Switching rosuvastatin to atorvastatin

This bulletin reviews a switch from rosuvastatin to atorvastatin. This project is an update of PrescQIPP Bulletin 18 which was originally written in June 2012. This project incorporates the new National Institute for Health and Care Excellence (NICE) guideline on lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular risk. It is acknowledged that there are strong views on the impact of this guideline and that it will take time for commissioners to digest and incorporate the guideline into pathways.

There are still potential annual savings of over £40 million across England (ePACT Jul - Sep 14) in implementing a switch from rosuvastatin to atorvastatin.

Support material is available on the PrescQIPP website, available at www.prescqipp.info

Recommendations

- Offer atorvastatin 20mg* for the primary prevention of cardiovascular disease (CVD) to people who have a 10% or greater 10-year risk of developing CVD (including type 2 diabetes). Estimate the level of risk using the QRISK2 calculator.¹
- Offer atorvastatin 20mg* for the primary prevention of type 1 diabetes in people who are older than 40 years, have had diabetes for more than 10 years, have established nephropathy or have other CVD risk factors.¹
- Offer atorvastatin 20mg* for the primary or secondary prevention of CVD to people with chronic kidney disease (CKD).¹
- Offer atorvastatin 80mg for secondary prevention to people with existing CVD. Consider a lower dose of atorvastatin if there are potential drug interactions, a high risk of adverse effects, or where there is patient preference for this. If people are not able to tolerate a high intensity statin, take the most clinically effective dose of statin.¹
- In primary and secondary prevention, measure total cholesterol, high-density lipoprotein (HDL) cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment after 3 months of treatment and aim for a >40% reduction in non-HDL cholesterol. Non–HDL refers to non-high density lipoprotein (non-HDL) cholesterol rather than low density lipoprotein (LDL) cholesterol. Non-HDL cholesterol is total cholesterol minus HDL cholesterol and is recommended instead of low density lipoprotein (LDL) cholesterol.¹
- Rosuvastatin is not recommended in primary or secondary prevention¹ as it is not a cost effective treatment choice.
- Review patients on rosuvastatin for a switch to atorvastatin. Exclude any patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal, raised creatine kinase levels greater than 5 times the upper limit of normal, concomitant use of CYP3A4 inducers or CYP3A4 inhibitors, patients with porphyria, HIV, children and adolescents under 18 years of age or where treatment has been initiated by the lipid clinic.

* starting dose
**Background**

Generic atorvastatin was launched in 2012. Rosuvastatin is approximately 18 times more expensive than atorvastatin. NICE guidance (lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular risk) recommends atorvastatin as the preferred high intensity statin with a low acquisition cost.\(^1\) In the absence of trial evidence of greater effectiveness than atorvastatin 80mg and the considerably higher cost, NICE guidance does not recommend the use of rosuvastatin. NICE guidance also states that if someone is not able to take the highest intensity statin recommended it will still be cost effective for them to take the most clinically effective dose of a statin that they can tolerate with the exception of rosuvastatin, which is much more costly than the other available statins and so would not be cost effective.\(^1\)

Table 1 states the percentage and absolute reductions in low-density lipoprotein cholesterol for statin therapy.

**Table 1: Absolute reductions (mmol/L) and percentage reductions in serum LDL-cholesterol\(^{2,3}\)**

<table>
<thead>
<tr>
<th>Statin</th>
<th>5mg</th>
<th>10mg</th>
<th>20mg</th>
<th>40mg</th>
<th>80mg</th>
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<tbody>
<tr>
<td>Simvastatin</td>
<td>Absolute reduction</td>
<td>1.31 (1.22-1.40)</td>
<td>1.54 (1.46-1.63)</td>
<td>1.78 (1.66-1.90)</td>
<td>2.01 (1.83-2.19)</td>
</tr>
<tr>
<td></td>
<td>Reduction in serum LDL-cholesterol</td>
<td>27%</td>
<td>32%</td>
<td>37%</td>
<td>42%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Absolute reduction</td>
<td>1.79 (1.62-1.97)</td>
<td>2.07 (1.90-2.25)</td>
<td>2.36 (2.12-2.59)</td>
<td>2.64 (2.31-2.96)</td>
</tr>
<tr>
<td></td>
<td>Reduction in serum LDL-cholesterol</td>
<td>37%</td>
<td>43%</td>
<td>49%</td>
<td>55%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Absolute reduction</td>
<td>1.84 (1.74-1.94)</td>
<td>2.08 (1.98-2.18)</td>
<td>2.32 (2.20-2.44)</td>
<td>2.56 (2.42-2.70)</td>
</tr>
<tr>
<td></td>
<td>Reduction in serum LDL-cholesterol</td>
<td>38%</td>
<td>43%</td>
<td>48%</td>
<td>53%</td>
</tr>
</tbody>
</table>

Table 2 groups the statins into three different intensity categories.

