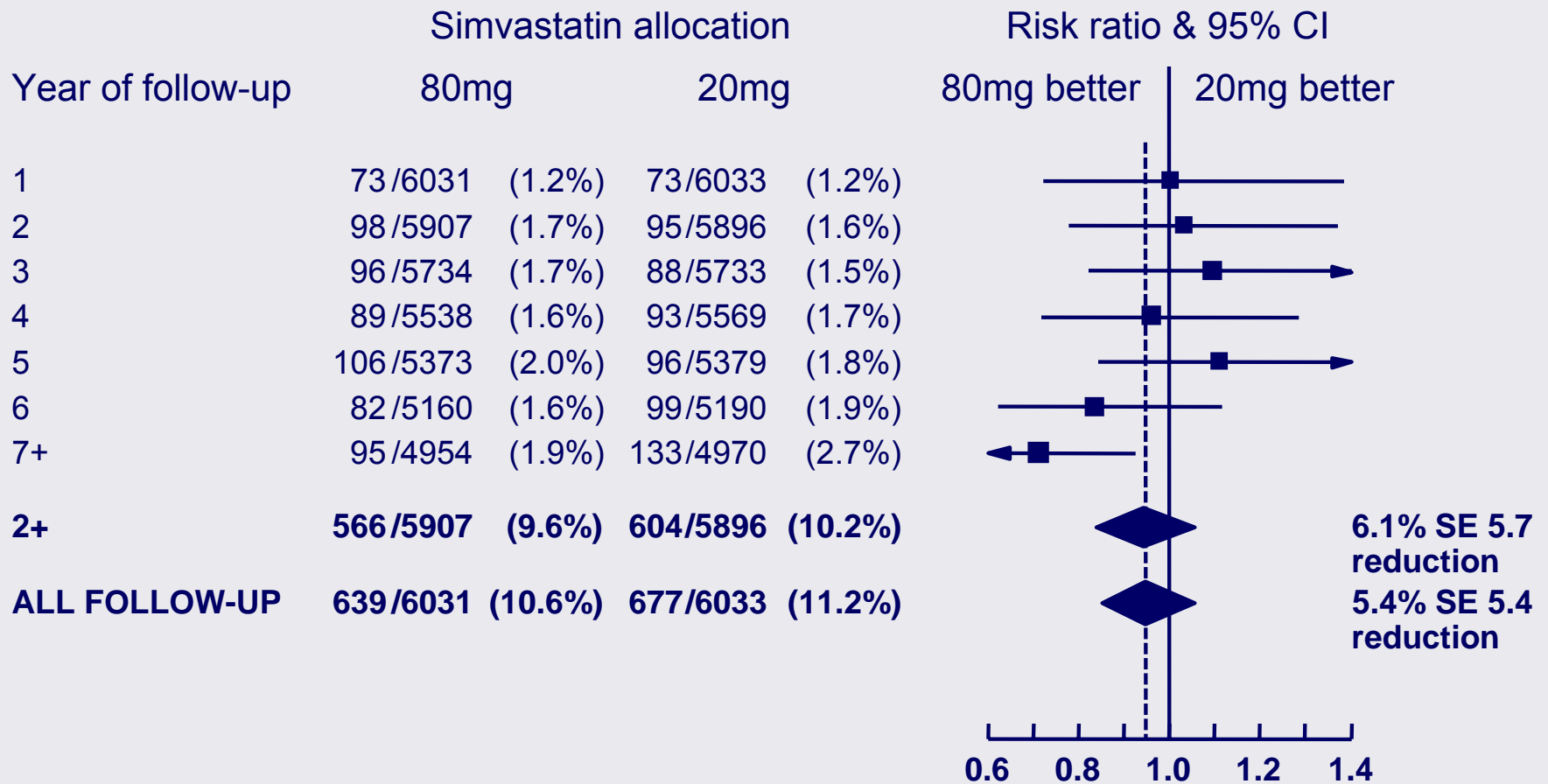
Myopathy: New, unexplained muscle pain or weakness
plus CK>10x ULN (7 vs 0 developed rhabdomyolysis)

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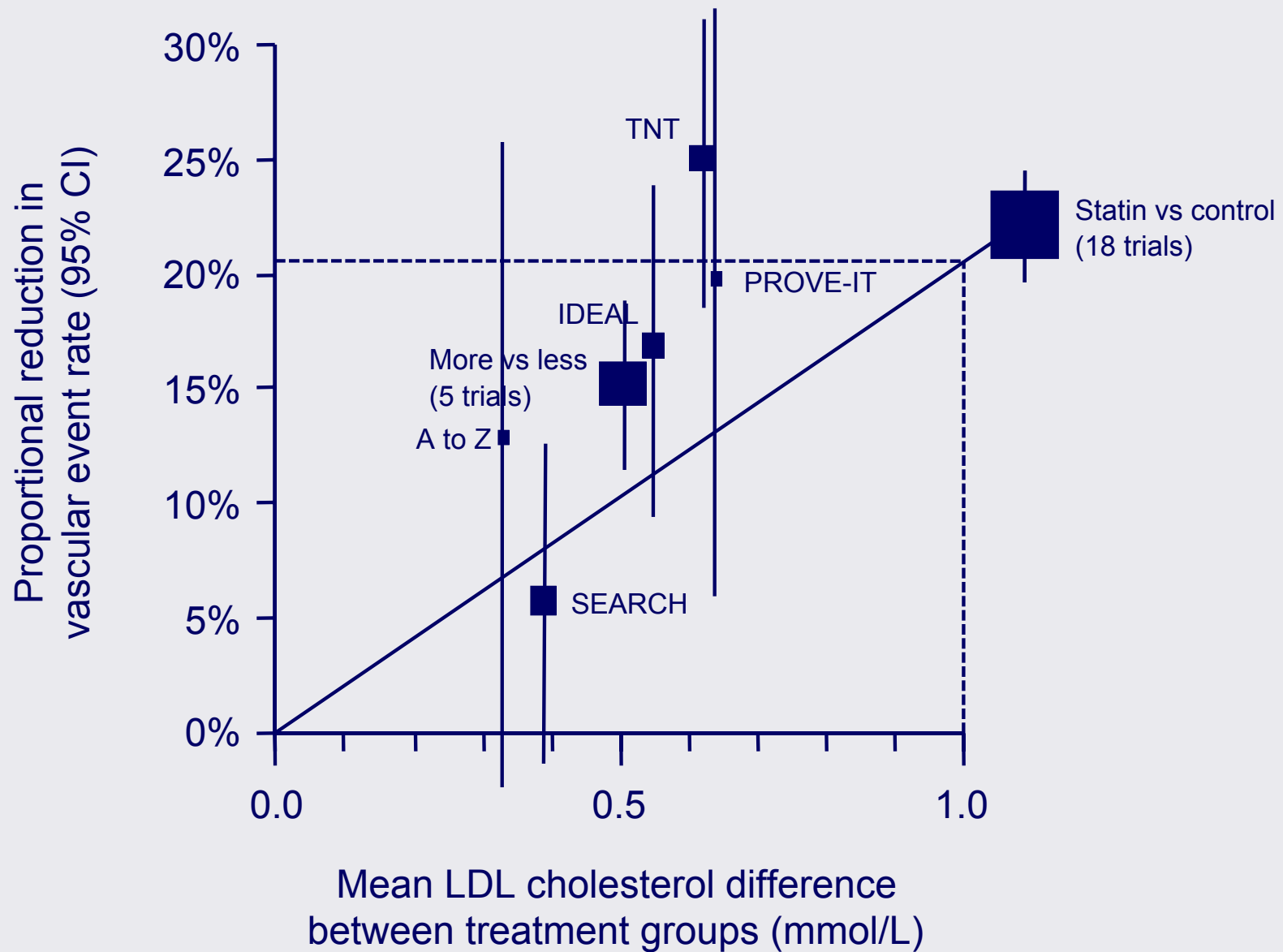
SEARCH: Effects of more vs less STATIN on MORTALITY



