NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

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REVIEW OF LINCOLNSHIRE LIPID MODIFICATION GUIDELINES

Executive Summary

Primary prevention of cardiovascular disease (CVD)

- **The primary prevention of CVD is appropriate for patients without known CVD but with a calculated cardiovascular (CV) risk ≥20% over the next 10 years.**
- **Before offering lipid modification therapy for primary prevention, all other modifiable risk factors should be considered and their management optimised. Key lifestyle interventions are summarized in *Appendix 1*.**
- **A systematic strategy should be used to identify and risk assess all people aged between 40 and 74 in order to identify those at high risk. QRISK is the preferred risk assessment tool and is available through SystmOne; alternatively the Framingham risk assessment tool can be used. Cholesterol lowering medication should not be prescribed unless a risk assessment has been carried out.**
- **People should be offered information about their absolute risk of CVD and about the absolute benefits and harms of an intervention over a 10-year period.**
- **Treatment for primary prevention of CVD should be initiated with generic simvastatin 40mg once daily in the evening unless the patient is receiving concurrent interacting medication or simvastatin is contraindicated (see *Appendix 2*).**
- **Where simvastatin is poorly tolerated or contra-indicated, generic atorvastatin 10mg or generic pravastatin 40mg are the preferred alternatives; generic atorvastatin is already lower in price than generic pravastatin.**
- **Simvastatin should not be prescribed in doses higher than 20mg in patients taking concurrent amlodipine, diltiazem or verapamil. Simvastatin is licensed for the primary prevention of CVD at a dose of 20mg once daily and in most patients requiring the lower dose this should be sufficient. Alternatively, for patients taking concurrent amlodipine, generic atorvastatin 10mg could also be considered; atorvastatin is licensed for primary prevention of CVD at the 10mg dose. For patients taking concurrent diltiazem or verapamil, generic pravastatin 40mg is preferred; pravastatin is licensed for primary prevention of CVD at the 40mg dose. Generic atorvastatin could also be considered within this context, although careful clinical monitoring is recommended, particularly at the higher doses or if the dosage of diltiazem or verapamil is changed or stopped (see *PACE Bulletin* Vol 6 No 15 (October 2012) for more detail).**

- **No targets for Total Cholesterol (TC) or Low Density Lipoprotein-Cholesterol (LDL-C) are recommended for primary prevention. For most patients started on primary prevention with a statin, repeat lipid measurement is unnecessary.**

<u>Secondary prevention of cardiovascular disease (CVD)</u>

- **Secondary prevention is appropriate for patients with known CVD or other atherosclerotic vascular disease (such as ischaemic stroke, transient ischaemic attack (TIA) or peripheral vascular disease), familial hypercholesterolaemia and in all patients with diabetes over 40 years of age.**
- **Treatment for secondary prevention of CVD should be initiated with generic simvastatin 40mg once daily in the evening unless the patient is receiving concurrent interacting medication (see below) or simvastatin is contraindicated (see Appendix 2). Where simvastatin is insufficiently effective, poorly tolerated or contra-indicated, generic atorvastatin 10mg/20mg is the preferred alternative; atorvastatin is already lower in price than generic pravastatin. Generic pravastatin remains an option where simvastatin and atorvastatin are poorly tolerated or contra-indicated.**
- **All patients taking amlodipine, diltiazem or verapamil should not be prescribed simvastatin in a dose in excess of 20mg daily. For patients taking concurrent amlodipine who do not reach target on simvastatin 20mg, generic atorvastatin 10mg or 20mg should be considered as an alternative. For patients taking concurrent diltiazem or verapamil who do not reach target on simvastatin 20mg, generic pravastatin 40mg is preferred. Generic atorvastatin could also be considered, although careful clinical monitoring is recommended particularly at the higher doses or if the dosage of the concurrent diltiazem or verapamil is changed or stopped (see *PACE Bulletin* Vol 6 No 15 (October 2012) for more detail).**
- **Secondary prevention targets of 4mmol/litre (Total Cholesterol (TC)) and 2mmol/litre (Low Density Lipoprotein – Cholesterol (LDL-C)) should be used in secondary prevention where it is cost-effective to do so. NICE recommend pursuit of 4 and 2 as long as these targets can be achieved using either simvastatin or a drug of similar efficacy and acquisition cost (e.g. generic atorvastatin). If the patient does not reach these targets on simvastatin 40mg, initiate atorvastatin 20mg and titrate up as necessary.**
- **Following the *Lipitor* patent expiry, rosuvastatin is the only remaining high cost, high intensity, branded statin available on the UK market. It should be used solely in patients where all low cost, high-intensity statins have been considered and have either been demonstrated to be insufficiently effective, poorly tolerated or contra-indicated in some way. Even in secondary prevention of CVD, rosuvastatin is not cost-effective in most patients. It is, however, preferred, to less cost-effective and less well proven treatments such as ezetimibe, fibrates, anion exchange resins, nicotinic acid and omega 3 marine triglycerides.**
- **Fibrates, nicotinic acid and anion exchange resins should only be considered for secondary prevention of CVD in people unable to tolerate any statin (including rosuvastatin). If statin therapy is contraindicated or none of the available statins are tolerated, consider**

