

# SEARCH

## Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine

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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 vs Simvastatin
- 80 mg daily 20mg daily

Homocysteine-lowering comparison:

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

Mean (SD) duration: 6.7 (1.5) years

# 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

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

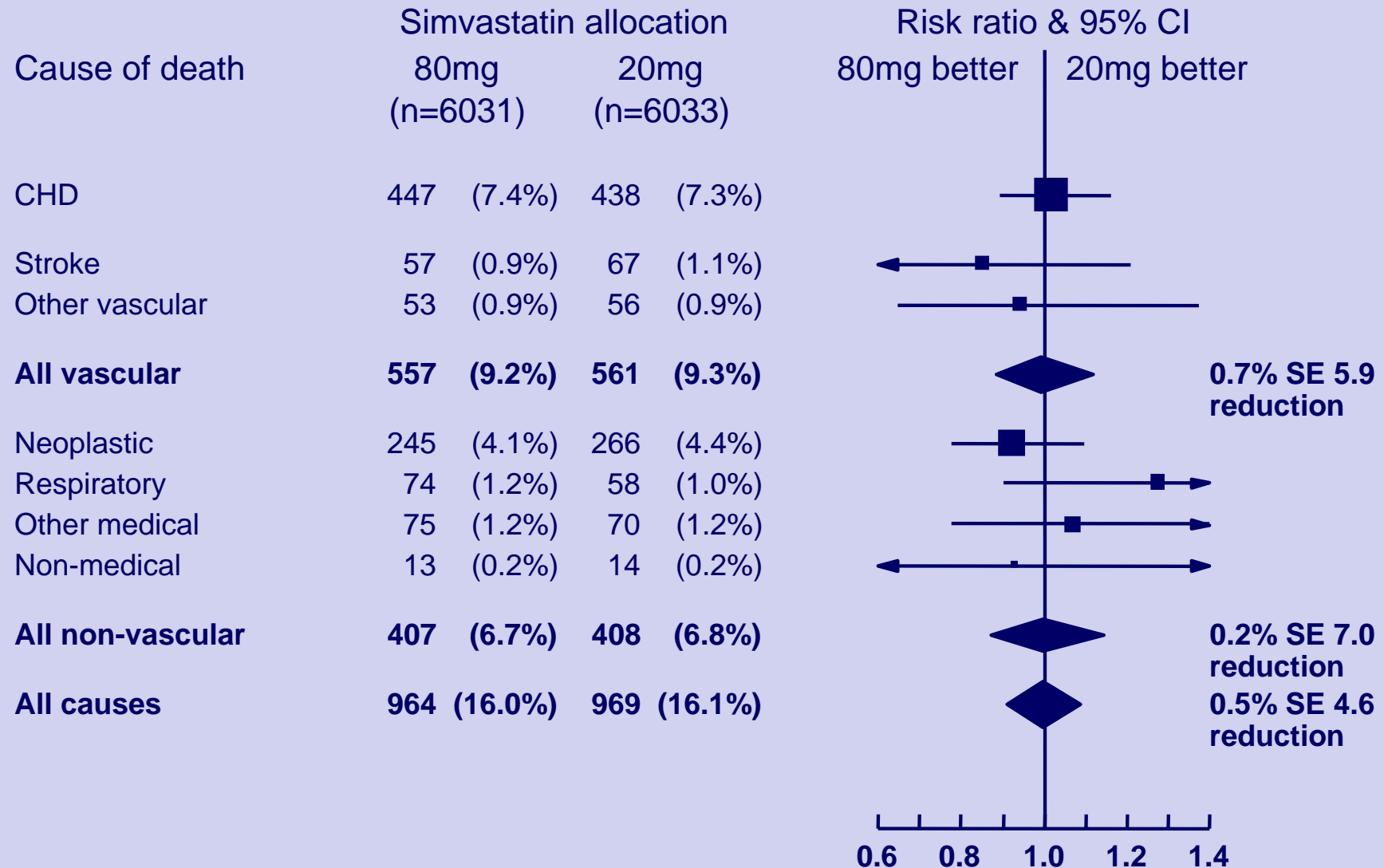
	Reduction: 20mg – 80mg		
	mmol/l	mg/dl	percent
Month 4	0.51	20	20%
Year 1	0.39	15	16%
Year 5	0.29	11	12%
AVERAGE	0.35	14	14%

# SEARCH: Myopathy rates by SIMVASTATIN comparison

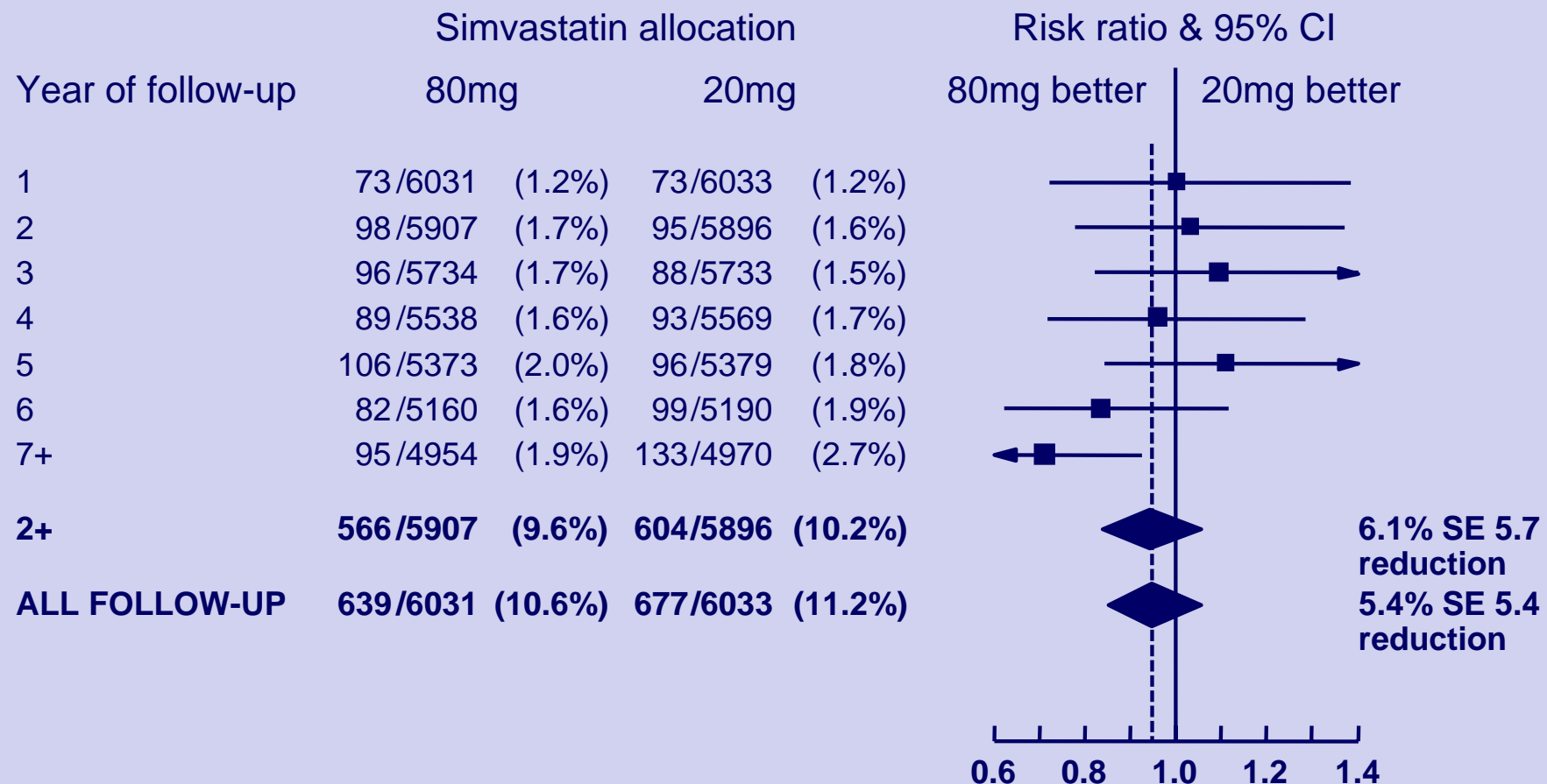
	Simvastatin allocation (per 1000 person-years)	
Years of follow-up	80 mg (6031)	20 mg (6033)
0-1	25 (4.2)	1 (0.2)
2-7	28 (0.8)	2 (0.1)
Total	53	3

