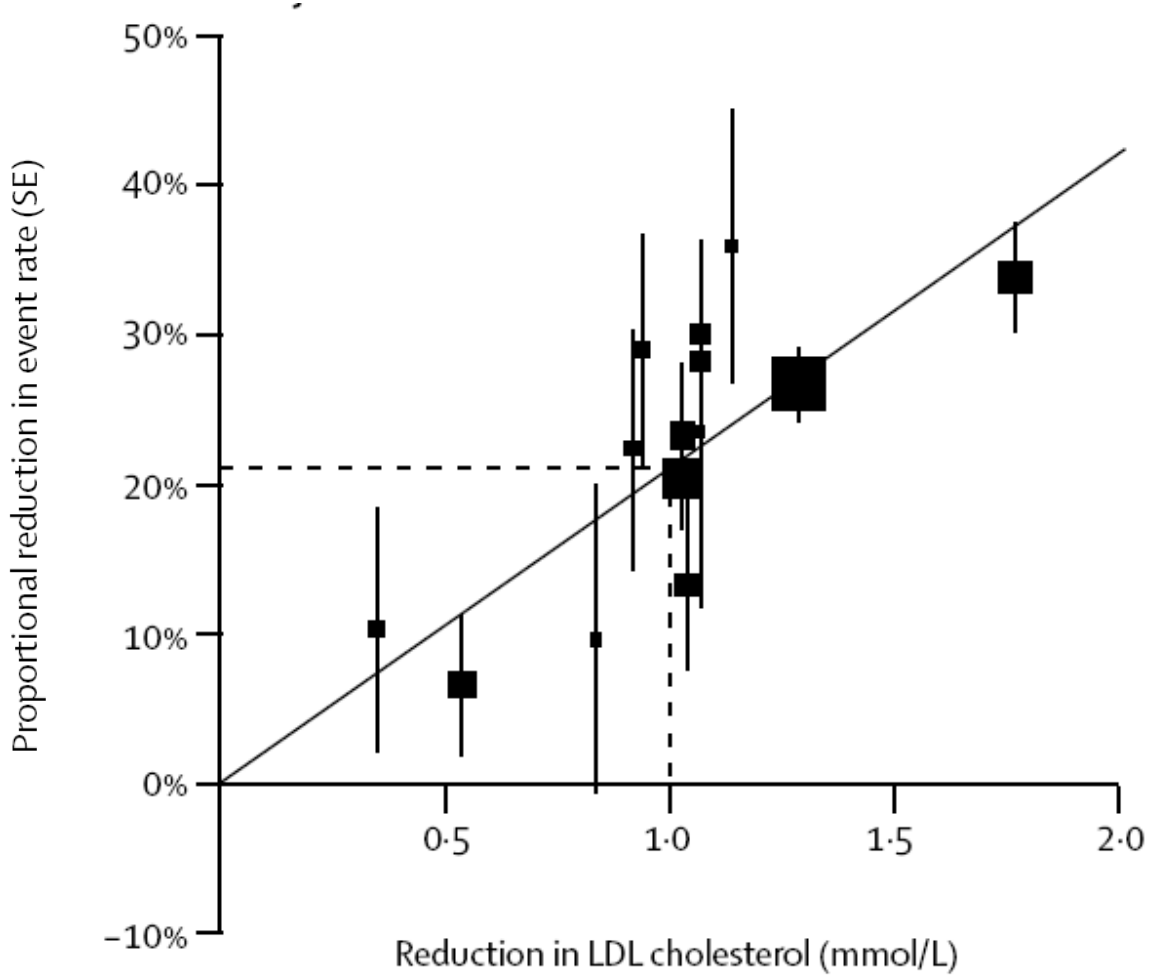
Statins for primary prevention

Colin Baigent

Professor of Epidemiology

CTSU, University of Oxford

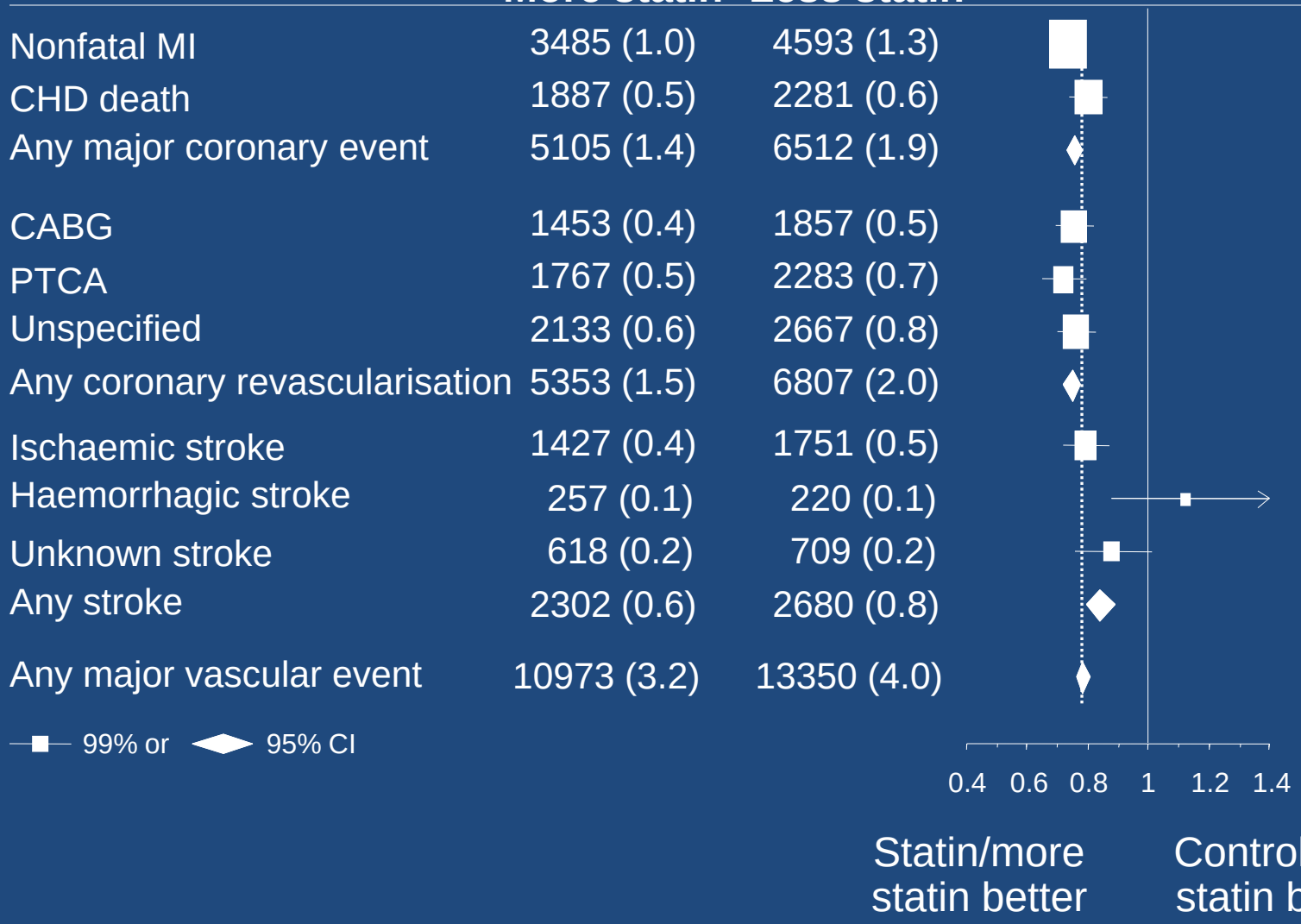
First CTT cycle: Relation between the proportional reduction in MAJOR VASCULAR EVENTS and mean absolute LDL-C reduction at 1 year in 14 statin trials



