


# Cholesterinsenkung im Alter – was ist gesichert ?

Symposium „Sekundärprävention des Schlaganfalls“

Deutsche Gesellschaft für Geriatrie (DGG)  
13. Jahrestagung      Fulda      05.11.2005

*M. Gogol      Klinik für Geriatrie*



**KRANKENHAUS LINDENBRUNN**

*Coppenbrügge*

# Atherosklerose

- **Chronisch-inflammatorischer Prozess**
- **Plaqueruptur**
  1. Endotheliale Blockade
  2. Aggressive LDL-Chol.-Senkung
  3. Inhibition der LDL-Oxidation
  4. Inhibition entzündl. Zytokine
  5. Thrombozytenfunktionshemmung

RS Munford – Statins and the acute-phase response. *N Engl J Med* 2001;344:2016-2018

P Libby – Inflammation in atherosclerosis. *Nature* 2002;420:868-874

JS Forrester – Prevention of plaque rupture: a new paradigm of therapy. *Ann Intern Med* 2002;137:823-833

# NCEP Adult Treatment Panel III – Guidelines I

## Hochrisikopatienten

- Bekannte Cardiovasculäre Erkrankung plus
- Diabetes mellitus oder
- Schwere / nicht beherrschte RF (z.B. weiteres Rauchen) oder
- Metabolisches Syndrom oder
- Akute Koronarsyndrome (Angina, AMI)

SM Grundy et al. – Implications of recent clinical trial for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. **Circulation** 2004;110:227-239

**National Cholesterol Education Program** (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. **Circulation** 2002;106:3143

Symposium „Sekundärprävention des Schlaganfalls“ Deutsche Gesellschaft für Geriatrie (DGG) Fulda 05.11.2005

M. Gogol – Cholesterinssenkung im Alter – was ist gesichert ?

# NCEP Adult Treatment Panel III – Guidelines II

- Very High Risk (< 70 mg/dl)
- High Risk (< 100 mg/dl)
- Moderately High Risk (2 o. >2 RF) (< 130 mg/dl)
- Lower Risk (0-1 RF) (< 160 mg/dl)
- **KHK:** MI, Angina, Koronarienprozedur
- **Risikoäquivalente Krankheiten:** pAVK, Aortenaneurysma, Carotisstenose, TIA, Diabetes
- **Risikofaktor:** Nikotin, Hypertonie, HDL < 40, positive Familienanamnese, Alter (Männer > 45 a, Frauen > 55 a)

SM Grundy et al. – Implications of recent clinical trial for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. **Circulation** 2004;110:227-239

**National Cholesterol Education Program** (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. **Circulation** 2002;106:3143

Symposium „Sekundärprävention des Schlaganfalls“ Deutsche Gesellschaft für Geriatrie (DGG) Fulda 05.11.2005

M. Gogol – Cholesterinssenkung im Alter – was ist gesichert ?

# Metanalyse Statine in RCTs

- 182 primäre Abstracts bzw. Originalarbeiten
- 29 bezüglich der Nutzung von Statinen selektiert, fünf erfüllten die Kriterien :
- die **Scandinavian Simvastatin Survival Study (4S)**  
[Simvastatin, Sek.präv.]
- die **West of Scotland Coronary Prevention Study (WOSCOPS)**  
[Pravastatin, Prim.präv]
- die **Cholesterol and Recurrent Events Trial (CARE)**  
[Pravastatin, Sek.präv.]
- die **Long-term Intervention With Pravastatin in Ischaemic Disease Trial (LIPID)** [Pravastatin, Sek.präv.]
- die **Airforce/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)** [Lovastatin, Prim.präv.]
- **30.817 Patienten eingeschlossen / mittlere Follow up-Zeit von 5,4 a / mittleres Alter 59 a (WOSCOP: Ausschluss Frauen + Alter > 65a)**

JC LaRosa et al. – Effect of statin on risk of coronary disease:  
A meta-analysis of randomised controlled trials. **JAMA** 1999;282:2340-6

# Statine bei alten Menschen ?

- CSE-Hemmer werden häufig genutzt
- Alle gut validierten, prospektiven RCT's mit signifikanter Überlegenheit bei
- **Männern, (Frauen), Weisse Rasse, Alter ca. 60 ± 10 a, selektierte Studienpopulation (wenig RF)**
  
- Bisher unzureichende Datenbasis bei
- Patienten > 75 a generell ?
- Patienten > 75 a mit Multimorbidität, insbes. dementiellen Syndromen und Frailty-Syndrom ?

LM Birch – Unanswered questions: The use of statins in older people to prevent cardiovascular event effects of statins on risk of coronary disease: A meta-analysis of randomized controlled trials.  
J Am Ger Soc 2002;50:391-393

# Limitationen im Alter / bei Frauen

- 47 RCTs 1990-2001
- 38 Sek.präv. oder Sek. + Primärpräev.
- 8 (17 %) Ausschluss von Frauen
- 18,6 (11,8-30) % Frauenanteil
- 14 berichten geschlechtskorrelierte Ergebnisse
- 31 (66 %) mit Altersausschluss (Median 70 a)
- 13 (28 %) Einschlussalteranteil  $\geq 65$  a mitgeteilt
- Nur 11 berichten alterskorrelierten Ergebnisse

C Bartlett et al. – Women, older persons, and ethnic minorities: factors associated with their inclusion in randomised trials of statin 1990 to 2001. **Heart** 2003;89:327-328

# Heart Protection Study HPS

- 20.536 Pat.,
- 40-80 a, 24 % > 70 a
- 40 mg Simvastatin vs. Placebo
- LDL  $\leq$  132 mg%
- Follow-up 5 a
- Ges.Mortalität  $\downarrow$  13 % (p=0,0003)
- Non-fatal MI, Koronarer Tod + Stroke  $\downarrow$  25 % (p<0,0001)
- Keine Unterschiede i.d. Ergebnissen bei Diabetes, Frauen, Alten (> 70a)
- Placebogruppe : 17 % Statine

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20.536 high-risk individuals: a randomised placebo-controlled trial. **Lancet** 2002;360:7

# PROSPER I

## Prospective Study of Pravastatin in the Elderly at Risk

- 2.804 M., 3.000 F.
- 75,3 ± 3,4 a
- Follow-up 3,2 a
- RF für cardiovaskuläre Erkrankungen
- 40 mg Pravastatin vs. Placebo
- Prim. EP: KHK Tod, n-fatal MI, fatal o. n-fatal Stroke

J Shepherd et al. – Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623

# PROSPER II

## Prospective Study of Pravastatin in the Elderly at Risk

- Kombin. Prim. EP ↓ 15 % (p=0,014)
- KHK Tod ↓ 24 % (p=0,043)
- N-fatal MI ↓
- New cancer ↑
  
- Effekte **NICHT** bei Frauen
- Effekte bei HDL < 1,11 mmol/l und **KEIN** Diabetes
- Primärprävention **NS**
- Sekundärprävention TIA/Stroke **NS**

J Shepherd et al. – Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623

# ALLHAT-LLT

## Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

- 10.355 Pat., 48 % Frauen
- $66 \pm 7,6$  a
- LDL mäßig  $\uparrow$  ( $129 \pm 21$  mg%)
- BMI  $29 \pm 6$
- Hypertonie + 1 kardiovaskulärer RF
- 40 mg Pravastatin vs. Placebo
- Kein Vorteil, da 30 % Statine in der Pl.gr.
- LDL-Senkung 17 vs. 8 %

The ALLHAT officers and coordinators for the ALLHAT collaborative research group.

Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care:

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). **JAMA** 2002;288:2998

**Symposium „Sekundärprävention des Schlaganfalls“ Deutsche Gesellschaft für Geriatrie (DGG) Fulda 05.11.2005**

**M. Gogol – Cholesterinssenkung im Alter – was ist gesichert ?**

# ASCOT-LLA

## Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm I

- 10.305 Pat., 63 ± 8,5 a, 19 % Frauen, 95 % weiss, Ges.Chol. ≤ 242 mg%
- Hypertonie + 3 weitere kardiovaskul. RF
- Follow-up 3,3 a
- Prim. EP: n-fatal MI + fatal KHK
- **Signifikanz:** Prim. EP (p 0,0005)
- **Sek. EP:** alle CV-Ereignisse + Prozeduren, alle Koronarereignisse, Stroke
- **Tert. EP:** Chronische KHK

PS Sever et al. – Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentration, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. **Lancet** 2003;361:1149

# ASCOT-LLA

## Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm II

### Sek. / Tert. EP n.s.

- Gesamtmortalität
- Kardiovaskul. Mortalität
- Herzinsuffizienz
- Stummer MI
- Instabile AP
- pAVK
- Diabetes-Entwicklung
- Niereninsuff.-Entwicklung

### Subgruppenanalyse n.s.

- Diabetes
- LVH
- Frauen
- Vorbesteh. Gefäßerkrankungen
- Niereninsuffizienz
- Metabol. Syndrom
- Alter  $\leq 60$  a

**PS Sever et al.** – Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentration, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. **Lancet** 2003;361:1149

# PROVE-IT

## Pravastatin or Atorvastatin Evaluation and Infection Therapy

- Akutes Koronarsyndrom
- 4.162 Pat.,  $58 \pm 11$  a, 78 % Männer, 90 % Weisse, LDL 106, HDL 39 mg%
- Follow-up 24 (18-36) Monate
- 40 mg Pravastatin vs. 80 mg Atorvastatin
- Atorv.  $\downarrow$  16 % LDL ( $p < 0,005$ )
- **NS:**  $> 65$ a, Diabetes, vorh. Statintherapie, LDL  $< 125$ , HDL  $\geq 40$

CP Cannon et al. – Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes.  
N Engl J Med 2004;350;1495

# CARDS

## Collaborative Atorvastatin Diabetes Study

- 2.838 Pat., 32 % Frauen, 94 % Weisse
- 61 a ± 8 a, 12 % ≥ 70 a, 38 % ≤ 60 a
- Diabetesdauer 7,8 ± 6,3 a, HbA1c 7,8 ± 1,4, BMI 28,8 ± 3,5
- Keine kardiovask. Vorerkrankung, LDL < 4,4, TG < 6,8 mmol/l
- 10 mg Atorvastatin vs. Placebo
- Median follow-up 3,9 a
- Prim. EP: Akute Koronarerereignisse, Coronare Revaskularisation, Stroke (p < 0,001)
- Nicht: Revaskularisation, Mortalität p = 0,059
- ALLHAT-LIT + ASCOT-LLA **negativ**
- HPS **positiv**

HM Colhoun et al. – Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685  
 A Garg – Statins for all patients with type 2 diabetes: not to soon. *Lancet* 2004;364:641  
 AS Gami et al. – Comment. *ACP Journal Club* 2005 March/April;142:29

# Observationsstudie

- 488 M + 922 F
- 81 ± 9 a
- LDL-Cholesterin > 125 mg%
- Follow-up 36 ± 21 Monate

	<u>Coronar events</u>	<u>New brain infarction</u>
<b>60 – 70 a</b>	36 vs 51 % (p 0,038)	13 vs 28 % (p 0,005)
<b>71 – 80 a</b>	43 vs 75 % (p <0,0001)	16 vs 33 % (p 0,0001)
<b>81 – 90 a</b>	49 vs 74 % (p <0,0001)	14 vs 24 % (p 0,002)
<b>91 – 100 a</b>	56 vs 81 % (p <0,0004)	14 vs 20 % (p 0,323)

**WS Aronow et al.** – Incidence of new coronary events in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol > 125 mg/dl treated with statins versus no lipid-lowering drug. **Am J Cardiol** 2002;89:67

**WS Aronow et al.** – Incidence of new atherothrombotic brain infarction in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol > 125 md/dl treated with statins versus no lipid-lowering drug. **J Gerontol** 2002;57A:333

**WS Aronow** – Should the NCEP III guidelines be changed in elderly and younger persons at high risk for cardiovascular events? **J Gerontol** 2005;60A:591-2(593—602)



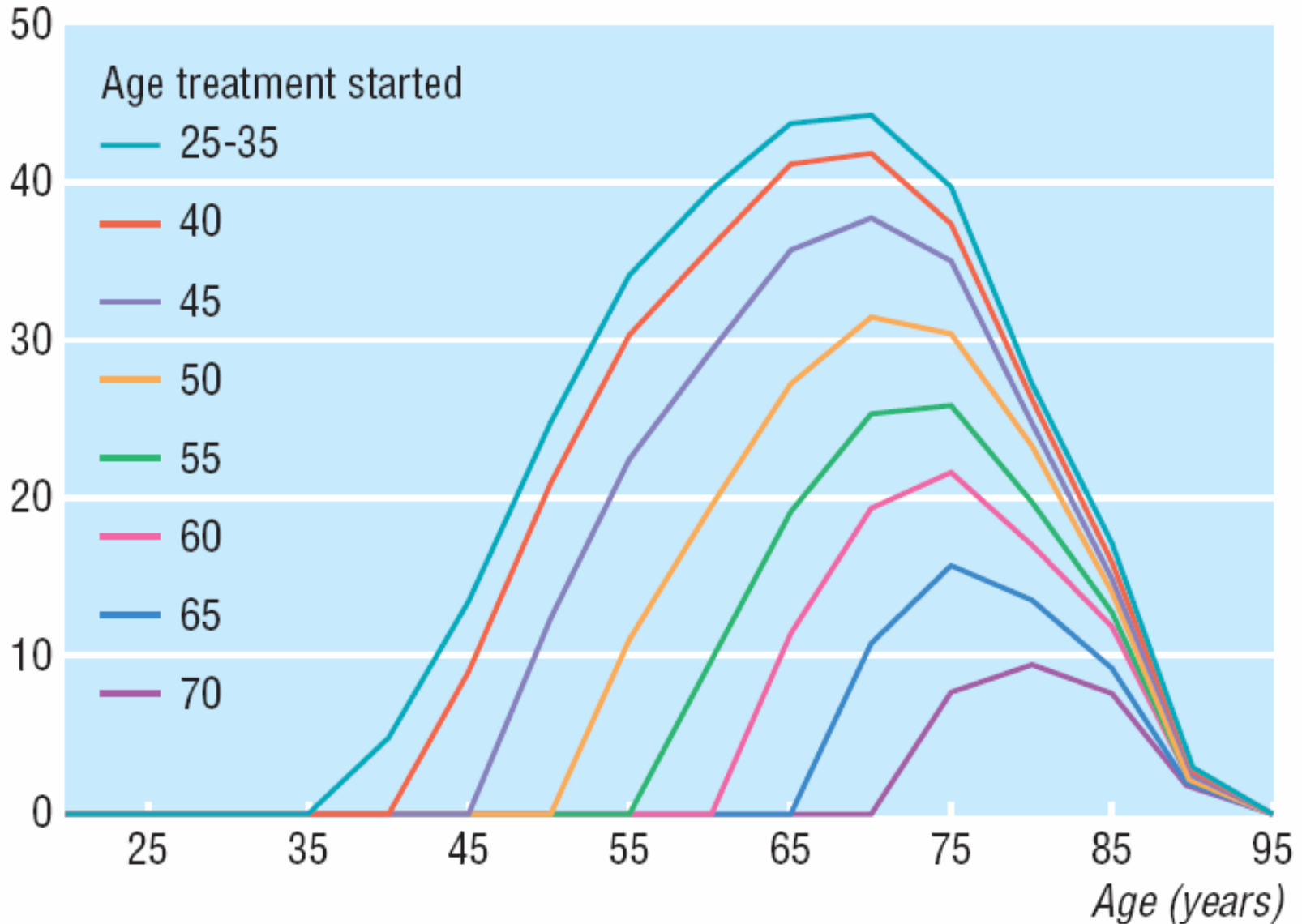
## Randomisierungsrate

**HPS:** von 63.603 Pat. → 20.536 (32 %)  
**PROSPER:** von 23.770 Pat. → 5.804 (25 %)  
**ALLHAT-LLT:** von 42.418 Pat. → 10.355 (25 %)  
**ASCOT-LLA:** von 19.342 Pat. → 10.305 (52 %)  
**PROVE-IT:** k.A.  
**REVERSAL:** von 2.163 Pat. → 657 (30 %)  
**CARDS:** von 4.053 Pat. → 2.841 (70 %)

