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Statin tolerability: In defence of placebo-controlled trials

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Abstract

Background: Statin intolerance is a barrier to effective lipid-lowering treatment. A significant number of patients stop prescribed statins, or can take only a reduced dose, because of adverse events attributed to the statin, and are then considered statin-intolerant.

Methods: Examination of differences between statin and placebo in withdrawal rates due to adverse events – a good measure of tolerability – in statin cardiovascular outcome trials in patients with advanced disease and complex medical histories, who may be more vulnerable to adverse effects. The arguments commonly used to dismiss safety and tolerability data in statin clinical trials are examined.

Results: Rates of withdrawal due to adverse events in trials in patients with advanced disease and complex medical histories are consistently similar in the statin and placebo groups. We find no support for arguments that statin cardiovascular outcome trials do not translate to clinical practice.

Conclusions: Given the absence of any signal of intolerance in clinical trials, it appears that statin intolerance in the clinic is commonly due to the nocebo effect causing patients to attribute background symptoms to the statin. Consistent with this, over 90% of patients who have stopped treatment because of an adverse event can tolerate a statin if re-challenged. Consequently, new agents, including monoclonal antibodies to proprotein convertase subtilisin/kexin type 9, will be useful when added to statin therapy but should rarely be used as a statin substitute.

Keywords

Statin intolerance, nocebo effect, re-challenge, PCSK9 antibody, statin side effects, stopping statins, statin muscle effects

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Inhibitors of HMG-CoA reductase (statins) substantially reduce the risk of myocardial infarction, stroke and other manifestations of atherosclerotic disease[1–3] and for most of the 28 years since their introduction have been considered to be safe and well tolerated. Recently, however, their perceived tolerability has declined: some investigators[4,5] state that 10–20% of patients are unable to tolerate statins, either completely or at a sufficient dose. Intolerance is commonly due to muscle symptoms (usually without significantly increased creatine kinase (CK)).[6] Tertiary care settings such as lipid clinics see an even higher fraction of patients labelled statin-intolerant.[7]

Randomised controlled trials (RCTs), especially when large, double-blind and placebo-controlled, have long been recognised as the best method yet devised for evaluating the efficacy, safety and tolerability of any treatment. Those who claim that a substantial fraction of patients cannot take statins may acknowledge the lack of any signal of intolerance in RCTs, but often contend[5,8] that, in the particular case of statins, RCTs are not relevant to clinical practice for the following overlapping reasons. First, these trials excluded patients with a history of statin intolerance, so that the randomised groups comprised only patients unlikely to experience statin-induced adverse effects.

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Second, the trials screened out potential participants with complex medical histories, women and the elderly – patient types who are probably more vulnerable to adverse events. Third, RCTs are insensitive instruments for the detection of intolerance. Similar objections could be raised to many clinical trials of therapeutic agents of any kind. We shall address all these arguments as they apply to statins. In addition, we comment on the paradox that statins, which can cause serious muscle injury including rhabdomyolysis, do not appear to cause less dramatic muscle symptoms, such as myalgia without significant elevations of CK.

Table 1 shows RCTs with statins, selected on the basis that they enrolled patients with substantial medical histories in randomised trials evaluating cardiovascular outcomes, were double-blind and placebo-controlled and the withdrawal rates due to adverse events collectively have been published. The withdrawal rates due to adverse events are consistently similar in the statin and placebo groups, as previously shown for RCTs in generally less complicated patient types.[9] Of the statins represented in Table 1, fluvastatin and rosuvastatin are not CYP3A4 substrates and are less prone to drug interactions[10], which elevate statin plasma concentrations and thus increase the risk of myopathy (muscle symptoms with CK elevations above 10X the upper limit of normal (ULN)). Otherwise statins differ little in terms of safety and tolerability at recommended doses.

Are statin-intolerant patients excluded from cardiovascular outcome trials?

Alone among the studies in Table 1, the Heart Protection Study (HPS)[11] included active drug in its pre-randomisation run-in period, which consisted of simvastatin 40 mg for 4–6 weeks following 4 weeks on placebo. (Active drug enabled a blinded pre-randomisation assessment of the sensitivity of each participant to the effect of simvastatin on low-density lipoprotein (LDL) cholesterol needed for a pre-specified subgroup analysis.) This brief exposure to simvastatin did not prevent randomisation of a large number of patients who later complained of muscle symptoms, approximately 6% at every visit for a total of 32.9% of those allocated to simvastatin 40 mg and 33.2% of those allocated to placebo.[11] In HPS patients were directly questioned at each visit about muscle symptoms (in addition to the standard general query about adverse events). HPS illustrates the high prevalence of muscle symptoms whether or not a patient takes a statin.

