

FORTH VALLEY

LIPID LOWERING GUIDELINES v4

May 2010

This guideline applies to people over 16 years of age. This guideline is not intended to serve as a standard of medical care or be applicable in every situation. Decisions regarding the treatment of individual patients must be made by the clinician in light of that patient's presenting clinical condition and with reference to current good medical practice.

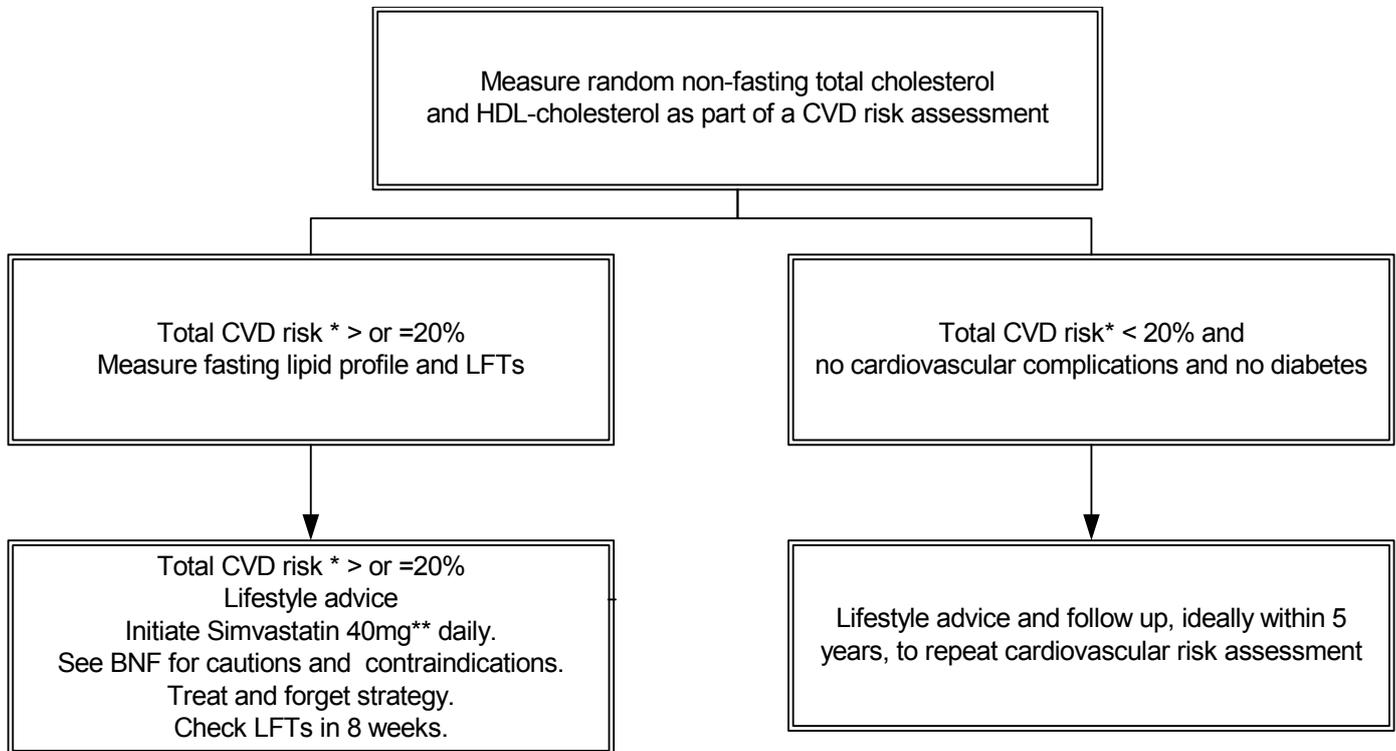
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PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

1. WITH NO DIABETES

All adults from 40 years onwards should have their total cholesterol measured as part of an opportunistic CVD risk assessment in Primary Care.



*Assess CVD risk using the ASSIGN score.

Consider secondary and familial hyperlipidaemia if cholesterol > 8.0mmol/L.
Discuss with lipid clinic if in doubt.

