SEARCH

Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine

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<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: 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)

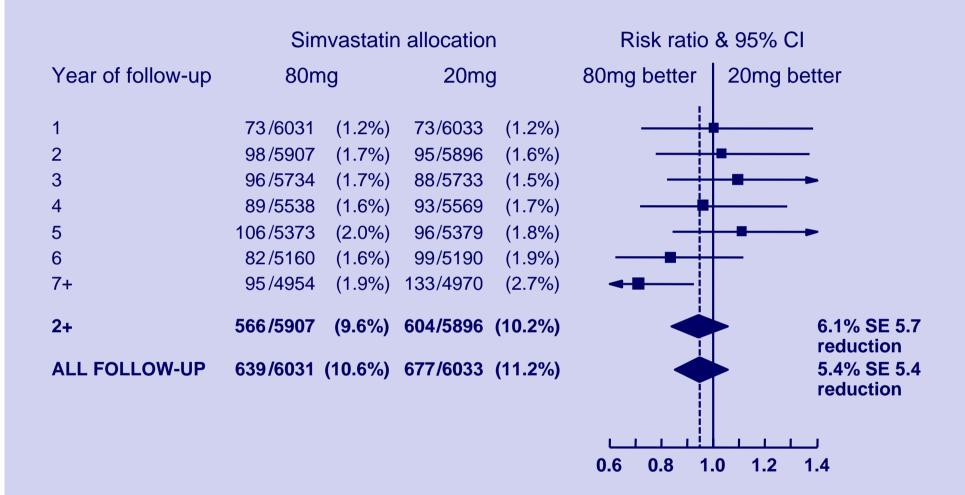
Total 53 3

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

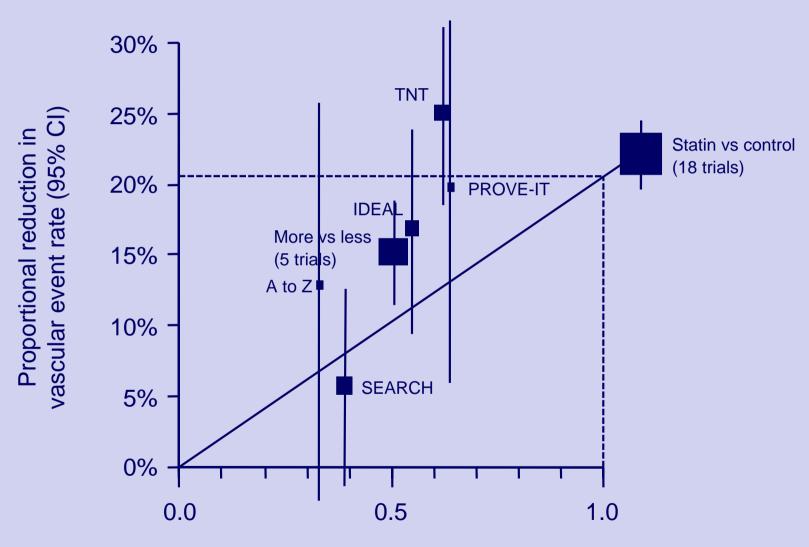
SEARCH: Effects of more vs less STATIN on MORTALITY

Cause of death	80	Simvastatin 80mg (n=6031)		eation Omg 6033)	Risk ratio & 95% CI 80mg better 20mg better	
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: Effects of more vs less STATIN on ANY CANCER by year of follow-up