**Table 2: Statin groupings for percentage reduction in LCL-cholesterol\(^{1,2}\)**

<table>
<thead>
<tr>
<th>Dose(mg/day)</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>21%</td>
<td>27%</td>
<td>33%</td>
<td></td>
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</tr>
<tr>
<td>Pravastatin</td>
<td>20%</td>
<td>24%</td>
<td>29%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>27%</td>
<td>32%</td>
<td>37%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>Atorvastain</td>
<td>37%</td>
<td>43%</td>
<td>49%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>38%</td>
<td>43%</td>
<td>48%</td>
<td>53%</td>
<td></td>
</tr>
</tbody>
</table>

*Advice from the MHRA:\(^4\) ‘there is an increased risk of myopathy associated with high-dose (80 mg) simvastatin. The 80 mg dose should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks’.

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Primary prevention

- For the primary prevention of CVD, a systematic strategy is needed to identify people who are likely to be at high risk. Prioritise people for a full formal risk assessment if their estimated 10-year risk of CVD is 10% or more using the QRISK2 assessment tool.¹

- The decision on whether to start statin therapy should be made after an informed discussion between the clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, co-morbidities, general frailty and life expectancy.¹

- Before offering lipid modification therapy for primary prevention, discuss the benefits of lifestyle modification and optimise the management of other modifiable risk factors if possible. Recognise that people may need support to change their lifestyle. Refer them to programmes such as exercise referral schemes. [http://pathways.nice.org.uk/pathways/behaviour-change](http://pathways.nice.org.uk/pathways/behaviour-change)

- Include all the following in the assessment:
  - Smoking status
  - Alcohol consumption
  - Blood pressure
  - Body mass index or other measure of obesity
  - Fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels not already available), HbA1c, renal function, liver function (transaminases) and TSH.

- Risk equations should not be used for people who are already considered at high risk of CVD because of familial hypercholesterolaemia or other inherited disorder of lipid metabolism. Clinical assessment is needed for these patients. Other high risk groups include people treated for HIV or with antipsychotic disorders, people with chronic kidney disease and people with autoimmune disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis.¹ ⁵

- If lifestyle modification is ineffective or inappropriate, offer atorvastatin 20mg for the primary prevention of CVD to people who have a 10% or greater 10 year risk of developing CVD.¹

- The updated guidelines recommend that for people aged 85 years or older, consider atorvastatin 20mg, as a statin may be of benefit in specifically reducing the risk of non-fatal myocardial infarction. The guidance also recommends prescribers to be aware of factors such as polypharmacy, comorbidity, frailty and life expectancy that may make treatment inappropriate. Current opinion and guidance on problematic polypharmacy suggests to re-evaluate the patient’s risk profile for primary and secondary prevention of cardiovascular disease and to check if there is a valid indication for prescribing. The systemic strategy outlined by NICE also recommends including frailty and life expectancy.

- A review of the few randomised controlled trials of patients over 80 years old did not provide evidence of an effect of lipid-lowering treatment on total mortality in this age group.⁶-⁸ NICE made a recommendation that statin treatment should be considered in people over 85 years but added detail to make it explicit that the benefit may only be in reduced non-fatal myocardial infarction (MI).¹

- Offer atorvastatin 20mg for the primary prevention of CVD in people with type 1 diabetes who are older than 40 years, have had diabetes for more than 10 years, have established nephropathy or have other CVD risk factors.¹

- Offer atorvastatin 20mg for the primary prevention of CVD to people with type 2 diabetes who have a 10%-year risk of developing CVD.¹

- Measure total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment after three months of treatment and aim for a greater than 40% reduction in non-HDL cholesterol. Note that this now applies to both primary and secondary prevention.¹
If the person is unable to tolerate atorvastatin 20mg, consider the following strategies:\(^1\):

» Stop the statin and try again when the symptoms have resolved to check the symptoms are related to the statin.

» Reduce the dose and offer atorvastatin 10mg.

