

# **Cholesterol Treatment Trialists' (CTT) Collaboration**

**Slide deck**

# CTT Collaboration: Background\*

## History:

- Founded in 1993 (prior to publication of 4S trial in 1994)
- Original protocol published in 1995

## Trial eligibility for inclusion in CTT:

- Randomized
- Principal effects of treatment is modification of blood lipids
- Unconfounded (i.e. treatment arms differ only by lipid intervention)
- Recruited at least 1000 participants
- Scheduled study treatment duration of at least 2 years

\*American Journal of Cardiology 1995; 75: 1130-4

## CTT Collaboration: Analyses\*

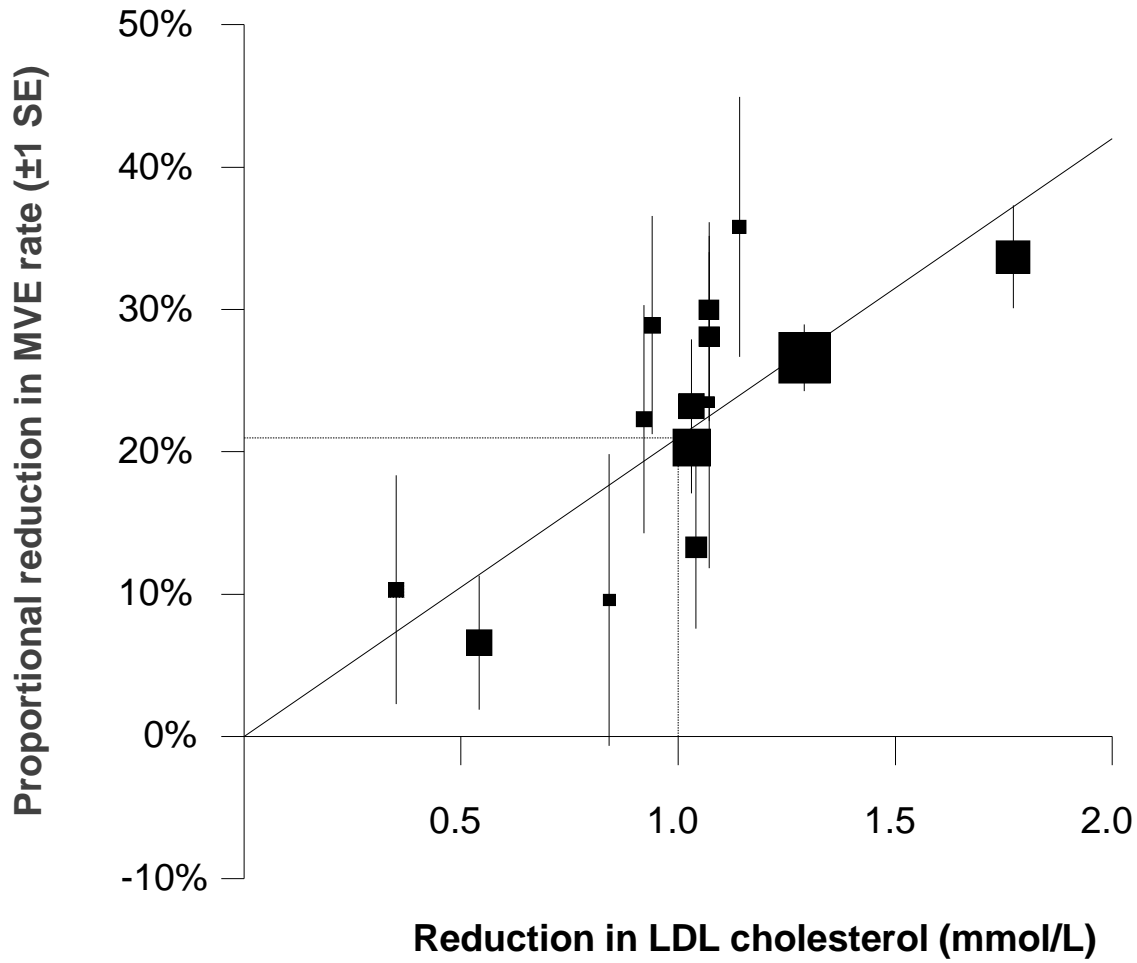
- Based on individual participant data (as opposed to tabular data)
- Intention-to-treat analyses
- Main results standardised per mmol/L LDL-cholesterol reduction

\*American Journal of Cardiology 1995; 75: 1130-4

## CTT Lancet 2005: included 14 trials of statin vs control

Study	Treatment comparison	N	Target population	Entry lipid criteria
4S	S20-40 vs. placebo	4444	Angina or previous MI	Total cholesterol 5.5-8.0 mmol/L
WOSCOPS	P40 vs. placebo	6595	Primary prevention	LDL-C at least 4.0 mmol/L
CARE	P40 vs. placebo	4159	Previous MI	Total cholesterol <6.2 mmol/L; LDL-C 3.0 to 4.5 mmol/L
Post-CABG	L40-80 vs. L2.5-5	1351	Previous bypass surgery	LDL-C 3.4-4.5 mmol/L
AFCAPS/TexCAPS	L20-40 vs. placebo	6605	Primary prevention	Total cholesterol 4.65-6.82 mmol/L; LDL-C 3.36-4.91 mmol/L
LIPID	P40 vs. placebo	9014	Previous MI or hospitalization for unstable angina	Total cholesterol 4.0-7.0 mmol/L
GISSI-P	P20 vs. no treatment	4271	Recent MI	Total cholesterol $\geq$ 5.2 mmol/L
LIPS	F80 vs. placebo	1677	Previous PCI	Total cholesterol 3.5-7.0 mmol/L
HPS	S40 vs. placebo	20,536	CHD, other occlusive arterial disease or DM	Non-fasting total cholesterol $\geq$ 3.5 mmol/L
PROSPER	P40 vs. placebo	5804	History of or risk factors for vascular disease	Total cholesterol 4.0-9.0 mmol/L
ALLHAT-LLT	P40 vs. usual care	10,355	Hypertension + at least 1 additional CHD risk factor	Fasting LDL-C 3.1-4.9 mmol/L (no known CHD); 2.6 to 3.3 mmol/L (known CHD; upper limit 4.1 mmol/L)
ASCOT-LLA	A10 vs. placebo	10,305	Hypertension CVD risk factors	Non-fasting total cholesterol $\leq$ 6.5 mmol/L
ALERT	F40 vs. placebo	2102	Renal transplant patients	Total cholesterol 4.0-9.0 mmol/L.
CARDS	A10 vs. placebo	2838	Type 2 DM	LDL-C $\leq$ 4.14 mmol/L

# Relation between the proportional reduction in MAJOR VASCULAR EVENTS and mean absolute LDL-C reduction in 14 statin trials



## CTT Lancet 2010\*: additional trials of statin vs control

Study	Treatment comparison	N	Target population	Entry lipid criteria
MEGA	P 10-20 vs. usual care	8214	Primary prevention	TC 220-270 mg/dL
JUPITER	R 20 vs. placebo	17 802	Primary prevention (but CRP>2 mg/dL)	LDL-C <130 mg/dL, TG <500 mg/dL
4D	A 20 vs. placebo	1255	Type 2 DM + haemodialysis	LDL-C 80-190 mg/dL TG <1000 mg/dL
AURORA	R 10 vs. placebo	2773	Haemodialysis	None
ALLIANCE	A 10-80 (until LDL <80 mg/dL) vs. usual care	2442	Prior CHD	LDL-C 110-200 mg/dL on lipid lowering drugs, 130-250 mg/dL if not
ASPEN	A 10 vs. placebo	2410	Type 2 DM + CHD or risk factors	LDL-C <150, TG ≤445 mg/dL with CHD; LDL-C <159, TG ≤600 mg/dL without
GISSI-HF	R 10 vs. placebo	4574	CHF	None

