



Prescribing Points

A NEWSLETTER FOR ALL HEALTH CARE PROFESSIONALS IN OXFORDSHIRE, WRITTEN BY THE MEDICINES MANAGEMENT TEAM, OXFORDSHIRE PCT, JUBILEE HOUSE, OXFORD BUSINESS PARK SOUTH, OXFORD, OX4 2LH.

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Inside this issue:

<i>NICE Dementia Guidance</i>	1
<i>Dalteparin prescribing in Primary Care</i>	
<i>Atrial Fibrillation in Primary Care</i>	3
<i>Hypertriglyceridaemia in Primary Care</i>	

NICE Guidance on Drug Treatment in Alzheimer's Disease

A NICE review and re-appraisal of [donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease](#) has resulted in a change in the [dementia guidance CG42](#).

NICE technology appraisal TA217 has introduced the following changes:

- The three acetylcholinesterase (AChE) inhibitors*(donepezil, galantamine and rivastigmine) are now recommended as options for managing mild as well as moderate Alzheimer's disease. Memantine is now recommended as an option for managing moderate Alzheimer's disease for people who are intolerant to or have a contraindication to AChE inhibitors, and as an option for managing severe Alzheimer's disease.

There is a three month period for adoption of these new recommendations, and therefore this new guidance will take effect in August 2011. The shared care protocol will be updated in the intervening time. Until then **patients with mild disease should only be treated in secondary care and no memantine prescribing should be seen in primary care.**

So What?

Prescribers should not accept shared care referrals in line with the new recommendations until after August 2011.

Dalteparin – Guidelines for Prescribing in Primary Care

Historically patients requiring subcutaneous anticoagulation have received treatment through specialists and the acute sector. Concerns have been expressed at the increasing requests for prescribing in primary care and the lack of information or guidance to support prescribers. The following guidance has been agreed with the ORH in attempt to clarify these issues giving information for various indications including:

- Dosage
- Monitoring requirements
- Duration of treatment
- Shared Care arrangements

The [full Oxfordshire guidance](#) is available at www.oxfordshirepct.nhs.uk. A quick reference summary table is also enclosed overleaf.

Traffic Light Classifications for Dalteparin Prescribing in Primary Care

Yellow —Suitable for shared care, in line with guidelines	<ul style="list-style-type: none"> • DVT in patients with cancer, • significantly subtherapeutic INRs within one month of acute VTE, • dalteparin for Intra-venous drug users • pregnant women with a high risk of VTE (initial doses only whilst referral to a specialist is processed)
Red —Specialist prescribing only, in line with guidelines	<ul style="list-style-type: none"> • peri-operative anti-coagulation, • extended thrombophlebitis, • prophylaxis in intermediate risk pregnancy, postpartum patients
Brown —Prescribe only in restricted circumstances, in line with guidelines	<ul style="list-style-type: none"> • long haul flight prophylaxis
Green —suitable for primary care prescribing in line with guidelines	<ul style="list-style-type: none"> • DVT patients – first dose only when outside DVT clinic hours (as per DVT LES), • patients with superficial thrombophlebitis

Dalteparin – Guidelines for Prescribing in Primary Care

Quick Reference Summary:

Indication	Dose		Duration
dateparin for sub-therapeutic INRs	Body Weight (kg)	Dose (units)	Until therapeutic levels are reached. Three doses would be appropriate to be prescribed in first instance, as most patients should reach therapeutic levels within this time.
	<46	7 500	One initial dose only where patient presents outside of (or near to) VTE clinic opening hours.
DVT patients:	46-56	10 000	
	57-68	12 500	
	69-82	15 000	
	83-120	18 000	
	>120	100 units / kg twice daily	
DVT in patients with cancer	Dose dependent on weight, full treatment dose as per table above for 1st month (provided by secondary care) and then the dose reduced to the pre-filled syringe in the band below, i.e. to approx 75-80% of full dose (table below shows dose from month 2 onwards)		Secondary care will provide first month of treatment. Specialist review to be carried out at 6 months to decide on subsequent treatment.
	Months 2-6:		
	Body Weight (kg)	Dose (units)	
	Less than or equal to 56	7 500	
	57 to 68	10 000	
	69 to 82	12 500	
	83 to 98	15 000	
	Greater than or equal to 99	18 000	
INDU patients:	Sufficient written info should be provided alongside the TTO specifying full details around the dose, duration, reviews etc		
Patients with superficial thrombophlebitis:	dateparin 5000 units sc od		Treatment should continue until pain and redness have settled (usually within 4 weeks)
Prophylaxis in pregnancy	High risk patients (specified on page 8): Weight <50kg 2500u od Weight 50-90kg 5000u od Weight 91-130kg 7500u od Weight 131-170kg 10000u od Weight >170kg 75u/kg od		Treatment for high risk patients should begin as soon as possible after positive pregnancy test and be continued until the patient attends their first appointment with the specialist, at which stage secondary care will assume responsibility for continued treatment. Referral for high risk patients (specified on page 8) should be marked as urgent.
Long haul flight prophylaxis	dateparin 5000 units sc od		Dalteparin should only rarely be recommended for this indication.

