

FATS3

A district wide strategy for the use of cholesterol lowering drugs in Newcastle and North Tyneside

A summary of the evidence to develop FATS3 from FATS2

This should be read in conjunction with the new laminated summary

FATS Steering Group June 2002

FATS3 : 2002

- *This is a lipid lowering drug strategy which should only be used within an overall lifestyle and clinical management strategy*
- *It is assumed that people with contraindications will be identified and excluded (refer to the BNF)*

This should be used with the supporting documentation

People with symptomatic or prior occlusive vascular disease or people ≥ 40 years with Type 2 diabetes

- Measure total cholesterol, HDL cholesterol and triglycerides
- Measure ALT/AST
- If ALT/AST < 2 fold normal, prescribe simvastatin 40 mg nocte
- Monitoring: Cholesterol at 8-12 weeks initially
Cholesterol at least annually thereafter

Notes:

1. If total cholesterol > 8.0 mmol/l, triglycerides > 4.5 mmol/l, or ALT/AST > 2 x normal - treat individually, consider discussion with local advisor (see supporting notes for tel.); Newcastle; fatsinfo@nuth.northy.nhs.uk North Tyneside; paul.mckenna@northumbria-healthcare.nhs.uk
2. Consider secondary causes of hyperlipidaemia – alcohol / thyroid / diabetes / nephrotic syndrome
3. Simvastatin potentiates warfarin – initiate 3 - 5 days before INR check
4. Consider initiating at lower dose if potential for interactions with concomitant medication, especially in significant renal impairment
5. Review if cholesterol falls less than 1 mmol/l, or cholesterol on treatment is ≥ 5 mmol/l (see supporting notes)
6. If considering the metabolic syndrome measure fasting glucose and triglycerides (see ‘primary prevention’ and supporting notes)

High risk people not with symptomatic or prior occlusive vascular disease nor aged ≥ 40 years with Type 2 diabetes

FATS advice is based **on risk** not **cholesterol**

In people at high risk of developing vascular disease

- Measure total and HDL cholesterol, triglycerides (non fasting acceptable)
- Estimate 10 year CHD risk from coronary risk prediction chart
- If confirmed female menopause < 45 years treat as male in the charts
- Consider other additional risk factors:
 - Family history of premature CHD (men < 55 yrs, women < 65 yrs)
 - LVH on ECG (if not already included)
 - South Asian raceIf 1 other additional risk factor, double estimated 10 year CHD risk
If 2 other additional risk factors, treble estimated 10 year CHD risk
- If metabolic syndrome ie 3+ of the following factors;
 - Central obesity ie waist > 40 in (100 cm) men, > 35 in (90 cm) women
 - HDL cholesterol < 1.0 mmol/l (men), < 1.2 mmol/l (women)
 - Fasting triglycerides > 2.0 mmol/l
 - BP > 130/85 mmHg
 - Fasting glucose > 6.0 mmol/lwill benefit from intensive therapeutic lifestyle interventions (see supporting notes)
- Consider drug treatment if 10 year CHD risk $\geq 30\%$ and or microalbuminuria/proteinuria in people with Type 1 diabetes
- If considering drug treatment measure fasting lipid profile for accurate HDL cholesterol and triglycerides, and ALT/AST
- Drugs, monitoring and notes: see under ‘People with symptomatic or prior occlusive vascular disease or Type 2 diabetes’

FATS3 developed in the light of new evidence and monitoring of FATS1&2
FATS4 will be developed in the light of new evidence and progress with FATS3
Agreed with Public Health, and Primary and Secondary Care Users

FATS3

Introduction

FATS is the Newcastle and North Tyneside strategy to guide prescribing of lipid lowering drugs. The aim is to offer a pragmatic, extensively discussed strategy based on up to date evidence. FATS is a drug treatment strategy, but must be considered as part of an overall treatment strategy for the intended recipients of the drugs. As new evidence is published FATS has been reviewed, and revised if appropriate, and this is its third iteration. The main reason for FATS2 being reviewed to develop FATS3 is the results of the Heart Protection Study¹, a study of cholesterol lowering with simvastatin in 20,536 high-risk individuals.

