SUMMARY GUIDELINES JUNE 2015

Statin guidance update

Key messages

IHD, stroke, PAD

Start treatment with atorvastatin 80 mg
Use lower dose of atorvastatin if indicated.

Type 2 diabetes ≥10% CVD risk
Type 1 diabetes ≥ 40yrs /10 yrs duration

Start atorvastatin 20mg increasing up to 80mg if other CVD risk factors present.

Established CVD: start with atorvastatin 80mg as above.

Primary prevention (including people >75 years)

Treat with atorvastatin 20mg
(or simvastatin 40mg if already on it)

Prioritise ≥20% CVD risk
Prioritise 10-19% CVD risk + other factors
ie. hypertension, positive FH 1^{O} relative under 60yrs, pre-diabetes or BMI ≥40
In others at 10-19% CVD risk support informed patient preference.

Liver Function Tests

Request one ALT if monitoring for statins
NOT full LFTs

Aim of the guideline

To increase use of atorvastatin 40mg and 80mg in people with CVD or diabetes with CVD risk factors.

To prioritse primary prevention in people with CVD risk 20% or more or in those at 10% or more who have other major risk factors.

To decrease inapproriate use of liver functions tests.

What this guidance covers

The guidance is for adults 18 years and over.

It concerns statins and lipid modification for primary and secondary prevention and routine LFTs.

Statins should not be usd in pregnancy- as there is a teratogenic risk.

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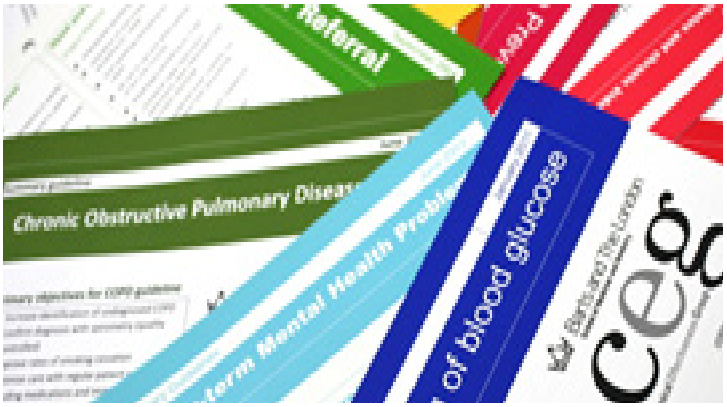
CEG Website

This guideline is available on the CEG website

http://www.blizard.qmul.ac.uk/ceg-home.html



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John Robson and Sotiris Anthoniou compiled the document after extensive stakeholder discussion with GPs, consultants, patients, prescribing advisors, pharmacists and other stakeholders and it was approved by Barts Health NHS Trust & Local CCGs Joint Prescribing Group in March 2015.

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About the guideline

The guidance is for clinicians prescribing and monitoring statin use for both secondary and primary prevention. It is a SUMMARY intended to make the main points. It is not intended to replace NICE guidance or more detailed advice. It is an aid to clinical judgement and individual patient circumstance may lead patients and clinicians to alternative options.

NICE guidance 2014 is reported in **bold**

see NICE website:
www.nice.org.uk/guidance/cg181/resources

All guidance is consistent with NICE 2014 except where stated and local opinion considers some modification is preferable - in particular on liver function tests and also on the need to consider prioritisation of treatment for primary prevention to those at highest CVD risk; including those with a BMI 40 or more, pre-diabetes or positive FH of premature IHD.The use of atorvastatin 40mg rather than 80mg might often be prudent in the very old or frail.

The guideline is a consensus document and does not necessarily represent the views of individual contributors.

