



WISER HEALTHCARE

A RESEARCH COLLABORATION FOR REDUCING
OVERDIAGNOSIS AND OVERTREATMENT

What is the evidence for legacy effects of statins? A Systematic Review

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THE UNIVERSITY OF
SYDNEY

Background

Large statin trials → evidence of clear benefit

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PREVENTION OF CORONARY HEART DISEASE WITH PRAVASTATIN IN MEN WITH
HYPERCHOLESTEROLEMIA

THE LANCET

0169-5106/95/33320-0

**Randomised trial of cholesterol lowering in 4444 patients with
coronary heart disease: the Scandinavian Simvastatin Survival
Study (4S)**

ARTICLES

**Long-term effectiveness and safety of pravastatin in 9014
patients with coronary heart disease and average cholesterol
concentrations: the LIPID trial follow-up**

The LIPID Study Group*

**MRC/BHF Heart Protection Study of cholesterol lowering with
simvastatin in 20 536 high-risk individuals: a randomised placebo-
controlled trial**

Heart Protection Study Collaborative Group*

Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins



Cholesterol Treatment Trialists' (CTT) Collaborators*

	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 (%)	Baseline history of vascular disease (%)			
									MI	Other CHD‡	Other vascular§	None¶
4S	5/1988–8/1989	1994	5.2	S20–40 vs placebo	4444	35–70	827 (19%)	202 (5%)	3530 (79%)	914 (21%)	126 (3%)	0
WOSCOPS	2/1989–9/1991	1995	4.8	P40 vs placebo	6595	45–64	0	76 (1%)	0	338 (5%)	193 (3%)	6096 (92%)
CARE	12/1989–12/1991	1996	4.8	P40 vs placebo	4159	21–75	576 (14%)	586 (14%)	4159 (100%)	0	0	0
Post-CABG	3/1989–8/1991	1997	4.2	L40–80 vs L2.5–5	1351	21–74	102 (8%)	116 (9%)	662 (49%)	689 (51%)	37 (3%)	0
AFCAPS/ TexCAPS	5/1990–2/1993	1998	5.3	L20–40 vs placebo	6605	45–73 (men) 55–73 (women)	997 (15%)	155 (2%)	0	10 (<1%)	9 (<1%)	6431 (97%)
LIPID	6/1990–12/1992	1998	5.6	P40 vs placebo	9014	31–75	1516 (17%)	782 (9%)	5754 (64%)	3248 (36%)	905 (10%)	10 (<1%)
GISSI Prevention	1/1994–5/1996	2000	1.9	P20 vs no treatment	4271	19–90	587 (14%)	582 (14%)	4271 (100%)	0	179 (4%)	0
LIPS	4/1996–10/1998	2002	3.1	F80 vs placebo	1677	18–80	271 (16%)	202 (12%)	744 (44%)	933 (56%)	142 (8%)	0
HPS	7/1994–5/1997	2002	5.0	S40 vs placebo	20 536	40–80	5082 (25%)	5963 (29%)	8510 (41%)	4876 (24%)	8865 (43%)	3161 (15%)
PROSPER	12/1997–5/1999	2002	3.2	P40 vs placebo	5804	70–82	3000 (52%)	623 (11%)	776 (13%)	1105 (19%)	1026 (18%)	3254 (56%)
ALLHAT–LLT	3/1994–5/1998	2002	4.8	P40 vs usual care	10 355	≥55	5051 (49%)	3638 (35%)	0	1188 (11%)	0	9167 (89%)
ASCOT–LLA	2/1998–5/2000	2003	3.2	A10 vs placebo	10 305	40–79	1942 (19%)	2527 (25%)	0	15 (<1%)	1435 (14%)	8860 (86%)
ALERT	6/1996–10/1997	2003	5.1	F40 vs placebo	2102	30–75	715 (34%)	396 (19%)	319 (15%)	81 (4%)	241 (11%)	1702 (81%)
CARDS	11/1997–6/2001	2004	3.9	A10 vs placebo	2838	40–75	909 (32%)	2838 (100%)	0	9 (<1%)	97 (3%)	2738 (96%)
Total	4.7	..	90 056	..	21 575 (24%)	18 686 (21%)	28 725 (32%)	13 406 (15%)	13 255 (15%)	41 354 (46%)