We agree that statin-intolerant patients are unlikely to volunteer for a RCT and likely to be excluded if they did (to reduce loss of statistical power from post-randomisation cessation of study medication). Let us postulate that 10% or more of patients are statin-intolerant, as is often asserted.[4,5,12] The recruiting periods for the trials in Table 1 generally preceded widespread usage of statins in the relevant patient population. However, even if as many as half the patients randomised had been previously exposed to a statin and all the intolerant patients among them had been excluded, intolerance in the statin-naïve other half of the study population would produce an absolute excess of discontinuation due to adverse events among patients allocated to the statin of at least 5% compared to placebo; this would have been detectable in these large long-term trials. But the RCTs show no such excess (Table 1). Withdrawal due to adverse events in the 8 studies pooled was 8.0% (1814/22714) and 8.1% (1843/22715) in patients allocated to statin and placebo respectively.

In any event, this potential bias could not affect the Scandinavian Simvastatin Survival Study (4S), the first of the statin cardiovascular outcome trials, which

Table 1. Discontinuation due to adverse events in randomised double-blind placebo-controlled cardiovascular outcome trials of statins.[a]

Trial	N	Drug, dose (mg)	Duration (years)[b]	Patient type	Age (years)[b]	% Female	Discontinuation due to AEs (%)	
							Statin	Placebo
4S	4444	S 20–40	5.4	CHD	59	19	5.7	5.7
HPS	20536	S 40	4.9	Mixed[c]	64	25	4.8	5.1
ALERT	2102	F40–80	5.1	Renal transplant	50	34	14.8	16.3
4D	1255	A20	4.0	Diabetes, on dialysis	66	46	11.8	8.2
SPARCL	4731	A 80	4.9	Stroke/TIA[d]	63	40	17.5	14.5
CORONA	5011	R10	2.7	Heart failure	73	24	9.6	12.1
GISSI-HF	4574	R10	3.9	Heart failure	68	23	4.6	4.0
AURORA	2776	R10	3.8	Haemodialysis	64	38	14.9[e]	16.8[e]

AEs: adverse events; S: simvastatin; CHD: coronary heart disease; F: fluvastatin; 4D: A: atorvastatin; TIA: transient ischaemic attack; R, rosuvastatin.
[a]Trials are listed in order of publication date of the main results. [b]Mean or median. [c]65% CHD, 16% cerebrovascular disease and 29% diabetes.
[d]69% stroke and 31% TIA. [e]Included end point events. For study references, see Appendix in supplementary material.

began enrolling participants in February 1988.[13] Simvastatin became available for prescription in Scandinavia later that year (preceding all other statins).[14] Because of the newness of the drug and the conservatism of Scandinavian physicians at that time,[13] usage in clinical practice was minimal during the enrolment period, which ended in 1989. For example, in 1990 prescription of simvastatin in Sweden was still limited to a few thousand patients;[15] in contrast, about 600,000 patients were taking it by 2008.[15] Therefore, exclusion of participants from 4S because of statin intolerance was negligible, but the rates of withdrawal due to adverse events in the simvastatin and placebo groups were virtually identical (Table 1).

Finally, patients with well-documented statin intolerance due to muscle symptoms usually tolerate a statin under double-blind conditions.[16,17] Therefore, any exclusion of patients with statin-associated muscle symptoms from RCTs would have had little impact.

Are patients in the cardiovascular outcome RCTs less vulnerable to statin adverse events?

Another frequent assertion is that, because of the screening process for entry into the RCTs, patients randomised were healthier and therefore less vulnerable to statin adverse effects than patients in clinical practice. While some trials excluded potential participants with renal disease, heart failure or advanced age, other trials included them and collectively there were thousands of patients with these characteristics. There was minimal exclusion of concomitant medications other than lipid-lowering agents and drugs known to interact with the statin studied. The RCTs in Table 1 included the elderly, women, patients with a history of coronary heart disease or stroke, diabetes, heart failure and end-stage renal disease – collectively, a population with medical histories at least as complex as in most clinical practices. Nevertheless, the withdrawal rate due to adverse events was consistently similar in the statin and placebo groups.