The decision to treat

"The decision whether to start statin therapy should be made after an informed discussion between the clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy"
NICE guideline 2014

"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. "
NICE guideline 2014

The guideline stresses the need for lifestyle change and optimising other modifiable risk factors such as blood pressure. The need for increased physical activity has in the past been substantially underestimated in CVD prevention. Even modest increases in activity e.g. walking 20 minutes a day, are important and the more the better. Smoking remains the single most important modifiable risk factor. A diet low in saturated fats (cheese, butter, full fat milk and visible fat on meat) with reduction in sugars (in particular sweet drinks including fruit juice) and alcohol also remain important.

Since the peak of the CVD epidemic in the 1970's rates of CVD have fallen more than threefold. Much of this is due to reduction in smoking, saturated fat and dietary salt. However, atherosclerosis remains one of the major causes of premature death and serious disability including peripheral arterial disease, atrial fibrillation and heart failure as well as stroke and heart attack. Medical treatments account for around half the recent reduction in CVD.

Statins are an important part of that medical intervention along with smoking cessation, blood pressure reduction and support for behavioural change.

Starting statin

Existing statin

Primary Prevention: Atorvastatin 20mg

If on simvastatin 40mg then stay on it

IHD, Stroke/TIA, PAD*
<75 yrs atorvastatin 80mg
≥75 yrs atorvastatin 40mg or 80mg

Secondary prevention: if on simvastatin 40mg change to atorvastatin

Diabetes T1 >10yrs: atorvastatin 20mg
Diabetes T2 > 10% CVD risk: atorvastatin 20mg
Increase atorvastatin dose up to 80mg if other CVD risk factors
ie. BMI >40, FH IHD<60yrs, hyptn **(or if pre-existing CVD as above)**
or non-HDL cholesterol not reduced by 40%.

Renal disease CKD <60 ml/min: atorvastatin 20mg
Atorvastatin 40-80mg if CVD, diabetes, hypertension
but if <30ml/min consult renal specialist about higher dose

*Use highest tolerated statin dose. If lower dose atorvastatin is not tolerated, try a trial of pravastatin 10-20mg, increasing if tolerated to atorvastatin 10mg or more. Record "adverse reaction to statin" with persistent QOF code U60CA (in template).

Recommended high intensity statins are atorvastatin 40mg or 80mg. Where patients are already stable on simvastatin 80mg this may be continued if preferred. In patients already on simvastatin 40mg for secondary prevention, review to uptitrate to atorvastatin 80mg or 40mg if more appropriate.

For primary prevention, where patients are already on simvastatin 40mg this can be continued.
New patients starting on a statin for primary prevention are recommended to use atorvastatin 20mg.

NICE guidance recommends statin treatment for primary prevention in people over 75 years almost **all** of whom have CVD risks of 20% or more, in whom atorvastatin 20mg is approriate.

Statins with CVD

"Start statin treatment in people with CVD with atorvastatin 80 mg. Use a lower dose of atorvastatin if …potential drug interactions; high risk of adverse effects; patient preference."

NICE guideline 2014.

In people with CVD (CHD, stroke, TIA and peripheral arterial disease) high intensity statins (ie. atorvastatin 80mg or simvastatin 80mg,) versus a standard dose, reduce LDL cholesterol by a further 0.5mmol/L, CVD events by an extra 15% and total mortality by a further 5%.

Cholesterol Treatment Trialists Collaboration. Lancet 2010;376:1670-81.

Both 2014 NICE and American guidance now recommend high intensity statins for people with CVD.

Both recommend that targets for lipid lowering are not the best reason to initiate high intensity statins. High intensity statins should be prescribed irrespective of baseline lipid levels.

(Cholesterol levels may continue to be useful to monitor/audit improvement and check adherence).

CVD under 75 years

Start treatment with atorvastatin 80mg

Treat irrespective of serum cholesterol – aim to optimise dose rather than achieve a target.

If 80mg not tolerated use lower dose.

CVD over 75 years

Atorvastatin 40mg is an alternative to 80mg

Some people at older ages may be more susceptible to adverse events so clinicians may prefer to choose either 40mg or 80mg in this age group depending on clinical circumstance.

