

Statin Prescribing & Lipid Modification Guideline for the Prevention of Cardiovascular Disease

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Document control

Date	Version	Amendments
Dec 2015	1	New Guideline
Jan 2020	2	Change from QRISK2 to QRISK for CV risk stratification Removal of “last line option” for rosuvastatin Linking NCL JFC documents on omega fatty acids and management of hypertriglyceridemia Addition of PCSK9i paragraph Update of content in appendix 1 and appendix 2

Document management

Groups / Individuals who have overseen the development of this guidance:	Shalina Dhalla, RFL Senior Cardiology Pharmacist
Groups which were consulted and have given approval:	Dr Catherine Lunken, UCLH Lipid & Endocrinology Specialist Dr Devaki Nair, RFH Clinical Lead for Lipids & CVD Prevention NCL JFC Formulary Pharmacists (UCLH, RFH, WH, MEH, NMUH, GOSH, RNOH, BEH & C&I MH Trusts) NCL JFC CCG Representatives (Camden, Islington, Barnet, Haringey, Enfield)
File name:	Statin Prescribing & Lipid Modification Guideline
Version number:	2
Available on:	https://www.ncl-mon.nhs.uk/wp-content/uploads/Guidelines/2_Lipid_modification_prevention_cardiovascular_disease.pdf
Disseminated to:	NCL JFC Formulary Pharmacists and CCG Leads
Equality impact assessment:	Low
NCL Joint Formulary Committee Approval date:	January 2020
Review date:	January 2023

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1. Target audience

Hospital clinicians, GPs, non-medical prescribers, specialist nurses and pharmacists.

2. Purpose

To provide guidance on appropriate prescribing of statins in different adult patient groups and use of other lipid modifying therapies e.g. ezetimibe.

3. Introduction

NICE issued updated guidance on lipid modification (CG181) in September 2016. This NCL JFC guidance reflects updated information based on NICE guidance, current pricing of statins and a search of interactions and contraindications.

4. Cardiovascular Disease (CVD) Risk Assessment

Be aware that all CVD risk assessment tools can provide only an approximate value for CVD risk. Interpretation of CVD risk scores should always reflect informed clinical judgement.

Use the QRISK risk assessment tool to assess CVD risk for primary prevention – available via <http://www.qrisk.org/> or automatically via GP patient record systems.

The following treatment groups are at higher baseline CVD risk, and therefore a further risk assessment is not required:

- patients ≥85 years old
- patients with type 1 diabetes (see section 7.2.1)
- eGFR <60ml/min/1.73m² and/or albuminuria
- pre-existing CVD (secondary prevention)
- familial hypercholesterolaemia or other inherited disorders of lipid metabolism

Be aware that standard CVD risk scores will underestimate risk in people who have additional risk because of underlying medical conditions or treatments. These groups include:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotic medication, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders such as systemic lupus erythematosus, and other systemic inflammatory disorders.

Use clinical judgement when using risk scores to inform treatment decisions in these patient groups.

Also recognise that CVD risk will be underestimated in people who are already taking antihypertensive or lipid modification therapy, or who have recently stopped smoking. Use clinical judgement to decide on further treatment of risk factors in people who are below the CVD risk threshold for treatment.

Refer to NICE CG181 (<http://www.nice.org.uk/guidance/cg181/>) for further information on identifying patients and assessing CVD risk.

5. Lifestyle Advice for Primary & Secondary Prevention of CVD

Advise all patients to make lifestyle modifications to reduce their CVD risk including cardio-protective diet, physical activity, weight management, reduced alcohol consumption and smoking cessation.

6. Statin Treatment Guidance

See Appendix 1 for flow chart and guidance on statin treatment in primary and secondary prevention. Common interactions of statins and management advice are listed in Appendix 2; please note that this list is not exhaustive and users should also refer to product Summary of Product Characteristics (SPCs) or ask a pharmacist for up-to-date advice.