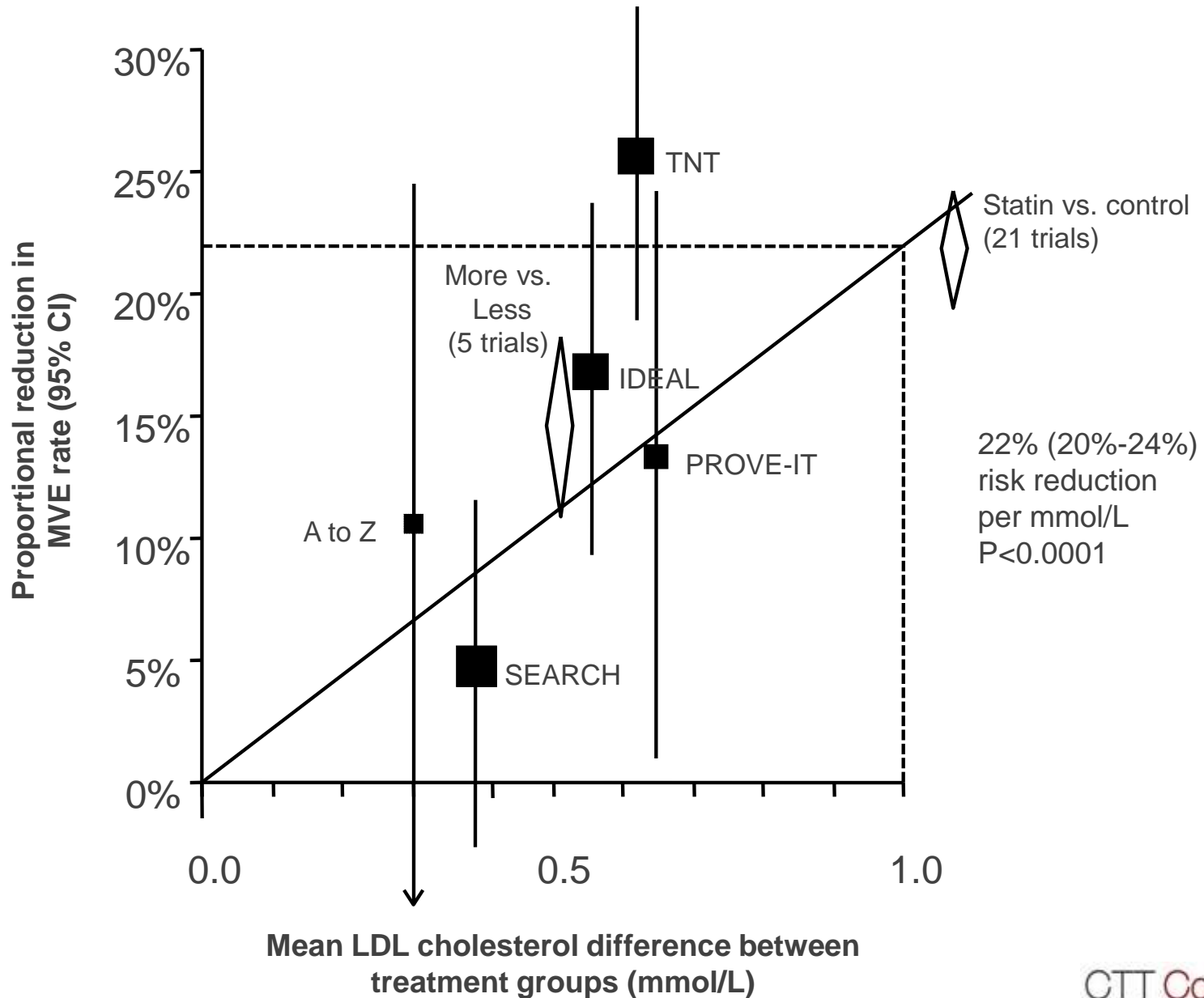
\*Lancet 2010; 376: 1670-81

## CTT Lancet 2010\*: more vs less intensive statin therapy

Study	Treatment comparison	N	Target population	Entry lipid criteria
PROVE-IT	A 80 vs. P 40	4162	ACS	TC ≤240 mg/dL
A to Z	S 40 then S 80 vs. placebo then S 20	4497	ACS	TC ≤250 mg/dL
TNT	A 80 vs. A 10	10,001	Prior CHD	LDL-C 130-250 mg/dL TG ≤600 mg/dL
IDEAL	A 80 vs. S 20-40	8888	Prior CHD	TG ≤600 mg/dL
SEARCH	S 80 vs. S 20	12,064	Prior CHD	TC ≥4.5 mmol/L or ≥3.5 if on statins

\*Lancet 2010; 376: 1670-81

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



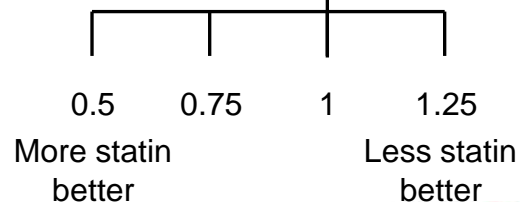




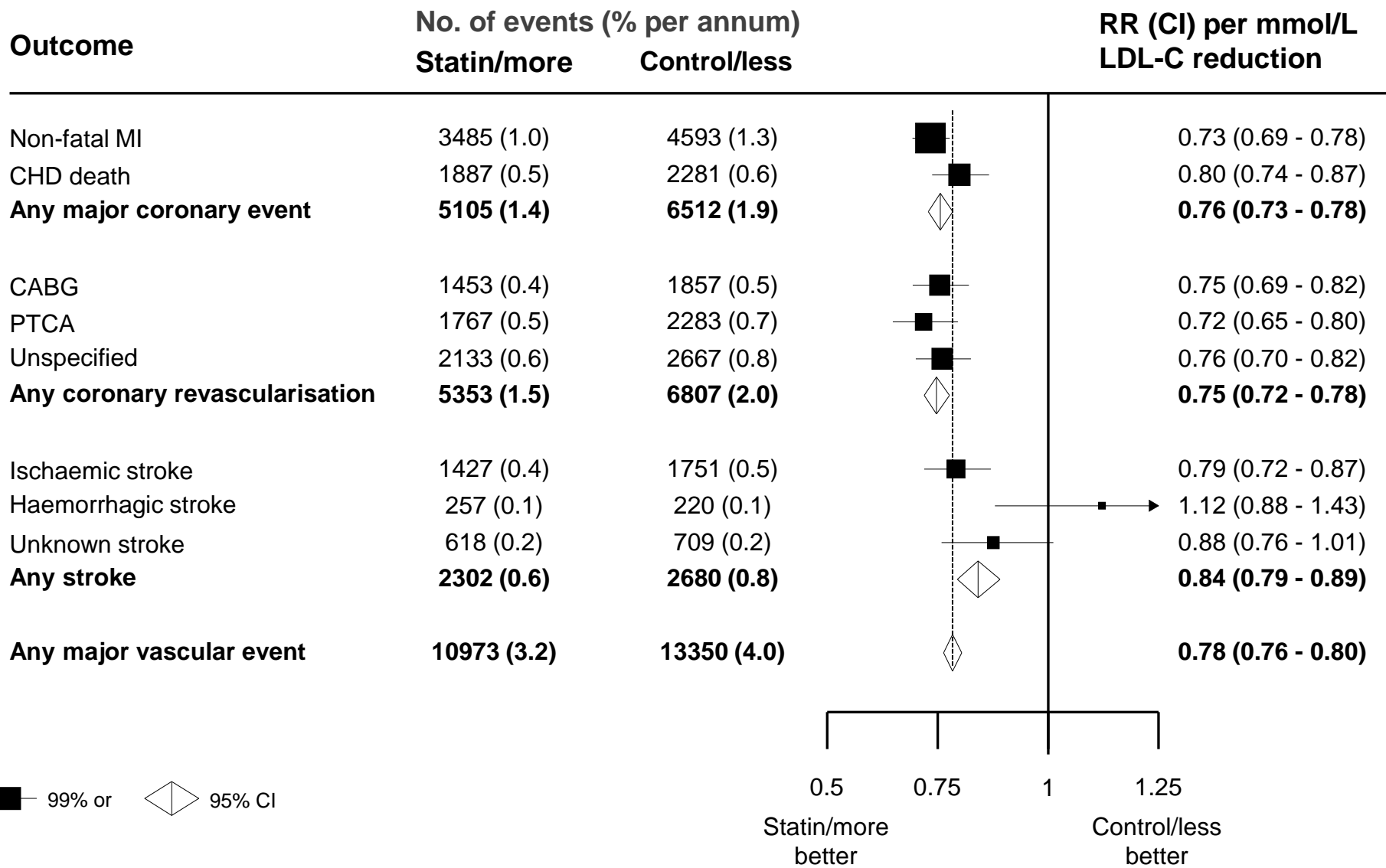
# More vs less statin: Proportional effects on MAJOR VASCULAR EVENTS per mmol/L LDL-C reduction

Outcome	No. of events (% per annum)		RR (CI) per mmol/L LDL-C reduction
	More statin	Less statin	
Non-fatal MI	1175 (1.3)	1380 (1.5)	0.71 (0.58 - 0.87)
CHD death	645 (0.7)	694 (0.7)	0.85 (0.63 - 1.15)
<b>Any major coronary event</b>	<b>1725 (1.9)</b>	<b>1973 (2.2)</b>	<b>0.74 (0.65 - 0.85)</b>
CABG	637 (0.7)	731 (0.9)	0.72 (0.55 - 0.95)
PTCA	1166 (1.3)	1508 (1.8)	0.60 (0.50 - 0.71)
Unspecified	447 (0.5)	502 (0.6)	0.78 (0.58 - 1.04)
<b>Any coronary revascularisation</b>	<b>2250 (2.6)</b>	<b>2741 (3.2)</b>	<b>0.66 (0.60 - 0.73)</b>
Ischaemic stroke	440 (0.5)	526 (0.6)	0.69 (0.50 - 0.95)
Haemorrhagic stroke	69 (0.1)	57 (0.1)	1.39 (0.57 - 3.39)
Unknown stroke	63 (0.1)	80 (0.1)	0.63 (0.24 - 1.66)
<b>Any stroke</b>	<b>572 (0.6)</b>	<b>663 (0.7)</b>	<b>0.74 (0.59 - 0.92)</b>
<b>Any major vascular event</b>	<b>3837 (4.5)</b>	<b>4416 (5.3)</b>	<b>0.72 (0.66 - 0.78)</b>

■ 99% or ◊ 95% CI



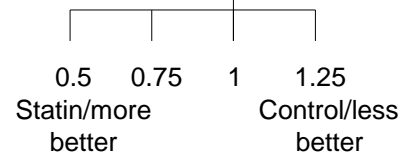
# All trials (statin vs control OR more vs less statin): Proportional effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL-C



