NHS Sunderland Clinical Commissioning Group

City Hospitals Sunderland NHS
NHS Foundation Trust

SLiMS

SOUTH OF TYNE LIPID MODIFICATION STRATGEY

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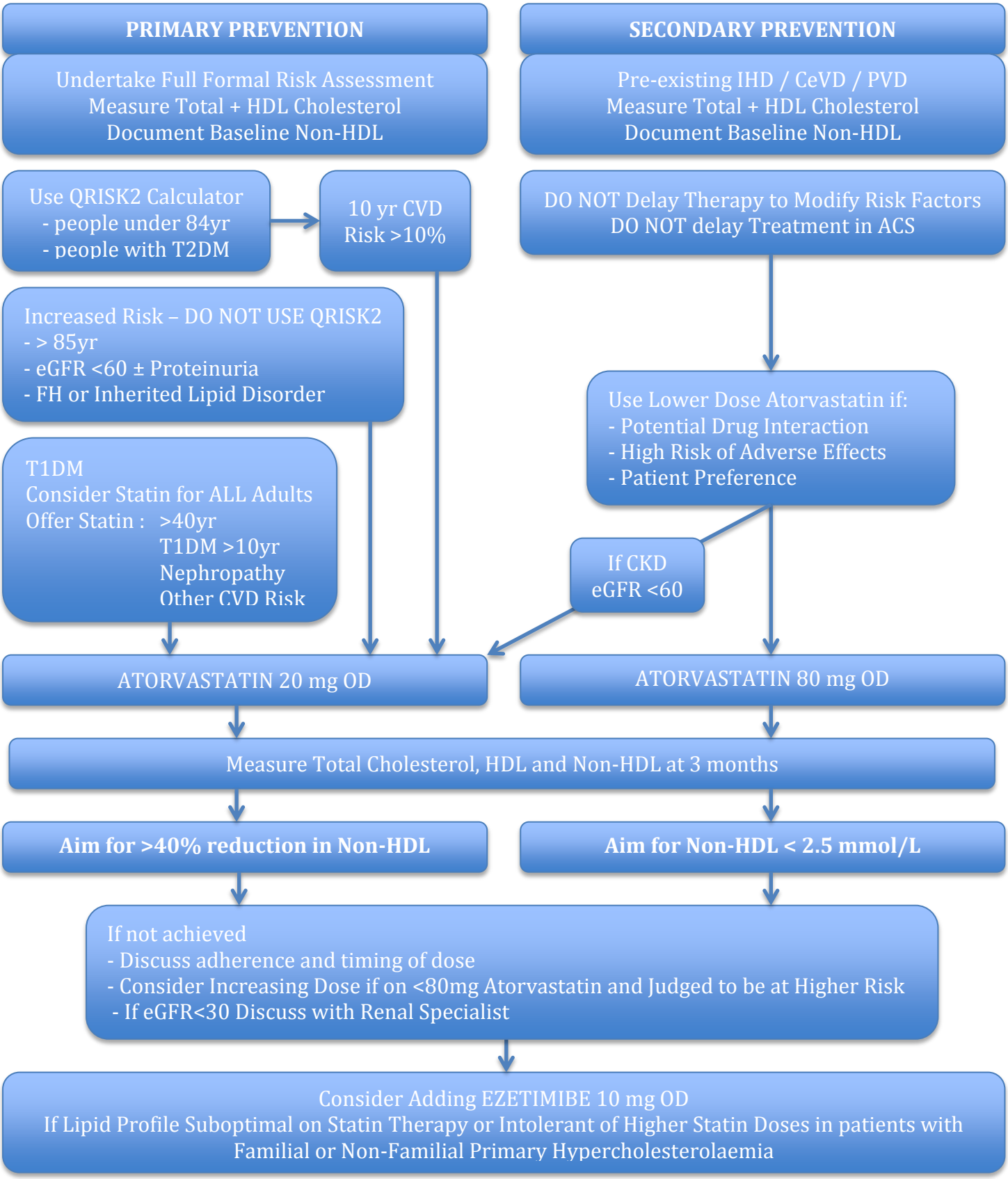
INTEGRATED VASCULAR CENTRE
SOUTH OF TYNE

SLIMS GUIDELINE 2015 - LIPID MODIFICATION THERAPY



Before Starting Therapy

Measure Full lipid profile (Total, HDL and Non-HDL Cholesterol plus Triglycerides) at least once