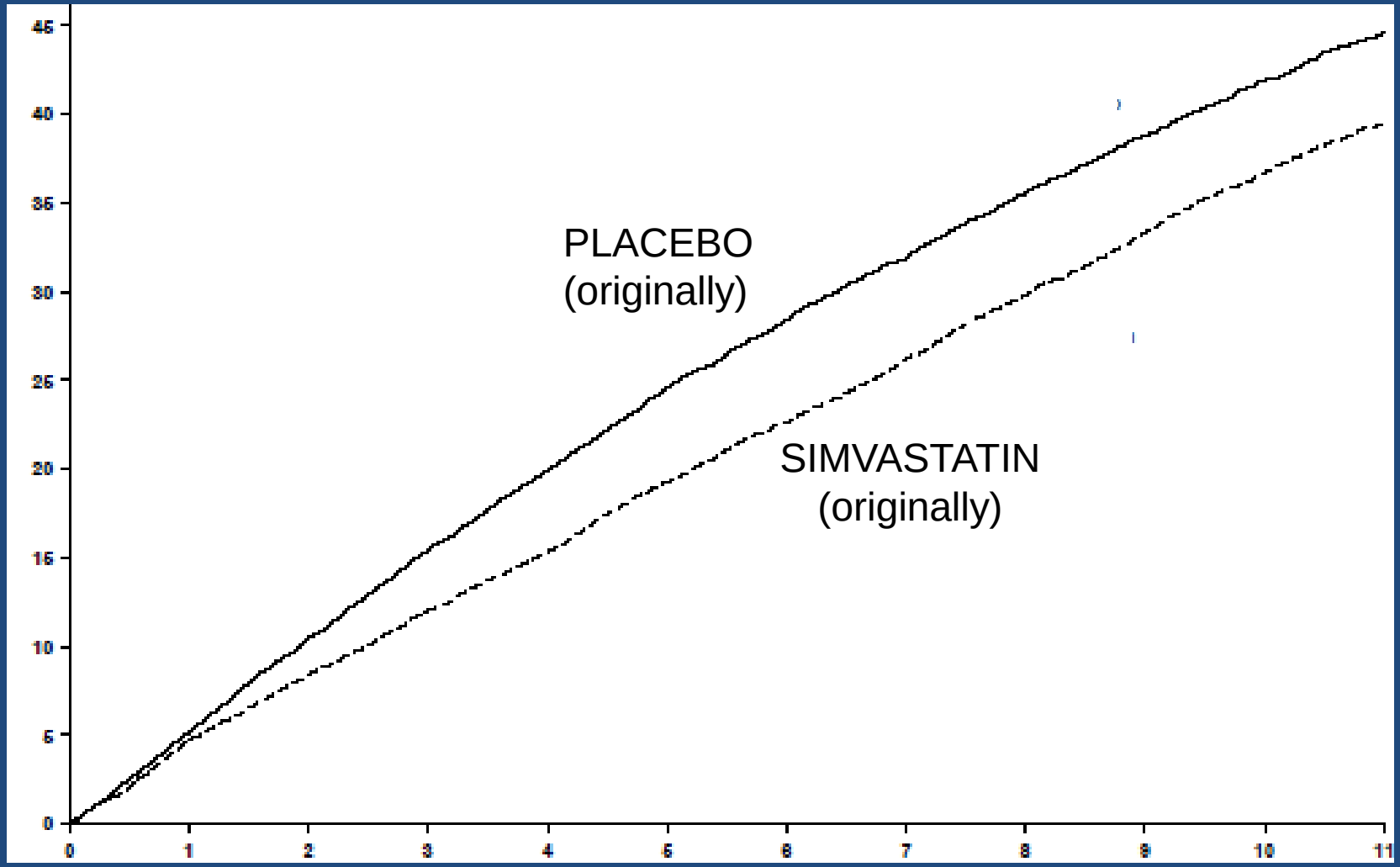
Lancet 2005; 366: 1267–78

Proportional effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol

	No. of events (% pa) Statin/ More statin	Control/ Less statin	Relative risk (CI)
Nonfatal MI	3485 (1.0)	4593 (1.3)	0.73 (0.69 - 0.78)
CHD death	1887 (0.5)	2281 (0.6)	0.80 (0.74 - 0.87)
Any major coronary event	5105 (1.4)	6512 (1.9)	0.76 (0.73 - 0.78)
CABG	1453 (0.4)	1857 (0.5)	0.75 (0.69 - 0.82)
PTCA	1767 (0.5)	2283 (0.7)	0.72 (0.65 - 0.80)
Unspecified	2133 (0.6)	2667 (0.8)	0.76 (0.70 - 0.82)
Any coronary revascularisation	5353 (1.5)	6807 (2.0)	0.75 (0.72 - 0.78)
Ischaemic stroke	1427 (0.4)	1751 (0.5)	0.79 (0.72 - 0.87)
Haemorrhagic stroke	257 (0.1)	220 (0.1)	1.12 (0.88 - 1.43)
Unknown stroke	618 (0.2)	709 (0.2)	0.88 (0.76 - 1.01)
Any stroke	2302 (0.6)	2680 (0.8)	0.84 (0.79 - 0.89)
Any major vascular event	10973 (3.2)	13350 (4.0)	0.78 (0.76 - 0.80)



HPS: In-trial and post-trial effects on MVE risk of 5-year allocation to simvastatin vs placebo



Lancet 2011

Cochrane Library press release (2011)

"Statins: Benefits Questionable In Low-Risk Patients

Cholesterol-lowering statins are first line treatments for heart patients and the benefits are well established

….. less evidence that statins are beneficial in those who have no history of CVD, given that the absolute numbers of people who benefit will inevitably be lower, and statins are recognised as having harmful effects in some people.

….Therefore, in people at low risk of heart disease, statins might do more harm than good."

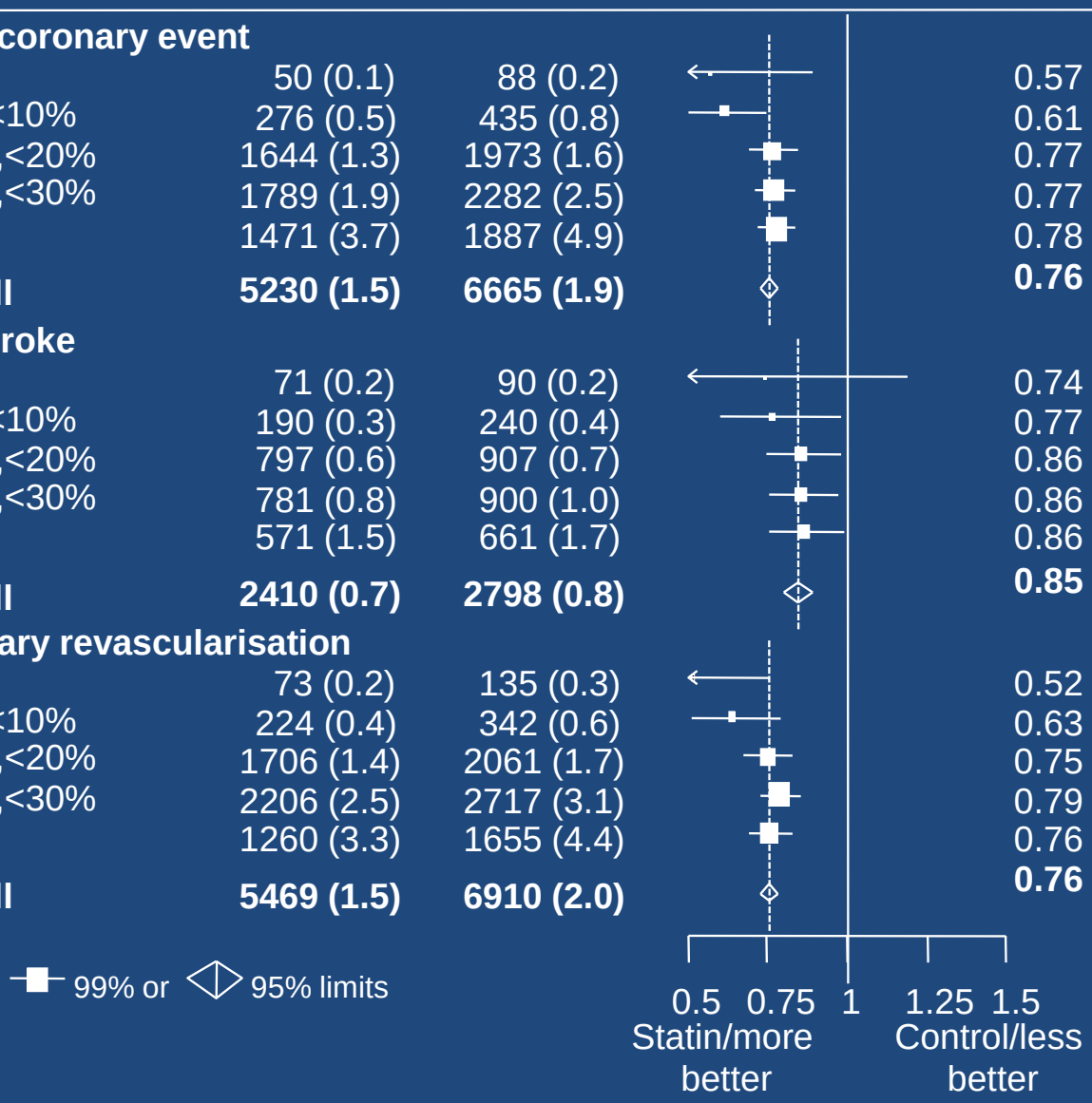
CTT meta-analysis: Effects on MAJOR VASCULAR EVENTS per mmol/L LDL-C reduction subdivided by RISK