These notes are intended to support the revisions made to FATS2 and should be read in conjunction with the new laminated summary and the summary of the research evidence for FATS2. The statements in the laminated summary are highlighted in boxes in these notes. Information in the summary of the research evidence for FATS2 has not generally been duplicated here.

Revisions in FATS3 compared to FATS2 are mainly in the following areas:-

- FATS3 acknowledges the publishing of new evidence and the now robust evidence that simvastatin reduces ischaemic stroke and all ischaemic vascular events as well as coronary events in people with any form of symptomatic or prior occlusive vascular disease or in people aged ≥ 40 years with Type 2 diabetes.
- There are two sections in FATS3; the first outlining treatment in people with symptomatic or prior occlusive vascular disease or people ≥ 40 years with Type 2 diabetes and the second outlining treatment in people not with symptomatic or prior occlusive vascular disease nor aged ≥ 40 years with Type 2 diabetes, and includes those with Type 1 diabetes.

MRC/BHF Heart Protection Study

More detailed information about the guidance in FATS3 is given below, but firstly the results of the Heart Protection Study (HPS) are summarised.

The study was funded by the Medical Research Council (MRC), the British Heart Foundation (BHF), MSD and Roche. The respective pharmaceutical companies provided simvastatin and the vitamins. The results were analysed independently of any pharmaceutical company.

HPS recruited people:-

¹ Heart Protection Collaborative Group Lancet 2002;360:7-22

At increased risk of coronary heart disease (CHD) death due to one or more of the following;

- History of myocardial infarction (MI) or other CHD
- History of other vascular disease (cerebro-vascular, carotid and peripheral)
- Diabetes mellitus
- Hypertension in men aged at least 65 years

Age 40 - 80 years

Total cholesterol > 3.5 mmol/l

Randomisation felt to be appropriate by the doctor

There was no cut off triglyceride level above which patients could not be randomised (although the patient's doctor could elect that the patient was not randomised).

People were excluded if the ALT was 1.5 fold or more above normal, creatinine kinase was 3 fold or more above normal or creatinine was > 200 umol/l.

The study was a factorial design with simvastatin 40 mg daily vs placebo and vitamins vs placebo.

The main outcome measures were;

- Total CHD (non-fatal MI and CHD death)
- Stroke (fatal and non-fatal of any aetiology, including subarachnoid haemorrhage)
- Revascularisation (coronary, carotid, peripheral)
- Major vascular events (total CHD, stroke and revascularisation)

Results of HPS

There was no benefit (or harm) from the vitamins.

10,269 people were randomised to simvastatin 40 mg daily and 10,267 to placebo. Those with non-coronary vascular disease and or diabetes, as well as those with coronary heart disease were well represented, although there were too few with hypertension alone to come to any meaningful conclusions in people with hypertension without vascular disease or diabetes.

There was an average fall in total cholesterol of 1.2 mmol/l and in LDL cholesterol of 1.0 mmol/l with simvastatin compared to placebo.

This led to;

- 17% reduction (7.6% vs 9.1%) in vascular death with no increase in non-vascular death
- 24% reduction (19.8% vs 25.2%) in major vascular events
- 27% reduction (8.7% vs 11.8%) in non-fatal MI and CHD death
- 25% reduction (4.3% vs 5.7%) in stroke of any cause, with the most marked reduction being a reduction in ischaemic stroke

These reductions were consistent in those with and without CHD, and in those with LDL cholesterol above and below 3 mmol/l, and irrespective of age and gender, or the presence of diabetes.