Check U+E, LFT, TFT. Fasting Glu / HbA1c and for Proteinuria

On Treatment

Do not routinely measure CK in asymptomatic people

Repeat ALT/AST at 3 and 12 months

Do Not Routinely Offer

Fibrates

Nicotinic Acid

Bile acid Sequestrants

Omega 3 Fatty Acids

Plant Stanols and Sterols

SLIMS GUIDELINE 2015

1. Full Formal Risk Assessment

Use QRISK2 calculator to assess CVD for primary prevention in people up to the age of 84
Consider people aged over 85 to be at increased risk of CVD because of age alone, particularly those who smoke or have raised BP
People older than 40 should have estimation of their CVD risk on an ongoing basis

Use QRISK2 to assess CVD risk in patients with Type 2 Diabetes.
Do not use QRISK2 for patients with Type 1 diabetes

Do not use risk assessment tool for
- people with eGFR <60 and/or Proteinuria – at increased risk of CVD
- people with pre-existing CVD (cerebrovascular disease, ischaemic heart disease or peripheral vascular disease)
- people with familial hypercholesterolaemia of other inherited disorders of lipid metabolism

Be aware that CVD risk scores will underestimate risk in the following groups
- people treated for HIV
- people with serious mental health problems
- patients on medications that can cause dyslipidaemia
- patients with autoimmune disorders (eg SLE) and other systemic inflammatory disorders

Recognise that CVD risk will be underestimated in
- people taking antihypertensive therapy
- people taking lipid modification therapy
- people who have recently stopped smoking

Be aware that CVD risk may be underestimated if triglycerides >4.5 mmol/L

Take into account increased risk of CVD in patients with BMI >40 kg/m^2

2. Lipid Measurement and Referral

Measure both total cholesterol and HDL cholesterol for best estimation of CVD risk

Take at least 1 full lipid sample (consisting of total cholesterol, triglycerides, HDL, LDL and/or Non-HDL cholesterol) **before starting lipid lowering therapy**. A fasted sample is not needed **unless** significant hypertriglyceridaemia (>10 mmol/L).

Include in assessment
- smoking
- alcohol consumption
- blood pressure
- BMI or other measure of obesity

Consider secondary causes of dyslipidaemia before considering referral for specialist opinion (See Appendix 1). Arrange the following investigations:-
- Fasting Glucose and HbA1c
- U+E
- LFT
- TFT
- Screen urine for proteinuria

If triglycerides 10-20 mmol/L repeat full fasted lipid profile after interval of 5 days (but within 2 weeks). Consider secondary causes.

Refer to specialist (See Appendix 6) if

- clinical diagnosis of Familial Hypercholesterolaemia (according to Simon Broome criteria) (See Appendices 3 and 4)
- total cholesterol >9 mmol/L or Non-HDL >7.5 mmol/L even if absence of first degree family history of premature heart disease
- triglycerides >10 mmol/L (not due to alcohol or poor glycaemia control)
- **refer urgently if triglycerides >20 mmol/L; consider starting Fenofibrate**

3. Lifestyle Advice (see NHS Choices website)

Diet

- total fat <30% of total energy intake
- saturated fat <7% of total energy intake
- dietary cholesterol <300mg/day

- replace saturated fats with mono-unsaturated and polyunsaturated fats
- reduce fat intake from animal sources reduces both saturated and monounsaturated fat
- replace saturated and mono-unsaturated fat intake with olive oil, rape seed oil and spreads

- choose wholegrain varieties of starchy foods

- reduce intake of sugar and food products containing refined sugars including fructose

- eat at least 5 portions of fruit and vegetables a day

- eat at least 2 portions of fish per week including a porion of oily fish (salmon, mackerel, sardines of fresh tuna)

- eat 4 to 5 portions of unsalted nuts, seeds and legumes a week

Physical Activity

- take into account person's needs preferences and circumstances
- at least 150 min of mod intensity aerobic activity (eg cycling or fast walking) a week or
- 75 min vigorous intensity aerobic activity (eg running, playing football) or a mix of moderate and vigorous aerobic activity
- muscle strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back abdomen, chest shoulders, arms)
- encourage people unable to perform moderate intensity physical activity to exercise at their maximum safe capacity

Weight Management

- offer advice and support to those who are overweight or obese

Alcohol consumption

- men should not drink regularly more than 3-4 units a day
- women should not drink more than 2-3 units a day
- people should avoid binge drinking

Smoking

- advise all who smoke to stop
- offer advice and support, referral to intensive support service or pharmacotherapy in line with smoking cessation services.

