Statins: may cause diabetes but patients still better off

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Professor Malik demonstrates that the risk of developing diabetes when taking statins is heavily outweighed by the observed reduction in cardiovascular events.

A recent population-based cohort study of over 1.5 million Canadians who had been prescribed a statin between 1997 and 2010 confirms the link between statin therapy and incident diabetes.\(^2,3\)

The JUPITER study (Justification for the use of statins in primary prevention: An intervention trial evaluating rosuvastatin) first highlighted this potential association, when the risk of incident diabetes was found to be increased by 27 per cent compared to placebo in a low-risk primary prevention cohort.\(^4\)

This was, of course, in contrast with the original observations from the West of Scotland coronary prevention study (WOSCOPS), which demonstrated a 30 per cent reduced risk of diabetes.\(^5\)

However, with all such analyses it is important to take into consideration the definitions applied to identify cases. Thus in WOSCOPS the criterion used to define diabetes was nonstandard, ie a 2mmol per litre rise in glucose from baseline, and indeed when standard criteria were subsequently applied the protective benefit disappeared.\(^3\)

More likely to develop diabetes?

Given the overwhelming benefit of statins in the primary and secondary prevention of CHD, there is clearly disquiet and considerable debate regarding the validity of the data linking statins with diabetes.\(^2,3,6\) Such associations are not

<table>
<thead>
<tr>
<th>Statin</th>
<th>No. patients</th>
<th>No. outcomes</th>
<th>HR (95% CI) adjusted</th>
<th>Number needed to treat to harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>pravastatin</td>
<td>38 470</td>
<td>1 443</td>
<td>reference</td>
<td>-</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>268 254</td>
<td>15 261</td>
<td>1.22 (1.15–1.29)</td>
<td>172</td>
</tr>
<tr>
<td>fluvastatin</td>
<td>5 636</td>
<td>167</td>
<td>0.95 (0.81–1.11)</td>
<td>-</td>
</tr>
<tr>
<td>lovastatin</td>
<td>6 287</td>
<td>211</td>
<td>0.99 (0.86–1.14)</td>
<td>-</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>76 774</td>
<td>3 732</td>
<td>1.18 (1.10–1.26)</td>
<td>210</td>
</tr>
<tr>
<td>simvastatin</td>
<td>75 829</td>
<td>3 727</td>
<td>1.10 (1.04–1.17)</td>
<td>363</td>
</tr>
</tbody>
</table>

Table 1. Diagnoses of diabetes (outcomes) and hazard ratio compared to pravastatin in new users of statins; after reference 1 (lovastatin not available in the UK).  

de facto causal and therefore they should be interpreted in relation to the fact that statins lower CVD events and hence allow patients to live longer and by default develop diabetes.

Furthermore, patients prescribed statins are more likely to be obese and therefore at a greater risk of diabetes, and of course they are going to be subject to more intensive follow-up and assessment, including blood glucose measurements, and consequently a diagnosis of diabetes.

However, it is difficult to reconcile these reassuring views with the finding that the most potent and effective statins have the highest risk, thus when compared with pravastatin there was a significantly increased risk (adjusted hazard ratio, 95% CI) of incident diabetes with atorvastatin (1.22, 1.15–1.29), rosuvastatin (1.18, 1.10–1.26) and simvastatin (1.10, 1.04–1.17), but not with fluvastatin (0.95, 0.81–1.11) or lovastatin (0.99, 0.86–1.14), as shown in Table 1.\(^1\)

Furthermore, there is an increased risk of diabetes with intensive compared to moderate-dose statin therapy.\(^2\)
odds ratio was 1.12 (95% CI, 1.04–1.22) compared with 0.84 (95% CI, 0.75–0.94) for cardiovascular events for participants receiving intensive compared with moderate doses. Thus while there were 6.5 fewer cases with cardiovascular events there were 2.0 additional cases of diabetes in the intensive-dose group per 1000 patient-years.

**Mechanism**

The essential paradigm for the development of diabetes per se is that of increasing insulin resistance and a reduction in beta-cell function. In animal models, pravastatin improves insulin sensitivity and inhibits gluconeogenesis, while simvastatin reduces insulin secretion and atorvastatin and lovastatin both impair glucose tolerance.\(^7\)

Indeed in a recent study in hypercholesterolaemic patients, rosuvastatin decreased adiponectin, which is a key adipokine for vascular protection\(^8,9\) and regulates insulin sensitivity, with a resultant increase in fasting insulin and HbA\(_{1c}\), while pravastatin did exactly the opposite.\(^10\)

Statins have also been shown to increase beta-cell inflammation and apoptosis, inhibit calcium-mediated pancreatic insulin release and decrease expression of glucose transporters GLUT-2 and GLUT-4.\(^11\)

A direct effect of inhibiting HMG-CoA reductase is inhibition of mevalonate synthesis, which regulates the formation of secretory granules and insulin secretion from the pancreatic beta-cells.\(^12\) The inhibition of HMG-CoA reductase also causes up-regulation of LDL receptors and enhanced cellular uptake of LDL-cholesterol, which undergoes oxidation, thus inciting inflammation and deranged beta-cell release of insulin.\(^7\)

The cumulative effect of all these molecular alterations is to disrupt glucose handling and hence increase the incidence of diabetes.

**Conclusion**

As with all interventions, the physician must weigh up the risk/benefit ratio and must always remember *primum non nocere* (first, do no harm). But of course preventing diabetes, which may eventually ‘cause harm’, needs to be balanced against denying one of the most effective therapies we have to date for CHD.\(^13\)

Hence as physicians we are often caught between ‘a rock and hard place’ but clinical judgement and evidence for ‘less harm’ must prevail.

**References**


Declaration of interests
None to declare.

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