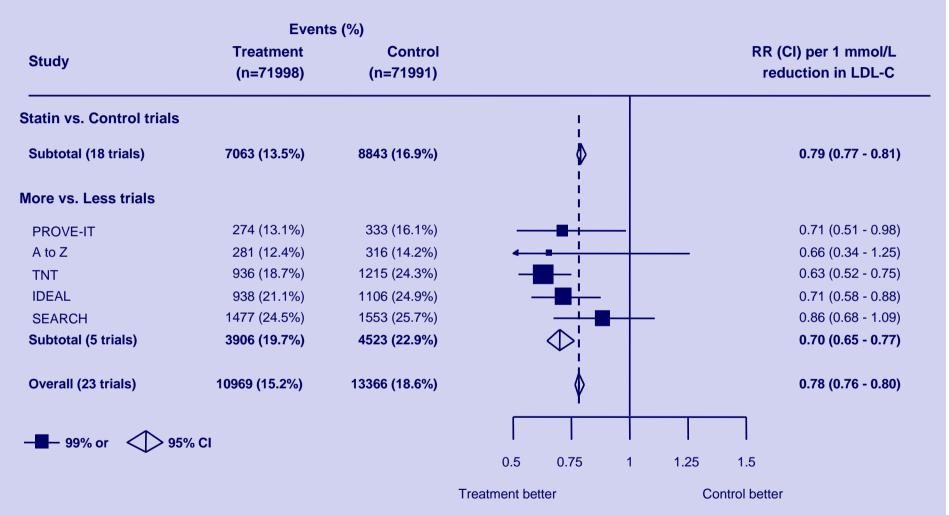


CTT meta-analysis: Proportional reduction in MAJOR VASCULAR EVENTS versus absolute LDL-C reduction



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

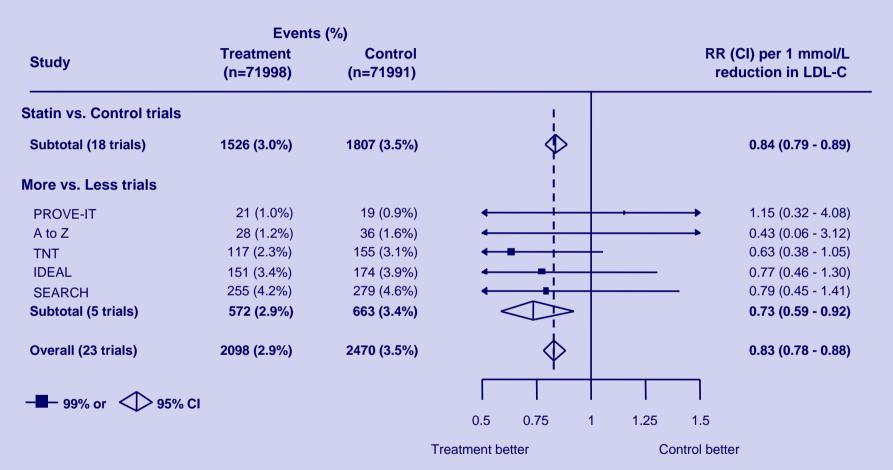
CTT meta-analysis: Effects of STATIN on MAJOR VASCULAR EVENT per mmol/l LDL-C reduction



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

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

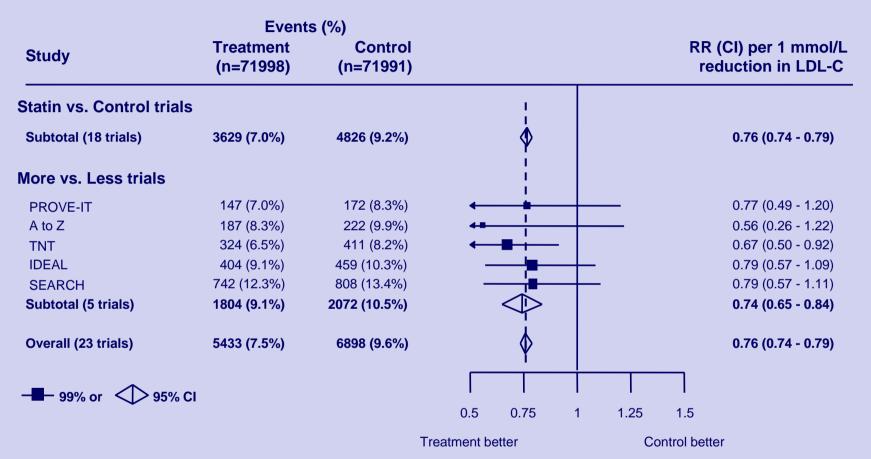
CTT meta-analysis: Effects of STATIN on STROKE per mmol/l LDL-C reduction



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)