6.1. Statins in Patients with Renal Impairment

For primary and secondary prevention of CVD in patients with chronic kidney disease (CKD) offer atorvastatin 20mg daily. The dose can be increased if >40% reduction in non-HDL cholesterol is not achieved and eGFR is $\geq 30\text{ml/min/1.73m}^2$. Agree the use of higher doses with a renal specialist if eGFR is $< 30\text{ml/min/1.73m}^2$

6.2. Statins in Patients with Diabetes

6.2.1. Type 1 Diabetes

Consider statin therapy in all patients with type 1 diabetes as this patient group has a higher baseline CVD risk. Offer atorvastatin 20mg for primary prevention of CVD to adults with type 1 diabetes who have one or more of the following risk factors:

- Age >40 years
- Had diabetes for >10 years
- Established nephropathy
- Other CVD risk factors

6.2.2. Type 2 Diabetes

Offer atorvastatin 20mg for primary prevention of CVD to all patients with type 2 diabetes and with an estimated 10-year CVD risk $\geq 10\%$.

6.3. Statins in Pregnancy & Breastfeeding

Statins are contraindicated in pregnancy due to reports of congenital anomalies and effects on foetal development. Advise women of childbearing potential of the potential teratogenic risk of statins and to stop taking them if pregnancy is a possibility. Statins should ideally be discontinued 3 months before women attempt to conceive.

Statins are contraindicated in women who are breastfeeding.

6.4. Relative Statin Intensities¹

Statin Intensity	Daily Dose (reduction in LDL cholesterol)
High-Intensity	Atorvastatin 80mg (55%)
	Atorvastatin 40mg (49%)
	Atorvastatin 20mg (43%)
	Simvastatin 80mg (42%) <i>see note below</i>
	Rosuvastatin 40mg (53%)
	Rosuvastatin 20mg (48%)
	Rosuvastatin 10mg (43%)

Medium-Intensity	Atorvastatin 10mg (37%)
	Simvastatin 40mg (37%)
	Simvastatin 20mg (32%)
	Rosuvastatin 5mg (38%)
Low-Intensity	Pravastatin 40mg (29%)
	Pravastatin 20mg (24%)
	Pravastatin 10mg (20%)
	Simvastatin 10mg (27%)

- Atorvastatin is the first line statin for primary and secondary prevention of CVD.
- Fluvastatin is not included in this table as it is not recommended or included on the NCL JFC formulary.
- There is a particularly high risk of myopathy associated with high dose (80mg) simvastatin, and it is therefore not recommended for patients newly initiated on a statin. Please see further details on the MHRA Drug Safety Update see MHRA Drug Safety Update at <https://www.gov.uk/drug-safety-update/simvastatin-increased-risk-of-myopathy-at-high-dose-80-mg>

7. Monitoring

Prior to initiating lipid modification therapy a baseline full lipid profile should be measured (this does not need to be fasting) if these have not been done in the last 3 months. This should include total cholesterol (TC), HDL cholesterol, non-HDL cholesterol, LDL cholesterol (LDL-C) and triglyceride levels. Urea and electrolytes, Liver Function Tests (LFTs), HbA1c and thyroid stimulating hormone (TSH) should also be taken. Secondary causes of dyslipidaemia should be excluded. The following groups should be referred to a lipid clinic (see contact details in section 10):

- Patients with baseline TC >7.5 mmol/L and family history of premature CHD
- Any patient with baseline TC >9.0mmol/L **or** non-HDL cholesterol >7.5mmol/L
- Patients with a triglyceride level >10mmol/L after two measurements (see NICE CG181 for further details). Please consult NCL [Guidance for the management of hypertriglyceridaemia](#)
- Urgently refer patients with triglyceride level >20 mmol/L that is not related to excess alcohol or poor glycaemic control. Please consult JFC [NCL Guidance for the management of hypertriglyceridaemia](#)
- Patients at high-risk of CVD who are intolerant to 3 different statins

Lipid profiles should be measured at baseline and 3 months. Consider measuring every 12 months thereafter (or after 6 months if the dose/statin changes). The results should be used to inform annual medication reviews where adherence, lifestyle modifications and CVD risk factors can be discussed. Aim for $\geq 40\%$ reduction in non-HDL cholesterol. If a 40% reduction in non-HDL cholesterol is achieved, there is no need to continue repeating the full lipid profile in primary prevention.

LFTs should be measured at baseline, 3 months and 12 months. Statins do not require further routine LFT monitoring if stable at 12 months unless clinically indicated.