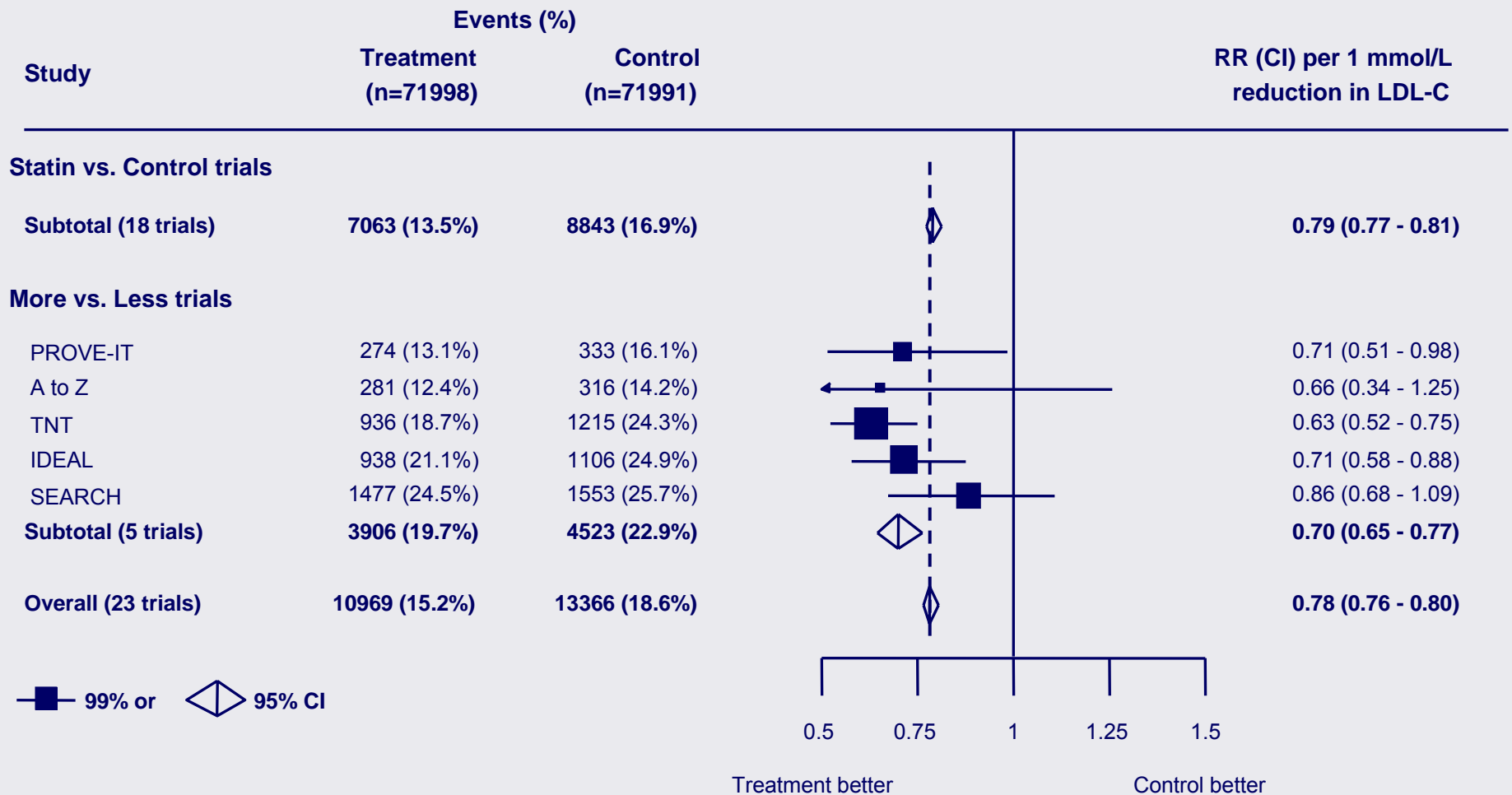
SEARCH: Effects of more vs less STATIN on ANY CANCER by year of follow-up