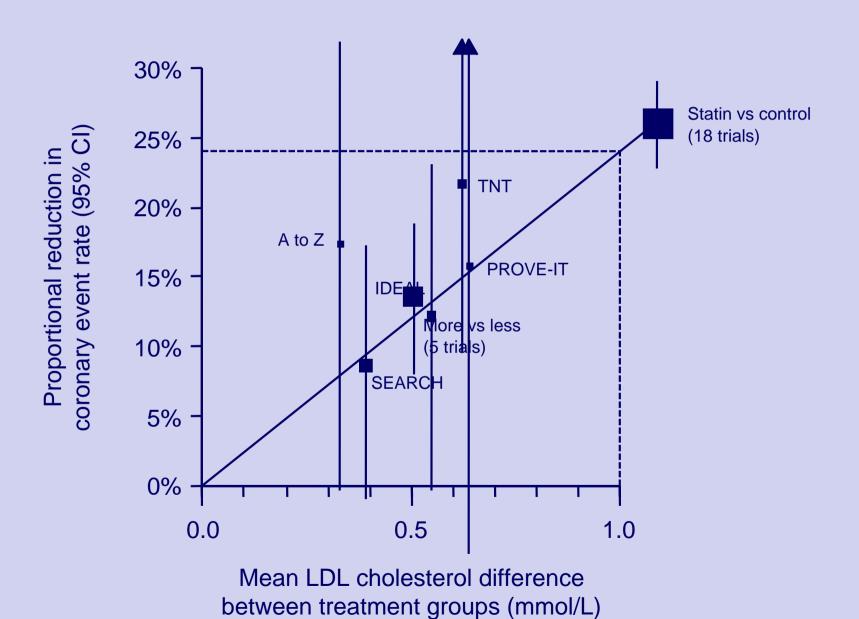
CTT meta-analysis: Effects of STATIN on NON-FATAL MI or CHD DEATH per mmol/l LDL-C reduction



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

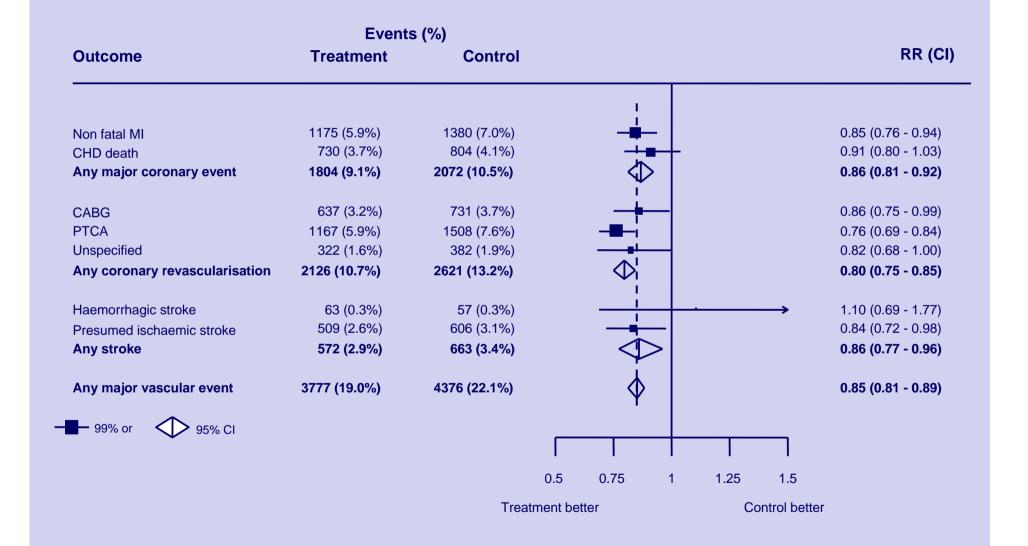
Difference between more vs less and statin vs control trials: $\chi_1^2 = 0.23$ (p=0.63)