Recent reports on long term follow up after the initial statin trials



Long-Term Follow-up of the West of Scotland Coronary Prevention Study

Ian Ford, Ph.D., Heather Murray, M.Sc., Chris J. Packard, D.Sc., James Shepherd, M.D., Peter W. Macfarlane, D.Sc., and Stuart M. Cobbe, M.D., for the West of Scotland Coronary Prevention Study Group

Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial



Heart Protection Study Collaborative Group*

Summary

Background Findings of large randomised trials have shown that lowering LDL cholesterol with statins reduces vascular morbidity and mortality rapidly, but limited evidence exists about the long-term efficacy and safety of statin treatment. The aim of the extended follow-up of the Heart Protection Study (HPS) is to assess long-term efficacy and safety of lowering LDL cholesterol with statins, and here we report cause-specific mortality and major morbidity in the in-trial and post-trial periods.

Lancet 2011; 378: 2013-20
Published Online
November 23, 2011
DOI:10.1016/S0140-6736(11)61125-2

Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S)

Timo E Strandberg, Kalevi Pyörälä, Thomas J Cook, Lars Wilhelmsen, Ole Faergeman, Gudmundur Thorgeirsson, Terje R Pedersen, John Kjekshus, for the 4S Group*

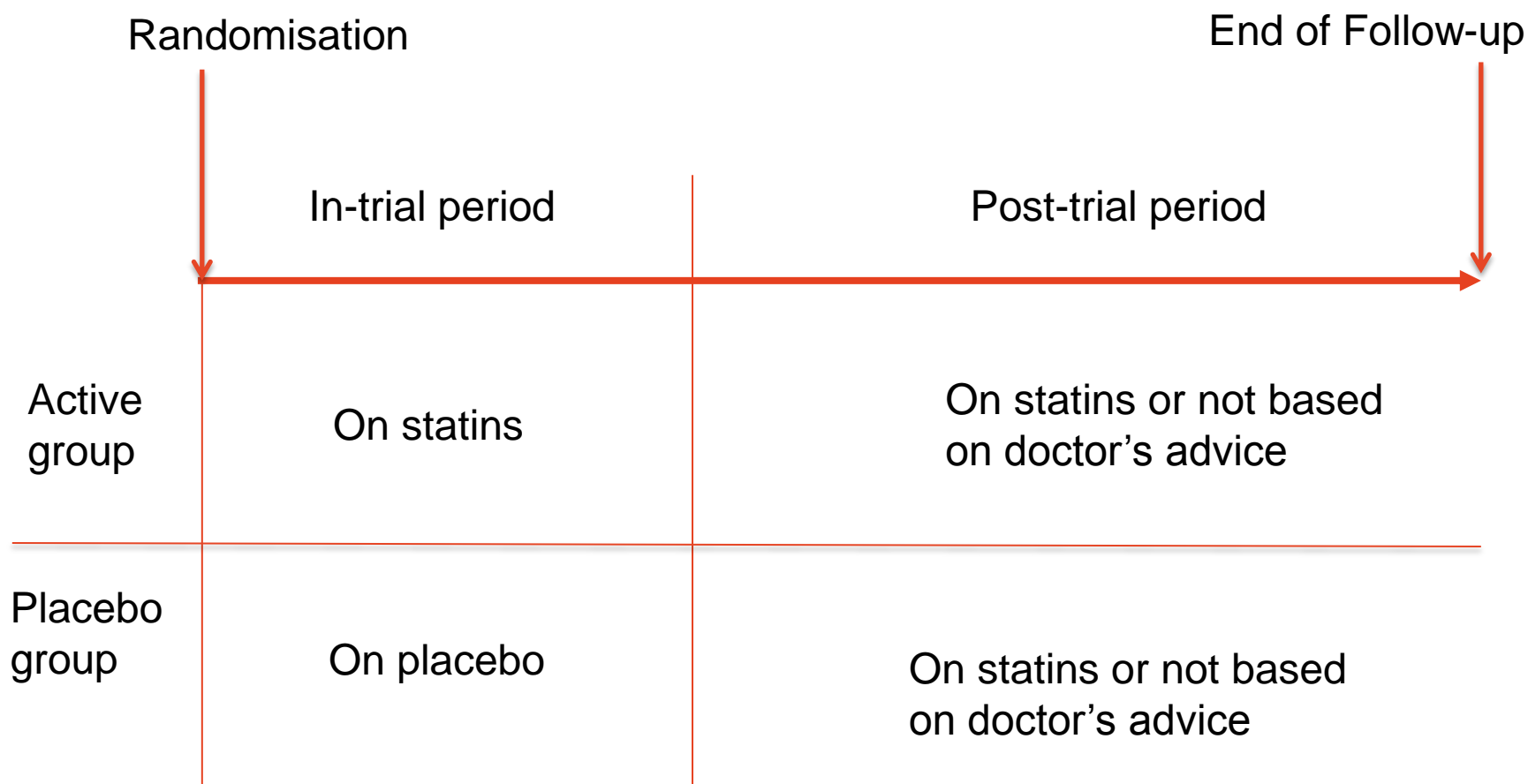
Lancet 2004; 364: 771-77
Department of Medicine,
University of Helsinki, Helsinki,