Are RCTs insensitive for detecting adverse effects compared to observational studies?

In observational studies of patients prescribed statins in clinical practice[18,19], adverse event rates – especially muscle symptoms obtained via a questionnaire – are substantial, but muscle symptoms are also very common in patients allocated to placebo in RCTs, when queried.[11] Association is not causation and an adverse event is not necessarily an adverse effect,[20,21] but this is sometimes forgotten.[22] A recent large and carefully conducted cohort study[23] has provided valuable information on withdrawal from statins, including the fact that statin therapy could be restored in 92% of the 6579 patients who stopped it because of an adverse event and were then re-challenged. Similarly, a review of 1605 patients referred to a specialist clinic because of statin intolerance found that statin therapy could be restored in 73%.[24] This slightly lower success rate may reflect the more challenging patients referred to a specialist clinic.

The statin cardiovascular outcome RCTs each followed thousands of patients for several years. The main focus was to test the hypothesis that reducing LDL cholesterol with a statin would reduce atherosclerotic cardiovascular disease end points in various patient populations. It is possible that participants volunteering for clinical trials are more motivated and more stoical than average but, if so, this will affect the stain and placebo groups equally. Also, tolerability data tend to be presented in less detail in the published papers. Nevertheless, all adverse event data in clinical trials must be communicated via comprehensive clinical study reports to regulatory agencies by the sponsor and, if new and clinically significant, incorporated into prescribing information.

Observation, usually in the form of adverse event reporting by clinicians to regulatory agencies or pharmaceutical companies, can suggest and sometimes prove drug adverse effects too rare to be detectable even in very large clinical trials. However, in the case of statins, all adverse effects were established through RCTs.[20] In brief, the risk of myopathy and rhabdomyolysis is long established, but a cardiovascular outcome RCT showed this risk to be unacceptably high (about 1%) for simvastatin 80 mg[25] (compared to <0.1% for lower doses).[25,26] Consequently, the maximum generally recommended dose of simvastatin is now 40 mg. In patients with a history of recent stroke or transient ischaemic attack, atorvastatin increased the risk of haemorrhagic stroke while reducing the risk of ischaemic stroke and stroke overall[27] and this may be a class effect.[3] A recent finding from a meta-analysis of outcome trials is that statins increase the risk of new onset diabetes by about 10%, equivalent to an absolute risk of about 0.1% per year,[28] more with high-intensity statin treatment.[29] When there are serious adverse effects to detect, large RCTs have the sensitivity to detect them, even when very uncommon. As noted below, sensitivity is reduced if the incidence of an adverse event in the placebo group is high, as is often the case for non-serious adverse events. Nevertheless, if the absolute withdrawal rate due to statin adverse events were as high as 10% above placebo, failure to detect a significant difference in any of the RCTs in Table 1 would be inconceivable.

Why is there no evidence that statins cause minor muscle symptoms?

The most common adverse event during statin therapy is muscle symptoms without significant CK elevations,[6,23] which we have examined previously.[16] The risk of myopathy, defined here and in the prescribing information for most statins as unexplained muscle pain or weakness accompanied by CK increased over 10 X ULN (and including its more severe form, rhabdomyolysis) is well established, but the difference vs. placebo in long-term RCTs is less than 0.1% for any statin at its maximal recommended dose.[16,20] Adverse effects of drugs are typically manifested as a continuum, with a few subjects having a severe form and a larger number a milder form. Therefore, minor muscle adverse effects in some small percentage of statin-treated patients would be expected. However, if this is the case, it has been undetectable in large RCTs under double-blind conditions.[9,16,20,30]

One possible explanation is that a high background rate of any symptom leads to a high incidence in a placebo control group, which reduces statistical power: a small signal may be lost in the noise. For example, if the true rate of minor muscle symptoms in statin-treated patients were around 0.5%, which would be an order of magnitude greater than the risk of myopathy/rhabdomyolysis, it would be difficult to detect even in a large RCT, because the rate in the placebo group will be several percentage points[16] or more if patients were queried about muscle symptoms specifically.[11]