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

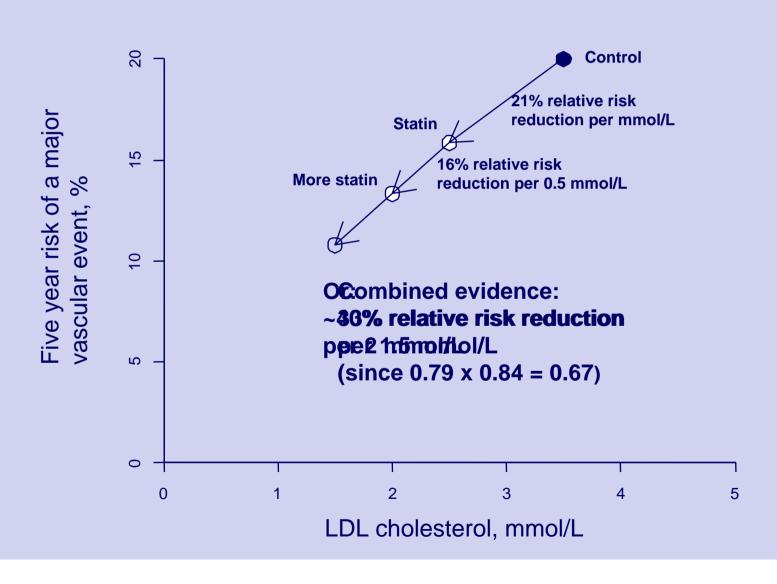


CTT meta-analysis: Effects of MORE vs LESS STATIN C) on MAJOR VASCULAR EVENTS

(0.5 mmol/l lower LDL-



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

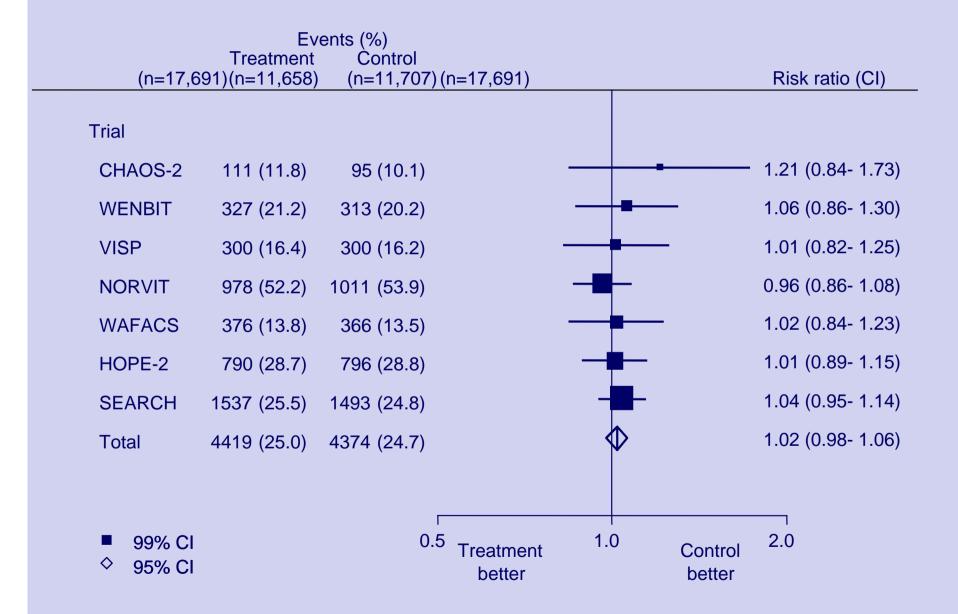
Mean (SD) duration: 6.7 (1.5) years

HOMOCYSTEINE with allocation to FOLATE/B12 versus placebo