The absolute risk reduction in major vascular events from treatment with simvastatin 40 mg daily was;

- 2,033 (19.8%) vs 2,585 (25.2%) in the study population NNT 19
- 598 (17.7%) vs 756 (22.2%) with a baseline LDL < 3.0mmol/l NNT 22
- 1,435 (20.9%) vs 1,829 (26.7%) with a baseline LDL ≥ 3.0mmol/l NNT 17
- 690(23.6%) vs 829 (28.7%) if age ≥ 70 years NNT 20
- 367 (14.4%) vs 450 (17.7%) if female NNT 30
- 325 (33.4%) vs 381 (37.8%) if diabetes and prior CHD NNT 23
- 276 (13.8%) vs 367 (18.6%) if diabetes and no prior CHD NNT 21

The relative risk reduction was similar in the three sub groups with triglycerides less than 2.0 mmol/l; equal to, or greater than 2.0 mmol and less than 4.0 mmol/l; and greater than 4.0 mmol/l.

The benefit of simvastatin was additive to other treatment such as aspirin, beta blockers, and ACE inhibitors, and in people with diabetes, was not effected by diabetes control.

During the study people could be treated with a non-study statin if this was clinically indicated, which later in the study was in addition to the study statin or placebo. More people in the placebo arm were taking a non-study statin at the end of the study than in the simvastatin arm. The average difference in total and LDL cholesterol and the differences in outcome from treatment with simvastatin 40 mg daily are expected to be at least those in the study.

There were very few people with a significant rise in ALT or creatinine kinase during follow up; 43 (0.42%) randomised to simvastatin and 32 (0.31%) to placebo had a ALT greater than 4 times the upper limit of normal, and 11 (0.11%) and 6 (0.06%) respectively a creatinine kinase greater than 10 times the upper limit of normal.

NNT of other interventions in comparison with HPS

In summary, in the Heart Protection Study;

- to prevent one major vascular events at 5.5 years – NNT = 19
- to prevent one CHD event at 5.5 years – NNT = 32
- to prevent one cerebro-vascular event at 5.5 years – NNT = 71

The benefits of treatment with simvastatin 40 mg daily in the heart protection study population can be compared with treatments in other patient populations. For example;

Treatment of hypertension in people aged 60 years or more;²

- to prevent 1 cardiovascular event (summed coronary heart disease, cerebro-vascular disease, aneurysm, congestive heart failure and transient ischaemic attack) at 5 years – NNT = 18;
- to prevent 1 CHD event (fatal CHD and non-fatal MI) at 5 years – NNT = 61
- to prevent 1 cerebro-vascular event (fatal and non-fatal stroke) – NNT = 43

² <http://www.jr2.ox.ac.uk/bandolier>

Streptokinase and aspirin in MI to prevent 1 vascular death at 5 weeks³ – NNT = 19

Captopril after acute MI and ejection fraction < 40% to prevent 1 death at 42 months⁴ – NNT = 20

Ramipril after acute MI with heart failure to prevent 1 death at 15 months⁵ – NNT = 17

Exercise, diet and weight reduction in obese people with impaired glucose tolerance to prevent 1 case of diabetes in 3 years⁶ – NNT = 7

Non smoking men aged 61-81 years walking an average of 2 miles per day over 12 years to prevent 1 death⁷ – NNT = 5

Men and women surviving acute MI within last 6 months advised to follow a Mediterranean diet over 27 months to prevent 1 cardiovascular death or non-fatal MI⁸ – NNT = 24

Men surviving an acute MI advised to follow a oily fish diet or to take Maxepa capsules over 2 years to prevent 1 IHD death⁹ – NNT = 27

Costs of simvastatin in HPS

The average follow up in HPS was five and a half years. Simvastatin 40 mg daily at current costs is £29.69 for 28 days treatment, approximately £2129 for five and a half years. Using a NNT to prevent one major vascular event of 18, the direct drug costs per major vascular event saved are approximately £38,322 with current pricing. However, this is not the net cost of treatment which may be substantially lower if one takes account of the reduction in hospital admissions, revascularisation procedures, rehabilitation, and disability.

The direct drug costs are likely to fall when the patent on simvastatin expires in May 2003. It is also worth noting that during each year of study treatment, the surviving patients originally allocated cholesterol-lowering statin therapy did better than those allocated placebo, so the absolute benefits increased with increasing treatment duration. More prolonged treatment than in HPS might produce bigger benefits, with a reduction in the cost per event saved.