## Thrombozytenaggregationshemmer

**HPS:** KA  
**Prosper:** KA  
**ALLHAT-LLT:** 30,3 vs. 31,6 %  
**ASCOT-LLA:** 17,1 vs. 16,9 %  
**CARDS:** 15 %

# Total number of life years free of cv events



S Ulrich et al. – What is the optimal age for starting lipid lowering treatment? A mathematical model. **BMJ** 2000;320:1134

# PROSPER – Stroke outcome

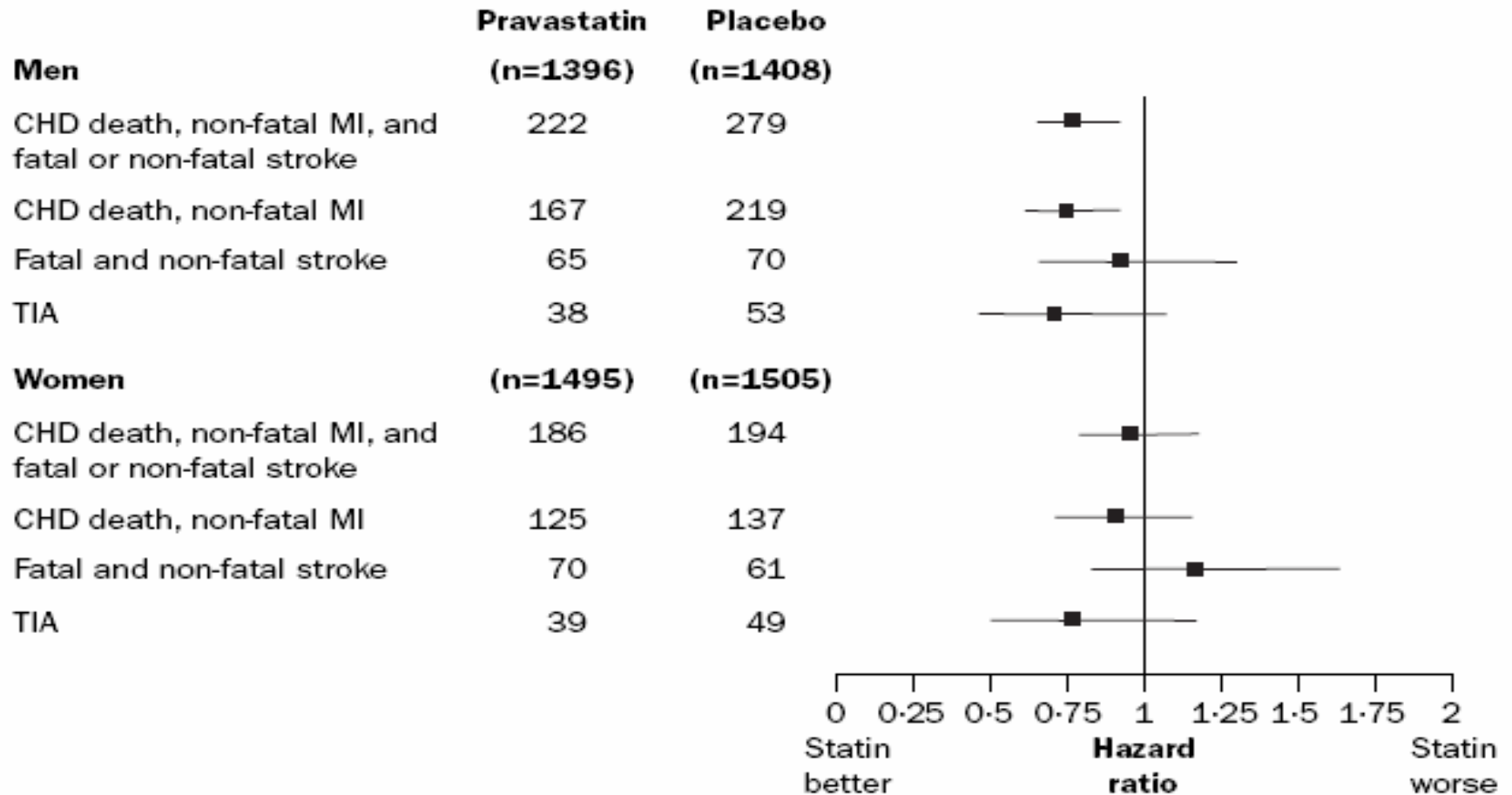


Figure 3: Major cardiovascular outcomes, according to sex

CHD=coronary heart disease. MI=myocardial infarction. TIA=transient ischaemic attack. The primary endpoint of the study is reproduced for comparative purposes.

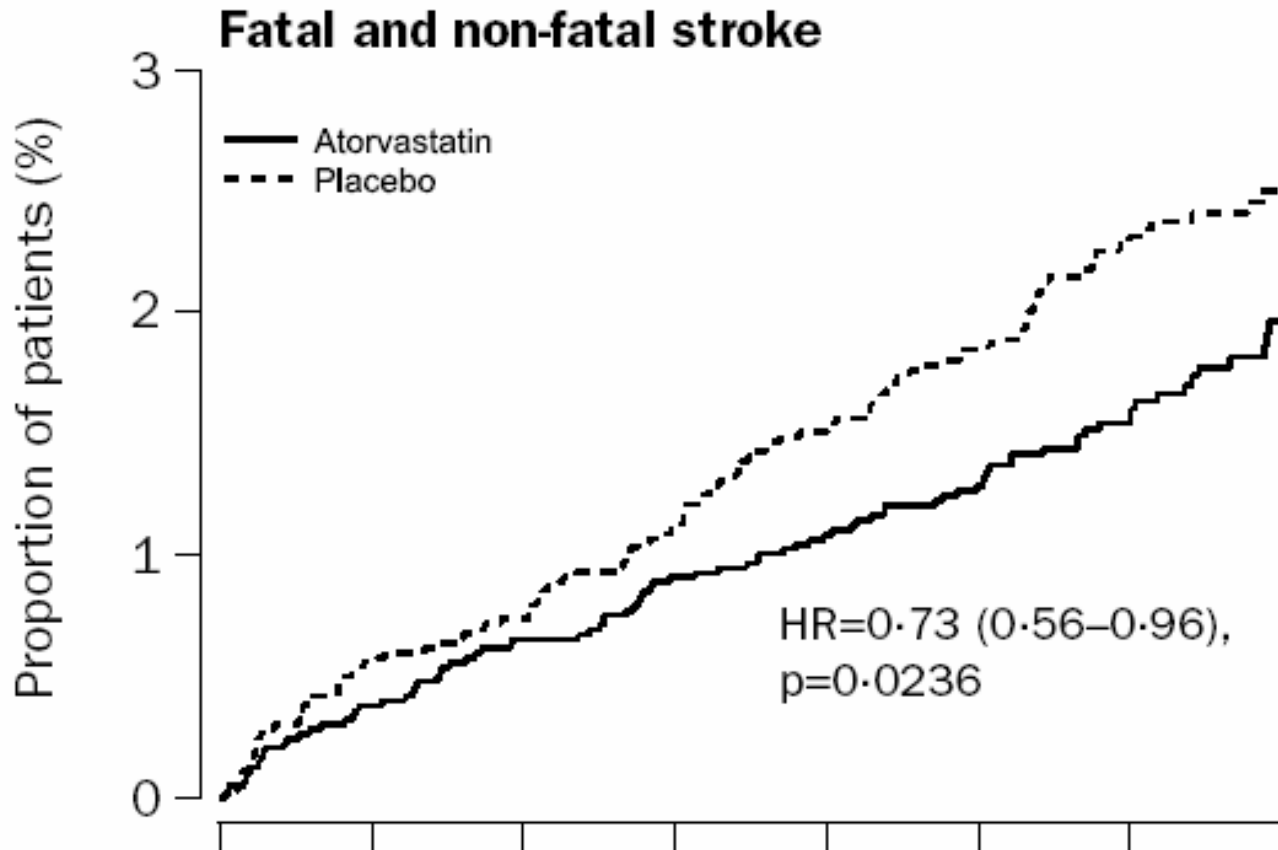
J Shepherd et al. – Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623

