Lincolnshire NHS

Prescribing and Clinical Effectiveness Bulletin

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CONTENTS

NICE CLINICAL GUIDELINE 67: *LIPID MODIFICATION - CARDIOVASCULAR RISK ASSESSMENT AND THE MODIFICATION OF BLOOD LIPIDS FOR THE PRIMARY AND SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE* (MAY 2008)

PACEF Recommendations in Brief

Primary prevention of cardiovascular disease (CVD)

- Before offering lipid modification therapy for primary prevention, all other modifiable risk factors should be considered and their management optimised.
- For primary prevention, statin therapy is recommended first line in adults who have a 20% or greater 10-year risk of developing CVD.
- Initiate treatment with simvastatin 40mg. If there are potential drug interactions, or simvastatin 40mg is contraindicated or not tolerated, a lower dose or a low cost alternative, such as pravastatin, should be used.
- 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.
- Practices should ensure that atorvastatin, rosuvastatin, omega 3 fatty acid supplements (such as Omacor and Maxepa), fibrates, nicotinic acid and anion exchange resins are not used for primary prevention. Ezetimibe may be appropriate within licensed indications (i.e. primary hypercholesterolaemia).

Secondary prevention of cardiovascular disease

- For secondary prevention, lipid modification therapy should be offered and should not be delayed by management of modifiable risk factors.
- Statin therapy is recommended for adults with clinical evidence of CVD.
- Treatment for secondary prevention of CVD should be initiated with simvastatin 40mg. If there are potential drug interactions, or simvastatin 40mg is contraindicated, an alternative low-cost preparation such as pravastatin should be chosen. If simvastatin 40mg is not tolerated, a lower dose or pravastatin should be chosen.
- Targets of 4mmol/litre (TC) and 2mmol/litre (LDL-C) have been endorsed by NICE as an aspiration, but achievement is not an absolute necessity.
- If the patient does not reach target on simvastatin 40mg, increase the dose to 80mg. If the patient does not reach the 4mmol/l and 2mmol/l targets on

simvastatin 80mg (over half of patients will not), reduce aspiration to the minimum audit standard and QOF target of 5mmol/l (TC).

- **Maintain the patient on the dose of simvastatin that has either reached the 4 and 2mmol/l targets or the minimum audit standard of 5mmol/l (TC). Only consider higher-cost, higher-potency agents in those patients that remain above the minimum audit standard of 5mmol/l (TC) despite taking simvastatin 80mg or who are intolerant to simvastatin and pravastatin or have contra-indications or potential interactions.**
- **Remember that high-cost high-potency statins like atorvastatin and rosuvastatin are effective, but have emerged from NICE cost-effectiveness evaluations as not cost-effective in most patients. As a result of this, their use for secondary prevention of CVD should be restricted to the exceptional circumstances outlined above. The role of atorvastatin in acute coronary syndrome (ACS) is detailed below.**
- **Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention of CVD in people unable to tolerate statins. Ezetimibe may be appropriate within licensed indications (i.e. primary hypercholesterolaemia)**

Acute Coronary Syndrome

- **If a person has acute coronary syndrome, statin treatment should not be delayed until lipid levels are available.**
- **Initiate simvastatin 80mg as the treatment of first choice; atorvastatin 80mg can be considered second line for patients who are inappropriate for simvastatin therapy or are intolerant to simvastatin 80mg. For both agents, treatment should be initiated at the 80mg dose.**

Introduction

It is the purpose of this special edition of the *PACE Bulletin* to summarize the key points of the new NICE Clinical Guideline on Lipid Modification. The bulletin also updates Lincolnshire policy on the prescribing of lipid lowering therapy and includes PACEF recommendations for implementation.