using gemfibrozil at a dose of 900mg once daily or 600mg twice daily. Statin therapy must be discontinued before gemfibrozil is initiated.

- **Ezetimibe should only be used within licensed indications (i.e. primary hypercholesterolaemia). Prescribers are strongly urged not to prescribe ezetimibe for secondary or primary prevention of CVD unless the patient has primary hypercholesterolaemia. Ezetimibe should only be used where all other options including high intensity statins and fibrates, have been exhausted. The cost effectiveness, even within this context remains questionable.**

Acute Coronary Syndrome (ACS)

- **In view of the safety concerns with simvastatin 80mg, generic atorvastatin 80mg is recommended as the first line statin of choice for patients with ACS regardless of Global Registry of Acute Coronary Events (GRACE) score.**
- **If a person has ACS, statin treatment should not be delayed until lipid levels are available.**

Introduction

Since PACEF published their last review of the *Lincolnshire Lipid Modification Guidelines* in August 2010, there have been a number of key developments. Most significant of these has been the patent expiry of *Lipitor* (atorvastatin) in May 2012 followed by the emergence of generic atorvastastin and rapidly falling atorvastatin reimbursement prices. The publication of the MHRA *Drug Safety Update* in August 2012 significantly raised the profile of safety concerns surrounding the use of simvastatin 40mg when used concurrently with amlodipine, diltiazem or verapamil and began to challenge the supremacy of simvastatin 40mg as the preferred first line statin in the primary and secondary prevention of cardiovascular disease that had existed since the publication of the Heart Protection Study in 2005. Prescribers will remember that this is not the first time that simvastatin has featured in the MHRA *Drug Safety Update*; in May 2010 the MHRA advised that, following their review of the SEARCH study, simvastatin 80mg should only be considered in patients with severe hypercholesterolaemia and at high risk of cardiovascular complications who had not achieved their treatment goals on lower doses. This advice significantly compromised the role of simvastatin 80mg as the high intensity statin of choice. PACEF have endeavoured to keep pace with all of these changes and have published updates to existing guidance as and when circumstances have arisen. It is the purpose of this review to incorporate all of the recent changes into a single text and to provide practical guidance on product selection at each stage of the treatment pathway. It is acknowledged that NICE are in the process of reviewing their Lipid Modification guidelines with a publication date yet to be confirmed. Lincolnshire PACEF guidance will be reviewed again once NICE publish their updated guidance.

Primary prevention of cardiovascular disease (CVD)

- **The primary prevention of CVD is appropriate for patients without known CVD but with a calculated cardiovascular (CV) risk ≥20% over the next 10 years.** This threshold was established by NICE in their Clinical Guideline on Lipid Modification in 2008. This primary prevention of CVD guidance should not be applied to patients with: proven coronary heart disease (CHD), peripheral vascular disease, diabetes or familial hypercholesterolaemia or following ischaemic stroke; these patients are more

appropriately managed using the secondary prevention of CVD guidance (see below).