# ALLHAT-LLT – Stroke outcome

	<b>Pravastatin</b> Event rate % + SD	<b>Usual care</b> Event rate % + SD	Relative Risk (95 % CI)
<b>Stroke mortality</b>	2,1 ± 0,3	2,0 ± 0,3	0,95 (0,66 – 1,39)
<b>Stroke <i>fatal and non-fatal</i></b>	5,3 ± 0,4	5,8 ± 0,4	0,91 (0,75 – 1,09)

The ALLHAT officers and coordinators for the ALLHAT collaborative research group.  
 Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT).  
 JAMA 2002;288:2998

# ASCOT-LLA – Stroke outcome

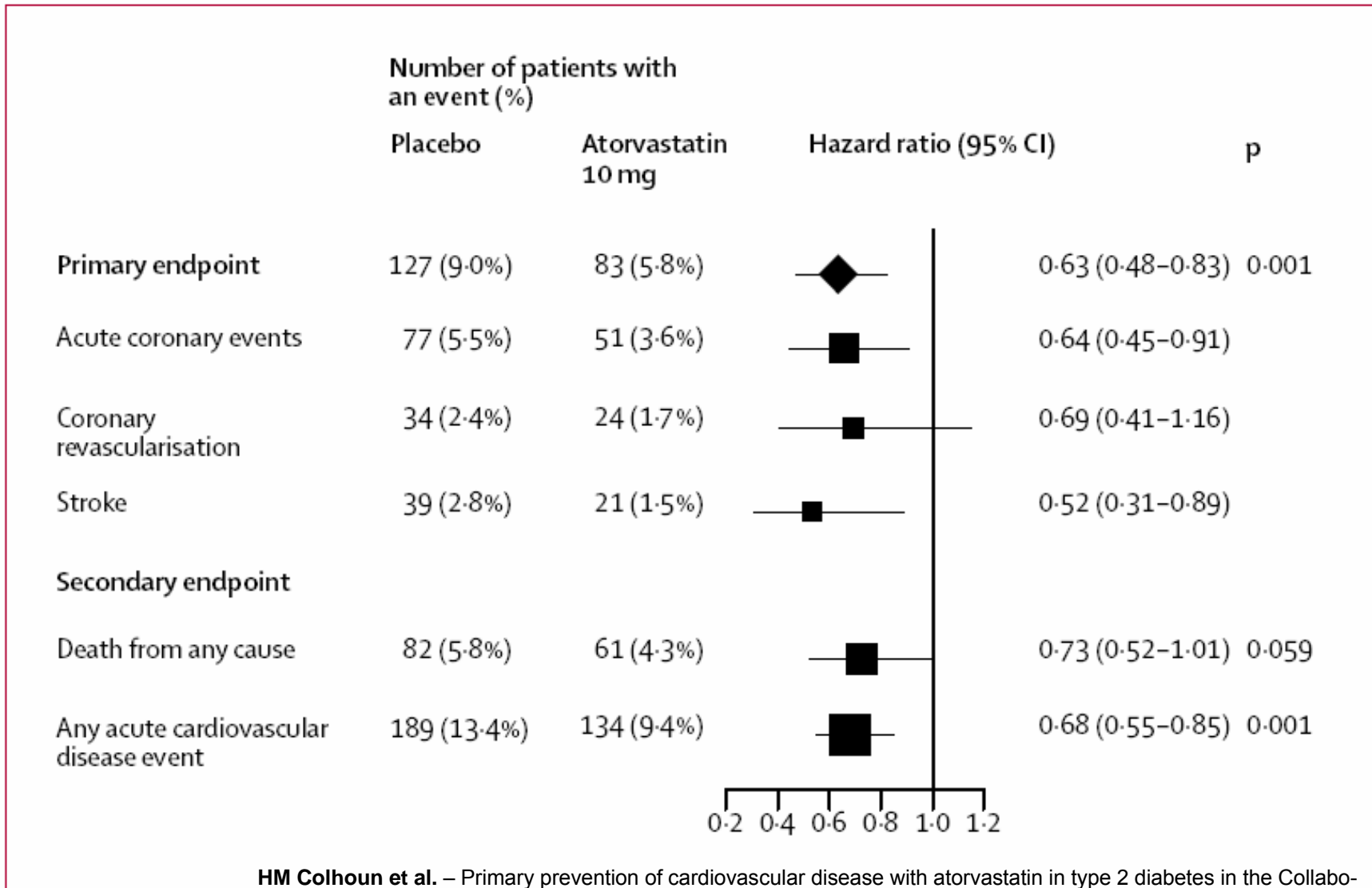


**Number at risk**

Placebo	5137	5085	5051	5014	4968	4609	3257	1808
Atorvastatin	5168	5128	5093	5054	5022	4669	3257	1797

