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REVIEW

Lipids

Reasons for disparity in statin adherence rates between clinical trials and real-world observations: a review

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With statins, the reported rate of adverse events differs widely between randomized clinical trials (RCTs) and observations in clinical practice, the rates being 1–2% in RCTs vs. 10–20% in the so-called real world. One possible explanation is the claim that RCTs mostly use a run-in period with a statin. This would exclude intolerant patients from remaining in the trial and therefore favour a bias towards lower rates of intolerance. We here review data from RCTs with more than 1000 participants with and without a run-in period, which were included in the Cholesterol Treatment Trialists Collaboration. Two major conclusions arise: (i) the majority of RCTs did not have a test dose of a statin in the run-in phase. (ii) A test dose in the run-in phase was not associated with a significantly improved adherence rate within that trial when compared to trials without a test dose. Taken together, the RCTs of statins reviewed here do not suggest a bias towards an artificially higher adherence rate because of a run-in period with a test dose of the statin. Other possible explanations for the apparent disparity between RCTs and real-world observations are also included in this review albeit mostly not supported by scientific data.

Keywords Statin therapy • Adherence • Run in phase • Intolerance

Introduction

Randomized controlled trials (RCTs), especially when large, double-blind, and placebo-controlled, are the best method for evaluating the efficacy, safety, and tolerability of statin treatment.[1,2] A further advantage is that both, known and—more importantly—unknown confounders are equally distributed between the treatment arms.

There is overwhelming evidence from numerous RCTs that inhibitors of HMG-CoA reductase (statins) substantially reduce the risk of myocardial infarction, stroke, and other manifestations of atherosclerotic cardiovascular disease. Furthermore, analysis of the Cholesterol

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Treatment Trialists' Collaboration (CTTC) showed that statin therapy substantially reduces the risk of vascular mortality by about one-fifth per each mmol/L reduction in LDL cholesterol (*Table 1*).[3]

In addition to results from RCTs, during the approximately 4 decades since their introduction, statins have been demonstrated to be safe and well tolerated.[4,5] Adverse effects of statin in RCTs, as recently reviewed[6] are mainly myopathy with reportedly 1–2% under statin, with similar incidence in placebo arms.[3] Sometimes, however, their perceived tolerability has declined. Some investigators nowadays suggest that 10–20% of patients are unable to tolerate statins, either completely or at a higher dose. Consequently, poor adherence in the real-world setting has become an important problem.[7,8]

Specifically, for the case of statin trials, there is an often raised claim that RCT's excluded patients with statin intolerance in the pre-randomization or run-in periods in order to minimize losses from follow-up, a fact that could explain why randomized trials had lower rates of side effects in the active treatment phase than will be observed in the real world.[9]

The Physicians' Health Study exemplifies the use of a pre-randomization run-in period to exclude subjects who are more likely to become non-adherent. The underlying rationale was that run-in periods can dilute or enhance the clinical applicability of the results of a clinical trial, depending on the patient group who will receive the therapy.[10] Thus, adherence data from clinical trials using run-in periods should clarify how this aspect of their design affects the applicability of the results to clinical practice.

The hypothesis of the present investigation was that there are more side effects and non-adherence in trials without a run-in period. We analysed the data from RCTs selected by the CTTC involving 175 000 participants.[3]

Selection of sources

We aimed to include all eligible statin trials from the CTTC protocols. The CTTC protocol was first established in 1994 to reliably assess mortality outcome in particular types of patients. Randomized trials were eligible for inclusion if the main effect of at least one of the trial interventions was to modify lipid levels, the trial was un-confounded with respect to the intervention and the trial aimed to recruit at least 1000 participants with treatment duration of at least 2 years.[11] The main outcome measure in these trials were major vascular events.

From the 27 trials included in CTTC and the Heart Protection Study (HPS)-2 trial, 15 trials had a run-in period (*Figure 1*). Among the 15 trials with a run-in period, 12 trials used no statin in the run-in period and 3 trials used a statin therapy in the run-in phase. We here evaluate the adherence rates in these trials, both for statins and for placebo.

