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Long term follow up of lipid lowering trials.

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Abstract

Purpose of Review:
Most LDL lowering trials are limited in duration while the disease process occurs over decades. It is informative therefore to evaluate the long-term effects of treatment by undertaking extended observation beyond the formal double-blind phase of intervention studies. This review brings together the findings of major trials that have conducted such long-term follow up.

Recent findings:
Extended observation of trial cohorts has reinforced the long-term safety of LDL lowering therapy (with statins and other agents), with no evidence of late development of cancers or other adverse outcomes. Post-trial follow up reveals also legacy benefits in terms of improved survival (due principally to decreased cardiovascular death rates), and lower hospitalization rates for cardiovascular disease. A number of trials report further risk reduction even after the formal intervention has ceased, and the appearance of delayed benefits such as reduced rate of heart failure.

Summary:
The perceived value of LDL lowering is enhanced significantly by the legacy benefits that persist after administration of treatment to individuals with established CHD or to those at high risk of developing disease. Safety, efficacy and the economics of intervention can be judged more fully in light of the knowledge gained from extended observation in clinical trials.

Introduction

Cholesterol lowering to prevent major cardiovascular events in both asymptomatic individuals and patients with established vascular disease is one of the best-evidenced interventions in medicine. A raft of large-scale, well-conducted clinical trials comparing active treatment with placebo, or more versus less intensive therapy has shown the benefits of reducing circulating levels of LDL. [Examples are 1,2,3; see 4,5 for meta-analysis]. This has led to the widespread use of statins, especially in secondary prevention and high-risk primary prevention and the promulgation of international treatment guidelines [6,7]. However, concerns remain that are voiced in both the scientific and lay media [8-10]. These relate to side-effects and the size of the benefit in lower risk recipients, and this in turn may contribute to the incomplete uptake of, and adherence to, proven medication [11].

The trials that comprise the evidence base were typically about 5 years in duration (ranging from 2.5 years in JUPITER [12] to 8 years in IMPROVE-IT [13]). This is long enough to document clinical efficacy and detect early adverse events but since treatment is lifelong there have been questions over the size of the lifetime benefit and the risk of delayed onset diseases such as cancer. To address these issues, a number of investigating teams have extended the observation period with further follow up of trial cohorts for 2 to 15 years [14-26] (see Table 1 below). The quality of long-term follow up depends on resources, the availability of accessible death and hospital records, and whether or not medication use is known after the end of the formal trial. Compromises have to be made in the rigour of the analyses but it is clear now that a consistent picture is emerging that is helpful in establishing the use of LDL lowering as safe and highly effective prevention strategy

Methodological approaches

The core methodological approach in most of the extended follow up studies is to interrogate national death registers which give cause-specific mortality rates. Further information has been derived from patient questionnaires sent at intervals after the conclusion of the double-blind period, review of case records by the investigating team, and increasingly interrogation of electronic health/ hospital records. Depending on how comprehensive an evaluation was possible, post-trial use of lipid-lowering medication and relevant plasma (LDL) cholesterol levels may be known. The success and completeness of follow up depends, therefore, on the stability of the population and accuracy of patient recall and of records collected for other purposes. Assumptions are usually made as to ongoing differential use of lipid lowering drugs in the treatment arms of the original study, and the validity of surrogates (hospitalizations) for clinical events. The ideal scenario for long-term follow up is where the placebo group continues to receive no active treatment. However, this is unlikely for ethical reasons (especially in the case of statins). A trial where a significant proportion of the placebo group do not take up therapy yields substantial information. On the other hand, exploration of studies where the majority of participants receive active treatment post-trial gives only short-term useful insight into legacy benefits since the difference in statin exposure diminishes with time.

A further issue as follow up continues into old age is the impact of competing risk as prevention of early vascular disease that may have been fatal leads to the appearance of increased rates of non-vascular disease such as cancer or other disorders

associated with ageing. This requires that statistical analyses take into account length of exposure and survivor bias

Non-statin trials: long-term follow up
During the course of the Coronary Drug Project conducted between 1966 and 1975, some treatment arms were terminated due to emergent serious adverse events and there was no clear result by the end of the randomized period. However, long-term follow up revealed after 15 years an 11% decrease in mortality in niacin treated subjects compared to placebo [26] and this led to optimism that the agent would be useful in preventing CHD. Recent trials, unfortunately, did not bear out this supposition, at least when nicotinic acid was added to background statin therapy [27, 28].