» Change to a lower intensity group, e.g. simvastatin (see table 2, page 2).

See below for monitoring of adverse events.

**Secondary prevention**

These patients are at highest risk of a vascular event. They have a history of MI, angina, or coronary revascularisation, peripheral vascular disease (PVD), transient ischaemic attack (TIA) or ischaemic stroke, patients with type I and II diabetes over the age of 40, familial lipid disorders, clotting disorders or other conditions known to be associated with increased CVD risk. In addition, patients with chronic renal failure are considered to be high risk. Do not delay statin treatment for secondary prevention to manage modifiable risk factors.

- Offer people with CVD atorvastatin 80mg.\(^1\)
- Use a lower dose of atorvastatin if there are potential drug interactions, high risk of adverse effects or there is patient preference.\(^1\)
- If someone reports adverse effects when taking high-intensity statins discuss the following possible strategies with them:
  - Stopping the statin and trying again with the same dose when the symptoms have resolved, to check if the symptoms are related to the statin.
  - Reducing the dose of the statin within the same intensity group.
  - Changing the statin to a lower intensity group, e.g. simvastatin. Note the advice from the MHRA.\(^4\)
- If a person has acute coronary syndrome, do not delay statin treatment. Take a lipid sample on admission and about 3 months after the start of treatment.\(^1\)
- Measure total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment after three months of treatment and aim for a greater than 40% reduction in non-HDL cholesterol.
- If a greater than 40% reduction in non-HDL cholesterol is not achieved, discuss the following:
  - Adherence and timing of dose.
  - Optimise adherence to diet and lifestyle measures.
  - Consider increasing the dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement.\(^1\)

Seek specialist advice about options for treating people at high risk of CVD such as those with CKD, type 1 diabetes, type 2 diabetes or genetic dyslipidaemias, and those with CVD, who are intolerant to three different statins.\(^1\)

**Chronic kidney disease**

Offer atorvastatin 20mg for the primary or secondary prevention of CVD to people with CKD. Increase the dose if greater than 40% reduction in non-HDL cholesterol is not achieved and eGFR is 30ml/min/1.73m\(^2\) or more. Higher doses need to be agreed with a renal specialist if eGFR is less than 30ml/min.\(^1\)
**Familial hypercholesterolaemia**

Consider familial hypercholesterolaemia (FH) if cholesterol >7.5 mmol/litre and there is family history of premature coronary heart disease. Arrange for specialist assessment of people with a total cholesterol concentration of more than 9.0 mmol/litre or a non-HDL cholesterol concentration of more than 7.5 mmol/litre even in the absence of a first-degree family history of premature coronary heart disease.¹ ⁵

For FH, treat with a high intensity statin to achieve a recommended reduction in LDL-C concentrations of greater than 50% from baseline.⁵ If treatment with the maximum tolerated dose of a high-intensity statin (and ezetimibe) does not reduce LDL-C concentrations by greater than 50% from baseline, offer a referral to a specialist in FH. Prescribe drugs for the treatment of homozygous FH in a specialist centre.⁵

If target lipid levels are not achieved, lipid clinic advice or referral may be needed in line with your local Trust policy.

NICE guidance for familial hypercholesterolaemia does not exclude rosuvastatin as a high intensity statin, although this guidance is due for review.⁵

Rosuvastatin 40mg should only be prescribed under specialist supervision (through lipid, cardiac or diabetic clinics) as it is contraindicated in patients with predisposing risk factors for muscle toxicity. The 40mg dose should only be necessary for the minority of patients with severe hypercholesterolaemia at high cardiovascular risk.⁹

**Monitoring of adverse effects**

**Statin intolerance**

Intolerance to initial statin therapy should be defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. Adverse effects should be interpreted and balanced against the individual CV risk of the patient. Adverse effects include evidence of new-onset muscle pain (often associated with levels of muscle enzymes in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests.⁵

**Myalgia**

Myalgia is defined as muscle pain, tenderness, or weakness without creatine kinase elevation that is generalised and symmetrical and present for three or more days. It is clear that statins can rarely cause myositis (muscle symptoms with increased CK levels) and even more rarely, rhabdomyolysis (muscle symptoms with marked creatine kinase levels that are typically >20 times the upper limit of normal (ULN) with creatinine elevation and renal failure). It is much less clear that statins are responsible for myalgia with normal (or even mildly raised) CK levels.¹⁰

Muscular symptoms of statin therapy mostly occur on initiation of treatment. It is often also associated with some other pathology (weight gain, deterioration of diabetic control, renal impairment, untreated hypothyroidism, alcohol abuse, concomitant use of other lipid lowering agents or interactions with drugs inhibiting cytochrome P450).¹⁰

**Pre-statin therapy**

Before starting statin therapy, if the person has had persistent generalised unexplained muscle pain, measure CK levels.