5-year MVE risk at baseline	Events (% per annum) Statin/more	Control/less	RR (CI)	Trend test
<5%	167 (0.4)	254 (0.6)	0.62 (0.47 - 0.81)	
≥5%,<10%	604 (1.1)	847 (1.6)	0.69 (0.60 - 0.79)	
≥10%,<20%	3614 (3.0)	4195 (3.5)	0.79 (0.74 - 0.85)	χ^2_1=4.29
≥20%,<30%	4108 (4.7)	4919 (5.8)	0.81 (0.77 - 0.86)	(p=0.04)
≥30%	2787 (7.6)	3458 (9.8)	0.79 (0.74 - 0.84)	
Overall	**11280 (3.3)**	**13673 (4.0)**	**0.79 (0.77 - 0.81)** **p<0.0001**	

Lancet 2012

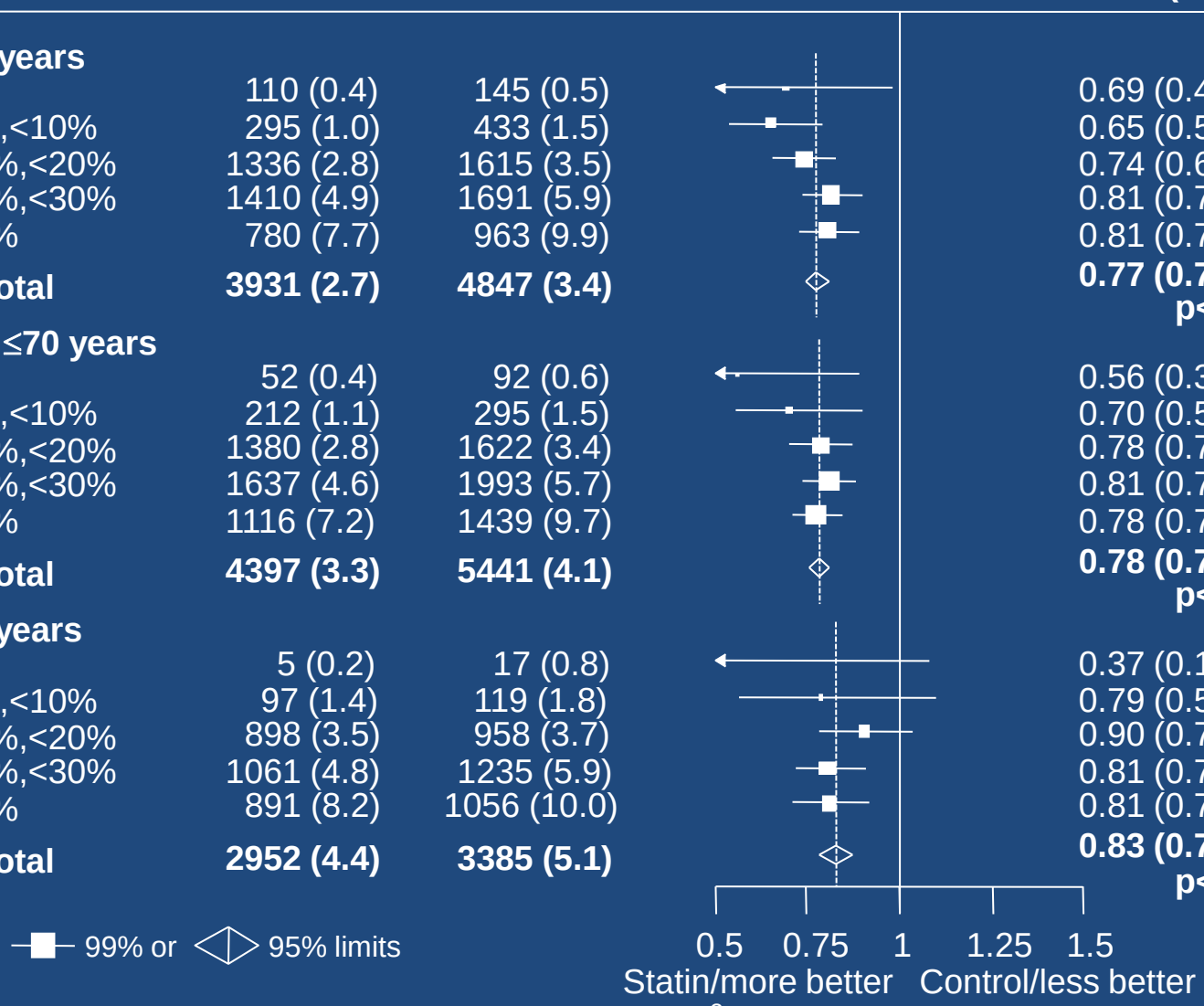
Proportional effects on components of MAJOR VASCULAR EVENT per mmol/L LDL-C reduction

5-year MVE risk at baseline	Events (% per annum) Statin/more	Control/less	RR (CI)	Trend test
Major coronary event				
<5%	50 (0.1)	88 (0.2)	0.57 (0.36 - 0.89)	
≥5%,<10%	276 (0.5)	435 (0.8)	0.61 (0.50 - 0.74)	
≥10%,<20%	1644 (1.3)	1973 (1.6)	0.77 (0.69 - 0.85)	χ^2_1=5.66
≥20%,<30%	1789 (1.9)	2282 (2.5)	0.77 (0.71 - 0.83)	(p=0.02)
≥30%	1471 (3.7)	1887 (4.9)	0.78 (0.72 - 0.84)	
Overall	**5230 (1.5)**	**6665 (1.9)**	**0.76 (0.73 - 0.79) p<0.0001**	
Any stroke				
<5%	71 (0.2)	90 (0.2)	0.74 (0.46 - 1.19)	
≥5%,<10%	190 (0.3)	240 (0.4)	0.77 (0.60 - 0.98)	
≥10%,<20%	797 (0.6)	907 (0.7)	0.86 (0.75 - 0.98)	χ^2_1=1.03
≥20%,<30%	781 (0.8)	900 (1.0)	0.86 (0.75 - 0.97)	(p=0.3)
≥30%	571 (1.5)	661 (1.7)	0.86 (0.75 - 0.99)	
Overall	**2410 (0.7)**	**2798 (0.8)**	**0.85 (0.80 - 0.89) p<0.0001**	
Coronary revascularisation				
<5%	73 (0.2)	135 (0.3)	0.52 (0.35 - 0.75)	
≥5%,<10%	224 (0.4)	342 (0.6)	0.63 (0.51 - 0.79)	
≥10%,<20%	1706 (1.4)	2061 (1.7)	0.75 (0.67 - 0.83)	χ^2_1=4.93
≥20%,<30%	2206 (2.5)	2717 (3.1)	0.79 (0.73 - 0.86)	(p=0.03)
≥30%	1260 (3.3)	1655 (4.4)	0.76 (0.69 - 0.83)	
Overall	**5469 (1.5)**	**6910 (2.0)**	**0.76 (0.73 - 0.79) p<0.0001**	