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

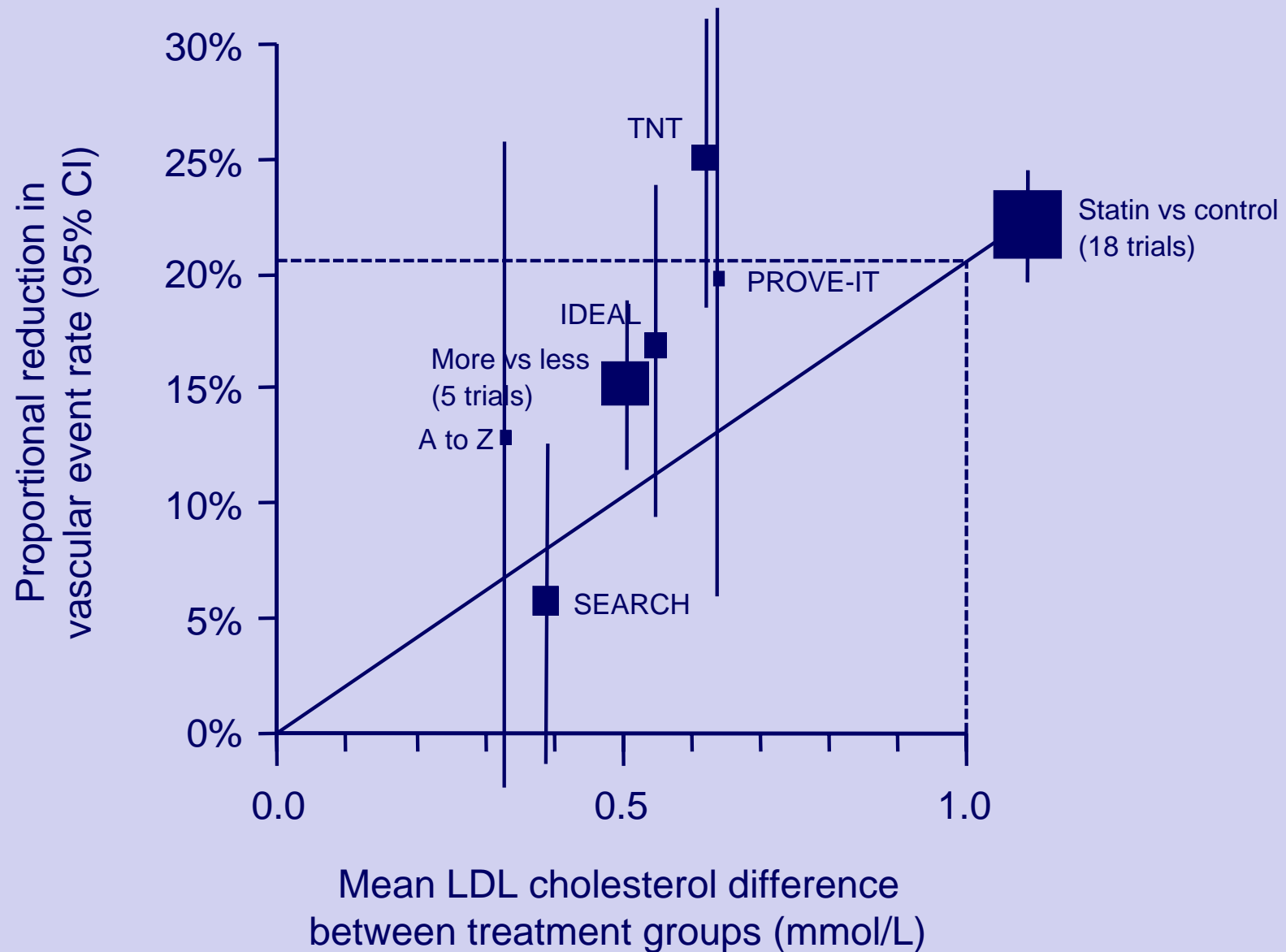
## SEARCH: Effects of more vs less STATIN on MORTALITY



