

National Institute for Health and Care Excellence

**Lipid Modification
Guideline Consultation Table
12/02/14-26/03/14**

ID	Type	Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
180	SH	Royal College of General Practitioners	7	FULL			<p>Summary Comment:</p> <p>NICE have reduced the statin intervention threshold understandably in the light of recent meta-analyses which show persisting risk reduction among lower risk patients. This is probably the right thing to do but definitely will lead to most of the population > 50 becoming candidates for treatment.</p> <p>The solution to avoiding overtreatment whilst also making available treatment to those who want it, is a clear presentation of ABSOLUTE benefits on risk in the ways described above. This needs to be easy for patients, GPs, nurses and the media to understand. Quite a challenge, but I am sure could be done with clever use of graphics and publicity/communication .</p>	Thank you for your comment. We have added information to the guideline about numbers needed to treat in section 11.5. The absolute benefit can also be read from the GRADE tables. The GDG will work with the NICE implementation team to highlight this information.
241	SH	Cholesterol Treatment Trialists' Collaboration	16	FULL		P181 Other considerations	In the first paragraph the meaning of the second sentence is unclear.	Thank you for your comment. We have re-written this paragraph.
242	SH	Cholesterol Treatment Trialists' Collaboration	17	FULL		P184 CKD	It would be helpful to have a statement about the management of stage 5 CKD here.	We have clarified the people to whom this section refers. We have adopted the classification recommended by the NICE CKD guideline which uses a combination of egfr and albuminuria.
243	SH	Cholesterol	18	FULL		P185	The comments made on the GDG's discussion on the	Thank you for your comment. We have

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		Treatment Trialists' Collaboration		L			grouping of statins are unclear. The relationship between magnitude of LDL cholesterol reduction and the proportional effect of statin therapy was established in the 2005 CTT paper (ref 26) and many other independent groups since that time. The alternative paper referenced (ref 269) does not address this issue.	added more detail to the discussion on grouping of statins to explain the position taken in the guideline and corrected the references.
244	SH	Cholesterol Treatment Trialists' Collaboration	19	FULL		P198 Adverse effects	There is no mention in this section of haemorrhagic stroke, which the CTT has demonstrated is increased by statins.	Thank you for your comment. Haemorrhagic stroke was considered in the statin efficacy chapter. We reported total stroke as an outcome, which included both haemorrhagic and ischaemic stroke. A number of meta-analyses exist on this topic which differ in their conclusions with regards to the effects of statins on haemorrhagic stroke probably dependent on the trials included in the analyses. The largest and latest meta-analysis including 31 trials and 180,000 patients showed no difference in haemorrhagic stroke in the active treatment group versus control (Stroke. 2012;43:2149-2156). Some of the RCTs included in our review did not report haemorrhagic stroke separately within the published data so an independent analysis was not possible.
40	SH	New Devon CCG	13	FULL	Appendices	L	Table 80 is confusing - if all drugs are assumed to be equally clinically effective within their intensity group, as stated elsewhere in the text, why are some shown as providing more health benefit than others? Table 99, on which the recommendation to move to a 10% risk threshold appears to be based, is calculated from a male aged 60 perspective. There is no evidence presented to suggest that the results will also apply to younger men and women who have lower absolute risks and hence will	Thank you for your comment. Table 80 shows Net Health Benefit (NHB). NHB (which is explained in Section L.2.7) is a measure of cost effectiveness, incorporating both clinical benefit (QALYs) and cost, and therefore differing NHBs do not imply that one treatment necessarily provides better health (more QALYs) than another.

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							receive lower absolute benefit. As this move to a 10% threshold is a major change in practice with an impact on many people who will be asked to take a lifelong drug with a lower expectation of benefit, it seems crucial that these additional analyses are done (though note the caveats in the structure of the cost effective modelling).	Only the risk thresholds for men aged 60 were published in the draft guideline, although the GDG had had regard to the threshold for some other subgroups in formulating their recommendations. The equivalent thresholds for all age and sex subgroups have now been added to the guideline and can be found in Table 99.
87	SH	Weightwatchers UK	4	FULL	General		<p>As the draft guidance states 'Severe Obesity (BMI greater than 40 kg/m²) increases CVD risk. Take this into account when using risk scores to inform treatment decisions in this group'.</p> <p>While we feel this is an important (and welcomed) statement, we feel this is not commanding enough and does not provide practitioners with a clear enough directive. We would like to see a clearer mandate for what effective lifestyle treatment should be offered for this group for both primary and secondary prevention.</p> <p>The need for effective lifestyle weight management in primary and secondary prevention of CVD is absolutely essential and it is imperative that clinicians and practitioners are offering the most effective treatments according to evidence base. There needs to be specific recommendations for specific lifestyle weight management programmes (we recommend specific naming of programmes from proven providers) that have evidence of meeting the best practice guidance and are proven to be effective. This is only fair and transparent and ultimately in the best interests of patients.</p>	Thank you for your comment. We agree that the management of obesity is important but this was not included in the scope for this guideline. We will cross-refer to the NICE Clinical Guideline on Obesity which is currently being updated as well as NICE Public Health guidance which includes guidance on behaviour change. These will also be linked using NICE Pathways on NICE website.
41	SH	Cardiff and Vale University Health Board	1	FULL	General	General	The lipid modification consultation document has selected 7 key priorities for implementation. These do not include any lifestyle measures in these 7 key priorities and seems to be promoting the use of medicines (statins) over any	Thank you for your comment. The GDG have identified the recommendations they consider will have the highest impact on outcomes that are important to

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							<p>lifestyle measures for primary prevention patients, particularly those at low risk.</p> <p>Clinical trials typically have a run in period where patients that may have an adverse event to one of the medicines being studied are excluded. Therefore the adverse event rates seen in the clinical trials may not be representative of the true rates seen in the general population.</p>	<p>patients and include actions that are measurable.</p> <p>The adverse event rates in the clinical trials may be lower than the general population. We explored this in a sensitivity analysis in the model. We examined the relative risk of outcomes for an intervention versus control from RCT evidence because this is the most robust method for evaluating interventions. However we also looked at the effects which higher rates of adverse events would have in additional analyses carried out as part of the original economic modelling in Appendix L.</p>
226	SH	Cholesterol Treatment Trialists' Collaboration	1	Full	General	General	The text refers to 'myalgia' as an outcome, but this simply means muscle pain. The relevant outcome to consider is 'myopathy', generally defined as muscle pain or weakness in association with elevation of creatine kinase to at least 10 times the upper limit of normal (i.e. muscle symptoms in association with biochemical evidence of muscle damage)	Thank you for your comment. The GDG were interested in myalgia as an outcome as subjective muscle pain is considered to be a frequent complaint of people taking statins and a common cause of statin intolerance.
227	SH	Cholesterol Treatment Trialists' Collaboration	2	Full	General	General	Although we welcome the NICE proposal to lower to 10% the 10 year risk threshold that determines when to offer statin treatment, we feel that NICE should be doing more in this report to emphasise the importance of ensuring that the risks of statins (ie the low rate of side effects) are better understood. This might include requesting that MHRA review the side-effect statements in the data sheet as these are frequently not based on reliable evidence (such as individual case reports)	Thank you for your comment and support for our recommendations. NICE have passed your comments to the MHRA.
325	SH	Heart UK- The Cholesterol Charity	72	Full	General	General	All of the previous points from the NICE guideline also apply to any relevant sections of the Full Guideline.	Thank you.
28	SH	New Devon	1	FUL	General	General	The constitution of the guideline committee was not a	Thank you for your comment. This

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		CCG		L		al	<p>Please insert each new comment in a new row.</p> <p>representative sample of the stakeholders and this has affected the final policy direction of the document in favour of screening and intervention. In particular there was no public health or epidemiological representation and only one primary care representative who is an academic practitioner and not primarily a clinician.</p> <p>In addition, the use of expert opinion to fill in the gaps where evidence was sparse, rather than not making a recommendation, has diminished its credibility as evidence based guidance. Taken with the comments below detailing reservations about the population impact of the systematic searching process, and the bias within the modelling process, our concern is that this guideline gives recommendations that are too narrowly focused on certain health outcomes, and are not desirable in their approach to statin treatment. Even if one accepts the conclusion that 80mg atorvastatin is an appropriate choice of therapy for secondary prevention, there is no rationale for the recommendation to start at that dose as opposed to titrate up to it. At least some people who experience side effects with a drug will decline to try a smaller dose, and as side effects are more common at higher doses, this approach seems less likely to achieve the stated aim than starting with a smaller dose and increasing.</p>	<p>Please respond to each comment</p> <p>guideline is an update of Clinical Guideline 67 and the sections updated are those agreed following a review of CG67 and a public consultation process. The sections on identifying people who might be at risk were not updated.</p> <p>The membership of the GDG was discussed at consultation. This included 2 GPs, who were recruited to the GDG. GDG members are chosen following public advertisement and interview and a balance is required between members from different areas and with different expertise. The consultation on the draft guideline is part of the process of engaging a wide group of stakeholders each of whose comments have to be considered and answered.</p> <p>Any recommendations that are made which are informed by expert opinion are also subject to scrutiny during this stakeholder consultation.</p> <p>High-intensity statins were recommended for secondary prevention in the previous guideline. At that time simvastatin 80 mg was the only high-intensity generic statin available and the recommendation to use this was based on cost effectiveness.</p> <p>The recommendations do allow healthcare practitioners and patients to start on a lower dose than atorvastatin</p>

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								80mg in secondary prevention if there are good reasons for this, but otherwise the GDG believed that secondary prevention patients should be started on atorvastatin 80 mg as this is likely to be most clinically effective dose and so patients would receive a greater benefit from receiving this from the start. The GDG also noted that it would be more costly and time consuming to start all patients on a lower dose but then review them and increase to 80 mg if there are no adverse events, than to start all patients at 80 mg and reduce only those who were not able to tolerate this dose, and so that strategy is unlikely to be cost effective.
29	SH	New Devon CCG	2	FULL	General	general	The guideline does not use standard academic methods and is inconsistent in its use of evidence, again in favour of intervention. The use of placebo-based comparisons as estimates of effect rather than head to head comparisons when the primary aim is to make recommendations about drugs compared to one another is not accepted practice. The use of actual case analysis to estimate effect as opposed to intention to treat is likely to overestimate effect and underestimate adverse effects. There is inconsistency between the rationale behind the recommendations. For example, the recommendation in favour of ezetimibe is based on the surrogate outcome of cholesterol measurement and not clinical outcome data. However in the statin chapter the comment is made that the guideline group did not consider the use of a surrogate outcome was sufficient to make a recommendation.	This guidance was developed in accordance with the methods outlined in the NICE guidelines manual (http://publications.nice.org.uk/the-guidelines-manual-pmg6/). Meta-analysis and assessment of quality of evidence using GRADE are standard practice for evaluation of an intervention versus control. In the statin efficacy chapter head-to-head statin RCT evidence was reviewed. Statin versus placebo RCTs were included to provide further evidence because the head-to-head RCTs did not include all statins and doses. Most of the statin RCTs used intention-to-treat analysis. Other drug intervention reviews in the guideline were not recommending one drug versus another, and so intervention versus placebo/control RCTs

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								were appropriate. The recommendation for ezetimibe comes from the NICE Technology Appraisal programme who recommend that it is an option for treatment; this was not within the scope of this guideline to review (http://guidance.nice.org.uk/TA132). The GDG considered it important to be confident that the drugs they were recommending to large groups of people have an effect on hard outcomes.
Was 30	SH	New Devon CCG	3	FULL	General	General	The guideline does not take a holistic approach to health, and appears to be based on the premise that the prevention of certain (but not all) cardiovascular events is <i>a priori</i> more important than other aspects of quality of life. The following is a direct quotation 'One of the key challenges in the field of CVD preventionis how to convince people who feel well...that they may need to take lifelong drug therapy'. This neglects to take into account the psychological impact of being designated and treated as high risk for cardiovascular disease, and potential adverse effects of treatment.	Thank you for your comment. The guideline is not suggesting that all those eligible for treatment are at high risk, rather their risk is such that they could benefit from statins. The GDG recognise that discussions about primary prevention are difficult and do recommend that people are informed about the risks and benefits of treatment and a decision to take statins should be the informed choice of the patient.
135	SH	NHS England	1	FULL	General	General	Thank you for the opportunity to comment on the consultation for the above clinical guideline. I wish to confirm that NHS England has no substantive comments to make regarding this consultation.	Thank you for your comment
83	SH	Roche Products Ltd	1	FULL	General	General	Roche Products Ltd has no comments.	Thank you for your comment
136	SH	Royal College of Physicians (RCP)	1	FULL	General	General	The RCP is grateful for the opportunity to comment on the draft guidelines. We wish to endorse the comments submitted jointly by the ABCD/DUK.	Thank you for your comment

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433	SH	The Royal College of Pathologists	19	Full	General	General	All of the previous points also apply to the relevant sections of the Full Guideline.	Thank you for your comment
128	SH	Unilever	1	FULL	General	General	Unilever welcomes the review of the Lipid Modification Guidelines. We hope that the NICE guidelines complement those of JBS3 to be launched imminently.	Thank you for your comment. NICE guidelines are developed independently of other organisations and according to the NICE guideline manual.
81	SH	University of Nottingham	25	FULL	General	General	<p>Competing interest statement</p> <p>JHC is professor of clinical epidemiology at the University of Nottingham and co-director of QResearch[®] – a not-for-profit organisation which is a joint partnership between the University of Nottingham and EMIS (leading commercial supplier of IT for 60% of general practices in the UK). JHC is also director of ClinRisk Ltd which produces open and closed source software to ensure the reliable and updatable implementation of clinical risk algorithms within clinical computer systems to help improve patient care. CC is associate professor of Medical Statistics at the University of Nottingham and a consultant statistician for ClinRisk Ltd. PB has received no financial support for undertaking this work. This work and any views expressed within it are solely those of the co-authors and not of any affiliated bodies or organisations.</p>	Thank you for declaring competing interests.
84	SH	Weightwatchers UK	1	FULL	General	General	<p>Weight Watchers welcomes NICE's draft update to the clinical guidance on Lipid Modification. Once final, the guidance will be an immense help to those working with patients at risk of developing CVD and will provide guidance in an area where the correct, evidence-based approach will provide patients with the best possible care to reduce their risk.</p> <p>It is a surprise that the project did not review evidence on the impact of weight management on the primary and secondary prevention of CVD. This area does not seem to</p>	Thank you for your comment. We agree that the management of obesity is important but this was not included in the scope for this guideline. We will cross-refer to the NICE Clinical Guideline on Obesity which is currently being updated as well as NICE Public Health guidance which includes guidance on behaviour change. These will also be linked using NICE Pathways on NICE website.

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							<p>have been given much focus, despite its ability to offer multiple risk factor reductions via multiple lifestyle changes as outlined in the recommendations, for example diet and physical activity.</p> <p>There is almost no discussion about the evidence of effectiveness for weight management in this specific population group. This is a real shame and a missed opportunity.</p>	
403	SH	Merck Sharp & Dohme	10	FULL	General	n/a	<p>In MSD's comments 11 to 17, we have provided a detailed critique of the methodology that the GDG and NCCPC used to justify critical decisions in the development of this guideline. We believe that there are some fundamental flaws in the approach that has been used, and these responses are some of the methodological issues that we have identified.</p> <p>Furthermore, Appendix L (page 550) that summarises the de novo cost-effectiveness analyses states that "There are no deviations from the NICE reference case". This is not a true reflection, as the approach used by the NCCPC for determining the cost-effectiveness of atorvastatin 80 mg in comparison to atorvastatin 40 mg and 20 mg does not follow the NICE reference case (see comment 11 for further details).</p> <p><u>References</u></p> <ul style="list-style-type: none"> - NICE. (2013) Guide to the methods of technology appraisal 2013. [online] Available at: http://www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyAppraisal2013.pdf Accessed March 25th 2014 	<p>Thank you for your comments.</p> <p>Please note that this guideline update was conducted by the National Clinical Guideline Centre (NCGC) for NICE. The NCCPC developed the original clinical guideline 67, and so were responsible for the sections which have not been updated only.</p> <p>Our response to your comment regarding the NICE reference case are responded to alongside comment 11 (ID 404).</p>
141	SH	George Eliot Hospital NHS Trust	1	Full	General	General	Currently most clinicians are attuned to treating the total cholesterol or the LDL and not the non-HDL cholesterol.	Thank you for your comment. We have highlighted to the NICE Implementation team that this is a change in usual

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							Education will be key to allowing dissemination of this concept and require educational aids such as slide sets attached to the website pages and a clear explanation of its rationale	practice and will require education and explanation.
142	SH	George Eliot Hospital NHS Trust	2	Full	General	General	<p>Aiming for $\geq 40\%$ reduction in non-HDL cholesterol is laudable but what happens to the patient who still ends up with a high level such as 5 mmol/l?</p> <p>This will be particularly important in patients that are at highest risk and include FH patients as well as those with isolated high cholesterol levels.</p> <p>One could argue that we should target an equivalent non-HDL level equivalent to $LDL \leq 2.0$. The rationale for this would be the fact that in the TNT study, atorvastatin 80mg (average LDL 1.99 mmol/l attained) versus Atorvastatin 10mg, in patients with CHD, resulted in 16% less major adverse cardiac events.</p> <p>In patient with diabetes or metabolic syndrome this was 25% less. Both statin doses are generic and very cheap. I would expect the reduction in CV to pay for itself through less CABG, coronary stenting and the like.</p> <p>Beyond, high dose statins however, we would need to consider adding on other agents such as ezetimibe or fenofibrate.</p> <p>Ref:</p> <p>LaRosa JC, Grundy SM, Waters DD; Treating to New Targets (TNT) Investigators. Intensive lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352.</p>	<p>Thank you for your comment. The recommendations allow for people to take their highest tolerated dose of statin. The GDG did not think it appropriate to recommend additional drugs which had not been shown to reduce morbidity or mortality. The evidence from clinical trials is that a significant proportion of people will not reach $LDL \leq 2$ mmol/l and there are very few 'treat to target' studies. The recommendations do allow for discussion with a specialist if people are considered at significantly high risk.</p> <p>People with FH are outside the scope of this guideline and these recommendations do not refer to them. There is separate NICE guidance for people with FH; http://publications.nice.org.uk/identification-and-management-of-familial-hypercholesterolaemia-cg71.</p> <p>Ezetimibe is not in the scope of this guideline update, please refer to the NICE Ezetimibe Technology Appraisal; http://guidance.nice.org.uk/TA132.</p>

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143	SH	George Eliot Hospital NHS Trust	3	Full	General	General	<p>Please consider a clear distinct table that explains benefits and risks of treatment for various groups of patients eg Diabetes, Primary Prevention, Secondary Prevention, Young , Elderly</p> <p>This should be expressed in NNTs (Number needed to treat) and relative risk reductions- together with the number needed to harm or have side-effects.</p> <p>The risks of diabetes should also be stated.</p> <p>Eg less CVD by x% and increase risk of diabetes by y%. If 100 people took statins then x CVD events would be prevented with y extra cases of diabetes over z years.</p>	<p>Thank you for your comment. We have added information on statin therapy NNT for primary prevention in Section 11.5, including a NNT for new onset diabetes.</p> <p>We have indicated to NICE Implementation team that this information as you suggest would benefit implementation of the guideline.</p>
446	SH	Royal College of Physicians (RCP)	2	Full	General	General	The RCP is grateful for the opportunity to comment on the draft guidelines. From the perspective of our experts in diabetes we wish to endorse the comments submitted jointly by the ABCD/DUK. The following comments represent the thoughts of our experts in renal medicine following liaison with the Renal Association.	Thank you for your comment.
445	SH	United Kingdom Clinical Pharmacy Association	6	Full	General		Generally the level of myopathy is under reported in clinical trials which may lead to a more favourable risk benefit profile. As the CVD risk criteria has been lowered the risks of treatment need further attention as the recommendation is for high intensity statin usage and with this an increase in associated myopathy.	Thank you for your comment. Following stakeholder consultation we have done additional cost-effectiveness sensitivity analyses increasing the number of people who have side effects and need additional consultations and monitoring. These have not resulted in a change to the recommended threshold for treatment.
434	SH	Royal College of Nursing	1	Full	General	General	The Royal College of Nursing welcomes proposals to update the existing guidance for lipid modification.	Thank you for your comments.

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435	SH	Royal College of Nursing	2	Full	General	General	<p>The Royal College of Nursing is a registered stakeholder for Clinical Guideline for Lipid Modification.</p> <p>The Royal College of Nursing was invited to comment on recommendations to update this guideline.</p> <p>The document was circulated to nurses caring for people with cardiac disease and comments below were received from the reviewers.</p>	Thank you.
439	SH	Royal College of Nursing	6	Full	General	General	<p>It is welcomed that the updated guidelines recognise that non HDL C may be a better predictor of CV risk due to it encompassing all cholesterol present in potentially atherogenic lipoprotein particles. It is still extremely important to recognise that if there is any suspicion of familial hypercholesterolemia (FH) then the NICE CG71, clinical guidelines for FH should be referred to.</p>	Thank you for your comment and support of the decision to use non-HDL cholesterol. We recognise the need to identify people who may have inherited disorders in the recommendations.
344	SH	AstraZeneca UK Ltd	1	Full	General		<p>Executive summary:</p> <p>AstraZeneca recognises the important role that treatment guidelines have in reducing the burden of CVD by guiding clinical practice. We welcome the opportunity to provide comments.</p> <ol style="list-style-type: none"> 1. We recommend that rosuvastatin is explicitly recommended in the 2014 NICE guidelines as a treatment option for patients at higher CV risk. Risk: benefit is an important consideration when choosing which statin is most appropriate to treat an individual patient. The percentage LDL reduction with rosuvastatin is higher compared with that for atorvastatin across the doses (see Table 36, page 123, full NICE guideline). An alternative high-intensity statin is needed for high 	Thank you. We have responded to these comments where they are stated in individual sections.

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							<p>risk patients failing on atorvastatin.</p> <p>2. Statins are generally well tolerated¹⁴, although some drug-drug interactions may increase the risk of adverse events such as myopathy.¹⁵ For example, the risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with potent inhibitors of CYP3A4 and alternative (non-interacting) therapies should be considered.¹⁶ Rosuvastatin is not expected to be associated with drug interactions resulting from cytochrome P450-mediated metabolism.¹⁷ In addition, tolerability should be considered as rosuvastatin 40 mg is associated with lower rates of liver adverse events compared with atorvastatin 80mg.^{28, 29}</p> <p>3. AstraZeneca welcomes the assessment of CV risk with a view to reducing this risk appropriately. The Joint British Society (JBS3) guidelines have been launched on the 26th March. The JBS3 includes a new JBS3 risk calculator, whereas the NICE guideline recommends the QRISK2 risk calculator. In order to ensure consistency of use of risk calculators, AstraZeneca ask for specific reference and acknowledgement of the JBS3 risk calculator as an alternative option alongside the QRISK2.</p>	
130	SH	Unilever	3	FULL		Section 8 - 106	When replacement of saturated fat by polyunsaturated fat is noted, examples should be given e.g. to say vegetable oils and vegetable oil based spreads/products to include the broader range of products as the focus of the messaging appears to be on monounsaturated fats - only olive oil and rapeseed oil are mentioned. We would suggest that this is amended.	Thank you for your comment. In the Lyon Heart study examining Mediterranean diet, the control diet was based on sunflower oil. CV events were reduced in the intervention Mediterranean diet group. The GDG considered the use of sunflower oil could not be recommended over the consumption of olive and rapeseed which were in the experimental diet. The

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								<p>intervention group in the PREDIMED study were specifically advised to limit their consumption of spreading fats to less than one portion per day and the control to one portion per week. Given the low rate of events in both groups and other supporting evidence the guideline development group considered it inadvisable to specifically recommend this class of foods.</p> <p>Rapeseed oil was recommended as a replacement for saturated fat because it is a moderately good source of poly- as well as mono- unsaturated fats in addition to omega 3. Olive oil was recommended because it contains monounsaturated fats and proportionately small amounts of poly-unsaturated fats. The GDG did not recommend vegetable oils as a group as this would include coconut and palm oils which are sources of saturated fat.</p>
195	SH	Erewash CCG	15	Full		166-176	<p>We presume this section informs the QALY. In high quality studies this contradicts the using of high intensity statins Vs medium intensity statins.</p> <p>On page 175 last point and page 176 1st points you mention cost utility of cost effectiveness with no cross references. Please provide references.</p>	<p>Thank you for your comment. These are summary statements of the evidence. The GDG acknowledge that for individual outcomes the differences between statins may not be significant. These results are however then combined and integrated with the cost-effectiveness analysis to inform the final recommendations.</p> <p>The economic evidence statements on pages 175 and 176 (of the draft guideline) summarise the original cost-effectiveness modelling carried out for</p>

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								<p>this guideline, the detail of which can be found in Appendix L, summarised in Section 11.6, and further discussed in Section 11.8.</p> <p>As with the standard style for evidence statements in NICE guidelines, the evidence statements do not themselves include references, but summarise evidence detailed above, which is referenced.</p>
102	SH	Southern Derbyshire CCG	15	FULL		166-176	<p>We presume this section informs the QALY. In high quality studies this contradicts the using of high intensity statins Vs medium intensity statins.</p> <p>On page 175 last point and page 176 1st points you mention cost utility of cost effectiveness with no cross references. Please provide references.</p>	<p>Thank you for your comment. These are summary statements of the evidence. The GDG acknowledge that for individual outcomes the differences between statins may not be significant. These results are however then combined and integrated with the cost-effectiveness analysis to inform the final recommendations.</p> <p>The economic evidence statements on pages 175 and 176 (of the draft guideline) summarise the original cost-effectiveness modelling carried out for this guideline, the detail of which can be found in Appendix L, summarised in Section 11.6, and further discussed in Section 11.8.</p> <p>As with the standard style for evidence statements in NICE guidelines, the evidence statements do not themselves include references, but summarise evidence detailed above, which is referenced.</p>

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232	SH	Cholesterol Treatment Trialists' Collaboration	7	FULL		Recommendation 12	The way this recommendation is written, it does not make clear how treatment decisions in patients with CKD stage 3 or beyond are to be made, since no alternative to using a risk score is proposed.	Thank you for your comment. We have added to this recommendation that these people are at risk of CVD and statin treatment should be considered.
191	SH	Erewash CCG	11	Full		Page 46	<p>Given that GPs may run out of options can we have a statement on rosuvastatin NOT to recommend or carry at an economic analysis or REMOVE. State also which 3 generic statins you recommend.</p> <p>"Seek specialist advice about options for treating people at high risk of CVD such as those with established CVD, CKD, diabetes or genetic dyslipidaemias who are intolerant to <u>3 statins</u>. Advice can be sought for example, by telephone, virtual clinic or referral."</p>	Thank you for your comment. We have added a recommendation to say that that statins of low acquisition cost should be used.
98	SH	Southern Derbyshire CCG	11	FULL		Page 46	<p>Given that Gps may run out of options can we have a statement on rosuvastatin NOT to recommend or carry at an economic analysis or REMOVE. State also which 3 generic statins you recommend.</p> <p>"Seek specialist advice about options for treating people at high risk of CVD such as those with established CVD, CKD, diabetes or genetic dyslipidaemias who are intolerant to <u>3 statins</u>. Advice can be sought for example, by telephone, virtual clinic or referral."</p>	Thank you for your comment. We have added a recommendation to say that that statins of low acquisition cost should be used.
443	SH	United Kingdom Clinical Pharmacy Association	4	full		69	Taking statins at night is likely to worsen adherence – what is the evidence for improving cholesterol reduction by taking at night – the licence for atorvastatin is daily I,e, anytime of the day due to its longer half life.	Thank you for your comment. We have removed the reference to take statin at night – this was an error.

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338	SH	Association of British Clinical Diabetologists, Diabetes UK	13	FULL		74	<p>'The GDG concluded.... patients with type 1 diabetes are likely to met (sic) clinical criteria for having a CV risk substantially in excess of the general population of the same age and gender.'</p> <p>There is important observational longitudinal data from Scotland that puts this in perspective and makes clear the event rates linked to risk is not nearly as excessive as implied, and certainly not enough to justify 20-80 mg atorvastatin in Type 1 diabetes from the age of 18-40. See previous comment and reference :</p> <p>Livingstone SJ, Looker HC, Hothersall EJ, Wild SH, Lindsay RS, Chalmers J, Cleland S, Leese GP, McKnight J, Morris AD, Pearson DW, Peden NR, Petrie JR, Philip S, Sattar N, Sullivan F, Colhoun HM. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. PLoS Med. 2012;9(10):e1001321. doi: 10.1371/journal.pmed.1001321. Epub 2012 Oct 2. PubMed PMID: 23055834; PubMed Central PMCID: PMC3462745.</p> <p>In contrast to the lack of evidence of statin benefit for CVD in type 1 diabetes, the 25 year follow up of DCCT clearly demonstrated that improved glycaemic control over that period reduced CVD event rates.</p>	<p>Thank you for your comment. The GDG reviewed the recommendations following stakeholder consultation and have developed a more nuanced recommendation in recognition of the information provided. This is to consider statin treatment in adults with type 1 diabetes. The GDG agreed that many adults with type 1 diabetes will have had diabetes since childhood and therefore many will have the condition for 10 years or more in early adulthood.</p> <p>The GDG have made a second recommendation to offer statins to adults with type 1 diabetes who have other risk factors, evidence of nephropathy, are more than 40 years or have diabetes for 10 years or more.</p>
229	SH	Cholesterol Treatment Trialists' Collaboration	4	FULL		66 (page 46)	Please clarify whether CKD stage 4 and beyond includes dialysis patients (stage 5D).	Thank you for your comment. People on renal replacement are outside the scope of the guideline. We have added a footnote to the recommendations to clarify this.
230	SH	Cholesterol Treatment Trialists' Collaboration	5	FULL		87 (page 48)	Include muscle weakness, not just pain.	Thank you for your comment. We have changed the recommendation as you suggest.

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194	SH	Erewash CCG	14	Full		180	<p>Economic considerations did not take account of adverse effects other than that of diabetes, Statin association with liver dysfunction/acute renal failure and cataracts, cognitive symptoms, neuropathy, myalgia, musculoskeletal disorders, etc. Trial evidence of adverse events exist e.g. Jupiter</p> <p>Why not carry these out?</p> <p>We presume CTT had access to patient level data- why is it not possible to undertake this work?</p>	<p>Thank you for your comment. A full discussion of adverse events, including which were included, how they were included, and why some were not included, can be found in Appendix L, Section L.2.3.7.</p> <p>The GDG did not have access to individual patient-level data from CTT.</p>
101	SH	Southern Derbyshire CCG	14	FULL		180	<p>Economic considerations did not take account of adverse effects other than that of diabetes, Statin association with liver dysfunction/acute renal failure and cataracts, cognitive symptoms, neuropathy, myalgia, musculoskeletal disorders, etc. Trial evidence of adverse events exist e.g. Jupiter</p> <p>Why not carry these out?</p> <p>We presume CTT had access to patient level data- why is it not possible to undertake this work?</p>	<p>Thank you for your comment. A full discussion of adverse events, including which were included, how they were included, and why some were not included, can be found in Appendix L, Section L.2.3.7.</p> <p>The GDG did not have access to individual patient-level data from CTT.</p>
239	SH	Cholesterol Treatment Trialists' Collaboration	14	FULL		P 180. Primary prevention	It is stated that high intensity statins are cost-effective compared to other options, but the validity of this is dependent on the use of <u>low-cost generic</u> statins (eg atorvastatin 20mg daily).	Thank you for your comment. We have added a recommendation to highlight the use of statins at low acquisition costs.
240	SH	Cholesterol Treatment Trialists' Collaboration	15	FULL		P 181. Type 1 diabetes	In the 2008 CTT paper on diabetes (Lancet 2008; 371:117-25), allocation to a statin reduced major vascular events by 21% per mmol/L reduction in LDL cholesterol (p=0.01) among patients with type 1 diabetes. This evidence might be useful in validating the approach of the guideline.	Thank you for alerting us to this information.
340	SH	Association of British Clinical Diabetologists , Diabetes UK	15	FULL		182	Primary prevention – States 'for those at 10% 10 year risk atorvastatin 20 mg likely to decrease risk by a large proportion and higher doses would decrease it by only a modest extra amount. It is not clear whether this extra benefit would be large enough to justify additional cost and possible increase in adverse events '	Thank you for your comment. The GDG reviewed the recommendations following stakeholder consultation and have developed a more nuanced recommendation in recognition of the information provided. This is to consider

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						183	<p>However earlier, in Appendix stated 80 mg in type 1 diabetes where 10 year risk is clearly < 10 % over 10 years till over age of 40.</p> <p>Please see again the reference. This represents contemporary data on CVD risk in T1DM Livingstone SJ, Looker HC, Hothersall EJ, Wild SH, Lindsay RS, Chalmers J, Cleland S, Leese GP, McKnight J, Morris AD, Pearson DW, Peden NR, Petrie JR, Philip S, Sattar N, Sullivan F, Colhoun HM. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. PLoS Med. 2012;9(10):e1001321. doi: 10.1371/journal.pmed.1001321. Epub 2012 Oct 2. PubMed PMID: 23055834; PubMed Central PMCID: PMC3462745.</p> <p>The informal consensus for the recommendations in type 1 diabetes is a concern given the referenced papers in JBS3 that more clearly record a lower contemporary CVD risk in type 1 diabetes than the GDG appear to have appreciated. Furthermore in this section it stated 20 mg atorvastatin having mentioned 80 mg high intensity in the Appendix section of the recommendations.</p> <p>The GDG later states that for type 2 diabetes atorvastatin 80 mg IS cost effective at UKPDS thresholds of below 10%.</p>	<p>statin treatment in adults with type 1 diabetes. The GDG agreed that many adults with type 1 diabetes will have had diabetes since childhood and therefore many will have the condition for 10 years or more in early adulthood.</p> <p>The GDG have made a second recommendation to offer statins to adults with type 1 diabetes who have other risk factors, evidence of nephropathy, are more than 40 years or have diabetes for 10 years or more.</p> <p>We have clarified the recommendations for Type 2 diabetes. In general atorvastatin 80mg is cost effective but the GDG recommend starting at atorvastatin 20mg.</p>
177	SH	Royal College of	4	Full	Rec 63-65		Up-titration of statins in CKD. This is complicated and could there be a statement about the absolute risk	Thank you for your comment. We have simplified the recommendations for

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		General Practitioners					reduction achieved by doing this?	people with kidney disease. The main concern for people with kidney disease is potential adverse effects so we now recommend that all people with kidney disease are started on atorvastatin 20mg.
116	NICE	CPH	1	FULL	1.2	15	Much of this section discusses the significance of prevention, and population level approaches to prevention. This suggests that the section heading ('management') is misleading and that possibly an earlier section ('prevention') should be inserted.	Thank you for your suggestion. The section is addressing management of risk and we have clarified this.
117	NICE	CPH	2	FULL	1.2	16	<p>As indicated above, much of this section refers to the importance of population level prevention. NICE has produced many pieces of relevant public health guidance related to this – PH25 (prevention of CVD) and guidance related to risk behaviours such as smoking and tobacco use (PH1, PH5, PH10, PH14, PH15, PH23, PH26, PH39, PH45, PH48); physical activity (PH8, PH13, PH17, PH41, PH44); obesity (PH27, PH44, PH46, CG43); alcohol (PH24). The recommendations are summarised in several relevant public health Pathways.</p> <p>While it might not necessarily be helpful for this guideline to repeat these recommendations many are directed at least in part at clinicians and others who would be the target audiences of this guideline. I note that section 2.3 indicates that the guideline covers 'risk assessment and prevention of CVD in...adults without established CVD'. It would be appropriate for this section to refer to them and provide links to enable them to navigate to NICE's outputs relevant to prevention, in lines with the wishes of the GDG in the final sentence of this section.</p>	Thank you for your comment. The NICE editors have informed us that they do not list clinical guidelines separately from public health guidelines in their standard template.
341	SH	Association of British Clinical Diabetologist	16	NICE	1.1.22		All aged above 85 recommended for statins given inevitable high CVD risk. This is controversial given life expectancy, and failure to specify applicability in those with dementia or marked frailty through other conditions. There	Thank you for your comment. The recommendation suggests that consideration should be given to giving statins to people over 85 years. We have

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		s , Diabetes UK					are inevitable ethical concerns in these areas which should be discussed	added more detail to the recommendation to explain possible benefits in older people and also expanded recommendation 1.3.12 which suggests the areas that need consideration such as frailty and polypharmacy, before statins are prescribed. The GDG have also made a research recommendation about the use of statins in older people.
6	SH	The Institute of Diabetes for Older People	1	NICE	1.1.22	13	No mention of erectile dysfunction as part of the risk assessment. It is in the ESC guideline and JBS3	<p>Thank you for your comment. The guideline has not addressed who should be identified to undergo risk assessment and erectile dysfunction might be considered an important complaint which should initiate CVD risk assessment.</p> <p>The guideline aimed to provide advice on which risk tool could be used to provide a risk score. The GDG were not aware of any tools including erectile dysfunction or evidence that of how the presence of erectile dysfunction would alter the assessment of overall cardiovascular risk.</p>
336	SH	Association of British Clinical Diabetologists , Diabetes UK	11	NICE	1.1.22	48 14	<p>Statin use aged over 85 – Need to include research need to examine polypharmacy impact on safety data in this age group with CKD – current lack of muscle-renal safety data in this situation.</p> <p>NB: evidence from PROSPER follow-up – whilst CVD events were reduced, there was no overall increase in life expectancy from pravastatin commencement at age 75 at least with pravastatin.</p>	Thank you for your comment. The recommendation suggests that consideration should be given to giving statins to people over 85 years. We have added more detail to the recommendation to explain possible benefits in older people and also expanded rec 1.3.12 which suggests the areas that need consideration such as frailty and polypharmacy, before statins

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							<p>Lloyd SM, Stott DJ, de Craen AJ, Kearney PM, Sattar N, Perry I, Packard CJ, Briggs A, Marchbank L, Comber H, Jukema JW, Westendorp RG, Trompet S, Buckley BM, Ford I. Long-term effects of statin treatment in elderly people: extended follow-up of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PLoS One. 2013 Sep 2;8(9):e72642. doi:10.1371/journal.pone.0072642. eCollection 2013. PubMed PMID: 24023757; PubMed Central PMCID: PMC3759378.</p>	are prescribed. We have clarified the need to include adverse events in the research recommendation.
343	SH	Association of British Clinical Diabetologists, Diabetes UK	18	NICE	1.3.10		<p>Is there evidence that CVD risk scores are meaningfully underestimated if triglycerides between 4.5 and 9.9 mmol/l? The ERFC paper does not fully agree with this, and there is no clarity regarding this issue in the diabetes population.</p> <p>Emerging Risk Factors Collaboration (ERFC), Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009 Nov 11;302(18):1993-2000. doi:10.1001/jama.2009.1619. PubMed PMID: 19903920; PubMed Central PMCID: PMC3284229.</p> <p>Given the limited epidemiology and evidence base for intervention in this group, we feel further research is needed to best manage this issue.</p> <p>Patients with triglycerides between 4.5 to 9.9mmol/l could be referred to specialist centres on the basis of this NICE advice which may be unnecessary. If they not already are on high intensity statins, then this is the first option which GPs can deliver. There is also evidence that statins (but not fibrates) lowered pancreatitis risk in clinical trials.</p>	<p>Thank you for your comment. The Emerging Risk Factors Collaboration is only one source for this data. The Copenhagen City Heart Study (2011; 2013) identified non-fasting triglycerides >5mmol/L, increased quantities of remnant (triglyceride-rich) lipoproteins and genetic variants predisposing to higher triglycerides as an additional risk factors for cardiovascular disease in papers published since the ERFC collaboration report in 2009.</p> <p>A specific research recommendation has been made with regards to the optimal treatment option for cardiovascular disease in patients with elevated triglycerides in chapter 12.</p> <p>We do not think people with triglycerides between 4.5 to 9.9mmol/l will be referred to specialist centres on the basis of this unless they also have elevated cholesterol when referral would be appropriate.</p>

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							<p>Preiss D, Tikkanen MJ, Welsh P, Ford I, Lovato LC, Elam MB, LaRosa JC, DeMicco DA, Colhoun HM, Goldenberg I, Murphy MJ, MacDonald TM, Pedersen TR, Keech AC, Ridker PM, Kjekshus J, Sattar N, McMurray JJ. Lipid-modifying therapies and risk of pancreatitis: a meta-analysis. JAMA. 2012 Aug 22;308(8):804-11. doi: 10.1001/jama.2012.8439. PubMed PMID: 22910758.</p> <p>Please also see letter below which elaborates this point.</p>	

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Correspondence

Treatment of severe hypertriglyceridaemia

We welcome the Review by Robert Hegele and colleagues¹ about the definition, diagnosis, and management of hypertriglyceridaemia.¹ In particular, we note that the simplification of hypertriglyceridaemia into two easily identifiable groups (individuals with mild-to-moderate hypertriglyceridaemia [2–10 mmol/L] and those with severe hypertriglyceridaemia [≥10 mmol/L]) is a logical step that allows clinicians to focus on the clinical priority in each group—ie, prevention of cardiovascular disease in patients with mild-to-moderate hypertriglyceridaemia and acute pancreatitis in those with severe hypertriglyceridaemia.