Proportional effects on MAJOR VASCULAR EVENTS per mmol/L LDL-C reduction, by age at baseline

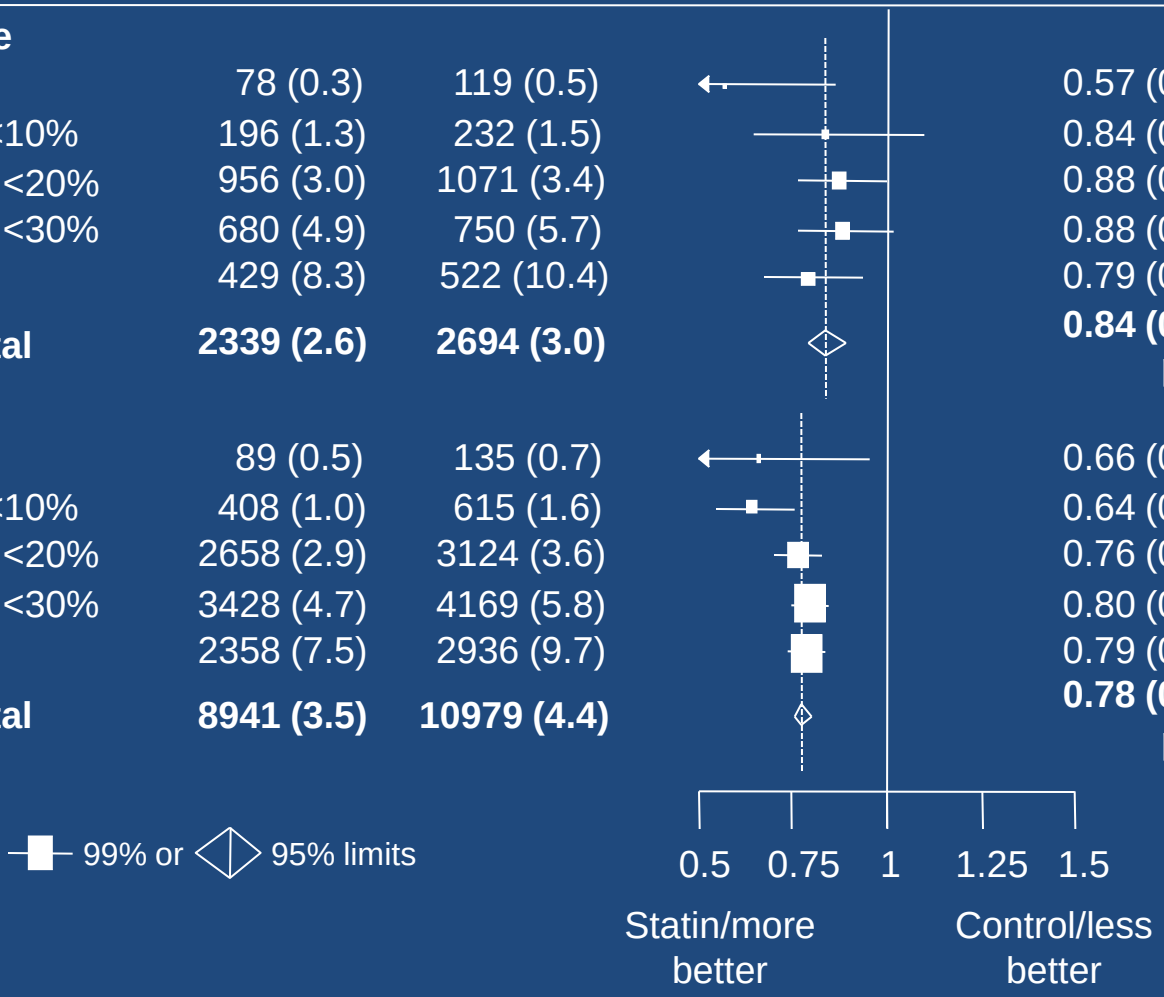
5-year MVE risk at baseline	Events (% per annum) Statin/more	Control/less	RR (CI)	Trend test
≤60 years				
<5%	110 (0.4)	145 (0.5)	0.69 (0.49 - 0.98)	
≥5%,<10%	295 (1.0)	433 (1.5)	0.65 (0.54 - 0.79)	
≥10%,<20%	1336 (2.8)	1615 (3.5)	0.74 (0.66 - 0.83)	χ^2_1=7.37
≥20%,<30%	1410 (4.9)	1691 (5.9)	0.81 (0.74 - 0.90)	(p=0.007)
≥30%	780 (7.7)	963 (9.9)	0.81 (0.73 - 0.89)	
Subtotal	**3931 (2.7)**	**4847 (3.4)**	**0.77 (0.74 - 0.81) p<0.0001**	
>60, ≤70 years				
<5%	52 (0.4)	92 (0.6)	0.56 (0.35 - 0.89)	
≥5%,<10%	212 (1.1)	295 (1.5)	0.70 (0.55 - 0.90)	
≥10%,<20%	1380 (2.8)	1622 (3.4)	0.78 (0.70 - 0.87)	χ^2_1=0.96
≥20%,<30%	1637 (4.6)	1993 (5.7)	0.81 (0.74 - 0.89)	(p=0.3)
≥30%	1116 (7.2)	1439 (9.7)	0.78 (0.71 - 0.85)	
Subtotal	**4397 (3.3)**	**5441 (4.1)**	**0.78 (0.75 - 0.81) p<0.0001**	
>70 years				
<5%	5 (0.2)	17 (0.8)	0.37 (0.13 - 1.08)	
≥5%,<10%	97 (1.4)	119 (1.8)	0.79 (0.56 - 1.10)	
≥10%,<20%	898 (3.5)	958 (3.7)	0.90 (0.79 - 1.04)	χ^2_1=0.42
≥20%,<30%	1061 (4.8)	1235 (5.9)	0.81 (0.72 - 0.91)	(p=0.5)
≥30%	891 (8.2)	1056 (10.0)	0.81 (0.71 - 0.91)	
Subtotal	**2952 (4.4)**	**3385 (5.1)**	**0.83 (0.78 - 0.87) p<0.0001**	



Test for trend in overall effects across age groups: χ^2_1=3.29(p=0.1)

Proportional effects on MAJOR VASCULAR EVENTS per mmol/L LDL-C reduction, by gender

5-year MVE risk at baseline	Events (% per annum) Statin/more	Control/less	RR (CI)	Trend test
Female				
<5%	78 (0.3)	119 (0.5)	0.57 (0.38 - 0.86)	
≥5%,<10%	196 (1.3)	232 (1.5)	0.84 (0.64 - 1.10)	
≥10%,<20%	956 (3.0)	1071 (3.4)	0.88 (0.77 - 1.00)	χ^2_1=0.23
≥20%,<30%	680 (4.9)	750 (5.7)	0.88 (0.76 - 1.02)	(p=0.6)
≥30%	429 (8.3)	522 (10.4)	0.79 (0.67 - 0.94)	
Subtotal	**2339 (2.6)**	**2694 (3.0)**	**0.84 (0.79 - 0.89) p<0.0001**	
Male				
<5%	89 (0.5)	135 (0.7)	0.66 (0.46 - 0.95)	
≥5%,<10%	408 (1.0)	615 (1.6)	0.64 (0.55 - 0.75)	
≥10%,<20%	2658 (2.9)	3124 (3.6)	0.76 (0.70 - 0.83)	χ^2_1=6.73
≥20%,<30%	3428 (4.7)	4169 (5.8)	0.80 (0.75 - 0.85)	(p=0.009)
≥30%	2358 (7.5)	2936 (9.7)	0.79 (0.74 - 0.84)	
Subtotal	**8941 (3.5)**	**10979 (4.4)**	**0.78 (0.76 - 0.80) p<0.0001**	