Next, we tested whether the use of statins in the run-in phase affected the rate of non-compliance during the trial both in patients receiving statins and those receiving placebo.

Medication in run-in phase

Adherence rate in Cholesterol Treatment Trialists Collaboration trials without a run-in period

From the 27 CTTC trials, 13 trials had no run-in period.

In the MEGA trial 8214 men and postmenopausal women aged 40–70 years were included and randomized to diet or diet plus pravastatin (10–20 mg daily). The mean follow-up was about 5.3 years. The adherence rate was 65.6% in the diet and 65.8% in the diet plus pravastatin group over 5-year follow-up.[12]

In the ALERT trial 2102 renal transplant recipients, men and women aged 30–75 years, were included and randomized to fluvastatin XL (80 mg/day) or placebo. Patients with a pre-existing statin therapy were excluded. The mean follow-up was about 5.1 years. The adherence rate was 74.9% in the fluvastatin group and 71.5% in the placebo group.[13]

The CARDS trial with 2838 men and women with type 2 diabetes aged 40–75 years in 132 UK and Ireland centres to placebo or

Table 1 Studies with a run-in phase

Study with run-in period	Number of patients	Placebo/comparator	Study drug	Duration
SSSS	4444	Placebo	Simvastatin 20 mg	5.4 years
ASCOT	10 305	Placebo	Atorvastatin 0 mg	5 years
ASPEN	2901	Placebo	Atorvastatin 10 mg	4 years
AFCAPS/TexCAPS	6695	Placebo	Lovastatin 20 mg (40 mg)	5.2 years
GISSI	4271	Placebo	Pravastatin 20 mg	23 months
HPS	20 536	Placebo	Simvastatin 20 mg	5 years
HPS 2	36 059	Placebo	ERN/LRPT	3.6 years
CORONA	5459	Placebo	Rosuvastatin 10 mg	32.8 months
TNT	10 003	Atorvastatin 10 mg	Atorvastatin 80 mg	5.5 years
Lipid Study Group	9014	Placebo	Pravastatin	6.1 years
PROSPER	5804	Placebo	Pravastatin 40 mg	3.2 years
JUPITER	17 802	Placebo	Rosuvastatin 20 mg	1.9 years
SEARCH	12 064	Simvastatin 20 mg	Simvastatin 80 mg	84 months
WOSCOPS	6596	Placebo	Pravastatin 40 mg	4.9 years
German Diabetes and Dialysis Study	1255	Placebo	Atorvastatin 20 mg	4 years

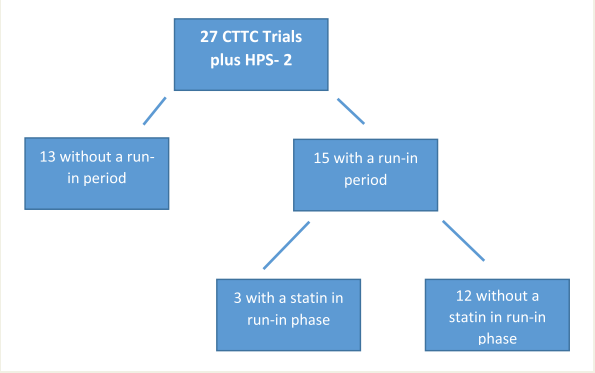

Figure 1 Included trials. HPS, Heart Protection Study; CTTC, Cholesterol Treatment Trialist Collaboration.

atorvastatin. The mean duration of follow-up was 3.9 years. The trial was terminated earlier because of the pre-specified rule for efficacy. The adherence rate was >99% in both groups.[14]

In the ALLHAT-LLT trial, a subset of 10 355 patients were randomized to a lipid-lowering component with pravastatin 40 mg/day or usual care. The follow-up was 4.9 years. There is no concrete information on adherence in the lipid subgroup.[15]