- **Before offering lipid modification therapy for primary prevention, all other modifiable risk factors should be considered and their management optimised.** Key lifestyle interventions are summarized in *Appendix 1*. It should be explained to all patients that they will only gain the maximum benefit from any intended drug treatment if they comply with all of the lifestyle interventions that have been suggested to them. Lifestyle issues should continue to be revisited regularly and opportunistically with each patient.
- **A systematic strategy should be used to identify and risk assess all people aged between 40 and 74 in order to identify those at high risk (i.e. CV risk ≥20% over the next 10 years). QRISK is the preferred risk assessment tool and is available through SystmOne; alternatively the Framingham risk assessment tool can be used.**
- **Cholesterol lowering medication should not be prescribed unless a risk assessment has been carried out**. Treatment decisions should be based on total cholesterol/HDL ratio and not purely on total cholesterol levels.
- **It is important to involve the patient in the decision to commence treatment.** People should be offered information about their absolute risk of CVD and about the absolute benefits and harms of an intervention over a 10-year period (e.g. individualised risk and benefit scenarios, absolute risk of events numerically, diagrams etc).
- **Subject to the patient fulfilling all of the criteria detailed above, statin therapy should be initiated.**
- Liver function tests should be performed before treatment is initiated and repeated within the first three months of treatment and again after 12 months. Statins should be used with caution in those with a history of liver disease or with high alcohol consumption.
- **Treatment for primary prevention of CVD should be initiated with generic simvastatin 40mg once daily in the evening unless the patient is receiving concurrent interacting medication or simvastatin is contraindicated.** Simvastatin is well proven and, prescribed generically, remains the most cost-effective intervention. Where simvastatin is poorly tolerated or contra-indicated, generic atorvastatin 10mg or generic pravastatin 40mg are the preferred alternatives; generic atorvastatin is already lower in price than generic pravastatin. Specific advice around the interaction between simvastatin and amlodipine, diltiazem or verapamil is given below.
- **Simvastatin should not be prescribed in doses higher than 20mg in patients taking concurrent amlodipine, diltiazem or verapamil. Simvastatin is licensed for the primary prevention of CVD at a dose of 20mg once daily and in most patients requiring the lower dose this should be sufficient. Alternatively, for patients taking concurrent amlodipine, generic atorvastatin 10mg could also be considered; atorvastatin is licensed for primary prevention of CVD at the 10mg dose. For patients taking concurrent diltiazem or verapamil, generic pravastatin 40mg is preferred; pravastatin is licensed for primary prevention of CVD at the 40mg dose. Generic atorvastatin could also be considered within this context, although careful clinical monitoring is recommended, particularly at the higher doses or if the dosage of diltiazem or verapamil is changed or stopped (see *PACE Bulletin* Vol 6 No 15 (October 2012) for more detail).**
- **No targets for Total Cholesterol (TC) or Low Density Lipoprotein-Cholesterol (LDL-C) are recommended for primary prevention. For most**

primary prevention patients started on a statin, repeat lipid measurement is unnecessary. There is no evidence to support the pursuit of targets in primary prevention of CVD or the utilization of higher intensity statins (e.g. simvastatin 80mg, atorvastatin 20mg and above, and rosuvastatin all strengths).

- **If none of the lower cost, generically available, statins are tolerated and the patient has no known CVD or diabetes and does not fulfil the criteria for familial hypercholesterolaemia (total cholesterol >7.7mmol/l), statin therapy should be discontinued and the patient advised to continue to manage their raised lipids with recommended lifestyle change. Prescribers should ensure that rosuvastatin, ezetimibe, omega 3 fatty acid supplements (such as *Omacor* and *Maxepa*), fibrates, nicotinic acid and anion exchange resins are <u>not</u> used for the primary prevention of CVD within this context.** All patients currently receiving these lipid lowering therapies for primary prevention of CVD should have their treatment reviewed and if clinically appropriate switched to simvastatin 40mg or an alternative low cost, licensed, well-proven statin (e.g. atorvastatin 10mg or pravastatin 40mg).
- Ezetimibe should only be continued within its licensed indications (i.e. for those patients with a proven diagnosis of primary familial hyper-cholesterolaemia (total cholesterol >7.7mmol/l)). If these patients have not been reviewed by a lipidologist for the management of primary familial hypercholesterolaemia then they should be referred for a specialist opinion. Within the context of familial hypercholesterolaemia, rosuvastatin (*Crestor*), a high-cost, high-potency statin, should be used in preference to ezetimibe as it is likely to have a much more significant effect on the patient's lipid profile, is associated with much stronger evidence of improved outcomes and is much more cost-effective.