Guidelines for the management of AF in Primary Care

Local guidelines for the management of AF in primary care have been developed with the ORH and approved by APCO. In a patient with AF consider both risk of stroke and rate control.

Key messages:-

- Atrial fibrillation is directly responsible for 14% of all strokes. Paroxysmal AF carries the same risk as persistent AF.
- *Appropriate* anticoagulation is an important early consideration. Warfarin is currently underused in the treatment of AF.
- Use CHADS₂ score for assessment of stroke:

CHADS2 item	Points	Total Score	Risk of Stroke	Antithrombotic Therapy Indicated
Congestive Heart Failure	1	0	Low	Nothing (pref) or Aspirin
History of Hypertension	1			
Age greater than 75yrs	1			
Diabetes	1	1	Moderate	Warfarin (pref) or Aspirin
Prior Stroke or TIA	2	2 or more	High	Warfarin

- In the over 75s the bleeding risks with aspirin and warfarin are similar.
- In the over 65s rate control is a reasonable initial strategy for patients with mild or no symptoms. Aim for a resting heart rate <100bpm.
- Recommended drugs for rate control are beta-blockers (bisoprolol) or non-dihydropyridine calcium channel blockers (verapamil, diltiazem). Digoxin may be used as an alternative or second agent.

Guideline for Management of Hypertriglyceridaemia in Primary Care

The [Oxfordshire guideline for Management of Hypertriglyceridaemia in Primary Care](http://www.oxfordshirepct.nhs.uk) is available at: www.oxfordshirepct.nhs.uk

Local guidelines have been developed in order to achieve a consistent approach to raised triglycerides in patients in primary care, and appropriate referral to the Oxfordshire Lipid Clinic.

A wide variation in treatment approaches to raised triglycerides has been observed in primary care in Oxfordshire, as there is currently no national guidance available. This guideline has therefore been developed in line with Oxfordshire Lipid Clinic expert opinion, to aid clinicians in their management of the condition by providing recommendations around diagnosis, treatment and possibly referral.

As debate continues around quantifying the level of risk imparted by raised triglycerides, it is essential that a patient's overall cardiovascular risk and severity of history is used to inform decisions regarding treatment commencement and review. The risks and benefits of raised triglycerides against treatment must be considered in this context. Triglyceride levels should not be considered in isolation. It is therefore recommended that treatment is only considered at triglyceride levels above 3 to 5 mmol/l, depending on background cardiovascular risk. The role of treating secondary causes and addressing lifestyle issues is paramount.

Much of the evidence available for treatments of triglycerides is based on sub-group analyses and secondary endpoints, but there is consistency in the results. This makes absolute recommendations difficult, and therefore a pragmatic approach is required when choosing, initiating and reviewing treatment.

Why treat raised triglycerides?

The role of raised triglycerides in cardiovascular risk has been difficult to assess in the past, with LDL cholesterol considered to be a more significant indicator of risk. There is support of an association between triglycerides and elevated risk in a 26 year study published in 2007. For example, for triglyceride levels above 5mmol/l a hazard ratio for myocardial infarction was found to be 2.4 in men and 5.5 in women. Associated increases in IHD and death were also observed.

High levels of triglycerides above 10mmol/l have long been associated with an increased risk of pancreatitis. The incidence rate of pancreatitis with hypertriglyceridaemia has not been quantified but the condition is sufficiently serious to merit immediate attention. The referral threshold has been set at 10mmol/l, as levels above this become very labile and unpredictable.

Secondary causes and lifestyle changes

Identification and management of secondary causes and appropriate lifestyle interventions are essential for patients with hypertriglyceridaemia. These should be continuously reinforced.