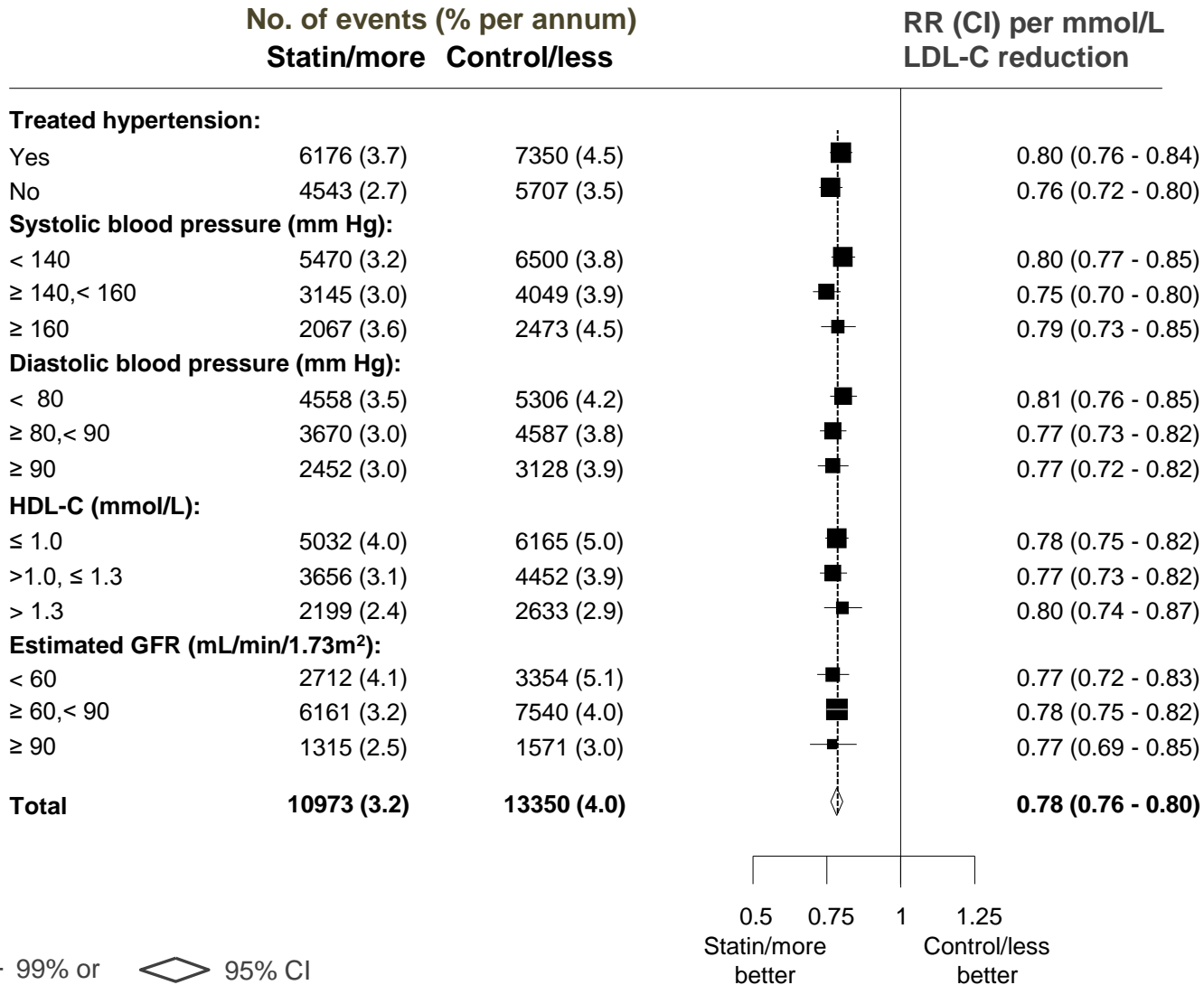
# Proportional effects on MAJOR VASCULAR EVENTS per mmol/L LDL-C reduction, by baseline prognostic factors

	No. of events (% per annum)			RR (CI) per mmol/L LDL-C reduction
	Statin/more	Control/less		
<b>Previous vascular disease:</b>				
CHD	8395 (4.5)	10123 (5.6)		0.79 (0.76 - 0.82)
Non-CHD vascular	674 (3.1)	802 (3.7)		0.81 (0.71 - 0.92)
None	1904 (1.4)	2425 (1.8)		0.75 (0.69 - 0.82)
<b>Diabetes:</b>				
Type 1 diabetes	145 (4.5)	192 (6.0)		0.77 (0.58 - 1.01)
Type 2 diabetes	2494 (4.2)	2920 (5.1)		0.80 (0.74 - 0.86)
No diabetes	8272 (3.2)	10163 (4.0)		0.78 (0.75 - 0.81)
<b>Sex:</b>				
Male	8712 (3.5)	10725 (4.4)		0.77 (0.74 - 0.80)
Female	2261 (2.5)	2625 (2.9)		0.83 (0.76 - 0.90)
<b>Age (years):</b>				
≤ 65	6056 (2.9)	7455 (3.6)		0.78 (0.75 - 0.82)
> 65, ≤ 75	4032 (3.7)	4908 (4.6)		0.78 (0.74 - 0.83)
> 75	885 (4.8)	987 (5.4)		0.84 (0.73 - 0.97)
<b>Body mass index (kg/m<sup>2</sup>):</b>				
< 25	3030 (3.0)	3688 (3.7)		0.79 (0.74 - 0.84)
≥ 25, < 30	5033 (3.3)	6125 (4.1)		0.78 (0.74 - 0.82)
≥ 30	2732 (3.3)	3331 (4.1)		0.78 (0.73 - 0.84)
<b>Smoking status:</b>				
Current smokers	2268 (3.6)	2896 (4.7)		0.78 (0.73 - 0.84)
Non-smokers	8703 (3.1)	10452 (3.9)		0.78 (0.75 - 0.82)
<b>Total</b>	<b>10973 (3.2)</b>	<b>13350 (4.0)</b>		<b>0.78 (0.76 - 0.80)</b>

■ 99% or ◊ 95% CI



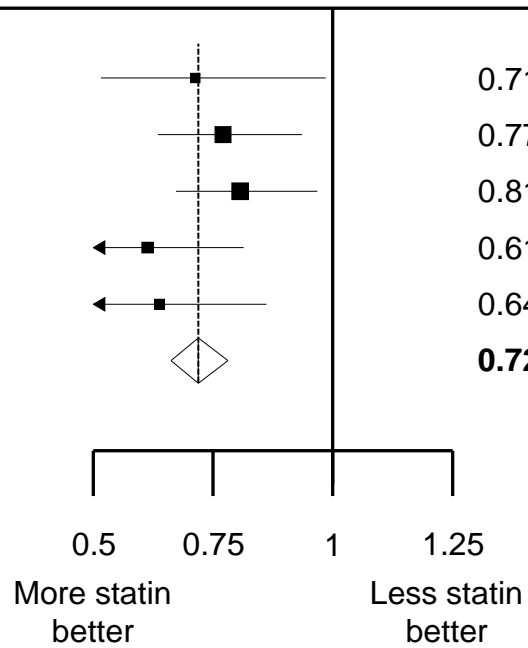
# Proportional effects on MAJOR VASCULAR EVENTS per mmol/L LDL-C reduction, by baseline prognostic factors



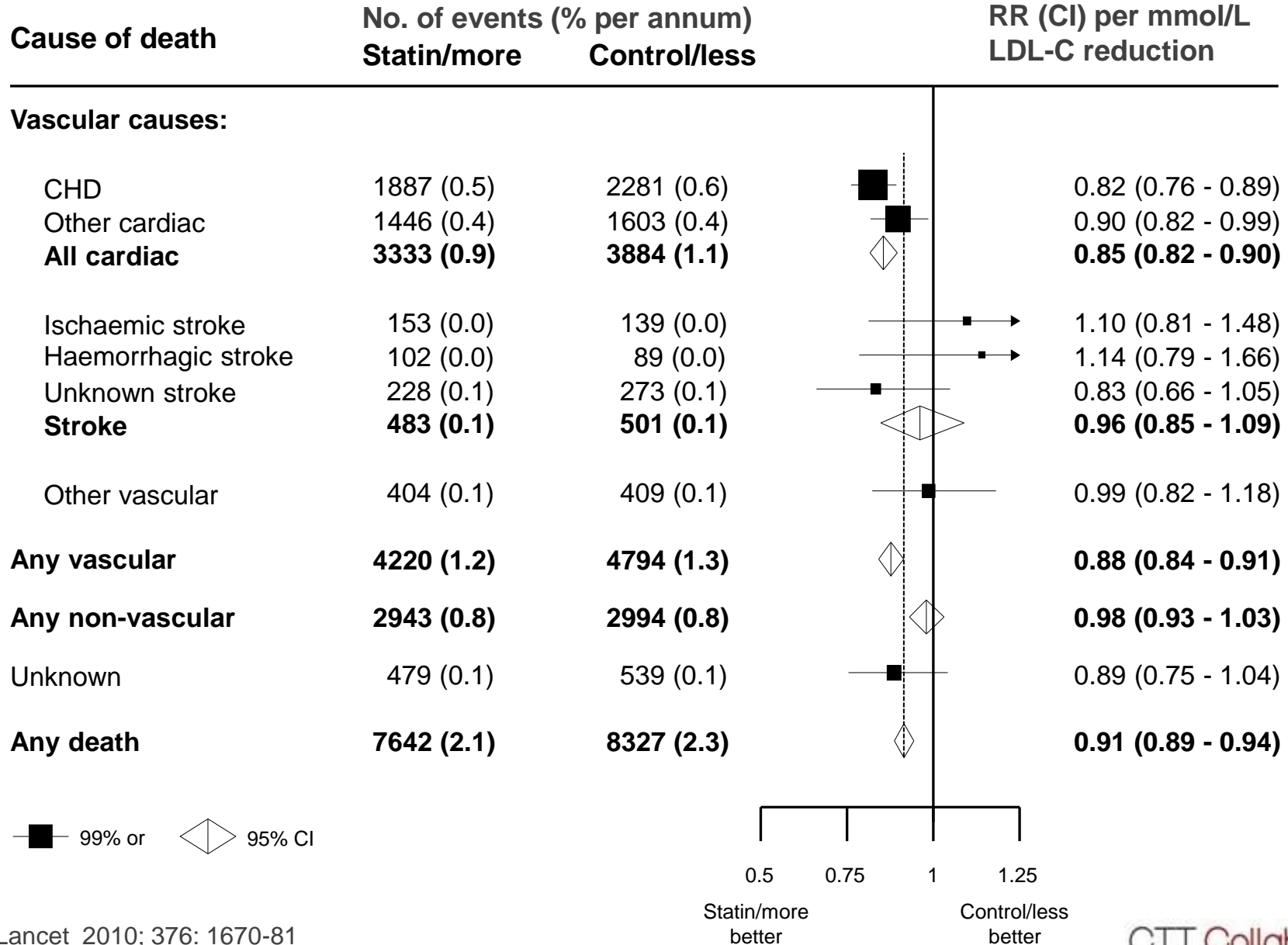
# More vs less trials: Proportional effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL-C, by baseline LDL-C