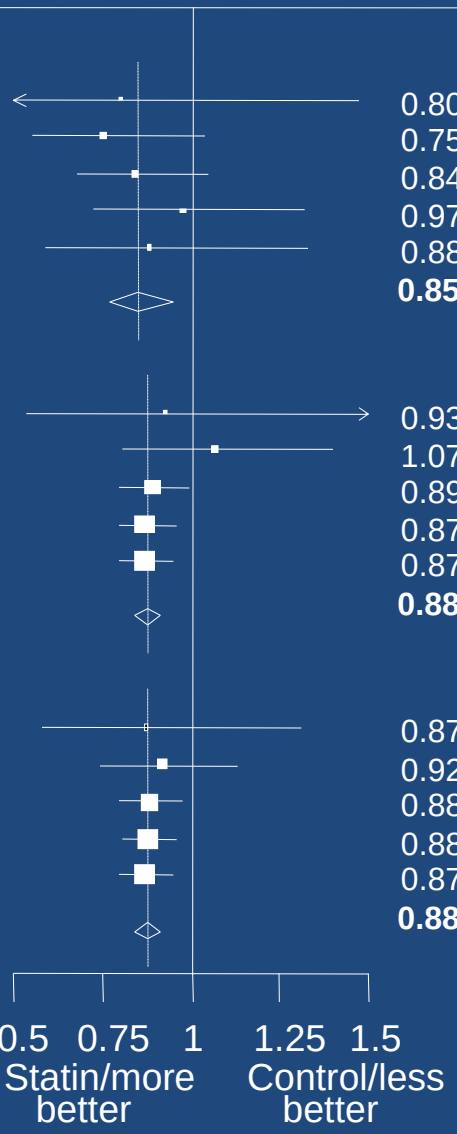
Difference in overall effect between men and women: χ^2_1=5.23(p=0.02)

Proportional effects on VASCULAR DEATH per mmol/L LDL-C reduction, by history of vascular disease

5-year MVE risk at baseline	Deaths (% per annum) Statin/more	Control/less	RR/mM (CI)	Trend test
Participants without prior vascular disease				
<5%	31 (0.1)	40 (0.1)	0.80 (0.43 - 1.47)	
≥5%,<10%	117 (0.2)	153 (0.3)	0.75 (0.55 - 1.04)	
≥10%,<20%	307 (0.9)	342 (1.0)	0.84 (0.67 - 1.05)	χ^2_1=1.46
≥20%,<30%	164 (2.3)	168 (2.3)	0.97 (0.72 - 1.32)	(p=0.2)
≥30%	93 (5.2)	98 (5.8)	0.88 (0.59 - 1.33)	
Subtotal	**712 (0.5)**	**801 (0.6)**	**0.85 (0.77 - 0.95) p= 0.004**	
Participants with prior vascular disease				
<5%	48 (2.2)	52 (2.4)	0.93 (0.53 - 1.62)	
≥5%,<10%	193 (2.5)	177 (2.3)	1.07 (0.81 - 1.41)	
≥10%,<20%	1166 (1.2)	1249 (1.3)	0.89 (0.79 - 1.00)	χ^2_1=1.49
≥20%,<30%	1432 (1.6)	1665 (1.9)	0.87 (0.80 - 0.95)	(p=0.2)
≥30%	1247 (3.1)	1435 (3.6)	0.87 (0.79 - 0.95)	
Subtotal	**4086 (1.8)**	**4578 (2.0)**	**0.88 (0.84 - 0.92) p<0.0001**	
All participants				
<5%	79 (0.2)	92 (0.2)	0.87 (0.58 - 1.31)	
≥5%,<10%	310 (0.6)	330 (0.6)	0.92 (0.74 - 1.13)	
≥10%,<20%	1473 (1.1)	1591 (1.2)	0.88 (0.79 - 0.97)	χ^2_1=0.18
≥20%,<30%	1596 (1.7)	1833 (1.9)	0.88 (0.81 - 0.96)	(p=0.7)
≥30%	1340 (3.2)	1533 (3.7)	0.87 (0.80 - 0.95)	
Overall	**4798 (1.3)**	**5379 (1.5)**	**0.88 (0.84 - 0.91) p<0.0001**	

Heterogeneity between patients with and without prior vascular disease: χ^2_1 =0.28 (p=0.6)

99% or 95% limits

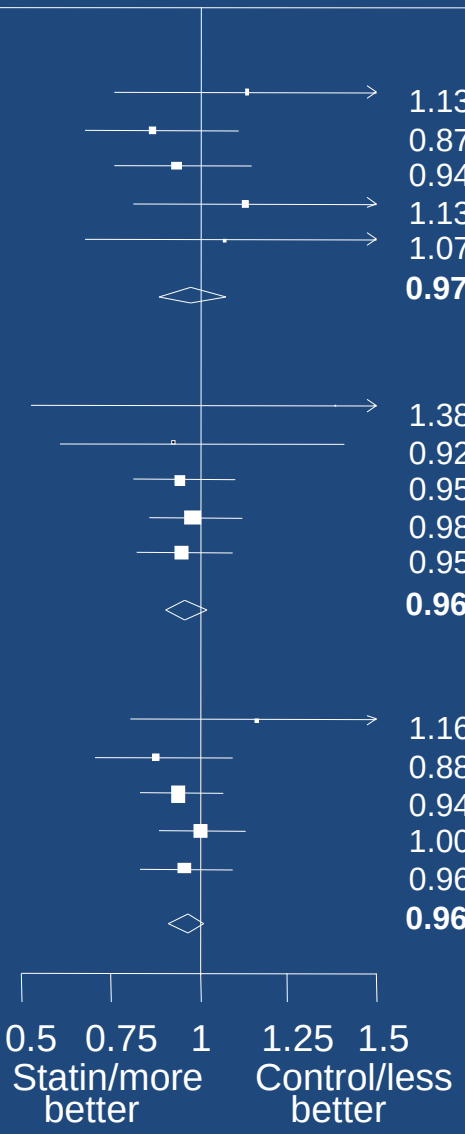


Proportional effects on NON-VASCULAR DEATH per mmol/L LDL-C reduction, by history of vascular disease

5-year MVE risk at baseline	Deaths (% per annum) Statin/more	Control/less	RR/mM (CI)	Trend test
Participants without prior vascular disease				
<5%	98 (0.2)	87 (0.2)	1.13 (0.76 - 1.69)	
≥5%,<10%	205 (0.4)	238 (0.5)	0.87 (0.67 - 1.11)	
≥10%,<20%	352 (1.0)	377 (1.1)	0.94 (0.76 - 1.15)	χ^2_1=0.47
≥20%,<30%	169 (2.4)	148 (2.1)	1.13 (0.81 - 1.57)	(p=0.5)
≥30%	79 (4.4)	71 (4.2)	1.07 (0.68 - 1.69)	
Subtotal	**903 (0.7)**	**921 (0.7)**	**0.97 (0.88 - 1.07) p= 0.60**	
Participants with prior vascular disease				
<5%	18 (0.8)	14 (0.6)	1.38 (0.53 - 3.63)	
≥5%,<10%	65 (0.8)	71 (0.9)	0.92 (0.61 - 1.41)	
≥10%,<20%	702 (0.7)	727 (0.8)	0.95 (0.81 - 1.11)	χ^2_1=0.04
≥20%,<30%	794 (0.9)	793 (0.9)	0.98 (0.86 - 1.12)	(p=0.8)
≥30%	602 (1.5)	634 (1.6)	0.95 (0.82 - 1.09)	
Subtotal	**2181 (0.9)**	**2239 (1.0)**	**0.96 (0.90 - 1.02) p= 0.18**	
All participants				
<5%	116 (0.3)	101 (0.2)	1.16 (0.80 - 1.68)	
≥5%,<10%	270 (0.5)	309 (0.6)	0.88 (0.71 - 1.09)	
≥10%,<20%	1054 (0.8)	1104 (0.9)	0.94 (0.83 - 1.07)	χ^2_1=0.02
≥20%,<30%	963 (1.0)	941 (1.0)	1.00 (0.89 - 1.13)	(p=0.9)
≥30%	681 (1.6)	705 (1.7)	0.96 (0.83 - 1.10)	
Overall	**3084 (0.8)**	**3160 (0.9)**	**0.96 (0.92 - 1.01) p= 0.16**	

