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COMMENTARY

Statins and mortality: the untold story

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Statins are first-line evidence-based drugs for the management of dyslipidaemias and to reduce the risk of cardiovascular events. However, statin clinical trials have shown marginally significant benefits on mortality, especially in the primary prevention setting. A major limitation of those trials is their relatively short follow-up. A reduced number of fatal events within a 5-year follow-up make mortality benefits unlikely to arise. This is particularly relevant for the primary prevention trials, where the risk of cardiovascular death is low. The short follow-up is a limitation for safety assessments too. However, extended major statin trials failed to detect any major safety concerns. Safety and efficacy assessments are even more complicated considering the differences of cardiovascular risk status in primary prevention individuals, and also given some potential ethnic and inter-individual genetic variations in response to statin treatment. Considerable evidence suggests a favourable risk–benefit balance for statin treatment. It can be assumed that statins reduce mortality in the long term by preventing cardiovascular events with complications that reduce lifespan. Unfortunately, this hypothesis cannot be proven as there is no current ethical basis on designing long-term placebo-controlled statin trials. Nevertheless, by effectively reducing disabilities related to cardiovascular events, statins have major benefits for public health. Therefore, clinicians should not withhold statin treatment awaiting proof of mortality benefits, as this may remain an 'untold story'.

Tables of Links

TARGETS
Enzymes [2]
Hydroxymethylglutaryl-CoA reductase
Proprotein convertase subtilisin/kexin type 9

LIGANDS	
Alirocumab	Mevastatin
Evolocumab	Pitavastatin
Fluvastatin	Pravastatin
Lovastatin	Simvastatin

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

In a recent issue of the *British Journal of Clinical Pharmacology*, Warren *et al*. assessed the effect of statin treatment on mortality in clinical trials [3]. Some comments may be of interest.

Statins are first-line evidence-based drugs for the management of dyslipidaemias and to reduce the risk of cardiovascular (CV) events [4]. There seems to be a linear association between this benefit and low density lipoprotein cholesterol (LDL-C) reduction [5]. The latter is the predominant lipid profile modification to prevent CV outcomes. Recent studies using proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors suggested that CV benefits extend to very low post-treatment LDL-C levels, not previously encountered in statin trials [6, 7]. Moroever, safety concerns associated with aggressive LDL-C reduction (e.g. the risk of haemorrhagic stroke) have not been confirmed by meta-analyses [8].

Statin-related CV risk reduction might not be explained by LDL-C lowering only [9]. In this context, statins were suggested to exert various anti-atherogenic *pleiotropic* actions [10]. It is still debated whether these properties are simply

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explained by cholesterol lowering or not. A proposed explanations is the inhibition of the synthesis of mevalonate products (i.e. isoprenoids), which regulate various cellular functions [10]. The latter was suggested to mediate several dose-dependent adverse effects too [11].

Despite the significantly decreased risk of CV events with statins, benefits on mortality in clinical trials were marginally significant, particularly in the primary prevention setting [3]. However, most trials were underpowered to show such an effect, and insufficient data should be interpreted with caution.

A major limitation of these trials is their relatively short follow-up. Hypercholesterolaemia, like other vascular risk factors, has a long natural history, and, unlike other diseases (e.g. cancer), is not always lethal. Specifically, the predicted 10-year CV mortality is <1% and 1–5% in low and moderate CV risk individuals respectively [12]. Therefore, within a 5-year primary prevention trial, CV mortality is expected to be <5%. In contrast, more CV deaths are anticipated in secondary prevention trials in which the 10-year CV mortality of participants is ≥10%. Namely, in the West of Scotland Coronary Prevention Study Group (WOSCOPS) total mortality rates were 3.2% *vs*. 4.1% in the pravastatin *vs*. placebo group respectively after 4.9 years (average) [13]. These rates were higher in the Heart Protection Study (HPS) within a similar follow-up: 12.9% *vs*. 14.7% in the simvastatin *vs*. placebo group [14].

Such increased mortality rates make secondary prevention statin trials more powered to identify significant mortality benefits than the primary prevention ones within a limited timeframe. In the latter studies the survival curves of the statin-treated and the placebo group might well become distant later in the course of treatment with an increasing number of fatal events. This assumption is not unreasonable considering statin-related reductions in non-fatal CV events with complications (e.g. heart failure) that limit lifespan. Unfortunately, no long-term placebo-controlled primary prevention statin trials are available, nor is there a current ethical basis for designing one.