However, we disagree with the authors' recommendation that fibrate therapy in particular, along with nicotinic acid and omega-3 fatty acids, and not statins, should be used as the optimum drug option in severe hypertriglyceridaemia to prevent pancreatitis.¹ Treatment with high-dose statins can lower triglycerides to a similar extent as noted with nicotinic acid and omega-3 fatty acids and, as Hegele and colleagues highlight, statins are only moderately weaker than are fibrates in this regard. Moreover, pooled data from major placebo-controlled and standard care-controlled randomised trials for statins

(16 trials, 113 800 participants) and fibrates (7 trials, 40 162 participants), suggest that medium-term treatment (2–7 years) with a statin reduces the risk of pancreatitis by more than 20%, whereas fibrates might actually increase risk of pancreatitis,² possibly because of contrasting effects on the development of gallstones.^{3,4} These meta-analyses had design weaknesses: the trials were not done in people with severe hypertriglyceridaemia, identification of pancreatitis was not recorded in a standardised way, and no pancreatitis analyses were prespecified. Nonetheless, these results provide the only source of unbiased, large-scale, randomised trial data on whether lipid-modifying drugs affect pancreatitis risk in any population. Data from a drug application document⁵ submitted to the US Food and Drug Administration in 2011 about the SHARP trial also suggested that the risk of development of pancreatitis in patients given combination treatment of simvastatin and ezetimibe was reduced by 40% compared with placebo.

Our view is that—along with attention to lifestyle and secondary factors, as Hegele and colleagues discussed—clinicians should treat severe hypertriglyceridaemia mainly with statins. For individuals with particularly severe hypertriglyceridaemia at diagnosis, plus patients whose triglyceride concentrations do not respond adequately to statin

monotherapy (ie, triglycerides remain >10 mmol/L), clinicians should add a fibrate or omega-3 fatty acid to this regimen. For most people with triglyceride concentrations less than 20 mmol/L at diagnosis, statin monotherapy will be adequate and it seems to be the option best supported by evidence for both cardiovascular risk and pancreatitis risk reduction.

We declare that we have no competing interests.

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- 1 Hegele RA, Ginsberg HN, Chapman MJ, et al. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. *Lancet Diabetes Endocrinol* 2013; published online Dec 23. [http://dx.doi.org/10.1016/S2213-8587\(13\)70191-8](http://dx.doi.org/10.1016/S2213-8587(13)70191-8).
- 2 Preiss D, Tikkanen MJ, Welsh P, et al. Lipid-modifying therapies and risk of pancreatitis: a meta-analysis. *JAMA* 2012; 308: 804–11.
- 3 Bodmer M, Brauchli YB, Krahenbuhl S, Jick SS, Meier CR. Statin use and risk of gallstone disease followed by cholecystectomy. *JAMA* 2009; 302: 2001–07.
- 4 The Coronary Drug Project Research Group. Gallbladder disease as a side effect of drugs influencing lipid metabolism. Experience in the Coronary Drug Project. *N Engl J Med* 1977; 296: 1185–90.
- 5 FDA. Endocrinologic and Metabolic Drugs Advisory Committee briefing document: SHARP (Study of Heart and Renal Protection). 2011. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetings/Meetings/Drugs/EndocrinologicandMetabolic/DrugsAdvisoryCommittee/UCM277652.pdf> (accessed Jan 29, 2014).

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7	SH	The Institute of Diabetes for Older People	2	NICE	1.2.2	14	Mediterranean diet should be discussed	Thank you for your comment. The GDG decided not to use the term 'Mediterranean diet' in the recommendations as the label lacks precision. This issue is discussed in the linking evidence Section 8.6.
332	SH	Association of British Clinical Diabetologists, Diabetes UK	7	NICE	1.2.4		Fibrates – Consistent with JBS3 with exception of comment regarding potential microvascular potential benefit in JBS3	Thank you for your comment.
327	SH	Association of British Clinical Diabetologists, Diabetes UK	2	NICE	1.3.1	18	States drugs are preferred for where evidence in clinical trials – Atorvastatin 10 mg in CARDS in Type 2 DM yet 20 up to 80 mg recommended in NICE document. Simvastatin in 4T study in T2DM studied but not stated There is an evidence base for use of atorvastatin 80 mg in DM CKD in the TNT study which has not been referenced	Thank you for your comment. There is trial evidence for the beneficial effects of each statin, and for most statin doses, but the GDG recognises that evidence is not available for all populations (such as people with type 2 diabetes or chronic kidney disease) for each statin. However, the clinical evidence review conducted for the guideline did not show significant heterogeneity in effectiveness between different populations. The TNT study data is included in the guideline and referenced as LaRosa 2005.
8	SH	The Institute of Diabetes for Older People	3	NICE	1.3.12	20	Introducing non HDL cholesterol will be new to GPs. The simple approach is to add 0.8 to the LDL figure	Thank you for your comment and for this information. The information will be passed on to the NICE implementation team to support the development of the implementation tools.
9	SH	The Institute of Diabetes for Older	4	NICE	1.3.16	21	Why not 40mg?	Thank you for the comment. The GDG did discuss whether people should be started on atorvastatin 40mg for primary

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		People						prevention. They were aware however that the risk threshold for use of statins was lower than previously and that there was concern about side effects with higher doses of statins. The recommendations do allow for up titration to atorvastatin 40mg or 80mg for people at higher risk.
328	SH	Association of British Clinical Diabetologists, Diabetes UK	3	NICE	1.3.21	21	<p>'Offer high intensity statin ...primary prevention to people with type 1 diabetes'. We feel there has been over-extrapolation in reaching this recommendation</p> <p>JBS3 concludes – no evidence base, no safety data to support those aged 18-40 take 20 mg atorvastatin for over 30 years before manifest 10 year 10% CVD risk.</p> <p>:</p> <p>Livingstone SJ, Looker HC, Hothersall EJ, Wild SH, Lindsay RS, Chalmers J, Cleland S, Leese GP, McKnight J, Morris AD, Pearson DW, Peden NR, Petrie JR, Philip S, Sattar N, Sullivan F, Colhoun HM. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. PLoS Med. 2012;9(10):e1001321. doi: 10.1371/journal.pmed.1001321. Epub 2012 Oct 2. PubMed PMID: 23055834; PubMed Central PMCID: PMC3462745.</p> <p>This critical recent paper from Scotland shows that although higher relative CVD risk of 2-3 in T1DM this is concentrated in longer duration of diabetes with complications, especially nephropathy. The 10 year CVD event rates in T1DM in populations aged less than 50 is consistently < 10% outside the higher risk categories.</p> <p>The current proposed NICE guidance fails to take account</p>	<p>Thank you for your comment. The GDG reviewed the recommendations following stakeholder consultation and have developed a more nuanced recommendation in recognition of the information provided. This is to consider statin treatment in adults with type 1 diabetes. The GDG agreed that many adults with type 1 diabetes will have had diabetes since childhood and therefore many will have the condition for 10 years or more in early adulthood.</p> <p>The GDG have made a second recommendation to offer statins to adults with type 1 diabetes who have other risk factors, evidence of nephropathy, are more than 40 years or have diabetes for 10 years or more.</p>

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							<p>of this UK and US data examining CVD risk in T1DM which consistently records the risk is most clearly related to long duration of T1DM linked with poor control, and/or with diabetic nephropathy characterised by persistent albuminuria, or other risk factors as stated in JBS3 .</p> <p>In other words, whilst T1DM is a risk factor for CVD, its level of risk is very low in younger populations and if one examines the risk models developed in JBS3, it is clear there is no benefit from earlier prescription of statins in the vast majority of individuals aged 18-30 . It is also clear, that if anything, risk for CVD is higher in age and duration matched individuals with type 2 diabetes compared to type 1. Please see:</p> <p>Constantino MI, Molyneaux L, Limacher-Gisler F, Al-Saeed A, Luo C, Wu T, Twigg SM, Yue DK, Wong J. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. Diabetes Care. 2013 Dec;36(12):3863-9. doi: 10.2337/dc12-2455. Epub 2013 Jul 11. PubMed PMID: 23846814; PubMed Central PMCID: PMC3836093.</p> <p>The concept of intensive statins for young type 1 extrapolates well beyond what the data allow us to say presently. Finally, if cost effectiveness in younger type 2 patients under 40 or 45 cannot be made, it certainly cannot be made for younger type 1 DM without complications, a group at lower average CVD and total mortality risk than an age matched young individual with type 2 diabetes with similar duration of diabetes.</p>	
329	SH	Association of British Clinical	4	NICE	1.3.24	22	'When offering statin treatment for people with type 2 diabetes, start with atorvastatin 80 mg '	Thank you for your comment. Following stakeholder consultation the GDG have recommended the use of QRISK2 to

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		Diabetologists, Diabetes UK					<p>We cannot agree with the basis for starting high intensity statin on a routine basis. The average CVD risk is not exceptionally high in uncomplicated type 2 DM and event rates have substantially declined over time given earlier diagnosis – the highest at risk groups with type 2 are those with existing CVD, and/or proteinuria and stage 3b CKD where there are data supporting the safe effective use of atorvastatin 80 mg (Shepherd et al, TNT study). For the majority, there is an evidence base of efficacy and safety that demonstrates 40 mg simvastatin or 10-20 mg atorvastatin would suffice.</p> <p>Moreover, we do not know, as yet, the extent to which intensive statin may lead to more side effects and any measurable effect on glycaemia – so these factors need discussion.</p>	assess risk in people with Type 2 diabetes and to start treatment when they have 10% risk of CVD in the next 10 years. The recommendation has been changed to start treatment with atorvastatin 20mg. Following stakeholder comment we have done additional sensitivity analyses to ensure adverse events are included. The use of high intensity statins remains cost effective following these analyses.
10	SH	The Institute of Diabetes for Older People	5	NICE	1.3.26	22	<p>Why 40%? plaque regression occurs at > 50% reduction. Why is ezetimibe not being position after atorvastatin 80mg as per TA 132?</p>	Thank you for your comment. 40% reduction in non-HDL is used as this the benefit people should get with the use of high intensity statins. The general statin recommendations are based on such as plaque regression when assessing the evidence. Ezetimibe is not in scope of this guideline update, Please follow the recommendation for Ezetimibe in NICE Ezetimibe Technology Appraisal; http://guidance.nice.org.uk/TA132 .
330	SH	Association of British Clinical Diabetologists, Diabetes UK	5	NICE	1.3.27	23	<p>There was no comment on the TNT study in this draft document where in T2DM with CKD 3 atorvastatin 80 mg was indeed of benefit and safe?</p>	That you for your comment and statement about the safety of atorvastatin 80mg in people with T2DM and CKD3. The clinical evidence is discussed in the Full guideline. Individual studies are not discussed in detail in the review but the results extracted to enter into a meta-analysis.

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11	SH	The Institute of Diabetes for Older People	6	NICE	1.3.29	23	As above + a reduction of 40% from 7.5 is 4.5 which is still too high	Thank you for your comment. The recommendations allow for people to take their highest tolerated dose of statin. The GDG did not think it appropriate to recommend additional drugs which had not been shown to reduce morbidity or mortality.
342	SH	Association of British Clinical Diabetologists, Diabetes UK	17	NICE	1.3.3		Need to explain what non-HDL-c is – JBS3 covers this.	Thank you for your comment. We have added explanation of non-HDL to the introduction to the NICE guideline.
12	SH	The Institute of Diabetes for Older People	7	NICE	1.3.32	24	Provide advice on dealing with statin intolerance referrals cost CCGs £ Also what about people who cannot tolerate 80mg atorvastatin What next?? suggest: Low dose, Alternate day hydrophilic statins, Fluvastatin +/- ezetimibe (Stein E Am J Cardiol 2008;101:490-496) Non statin Rx (ezetimibe, resins, plant sterols) Jacobson T.A. Mayo Clin Proc 2008; 83(6): 687-700. Available from http://www.mayoclinicproceedings.org/article/S0025-6196%2811%2960897-5/abstract Stein e. Am J Cardiol 2008; 101:490-496. Available from http://www.ajconline.org/article/S0002-9149%2807%2902043-7/abstract	<p>Thank you for your comment. The guideline proposes that specialist advice should be sought only for patients at high risk of CVD events such as those who have already had an event or who have CKD or diabetes who have tried and failed to tolerate 3 different statins (and therefore potentially a larger number of doses) and so cannot find any statin that they can take. We believe that this will be a small proportion of patients. We do not recommend specialist advice for primary prevention patients.</p> <p>We note that specialist advice can be sought by phone which may be quicker and less costly than booking a referral appointment.</p> <p>The GDG recognise that there are will be people who are not able to take statins</p>

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								and in these cases emphasis on other interventions such as diet, exercise and blood pressure may be more appropriate than the use of drugs without data on outcomes. Ezetimibe is beyond the scope of this guideline update, please refer to the NICE Ezetimibe Technology Appraisal; http://guidance.nice.org.uk/TA132
13	SH	The Institute of Diabetes for Older People	8	NICE	1.3.34	24	This will not take into consideration poor concordance. The cholesterol level achieved will be more accurate and what about people already on statins – no advice on testing or targets. No special high risk groups identified to audit to make sure they are on an appropriate statin dose	Thank you for your comment. Following stakeholder comment we have removed this recommendation.
331	SH	Association of British Clinical Diabetologists, Diabetes UK	6	NICE	1.3.45	25	Needs to be fully aligned with recommendations for women of child bearing age with diabetes in pre-pregnancy with advice to stop statins before planning conception.	Thank you for your comment. The GDG preferred the works 'if pregnancy is a possibility' as not all pregnancies are planned and we have added that statins should not be started again until breast feeding has stopped.
333	SH	Association of British Clinical Diabetologists, Diabetes UK	8	NICE	1.3.52	27	No comment regarding ezetimibe in diabetes – stated in other NICE guidance to support statin use Please note there is a section in JBS3 on statin intolerance. Given that ezetimibe avoids statin side effects, patients with existing CVD or at elevated risk with genuine documented intolerance to all statins at all doses should be offered ezetimibe since alone it can reduce cholesterol by up to 20% as the NICE committee recognise. The safety and efficacy evidence base comes from the SHARP trial. Its use should not therefore be restricted to those with FH alone since many very high risk patients who cannot take statin or sufficient dose to reach targets, can be helped to do so with ezetimibe.	Thank you for your comment. The use of Ezetimibe is outside the scope of this guideline, please refer to the NICE Ezetimibe Technology Appraisal; http://guidance.nice.org.uk/TA132 .

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112	SH	National Clinical Guidelines centre CKD GDG	4	FULL	1.8.1 Rec 63	183	<p>The guidelines state that:</p> <p>“For CKD stages 1 and 2, the GDG concluded that their risk was similar to those without CKD and hence that they should also be recommended atorvastatin 20 mg as for the general primary prevention if at greater than 10% risk as assessed using QRISK2”.</p> <p>Again we feel this downplays the importance of albuminuria. Although we recognise that better risk tools in CKD are needed, we do know from large scale epidemiological data that CV mortality is doubled in people with an eGFR>60 and albuminuria http://www.kdigo.org/pdf/ASL-DEFINITION-KDIGO.pdf)</p>	Thank you for your comment. We have altered these recommendations and now make reference to the presence or absence of albuminuria.
334	SH	Association of British Clinical Diabetologists, Diabetes UK	9	NICE	2.4	29	Need to add uncertainty regarding safety of long term administration of statins in type 1 diabetes. No mention of key issue of duration of diabetes linked with glycaemia control as factor	Thank you for your comment. This paragraph outlines why the research should be done. We have added more detail to this paragraph. There is further detail about the issues that should be considered in this research question in the Appendix N.
31	SH	New Devon CCG	4	FULL	3	34	No justification is given for the decision to include non-fatal AMI, for example, as a critical outcome whereas sudden cardiac death and stroke are only important outcomes, and adverse effects are ‘relevant’. This prioritisation of certain outcomes above others implies a bias in the writing of the guideline.	The guideline development group considered all outcomes when making recommendations. Stroke has been changed to a critical outcome.
32	SH	New Devon CCG	5	FULL	4		The recommendation to use a systematic search in primary care is essentially to institute a screening programme to identify high risk individuals. However, it has not been assessed formally as a screening programme, so the analysis is inadequate. For example, the costs of systematic searching in primary care, the psychological impact of being identified as at high risk, and the adverse effects of medication have not been taken into account.	Thank you for your comment. Strategies for identifying people at risk was not in the scope for this update.
440	SH	United	1	Full	4.1	Line	Whilst we recognise the improvement in cost effective of	Thank you for your comment. It is cost

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		Kingdom Clinical Pharmacy Association				15	generic statins, they are not without risk and we question the appropriateness of high intensity statin for people with a CVD risk of just 10% and wonder whether atorva 10 would suffice recognising the dose relationship associated with side effects and majority effect with lowest dose statin etc	effective to treat people at 10% risk with atorvastatin 40mg. The GDG considered that such a dose may not be acceptable at this level of risk and made a consensus recommendation to recommend 20mg atorvastatin as the initial dose. Using a lower dose of atorvastatin would potentially increase the number of people who required up titration. The GDG were aware that people will be identified for primary prevention who are at much higher risks than 10% and that these people would benefit from being on higher rather than medium intensity statin (such as atorvastatin 10mg).
441	SH	United Kingdom Clinical Pharmacy Association	2	Full	4.1	Line 18	See above comments	Thank you for your comment.
175	SH	Royal College of General Practitioners	1	Full	4.1	40	Offer high intensity statins for those at >10% risk CVD This will be the biggest headline from the new guidelines. Reading through the full guideline, it is clear that you recommend this as a patient choice , including recommending the use of decision aids to assist informed decision making, This is excellent, but without this being made really explicit, it is likely/inevitable that the message that goes out to GPs, patients and the media is that NICE recommends statins for all >10% risk which is a very large section of the population, heading towards "statins for all". A more accurate message would be something like: "NICE recommends that statins may be offered to those at > 10% CVD risk as they have been shown to reduce relative risk of future CV events. However, the decision to take them or not is dependent on patient preference after	Thank you for your comment and detailed appraisal of the guideline. The GDG consider that informed patient choice is important and we are working with NICE implementation team and NICE medicine and prescribing centre to make available information and decision aids as you suggest. The decision aid that was included has now been removed as some of the content was out of date. We have added recommendations to highlight the importance of lifestyle

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					27	85	<p>explanation of the likely absolute benefits to them as an individual"</p> <p>Then: to assist understanding, a table or graphic should be presented demonstrating the benefit in terms of ARR, NNT as well as RRR at varying levels of background risk.</p> <p>This should be "on the front page". ie in the summary guideline and on NICE pathways as well as on press releases.</p> <p>I note that there is a link to decision aids embedded within the full guideline but this will not be noticed by many people. The recommendation (27) addresses this but needs to be put in the spotlight</p> <p>This is a more complex type of recommendation, but is essential is we are to avoid overtreatment and harmful polypharmacy. It will be a challenging message for public and media to absorb but this is an ideal opportunity to expand understanding about risk modification.</p>	modification and for re-assessment of risk if a patient wishes this.
175	SH	Royal College of General Practitioners	2	Full	4.1 Table 36	40 123	<p>"High intensity statins"</p> <p>This phrase is used throughout the guideline.</p> <p>I note that table 36 explains the definition of this, but it is likely that GPs will misinterpret the phrase to mean something like atorvastatin 80mg, so to avoid unnecessary overtreatment and side effects perhaps this phrase should be avoided and use something like "atorva 20 or comparable potency"</p>	Thank you for your comment. We have removed reference to 'high intensity' statins where possible in the recommendations.
59	SH	University of Nottingham	3	FULL	4.1	41	Point 12: why not use in CKD stage 1 or 2?	Thank you for your comment. These recommendations have been altered since consultation in line with classification recommended by the NICE Chronic Kidney Disease guideline. This indicates that a label of kidney disease requires evidence of damage to

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								<p>kidney and this is not necessarily present in people with $\text{egfr} > 60 \text{mls/min/1.73m}^2$. These people should not be considered to have kidney disease without other evidence such as presence of albuminuria.</p> <p>The information available on codes included in CKD in QRISK indicates that this includes people with a diverse range of kidney related disorders e.g. pyelonephritis many of whom will not have evidence of kidney damage.</p>
57	SH	University of Nottingham	1	FULL	4.2	40/41	<p>Recommendation 1 states "For the primary prevention of CVD in primary care, use a systematic strategy to identify people aged 40–74 who are likely to be at high risk"</p> <p>Recommendation 22 states "Consider people aged 85 or older to be at increased risk of CVD because of 7 age alone, particularly people who smoke or have raised blood pressure".</p> <p>There is a gap relating to patients aged 75 to 84 years - please clarify what recommendation applies to patients in this age group?</p>	<p>Thank you for your comment. The first recommendation was not updated in this guideline and was developed as a strategy to target people at highest risk. When the recommendation was developed the available risk tools did not cover people older than 74 years. Risk tools now include people up to 84 years and so we have amended the recommendation.</p>
58	SH	University of Nottingham	2	FULL	4.2	41	<p>Point 9. Unclear why not to do CVD risk assessment in people with type 1 diabetes?</p>	<p>Thank you for your comment. There is no validated risk assessment tool in this population. The GDG considered that the number of people with type 1 diabetes included in the QRISK2 development cohort was not high enough to recommend the tool in this population.</p>
60	SH	University of Nottingham	4	FULL	4.2	42	<p>Point 27. Mentions the "high cholesterol shared decision making aid" please also consider the www.qintervention.org which also presents absolute individualised risk/benefit scenarios.</p>	<p>Thank you for your comment. We have removed this decision aid from the recommendations as it was out of date. We are working with the NICE implementation team and NICE medicine</p>

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								and prescribing centre to make information and decision aids available.
61	SH	University of Nottingham	5	FULL	4.2	45	Point 61 – recommends use of UKPDS. Please see validation study for evidence demonstrating that this decision is NOT in the best interest of people with diabetes. The reasons for this are briefly summarised at points below.	Thank you for your comment and report. Following stakeholder comments the GDG discussed the available evidence for UKPDS and QRISK2. They agreed to recommend QRISK2 for use in people with Type 2 diabetes because UKPDS is relatively out of date and has been not validated in a large population. QRISK2 is also more readily available and GPs have experience of its use. Thank you for submitting your validation study. We look forward to external validation and further publication.
156	SH	Greater Manchester Commissioning Support Unit GMCSU	13	Full	4.2	49	Should clearly state that this applies to both primary and secondary prevention (i.e. this might be not clear to people using this guideline for first time and not familiar with previous version(s)).	Thank you for your comment. We have clarified that combination treatment is not recommended in primary or secondary prevention.
228	SH	Cholesterol Treatment Trialists' Collaboration	3	FULL	4.2	Recommendation 50 (page 44)	Correction of a dyslipidaemia is only really relevant when a person's excess risk of CVD is judged to be attributable (at least in part) to that dyslipidaemia. For example, a patient with CKD may have raised triglycerides, but below average LDL cholesterol, and still be at increased risk of CVD for reasons that may not be related to the dyslipidaemia. So it may not be necessary to reverse the raised triglycerides, although it may be appropriate to treat with a statin because that person is at increased risk of CVD. This is an important distinction because the guideline needs to change perceptions away from 'treating lipid abnormalities' to 'treating elevated risk'.	Thank you for your comment. The guideline is recommending treatment on the basis of overall risk. The baseline investigations are to identify any significant inherited disorders or any factors relevant to ongoing assessment and monitoring.
442	SH	United Kingdom Clinical Pharmacy	3	Full	4.2	61 and 62	Both points seem to relate to the same patient group but offer different advice – one states atorvastatin 80 mg the other high intensity statin – could one line be deleted?	Thank you for your comment. These recommendations have changed since stakeholder consultation.

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		Association						
163	SH	Greater Manchester Commissioning Support Unit GMCSU	20	Full	4.2.53	45	The 10% threshold seems unjustified in terms of benefit over significant input of resources. This takes on account current financial constraints.	Thank you for your comment, The GDG chose the 10% risk threshold after taking into account all the evidence, including the cost-effectiveness analysis detailed in Appendix L, which balances the financial costs of statins against their clinical benefits. The GDG's reasoning is explained in Section 11.8.1. The cost-effectiveness analysis found that it was cost effective to give high-intensity statin treatment to people with this level of cardiovascular risk, based on the same threshold of cost effectiveness (£20,000 per QALY gained) and the same methodology as used in all NICE guidance. The cost effectiveness analysis includes costs of consultations with healthcare professionals, costs monitoring and costs of adverse events.
164	SH	Greater Manchester Commissioning Support Unit GMCSU	21	Full	4.2.54	45	It is difficult to quantify an individual's benefit from switching from simvastatin 40mg, now classed as a medium intensity statin, to a high intensity statin. There is no clinical trial data available (listed in the 'Evidence statements' section) comparing simvastatin 40mg with any strength atorvastatin. There are studies comparing simvastatin 20mg with atorvastatin, and simvastatin 20mg and 40mg have been newly reclassified as belonging to same group of medium intensity statins. Therefore it has been assumed that use of simvastatin 20mg and 40mg brings similar outcomes. However, it needs highlighting that the new classification of statins for the use of this guideline is arbitrary. Cheaper simvastatin 20mg was also used for the economic evaluation rather than currently recommended	Thank you for your comment. We agree that it is unfortunate that there are not more head-to-head studies comparing different doses of statins, and that there were not enough comparable data for us to analyse each dose of statin separately, but instead it was necessary to group the statins into 3 classes. We agree that simvastatin 40 mg is likely to be more clinically effective than simvastatin 20 mg, although it is also more expensive and may give rise to more side effects. We would however wish to note that the clinical effectiveness data used for medium

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							simvastatin 40mg.	intensity statins in the economic evaluation is an average of the effectiveness of all statins included in medium intensity, including simvastatin 40 mg, and so this probably overstates the effectiveness of simvastatin 20 mg, whilst the cost used for medium intensity statins was that of simvastatin 20 mg, the cheapest statin in that group. If high intensity statins were cost effective compared to medium intensity statins under these assumptions, it is very unlikely that using a more expensive statin (simvastatin 40 mg) would make the results for medium intensity statins more favourable, even if slightly more effective results were to be generously assumed. We recognise that the grouping of statins is arbitrary but similar grouping has been used by other investigators (Ribeiro et al. 2013, Int J Card 166: 431-439).
150	SH	Greater Manchester Commissioning Support Unit GMCSU	7	Full	4.2.55	45	It needs to be clearly stated that the evidence on use of statins for people >85 is very limited (especially in the NICE version of guideline).	Thank you for your comment. The NICE version of the guideline does not usually refer to level of evidence. The term 'consider' in the recommendation denotes a less strong recommendation.
165	SH	Greater Manchester Commissioning Support Unit GMCSU	22	Full	4.2.62	45	Concerns regarding the use of high strength atorvastatin. Compliance might be affected as patients often believe that higher strength of a drug will have higher profile of side effects.	Thank you for your comment. Following stakeholder comments we have changed this recommendation to start on atorvastatin 20mg and uptitrate if appropriate.
167	SH	Greater Manchester Commissioning Support	24	Full	4.2.69	46	Concerns expressed by GPs representative regarding the consequences of treating to lipid reduction targets. Also, there is no clear indication on how to treat patients who do not respond to 3 stains.	Thank you for your comment. The guideline is not recommending treatment to target. The guideline recommends discussion

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		Unit GMCSU						with a specialist if patient is intolerant of 3 statins. The other available drugs do not have evidence of effect on hard outcomes and treatment with lipid modification drugs may therefore not be possible.
138	SH	Sanofi	2	FULL	4.2.69	46	For secondary prevention recommendation 69 should include an option for referral to a specialist when the necessary reduction in non-HDL cholesterol is not achieved. Currently the guideline only allows for escalation to a specialist when statins are not tolerated. High CV risk patients with a prior event need to be referred to a specialist when they are not achieving the necessary response and control, regardless of statin tolerance or dose.	Thank you for your comment. The guideline is not recommending treatment to target. The guideline recommends discussion with a specialist if patient is intolerant of 3 statins. The other available drugs do not have evidence of effect on hard outcomes and treatment with lipid modification drugs may therefore not be possible.
139	SH	Sanofi	3	FULL	4.2.70	46	Sanofi do not believe this recommendation is appropriate for secondary prevention. If these patients cannot tolerate the dose that is necessary for them to achieve appropriate LDLc levels, they should be escalated to a specialist, not simply have their dose reduced.	Thank you for your comment. The guideline is not recommending a treatment target. The GDG considered that people treated for secondary prevention of CVD include a spectrum of patients whose absolute risk varies. People will benefit from being on any statin and the other available drugs do not have evidence of effect on hard outcomes. Healthcare professionals can use their judgement as to who requires referral.
140	SH	Sanofi	4	FULL	4.2.72	46	Sanofi suggests the wording of recommendation 72 is made clearer. Does failure on three statins mean three different statins, or one statin at three different doses? Presuming the former, does this mean at the highest or lowest dose? Sanofi do not believe the recommendation for referral to a specialist after failing on three statins is appropriate for	Thank you for your comment. We have clarified that this means 3 different statins. The GDG considered that people treated for secondary prevention of CVD include a spectrum of patients whose absolute risk varies. Healthcare professionals can use their judgement as to who requires

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							secondary prevention patients. These very high risk patients need to be escalated through the system more quickly.	referral.
137	SH	Sanofi	1	FULL	4.2.8	41	Sanofi welcomes the recommendation to assess 10 year CV risk using the QRisk Tool. However, the decision over whether to commence statin therapy needs to better account for baseline LDLc. While LDLc is one of the determinants of risk in QRisk tool, the approach overlooks the greater reduction in LDLc (and hence greater reduction in CV risk) in response to statin therapy that is achieved by patients with a higher baseline LDLc (CTT, 2012). For example, assume patient A meets the 10% CV risk requirement to commence statin therapy. Patient B does not meet this requirement but has a higher baseline LDLc than patient A. Patient B might actually receive greater benefit from statin therapy than patient A. Basing the decision on whether to commence statin therapy solely on the QRisk assessment of 10 year risk will lead to sub-optimal allocation of resources because statin therapy only modifies one of the components of risk in the QRisk tool.	<p>Thank you for your comment. We agree that the scenario you suggest is plausible and that a study is required which looks at risk estimation using validated tools and examining interaction of treatments with baseline LDL levels. The GDG made a research recommendation on the use of IPD data for such an analysis.</p> <p>While statin therapy may modify only one component of risk the current evidence suggests that reduction of that component is associated with reduction in CV events at all risk levels.</p> <p>The decision to recommend high statin intensity was based on the RCT evidence of reduction of CV events and the HE model which included patient CV risk. We could not examine the magnitude of LDL-cholesterol and associated reduction in clinical events because many RCTs did not report the appropriate LDL-cholesterol lowering data.</p>
33	SH	New Devon CCG	6	FULL	5	53	With respect to the risk prediction for CVD, and using the figures given, the calculated sensitivity and specificity of the model for the correct future diagnosis of CVD is 79% and 99.6% respectively. This does not appear realistic (see comment 9) and calls into doubt the cost effectiveness calculations that are based on this model. .	Thank you for your comment. This chapter was not included in the guideline update. The cost effectiveness of statins is not based upon this model.
34	SH	New Devon	7	FULL	5	75	The use of the UKPDS score for diabetes acknowledges	Thank you for your comment. Following

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		CCG		L			there is some degree of double counting but considers this justified on the grounds that people with diabetes are at higher risk of CVD than others. The specificity and AUC of this risk tool are relatively low, again leading to considerable over treatment (see below). This is a further example of the pervading underlying presumption in favour of treatment within the guideline.	stakeholder comments the GDG discussed the available evidence on UKPDS and QRISK2. They have changed the recommendation to recommend QRISK2 for people with Type 2 diabetes as UKPDS is relatively out of date and has been not validated in a large population.
35	SH	New Devon CCG	8	FULL	5	76	The recommendations in the population of people with CKD are not based on any evidence of benefit. It is not clear why firm recommendations are made here, but not in other situations where there is no evidence.	Thank you for your comment. The GDG interpretation of the evidence and development of the recommendations is detailed in the evidence to recommendations tables for all the recommendations. In the analysis for efficacy of statin therapy we conducted subgroup analysis by strata, and one of the strata considered is people with CKD. There is evidence of benefit for all-cause mortality and non-fatal MI. In addition to the evidence, in formulating recommendations for this subgroup, the GDG took advice from the co-opted renal physician with a specialist interest in CVD prevention.
201	SH	Greater Manchester, Cumbria and South Lancashire Strategic Clinical Network	1	Full	5.2	51	The guidance states that: "A systematic approach to selection requires prior stratification of risk so that those at highest risk are reviewed first. This will result in a more effective choice of people for inclusion and a more efficient use of staff time and health service resources than an opportunistic approach." This indicates that low risk people should still be selected but later which is incompatible with the logic of the rest of the statement. This has been implications locally as after the initial risk assessment, greater priority will have to be given to inviting low risk individuals than high risk individuals who failed to attend in	Thank you for your comment. This section of the guideline was not updated. The strategy outlines a systematic strategy to identify those at highest risk. We agree that the implementation of the strategy requires consideration of local circumstances and previous invitations to attend for assessment.