³ ISIS2 Lancet 1988;2:349-60

⁴ New England Journal of Medicine 1992;327:669

⁵ Lancet 1993;342:821

⁶ New England Journal of Medicine 2002;346:393

⁷ New England Journal of Medicine 1998;338:94

⁸ de Lorgeril Lancet 1994;343:1454

⁹ Burr et al Lancet 1989;ii:757

FATS3: 2002

- ***This is a lipid lowering drug strategy which should only be used within an overall lifestyle and clinical management strategy***

This is the same as in FATS2 and an overall strategy requires explanation and negotiation with the individual patient. Lifestyle changes (including for example smoking cessation, dietary changes and alcohol reduction, increased physical activity and weight reduction as appropriate), drug therapy and other interventions should be considered.

Patients with symptomatic or prior occlusive vascular disease or people ≥ 40 years with Type 2 diabetes

This is consistent with the recruitment criteria to the Heart Protection Study. People under the age of 40 years with Type 2 diabetes should be assessed and managed individually for cardiovascular risk reduction. It is important to remember that statins are contra-indicated in pregnancy and should only be used in women of child bearing age who do not intend to become pregnant, and following appropriate counselling.

Measure total, HDL cholesterol and triglycerides

This is consistent with FATS2, but there was a consensus to include HDL cholesterol in FATS3. People with low HDL cholesterol are at increased vascular risk and measurement is also needed if a diagnosis of the metabolic syndrome is also being considered. LDL cholesterol may be calculated from this and used if this is preferred. However, it was acknowledged that there would need to be additional patient education if only LDL cholesterol was used as most patients are more familiar with total cholesterol values. Blood can be taken either fasting or non-fasting. However, triglyceride levels are higher in the non-fasting state compared to the fasting state. LDL cholesterol is calculated from total cholesterol, HDL cholesterol and triglycerides and will thus be less accurate from a non-fasting sample. Fasting samples should be obtained if LDL cholesterol is being relied on to make treatment decisions.

Measure ALT/AST

The main purpose of measuring ALT or AST before treatment is to identify people with abnormal results prior to starting drug treatment. If people on a statin are later found to have a raised ALT or AST having had a normal enzyme measurement before treatment, it is possible (although not diagnostic) that the statin could be contributing. This avoids finding people with raised ALT or AST being treated with a statin and not knowing if the abnormality was present before the statin was started. It is recommended that the locally available liver enzyme assay be used.

If ALT/AST < 2 fold normal, prescribe simvastatin 40 mg

Patients with significantly raised ALT were excluded from the Heart Protection Study. It was agreed to use the threshold of > 2 fold normal to make calculation easy. Patients with an ALT/AST > 2 fold normal should be managed individually.

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| <ul style="list-style-type: none">• Monitoring: Cholesterol at 8-12 weeks initially
 Cholesterol at least annually thereafter |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

In the Heart Protection Study patients were not treated to specific targets, but maintained taking simvastatin 40 mg. However, there was a consensus in the group to recommend cholesterol be measured 8-12 weeks after starting treatment and annually (see summary notes). The incidence of raised liver enzymes and creatinine kinase in the Heart Protection was so small that routine monitoring is not recommended unless symptoms develop.

Notes:

1. If total cholesterol > 8.0 mmol/l, triglycerides > 4.5 mmol/l, or ALT/AST > 2 x normal - treat individually, consider discussion with local advisor (see supporting notes for tel.); Newcastle; fatsinfo@nuth.northy.nhs.uk North Tyneside; paul.mckenna@northumbria-healthcare.nhs.uk

Patients with biochemical parameters outside these limits should be managed individually. The local advisor (Dr Neely in Newcastle, Dr McKenna in North Tyneside) can be contacted for advice if necessary using e mail. If telephone discussion is preferred the numbers are;

- Newcastle; (0191) 2824554
- North Tyneside; (0191) 2932546

The steering group noted that if non-fasting triglycerides are greater than 4.5 mmol/l fasting triglycerides should be measured before making any treatment decisions. There are some patients with high triglycerides who respond particularly well to dietary interventions.