7.1. Advice and monitoring for adverse effects

The most common adverse effects associated with statins include: muscle related adverse effects (see Section 7.2 below), headaches, gastrointestinal disturbances, nasopharyngitis and sleep disturbances. If significant; consider changing time of dose, reducing the dose or switching to an alternative agent.

Advise people who are being treated with a statin that other drugs, some foods (for example, grapefruit juice) and some supplements may interfere with statins and to always consult the patient information leaflet, a pharmacist or prescriber for advice when starting other drugs or thinking about taking supplements.

Remind the person to restart the statin if they stopped taking it because of drug interactions or to treat intercurrent illnesses.

Advise people who are being treated with a statin to seek medical advice if they develop muscle symptoms such as pain, tenderness or weakness (see section 7.2 below).

7.2. Muscle-Related Adverse Effects

Muscle-related problems are the most frequently reported side effect of statins. All statins have a dose-dependent increased risk of myopathy. Interactions with other medications may also increase the risk of myopathy (see Appendix 2).

Patients should be counselled to report any unusual muscle pain, tenderness or weakness. Creatine kinase (CK) levels should be measured in patients reporting these symptoms, and appropriate action taken as below.

- Where CK levels are (in the absence of strenuous exercise) >5x the upper limit of normal, stop/avoid statins. If symptoms resolve and CK levels return to normal, then re-introduction of the statin or of an alternative statin may be considered at the lowest dose and with close monitoring.
- Where CK levels are (in the absence of strenuous exercise) raised but <5x the upper limit of normal, consider a reduced statin dose.
- Where patients reporting muscle pain/weakness have previously tolerated statin therapy for >3 months, explore other possible causes of muscle pain/weakness.

There is a particularly high risk of myopathy associated with high dose (80mg) simvastatin, and it is therefore not recommended for patients newly initiated on a statin. For patients already established on simvastatin 80mg, continue only if the patient has not experienced muscle-related side effects.

7.3. Intolerance of statins

If a patient is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose.

Tell the person that any statin at any dose reduces CVD risk. If someone reports adverse effects when taking high-intensity statin discuss the following possible strategies with them:

- stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin
- reducing the dose within the same intensity group
- changing the statin to a lower intensity group.

Patients at high risk of CVD who are intolerant to 3 different statin should be referred to a lipid clinic (see contact details in section 9).

7.4. Liver Function Tests (LFTs)

Measure LFTs at baseline, 3 months and 12 months. Thereafter only test if clinically indicated. Consider stopping/reducing statins when LFTs are raised >3x the upper limit of normal.

8. Lipid-Lowering Therapies

8.1. Ezetimibe

Ezetimibe is licensed and recommended by NICE (TA385) for patients with primary hypercholesterolaemia where a statin is contraindicated, not tolerated (consider referral to lipid specialist) or as an adjunct where high intensity statins have failed to sufficiently reduce cholesterol levels.

8.2. PCSK9 inhibitors (alirocumab and evolocumab)

Alirocumab and evolocumab are monoclonal antibodies that target proprotein convertase subtilisin/kexin type 9 (PCSK9). They stop low-density lipoprotein receptors in the liver from degrading, helping to lower levels of LDL-C in the blood. Alirocumab and evolocumab are licensed and recommended by NICE (TA393 and TA394 respectively) for patients with primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin, or a statin plus other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who cannot tolerate or cannot be given statins.

If the patients meets the NICE criteria below for a PCSK9i, a referral should be made to the lipid clinic for further monitoring and prescribing. PCSK9i can only be prescribed in secondary care.

	Without CVD	With CVD	
		High risk of CVD ¹	Very high risk of CVD ²
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre	

¹ High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; peripheral arterial disease.

² Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

Abbreviations: CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

8.3. Therapies that are NOT Recommended

The following therapies should NOT be prescribed due to limited evidence of benefit.

- Fibrates (unless advised by a lipid specialist)

- Bile acid sequestrants (unless advised by a lipid specialist)
- Nicotinic acid (no longer available in the UK)
- Omega-3 fatty acid compounds (please refer to NCL JFC [Guidance for the review of omega-3 fatty acids \(including Omacor®\)](#))
- Plant stanols and sterols
- Co-enzyme Q10 or vitamin D to increase adherence to statin

For patients established on these therapies, consider stopping and optimising statin therapy where appropriate. If patients wish to purchase omega-3 fatty acids, plant stanols/sterols, co-enzyme Q10 or vitamin D over the counter, there is no evidence of harm in this.