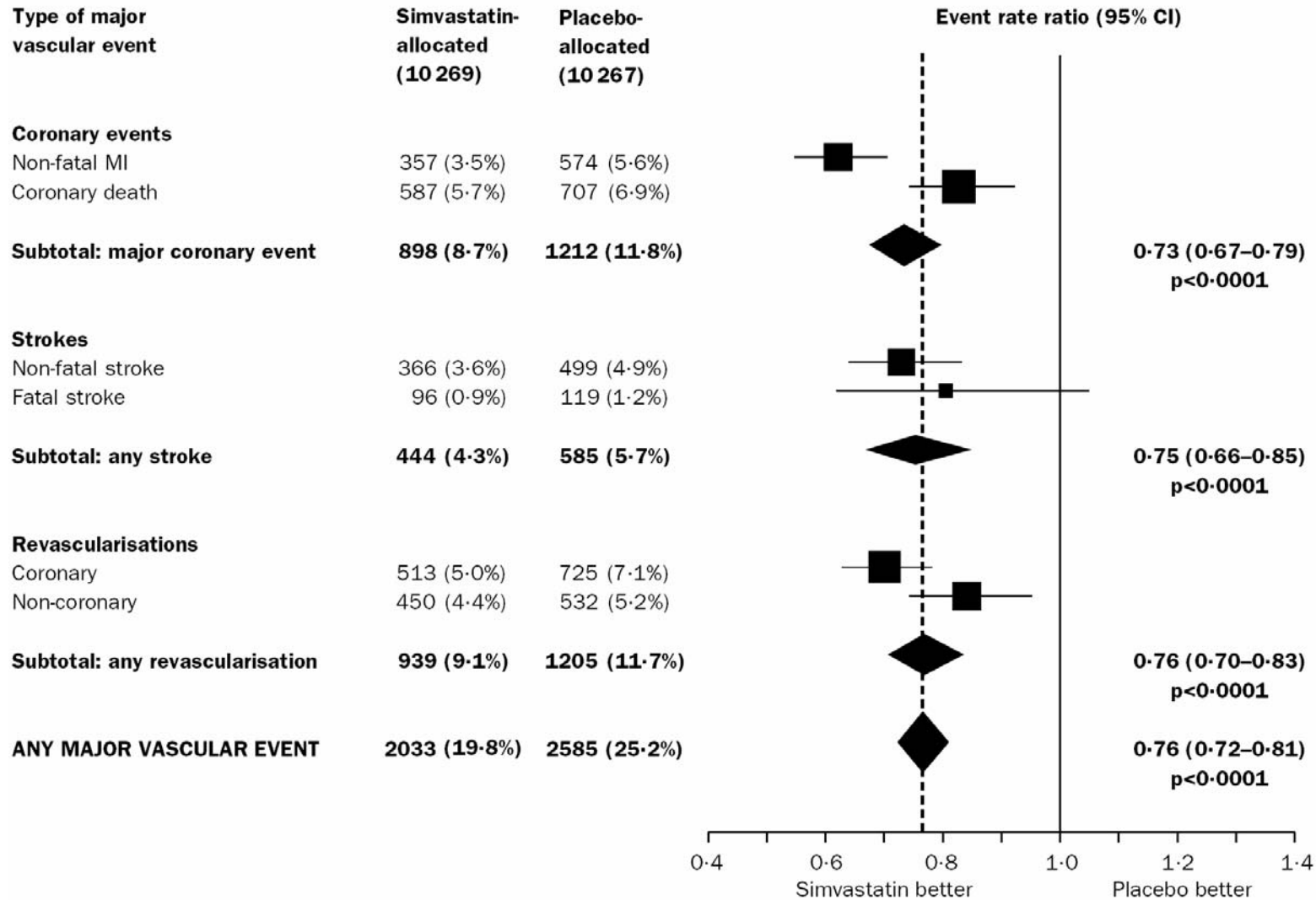
PS Sever et al. – Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentration, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. **Lancet** 2003;361:1149

# CARDS – Stroke outcome



HM Colhoun et al. – Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685

# HPS - Stroke outcome I



MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7

Figure 3: Effects of simvastatin allocation on first major coronary event, stroke, and revascularisation (defined prospectively as “major vascular events”)