2. Consider secondary causes of hyperlipidaemia – alcohol / thyroid / diabetes / nephrotic syndrome

This is the same as in FATS1 and FATS2.

3. Simvastatin potentiates warfarin – initiate 3 - 5 days before INR check

There was a consensus to advise that simvastatin still be used in patients taking warfarin. Patients can be advised to start simvastatin 3 to 5 days before the date of the next INR and a note made in the yellow book that the drug has been started. Any adjustments to the warfarin dose can be made when the INR is checked.

4. Consider initiating at lower dose if potential for interactions with concomitant medication, especially in significant renal impairment

People taking fibrates, cyclosporin and niacin (nicotinic acid) were excluded from recruitment to the Heart Protection Study. Patients with significant renal impairment who take a statin are at increased risk of developing myositis and initiation with a lower dose should be considered in these patients.

5. Review if cholesterol falls less than 1 mmol/l, or cholesterol on treatment is \geq 5 mmol/l (see supporting notes)

The protocol of the Heart Protection Study did not treat people to target cholesterol, but used a single dose of simvastatin. However, the FATS steering group recommended that total cholesterol (or LDL cholesterol if that is preferred) be measured after 8 to 12 weeks. If cholesterol falls less than 1 mmol/l from baseline or total cholesterol on treatment is \geq 5mmol/l (LDL cholesterol \geq 3 mmol/l) a medication review should be initiated. This review includes checking compliance with medication and a review of diet and other lifestyle. Patients who fail to reach target cholesterol might be treated with a higher dose of simvastatin (80 mg) and may obtain additional benefit, or alternatively might be maintained on simvastatin 40 mg in line with the protocol of the Heart Protection Study. This should be negotiated between the patient and clinician. The FATS steering group felt it was important to emphasise that the effect of doubling the dose of any statin was not to double the cholesterol lowering effect, but was substantially lower.

6. If considering the metabolic syndrome measure fasting glucose and triglycerides (see 'primary prevention' and supporting notes)

Further details of the metabolic syndrome are given in the next section. Fasting glucose and triglycerides must be measured if this diagnosis is being considered.

High risk people not with symptomatic or prior occlusive vascular disease nor aged \geq 40 years with Type 2 diabetes

FATS advice is based on risk not cholesterol

In people at high risk of developing vascular disease

- **Measure total and HDL cholesterol, triglycerides (non fasting acceptable)**

This is consistent with the recommendations in FATS2, but there was a consensus to also measure serum triglycerides in FATS3, particularly in those who may have the metabolic syndrome (see below).

- **Estimate 10 year CHD risk from coronary risk prediction chart**

This is the same as in FATS2. Age, gender, blood pressure, smoking status and the presence or absence diabetes are included. Risk increases exponentially with age and, as the person approaches the next age category, their risk will be greater than indicated

by the charts. Charts and an excel programme of the Joint British Societies recommendations were disseminated with FATS2 (the excel programme includes left ventricular hypertrophy on the ECG which the charts do not – see below).

- **If confirmed female menopause < 45 years treat as male in the charts**

Women with a premature menopause are at a higher risk than those of the same age who have not yet reached the menopause. It was agreed an estimate of this increased risk could be made by using the male charts instead of the female charts to estimate coronary heart disease risk. The diagnosis of a premature menopause should be secure (eg typical clinical symptoms, raised FSH).

- **Consider other additional risk factors:**
 - Family history of premature CHD (men < 55 yrs, women < 65 yrs)**
 - LVH on ECG (if not already included)**
 - South Asian race**
 - If 1 other additional risk factor, double estimated 10 year CHD risk**
 - If 2 other additional risk factors, treble estimated 10 year CHD risk**

These three variables which increase risk were included in FATS2 in this way. **Note:** If initial CHD risk is estimated from the computerised version of the charts, left ventricular hypertrophy is already included and should not be included a second time. In the light of experience of implementing FATS2 additional guidance about left ventricular hypertrophy on the ECG is included below.

Other factors (central obesity and microalbuminuria in people with Type 1 diabetes) were also included in FATS2, but are included in a different way in FATS3 (see below).