<u>Secondary prevention of CVD</u>

- **Secondary prevention is appropriate for patients with known CVD or other atherosclerotic vascular disease (such as ischaemic stroke, transient ischaemic attack (TIA) or peripheral vascular disease), familial hypercholesterolaemia and in all patients with diabetes over 40 years of age.** For patients fulfilling any of these criteria, lipid modification therapy should be offered and should not be delayed as other modifiable risk factors are brought under control (see *Appendix 1*).
- Liver function tests should be performed before treatment is initiated and repeated within the first three months of treatment and again after 12 months. Statins should be used with caution in those with a history of liver disease or with high alcohol consumption.
- **Treatment for secondary prevention of CVD should be initiated with generic simvastatin 40mg once daily in the evening unless the patient is receiving concurrent interacting medication (see below) or simvastatin is contraindicated (see *Appendix 2*).** Where simvastatin is insufficiently effective, poorly tolerated or contra-indicated, generic atorvastatin 10mg/20mg is the preferred alternative; atorvastatin is already lower in price than generic pravastatin. Generic pravastatin remains an option where simvastatin and atorvastatin are poorly tolerated or contra-indicated.
- **All patients taking amlodipine, diltiazem or verapamil should not be prescribed simvastatin in a dose in excess of 20mg daily. For patients taking concurrent amlodipine who do not reach target on simvastatin 20mg, generic atorvastatin 10mg or 20mg should be considered as an**

alternative. For patients taking concurrent diltiazem or verapamil who do not reach target on simvastatin 20mg, generic pravastatin 40mg is preferred. Generic atorvastatin could also be considered, although careful clinical monitoring is recommended particularly at the higher doses or if the dosage of the concurrent diltiazem or verapamil is changed or stopped. Rosuvastatin (*Crestor*) is licensed for purpose but is high-cost and not cost-effective in most scenarios; it should only be considered where all other alternatives have been poorly tolerated or insufficiently effective (see *PACE Bulletin* Vol 6 No 15 (October 2012) for more detail).

- **Secondary prevention targets of 4mmol/litre (Total Cholesterol (TC)) and 2mmol/litre (Low Density Lipoprotein – Cholesterol (LDL-C)) should be used in secondary prevention where it is cost-effective to do so. NICE recommend pursuit of 4 and 2 as long as these targets can be achieved using either simvastatin or a drug of similar efficacy and acquisition cost (e.g. generic atorvastatin). If the patient does not reach these targets on simvastatin 40mg, initiate atorvastatin 20mg and titrate up as necessary.**
- NICE Clinical Guideline 67: *Lipid Modification* (May 2008) includes a health economic model that challenges the use of high-cost, high potency statins (atorvastatin at 2008 *Lipitor* prices was used) in the pursuit of the 4mmol/litre (TC) and 2mmol/litre (LDL-C) targets on the grounds of poor cost-effectiveness. Extrapolating from this conclusion, the full range of low acquisition cost statins (generic simvastatin 40mg, generic pravastatin 40mg and generic atorvastatin 10mg, 20mg, 40mg and 80mg) should be considered preferentially before the higher-cost branded agent rosuvastatin (*Crestor*) is tried.
- **Following the *Lipitor* patent expiry, rosuvastatin is the only remaining high cost, high intensity, branded statin available on the UK market. It should be used solely in patients where all low cost, high-intensity statins have been considered and have either been demonstrated to be insufficiently effective, poorly tolerated or contra-indicated in some way. Even in secondary prevention of CVD, rosuvastatin is not cost-effective in most patients. It is, however, preferred, to less cost-effective and less well proven treatments such as ezetimibe, fibrates, anion exchange resins, nicotinic acid and omega 3 marine triglycerides.**
- **New initiations of simvastatin 80mg are no longer recommended; existing patients can be maintained on simvastatin 80mg subject to MHRA criteria (see *PACE Bulletin* Vol 4 No 11 (August 2010)).**
- **Fibrates, nicotinic acid and anion exchange resins should only be considered for secondary prevention of CVD in people unable to tolerate any statin (including rosuvastatin).** If statin therapy is contraindicated or none of the available statins are tolerated, consider using gemfibrozil at a dose of 900mg once daily or 600mg twice daily. **Statin therapy must be discontinued before gemfibrozil is initiated.**
- If the patient does not respond to or cannot tolerate gemfibrozil consider an alternative fibrate or an anion exchange resin (e.g. colestyramine), nicotinic acid or ezetimibe. None of these options are licensed for the secondary prevention of cardiovascular events; therefore any benefits can only be assessed in terms of reductions in lipid levels. There is no published data on their effectiveness in the reduction of further cardiovascular events.
- **Ezetimibe should only be used within licensed indications (i.e. primary hypercholesterolaemia). Prescribers are strongly urged not to prescribe ezetimibe for secondary or primary prevention of CVD unless the patient**

has primary hypercholesterolaemia. There is no published data to show reduction in mortality or morbidity with ezetimibe. In addition, the product is expensive and shows only modest reduction in TC (12 to 13%) and LDL-C (17 to 22%) in comparison with statins. Even a high-cost high-potency branded statin is more cost-effective. Ezetimibe should only be used where all other options including high intensity statins and fibrates, have been exhausted. The cost effectiveness, even within this context remains questionable.