9. Lipid Clinic Contact Details

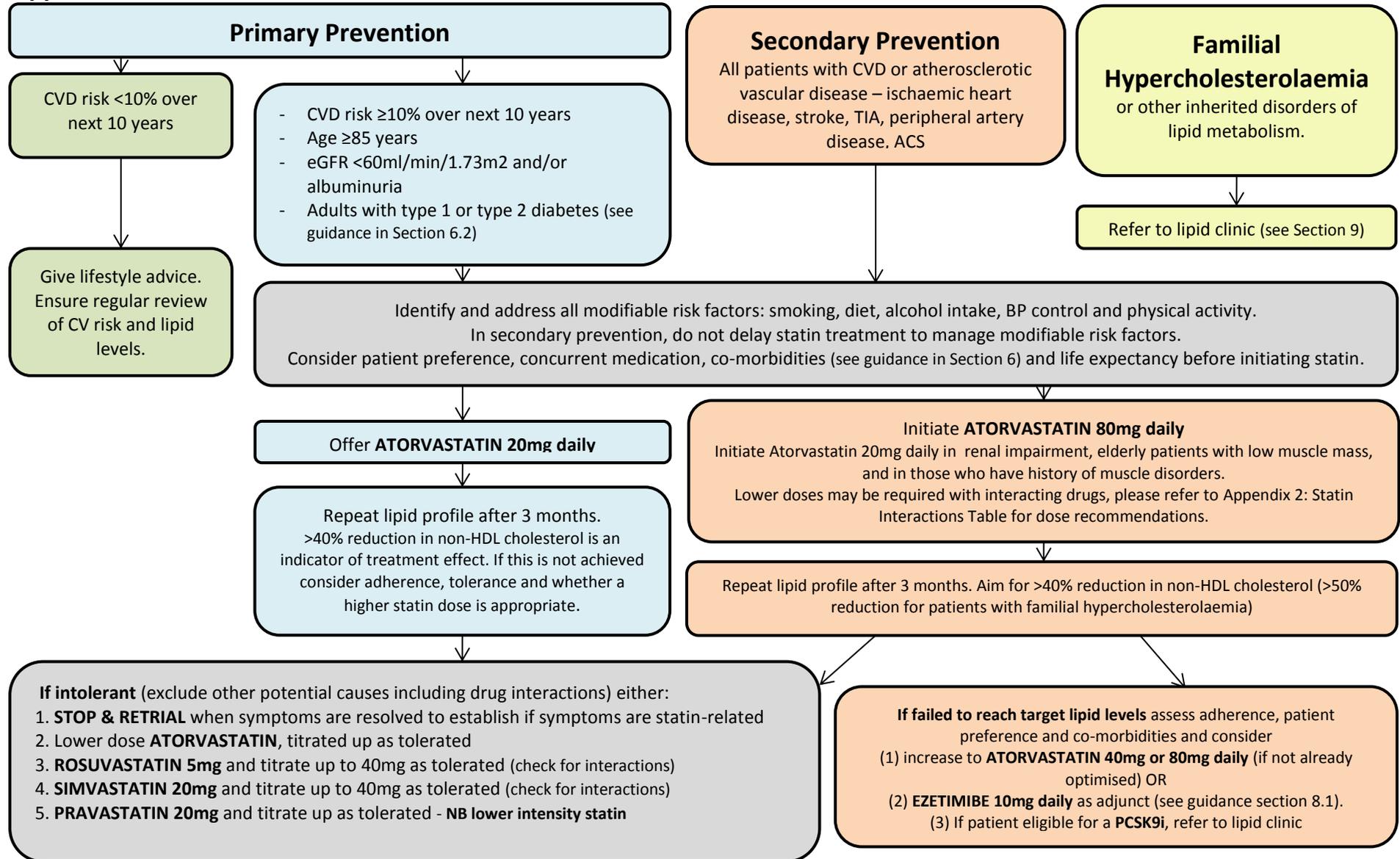
Royal Free London NHS Foundation Trust	UCLH NHS Foundation Trust
Dr Devaki Nair Clinical Lead for Lipids & CVD Prevention Devaki.nair@nhs.net Tel: 020 7472 6694 Ext 33489 Clinical Nurse Specialist Tel: 0207 317 7723	Dr Catherine Lunken Department of Diabetes & Endocrinology 250 Euston Road, London NW1 2PG Catherine.lunken@nhs.net Tel: 020 3447 9336