4. Drug Therapy

   See Main Diagram. Consider potential drug interactions (See Appendix 7)

   Before offering statin therapy for primary prevention discuss benefits of lifestyle modification and optimize management of all other modifiable CVD risk factors.
   Recognize that people may need support to change their lifestyle
   Offer people the opportunity to have their CVD risk re-assessed after making lifestyle changes.
   Offer statin therapy after risk assessment if lifestyle modification ineffective or inappropriate

5. Follow up of Patients started on Statin Therapy
   All patients started on high intensity statin therapy should have the following checked at 3 months :- Total Cholesterol
   HDL Cholesterol
   Non-HDL Cholesterol
   Aim for >40% reduction in Non HDL Cholesterol
   Aim for a Non –HDL Cholesterol < 2.5 mmol/L if pre-existing cardiovascular disease (JBS3)

   If not achieved
   - discuss adherence and timing of dose
   - optimize diet and lifestyle measures

   Consider increasing dose if
   - started on less than Atorvastatin 80mg
   - person judged to be at higher clinical risk because of co-morbidities, risk score or clinical judgement

   Provide annual medication reviews for patients taking statins
   - discuss medicines adherence, lifestyle modification and CVD risk factors
   - consider annual measurement of Non-HDL (non fasting)
   - discuss risks / benefits of changing patients on low- or middle-intensity statin to high intensity statin and make joint decision as to whether change required

6. Advice and Monitoring for Adverse Effects
   Advise people on stains that
   - other drugs, some foods (eg grapefruit juice) and supplements may interfere with statins
   - they should always consult patient information leaflet, a pharmacist or a prescriber for advice when starting other drugs or considering taking supplements

   Remind person to restart statin if discontinued temporarily because of intercurrent illness or following course of treatment with interacting drug when safe to do so.

   Enquire about persistent generalized unexplained muscle pain and whether or not this was associated with previous lipid lowering therapy before offering a statin

   Measure Creatine Kinase (CK) if history of myalgia
   - if CK >5x upper limit of normal re-measure after 7 days
   - **do not start statin** if remains >5x upper limit of normal
   - if CK raised but <5x upper limit of normal start stain at lower dose

   Advise patients on statin to seek medical advice if develop muscle pain, tenderness or weakness
   Measure CK if patient has muscle symptoms
   Explore other causes of symptoms or raised CK if previously tolerated stain for >3 months
   Do not measure CK in asymptomatic patients on statins

Measure baseline ALT or AST before commencing statin therapy
Re-measure within 3 months and at 12 months but not again unless clinically indicated
Avoid statin therapy if AST/ALT >3x upper limit of normal
Do not exclude patients from statin therapy if AST/ALT raised but <3x upper limit of normal

Do not stop statins because of increase in blood glucose or HbA1c

Statins are contraindicated in pregnancy
Advise women of childbearing potential of potential tetratogenic risks and to stop taking stains if pregnancy a possibility
Women planning pregnancy should stop statins 3 months before they attempt to conceive and not restart them until breast feeding is finished

7. Intolerance of Statins (Appendix 5)
If patient unable to tolerate a high intensity statin aim to treat with maximum tolerated dose

Advise patient that any statin at any dose reduces CVD risk

If patient reports adverse effects from high intensity statin discuss
- stopping statin (6 week washout period) and restarting when symptoms have resolved to see if symptoms related to statin
- reducing dose with same intensity group
- changing statin to lower intensity group

Seek specialist advice about options for treating patients at high risk of CVD who are intolerant of 3 separate statins
Do not offer coenzyme Q10 or vitamin D to increase adherence to statin therapy

8. Other Therapeutic Options

Do not routinely offer
- Fibrates
- Nicotinic Acid
- Bile acid Sequestrants
- Omega 3 Fatty Acids
- Plant Stanols and Sterols

for the prevention of cardiovascular disease to any of the following:
- people being treated for primary prevention
- people being treated for secondary prevention
- people with CKD
- people with Type 1 or Type 2 diabetes

Consider Ezetimibe 10 mg as an option for the treatment of adults with heterozygous familial or non-familial (polygenic) primary hypercholesterolaemia