The key points of the Clinical Guideline are as follows:

Primary prevention of cardiovascular disease

- **Before offering lipid modification therapy for primary prevention, all other modifiable risk factors should be considered and their management optimised**. Assessment should include: smoking status, alcohol consumption, BP, BMI, fasting total cholesterol (TC), LDL-C, HDL-C and triglycerides, fasting blood glucose, renal function, liver function and thyroid stimulating hormone (TSH) if dyslipidaemia is present.
- For the primary prevention of CVD in primary care, a systematic strategy should be used to identify people aged 40-74 who are likely to be at high risk. The 1991 Framingham 10-year risk equations should be used to assess CVD risk.
- 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).

PACEF Recommendation:
The National Prescribing Centre (NPC) has produced a useful leaflet entitled *Statins – a guide for patients.* They have also made some useful 'smiley face diagrams' available on their website that can help to explain to patients the meaning of different levels of CVD risk and the potential benefits of statin therapy. These resources can be accessed through www.npc.co.uk and by clicking on National Support Materials.

- For **primary prevention**, statin therapy is recommended first line as part of the management strategy for the primary prevention of CVD in adults who have a **20% or greater 10-year risk of developing CVD**.
- **Treatment for primary prevention of CVD should be initiated with simvastatin 40mg. If there are potential drug interactions, or simvastatin 40mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.**
- **A target for TC or LDL-C is not recommended for people treated with a statin for primary prevention. Once a person has been started on a statin for primary prevention, repeat lipid measurement is unnecessary ('fire and forget').**
- **There is no evidence to support the pursuit of targets in primary prevention or the utilization of higher intensity statins.** NICE define 'higher intensity statins' as those used in doses that produce greater cholesterol lowering than simvastatin 40mg, for example simvastatin 80mg, atorvastatin all strengths, particularly 20mg and above, and rosuvastatin all strengths.
- Fibrates, nicotinic acid and anion exchange resins should not routinely be offered for the primary prevention of CVD. If statins are not tolerated, an anion exchange resin may be considered. People should not routinely be recommended to take omega-3 fatty acid supplements (e.g. Omacor, Maxepa) for the primary prevention of CVD. Combination therapy (i.e. a statin plus any of the above options) is not appropriate in primary prevention.
- Ezetimibe should be considered in patients with primary hypercholesterolaemia in accordance with NICE TA 132 (see below).

PACEF Recommendations:
Practices should ensure that they do not inadvertently target chase in primary prevention. For the majority of patients, simvastatin 40mg once daily (unless poorly tolerated) will be sufficient.
Practices should ensure that atorvastatin, rosuvastatin, omega 3 fatty acid supplements (such as Omacor and Maxepa), fibrates, nicotinic acid and anion exchange resins are not in routine use for primary prevention.

Secondary prevention of cardiovascular disease

- **For secondary prevention, lipid modification therapy should be offered and should not be delayed by management of modifiable risk factors.** Assessment should include: smoking status, alcohol consumption, BP, BMI, fasting total cholesterol (TC), LDL-C, HDL-C and triglycerides, fasting blood glucose, renal function, liver function and thyroid stimulating hormone (TSH) if dyslipidaemia is present.
- **Statin therapy is recommended for adults with clinical evidence of CVD.**
- **Treatment for secondary prevention of CVD should be initiated with simvastatin 40mg.** If there are potential drug interactions, or simvastatin 40mg is contraindicated, an alternative low-cost preparation such as

pravastatin should be chosen. If simvastatin 40mg is not tolerated, a lower dose or pravastatin should be chosen.

- **Targets of 4mmol/litre (TC) and 2mmol/litre (LDL-C) have been endorsed by NICE as an aspiration, but achievement is not an absolute necessity.**
- **If the patient does not reach target on simvastatin 40mg, increase the dose to 80mg. If the patient does not reach the 4mmol/l and 2mmol/l targets on simvastatin 80mg (over half of patients will not), reduce aspiration to the minimum audit standard and QOF target of 5mmol/l (TC).**
- **Maintain the patient on the dose of simvastatin that has either reached the 4 and 2mmol/l targets or the minimum audit standard of 5mmol/l (TC). Only consider higher-cost, higher-potency agents in those patients that remain above the minimum audit standard of 5mmol/l (TC) despite taking simvastatin 80mg or who are intolerant to simvastatin and pravastatin or have contra-indications or potential interactions.**
- **Remember that high-cost high-potency statins like atorvastatin and rosuvastatin are effective, but have emerged from NICE cost-effectiveness evaluations as not cost-effective in most patients. As a result of this, their use for secondary prevention of CVD should be restricted to the exceptional circumstances outlined above. The role of atorvastatin in acute coronary syndrome (ACS) is detailed below.**
- **Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention of CVD in people unable to tolerate statins. Ezetimibe may be appropriate within licensed indications (i.e. primary hypercholesterolaemia).**