[Local agreement on atorvastatin 40mg as above]

See *Sniderman. J Clin Lipidology 2012; 6:303-309.*

Atorvastatin 80mg is preferred for people starting statins with CVD under 75 years. Both the MHRA and FDA have safety warnings on simvastatin 80mg as it has more major adverse events. However, there is no need to change people already stable on simvastatin 80mg. People with CVD on simvastatin 40mg should be changed to atorvastatin 40mg or 80mg. Increases in statin dose can take place at the next review after an informed patient discussion.

Statins and diabetes

Type 1 diabetes: diabetes for ≥ 10 years or age ≥40 years or nephropathy.

Start with atorvastatin 20mg. Increase to atorvastatin 80 mg if other risk factors.

Type 2 diabetes: if CVD risk 10% or more.

Start with atorvastatin 20mg.
Increase up to atorvastatin 80 mg if there are other risk factors*.

People with diabetes and CVD should be on atorvastatin 80mg or 40mg.

***Other CVD risk factors** include: positive FH of premature IHD under age 60 years in 1st degree relative, obesity > BMI 40; hypertension, eGFR<60ml/min; microalbuminuria.

NICE recommends increasing statin dose if non-HDL cholesterol is not reduced by 40%. However, this is unlikely to be relevant to most people who will qualify for high intensity statins anyway after an informed discussion at the next review.

Renal disease (CKD=eGFR <60ml/min)

"Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD" *NICE guideline 2014.*

Increase the dose if other major risk factors or 40% reduction in non-HDL cholesterol is not achieved and eGFR is 30 ml/min/1.73m^2 or more. If eGFR <30 ml/min, agree higher doses with a renal specialist.

Statins for primary prevention

High CVD risk of 20% or more:

treat with atorvastatin 20mg
(or continue simvastatin 40mg)

10-19% CVD risk + other risk factors:

treat with atorvastatin 20mg
(or continue simvastatin 40mg)

10-19% CVD risk without major risk factors:

advise statins confer modest benefit and lifestyle change will be beneficial.
Treat if requested.
[local agreement on this wording]

CVD Risk 5% -7.5%

Statins have evidence of benefit for primary prevention in people with a 10 year CVD risk of 5-7.5%. 50-60% population over age 40 have CVD risk above this level.

CVD Risk 10% -19%

Statins have robust evidence of benefit at this level. Statin recommended at 10% CVD risk in NICE 2014 guidance. 30% of the population age > 40 yrs have a risk of 10% or more

CVD Risk 20% or more

This is the level at which statins were previously recommended. 10% of the population age > 40 yrs have a risk of 20% or more.

Annual review

People on statins and those identified at high CVD risk (>20%) should be reviewed annually.

Include lifestyle advice, risk factor assessment including blood pressure, lipids and glycaemic indicators where appropriate.

Strategies for reducing CVD risk

Treating >30% of the adult population at the 10% CVD threshold is not attainable. There are other strategies that can achieve greater benefit: legislation and public health measures would have far bigger impact on CVD from changes in dietary salt, saturated fats, sugars, alcohol and cigarette consumption, air pollution and a built and social environment promoting physical activity.

Two-thirds of the population at high CVD risk of 20% or more are not currently treated through the NHS Health Check programme and it is a priority to improve this.

"Interpretation of CVD risk scores should always reflect informed clinical judgement" *NICE 2104.*

GPs already recognise this and are treating a minority of people in the 10% -19% CVD risk band – usually those with hypertension, obesity, positive family history of premature IHD, pre-diabetes. This is appropriate on a case by case basis.

Statins over 75 years

Rather than extending treatment to people at lower risk at younger ages, there would be considerably greater gain by treating those 75 years and older with a statin. This would have more benefit both for the individual patients and the population as a whole.

Almost everyone over 75 years as a CVD risk of 20% or more.