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							response to earlier invites. Our view is that if on prior stratification of risk, a person has a ten year risk of below 8%, they should not be invited for the NHS Health Check as this is likely to identify almost all individuals who have a risk of at least 10% after a full assessment.	
36	SH	New Devon CCG	9	FULL	6	general	The document neglects to provide some basic information about actual numbers of people who would be treated under these guidelines. All risk tools have a degree of individual misclassification i.e. some people are classified as high risk and recommended treatment whereas in reality they are at low risk (and vice versa). Using the ROC curves displayed in the document (even though these are at population level and not individual level, hence they will underestimate the degree of misclassification) it is possible to see that at a sensitivity of 90%, the specificity is about 40%. From this information, it is calculated that between 63% and 76% % of the assessed population will be classified as high risk, if between 10%and 25% of the assessed population are truly at high risk. This will lead to considerable over treatment, and adverse effects.	Thank you for your comment. Information about number of people treated after implementing this guideline can be found in the costing tool, released at the time of the publication of the final guideline. The ROC curves in chapter 6 are reproduced from published papers based on a simulated population of 500,000 individuals, and there is uncertainty on whether they are truly representative of a real cohort of patients. Therefore the GDG would not draw any definite conclusions based on these studies alone. From the data reported from the other validation studies on cohort populations, it has not been possible to establish exactly what the sensitivity and specificity of QRISK2 is at the 10% intervention threshold.
62	SH	University of Nottingham	6	FULL	6.2	55	Table 7 lists risk factors included in the risk assessment tools. Whilst HBA1C was included in the UKPDS model for CHD, it was NOT included in the UKPDS stroke model. Please can the table be updated to clarify this. Also the HBA1C values included in the UKPDS CHD model are entered as % rather than as the new mmol/l IFCC values which are now in routine use within the NHS. If the UKPDS is to be used, then please clarify what units should be used, the conversion formula and how the UKPDS risk engine might easily be used by GPs.	Thank you for your comment. We have now amended table 7 accordingly.
63	SH	University of	7	FULL	6.2	55	Table 7: The UKPDS risk engine suggests that some	Thank you for your comment. We have

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		Nottingham		L			aspects of ethnicity are taken into account, this is minimal at best. Whilst they did look at 3 ethnic groups in the study, only Afro-Caribbean ethnicity came out as significant in the CHD model and none were significant in the stroke model. Hence ethnicity is only included in the CHD model as a binary variable (afro-Caribbean vs other) and ethnicity is not included in the UKPDS stroke model at all. Lots of studies have demonstrated a wide range of CVD risk and distribution of risk factors across different ethnic groups. As the UKPDS risk engine does not account for most of these differences, its use in people from different ethnic groups will be unreliable. Please can the table be updated to make this clear.	now amended table 7 accordingly.
64	SH	University of Nottingham	8	FULL	6.2	55	Table 7. Whilst the number of CHD events was not reported in the UKPDS CHD model, the number of strokes was included in the UKPDS stroke paper. There were 188 strokes. Can this be added to table 7 please?	Thank you for your comment. We have now amended table 8 accordingly.
65	SH	University of Nottingham	9	FULL	6.2	55	Table 7: UKPDS includes two levels of smoking (current smoker vs other) in the models not three levels as possibly implied by the entry in the table. Patients who are ex-smokers are therefore treated as if they are non-smokers. This will tend to under-estimate CHD and stroke risk in ex-smokers. QRISK2 has 5 levels for smoking status so will provide better quantification of risk for this important exposure.	Thank you for your comment. We have now amended table 7 accordingly.
66	SH	University of Nottingham	10	FULL	6.2	55	Table 7: mentions that atrial fibrillation is included in the UKPDS model. Atrial fibrillation is not included in the UKPDS CHD model. It is included in the stroke model. Please clarify this in the table	Thank you for your comment. We have now amended table 7 accordingly.
68	SH	University of Nottingham	12	FULL	6.2.2	60	There are no references to validation studies testing the modification of UKPDS suggested by NICE ie the arithmetic addition of CHD risk + stroke risk as calculated by two separate equations with different input variables. Table 10: the Guzder (2005) paper validated UKPDS in newly diagnosed diabetics based on affluent white patients living in the Poole area. The results do not necessarily	Thank you, we agree with your comment. In the evidence to recommendation section the GDG acknowledged that there would be a certain amount of double-counting. Following stakeholder consultation, the GDG have recommended the use of QRISK2 for

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							apply to prevalent cases of diabetes. Can this caveat be added.	people with type 2 diabetes. Regarding the Guzder 2005 paper, we do not think it is necessary to include further details in table 10, More details, including baseline characteristics, are available in the evidence tables in appendix G.1.
69	SH	University of Nottingham	13	FULL	6.2.2.	60	The Elkes (2008) study included patients with Type 2 diabetes aged 50-75 years from an outpatient clinic in West London. It used version 3 of UKPDS rather than version 1 which the guideline is recommending. Can the version of UKPDS included in the validation be clarified? The results were very similar for both UKPDS and for Framingham (both had a ROC of 0.63 which was poor). The original UKPDS was developed in patients aged 25-65 so the validation was outside of the range applicable to the UKPDS score. The validation cohort also excluded Black people. Overall, there is a lack of satisfactory evidence for the performance of UKPDS in unselected ethnically diverse patients from primary care across England . See validation study	Thank you for your comment. We have clarified UKPDS version 3 for the Elkes 2008 study in table 10.
70	SH	University of Nottingham	14	FULL	6.2.2.	60	The Simmons (2009) study used version 3 of UKPDS. Can this be clarified? All patients in the Simmons study were from Norfolk and were white. The study reported higher ROC values for Framingham than UKPDS.	Thank you for your comment. We have clarified UKPDS version 3 for the Simmons 2009 study in table 10. More details on patient characteristics are available in the evidence tables in appendix G.1.
71	SH	University of Nottingham	15	FULL	6.2.2.	61	The footnote for Table 10 states there are no separate validation results for QRISK2 in the diabetes population only. The QRISK authors have now calculated the relevant validation statistics in (a) patients with type 1 diabetes and (b) patients with type 2 diabetes. The results have been published here [validation study] and are summarised below.	Thank you for your comment and for sending us the report. The GDG have considered tools which have been externally validated only and look forward to external validation of QRISK2 in population with diabetes. However the GDG reviewed the available externally validated evidence and have changed their recommendation

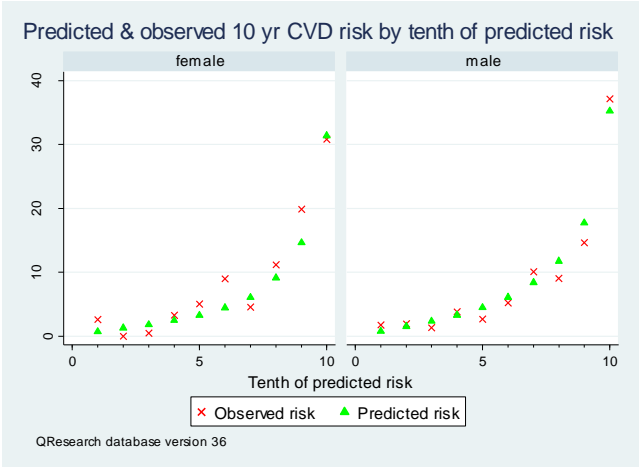
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								to recommend QRISK2 for people with Type 2 diabetes.
72	SH	University of Nottingham	16	FULL	6.2.2.	62	Guzder (2005) study results show significantly poor calibration. The calibration of QRISK2 in patients with diabetes is better with a close correspondence between predicted and observed risk as shown in Figures 1-3. [validation study] .	Thank you for your comment. Data on calibration (ratio predicted to observed) are reported in table 13.
231	SH	Cholesterol Treatment Trialists' Collaboration	6	FULL	6.5	Page 70	All-cause mortality is not a CV event. This is important in low risk populations because a minority of deaths will be due to CHD, and hence effects on all-cause mortality are likely to be small. All-cause mortality is therefore an insensitive outcome for assessing effects on CVD.	Thank you for your comment. We have removed all-cause mortality from the evidence to recommendation tables in section 6.5.
345	SH	AstraZeneca UK Ltd	2	Full	6.5	70	AstraZeneca welcomes the assessment of CV risk with a view to reducing this risk appropriately. The Joint British Society (JBS3) guidelines have been launched on the 26th March (jbs3risk.com). The JBS3 includes a new JBS3 risk calculator, whereas the NICE guideline recommends the QRISK2 risk calculator. In order to ensure consistency of use of risk calculators, AstraZeneca ask for specific reference and acknowledgement of the JBS3 risk calculator as an alternative option alongside the QRISK2.	Thank you for your comment. The risk tools assessed in the guideline were those for which external validation has taken place. The guideline is not recommending the use of a lifetime risk calculator as discussed in section 6.5. The JBS3 lifetime calculator is based on QRISK lifetime calculator; JBS3 are recommending this calculator for education and not for making decisions on lipid modification therapy, which they recommendation basing on 10-year cardiovascular risk.
337	SH	Association of British Clinical Diabetologists, Diabetes UK	12	FULL	6.5	72	<p>NICE stated that awareness of JBS3 but unfortunately the lack of consensus in two national documents being produced within same period will create real confusion for clinicians.</p> <p>These concerns apply not only to the section on diabetes but the issue of lifetime risk – evidence in younger type 2 DM aged less than 40 appear to have higher lifetime risk and worse prognosis than T1 DM of same age.</p> <p>Constantino MI, Molyneaux L, Limacher-Gisler F, Al-</p>	Thank you for your comment. The two guidelines agree in a number of important areas. JBS3 recommended that NICE guidance on the threshold for lipid modification is followed. We have also referred to the potential use of instruments such as JBS3 lifetime calculator for education particularly about life-style modification.

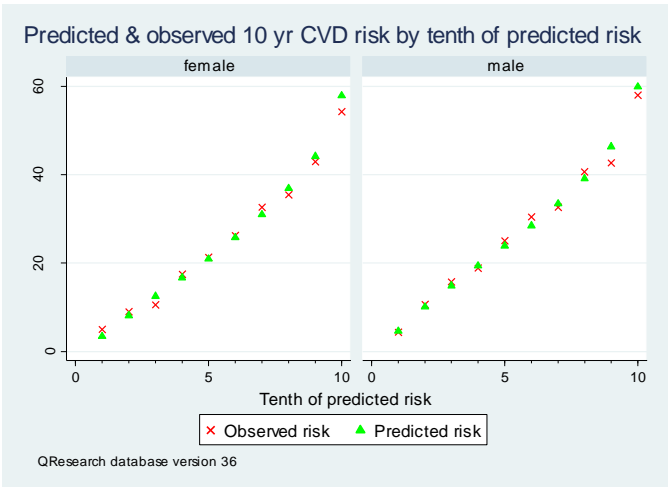
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							Saeed A, Luo C, Wu T, Twigg SM, Yue DK, Wong J. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. Diabetes Care. 2013 Dec;36(12):3863-9. doi: 10.2337/dc12-2455. Epub 2013 Jul 11. PubMed PMID: 23846814; PubMed Central PMCID: PMC3836093.	
42	SH	Cardiff and Vale University Health Board	2	FULL	6.5	72	<p>The following statement appears</p> <p><i>Following the health economics modelling, the GDG have chosen 10% 10-year CV risk as measured by QRISK2 as the threshold for offering drug therapy. None of the included studies reported data on this specific threshold;</i></p> <p>Offering a high intensity statin for the primary prevention of CVD to people who have a 10% (or greater) risk of CVD seems to be a low level of risk to be offering a drug for life. This means that there will be 10 people in 100 who in the next ten years will have a heart attack or stroke (assuming all at the 10% risk). All will need to take a statin for the 10 years and this means that 2 or 3 people will not have a stroke or heart attack, 7 or 8 people will still have their heart attack or stroke and for 90 people will not have a heart attack or stroke whether they had been on treatment or not. This is the benefit and this does not take into account any adverse effects people may have.</p> <p>Can the CVD risk be increased to a higher level than 10% to which offer drug treatment (20% at the moment)?</p>	<p>Thank you for your comment. The recommendations are based on clinical and cost-effectiveness evidence and do include consideration of adverse events. The GDG acknowledge the number needed to treat and have added this information to the guideline in Section 11.5.</p> <p>We also note that the figures given refer to the number of events predicted and averted in the first 10 years or treatment. As risk rises over time a higher number of events will be expected in following years, and this number will be reduced by the effect of several years of statin treatment already experienced.</p>
73	SH	University of Nottingham	17	FULL	6.5	73	<p>Recommendation 9. "Do not use risk assessment tool to assess CVD in people with Type 1 diabetes"</p> <p>We disagree with this statement – if the purpose of risk assessment includes explaining levels of risk to patients and highlighting potentially modifiable risk factors, then we can see no logical reason why patients with type 1 diabetes would not want to have this information as with</p>	<p>Thank you for your comment. The GDG discussed this issue at length, and concluded not to change this recommendation. The guideline has assessed tools that are externally validated only and await external validation of QRISK2 in population with</p>

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							<p>other patients. Given the lifelong nature of type 1 diabetes and risk of other complications, then this information could be useful to both the patient and the GP in terms of managing expectations and risk factors.</p> <p>Validation results for QRISK2 in 5588 patients which type 1 diabetes have been published here [validation study].</p> <p>In summary, for women</p> <ul style="list-style-type: none"> - R2 40.8 (33.2 to 48.4) - D statistic 1.698 (1.432 to 1.965) - ROC value 0.822 (0.788 to 0.856) <p>For men</p> <ul style="list-style-type: none"> - R2 48.1 (42.0 to 54.3) - D statistic 1.972 (1.729 to 2.215) - ROC value 0.841 (0.812 to 0.872) <p>The calibration is good with a close correspondence between predicted and observed risk as shown in the next graph</p> 	<p>diabetes. The GDG acknowledged that the QRISK2development cohort includes 5588 patients with type 1 diabetes, but concluded this was not a sufficient number of people to recommend the use of QRISK2 for this population and the decision to prescribe statin should be based on individual characteristics.</p>
74	SH	University of	18	FUL	6.5	74	Recommendation 10 "Use UKPDS to assess risk inl	Thank you for your comment and report.

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		Nottingham		L			<p>Please insert each new comment in a new row.</p> <p>patients with type 2 diabetes". "there have been no specific validations of QRISK2 in patients with diabetes"</p> <p>Validation results for QRISK2 in 26,759 patients with type 2 diabetes have now been published here [validation study].</p> <p>In summary for women with type 2 diabetes</p> <ul style="list-style-type: none"> - R2 23.2 (21.0 to 25.4) - D statistic 1.124 (1.054 to 1.195) - ROC value 0.703 (0.691 to 0.715) <p>For men</p> <ul style="list-style-type: none"> - R2 20.2 (18.2 to 22.2) - D statistic 1.031 (0.967 to 1.095) - ROC value 0.696 (0.685 to 0.706) - <p>The calibration is good with a close correspondence between predicted and observed risk as shown in the next graph</p> 	<p>Please respond to each comment</p> <p>The GDG discussed the available evidence on UKPDS and QRISK2, and they agreed that because UKPDS is relatively out of date and has been not validated in a large population that they would change the recommendation to use QRISK2 in type 2 diabetes. They accepted that QRISK2 is available and that people are familiar with its use.</p>

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75	SH	University of Nottingham	19	FULL	6.5	74	<p>UKPDS includes both HBA1C and duration of diabetes and the GDG "concluded that the UKPDS is the more relevant risk calculator system for type 2 diabetes".</p> <p>We have concerns about this statement in relation to duration of diabetes. According to the UKPDS paper (Stevens et al), the risk score for CHD was developed on patients with newly diagnosed diabetes who were then followed up over 10 years. We are unsure how such a model could then be applied to prevalent cases of diabetes and include duration of followup.</p> <p>Also HBA1C was not significant and not included in the stroke model. We don't know whether HBA1C would be significant in an overall model for CVD as the research presenting this is not cited.</p>	Thank you for your comment. Thank you, the GDG agree with your comment and have changed the recommendation on risk assessment in people with type 2 diabetes to reflect this.
76	SH	University of Nottingham	20	FULL	6.5	74	<p>"The GDG recommended that UKPDS score used should be the addition of score for CHD and stroke. They acknowledge that this is potentially double counting".</p> <p>We have considerable concerns about this since the calibration of UKPDS in the validation studies included in the draft guideline is generally poor. The simple addition of CHD and stroke risks will make this worse. The result would be to present an inaccurate level of CVD risk to patients which is misleading. For this reason the authors of the UKPDS website specifically recommend <i>against</i> adding CHD and stroke risks together.</p> <p>Fundamentally it is unsound to simply add the results of two completely different models with different risk factors.</p> <p>Recommending the continued use of QRISK2 would be the logical approach as it is already in common usage across the NHS and well integrated into the GP computer systems. A recommendation to now stop using QRISK2 in</p>	Thank you, the GDG agree with your comment and have changed the recommendation on risk assessment in people with type 2 diabetes to reflect this.

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							<p>people with diabetes and move to a risk score that is old and unfamiliar in primary care derived from an unrepresentative hospital population, with a limited range of variables that are important for individuals, is likely to disrupt the ambition for CVD risk assessment to be a routine part of clinical care.</p> <p>The main advantages of QRISK2 compared with UKPDS can be summarised as:</p> <ol style="list-style-type: none"> 1. QRISK2 is updated annually and so accounts for changes in evolving requirements (eg changes in age range), improvements in data quality, falling incidence of CVD and changing prevalence of risk factors (eg increasing obesity). UKPDS was based on data from 1977-1997 and has not been updated for more than 15 years and there is little prospect now of the original UKPDS score being updated. 2. QRISK2 is now integrated into all major GP systems and a number of pharmacy and other systems. This includes requirements to update annually. Introducing a separate score (UKPDS) to replace parts of the functionality would be an additional burden to the GP suppliers & could lead to inconsistent results. Eg if a patient is south Asian, from a deprived area, has rheumatoid arthritis, a positive family history of CHD, and type 2 diabetes, then which score should be used? Should it be QRISK2 which will take account of their rheumatoid arthritis, deprivation and ethnicity or UKPDS which will ignore those factors and potentially give a misleading risk estimate and potentially false reassurance 3. QRISK2 is modelled over the desired age range (including up to 85 years) whereas UKPDS is only modelled up to the age of 65 years. 4. QRISK2 predicts the required outcome of CVD whereas the version of UKPDS in the draft guideline, 	

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							<p>predicts stroke and CHD as separate outcomes which then need to be added together</p> <p>5. QRISK2 has been validated in primary care across England whereas the validation studies presented in the draft guidance are based on white affluent local populations from Dorset, Norfolk and hospital clinics in London. There is a lack of evidence for how UKPDS would perform in the setting into which NICE is recommending it is used. The current evidence for validation of UKPDS shows that the calibration is poor and there is no clear advantage over Framingham..</p> <p>6. QRISK2 accounts better for established risk factors including ethnicity (known to affect CV risk) and deprivation. Failure to incorporate these factors could lead to widening health inequalities.</p> <p>7. There are no references to validation studies of the modification to the UKPDS suggested in the guideline.</p>	
109	SH	National Clinical Guidelines centre CKD GDG	1	FULL	6.5 Recommendation 11	76	<p>The recommendations do not recognise the incontrovertible evidence that albuminuria (even low level albuminuria) is a powerful CVD risk factor. Whilst we agree we need better risk tools in CKD, ticking the CKD box on QRISK increases the relative risk by a factor of circa 2 in younger people, reducing with increasing age as one would predict. Most people with stage 1 and 2 CKD will have their CKD diagnosis on account of albuminuria, and to regard these people as being at the same risk as those with a normal ACR is surely not correct. All-cause mortality in stage 1&2 is at least as high as 3A without proteinuria. Also it is very likely that the stage 1&2 population are at increased risk from exactly the same pathological processes as in the non-renal population.</p>	Thank you for your comment. We have altered the recommendations in line with the classification of CKD in the updated NICE CKD guideline. These changes recognise the importance of albuminuria.
110	SH	National Clinical	2	FULL	6.5 Recommendation	76	<p>Taken together, neither of these recommendations inform what should be done to assess CV risk associated with</p>	Thank you for your comment. The recommendations on risk assessment

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		Guidelines centre CKD GDG			mendations 11&12		<p>CKD. They simply tell you what you should not do.</p> <p>If the tick box for CKD should not be used, perhaps should recommend that this box be removed?</p> <p>CV risk in the presence of isolated albuminuria should be considered. Therefore the QRISK2 score should be recommended in all individuals (including those with ACR>3, eGFR<60) – thus taking into account the risk consequent upon smoking, family Hx etc etc) – but with specific mention of the fact that CKD amplifies CV risk, and this amplification increases with increasing severity of CKD. Perhaps a reference to the NICE CKD guidelines, for example:</p> <p>1) When interpreting the QRISK2 score in patients with CKD stage 1-2, a decision to initiate risk-reduction should take into account the direct relationship between increased CV risk and albumin: creatinine ratio (ACR). [see NICE CKD Guideline]</p> <p>2) Do not use QRISK2 to assess the requirement for lipid-lowering therapy in people with CKD stage 3-5 [see recommendations 65-66]</p>	<p>are separated from the recommendations on treatment which are found in section on Lipid modification therapy (chapter 11), but we have clarified that people should be considered to be at risk and statin treatment considered.</p> <p>The QRISK2 tool is an independent tool and we cannot recommend that it is changed.</p> <p>We have altered the recommendations in line with classification in updated CKD guideline.</p>
77	SH	University of Nottingham	21	FULL	6.5	76	<p>Recommendation 12 – do not use risk assessment tool to assess CVD risk in patients with CKD stage 3 or greater.</p> <p>While we agree that the QRISK2 CKD term does not distinguish between different stages and may include a few other pathological processes, the bottom line is people who are classified in this way DO have increased risk and this needs to be considered in the risk assessment process.</p> <p>We accept the QRISK2 score, like all risk scores, is imprecise, but it is more precise than the approach that the</p>	<p>Thank you for your comment. The guideline considers that people with CKD should be considered to be at high and considered for treatment without the use of a risk tool.</p> <p>The GDG have altered the recommendations to recommend use of QRISK2 for Type 2 diabetes.</p>

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							<p>GDG are currently recommending in this draft guidance. For example, this draft is recommending the UKPDS risk engine that does not distinguish between the recognised differences between ethnic groups or amount of smoking. It seems illogical to change recognised practice because of imprecision, and recommend an approach with even more imprecision in many different areas. Furthermore, the current recommendation does not explain how to risk assess people with combinations of different risk factors eg with T2DM and CKD, or CKD and RA +/- T2DM. Decision making for individuals is important and leaving significant gaps, or recommending an old risk score unknown to GPs, will undermine the faith of practitioners in the whole risk assessment process.</p> <p>While recognising the limitations of any CVD risk assessment, it is much better that one is done, rather than for individuals to be missed and clinicians confused. QRISK2 is a simple tool to use that can be used with reasonable confidence in most primary care patients. The decision to change accepted practice needs to be made only when there is considerable evidence that patients and the clinicians will be better served. In this case, the evidence points to the changes resulting in a worse service than sticking with a tried and tested approach that is integrated into routine clinical systems.</p>	
202	SH	Greater Manchester, Cumbria and South Lancashire Strategic Clinical Network	2	Full	6.6	77	It should state that people who, as a result of cascade screening, are found to have the gene but do not have raised cholesterol, should be followed up whether by the NHS Health Check or other means	Thank you for your comment. The appropriate monitoring and treatment of people with FH or identified by FH cascade screening are outside the scope of this guideline. There is separate NICE guidance for people with FH; http://publications.nice.org.uk/identification-and-management-of-familial-hypercholesterolaemia-cg71 .

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78	SH	University of Nottingham	22	FULL	6.6	77	Point 19 – states that standard risk scores will underestimate risk in patients who have an additional risk such as...rheumatoid arthritis. QRISK2 includes rheumatoid arthritis as a variable so this is accounted for. Please can you update the text to reflect this.	Thank you for your comment. We have made this change as you suggest.
79	SH	University of Nottingham	23	FULL	6.6	77	Point 20. Please note that unlike UKPDS, QRISK2 does include categories for ex-smoker and taking antihypertensive medication which is relevant here.	Thank you for your comment. The recommendation is highlighting that clinical judgement may be required in this circumstances. For example an ex-smoker may be someone who stopped smoking 10 years ago or 3 months ago.
80	SH	University of Nottingham	24	FULL	6.7	78	<p>There is a research recommendation to simplify risk assessment. The current draft guidance is recommending an unfamiliar risk score that does not apply to lots of people from different ethnic groups and with different comorbidities. This is certain to make clinical decision making much more complex.</p> <p>While a risk score model such as QRISK2 may appear complex, it is actually very simple to use in practice due to its integration with the GP clinical systems that means data does not have to be manually entered which would be the case with using the UKPDS risk engine. The number of variables is irrelevant to a score's ease of use if the data is populated automatically.</p> <p>We do not agree that more research is needed in producing 'simpler' risk scores. It is well known that reducing the number of risk factors will reduce the accuracy and a more accurate multifactorial risk score, well integrated in GP systems is very easy to use. The key research questions are around widening access to risk assessment and appropriate primary prevention. Doing more research on the statistics around CVD risk scores is a distraction from the much more important and challenging issue of implementation.</p>	<p>Thank you for your comment. Following stakeholders consultation, the GDG re-discussed the evidence on risk assessment tools in people with type 2 diabetes, and concluded to recommend QRISK2 and not UKPDS for this population.</p> <p>The GDG however decided that the research recommendation on simplified risk tools should remain in the guideline. There are published studies on simulated populations that conclude that risk assessment based on age-alone has performances similar to multi-factorial risk assessment tools. The GDG considered it important that before such more simplified methods are introduced studies should examine issues such as misclassification using simpler methods.</p>

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67	SH	University of Nottingham	11	FULL	Table 7		Table 7 states that UKPDS algorithm accepts two input variables (total and HDL-C). However the input to the published algorithm only accepts the ratio value and is in this respect the same as QRISK2. Please can this be updated.	Thank you for your comment. The table has been amended accordingly.
323	SH	Heart UK- The Cholesterol Charity	70	Full	7.5	85	Section 7.5 contains a great deal of information about communication of <i>risk</i> through numerical, graphical and visual means. HEART UK believes that patients often respond well to information about their actual cholesterol levels, including the numbers for those levels. Knowing their actual cholesterol level and its relationship with risk (and what sort of level it needs to be to reduce risk) would be useful to include in communication to patients. HEART UK receives many calls on its helpline, asking for assistance with understanding their cholesterol numbers. This information could be better conveyed by healthcare professionals. At present, the revised Guideline does not deal sufficiently with the communication of <i>numbers</i> to patients.	Thank you for your comment. The guideline is recommending treatment on the basis of overall cardiovascular risk and not on the basis of cholesterol numbers. The GDG recognise that people often place emphasis on cholesterol levels and consider that there is a need to communicate better about overall risk modification and absolute risk.
131	SH	Unilever	4	FULL	Section 8		Plant stanols/sterols have been independently evaluated by EFSA to reduce a major risk factor in the development of Coronary Heart Disease. We therefore believe the consumption of these foods should be included in the diet, in the primary prevention of coronary heart disease. .	Thank you for your comment. The GDG wished to see effects on hard outcomes such as morbidity and mortality rather than surrogate outcomes before making recommendations.
380	SH	British Dietetic Association	8	Full	8	general	Dietitian spelt incorrectly throughout	We apologise for this and have corrected this error.
37	SH	New Devon CCG	10	FULL	8	general	The evidence base for dietary recommendations is all of low or very low quality, and the majority of it shows no effect. Nevertheless the guideline group felt it appropriate to make firm recommendations.	Thank you for your comment. The updated guideline included RCT evidence on diet and were also informed by the guideline development group which included a dietician, consideration of epidemiological evidence and government policy.

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382	SH	British Dietetic Association	10	Full	8	Studies included	DART2 was excluded from the original group of papers for consideration by the GDG because of its poor methodological quality and it is included in this consultation paper. The inclusion or exclusion of this study has a key influence on the results of the metanalysis. It has been excluded from other recent systematic reviews for the same reasons it was originally excluded from this review. It will enhance the credibility of the guideline if an explanation of its inclusion is given.	The guideline development group considered that this study should be included. The quality of studies in the review is reported in the GRADE tables and in the evidence extractions in Appendix G. Further information has been added on the quality of DART 2 in the recommendations and link to evidence section.
388	SH	Johnson & Johnson Ltd.	1	Full	8.6	106-108	We note that formal searches for evidence were limited to randomised controlled trials with outcomes that include cardio vascular events. No evidence of benefit was found for the following interventions; low fat, increased fibre, increased fruit and vegetables and increased oily fish. Yet, for example – ‘eat at least 5 portions of fruit and vegetables per day’ was recommended for those at high risk of or with CVD despite evidence that the effect could favour usual diet. The GDG were cognisant that the dietary recommendations would be unlikely to cause harm and recognised that they might impose costs and that the long term benefit may appear less important to those on reduced budgets . However, they considered it would not be adequate to overturn the principles of healthy eating.	Thank you for your comment. This guideline is concerned with Lipid modification and the evidence reviews on diet looked specifically at this area. The recommendations were based on the evidence from RCTs and the opinion of the guideline development group which included a dietitian. Diet however is important for areas other than cardiovascular health and the GDG judged that the specific evidence on CVD outcomes was not adequate to overturn general dietary recommendations made as part of wider government policy.
373	SH	British Dietetic Association	1	Full	8.8.5	General	The control for interventions have been incorrectly described as usual diet. For example, in the case of the Lyon Heart Study the control intervention is described as a prudent diet or what we would translate as healthy eating, in the Predimed study the control intervention is the AHA Step 1 diet. Other key differences are that in the Lyon Heart study the control intervention was physician led and the study intervention was Dietitian led. The Predimed trial study arm was a Dietetic intervention. It is important to check for each of the studies cited what the control arm intervention was and if there was no	Thank you for your comment. Further information on the control for interventions has been added to the summary tables describing the studies, the evidence statements and other considerations section.

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							<p>intervention. The term usual diet implies that there has been no control dietary intervention.</p> <p>This is also referred to in the section on other considerations where it says "control group may have been following an atypical diet". The control group were not advised to follow their usual diet they were given the usual intervention diet which is not typical of the wider population.</p> <p>The control group in each study cited should be accurately described and this reflected in the evidence statements.</p>	
206	SH	Greater Manchester, Cumbria and South Lancashire Strategic Clinical Network	6	Full	8.8.5	General	<p>The control for interventions have been incorrectly described as usual diet. For example, in the case of the Lyon Heart Study the control intervention is described as a prudent diet or what we would translate as healthy eating, in the Predimed study the control intervention is the AHA Step 1 diet. Other key differences are that in the Lyon Heart study the control intervention was physician led and the study intervention was Dietitian led. The Predimed trial study arm was a Dietetic intervention.</p> <p>It is important to check for each of the studies cited what the control arm intervention was and if there was no intervention. The term usual diet implies that there has been no control dietary intervention.</p> <p>This is also referred to in the section on other considerations where it says "control group may have been following an atypical diet". The control group were not advised to follow their usual diet they were given the usual intervention diet which is not typical of the wider population.</p>	Thank you for your comment. Further information on the control for interventions has been added to the summary tables describing the studies, the evidence statements and other considerations section.
375	SH	British Dietetic Association	3	Full	8.8.6	General	<p>Predimed results</p> <p>This trial is particularly important as it is the only study to have taken place since the publication of the last</p>	Thank you for your comment. The guideline development group considered that for consistency only individual

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							guidelines. The guidelines report some of the results but omit the primary endpoint of a composite of MI, stroke and CV causes.	outcomes should be meta-analysed across all reviews, rather than composite outcomes. Information on the primary composite outcome in PREDIMED has been added the recommendations and link to evidence section.
208	SH	Greater Manchester, Cumbria and South Lancashire Strategic Clinical Network	8	Full	8.8.6	General	Predimed results This trial is particularly important as it is the only study to have taken place since the publication of the last guidelines. The guidelines report some of the results but omit the primary endpoint of a composite of MI, stroke and CV causes.	Thank you for your comment. The guideline development group considered that for consistency only individual outcomes should be meta-analysed across all reviews, rather than composite outcomes. Information on the primary composite outcome in PREDIMED has been added the recommendations and link to evidence section.
377	SH	British Dietetic Association	5	Full	8.8.6	Other Considerations	You make the point that there are cultural differences in the intervention in the Spanish, French and Indian studies. The cardioprotective diet can be achieved with different food types and cuisines including foods of the "British diet". The differences between the nutrient intake of the study participants is demonstrated to have been influenced by the intervention and the extent of the effect of cultural difference in the cuisine is not known. One of the problems in using the term Mediterranean is that it suggest that it is the cuisine that is recommended rather than a set of nutrient and food guidelines.	Thank you for your comment. We agree that the term Mediterranean diet may not be helpful and have not used it in the recommendations. Some studies in the evidence review reported on Mediterranean diet, hence the review of the evidence used this term.
210	SH	Greater Manchester, Cumbria and South Lancashire Strategic Clinical Network	10	Full	8.8.6	Other Considerations	You make the point that there are cultural differences in the intervention in the Spanish, French and Indian studies. The cardioprotective diet can be achieved with different food types and cuisines including foods of the "British diet". The differences between the nutrient intake of the study participants is demonstrated to have been influenced by the intervention and the extent of the effect of cultural difference in the cuisine is not known. One of the problems in using the term Mediterranean is that it suggest that it is the cuisine that is recommended rather than a set	Thank you for your comment. We agree that the term Mediterranean diet may not be helpful and have not used it in the recommendations. Some studies in the evidence review reported on Mediterranean diet, hence the review of the evidence used this term.

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							of nutrient and food guidelines.	
376	SH	British Dietetic Association	4	Full	8.8.6	Quality of Evidence	"The majority of studies of studies were underpowered". In the results of the Predimed trial they report the data for a composite primary endpoint that was significantly positively affected by the study intervention (30% reduction RR). Whilst it is understood that this combined endpoint was not included in the scope of the guidelines it is worth including this in the narrative at this point given the significance of this trial and the paucity of dietary studies with mortality as an endpoint. Of course it is influenced by the positive outcomes for stroke.	Thank you for your comment. The guideline development group considered that for consistency only individual outcomes should be meta-analysed across all reviews, rather than composite outcomes. Information on the primary composite outcome in PREDIMED has been added the recommendations and link to evidence section.
209	SH	Greater Manchester, Cumbria and South Lancashire Strategic Clinical Network	9	Full	8.8.6	Quality of Evidence	"The majority of studies of studies were underpowered". In the results of the Predimed trial they report the data for a composite primary endpoint that was significantly positively affected by the study intervention (30% reduction RR). Whilst it is understood that this combined endpoint was not included in the scope of the guidelines it is worth including this in the narrative at this point given the significance of this trial and the paucity of dietary studies with mortality as an endpoint. Of course it is influenced by the positive outcomes for stroke.	Thank you for your comment. The guideline development group considered that for consistency only individual outcomes should be meta-analysed across all reviews, rather than composite outcomes. Information on the primary composite outcome in PREDIMED has been added the recommendations and link to evidence section.
374	SH	British Dietetic Association	2	Full	8.8.6	30 32	These are key principles of the AHA step 1 diet which are the control intervention for the Predimed study. The AHA no longer uses this terminology and their recommendations have changed; for example they now recommend saturated fat to contribute 6% of less of the energy in the diet. They also include a recommendation to consume nuts	Thank you for your comment. We have amended the recommendation.
207	SH	Greater Manchester, Cumbria and South Lancashire	7	Full	8.8.6	30 32	These are key principles of the AHA step 1 diet which are the control intervention for the Predimed study. The AHA no longer uses this terminology and their recommendations have changed; for example they now recommend saturated fat to contribute 6% of less of the	Thank you for your comment. We have amended the recommendation.

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		Strategic Clinical Network					energy in the diet. They also include a recommendation to consume nuts	
378	SH	British Dietetic Association	6	Full	8.8.6	31	<p>In the first bullet point in addition to telling people that their monounsaturated intake will be reduced by reducing their intake of animal sources it should also say here that this can be readily is replaced by use of olive oil and rapeseed oil in food preparation.</p> <p>This is a separate point from the one about using these oils to replace saturated fat.</p>	Thank you for your comment. We have amended the recommendation.
211	SH	Greater Manchester, Cumbria and South Lancashire Strategic Clinical Network	11	Full	8.8.6	31	<p>In the first bullet point in addition to telling people that their monounsaturated intake will be reduced by reducing their intake of animal sources it should also say here that this can be readily is replaced by use of olive oil and rapeseed oil in food preparation.</p> <p>This is a separate point from the one about using these oils to replace saturated fat.</p>	Thank you for your comment. We have amended the recommendation.
379	SH	British Dietetic Association	7	Full	8.8.6	32	<p>Nuts and pulses are also key features of the cardioprotective diet and these should be included; Unsalted nuts included as a regular part of the diet Pulses; peas beans and lentils to be consumed on a regular basis.</p> <p>This was part of the Lyon Heart Study Intervention.</p>	Thank you for your comment. We have amended the recommendation.
212	SH	Greater Manchester, Cumbria and South Lancashire Strategic Clinical Network	12	Full	8.8.6	32	<p>Nuts and pulses are also key features of the cardioprotective diet and these should be included; Unsalted nuts included as a regular part of the diet Pulses; peas beans and lentils to be consumed on a regular basis.</p> <p>This was part of the Lyon Heart Study Intervention.</p>	Thank you for your comment. We have amended the recommendation.