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

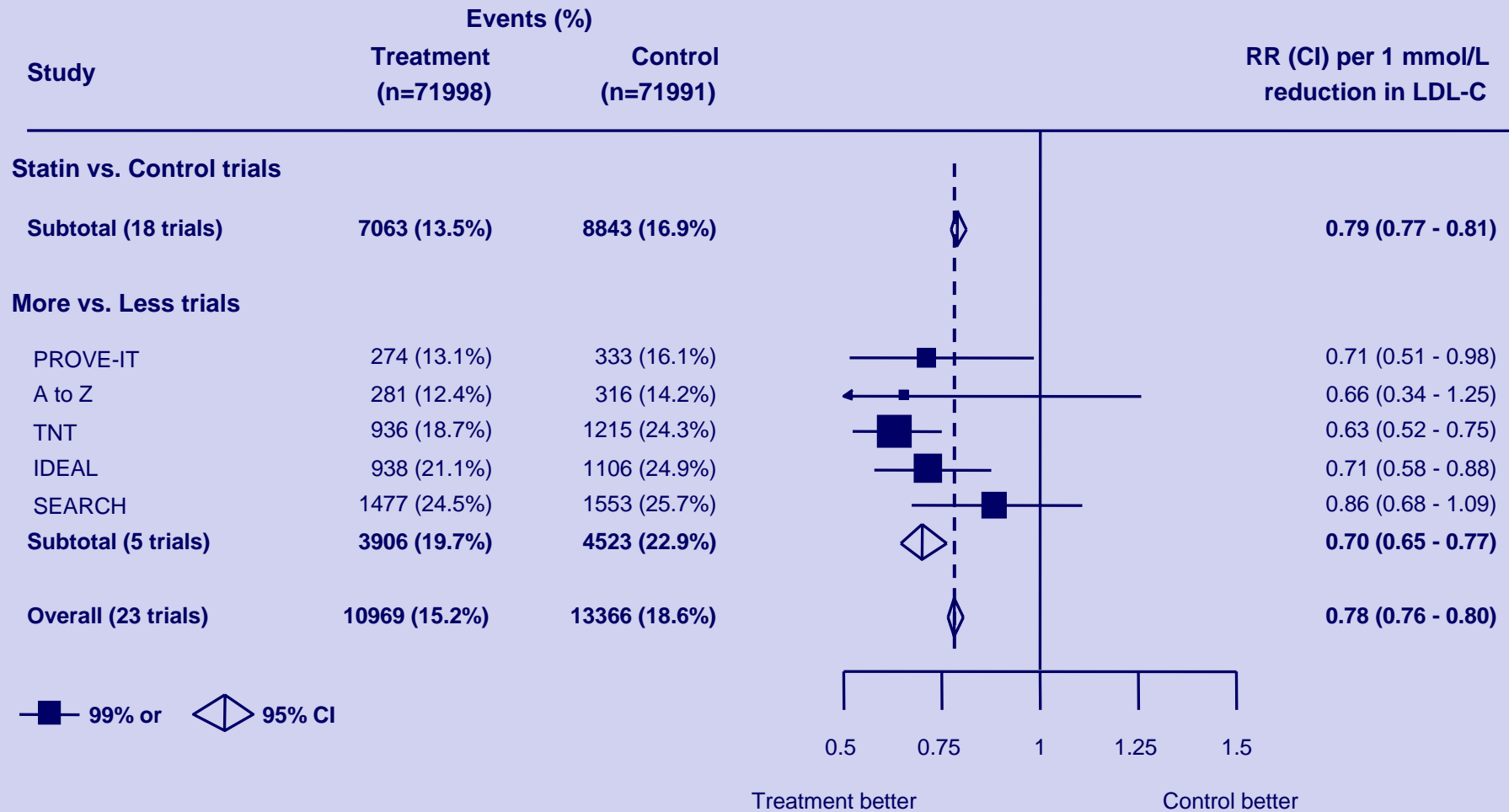


## CTT meta-analysis: Proportional reduction in MAJOR VASCULAR EVENTS versus absolute LDL-C reduction





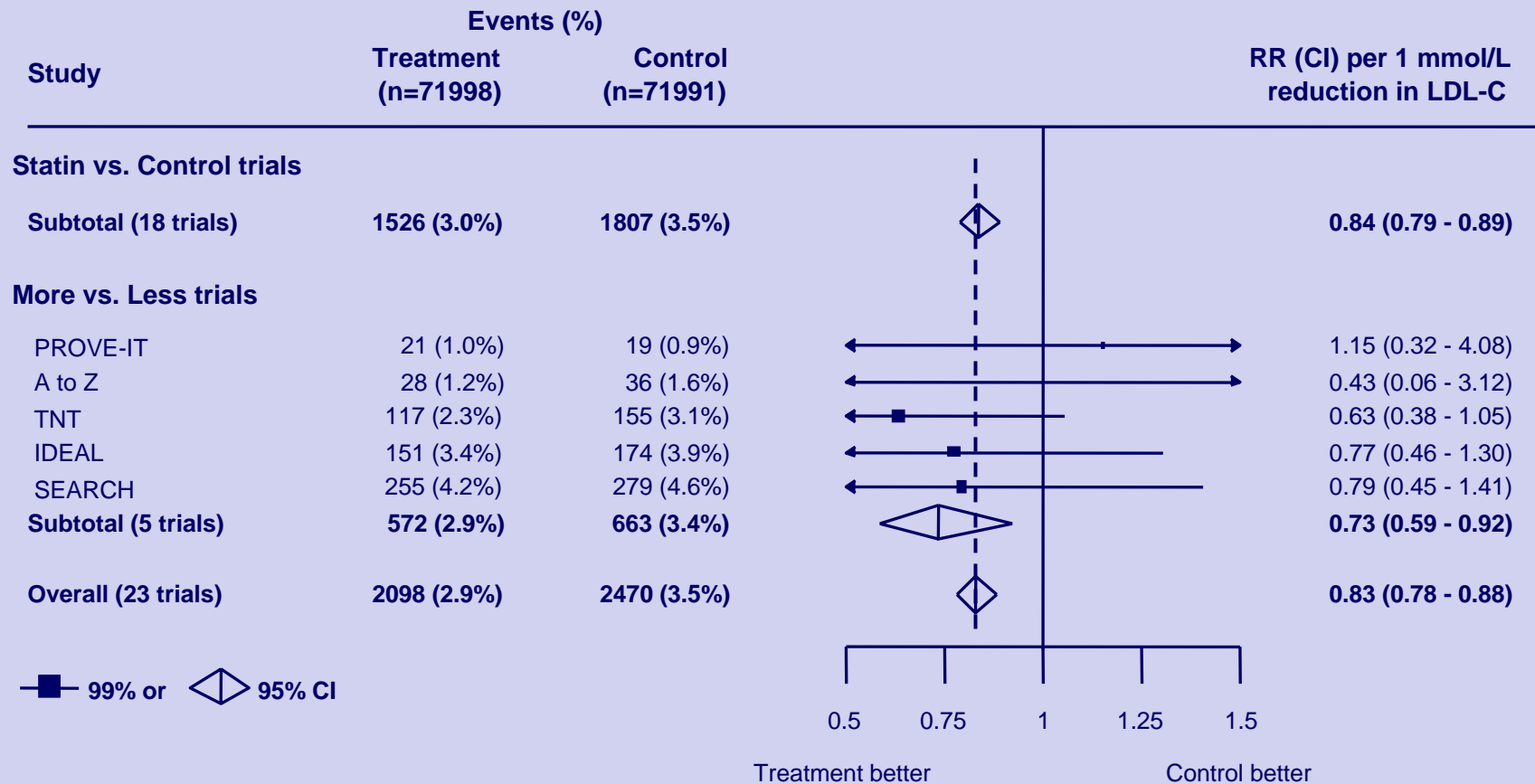
# CTT meta-analysis: Effects of STATIN on MAJOR VASCULAR EVENT per mmol/L LDL-C reduction



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)

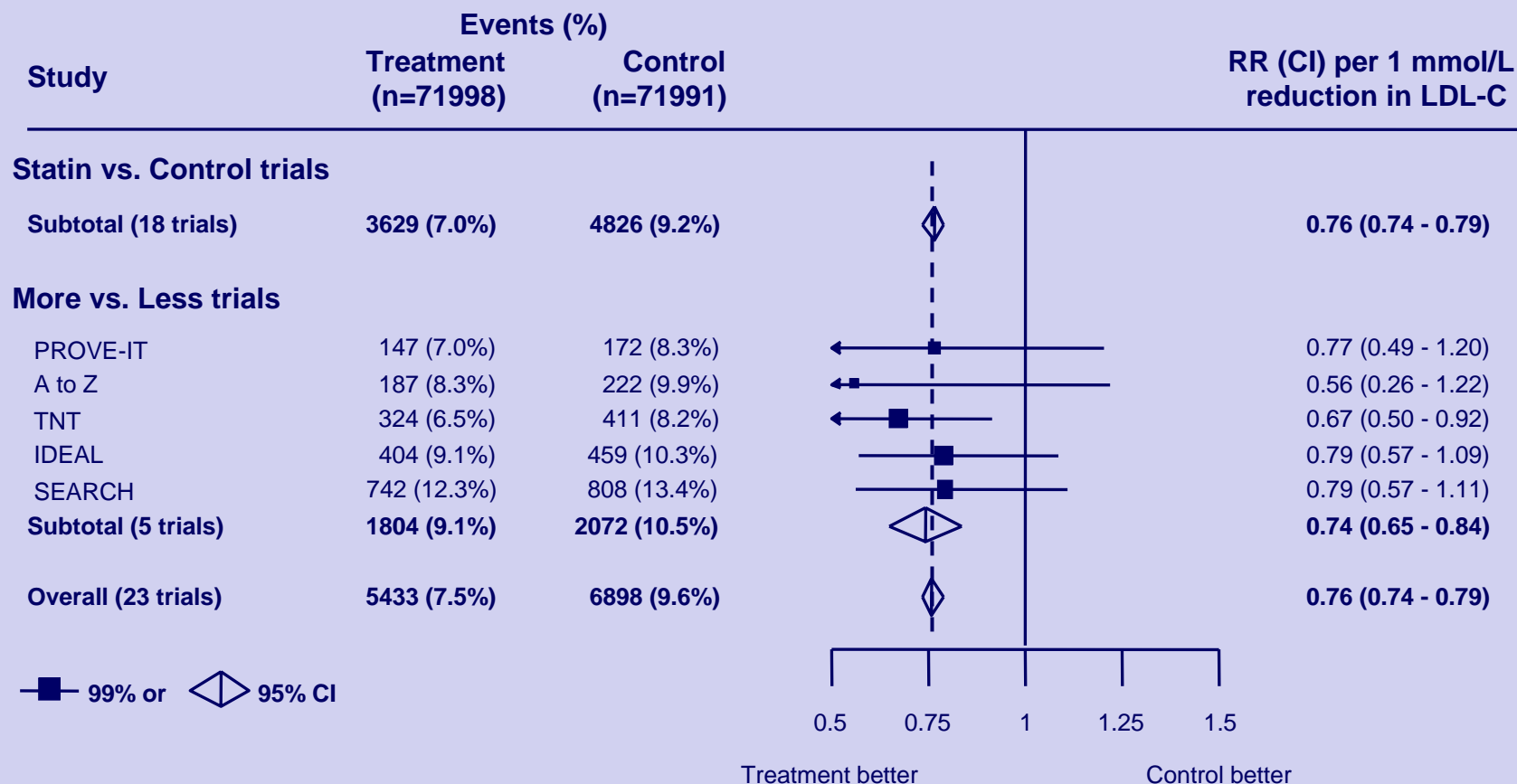
# CTT meta-analysis: Effects of STATIN on STROKE per mmol/L LDL-C reduction