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial

Heart Protection Study Collaborative Group*

'Legacy Effect'

Reports of survival benefit at long term follow-up from time of randomisation



Findings being extropolated to clinical practice

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<http://dx.doi.org/10.1016/j.jacc.2014.04.009>

VIEWPOINTS AND COMMENTARY

Viewpoint

Curing Atherosclerosis Should Be the Next Major Cardiovascular Prevention Goal



Jennifer G. Robinson, MD, MPH,* Samuel S. Gidding, MD†‡

Iowa City, Iowa; Wilmington, Delaware; and Philadelphia, Pennsylvania

'short-term, aggressive LDL-C-lowering intervention... [starting] early in adolescence and early adulthood'

'Legacy Effect'

Figure 1. Cumulative events over the 20-year follow-up period.

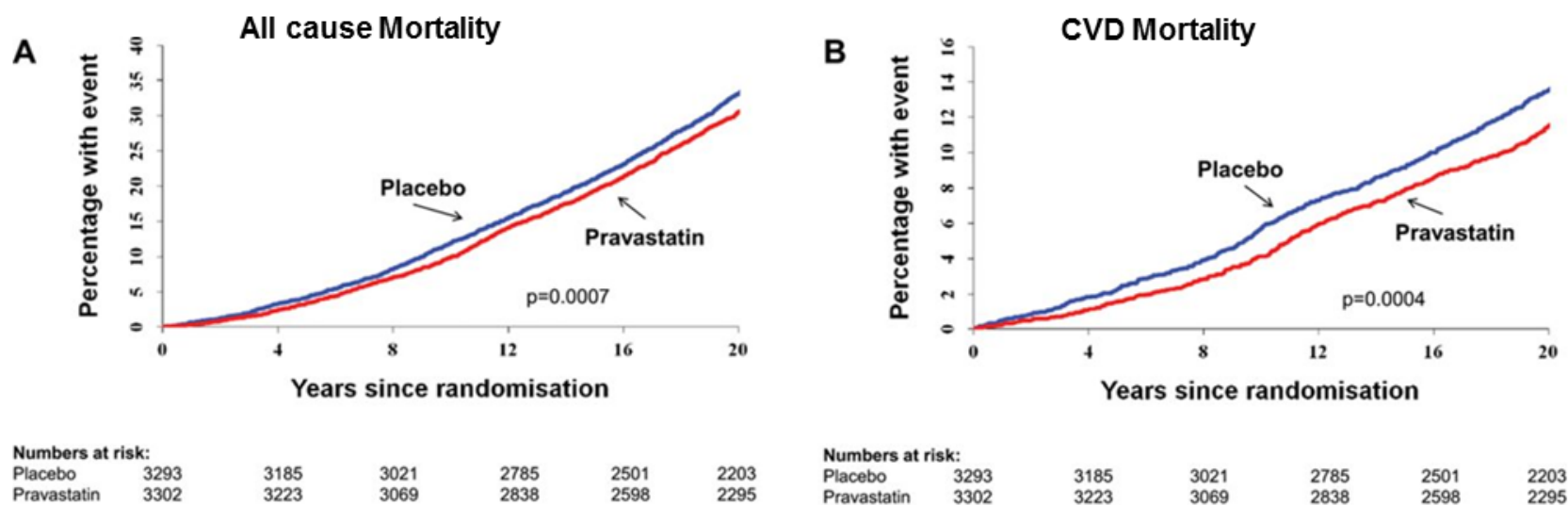
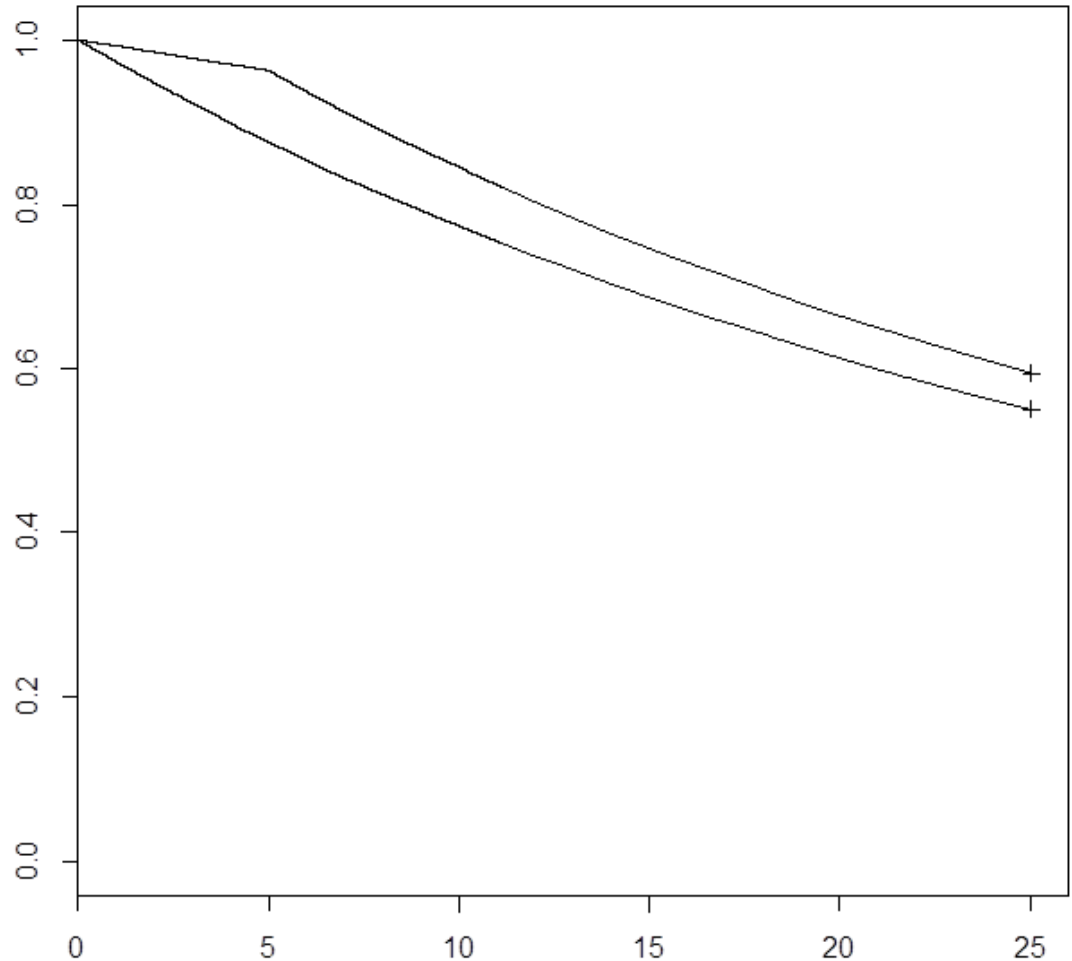