**In case of side effects with simvastatin 40mg daily try pravastatin 40mg daily
(see BNF for cautions and contraindications).

PREVENTION OF ATHEROSCLEROTIC ARTERIAL DISEASE REQUIRES CONTROL OF ALL RISK FACTORS. NO SINGLE RISK FACTOR, INCLUDING CHOLESTEROL, SHOULD BE VIEWED IN ISOLATION.

- All other risk factors (e.g. smoking, hypertension) should be addressed.
- Dietary and other lifestyle advice (e.g. alcohol, obesity, physical activity) should be given.

**Certain individuals are at higher risk than CVD risk charts predict.
Higher risk occurs in:**

- Familial dyslipidaemia (e.g. hypercholesterolaemia, familial combined hyperlipidaemia, or other inherited dyslipidaemia)
- People with raised triglyceride levels (>1.7mmol/l fasting)
- Those who are not yet diabetic, but have impaired fasting glucose (6.1-6.9 mmol/l) or impaired glucose tolerance (7.8-11mmol/l).
- Women with premature menopause
- People of south Asian descent, i.e. originating from the Indian subcontinent
- People with central obesity (waist circumference >102cm in men and >88cm in women)

2. WITH DIABETES

SIGN 116 recommends:

- Lipid lowering therapy with simvastatin 40mg for primary prevention in patients with type 2 diabetes aged > 40 years regardless of baseline cholesterol.
- Lipid lowering therapy with simvastatin 40mg should be considered for primary prevention in patients with type 1 diabetes aged > 40 years.
- Patients < 40 years with type 1 or type 2 diabetes and other important risk factors* should be considered for primary prevention lipid lowering therapy with simvastatin 40mg.

*Further risk factors

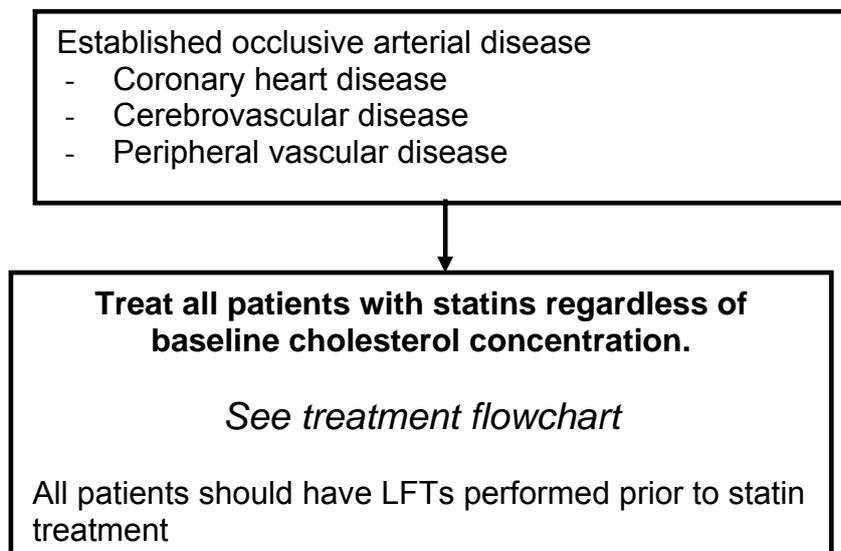
- Retinopathy (preproliferative, proliferative, maculopathy)
- Nephropathy, including persistent microalbuminuria
- Poor glycaemic control (HbA1c>9%)
- Features of metabolic syndrome (central obesity; fasting triglycerides >1.7 mmol/l [non-fasting >2.0 mmol/l] and/or HDL cholesterol <1.0 mmol/l in men or <1.2 mmol/l in women; impaired glucose tolerance).

Goals of Treatment

For primary prevention a “treat and forget” strategy is recommended i.e. there is no need to recheck cholesterol level.

LFTs should be checked before initiation of statin, at 8 weeks (NICE recommends within 3 months) and at 12 months. If LFTs remain normal, there is no need to repeat again unless clinically indicated.

SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE



ATHEROSCLEROTIC ARTERIAL DISEASE IS OF MULTIFACTORIAL ORIGIN. NO SINGLE RISK FACTOR, INCLUDING CHOLESTEROL CONCENTRATION, SHOULD BE VIEWED IN ISOLATION.

- Encourage smoking cessation (consider nicotine replacement therapy)
- All other risk factors hypertension, diabetic control, should be addressed (see separate guidelines)
- An antiplatelet agent (see separate guideline) should be taken by all those with occlusive arterial disease in the absence of contraindications (active peptic ulceration, a bleeding disorder, or true hypersensitivity)
- Treat with ACE-inhibitors unless contraindicated
- Consider β -blockers, and ensure attendance at a rehabilitation programme, for patients after MI
- Dietary and other lifestyle advice e.g. alcohol, obesity, physical activity, should be given.

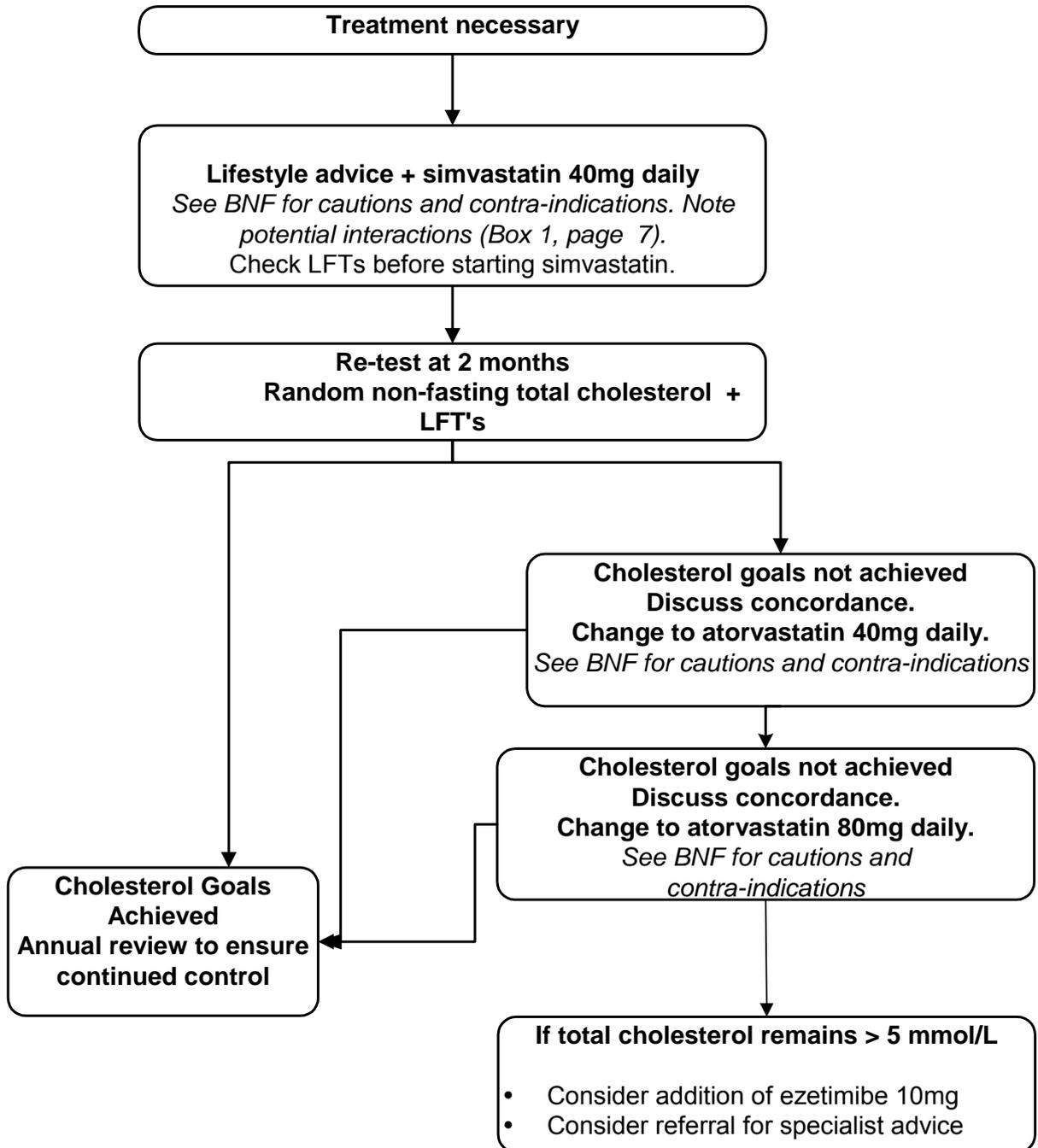
Goals of Treatment

For secondary prevention, the ideal target is total cholesterol concentration of ≤ 4 mmol/L.

NICE recommends an audit target of total cholesterol of < 5 mmol/L in recognition that more than half of patients will not achieve a total cholesterol < 4 mmol/L.

- Although relative risk reduction of major coronary events remains constant at about 23% reduction at 1mmol/L reduction in LDL absolute risk reduction is smaller at lower cholesterol levels.
- Two thirds of the gain from a statin is realized from the initial dose.

TREATMENT FLOWCHART



Acute Coronary Syndrome

All Forth Valley patients suffering acute coronary syndrome, who have no contraindication, will be commenced on or changed to atorvastatin 80mg daily whilst an inpatient. For those not tolerating 80mg atorvastatin two possible pathways are suggested.

- Reduce atorvastatin to maximum tolerated dose and add ezetimibe, if required to attain target.

Or

- Substitute rosuvastatin for atorvastatin. All patients must start on an initial dose of no more than 10mg rosuvastatin daily (5mg in those > 70 years and those of Asian ancestry).

Please note: there is not evidence to recommend changing all those with previous acute coronary syndrome to atorvastatin 80mg daily. Initiation of this dose without following the treatment flowchart should only be at the time of acute coronary syndrome.

Diabetes