PACEF Recommendation:
Having scrutinized the NICE cost-effectiveness models in the text of the Full Guideline, PACEF are satisfied that it is a cost-effective use of NHS resource to aspire to the lower targets of 4mmol/l (TC) and 2mmol/l (LDL-C) in secondary prevention of CVD, subject to the following qualifications: (1) it is only cost effective to treat to the lower targets using low cost generically available statins. Simvastatin 40mg is recommended first line; beyond this prescribers should utilize simvastatin 80mg as their preferred second line choice; (2) NICE have endorsed the 4 and 2 secondary prevention targets as helpful in guiding treatment rather than as an absolute measure of success or failure. As a consequence of this, PACEF recommend aspiration toward the 4mmol/l and 2mmol/l targets, but not pursuit at any cost. According to NICE, more than half of patients will not achieve a TC of less than 4mmol/litre or an LDL-C of less than 2mmol/litre and it is not cost-effective to utilize high-cost, high-potency branded agents (e.g. atorvastatin and rosuvastatin) in an attempt to realise these targets; (3) NICE have endorsed a minimum audit standard of 5mmol/l (TC) and this corresponds the current QOF target; (4) Prescribers should strive to ensure that the majority of secondary prevention patients are managed on either simvastatin or pravastatin. PACEF do not envisage that the implementation of this NICE CG will significantly impair practice performance against the national low cost statins prescribing indicator.

- Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention of CVD in people unable to tolerate statins.
- Ezetimibe should be considered in patients with primary hypercholesterolaemia in accordance with NICE TA 132 (see below).

PACEF Recommendation:
Prescribers are reminded that PACEF remain unconvinced of the cost-effectiveness of Omacor post-MI and the drug has been classified RED-RED, both for this indication and for hypertriglyceridaemia. NICE have emphasized that omega 3 fatty acid supplements also have no role in angina, PAD or stroke.

Acute Coronary Syndrome

- Acute coronary syndrome (ACS) is defined as a range of acute myocardial ischaemic states including unstable angina, non-ST segment elevation MI (NSTEMI) and ST segment elevation MI (STEMI).
- **If a person has ACS, statin treatment should not be delayed until lipid levels are available. People with ACS should be treated with a 'higher intensity statin'** (see definition of 'higher intensity statins' quoted above).
- 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.

PACEF Recommendation:
PACEF are satisfied that there is a case in terms of both effectiveness and cost-effectiveness to support higher intensity statins at the outset for this sub-group of patients. Simvastatin 80mg is recommended as the treatment of first choice on the grounds of proven effectiveness and superior cost-effectiveness; atorvastatin 80mg should be considered second line for patients who are inappropriate for simvastatin therapy or are intolerant to simvastatin 80mg. Treatment should be initiated at the 80mg dose. Patients intolerant of simvastatin 80mg or atorvastatin 80mg will need to be maintained on a lower dose statin where possible.

Lifestyle modifications for the primary and secondary prevention of CVD

- People at high risk of or with CVD should be advised to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 10% or less of total energy intake, intake of dietary cholesterol is less than 300mg per day and where possible saturated fats are replaced by monounsaturated and polyunsaturated fats. At least 5 portions a day of fruit and vegetables and at least 2 portions of fish a week (including a portion of oily fish) should be consumed.
- People at high risk of or with CVD should be advised to take 30 minutes of physical activity a day of at least moderate intensity at least 5 days a week. Recommended types of physical activity include brisk walking, using stairs and cycling.
- People at high risk of or with CVD who are overweight or obese should be offered advice and support to work towards achieving and maintaining a healthy weight.
- Alcohol consumption for men should be limited to 3 to 4 units a day; for women 2 to 3 units a day. Binge drinking should be avoided.
- Smokers should be advised to stop and offered support, advice and referral to an intensive support service (e.g. NHS Stop Smoking Services).

