Prescribing Policy: Lipid Modification - Secondary Prevention

Policy Statement: Date of Approval: 9th September 2010

This policy defines the decision made by the NHS Western Cheshire Clinical Commissioning and Strategy Committee

Lipid-modifying agents should only be prescribed in accordance with NICE guidance and local guidance for secondary prevention. **Simvastatin 40mg** is first line therapy.

Patients who cannot tolerate simvastatin 40mg should be prescribed pravastatin 40mg or a lower dose of simvastatin.

Patients who do not achieve target should be prescribed simvastatin 80mg second line. Other high intensity statins are not cost-effective and should therefore only be considered after an adequate trial of simvastatin 80mg. Atorvastatin 40mg should be prescribed in these circumstances.
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| Polish |


| Punjabi |

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| Urdu |

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Appendix 1 Flowchart for lipid modification in secondary prevention of CVD

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<td>CHD</td>
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<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>LDL-C</td>
<td>Low density lipoprotein cholesterol</td>
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<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
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<td>PCT</td>
<td>Primary Care Trust</td>
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<td>TC</td>
<td>Total cholesterol</td>
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Rapid Review: Statin prescribing for secondary prevention of cardiovascular disease

J.P. Hampson
Public Health Specialist
8th March 2010

1 Introduction/ method

This short report reviews the evidence for use of statins in secondary prevention of cardiovascular disease. Medline, EMBASE and PharmLine were searched together with the databases from Cochrane, NICE and SIGN.

The main findings are summarised and recommendations for the appropriate use of statins in this context are suggested.

2 Epidemiology/ background

Statins inhibit cholesterol synthesis in the liver which ultimately results in increased uptake of LDL from the circulation. The Multiple Risk Factor Intervention Trial (MRFIT), which was published over 20 years ago, followed 356,000 men for six years and showed a continuous, graded, strong relationship between serum cholesterol and coronary heart disease (CHD) mortality.

Later evidence showed that a reduction in LDL cholesterol of 1.6 mmol per litre halves the risk of CHD events after two years -- a reduction which can be achieved with standard doses of statins. Further, the principal action of statins is to lower LDL cholesterol with only small effects on HDL cholesterol or triglyceride levels. In addition, standard doses of statins are also associated with a 20-50% reduction in LDL level with a similar reduction in the risk of CHD events.¹

Data for the secondary prevention of stroke are less convincing. Evidence suggests that stroke recurrence or mortality are not reduced. However, serious vascular events are reduced and, consequently, routine administration of statins for secondary stroke prevention is still recommended.² ³ ⁴

In another Cochrane review, sub-group analysis showed a reduction in coronary events in patients with peripheral arterial disease. Statins are thus recommended especially in patients with a total cholesterol level ≥3.5mmol/litre.⁵
3 High intensity statin treatment

In general, for secondary prevention, one mmol drop in LDL cholesterol is expected to reduce cardiovascular events by 21%. Further, an editorial stated that high dose statins reduced the average LDL cholesterol from 2.6 to 1.93 mmol/litre. However, a closer inspection of the meta-analysis on which these figures are based shows that the 2 trials which included coronary artery disease patients gave reductions in event rates of between 12% to 21%. Such a large difference in event rate occurred despite both trials achieving a 16% reduction in LDL cholesterol and a final LDL cholesterol of 2mmol/litre.

Thus, it is suggested that whilst the effect of using high dose statins does confer an additional benefit, it cannot be assumed that the relationship between LDL cholesterol reduction and event rate reduction is a linear one. Also, the pooled results from this meta-analysis (which also included 2 acute coronary syndrome trials) demonstrated an overall event rate reduction of 16% by using high dose statins – the 95% confidence limits were between 9% and 23%.

For secondary prevention of cardiovascular disease, NICE recommends simvastatin 40 mg as a starting point. This should be increased to 80 mg (high intensity) dependent on cholesterol levels (see below). In stable coronary artery disease, high intensity atorvastatin is not considered to be cost-effective. A possible alternative to simvastatin is pravastatin. In acute coronary syndrome, NICE recommends high intensity simvastatin or atorvastatin. However, a recent Health Technology Assessment warned against the use of high dose simvastatin because of a higher incidence of side effects (in comparison to low dose simvastatin) although it was acknowledged that these were still rare. The same technology assessment (partially written by an ex-employee and shareholder of Astra Zeneca) goes on to recommend that rosuvastatin 40mg is the most cost-effective option although this was based on mathematical modelling rather than pure clinical trial data.

Clearly, high intensity therapy is more likely to produce side-effects. In one review, high dose statins were responsible for significant myopathy and raised liver transaminases but the absolute increases were small. A recent safety alert from the Medicines and Healthcare products Regulatory Agency (MHRA) warns of potential sleep disturbances, memory loss, sexual dysfunction, depression and exceptional cases of interstitial lung disease.

Other data have shown that high intensity atorvastatin (80 mg) would cost £96,000 per year to prevent one major cardiovascular event in patients with myocardial infarction.