Investigators from the Helsinki Heart Study (which was initiated in 1980 and compared a fibrate – gemfibrozil – with placebo in hypercholesterolemic men) published the results of a 3.5 year open-label extension [14] and then an 18 year follow up [19]. Over the full observation period, subjects originally randomized to receive gemfibrozil experienced overall a 24% lower CHD mortality rate with greater effects seen in those at study initiation who had a raised triglyceride/ low HDL profile (as in the original trial [29]). The investigators reported also that younger subjects (40 to 47 years) had a 42% reduction in CHD death rate compared to 24% in 48 to 57 year olds. This finding is in line with the postulate based on genomic and pharmacologic intervention studies that earlier intervention gives better results, possibly regardless of the agent used [30]. It is noted that gemfibrozil therapy was associated with an approximate 0.5 mmol/l reduction in LDL cholesterol and this should be borne in mind when evaluating this study alongside statin-based trials.

Statin trials: long-term follow up
Two major primary prevention trials – WOSCOPS [20] and ASCOT:LLA [21,23] – have reported long term follow up morbidity and mortality data (Table 1). Other studies - PROSPER [25] and ALLHAT [24] – included a substantial proportion of subjects without prior overt signs or symptoms of CHD. It is in these lower risk groups that evaluation of extended observations is particularly pertinent since the decision to start LDL lowering therapy depends on the perceived balance of benefit and risk both of which may occur years in the future.

Over 15 years of follow up in the WOSCOPS trial [20], we observed an apparent ever widening risk reduction for cardiovascular disease outcomes, and for all-cause mortality a 12% decrease (P=0.03) across the total period. These results are replicated in the recently reported 20-year follow up of this trial [31]. It was noteworthy that there was a significantly decreased risk of CHD related death or hospitalization both during the 5 years of formal randomized therapy (33%, P<0.001) and during the 10 year post-trial period (20%, P<0.001) - when both original treatment arms had the same level of statin use [20]. That is, there appeared to be a carry-forward or 'legacy' benefit arising from the initial 5 years of LDL lowering. No difference was seen over the 15 years of observation in non-cardiovascular deaths or fatal/non-fatal cancers ([20], or even after 20 years - Packard and Ford unpublished data). The economics of LDL lowering with statins in WOSCOPS was explored using long-term data and it was reported [32**] that treatment of 1000 individuals with

statin (for 5 years) saved the healthcare system £710,000 over the whole term. In this analysis, we noted also a late benefit in the form of a 43% (P=0.002) reduction in heart failure admissions in the original actively treated group.

ASCOT:LLA investigators examined the impact of LDL lowering on outcomes over extended observation periods of 2 years [21] and 11 years [23]. In the first report it was seen that despite equalization of LDL cholesterol levels due to high use of statins in both arms, the risk reduction for major coronary events was undiminished (at 37%, P=0.005) compared to the position at the end of the formal 3.3 year trial. Event rates in those initially assigned to statin continued to decline indicating as with in WOSCOPS a legacy benefit. The 11-year extension used only mortality data. Here, it was found that all-cause mortality (similar to WOSCOPS at 15 years) was reduced by 14% (P=0.02) in subjects originally in the statin arm and there was no difference in cancer deaths. However, in ASCOT reduced mortality appeared to be due to an impact on both cardiovascular and non-cardiovascular deaths (mainly due to infection and respiratory disease). The mechanistic reasons for this are speculative [23], and the finding may be confounded by small numbers of events and accuracy of attribution of cause of death.

Extended follow up of the elderly cohort in the PROSPER trial [25] showed no difference over 8.6 years in all-cause mortality despite a 20% reduction in coronary death (P=0.009); there were compensating trends to increased strokes and non-cardiovascular fatal outcomes in those allocated to active therapy. In the original PROSPER publication [33] we reported increased cancer risk in the statin treated group but this difference diminished with time so that there was no significant excess cancers over the full observation period [25]. It was possible to follow both fatal and non-fatal events in the Scottish recruits. Here, the clear reduction in CHD risk during the 3.5 years of the trial (HR=0.74, P=0.019) became a non-significant trend (HR =0.86, P=0.14) over the next 5.1 years. ALLHAT [24]provided long-term follow up data (out to 8 - 13 years post randomisation) that largely reflected the main findings of the formal trial; that is, no overall reduction in CHD risk probably attributable to the small difference in LDL in the two treatment arms but a significant persistent benefit in black participants.