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85	SH	Weightwatchers UK	2	FULL	9.5 9.7.3	118-119	<p>With reference to weight management, the draft guidance simply refers readers to the clinical guidance on Obesity CG43 stating: "For guidance in weight management in people at high risk of CVD refer to the NICE guideline..."</p> <p>However, the NICE CG43 does not specifically offer recommendations for weight management in people at high risk of or diagnosed with CVD; it offers general advice for the identification and treatment of unhealthy weight.</p> <p>This lipid guidance has the opportunity to be the source of recommendations for weight management in people at high risk of or diagnosed with CVD, but currently does not deliver that. At present therefore, there are no guidance available to support decision making specifically for this population group.</p> <p>It is recommend to adapt this sentence to; "For guidance on identification and treatment of overweight and obesity refer to the NICE guideline...".</p> <p>Within the recommendations section it states; "Offer people at high risk of or with CVD who are overweight or obese appropriate advice and support to work towards achieving and maintaining a healthy weight, in line with NICE CG43".</p> <p>Firstly, it is questioned how the use of the current CG43 links with the forthcoming PH guidance on adult lifestyle weight management, in which elements are vastly updated vs CG43. Is the proposed guidance future proof? Will guidance 9.5 be expanded to reflect all the NICE guidance documents in this area, as has been done for the smoking cessation section? There are more useful sources to reference than just CG43.</p>	<p>Thank you for your comment. We will refer to the NICE guideline on Obesity and all other relevant clinical and public health guidelines. These will also be linked on the NICE website using NICE pathways.</p> <p>This guideline did not attempt to cover all interventions likely to improve cardiovascular health but examined Lipid modification only.</p> <p>All NICE guidance is reviewed and updated and regular intervals as it is recognised that evidence changes.</p>

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							<p>In addition, it seems that there has been a missed opportunity to offer valuable and impactful guidance relating specifically to weight management for those at high risk of or diagnosed with CVD; simply referring readers to another piece of general guidance. It is suggested that the recommendation (recommendation 42) is expanded and enhanced to be far more useful for readers, for example:</p> <ol style="list-style-type: none"> 1. Advise all people who are overweight or obese that aiming to lose and maintain modest amounts of weight loss (5-10%) can significantly improve blood lipids and other risk factors of CVD 2. Aligned with the smoking cessation statement (9.7.5 / 45), the language and content is recommended to be changed to: "Offer people at high risk of or diagnosed with CVD who are overweight or obese and want to lose weight, appropriate advice and support, and referral to an effective lifestyle weight management service operating in line with NICE CG43 and PH xx (relating to the adult lifestyle weight management guidance due in May 2014'. 3. If a person is unable or unwilling to accept a referral to an effective lifestyle weight management service, ensure that they are aware they can access the service another time when they may be ready and more able to commit to making lifestyle changes. <p>We would like see advice about lifestyle weight management services to have more specific directives that people are referred to or offered interventions with proven efficacy. Weight Watchers has a depth of experience in</p>	

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							<p>developing, operating, evaluating and improving behavioural weight management programmes for the public sector. There is strong acknowledgement of the availability and efficacy of service providers such as Weight Watchers. Previous submissions to NICE have detailed the evidence underpinning this experience.</p> <p>In reality lifestyle weight management services are a very broad category of programmes and providers which differ in the methods they use, the type of training they provide to their facilitators, the materials they provide for their participants, the level and types of behavioural interventions, target audiences, whether physical activity is incorporated into delivery of the intervention, governance and QA in place, evidence of efficacy and effectiveness, costs and cost effectiveness etc. Most fundamental is the difference in the amount and quality of studies underpinning the effectiveness of different programmes. Some programmes, such as Weight Watchers, have good quality data on self-referring / self-funding participants and those referred via health professionals and / or services, derived from RCTs published in high impact peer reviewed journals such as the BMJ and the Lancet. Others have none. Each and every service / programme needs to be assessed in their own right and not amalgamated into to simply 'lifestyle weight management services', rather 'lifestyle weight management services that have proven efficacy'.</p>	
389	SH	Johnson & Johnson Ltd.	2	Full	9.2.4	112-119	<p>With regard to regular physical activity due to lack of clinical outcome data the GDG based their recommendations on The Chief Medical Officer's report, NICE Public Health Intervention Guidance and The Joint British Societies' Guidelines on prevention of CVD in clinical practice. For combined effects of diet and physical exercise the advice was based on National</p>	Thank you for your comment. Please see our response to comment 393.

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							Guidance.	
203	SH	Greater Manchester, Cumbria and South Lancashire Strategic Clinical Network	3	Full	9.6	118	Nortriptyline (Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. <i>Cochrane Database of Systematic Reviews</i> 2007(1):CD000031) should be included in drugs to aid smoking cessation as its effectiveness has been shown by a Cochrane Review.	Thank you for your comment. Smoking cessation was not specifically examined in this guideline. We have referenced existing NICE guidance on smoking cessation.
393	SH	Johnson & Johnson Ltd.	6	Full	10	120-122	<p>A key Public Health England priority is 'helping people to live longer by reducing preventable deaths from conditions, such as, heart disease, stroke, cancer and liver disease'. Over 6 percent total years of life are lost in UK due to the risk factor high cholesterol alone based on 2010 data (Tedstone, 2014, Public Health England and Registered Nutritionists). Diet plays a key role in prevention of CVD with 70,000 premature deaths preventable in the UK if nutritional recommendations on salt, saturated fat and added sugar were matched. The economic burden of diet related ill health is estimated at 5.8 billion to the NHS (Tedstone, 2014, Public Health England and Registered Nutritionists). Given these statistics it is imperative that all efficacious foods/ ingredients are included in a cardio-protective diet particularly those where evidence supports effects on CVD risk-factors.</p> <p>In the current Lipid Modification (Update) Guidelines, certain recommendations have been based singly or in combination on the following :</p> <p>National dietary guidelines Recommendations of expert bodies Recommendations of expert body based on surrogate markers. Yet in relation to phytosterols there appears to be an inconsistency as these lines of evidence were not</p>	Thank you for your comment. The GDG considered stanols and sterols to be additions to dietary measures rather than part of standard diet. As such they wished to see outcomes on morbidity and mortality outcomes rather than on surrogate markers.

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							<p>considered as appropriate evidence. We would respectively ask for a re-consideration of the recommendation on phytosterols, particularly in relation to foods with added phytosterols.</p> <p>Given the body of evidence demonstrating significant cholesterol lowering we urge the GDG to modify their recommendations to include foods with added phytosterols as part of cardio-protective diet and lifestyle modifications, at least in primary prevention, particularly given the significant impact of these foods on the surrogate marker that has been accepted as sufficient evidence in the case of Ezetimibe. This request is supported by the recommendations of the recent European Atherosclerosis Society Panel (2014) 'foods containing phytosterols may be considered in individuals with high cholesterol levels at intermediate or low global risk who do not qualify for pharmacotherapy; as an adjuvant to pharmacological therapy in high and very high risk patients who fail to reach LDL cholesterol targets on statins or who are intolerant to statins...' ((European Atherosclerosis Society, 2014) and the Joint British Societies Consensus recommendations for the prevention of CVD (JBS3) published today which state in relation to phytosterols that 'it is reasonable to postulate a beneficial effect on CVD outcomes based on the LDL lowering hypothesis'. (JBS3, Heart 2014: 10, ii1-i67).</p>	
339	SH	Association of British Clinical Diabetologists, Diabetes UK	14	FULL	Recn. 10	74-75	<p>Please see following paper for cost effectiveness in type 2 albeit from Netherlands. Same concepts apply</p> <p>de Vries FM, Denig P, Visser ST, Hak E, Postma MJ. Cost-effectiveness of statins for primary prevention in patients newly diagnosed with type 2 diabetes in the Netherlands. Value Health. 2014 Mar;17(2):223-30.</p>	Thank you for your comment. Following stakeholder consultation the GDG have reviewed the recommendation to use UKPDS in people with Type 2 diabetes and now recommending the use of QRISK2 for people with Type 2 diabetes and to start treatment with atorvastatin

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							<p>doi:10.1016/j.jval.2013.12.010. PubMed PMID: 24636380.</p> <p>It seems a backward step to revert to risk scoring in type 2 patients >40 years of age – fire and forget has considerable benefits. With CVD risk threshold proposed at 10%, then this has even more advantages. The dose of statin used is contentious but could be argued for simvastatin 40 or atorvastatin 20 rather than high dose atorvastatin – JBS3 recommends intensive statin if DM plus CVD or proteinuria or renal disease since these are the high risk groups but if no proteinuria or renal disease, lower risks do not justify intensive statins</p> <p>Preiss D, Sattar N, McMurray JJ. A systematic review of event rates in clinical trials in diabetes mellitus: the importance of quantifying baseline cardiovascular disease history and proteinuria and implications for clinical trial design. Am Heart J. 2011 Jan;161(1):210-219.e1. doi: 10.1016/j.ahj.2010.10.019.</p> <p>Tonelli M, Muntner P, Lloyd A, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet 2012;380(9844):807-14.</p> <p>NICE GDG state 'UKPDS and Framingham performance equivalent in type 2 diabetes' but this has been refuted in several papers and the contemporary relevance can be questioned. In addition the utility of these risk engines has not been effectively validated in the BME diabetes population:</p> <p>Assessing 10-year coronary heart disease risk in people with Type 2 diabetes mellitus: Framingham versus United Kingdom Prospective Diabetes Study.</p>	<p>20mg.</p> <p>The paper by deVries looks at the cost effectiveness of using simvastatin 40mg for primary prevention in people with T2D.</p> <p>The base case is highly cost effective, but it also looks at various age and risk subgroups.</p> <p>For people <45 it is not cost effective for 3/5 risk subgroups</p> <p>For people 45-55 it is not cost effective for the lowest risk subgroup</p> <p>Their conclusions include that treating people under 45 is not cost effective. This would seem to support risk scoring rather than treating on age alone in a population with Type 2 diabetes.</p>

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							<p>Patricia A. Metcalf, Susan Wells, Rod T. Jackson, Journal of Diabetes Mellitus. Vol.4 No.1, February 2014</p> <p>Coronary heart disease risk assessment in diabetes mellitus: comparison of UKPDS risk engine with Framingham risk assessment function and its clinical implications. S. H. Song and P. M. Brown .Diabetic Medicine Volume 21, Issue 3, pages 238–245, March 2004</p> <p>Prediction models for the risk of cardiovascular disease in patients with type 2 diabetes: a systematic review. S van Dieren¹ J W J Beulens¹, A P Kengne^{1,2,3}, L M Peelen¹, G E H M Rutten¹, M Woodward³, Y T van der Schouw¹, K G M Moons¹ Heart 2012;98:360-369</p> <p>In the latter paper it states: The UKPDS risk engine for stroke was validated in two studies, which obtained very different results. One study observed an AUC of 0.61 and a poor calibration, while the other observed an AUC of 0.86 and good calibration. The UKPDS risk engine for CHD was validated in eight studies. Discrimination ranged from 0.65 to 0.76, and most of these studies observed poor calibration with an overestimation of the risk.</p> <p>Thus whether adoption of UKPDS risk screen into clinical care will actually improve clinical outcomes or potentially worsen them is currently uncertain</p>	
129	SH	Unilever	2	FULL	10	page 120	<p>We would suggest considering, as an adjunct to this guidance, the findings of the recent EAS Consensus Panel Paper on <i>“Plant sterols and plant stanols in the management of dyslipidaemia and the prevention of cardiovascular disease”</i>, published in Atherosclerosis 2014. (Gylling <i>et al</i> Atherosclerosis 2014: 232; 346-360</p>	<p>Thank you for your comment. The GDG considered stanols and sterols to be additions to dietary measures rather than standard dietary interventions. As such they wished to see outcomes on morbidity and mortality outcomes rather</p>

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							<p>doi:10.1016/j.atherosclerosis.2013.11.043).</p> <p>This paper recommends that foods with added plant sterols and plant stanols in an amount up to 2 g/d are equally effective in lowering plasma atherogenic LDL cholesterol levels by up to 10%. Thus, plant sterols/stanols may be considered as an adjunct to diet and lifestyle approaches in subjects at all levels of CVD risk.</p> <p>On the basis of their critical assessment the Consensus Panel of 21 international experts concluded that foods with added plant sterols/stanols may be considered in the following populations:</p> <ul style="list-style-type: none"> • Individuals with high blood cholesterol levels but with intermediate or low global CVD risk who therefore do not (yet) qualify for drug treatment. • Subjects receiving lipid-lowering therapy such as statin treatment who fail to achieve LDL-cholesterol targets, or in those who are statin-intolerant, in conjunction with other lifestyle interventions. • Adults and children (>6 years) with familial hypercholesterolemia especially in light of the increasing importance of early preventive strategies in hypercholesterolemia. <p>In addition two commentaries on the consensus paper have been published. Stock, Atherosclerosis 2014 and Zampelas, Atherosclerosis 2014.</p>	than on surrogate markers
390	SH	Johnson & Johnson Ltd.	3	Full	10.6	120-122	Substantiation that phytosterols are CVD risk factors in their own right should be referenced and requires more specificity.	Thank you for your comment. The approach of the guideline was to look for effect of interventions on morbidity and mortality outcomes and to outline specific

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							Phytosterols are also incorporated into food products which can form part of a healthy balanced diet, in addition to being available as food supplements and thus foods with added phytosterols should be mentioned in the introduction and considered.	risk factors. The GDG considered stanols and sterols to be additions to dietary measures rather than standard dietary interventions. As such they wished to see outcomes on morbidity and mortality outcomes rather than on surrogate markers. Phytosterol enriched foods were included in the search strategy. Following stakeholder comments the GDG discussed whether a distinction should be made between phytosterols incorporated into foods and food supplements. They considered that they would need to see evidence of beneficial effect of stanols and sterols on hard outcomes before making specific recommendation that people should buy foods with added phytosterol. We have added reference to foods with added phytosterols to the introduction.
391	SH	Johnson & Johnson Ltd.	4	Full	10.6	121-122	<p>While foodstuffs with no clinical evidence were recommended (Section 8) by the GDG, the plant stanols and sterols recommendation was 'Do not advise plant stanols or sterols for the prevention of CVD to any of the following:</p> <ul style="list-style-type: none"> • people who are being treated for primary prevention • people who are being treated for secondary prevention • people with CKD • people with type 1 diabetes • people with type 2 diabetes'. <p>The GDG noted that supplementation of phytosterols to the diet would impose additional costs and may impact on the healthiness of the individual or family's diet as a whole.</p>	<p>Thank you for your comment. The guideline update looked for RCT evidence for recommendations on diet and used these to inform the recommendations. Diet is important for conditions other than CVD and so the recommendations include those informed by specific evidence from recent RCTs and general recommendations for healthy diet in line with government recommendations.</p> <p>Stanols and sterols whether as supplements or in enriched foods are marketed for benefit on cholesterol lowering and hence cardiovascular</p>

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							<p>However, foods with added phytosterols are not supplemental to the diet but form part of the daily diet (replacing equivalent products) in the millions of consumers that consume these products daily. It is also noteworthy that the incremental costs per serving for a typical food with an added phytosterol are only in the region of 4 pence (spread) to 11 pence (yoghurt) per serving which amounts to 8 to 22 pence per day for proven cholesterol lowering benefits.</p> <p>It is important to note that foods with added phytosterols are not considered as food supplements from a regulatory perspective in UK.</p> <p>The GDG considered that evidence for reduction of CVD outcomes was necessary in order for healthcare professionals to be able to advise people to use phytosterol supplements. They did not accept that an effect on a surrogate outcome was appropriate to allow a recommendation. The GDG did not specifically comment on foods with added phytosterols.</p> <p>It was highlighted that advice should emphasise appropriate diet rather than supplementation. However, foods with phytosterols, despite their recognised efficacy in lowering a major risk factor of CVD were also excluded from the components of the cardio-protective diet (Section 8). The cholesterol lowering efficacy of foods with added-phytosterols is recognised worldwide and these foods have been authorised to bear health claims in relation to lowering cholesterol in several jurisdictions worldwide, for example, in EU, USA, Canada, Japan. In addition, International/National Medical Bodies support phytosterols as part of a cardio-protective diet in relation to CVD prevention. Examples provided below:</p>	<p>disease. Phytosterol enriched food were included in the search strategy. Following stakeholder comments the GDG discussed whether a distinction should be made between phytosterols incorporated into foods and food supplements. They considered that they would need to see evidence of beneficial effect of stanols and sterols on hard outcomes before making specific recommendation that people should buy foods with added phytosterol.</p>

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							<p>Joint British Societies', 2014 <i>Joint British Societies' Consensus Recommendations for the Prevention of Cardiovascular Disease (JBS3. Heart 2014:ii1-ii67).</i> http://heart.bmj.com/content/100/Suppl_2/ii1.full.html.</p> <p>European Atherosclerosis Society, 2014, Atherosclerosis 2014, 232, 2, 346-360. http://www.sciencedirect.com/science/article/pii/S0021915013006941?via=ihub</p> <p>International Atherosclerosis Society, 2013 <i>An International Atherosclerosis Society Position Paper: Global Recommendations for the Management of Dyslipidemia.</i> http://www.athero.org/IASPositionPaper.asp</p> <p>American Diabetes Association, 2013 Evert AB et al. Nutrition therapy recommendations for the management of adults with diabetes. A position statement of American Diabetes Association. <i>Diabetes Care</i> 2013; doi: 10.2337/dc13-2042</p> <p>European Society of Cardiology 2012 The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice, 2012 <i>European Guidelines on cardiovascular disease prevention in clinical practice (version 2012).</i> <i>Eur Heart J</i> 2012; 33: 1635–1701.</p>	

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							<p>National Heart, Lung, and Blood Institute, 2011 <i>Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics 2011; 128: Suppl 5: S1-S44. NHLBI website</i></p> <p>European Society of Cardiology & European Atherosclerosis Society, 2011 <i>The Task Force for the management of dyslipidemias of the European Society of cardiology (ESC) and the European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidemias. Eur Heart J 2011; 32: 1769–1818.</i></p> <p>The Australian Heart Foundation, 2009 <i>The Australian Heart Foundation. Position statement on phytosterol/sterol enriched foods 2007, updated December 2009. AHF Website</i></p> <p>American Academy of Pediatrics, 2008 <i>Stephen R. Daniels, Frank R. Greer and the Committee on Nutrition. Lipid Screening and Cardiovascular Health in Childhood. Pediatrics 2008; 122: 198-208.</i></p> <p>American Diabetes Association & American College of Cardiology Foundation, 2008 <i>Brunzell JD, Davidson M, Furberg CD et al. Lipoprotein Management in Patients With Cardiometabolic Risk: Consensus Conference Report From the American Diabetes Association and the American</i></p>	

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							<p><i>College of Cardiology Foundation. J Am Coll Cardiol 2008; 51: 1512-24.</i></p> <p>American Heart Association / American College of Cardiology, 2006</p> <p><i>Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pasternak RC, Pearson T, Pfeffer MA, Taubert KA. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update. Endorsed by National Heart, Lung and Blood Institute. Circulation 2006; 113: 2363-72.</i></p> <p>Joint British Societies' Guidelines, 2005</p> <p><i>JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart 2005; 91(Suppl V): V1-V52.</i></p> <p>Joint WHO/FAO Expert Consultation, 2003</p> <p><i>Report of a Joint WHO/FAO Expert Consultation, Diet, nutrition, and the prevention of chronic diseases. WHO Technical Report Series, No.797 - TRS 797, 2003.</i></p>	
111	SH	National Clinical Guidelines centre CKD GDG	3	FULL	10.6 Recommendation 47	121	Suggest that CKD should be defined (e.g. eGFR and ACR level).	Thank you for your comment. We have altered the recommendations to be consistent with how CKD is classified in the NICE CKD guideline.
39	SH	New Devon	12	FUL	11		The adverse effects of statins, as described in the trials,	Thank you for this information. We

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		CCG		L			are considerably underestimated compared to real life. An audit in a local practice of 15,000 patients showed that less than 75% of people on the CHD register were taking a statin, despite repeated efforts to ensure everyone eligible was offered and tried one.	recognise that adherence to long term medication may be less than desired. Adherence however is known to be affected by many factors and not only by adverse effects.
38	SH	New Devon CCG	11	FULL	11	165	<p>The cost -effectiveness modelling produces results which are inevitable given the structure and inputs of the model.</p> <p>It does not incorporate all cause mortality which will have the effect of overestimating the impact of cardiovascular mortality. The point estimates of effect are taken from placebo controlled studies from different populations are hence are not directly comparable. In head to head studies there is high quality evidence that there is no difference between atorvastatin 80 mg and atorvastatin 10mg in terms of all cause mortality and cardiovascular mortality, with a difference in non-fatal MI of an effect size too small to be clinically important.</p>	<p>Thank you for your comment. All cost-effectiveness modelling produces results which are inevitable given their structure and inputs; we therefore agree that it is important that the structure and inputs of the model are carefully considered.</p> <p>The model incorporates cardiovascular (CV) mortality and non-CV mortality, which collectively make up all-cause mortality.</p> <p>We acknowledge that effect sizes are small but the GDG considered that the evaluation of individual outcomes may underestimate the total clinical benefit of statins. We did not examine composite outcomes (for example reduction in all CV events) because of the inconsistent reporting of combined outcomes in the RCT evidence.</p> <p>The comparison of high-intensity versus high intensity referred to (with relative risks of 1 for both CV mortality and non-fatal MI) refers to comparison of atorvastatin 80 mg and rosuvastatin 40 mg (SATURN trial). This is not relevant to the difference between different doses of atorvastatin.</p>

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							<p>However, the model uses an assumption that atorvastatin 80mg is 2% more effective than atorvastatin 20mg. This is not based on any evidence, indeed the comparison of high intensity statins show a relative risk of 1 for cardiovascular mortality and non-fatal AMI.</p>	<p>There have been no head-to-head trials of atorvastatin 80 mg versus atorvastatin 20 mg (or 40 mg), hence this conclusion could only be based on expert opinion. The GDG assumed that atorvastatin 80 mg is 2% relatively more effective than atorvastatin 20 mg. This means that if atorvastatin 20 mg causes an absolute reduction in the rate of MIs by 54%, strokes by 20% and CV mortality by 27%, atorvastatin 80 mg would be assumed to reduce MIs by 55.08%, strokes by 20.4% and CV mortality by 27.54%. The GDG believes this is a very cautious assumption. By contrast atorvastatin 80 mg reduces LDL cholesterol by 28% relative to atorvastatin 20 mg (absolute reduction of 55% compared to 43%).</p> <p>The scenario analysis in Section L.3.3.1 has been repeated with the drop-out and switching rates doubled. The high-intensity strategy remains cost effective.</p>
							<p>Adverse effects are assumed to lead to a low drop out rate which does not match current experience in practice, and would have a significant impact (as shown in section 3.3.1 appendix L) if they were included. In head to head studies there are more adverse effects in the atorvastatin 80mg group but this is not included.</p>	<p>All costs have been reviewed and brought up to date. The costs for unstable angina and stable angina have both been greatly increased. The GDG believe the costs for primary care appointments are reasonable, but have nevertheless added one extra appointment per year to take account of patients booking additional unscheduled</p>

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							<p>The costs for primary care and unstable angina are unrealistically low, no nurse visits and only 1 GP visit per year despite the requirement for GPs to follow up patients with cardiovascular disease in the QoF, and an average of 3-4 visits being more likely.</p> <p>The utility values used are inconsistent e.g. the utility for PAD is higher than that for angina, and no utility decrement is included for adverse effects or for the psychological impact of being identified as at high risk of disease and the recommendation to take lifelong treatment.</p>	<p>appointments (conservatively assuming this appointment is with a GP). It should be noted that these do not represent all the appointments that a person with CVD would receive during the year, but those additional appointments which a patient with (or without) CVD taking statins would receive that a patient with (or without) CVD would not receive. As such we think the assumptions are conservative.</p> <p>The GDG have reconsidered the utility value used for PAD and have decided to change this to 0.808 to be the same as that for stable angina.</p> <p>No utility decrement is included for the negative effects on quality of life of taking statins themselves per se, in line with the findings of a review conducted for Ward 2005 (which informed TA94), as stated in Section L.2.3.5. Utility decrements are included for complications of diabetes in the sensitivity analysis for the effects of increasing new-onset diabetes, but are not included for other adverse events, as those events are assumed to be short-lasting as statin therapy would be halted or modified as a result of the event.</p> <p>Given the explanations given above, and the additional sensitivity analyses conducted for the cost-effectiveness analysis, the GDG have confidence in the recommendations made.</p>

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							Given all the above, the conclusions that a move to a 10% threshold for primary prevention, and that atorvastatin 80mg should be used for secondary prevention and atorvastatin 20mg for primary prevention are unjustified.	
43	SH	Cardiff and Vale University Health Board	3	FULL	11.1	123	The table at the bottom of page 123 gives details of the statins, the doses and the LDL lowering in terms of percentages and then classifies the statins into low, medium and high intensity. The detail on how these groupings were decided on seems vague "agreed by the GDG consensus, informed by analyses in the literature".	Thank you for your comment. We have added more detail to the discussion on grouping of statins.
346	SH	AstraZeneca UK Ltd	3	Full	11.1	123	As an example of primary prevention study , the JUPITER trial should be included in the clinical evidence review conducted for statin therapy. ^{1,2} Rosuvastatin 20mg has been shown to be effective in primary prevention of CVD in the placebo controlled randomised JUPITER study. A post-hoc analysis of JUPITER conducted at the request of the European regulatory authorities, in the sub-population with Framingham risk score >20 or SCORE risk ≥ 5%, showed rosuvastatin 20mg to be effective in reducing the risk of first major CV event. ^{1,2}	Thank you for your comment. The JUPITER trial is included as Ridker (2008) as this is the primary publication. Reference 1 is a post-hoc analysis according to risk and the guideline development group decision was not to examine this type of evidence. Reference 2 is the protocol publication for JUPITER and does not contain follow-up data.
347	SH	AstraZeneca UK Ltd	4	Full	11.1 11.3	123 125 129 130 148 158 159 160	Table 36, Table 38, Table 39, Table 40, Table 46, Table 52, Table 54, Table 55: Disclaimer should be in place where simvastatin 80 mg is mentioned. There is an increased risk of myopathy associated with simvastatin 80mg. The MHRA recommends that the 80mg dose should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the	Thank you for your comment. The tables provide evidence of outcomes considered by the GDG. We have included reference to the MHRA advice in the Table 36, Section 11.1

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							benefits are expected to outweigh the potential risks. ³	
410	SH	Merck Sharp & Dohme	17	Full	11.1 11.3	123 126	<p><u>The grouping of statins is based on out-of-date evidence</u></p> <p>In the development of the draft guideline the evidence used to support the grouping of statins is from a meta-analysis published by Law et al. in 2003 (Law et al., 2003). Atorvastatin 20 mg to 80 mg is defined as high intensity and a critical part of the methodology used in the development of the cost-effectiveness analysis. This analysis is 11 years out-of-date and does not offer the most recent evidence on which to make the decision on statin grouping. In the recent ACC/AHA guidelines the grouping of statins utilised evidence up to 2009 (ACC/AHA, 2013). Percent reductions in LDL-c for a specific statin and dose were calculated for the RCTs included in individual meta-analyses conducted by the CTTC (CTTC, 2010). This grouped the statins as follows: high-intensity statin therapy on average lowers LDL-c by approximately ≥50%, moderate-intensity statin therapy lowers LDL-c by approximately 30% to <50%, and lower-intensity statin lowers LDL-c by <30%. This categorises atorvastatin 20 mg as a moderate-intensity statin and atorvastatin 40 mg and 80 mg as a high-intensity statin. We recommend that the GDG and NCCPC base their statin grouping on more up-to-date evidence than the Law analysis.</p> <p><u>References</u></p> <ul style="list-style-type: none"> - Law MR, Wald NJ, Rudnicka AR. (2003) Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ doi: 10.1136/bmj.326.7404.1423. - ACC/AHA. (2013) Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular 	<p>Thank you for your comment.</p> <p>The meta-analysis by Law et al. 2003, a includes 164 short term trials of statins versus placebo that determined the efficacy of statins in reducing total cholesterol and LDL cholesterol. Their analysis included RCTs of 2 weeks minimum duration and with fixed statin dose throughout the RCTs. Absolute and percentage reductions in LDL cholesterol were reported. More recent systematic reviews have included fewer studies. For example CTT 2010 only included 26 RCTs because they limited their inclusion criteria to RCTs with >1000 participants and study duration of >2 years.</p> <p>In the clinical effectiveness review for the guideline we examined studies with greater than or equal to 1 year follow-up, with no limit on number of participants when determining the efficacy of statins in reducing all-cause mortality and CV events, and adverse events. Tests for subgroup differences in the statin versus placebo RCTs showed that heterogeneity in our meta-analyses could be explained by grouping the statins according to Law 2003. Hence our findings for reductions in mortality and CV outcomes were consistent with the GDG's decision on statin intensity grouping.</p> <p>Having decided to use the reductions in</p>

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							<p>Please insert each new comment in a new row.</p> <p>risk in adults. Journal of the American College of Cardiology doi: 10.1016/j.jacc.2013.11.002.</p> <p>- CTTC. (2010) The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 380: 581-590.</p>	<p>Please respond to each comment</p> <p>LDL cholesterol shown in Law 2003, and having decided that there are insufficient trial results to split the data into more than 3 groupings, the statin doses naturally cluster into the 3 groups chosen:</p> <ul style="list-style-type: none"> • 6 doses giving a reduction in LDL cholesterol of between 21% and 27% • 5 doses giving a reduction in LDL cholesterol of between 32% and 38% • 7 doses giving a reduction in LDL cholesterol of 42% or over. <p>A recent meta-analysis, which also based its categorisations on Law 2003, independently selected the same cut-off points as we have chosen (Ribeiro et al. 2013, Int J Card 166: 431-439).</p> <p>The 2013 ACC/AHA US guidelines used the CTT meta-analyses as their source of cholesterol reductions for grouping rather than Law 2003, but similarly chose to use 3 intensity groupings. They chose a smaller high-intensity group including just 4 doses (atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg) and hence a larger moderate-intensity group. They categorised atorvastatin 20 mg as moderate intensity on the basis of expert assumption as none of the trials they included assessed cholesterol reduction for atorvastatin 20 mg. With the exception of pravastatin 40 mg (which</p>

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								we have classified as low intensity and ACC/AHA classified as medium intensity), the remaining doses are classified in the same class by both ACC/AHA and our guideline.
369	SH	AstraZeneca UK Ltd	26	Full	11.10	196	<p>We welcome the Recommendation 82, not to offer Coenzyme Q10 and vitamin D to improve adherence. In addition, we suggest encouraging physicians to optimise the choice of statin and the dose, take into account the potential drug-statin interaction E.g.^{18,19,22}.</p> <p><u>Special warnings and precautions for use of simvastatin:</u>²² The combined use of simvastatin at doses higher than 20 mg daily with amiodarone, amlodipine, verapamil, or diltiazem should be avoided.</p> <p><u>Contraindications for simvastatin use:</u>²² Concomitant administration of potent CYP3A4 inhibitors (agents that increase AUC approximately 5 fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) Concomitant administration of gemfibrozil, ciclosporin, or danazol isn't recommended either.</p> <p><u>Special warnings and precautions for use of atorvastatin:</u>¹⁸ Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc).</p>	Thank you for your comment and this information. Prescribers are expected to always take into account information in the BNF and in the SPC of each drug.

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							<p>The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivatives, erythromycin, niacin, ezetimibe, telaprevir, or the combination of tipranavir/ritonavir. If possible, alternative (noninteracting) therapies should be considered instead of these medicinal products.</p> <p><u>Special warnings and precautions for use of rosuvastatin:</u>¹⁹ Concomitant use of Crestor and gemfibrozil resulted in a 2-fold increase in rosuvastatin C max and AUC. The concomitant use of Crestor and some protease inhibitor(atazanavi, ritonavir) combinations may be considered after careful consideration of Crestor dose adjustments based on the expected increase in rosuvastatin exposure .Crestor is contraindicated in patients receiving concomitant ciclosporin.</p>	
370	SH	AstraZeneca UK Ltd	27	Full	11.1	198	<p>Statins are generally well tolerated¹⁶, although some drug-drug interactions may increase the risk of adverse events such as myopathy.¹⁷ For example, the risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with potent inhibitors of CYP3A4 or transport proteins and alternative (non-interacting) therapies should be considered.¹⁸ Rosuvastatin is not expected to be associated with drug interactions resulting from cytochrome P450-mediated metabolism.¹⁹ In addition, tolerability must be considered as NICE present data (Table 50 Full report) on differences in liver adverse events with atorvastatin 80mg and rosuvastatin 40mg.</p> <p>Also, among the statins mentioned, lovastatin, simvastatin, atorvastatin, and fluvastatin are lipophilic, whereas pravastatin and rosuvastatin are more hydrophilic. The lipophilic properties of the statins are accompanied, except for pitavastatin, by low systemic bioavailability because of</p>	Thank you for your comment and this information. Prescribers are expected to always take into account information in the BNF and in the SPC of each drug.

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							<p>an extensive first-pass effect at the hepatic level. Although this effect can be desirable, the statins' lipophilicity enables them to passively penetrate the cells of extrahepatic tissues, possibly leading to side effects that in some cases can be undesirable.^{23,24}</p> <p>Consideration should be given to the above points within guidelines document.</p>	
371	SH	AstraZeneca UK Ltd	28	Full	11.11	205	<p>We welcome the Recommendation 83, to advise people who are being treated with a statin, to be aware of drug-statin or food-statin interactions. To compliment the recommendation, we suggest adding a table comparing the pharmacokinetics properties of the available statins, and another table detailing specific drug-statin interactions via the cytochrome P450 pathway. E.g.^{18,19,22}.</p> <p><u>Special warnings and precautions for use of simvastatin:</u>²²</p> <p>The combined use of simvastatin at doses higher than 20 mg daily with amiodarone, amlodipine, verapamil, or diltiazem should be avoided.</p> <p><u>Contraindications for simvastatin use:</u>²²</p> <p>Concomitant administration of potent CYP3A4 inhibitors (agents that increase AUC approximately 5 fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone)</p> <p>Concomitant administration of gemfibrozil, ciclosporin, or danazol isn't recommended either.</p> <p><u>Special warnings and precautions for use of atorvastatin:</u>¹⁸</p> <p>Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products</p>	Thank you for your comment and this information. Prescribers are expected to always take into account information in the BNF and in the SPC of each drug. It is not considered appropriate to repeat this information in a guideline.