Treatment choices

- A statin has been recommended as the first line drug of choice as it confers an overall reduction in CV risk, and also shows a modest lowering of triglycerides in many patients.
- Fibrates have also been recommended within the guideline as there is good evidence of improved patient oriented outcomes in analyses of subgroups of hypertriglyceridaemic patients in major studies. Cardiovascular event reduction ranges from 27% to 71% (relative risk reductions) in these analyses, suggesting numbers needed to treat in the range of 10 to 20. These studies provide consistent evidence in high-risk patients (type 2 diabetes and secondary prevention); the situation is less clear for the general population. The FIELD study suggests that side effects are encountered in less than 1% of fibrate patients and possibly only 0.12% are associated with myopathy. Ensure creatine kinase and liver function tests are carried out before initiating a fibrate, and again after 8 weeks. Regular monitoring is particularly important if prescribing the combination of a statin with a fibrate. If you are concerned about prescribing combination therapy, consult the Lipid Clinic for advice.
- Omega-3-acid has been included as it is a well tolerated option. Although there is evidence of a reduction in CHD events with lower doses, there is an absence of evidence for patient oriented outcomes with triglyceride lowering doses (2g twice daily).
- Nicotinic acid has been shown to be effective at lowering triglycerides. There is mixed evidence around patient oriented outcomes but there is meta-analysis evidence to suggest that nicotinic acid may reduce MI and stroke by approximately 25%. It has tolerability issues, however, which makes it an option only after trying a fibrate in patients with high CV risk.

In most cases, patients with high levels of triglycerides will be identified incidentally following a lipid profile ordered for other reasons.

Diagnosis of patients

If a patient's original lipid profile was determined on a sample taken during a non-fasting state, recall the patient and order a fasting lipid profile. Caution is required when interpreting triglyceride levels as they are very susceptible to recent lifestyle and dietary effects.

Primary hypertriglyceridaemia

Some types of hypertriglyceridaemias have a more or less well-defined molecular basis and are therefore denoted primary hypertriglyceridaemias. Primary hypertriglyceridaemias tend to be more severe than secondary causes.

The types of primary hypertriglyceridaemia are:

- familial hypertriglyceridaemia
- familial combined hyperlipidaemia
- familial dysbetalipoproteinaemia
- lipoprotein lipase deficiency/apolipoproteinase CII deficiency

All of these types of hypertriglyceridaemias will be aggravated by the presence of secondary causes. The first three are high risk syndromes for CV disease. The fourth conveys a very high risk of pancreatitis but is rare.

Secondary hypertriglyceridaemia

Secondary hypertriglyceridaemia is much more common than primary hypertriglyceridaemia:

Common secondary causes of hypertriglyceridaemia are:

- **hypothyroidism**
- **diabetes/impaired glucose tolerance**
- **excessive alcohol consumption**
- obesity
- smoking
- liver disease
- kidney disease
- drugs

A number of rarer causes also exist.

A patient may have more than one secondary cause of hypertriglyceridaemia, and some of the causes are, in themselves, factors that increase the risk of cardiovascular events.

The extra pressure of another stressor such as an infection, excess alcohol, or pregnancy can exacerbate both primary and secondary cases of hypertriglyceridaemia.

Request a lipid profile in patients with stigmata of high triglycerides, such as eruptive xanthomata, as they are more likely to have a primary hyperlipidaemia and referral to a lipid specialist may be necessary.

Physical examination of any patient with increased levels of triglycerides should include the following:

Physical examination

- waist circumference
- body mass index (BMI)

- blood pressure
- lipid stigmata (e.g. eruptive and palmar xanthomata)
- ankle oedema

Laboratory investigations

For any patient with increased levels of triglycerides, the following laboratory investigations should be ordered:

- urine dipstick test (protein could indicate nephrotic syndrome; glucose could indicate diabetes)
- fasting lipid profile
- fasting blood glucose
- liver function tests (LFTs)
- renal function tests (RFTs)
- thyroid function tests (TFTs)
- creatine kinase (especially if you are considering prescribing a fibrate with or without a statin)

Be aware that very high levels of triglycerides can lead to a falsely low sodium measurement.

Management

The management of hypertriglyceridaemia is multifaceted, involving a combination of lifestyle changes, risk factor modification, and drug therapy.

For the purposes of management, patients can be divided into five categories:

- isolated hypercholesterolaemia (increased levels of LDL cholesterol only)
- combined hypercholesterolaemia and hypertriglyceridaemia (increased levels of LDL cholesterol and triglycerides) in secondary prevention and high risk patients
- combined hypercholesterolaemia and hypertriglyceridaemia in primary prevention low risk patients
- isolated hypertriglyceridaemia (increased levels of triglycerides with relatively normal levels of cholesterol) in primary prevention low risk patients
- isolated hypertriglyceridaemia in secondary prevention or high risk patients

The management of each is considered separately below.

If you are unfamiliar with any of the drugs mentioned in this guideline, refer to the individual summary of product characteristics before prescribing.