Baseline LDL-C (mmol/L)	No. of events (% per annum)			RR (CI) per mmol/L LDL-C reduction
	More statin	Less statin		
< 2.0	704 (4.6)	795 (5.2)		0.71 (0.52 - 0.98)
≥ 2.0, <2.5	1189 (4.2)	1317 (4.8)		0.77 (0.64 - 0.94)
≥ 2.5, <3.0	1065 (4.5)	1203 (5.0)		0.81 (0.67 - 0.97)
≥ 3.0, <3.5	517 (4.5)	633 (5.8)		0.61 (0.46 - 0.81)
≥ 3.0	303 (5.7)	398 (7.8)		0.64 (0.47 - 0.86)
<b>Total</b>	<b>3837 (4.5)</b>	<b>4416 (5.3)</b>		<b>0.72 (0.66 - 0.78)</b>

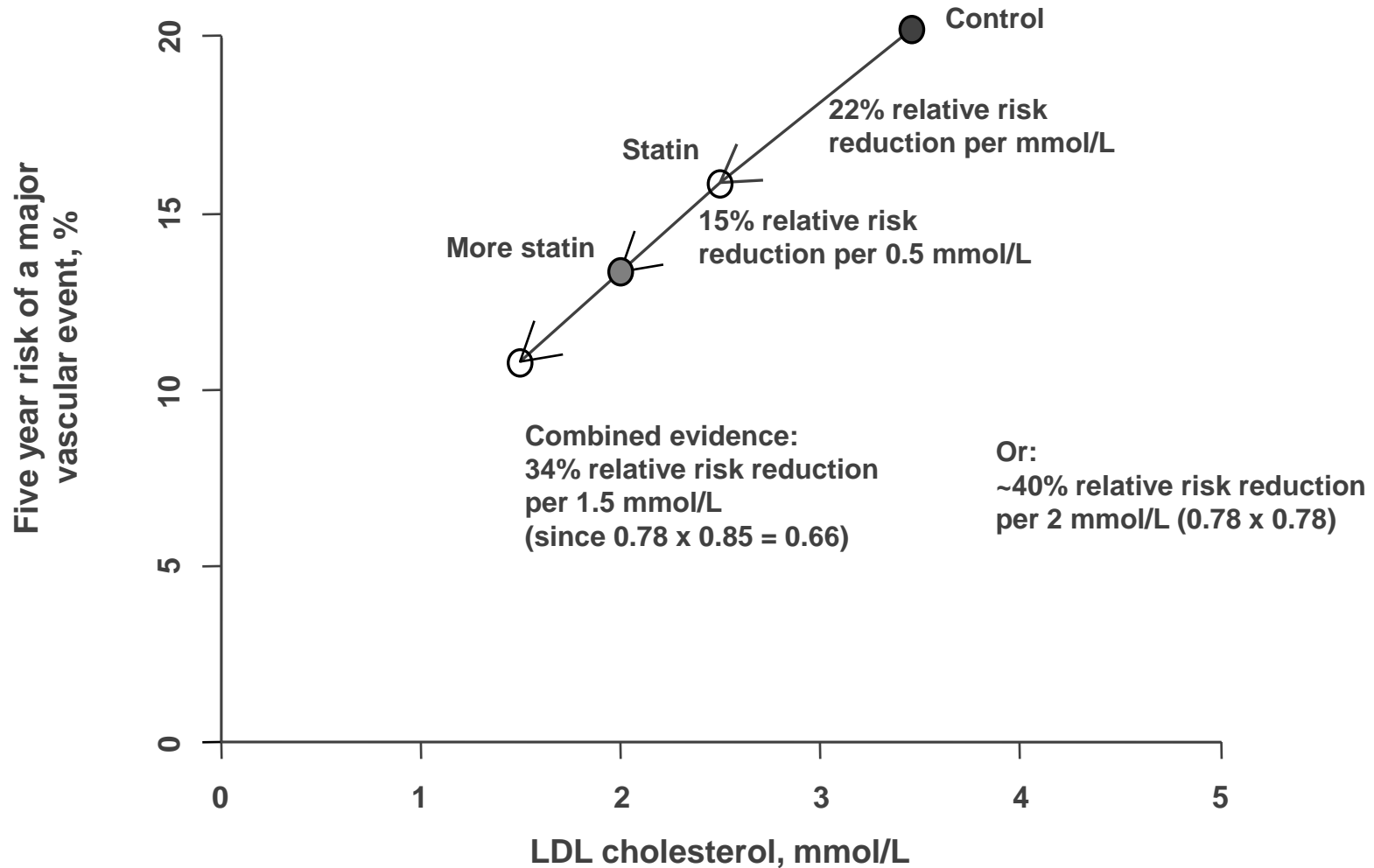
99% or 95% CI      95% CI