- If creatine kinase levels are > 5 times the ULN, re-measure creatine kinase after seven days. If creatine kinase levels are still 5 times the ULN, do not start statin treatment.
- If creatine kinase levels are raised but < 5 times the ULN, start statin treatment at a lower dose.¹
**Post–statin therapy**

A working party has developed a pathway to review the risk versus benefit of continuing statin therapy in patients with symptoms of myalgia:

- If CK <3 x ULN: Safe to continue statin and monitor symptoms.
- If CK 3-5 x ULN: Safe to continue statin, monitor for symptoms and repeat CK levels after 48 hours. If the symptoms are acceptable to the patient, continue the statin at the same or lower dose OR switch to a different statin at a lower dose and uptitrate.
- If CK >5 x ULN: Discontinue the statin and seek specialist advice.

CK should not be routinely monitored in asymptomatic people who are being treated with a statin.¹

**Liver function tests**

Baseline liver transaminases should be measured before starting a statin. Liver function (transaminases) should be measured within three months of starting treatment and at 12 months, but not again unless clinically indicated. People who have liver enzymes (transaminases) that are raised but are less than three times the ULN should not be routinely excluded from statin therapy.¹

**Other considerations**

- Stop statins and seek specialist advice if unexplained peripheral neuropathy develops.
- Do not offer the combination of a bile acid sequestrant (anion exchange resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for the primary or secondary prevention of cardiovascular disease.¹

Note that in secondary prevention, the combination of statin plus fibrate increases the risk of side effects including rhabdomyolysis.

**Statin comparison**

NICE recommends that when a decision is made to prescribe a statin for primary or secondary prevention, to use a high intensity statin with a low acquisition cost. High intensity refers to greater than 40% lowering in low-density lipoprotein cholesterol and guidance specifically refers to atorvastatin 20mg to 80mg. NICE does not recommend rosuvastatin.¹

The following statements compare the statins if there is a need to use an alternative high or lower intensity statin.

- Pravastatin and rosuvastatin unlike atorvastatin and simvastatin are not metabolised via P450 CYP3A4 so there is no interaction with amiodarone, macrolides, calcium channel blockers; diltiazem, verapamil, anti-retrovirals.¹¹-¹³
- Pravastatin and rosuvastatin are hydrophilic rather than lipophilic which may alter side effect patterns but in relation to muscle side effects this is not clear. It is prudent to use lower doses of statins in patients with pre-existing muscle disease.¹¹-¹³
- In August 2012, MHRA guidance highlighted the potential interaction between simvastatin and amlodipine and diltiazem and the increased risk of myopathy. Consequently the maximum recommended dose of simvastatin is now 20mg if used in conjunction with either drug. For secondary prevention, if a more potent statin is needed a switch from simvastatin 40mg to atorvastatin 20mg to 40mg may be an option.¹⁴-¹⁶
- Atorvastatin has hepatic excretion and is therefore favoured over higher simvastatin doses in patients with impaired kidney function.¹³ In severe renal insufficiency (creatinine clearance <30 ml/ min), simvastatin doses above 10mg/day should be carefully considered and, if deemed necessary, implemented cautiously.
- Atorvastatin 80mg has a similar incidence of myopathy to atorvastatin 10mg but a higher incidence of raised liver function tests (LFTs) (2%).
- Simvastatin 80mg should only be used under exceptional circumstances as it is clearly associated with myopathy side effects.
- Any statin (even low doses) is preferred to none, as the benefit of monotherapy with ezetimibe or a fibrate, or the two in combination, instead of statin treatment has a very limited evidence base.
- Statins are unlikely to be the first line treatment in cases with plasma triglyceride concentrations above 10 mmol/litre and referral to the lipid clinic should be considered in line with local Trust policy.
- There is a significant difference in cost between rosuvastatin and atorvastatin; the patent for rosuvastatin is also set to expire in 2017. Table 3 illustrates the current cost differences at comparable doses.

