Greater East Midlands Commissioning Support Unit

Prescribing and Clinical Effectiveness Bulletin

Volume 8; Number 23 **December 2014**

REVIEW OF LINCOLNSHIRE LIPID MODIFICATION GUIDANCE IN RESPONSE TO THE NEW NICE CLINICAL GUIDELINE

Introduction

Since PACEF published their last review of the *Lincolnshire Lipid Modification Guidelines* in 2013, NICE have published Clinical Guideline 181: *Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease* (July 2014). Now that atorvastatin is available in all strengths as a low cost generic, NICE have concluded that low cost, high-intensity statin therapy can be offered to a wider range of patients than ever on the NHS. It is the purpose of this special edition of the *PACE Bulletin* to summarize the key recommendations of the NICE CG and to offer PACEF advice on implementation.

Inputting Lincolnshire CCG population figures into the NICE Costing Template reveals that approximately 50,000 additional people in the county are eligible for lipid modification therapy if the primary prevention threshold is lowered to 10% or greater 10 year risk of CVD as advocated by NICE. Understandably, Lincolnshire CCGs and some of their constituent practices have expressed concern around lack of sufficient capacity in primary care to prioritise rigorous and systematic implementation of this guidance across both new and existing patients. NICE acknowledge this issue in the supporting text to their Costing Template and anticipate a 5 year implementation period. Information from the NICE Costing Template around the likely number of new patients in each CCG, the potential financial impact in terms of increased treatment volume and cost and the potential saving in terms of prevented cardiovascular events are included as an Appendix.

After careful consideration, PACEF are in support of the implementation of the recommendations in CG181, primarily in new patients in the first instance identified either through NHS Health Check or through normal GP or practice nurse consultations and reviews. It is also recommended that existing patients on statins are given the opportunity to discuss the risks and benefits of higher intensity statin therapy as part of their annual medication review. PACEF are not supportive of a systematic approach to identifying new patients or systematic switching of existing patients from low or medium intensity statin therapy to higher intensity therapy, although practices are free to follow this approach if they feel that they have the capacity to do so.

Summary of guidance for new patients

Primary prevention of CVD in new patients	**Preferred first line treatment**
Primary prevention of CVD in adults	Generic atorvastatin 20mg once daily in patients with a 10% or greater 10 year risk of developing CVD as assessed by QRISK2. If atorvastatin 20mg is poorly tolerated consider stepping down to 10mg before moving to an alternative statin.
Primary prevention of CVD in adults with type 1 diabetes	Generic atorvastatin 20mg once daily, if the patient is: (1) older than 40 or (2) has had diabetes for more than 10 years or (3) has established nephropathy or (4) has other CVD risk factors. If atorvastatin 20mg is poorly tolerated consider stepping down to 10mg before moving to an alternative statin.
Primary prevention of CVD in adults with type 2 diabetes	Generic atorvastatin 20mg once daily in patients with a 10% or greater 10 year risk of developing CVD as assessed by QRISK2. If atorvastatin 20mg is poorly tolerated consider stepping down to 10mg before moving to an alternative statin.
Primary prevention of CVD in adults with Chronic Kidney Disease (CKD)	Generic atorvastatin 20mg once daily in all patients. Increase the dose if greater than 40% reduction in non-HDL cholesterol is not achieved and eGFR is at least 30ml/min/1.73m^2. If eGFR is less than 30ml/min/1.73m^2, only use higher doses of atorvastatin on the advice of a renal specialist. If atorvastatin 20mg is poorly tolerated consider stepping down to 10mg before moving to an alternative statin.
Primary prevention of CVD in people 85 years and older.	Consider atorvastatin 20mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate (e.g. polypharmacy, frailty, comorbidities, life expectancy). If atorvastatin 20mg is poorly tolerated consider stepping down to 10mg before moving to an alternative statin.
Secondary prevention of CVD in new patients	
Secondary prevention of CVD in adults	Generic atorvastatin 80mg once daily preferred unless there is a risk of interaction with concurrent therapy or if there is a risk of adverse effects or if the patient prefers a lower dose. If atorvastatin 80mg is poorly tolerated or

	considered to be more than the patient can tolerate, step down or initiate at a lower dose of atorvastatin (e.g. 40mg).
Secondary prevention of CVD in adults with Chronic Kidney Disease (CKD)	Generic atorvastatin 20mg once daily in all patients. Increase the dose if greater than 40% reduction in non-HDL cholesterol is not achieved and eGFR is at least 30ml/min/1.73m^2. If eGFR is less than 30ml/min/1.73m^2, only use higher doses of atorvastatin on the advice of a renal specialist. If atorvastatin 20mg is poorly tolerated consider stepping down to 10mg before moving to an alternative statin.