# Proportional effects on CAUSE-SPECIFIC MORTALITY per mmol/L LDL-C reduction

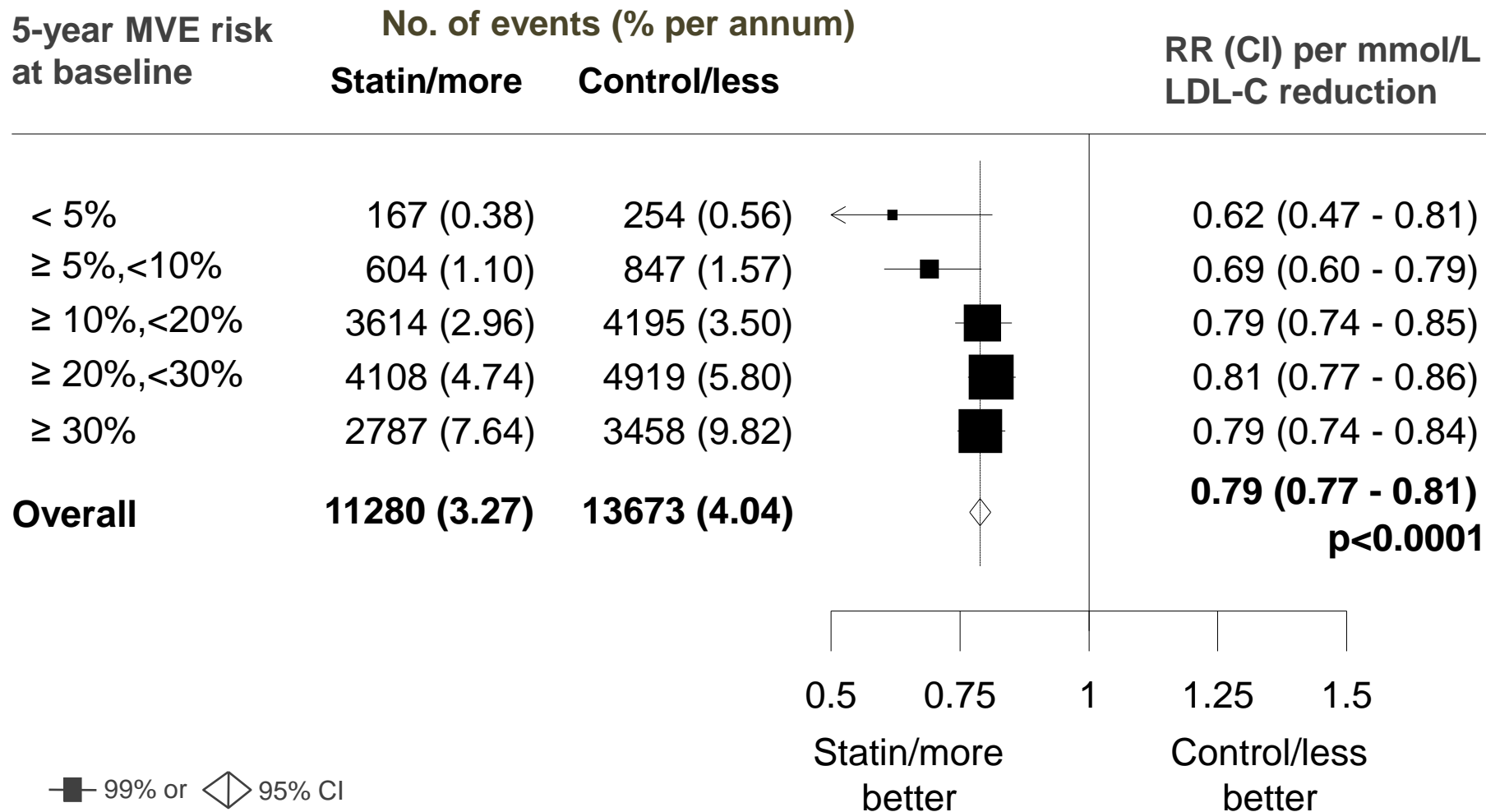


# Expected reduction in MAJOR VASCULAR EVENT risk from lowering LDL-C with STATIN therapy

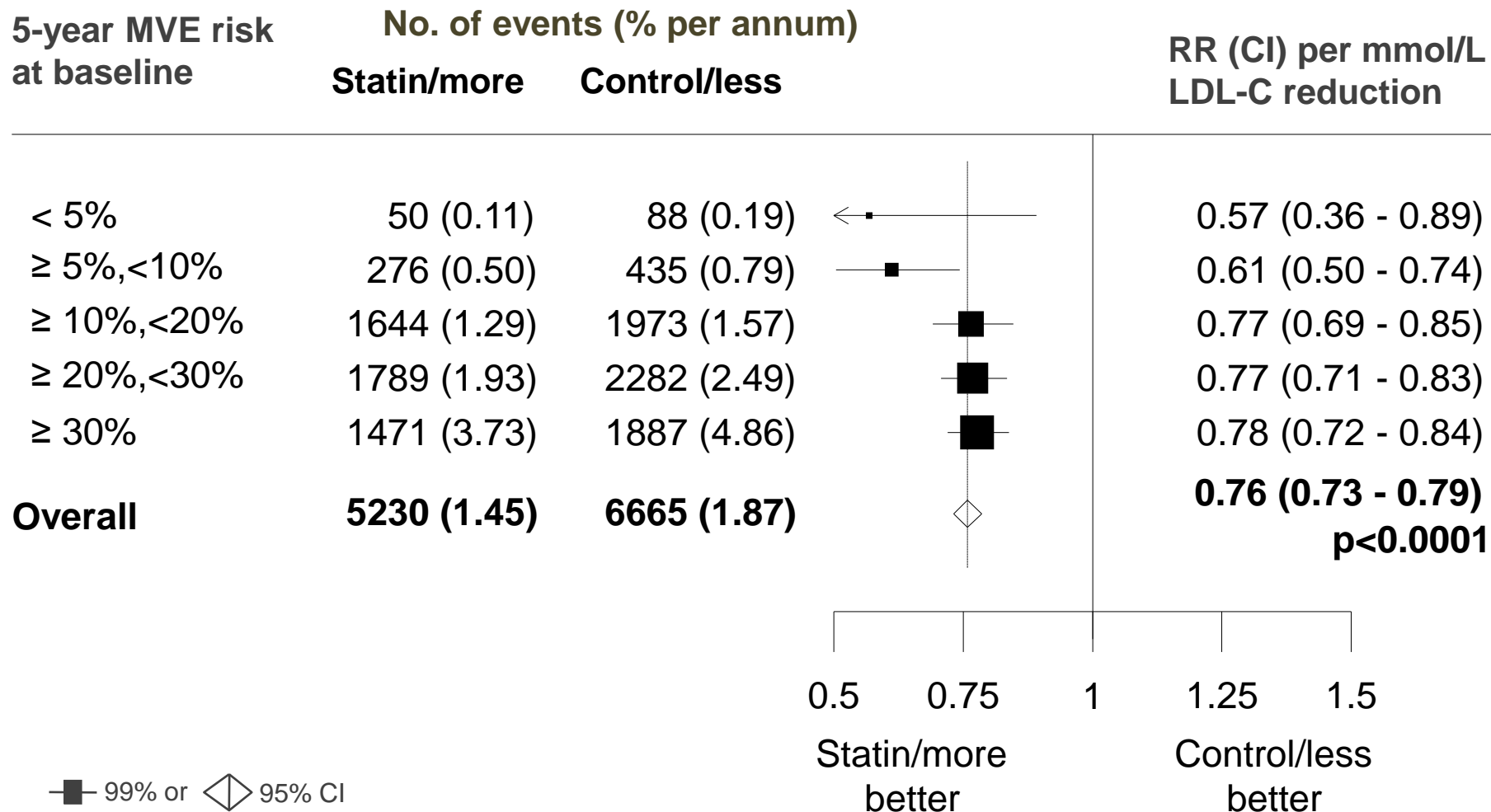




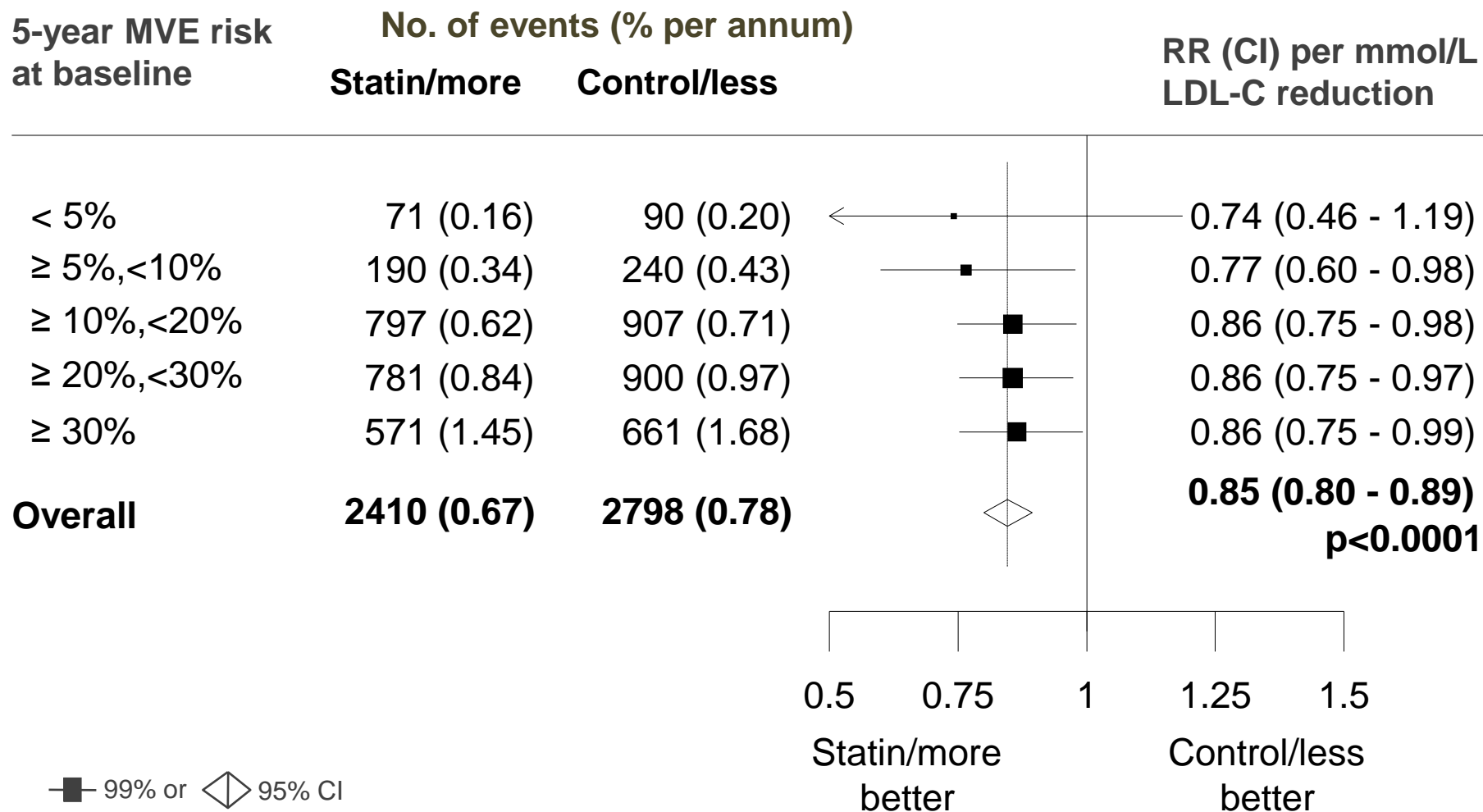
## Effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL-C at different levels of risk



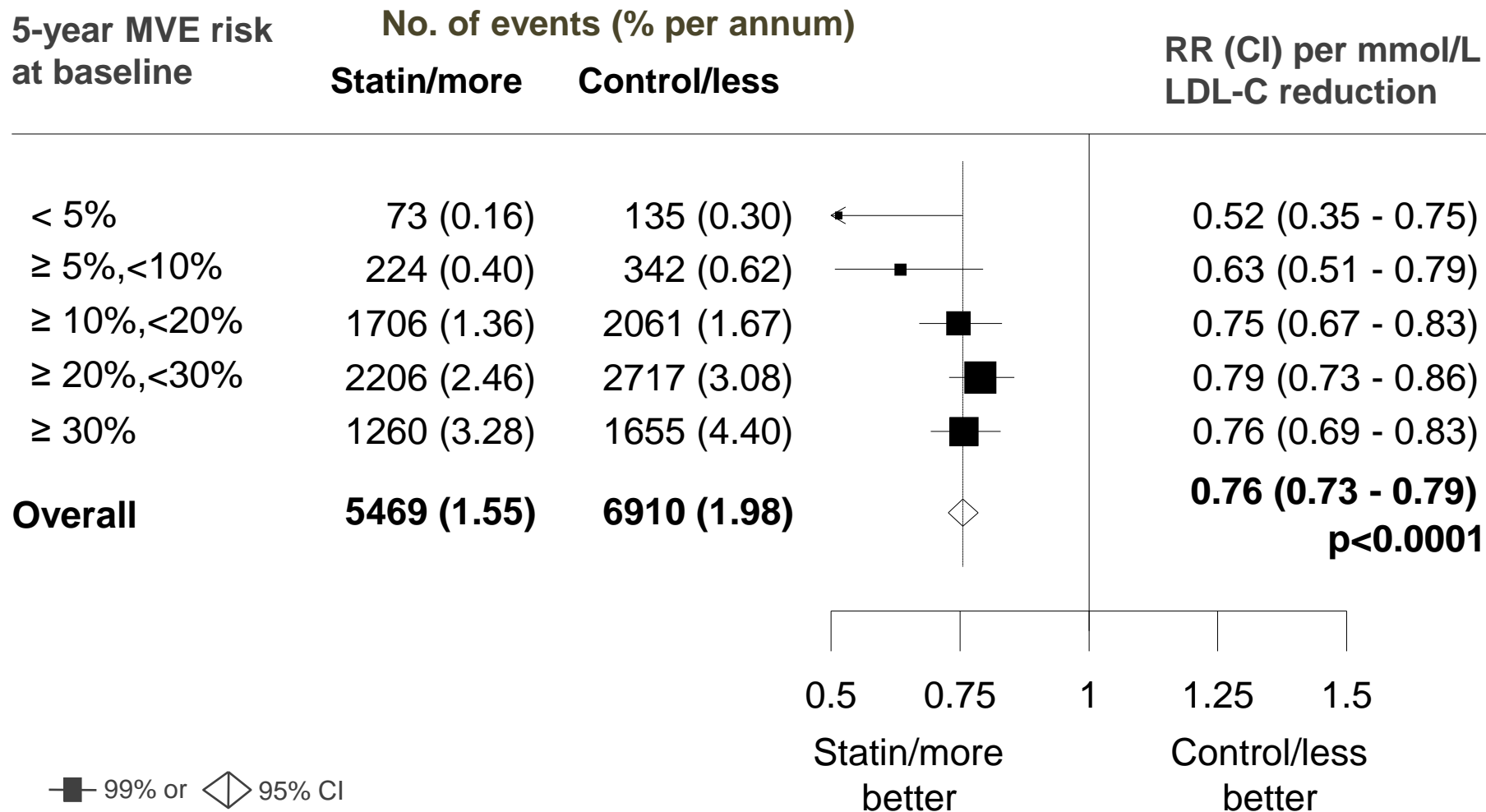
## Effects on MAJOR CORONARY EVENTS per mmol/L reduction in LDL-C at different levels of risk