Acute Coronary Syndrome (ACS)

- **The NICE review of statins for ACS published as part of Clinical Guideline 67: *Lipid Modification* (May 2008) concluded that: 'there is good evidence that higher intensity statins (specifically simvastatin 80mg and atorvastatin 80mg) are associated with additional cost-effective reductions in CV events for people after recent MI and in ACS'.**
- **In view of the safety concerns with simvastatin 80mg, generic atorvastatin 80mg is recommended as the first line statin of choice for patients with ACS regardless of Global Registry of Acute Coronary Events (GRACE) score.**
- **If a person has ACS, statin treatment should not be delayed until lipid levels are available.**

Appendix 1

Lifestyle change

Before offering lipid modification therapy for primary prevention and concurrently with offering lipid modification therapy for secondary prevention, all other modifiable risk factors should be considered and their management optimised. These include:

- Smoking cessation.
- Weight loss. Aim for a Body Mass Index (BMI) of 19-25kg/m^2. Provide dietary advice including: reduced intake of saturated fats, adoption of a Mediterranean style diet and, ideally, consumption of two portions of oily fish a week and five portions of fruit and vegetables per day.
- Moderate alcohol intake; should be within accepted safe limits (up to 21units/week for men and 14units/week for women).
- Exercise. Aim for a total of 30 minutes of moderate to high intensity physical activity at least five times a week (e.g. brisk walking).
- Blood pressure control – Treat if BP over 140/90mmHg to achieve BP of less than 140/90mmHg,
- Take the opportunity to review medication that may increase cardiovascular risk e.g. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) with high risk cardio-toxicity (e.g. diclofenac).

Appendix 2

Drug interactions associated with an increased risk of myopathy/ rhabdomyolysis with simvastatin:

Interacting agents	Prescribing recommendations
Itraconazole Ketoconazole Posaconazole	

Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (e.g. nelfinavir) Nefazodone Ciclosporin Danazol Gemfibrozil	Contraindicated with simvastatin
Other fibrates (except fenofibrate)	Do not exceed 10mg simvastatin daily
Amiodarone Amlodipine Verapamil Diltiazem	Do not exceed 20mg simvastatin daily
Fusidic acid	Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Appendix 3

Cost Comparison and Percentage Reductions in LDL Cholesterol and Total Cholesterol

Statin	28 day cost	Percentage reduction in LDL-C	Percentage reduction in total cholesterol	Incidence of myopathy
Atorvastatin 10mg	£1.30	37%	32%	0.4%
Atorvastatin 20mg	£1.76	43%	36%	0.4%
Atorvastatin 40mg	£1.99	49%	42%	0.4%
Atorvastatin 80mg	£3.73	55%	47%	0.5%
Pravastatin 40mg	£2.75	29%	29%	
Rosuvastatin 5mg	£18.03	38%	33%	0.2%
Rosuvastatin 10mg	£18.03	43%	37%	0.1%
Rosuvastatin 20mg	£26.02	48%	40%	0.1%
Simvastatin 40mg	£1.05	37%	31%	0.4%

(Prices quoted are from the *Drug Tariff*, February 2013)

% LDL Reduction (approx.)	Atorvastatin	Fluvastatin	Pravastatin	Rosuvastatin	Simvastatin
10-20%	--	20 mg	10 mg	--	--
20-30%	--	40 mg	20 mg	--	10 mg
30-40%	10 mg	80 mg	40 mg	5 mg	20 mg
40-45%	20 mg	--	80 mg	5–10 mg	40 mg
46-50%	40 mg	--	--	10–20 mg	80 mg
50-55%	80 mg	--	--	20 mg	--
56-60%	--	--	--	40 mg	--
Starting dose	10–20 mg	20 mg	40 mg	10 mg; 5 mg if hypothyroid, >65, Asian	20 mg
If higher LDL reduction goal	40 mg if >45%	40 mg if >25%	--	20 mg if LDL >190 mg/dL (4.87 mmol/L)	40 mg if >45%
Optimal timing	Anytime	Evening	Anytime	Anytime	Evening

References

Boston Clinical Effectiveness Forum (BOCEF) *Lipid Modification Guidance*
Medicines and Healthcare Products Regulatory Agency (MHRA), *Drug Safety Update* (May 2010)

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