New patients requiring 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 of 10% or greater 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*.**
- **Due to concerns over primary care capacity, PACEF do not support implementation of a systematic strategy to identify and risk assess all people who are likely to be at high risk at this stage. The NICE Costing Template estimates that lowering the primary prevention risk threshold will potentially increase the number of patients on statin therapy in Lincolnshire by nearly 50,000 people. In order to gradually phase in the new threshold and higher intensity therapy, it is recommended that the initial focus should be on new patients and patients going through NHS Health Check.**
- **The QRISK2 risk assessment tool should be used to assess CVD risk for the primary prevention of CVD in people up to and including age 84. Cholesterol lowering medication should not be prescribed for primary prevention 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. NICE have produced a patient decision aid to help with these discussions which is available from the NICE website (see References).**
- **Where a decision is made to start statin therapy, NICE recommend high intensity statins of low acquisition cost. Taking into account the well documented problems associated with simvastatin 80mg, atorvastatin in doses of 20mg to 80mg daily emerges as the first line statin of choice. Appendix 2 tabulates the NICE definition of low, medium and high intensity statins.**
- **New patients requiring primary prevention of CVD for the first time should be initiated on generic atorvastatin 20mg once daily. If atorvastatin 20mg is poorly tolerated consider stepping down to 10mg before moving to an alternative statin.**
- **Primary prevention of CVD should be considered for all adults with type 1 diabetes. Offer statin treatment to adults with type 1 diabetes who (1)**

are older than 40 years or (2) who have had diabetes for more than 10 years or (3) have established nephropathy or (4) have other CVD risk factors. Generic atorvastatin 20mg once daily is preferred. If atorvastatin 20mg is poorly tolerated consider stepping down to 10mg before moving to an alternative statin.

- **Primary prevention of CVD should be offered to all adults with type 2 diabetes who have a 10% or greater 10 year risk of developing CVD as assessed by QRISK2. Generic atorvastatin 20mg once daily is preferred. If atorvastatin 20mg is poorly tolerated consider stepping down to 10mg before moving to an alternative statin.**
- **All patients with Chronic Kidney Disease (CKD) should be offered atorvastatin 20mg either for the primary or secondary prevention of CVD. Increase the dose if greater than 40% reduction in non-HDL cholesterol is not achieved and eGFR is at least 30ml/min/1.73m^2. If eGFR is less than 30ml/min/1.73m^2, only use higher doses of atorvastatin on the advice of a renal specialist. If atorvastatin 20mg is poorly tolerated consider stepping down to 10mg before moving to an alternative statin.**
- **For people 85 years or older, consider atorvastatin 20mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate (e.g. polypharmacy, frailty, comorbidities, life expectancy). If atorvastatin 20mg is poorly tolerated consider stepping down to 10mg before moving to an alternative statin.**
- **Before starting lipid modification therapy for the primary prevention of CVD, take at least one lipid sample to measure a full lipid profile. This should include measurement of total cholesterol, high density lipoprotein (HDL-C), non-HDL cholesterol and triglycerides. A fasting sample is not needed.**
- **Measure total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment at 3 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: (1) discuss adherence and timing of dose (take at night); (2) optimise adherence to diet and lifestyle measures; and (3) consider increasing dose if the person is judged to be at higher risk because of co-morbidities, risk score or using clinical judgement.**

<u>New patients requiring 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) and familial hypercholesterolaemia.**
- **New patients requiring secondary prevention of CVD for the first time should be initiated on generic atorvastatin 80mg once daily. If any of the following apply use a lower dose of atorvastatin: (1) potential drug interactions; (2) risk of adverse effects and (3) patient preference. If atorvastatin 80mg is poorly tolerated or considered on reflection to be more than the patient can tolerate, step down or initiate at a lower dose of atorvastatin (e.g. 40mg).**
- **Measure total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment at 3 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: (1) discuss adherence and timing of dose (take at night); (2) optimise adherence to diet and lifestyle measures; and (3) consider increasing dose if started on less than atorvastatin 80mg and the person is judged to be at higher risk because of co-morbidities, risk score or using clinical judgement.