In the post-coronary artery bypass graft (CABG) trial 1351 men and women, aged 21 to 74 years, who had undergone a coronary bypass surgery 1–11 years before baseline. Patients were randomized to aggressive vs. moderate lipid-lowering therapy with lovastatin (mean 76 mg daily) and cholestyramine (8 g per day) if necessary. An angiography was repeated after an average of 4.2 years. The adherence in both statin groups was 85 to 90%. The cholestyramine adherence was lower (65%).[16]

The CARE trial included 4159 patients, men and postmenopausal women aged 21–74 years with myocardial infarction who were randomized to pravastatin (40 mg/day) or placebo. In the last year of follow-up, 86% of the placebo group and 94% of the treatment group were taking their study medication. The median duration of follow-up was 5.0 years.[17]

In the ALLIANCE trial 2442 patients, men and women >18 years, with coronary heart disease were randomized to an aggressive treatment arm using atorvastatin (80 mg/day) or usual care followed over 51.5 months. The adherence was 78.7% in the aggressive treatment arm and 76.8% in the usual care arm.[18]

In the LIPS trial 1677 patients, men and women aged 18–80 years with stable or unstable angina, were randomly assigned to treatment with fluvastatin or placebo. The median follow-up was 3.9 years. The adherence was 93.1% in the fluvastatin group and 92.1% in the placebo group.[19]

The AURORA trial included 2776 men and women aged 50–80 years who were undergoing maintenance dialysis. They were randomized to rosuvastatin 10 mg daily or placebo. The median follow-up period was 3.8 years. According to tablet counts, 91.7% of rosuvastatin and 89.5% of placebo tablets were taken as prescribed.[20]

The 4D trial included 1255 subjects, men and women 18–80 years, with type 2 diabetes receiving maintenance haemodialysis. They were randomly assigned to atorvastatin 20 mg per day or placebo. The median follow-up time was about 4 years. In the placebo group, 82% of patients took the study medication without interruption and in the atorvastatin group 80% of patients did so.[21]

The A-Z trial compared in phase Z in 4497 patients with acute coronary syndrome aged 21–80 years with a less aggressive treatment strategy with placebo (for 30 days) then simvastatin 20 mg or more aggressive with simvastatin 40 mg (for 30 days) and then 80 mg. The adherence rate was about 68% in the low aggressive group and about 66% in the more aggressive group. They were randomized to either an early intensive treatment strategy (40 mg/day of simvastatin for 30 days and then 80 mg/day of simvastatin thereafter) or a less aggressive strategy (placebo for 4 months and then 20 mg/day of simvastatin thereafter).[22]

The PROVE-IT trial randomized 4162 patients, men and women at least 18 years old, who were hospitalized for an acute coronary syndrome to a treatment group with pravastatin 40 mg or a group with atorvastatin 80 mg. The follow-up was up to 36 months. The adherence rate has not been reported in detail from this trial.[23]

The IDEAL trial enrolled 8888 patients, men and women, aged <80 years with a history of acute myocardial infarction. They compared usual dose simvastatin (20 mg/day) or high dose of atorvastatin (80 mg/day). The follow-up was about 4.8 years. The adherence was 95% in both groups.[24]

In synopsis, thus, in those trials that had no run-in phase, the adherence rate was very similar in patients receiving statins and in those receiving placebo.

Adherence rate in Cholesterol Treatment Trialists Collaboration trials with a run-in period

From the 27 CTTC trials plus HPS-2, 15 trials had a run-in period (*Figure 1*).