# HPS - Stroke outcome II

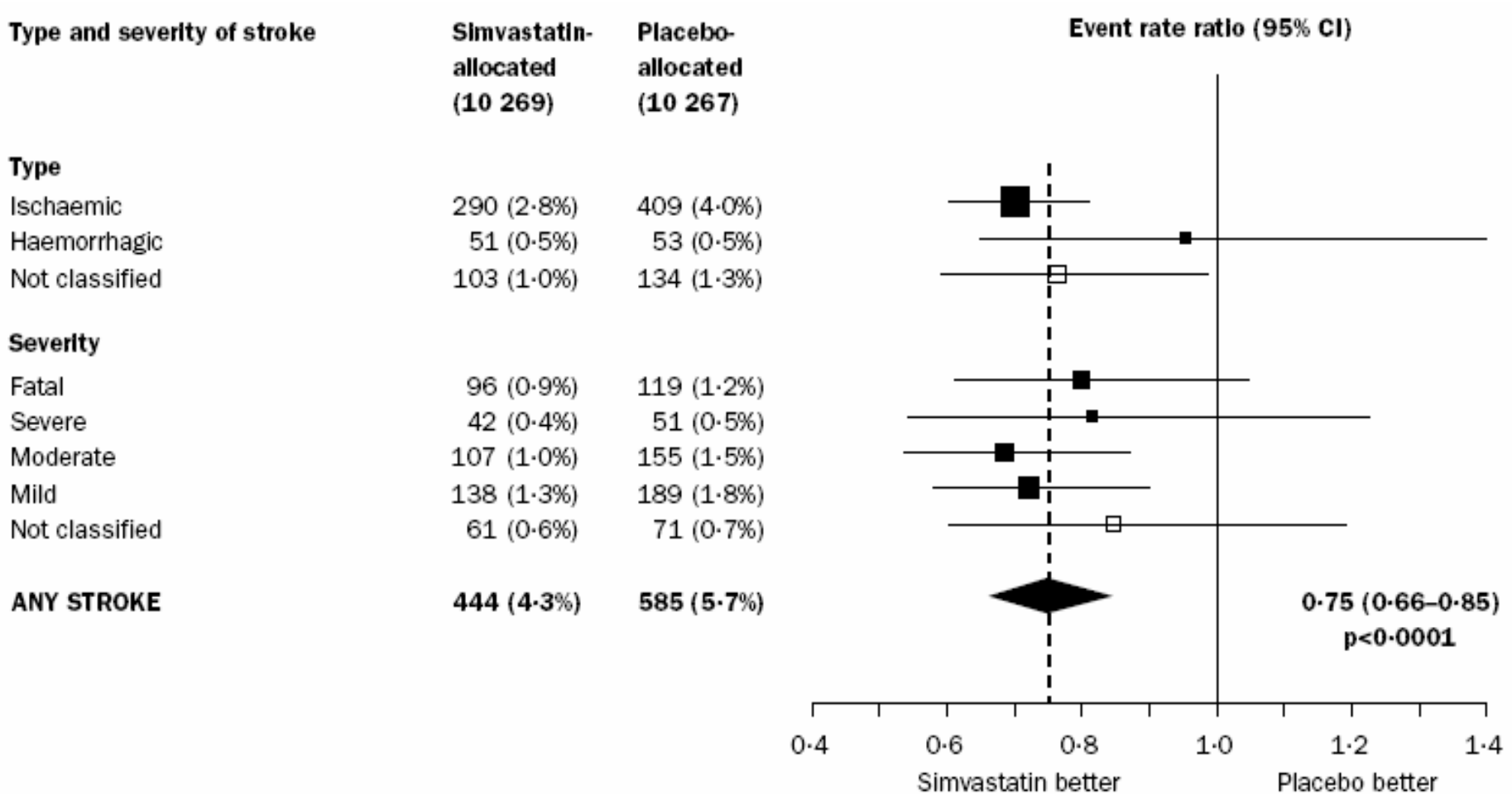


Figure 4: Effects of simvastatin allocation on first stroke

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7

	Dates of recruitment	Year of publication of primary results	Mean duration of follow-up (years)*	Treatment comparison (mg/day)†	Number of patients	Age range (years)	Women (%)	Diabetes (%)
4S	5/1988–8/1989	1994	5.2	S20–40 vs placebo	4444	35–70	827 (19%)	202 (5%)
WOSCOPS	2/1989–9/1991	1995	4.8	P40 vs placebo	6595	45–64	0	76 (1%)
CARE	12/1989–12/1991	1996	4.8	P40 vs placebo	4159	21–75	576 (14%)	586 (14%)
Post-CABG	3/1989–8/1991	1997	4.2	L40–80 vs L2.5–5	1351	21–74	102 (8%)	116 (9%)
AFCAPS/ TexCAPS	5/1990–2/1993	1998	5.3	L20–40 vs placebo	6605	45–73 (men) 55–73 (women)	997 (15%)	155 (2%)
LIPID	6/1990–12/1992	1998	5.6	P40 vs placebo	9014	31–75	1516 (17%)	782 (9%)
GISSI Prevention	1/1994–5/1996	2000	1.9	P20 vs no treatment	4271	19–90	587 (14%)	582 (14%)
LIPS	4/1996–10/1998	2002	3.1	F80 vs placebo	1677	18–80	271 (16%)	202 (12%)
HPS	7/1994–5/1997	2002	5.0	S40 vs placebo	20 536	40–80	5082 (25%)	5963 (29%)
PROSPER	12/1997–5/1999	2002	3.2	P40 vs placebo	5804	70–82	3000 (52%)	623 (11%)
ALLHAT–LLT	3/1994–5/1998	2002	4.8	P40 vs usual care	10 355	≥55	5051 (49%)	3638 (35%)
ASCOT–LLA	2/1998–5/2000	2003	3.2	A10 vs placebo	10 305	40–79	1942 (19%)	2527 (25%)
ALERT	6/1996–10/1997	2003	5.1	F40 vs placebo	2102	30–75	715 (34%)	396 (19%)
CARDS	11/1997–6/2001	2004	3.9	A10 vs placebo	2838	40–75	909 (32%)	2838 (100%)
Total	..	..	4.7	..	90 056	..	21 575 (24%)	18 686 (21%)

**Cholesterol Treatment Trialists' (CTT) Collaborators** – Efficacy and safety of cholesterol-lowering treatment: prospective Meta-analysis of data from 90 056 participants in 14 randomised trials of statins. **Lancet** 2005;366:1267-78

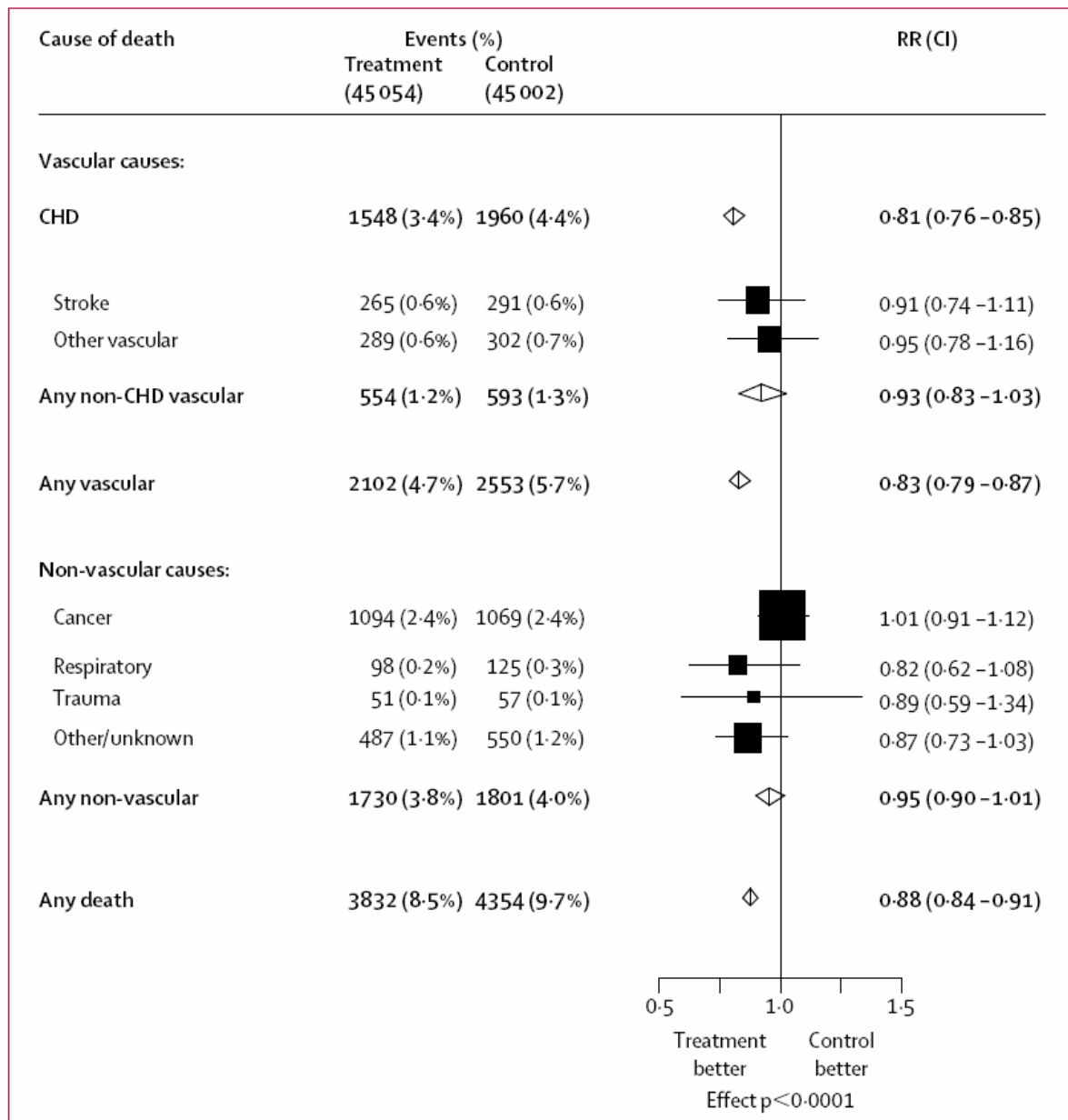
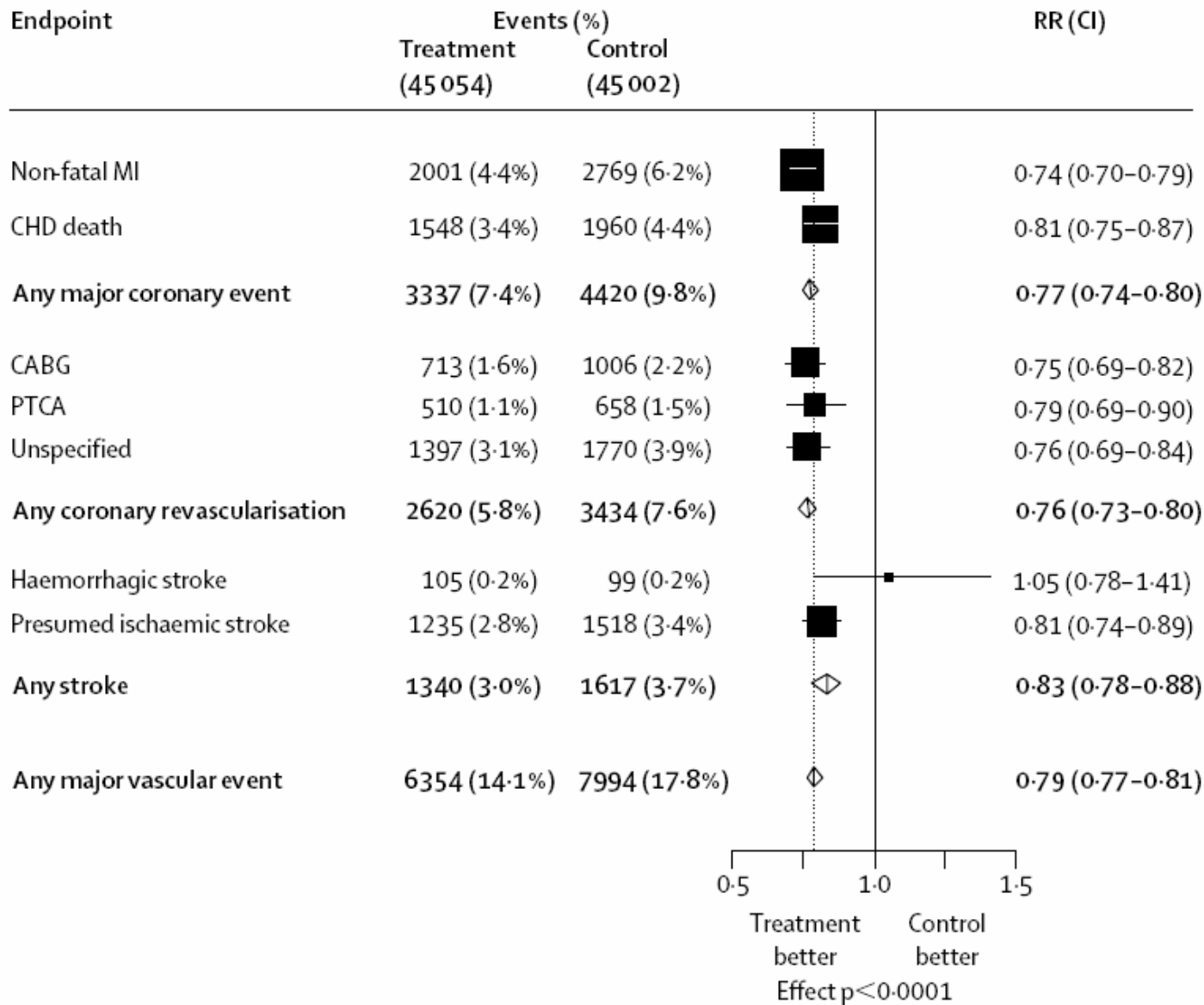