Heterogeneity within more vs less trials:  $\chi^2_4 = 2.06$  (p=0.73)

Difference between more vs less and statin vs control trials:  $\chi^2_1 = 1.25$  (p=0.26)

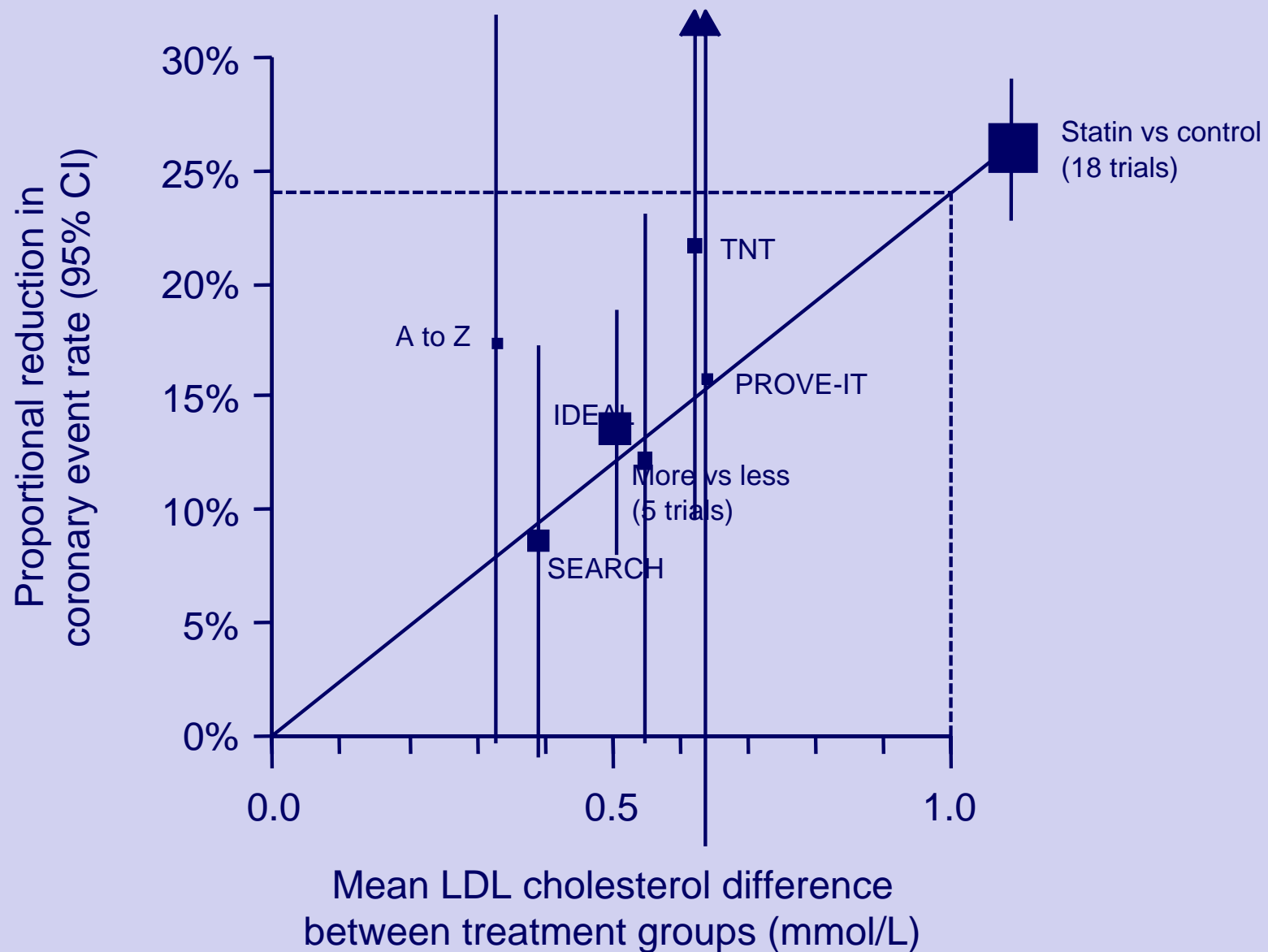
# CTT meta-analysis: Effects of STATIN on NON-FATAL MI or CHD DEATH per mmol/l LDL-C reduction



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)

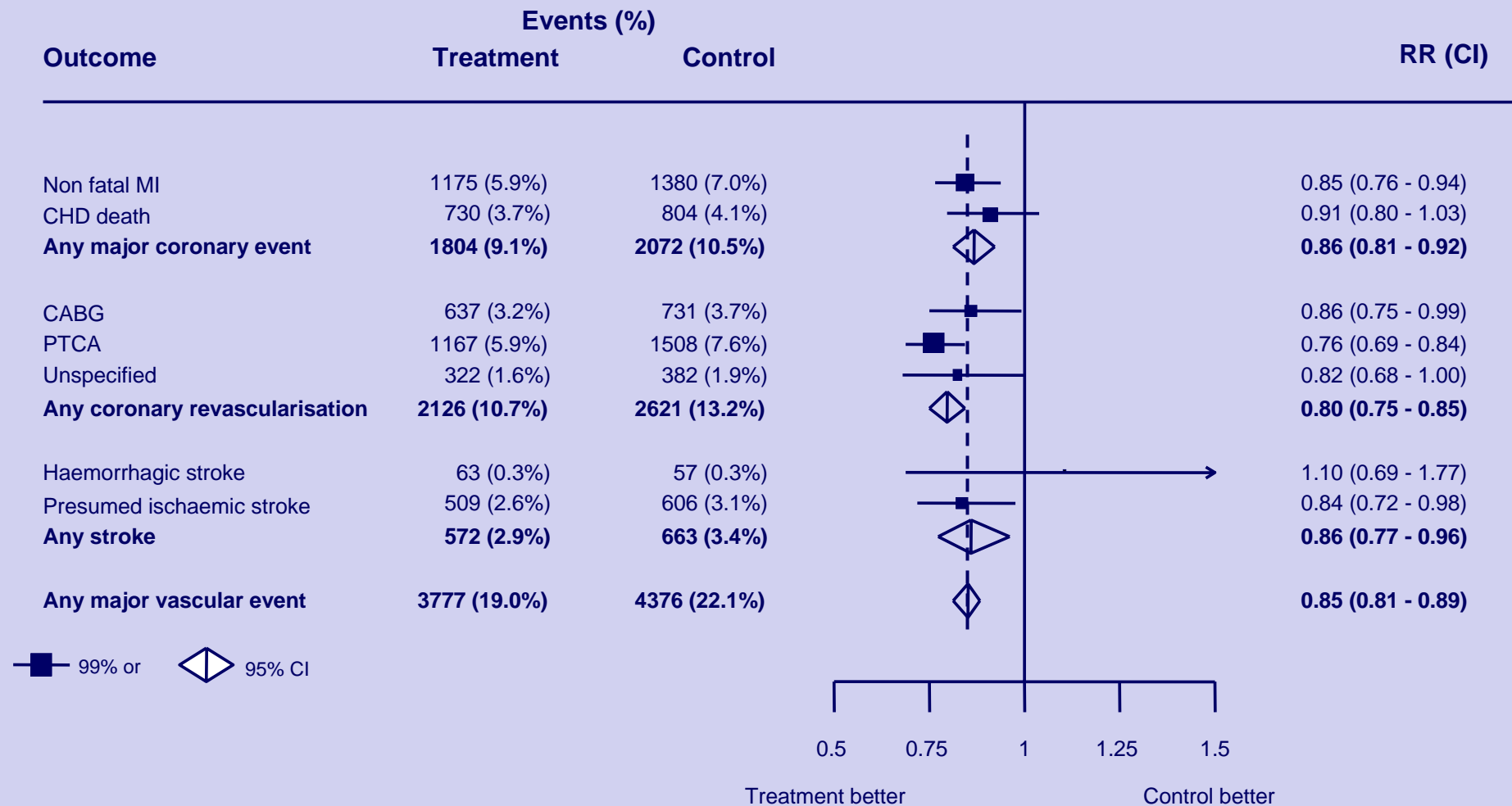
# CTT meta-analysis: Proportional reduction in NON-FATAL MI or CHD DEATH versus absolute LDL-C reduction