A 2 year post-trial follow up of ALERT, a trial of fluvastatin therapy in renal transplant patients without a history of recent myocardial infarction, was published in 2005 [18]. It was a relatively small study with 2102 subjects and therefore had limited power. While LDL lowering produced a trend to benefit during the trial, it was only with extended follow up that a significant result appeared. That is, over the entire 6.7 years, relative risk of a major coronary event was reduced 29% in the group assigned to statin.

A number of secondary prevention trials have been able to conduct long term follow up of both mortality and morbidity outcomes (Table 1). HPS was the largest trial of statin versus placebo and using annual survey questionnaires, investigators were able to determine event rates, statin use, and LDL levels during a 6 year post-trial period [22]. Over the total follow up of 11 years in HPS, there was a substantial reduction in vascular events in the subjects originally allocated to simvastatin, and as for other studies described above no emergent issues relating to cancer or non-cardiovascular mortality. For a range of outcomes, the investigators were able to show that the

benefits during the in-trial period (risk ratios for major coronary events and strokes of 0.73 to 0.77, all P<0.0001) were not present in the extension (risk ratios of 0.93 to 0.98). Further, in a detailed year-by-year analysis (which was possibly due to the inherent power of the study), it could be seen that the differential rates for new major vascular events in the active vs placebo groups were established within 12 months of initiating therapy but at the end of the double-blind phase were lost within 12 months of both groups receiving the same treatment (self-reported statin use was the same at 59% rising to 84% in the post-trial period; LDL levels were also identical). This finding is in contrast to the reported risk reductions in the post-trial follow up noted above for WOSCOPS and ASCOT.

Long-term follow up findings in the 4S trial were reported using mortality data acquired at 2 years and 5 years after the end of the formal study [15, 17]. 4S was the first statin trial to show a reduction in coronary and total mortality, and the 10.4 year extended observation period [17] reinforced the strength of the benefit with a 15% overall decrease in all-cause death (P=0.02) and a 24% fall in coronary death (P=0.0018). Splitting the in-trial and post-trial events, as in HPS, it was noted that the large risk reduction for coronary mortality during the trial (relative risk = 0.57, P<0.0001) was not present in the 5 year extension (relative risk = 1.08). During the extension >80% of subjects were taking open label statin.

In the LIPID trial an extended follow up was conducted for 2 years (making 8 years in total of observation) during which time face-to-face interviews were undertaken, and LDL cholesterol levels monitored and found to be equal in the two original treatment arms [16]. Morbidity and mortality outcomes were reported and in general the risk reductions seen in the formal trial persisted during the extension. All-cause mortality was reduced in subjects originally assigned pravastatin by 22% in-trial and 18% (P=0.029) post-trial; CVD death rates were reduced 25% and 24% respectively (P=0.019 for post-trial). Other endpoints, however, showed a smaller, non significant risk reduction post-trial; the relative risk of CHD death and myocardial infarction was 24% (P<0.0001) during the trial but 16% (P=0.08) in the extension; the respective figures for revascularization were 20% (P<0.0001) and 16% (P=0.1).

Lv et al [34**] have published recently a meta-analysis of outcome data from statin trials with extended follow up. Attention was given to aggregate risk reductions at 2 years post-trial - a time point used in a number of studies, and total follow up. Across the six studies included in the analysis a significant risk reduction was seen for all-cause mortality at 2 years with a relative risk of 0.83 (0.74-0.93) but not for the total follow up period, relative risk = 0.94 (0.88-1.01). Major coronary events were reduced by 23% at 2 years (relative risk 0.77(0.63-0.95)) and by 14% for the total post-trial extension (relative risk 0.86(0.75-0.97).