Consider Ezetimibe in combination with statin therapy
- if Non-HDL or LDL cholesterol target is not reached after appropriate statin dose titration
- if statin dose titration is limited by intolerance to statin therapy
- if LDL ≥ 1.8 mmol/L after NSTEMI / ACS despite maximally tolerated dose of statin

Consider Ezetimibe monotherapy in adults who
- would otherwise be commenced on statin therapy but are unable to do so because of contraindications to initial statin therapy
- are intolerant of statin therapy (see section 7 and Appendix 5)

APPENDIX 1 – SECONDARY CAUSES OF DYSLIPIDAEMIA

Diabetes mellitus / Poor glycaemic control
Hypothyroidism
Chronic kidney disease
Nephrotic syndrome
Cholestatic liver disease
Alcohol excess
Obesity / Diet / Anorexia
Cigarette smoking

Drugs
Beta Blockers
Thiazide diuretics; Loop diuretics (temporary increase)
Oestrogens
Steroids – anabolic steroids and glucocorticoids
Atypical antipsychotics
Anti Depressants - Paroxetine, Sertraline, Venlafaxine, Duloxetine
Anti Epileptics - Carbamazepine, Phenytoin, Phenobarbital
Cyclosporin
Protease inhibitors
Retinoids

APPENDIX 2 – GROUPING OF STATINS

	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%	

20-30% - low intensity

31-40% - medium intensity

>40% - high intensity

Advice from MHRA – there is an increased risk of myopathy associated with high-dose (80 mg) simvastatin

APPENDIX 3 – SIMON BROOME CRITERIA FOR FAMILIAL HYPERCHOLESTEROLAEMIA

Definite Familial Hypercholesterolaemia is defined as:

Total cholesterol > 7.5 mmol/l or LDL-C > 4.9 mmol/l in an adult

Total cholesterol > 6.7 mmol/l or LDL-C > 4.0 mmol/l in a child (< 16 years)
(Levels either pre-treatment or highest on treatment)

Plus

Tendon Xanthomas in
- patient
- 1st degree relative (parent, sibling or child) or
- 2nd degree relative (grandparent, uncle or aunt)

Or

DNA-based evidence of an
- LDL receptor mutation
- Familial Defective Apo B-100 or
- PCSK9 mutation.

Possible Familial Hypercholesterolaemia is defined as:

Total cholesterol > 7.5 mmol/l or LDL-C > 4.9 mmol/l in an adult

Total cholesterol > 6.7 mmol/l or LDL-C > 4.0 mmol/l in a child (< 16 years)
(levels either pre-treatment or highest on treatment)

And at least one of the following

Family history of premature myocardial infarction:
- < 60 years of age in 1st degree relative
- < 50 years of age in 2nd degree relative