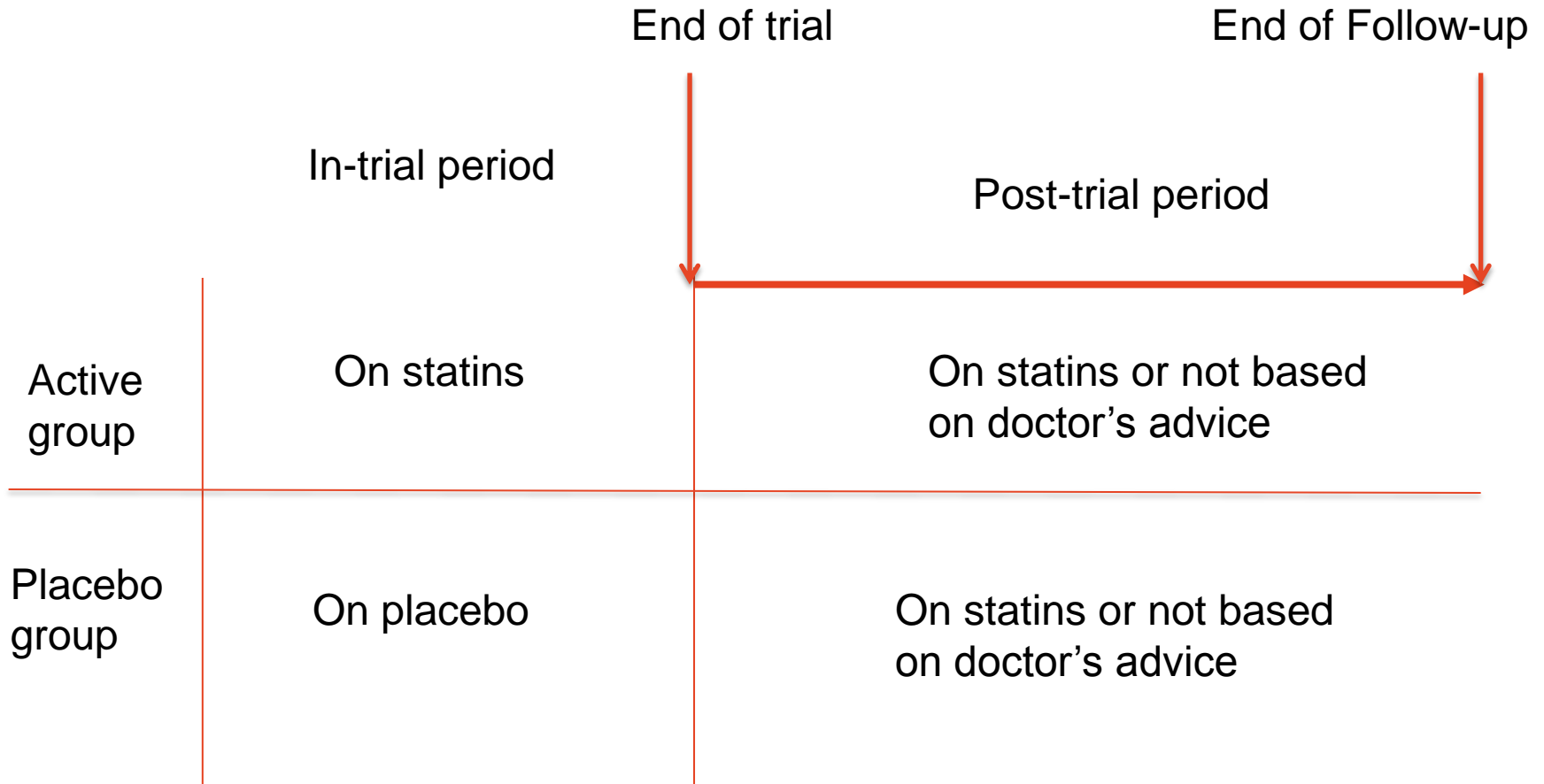
Figure modified from one presented in : Ian Ford et al.
Circulation. 2016;133:1073-1080