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							<p>that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivatives, erythromycin, niacin, ezetimibe, telaprevir, or the combination of tipranavir/ritonavir. If possible, alternative (noninteracting) therapies should be considered instead of these medicinal products.</p> <p><u>Special warnings and precautions for use of rosuvastatin:</u>¹⁹ Concomitant use of Crestor and gemfibrozil resulted in a 2-fold increase in rosuvastatin C max and AUC. The concomitant use of Crestor and some protease inhibitor(atazanavi, ritonavir) combinations may be considered after careful consideration of Crestor dose adjustments based on the expected increase in rosuvastatin exposure .Crestor is contraindicated in patients receiving concomitant ciclosporin.</p>	
233	SH	Cholesterol Treatment Trialists' Collaboration	8	FULL	11.2		<p>No consideration is given to haemorrhagic stroke. The CTT has shown that there is about a 20% increased risk of such strokes.</p>	<p>Thank you for your comment. Haemorrhagic stroke was considered in the statin efficacy chapter. We reported total stroke as an outcome, which included both haemorrhagic and ischaemic stroke. A number of meta-analyses exist on this topic which differ in their conclusions with regards to the effects of statins on haemorrhagic stroke probably dependent on the trials included in the analyses. The largest and latest meta-analysis including 31 trials and</p>

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								180,000 patients showed no difference in haemorrhagic stroke in the active treatment group versus control (Stroke. 2012;43:2149-2156). Some of the RCTs included in our review did not report haemorrhagic stroke separately within the published data so an independent analysis was not possible.
444	SH	United Kingdom Clinical Pharmacy Association	5	full	11.2	Table 36 and 37	Although the review group state the intensity level of statin is arbitrary, atorvastatin 20mg would not usually be deemed high intensity and may be miss leading.	Thank you for your comment. The GDG accept that division of statins into different intensity groups requires judgement. On the basis of the analysis by Law atorvastatin 20mg results in an LDL reduction of 43% which is similar to rosuvastatin 10mg and simvastatin 80mg both of which have been generally accepted as being high intensity statins.
348	SH	AstraZeneca UK Ltd	5	Full	11.2	123 125	Table 36: consider LDL-C lowering efficacy data of simvastatin, atorvastatin and rosuvastatin from VOYAGER meta-analysis. It is noted that rosuvastatin data is under-represented in the systematic review and meta-analysis referenced in Table 36; only 2 of the 164 RCTs analysed involved rosuvastatin. The VOYAGER is an individual patient data pooled analysis of simvastatin, atorvastatin and rosuvastatin from 37 RCTs with 32,325 patients in total. We believe this is a more reliable evidence to compare LDL-C lowering efficacy of the 3 agents. ⁴	Thank you for your comment. The VOYAGER meta-analysis examined LDL-cholesterol lowering of atorvastatin rosuvastatin (reference 4). The guideline development group decided to base the grouping of type of statin and dose on Law 2003, a meta-analysis of 164 short term trials of statins versus placebo that determined the efficacy of statins in reducing total cholesterol and LDL-cholesterol. The Law 2003 meta-analysis was more appropriate compared with VOYAGER because it provided a comparison of atorvastatin, rosuvastatin, pravastatin, fluvastatin and simvastatin at 5 doses
349	SH	AstraZeneca	6	Full	11.2	123	Table 36 and throughout the guideline: The NICE	Thank you for your comment. The GDG

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		UK Ltd					<p>proposed definition for categorising high statins (40% lowering LDL-C) is less stringent than that which is currently proposed by others (50% lowering LDL-C).²⁰ In addition, the ESC/EAS recommendation to reduce LDL-C by 50% when treating very high CV risk patients⁹ makes it important to align this to the classification of statins. Using the 50% lowering of LDL-C criteria, atorvastatin 10mg and simvastatin 80 mg are not classified as high intensity statins.</p>	<p>recommendations are for treatment with statins and not with aim of reaching specific LDL cholesterol targets. The recommendations will result in people at risk being given the highest dose of statin they can tolerate within the NICE threshold for cost effectiveness.</p> <p>We also note that the 50% reduction is LDL cholesterol cut-off for high-intensity statins used in the AHA/ACC guidelines used a difference source of LDL cholesterol reductions. This guideline uses Law 2003, a meta-analysis of 164 short-term trials. The division into groups in the AHA/ACC guidelines are based on the cholesterol lowering seen in the 26 long-term RCTs reported in the CTT analysis. The CTT analysis reported on average larger reductions in cholesterol for each statin than seen in Law, as might be expected for longer-term trials. Hence, for example rosuvastatin 20 mg gives an LDL-cholesterol reduction of over 50% in CTT and 48% in Law 2003, but is classified as high-intensity in both classifications due to different cut-off points. The AHA/ACC guideline also chose to select a smaller group of high-intensity statins than for this guideline.</p> <p>We agree that atorvastatin 10 mg is not a high-intensity statin; it is not classified as such in this guideline, or in any other guidelines of which we are aware.</p>
44	SH	Cardiff and Vale	4	FULL	11.2	124	The comparisons here are pravastatin 10mg – 40mg (low) simvastatin 40mg (medium) and atorvastatin 80mg (high).	Thank you for your comment. The GDG accept that any grouping of statins

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		University Health Board					Atorvastatin 80mg according to the table on page 123 gives an LDL-cholesterol lowering of 55% and simvastatin 40mg gives an LDL- cholesterol lowering of 37% whereas atorvastatin 20mg gives an LDL-cholesterol lowering of 43%. It seems to be that atorvastatin 20mg is much nearer to the effect that would be seen with simvastatin 40mg than atorvastatin 80mg is to atorvastatin 20mg. By grouping the statins into low, medium and high intensity as the GDG have done with atorvastatin 80mg and atorvastatin 20mg both being labelled high intensity statins the benefits of atorvastatin 20mg may be overstated over simvastatin 40mg in terms of meaningful outcomes to patients of less heart attacks and strokes	requires judgement and there will be some decisions at cut-off points which are more likely to be contested. Tests for subgroup differences in the statin versus placebo RCTs included in the evidence review showed that heterogeneity in our meta-analyses could be explained by the grouping of statins agreed by the GDG. Hence our findings for reductions in mortality and CV outcomes were consistent with the GDG's decision on statin intensity grouping.
234	SH	Cholesterol Treatment Trialists' Collaboration	9	FULL	11.3		It might be helpful to mention the SHARP trial on page 15, even if only in parenthesis, since it does provide important information about the effects of reducing LDL cholesterol in patients with CKD.	Section 11.3 details the studies included in our review on statins versus placebo and head to head statin studies. The SHARP RCT compares ezetimibe plus simvastatin in CKD and it does not meet our inclusion criteria.
352	SH	AstraZeneca UK Ltd	9	Full	11.3	128-130	The two studies presented on rosuvastatin (VIRHISTAMI study (Egede 2013) and Lemos analysis) are not within licensed indications, disclaimer should be in place.	Thank you for your comment. NICE process requires unlicensed indications to be highlighted in recommendations and not in analysis of evidence.
46	SH	Cardiff and Vale University Health Board	6	FULL	11.3	129/130/ 131	In the placebo studies there was one study looking at atorvastatin 20mg (54 patients over 1 year). In the head to head studies with 2 active comparators there were no studies that involved atorvastatin 20mg	Thank you. We agree that there are very few studies using atorvastatin 20mg
45	SH	Cardiff and Vale University Health Board	5	FULL	11.3	125	<i>"The statin grouping was based on GDG consensus informed by 4 clinical consensus and an analysis of LDL-cholesterol reduction from 164 short-term trials (minimum 5 duration 2 weeks)"</i> The statement gives a little more information on how the statins were grouped. However a better grouping of the statins would have been on patient	Thank you for your comment. We have added more detail to the discussion. Tests for subgroup differences in the statin versus placebo RCTs showed that heterogeneity in our meta-analyses could be explained by the grouping chosen by

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							outcomes and not on ability to lower LDL-cholesterol	the GDG.
350	SH	AstraZeneca UK Ltd	7	Full	11.3	125	Seventeen studies were included in the head-to-head statin comparison review - JUPITER data should be included. ^{1,2} Rosuvastatin 20mg has been shown to be effective in primary prevention of CVD in the placebo controlled randomised JUPITER study (in the UK the population with Framingham risk score >20 or SCORE risk ≥5%), but LDL-C levels not requiring pharmacologic treatment). A post-hoc analysis conducted at the request of the European regulatory authorities showed rosuvastatin 20mg to be effective in reducing the risk of first major CV event also in patients at high CV risk. ^{1,2}	Thank you for your comment. The JUPITER trial is included as Ridker (2008) as this is the primary publication. Reference 1 is a post-hoc analysis according to risk and the guideline development group decision was not to examine this type of evidence. Reference 2 is the protocol publication for JUPITER and does not contain follow-up data.
407	SH	Merck Sharp & Dohme	14	Full	11.3	128	The de novo clinical effectiveness analysis conducted as part of this guideline appears to have misclassified the ALLIANCE study (Koren et al., 2004) as a study evaluating atorvastatin 80 mg versus placebo. However, patients in the study were initiated on atorvastatin 10 mg and up-titrated to reach the target cholesterol level specified in the study. The median daily dose used in the study was 40.5 mg and 45% of patients received the 80 mg dose. As such, this study should have been classified as an atorvastatin 40 mg study rather than 80 mg. This would have significant implications on the clinical and cost-effectiveness analysis conducted as part of this guideline update – and brings into question the reliability of the underlying analyses used to generate the recommendations.	Thank you for your comment. The clinical effectiveness review was based on intensity of statin and both atorvastatin 40 mg and atorvastatin 80 mg were classified as high-intensity statins. Therefore the classification of this study has no effect on the clinical or cost-effectiveness analyses conducted. ALLIANCE was a treat-to-target study and the table cites the maximum atorvastatin 80 mg dose. Further information has been added to the table noting it was a treat-to-target study.
351	SH	AstraZeneca UK Ltd	8	Full	11.3 11.5 11.5	130 158 161	Table 40, Table 53, Table 59: The VIRHISTAMI study (Egede 2013) is off label. Rosuvastatin is not indicated to affect the necrotic core content in coronary plaques of angiographic lesions.	Thank you for your comment. We acknowledge that the study is off label. Egede 2013 VIRHISTAMI was included in the review because it reported on LDL-cholesterol lowering of rosuvastatin

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							Disclaimer should be in place.	40 mg versus rosuvastatin 5 mg in one of our included population of patients after ST-elevation MI.
353	SH	AstraZeneca UK Ltd	10	Full	11.3	130 161	Table 40: Fourth line of the table contain 2 typos in rosuvastatin Table 58 Typos in rosuvastatin	Thank you for your comment. These have been corrected.
152	SH	Greater Manchester Commissioning Support Unit GMCSU	9	Full	11.10.2	192	NB one of the interventions was 'vitamin E' not 'vitamin D'. See line 22 and relevant study abstract. Consequently all errors will need amending.	Thank you for your comment. The interventions considered for the adherence to statin therapy review are either coenzyme Q ₁₀ or Vitamin D (not vitamin E), as described in the review protocol (see Appendix C, Section C.10). The Caso 2007 paper compares coenzyme Q ₁₀ (intervention group) with vitamin E (control group). We have now amended the table to clarify this.
235	SH	Cholesterol Treatment Trialists' Collaboration	10	FULL	General and 11.4 in particular		The NICE evaluation team has conducted its own meta-analyses, subdivided by intensity of statin regimen. But in reaching its conclusions it has not given any explicit consideration to the results of the CTT, which had access to individual participant data and has addressed many of the questions posed in a more reliable way than is possible with (incomplete) summary data. Many of the recommendations do not appear to follow naturally from the results of the NICE team's analyses (eg, Tables 43 – 50), but could be supported by reference to the CTT analyses.	Thank you for your comment. Our recommendations are based on the clinical review of RCTs conducted for this guideline in line with NICE methodology, although we are aware that many of our conclusions agree with results of the CTT analyses. Our clinical review included many of the same RCTs as CTT, as well as some additional smaller trials. We agree that individual patient-level data (IPD) can be extremely useful. For this guideline the GDG wished to determine not just the effectiveness of all statins collectively against placebo, which is given in the CTT analyses (per 1 mmol/l reduction in LDL cholesterol),

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								but the effectiveness of different intensities of statin against each other. To answer that question we would have needed to analyse IPD by statin intensity class, but unfortunately this data was not available to us.
354	SH	AstraZeneca UK Ltd	11	Full	11.4	137-138	Table 42: presented data on rosuvastatin 20mg study JUPITER ¹ and ALLIANCE ⁵ on atorvastatin 80 are not comparable and shouldn't be analysed the same way.	The two studies were analysed together because atorvastatin 80 mg and rosuvastatin 20 mg were both classified as high intensity statin.
47	SH	Cardiff and Vale University Health Board	7	FULL	11.4	132 - 139	The studies are then looked at in terms of clinically meaningful outcomes for patients (mortality, CV events and adverse events) but have used the classification as stated above in terms of low, medium and high intensity. As stated in 5 there are no head to head studies that used atorvastatin 20mg that were identified by the GDG. Looking at the data compared to placebo medium intensity statins performed better against placebo in terms of all cause mortality, non-fatal MI, and stroke compared to high intensity statins compared to placebo. They seemed to better tolerated (less numbers of adverse events though these were broadly similar). Table 42 shows the greatest benefit in terms of reducing CV events is for those with the highest risk.	High intensity statins compared with medium intensity statins performed better in terms of reduction in CV mortality and MI. All-cause mortality was comparable in the two intensities, moderate intensity statin performed better for stroke. The GDG made recommendations based on the individual outcomes and the overall benefits in reduction in mortality and CV events, together with the cost effectiveness. Statins performed better in higher risk individuals for CV mortality, however for the outcomes of MI and stroke the results were comparable across all risk groups. In this table 'high' refers to intensity of statin and not risk level and we have altered the labelling to make this clear.
48	SH	Cardiff and Vale University Health Board	8	FULL	11.4	148	This table compares high intensity statin (atorvastatin or simvastatin 80mg) to medium intensity statin (atorvastatin 10mg or simvastatin 20mg) and shows some benefit in terms of reduced mortality when all of the studies are combined together. This still does not directly look at atorvastatin 20mg and how it compares to the most	Thank you for your comment. We accept that there is no study which directly compares simvastatin 40mg and atorvastatin 20mg. The recommendations are not suggesting that those people stable on

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							commonly prescribed statin in the UK of simvastatin 40mg, particularly in patient populations that may be at lower risk than in the clinical trials.	simvastatin 40mg have to change their medication. The GDG did consider however that patient newly initiated on statins should start on atorvastatin 20mg as the analysis indicates that this is a more cost-effective option.
49	SH	Cardiff and Vale University Health Board	9	FULL	11.4	154	This table compares high intensity statin (atorvastatin 80mg) and medium intensity statin (simvastatin 20mg) to a low intensity statin (simvastatin 10mg and pravastatin 40mg) in the prevention of CVD and finds no difference between the groups in terms of benefit. If this is in a primary prevention population this does not determine that high intensity statin has the greatest benefit here.	Thank you for your comment. The recommendation is based on integration of all individual outcomes with cost effectiveness analysis..
359	SH	AstraZeneca UK Ltd	16	Full	11.5	160-161	<p>Table 57: study on primary prevention JUPITER data should be included. ^{1,2}</p> <p>Rosuvastatin 20mg has been shown to be effective in primary prevention of CVD in the placebo controlled randomised JUPITER study (in the UK the population with Framingham risk score >20 or SCORE risk ≥5%), but LDL-C levels not requiring pharmacologic treatment). A post-hoc analysis of JUPITER conducted at the request of the European regulatory authorities, in the sub-population with Framingham risk score >20 or SCORE risk ≥ 5%, showed rosuvastatin 20mg to be effective in reducing the risk of first major CV event also in patients at high CV risk. ^{1,2}</p>	<p>Thank you for your comment. Table 57 concerns LDL lowering in trials of high intensity statins versus medium intensity statins and not high intensity versus placebo trials. Table 55 concerns LDL lowering in trials of statins versus placebo. The JUPITER trial is included as Ridker (2008) in the clinical effectiveness review on mortality and CV outcomes, because this is the primary publication and it reports on mortality and CV outcomes for rosuvastatin versus placebo. Ridker 2008 did not report LDL-cholesterol as final mean (SD) values for statin and placebo groups at median follow-up of 1.9 years.</p> <p>Reference 1 is a post-hoc analysis according to risk and the guideline development group decision was not to examine this type of evidence.</p> <p>Reference 2 is the protocol publication for JUPITER and does not contain</p>

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								follow-up data.
236	SH	Cholesterol Treatment Trialists' Collaboration	11	FULL	11.5	Table 54	The mean differences in LDL cholesterol in this table are misleading, for several reasons. First, it is important, when assessing the LDL cholesterol difference between statin-allocated and control-allocated patients, to ensure that it is based on an intention-to-treat analysis (as opposed to data-derived subgroups such as available case analyses), so as to avoid introduction of bias. In particular, for those patients who did not have an LDL cholesterol measured at follow-up, an imputed value corresponding to baseline is appropriate to ensure that the effects of non-compliance are estimated. Secondly, the absolute difference in LDL cholesterol in a trial depends BOTH on intensity of the statin regimen AND the baseline LDL cholesterol. Hence the LDL cholesterol differences presented in Table 54 are dependent on characteristics of the populations studied in those trials with published data available. Finally, the subset of trials publishing results on LDL cholesterol at baseline and follow-up is very limited, and does not reflect the totality of the evidence. The authors should note that these analyses have been presented comprehensively by the CTT collaboration papers, and it may be valuable to refer to these.	Available case data was used for the LDL-cholesterol outcome as it was beyond the scope of the review to do imputation. We agree the absolute difference in LDL-cholesterol in a trial depends both on intensity of the statin regimen and the baseline LDL cholesterol, and have added a footnote to the table stating this. We have stated that the results for LDL-cholesterol reduction do not represent the totality of the evidence.
355	SH	AstraZeneca UK Ltd	12	Full	11.5	157	Table 52: study on primary prevention JUPITER data should be included. ^{1,2} Rosuvastatin 20mg has been shown to be effective in primary prevention of CVD in the placebo controlled randomised JUPITER study (in the UK the population with Framingham risk score >20 or SCORE risk ≥5%), but LDL-C levels not requiring pharmacologic treatment). A post-hoc analysis of JUPITER conducted at the request of the European regulatory authorities, in the sub-population with Framingham risk score >20 or SCORE risk ≥ 5%, showed rosuvastatin 20mg to be effective in reducing the risk of first major CV event also in patients at high CV risk. ^{1,2}	Thank you. Table 52 reports final LDL-cholesterol levels in statin versus placebo studies. The JUPITER trial is included as Ridker (2008) as this is the primary publication. LDL-cholesterol results were not reported as final mean (SD) values for statin and placebo groups at in this primary publication at median 1.9 years median follow-up. Reference 1 is a post-hoc analysis according to risk and the guideline development group decision was not to examine this type of evidence.

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							Lemos et al analysis is off label (rosuvastatin is not indicated for slowing progression of coronary artery calcification in chronic kidney disease). ⁶	Reference 2 is the protocol publication for JUPITER and does not contain follow-up data Lemos et al was included in the review because it reported on final values of LDL-cholesterol lowering at study follow-up.
356	SH	AstraZeneca UK Ltd	13	Full	11.5 1.2	157 15	<p>Clinical evidence review: Information below should be considered: There is compelling evidence that lowering LDL-C can reduce the risk of CVD. Experts have quantified this effect by analyzing data from 26 randomized clinical trials, which included 170,000 participants, to show that every 1.0 mmol/L (~40 mg/dL) reduction in LDL-C is associated with a 22% reduction in CVD mortality and morbidity.⁷</p> <p>Others estimate that every 1% decrease in LDL-C reduces the risk of CHD by 1%⁸, showing the potential benefits of incremental decreases in LDL-C.</p> <p>Effective lowering LDL-C is particularly important in those patients at very high CV risk, and the 2011 EAS/ESC Guidelines for management of dyslipidaemia recommend an LDL-C treatment target of <1.8mmol/L (less than ~70mg/dL) and/or a 50% reduction when the target cannot be reached.⁹</p>	The guideline development group decided to perform meta-analyses of RCTs at the study level for the clinical effectiveness review rather than using results of the CTT 2010 (ref 7) or the Adult Treatment Panel III Guidelines (ref 8). Recommendations were based on clinical and cost effectiveness.
357	SH	AstraZeneca UK Ltd	14	Full	11.5	159	<p>Table 54: study on primary prevention JUPITER data should be included.^{1,2}</p> <p>Rosuvastatin 20mg has been shown to be effective in primary prevention of CVD in the placebo controlled randomised JUPITER study (in the UK the population with Framingham risk score >20 or SCORE risk ≥5%), but LDL-</p>	Table 54 reports final LDL-cholesterol levels in statin versus placebo studies according to statin intensity. JUPITER data from Ridker 2008 (primary publication) has not been included because the LDL-cholesterol results were not reported as final mean (SD)

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							C levels not requiring pharmacologic treatment). A post-hoc analysis of JUPITER conducted at the request of the European regulatory authorities, in the sub-population with Framingham risk score >20 or SCORE risk \geq 5%, showed rosuvastatin 20mg to be effective in reducing the risk of first major CV event also in patients at high CV risk. ^{1,2}	values for statin and placebo. Reference 1 is a post-hoc analysis according to risk and the guideline development group decision was not to examine this type of evidence. Reference 2 is the protocol publication and does not contain follow-up data.
358	SH	AstraZeneca UK Ltd	15	Full	11.5	160	Data from STELLAR ¹⁰ , LUNAR ¹¹ , MERCURY ¹² , ANDROMEDA ¹³ should be included in the efficacy review of statins for the ezetimibe data included in the guideline utilises surrogate endpoint (not outcome) data as a marker of efficacy.	These trials were not included in the clinical review on statin efficacy because their follow-up was less than 1 years; STELLAR (6 weeks), LUNAR (4 day), MERCURY (16 weeks), ANDROMEDA (16 week).
360	SH	AstraZeneca UK Ltd	17	Full	11.5	160	Table 57: Data from STELLAR should be included. ¹⁰ Please see comment 12.	STELLAR was not included in Table 57 because its follow-up was less than 1 year (6 weeks).
237	SH	Cholesterol Treatment Trialists' Collaboration	12	FULL	11.7 Evidence statements		<p>The evidence statements are written in a formulaic way, and it is unclear how they are to be interpreted. They are effectively subgroup analyses for each endpoint and statin intensity category. The literal interpretation of subgroup findings generates statements that are inconsistent with established facts about the properties of statins (eg, the statement that 'moderate quality evidence suggested that medium intensity statins when compared to placebo caused fewer rhabdomyolysis events at up to 5 years...' on page 168, as well as the other statements on rhabdomyolysis appear to have been written without reference to the known effects of statin therapy on muscle.</p> <p>There are repeated statements that 'the effect size is too small to be clinically important', but no explanation to guide the reader on how this judgement has been made. In particular, we know from the CTT meta-analysis that the absolute benefit of statins on major vascular events depends on the absolute size of the LDL cholesterol difference and a patient's baseline risk, so a statement that</p>	<p>The evidence statements refer to the effect estimate for single outcomes and GRADE quality assessment. They are written in a consistent standard format. Rhabdomyolysis was one of the outcomes chosen by the guideline development group and was defined as CK more than 10 times the upper limit of normal. These evidence statements summarise the data found in the RCTs included in this review, and we are aware that the data on adverse events in particular is reported in only a few studies and does not always agree with adverse event rates reported in observational studies. This is discussed further in Section 11.8.1 and Appendix L.</p> <p>The effect estimates and the confidence intervals were assessed using default</p>

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							the benefit is too small to be clinically important has meaning only in the context of a particular patient population.	minimal important differences (imprecision in GRADE) to determined confidence in the effect. We used default minimal important differences because there are no established values in the literature for the outcomes examined in the guideline. Further information is given in the Methods chapter (chapter 3) of the full guideline. We have added a comment that total reduction of all CV outcomes may be of greater magnitude at the start of the evidence statements section.
51	SH	Cardiff and Vale University Health Board	11	FULL	11.7	171 / 172 / 173	<p>There are the statements: <i>"High quality evidence showed that there is no clinical difference between high intensity and medium intensity statin at reducing all-cause mortality at up to 7 years"</i></p> <p><i>High quality evidence showed that there is no clinical difference between simvastatin 20 mg and atorvastatin 80 mg at reducing all-cause mortality at up to 5 years</i></p> <p><i>High quality evidence showed that high intensity statin is more effective when compared to medium intensity statin at reducing non-fatal MI at up to 7 years, but the effect size is too small to be clinically important</i></p> <p><i>High quality evidence showed that there is no clinical difference between high intensity and medium intensity statin at reducing stroke at up to 7 years</i></p> <p><i>High quality evidence showed that medium intensity statin is more clinically effective when compared to high intensity statin in showing less myalgia at up to 5 years</i></p> <p><i>High quality evidence showed that medium intensity statin</i></p>	<p>Thank you for your comment. The evidence statements provide a summary of evidence for each outcome and as indicated the difference may be small. The recommendations are based on the integration of the effect of intervention on each outcome with the health economic evidence. From this analysis it is cost effective to given atorvastatin 80mg to the majority of people at risk.</p> <p>The GDG however agreed that for populations other than those treated for secondary prevention statin treatment should be initiated with atorvastatin 20mg because of concern about higher doses.</p>

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							<p><i>is more clinically effective when compared to high intensity statin in showing fewer rhabdomyolysis events at up to 7 years</i></p> <p><i>Moderate quality evidence showed that atorvastatin 10 mg is potentially more clinically effective when compared to atorvastatin 80 mg in people with CKD in showing fewer liver adverse events at up to 5 years</i></p> <p>All of these statements seem to indicate that medium intensity statins as defined by the GDG are equally efficacious as high intensity statins and seem to have less risk of side effects.</p> <p>Why was the choice then made to go for a high intensity statin as the statin to be offered?</p>	
361	SH	AstraZeneca UK Ltd	18	Full	11.6.1 11.6.2.3	161 165	<p>In this chapter should be included data from this publication:</p> <p>The overall JUPITER population (in the UK the population with Framingham risk score >20 or SCORE risk ≥5%), rosuvastatin was dominant for the lifetime horizon. In the sensitivity analysis, rosuvastatin was the dominant treatment strategy over a 20-year time horizon, and cost-effective with an incremental cost-effectiveness.^{1,2,14}</p>	<p>Thank you for your comment. The JUPITER trial is included as Ridker (2008) as this is the primary publication. Reference 1 is a post-hoc analysis according to risk and the guideline development group decision was not to examine this type of evidence. Reference 2 is the protocol publication for JUPITER and does not contain follow-up data.</p> <p>Ref 14 (Ohsfeldt et al 2012) was considered for the economic review and was selectively excluded due to the existence of alternative evidence which was judged to be more applicable (see Appendix K.4).</p>
162	SH	Greater Manchester	19	Full	11.7	166, and in	Evidence statements – not clearly presented - do they apply to primary or secondary prevention? This chapter is	Thank you for your comment. The populations in the evidence statements

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		Commissioning Support Unit GMCSU				general for whole chapter	not laid out clearly and reading evidence does not follow in a logical order. Some statements e.g. regarding economic evidence are repeated. Also, it should be clearly stated (not only in the full guideline, but also in the NICE guideline) that the classification of statins in terms of intensity is arbitrary and was created for the need of this guideline.	has been clarified in the text. The economic evidence statements are not repeated as each statement applies to a different population (secondary prevention, primary prevention using QRISK2 or UKPDS tools, people with CKD). The statin chapter introduction and the linking evidence to recommendations section (Section 11.8) states that intensity grouping was based on Law 2003 and GDG consensus. This is also included in the introduction of the NICE guideline.
50	SH	Cardiff and Vale University Health Board	10	FULL	11.7	167	Under the evidence on rates of myalgia please refer to the general comments regarding clinical trials and run in periods where patients exhibiting this side effect may have been excluded.	Thank you for your comment. The evidence statements are written based on the results of the overall meta-analysis, and do not include details about single RCTs. For details about exclusion criteria for single RCTs please refer to the clinical evidence tables in Appendix G. The GDG recognise that clinical trials may have run in periods and this has consequences for the populations included in trials. We have conducted additional sensitivity analyses where the number of people suffering side effects is increased and have not recommended the highest doses of atorvastatin although these are cost effective.
363	SH	AstraZeneca UK Ltd	20	Full	11.7	167	Data on stroke should include data from study on primary prevention JUPITER. ^{1,2} Rosuvastatin 20mg has been shown to be effective in primary prevention of CVD in the placebo controlled randomised JUPITER study (in the UK	Thank you for your comment. The JUPITER trial is included as Ridker (2008) as this is the primary publication. Stroke data from this trial has been

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							the population with Framingham risk score >20 or SCORE risk \geq 5%), but LDL-C levels not requiring pharmacologic treatment). A post-hoc analysis of JUPITER conducted at the request of the European regulatory authorities, in the sub-population with Framingham risk score >20 or SCORE risk \geq 5%, showed rosuvastatin 20mg to be effective in reducing the risk of first major CV event also in patients at high CV risk. ^{1,2}	included in the clinical effectiveness review. Reference 1 is a post-hoc analysis according to risk and the guideline development group decision was not to examine this type of evidence. Reference 2 is the protocol publication for JUPITER and does not contain follow-up data.
161	SH	Greater Manchester Commissioning Support Unit GMCSU	18	Full	11.7	173 row 4&5	Reads 'atorvastatin 80mg vs. atorvastatin 80mg'. Should be '80mg vs. 10mg'	Thank you for your comment, this has been corrected.
401	SH	Merck Sharp & Dohme	8	Full	11.7	166 176	<p><u>Epidemiological data on the safety and tolerability of statins in clinical practice</u></p> <p>The levels of statin intolerance have been reported to be much higher in clinical practice than seen in RCTs. For example, the PRIMO observational study found that 10.5% of patients on high-dose statins reported muscle-related symptoms (Bruckert et al., 2005). While it has been reported as high as 20% in other cases (Fernandez et al., 2011). This is expected to be associated with the manner in which RCTs are conducted. For example, RCTs exclude those patients that cannot tolerate the treatment during the run-in period and these people are subsequently not included in the intention-to-treat analysis. In TNT, for example, of the 15,464 patients that were eligible to enter the run-in period, 5,461 patients (35.3%) were excluded. Furthermore, the controlled environment of RCTs and the extensive follow-up of patients is not the same as routine clinical environment. As such, the GDG needs to consider epidemiological evidence in addition to RCTs to assess the safety of statins, and the subsequent impact of implementing their current recommendations in clinical</p>	<p>Thank you for your comment. At the protocol setting stage, the GDG decided to use only RCT evidence for both CV outcomes and adverse events. RCT evidence is of higher quality compared to observational studies. The GDG considered that a well conducted RCT reporting long term outcomes ought to report also adverse events at short term.</p> <p>We note that the imperfect and varied data available mean that the true rates of intolerance to statins are unclear. The paper by Fernandez et al. cites Franc et al 2003 Cardiovasc Drugs & Ther, a study of muscle symptoms associated with lipid-lowering therapy in general – fibrates or statins – and provides no figures for adverse events due specifically to statins.</p> <p>This guideline recommends that those</p>

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							<p>practice.</p> <p><u>References</u></p> <ul style="list-style-type: none"> - Bruckert et al. Mild to Moderate Muscular Symptoms with High-Dosage Statin Therapy in Hyperlipidemic Patients —The PRIMO Study. <i>Cardiovascular Drugs and Therapy</i> 2005; 19, 403–414. - Fernandez G, Spatz ES, Jablecki C, Phillips PS. Statin myopathy: a common dilemma not reflected in clinical trials. <i>Cleve Clin J Med</i> 2011;78:393-403 	<p>who experience adverse events whilst taking statins should first check – by stopping and re-starting statins – whether the adverse event does appear to be related to the statin, and if so then to change to an alternative statin, or cease taking statins if the individual prefers. This advice is relevant whatever the prevalence of statin intolerance. Good practice in monitoring the patient during initial use of statins should ensure that any problems are identified early, and it is hence very unlikely there would be lasting harms.</p> <p>Sensitivity analyses conducted as part of the cost-effectiveness analysis undertaken for this guideline (Appendix L) indicate that the recommendations for the use of statins will be cost effective even for high rates of patients changing statins or ceasing treatment as a result of adverse events.</p>
238	SH	Cholesterol Treatment Trialists' Collaboration	13	FULL	11.8	P179 'Trade-off between clinical benefits and harms'	<p>It is stated that 'There was no evidence of benefit for statins on all-cause mortality'. In the CTT 2012 paper (reference 166), there were clearly significant effects on all-cause mortality (as well as key cardiovascular outcomes) in people without vascular disease.</p> <p>In this section, the term 'myopathy' should be used rather than 'myalgia' – see comment above.</p>	The evidence statement reports the results of our meta-analyses. Myalgia was used as this was the outcome analysed from RCT evidence.
114	SH	Type 1 Diabetes Guideline Development	1	FULL	11.8	177 - 185	<p>We note the recommendations relevant to type 1 diabetes: Recommendation 9: Do not use a risk assessment tool to assess CVD risk in type 1 diabetes. Recommendation 47: Do not advise plant sterols or</p>	Thank you for your comment. The GDG reviewed the recommendations for adults with type 1 diabetes following stakeholder consultation and have

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		Group					<p>stanols for the prevention of CVD in those with type 1 diabetes</p> <p>Recommendation 59: Offer high-intensity statin treatment for the primary prevention of CVD to people with type 1 diabetes</p> <p>Recommendation 60: When offering statin treatment for the prevention of CVD to people with type 1 diabetes, start with atorvastatin 20 mg</p> <p>Recommendations 93,94,95,96; Do not routinely offer fibrates, nicotinic acid, bile acid sequestrants, omega-3 fatty acid compounds</p> <p>We note that one of the key research recommendations is: Research recommendation 4: What is the effectiveness of statin and/or other LDL cholesterol lowering treatment in patients with type 1 diabetes?</p> <p>Further we note that no studies were identified which considered the use of statins in those with type 1 diabetes. The recommendations on statin therapy were therefore based on the professional judgement of the GDG and knowledge from epidemiological studies.</p> <p>The Type 1 Diabetes GDG acknowledge that in the absence of evidence to support a recommendation that an expert consensus view is needed, and that with the low acquisition costs of generic statin drugs there is an argument that all those with type 1 diabetes should be offered statin therapy. However both clinicians and patient representatives on the group had reservations about such a blanket policy.</p> <p>The clinicians on the GDG currently favour the approach outlined in the draft guidance, whereby statin therapy is given to those with any evidence of nephropathy, those with other cardiovascular risk factors and possibly those who are older than a certain age threshold (?40, ?50 or</p>	<p>developed a more measured recommendation in recognition of the information provided. This is to consider statin treatment in adult Type 1 diabetics. The GDG agreed that many Type 1 diabetics will have had diabetes since childhood and therefore many will have the condition for 10 years or more in early adulthood.</p> <p>The GDG have made a second recommendation to offer statins to adults with type 1 diabetes who have other risk factors, evidence of nephropathy, are more than 40 years or have diabetes for 10 years or more.</p> <p>The guideline includes a recommendation to advice women of child-bearing age about the risks of statins and to stop these until after breast feeding is considered.</p>

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							<p>older) or have had type 1 diabetes for a longer duration (?20, ?30 years or longer). The patient representatives were concerned that if the draft guidance were implemented without taking additional risk factors into account, then many low-risk individuals would have to be treated for any to benefit, and so may be unnecessarily exposed to harm from the side effects of statin therapy.</p> <p>Whilst accepting that people with type 1 diabetes are at greater risk of CV mortality than the population without diabetes, there is increasing evidence from the EDIC and other large cohorts that glycaemic control plays an important role in conveying this risk, with intensive glycaemic control having a legacy effect in reducing CV risk. Furthermore much of the CV risk in younger patients is not necessarily related to atheromatous vascular disease, but rather to the adverse impact of cardiac autonomic neuropathy.</p> <p>Given that in those with type 1 diabetes who do not have the other CV risk factors we have considered, any excess CV risk may be mediated by pathology that is not altered by statin therapy, we would urge caution in making the recommendation that all those with type 1 diabetes should be offered statin therapy.</p> <p>If the Lipid Modification GDG did wish to extend the use of statin therapy beyond current usage, we would be more comfortable with a recommendation that statins should definitely be offered to those with established nephropathy or other CV risk factors, including elevated LDL-cholesterol levels as for those without diabetes, and considered for those over 40 years of age and/or with diabetes duration of greater than 20 years.</p> <p>We would also want to see a statement in the guidance warning about the use of statins in women of childbearing age, and the importance of counselling women in this group who definitely need statin therapy that they must stop treatment before attempting to conceive.</p>	

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52	SH	Cardiff and Vale University Health Board	12	FULL	11.8	177	Offering a high intensity statin for the primary prevention of CVD to people who have a 10% (or greater) risk of CVD seems to be a low level of risk to be offering a drug for life. This means that there will be 10 people in 100 who in the next ten years will have a heart attack or stroke (assuming all at the 10% risk). All will need to take a statin for the 10 years and this means that 2 or 3 people will not have a stroke or heart attack, 7 or 8 people will still have their heart attack or stroke and for 90 people will not have a heart attack or stroke whether they had been on treatment or not. This is the benefit and this does not take into account any adverse effects people may have. Can the CVD risk be increased to a higher level to which offer drug treatment (20% at the moment)	Thank you for your comment. The recommendations are based on clinical and cost-effectiveness evidence and do include consideration of adverse events. The GDG acknowledge the number needed to treat and have added this information to the guideline in Section 11.5. We also note that the figures given refer to the number of events predicted and averted in the first 10 years or treatment. As risk rises over time a higher number of events will be expected in following years, and this number will be reduced by the effect of several years of statin treatment already experienced.
53	SH	Cardiff and Vale University Health Board	13	FULL	11.8	177 / 178	As detailed above the choice of atorvastatin 20mg as the statin of choice for primary and secondary prevention seems arbitrary. This does not seem to be supported by the evidence (see row 10) There is an immediate cost implication of a change to atorvastatin 20mg of at least £100,000 a year for Cardiff and Vale UHB. This does not take into account the increased costs associated with the lowering of the risk threshold to 10%	Thank you for your comment. Costs for atorvastatin have decreased several times in the past year. Current costs (NHS Drug Tariff May 2014) for atorvastatin 20 mg are £16.44 per year, compared to £14.22 for simvastatin 40 mg, currently recommended as the standard therapy. Atorvastatin 20 mg is being recommended in preference to simvastatin 40 mg because it is believed to be more effective at decreasing clinical events (it is proven to be more

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								<p>effective at reducing LDL cholesterol). There are therefore expected to be some savings in future costs of treating CVD, although we acknowledge that these will take several years to take effect.</p> <p>The recommendations to use atorvastatin 20 mg are primarily addressed to those newly initiating statins. We recommend that people stable on other statins have a discussion about risk and benefits of any change and an agreement is made between healthcare professional and patient about any change.</p>
54	SH	Cardiff and Vale University Health Board	14	FULL	11.8	182	<p>This statement appears in the guide. Can this be made into a recommendation</p> <p><i>Given the considerably higher cost of using rosuvastatin, the GDG were unable to recommend the use of rosuvastatin in the absence of trial evidence of greater effectiveness.</i></p>	Thank you for your comment. We have added a recommendation to say that that statins of low acquisition cost should be used.
55	SH	Cardiff and Vale University Health Board	15	FULL	11.8	186	<p><i>Therefore, if someone is not able to take the highest intensity statin recommended it will be cost effective for them to take the most clinically effective dose of a statin (other than rosuvastatin) which they can tolerate.</i></p> <p>Same comment as row 14</p>	Thank you for your comment. We have added a recommendation to say that that statins of low acquisition cost should be used.
204	SH	Greater Manchester, Cumbria and South Lancashire Strategic Clinical Network	4	Full	11.8.1	177	<p>This suggests that blood pressure should only be considered if there is hypertension. A meta-analysis (Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338(May 19, 2009):b1665) A Cochrane review of mild hypertension was much more limited (Diao D,</p>	Thank you for your comment. The recommendation is listing the investigations that should be carried out before starting lipid modification treatment. The reference to the NICE Hypertension guideline is to alert people to the importance of assessing and treating raised blood pressure as

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							Wright JM, Cundiff DK, Gueyffier F. Pharmacotherapy for mild hypertension. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD006742. DOI: 10.1002/14651858.CD006742.pub2.) but although the results were not significant, they were compatible with the larger meta-analysis.	appropriate.
168	SH	Greater Manchester Commissioning Support Unit GMCSU	25	Full	11.8.1	177	<p>We believe that this advice targets essentially healthy people and increases costs to the local NHS with very little improvement in outcomes. At a time when the NHS is struggling to balance its books, this is very unwelcome.</p> <p>The numbers needed to treat to prevent a serious vascular event are high, even assuming good compliance with treatment. With a risk of developing diabetes from statin therapy of ~2% absolute risk over five years. Then, at a threshold risk of 10%, we might be preventing 3 CVD events per 100 treated over ten years but we cause 4 new cases of diabetes.</p>	<p>These recommendations are based on the same principles and the same cost-effectiveness threshold that NICE uses for all its advice. Hence the statin treatment recommended in these guidelines is as beneficial and cost effective as other treatments already routinely provided in the NHS, and to not offer this treatment would be unfair towards those who could benefit from it.</p> <p>The GDG acknowledges the NNT for primary prevention and has added this information to the guideline in Section 11.5. The number of cases of new-onset diabetes is discussed in Section 11.2. Statins give rise to an increased relative risk of diabetes onset, but since baseline risk of diabetes will vary in different populations the absolute increased risk with statins will vary, and we do not agree with an absolute cumulative risk of 2% cases of new-onset diabetes per 5 years. We believe that treating 100 people will at most lead to diagnosis of 1 additional case of diabetes, which is likely to represent a case which would have occurred later but is being brought forward by statin treatment. We are hence confident that the benefits of statin</p>