Left ventricular hypertrophy

In summary;

- Possible ECG-LVH with only voltage criteria for LVH is not associated with a marked excess vascular risk over and above that associated with the raised blood pressure, and should not be included as an additional factor in the risk assessment.
- Definite ECG-LVH with ST flattening or more marked ST / T wave changes as well as increased voltages is associated with a significantly increased risk independent of the raised blood pressure and should be included as an additional risk factor in the risk assessment.
- If the significance of the voltages on an ECG is uncertain, the ECG might be repeated after 2 years looking for progression of ECG changes of LVH and thus an increased risk, particularly if this would lead to a change in treatment.

Background information;

In the Framingham Study the criteria for definite ECG-LVH included, some but not all, of the following:

- an increased R wave amplitude in leads reflecting potentials from the left ventricle associated with S-T segment depression and T wave flattening or inversion;

- deep S waves over the right precordial leads;
- left axis deviation (> -30 degrees); and,
- a slight prolongation (at least 0.05 seconds) of ventricular activation time (ie QRS duration).

Possible ECG-LVH was defined if tracings showed similar abnormalities which were less marked and for which the principal findings included in this category were increased R wave amplitude without prominent ST and T wave abnormalities¹⁰.

After adjustment for blood pressure, vascular risk became markedly attenuated or disappeared in those with possible ECG-LVH. In those with definite ECG-LVH the four fold increased risk was reduced by about 25% after adjustment for blood pressure¹¹.

Patients with the greatest increases in voltages and those with the most marked repolarisation changes are at greatest risk¹². Serial change in voltages and repolarisation changes also predicted future risk, with a reduction associated with a lower risk and an increase with a higher risk¹³.

- **If metabolic syndrome ie 3+ of the following factors;**
Central obesity ie waist > 40 in (100 cm) men, > 35 in (90 cm) women
HDL cholesterol < 1.0 mmol/l men, < 1.2 mmol/l (women)
Fasting triglycerides > 2.0 mmol/l
BP $> 130/85$ mmHg
Fasting glucose > 6.0 mmol/l)
will benefit from intensive therapeutic lifestyle interventions (see supporting notes)

Some people have a combination of risk factors which significantly increase their cardiovascular risk¹⁴. This combination makes up the condition known as the metabolic syndrome and for FATS3 the diagnosis is made when 3 or more of the risk factors are present;

- Excess body fat, particularly abdominal fat – ‘central obesity’. The measurements recommended in FATS3 facilitate them being remembered. For example, 100 cm rather than 102 cm and 90 cm rather than 88 cm. People may be asked during assessment what their waist measurement is from their clothes size, but care should be taken to ensure this truly reflects maximum girth.
- Raised fasting triglycerides – there was a consensus to use > 2.0 mmol/l in FATS3.
- Low HDL cholesterol – there was a consensus to use < 1.0 mmol/l in men and < 1.2 mmol/l in women in FATS3
- Hypertension – BP $> 130/85$ mmHg in FATS3 (using the large cuff if appropriate)
- Impaired fasting glycaemia – fasting glucose > 6.0 mmol/l, but < 7.0 mmol/l (or impaired glucose tolerance)

¹⁰ Kannel WB Ann Intern Med 1970;72:813

¹¹ Kannel WB Ann Intern Med 1970;72:813

¹² Levy D Circulation 1994;90:1786-1793

¹³ Levy D Circulation 1994;90:1786-93

¹⁴ Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-2497

The criteria for diabetes is a confirmed fasting venous plasma glucose ≥ 7.0 mmol/l. Impaired fasting glycaemia is defined as a fasting venous plasma glucose of 6.1 - 6.9 mmol/l. Impaired glucose tolerance is diagnosed from a 75 g OGTT - fasting venous plasma glucose < 7.0 mmol/l and 2 hour venous plasma glucose 7.8 - 11.0 mmol/l.

Women who develop gestational diabetes are at increased risk of developing impaired fasting glycaemia and Type 2 diabetes and it is recommended that a fasting plasma glucose is measured annually.