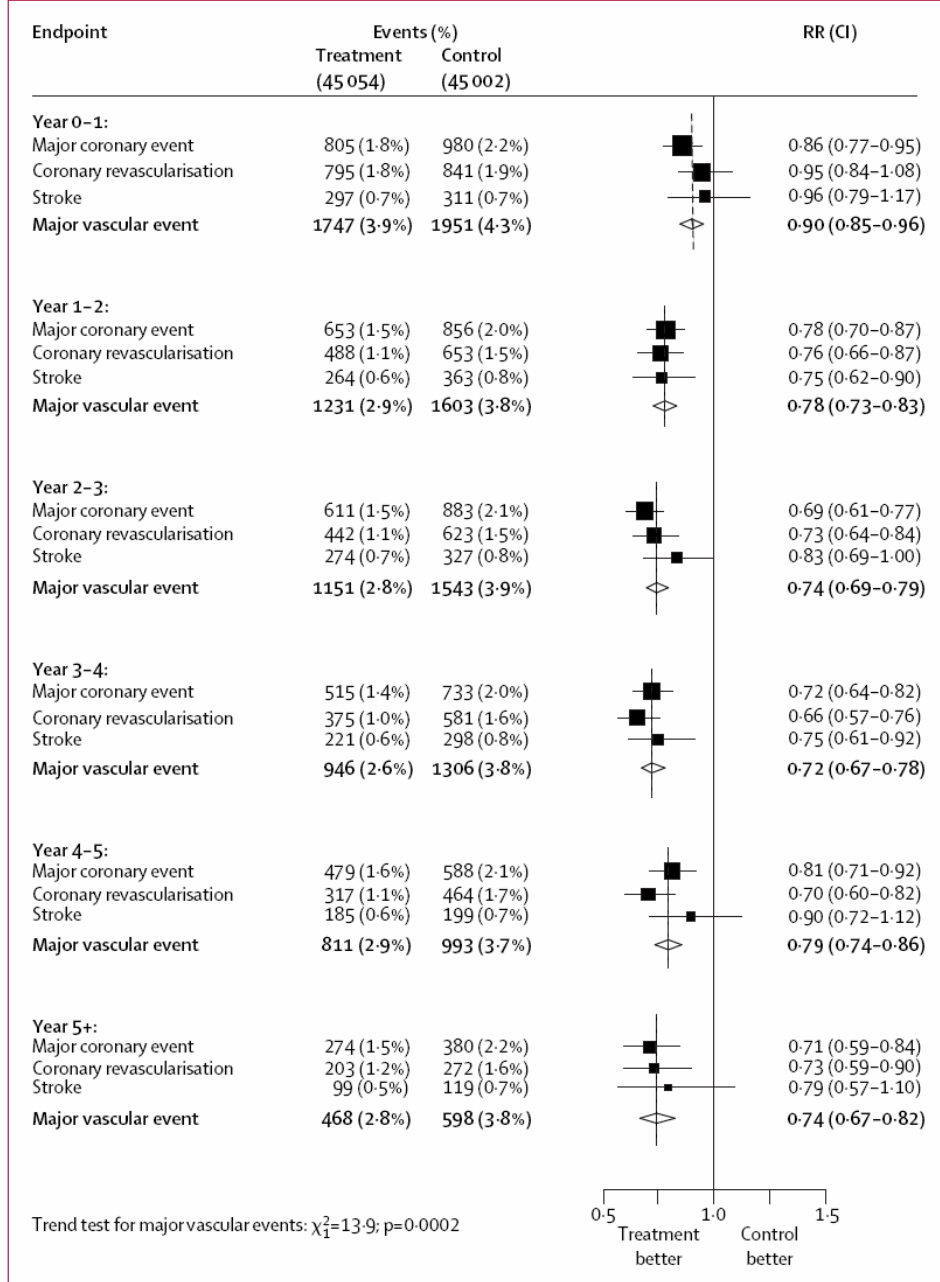
Figure 1: Proportional effects on cause-specific mortality per mmol/L LDL cholesterol reduction

**Cholesterol Treatment Trialists' (CTT) Collaborators** – Efficacy and safety of cholesterol-lowering treatment: prospective Meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-78



**Cholesterol Treatment Trialists' (CTT) Collaborators** – Efficacy and safety of cholesterol-lowering treatment: prospective Meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-78

Figure 2: Proportional effects on major vascular events per mmol/L LDL cholesterol reduction