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



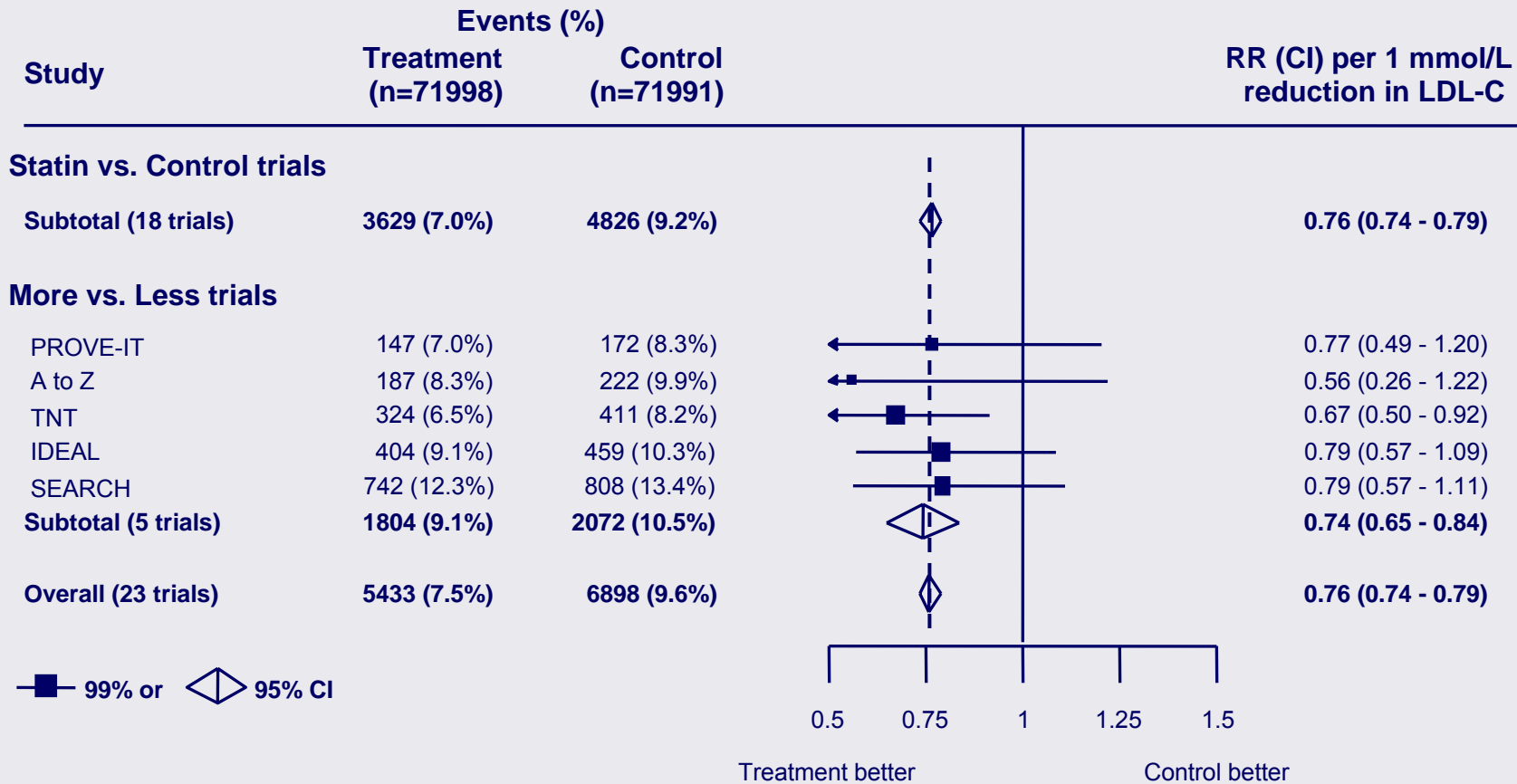
CTT meta-analysis: Effects of STATIN on MAJOR VASCULAR EVENT per mmol/L LDL-C reduction



Heterogeneity within more vs less trials: $\chi^2_4 = 7.34$ (p=0.12)

Difference between more vs less and statin vs control trials: $\chi^2_1 = 6.73$ (p=0.01)

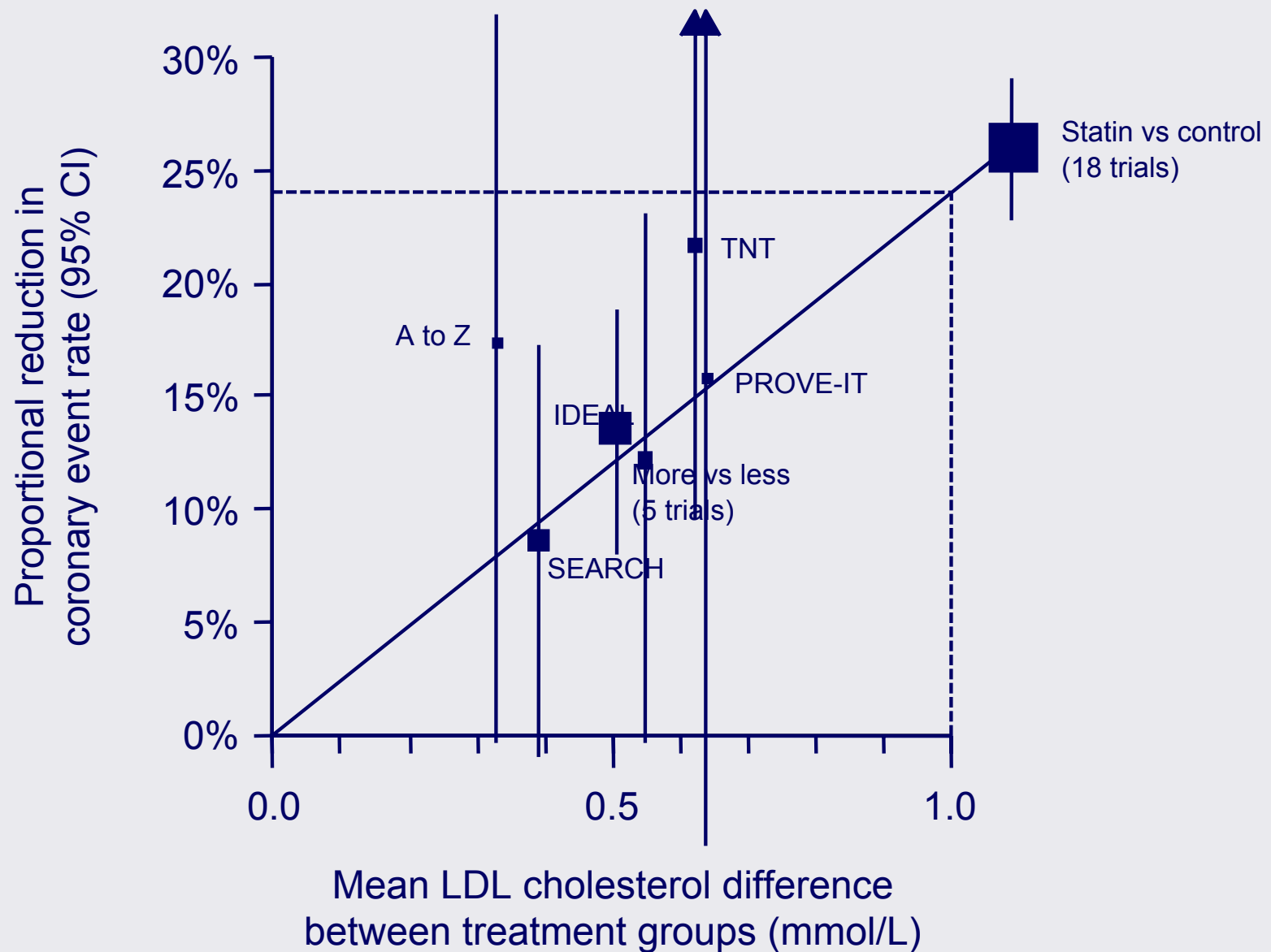
CTT meta-analysis: Effects of STATIN on NON-FATAL MI or CHD DEATH per mmol/L LDL-C reduction