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- 14) Liverpool HIV drugs interaction checker. Accessed online on 27/08/19 via <https://www.hiv-druginteractions.org/checker>
- 15) NCL Right Test Right Time Pathology Guidance – Updated Phase 1 & 2 July 2019

Appendix 1: Statin Guidelines



Appendix 2: Statin Interactions Table

(please also refer to the most up to date SPC or ask a pharmacist for advice as this list is not exhaustive)

Interacting Drug	Atorvastatin Advice	Simvastatin Advice	Rosuvastatin advice	Pravastatin Advice
Macrolides - clarithromycin, erythromycin, telithromycin Azoles – itraconazole, ketoconazole, posaconazole	Avoid if possible (i.e. stop atorvastatin for duration if short course). If required, counsel patient to report any symptoms of myopathy. Monitor lipid levels to ensure lowest necessary dose of atorvastatin. Clarithromycin: do not exceed 20mg daily Itraconazole: do not exceed 40mg daily.	Contraindicated with simvastatin	Macrolides: Use with caution. Counsel patient to report any symptoms of myopathy. Azoles: Nil significant interaction reported – dose as normal	Nil significant interaction reported – dose as normal
Amiodarone, verapamil, diltiazem, amlodipine	May increase statin levels – counsel patient to report any symptoms of myopathy. Monitor lipid levels to ensure lowest necessary dose of atorvastatin is used.	Do not exceed simvastatin 20mg daily	Nil significant interaction reported – dose as normal	Nil significant interaction reported – dose as normal
HIV Protease Inhibitors e.g. tipranavir, ritonavir, nelfinavir, lopinavir	Initiate atorvastatin 10mg daily. If target lipid levels not achieved, consider atorvastatin 20mg and seek advice from pharmacist/HIV team/lipid team. Counsel patient to report any symptoms of myopathy.	Contraindicated with simvastatin	Atorvastatin in the preferred option. If high risk patient or target lipid levels not achieved with atorvastatin, start with the lowest possible dose of rosuvastatin and seek advice from pharmacist/HIV team/lipid team.	Atorvastatin is the preferred option. If pravastatin required due to intolerance to other statins, initiate pravastatin 20mg daily and if tolerated titrate up to 40mg daily with caution. Counsel patient to report any symptoms of myopathy.
Ciclosporin, gemfibrozil, danazol, nefazodone	Do not exceed atorvastatin 10mg daily	Contraindicated with simvastatin	Contraindicated with rosuvastatin	Ciclosporin: Initiate pravastatin 20mg daily and if tolerated titrate up to 40mg daily with caution. Gemfibrozil: Avoid combined use. If required, monitor lipid levels to ensure lowest necessary dose of pravastatin is used. Counsel patient to report any symptoms of myopathy.
Other fibrates (for gemfibrozil see above)	Counsel patient to report any symptoms of myopathy. Monitor lipid levels to ensure lowest necessary dose of atorvastatin is used.	Do not exceed simvastatin 10mg daily. (except fenofibrate - no dose alteration required, but monitor for adverse effects)	Counsel patient to report any symptoms of myopathy. Monitor lipid levels to ensure lowest necessary dose of rosuvastatin is used. Avoid rosuvastatin 40mg daily.	Counsel patient to report any symptoms of myopathy. Monitor lipid levels to ensure lowest necessary dose of pravastatin is used.
Fusidic Acid (systemic)	Avoid if possible (i.e. if short course stop statin until 7 days after course is finished). If required, counsel patient to report any symptoms of myopathy. Monitor lipid levels to ensure lowest necessary dose of statin is used.			
Ezetimibe	Possible additive risk of myopathy. Counsel patient to report any signs of myopathy.			
Warfarin/Coumarins	Monitor INR on initiation and with dose changes.			Nil significant interaction reported
Grapefruit Juice	Avoid large quantities (>1.2L a day), the occasional glass is thought to be safe	Avoid while taking simvastatin.	Information is lacking but no interaction would be expected	Nil significant interaction