The 4S trial randomized 4444 men and women aged 35–70 with a history of angina pectoris or myocardial infarction from 94 Scandinavian centres. The protocol included a 2-week placebo run-in phase. There was no significant difference in discontinuation [288 (13%) patients in placebo group vs. 231 (10%) in the statin group].[25]

A similar report exists from the ASCOT-LLA trial with 10 305 hypertensive patients aged 40–79 and a total cholesterol of 6.5 mmol/L or less. There was a 4-week run-in period. In the atorvastatin group (10 mg/day), 240 patients (2.3%) discontinued atorvastatin vs. 276 (2.6%) in the placebo group.[26]

In the ASPEN trial, 3598 men and women with type 2 diabetes aged 40–75 years had a 6-week run-in phase, 67.5% in the Atorvastatin group (10 mg/day) and 57.6% in placebo group were taking study medication at study completion.[27]

The AFCAPS/TexCAPS included 6605 men and women aged 45–73 years. There was a 2-week placebo run-in phase, 969 patients (14.6%) withdraw in the Lovastatin group vs. 1220 (18.4%) in the placebo group.[28]

The HPS study with 20 536 participants (men and women) with coronary disease or other occlusive arterial disease aged 40–80 years had a 4-week placebo run-in phase and showed an adherence rate of 99.6% in the simvastatin (20 mg/day) intervention group vs. 99.7% in the placebo group.[29]

The CORONA trial included 5459 participants of at least 60 years of age. Eligible patients were treated with single blind placebo for 2–4 weeks before randomization to demonstrate compliance. After 33 months of follow-up, median rosuvastatin (10 mg/day) was discontinued in 546 patients in the rosuvastatin group (10%) vs. 490 in the placebo group (8.9%), the difference was not statistically significant.[30]

A similar result was shown in the PROSPER trial with 5804 men and women aged 70–82 years, with a history or risk for vascular disease. The eligible patients entered a 4-week single blind placebo lead-in period. Participants who used less than 75% or more than 120% of the placebo medication were excluded: 725 (12.5%) patients discontinued in the placebo group vs. 724 (12.5%) in the pravastatin group (40 mg/day) during a follow-up of 3.2 years.[31]

In the JUPITER trial, 17 802 healthy men 50 years and women 60 years or older were included. They had no history of coronary artery disease (CAD) or lipid-lowering medication. All eligible subjects underwent a 4-week run-in phase during which they received placebo. The adherence rate was about 75% at the time the study was terminated. There are no data on the comparison of placebo and verum. We should mention that the patients received rosuvastatin 20 mg daily. The trial was stopped after a median follow-up of 1.9 years.[32]

The SEARCH study with 12 064 patients aged between 18 and 80 years with a history of myocardial infarction had a run-in phase with simvastatin 20 mg. In the active phase of the trial, the patients were then randomized to 80 mg simvastatin or 20 mg simvastatin. The adherence after 84 months was 77% in the simvastatin 80 mg group vs. 69% in the simvastatin 20 mg group.[33]

The WOSCOPS trial compared pravastatin 40 mg with placebo in 6596 patients in a 4.9 year follow-up. The patients got a lipid-lowering advice after 1 week and a control diet for 4 weeks before randomization. The adherence rate was 69.2% in the placebo group and 71.4% in the pravastatin group, respectively.[34]

The GDDS trial included 1255 patients with type 2 diabetes at the age of 18–80 years with haemodialysis for less than 2 years. The patients were randomized to atorvastatin 20 mg or placebo, after a 4-week run-in phase with placebo. After a 4 year follow-up, the adherence rate was 80% in the treatment group and 82% in the placebo group.[35]

The HPS 2 trial included 25 673 patients with occlusive arterial disease. There was a 4-week run-in phase with simvastatin 40 mg. If the participants did not reach the treatment goal they received ezetimibe on top. The proportion of participants taking at least 80% of their study medication was 92, 89, and 85% after 1, 2, and 3 years follow-up, respectively.[29]

The GISSI-P trial included 4271 patients with acute myocardial infarction. The population on which the cholesterol-lowering treatment was tested (pravastatin 20 mg daily) was derived from a broader cohort randomized to supplements of n-3 polyunsaturated fatty acids, vitamin E, or standard treatment over 6 months. The median follow-up was about 23 months.[36]

In synopsis thus, there is no indication that—in studies using a run-in phase—a difference existed in adherence between participants allocated to placebo or to statins. Moreover, and most importantly, there is no significant difference in adherence rates between trials using or not using statins in the run-in phase (*Figure 2*). A run-in phase statin use cannot be a cause for the low rate of statin non-adherence in RCTs.