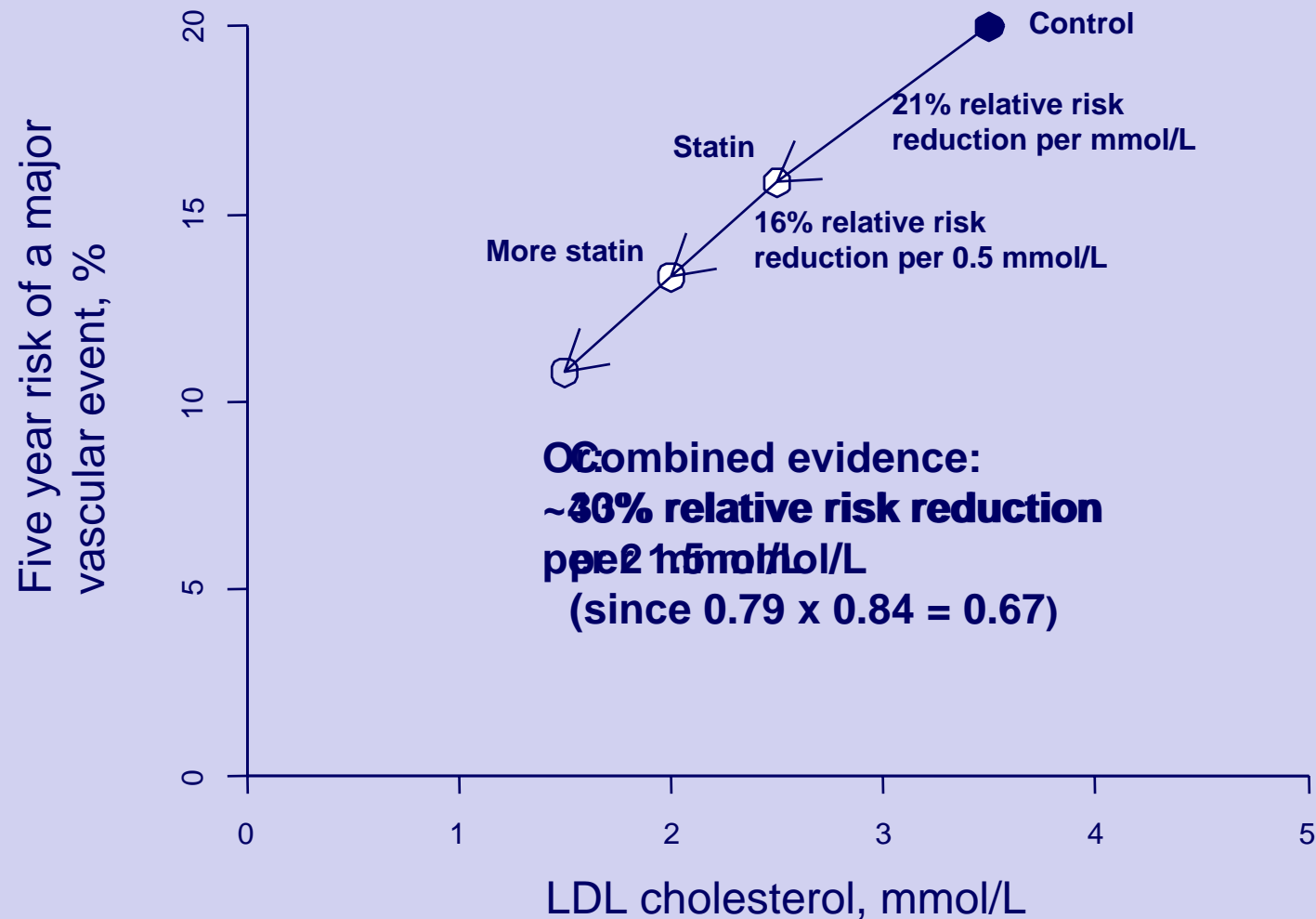
# CTT meta-analysis: Effects of MORE vs LESS STATIN

## C) on MAJOR VASCULAR EVENTS

(0.5 mmol/l lower LDL-C)



# 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

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Homocysteine-lowering comparison:

Folic acid 2mg plus vitamin B12 1mg daily	vs	Placebo tablets
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Mean (SD) duration: 6.7 (1.5) years

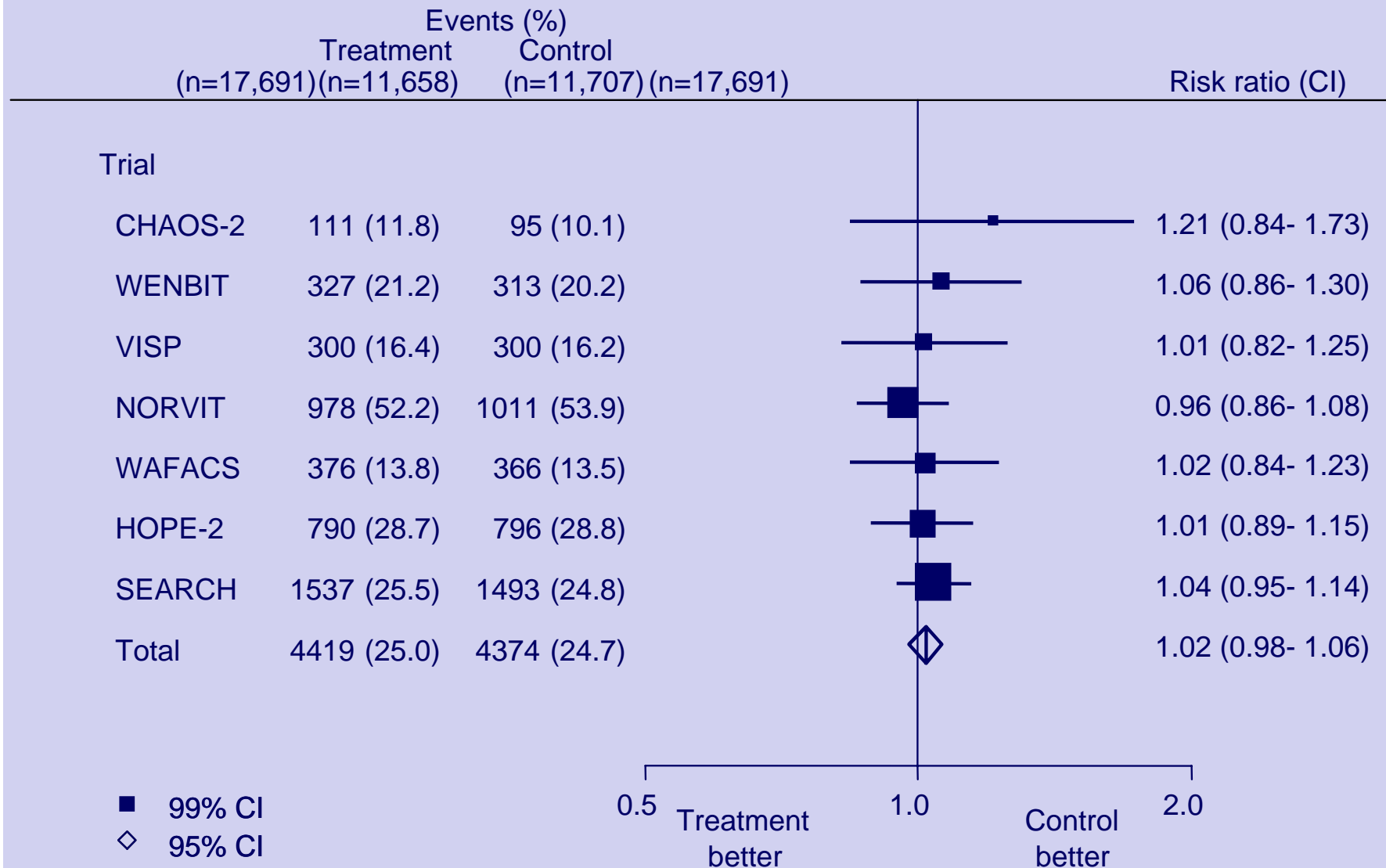
# HOMOCYSTEINE with allocation to FOLATE/B12 versus placebo

