The effect of statins on muscle symptoms in primary care: the StatinWISE series of 200 N-of-1 RCTs

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Scientific summary

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Scientific summary

Background

Statins effectively reduce cardiovascular disease in primary and secondary prevention among men and women across all age groups. Meta-analyses have demonstrated the safety of statins; however, uncertainty persists about whether or not statins cause symptomatic muscle adverse effects in the absence of myopathy. Many people strongly believe that statins commonly cause muscle symptoms, such as stiffness, pain and weakness. This has been driven by unblinded observational studies and exacerbated by media reports worldwide. Because some patients think that their muscle symptoms are caused by statins, discontinuation is common, which leads to increased cardiovascular disease mortality and a substantial public health burden.

Objective

Our aims were to establish (1) the effect of statins on all muscle symptoms and (2) the effect of statins on muscle symptoms that are perceived to be statin related.

Methods

We conducted a series of 200 double-blinded, placebo-controlled N-of-1 trials in UK primary care. We recruited patients who were considering discontinuing statin use and those who had discontinued in the last 3 years because of perceived muscle symptoms.

Participants were randomly assigned to a sequence of six 2-month treatment periods during which they received 20 mg of atorvastatin daily or a matched placebo. The trial treatment packs were posted to patients prior to the start of each treatment period. Patients, general practice staff and trial staff were blind to allocation in each treatment period.

The primary outcome was self-reported muscle symptoms, defined as pain, weakness, tenderness, stiffness or cramp to the body of any intensity. On the last week of each treatment period, participants rated their muscle symptoms on a visual analogue scale (0 = no symptoms, 10 = worst possible symptoms) online, over the telephone, using a mobile phone application or on paper.

Secondary outcomes were collected on the last day of each treatment period and included binary measures for experience of muscle symptoms and attribution of symptoms to the study medication, site of muscle symptoms, visual analogue scale scores for the effect of their muscle symptoms on general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life, and any other symptoms that the participant believed were attributable to the study medication. Adherence to study medication was self-reported and verified by a drug accountability count of returned treatment packs containing the trial medication.

At the end of their trial, each participant was provided with a summary of their symptom data during the statin periods and the placebo periods. Three months after the end of the final treatment period, we asked the participants if they intended to continue or cease statin treatment. All participants were asked if they found the trial useful in making a decision about future statin use, and we determined the relationship between this decision and the participant's primary outcome.

The primary analysis aggregated data from all participants' muscle symptom scores, comparing statin with placebo periods.

Results

Two hundred patients were recruited between December 2016 and April 2018. The median age was 69.5 years (interquartile range 63–76 years) and 115 (57.5%) were male. Fourteen participants (7.0%) were current smokers, 105 (52.5%) were ex-smokers, 33 (16.5%) had diabetes and 140 (70.0%) had a history of cardiovascular disease. The mean total cholesterol level was 5.4 mmol/l (standard deviation 1.4 mmol/l).

Primary outcome

A total of 151 out of 200 (75.5%) randomised participants provided one or more visual analogue scale measurements in a placebo period and one or more in a statin period, and are therefore included in the primary analysis. A total of 86 (43.0%) participants did not complete the whole trial (two died, four were lost to follow-up and 80 withdrew).

There was no evidence of a difference in aggregated muscle symptom scores between statin and placebo periods (mean difference statin minus placebo −0.11, 95% confidence interval −0.36 to 0.14; $p = 0.398$).

Secondary outcomes

Among the 152 patients who contributed at least one secondary outcome measurement in a placebo period and one in a statin period (note that one additional participant provided secondary outcome data compared with primary outcome data), there was no evidence of an effect of statins on muscle symptoms overall (odds ratio 1.11, 99% confidence interval 0.62 to 1.99), nor was there evidence of an effect of statins when restricting to muscle symptoms that could not be attributed to another cause (odds ratio 1.22, 99% confidence interval 0.77 to 1.94). Of the other secondary outcomes (e.g. general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life), there was no evidence of a difference in symptom scores between the statin and placebo periods.

Adherence to the study medication was high, with the proportion of participants reporting taking their study medication 'every day' or 'most days' being at least 80% during each period, among participants who had not yet withdrawn.

Of the 114 patients who completed the full six treatment periods, 113 received their results during an end-of-trial discussion with their general practitioner or research nurse (56.5% of randomised participants) (one participant did not attend). At 15 months, 58 (51.3%) of these 113 participants had a prescription for statins, 74 (65.5%) said that they intended to resume statins or had already done so, and 99 participants (87.6%) said that their trial had been helpful.

Conclusions

The evidence from StatinWISE (Statin Web-based Investigation of Side Effects) suggests that, on re-challenge among patients who have previously experienced muscle symptoms that they attribute to statins, 20 mg of atorvastatin (Lipitor, Pfizer) has no effect on muscle symptoms at the population level.

Among individual patients, a majority of those completing the trial decided to restart statins. Therefore, the N-of-1 trial design could be a useful method of encouraging patients to find out whether or not statins are causing their pain and guide individual therapy.

Implications for practice

The evidence from our series of N-of-1 trials suggests that this methodology could be a useful tool to aid decision-making about future statin use, and could encourage patients to find out whether or not statins are causing their symptoms.

General practitioners who are managing patients who believe that they are experiencing muscle symptoms because of their statin use should be aware that the majority of StatinWISE participants did not experience a difference in symptoms between the statin and the placebo periods.

Recommendations for future research

1. We would recommend that series of N-of-1 trials be undertaken for other types of statins, higher dosages and non-muscle symptoms that are frequently attributed to statins. In particular, we would recommend this methodology among patients with existing cardiovascular disease who require higher doses of statin than tested in our series of N-of-1 trials.
2. We would recommend that N-of-1 trials could be used in the context of transient symptoms that occur during use of other medications.

Trial registration

This trial is registered as ISRCTN30952488 and EudraCT 2016-000141-31.

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This report

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