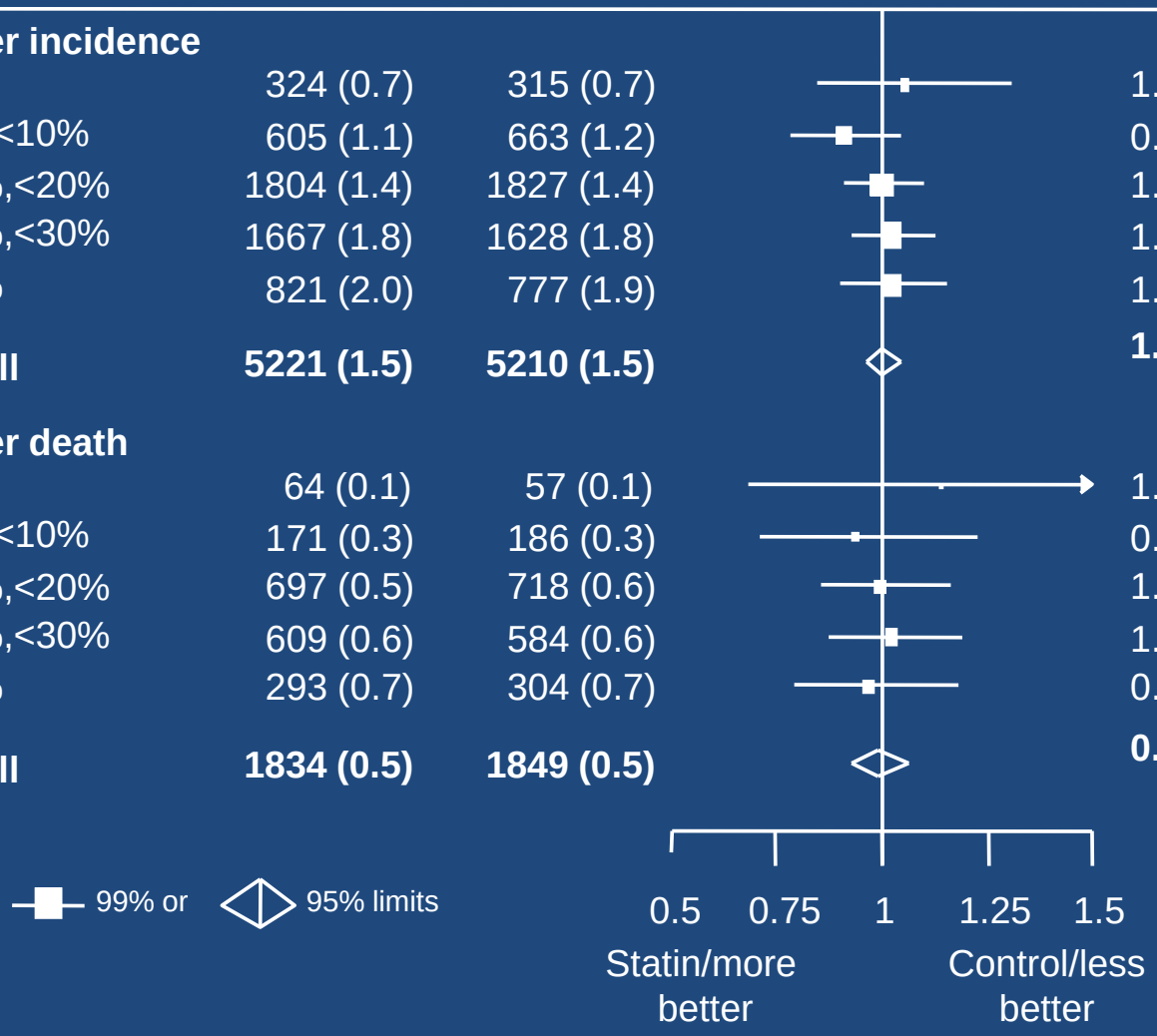
Heterogeneity between patients with and without prior vascular disease: χ^2_1 =0.17 (p=0.8)

99% or 95% limits

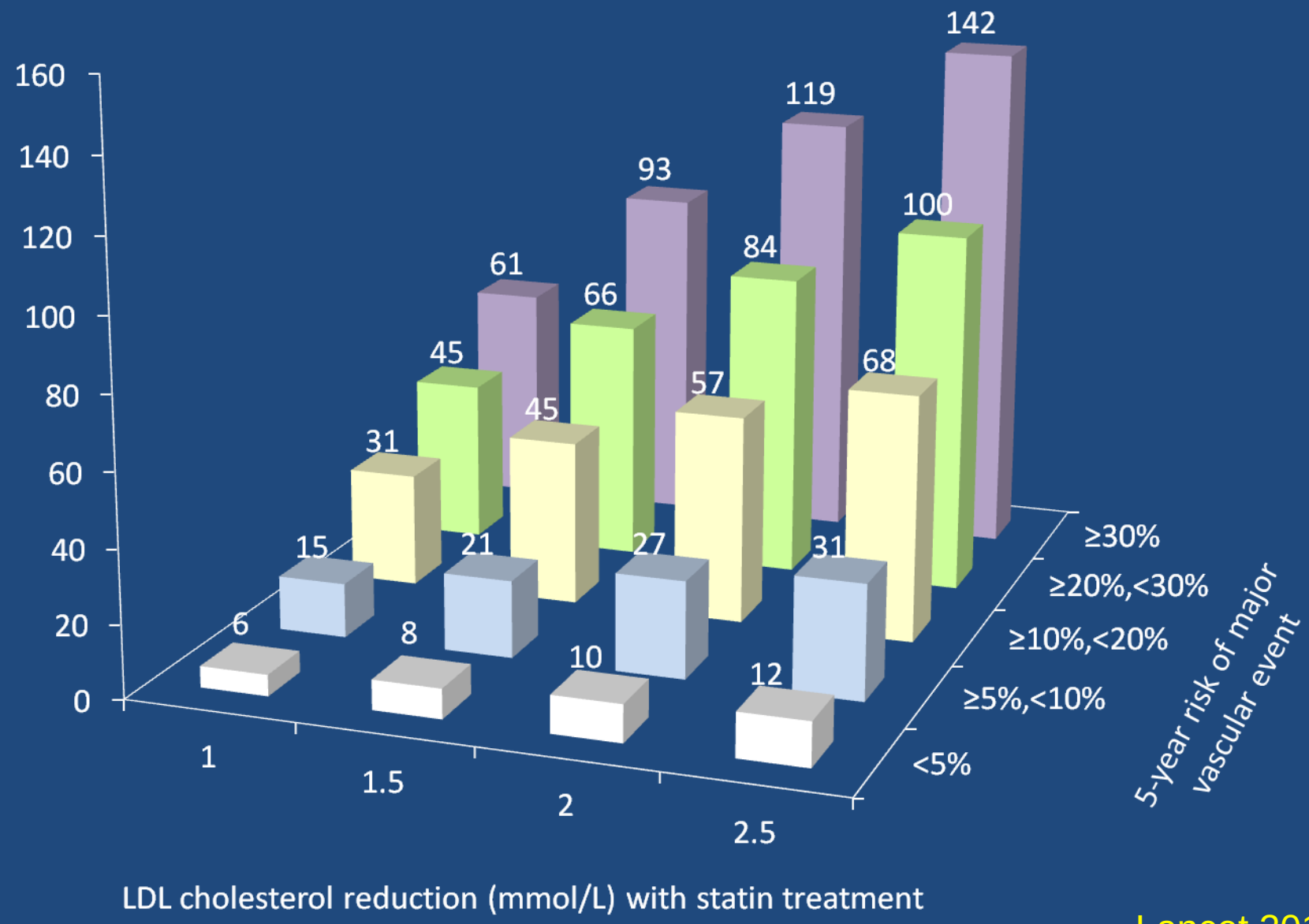


Proportional effects on CANCER INCIDENCE and CANCER MORTALITY per mmol/L LDL-C reduction