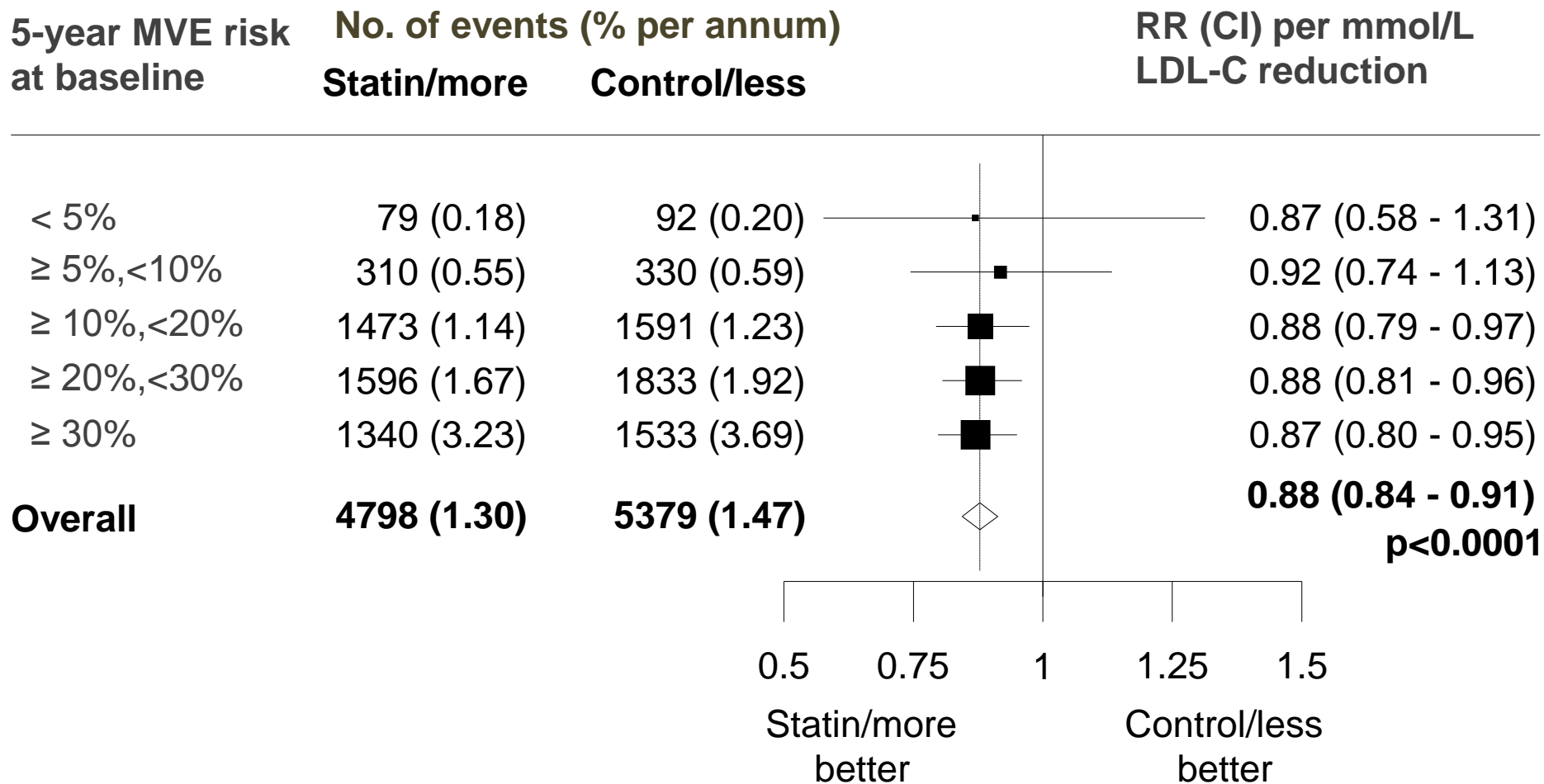
## Effects on ANY STROKE per mmol/L reduction in LDL-C at different levels of risk