Review of existing patients on lipid modification therapy

- **People taking statins should be reviewed annually. The results of a non-fasting blood test for non-HDL cholesterol could be used to inform the discussion. These reviews need to address medicines adherence, lifestyle modification and any CVD risk factors. For patients taking low or medium intensity statins the benefits and risks of changing to high-intensity statin therapy should be discussed and any proposed change agreed with the patient. The NICE definition of low, medium and high intensity statins is tabulated in Appendix 2.**

Avoiding and managing intolerance to treatment

- **Before offering a statin, ask the person if they have had persistent generalised unexplained muscle pain, whether associated or not with previous lipid-lowering therapy, and if present, measure creatinine kinase (CK) levels. If CK levels are more than 5 times the upper limit of normal, re-measure CK after 7 days. If CK levels are still 5 times the upper limit of normal, do not start statin treatment. If CK levels are raised but less than 5 times the upper limit or normal, start statin treatment at a lower dose.**
- **Advise people who are being treated with a statin to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, measure creatinine kinase.**
- **If people report muscle pain or weakness while taking a statin, explore other possible causes of myalgia and raised creatinine kinase if they have previously tolerated statin therapy for more than 3 months.**
- **Measure baseline liver transaminase enzymes (alanine aminotransferase or aspartate aminotransferase) before starting a statin. Measure liver transaminase within 3 months of starting treatment and at 12 months, but not again unless clinically indicated.**
- **If a person cannot tolerate a high-intensity statin aim to treat with the maximum tolerated dose. Any statin at any dose reduces CVD risk. If someone reports adverse effects when taking high-intensity statins consider: (1) stopping the statin and trying again when symptoms resolve to check if the symptoms are related to the statin; (2) reduce the dose within the same intensity group; (3) change the statin to a lower intensity group.**

Simvastatin and other second line options

- **Where low cost, high intensity statin therapy with generic atorvastatin is not tolerated, low cost, medium intensity therapy should be considered. (i.e. atorvastatin 10mg or simvastatin 20mg or 40mg). Prescribers should remember that the lower 10% 10 year risk of developing CVD threshold for primary prevention is only affordable if *low cost* medium or high intensity statins are prescribed. As a result of this, the role of**

the high cost, high intensity statin, rosuvastatin within this guidance is extremely limited.

Rosuvastatin (*Crestor*) and other third line options

- **Rosuvastatin (*Crestor*) 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 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, there are concerns around the high cost of rosuvastatin and its poor cost-effectiveness compared to alternative statins. 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 where all other options including high intensity statins and fibrates, have been exhausted. The cost effectiveness, even within this context remains questionable.**

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. Advise people at high risk of or with CVD to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 7% or less of total energy intake, intake of dietary cholesterol is less than 300mg/day and where possible saturated fats are replaced by mono-unsaturated and polyunsaturated fats.
- Healthy eating. Provide dietary advice including: reduced intake of saturated fats from animal sources and, ideally, consumption of two portions of fish a week, including one portion of oily fish, at least five portions of fruit and vegetables per day and at least 4 to 5 portions of unsalted nuts, seeds and legumes per week. Advise people to choose wholegrain varieties of starchy foods and reduce their intake of sugar and food products containing refined sugars, including fructose.
- Moderate alcohol intake; should be within accepted safe limits (no more than 3-4 units a day for men and 2-3 units a day for women).
- Exercise. Advise people at high risk of or with CVD to take at least 150 minutes of moderate intensity aerobic activity per week or 75 minutes of vigorous intensity aerobic activity or a mix of moderate and vigorous aerobic activity per week (e.g. brisk walking, using stairs, cycling)
- Blood pressure control.
- 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).

- Do not advise plant stanols or sterols for the prevention of CVD in: (1) people receiving primary or secondary prevention therapy; (2) people with CKD; (3) people with type 1 diabetes or type 2 diabetes.