Other clinical studies have examined possible statin effects on muscle function. In the largest of these,[31] 420 healthy statin-naïve subjects were randomised to atorvastatin 80 mg or placebo for 6 months. Normally, a clinical trial has a single primary outcome (with other questions of interest defined as secondary or tertiary outcomes). This study had six predefined primary outcome measures, listed as myopathy frequency (undefined, but appears to signify myalgia), arm isokinetic force, leg isokinetic force, handgrip isometric force, leg dynamic endurance and maximal aerobic power.[32] The standard statistical approach of adjusting p values to take into account the multiplicity of primary comparisons[33] was not followed. Even so, there were no significant differences between the treatment groups for any end point.[31,34] This study therefore provides no evidence for any effect of a maximal dose of atorvastatin on muscle function or symptoms. There were, however, small but significant increases in mean plasma CK (21 U/L) and also alanine aminotransferase. There was no correlation between CK increases and muscle function or myalgia.[34] Small increases in the mean plasma levels of muscle and liver enzymes have long been known to be a class effect of statins,[35] but have never been shown to be clinically significant. Studies of possible effects of statins on muscle morphology and biochemistry, reviewed elsewhere,[21] have not produced a consistent pattern.

Conclusions and implications

The reliability of large randomised, double-blind, placebo-controlled clinical trials for evaluating both beneficial and adverse effects of any treatment is long established and there is no good reason to suppose they are not reliable in the case of statin tolerability. The arguments that the adverse events reported in cardiovascular outcome trials with statins cannot be generalised to patient care are not sustainable.

We have previously put forth evidence[16] that, in most patients, statin-associated muscle symptoms are not of pharmacological origin, but rather a consequence of the high prevalence of background muscle symptoms in the population prescribed statins,[7] coupled with patient expectations that muscle damage may occur, a problem aggravated by media misinformation. The result is that background symptoms are attributed to the statin. This phenomenon is known as the nocebo effect,[36] the lesser known opposite of the placebo effect.

In RCTs, in which treatment is blinded and the nocebo effect applies equally to the statin and placebo groups, there is little difference between statin and placebo in the rates of withdrawal due to adverse events of any kind, showing that statins can be tolerated by nearly all patients, including those with advanced disease and complex medical histories.

Nevertheless, in clinical practice, management of patients with statin intolerance, particularly those with statin-associated muscle symptoms, is often difficult. Strategies for keeping patients with statin-associated muscle symptoms on statin therapy have been proposed,[21] most recently by the European Atherosclerosis Society Consensus Panel.[6] In discussion with patients, contrasting the small risk of adverse effects with the proven substantial cardiovascular benefit of statins may be helpful.[6,37] Some patients who do not tolerate a full dose can at least tolerate lower doses[23] or longer dosing intervals.[24]

This is of particular current relevance because several new drugs that lower LDL cholesterol are in development or newly available. Among them, monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9) have been studied in nominally statin-intolerant patients[4,5] and became available for prescription in Europe and the United States in July 2015. The United States Food and Drug Administration has written:

> '... new lipid-lowering guidelines ... focus on statins as first-line cholesterol-lowering therapy for primary and secondary prevention of atherosclerotic cardiovascular

> disease. However, much discussion has been made of statin-intolerance in recent years . . . we have concerns that many patients who have symptoms that may be entirely unrelated to statins could prematurely discontinue their statins and turn, instead, to a PCSK9 inhibitor, which will lack long-term safety data and CV outcomes'.[38]

We share these concerns. In addition, as biological products, PCSK9 antibodies are expensive to manufacture and will cost orders of magnitude more than the five statins that are already generic products and more than the cholesterol absorption inhibitor ezetimibe. The latter has recently been shown to reduce major cardiovascular events[39] and will become generic and therefore low cost in 2017. One PCSK9 antibody, alirocumab (Praluent, Sanofi/Regeneron), has a 2015 US list price of $14,600 per year of treatment.[40] PCSK9 antibodies will be useful to further reduce LDL cholesterol when added to therapy with a statin or a statin plus ezetimibe, but to use them widely as a statin substitute would be a poor use of health care resources. The vast majority of patients can tolerate a statin, although re-challenge will be necessary in some cases.[2,6,23] This observation is strongly supported by the large randomised double-blind placebo-controlled cardiovascular outcome trials.

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The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Tobert reported receiving consultant fees from Johnson & Johnson and Esperion and that, as a retired (2004) employee of Merck, he receives a fixed pension. Dr Newman reports no conflict of interest. The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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