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							<p>The impact/ costs of side effects appear to be under-represented and the costs of blood monitoring and of cases of rare but severe side effects appear to be ignored. GPs are predicting a large increase in consultations that have not been costed either.</p> <p>Up to 50% of patients do not comply with statin medication and cardiovascular risk is reduced by a healthy lifestyle (non-smoking, healthy weight, physically active and a healthy diet). We feel that this guidance may result in waste, false reassurance by relying on statin medication, transfers the responsibility for health from patients to professionals and discounts the value of behaviour modification, for example, a brisk 30 minute walk.</p>	<p>treatment outweigh the risks.</p> <p>The impact of adverse events is included in the modelling where appropriate. Full details are given in Appendix L, Section L.2.3.7.</p> <p>The cost of blood monitoring tests and additional GP consultation are included (see Section L.2.3.6, Table 78).</p> <p>We agree that both lifestyle measures (Chapters 8 and 9) and statins (Chapter 11) are useful to reduce CV risk, and we strongly encourage GPs and other healthcare professionals to fully discuss all means of reducing CV risk with their patients. We agree that no-one should 'rely on' statins and not make any efforts to improve their other risk factors. It is important that clinicians make this clear to their patients.</p>
108	SH	NHS Stockport CCG	1	FULL	11.8.1	177	<p>We believe that this advice targets essentially healthy people and increases costs to the local NHS with very little improvement in outcomes. At a time when the NHS is struggling to balance its books, this is very unwelcome.</p> <p>The numbers needed to treat to prevent a serious vascular event are high, even assuming good compliance with treatment. With a risk of developing diabetes from statin therapy of ~2% absolute risk over five years. Then, at a</p>	<p>These recommendations are based on the same principles and the same cost-effectiveness threshold that NICE uses for all its advice. Hence the statin treatment recommended in these guidelines is as beneficial and cost effective as other treatments already routinely provided in the NHS, and to not offer this treatment would be unfair towards those who could benefit from it.</p> <p>The GDG acknowledges the NNT for primary prevention and has added this information to the guideline in Section 11.5. The number of cases of new-onset</p>

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							<p>threshold risk of 10%, we might be preventing 3 CVD events per 100 treated over ten years but we cause 4 new cases of diabetes.</p> <p>The impact/ costs of side effects appear to be under-represented and the costs of blood monitoring and of cases of rare but severe side effects appear to be ignored. GPs are predicting a large increase in consultations that have not been costed either.</p> <p>Up to 50% of patients do not comply with statin medication and cardiovascular risk is reduced by a healthy lifestyle (non-smoking, healthy weight, physically active and a healthy diet). We feel that this guidance may result in waste, false reassurance by relying on statin medication, transfers the responsibility for health from patients to professionals and discounts the value of behaviour modification, for example, a brisk 30 minute walk.</p>	<p>diabetes is discussed in Section 11.2. Statins give rise to an increased relative risk of diabetes onset, but since baseline risk of diabetes will vary in different populations the absolute increased risk with statins will vary, and we do not agree with an absolute cumulative risk of 2% cases of new-onset diabetes per 5 years. We believe that treating 100 people will at most lead to diagnosis of 1 additional case of diabetes, which is likely to represent a case which would have occurred later but is being brought forward by statin treatment. We are hence confident that the benefits of statin treatment outweigh the risks.</p> <p>The impact of adverse events is included in the modelling where appropriate. Full details are given in Appendix L. The cost of blood monitoring tests and additional GP consultation are included (see Section L.2.3.6, Table 78).</p> <p>We agree that both lifestyle measures (Chapters 8 and 9) and statins (Chapter 11) are useful to reduce CV risk, and we strongly encourage GPs and other healthcare professionals to fully discuss all means of reducing CV risk with their patients. We agree that no-one should 'rely on' statins and not make any efforts to improve their other risk factors. It is important that clinicians make this clear to their patients.</p>
86	SH	Weightwatch	3	FUL	11.8.1	177	With reference to the following point:	Thank you for your comment. The

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		ers UK		L			<p>"51. Before offering statin treatment for primary prevention, optimise the management of all other modifiable CVD risk factors if possible. [2014]"</p> <p>We would like to see a more unequivocal recommendation here for lifestyle weight management as an option for managing one such risk factor of CVD. Suggest the following: 'such as an evidence-based lifestyle weight management intervention as detailed in the Obesity CG43 guidance'</p>	recommendations from NICE Obesity guideline will be linked using NICE pathways.
364	SH	AstraZeneca UK Ltd	21	Full	11.8.1	177	<p>Recommendation 54. "Offer atorvastatin 20mg for the primary prevention of CVD". [new 2014] should be changed to:</p> <p>"Offer atorvastatin 20mg for the primary prevention of CVD. Alternatively, consider rosuvastatin or other high intensity statins at tolerated dose."</p> <p>Rosuvastatin 20mg has been shown to be effective in primary prevention of CVD in the placebo controlled randomised JUPITER study (in the UK the population with Framingham risk score >20 or SCORE risk ≥5%), but LDL-C levels not requiring pharmacologic treatment). A post-hoc analysis of JUPITER conducted at the request of the European regulatory authorities, in the sub-population with Framingham risk score >20 or SCORE risk ≥ 5%, showed rosuvastatin 20mg to be effective in reducing the risk of first major CV event also in patients at high CV risk.^{1,2}</p>	This recommendation is based on clinical and cost effectiveness evidence. The cost-effectiveness modelling conducted for this guideline showed that the use of atorvastatin 20 mg would be cost effective in primary prevention but that the use of rosuvastatin would not be cost effective.
144	SH	Greater Manchester Commissioning Support Unit GMCSU	1	Full	11.8.1	178	<p>65 – It is not clearly stated if the treatment would be primary or secondary prevention. Presumably secondary prevention as mentions reducing raised cholesterol. If so, what are the recommendations for primary prevention for people with CKD stage 3&4?</p>	Thank you for your comment. We have clarified which recommendations refer to primary and secondary prevention.
146	SH	Greater Manchester	3	Full	11.8.1	178	<p>66 – Not clearly stated if refers to primary or secondary prevention.</p>	Thank you for your comment. We have clarified which recommendations refer to

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		Commissioning Support Unit GMCSU						primary and secondary prevention.
205	SH	Greater Manchester, Cumbria and South Lancashire Strategic Clinical Network	5	Full	11.8.2	186	It is not clear why cholesterol should only be measured after three months. The problems of adherence and the failure of a fire and forget approach (Wei L, MacDonald TM, Watson AD, Murphy MJ. Effectiveness of two statin prescribing strategies with respect to adherence and cardiovascular outcomes: observational study. Pharmacoepidemiol Drug Saf 2007 16: 385-92) indicates that one follow up is probably insufficient. It is also not clear why the target is in relation to cholesterol (40% may be too high for testing adherence – 30% may be better) rather than a reduction in cardiovascular risk.	Thank you for your comment. The GDG considered that people will benefit from being on a statin. The measurement of cholesterol is to indicate what reduction they have achieved and whether they might benefit further from a higher dose of atorvastatin and to allow discussion of adherence. This measurement can be combined with monitoring required when statins initiated at 3 months. It is not appropriate to use cardiovascular risk as a means of monitoring treatment- risk will increase for example by age even if patient has a better lipid profile.
365	SH	AstraZeneca UK Ltd	22	Full	11.8.2	186 Table 36	<p>Recommendation 69: Should be rephrased from</p> <p>“consider increasing dose if started on less than atorvastatin 80mg and person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement” [new 2014]</p> <p>to:</p> <p>“ - consider increasing dose - alternatively, consider switching to another high intensity statin at tolerated dose such as rosuvastatin.”</p> <p>Risk: benefit is an important consideration when choosing which statin is most appropriate to treat an individual patient. Therefore, given the greater efficacy of rosuvastatin⁴ in lowering LDL-C compared with atorvastatin, and the need for an alternative high intensity statin we recommend that rosuvastatin to be included in the 2014 NICE guidelines as a treatment option for</p>	<p>Thank you for your comment. Recommendations are based on effectiveness at reducing CV events and death, not at lowering LDL cholesterol levels.</p> <p>Given the available data the GDG agreed that rosuvastatin 10 mg, 20 mg and 40 mg should be classified as high-intensity statins along with atorvastatin 20 mg, 40 mg and 80 mg. Within this group it may be cost effective to increase the dose of atorvastatin but it would not be cost effective to offer rosuvastatin at current prices.</p>

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							patients at higher CV risk.	
366	SH	AstraZeneca UK Ltd	23	Full	11.8.2	186	<p>Recommendation 70. Should be rephrased: from: “If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose.” to If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose or consider switching to another high intensity statin at tolerated dose such as rosuvastatin.”</p> <p>Recommendation 71. Consider adding to: “Tell the person that any statin at any dose reduces CVD risk. If someone reports adverse effects when taking high-intensity statins discuss the following possible strategies with them : The following: “Alternatively, consider switching to another high intensity statin at tolerated dose such as rosuvastatin.” Statins are generally well tolerated ¹⁶, although some drug-drug interactions may increase the risk of adverse events such as myopathy ¹⁷. For example, the risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with potent inhibitors of CYP3A4 and alternative (non-interacting) therapies should be considered. ¹⁸ Rosuvastatin is not expected to be associated with drug interactions resulting from cytochrome P450-mediated metabolism. ¹⁹ In addition, tolerability must be considered and NICE present data (Table 50 Full report) on differences in liver adverse events with atorvastatin 80mg and rosuvastatin 40mg.</p>	Thank you for your suggested re-wording of the recommendations. The use of rosuvastatin was not cost-effective and the recommendations have not been changed as you suggest.
367	SH	AstraZeneca UK Ltd	24	Full	11.8.2	186	In Economic considerations:	Thank you for your comment. The guideline states that for people unable to

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							Removal of: "other than rosuvastatin" due to the benefits listed in ^{1,2,4,7,10,14,15}	take the high-intensity statin that they have been prescribed, it will be cost effective for them to take the most clinically effective dose of a statin that they can tolerate, other than rosuvastatin. This is correct. It would not be cost effective for them to take rosuvastatin due to the cost of rosuvastatin compared to other statins.
174	SH	Pfizer Ltd	6	Full	11.8.2	187	We note that there is an error on line 9 of page 187, in 'other considerations' ; the word "higher" appears twice.	Thank you for comment this has been corrected.
362	SH	AstraZeneca UK Ltd	19	Full	11.6.2.3	166	CV mortality section should include data from study on primary prevention JUPITER. ^{1,2}	Thank you for your comment. The JUPITER trial is included as Ridker (2008) as this is the primary publication. It did not report CV mortality as a single outcome. Reference 1 is a post-hoc analysis according to risk and the guideline development group decision was not to examine this type of evidence. Reference 2 is the protocol publication for JUPITER and does not contain follow-up data. Reference 2 is the protocol publication and does not contain follow-up data.
368	SH	AstraZeneca UK Ltd	25	Full	11.8.3	189	<p>"The GDG decided that the use of non-HDL cholesterol was preferable to calculated or measured LDL-cholesterol given its greater practicality"</p> <p>The Expert Panel 2013 ACC/AHA Guideline was unable to find RCT evidence to support continued use of specific LDL-C and/or non-HDL-C treatment targets. No trials reported on-treatment non-HDL-C levels in primary prevention. Therefore, given the absence of data on titration of drug therapy to specific goals, no recommendations are made for or against specific LDL-C or non-HDL-C goals for the primary or secondary</p>	Thank you for your comment. We agree on the lack of evidence for use of targets. Non-HDL is recommended as the preferred measure when checking baseline tests and to inform discussions with patients.

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							<p>prevention of ASCVD by 2013 ACC/AHA Guideline.</p> <p>No evidence was found that titration or combination drug therapy to achieve specific LDL-C or non-HDL-C levels or percent reduction improved ASCVD outcomes. Therefore, 2013 ACC/AHA Guideline does not recommend their use as performance measures.^{20,21}</p> <p>Therefore we propose that non-HDL-C should be suitable for patients with:^{20,21}</p> <ul style="list-style-type: none"> - metabolic syndrome - diabetes - triglyceride levels are high (above 400 mg/dL or 4.52 mmol/L) - non- fasting patient. 	
387	SH	ABBOTT EPD	5	Full	12.5 Evidence statements 12.6	217 219	<p>The current indication of fenofibrate is the following: Indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the following:</p> <ul style="list-style-type: none"> - Treatment of severe hypertriglyceridaemia with or without low HDL cholesterol. - Mixed hyperlipidaemia when a statin is contraindicated or not tolerated. - Mixed hyperlipidaemia in patients at high cardiovascular risk in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled. <p>It is also specified in the section 5.1 Pharmacodynamic properties the following:</p> <p>There is evidence that treatment with fibrates may reduce coronary heart disease events but they have not been shown to decrease all cause mortality in the primary or secondary prevention of cardiovascular disease.</p> <p>The Action to Control Cardiovascular Risk in Diabetes</p>	<p>Thank you for your comment. The Guideline Development Group reviewed the evidence for use of fibrates both in monotherapy and when added to baseline statin. While a small reduction in non-fatal myocardial infarction was observed with monotherapy no additional benefit was found for fibrates added to statins. The effects of fibrates were considerably smaller than those observed with statins.</p> <p>The guideline is not recommending a strategy based on lipid levels but on use of drugs which have demonstrated effect on morbidity and mortality outcomes. .</p> <p>It was noted that there was clinical uncertainty about the role of fibrates and other triglyceride-reducing medications in</p>

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							<p>(ACCORD) lipid trial was a randomized placebo-controlled study of 5518 patients with type 2 diabetes mellitus treated with fenofibrate in addition to simvastatin. Fenofibrate plus simvastatin therapy did not show any significant differences compared to simvastatin monotherapy in the composite primary outcome of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death (hazard ratio [HR] 0.92, 95% CI 0.79-1.08, p = 0.32 ; absolute risk reduction: 0.74%). In the pre-specified subgroup of dyslipidaemic patients, defined as those in the lowest tertile of HDL-C (≤ 34 mg/dl or 0.88 mmol/L) and highest tertile of TG (≥ 204 mg/dl or 2.3 mmol/L) at baseline, fenofibrate plus simvastatin therapy demonstrated a 31% relative reduction compared to simvastatin monotherapy for the composite primary outcome (hazard ratio [HR] 0.69, 95% CI 0.49-0.97, p = 0.03; absolute risk reduction: 4.95%).</p> <p>European Medicine Agency approved this new indication early 2011 considering there is evidence that residual cardiovascular risk remains even after effective reduction in TC and LDL-C levels by statins. This residual risk may be partly attributable to high triglyceride (TG) and reduced high-density lipoprotein cholesterol (HDL-C) levels, both of which are now recognised as independent risk factors for CHD.</p> <p>The current Clinical guideline focuses essentially on TC and LDL-C management which reflects the epidemiological evidence that a high LDL-C level is a strong risk factor for CVD, and the consistent finding in clinical trials that lowering raised LDL-C levels significantly reduces the incidence of CVD.</p> <p>So, it is then understandable to limit the indication as in Recommendation 93: Do not <u>routinely</u> offer fibrates for the prevention of CVD to any of the following:</p>	subgroups within these trial of patients with high residual triglycerides after statin therapy. A research recommendation has been made on this topic.

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							<ul style="list-style-type: none"> • People who are being treated for primary prevention • People who are being treated for secondary prevention • People with CKD • People with type 1 diabetes • People with type 2 diabetes. <p>However, it is important to mention that for patients at high cardiovascular risk, as patients with type 2 diabetes, for which triglycerides are elevated and HDL-C is low, combination of fenofibrate and a statin could be considered.</p> <p>A retrospective analysis, conducted using the UK General Practice Research Database, the PRIMULA study, has recently been published. The aim was to estimate the prevalence of dyslipidaemias in high-risk patients new to lipid-modifying therapy, and establish the extent to which these lipid abnormalities are addressed by treatment in UK clinical practice. Data were assessed between April 2006 and December 2008 (i.e. after the introduction of the Quality and Outcomes Framework in April 2004).</p> <p>Two periods were studied as follows: a pretreatment period, defined as the 12 months before initiation of lipid-modifying therapy (the index date), and a follow-up period of at least 12 months. Patients included in the study (n = 25,011) had dyslipidaemia with at least one abnormal lipid measurement [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) or triglycerides (TG)] in the pretreatment period. All patients were at high risk of cardiovascular events, which was defined as having a history of cardiovascular disease, a 10-year Framingham</p>	

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							<p>risk score higher than 20%, diabetes or hypertension, as defined by the Joint British Societies 2 guidelines. The patients are representative of the general population in terms of age and gender.</p> <p>At the index date, 98% of patients were initiated on statin monotherapy. After 12 months of treatment, 15.2% (sub-group range: 11.0–22.9%) of all high-risk patients had no lipid abnormalities. The proportions of patients with high TC or LDL-C levels decreased from 98.8% to 68.9%, and from 99.2% to 68.7%, respectively, over 12 months. The prevalence of high TG levels decreased from 45.0% to 26.9%, whereas that of low HDL-C levels increased, from 16.6% to 18.0%.</p> <p>The prevalence of high TG or low HDL-C levels, or a combination of these, was highest in patients with diabetes, both at baseline and after 1 year. In the diabetes subgroup, the proportion of patients with mixed dyslipidaemia consisting of high TG with low HDL-C levels decreased from 17.3% at baseline to 12.6% after 1 year of LMT. The proportion of patients with diabetes who had either high TG or low HDL-C levels decreased from 57.4% at baseline to 44.9% after 1 year.</p> <p>The results of this study indicate that HDL-C and TG levels are poorly managed in primary care in the UK.</p> <p>This finding applies both to the overall study population and the specific subgroups such as patients with a history of CVD and those with hypertension or diabetes. This is consistent with the results of other observational studies (including analyses from other PRIMULA studies in Europe and Asia, the DYSlipidemia International Study (DYSIS) in Europe and Canada and the EUROASPIRE III study in eight European countries), which have all shown that lipid</p>	

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							<p>abnormalities persist in a significant proportion of patients despite effective lowering of LDL-C and TC levels with statins. In DYSIS, for example, 48% of statin-treated patients did not achieve target LDL-C levels. The present findings are also consistent with a previous study in the UK, which suggested that, while LDL-C and TC levels appeared to be managed appropriately in primary care, more than half of statin-treated patients were not reaching optimal levels of HDL-C or TG.</p> <p>In conclusion it is important to recommend treating elevated triglycerides and/or low HDL-C persisting after statin therapy. The only lipid-lowering agent having demonstrated a clinical benefit to patients with this lipid profile is fenofibrate and ignoring this fact may on the long run diminish the improvement in UK patients'health, this guideline is aiming to.</p> <p>REFERENCES</p> <p>Ginsberg NH. DIABETES CARE, VOLUME 34, SUPPLEMENT 2, MAY 2011. Jameson K, Amber V, D'Oca K, Mills D, Giles A, Ambegaonkar B. Int J Clin Pract, December 2013, 67, 12, 1228–1237.</p>	
381	SH	British Dietetic Association	9	Full	15.6	97	<p>It states that there is no evidence that omega 3 help to prevent CVD. This is not an accurate statement. There is evidence for this from some studies but other studies have more equivocal results. The Nilson study for example was undertaken in a coastal town in Norway and dietary intake of omega 3 fatty acids was not controlled for. There is other evidence that no additional benefit is conferred by having very high intakes of omega 3 fatty acids and in this study habitual intakes of oily fish could reasonably</p>	<p>Thank you for your comment. The recommendation is worded to provide as clear advice as possible which is why the it is stated in the way it is.</p>

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							<p>expected to be high.</p> <p>The recommendation could read; On balance there is insufficient evidence to support a recommendation for omega 3 supplementation.</p>	
386	SH	ABBOTT EPD	4	Full	15.6 Recommendation and link to evidence	247	<p>As a global conclusion for the three above mentioned points we could conclude that triglyceride lowering agents such as fibrates and omega-3 fatty acids lower triglycerides more effectively than statins and therefore triglyceride lowering agents should be recommended to be used to treat people with predominantly elevated triglycerides and slightly elevated LDL cholesterol levels whilst statins should be recommended to lower LDL cholesterol when triglycerides are normal or only moderately elevated.</p> <p>REFERENCES:</p> <ul style="list-style-type: none"> National Evidence Based Guidelines for the Management of Type 2 DM prepared by the Australian Centre for Diabetes Strategies 	Thank you for your comment. Please see response to comment number 387
56	SH	Cardiff and Vale University Health Board	16	FULL	16	249 / 250 / 251	<p>The information on ezetimibe all relates to the information from the TA 132. There does not seem to be a distinction between people with primary familial hypercholesterolaemia and those people that are primary and secondary prevention patients of CVD.</p> <p><i>Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia' did not identify any randomised controlled trials that reported health-related quality of life or clinical endpoints such as cardiovascular morbidity and mortality; in the trials identified, surrogate outcomes such as total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels</i></p>	Thank you for your comment. This information is from the ezetimibe NICE Technology Appraisal. Consideration of ezetimibe was outside the scope of this guideline update, please refer to the NICE Ezetimibe Technology Appraisal; http://guidance.nice.org.uk/TA132 .

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							<p><i>were used as indicators of clinical outcomes</i></p> <p>This statement appears a number of times.</p> <p>If there is no evidence of benefit of ezetimibe both when added to a statin or on its own why is it continued to be recommended as an option for primary or secondary prevention of CVD. In the absence of primary hypercholesterolaemia should it be recommended? (even then there is no evidence of benefit). This is inconsistent when other treatments with no evidence of benefit are not recommended.</p>	
392	SH	Johnson & Johnson Ltd.	5	FULL	16.1	249-251	<p>It is noteworthy that in relation to Ezetimibe the GDG rely on recommendations of the 'NICE Technology Appraisal 132' which did not identify any randomised controlled trials that reported health-related quality of life or clinical endpoints such as CVD morbidity and mortality. Rather, it relied on surrogate outcomes such as, total and LDL cholesterol as indicators of clinical outcomes. These same surrogate end-points are successfully impacted by foods/food supplements with added phytosterols as evaluated by the European Food Safety Authority.</p>	<p>Thank you for your comment. This information is from the ezetimibe NICE Technology Appraisal. Consideration of ezetimibe was outside the scope of this guideline update, please refer to the NICE Ezetimibe Technology Appraisal; http://guidance.nice.org.uk/TA132.</p>
178	SH	Royal College of General Practitioners	5	Full	Evidence statements 17	166	<p>Composite endpoints.</p> <p>The message that comes out with statins is usually discussed in terms of Composite endpoints – all CV events and death.</p> <p>However, in the many evidence statements, it is clear that most of the gain seen in trials is for non fatal Coronary events and that the evidence is weak or of small effect size for total mortality or stroke.</p> <p>Extrapolation of the data may imply greater benefit over the long term (as the cardiologists tell us) but the important difference in different endpoint outcomes should be vital in considering benefit to individuals, especially in old age or those with severe multimorbidity.</p>	<p>Thank you for your comment. We have added information about NNT for different endpoints and will work with NICE Implementation team to present the evidence as clearly as possible.</p>

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					27	85	<p>Perhaps these different end points could be presented in table or graphic format as suggested in comment 1. Again, this would be very valuable to have on a summary guideline and information to the media.</p> <p>If we are to live up to the patient choice and information standards set out in recommendation 27, then this detail is vital.</p>	
176	SH	Royal College of General Practitioners	3	Full	Rec 22	78	<p>“Consider those age > 85 to be at increased risk”</p> <p>It is clear reading through that this statement is there because risk isn't valid above age 85 and so we should assume a > 10% risk for these patients. However, this is highly likely to be interpreted as a “Treat all those over age 85 with a statin”</p> <p>On page 184, there is a paragraph noting the paucity of older people in statin trials. Without good evidence, adding to polypharmacy in the very elderly should not be undertaken lightly – what are we hoping to achieve with statins in this age group? Decrease overall mortality (little evidence even in the young) Prevent stroke? (what the elderly may be most interested in, but statins have a weak to non significant effect in this- as detailed in your evidence reviews for statins vs placebo) Prevent non fatal MIs? (where statins show most benefit, but is this what the very elderly are after?)</p> <p>The pros and cons of statins in this age group and evidence supporting their use need to be summarised in an explicit and easily accessible manner, otherwise the message will be received as “Statins for all over 85”</p> <p>If there is a clear need for more research, then the summary guideline should be honest about it.</p>	Thank you for your comment. We have altered the recommendation for people over 85 years to indicate that they may benefit by a reduction in non-fatal MI and added more detail about issues to be considered when deciding on statin treatment for all people.
					Research Rec 4			

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406	SH	Merck Sharp & Dohme	13	Full	11.3 11.4	125 156	<p><u>Meta-analyses conducted by NCCPC</u></p> <p>In the synthesis of clinical effectiveness data for the cost-effectiveness analysis, the NCCPC conducted a number of meta-analyses for outcome trials for relevant endpoints, such as non-fatal MI and myopathy. However, there is concern regarding the appropriateness of the meta-analyses conducted due to the heterogeneity of RCTs included. For example, trials with different patient populations, such as those with heart failure, have been meta-analysed with those with primary prevention populations. Furthermore, a number of outcome trials conducted in Japan only, such as MEGA (Nakamura, 2006) and Yokoi (Yokoi, 2005), were included, which have limited relevance to UK clinical practice.</p> <p><u>References</u></p> <ul style="list-style-type: none"> - Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T et al. (2006) Primary prevention of 18 cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised 19 controlled trial. <i>Lancet</i> 368(9542): 1155-1163. - Yokoi H, Nobuyoshi M, Mitsudo K, Kawaguchi A, Yamamoto A. (2005) Three-year follow-up results of 36 angiographic intervention trial using an HMG-CoA reductase inhibitor to evaluate retardation 37 of obstructive multiple atheroma (ATHEROMA) study. <i>Circulation Journal</i> 69(8): 875-883. 	<p>Thank you for your comment. We acknowledge there was some heterogeneity in the meta-analysis, therefore we have conducted a number of subgroup analysis: please see forest plots in Appendix I, Section I.4. The primary subgroup analysis were by statin intensity (low, medium and high intensity), and by strata (primary prevention, secondary prevention, people with diabetes and people with CKD). RCTs conducted solely in patients with heart failure have been excluded, and if a RCT included a mixed population including heart failure, then it has been assigned to the secondary prevention strata.</p> <p>The GDG did not consider the country of intervention to be a discriminant factor for this guideline, and studies from all over the world were included (published in English language).</p> <p>In addition to the subgroup analysis by intensity and strata, we also conducted subgroup analysis by each single statin and dose, and by follow up time (up to three years, and more than 3 years), and these did not show any significant heterogeneity.</p>
113	SH	National Clinical Guidelines centre CKD GDG	5	FULL	12.6, 13.6, 14.5 R93-95	219, 231, 238	As no evidence was identified by CKD, it is unclear whether this would also relate to people with stage 1& 2 CKD. Perhaps would be more appropriate to say stage 3-5 CKD?	Thank you. This recommendation applies to all populations treated for prevention of CVD. We did not find any convincing evidence for the use of these drugs in any of the populations in which they were studied.
383	SH	ABBOTT	1	Full	15.5 line	246		Thank you for your comment and

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		EPD			13 Primary prevention of CVD		<p>Please insert each new comment in a new row.</p> <p>First of all, it would be important to summarise the current indication of Omega-3-acid ethyl esters 90. They are indicated in two conditions:</p> <ol style="list-style-type: none"> 1. Post Myocardial Infarction (one capsule daily); and 2. Hypertriglyceridaemia (Initial treatment two capsules daily. If adequate response is not obtained, the dose may be increased to four capsules daily). <p>In Section 5.1 Pharmacodynamic properties it is also specified:</p> <ul style="list-style-type: none"> • Omacor is active on the plasma lipids by lowering triglyceride levels as a result of a fall in VLDL (very low density lipoprotein), and the substance is also active on haemostasis and blood pressure. • Omacor reduces the synthesis of triglycerides in the liver because EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis and they inhibit esterification of other fatty acids. • The increase in peroxisomes of β-oxidation of fatty acids in the liver also contributes to the fall in triglycerides, by reducing the quantity of free fatty acids available for their synthesis. The inhibition of this synthesis lowers VLDL. <p>The new Clinical guideline focuses essentially on Total Cholesterol and LDL-C management which reflects the epidemiological evidence that a high LDL-C level is a strong risk factor for CVD, and the consistent finding in clinical trials that lowering raised LDL-C levels significantly reduces the incidence of CVD.</p> <p>However other risk factors should be taken into account when assessing and managing a person's overall CVD risk. One of them is the increased level of triglycerides (fasting triglyceride, 1.7 mmol/l; non-fasting 2.0 mmol/l) as it increases the risk of CVD in both diabetic and non-</p>	<p>Please respond to each comment</p> <p>information regarding the association between detail of lipid profiles and cardiovascular risk.</p> <p>For your information the current NICE Post MI guideline CG172 http://publications.nice.org.uk/mi-secondary-prevention-cg172 does not recommend use of omega fatty acid compounds following myocardial infarction..</p> <p>The GDG acknowledge that evidence that you provide for effect of omega fatty acid compounds on surrogate end-points. The guideline recommendations are based on effect of drug interventions on morbidity and mortality outcomes using RCT evidence and not on effect on lipid subfractions or TGs.</p>

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							<p>diabetic patients.</p> <p>Many prospective epidemiological studies have reported a positive relationship between serum triglyceride levels and incidence of coronary heart disease (CHD). However, early multivariate analyses generally did not identify serum triglycerides as an independent risk factor for CHD. This failure results from the large number of intercorrelated variables associated with elevated triglycerides. Lipoprotein metabolism is integrally linked, and elevations of serum triglycerides can be confounded by significant correlations with total, LDL, and HDL cholesterol levels. Nonlipid risk factors of obesity, hypertension, diabetes, and cigarette smoking are also interrelated with triglycerides as are several emerging risk factors (insulin resistance, glucose intolerance, and prothrombotic state. Thus, many persons with elevated triglycerides are at increased risk for CHD, even when this greater risk cannot be independently explained by triglycerides. Nevertheless, two meta-analyses found that raised triglycerides are in fact an independent risk factor for CHD.</p> <p>The meta-analysis conducted by Austin et al., reviewed 17 population-based prospective studies of triglyceride and cardiovascular disease (46,413 men and 10,864 women). This meta-analysis showed that increases in plasma triglyceride are associated with a significant increase in risk of cardiovascular disease among both men and women (32% in men and 76% in women). After adjustment for HDL cholesterol and other risk factors, these risks were decreased to a 14% increase in men and a 37% increase in women but remained statistically significant. These results, based on more than 46,400 men and 10,800 women, show that plasma triglyceride is an independent risk factor for cardiovascular disease.</p>	

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							<p>Three different prospective epidemiologic studies – the Physician's Health Study, the Stanford Five-City Project and the Quebec Cardiovascular study - have also shown that plasma triglyceride and LDL particle size, two highly interrelated risk factors, predicted subsequent coronary artery disease in three different Caucasian populations.</p> <p>More recently Morrison et al., conducted a meta-analysis to reassess whether serum levels of triglycerides should be considered independently of high-density lipoprotein-cholesterol (HDL-C) as a predictor of CHD. A total of 38 population-based cohort studies were included in this meta-analysis. Results showed that plasma triglyceride levels are predictive of CHD independently of HDL-C. The relationship between triglycerides and CHD is stronger and more consistently observed in populations without elevated CHD risk (e. g., without pre-existing CHD). Authors conclude that population based screening for elevated triglycerides may identify individuals at elevated risk for CHD who may not otherwise be detected.</p> <p>The European Society of Cardiology and the European Atherosclerosis Society has recognized triglycerides as an independent risk factor and thus the therapeutic strategy in atherogenic dyslipidaemia must include a reduction in triglycerides in both primary and secondary prevention.</p> <p>The JBS recommend to measure random (non-fasting) total cholesterol and a full fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and calculated LDL cholesterol and non-HDL cholesterol) either for primary or secondary prevention. The threshold of high blood triglycerides has been defined as 1.7 mmol/l by the JBS, the American Heart Association, the European Society of Cardiology/European Association for the Study of Diabetes and Diabetes UK. At triglyceride</p>	

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							<p>levels above 1.7 mmol/l there are adverse changes in the quality of LDL and HDL molecules. With high triglycerides plasma residence time of triglyceride-rich lipoproteins also rises, so there is increased interchange of triglyceride from chylomicrons and very low density lipoprotein (VLDL) into LDL and HDL, while cholesterol esters travel in the opposite direction, through the action of cholesterol-ester transfer (CETP) protein. The triglyceride enriched LDL is converted to small dense LDL which is cleared less rapidly from the circulation. So, when there are high levels of triglycerides, especially when HDL cholesterol values are low, the CVD risk increases.</p> <p>Due to these facts it seems convenient that triglycerides would be mentioned as a risk factor in the new guideline. The treatment of this risk factor would result in patient benefit and it would be aligned with NHS outcomes Framework Domain 2 helping to reduce premature death and improve patient health & wellbeing.</p> <p>The Guide Development Group (GDG) decided not to recommend the use of omega-3 fatty acids in primary prevention due to the lack of evidence of clinical benefits (all-cause mortality, cardiovascular mortality, presence of myocardial infarction and stroke) based in 2 studies. Only one of them was exclusively on primary prevention. In this study 563 healthy men with hypercholesterolemia in Norway were evaluated. Despite the low number of participants, a tendency toward reduction in all-cause mortality was observed in n-3 PUFA groups. The other study (JELIS study) considered a combined primary and secondary prevention in 18,645 patients with hypercholesterolaemia (14,981 primary prevention). In this study a reduction of 18% in major coronary events was observed in the EPA group compared with the controls,</p>	

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							<p>although it was not statistically significant. It is necessary to highlight that this study was conducted in Japan and the EPA levels of the participants were 10 times higher than in Western population (USA). In Japan, the average fish consumption is very high (x5) compared with that of Western populations and it is unclear if the EPA doses (1800 mg) proposed in this study would have the same effect that have a substantially lower fish consumption.</p> <p>LDL cholesterol is the primary target of treatment in clinical lipid management. However, different studies have shown that a high proportion of patients with metabolic syndrome, obesity and type 2 diabetes have complex lipid abnormalities (dyslipidaemia), which are not restricted to elevated LDL-C or total cholesterol (TC) levels, but often comprise reduced levels of high density lipoprotein cholesterol (HDL-C) and/or elevated triglycerides.</p> <p>In line with current guideline recommendations, patients at high cardiovascular risk are usually treated with statins for secondary as well as for primary prevention. While many studies investigated treatment goal achievement with regards to low-density lipoprotein (LDL-C) and total cholesterol there is paucity of data regarding high density lipoprotein (HDL-C), and/or triglycerides (TG). It has been demonstrated that statin treatment alone may be insufficient to achieve non-HDL-C targets. Gitt et al., conducted a large-scale cross-sectional study (4,282 patients) and found that despite statin treatment the lipid profile of only every fifth patient reached the target values as recommended by current practice guidelines, while the large majority of high-risk patients still had one or more manifestations of dyslipidaemia.</p> <p>The triglyceride-lowering effects of omega-3 fatty acids are well established. Briefly, results of a</p>	

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							<p>systematic review demonstrated dose dependent reductions in triglyceride levels with omega-3 fatty acids in clinical studies; net reductions in triglyceride levels of 10–33% were seen in most studies. The effect of omega-3 fatty acids tended to be greater in studies with higher triglyceride levels at baseline. Changes in total cholesterol and HDL-C levels were generally not significant, and small net increases occurred in LDL-C levels.</p> <p>Therefore, in patients with persistent hypertriglyceridemia while receiving statin therapy, the addition of a TG lowering agent is recommended as a therapeutic option to reduce levels of non-HDL-C. In such patients, one approach is to combine prescription omega-3-acid ethyl esters (P-OM3) with the statin.</p> <p>The effects on the lipid profile of the combination of omega-3 fatty acids with a statin for the treatment of dyslipidaemia have been assessed in several trials. One of the largest was the Combination of Prescription Omega-3 with Simvastatin (COMBOS) trial. The COMBOS study was a multicentre, randomized, double-blind, placebo-controlled, parallel-group study (n=254) in adults who had received >8 weeks of stable statin therapy and had mean fasting TG levels >200 and <500 mg/dL (>2 mmol/L and <than 6 mmol/L) and mean low-density lipoprotein cholesterol levels <10% above their NCEP ATP III goal. This study was conducted to measure the percent change in non-HDL-C from baseline to the end of treatment. The study regimen consisted of an initial 8 weeks of open label simvastatin 40 mg/d and dietary counselling, followed by 8 weeks of randomized treatment with double-blind P-OM3 4 g/d plus simvastatin 40 mg/d or placebo plus simvastatin 40 mg/d. In this study, the addition of P-OM3 4 g/d (465 mg EPA and 375 mg DHA per 1-g capsule) to ongoing simvastatin 40 mg/d in</p>	