Consider statins in everyone over 75 years unless clinically inappropriate including people over 85 years.

"For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate" *NICE 2014 Guidance*

Absolute reduction in CVD events

The reduction in CVD events or vascular death depends on the patient's risk. Those at higher risk will have a greater absolute reduction from statin treatment which reduces events by about 25% irrespective of baseline risk. It also depends on the extent to which their cholesterol is reduced.

The figure below shows the numbers of people per 1000 treated with a statin, who will benefit over 5 years; depending on baseline CVD risk and cholesterol reduction.

The figure[3] shows 5 year risks. Most clinicians are used to dealing with 10 year risks.
A 5 year 5 % - <10% CVD risk is equivalent to the new NICE guideline 10 year 10-19% CVD risk.

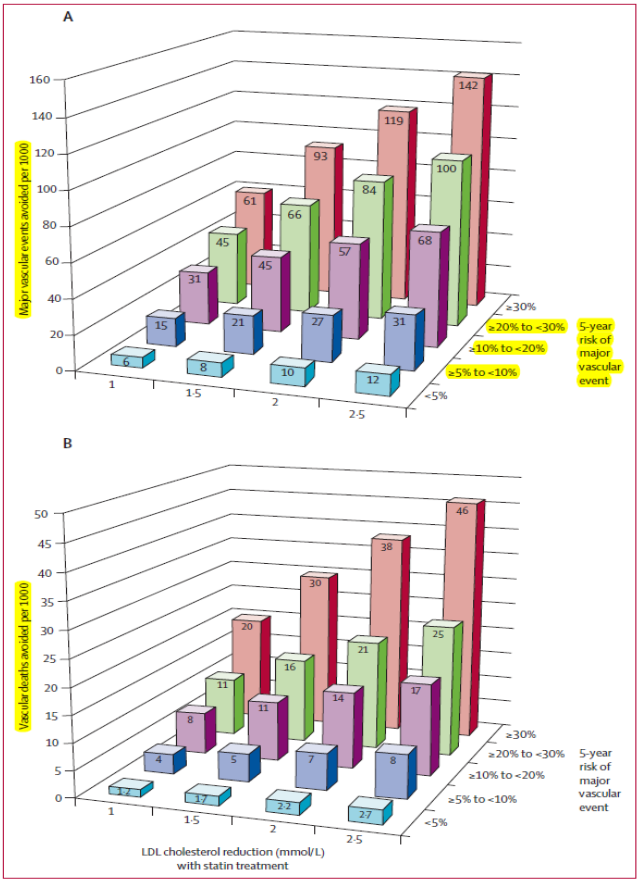

Figure 5: **Predicted 5-year benefits of LDL cholesterol reductions with statin treatment at different levels of risk**
(A) Major vascular events and (B) vascular deaths. Lifetable estimates using major vascular event risk or vascular death risk in the respective risk categories and overall treatment effects per 1·0 mmol/L reduction in LDL cholesterol with statin.

[3]Taken from1 Lancet May 17, 2012 DOI:10.1016.

This data can also be expressed as the number of people who need to be treated with a statin for five years to prevent one CVD event or death .

For example at a 20% or more CVD risk you would need to treat 22 people for five years to pevent one heart attack, stroke or CVD death. And you would need to treat 91 people to prevent a CVD death. At the 10-19% threshold 250 people would need to be treated to prevent 1 CVD death.

This is shown in the table below

Statins for Primary prevention: 5 yr NNT by CVD risk

10 year CVD risk	NNT CVD event	NNT CVD death	Annual CVD events in trials No statins vs statins
≥20%	22	91	5.4% vs 4.4%
10-19%	66	250	1.5% vs 1.0%

Other lipid lowering drugs

NICE recommends that .....

Fibrates: should not be routinely used

Nicotinic acid, omega-3 (fish oil) and anion exchange resins should not be used.