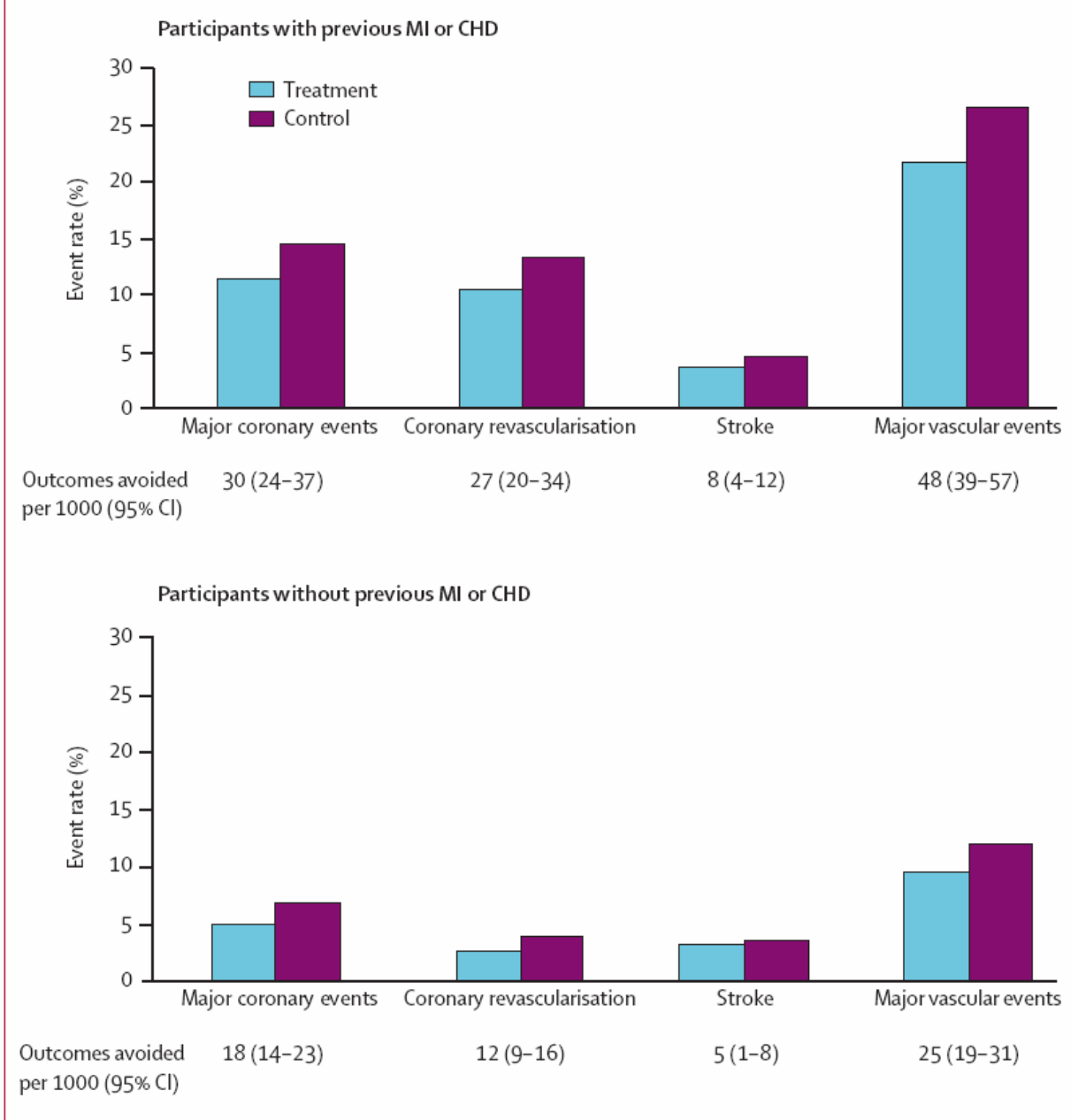


**Cholesterol Treatment Trialists' (CTT) Collaborators** – Efficacy and safety of cholesterol-lowering treatment: prospective Meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-78

Figure 4: Proportional effects on major vascular events per mmol/L LDL cholesterol reduction by year

Groups	Events (%)		RR (CI)	Heterogeneity/ trend test
	Treatment (45 002)	Control (45 054)		
<b>Previous disease:</b>				
Post-MI	1681 (11.7%)	2207 (15.4%)	0.78 (0.74-0.84)	$\chi^2=3.0$ ; $p=0.2$
Other CHD	568 (8.7%)	744 (11.4%)	0.77 (0.68-0.87)	
None	1088 (4.5%)	1469 (6.1%)	0.72 (0.66-0.80)	
<b>Age (years):</b>				
≤65	1671 (6.1%)	2344 (8.5%)	0.74 (0.69-0.79)	$\chi^2=6.6$ ; $p=0.01$
>65	1666 (9.5%)	2076 (11.9%)	0.81 (0.76-0.88)	
<b>Sex:</b>				
Male	2686 (7.8%)	3630 (10.6%)	0.76 (0.72-0.80)	$\chi^2=2.6$ ; $p=0.1$
Female	651 (6.1%)	790 (7.3%)	0.82 (0.73-0.93)	

**Cholesterol Treatment Trialists' (CTT) Collaborators** – Efficacy and safety of cholesterol-lowering treatment: prospective Meta-analysis of data from 90 056 participants in 14 randomised trials of statins. **Lancet** 2005;366:1267-78



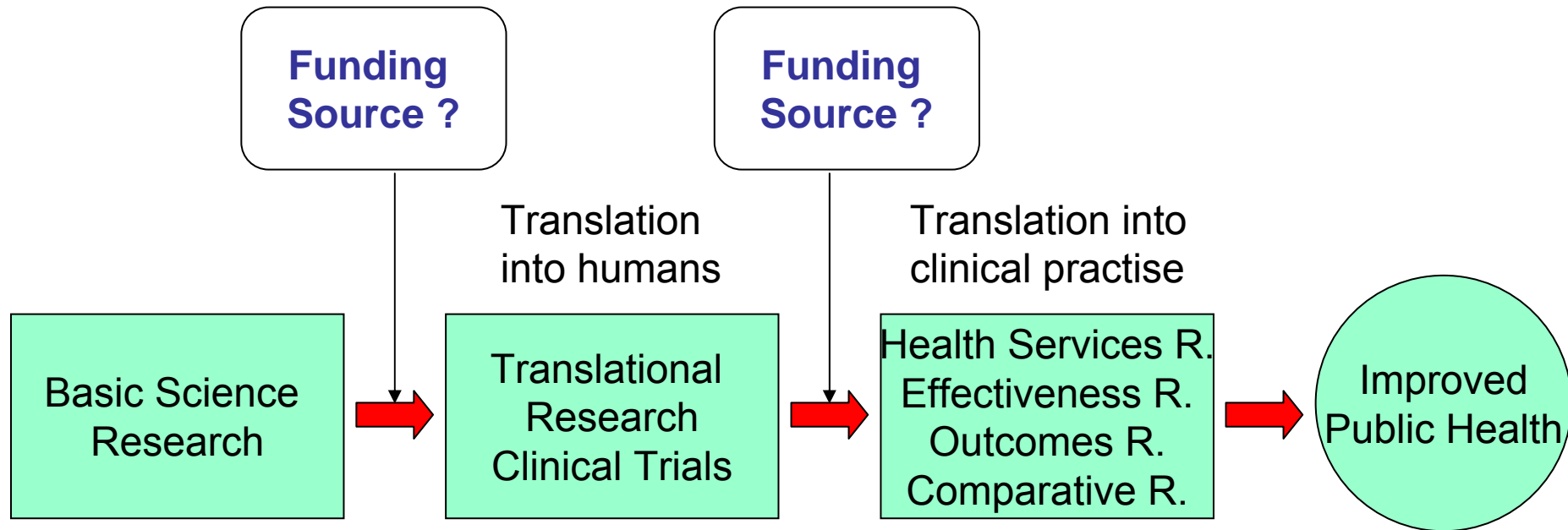
Cholesterol Treatment Trialists' (CTT) Collaborators – Efficacy and safety of cholesterol-lowering treatment: prospective Meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-78

Figure 6: 5-year absolute benefits on particular vascular outcomes per mmol/L LDL cholesterol reduction in participants with and without previous MI or CHD

# Statine Pro

**„All agree that the introduction of ... statins ... has revolutionized the practise of cardiovascular medicine. A series of well-known, well-designed, conclusive, and concordant studies has shown that statin therapy can reduce „hard“ end points, including myocardial infarction, stroke, and cardiovascular, and all-cause mortality in a broad variety of populations ...“**

P Libby, JT Willerson – Introduction. Circulation 2004;109[suppl II]:II-1



WP Crowley et al. – Clinical research in the United States at a crossroad. *JAMA* 2004;291:1120

# Take Home Message

- ✓ **Evidenz für KHK mit erhöhten LDL-Cholesterin bis 80 a**
- Zielgrösse der LDL-Senkung unklar
- Evidenz für Stroke, Diabetes etc. unklar
- RCT's mit Patienten > 80 a nicht existent
- Im Einzelfall diskutieren
- Cave Multipharmakotherapie
- Evidenz einzelne Substanz vs. Klasseneffekt unklar
- Evidenz für Kombinationstherapie (mit anderen lipidsenkenden Medikamenten) im hohen Lebensalter unklar
- Evidenz bei Multimorbidität unklar
- Evidenz bei vaskulärer und Alzheimer-Demenz unklar
- Lifestyle-Intervention generell empfohlen