Pathobiological basis of legacy benefits
Clearly, when LDL is lowered (using statins in the trials described above) there is a rapid reduction in risk of a coronary event that is established fully by about 12 months after starting treatment [4,5] and continues during the period of active therapy. This benefit is proportional to the degree of LDL lowering as shown in regression analysis of all major trials [5], including the recently reported IMPROVE-IT study using ezetimibe, a non-statin LDL lowering drug [13]. The pathobiological basis

of risk reduction has been attributed to a combination of stabilization of vulnerable atherosclerotic plaques in coronary arteries and other vascular beds, and plaque regression (diminution in size) [35,36]. The consistent finding that the risk reduction persists in a legacy benefit many years after differential treatment has ceased indicates that the intervention altered the 'natural history' of the disease process in those receiving active treatment and placed them on a new trajectory [37].

A remarkable finding particularly in the primary prevention trials described above is that there was a risk reduction for new major coronary events even in the post-trial period. The size of the reduction was less than during the formal double-blind phase but contributed to an apparent continued 'widening' of the incidence (Kaplan-Meier) curves over a long period – 15 years in the case of WOSCOPS. This additional risk reduction was not observed in HPS or 4S trials of secondary prevention.

It is tempting to speculate that an enhanced late benefit may be due to an effect of LDL lowering beyond plaque stabilization which comes into play when atherosclerotic disease is less advanced. In the scheme shown in Figure 1 it is postulated that risk of an event is related to the probability of plaque rupture and that while the main response to LDL lowering is to stabilize plaque (an action that can occur rapidly but be reversed equally quickly), if there is less severe disease and a profusion of fatty streaks (the progenitors of more complex, fragile plaque) then LDL lowering resolves these precursor lesions and it is a number years before new streaks reappear to re-establish an elevated risk level.

In considering the phenomenon of carry-forward or legacy benefit in intervention studies, it is informative to look at the experience with other modalities. Maintenance of excellent glucose control in type 2 diabetics in the UK Prospective Diabetes Study appears to be associated with a post-trial risk reduction for vascular disease [38]. Intriguingly this was not seen for tight blood pressure control in the same trial [39]. Possibly, there are agents that impact on the natural history of CVD in a way that leads to legacy benefits while others have an effect that is more transient.

Conclusions

Extended observation from 2 to 10 years after LDL lowering trials completed their formal double-blind phase gives added confidence in the efficacy and safety of the intervention. There is no late appearance of serious adverse events (such as cancer), and indeed evidence of emergent late benefit in terms of risk of heart failure prevention [32]. This data should increase confidence to initiate LDL lowering therapy widely in lower risk individuals. Economic evaluations also need to be set in the framework of the long-term/ lifetime impact of therapy and include recurrent as well as first events. This approach can yield a fuller picture of the net costs or savings to healthcare systems and remove perceived financial obstacles to effective prevention programmes.

In a new approach to presenting the benefits of intervention, it is now useful to consider assessment of both 'lifetime risk' (based possibly on the combination of informative gene scores and classical risk factors [40,41*]) and 'lifetime benefit' (based on long-term follow up). The former provides an indication of exposure to integrated risk factors such as 'LDL-years' and the latter a measure of the reduction in total disease burden [37]. Clinically, application of these metrics will lead to earlier and more aggressive intervention especially in younger, asymptomatic people that will be personalised and cost effective.

Key points

- Long-term follow up of LDL lowering trials demonstrates the safety of the intervention with no evidence for delayed onset of adverse outcomes such as cancer.
- Relative risk reduction on statins persists beyond the end of the formal double-blind phase and in some studies is augmented in a post-treatment legacy benefit.
- There can be the appearance of delayed benefits such as reduced risk of hospitalization due to heart failure.

References

1. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.

2. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333:1301–7.

3. LaRosa JC, Grundy SM, Waters DD et al. Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352:1425-35

4. Cholesterol Treatment Trialists Collaboration. 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.

5. Baigent C, Blackwell L, Emberson J et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670–81.

6. European Association for Cardiovascular Prevention & Rehabilitation, Z. Reiner, A.L. Catapano, G. De Backer et al for the ESC committee for practice guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology(ESC) and the European Atherosclerosis Society (EAS), Eur. Heart J. 2011;32:1769-1818.

7. Stone NJ, Robinson JG, Lichtenstein AH et al. American College of Cardiology/American Heart association task force on practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/ American Heart association task force on practice Guidelines, J. Am. Coll. Cardiol. 2014;63:2889-2934.

8. Clinical Decisions. The guidelines battle on starting statins. New Eng J Med. 2014;370: 1652-1658.

9. Odden MC, Plecher MJ, Coxson PG et al. Cost-effectiveness and population Impact of statins for primary prevention in adults aged 75 years or older in the United States. Ann Intern Med. 2015;162:533-541.