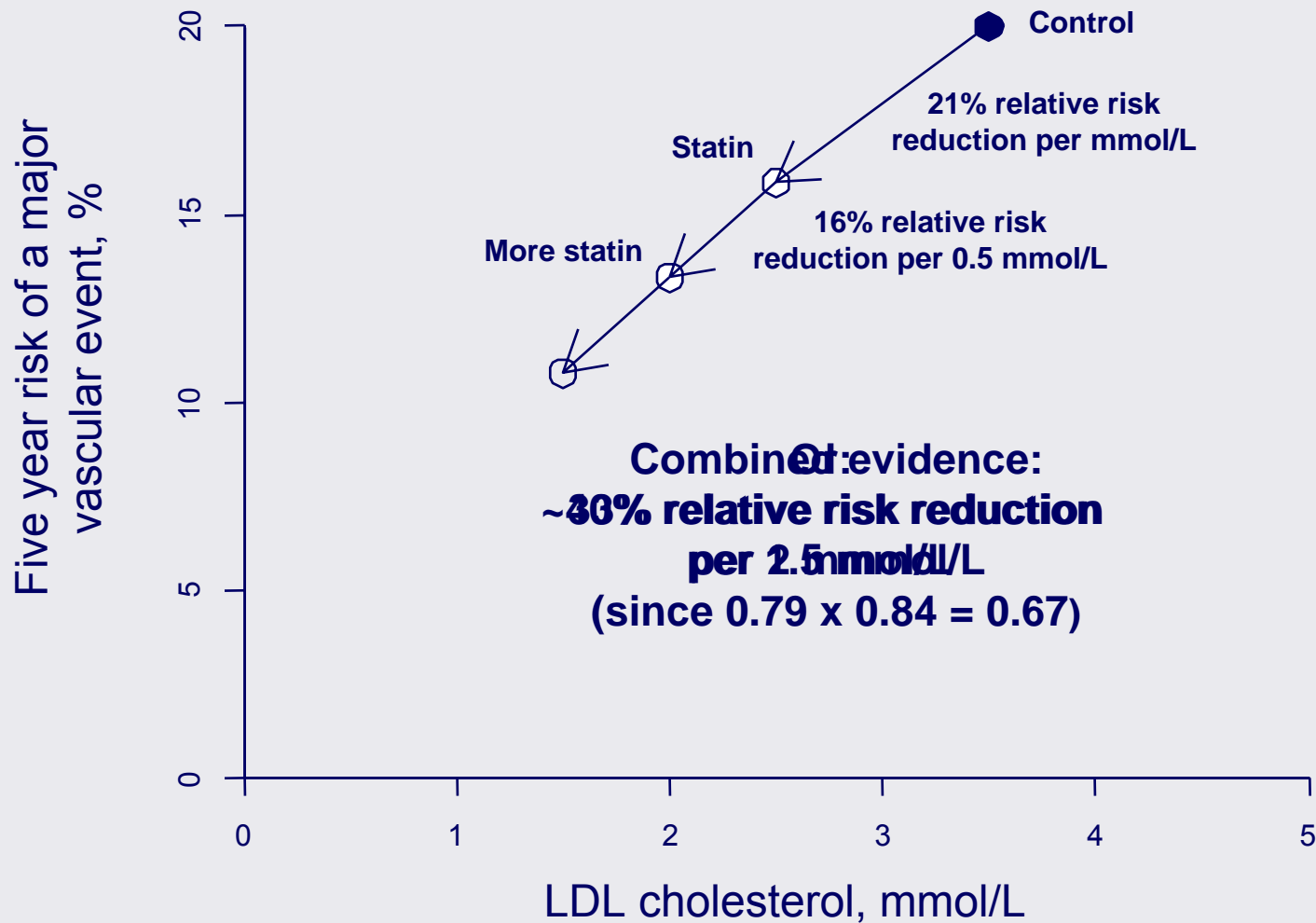
Heterogeneity within more vs less trials: $\chi^2_4 = 2.07$ (p=0.72)

Difference between more vs less and statin vs control trials: $\chi^2_1 = 0.23$ (p=0.63)

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



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



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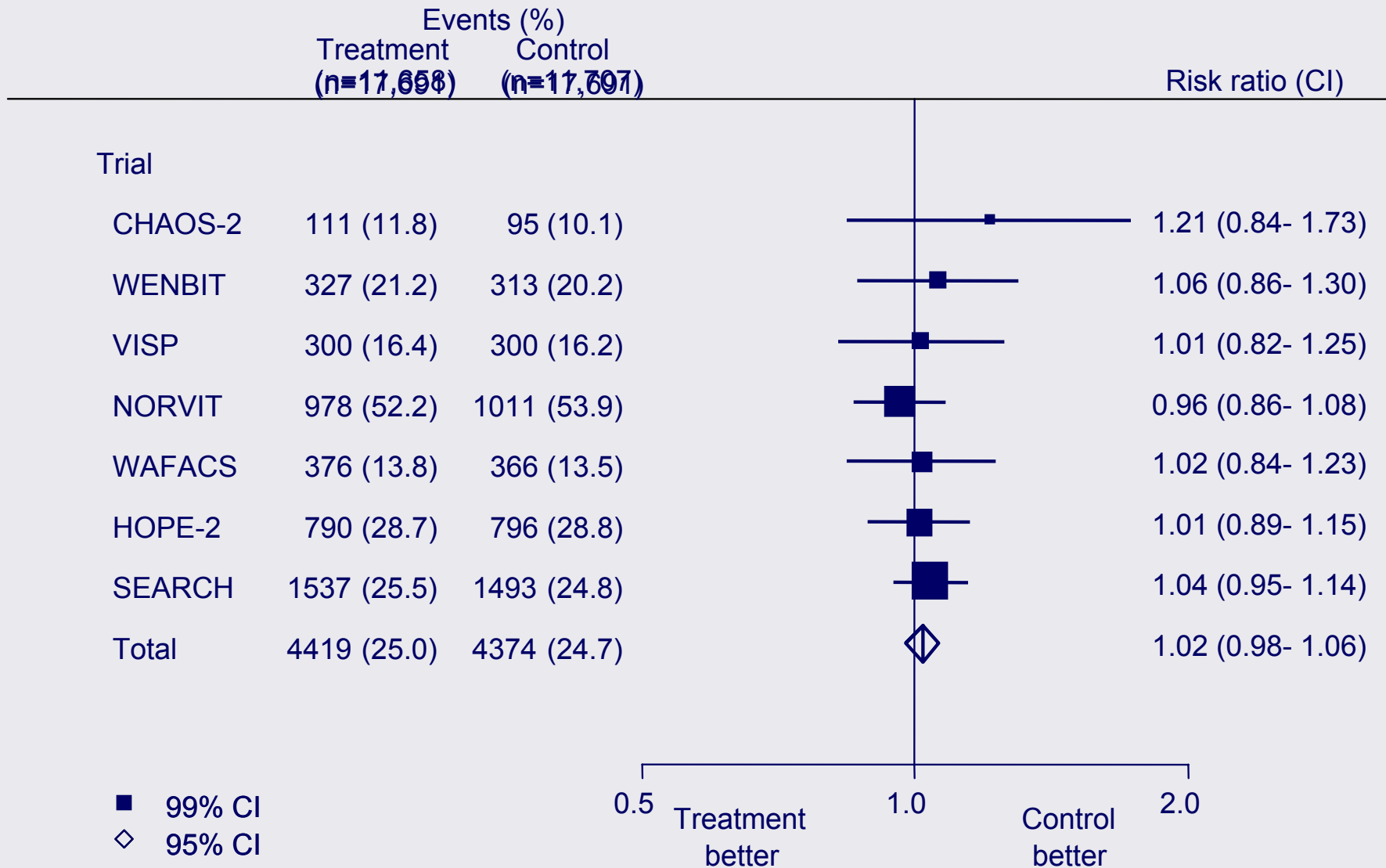
SEARCH: Reduction in HOMOCYSTEINE with allocation to FOLATE/B12 versus placebo