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

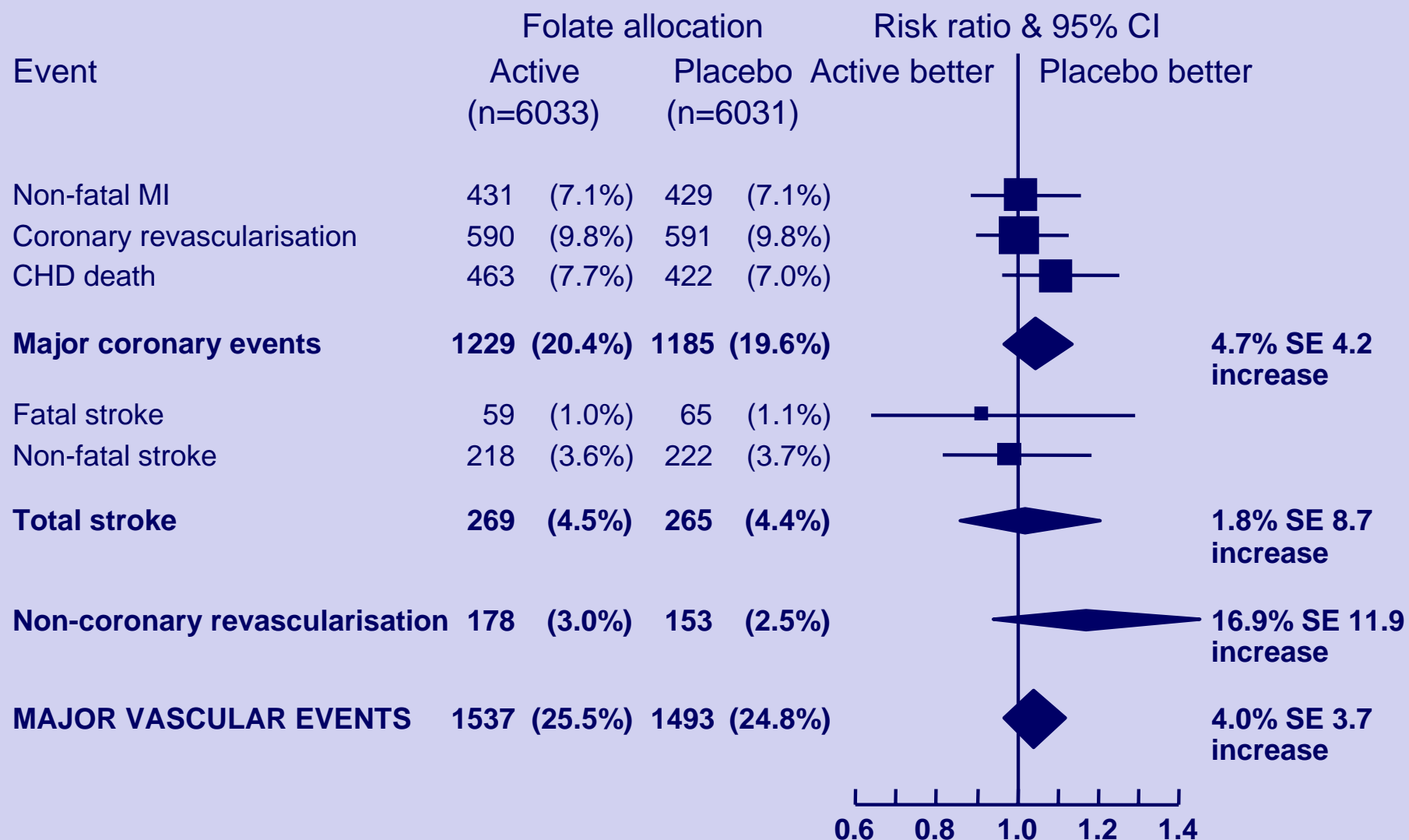
	Reduction	
	$\mu\text{mol/l}$	percent
Month 4	4.2	31%
Year 1	4.0	30%
Year 5	3.7	27%
AVERAGE	3.8	28%



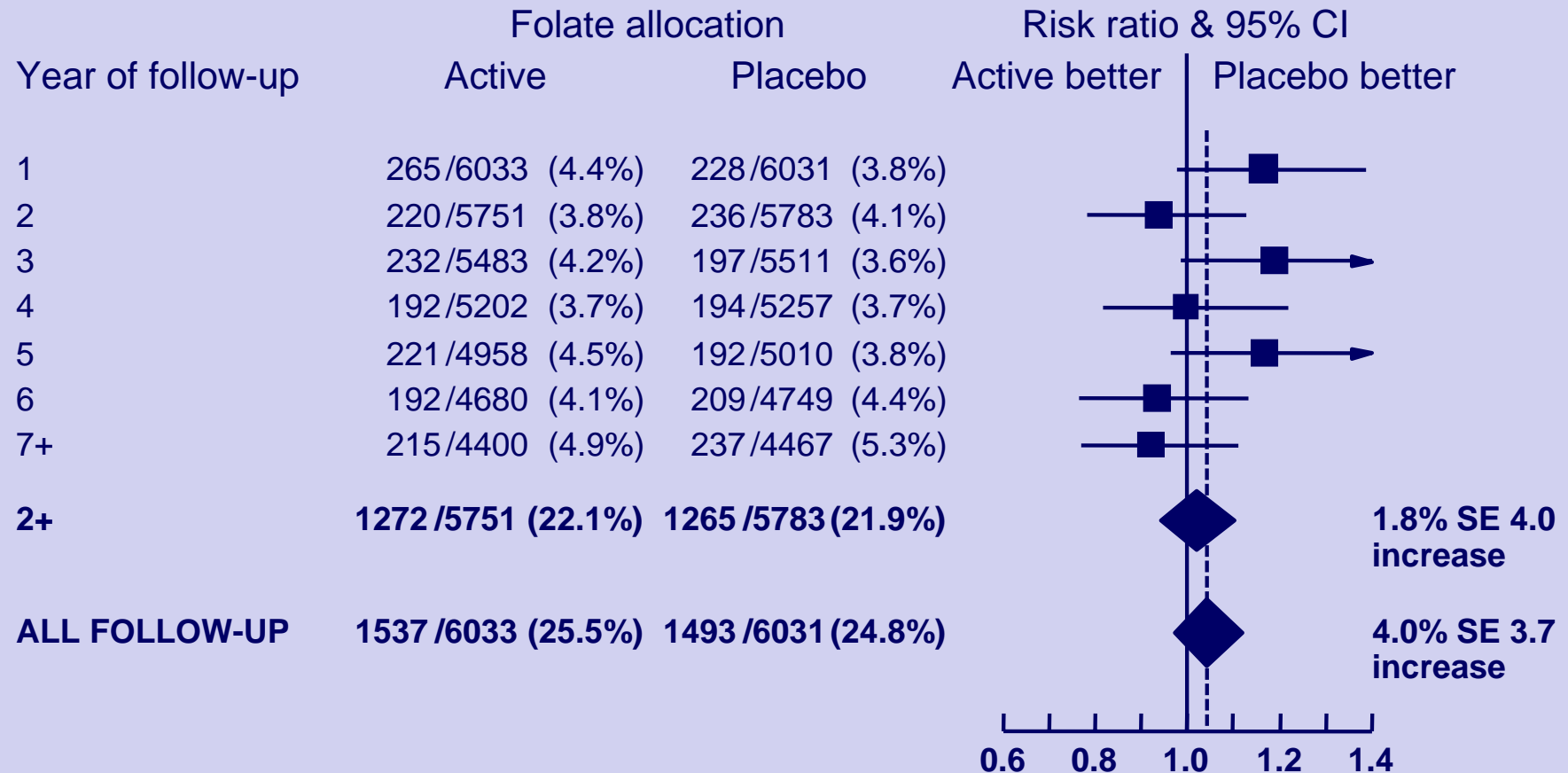
# BVTT meta-analysis: Effects of FOLATE on MAJOR VASCULAR EVENTS by trial