Previous versions of the Forth Valley Lipid Lowering Guideline have recommended treatment of diabetes as an equivalent to established vascular disease i.e. secondary prevention. SIGN 116 outlines the lack of evidence base for this approach and recommends that lipid lowering management in people with diabetes is divided to primary and secondary prevention on the basis of established vascular disease. The following recommendations are included within the SIGN guideline:

- Grade A evidence. "Lipid lowering drug therapy with simvastatin 40mg is recommended for primary prevention in patients with type 2 diabetes aged > 40 years regardless of baseline cholesterol." No treatment target is recommended by SIGN. QOF DM17 recommends a total cholesterol target in patients with diabetes of $\leq 5\text{mmol/l}$.
- Grade B evidence. "Lipid lowering drug therapy with simvastatin 40mg should be considered for primary prevention in patients with type 1 diabetes aged >40 years."
- Grade A evidence "Consider intensive lipid lowering therapy with atorvastatin 80mg for patients with diabetes and acute coronary syndrome, objective evidence of coronary heart disease and angiography of following coronary revascularisation procedures."

Cytochrome P450 Interactions

Simvastatin and atorvastatin are metabolized by cytochrome P450 CYP3A4 and co-administration of potent inhibitors of this enzyme increases the risk of side effects including rhabdomyolysis.

MHRA gives the following advice:

Box 1

Interacting Drug	Prescribing Advice
Potent cytochrome P450 CYP3A4 inhibitors: HIV protease inhibitors Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin	Avoid simvastatin
Ciclosporin Danazol Other fibrates (except fenofibrate) Niacin (>1g/day)	Do not exceed 10mg simvastatin
Gemfibrozil	Avoid but if necessary, do not exceed 10mg simvastatin daily
Verapamil, amiodarone	Do not exceed 20mg simvastatin
Diltiazem	Do not exceed 40mg simvastatin
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Please note - The FV antimicrobial guideline gives further advice on alternatives to macrolide antibiotics for various clinical indications. If an interacting drug, which would result in MHRA advice to avoid simvastatin is deemed essential, an assessment should be made of the individual's immediate cardiac risk. The PRISM trial suggests that stopping a statin in those suffering an acute coronary syndrome is associated with a significantly increased risk of death and non-fatal myocardial infarction within the first 30 days. In case of doubt seek specialist advice.