Some people from minority ethnic groups (for example those of Chinese and South Asian origin) are at particular risk of developing impaired fasting glycaemia and diabetes and extra vigilance is required to ensure the diagnosis is excluded in these groups.

Vascular risk factors in people with the metabolic syndrome are usually particularly responsive to intensive therapeutic lifestyle changes which include;

- Reduced intake of saturated fat and cholesterol
- Increased physical activity
- Weight reduction

In non-diabetic people with impaired glucose handling the recent diabetes prevention study¹⁵ reported a 58% reduction in the incidence of diabetes during a mean of 2.8 years with a regimen of exercise and diet compared to normal care. Metformin led to a 31% reduction. Thus, lifestyle intervention was more effective than metformin.

Thus, the approach recommended for specific treatment in people with the metabolic syndrome is one of intensive therapeutic lifestyle changes, alongside appropriate cholesterol lowering drugs and control of hypertension.

PCTs are developing strategies to facilitate intensive therapeutic lifestyle changes to which people motivated to change behaviour can be referred. For example, exercise referral schemes, schemes for the management of overweight and obesity. Clinicians should negotiate with individual people with the combination of risk factors which make up the metabolic syndrome a regimen of intensive therapeutic lifestyle change.

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| <ul style="list-style-type: none">• Consider drug treatment if 10 year CHD risk $\geq 30\%$ and or microalbuminuria/proteinuria in people with Type 1 diabetes |
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This 10 year coronary heart disease (CHD) risk threshold of 30% is that which is currently accepted nationally. It is important to note that risk is a continuum however, and for example, there is little difference between 29% and 30%. The decision not to introduce drug therapy in an individual should be reviewed regularly. With increasing age, the absolute risk of an individual may increase to a level at which drug therapy would be recommended.

¹⁵ NEJM 2002;346:393

There was a consensus that as microalbuminuria and proteinuria in people with Type 1 diabetes is a marker of high vascular risk, these people should be considered for drug treatment.

- **If considering drug treatment measure fasting lipid profile for accurate HDL cholesterol and triglycerides, and ALT/AST**

An estimate of HDL cholesterol and triglycerides can be obtained from a non fasting sample, but a fasting sample will provide a more accurate measurement. ALT/AST is the same as for 'People with symptomatic or prior occlusive vascular disease or people \geq 40 years Type 2 diabetes'.

- **Drugs and monitoring: see under 'People with symptomatic or prior occlusive vascular disease or people \geq 40 years with Type 2 diabetes'**

This is the same as for 'People with symptomatic or prior occlusive vascular disease or people aged \geq 40 years with Type 2 diabetes'.

Notes about use of other statins in FATS3

Information, endorsed by the Drugs and Therapeutic Committee, about the use of different statins was circulated in November 2001 after the withdrawal of cerivastatin. The recommendations about which statin to use remain similar for FATS3.

Simvastatin is the first line statin and now has the additional evidence from the Heart Protection Study to support its use. The safety data from using simvastatin 40 mg daily in the Heart Protection Study is very reassuring.

Pravastatin is included in the formulary and might be considered if there is concern about drug interactions. Pravastatin should also be considered if patients are intolerant of simvastatin (assuming there is no absolute contra-indication to all statins). The only dose of pravastatin shown to be effective to date is 40 mg daily. Higher dose titrations are not recommended and if target cholesterol is not reached it is necessary to switch to an alternative statin with more potent cholesterol lowering effects.

Atorvastatin is retained on the formulary as an alternative statin, starting at 10 mg daily and up titrating to 80 mg daily. There is less clinical outcome data with atorvastatin and it is recommended that this is reserved for people who do not respond to optimising the doses of other statins and lifestyle interventions, or if advised by specialist care. The FATS steering group did not feel that atorvastatin had any particular advantages for people with marked hypertriglyceridaemia compared with the other statins.