But Survival benefit may be explained by in-trial period

Survival Curves using simulated data where HR after trial = 1
i.e. no legacy effect



Need to focus on the post-trial period for evidence of legacy effect



What is the evidence for legacy effects of statins?

Is there evidence of a legacy effect on:

1. All cause mortality?
2. CVD mortality?

Systematic review of long term follow-up after placebo controlled RCTS of statins in adults

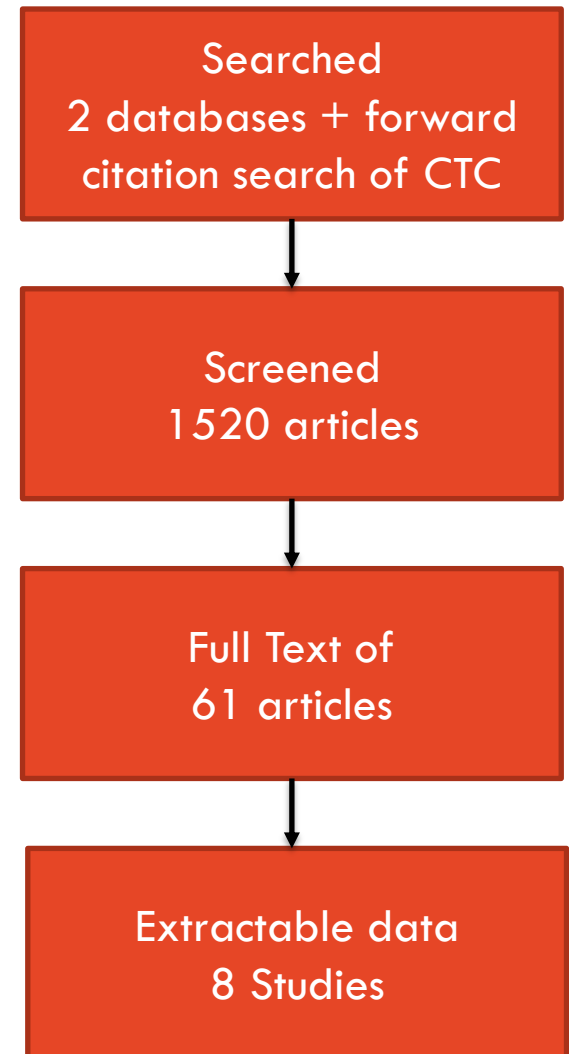
SEARCH FOR:

Reports on long term follow-up after placebo controlled RCTS of statins in adults