An important issue addressed by Warren *et al*. is that primary prevention trials did not recruit only low-risk participants [3]. Namely, among the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) participants, 41.2% and 8.1% had a Framingham risk score of 11–20% and >20% respectively [15]. It was estimated that absolute CV risk reduction was greater in those with a Framingham score of greater than rather than less than 10% [16]. Such an increased prevalence of 'non-low' CV risk in JUPITER might explain significant rosuvastatin benefits on mortality in only 1.9 years [17].

Nevertheless, the recent Heart Outcomes Prevention Evaluation (HOPE)-3 study including 12 705 moderate-to-risk individuals failed to show any significant mortality reduction of rosuvastatin compared with placebo after 5.6 years (mean) [17]. However, a smaller LDL-C reduction was noted in this study in line with the lower rosuvastatin dose used. Also, the ethnic background of the HOPE-3 population was diverse, with approximately 80% of participants being of non-white ancestry in contrast to the JUPITER study [17]. This raises the question whether ethnic differences impact statin effects on mortality. This issue needs to be addressed on a prospective basis. Another interesting concept is that, apart from the ethnic diversity, there might be inter-individual genetic variations associated with the LDL-C lowering efficacy of statin treatment [17]. Such genetic diversity might also apply to the efficacy of statins to prevent CV events and reduce mortality [17, 18].

It should be acknowledged that the short follow-up is a limitation for safety assessments too. Apparently, non-CV fatal events may fail to emerge in a 5-year-long study. To address this issue there have been follow-up studies of several major trials in which statins were offered to all living participants for a follow-up phase of >6 years (up to 14.7 years) [19–24]. A meta-analysis of such studies included 47 296 patients of the primary and secondary prevention. In this analysis, no significant differences in non-CV mortality or cancer incidence between the statin-treated and the placebo group were noted, suggesting no major safety concerns in the long term [19].

However, a major limitation of these studies for both safety and efficacy assessments is that in their follow-up phase the proportions of patients on statins within the original in-trial groups were similar. Besides, this proportion was variable in different studies ranging from up to >80% in the Scandinavian Simvastatin Survival Study (4S), Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) and Assessment of LEscol in Renal Transplantation (ALERT) studies, down to approximately 37% in the WOSCOPS. These factors reduce the possibility of demonstrating an ongoing benefit on mortality with respect to the original group assignment [19]. Relevant benefits could be shown by studies prospectively including patients on either statins or placebo for a long follow-up (e.g. >6 years). However, considering the well-established efficacy of statins to reduce outcomes, there is no current ethical basis on designing such studies. At least, this extension of the major statin trials showed that the differences in mortality between statin treatment and placebo were grossly attributed to the differences observed during the in-trial phase, suggesting a sustained statin benefit on mortality in the long term [19].

It has been largely shown that the risk–benefit balance is in favour of statin treatment [18]. A population-based study included >2 million primary care individuals in England and Wales [25]. Among high-risk individuals, the 5-year Numbers Needed to Treat (NNT) for CV events were significantly lower than the Numbers Needed to Harm (NNH) for a number of adverse effects [25]. Regarding organ-specific effects, statins might be protective rather than deleterious, especially for the kidneys and the liver [18, 26, 27]. Interestingly, statin treatment may result in even better CV outcomes in individuals with established chronic kidney disease or fatty liver [28, 29]. However, it should be acknowledged that there are discrepancies in the safety assessments between observational studies and randomized controlled studies, reflecting the differences between real life and clinical trials [30]. Namely, the latter tend to exclude individuals at risk for side effects, thus not entirely mirroring the population treated in everyday clinical practice.

In the end, not only a longer, but also a better life matters. Preventing strokes, myocardial infarctions, peripheral vascular disease and their accompanying disabilities is important in this regard, and statins can definitely 'do the job'. The existing data firmly support the efficacy and

cost-effectiveness of these drugs and there is no convincing evidence of major safety concerns. Profound effects of statins on mortality will remain an untold story. However, considering statin benefits on public health, it is not prudent for clinicians to withhold treatment, especially in high-risk populations. Meanwhile, several other widely prescribed drug classes have debated effects on mortality (e.g. anti-diabetic drugs), and non-steroidal anti-inflammatory drugs are sold over the counter.