In practice, however, there appears to be a wide gap between published guidance and real life prescribing patterns. In other studies, around 60% of

patients were above their respective LDL cholesterol targets \textsuperscript{14, 15, 16}. Another recent study has confirmed that non-adherence with statin therapy is associated with higher mortality. \textsuperscript{17}

## 4 Treatment targets

High intensity regimens were developed to achieve LDL cholesterol levels as low as possible. Exactly what the LDL target should be is a matter of debate. \textsuperscript{18}

A major Lancet meta-analysis of 14 trials found that there was a 20% reduction in cardiovascular events (over five years) for every millimole reduction in LDL cholesterol. However, the reduction in events was related to the absolute reduction and the authors concluded treatment regimens should be maximised to achieve this reduction rather than aiming for specific targets. \textsuperscript{19} Pragmatically, it has also been shown that few patients will achieve a low limit LDL cholesterol even despite aggressive regimen changes. \textsuperscript{20}

From above, NICE recommends high intensity statins in stable coronary artery disease for patients whose cholesterol levels are above 4 mmols per litre (total cholesterol) and 2 mmols per litre (LDL). However, these should not be regarded as targets since no further action is required beyond changing to a high intensity statin dosage. \textsuperscript{8} The Scottish Intercollegiate Guidelines Network (SIGN) recommends a higher limit of 5 mmol per litre (total cholesterol). \textsuperscript{1}

## 5 Diet

The relationship between saturated fats in the diet and impact on LDL cholesterol is well established. \textsuperscript{21} Further, patients on statin therapy can achieve even greater reductions in cholesterol (and subsequent vascular risk) through low-fat dieting. \textsuperscript{22} The product licenses for all statins stipulate that patients should be commenced on low fat diets before starting therapy and throughout the course of treatment.

## 6 Conclusions

1. Reduction in LDL Cholesterol is associated with reduction in cardiovascular events.
2. High intensity (dose) compared to low intensity statins do decrease the LDL cholesterol levels even further. The reduction in cardiovascular events is variable which clouds the ability to predict the exact benefits.
3. Side effects (although rare) are more likely to occur with high intensity therapy.
4. There is no universally acceptable target and it appears that the absolute reduction in LDL cholesterol gives a better predictor of coronary event reduction.
5. NICE suggest total/LDL cholesterol limits of 4mmol/litre or 2mmol/litre respectively. However, patients already receiving high intensity statins do not need additional therapy if these “targets” are not reached.

7 Recommendations

1. All at risk patients should be commenced on simvastatin 40mg.
2. Following review, if total cholesterol is \( \geq 4 \text{mmol/litre} \) and LDL cholesterol is \( \geq 2 \text{mmol/litre} \), the simvastatin dose should be increased to 80mg.
3. If side effects are troublesome, alternatives are pravastatin and atorvastatin.
4. In acute coronary syndrome, high intensity statins should be commenced.
5. The importance of cholesterol-lowering diets should be emphasised before and throughout treatment.

8 Responsibility for implementation

Responsibility For Implementation Lies With The Practice Based Commissioning Consortium And The Area Prescribing Committee.

9 References


(6) Ray KK, Schofield PM. Secondary prevention for coronary heart disease in the United Kingdom, low-density lipoprotein cholesterol


10 Route for policy development and ratification

- Evidence researched by Public Health Specialist
- Evidence reviewed by Task & Finish Group and draft policy developed
- Draft policy reviewed and agreed by Area Prescribing Committee
- Draft policy finalised and ratified by Clinical Commissioning and Strategy Committee
- Policy distributed to relevant stakeholders and uploaded on the PCT extranet and website
APPENDIX 1  Flowchart for lipid modification in secondary prevention of CVD

2. Secondary prevention (CG 67)

Acute Coronary Syndrome

Prescribe simvastatin 40mg nocte. If not tolerated / interacting drugs give a lower dose or pravastatin 40mg (see general information at end). If unable to tolerate any statin at low dose consider ezetimibe, fibrates, nicotinic acid or resins.

Other secondary prevention
- Post STEMI
- Other ischaemic heart disease
- Peripheral vascular disease
- Cerebrovascular disease (ischaemic stroke/TIA)

Atorvastatin 80mg od for 6 months then review as below

Monitor lipids and LFTs at 3 months and 12 months. Check lipids annually.

Where TC remains >4.0 mmol/L OR LDL-C >2.0 mmol/L on simvastatin 40mg (after checking compliance), consider increasing to simvastatin 80mg or a drug of similar efficacy and acquisition cost. Any decision to offer a higher intensity statin should take into account informed preference, co-morbidities, multiple drug therapy and the potential benefits and risks of treatment. Atorvastatin 40mg is third line choice and should only be used after an adequate trial of simvastatin at both 40mg and 80mg doses.

The audit level is TC<5mmol/L.

NICE recognises that more than 50% of patients will not achieve a TC<4mmol/L or LDL-C<2mmol/L and state that it is not cost effective to titrate treatment above simvastatin 80mg nocte.