Or

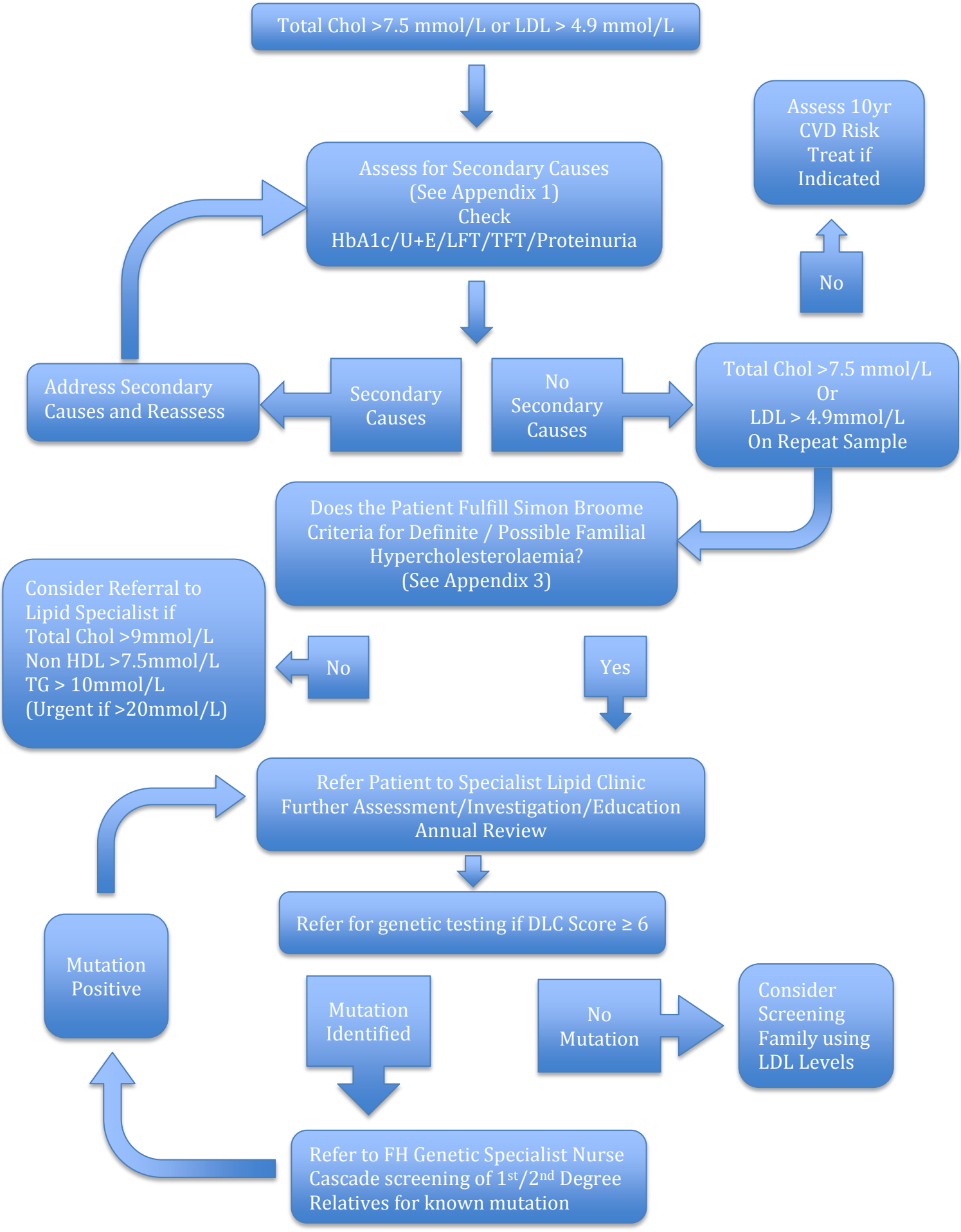
Family history of raised total cholesterol:
- > 7.5 mmol/l in adult 1st or 2nd degree relative or
- > 6.7 mmol/l in child or sibling < 16 years.

Do not use Simon Broome LDL-C criteria for relatives of index individuals with clinical diagnosis of Familial Hypercholesterolaemia because this will result in under diagnosis.