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							<p>patients with persistent hypertriglyceridemia prove to be effective in providing additional lowering of non-HDL-C, VLDL-C, and TG levels. The authors concluded that the combination of P-OM3 and simvastatin improved the overall lipid profile without attenuating the efficacy of the statin.</p> <p>Maki et al., reviewed the results from clinical trials regarding the use of omega-3 fatty acids for reducing cardiovascular morbidity and mortality and for the treatment of hypertriglyceridemia and concluded that clinical trials have demonstrated that POM3 treatment at a dose of 4.0 g/day is effective for reducing TG and non-HDL-C levels, while raising HDL-C. Efficacy for these improvements in the lipoprotein lipid profile have been also demonstrated when POM3 is administered as monotherapy or in combination with statins.</p> <p>CONCLUSION: Taking into consideration all the above mentioned data, it is important to recommend the use of P-OM3 in combination with statins for primary cardiovascular disease prevention in patients with hypertriglyceridemia. It is necessary to highlight that this combination therapy is aligned with NHS outcomes Framework Domain 2 helping to reduce premature death and improve patient health & wellbeing.</p> <p>REFERENCES</p> <ul style="list-style-type: none"> Catapano A.L, Reiner T, De Backer G., Graham, I., Taskinen, M.-R., Wiklund, O., Agewall, S., Alegria, E., Chapman, M.J., Durrington, P., Erdine, S., Halcox, J., Hobbs, R., Kjekshus, J., Perrone Filardi, P., Riccardi, G., Storey, R.F., Wood, D..ESC/EAS Guidelines for the management of dyslipidaemias. The Task Force 	

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							<p>Please insert each new comment in a new row.</p> <p>for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) Atherosclerosis Volume 217, Issue 1, July 2011, Pages 3-46.</p> <ul style="list-style-type: none"> • Austin MA, Hokanson JE, Edwards KL. <i>Am J Cardiol</i> 1998;81:7B-12B. • Assmann G, Schulte H, Funke H, von Eckardstein A. <i>Eur Heart J</i> 1998;19(suppl M):M8-M14. • Grundy SM. <i>Am J Cardiol</i> 1998;81:18B-25B. • Stampfer MJ, Krauss RM, Ma J, Blanche PJ, Holl LG, Sacks PM. Hennekens CH. <i>JAMA</i> 1996;276:882-888. • Gardner CD, Fortmann SP, Krauss RM. <i>JAMA</i> 1996;276:875-881. • Lamarche B, Tchernof A, Moorjani S, Catin B, Dagenais GR, Lupien PJ, Despres J-P. <i>Circulation</i> 1997;95:69-75. • Morrison A, Hokanson JE. <i>Vasc Health Risk Management</i> 2009 ; 5 : 89-95. • Joint British Societies. <i>Heart</i> 2005; 91 (suppl v): v1-v52. • La Rosa JC, He J, Vupputuri S. <i>JAMA</i> 1999; 282(24): 2340-6. • Davidson MH <i>et al. Clin Therapeutics</i> 2007; 29(7): 1354-67. • Gitt AK <i>et al. Clin Res Cardiol</i> 2010; DOI 10.1007/s00392-010-0177-z (published online). • National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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) final report. <i>Circulation</i>. 	Please respond to each comment

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							<p>2002;106: 3143-3421.</p> <ul style="list-style-type: none"> American Diabetes Association (ADA) (2004). Dyslipidemia management in adults with diabetes. Diabetes Care 27(90001):S68–S71 Snow V, Aronson MD, Hornbake ER, Mottur-Pilson C, Weiss KB (2004) Lipid control in the management of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med 140(8):644–649. Davidson MH, Maki KC, Pearson TA, et al. <i>Am J Cardiol</i>.2005;96:556-563. Maki KC <i>et al.</i> J Clin Lipidol 2009; 3: 3-38. Miller M et al. Circulation. Published online 18 April 2011; DOI: 10.1161/CIR.0b013e3182160726 Guidelines on diabetes, pre-diabetes, and cardiovascular diseases. Task Force on Diabetes and Cardiovascular Diseases, ESC and EASD. Eur Heart J 2007. doi:10.1093/eurheartj/ehl261 (published online). Diabetes UK blood lipid targets. http://www.diabetes.org.uk (accessed 07/03/14). Balk E, Chung M, Lichtenstein A, et al. Effects of omega-3 fatty acids on cardiovascular risk factors and intermediate markers of cardiovascular disease: evidence report/technology assessment no. 93 [AHRQ publication no. 04-E010-2]. Rockville (MD): Agency for Healthcare Research and Quality, 2004 Mar. 	
372	SH	AstraZeneca UK Ltd	29	Full	16.2.1 16.2.2	249-251	<p>The titles of 16.1 “Ezetimibe (for primary prevention)” and 16.2 “Ezetimibe (for secondary prevention)” <u>are misleading</u> ²⁵, because ezetimibe, either as monotherapy or add-on to statin, is not licensed for primary or secondary prevention of CVD.</p> <p>In addition, ezetimibe is excluded from the 2013</p>	Thank you for your comment. This is a reference to the NICE Technology Appraisal recommendations on Ezetimibe. Ezetimibe was outside the scope of this guideline update, please refer to the NICE Ezetimibe Technology Appraisal;

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							Please insert each new comment in a new row. ACC/AHA blood cholesterol guidelines. ²⁰ In the recent ENHANCE trial, in which patients with heterozygous familial hypercholesterolaemia were randomised to ezetimibe/simvastatin 10/80mg versus simvastatin 80mg alone, the primary endpoint of surrogate marker, mean change in carotid intima-media thickness was not met. To date, ezetimibe has not been shown to reduce risk of CVD in outcome studies. ²⁶	Please respond to each comment http://guidance.nice.org.uk/TA132 .
384	SH	ABBOTT EPD	2	Full	15.5 line 25 People with type 2 diabetes	246	<p>The GDG considered not to recommend the use of omega-3 fatty acids for the primary or secondary prevention of CVD in people with type 2 diabetes due to the lack of evidence of a beneficial effect of this therapy. The recommendations are based on one study, ORIGIN study which combined primary and secondary prevention in type 2 diabetic patients. In this study the levels of triglycerides were reduced by 14.5 mg per decilitre (0.16 mmol/l) more in patients taking O3FA versus placebo. However, no significant reduction in the rate of cardiovascular events in patients at high risk for cardiovascular events was observed.</p> <p>Lipid abnormalities are common in people with Type 2 diabetes and are a major contributor to the increase in cardiovascular disease experienced by people with Type 2 diabetes. Lipid abnormalities in Type 2 diabetes can be broadly categorised into 2 groups:</p> <ul style="list-style-type: none"> • Those which are common to the general population e.g. elevated total and LDL cholesterol • Additional diabetes related abnormalities e.g. elevated triglycerides and reduced HDL cholesterol <p>The typical pattern of dyslipidaemia in type 2 diabetes (T2DM) is characterised by hypertriglyceridaemia, raised total cholesterol and LDL-C, and low levels of HDL-C. According to the Australian National Evidence Based</p>	<p>Thank you for your comment and further references. As per agreed protocol, we only included RCTs, and triglycerides level reduction was not one of our specified outcomes. The guideline is based on evidence for morbidity and mortality outcomes and not on effect on lipid profiles.</p> <p>Although for the type 2 diabetes subgroup only 1 RCT was included, it included more than 12,000 patients, and the evidence was rated of high quality according to the GRADE methodology, The GDG discussed the evidence at length, and concluded that omega-3 fatty acids should not be recommended for people with type 2 diabetes.</p> <p>Regarding the list of references you provided, please see below the reason for exclusion:</p> <ul style="list-style-type: none"> • Sears AV, Ho CKM, Walker SV. D. <i>Pract Diab Int January/February 2010 Vol. 27 No. 1.</i>

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							<p>Guidelines for the Management of Type 2 DM thirty to fifty percent of patients with diabetes have triglycerides levels above 2.25mmol/l and the levels of HDL cholesterol and triglycerides are considered predict factors of cardiovascular disease in Type 2 diabetes (<i>Evidence level III-2</i>). Most of the statin primary and secondary prevention and fibrate primary and secondary prevention trials that have been done in diabetics, the mean baseline triglycerides have ranged between 1.50 and 2.59mmol/l.</p> <p>Epidemiologic studies and clinical trials have demonstrated that diabetic individuals are at increased risk for CVD compared to normoglycemic controls. Several additional factors may be associated with this increased risk, including persistent hyperglycemia, untreated hypertension, and dyslipidemia characterized by raised serum triglycerides (TG) and low concentrations of high-density lipoprotein cholesterol (HDL-C).</p> <p>Lehto et al., conducted a study to demonstrate the role of dyslipidaemia and glycemic control as predictors of coronary heart disease mortality and morbidity in middle-aged patients with type 2 diabetes. This was a 7 year follow up study including 1,059 subjects which provided evidence that patients with triglyceride levels > 2.3 mmol/l increased the risk of CHD events by approximately two fold independently of other risk factors.</p> <p>Fontbonne et al., conducted a separate analysis in 943 men with impaired glucose tolerance of diabetes who had been initially included in the large Paris Prospective Study (to evaluate the incidence of CHD in 7,038 working men). The aim of this sub-study was to assess the CHD mortality risk factors in patients with the above mentioned conditions. This study showed that in this population, hypertriglyceridaemia was the major risk factor of CHD</p>	<p>Not an RCT</p> <ul style="list-style-type: none"> The National Evidence Based Guidelines for the Management of Type 2 DM. The Australian Centre for Diabetes Strategies. 2004. <p>Not an RCT (Guideline)</p> <ul style="list-style-type: none"> Gitt AK <i>et al. Clin Res Cardiol</i> 2010; DOI 10.1007/s00392-010-0177-z (published online). <p>Not an RCT (cross-sectional study)</p> <ul style="list-style-type: none"> American Diabetes Association (ADA) (2004) Dyslipidemia management in adults with diabetes. <i>Diabetes Care</i> 27(90001):S68–S71 <p>Not an RCT (position statement)</p> <ul style="list-style-type: none"> Snow V, Aronson MD, Hornbake ER, Mottur-Pilson C, Weiss KB (2004) Lipid control in the management of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. <i>Ann Intern Med</i> 140(8):644–649. <p>Not an RCT (guideline)</p> <ul style="list-style-type: none"> Lehto S <i>et al. Diabetes</i> 1997; 46: 1354-1359.

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							<p>death in subjects with abnormal glucose tolerance or diabetes.</p> <p>In the Multiple Risk Factor Intervention Trial, a cohort study of approximately 350,000 men aged 35 to 57 years without diabetes and approximately 5000 men of the same ages with diabetes, the incidence of cardiovascular mortality over a mean follow-up of 12 years was 11.7% and 2.6% in diabetic and non-diabetic individuals, respectively. Similarly, the 5-year Helsinki Heart Study found that the incidence of myocardial infarction and cardiac death in diabetic individuals was more than twice that in individuals without diabetes (7.4% and 3.3%, respectively; $P < .02$),²⁵ while a study in approximately 13,000 Danish individuals who were followed prospectively for 20 years showed that those with diabetes had a 2- to 3-fold increased risk of MI or stroke compared with those without diabetes.</p> <p>Data from a Finnish population based cohort of 2432 diabetic and non diabetic individuals suggested that T2DM conferred as great a risk of CVD death as existing CHD.</p> <p>In 2012, Feher et al. conducted a cross-sectional, observational, systematic audit of patients with diagnosed diabetes from 40 primary care practices to assess the prevalence of residual hypertriglyceridemia and the potential need for intensified management among patients with statin-treated type 2 diabetes mellitus (T2DM) in primary care in the UK. The audit collected data from 14,652 patients with diagnosed diabetes: 89.5% ($n = 13,108$) of the total cohort had T2DM. Of the people with T2DM, 22.2% (2916) were not currently receiving lipid-lowering therapy. Up to approximately 80% of these people showed evidence of dyslipidemia. Among the group that received lipid-lowering therapy, 94.7% (9647) were on statin monotherapy, which was usually simvastatin (69.5%</p>	<p>Not an RCT (prospective cohort study)</p> <ul style="list-style-type: none"> Fontbonne A <i>et al.</i> Diabetologia 1989; 32: 300-304. <p>Not an RCT (prospective cohort study)</p> <ul style="list-style-type: none"> Haffner SM, Lehto S, Ronnema T, et al. N Engl J Med. 1998;339:229–234. <p>Not an RCT (cross-sectional study)</p> <ul style="list-style-type: none"> Stamler J, Vaccaro O, Neaton JD, et al. Diabetes Care. 1993;16:434–444. <p>Not an RCT (cohort study)</p> <ul style="list-style-type: none"> Almdal T, Scharling H, Jensen JS, et al. Arch Intern Med. 2004;164:1422–1426. <p>Not an RCT (prospective cohort study)</p> <ul style="list-style-type: none"> Koskinen P, Manttari M, Manninen V, et al. Diabetes Care. 1992;15:820–825. <p>RCT comparing gemfibrozil versus placebo: the outcomes in this paper are not relevant to our review on</p>

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							<p>Please insert each new comment in a new row.</p> <p>of patients receiving statin monotherapy; 6707). The currently available statins were prescribed, with the most common dose being 40 mg simvastatin (44.2%; 4267). Irrespective of the statin used, around half of the patients receiving statin monotherapy did not attain the European Society of Cardiology treatment targets for triglycerides, low-density lipoprotein, high-density lipoprotein, and total cholesterol. The authors concluded that despite the reduction in cardiovascular events produced by statins in patients with diabetes, which is broadly consistent with that in normoglycemic, dyslipidemic controls, a considerable residual cardiovascular risk remains among patients receiving statin therapy. Therefore, clinicians need to consider intensifying statin regimens, prescribing additional lipid-modifying therapies, and specific treatments aimed at triglyceride lowering to improve dyslipidemia control in statin-treated patients with T2DM.</p> <p>The effects of omega-3 PUFA supplementation on cardiovascular outcomes, cholesterol levels and glycemic control in people with type 2 diabetes mellitus have been evaluated in different studies. Hartweg et al carried out a comprehensive search of <i>The Cochrane Library</i>, MEDLINE, EMBASE, bibliographies of relevant papers and contacted experts for identifying additional trials to determine the effects of omega-3 PUFA supplementation on cardiovascular outcomes, cholesterol levels and glycemic control in this population. Eighteen of 23 trials reported data on triglycerides (comparison 01.01) including 969 participants. Omega-3 supplementation was associated with a mean (pooled weighted mean difference) lowering of plasma triglyceride concentration by 0.45 mmol/L (95% confidence interval (CI) -0.58 to -0.32) compared to controls (including a placebo of vegetable oils). This</p>	<p>Please respond to each comment</p> <p>omega-3 fatty acids, however, the original Helsinki Heart study was included in our systematic review on Fibrates (Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P et al. Helsinki Heart Study. New England Journal of Medicine. 1987; 317(20):1237-1245 and Manttari M, Elo O, Frick MH, Haapa K, Heinonen OP, Heinsalmi P et al. The Helsinki Heart Study: basic design and randomization procedure. European Heart Journal. 1987; 8 Suppl I:1-29).</p> <ul style="list-style-type: none"> Eriksson M <i>et al.</i> Eur J Cardiovasc Prev Rehab 2010; 18: 97-105. <p>Not an RCT (population-based survey)</p> <ul style="list-style-type: none"> Howard BV. J Lipid Res 1987; 28: 613-628. <p>Not an RCT (narrative paper)</p> <ul style="list-style-type: none"> Feher M, Greener M, Munro N. Diabetes Metab Syndr Obes. 2013;6:11-5. doi: 10.2147/DMSO.S35053. Epub 2013 Jan 10. <p>Not an RCT (cross-sectional, observational, systematic audit)</p>

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							<p>reduction was statistically significant ($P < 0.00001$).</p> <p>CONCLUSION Taking into consideration the above mentioned data Abbott believes that the administration of omega-3 PUFA in combination with statins in patients with type-2 diabetes is of benefit for these patients. It is necessary to highlight that this combination therapy is aligned with NHS outcomes Framework Domain 2 helping to reduce premature death and improve patient health & wellbeing.</p> <p>REFERENCES</p> <ul style="list-style-type: none"> Sears AV, Ho CKM, Walker SV. D. <i>Pract Diab Int January/February 2010 Vol. 27 No. 1.</i> The National Evidence Based Guidelines for the Management of Type 2 DM. The Australian Centre for Diabetes Strategies. 2004. Gitt AK <i>et al. Clin Res Cardiol</i> 2010; DOI 10.1007/s00392-010-0177-z (published online). American Diabetes Association (ADA) (2004) Dyslipidemia management in adults with diabetes. <i>Diabetes Care</i> 27(90001):S68–S71 Snow V, Aronson MD, Hornbake ER, Mottur-Pilson C, Weiss KB (2004) Lipid control in the management of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. <i>Ann Intern Med</i> 140(8):644–649. Lehto S <i>et al. Diabetes</i> 1997; 46: 1354-1359. Fontbonne A <i>et al. Diabetologia</i> 1989; 32: 300-304. Haffner SM, Lehto S, Ronnema T, et al. <i>N Engl J Med.</i> 1998;339:229–234. Stamler J, Vaccaro O, Neaton JD, et al. <i>Diabetes Care.</i> 1993;16:434–444. Almdal T, Scharling H, Jensen JS, et al. <i>Arch</i> 	<ul style="list-style-type: none"> Hartweg J. Cochrane Database Systematic Rev 2008; (1): CD003205. <p>This Cochrane review was excluded because it also included dietary supplement of omega-3 fatty acids, and we were only interested in pharmacological preparations. In addition, the Cochrane review states that no trials with vascular events or mortality endpoints were identified.</p>

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							<p>Intern Med. 2004;164:1422–1426.</p> <ul style="list-style-type: none"> • Koskinen P, Manttari M, Manninen V, et al. Diabetes Care. 1992;15:820–825. • Eriksson M <i>et al.</i> Eur J Cardiovasc Prev Rehab 2010; 18: 97-105. • Howard BV. J Lipid Res 1987; 28: 613-628. • Feher M, Greener M, Munro N. Diabetes Metab Syndr Obes. 2013;6:11-5. doi: 10.2147/DMSO.S35053. Epub 2013 Jan 10. • Hartweg J. Cochrane Database Systematic Rev 2008; (1): CD003205. 	
385	SH	ABBOTT EPD	3	Full	15.5, line 35, Secondary prevention	246	<p>The GDG considered that there was no clinical benefit in using omega-3 fatty acids for secondary prevention of CVD based on the lack of evidences. This conclusion is based in 6 different studies. One of them was the one conducted by Marchioli et al., to assess the time course of the benefit of Omega-3 fatty acids on mortality documented by the GISSI-P trial in patients surviving a recent (<3 months) myocardial infarction. This study showed that the administration of Omega-3 fatty acids led to a clinically important and statistical significant, reducing the total mortality (lowered after 3 months of treatment) and the risk of sudden death (significant at 4 months). Similar decreases were observed after 6 to 8 months for cardiovascular, cardiac and coronary deaths.</p> <p>Abbott would like to emphasize the current validity of the GISSI-P study although the use of statins was not so spread as it is at present time.</p> <p>Major clinical trials of secondary prevention of CHD with omega-3 fatty acids including DART, GISSI-Prevenzione, GISSI-Heart Failure, and JELIS generally indicate a significant reduction in cardiovascular morbidity or mortality.</p> <p>In 2012, the results of a retrospective, matched-cohort study which used data from the General Practice Research</p>	<p>Thank you for your comment.</p> <p>A meta-analysis was conducted on the use of omega-3 fatty acids for the prevention of CV disease following NICE methodology and the GDG based their decision on the result of the meta-analysis of RCTs, not on single studies. Only RCTs were included in the review, as per protocol; cohort studies were excluded.</p> <p>The GDG discussed the evidence at length, and agreed that for the secondary prevention of CV disease, the evidence showed that there was no clinical benefit in using preparations of omega-3 fatty acids compounds. In addition, there was evidence of increased gastro-intestinal adverse effects.</p> <p>Therefore the GDG disagreed with your suggestion of recommending omega-3 fatty acids in secondary prevention to reduce the risk of death in patients with MI, in addition to other cardiovascular</p>

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							<p>Database (GPRD) were published. In this retrospective study patients who have had a first myocardial infarction (MI) and had initiated treatment with 1 g of licensed n-3 fatty acids in the 90 days after the first MI were selected and each patient was matched to 4 non-exposed patients. Progression to death was compared using time-dependent Cox models to account for potential differences in exposure to other cardiovascular risk-modifying treatments. The authors identified 2,446 eligible first-MI patients subsequently exposed to n-3 fatty acids; 326 (13%) had a baseline diagnosis of type 2 diabetes. This study showed that treatment with licensed n-3 fatty acids was associated with a reduction of the all-cause mortality when this treatment was initiated early post-MI. When treatment started within 90 days of MI it was associated with a reduction of all-cause mortality of 21.8%, independently of other cardiovascular risk-modifying treatment. This study also demonstrated that earlier treatment initiation, within the 14 days after MI, seemed to increase survival benefit by as much as 40%. Similar results were observed in the subgroup of patients who had a baseline diagnosis of type 2 diabetes. These results are consistent with the 20% reduction in all-cause mortality reported in the GISSI-P study (2.1% - 3.2% absolute risk reduction in the GISSI-P randomised controlled trial and real world data (CPRD) .</p> <p>CONCLUSION: taking into consideration all the above mentioned data and especially the results from the routine clinical practice retrospective study, Abbott believes that n-3 fatty acid should have to be administered in secondary prevention to reduce the risk of death in patients with MI in addition to other cardiovascular risk-modifying treatment. It is necessary to highlight that this combination therapy is aligned with NHS outcomes Framework Domain 2 helping to reduce premature death and improve</p>	<p>risk-modifying treatment.</p> <p>Regarding the references you provided:,</p> <ul style="list-style-type: none"> the Poole 2012 study does not meet our inclusion criteria as it is not an RCT. (2) the Marchioli 2002 (not 2012) paper is a subsidiary publication of Marchioli 1999 (GISSI-Prevenzione trial), which we have fully included. The Marchioli 2002 paper did not add any useful data for our outcomes of interest and subgroups, therefore was excluded.

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							<p>patient health & wellbeing.</p> <p>REFERENCES</p> <ul style="list-style-type: none"> • Poole CD, Halcox JP, Jenkins-Jones S, Carr Emma SM, Schiffllers MS, Ray KK, Currie CJ. <i>Clinical Therapeutics</i> 2012. • Marchioli R. <i>Circulation</i>. 2012; 105: 1897-1903. 	
179	SH	Royal College of General Practitioners	6	Full	56	45	<p>Atorva 80 if established CVD.</p> <p>Can we have an easy to understand statement saying what the absolute gain in risk reduction is by doing this?</p>	<p>Thank you for your comment. We do not usually include details about risk reduction in recommendations. The absolute and relative risk are different for each outcome considered, and these can be found in the clinical evidence profiles (section 11.3.1). The absolute risk reduction for non-fatal MI for high intensity versus medium intensity for example is 11 per 1000. A narrative description of how the GDG interpreted the evidence and formulated the recommendation can also be found in the evidence to recommendation table (section 11.8.1).</p> <p>We have informed the NICE implementation team that information on benefits and harms of statins will be useful for implementation of the guideline.</p>
148	SH	Greater Manchester Commissioning Support Unit GMCSU	5	Full and NICE	general	general	<p>Approximately how many people are expected to be in the group benefiting from the primary prevention? Current NICE Lipid modification guideline states how large is the treated population. It would be beneficial, in terms of ability to define the financial impact, to state how many (or how many more than currently) patients are expected to be started on statin.</p>	<p>Thank you for your comment. The costing team at NICE will develop this information.</p>

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149	SH	Greater Manchester Commissioning Support Unit GMCSU	6	Full and NICE	general	general	What actions are to be taken for people aged 75-84? I.e. the draft reads that people aged 40-75 should be screened for risk and people over 85 considered for treatment. Shouldn't the screening upper limit age be changed to 84?	Thank you. We have changed the recommendation as suggested.
166	SH	Greater Manchester Commissioning Support Unit GMCSU	23	Full and NICE	general	general	If high dose atorvastatin recommended, the patient should be educated about the adverse effect profile and incidence. Prescribers should also inform patients that the effects are temporary and reversible. All this potentially could improve compliance.	Thank you for these suggestions. We agree that it is important for people to be appropriately informed about risks and benefits of treatment in a realistic way which allows them to maximise benefit from treatment they decide to take.
447	SH	Royal College of Physicians (RCP)	3	NICE			<ol style="list-style-type: none"> 1. Para 1.3.13: before offering statin therapy, optimise management of all other modifiable CVD risk factors if possible. This seems to suggest recommending managing BP before offering statin to reduce risk. Given that (as previous statement has made clear) patients with treated BP are higher risk than those without, we are not sure why you should wait for management of BP before initiating statin therapy, especially as 1.3.14 suggests starting statin "as soon as possible" after risk assessment. 2. 1.3.25: QRISK2 does not include proteinuria which most patients with CKD 1-2 will have. Proteinuria is a potent CV risk factor so it seems odd to suggest that "CKD" QRISK2 box is not ticked for CKD 1-2. It means QRISK2 will underestimate risk in these people and lead to undertreatment. 3. It is unclear from the guidelines what to do for patient with CKD 3 and type 2 DM: should they get atorva 20 (1.3.27) or atorva 80 (1.3.24). There are many such people. 4. 1.3.27: We are unsure why guidance on titration is needed here, given that is in general section later 5. Current guidance on CKD will lead to low-risk people (eg, young people with CKD3) getting treatment. However, as the bias is towards treating more rather 	<p>Thank you for your suggestions. We have altered recommendation. In primary prevention we have changed the recommendations to encourage and facilitate lifestyle interventions before statin treatment is appropriate as concern was raised by stakeholders that adequate emphasis was not placed on lifestyle modification. We agree that statin treatment should not necessarily be delayed.</p> <p>We have simplified the recommendations so that all people other than those treated for secondary prevention are started on 20mg of atorvastatin.</p> <p>The CKD recommendations have also changed in line with revised classification of CKD by the NICE CKD guideline. People on renal replacement are outside the scope of the guideline and we have clarified this.</p> <p>We now have one recommendation only</p>

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							<p>than fewer people, our experts think this bias can be accepted in the interests of simplicity.</p> <p>6. 1.3.28: This would be better if it read "in CKD 4 or greater start with atorva 20 and titrate upwards if required in discussion with local nephrology services". We believe that the emphasis should be on uptitration because (a) many people with CKD 4 will be high risk and (b) they will have lower LDL-C so probably need titration to achieve a 40% reduction (arbitrary as it may be), so it needs more emphasis. Furthermore, dialysis patients are not specifically mentioned - we believe that they should be treated just like CKD 4-5, but perhaps it would help to be clearer about this.</p> <p>7. 1.3.31: NICE should give some guidance about the likely adverse effects of statins (few) and those that are not statin-related (most, including many currently believed by many doctors to be related). There is a section on how to handle muscle symptoms (which we largely agree with), but at the moment it reads like any adverse effect is to be believed until proven otherwise, rather than suggesting that most adverse effects are not statin-related and patients should be advised accordingly</p> <p>8. The current statin/dose chart in the appendix includes simva 80 which is unnecessary and potentially dangerous</p> <p>9. Fibrates are no longer recommended at all. However, some patients may not be able to take statins (previous myopathy) in which case fibrates may be useful</p> <p>10. Section on niacin could be simplified to: do not use niacin. If not recommended for primary or secondary prevention it would seem that it's never recommended, so why not just say that?</p> <p>11. 2.4: to state that statins have never been tested in type 1 DM is unfair. HPS and CTT include substantial data</p>	<p>on titration.</p> <p>This information is included in the LETR section.</p> <p>We have now indicated in the table which statins are not available in the UK and that simvastatin 80mg is subject to a warning by the MHRA.</p> <p>The recommendation says fibrates should not routinely be used.</p> <p>The recommendations on niacin are in the form they are as the guideline is</p>

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							on such patients and we are not sure there is any remaining uncertainty	making recommendations for a number of different populations when the remainder of care is outlined in a different guideline. The GDG wished to make it clear that these other populations had been formally considered. It was an error to say that statins have never been tested in Type 1 diabetes and we have amended this.
190	SH	Erewash CCG	10	NICE		Appendix B	Rosuvastatin is mentioned in appendix (but see below)	Thank you for your comment
97	SH	Southern Derbyshire CCG	10	NICE		Appendix B	Rosuvastatin is mentioned in appendix (but see below)	Thank you for your comment
196	SH	Erewash CCG	16	NICE			For existing patients on established treatment with simvastatin, is NICE recommending the change to atorvastatin 20mg or high intensity Has the impact of this been factored into the costs associated with implementing this CG?	Thank you for your comment. We are not recommending that people who are stable on a statin have their dose changed but that there is a discussion between healthcare professional and patient about the benefits and risk of changing when medication review occurs.
103	SH	Southern Derbyshire CCG	16	NICE	General	General	For existing patients on established treatment with simvastatin, is NICE recommending the change to atorvastatin 20mg or high intensity Has the impact of this been factored into the costs associated with implementing this CG?	Thank you for your comment. We are not recommending that people who are stable on a statin have their dose changed but that there is a discussion between healthcare professional and patient about the benefits and risk of changing when medication review occurs.
198	SH	Erewash CCG	18	NICE	General	General	Some parts of the literature suggest that compliance with statins after one year may be as low as 50% which is much lower than that seen in clinical trials. Has this been factored into the economic analysis and the perceived net	Thank you. An additional sensitivity analysis has been conducted to assess the impact on cost effectiveness if there was a 50% drop in continuance with

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							benefit on CV mortality and morbidity?	statins after 1 year. This found that treatment would still be cost effective under this scenario. The results can be found in Appendix L.
105	SH	Southern Derbyshire CCG	18	NICE	General	General	Some parts of the literature suggest that compliance with statins after one year may be as low as 50% which is much lower than that seen in clinical trials. Has this been factored into the economic analysis and the perceived net benefit on CV mortality and morbidity?	Thank you. An additional sensitivity analysis has been conducted to assess the impact on cost effectiveness if there was a 50% drop in continuance with statins after 1 year. This found that treatment would still be cost effective under this scenario. The results can be found in Appendix L.
199	SH	Erewash CCG	19	NICE	General	General	Will the implementation tools or the final guidance give statements on organisational responsibilities? For example the role of; <ul style="list-style-type: none"> • Community pharmacists • Public health • CCGs • Secondary care 	Thank you for your comment. NICE clinical guidelines do not usually make recommendations on organisational responsibilities.
106	SH	Southern Derbyshire CCG	19	NICE	General	General	Will the implementation tools or the final guidance give statements on organisational responsibilities? For example the role of; <ul style="list-style-type: none"> • Community pharmacists • Public health • CCGs • Secondary care 	Thank you for your comment. NICE clinical guidelines do not usually make recommendations on organisational responsibilities.
200	SH	Erewash CCG	20	NICE	General	General	Will there be additional resources for implementation of this guidance which will have a significant impact on	Thank you for your comment. Implementation is a local decision of

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							primacy care management of CV disease?	CCG
107	SH	Southern Derbyshire CCG	20	NICE	General	General	Will there be additional resources for implementation of this guidance which will have a significant impact on primacy care management of CV disease?	Thank you for your comment. Implementation is a local decision of CCG
14	SH	British Medical Association General Practitioners Committee	1	NICE Full	General	General	We believe that the psychological effect on individuals of being advised that they are at high risk of cardiovascular disease (CVD) has been ignored. The act of prescribing medication, submitting to monitoring, and daily tablet taking impacts negatively on a person's psychological self-image, transforming them from people to patients, with an adverse effect on their perception of well-being and self-reliance, and influencing their future use of healthcare services.	Thank you for your comment. The guideline is not suggesting that people are at high risk but that their risk is sufficient for them to potentially benefit from statin treatment. This is a preventative medication which is cost effective. The recommendation is to offer this to people who can make their own informed choice on whether to take statins or not.
16	SH	British Medical Association General Practitioners Committee	3	NICE Full	General	General	We believe that the guidance fundamentally moves away from the accepted position that the priority of preventative medicine should be to reduce premature illness and death. Both illness and death are an inevitable consequence of life, and it is therefore their untimely arrival rather than their existence per se which should be the focus of NHS efforts in a resource-limited health economy.	<p>Thank you for your comment. Cardiovascular disease causes a very large burden of premature illness and death, which can be reduced by modifying lifestyle and/or taking statins. We therefore believe that the use of risk tools is integral to reducing premature illness and death. This is particularly the case for younger people at high risk of CVD, who are at risk of the largest losses of health and life if not identified early, which would be likely without the use of risk tool-based risk assessment.</p> <p>The cost effectiveness of the interventions in this guideline are assessed in line with NICE's standard methods as for any other intervention, ensuring that the NHS's limited resources are focused on all</p>

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								interventions which provide a gain in health at a reasonable cost.
17	SH	British Medical Association General Practitioners Committee	4	NICE Full	General	General	The guidance fails to address the lost opportunity costs in primary care. General practice currently does not have spare capacity, and this situation is likely to get worse due to demographic, medical, social, and workforce changes in coming years. The appointments required to assess, treat, and monitor patients according to this guidance can only result in fewer appointments being available for other reasons. With studies failing to show improvements in all-cause mortality the implementation of this guidance may well reduce and not increase the health of the nation, by denying primary care appointments for other conditions.	<p>Thank you for your comment recognising the importance of opportunity costs. NICE's methodology, and the consideration of cost effectiveness in particular, is designed precisely to ensure that opportunity costs are taken account.</p> <p>Recommendations regarding service configuration and service delivery are not within our remit, and the cost-effectiveness analysis is conducted with a neutral view between NHS services, considering opportunity costs between all NHS services not just within primary care. Hence, we do not take the position that the current capacity in general practice is necessarily the correct or sufficient capacity. It may be that if more primary care would reduce the need for subsequent secondary care then it would be cost effective to expend more resources in primary care and less in secondary care. Therefore we do not accept that there are a fixed number of appointments available in general practice. However, we do note that even if appointments connected to statin monitoring were in the short term to displace any other appointments, some of the appointments displaced may relate to treatments less cost-effective than statin treatment, and so it is not necessarily the case that this would</p>

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								<p>decrease overall population health.</p> <p>The GDG consider that effects on morbidity such as on non-fatal MI are important both for patients and for the NHS.</p> <p>We disagree that studies do not show improvement in all-cause mortality. The risk ratio for all statin trials versus placebo is 0.87 (95% CI 0.84 to 0.91), and for primary prevention trials 0.89 (95% CI 0.83 to 0.96). Risk ratios for additional subgroups are shown in the evidence tables in Section 11.4.</p>
18	SH	British Medical Association General Practitioners Committee	5	NICE Full	General	General	This guidance may increase health inequalities as those who engage with the programme are likely to be those who, by virtue of their socio-economic status, have less need of their GPs than others.	Thank you for your comment. The guideline recommends a strategy of prioritising those at highest risk for assessment. This provides practices with a mechanism to identify those at higher risk and target them for assessment.
19	SH	British Medical Association General Practitioners Committee	6	NICE Full	General	General	<p>The evidence base is too poor to on which to justify such a major change in health policy, both in terms of resource allocation and the clinical effects of pharmaceutical intervention in people who are not only healthy, but may well be more healthy than their peers. With regard to positive reported outcomes from trials, the phrase 'too small to be clinically important' occurs 22 times in the full document.</p> <p>There is also recognised uncertainty about whether the benefits from population trials can be applied to individuals, but it is individuals who GPs will be treating.</p>	Thank you for your comment. The guideline is recommending a lower threshold for statin treatment. This is cost effective for the NHS. The GDG acknowledge that effects on individual end-points are small. However cardiovascular disease is common and events occur in those who are a lower risk. The GDG acknowledge that evidence for treatments come from clinical trials on populations but this is a recognised issue with all interventions.
20	SH	British Medical Association	7	NICE Full	General	General	Even in NICE form, the guidance is voluminous and contains too many tasks to be covered properly, even in a number of consultations, even if the facilities and the	Thank you for your comment. The guideline updates CG67. Many of the recommendations are unchanged and

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		General Practitioners Committee					resources were available for this. With some of the evidence for benefit for some activities (such as increasing exercise or modifying diet) being unproven, these would be better omitted to make it easier to know what interventions are both achievable and beneficial. When patients are faced with too much to take on board, they often give up completely; we believe it is better to concentrate on one or two aspects that will have most benefit. Efforts to make the guidance comprehensive have reduced its worth as a treatment guide.	represent principles for treatment and different recommendations are included for different subgroups so all recommendations are not relevant to each patient. Many of the recommendations around assessment and lifestyle advice and modification are already part of Health Checks programme.
21	SH	British Medical Association General Practitioners Committee	8	NICE FULL	General	General	In places statins are recommended to be used in a dose different to that specified on the drug's Summary of Product Characteristics or Patient Information Leaflets. This will cause uncertainties for patients and places extra duties and risks on prescriber.	Thank you for your comment. We acknowledge that some recommendations are off label. The drugs and doses recommended in the guideline are however currently in widespread use in the NHS. Where recommendations are for off label indications this information is provided in a footnote.
15	SH	British Medical Association General Practitioners Committee	2	NICE Full	General	General	We believe that the guidance overvalues absolute and undervalues relative risk. The majority of patients accept increasing risks of CVD with advancing age and relate more easily to, and are more motivated to change by, relative risk; the 'how am I doing compared to my classmates' view.	Thank you for your comment. The best way to provide risk information is a matter for research. A recent paper in the British Journal of General Practice studied the use of prolongation of life and absolute risk reduction in regard to statin treatment Br J Gen Pract 2014; DOI: 10.3399/bjgp14X677824. This guideline and the Patient Experience guideline recommend using a variety of ways to discuss risk. The values and preferences of the patient are as important as how risk is described.
160	SH	Greater Manchester Commissioning Support	17	NICE	general	general	It should be clearly stated that this guideline refers to adult patients for all discussed groups. 'People' wording is used in most cases replacing 'adults' from current guideline. This makes the age range unclear, especially for people	Thank you for your comment. The guideline is relevant to adults only and we have clarified this particularly in the case of Type 1 diabetes.