Please refer to the [Oxfordshire PCT Statin Guidance](#) before initiating treatment.

It is not always necessary to refer a patient for an appointment at the Lipid Clinic. It may be possible to offer advice by email (see appendix A), providing full details are available.

Isolated hypercholesterolaemia

Refer to the NICE guidelines on [lipid management \(CG 67\)](#) and [familial hypercholesterolaemia \(CG71\)](#).

Combined hypercholesterolaemia and hypertriglyceridaemia in secondary prevention or high risk patients **OR** Isolated hypercholesterolaemia in secondary prevention or high risk patients:

Family history and high risk patients

High risk is defined as an absolute CVD risk of 20% or more over 10 years. QRISK2 is the Oxfordshire recommended risk assessment tool. Other high risk groups include patients on long-term antipsychotics, those with rheumatoid arthritis, erectile dysfunction or with systemic lupus.

Control secondary causes and make lifestyle changes:

excessive alcohol consumption; reduce alcohol intake or abstain completely when possible

obesity; reduce waist circumference, optimise BMI, reduce total calorie intake, pay more stringent attention to a low-fat diet
smoking; stop smoking (as part of general measures to achieve reduction in cardiovascular risk)

increase physical activity

hypothyroidism

diabetes/impaired glucose tolerance

liver disease

other drug treatments that increase triglyceride levels; consider alternative medications that are less likely to increase triglycerides if the patient's condition allows

modify diet; eat at least two portions of fish per week, including one portion of oily fish

Advice on lifestyle changes should be instigated in any patient with hypertriglyceridaemia and reinforced at every opportunity

Treatment:

The approach to management can be stratified according to the extent of hypertriglyceridaemia:

- Patients with levels up to 10 mmol/l initially can be managed within primary care.
- Patients with levels higher than 10 mmol/l require more specialist care due to the high risk of acute pancreatitis and should be referred to the Lipid Clinic.
- Although often common practice to aim for a triglyceride level <1.7 mmol/l, achieving levels between 3 to 5 mmol/l is realistic for many in this category.

Combined hypercholesterolaemia and hypertriglyceridaemia in primary prevention low risk patients OR Isolated hypertriglyceridaemia in primary prevention low risk patients**Control secondary causes and make lifestyle changes:**

Control secondary causes (see above).

Advice on lifestyle changes should be instigated in any patient with hypertriglyceridaemia and reinforced at every opportunity (see above).

Treatment

The approach to management can be stratified according to the extent of hypertriglyceridaemia.

- Patients with levels up to 10 mmol/l initially can be managed within primary care.
- Patients with levels higher than 10 mmol/l require more specialist care due to the high risk of acute pancreatitis and should be referred to the Lipid Clinic.
- Although often common practice to aim for a triglyceride level <1.7 mmol/l, achieving levels of 5 mmol/l is realistic for many in this category.

Throughout the management and treatment in low risk patients the risk/benefit and concordance issues should be reviewed. This should inform decisions in management, including whether to commence or continue treatment.

Special circumstances for referral

- Primary (familial) hypertriglyceridaemia. Please refer to [NICE CG 71](#), appendix E for the Simon Broome Criteria.
- Patients with triglyceride levels <10mmol/l but who have high CVD risk and do not achieve any lipid target, despite following recommended management and treatment (NICE CG67 and CG87, Oxfordshire Statin Guidelines and Oxfordshire Guidelines for Management of Hypertriglyceridaemia in Primary Care).
- Treatment failure in primary care (a minority of patients with very high levels of triglycerides may require plasmapheresis).
- Pregnancy: high triglycerides on treatment prior to pregnancy, hypertriglyceridaemia identified during pregnancy – please refer to Obstetrics, Women's Centre, John Radcliffe Hospital.
- HIV: pharmacological intervention leading to increase in triglycerides.
- Increased creatine kinase: due to any muscle disease, induced by drugs such as lipid-lowering drugs.
- LFT abnormalities: increase in transaminase activity to greater than three times the upper limit of normal.

Referral to the Lipid Clinic in OCDEM (Churchill Hospital)

It is not always necessary for the patient to be seen in the patient in the Lipid Clinic. With a clear description of the patient (see info suggested below) the clinic are happy to provide advice via email. This approach can avoid unnecessary appointments.