Monitoring of statin treatment for primary and secondary prevention

- People who are being treated with a statin should be advised to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, creatine kinase should be measured. Creatine kinase should not be routinely monitored in asymptomatic people treated with a statin.
- Baseline liver enzymes should be measured before starting treatment with a statin. Liver function should be measured within 3 months of starting treatment and at 12 months, but not again unless clinically indicated. People who have liver enzymes that are raised but are less than 3 times the upper limit of normal should not be routinely excluded from statin therapy.
- If unexplained peripheral neuropathy occurs, statins should be discontinued and specialist advice sought.

Percentage Reductions in LDL Cholesterol and Total Cholesterol

Statin	Daily Dose	28 day cost	Percentage reduction in LDL-C	Percentage reduction in total cholesterol
Atorvastatin	10mg	£18.03	37%	32%
Atorvastatin	20mg	£24.64	43%	36%
Atorvastatin	40mg	£28.21	49%	42%
Atorvastatin	80mg	£28.21	55%	47%
Pravastatin	40mg	£6.80	29%	29%
Rosuvastatin	5mg	£18.03	38%	33%
Rosuvastatin	10mg	£18.03	43%	37%
Rosuvastatin	20mg	£26.02	48%	40%
Simvastatin	**40mg**	**£1.40**	**37%**	**31%**
Simvastatin	80mg	£4.63	42%	35%

(Prices quoted are from the *Drug Tariff*, July 2008)

PACEF Comment:
The data in this table provides an update on information previously circulated. In particular, prescribers are asked to note the equipotency of simvastatin 40mg with atorvastatin 10mg and rosuvastatin 5mg and the almost thirteen-fold cost difference. Simvastatin 40mg remains the preferred first-line agent and all prescriptions for atorvastatin 10mg and rosuvastatin 5mg should be considered for therapeutic switching to simvastatin 40mg unless there is good reason not to do so (e.g. known intolerance to simvastatin, contra-indication or potential interaction). NICE define higher intensity statins as those used in doses that produce greater cholesterol lowering than simvastatin 40mg; this can be seen from this table to include simvastatin 80mg, most strengths of atorvastatin and all strengths of rosuvastatin. In people taking statins for secondary prevention, NICE recommend increasing to simvastatin 80mg (or a drug of similar efficacy and acquisition cost) if a TC of less than 4mmol/litre or an LDL-C of less than 2mmol/litre is not attained. This table reveals that there is no currently available agent that corresponds to simvastatin 80mg in terms of both efficacy and acquisition cost.

NICE TECHNOLOGY APPRAISAL 132: EZETIMIBE FOR THE TREATMENT OF PRIMARY (HETEROZYGOUS FAMILIAL AND NON-FAMILIAL) HYPERCHOLESTROLAEMIA (NOVEMBER 2007)

Following on from the article that featured in *PACE Bulletin*, Vol 2, No 1 (January 2008), a number of readers have asked for further clarity on the implementation of NICE TA 132. Prescribers are reminded that **ezetimibe is only licensed for the treatment of primary (heterozygous-familial or non-familial) hypercholesterolaemia** and NICE have only evaluated the drug within this context.

NICE define hypercholesterolaemia as the presence of high levels of cholesterol in the blood. For patients with familial hypercholesterolaemia (FH) a risk assessment is unnecessary as patients should automatically be considered to be at high risk and prioritized for lipid lowering therapy. FH should be considered if Total Cholesterol (TC) is >7.5mmol/L (or Low Density Lipoprotein Cholesterol (LDL-C) is >4.9mmol/L) and there is a family history of either early MI or raised cholesterol. The presence of tendon xanthoma in the patient or relative is also pathognomonic. The majority of people with TC >9mmol/L and normal triglycerides will have FH.