10. Robinson JG. Accumulating Evidence for Statins in Primary Prevention. JAMA. 2013; 310:2405-6.

11. Kotseva K, Wood D, De Bacquer D et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of

coronary patients from 24 European countries. Europ. J. Prev, Cardiol 2015; DOI: 10.1177/2047487315569401

12. Ridker PM, Danielson E, Fonseca FA et al for the JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet. 2009;373:1175-82

13. Cannon CP, Blazing MA, Giugliano RP et al for the IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015;372:2387-97

14. Huttunen JK, Heinonen OP, Manninen V et al. The Helsinki Heart Study: an 8. 5 -year safety and mortality follow up. J Intern Med 1994;235:31–9.

15. Pedersen TR, Wilhelmsen L, Faergeman O et al. Follow up study of patients randomized in the Scandinavian Simvastatin Survival Study (4S) of cholesterol lowering. Am J Cardiol. 2000;86:257–62.

16. Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow up. Lancet 2002;359:1379–87.

17. Strandberg TE, Pyorala K, Cook TJ et al. Mortality and incidence of cancer during 10-year follow up of the Scandinavian Simvastatin Survival Study (4S). Lancet 2004;364:771–7.

18. Holdaas H, Fellstrom B, Cole E et al. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin; the ALERT extension study. Am J Transplant 2005;5:2929–36.

19. Tenkanen L, Manttari M, Kovanen PT, Virkkunen H, Manninen V. Gemfibrozil in the Treatment of Dyslipidemia: An 18-Year Mortality Follow up of the Helsinki Heart Study. Arch Intern Med. 2006;166:743-748.

20. Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM. Long-term follow up of the West of Scotland Coronary Prevention Study. N Engl J Med. 2007;357:1477–86.

21. Sever PS, Poulter NR, Dahlof B et al. The Anglo-Scandinavian Cardiac Outcomes Trial lipid lowering arm: extended observations 2 years after trial closure. Eur Heart J. 2008;29:499–508.

22. Bulbulia R, Bowman L, Wallendszus K et al. 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. Lancet 2011;378:2013–20.

23. Sever PS, Chang CL, Gupta AK, Whitehouse A, Poulter NR. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow up of the lipid-lowering arm in the U.K. Eur Heart J. 2011;32:2525–32.

24. Margolis KL, Davis BR, Baimbridge C et al for the ALLHAT Collaborative Research Group. Long-term follow up of moderately hypercholesterolemic hypertensive patients following randomization to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). J Clin Hypertens. 2013;15(8):542-54.

25. Lloyd SM, Stott DJ, de Craen AJ et al. Long-term effects of statin treatment in elderly people: extended follow up of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PLoS One. 2013;8:e72642.

26. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in Coronary Drug project patients: long-term benefit with niacin. J Am Coll Cardiol. 1986;8:1245-55.

27. The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365:2255-67.

28. The HPS2-THRIVE Collaborative Group. Effects of extended release niacin with laropiprant in high-risk patients. N Engl J Med. 2014;371:203-12.

29. Frick MH, Elo O, Haapa K et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med. 1987;317:1237-45.

30. Ference BA, Majeed F, Penumetcha R, Flack JM, Brook RD Effect of naturally random allocation to lower low-density lipoprotein cholesterol on the risk of coronary heart disease mediated by polymorphisms in NPC1L1, HMGCR, or both: a 2 × 2 factorial Mendelian randomization study. J Am Coll Cardiol. 2015;65:1552-61.

31. Packard CJ, Ford I, Murray H, McCowan C. Long-term clinical and economic benefits of statin-based LDL lowering: 20-year follow up of West of Scotland Coronary Prevention Study. AHA abstract November 25, 2014, Volume 130, Suppl 2.

32**. McConnachie A, Walker A, Robertson M, Marchbank L, Peacock J, Packard CJ, Cobbe SM, Ford I. Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. Eur Heart J. 2014;35:290-8.
In this paper the authors provide an economic assessment of the value of LDL lowering with statins using 15 year follow up data based on death registers and comprehensive electronic hospitalization records available through the national healthcare system. It demonstrates more fully by using the complete information on first and recurrent events the potential financial benefits of the intervention with a net cost-saving when the entire period of observation is taken into account.