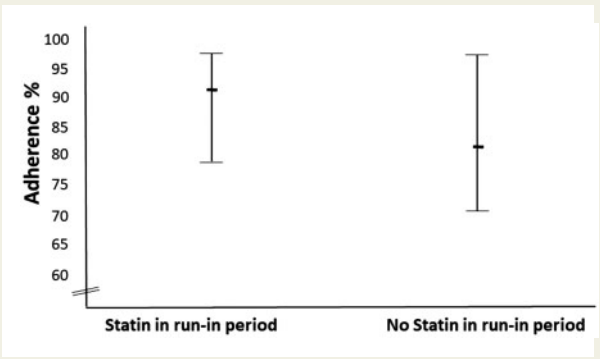

Figure 2 Adherence rates in relation to run-in phase. Mean ± SD adherence rates in statin trials with vs. without statin therapy in run-in period.

The general value of run-in phases in RCTs has recently been challenged in investigations on DPP4 inhibitors and statins.[37,38] The authors had focused on efficacy and safety, but not on adherence rates. Taken together with our results, statins in the run-in phase are time-consuming and appear not essential for the conduct of RCTs.

Other causes for non-adherence in the real world vs. RCT's

In general, non-adherence in real-world settings can exceed 50% in some populations, and this situation also pertains to non-medication treatment recommendations such as monitoring blood glucose or exercising regularly.[39,40] Multiple factors contribute to real-world non-adherence, including high medication costs, complexity and duration of the medication regimen, disruption of lifestyle, younger age, asymptomatic chronic disease, the patient's opinion of benefits and risks, and poor communication between doctor and patient.[41,42] Treatment factors, particularly side effects such as weight gain or sexual dysfunction, patient factors, such as the desire to be independent and eschew the healthcare system, and illness factors (including psychosis, depression, or cognitive impairment) are also important contributors to non-adherence.[43]

Importantly, non-adherence during the conduct of a clinical trial will include most types of non-adherence encountered in real world plus several behaviours unique to clinical trials that are termed, according to Shiovitz *et al.* as 'artifactual' non-adherence.[44] When adherence is not monitored, there is a general assumption that adherence is almost ideal in clinical trial settings.[45] However, there is extensive evidence to the contrary: both real world and the unique forms of non-adherence abound in clinical trials.[46] Artifactual non-adherence is completely different from real-world non-adherence; it is also contrary to both the clinical trial protocol and the agreements in the informed consent process. Examples of these specific and intentional behaviours include denying previous or ongoing study participation while enrolling in multiple studies with an intention to collect stipends, but pretending to have the medical interest.[44]

Although real-world studies have been extremely valuable for identifying associations of risk factors with disease (e.g. blood pressure, blood sugar, and cholesterol with cardiovascular disease), their

value for the assessment of treatment effects is more limited. Real-world studies also have the potential to detect large adverse event rates on health outcomes that would not normally be expected to occur. One of the best examples certainly is myopathy with statin therapy.[47] The HPS study exemplifies very well that patients asked about muscle complaints frequently agree to have muscle pain; however this statement was at the same frequency found in placebo patients.