## Effects on ANY CORONARY REVASCULARISATION per mmol/L reduction in LDL-C at different levels of risk

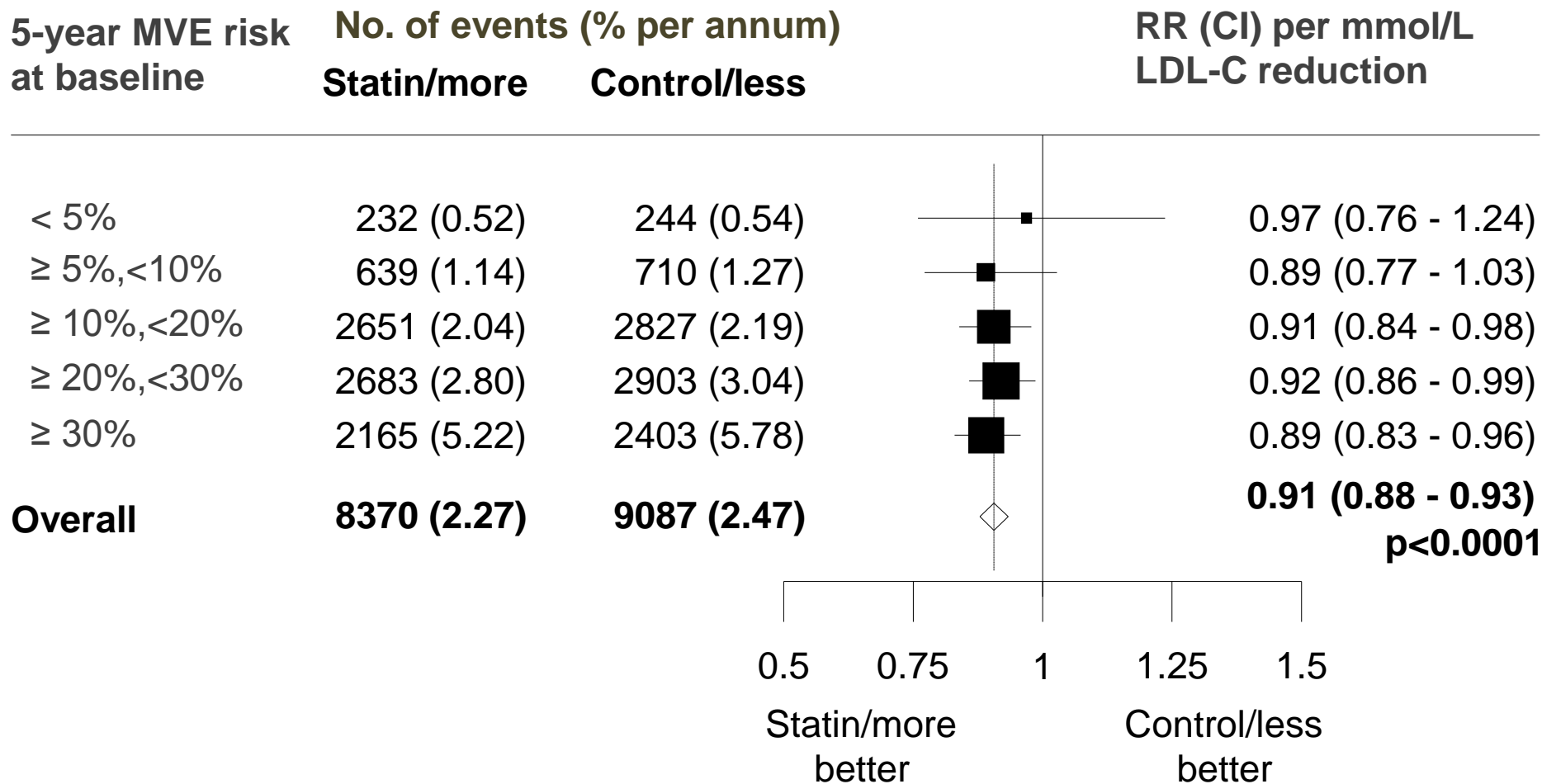


## Effects on VASCULAR MORTALITY per mmol/L LDL-C reduction at different levels of risk



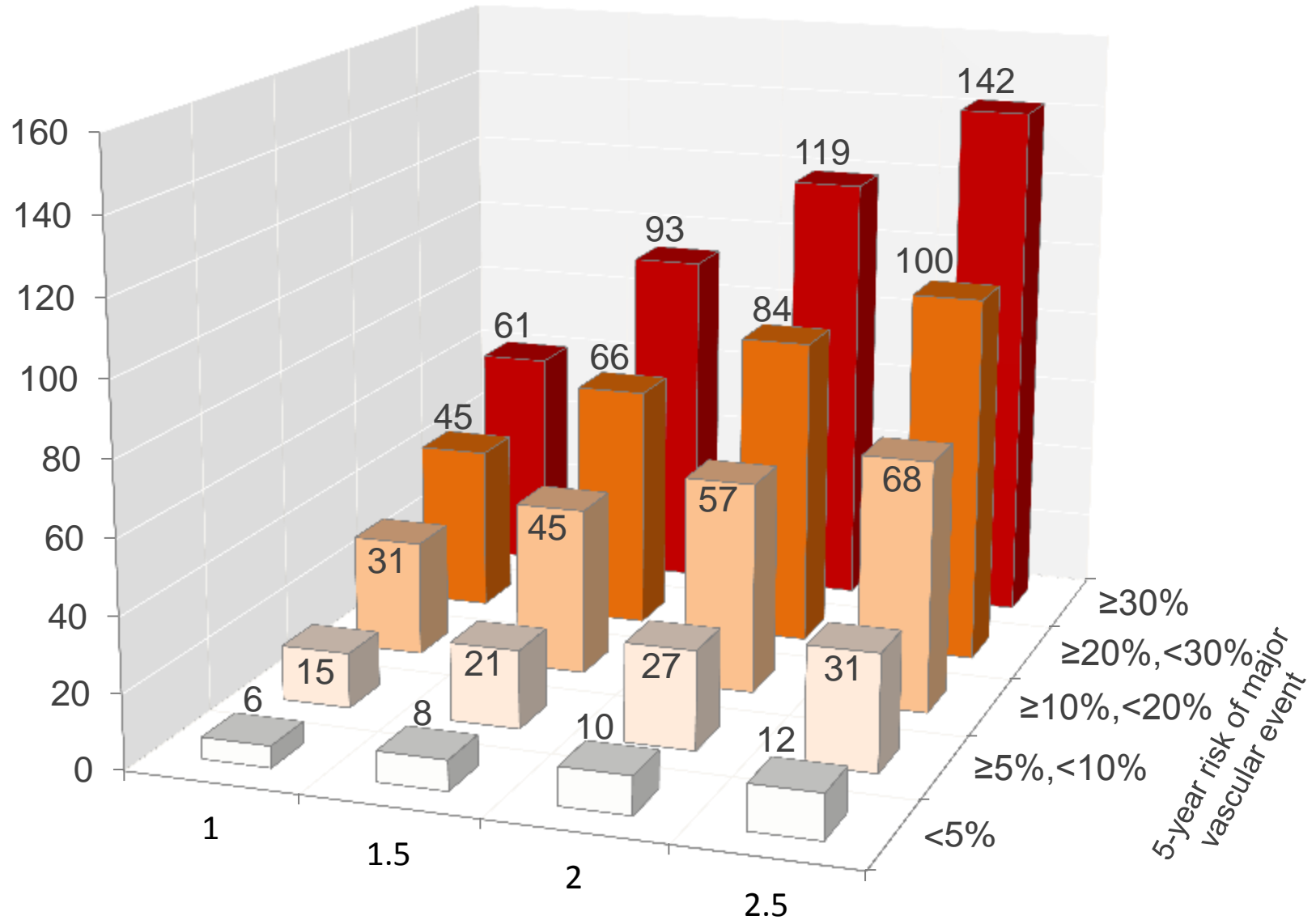
■ 99% or ◊ 95% CI

## Effects on ALL CAUSE MORTALITY per mmol/L LDL-C reduction at different levels of risk



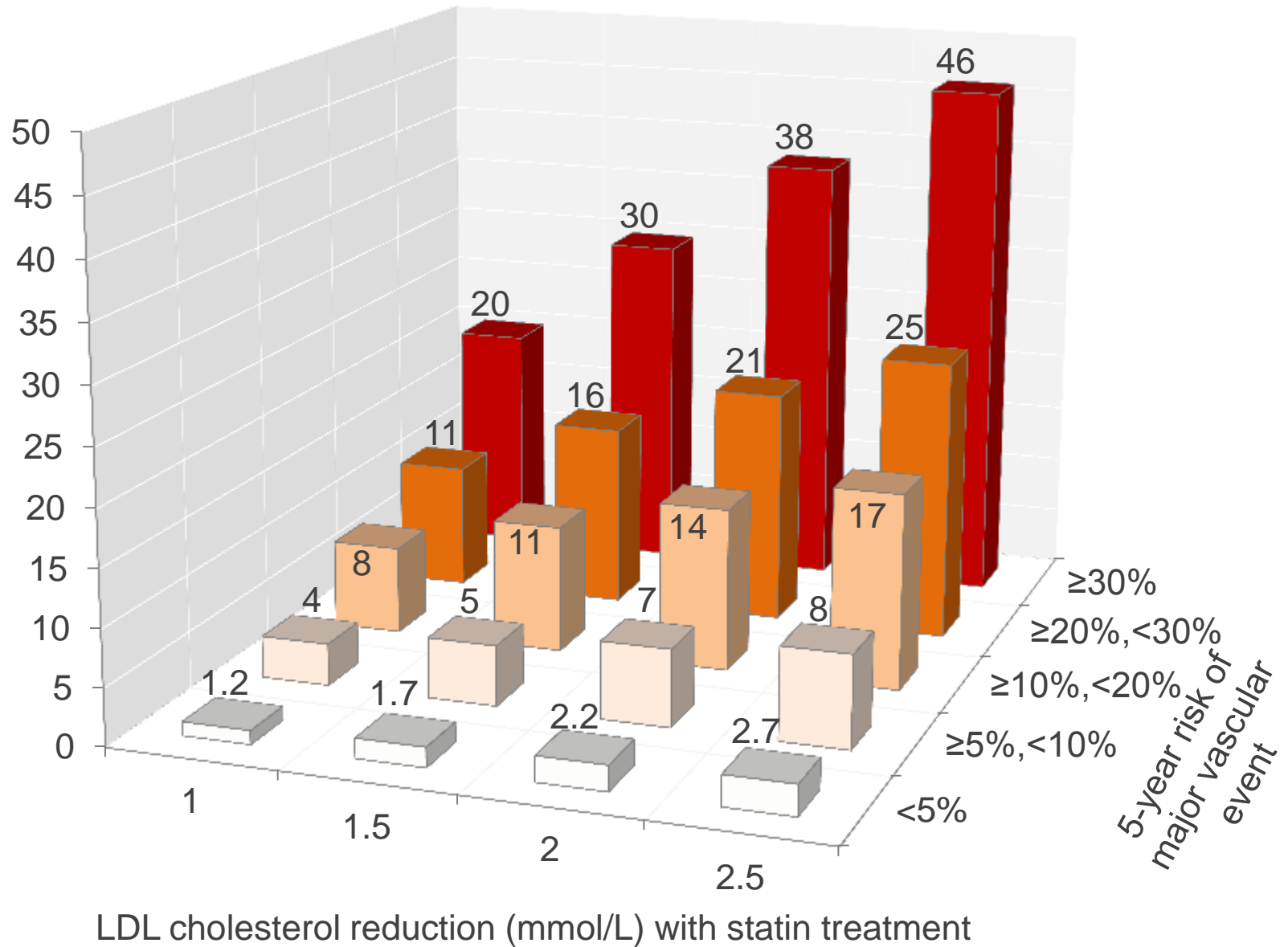
■ 99% or ◊ 95% CI

# MAJOR VASCULAR EVENTS avoided per 1,000 treated over 5 years



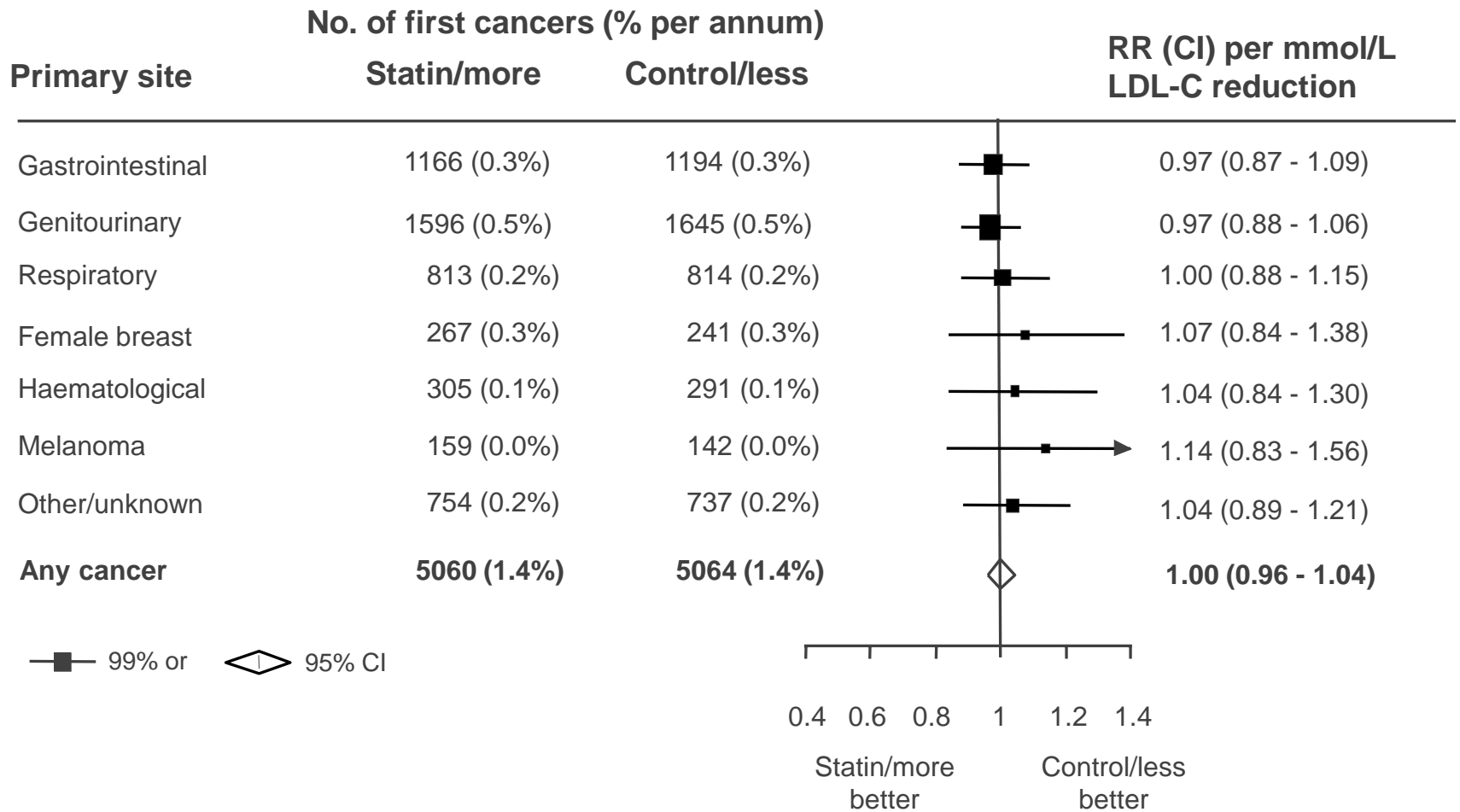
LDL cholesterol reduction (mmol/L) with statin treatment