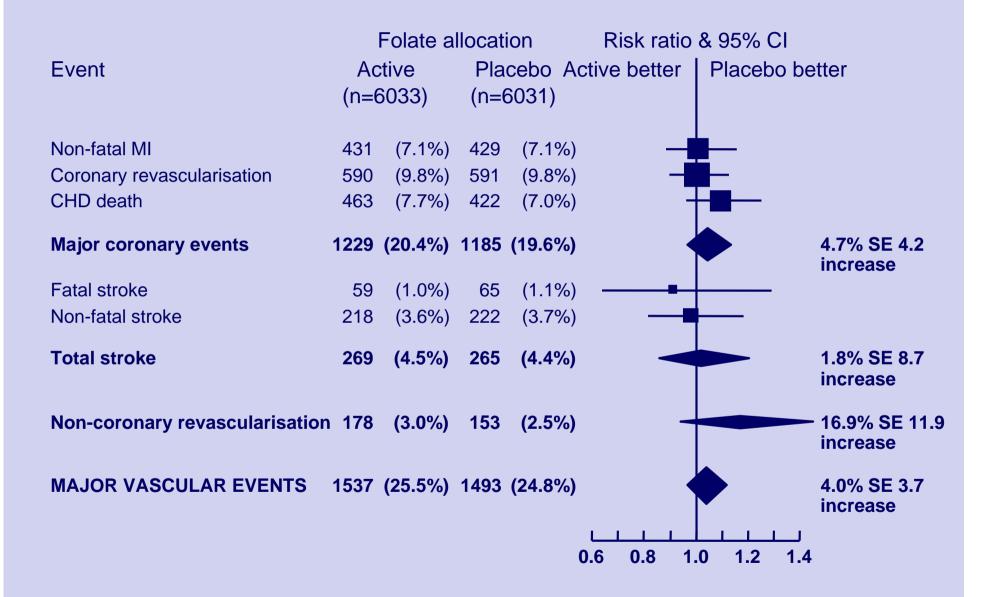
Mean (SD) baseline: 13.5 (5) µmol/l

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

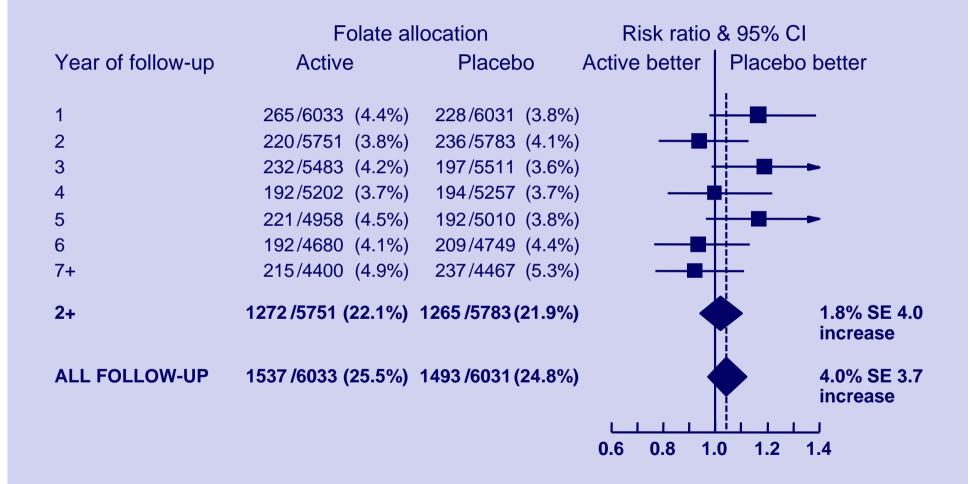
BVTT meta-analysis: Effects of FOLATE on MAJOR VASCULAR EVENTS by trial



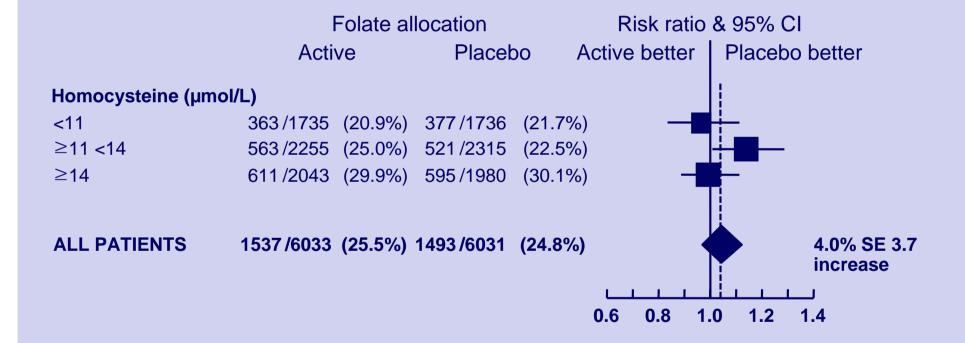
SEARCH: FOLATE/B12 on MAJOR VASCULAR EVENTS