Warfarin

Care is needed when prescribing some statins to patients taking warfarin - please check the specific product information for further advice on possible interactions.

Statin Side Effects

In cases of possible statin side effects with either simvastatin or atorvastatin, a statin of different solubility should be tried. In primary prevention, pravastatin (hydrophilic) should be substituted for simvastatin (lipophilic). In secondary prevention, rosuvastatin (hydrophilic) should be substituted for simvastatin or

atorvastatin (lipophilic). Prescribing a statin of different solubility may improve treatment and is recommended over alternative therapies.

Liver Function Tests (LFTs)

Statins should be used with caution in those with a history of liver disease or with a high alcohol intake. Use should be avoided in active liver disease.

Baseline liver enzymes should be measured before starting a statin. Liver function (transaminases) should be measured 8 weeks after starting treatment or dose changes (NICE recommends within 3 months) and at 12 months, but not again unless clinically indicated.

If transaminase concentrations reach 3 times the upper limit of normal, levels should be rechecked after a minimum 2 week period (a large percentage will return to normal with no intervention). If still elevated, reduce or stop statin. When transaminases return to normal a statin from a different class may be tried i.e. rosuvastatin (hydrophilic) if previously on simvastatin/atorvastatin (lipophilic).

Myopathy and Rhabdomyolysis

The CSM advises that myopathy and rhabdomyolysis are rare but clinically important adverse effects of statins. The exact mechanism by which statins cause rhabdomyolysis remains unclear, but the risk appears to be dose related. Risk factors include:

- Underlying muscle disorders, renal impairment, untreated hypothyroidism, alcohol abuse and age >70 years.
- Concomitant use of other lipid lowering agents i.e. gemfibrozil, fenofibrate, other fibrates or nicotinic acid.
- A history of myopathy with any lipid-lowering treatment.
- Interactions (e.g. drugs inhibiting cytochrome P450 CYP3A4) see table above).

Prescribers are reminded of the need to adjust doses of statins in accordance with the recommendations of each Summary of Product Characteristics.

Patients receiving any statin should be asked to report muscle pain, weakness or cramps immediately. If symptoms are severe or if creatine kinase is greater than 5 times the upper limit of normal, treatment should be withheld.

Ezetimibe

Ezetimibe is a cholesterol absorption inhibitor with moderate cholesterol lowering effect. Ezetimibe has no cardiovascular outcome data to show that its cholesterol lowering effect reduces cardiovascular morbidity or mortality.

- Strategies utilising the addition of ezetimibe to lower dose statins are expensive, not evidence based and not recommended.
- Ezetimibe is not recommended for primary prevention.
- Ezetimibe is not recommended for monotherapy. Every attempt should be made to improve concordance with a statin by changing to a statin of different solubility in the case of side effects.

Rosuvastatin

All patients must start on an initial dose of no more than 10mg rosuvastatin once daily (5mg in those aged > 70 years and those of Asian ancestry). Rosuvastatin should only be titrated to 20mg if considered necessary after a 4-week trial of 10mg daily.

The 40mg dose is contraindicated in patients with predisposing risk factors for muscular toxicity and specialist supervision is recommended if the 40mg dose is initiated.

Omega – 3 – Fatty Acid Compounds

NICE clinical guideline 67 advises that there is insufficient evidence to recommend omega 3 fatty acid supplementation in patients with angina, peripheral arterial disease or stroke. Use in primary prevention is also not recommended.

Fibrates

Fibrates act mainly by decreasing serum triglycerides; they have variable effects on cholesterol. All can cause a myositis-like syndrome, especially in those with impaired renal function. Combining a fibrate with a statin increases the risk of muscle effects (especially rhabdomyolysis) and should be used with caution and after specialist advice. Bezafibrate and fenofibrate are current FV formulary choice fibrates.

The routine use of additional lipid-lowering treatment is not recommended without specialist advice.