**Table 3: Rosuvastatin and atorvastatin price comparison and savings**

<table>
<thead>
<tr>
<th>Statin and strength</th>
<th>Cost per 28 days (June 2014 Drug Tariff)</th>
<th>% reduction in LDL cholesterol</th>
<th>Statin and strength</th>
<th>Cost per 28 days (June 2014 Drug Tariff)</th>
<th>% reduction in LDL cholesterol</th>
<th>Savings per 28 days with generic atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin 5mg tablets</td>
<td>£18.03</td>
<td>38%</td>
<td>Atorvastatin 10mg tablets</td>
<td>£1.03</td>
<td>37%</td>
<td>£17</td>
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<tr>
<td>Rosuvastatin 10mg tablets</td>
<td>£18.03</td>
<td>43%</td>
<td>Atorvastatin 20mg tablets</td>
<td>£1.26</td>
<td>43%</td>
<td>£16.77</td>
</tr>
<tr>
<td>Rosuvastatin 20mg tablets</td>
<td>£26.02</td>
<td>48%</td>
<td>Atorvastatin 40mg tablets</td>
<td>£1.51</td>
<td>49%</td>
<td>£24.51</td>
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<tr>
<td>Rosuvastatin 40mg tablets</td>
<td>£26.69</td>
<td>53%</td>
<td>Atorvastatin 80mg tablets</td>
<td>£2.48</td>
<td>55%</td>
<td>£24.21</td>
</tr>
</tbody>
</table>

**Switch savings**

There is a significant difference in cost between rosuvastatin and atorvastatin. Nationally the current annual spend for rosuvastatin is over £43 million (based on ePACT data Jul - Sep 14). Switching to atorvastatin could result in an annual potential saving of over £40 million, which equates to a saving of £70,874 per 100,000 patients.

As with all switches, individual patient circumstances need to be borne in mind, however, with tight switching criteria, assistance from practice nurses, support from your local CCG prescribing teams and the experiences of CCGs/GPs that have already undertaken this worked, it is hoped that GPs will participate in realising the cost savings.

**Switching criteria**

To identify patients on rosuvastatin who may be suitable for a switch to atorvastatin.

**Inclusion criteria**

- Adult patients currently taking rosuvastatin for primary prevention and secondary prevention.
- Adult patients taking rosuvastatin for familial hypercholesterolaemia.
Exclusion criteria

- Patients previously on atorvastatin which was withdrawn due to an intolerance or lack of clinical effectiveness.
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the ULN.
- Raised creatine kinase levels exceeding 5 times the ULN.
- Pregnancy, breast-feeding or in women of child-bearing potential not using appropriate contraceptive measures.
- CYP3A4 inducers (e.g. efavirenz, rifampicin, St. John’s Wort).
- CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole), colestipol, fusidic acid, digoxin.
- Children and adolescents under 18 years of age.
- Patients with hypersensitivity to the atorvostatin or any of the excipients in the medicinal product.
- Initiated by the lipid clinic.
- It is likely that the majority of patients on rosuvastatin 40mg dose would be excluded from switching to atorvastatin as they would have been initiated by the lipid clinic. If they are included in the switch to atorvastatin 80mg then the patient should be reviewed to ensure they are currently taking an appropriate dose of rosuvastatin.
- Patients not ordering prescriptions or with a low compliance history should be reviewed by their GP.

For primary prevention including patients with diabetes and CKD a switch to atorvastatin 20mg is recommended.

For secondary prevention, a switch to atorvastatin 80mg is recommended.

For familial hypercholesterolaemia only, use the absolute reductions as summarised in table 3.

All patients switched to atorvastatin should have their total cholesterol, HDL cholesterol and non-HDL cholesterol measured after three months of treatment.

Re-check prescribing patterns in six months time to ensure the intervention has continued to be a success.

Summary

- The atorvastatin patent expired in May 2012 releasing significant savings for the NHS. In line with this, NICE recommends atorvastatin as a high intensity statin with a low acquisition cost.
- Reviewing rosuvastatin prescribing and switching patients to atorvastatin could release over £40 million in savings per year nationally.

References

5. National Institute for Health and Care Excellence. NICE Clinical guideline 71. Familial


15. UKMI. MHRA recommendations on simvastatin interactions: What are the implications for patients taking amlodipine? September 2012.


Additional PrescQIPP resources

Available here: http://www.prescqipp.info/resources/viewcategory/301-rosuvastatin

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