Ezetimibe: Ezetimibe remains an option in NICE TA 132 for primary hypercholesterolaemia or homozygous familial hypercholesterolaemia. It is not licensed for the reduction of cardiovascular events.

Ezetimibe alone or in combination should not be routinely used.

Atorvastatin 40/80mg is likely to be more effective than ezetimibe combined with a lower dose statin.

The IMPROVE-IT trial of ezetimibe + simvastatin 40mg versus simvastatin 40mg in people at very high risk after acute coronary syndrome, reduced combined CVD events by 2% (a 6% relative reduction) achieving significance only after 7 years of use with no reduction in total mortality.

Simvastatin 40mg is now considered a suboptimal dose for established CVD. Atorvastatin 40/80mg is likely to reduce CVD events by a greater extent in a shorter time.

Statins and adverse events

There is a low risk of adverse events with statins. Minor and major adverse events are less frequent than many commonly used drugs such as aspirin, ACE inhibitors, or diabetes medications. The risk is higher in combination with certain other drugs, frail elderly and those with major illness/operation. A fuller list of drug interactions is given in the appendix at the end.

The risk of myopathy, neuropathy or intracranial haemorrhage with atorvastatin 80mg or simvastatin 80mg is 1/10,000 PA. This is similar to the risk of thrombosis with oral contraceptives. Rhabdomyolysis is very rare 1/100,000 PA.

Treating 255 patients with statins for 4 years led to 1 extra case of diabetes mellitus, whereas 5.4 cardiovascular events were prevented. *Sattar et al. Lancet 2010;375:735–742.*

Statins decrease total non-fatal strokes with a small increase in haemorrhagic strokes. Use of statins after haemorrhagic stroke should be made on a case-by-case basis with the stroke physician.

If the patient reports adverse symptoms on the starting dose of atorvastatin consider....

Restart with a trial of pravastatin 10-20mg (metabolised by an alternative pathway).
If tolerated increase to atorvastatin 10mg with further increases if appropriate.

If other strategies fail rosuvastatin 5mg may be suitable; though it is 10x the cost and is associated with more adverse reactions than other statins.

Use *persisting* QOF code "Adverse reaction to statin U60CA" if appropriate. The expiring code "Maximal tolerated statin therapy 8BL1." needing renewal each year, can also be used (both in CEG template).

Statins are contraindicated in pregnancy. Advise women of reproductive age of teratogenic risks; discontinue 3 months before attempting to conceive.

Liver function tests

Request ALT not LFTs for statin monitoring

Measure ALT before starting a statin but not again unless indicated*

Statins often cause a modest rise in transaminases. If less than 3x upper limit of normal, remain on statins.

Review dose/investigations above this level. If liver disease is suspected or known, measure before starting, at 3 and 12 months or as clinically indicated.

*This is a locally agreed view. NICE recommends testing before starting statins, and at 3 and 12 months but not again unless clinically indicated. NICE is obliged to stick to original licensing. 30 years experience confirm that statins do not cause liver disease. The American FDA advise a single test as stated above.

Clinicians checking liver function in people on statins can select ALT (alanine transaminase).
NB: Selecting "LFTs" automatically means 7 liver function tests costing 7x£6.50 = £45 in one local CCG.

In a single CCG about 4000 people are newly started on statins each year. NICE guidance means requesting 3x4000=12,000 LFTs at a cost of £540,000 per year. Over 5 years this costs £2.7 million in each CCG and in England at this price, costs £570 million. By choosing more prudent use of a single Alanine Transaminase (ALT) the 5 year saving per CCG would be £2.5 million, an estimated £500 million nationally (prices vary greatly in CCGs).

Statins do not cause liver disease and repeated testing is unnecessary unless at high risk of liver disease[1-3].
Statins increase transaminases but these are often transient and less than 3x upper limit of normal. Most people at high CVD risk with non-alcoholic fatty livers or other chronic liver disease are likely to benefit from statins.