Mean (SD) baseline: 13.5 (5) $\mu\text{mol/l}$

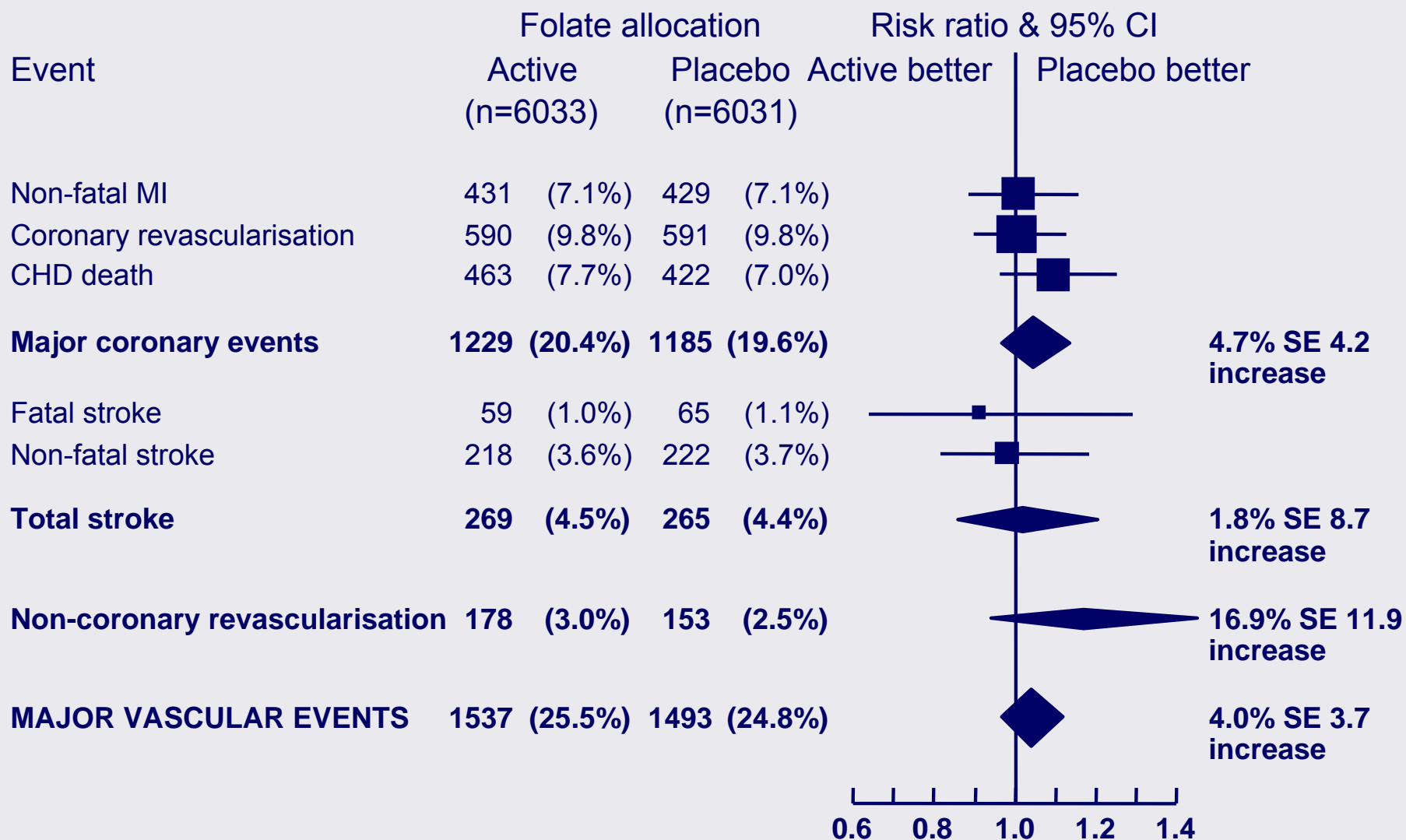
| | Reduction | |
|---------|-------------------|---------|
| | $\mu\text{mol/l}$ | percent |
| Month 4 | 4.2 | 31% |
| Year 1 | 4.0 | 30% |
| Year 5 | 3.7 | 27% |
| AVERAGE | 3.8 | 28% |