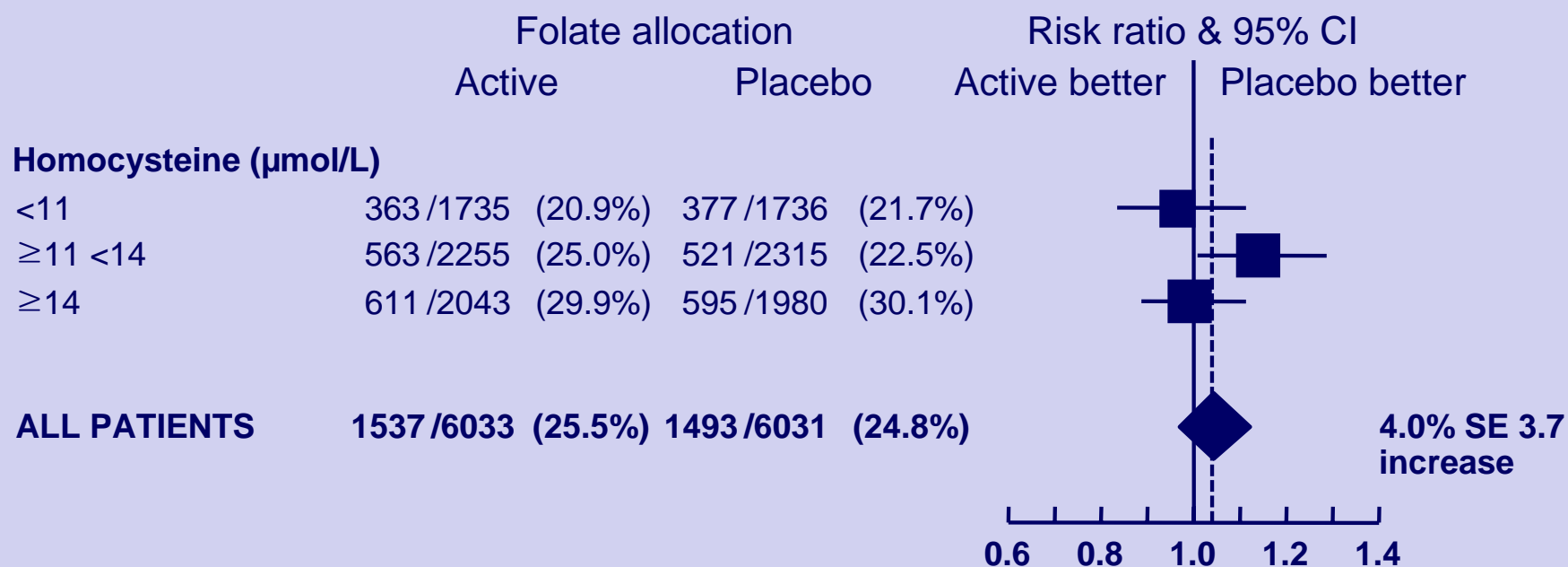
## SEARCH: FOLATE/B12 on MAJOR VASCULAR EVENTS



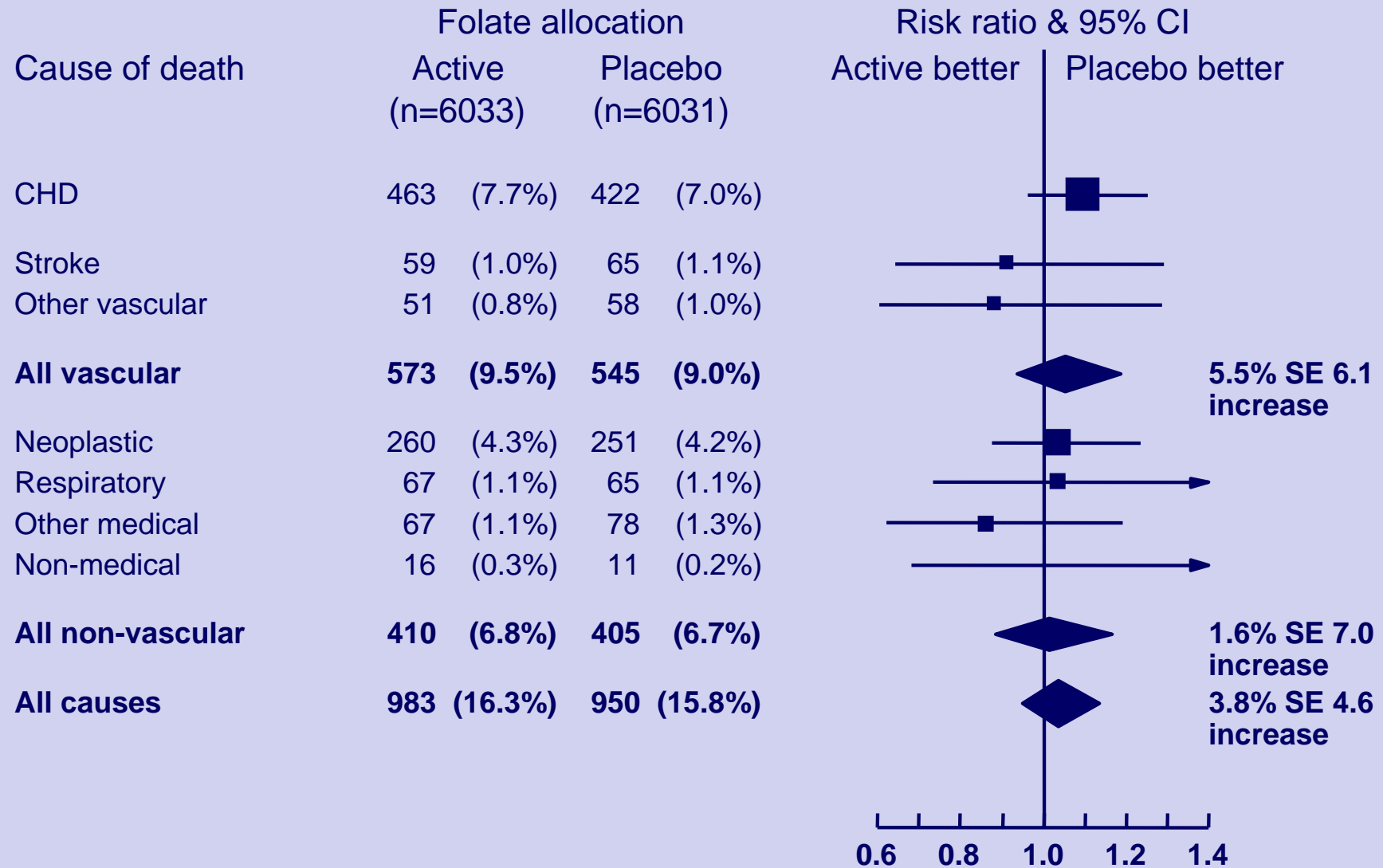
# SEARCH: FOLATE/B12 on MAJOR VASCULAR EVENTS by year of follow-up