Liver Function Tests [contd]

A rise in ALT <3x ULN should not affect statin therapy. If ALT is raised above 3xULN take a history including alcohol/drugs/medication/ transfusion pre 1991/treatment or birth abroad, perform clinical examination and further testing (e.g. platelets, full LFTs, viral hepatitis screen). In patients with raised transaminases in whom fatty liver disease is thought to be the cause, only patients with an ALT>100 or an AST:ALT ratio of >1 or a platelet count of less than 100 x10^9/L (normal 150---450 x10^9/L) are at high risk of liver disease progression. Such patients should be referred for consideration of a liver biopsy.

This LFT policy is not NICE guidance but has been endorsed by local specialists and GPs as a safe and prudent use of resources and is also recommended by the FDA in the USA.

1Lowe RN et al. Ther Adv Drug Saf (2013) 4(1) 9–17.
2Bader,T. The Myth of Statin-Induced Hepatotoxicity Am J Gastroenterol 2010;105:978–980;
3Lilford et al. What is the best strategy for investigating abnormal liver function tests in primary care? BMJ Open 2013;3:e003099.

MHRA 2012 interactions

Interacting drug or food	Simvastatin prescribing advice	Atorvastatin prescribing advice
Potent CYP3A4 inhibitors, including itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, and HIV protease inhibitors	All are contraindicated with simvastatin	Avoid if possible: consider temporary suspension of atorvastatin if interacting drug is taken for short period; Itraconazole: do not exceed 40 mg atorvastatin daily; Clarithromycin: do not exceed 20 mg atorvastatin daily; HIV protease inhibitors: monitor lipid levels to ensure lowest necessary dose of atorvastatin is used
Ciclosporin, danazol and gemfibrozil	Contraindicated	Do not exceed 10 mg atorvastatin daily
Verapamil, amiodarone, amlodipine, diltiazem	Do not exceed 20 mg simvastatin daily	Monitor lipid levels to ensure lowest necessary dose of atorvastatin is used
Grapefruit juice	Avoid grapefruit juice	Limit intake of grapefruit juice to very small quantities (or avoid altogether)
Warfarin/courmarins	Monitor INR before starting treatment and regularly during treatment, especially with dose changes	Monitor INR before starting treatment and regularly during treatment, especially with dose changes
Fibrates	Increased risk of myopathy when used with fibrates; do not exceed 10 mg simvastatin daily (except with fenofibrate); gemfibrozil increases systemic exposure to simvastatin	Increased risk of myopathy when used with fibrates; gemfibrozil increases systemic exposure to atorvastatin
Ezetimibe	Additive risk of myopathy cannot be ruled out	Additive risk of myopathy cannot be ruled out
Simvastatin 80mg	May be associated with more adverse events than atorvastatin	Atorvastatin 80mg is preferred optimal dose or atorvastatin 40mg in people age 75 years or more

	% Reduction in LDL cholesterol				
Dose mg/day	**5mg**	**10mg**	**20mg**	**40mg**	**80mg**
Fluvastatin	10	15	**21**	**27**	**33**
Pravastatin	15	**20**	**24**	**29**	33
Simvastatin	23	**27**	**32**	**37**	**42**
Atorvastatin	31	**37**	**43**	**49**	**55**
Rosuvastatin	**38**	**43**	**48**	**53**	58

1. Small light text not available UK
2. Recommended high intensity statins in yellow

Decision aids to assist in advising patients on treatment with statins for primary prevention are avialable at http://www.nice.org.uk/guidance/cg181/resources/cg181-lipid-modification-update-patient-decision-aid2
Of 100 people like you, 20 will have a heart attack or stroke in 10 yrs. With atorvastatin, 7 will be prevented

20(%) CVD in 10yrs no statin

7 prevented with atorvastatin

Yellow smileys show CVD events prevented by treatment

Green no events

Red CVD events per 100 people.

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