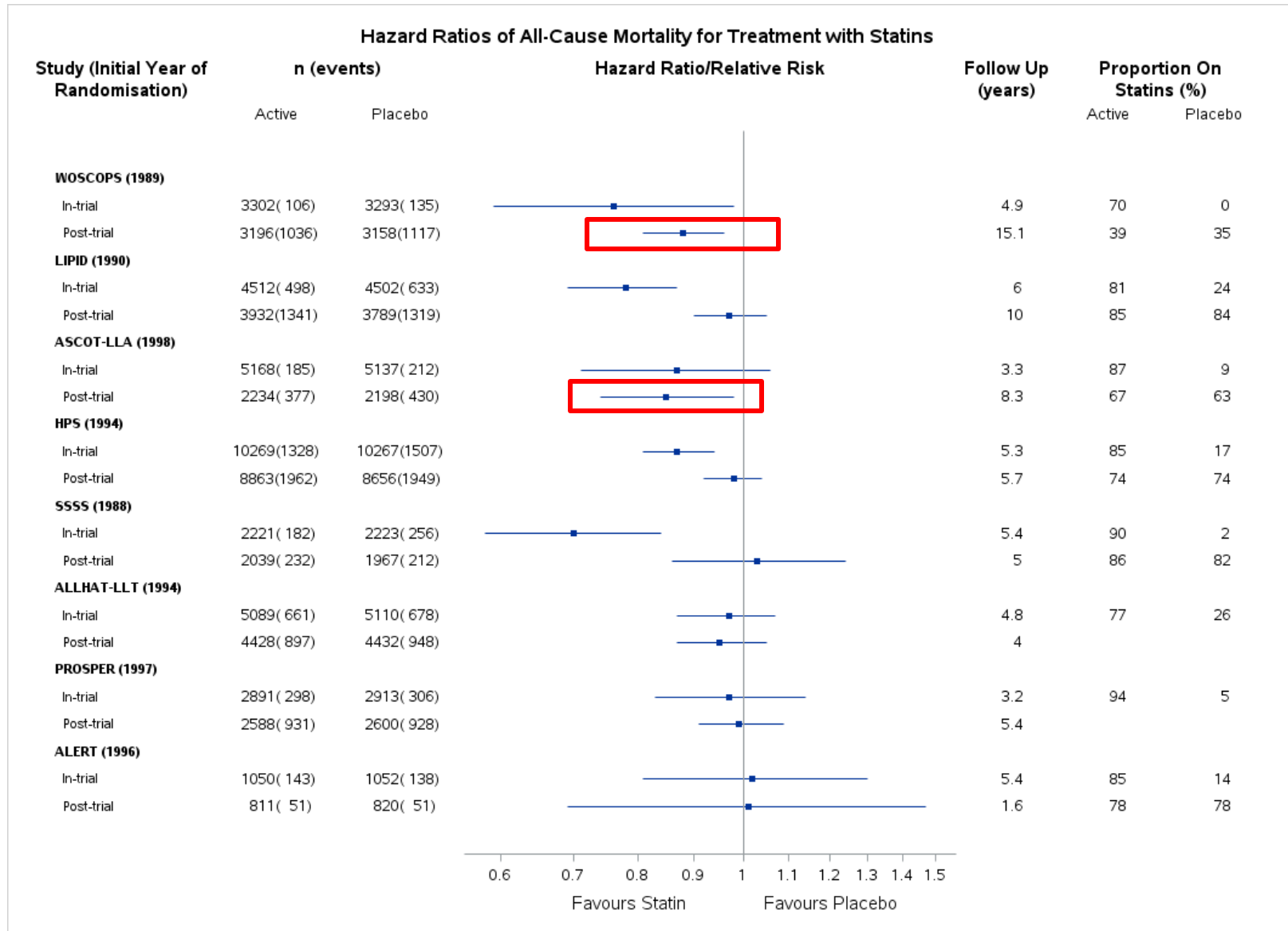
FOUND:

8 studies includable

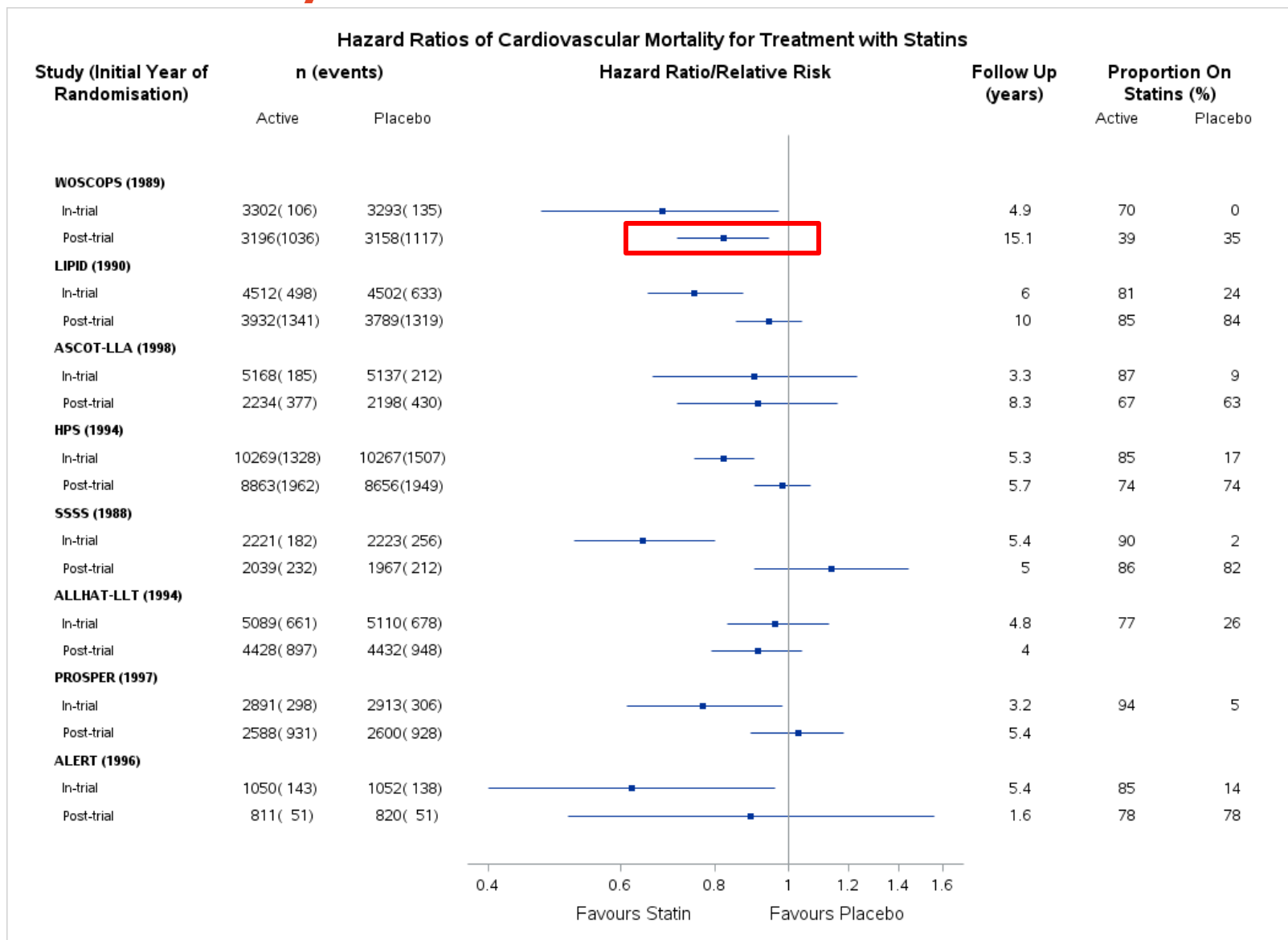
-relate to statin RCTs published 1988-1997



All-Cause Mortality



CVD Mortality



ASCOT-LLA

- Possible legacy effect on All-cause mortality, but not CVD-mortality
- Effect appeared to be mediated through infectious/resp causes (also seen in-trial period)
- ?Seems unlikely to be effect of statin

WOSCOPS

- Only trial to show possible legacy effect on All-cause mortality and CVD-mortality
- May be real legacy effect
- Participants would be above current treatment threshold (10% absolute risk of event over 10 years)
- Doesn't justify treatment of lower risk people at younger age

Limitations

- Post-trial period no longer a randomised comparison
- Aggregate data means can't allow for individual differences in statin use, cardiovascular risk factors and other potential confounders

Conclusion

Most reports showed no evidence of legacy effect of statins on All-cause or CVD mortality

WOSCOPS shows some evidence of possible legacy effects

→ **Analysis of individual patient data needed for more definitive evidence on legacy effects**