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

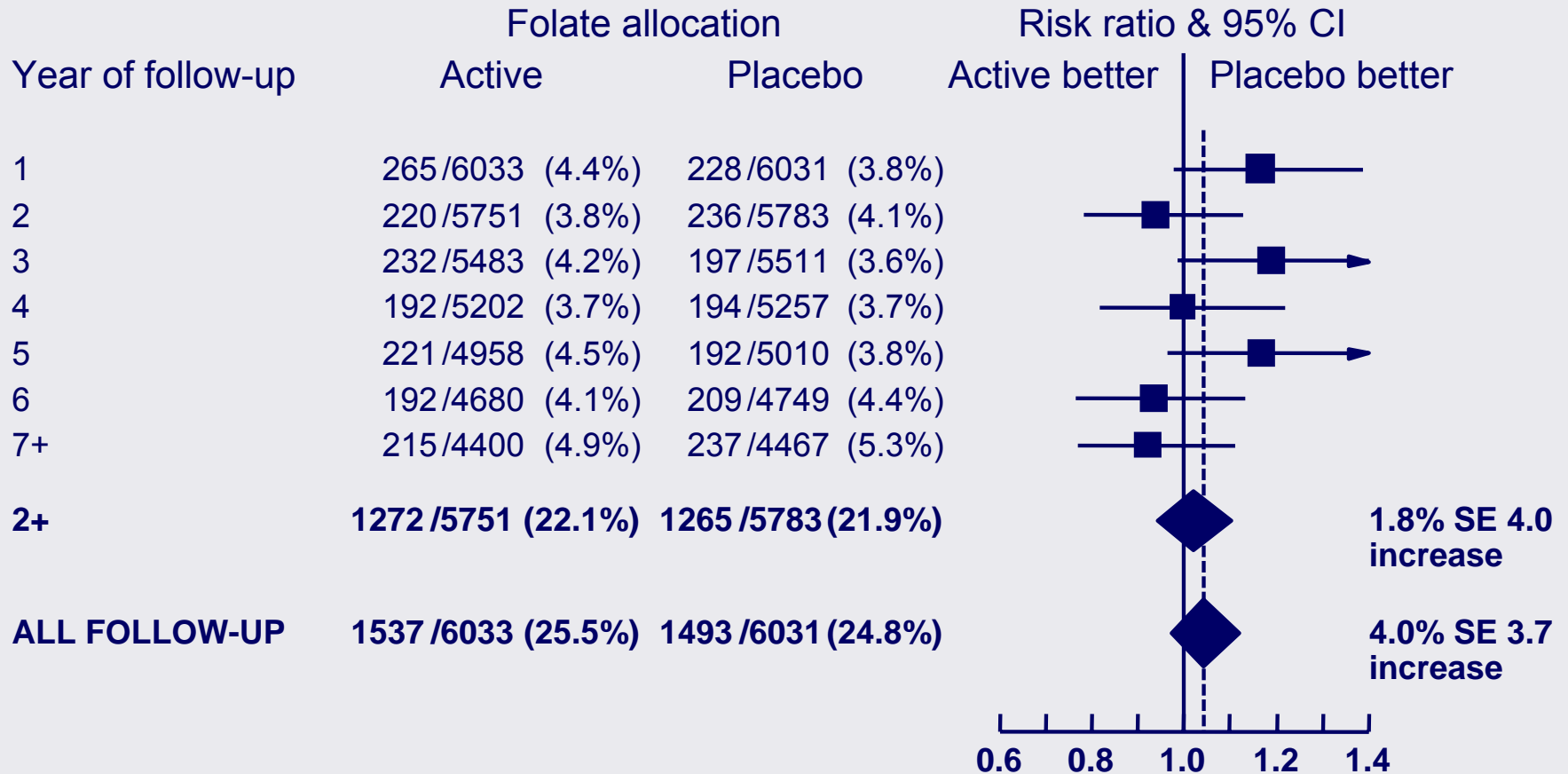


SEARCH: FOLATE/B12 on MAJOR VASCULAR EVENTS



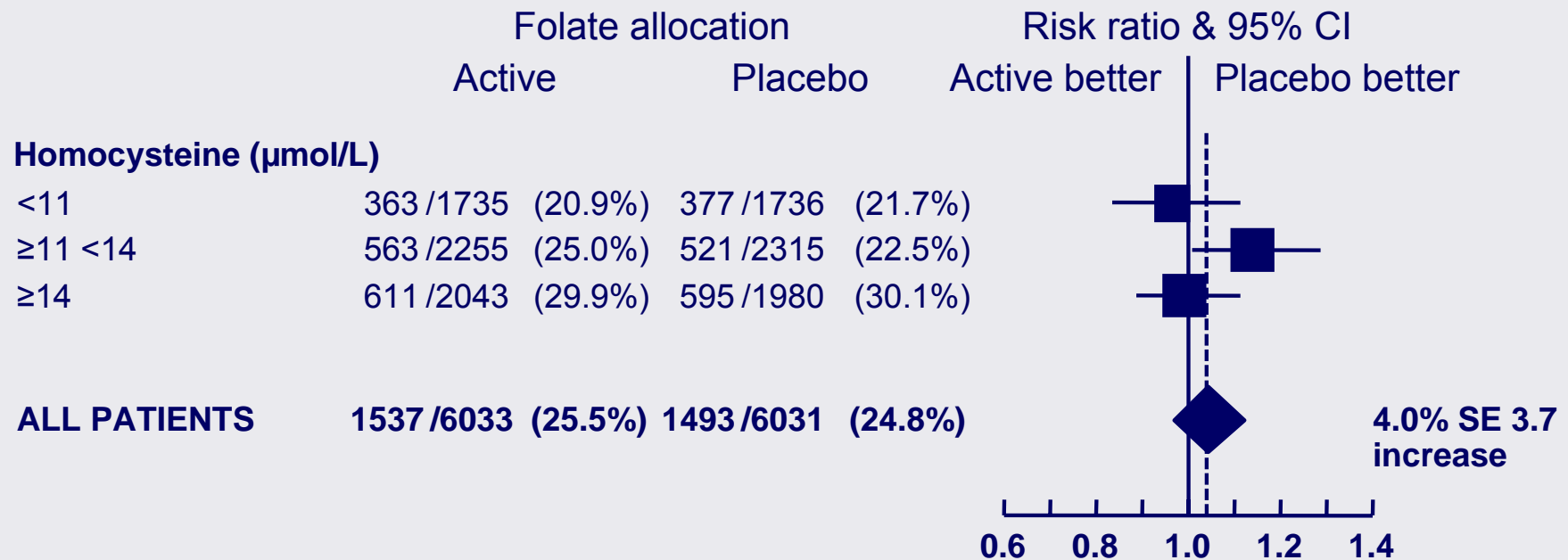
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SEARCH: FOLATE/B12 on MAJOR VASCULAR EVENTS by year of follow-up