Competing Interests

Michael S. Kostapanos is being reimbursed as a Study Physician at the GlaxoSmithKline (GSK) Clinical Trials Unit in Cambridge, UK. Moses S. Elisaf has given talks, attended conferences and participated in trials sponsored by various statin manufacturers. The authors declare that there is no duality of interest associated with this manuscript.

References

1 Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP, *et al*. The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 2016; 44: D1054–68.

2 Alexander SPH, Fabbro D, Kelly E, Marrion N, Peters JA, Benson HE, *et al*. The Concise Guide to PHARMACOLOGY 2015/16: Enzymes. Br J Pharmacol 2015; 172: 6024–109.

3 Warren JB, Dimmitt S, Stampfer H. Cholesterol trials and mortality. Br J Clin Pharmacol 2016; 82: 168–77.

4 Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, *et al*. 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 Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, *et al*. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 2015; 385: 1397–405.

6 Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, *et al*. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med 2015; 372: 1500–9.

7 Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, *et al*. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015; 372: 1489–99.

8 McKinney JS, Kostis WJ. Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials. Stroke 2012; 43: 2149–56.

9 West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation 1998; 97: 1440–5.

10 Kostapanos MS, Milionis HJ, Elisaf MS. An overview of the extra-lipid effects of rosuvastatin. J Cardiovasc Pharmacol Ther 2008; 13: 157–74.

11 Agouridis AP, Kostapanos MS, Elisaf MS. Statins and their increased risk of inducing diabetes. Expert Opin Drug Saf 2015; 14: 1835–44.

12 Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, *et al*. ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J 2011; 32: 1769–818.

13 Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, *et al*. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995; 333: 1301–7.

14 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7–22.

15 Ridker PM, MacFadyen JG, Nordestgaard BG, Koenig W, Kastelein JJ, Genest J, *et al*. Rosuvastatin for primary prevention among individuals with elevated high-sensitivity c-reactive protein and 5% to 10% and 10% to 20% 10-year risk. Implications of the Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial for 'intermediate risk'. Circ Cardiovasc Qual Outcomes 2010; 3: 447–52.

16 Ridker PM, MacFadyen JG, Fonseca FA, Genest J, Gotto AM, Kastelein JJ, *et al*. Number needed to treat with rosuvastatin to prevent first cardiovascular events and death among men and women with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). Circ Cardiovasc Qual Outcomes 2009; 2: 616–23.

17 Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, *et al*. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359: 2195–207.

18 Kostapanos MS, Rizos CV, Elisaf MS. Benefit–risk assessment of rosuvastatin in the treatment of atherosclerosis and related diseases. Drug Saf 2014; 37: 481–500.

19 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; 81: 64–73.

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

21 Ford I, Murray H, McCowan C, Packard CJ. Long-term safety and efficacy of lowering low-density lipoprotein cholesterol with statin therapy: 20-year follow-up of West of Scotland Coronary Prevention Study. Circulation 2016; 133: 1073–80.

22 LIPID Study Group. 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.

23 Heart Protection Study Collaborative Group, Bulbulia R, Bowman L, Wallendszus K, Parish S, Armitage J, *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.

24 Sever PS, Chang CL, Gupta AK, Whitehouse A, Poulter NR, ASCOT Investigators. The Anglo-Scandinavian Cardiac Outcomes

Trial: 11-year mortality follow-up of the lipid-lowering arm in the UK. Eur Heart J 2011; 32: 2525–32.

25 Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ 2010; 340: c2197.

26 Kostapanos MS, Liberopoulos EN, Elisaf MS. Statin pleiotropy against renal injury. J Cardiometab Syndr 2009; 4: E4–E9.

27 Athyros VG, Mikhailidis DP, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, *et al*. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. J Clin Pathol 2004; 57: 728–34.

28 Shepherd J, Kastelein JJ, Bittner V, Deedwania P, Breazna A, Dobson S, *et al*. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. J Am Coll Cardiol 2008; 51: 1448–54.

29 Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, *et al*. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study: a post-hoc analysis. Lancet 2010; 376: 1916–22.

30 Naci H, Brugts J, Ades T. Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. Circ Cardiovasc Qual Outcomes 2013; 6: 390–9.