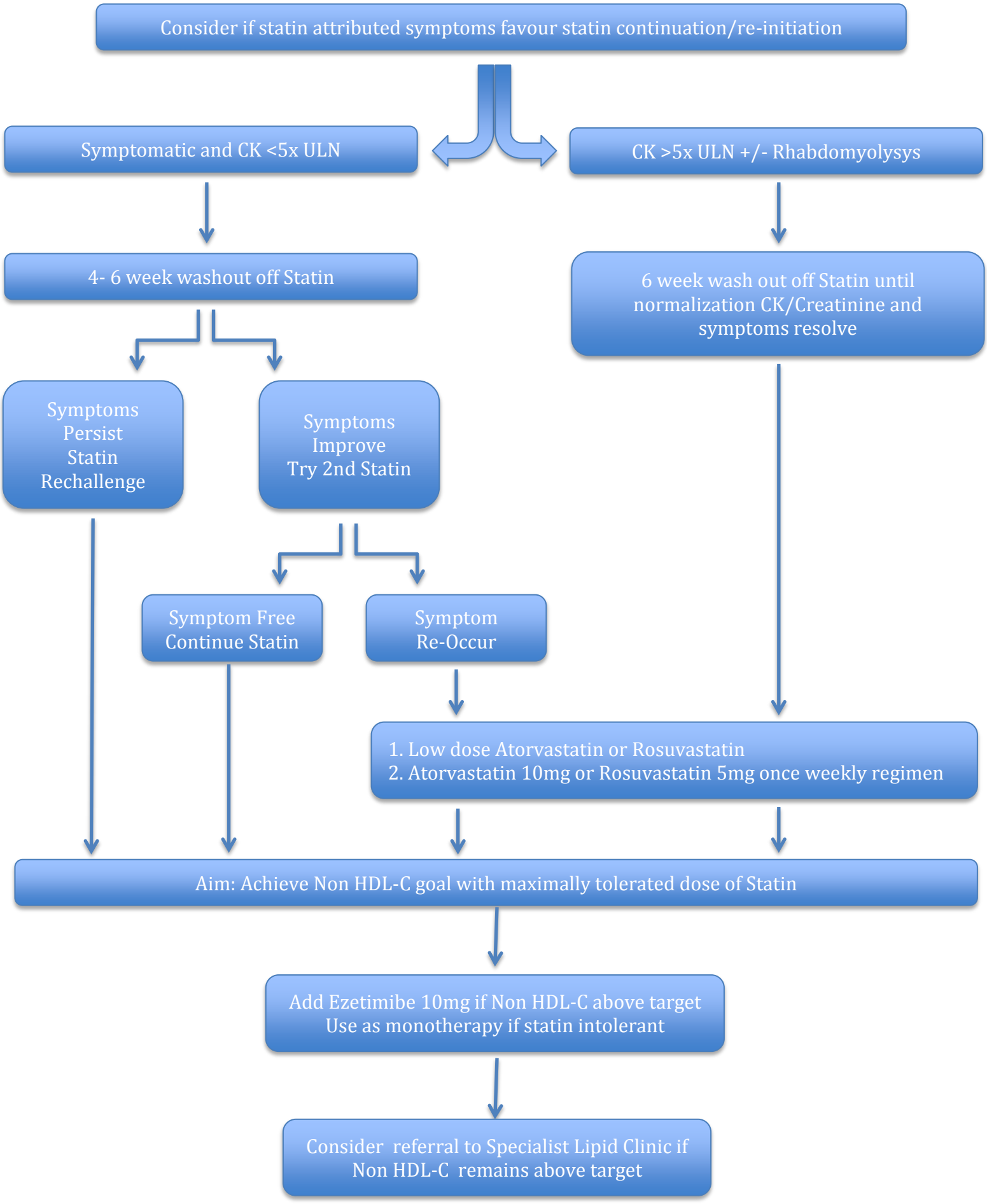
Do not use CVD risk estimation tools as people with Familial Hypercholesterolaemia are already at a high risk of premature coronary heart disease.

Homozygous Familial Hypercholesterolaemia
Consider a clinical diagnosis of homozygous familial hypercholesterolaemia in:
- adults with an LDL-C > 13 mmol/l
- children/young people with an LDL-C > 11 mmol/l.

APPENDIX 4 – PATHWAY FOR PATIENTS WITH SUSPECTED FAMILIAL HYPERCHOLESTEROLAEMIA



APPENDIX 5 – PATHWAY FOR STATIN INTOLERANT PATIENTS



APPENDIX 6 – LIPID CLINIC REFERRAL

Refer to specialist if

- Clinical diagnosis of Familial Hypercholesterolaemia according to Simon Broome criteria (see **Appendix 3**)

- Relatives of patients with FH who may require genetic screening (see **Appendix 4**)

- Children with FH

- Total cholesterol >9 mmol/L or Non-HDL >7.5 mmol/L even if absence of first degree family history of premature heart disease

- triglycerides >10 mmol/L (not due to alcohol or poor glycaemia control) – **refer urgently if triglycerides >20 mmol/L**

- Patients with other inherited disorders of lipid metabolism including Familial Combined Hyperlipidaemia (FCH), Familial Hypertriglyceridaemia (FH) and Remnant Dyslipidaemia

- Patients with non-HDL above target due to intolerance of Statins and/or Ezetimibe

Consider referral of

- Patients at high risk of CVD who are intolerant of 3 separate statins (see **Appendix 5**)

- Patients who do not achieve target lipid levels with first-line lipid-lowering treatment

- Patients for whom it is uncertain whether lipid-lowering therapy is indicated

APPENDIX 7 – COMMON DRUG INTERACTIONS

FOR FULL INFORMATION REFER TO BRITISH NATIONAL FORMULARY
www.bnf.org.uk

Anti-Biotics

Azithromycin	- possible increased risk of myopathy with Atorvastatin and Simvastatin
Clarithromycin	- increases plasma concentration of Atorvastatin - increases plasma concentration of Pravastatin - increased risk of myopathy with Simvastatin – avoid concomitant use
Erythromycin	- reduces plasma concentration of Rosuvastatin - possible increased risk of myopathy with Atorvastatin - increases plasma concentration of Pravastain - increased risk of myopathy with Simvastatin, avoid concomitant use
Daptomycin	- increased risk of myopathy with statins – avoid concomitant use
Fusidic Acid	- risk of myopathy and rhabdomyolysis when given with statins - avoid concomitant use and for 7 days after last dose fusidic acid
Rifampicin	- possibly reduces plasma concentration of Atorvastatin and Simvastatin - metabolism of Fluvastatin accelerated – reduced effect