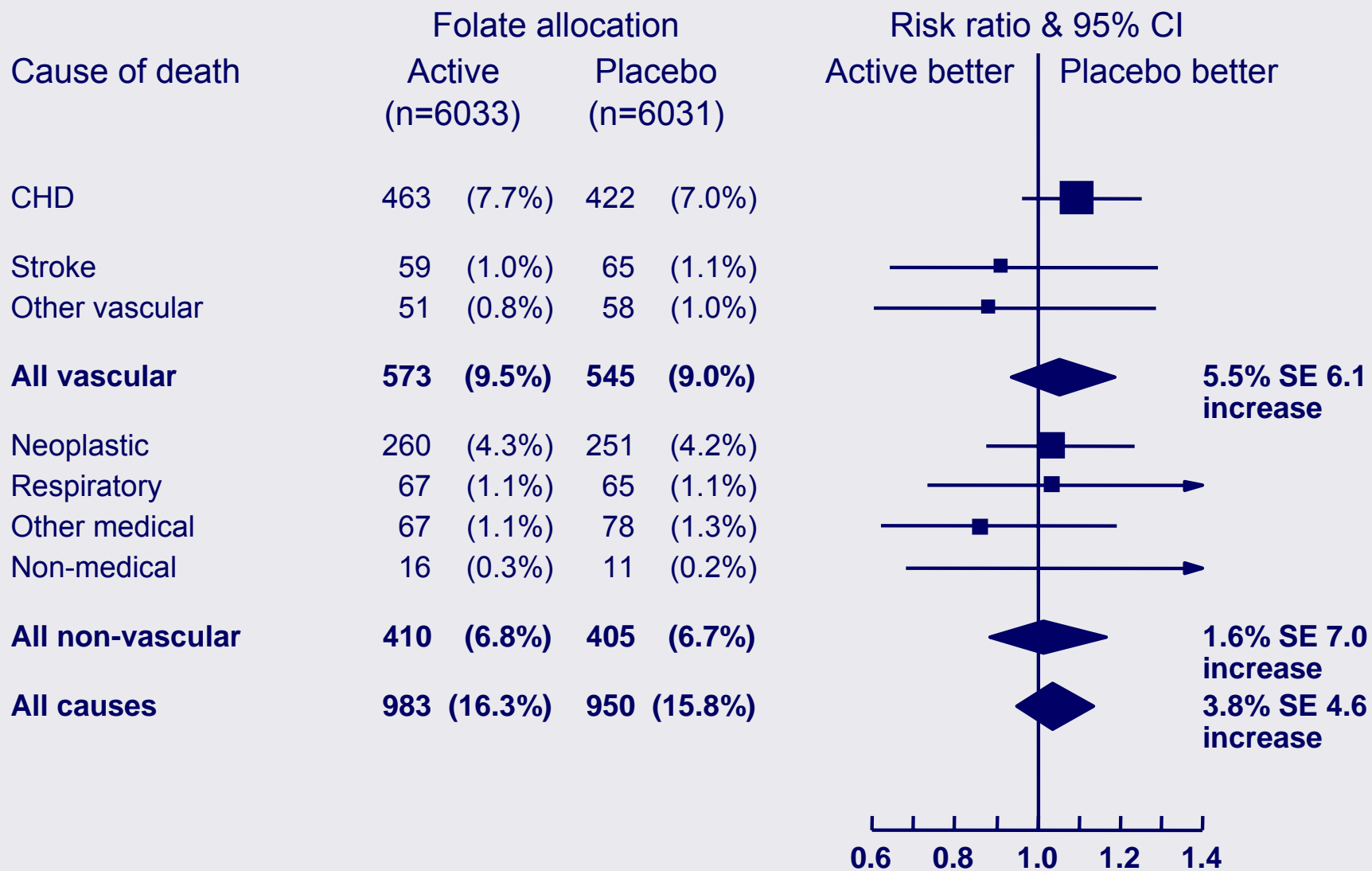


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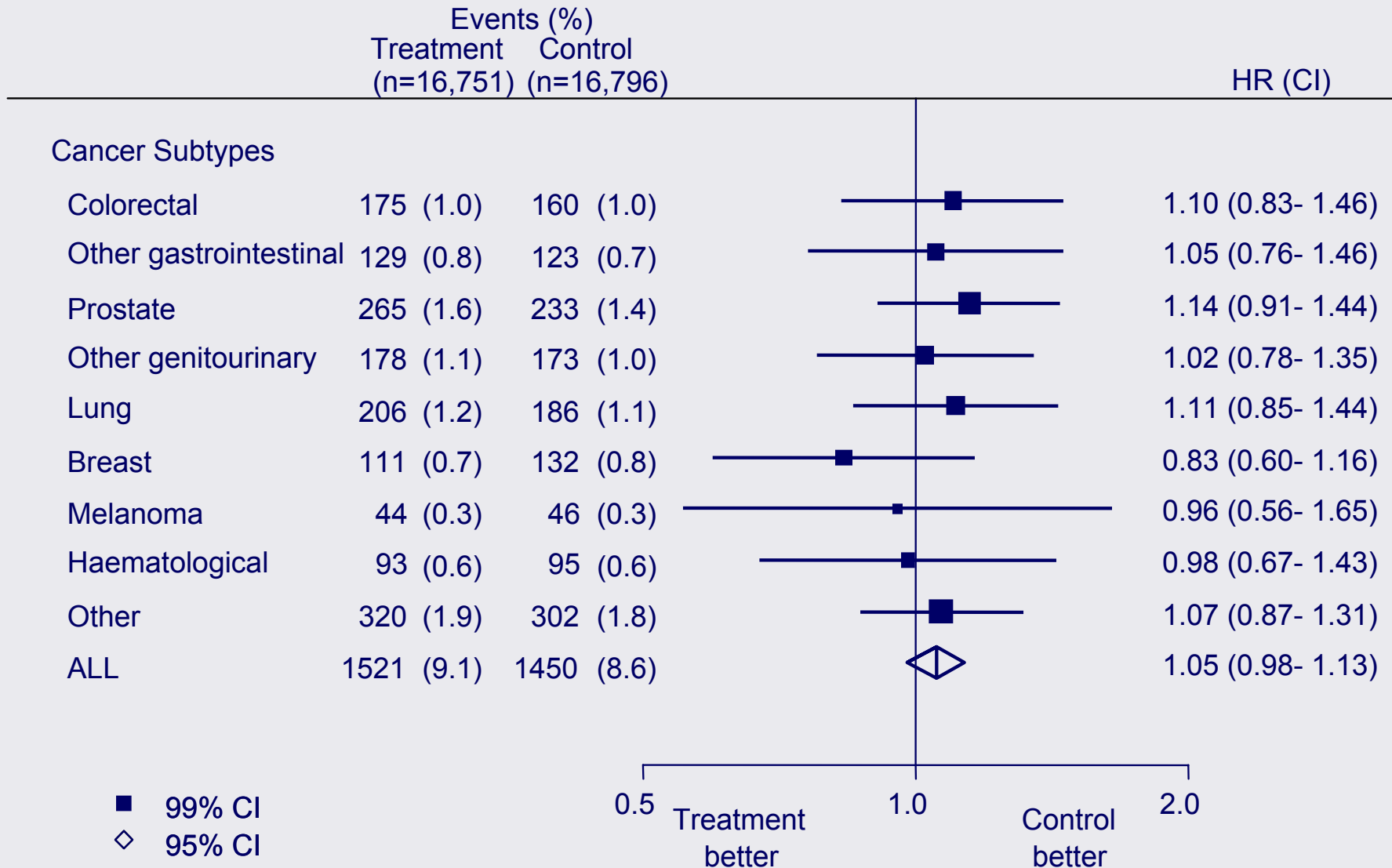
SEARCH: FOLATE/B12 on MAJOR VASCULAR EVENTS by baseline HOMOCYSTEINE