5-year MVE risk at baseline	Events (% per annum) Statin/more	Control/less	RR (CI)	Trend test
Cancer incidence				
<5%	324 (0.7)	315 (0.7)	1.05 (0.85 - 1.31)	
≥5%,<10%	605 (1.1)	663 (1.2)	0.91 (0.78 - 1.05)	
≥10%,<20%	1804 (1.4)	1827 (1.4)	1.00 (0.91 - 1.10)	$\chi^2_1 = 0.83$
≥20%,<30%	1667 (1.8)	1628 (1.8)	1.02 (0.93 - 1.12)	(p=0.4)
≥30%	821 (2.0)	777 (1.9)	1.02 (0.90 - 1.16)	
Overall	**5221 (1.5)**	**5210 (1.5)**	**1.00 (0.96 - 1.04) p= 0.99**	
Cancer death				
<5%	64 (0.1)	57 (0.1)	1.14 (0.69 - 1.89)	
≥5%,<10%	171 (0.3)	186 (0.3)	0.93 (0.71 - 1.23)	
≥10%,<20%	697 (0.5)	718 (0.6)	1.00 (0.86 - 1.16)	$\chi^2_1 = 0.01$
≥20%,<30%	609 (0.6)	584 (0.6)	1.02 (0.88 - 1.19)	(p=0.9)
≥30%	293 (0.7)	304 (0.7)	0.97 (0.80 - 1.19)	
Overall	**1834 (0.5)**	**1849 (0.5)**	**0.99 (0.93 - 1.06) p= 0.86**	



ABSOLUTE BENEFIT: Major Vascular Events avoided per 1,000 treated over 5 years



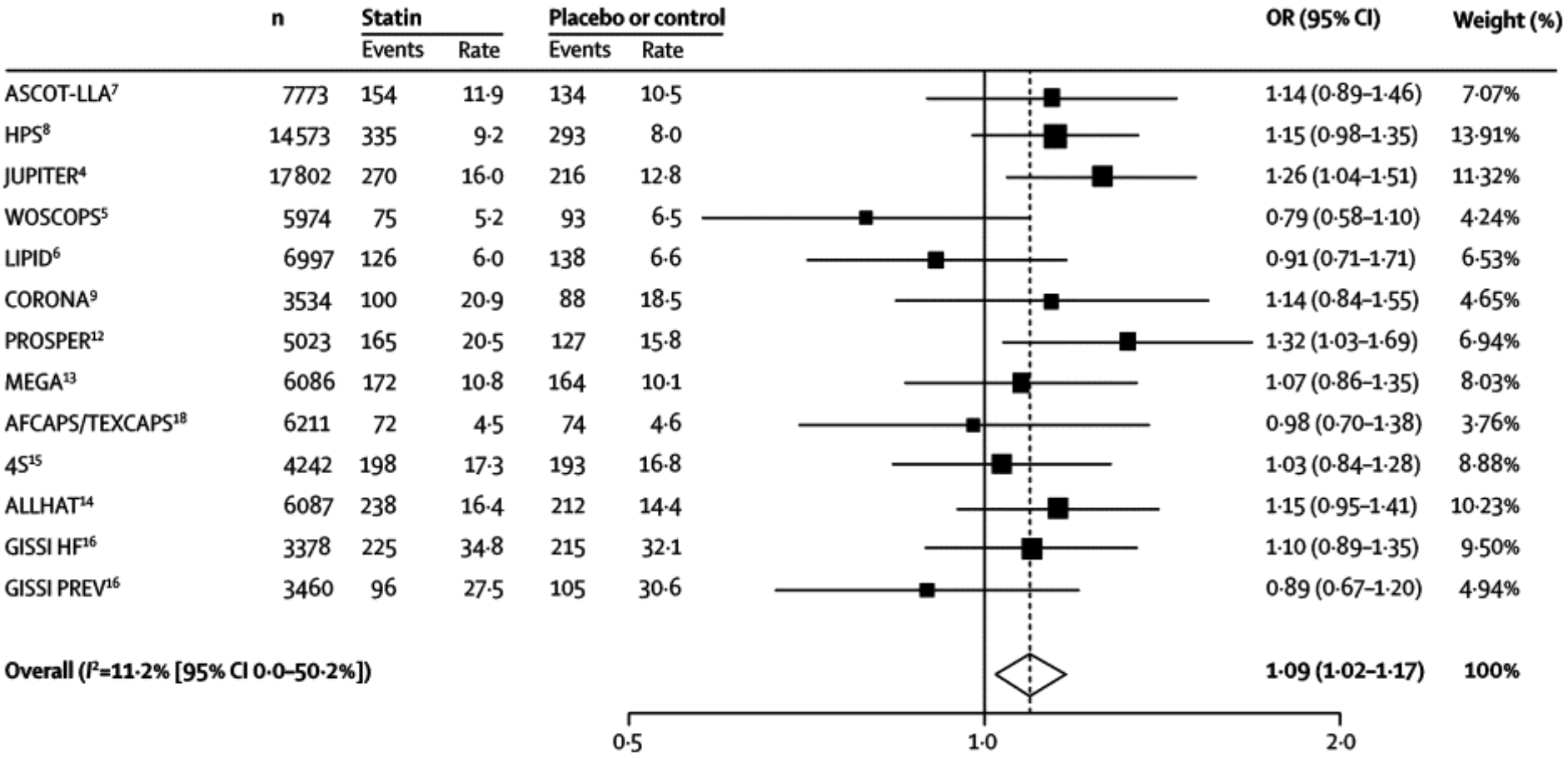
Lancet 2012

Statin-related myopathy/rhabdomyolysis

Muscle disorder	Definition	Frequency (per annum)
Myopathy	Creatine kinase (CK) >10x ULN with muscle symptoms	<1/10,000
Rhabdomyolysis	Myopathy with CK >40x ULN and evidence of renal dysfunction	~1/100,000

Risk influenced by dose (e.g. 10-fold increase with 40 vs 80 mg simvastatin), certain drugs and other factors (e.g. ethnicity)

Meta-analysis of statin trials: Diagnosis of diabetes (Sattar; Lancet 2010)



Balance of benefits and risks of statin therapy in LOWEST RISK individuals (<5% over 5 years)

5 year effects per mmol/L LDL-c reduction per 1000 individuals treated with a statin:

- 6 fewer major vascular events*

VERSUS

- 0.5 more myopathy cases (0.1 rhabdomyolysis)
- 5 new diagnoses of diabetes mellitus

* includes 0.5 extra haemorrhagic strokes

Mail Online

March 2010

The other side of statins: They've saved countless lives - but now doctors fear for some, the side effects could be devastating

Permanent nerve damage: Smallholder Paul Rhoades is now largely dependent on a wheelchair after taking statins

Effects of statins on risk of polyneuropathy

Gaist et al (Neurology 2002): Observational study

- 9 of 166 patients with idiopathic neuropathy had taken average of 15mg simvastatin daily (or equivalent of another statin) for 2.8 years
- Risk ratio of 3.7 (95%CI 1.8-7.6) for statin use

HPS (Lancet 2004): Randomised controlled trial

- 20,000 patients randomly allocated to receive 40mg simvastatin daily vs placebo for 5 years
- 11 (0.1%) statin vs 8 (0.1%) placebo cases

MHRA Drug Safety Update November 2009 Statins: updated product information in patient leaflets on adverse reactions

European-wide review on statins…. identified the need for the product information for all statins to reflect the issues identified from analyses of clinical trial and post-marketing data from case reports of adverse drug reactions….

- ….treatment with any statin may be associated with depression, sleep disturbances, memory loss and sexual dysfunction

- Statins may very rarely be associated with interstitial lung disease…

…there is sufficient evidence to support a possible causal relationship between statin use and the above adverse reactions.

Statins and interstitial lung disease: systematic review of literature and FDA reports (Fernandez; Chest 2008)

"The evidence linking statins to lung injury is not definite. These cases of ILD reported as being due to statins could simply reflect background prevalence of ILD and that statins are not the cause…. Nevertheless such an association is possible."