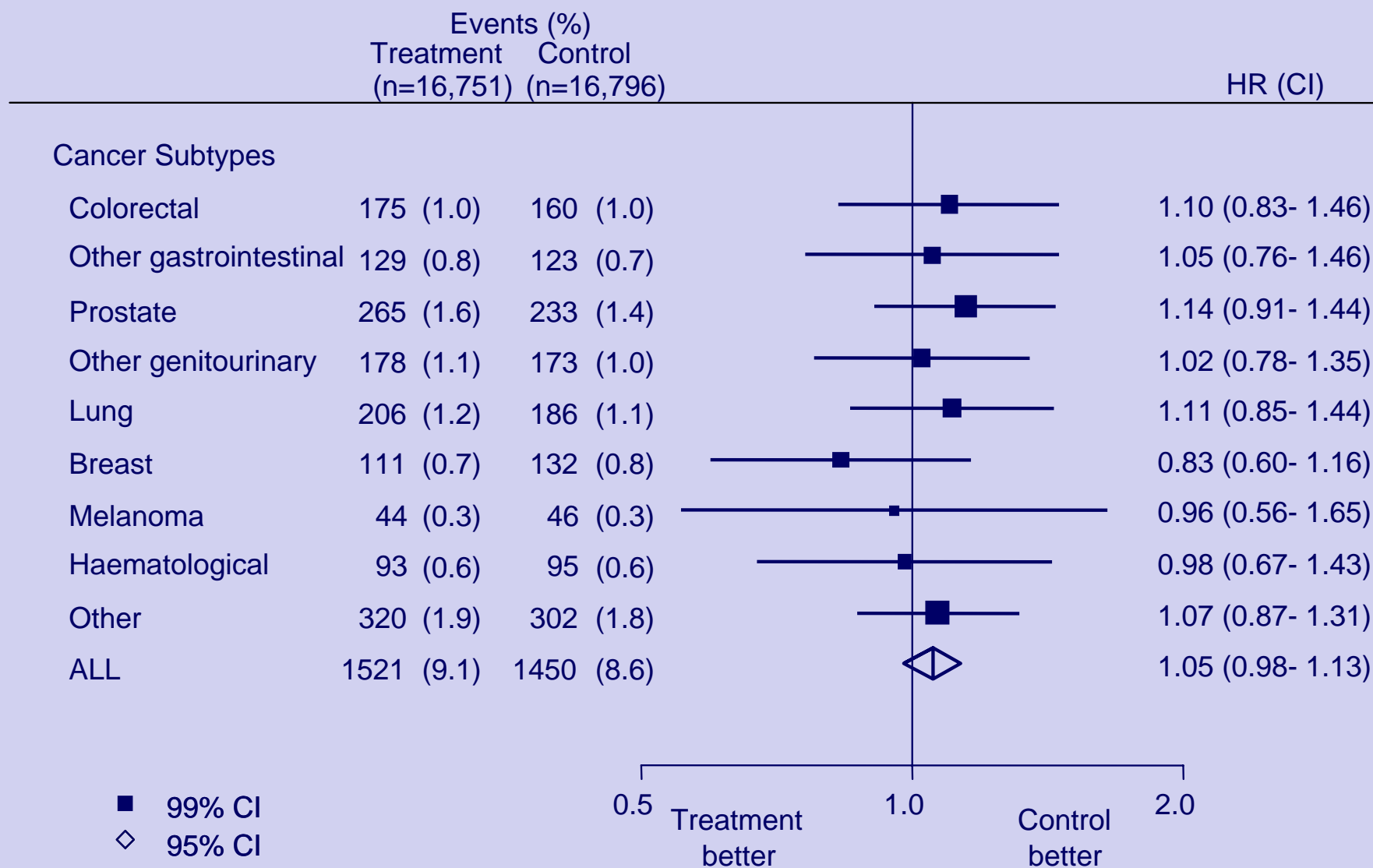
# SEARCH: FOLATE/B12 on MAJOR VASCULAR EVENTS by baseline HOMOCYSTEINE



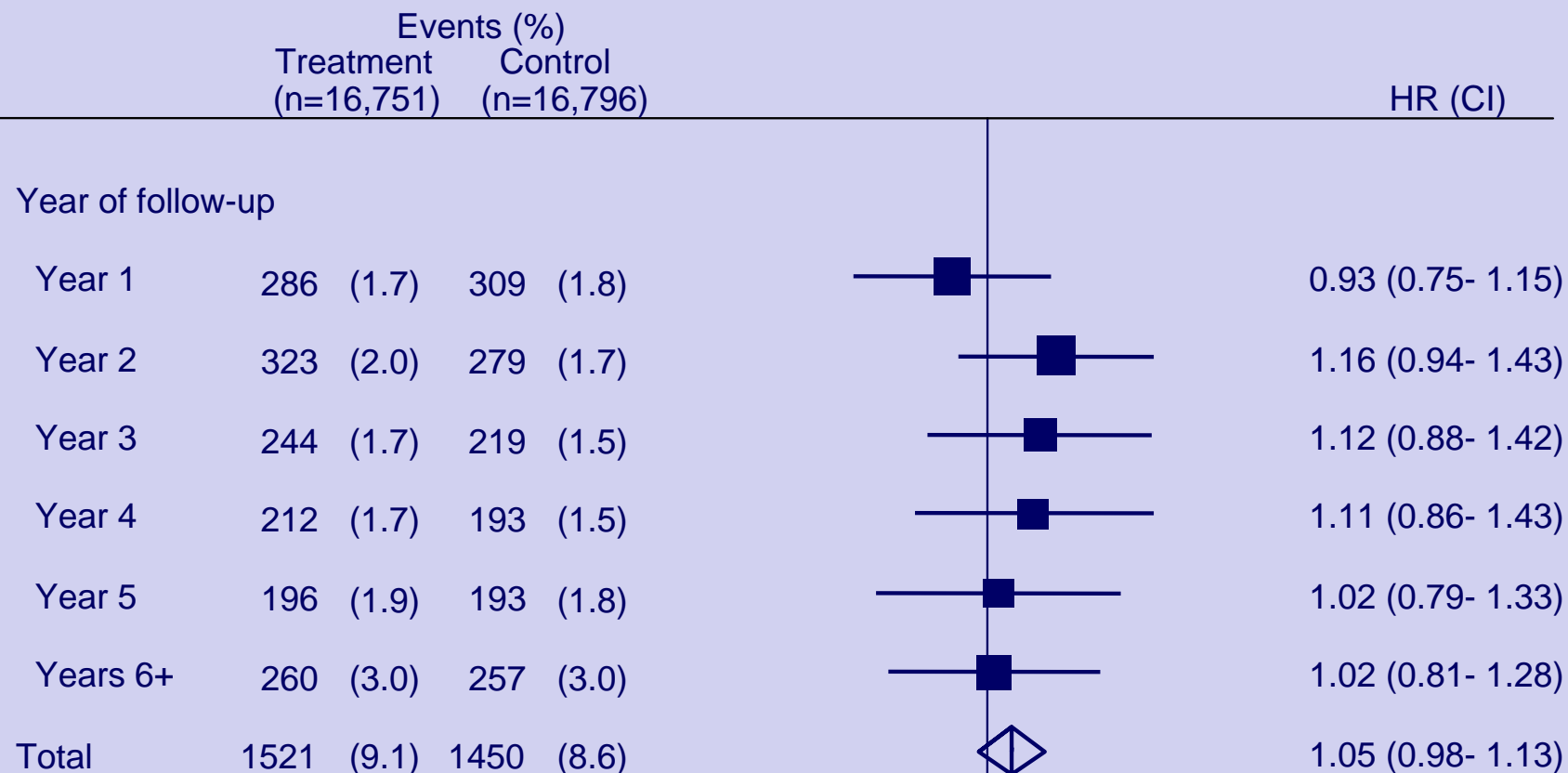
## SEARCH: Effects of FOLATE/B12 on MORTALITY



## 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