A table outlining the current costs of the recommended statins is enclosed. The patent for simvastatin expires in May 2003 and a significant fall in price is anticipated thereafter although no details are yet available. It is important to remember that it costs twice as much to prescribe any statin twice daily (or as two lower dose tablets) and is no more effective. For example, simvastatin 20 mg twice daily or simvastatin 20 mg two tablets daily costs twice as much as simvastatin 40 mg one tablet daily.

Costs of statins and percentage cholesterol reduction

Statin	Dose	Mean reduction in total cholesterol	Mean reduction in LDL cholesterol	Cost 28 days (MIMS May 2002)
Simvastatin	40 mg daily	30%	41%	£29.69
	80 mg daily	37%	48%	£29.69
Pravastatin	40 mg daily	24%	34%	£29.69
Atorvastatin	10 mg daily	28%	38%	£18.03
	20 mg daily	35%	46%	£29.69
	40 mg daily	40%	51%	£29.69
	80 mg daily	42%	54%	£29.69

APPENDIX

Membership of the FATS steering group

Dr I Spencer, Director of Clinical Governance, Northumberland, Tyne and Wear Health Authority (stood down as chair of the FATS steering group, May 2002)
Dr JS Skinner, Consultant Community Cardiologist, Royal Victoria Infirmary
Dr PC Adams, Consultant Cardiologist, Royal Victoria Infirmary
Dr S Blades, GP and Newcastle PCT PEC Chair, The Grove, Gosforth
Dr S Blair, GP, Village Green Surgery
Dr JP Bourke, Consultant Cardiologist, Freeman Hospital
Dr JC Doig, Consultant Cardiologist, North Tyneside Hospital
Dr AS Gandy, GP, North Shields
Dr I Haq, Consultant Cardiologist, Royal Victoria Infirmary
Dr E Harrison, GP, New York Surgery, North Shields
Prof P Home, Consultant Physician, Freeman Hospital
Dr MF Laker, Consultant in Clinical Biochemistry, Royal Victoria Infirmary
Dr P McKenna, Consultant Chemical Pathologist, North Tyneside Hospital
Dr E Milne, Consultant in Public Health Medicine, Newcastle and North Tyneside Health Authority (resigned from FATS steering group May 2002)
Dr D Neely, Consultant in Clinical Biochemistry, Royal Victoria Infirmary
Dr SH Roberts, Consultant Physician, North Tyneside Hospital
Deb Stone, Dietician, Healthy Hearts, North Tyneside Hospital
Dr S Thomas, Consultant Physician, Freeman Hospital
Mr G Trueman, Formulary Pharmacist, Freeman Hospital
Dr M Walker, Consultant Physician, Metabolic Office, Royal Victoria Infirmary
Dr Graeme Wilkes, GP, Prospect House, Newcastle
Dawn Solomon, Pharmaceutical advisor, Newcastle PCT
Clive Edwards, Pharmaceutical advisor, North Tyneside PCT
Tim Donaldson, Pharmaceutical advisor, Benfield Road
Dr Gillian Hawthorne, Consultant Community Diabetologist, Diabetes Resource Centre, NGH
Dr Nick Lewis-Barned, Consultant Physician, North Tyneside Hospital
Dr Trevor White, GP, Falcon House Surgery, Newcastle
Dr Andrew Chalmers, GP, Beaumont Park, Whitley Bay

Declared conflicts of interest

JSS has received travel grants and honoraria from various pharmaceutical companies that manufacture statins. PCA has received research support, travel grants, consultancy fees and honoraria from pharmaceutical companies that manufacture statins, including MSD the manufacturers of simvastatin, and was a HPS investigator. On behalf of the University of Newcastle PH provides advice to Merck Inc. from time to time. NL-B has received research support, travel grants and honoraria from pharmaceutical companies that manufacture statins and has been involved in original research into statins. ST has received research funding from Pfizer and AstraZeneca. PM was a HPS investigator. SHR was a HPS investigator. ML has until recently been a member of the Merck, Sharp and Dohme Advisory Board, is a member of the safety committee for the CARDS study (a study of atorvastatin), has received travel grants from various companies that make statins, and in the past has received research grants from various pharmaceutical companies, including from two that manufacture statins.