Clinical lead: Prof Fredrik Karpe (Fredrik.Karpe@nhs.net)

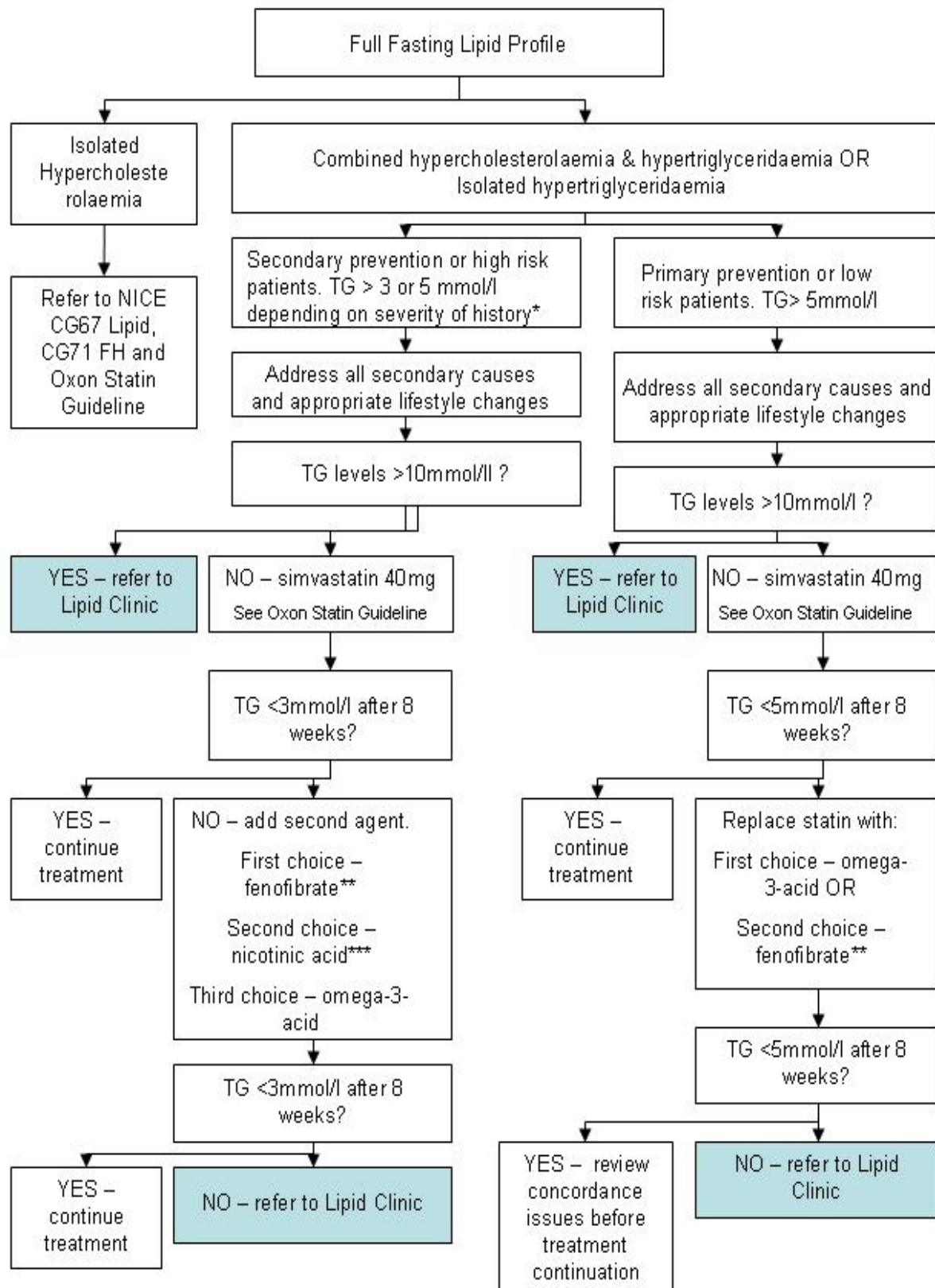
Patient information

Age, Gender, BMI/waist, Family history for cardiovascular and if available lipid phenotypes, Medication, Concomitant disorders, Alcohol/Smoking, Lipid management history

Lab

Fasting lipid profile (total cholesterol, triglycerides and HDL-C), FBG, LFT, TSH, HBA1c (if diabetic)

Algorithm for the Management of Hypertriglyceridaemia



Control of secondary causes and lifestyle changes should be reinforced throughout treatment.

*Severity of history should consider a patient's overall risk as well as early age of onset (eg < 40yrs) and levels of other lipids.

**Check creatine kinase and LFTs before fibrate initiation and repeat after 8 weeks.

***In diabetic patients nicotinic acid may raise HbA1c and glucose levels.

A template for referral to the Lipid Clinic is attached in appendix A.

- If there are concerns about prescribing the combination of a statin plus a fibrate, consult the Lipid Clinic for advice.