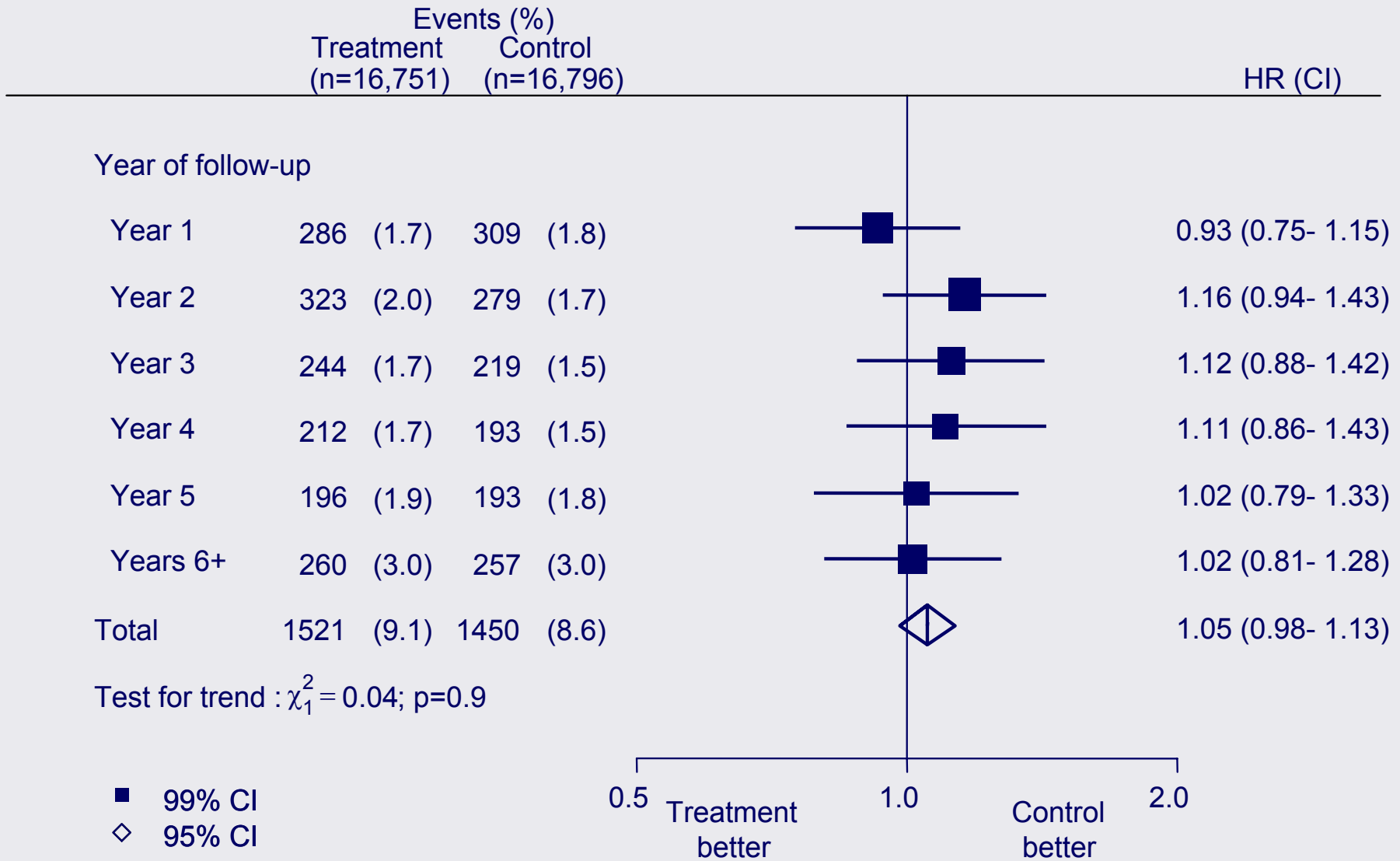
SEARCH: Effects of FOLATE/B12 on MORTALITY



BVTT meta-analysis: Effects of FOLATE on CANCER SUBTYPES



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



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

More versus less LDL-lowering comparison:

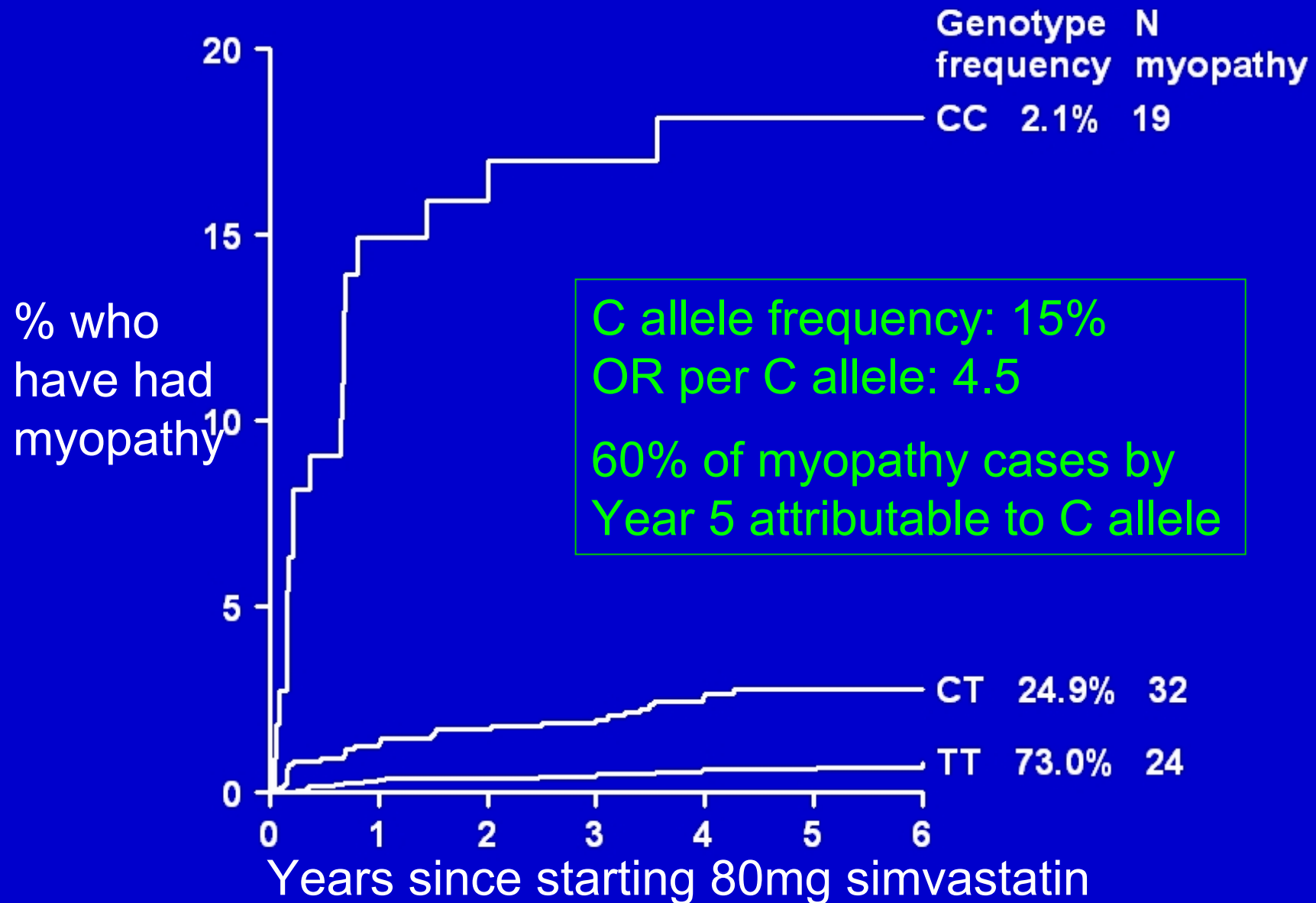
- SEARCH results are consistent with previous trials of statin vs control and of more vs less statin
- Larger reductions in LDL cholesterol with statin therapy produces larger reductions in major vascular events
- No excess of non-vascular outcomes (e.g. cancer) when LDL cholesterol is reduced to very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

Homocysteine-lowering comparison:

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

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



SEARCH: More vs less STATIN on MAJOR VASCULAR EVENTS

