Statins: association with increased risk of wider range of musculoskeletal conditions

A large US cohort study suggests that statin use increases the risk of musculoskeletal conditions, including musculoskeletal injury, musculoskeletal pain and, possibly, degenerative arthropathies. Health professionals should continue to follow current NICE guidance on lipid modification, and be aware of MHRA advice relating to statins and myopathy.

Overview and current advice

Statins are an important therapeutic component of primary and secondary prevention of cardiovascular disease. They are recommended in NICE guidance on lipid modification and care of people with type 1 and type 2 diabetes (all these guidelines are being updated and the update to the lipid guideline is expected in July 2014).

Although statins are generally well tolerated, myopathy (which can range from clinically benign myalgia to rare life-threatening rhabdomyolysis) is a known side effect of all statins, and the risk increases with higher doses. The Medicines and Healthcare Products Regulatory Agency (MHRA) has issued several warnings about the increased risk of myopathy with statins in Drug Safety Updates from May 2010, November 2011, August 2012 and October 2012.

This observational study aimed to determine whether the use of statins was associated with a wider range of musculoskeletal conditions, including degenerative arthropathies, musculoskeletal injury and drug-associated musculoskeletal pain.

See the Clinical Knowledge Summaries information on lipid modification for a general overview of prescribing considerations. The NICE Evidence topic page on statins provides links to other evidence related to statins and their use, including a Medicines Evidence Commentary on the effect that switching statins has on muscle symptoms.

New evidence

A retrospective cohort study evaluated the association of statin use with musculoskeletal conditions in a US military healthcare system¹. It included 46,249 people; 17% were active-
duty soldiers and 83% were veterans and families. They were divided into 2 groups; 13,626 statin users (who had received and collected a prescription for a statin for at least 90 days; mean age 60 years, 58% male) and 32,623 nonusers (who did not receive a statin at any time throughout the study; mean age 45 years, 44% male). Follow-up was from October 2005 to March 2010.

The most commonly taken statin was simvastatin (74%), with 17% taking atorvastatin, 7% pravastatin and 2% rosuvastatin. The mean cumulative duration of statin use was about 4.5 years, and about one-third of patients were prescribed maximal doses (simvastatin 80 mg/day, pravastatin 80 mg/day [maximum licensed UK dose of pravastatin is 40 mg/day], atorvastatin 80 mg/day or rosuvastatin 40 mg/day).

The occurrence of musculoskeletal conditions was determined using pre-specified groups of International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) codes: Msk1 (all musculoskeletal diseases), Msk1a (arthropathies and related diseases), Msk1b (injury-related diseases, such as dislocation, strain and sprain) and Msk2 (drug-associated musculoskeletal pain).

The results of the study are shown in the table below. The primary analysis assessed the risk of musculoskeletal conditions in 6967 statin users and 6967 nonusers in a propensity score-matched cohort (propensity score matching balances baseline characteristics).

**Table: outcomes for the primary analysis**

<table>
<thead>
<tr>
<th></th>
<th>Statin users (n=6967)</th>
<th>Nonusers (n=6967)</th>
<th>OR (95% CI)</th>
<th>p value</th>
<th>NNH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All musculoskeletal diseases (Msk1)</td>
<td>86.9%</td>
<td>84.8%</td>
<td>1.19 (1.08 to 1.30)</td>
<td>p&lt;0.001</td>
<td>47 (32 to 103)</td>
</tr>
<tr>
<td>Osteoarthritis/arthropathies (Msk1a)</td>
<td>73.6%</td>
<td>72.2%</td>
<td>1.07 (0.99 to 1.16)</td>
<td>p=0.07</td>
<td></td>
</tr>
<tr>
<td>Dislocation/strain/sprain (Msk1b)</td>
<td>35.2%</td>
<td>32.5%</td>
<td>1.13 (1.05 to 1.21)</td>
<td>p=0.001</td>
<td>37 (23 to 92)</td>
</tr>
<tr>
<td>Drug-associated musculoskeletal pain (Msk2)</td>
<td>73.4%</td>
<td>71.6%</td>
<td>1.09 (1.02 to 1.18)</td>
<td>p=0.02</td>
<td>58 (31 to 249)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio, NNH, number needed to harm

In secondary analyses, the risk of musculoskeletal conditions was determined for all patients who met the study criteria, and a subgroup of patients with no co-morbidities identified using the **Charlson co-morbidity index**. Sensitivity analyses determined the risks in a subgroup of patients with no musculoskeletal diseases at baseline and a subgroup who continued statins for 2 years or more. In all these cohorts, the risk of all musculoskeletal outcomes was higher with statin users compared with nonusers (with adjusted ORs ranging from 1.07 to 1.25).

This observational study has several limitations, as acknowledged by the authors. ICD-9-CM codes were used to identify baseline characteristics and musculoskeletal conditions. These do not provide any information on the severity of illness, may not account fully for variables such as smoking and obesity, and were not validated in the musculoskeletal diseases group (Msk1). Furthermore, the study could also only account for what statins were prescribed (and prescriptions filled), not what patients actually took. Although the authors of the study went to considerable effort to control for differences between the groups in baseline characteristics, and the primary analysis was based on propensity-score matched groups, not all potentially confounding factors were recorded and adjusted for and some imbalances may inevitably have remained.
Commentary provided by the NICE Medicines and Prescribing Centre:

Although observational studies, such as this, can only suggest an association not prove causation and are prone to confounding, this study does add to the well-established concerns about statin therapy and muscle symptoms. In this study, statins were not only associated with musculoskeletal pain, but also musculoskeletal injury and, possibly, degenerative arthropathies. Osteoarthritis or arthropathies were not statistically significantly increased with statin use in the primary analysis, but were in all secondary and sensitivity analyses.

The occurrence of musculoskeletal conditions was relatively high in both statin users and nonusers in this study. Over 70% of patients in both groups had osteoarthritis or arthropathies (Msk1a) or drug-associated musculoskeletal pain (Msk2) documented during follow-up, and over 30% had injuries, such as dislocation, strains or sprains (Msk1b). Muscle symptoms are known to be related to the dose of statins, but the analysis did not make any assessment of the association of the type or dose of statin used with musculoskeletal conditions.

Reported rates of statin-associated muscle symptoms are 1.5% to 5% from randomised controlled trials, and about 5% to 10% from observational studies1,2. Health professionals should be aware of MHRA advice about statins and myopathy (Drug Safety Updates from May 2010, November 2011, August 2012 and October 2012), and NICE lipid guidance which advises that creatine kinase should be measured in people who develop muscle symptoms (pain, tenderness or weakness) while taking statins.

The authors of this study express particular concern about these findings in relation to statin use for the primary prevention of cardiovascular disease in younger people and those with lower cardiovascular risk. The study found an increased risk of dislocations, strains or sprains with the use of statins, which may be of particular importance in people who are physically active. However, there is no information on the activity or exercise levels of the groups, and this could be a confounding factor. The study included active-duty soldiers, and the authors commented that further studies evaluating possible musculoskeletal adverse effects of statins in physically active people, in particular, are needed.

Overall, statins remain an important therapeutic component of primary and secondary prevention of cardiovascular disease. The NICE clinical guideline on lipid modification (which is currently being updated; expected July 2014) recommends that statin therapy should be considered as part of the management strategy for primary prevention in adults who have a 20% or greater 10-year risk of developing cardiovascular disease, and this should include an informed discussion about the benefits and risks of statin treatment, including myopathy. As the guidance says, the National Prescribing Centre decision aid may be helpful in this discussion.

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References


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