MHRA review: interstitial pneumonopathy

"Interstitial pneumopathy-related events that occurred in atorvastatin clinical trials were few and generally balanced among treatment groups.

In the WOSCOPS, CARE and PROSPER clinical studies, the incidence of interstitial pneumonopathy was similar in pravastatin-treated and placebo-treated patients… no reports of interstitial pneumonopathy in the LIPID study.

…4S trial: 3 vs 1; HPS trial: 3 vs 12; A-Z: 1 vs 1 for simvastatin versus placebo "

MHRA review: memory loss

"A total of 333 cases of memory loss were reported post-marketing … a causal relationship between simvastatin and memory loss cannot be ruled out.

In the WOSCOPS, CARE and PROSPER clinical studies … the incidence of memory loss was similar in pravastatin-treated and placebo-treated patients.

HPS: Cognitive impairment (TICS-m <22/39) at Final Follow-up (Lancet 2002)

Age (years) at randomisation	Simvastatin (8086)	Placebo (7834)
<65	17.1%	17.8%
65<70	25.8%	25.4%
70	34.6%	36.2%
ALL PATIENTS	23.7%	24.2%

P-value = 0.4

MHRA review: depression

"Depression-related event incidence was similar in the atorvastatin and placebo groups in all individual studies that included placebo…

In the WOSCOPS, CARE, LIPID and PROSPER clinical studies…the incidence of depression was similar in pravastatin-treated and placebo-treated patients.

… similar incidence of depression has been reported between simvastatin and placebo."

BBC NEWS

May 2010

Statin side-effect risk uncovered

GPs should think more carefully about prescribing cholesterol-busting drugs say researchers who highlighted a range of "unintended" side effects.

RISKS OF STATINS
For every 10,000 women treated with statins:
271 fewer cases of cardiovascular disease
8 fewer cases of oesophageal cancer
23 extra patients with acute kidney failure
73 extra patients with liver dysfunction
307 extra patients with cataracts
39 extra patients with muscle weakness Figures were similar for men, except there would be 110 extra cases of muscle weakness

Population-based cohort study: HR and NNT/NNH with statin over 5 years in men aged 35-74 with CV risk ≥20% over 10 years (Hippisley-Cox; BMJ 2010)

Outcome	HR (95% CI)	NNT/NNH (95% CI)
CV events	0.76 (0.67 to 0.86)	-33 (-57 to -24)
Cataract	1.32 (1.26 to 1.37)	52 (44 to 63)
Myopathy	6.15 (5.19 to 7.30)	91 (74 to 112)
Liver dysfunction	1.53 (1.42 to 1.66)	142 (115 to 180)
Acute renal failure	1.61 (1.39 to 1.87)	346 (245 to 539)

Based on average of only 2.5 years of statin exposure and partial adjustment for potential confounders

HPS randomised placebo-controlled trial of 40 mg simvastatin daily for 5 years: Effect on CATARACT

	Simvastatin (10,269)	Placebo (10,267)
Cataract report or extraction	393 (3.8%)	404 (3.9%)

Risk ratio (95% CI): 0.96 (0.84-1.11)

Low cholesterol and cancer

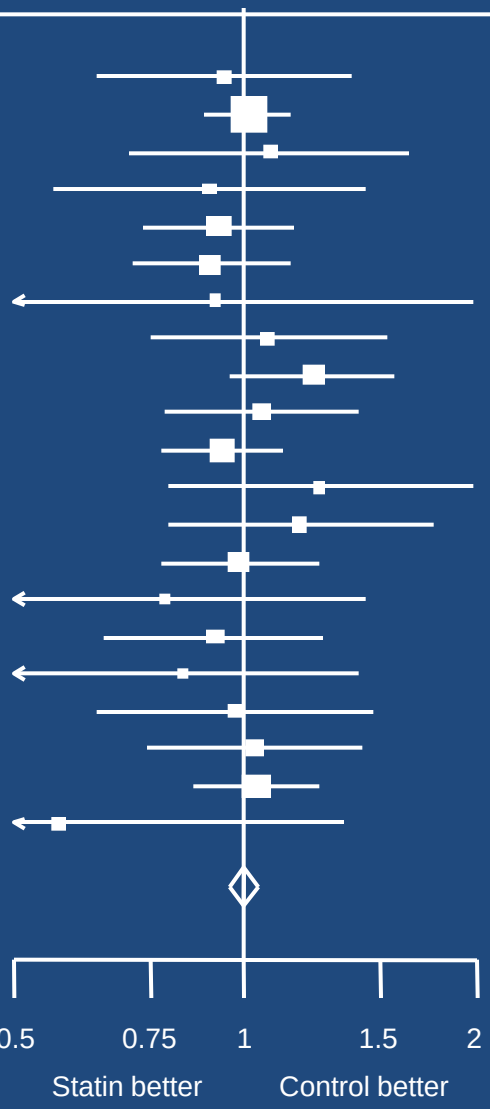
- Association between low blood cholesterol and increased cancer often seen in observational studies

- Previous tabular meta-analyses of randomised statin trials have generally been reassuring, but
  - Claims that statins might cause some types of cancer (eg, breast, gastrointestinal)
  - Concerns about reducing cholesterol to very low levels or reducing cholesterol in particular groups (eg, the elderly)

Cancer incidence in 21 statin vs control trials

Trial	LDL-C reduction (mmol/L)	Events (% p.a.) Statin	Control
SSSS	1.77	89 (0.8)	94 (0.8)
HPS	1.29	790 (1.6)	776 (1.6)
ALLIANCE	1.16	78 (1.5)	71 (1.4)
CARDS	1.14	57 (1.1)	62 (1.2)
JUPITER	1.09	253 (1.3)	274 (1.4)
ASCOT-LLA	1.07	220 (1.3)	242 (1.5)
Post CABG	1.07	21 (0.8)	23 (0.8)
WOSCOPS	1.07	108 (0.7)	100 (0.6)
PROSPER	1.04	241 (2.6)	198 (2.1)
CARE	1.03	158 (1.6)	149 (1.5)
LIPID	1.03	386 (1.6)	407 (1.7)
ASPEN	0.99	71 (1.7)	56 (1.3)
AURORA	0.99	92 (2.0)	78 (1.7)
AFCAPS/TexCAPS	0.94	239 (1.4)	242 (1.4)
LIPS	0.92	33 (1.2)	40 (1.6)
GISSI-HF	0.92	117 (1.5)	128 (1.6)
4D	0.89	43 (2.5)	51 (3.0)
ALERT	0.84	77 (1.5)	79 (1.5)
MEGA	0.67	130 (0.6)	130 (0.6)
ALLHAT-LLT	0.54	378 (1.6)	369 (1.5)
GISSI-P	0.35	13 (0.3)	23 (0.6)
Subtotal (21 trials)	**1.07**	**3594/64744 (1.4% p.a.)**	**3592/64782 (1.4% p.a.)**

Relative risk (CI)



Trend: $\chi^2_1 = 0.0$ (p=1.0)

1.00 (0.95 - 1.04)

Heterogeneity $\chi^2_{20} = 17.0$, p=0.65

99% or 95% CI

Requirements for evidence to support claims related to safety and efficacy of treatments

- Treatment not known to be effective

  → Lower threshold for safety concerns (compared with evidence for efficacy)

- Treatment known to be effective (e.g. statins)

  → Higher threshold for safety concerns (of similar strength to evidence that is typically required for efficacy)

Conclusions (1)

- Each 1 mmol/L LDL-C reduction reduces the annual rate of major vascular event by about one-fifth
- Larger LDL-C reductions safely produce definite larger reductions in the incidence of heart attack, revascularisation and ischaemic stroke
- Similar proportional reductions in all of the subgroups studied (including 1° prevention)
- No threshold within the cholesterol range studied, which implies that reducing LDL-C by 2-3 mmol/L would reduce vascular event risk by about 40-50%

Conclusions (2)

- Main determinants of the absolute benefit with statin therapy are the presenting vascular risk level and the achieved absolute LDL-C reduction

- Aim to target patients at highest risk (based on prior disease and standard risk factors) , even in the absence of raised LDL cholesterol, and to lower their LDL-C substantially with the highest safe statin dose