Patients with non-familial hypercholesterolaemia should be formally risk assessed. Individuals at high risk are likely to be those with a family history of premature CVD (i.e. a father or brother who had a vascular event before the age of 55 or a mother or sister before the age of 65), those with clinical signs of hyperlipidaemia, those originating from the Indian subcontinent, smokers and hypertensives.

NICE have endorsed the use of ezetimibe as follows:

- Ezetimibe monotherapy is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who would otherwise be initiated on statin therapy.
- Ezetimibe, co-administered with initial statin therapy, is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who have been initiated on statin therapy (as per NICE guidance TA 94 in adults with non-familial hypercholesterolaemia) when: (1) **serum total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) concentration is not appropriately controlled** either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to initial statin therapy or (2) **consideration is being given to changing from initial statin therapy to an alternative statin.**

PACEF Recommendation
Ezetimibe monotherapy in primary (heterozygous-familial or non-familial) hypercholesterolaemia
Patients should usually be initiated on simvastatin 40mg; if intolerant to the 40mg dose, 20mg should be tried. Alternative statins such as pravastatin or a higher intensity statin of lower acquisition cost (i.e. simvastatin 80mg) should also be tried before ezetimibe monotherapy is considered. This is because ezetimibe monotherapy is not as effective in terms of TC and LDL-C lowering as even a low dose of simvastatin. It should also be remembered that ezetimibe is currently a black triangle drug.

PACEF Recommendation

Ezetimibe/statin combination therapy in primary (heterozygous-familial or non-familial) hypercholesterolaemia

Simvastatin 40mg should be prescribed initially and should enable at least one third of patients to get below 4mmol/litre (TC) and 2mmol/litre (LDL-C). Increasing the simvastatin dose to 80mg may be necessary in those insufficiently responsive to simvastatin 40mg. If the patient does not reach the 4mmol/l and 2mmol/l targets on simvastatin 80mg (over half of patients will not), reduce aspiration to the minimum audit standard and QOF target of 5mmol/l (TC). If ezetimibe/statin combination therapy becomes necessary due to intolerance or inadequate response, an ezetimibe/simvastatin combination should be preferred. Co-prescribing of high-cost, high-potency statins with ezetimibe is prohibitively expensive and should be reserved for exceptional circumstances. Where exceptionally high TC or LDL-C reductions are required, a combination of ezetimibe and simvastatin 80mg should be considered. A fixed dose combination formulation of ezetimibe and simvastatin (Inegy) is available in a variety of strengths, but is significantly more expensive than separate components and should not be prescribed.

PACEF Recommendation

Ezetimibe in the primary prevention of Coronary Heart Disease (CHD)

NICE TA 94 and CG 67recommend statin therapy first line as part of the management strategy for the primary prevention of CVD in adults who have a 20% or greater 10-year risk of developing CVD. Simvastatin 40mg is recommended first line (see above). NICE CG 67 does not recommend targets for TC or LDL-C for people treated with a statin for primary prevention. There are no clinical trials in primary prevention that have evaluated the relative and absolute benefits of cholesterol lowering to different TC and LDL-C targets and target chasing is not recommended within this context. Ezetimibe is not licensed for the primary prevention of CHD and no published cardiovascular outcomes data is available. As a result of this, there should be very little need to prescribe ezetimibe within this context except in the circumstances already defined for the treatment of primary (heterozygous-familial or non-familial) hypercholesterolaemia.

PACEF Recommendation

Ezetimibe in the secondary prevention of CHD

Prescribers are reminded that ezetimibe is not licensed for secondary prevention of CHD and that no cardiovascular outcomes data exists. If ezetimibe is being considered within this context, it should be as a last resort and utilized as recommended above in the section entitled ezetimibe/statin combination therapy in primary hypercholesterolaemia.

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