Anti-Fungals

Fluconazole	- possible increased risk of myopathy with Atorvastatin and Simvastatin - increases plasma concentration of Fluvastatin - possible increased risk of myopathy with Fluvastatin
Itraconazole	- increases plasma concentration of Rosuvastatin, adjust dose of Rosuvastatin - increased risk of myopathy with Atorvastatin - increased risk of myopathy with Simvastatin, avoid concomitant use
Ketoconazole	- possible increased risk of myopathy with Atorvastatin, avoid concomitant use - increased risk of myopathy with Simvastatin, avoid concomitant use
Miconazole	- possible increased risk of myopathy with Simvastatin

Drugs used in HIV

Multiple interactions – seek specialist advice
Consult www.hiv-druginteractions.org

Anti-Coagulants

Coumarins	- anticoagulant effect possibly enhanced by Rosuvastatin - Rosuvastatin possibly enhances anticoagulant effect of Pheninidione - anticoagulant effect enhanced by Fluvastatin - anticoagulant effect can be enhanced by Simvastatin - anticoagulant effect possibly enhanced by Ezetimibe
Warfarin	- anticoagulant effect may be transiently reduced by Atorvastatin

Anti-Arrhythmics

Amiodarone	- increased risk of myopathy when given with Simvatatin - potential for drug interaction to occur weeks/moths after drug stopped
Digoxin	- plasma concentration possibly increased by Atorvastatin

Calcium Channel Blockers

Amlodipine	- possible increased risk of myopathy with Simvastatin; max dose 20 mg
Diltiazem	- increases plasma concentration of Atorvastatin - possible increased risk of myopathy - possible increased risk of myopathy with Simvastatin
Verapamil	- Atorvastatin increases plasma concentration - possible increased risk of myopathy with Atorvastatin - consider reducing dose of Atorvastatin - increased risk of myopathy with Simvastatin

Anti-Platelet Agents

Clopidogrel	- increases plasma concentration of Rosuvastatin; adjust dose of Rosuvastatin
Ticagrelor	- increases plasma concentration of Simvastatin; increased risk of toxicity

Anti-Epileptics

Carbamazepine	- reduces plasma concentration of Simvastatin; consider increasing dose of Simvastatin
Phenytoin	- combination with Fluvastatin may increase concentration of either drug

Oestrogens / Progesterones

Ethinyestradiol	- Rosuvastatin, Atorvastatin increase plasma concentration
Norethisterone	- Atorvastatin increases plasma concentration
Norgestrel	- Rosuvastatin increases plasma concentration

Lipid Lowering Agents

Fibrates	- increased risk of myopathy when given with statins - avoid concomitant use of Atorvastatin / Simvastatin and Gemfibrozil - preferably avoid concomitant use of Fluvastatin / Ptravastatin with Gemfibrozil - possible increased risk of myopathy with Simvastatin and Bezafibrate - reduce maximum dose of Fenofibrate when given with statins - increased risk of cholelithiasis and gallbladder disease when given with Ezetimibe – discontinue if suspected
Ezetimibe	- increases plasma concentration of Rosuvastatin; adjust dose of Rosuvastatin
Nicotinic Acid	- increased risk of myopathy when given with statins

Others

Antacids	- absorption of Rosuvastatin reduced by antacids - antacids should not be taken at same time
Ciclosporin	- increased risk of myopathy with Rosuvastatin, Atorvastatin, Fluvastatin, Simvastatin and Pravastatin - avoid concomitant use with Rosuvastatin and Simvastatin - max dose Atorvastatin 10mg daily
	- plasma concentration of both drugs may increase when given with ezetimibe
Colchicine	- possible increased risk of myopathy with statins
Glibenclamide	- plasma concentration possibly increased by Fluvastatin
Grapefruit Juice	- possibly increases plasma concentration of Atorvastatin - increases plasma concentration of Simvastatin; avoid concomitant use
Imatinib	- increases plasma concentration of Simvastatin
Midazolam	- Atorvastatin possibly increases plasma concentration
Ranolazine	- increases plasma concentration of Simvastatin
St John's Wort	- reduces plasma concentration of Simvastatin