Because of the potential biases inherent in observational studies, they cannot be relied on for demonstrating the causal nature of treatment-related associations when the relative risks are moderate or relate to health outcomes that are common in the types of patients studied.[48–53] Thus, when large-scale evidence from randomized controlled trials does exist, the additional value of information from non-randomized observational studies about treatment effects is very limited because no causal proof exists.[47]

Contrary to a common belief, adequate data about the use of a treatment in healthcare databases might not involve a duration of exposure that is longer than in the randomized trials.[54–56] Another important fact is that potential biases in observational studies of treatment are often underestimated in the interpretation of associations that are found with health outcomes. Compared with the situation in randomized controlled trials with masked treatment, patients are treated in daily practice knowing that they are taking a particular drug.[48–50,53,57] Confounding by indication, or contraindication, occurs when the treatment being considered tends to be provided more, or less, often to individuals with medical conditions or other characteristics that are associated with increased, or decreased, risks of various health outcomes (which is, of course, what would be expected to occur in clinical practice).[58] Hence, confounders for side effects occur in the real world that are controlled for by randomization in RCTs.

Moreover, there is a high probability of a nocebo effect. Typically, in a pre-medication discussion, physicians tell patients that the treatment could have potential side effects. This effect is so-called the nocebo effect which refers by definition to the induction or the worsening of symptoms induced by sham or active therapies. Examples are numerous and concern both clinical trials and daily practice. The underlying mechanisms are, on one hand, psychological (conditioning and negative expectations) and, on the other hand, neurobiological (role of cholecystokinin, endogenous opioids, and dopamine). Nocebo effects can modulate the outcome of a given therapy in a negative way, as do placebo effects in a positive way.[59] Importantly, in RCTs nocebo effects will be distributed evenly between active drug and placebo if the expected side effect is explained equally. As indicated above, myopathy rates in the HPS trial (high but equal with placebo and active drug) are a good example.

A recent review of the evidence from randomized trials and observational studies suggested that symptomatic adverse events may be misattributed to statins,[50] and there is further evidence from trials of statins of this misattribution.[60] Uncertainty about the association between muscle symptoms and statins persists due to limitations of observational studies and trials. For example, a major limitation of observational studies is a lack of blinding, patients taking a medication expect to experience adverse effects,[61] and therefore reporting of symptoms in statin users may be higher than in a comparable population not on statins. Furthermore, many patients start with exercise after a cardiovascular event at the same time as statin therapy is initiated, so the causal muscle pain is pushed to statin therapy.

Often forgotten is that tolerability is a patient-defined entity and not an objectively defined one but a feeling of treated subjects. In addition to all above-mentioned reasons, there is place for irrationality.

Data on adherence and persistence should ideally be derived from real-life studies. Several patient-related, physician-related, and health system-related factors influence adherence behaviour.[62] Non-adherence may arise from low social status, suboptimal health literacy, lack of involvement in treatment decision-making, comorbidity and subsequent polypharmacy, communication barriers, uncertainty about the drug effectiveness, serious adverse events occurring during therapy, limited access to care, and lack of health information technology and high copayments.[62,63]

Conclusion

If RCT's have no confounder, real-word data must have

In clinical practice, management of patients with statin intolerance or those with statin associated muscle symptoms is often difficult.[64] Strategies for keeping patients on statin therapy and improving the adherence have been proposed most recently by two position papers of the ESC working group of cardiovascular pharmacotherapy[7] and another group.[65]

In most patients, statin associated muscle symptoms are not of pharmacological origin, but rather a consequence of the high prevalence of any other background muscle symptoms coupled with patient expectations that muscle pain or damage may occur. This problem is aggravated by lay press misinformation. In observational studies of patients prescribed statins in clinical practice, adverse event rates, especially muscle symptoms, obtained per questionnaire are substantial, but muscle symptoms are also very common in patients allocated to placebo. Association is not causation and an adverse *event* is not necessarily an adverse effect. In RCT's, 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 history.

Ways to solution

There appear three levels for a possible progress in statin adherence rate. First, physicians should explain causality of benefit and lack of causation of side effects with statins. Second, patients must be educated on the long-term value to reduce hard endpoints. Third, the public high-quality media must be informed and convinced of the benefit/risk ratio of statins.

Conflict of interest: none declared.

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