PACEF Comment:
There is evidence that plant sterols incorporated into dietary supplements, such as *Benecol,* reduce LDL-C in a dose dependent manner. However, NICE could find no relevant clinical studies comparing plant sterol enriched foods or supplements with placebo that provided any relevant outcomes data. There are also no relevant economic evaluations that enable evaluation of cost-effectiveness to be done. Hence, due to absence of evidence, these products should not be recommended as an alternative or addition to treatment with well proven evidence based treatments such as statins. However, there is nothing to suggest that health conscious people outside the context of this guidance should not purchase and consume these products if they wish to do so.

Appendix 2: *NICE definition of low, medium and high intensity statins*

Intensity	Statin and dose	LDL-cholesterol reduction (%)
Low intensity	Fluvastatin 20mg, 40mg Pravastatin 5mg, 10mg, 20mg, 40mg Simvastatin 10mg	20-30%
Medium intensity	Atorvastatin 10mg Fluvastatin 80mg Rosuvastatin 5mg Simvastatin 20mg, 40mg	31 to 40%
High intensity	Atorvastatin 20mg, 40mg, 80mg Rosuvastatin10mg, 20mg, 40mg Simvastatin 80mg	Greater than 40%

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	£1.19	37%	32%	0.4%
Atorvastatin 20mg	£1.45	43%	36%	0.4%
Atorvastatin 40mg	£1.67	49%	42%	0.4%
Atorvastatin 80mg	£2.68	55%	47%	0.5%
Pravastatin 40mg	£2.00	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	£1.23	37%	31%	0.4%

(Prices quoted are from the *Drug Tariff*, December 2014)

PACEF Comment:
Generic price reductions have resulted in all strengths of atorvastatin becoming available in a range of low cost generic preparations. At present in Lincolnshire, atorvastatin is already the most widely prescribed statin. The NICE Costing Template predicts that full implementation of the recommendations of NICE CG181 will increase prescribing costs by £665,000pa offset by savings due to avoided CVD events of £321,000pa. The increased prescribing costs associated with the new CG are linked to an increase in patients eligible for statin therapy (approximately 50,000) and the higher cost of more intensive statin therapy (i.e. atorvastatin 20mg to 80mg).

Reduction in low-density lipoprotein cholesterol

Dose (mg/day)	5	10	20	40	80
Fluvastatin	-	-	21%	27%	33%
Pravastatin	-	20%	24%	29%	-
Simvastatin	-	27%	32%	37%	42%
Atorvastatin	-	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	-

Appendix 4: *Applying the NICE Costing Template to Lincolnshire CCGs*

	GP registered population	Cost of increased statin prescribing per annum	Saving from avoided CVD events per annum	Increase in number of people taking a statin assuming 20% non-compliance
LECCG	240,000	£213,600	£103,200	15,619
LWCCG	223,773	£199,158	£96,222	14,563
SLCCG	154,909	£137,869	£66,611	10,082
SWLCCG	128,329	£114,213	£55,181	8,352
Lincolnshire	747,011	£664,840	£321,215	48,616

Appendix 5: *Prescribing simvastatin*

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.

The MHRA advise that there is an increased risk of myopathy associated with high-dose 80mg simvastatin. The 80mg dose should be considered only in patients with severe hypercholesterolaemia and high risk of CV complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks.

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

Interacting agents	Prescribing recommendations
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin	Contraindicated with simvastatin

Telithromycin HIV protease inhibitors (e.g. nelfinavir) Nefazodone Ciclosporin Danazol Gemfibrozil	
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

Acknowledgements

In addition to PACEF, many thanks to members the various CCG GP prescribing groups for their input and comments into previous versions of this guidance. Also thanks to colleagues in the United Lincolnshire Hospitals Cardiology team, particularly Dr Richard Andrews and Alun Roebuck. Many thanks to Helen Marshall, Senior Pharmacy Technician for her help in testing the validity of the some of the figures emerging from the NICE Costing Template.

References

MHRA, *Drug Safety Update* (August 2012)
NICE Clinical Guideline 181: *Lipid Modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease* (July 2014)
NICE Costing Template: *Lipid Modification – Implementing the NICE guideline on lipid modification* (July 2014)
NICE CG181: *Patient Decision Aid* (November 2014)
NICE *Patient Decision Aid: User guide for healthcare professionals - Implementing the NICE guideline on lipid modification* (November 2014).

NICE documents can be accessed through www.nice.org.uk

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December 2014