# VASCULAR DEATHS avoided per 1,000 treated over 5 years

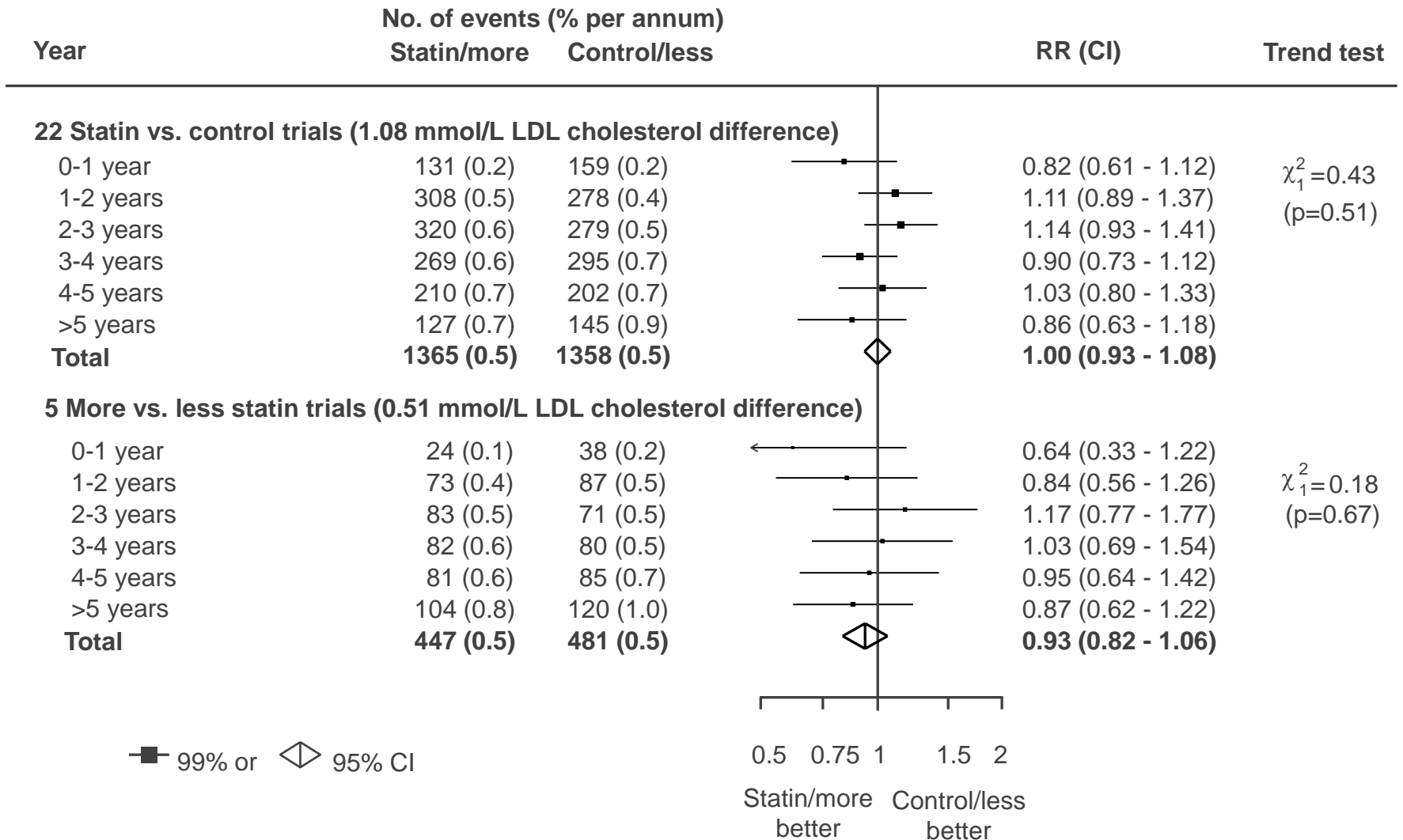




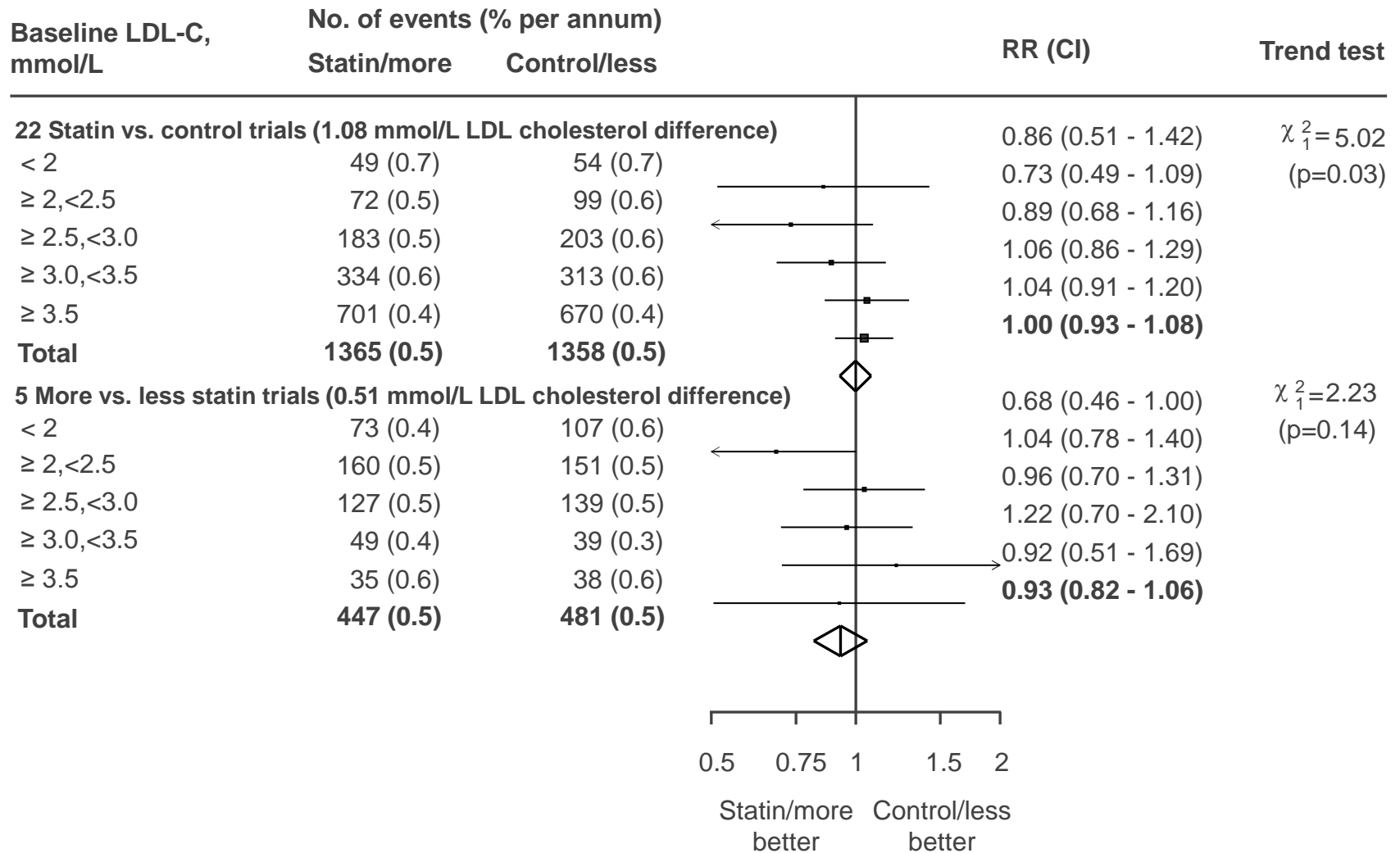
# Proportional effects on SITE SPECIFIC CANCER per mmol/L LDL-C reduction



# Effects of statin therapy on **CANCER MORTALITY** by duration of treatment



# Effects of statin therapy on **CANCER MORTALITY** by baseline LDL cholesterol



Thank you to our funders:



**Australian Government**  

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**National Health and  
Medical Research Council**

CTT Collaboration  
Cholesterol Treatment Trialists' Collaboration