33. Shepherd J, Blauw GJ, Murphy MB et al for the PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623-30.

34**. Lv HL, Jin DM, Liu M, Liu YM, Wang JF, Geng DF. Long-term efficacy and safety of statin treatment beyond six years: a meta-analysis of randomized controlled trials with extended follow up. Pharmacol Res. 2014 Mar;81:64-73.
This article provides a comprehensive description of long-term follow up studies up to the date of its publication, and a meta-analysis of the risk reductions observed during the post-trial phase at 2 years and for the whole observation period.

35. Libby P, Sasiela W. Plaque stabilization: Can we turn theory into evidence? Am J Cardiol. 2006;98(11A):26P-33P

36. Puri R, Libby P, Nissen SE et al. Long-term effects of maximally intensive statin therapy on changes in coronary atheroma composition: insights from SATURN. Eur Heart J Cardiovasc Imaging. 2014;15:380-8

37. Packard CJ, Weintraub WS, Laufs U. New metrics needed to visualize the long-term impact of early LDL-C lowering on the cardiovascular disease trajectory. Vascul Pharmacol. 2015 pii: S1537-1891(15)00046-4. doi: 10.1016/j

38. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577-89.

39. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow up after tight control of blood pressure in type 2 diabetes. N Engl J Med. 2008;359:1565-76.

40. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, Greenland P, Van Horn L, Tracy RP, Lloyd-Jones DM. Lifetime risks of cardiovascular disease. N Engl J Med. 2012 26;366:321-9

41*. Mega JL, Stitziel NO, Smith JG et al. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. Lancet 2015;385:2264-71
This paper presents a novel approach to selecting patients for aggressive intervention using a CHD gene score (comprising 27 genetic variants) adjusted for classical risk factors. Cohort studies and primary and secondary prevention trials were included in the analysis. As gene score increased in the populations studied so did both relative and absolute risk reduction. For primary prevention trials, in those with the highest gene score the number-needed-to-treat to prevent 1 event was threefold less than in subjects with the lowest score.

Table 1: Outcome trials of lipid lowering interventions with extended follow up.*

Figure legend

Figure 1: Potential mechanism for legacy benefit in LDL lowering trials.
This schema is based on the findings that in WOSCOPS long-term follow up [20] and the ASCOT-LLA 2 year extension [21] there was a persistent risk reduction in the incidence of new events after the formal trial ended. However, in HPS [22] there was clear evidence that the risk reduction was attenuated almost immediately on cessation of differential treatment and by 2 years there was no evidence of a difference in incidence rates (see Figure 2 in [22]). Likewise in 4S, during post-trial follow up there appeared to be more coronary events (non-significant) in the subjects allocated originally to simvastatin than those on placebo [17].

In the hypothetical trial depicted in the figure, the double-blind phase lasts 5 years and the period of extended observation, when subjects receive similar levels of LDL lowering therapy, is for a further 5 years. For the purposes of illustration the LDL decrease is set at 1.0mmol/l and the relative risk reduction at 22% (as per the CTTC analysis [5]). Since WOSCOPS and ASCOT-LLA are primary prevention studies and 4S and HPS secondary prevention, it is suggested that the difference in response in terms of the size of the post-trial legacy benefit is related to the underlying severity of disease (although as noted above the extent of statin use post-trial may also be important). Thus, in subjects with clinically manifest atherosclerotic vascular disease, there are a large number of complex lesions that are prone to rupture and the predominant effect of LDL lowering is to stabilise these. The data from HPS suggest either that stabilization is rapidly reversed and relative protection from further clinical events is lost within 12 to 24 months, or that post-trial statin use was so high that those originally on placebo caught up quickly with those originally on simvastatin.

In subjects with less severe disease – a mix of vulnerable plaque and precursor lesions such as fatty streaks - LDL lowering therapy impacts on both pathological structures leading to stabilization of the plaque and regression/ resolution of the lipid filled streaks. It takes a number of years before the fatty streaks reform and so there is a prolonged legacy benefit manifest in a post-trial relative risk reduction that lasts for a considerable period. This is of course a speculative mechanism and other factors may well explain the persistence of benefit in trials such as WOSCOPS. The stylized cumulative incidence curves can be compared to those found in references [20] and [22].