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



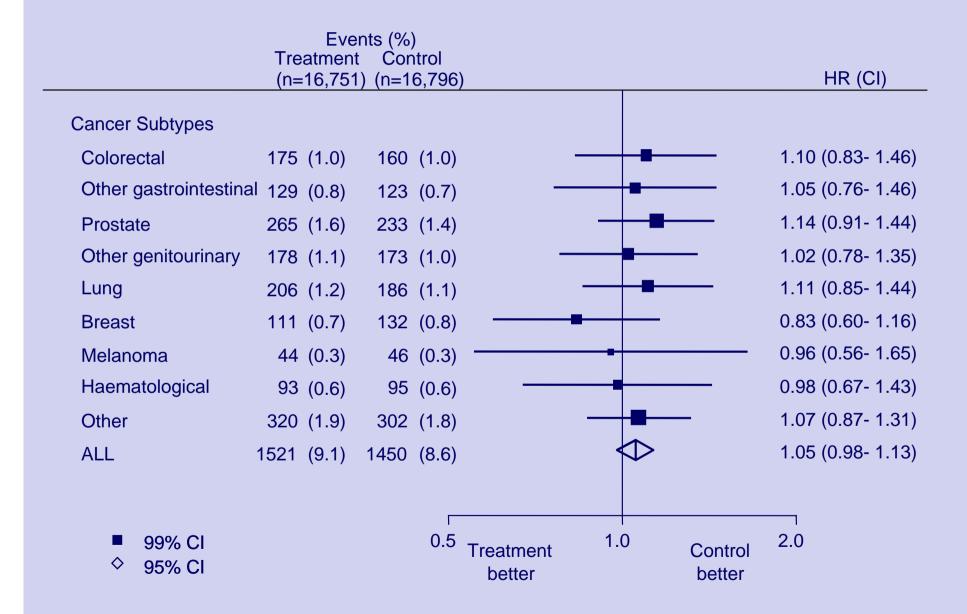
SEARCH: FOLATE/B12 on MAJOR VASCULAR EVENTS by baseline HOMOCYSTEINE



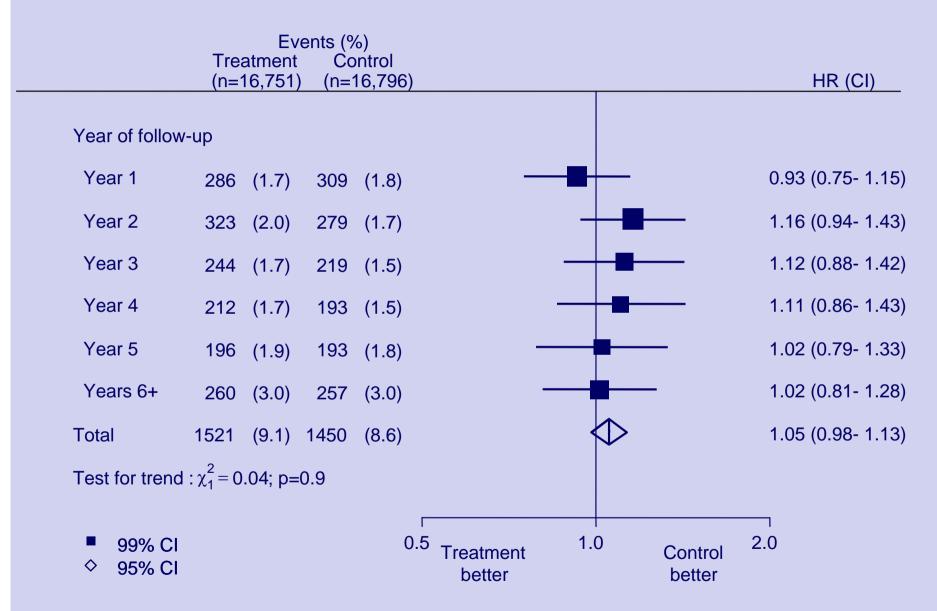
SEARCH: Effects of FOLATE/B12 on MORTALITY

	Folate allocation		Risk ratio & 95% CI	
Cause of death	Active (n=6033)	Placebo (n=6031)	Active better Placel	oo 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%	6) 545 (9.0%)		5.5% SE 6.1 increase
Neoplastic	260 (4.3%	%) 251 (4.2%)		IIICIease
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%	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



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