Figure 1

Primary Prevention trials	Length of extended followup	No. of subjects Age (y)	Baseline chol. (LDL)	Lipid Rx post trial	Major findings across full observation period (from randomisation)
HHS (gemfibrozil)	13 years	4081 (40-55y)	7.0 mmol/l (4.9 mmol/l)	Open label for 3.5 yr with 67% on gemfibrozil	At 18-years:– CHD mortality relative risk 0.76(0.59-0.99). No difference in all-cause or cancer mortality. Highest tertile BMI+triglyceride:- CHD mortality relative risk 0.30(0.15-0.58)
WOSCOPS (pravastatin)	10 years	6595 (55y)	7.0mmol/l (4.9mmol/l)	As per GP prescription - about 37% on statin	At 15 years:- Hazard ratio for all-cause mortality was 0.88 (0.79–0.99), and for cardiovascular mortality was 0.81(0.68-0.96). No difference in total cancer.
ASCOT-LLA (atorvastatin)	2 years 8 years	10,305 4,605 (63y)	5.5mmol/l (3.4mmol/l)	65% on statin at 2 y	At 11 years:- All-cause mortality hazard ratio 0.86(0.76-0.98).
ALERT (fluvastatin)	2 years	2,102 (49y)	6.5mmol/l (4.1mmol/l)	Open label fluvastatin (63%) or other statin (15%)	At 6.7 years:- hazard ratio for cardiac death/ non-fatal MI was 0.71(0.55-0.93). No difference in total mortality or graft loss.
Primary/secondary prevention trials					
PROSPER (pravastatin)	5 years	5,804 2,520 in UK (75y)	5.7mmol/l (3.8mmol/l)	As per GP prescription	At 8.6 years:- Hazard ratio for CHD mortality was 0.80 (0.68-0.95). No difference in all-cause mortality, cancer or stroke.
ALLHAT (pravastatin)	4 years	10,355 (67y)	5.8 mmol/l (3.8 mmol/l)	Open label statin	At 8.8 years:- Hazard ratio for CHD mortality for whole group was 0.92(0.81-1.04) and for Black participants was 0.79(0.64-0.98).
Secondary prevention trials					
Coronary Drug Project (niacin)	9 years	8,341 1,119 to niacin (30-64y)		Not known	At 15 years:- All-cause mortality in drug groups other than niacin was equal to placebo; mortality in niacin group was 11% lower (P=0.0004).
4S (simvastatin)	2 years 5 years	4,444 (35-70y)	6.8mmol/l (4.9mmol/l)	Open label – 83.5% on statin	At 10.4 years:- All-cause mortality relative risk was 0.85(0.74-0.97), and coronary mortality was 0.76(0.64-0.90). Relative risk for cancer death was 0.81(0.60-1.08).
HPS (simvastatin)	6 years	20,236 (40-80y)	5.9mmol/l (3.4mmol/l)	Self-reported – 84% on statin	In-trial risk ratio for vascular events was 0.77(0.72-0.81). During the post trial extension for 6 years this was 0.95(0.89-1.02). No difference in cancer deaths across whole 11.0 years of follow up.
LIPID (pravastatin)	2 years	9,014 (62y)	5.7mmol/l (3.9mmol/l)	Open label pravastatin-87% plus 3% on other agent	At 8.0 years:- Relative risk of all-cause mortality was reduced 21% (P<0.0001) and cardiovascular mortality by 25%(P<0.0001).

A Scenario 1

Cumulative events

0   5   10y

B Scenario 2

Cumulative events

0   5   10y

Stylised cumulative incidence curves

C

0   1   2   3   4   5   6   7   8   9   10   Years - timeline

| Double-blind phase | Extended observation |

Differential LDLc (1 mmol/l) | Equalised LDLc

Scenario 1 – severe atherosclerotic disease

CHD risk in placebo group

Risk reduction (of 22%)

Relative risk for new events in actively treated group

Predominantly plaque stabilisation

Vessel wall response

Scenario 2 – mild/ moderate atherosclerotic disease

CHD risk in placebo group

Risk reduction (of 22%) | Legacy risk reduction

Relative risk for new events in actively treated group

Plaque stabilisation
Resolution of precursor fatty streaks | Gradual formation of new lesions

Vessel wall response

Randomisation | End formal trial