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		Unit GMCSU					with type 1 diabetes.	
304	SH	Heart UK- The Cholesterol Charity	51	NICE	General	General	The draft seems to duck the cost-effectiveness issue of non-generic high intensity statin (rosuvastatin)	Thank you for your comment. The cost effectiveness of all statin doses is addressed in the cost-effectiveness modelling and the conclusions summarised in Recommendations and link to evidence, Section 11.8.1. We have also added a recommendation to say that that statins of low acquisition cost should be used.
321	SH	Heart UK- The Cholesterol Charity	68	NICE (& Full)	General	General	The lack of treatment targets is a major omission. It is very helpful in demonstrating benefit of treatment, in showing potential reduction in CVD risk to patients. The lack of follow-up protocol is a further major omission. Continuing a long-term or life-long therapy without measurement does very little to help concordance.	Thank you for your comment. The guideline recognises that individuals are interested in cholesterol levels and have suggested that people should have annual review and that measurement of cholesterol yearly can inform discussion.
322	SH	Heart UK- The Cholesterol Charity	69	NICE (& Full)	General	General	In discussing risk with a patient and the potential benefit that might be achieved requires various ways of presenting the data, depending on what the individual finds easiest to understand fully. There is no consideration of NNTs or NNHs for example.	Thank you for your comment. The GDG did discuss NNT and NNH and have added some information about this to the Full guideline I section 11.5.
324	SH	Heart UK- The Cholesterol Charity	71	NICE	General	General	Queries on the Guideline for consideration: Does NICE accept that rosuvastatin can be used as they have deleted all reference to generic statins to be used? Should there not be a target or targets for LDL-C, or now for non-HDL-C? Does NICE not accept evidence that better results are obtained when LDL-C (or now non-HDL-C) reach 1.7 mmol/l (or 2.5-2.9 for non-HDL-C)? Do we want "fire and forget" for all statin treatment whether for primary or for secondary prevention or for FH (after	Thank you for your comment. Rosuvastatin was not cost effective in the HE analysis and we have re-instituted a recommendation about using drugs of low acquisition cost. The guideline is not recommending a target but that people are treated with a high intensity statin to their maximum tolerated dose with a 40% reduction in non-HDL as a guide only. We have added a recommendation to indicate that

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							<p>possible one measurement at 3 months)?</p> <p>Will people refer to the FH TA or just use these guidelines?</p> <p>NICE keeps saying "Do not routinely offer fibrates (or niacin, or resins or stanols/sterols) for prevention of CVD to any of the following...", but does this mean there are any groups to whom one or other of these groups should be so offered, for CVD prevention or for other indication? Does NICE consider that the evidence for resins no longer applies?</p> <p>Does NICE recognise that many will read only the summary and will not look at FH, ezetimibe or other TAs or guidance, and therefore that there should be more explicit summaries of key points from these other NICE publications?</p> <p>Even if they are not prepared to take comments about their style changes, can NICE explain their English usage on page 46 where they say "...The threshold for treatment has been changed from 20% to 10% further the new health economic results..."? Did they mean "...following..." or "...as a result of..." rather than "...further..."?</p> <p>On page 48 and elsewhere, while HEART UK agrees that alcohol consumption should be assessed, does NICE have advice as to how that information should be used in advising/modifying treatment for CVD prevention?</p>	<p>annual review is required with a measurement of non-HDL cholesterol to inform the review. Since the guideline allows use of high intensity statins and little evidence was found for beneficial effect on hard endpoints for other possible drugs continued measuring of cholesterol and consideration of specific targets is not indicated.</p> <p>The GDG consider that these drugs should not generally be used given the lack of evidence for their effect on morbidity and mortality. People with inherited lipid disorders are outside the scope of this guideline. The GDG have recommended that discussion should take place with a specialist for people at high risk who are unable to tolerate statins.</p> <p>The different NICE products will be cross-referenced on NICE Pathways. We have cross-referenced within the guideline itself where relevant.</p> <p>We have changed the wording that you refer to and agree it was poorly expressed.</p> <p>This part of the guideline was not updated in the current update. NICE has developed guidance on Alcohol use Disorders:</p>

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							HEART UK could not find reference in the GDG papers as to an explanation as to the appearance of HbA1c and its logic, and is NICE going to explain and reference the newish use of HbA1c in the diagnosis of diabetes, something that GPs have not yet fully taken on board?	Alcohol dependence and harmful alcohol use (CG115). Alcohol use disorders: diagnosis and clinical management of alcohol-related physical complications (CG 100). The guideline did not review the evidence for the use of HbA1c to diagnose diabetes but accepted its use as recommended by the WHO. The test also has the advantage of not requiring a fasting sample.
213	SH	NHS Sheffield CCG	1	NICE	General	General	We welcome the inclusion of patients with Type 1 or Type 2 diabetes or with CKD into the update of CG67.	Thank you for your comment.
214	SH	NHS Sheffield CCG	2	NICE	General	General	There is a change in the recommendations in this draft from CG67 on the initial use of high intensity statins for both primary and secondary prevention. This is on the basis of their increased LDL lowering effect. There is also a target 40% reduction in non-HDL cholesterol. This represents a move away from the direct evidence from clinical trials as these did not treat to a target cholesterol reduction but used fixed doses of statins. Simvastatin 40mg has been recommended in the previous guideline and promoted in primary care partly on the basis of the strong evidence from clinical trials (principally the HPS study). There is no recommendation for this product despite the strong evidence base and current high prescribing in primary care. Emphasis seems to be on the economic analyses, with their wide assumptions, from the interpolated data rather than on the direct evidence from the clinical trials.	Thank you for your comment. There is significant trial evidence regarding atorvastatin 10 mg and 80 mg, but unfortunately there is much less trial evidence for atorvastatin 20 mg and 40 mg. On the basis of the pattern of effectiveness in reducing CV events with increasing dose in other statins, and the increase in cholesterol reduction with increasing dose in atorvastatin, the GDG does not believe it is unreasonable to assume that the clinical effectiveness of atorvastatin 20 mg and 40 mg at reducing CV events is intermediate between that of atorvastatin 10 mg and 80 mg, and that it would be unreasonable to prefer simvastatin 40 mg solely on the basis of a larger quantity of evidence.
438	SH	Royal College of	5	NICE	General	general	The NICE version seems comprehensive; however the detail in this version is considerable and would take some	Thank you for your comment. NICE will develop a NICE Pathway for the

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		Nursing					time to get through. It would be helpful to have a simplified flow chart for ease of access in clinical practice.	guideline and will link it with other guidance referred to.
115	SH	Royal Pharmaceutical Society	1	NICE	General	General	<p>The Royal Pharmaceutical Society welcomes an update to the NICE Lipid Modification guidance. Pharmacists play a significant role in raising awareness of cardiovascular disease (CVD) and its risk factors. Pharmacists as medicine experts are also intrinsically involved in the supplying of medicine for the prevention and management of CVD, counsel on drug interactions, identify adverse effects and are competent to provide healthcare and lifestyle advice.</p> <p>With an increase in pharmacies offering additional wellbeing assessment services eg Lipid measuring and blood pressure monitoring, pharmacists are well placed to identify at risk patients and recognise warning signs in patients who should be referred for formal CVD risk assessment. Equally, direct interaction with patients about the medicine they are taking and what services the pharmacy provides, allows pharmacists who specifically offer CVD risk assessment health checks an opportunity to manage the number of patients who have not yet been referred,</p> <p>As one of the public faces of healthcare, pharmacists are key to the provision of information on patient conditions and treatments and are on hand to explore patients concerns, offer evidence-based assurances and check patients understanding in a safe and confidential environment.</p> <p>Similarly, as pharmacists are regularly involved in the promotion of better public health such as healthy living campaigns, smoking cessation and advising on alcohol consumption, they are suitable healthcare professionals to support and encourage CVD patients on a cardio protective diet and appropriate lifestyle modifications. With a commitment to the delivery of public health services,</p>	Thank you for this information. We agree that pharmacists have an important role in the prevention of CVD

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							pharmacists and pharmacy teams should be considered in any further recommendations regarding best practice advice on the care of people at risk of CVD.	
415	SH	The Royal College of Pathologists	1	NICE	General	General	We are grateful for being asked to comment on this important update of the Lipid Guidelines and support the majority of recommendations.	Thank you for your comments.
394	SH	Merck Sharp & Dohme	1	NICE	General	n/a	<p>MSD commends the GDG on the following from the guideline:</p> <ul style="list-style-type: none"> • Putting emphasis on lifestyle modification in both primary and secondary prevention • Combining the lipid management of all high risk patient groups under one guideline • Emphasis on non-HDL-c as a marker for CV risk • Emphasis on intensive dose statin in patients with ACS and in secondary prevention <p>However, MSD have concerns on the significant changes in the guideline with regards to:</p> <ul style="list-style-type: none"> • the shift from LDL-c to non-HDL-c with no clarification on the association of the two parameters • the abolition of cholesterol targets. The JBSIII guidelines published recently continue to recommend targets in patients with ACS and secondary prevention • omitting individualised patient care for very high risk patients • the recommendation to routinely start patients on high dose atorvastatin (i.e. 80 mg) but no clear patient follow-up recommendation. <p>Among MSD's comments, we are asking for a number of key changes to the draft guideline in the best interest of patient healthcare management:</p>	<p>Thank you for your comment.</p> <p>We have altered the recommendations following stakeholder comment to use atorvastatin 20mg in all populations treated for primary prevention. The GDG did not recommend a cholesterol target approach as the guideline recommends people to take the maximum tolerated dose of statin.</p> <p>We have added a recommendation about yearly follow up for people stable on a statin but would expect that people treated for secondary prevention will be seen more regularly as they will be on other treatments.</p> <p>We have indicated to the NICE Implementation team that the change to non-HDL will require support and education for healthcare professionals.</p> <p>The comment article by Maningat and Breslow mentioned references its figure of 20% from a review article by Fernandez et al 2011 Cleve Clin J Med, which itself cites Franc et al 2003</p>

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							<ul style="list-style-type: none"> a clarification on the translation of LDL-C to non-HDL-c, given that there is wider awareness of LDL-c among HCPs and patients, and they have little knowledge on non-HDL-c. the inclusion of specific numerical targets for non-HDL-c attainment in secondary prevention in line with the recently published JBSIII. follow-up of all people initiated on statin treatment (primary and secondary prevention) with regular cholesterol testing particularly in high risk secondary prevention to ensure patient's CV risk is effectively managed and minimised over their lifetime. a high-intensity statin starting dose of atorvastatin 40 mg in people with established CVD (1.3.18) and people with type 2 diabetes (1.3.24). This is in the interest of patient adherence and with the knowledge that statin intolerance has been reported in up to 20% (Maningat, 2011) of patients in clinical practice. <p>The below sections detail our evidence to support these changes.</p> <p><u>References</u></p> <ul style="list-style-type: none"> Maningat P, Breslow JL. (2011) Needed: Pragmatic clinical trials for statin-intolerant patients <i>NEJM</i> doi: 10.1056/NEJMp1112023 	Cardiovasc Drugs & Ther. This is a study of muscle symptoms associated with lipid-lowering therapy in general (fibrates or statins), and not with statins in particular. This study cannot therefore be used to justify starting treatment with atorvastatin 40 mg instead of atorvastatin 80 mg. The GDG is not aware of any evidence indicating that adherence with atorvastatin 80 mg will be substantially lower than with atorvastatin 40 mg.
396	SH	Merck Sharp & Dohme	3	NICE	General	n/a	<p><u>Research investigating public and secondary care health care professional (HCP) views on health and cholesterol targets</u></p> <p>With the large amount of publicity on this draft guideline and the relevance to public health and HCP views, MSD</p>	Thank you for providing us with this information. This highlights the importance of GPs providing clear information and education to their patients when explaining why cholesterol targets should no longer be used and

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							<p>funded research to seek the public and secondary care HCP perspective on health and cholesterol targets. This was performed among members of the public aged 50 years and above (n=500) and secondary care healthcare professionals with a specialist interest in Lipidology and Diabetes (n=100). These views were collected in March, 2014.</p> <p>GENERAL PUBLIC RESEARCH KEY FINDINGS¹</p> <ul style="list-style-type: none"> Key demographics of members of the public surveyed: <ul style="list-style-type: none"> 54% of responders were male and 46% were female Average age was 63.7 years old (8% 50-54, 19% 55-59, 23% 60-64, 33% 65-69, 13% 70-74, 4% 75-79) 51% of those surveyed regularly check their cholesterol levels 35% had been set health targets for their cholesterol levels by their healthcare professional 49% found health targets very useful in helping them to understand how well their condition is managed, 29% find them a little useful, 17% were unsure, and only 4% of the survey participants found them not useful. This highlights the importance of retaining simple, clearly defined targets for patients. Of those who have a specific number describing their health target (n=58), a substantial proportion, 43%, said that it made them much more likely to take their medication as prescribed, 48% said that it did not affect how they take their medication, 9% were unsure. This suggests that the removal of simple, clearly defined cholesterol targets has the potential to compromise patient concordance. 42% of participants had heard of total cholesterol, whereas only 7% had heard of non-HDL cholesterol, 	<p>why non-HDL cholesterol is now being measured in preference to LDL cholesterol.</p> <p>The GDG believes that patients will welcome the use of non-fasting blood samples enabled by the use of non-HDL cholesterol instead of LDL cholesterol.</p>

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							<p>25% had heard of LDL cholesterol and 26% had heard of HDL cholesterol.</p> <ul style="list-style-type: none"> 45% of people find numerical values or target ranges easier to understand than reductions or increases, 30% of people find specific reductions or increases easier, 25% were unsure. There have been a series of campaigns over the years teaching patients and the public to 'Know your Numbers', highlighting the importance of total cholesterol and LDL-cholesterol numerical target values. Moving away from simple numbers may require a very substantial education programme to re-educate the public. It may be that this is not an either/or, but that simple numerical targets should be retained in the NICE Lipid Modification Guideline but based on this research alongside any newly proposed measures. <p>Health Care Professional Survey Finding²</p> <ul style="list-style-type: none"> 87% of HCP's who have a special medical interest in Lipidology or Diabetes participating in the survey thought that patients understood the concept and purpose of working towards a cholesterol target. 88% believed that having numerical cholesterol targets has a positive impact on cardiovascular events. 39% of healthcare specialists believed that removing numerical cholesterol targets would have a negative impact on patient concordance with their medicine. Healthcare specialists surveyed indicated that removing numerical cholesterol targets of total cholesterol <4.0 mmol/L or LDL cholesterol <2.0 mmol/L in secondary prevention from NICE guidance could lead to the following: 	

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							<ul style="list-style-type: none"> ○ 35% thought it could lead to lack of understanding by patients of their CVD risk. ○ 35% believed there would be an increase in referrals to secondary care. ○ 29% believed there would be an increase in CV events. ○ Only 11% of specialists surveyed thought that the removal of numerical cholesterol targets in secondary prevention would have no impact. • There was mixed opinion amongst healthcare specialists on the value of moving towards a percentage reduction target for cholesterol – 11% strongly support, 26% moderately support, 33% don't support, and 13% strongly oppose the move. 13% didn't have an opinion and 4% were unsure. There was also a mixed opinion on how well they thought patients would understand the concept of working towards a percentage reduction in non-HDL cholesterol from their baseline score. • This secondary care healthcare specialist view reinforces the general public findings that simple numerical targets that currently exist in CG87 for diabetes patients and CG67 for secondary prevention patients, should be retained alongside any new measures that may be proposed. <p>If NICE wishes to obtain further information regarding the survey, MSD can provide this upon request.</p> <p><u>References</u></p> <ol style="list-style-type: none"> 1. MSD. Data on file. General public research amongst the over 50s – March 2014 2. MSD. Data on file. Healthcare specialist research – March 2014 	

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400	SH	Merck Sharp & Dohme	7	NICE	General	n/a	<p>The proposed recommended start dose of 80 mg of atorvastatin will be received by many general practitioners with a significant degree of reticence due to their inexperience in using high doses of statins and the greater adverse event risk associated with the higher doses of statins (Davidson, 2007; Maningat, 2011). There is also a high degree of patient resistance to high doses of statins.</p> <p>A recent publication of a retrospective observational study in IMS Disease Analyzer of atorvastatin and cholesterol target attainment of those patients with CHD, atherosclerotic vascular disease, diabetes mellitus or familial hypercholesterolaemia showed that between November 2008 to November 2011, only 11.6% of these patients received atorvastatin 80 mg. Atorvastatin 40 mg was the most commonly used dose among these patients. This study also demonstrated that of those high risk patients on atorvastatin 40 mg, 88.4% had a TC of <5mmol/L. Of those high risk patients on atorvastatin 80 mg, 86.5% had a TC of <5mmol/L (Jameson et al., 2014). Given that for many patients, a lower dose of atorvastatin such as 40 mg will provide sufficient reduction in cholesterol to reduce their CV risk, it seems unnecessary to expose such a large group of patients to atorvastatin 80 mg when the incremental risk reduction of 80 mg vs 40 mg is likely small in most cases.</p> <p><u>References</u></p> <ul style="list-style-type: none"> - Davidson MH, Robinson JG. (2007) Safety of aggressive lipid management. <i>Journal of the American College of Cardiology</i> 49: 1753-1762. - Maningat P, Breslow JL. (2011) Needed: Pragmatic clinical trials for statin-intolerant patients. <i>NEJM</i> doi: 10.1056/NEJMp1112023. - Jameson K, Zhang Q, Zhao C, Ramey DR, Tershakovec AM, Gutkin SW, Marrett E. (2014) 	<p>Thank you for your comment. Some GPs may not yet be familiar with prescribing atorvastatin 80 mg, since this was not previously recommended due to the previous high price before the drug was available generically, but this is changing fast. Atorvastatin 80 mg is now a very commonly prescribed drug (2.1 million prescriptions dispensed in 2013, HSCIC). The GDG is confident that any GPs not yet familiar with atorvastatin 80 mg will quickly become so following the publication of this guideline.</p> <p>Maningat and Breslow 2011 do not argue or provide any evidence that high dose atorvastatin has higher rates of adverse events than other atorvastatin doses. Davidson and Robinson 2007 state that atorvastatin 80 mg gives rise to higher frequency of transaminase elevation compared to atorvastatin 10 mg or simvastatin 20–40 mg but do not compare rates of adverse events with atorvastatin 80 mg to atorvastatin 20 mg or 40 mg. There is clear evidence of increased adverse events with simvastatin 80 mg compared with simvastatin 40 mg, but the situation with atorvastatin is not analogous.</p> <p>No evidence is cited for patient resistance to high doses of statins, so we cannot comment on that assertion.</p> <p>We have not taken observational head-</p>

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							Total and Low-Density Lipoprotein Cholesterol in High Risk Patients Treated With Atorvastatin Monotherapy in the United Kingdom: analysis of a Primary-Care Database. <i>CMRO</i> : doi:10.1185/03007995.2014.890926.	to-head studies into account due to the lower quality of evidence compared with RCTs. The GDG acknowledged that the increased effectiveness of atorvastatin 80 mg over atorvastatin 40 mg may be modest, but note that the cost-effectiveness analysis shows that atorvastatin 80 mg would need to have an increased relative effectiveness of only 2% (an increased absolute effectiveness of under 1% for most outcomes) to be cost effective, and are content that this degree of increased effectiveness is highly likely.
255	SH	Heart UK-The Cholesterol Charity	2	NICE Full	General	General	Where "gender" is used it should state "sex". "Sex" is what you are while "gender" is what you might wish to be.	Thank you for alerting is to this.
157	SH	Greater Manchester Commissioning Support Unit GMCSU	14	NICE full	general	general	Note that the layout of chapter referring to drug treatment will change. The current guideline clearly divides the drug treatment into primary and secondary prevention sections. In the proposed guideline update the pharmacological interventions are organised by individual drug (or drug groups), but often it is not clearly stated if the treatment considers primary or secondary prevention.	Thank you for your comment. We have worked with the NICE editors to improve clarity of meaning in the recommendations.
252	SH	Aneurin Bevan University Health Board (Medicines & Therapeutics Committee)	8	NICE		46-47	my biggest concern is the statement included in most of the reason for change boxes (pages 46-47) which states that "the threshold for treatment has been changed from 20% to 10% further the (sic; but probably should say to) new health economic results, which suggests to me this is an overall cost saving exercise rather than designed to improve patient outcomes - something I really struggle with.	Thank you for your comment. We apologise for the error in the wording of this sentence in the draft version. What this statement means is that it is now cost effective to offer statin treatment to people at lower risks of CVD which previously was not cost effective for them. This reflects the fact that the cost of atorvastatin has decreased greatly since the previous guideline.

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								Reducing the threshold will not save money – the decision to lower the threshold, taken on its own, will increase NHS expenditure as more people will be entitled to receive statins – what this statement means is that a treatment which would improve patient outcomes but was previously unaffordable is now affordable and so can now be made available.
256	SH	Heart UK- The Cholesterol Charity	3	NICE	Intro	2	Lines 16-18: These state what are main non-modifiable and modifiable risk factors, but diabetes has been omitted even though it is a potent risk factor. It needs to be added here.	Thank you. This list is not intended to be definitive.
257	SH	Heart UK- The Cholesterol Charity	4	NICE	Intro	2	Lines 25-26: This guideline should be used in conjunction with NICE's other guidance. This is so, but difficult when some of the guidance related to has been fully or partly superseded e.g. CG15 & CG87	Thank you for your comment. The final guideline will refer to the latest NICE guidance.
254	SH	Heart UK- The Cholesterol Charity	1	NICE	Intro	3	Line 5: Instead of "...non-HDL does not..." it needs to say "...non-HDL cholesterol does not..."	Thank you for your comment, this has now been amended.
397	SH	Merck Sharp & Dohme	4	NICE	Introduction	3	MSD agrees with the recommendation for the use of non-high density lipoprotein cholesterol (non-HDL-c) rather than low density lipoprotein cholesterol (LDL-c). Non-HDL-c has been shown to be a better marker of risk in both primary and secondary prevention (Cui 2001; Kirby 2013). However, one concern is the widespread understanding among health care professionals (particularly GP's) and patients of non-HDL-c rather than LDL-c. Abolishing LDL-c without an evidence-based review of how LDL-c screening and treating to goal influence clinical practice would be premature and may have unanticipated negative consequences for public health. We recommend the continued inclusion of LDL-c in the guideline, a clarification on the translation of LDL-c to non-HDL-c, and additional	Thank you for your comment. We have added the definition of non-HDL cholesterol to the introduction.

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							<p>text on how non-HDL-c is calculated. We also recommend that an education programme be implemented (although we understand this is not within NICE's remit) in order to educate health care professionals and patients on this switch.</p> <p><u>References</u></p> <ul style="list-style-type: none"> - Cui Y, Blumenthal RS, Flaws JA, Whiteman MK, Langenberg P, Bachorik PS, Bush TL. (2001) Non-High-Density Lipoprotein Cholesterol Level as a Predictor of Cardiovascular Disease Mortality. <i>Arch Intern Med</i> 161: 1413-1419. - Kirby M. (2013) Managing dyslipidaemia in the context of diabetes. <i>Diabetes & Primary Care</i> 15: No 3, 141 – 148. 	
258	SH	Heart UK-The Cholesterol Charity	5	NICE	Priorities	9	QRISK2 will be embedded in NHS primary care computers but for all other users there will need to be online internet access – give website details here for this.	Thank you for your comment, Weblink to the QRISK2 risk tool is available in the full guideline.
259	SH	Heart UK-The Cholesterol Charity	6	NICE Full	Priorities & elsewhere	NICE 9	NICE normally works on evidence – there is no evidence for the primary use of atorvastatin 20mg, a dose not used in any RCTs, where 10 or 80mg have been used.	Thank you for your comment. The GDG acknowledge that there is no evidence for use of all drugs at all doses in all populations. The cost effectiveness analysis indicates that it is cost effective to use atorvastatin 80mg. The GDG recognised that there is concern about the use of these doses so agreed that people treated for primary prevention should start on lower doses.
260	SH	Heart UK-The Cholesterol Charity	7	NICE Full	Priorities & General	NICE 9 & elsewhere	The follow up of patients is essentially omitted from this guideline – this will lead to an inappropriate “fire & forget” for almost all patients – concordance will not be assessed – additional or altered treatments will not be considered as there will not be any further measurement carried out.	Thank you for your comment. We have added a recommendation about annual review.
437	SH	Royal	4	NICE	1.3.46/4	26	The guideline appears to be saying that fibrates, nicotinic	Thank you for your comment. The GDG

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		College of Nursing			7/48		acid and bile acid sequestrants have no place in the management of lipid disorders as they are not recommended for primary or secondary prevention which covers everyone. When should they be used? Is this guideline aimed at primary care or does it include lipid specialists? A statement of when these drugs are indicated and who should prescribe them would be useful.	consider that there are few situations where these drugs should be used given the lack of evidence for their effect on morbidity and mortality. People with inherited lipid disorders are outside the scope of this guideline. The GDG have recommended that discussion should take place with a specialist for people at high risk who are unable to tolerate statins as they recognise that guidelines will not cover all possible clinical circumstances where use of these drugs might be considered.
309	SH	Heart UK- The Cholesterol Charity	56	NICE	Fibrates	26	Is the guideline saying that there is NO indication for the use of fibrates i) in general or ii) for CVD reduction or iii) for triglycerides or iv) in type 2 diabetes eye disease? Fenofibrate can be a very effective treatment (and better than a statin) for type III hyperlipidaemia (remnant lipaemia).	Thank you for your comment. The GDG consider that these drugs should not generally be used given the lack of evidence for their effect on morbidity and mortality. People with inherited lipid disorders are outside the scope of this guideline. The GDG have recommended that discussion should take place with a specialist for people at high risk who are unable to tolerate statins.
310	SH	Heart UK- The Cholesterol Charity	57	NICE	Resins	26	Again this suggests that there is never indication and/or no evidence for resins. It is agreed that they are difficult with poor tolerance but where a statin is contraindicated, or where a statin is insufficient, they are an option. There are some outcome data.	Thank you for your comment. The GDG consider that these drugs should not generally be used given the lack of evidence for their effect on morbidity and mortality. People with inherited lipid disorders are outside the scope of this guideline. The GDG have recommended that discussion should take place with a specialist for people at high risk who are unable to tolerate statins.
318	SH	Heart UK- The Cholesterol	65	NICE	Appx A	36	Keep the definition of "premature" contained within 1.1.15	Thank you. This recommendation was included in CG67 to provide advice about adjustments to Framingham risk

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		Charity						equation. QRISK2 provides for this information to be included in its risk estimation.
319	SH	Heart UK- The Cholesterol Charity	66	NICE	Appx A	37	The 2008 paragraph 1.1.26 to be deleted is incomplete stopping in mid-sentence and should be clarified.	Thank you for your comment. After stakeholder consultation, most of Appendix A has been deleted, following the NICE process.
5	SH	NHS Leeds, University of Leeds	5	NICE	1.1.1	9	For primary prevention of cardiovascular disease and to identify high risk patients over age of 40 is too late for South Asians. They already have widespread atherosclerosis by that time. The identification ought to start in young adult South Asians with a tailor-made, in expensive, non- invasive simple risk engine (taking into account increased waist-height-ratio, systolic ankle pressures, microalbuminuria, family history of premature cardiovascular disease, personal history of diabetes, duration of diabetes, etc.)	Thank you for your comment. We have removed the age range in this recommendation. Practices can stratify by risk and invite patients for more formal risk assessment according to their local population. Ethnicity is included in QRISK2. The development of risk tools and their validation is outside the scope of a guideline.
261	SH	Heart UK- The Cholesterol Charity	8	NICE	1.1.3	10	Yes, but what is "ongoing"? – weekly, yearly, opportunistically or some other period?	Thank you for your comment. This recommendation was not included in the current update. The frequency of re-assessment is likely to depend on the risk of a patient and their individual circumstances.
22	SH	British Medical Association General Practitioners Committee	9	NICE	1.1.8	11	Although the QRISK2 calculator is the best available it still has limited specificity and sensitivity. This is more likely to be of clinical importance at lower risk levels, and we believe efforts to reduce CVD in these marginal groups would be better employed on population measures such as more controls on calorie-dense foods, tobacco, and the sedentary-encouraging environment.	Thank you, we agree with your comment. The GDG made several recommendations about life-style modification.
181	SH	Erewash CCG	1	NICE	1.1.8	11	QRISK- while we agree using a UK population risk tool is advantageous over the US Framingham. <ul style="list-style-type: none"> Has there been any consideration in the economic modelling to look at patient numbers and Gp appointments/ blood test/ screening costs/ training? 	Thank you for your comment. The costs of GP appointments, blood tests and of using a risk calculator are considered as part of the economic considerations relating to the relative cost effectiveness of different risk assessment tools (Full

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							<ul style="list-style-type: none"> Is there a requirement to re-assess patients already risk scored on Framingham? Is QRISK available on all GP clinical systems? Has QRISK been validated in pts with CVD>10%-20%? 	<p>guideline, Section 6.5). (The costs of GP appointments and blood test are also included in the economic modelling of statin therapy (Appendix L and Chapter 11)).</p> <p>Training costs have not been included, in line with our standard methodology, as training can be delivered in a wide variety of ways and is likely to be combined with training regarding other conditions. Training will be considered as part of the implementation and costing tools developed by the NICE Implementation team.</p> <p>Primary prevention patients previously assessed as eligible for statin therapy using Framingham do not need to be reassessed as they will still be eligible under these recommendations. Those previously found not to be eligible should continue to be reassessed every 5 years, in line with the NHS Health Check programme.</p> <p>We understand that QRISK2 is already available in all GP IT systems.</p> <p>The published QRISK2 validation studies include people at all risk levels, below and above 10% and 20% 10-year risk level.</p>
88	SH	Southern Derbyshire CCG	1	NICE	1.1.8	11	<p>QRISK- while we agree using a UK population risk tool is advantageous over the US Framingham.</p> <ul style="list-style-type: none"> Has there been any consideration in the economic 	The costs of GP appointments, blood tests and of using a risk calculator are considered as part of the economic

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							<p>modelling to look at patient numbers and Gp appointments/ blood test/ screening costs/ training?</p> <ul style="list-style-type: none"> • Is there a requirement to re-assess patients already risk scored on Framingham? • Is QRISK available on all GP clinical systems? • Has QRISK been validated in pts with CVD>10%-20%? 	<p>considerations relating to the relative cost effectiveness of different risk assessment tools (Full guideline, Section 6.5). (The costs of GP appointments and blood test are also included in the economic modelling of statin therapy (Appendix L and Chapter 11). Training costs have not been included, in line with our standard methodology, as training can be delivered in a wide variety of ways and is likely to be combined with training regarding other conditions. Training will be considered as part of the implementation and costing tools developed by the NICE Implementation team.</p> <p>Primary prevention patients previously assessed as eligible for statin therapy using Framingham do not need to be reassessed as they will still be eligible under these recommendations. Those previously found not to be eligible should continue to be reassessed every 5 years, in line with the NHS Health Check programme.</p> <p>We understand that QRISK2 is already available in all GP IT systems.</p> <p>The published QRISK2 validation studies include people at all risk levels, below and above 10% and 20% 10-year risk level.</p>
262	SH	Heart UK-	9	NICE	1.1.9	11	Before it is stated what NOT to do for a particular category	Thank you. We have clarified where

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		The Cholesterol Charity		(& Full)	(& General)		there should be a preceding statement as to what TO DO for a particular category. Here it might be assumed that if a risk assessment tool is not to be used for type 1 diabetes then no assessment or management is required for type 1 diabetes. This might be assumed as there have been no type 1 diabetes RCTs (and will not be done)	groups should be considered for treatment.
182	SH	Erewash CCG	2	NICE	1.1.9	11	What is the age start for Type 1 diabetes, we assume its 18 years of age but it's not clear	Thank you for your comment. We have amended the recommendations to indicate that they apply to adults with Type 1 diabetes.
89	SH	Southern Derbyshire CCG	2	NICE	1.1.9	11	What is the age start for Type 1 diabetes, we assume its 18 years of age but it's not clear	Thank you for your comment. We have amended the recommendations to indicate that they apply to adults with Type 1 diabetes.
183	SH	Erewash CCG	3	NICE	1.1.10	11	From an implementation perspective using a separate risk tool UKPDS for T2DM will be confusing.	Thank you for your comment. The GDG discussed this at length and have agreed to recommend the use of QRISK2 for people with type 2 diabetes.
90	SH	Southern Derbyshire CCG	3	NICE	1.1.10	11	From an implementation perspective using a separate risk tool UKPDS for T2DM will be confusing.	Thank you for your comment. The GDG discussed this at length and have agreed to recommend the use of QRISK2 for people with type 2 diabetes.
326	SH	Association of British Clinical Diabetologists, Diabetes UK	1	FULL NICE	1.1.10		UKPDS to assess CVD risk in DM – given the recent improvements in CVD risk in diabetes, and the simplicity of prescribing all patients with type 2 above age of 40 with statin, it seems a potentially backward step to revert to risk scoring for type 2 diabetes in this age group. The validity of the UKPDS risk engine has also been questioned (see later). The average cholesterol has fallen in 2 decades from around 5.9 mmol/l chol to around 4.2 mmol/l in 2008 Oluwatowoju et al Diab Med 2006	Thank you for your comment. The GDG discussed this at length and have agreed to recommend the use of QRISK2 for people with type 2 diabetes.

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							<p>The fire and forget approach in T2DM is simpler and makes sense. Moreover, it is also now clear that cholesterol lowering and BP management do more to lessen CVD risk in T2DM than managing glycaemia:</p> <p>Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009 May 23;373(9677):1765-72. doi: 10.1016/S0140-6736(09)60697-8. PubMed PMID: 19465231)</p> <p>Hence a blanket statement to give all diabetes patients >40 statins makes sense, is well accepted and appears to be an important contributor to reductions in CVD in DM.</p> <p>A recent paper on cost effectiveness suggest cut off around 40 or 45 support this view :</p> <p>de Vries FM, Denig P, Visser ST, Hak E, Postma MJ. Cost-effectiveness of statins for primary prevention in patients newly diagnosed with type 2 diabetes in the Netherlands. Value Health. 2014 Mar;17(2):223-30. doi:10.1016/j.jval.2013.12.010. PubMed PMID: 24636380.</p> <p>There is a need for CVD risk scores in T2DM below the age of 40 to determine who would benefit. The above paper suggest not cost effective to give ALL patients with T2DM under 45 statins.</p>	<p>As you note, de Vries et al. 2014 state that (in a Netherlands population and using Dutch prices for simvastatin 40 mg, which are lower than those in the UK) treating all patients below 45 is not cost effective. For those between 45 and 55 they note that treatment is not cost effective in the lowest CVD risk group. (Cost effectiveness above and below the age of 40 is not considered.) They do not advocate an age-based cut-off but suggest "the efficiency of the treatment could be increased by targeting patients with relatively higher cardiovascular risk and higher ages."</p>
4	SH	NHS Leeds, University of Leeds	4	NICE	1.1.10	11	UKPDS risk assessment tool uses total cholesterol, atrial fibrillation and smoking all of which are not increased in South Asians when compared to Europeans.	Thank you for this information

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215	SH	NHS Sheffield CCG	3	NICE	1.1.11 1.1.12	11	The recommendations regarding using QRISK assessment tool in people with CKD stage 1 or 2 but not ticking the CKD box (1.1.11) and not using the tool in CKD stage 3 or greater (1.1.12) is likely to be confusing for primary care practitioners.	Thank you for your comment. We have altered these recommendations to increase clarity and adopted the classification of CKD recommended by the NICE CKD guideline.
263	SH	Heart UK- The Cholesterol Charity	10	NICE (& Full)	1.1.12 (& General)	11	As for type 1 diabetes, there needs to be a preceding comment that treatment is needed for those with CKD3 & what should be done. Otherwise superficial reading (& most users will not read the 250 pages) may lead to no CKD being treated or just CKD1 or CKD2.	Thank you. We have altered the recommendations to increase clarity.
184	SH	Erewash CCG	4	NICE	1.1.13	11	Can NICE outline the accuracy of QRISK when fields are left incomplete, i.e. at what point is it inaccurate?	Thank you for your comment, but, at the best of our knowledge, there are not published validation studies to answer your question. We have reviewed the accuracy of the risk tools as structured multi-factorial risk assessment tools; it is outside our remit to review how accurately each risk factor is reflected in the tool.
91	SH	Southern Derbyshire CCG	4	NICE	1.1.13	11	Can NICE outline the accuracy of QRISK when fields are left incomplete, i.e. at what point is it inaccurate?	Thank you for your comment, but, at the best of our knowledge, there are not published validation studies to answer your question. We have reviewed the accuracy of the risk tools as structured multi-factorial risk assessment tools; it is outside our remit to review how accurately each risk factor is reflected in the tool.
264	SH	Heart UK- The Cholesterol Charity	11	NICE (& Full)	1.1.16	12	Again, state that pre-existing CVD (of all types) needs treatment	Thank you for your comment. The GDG considered your suggestions but did not agree that further information was required.
265	SH	Heart UK-	12	NICE	1.1.17	12	State positive – all patients with FH should be assessed	Thank you for your comment. The

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		The Cholesterol Charity		(& Full)			and almost all should be intensively treated (not females from conception-planning to the end of breast-feeding).	guideline is recommending appropriate assessment and diagnosis for people who may have FH in the section on Lipid measurement. People with FH should be treated according to the FH guideline (http://publications.nice.org.uk/identification-and-management-of-familial-hypercholesterolaemia-cg71).
185	SH	Erewash CCG	5	NICE	1.1.19	12	Do we know how much risk will be underestimated in these at risk groups?	Thank you for your comment. We are unable to provide accurate figures for this and clinical judgement will be required on a decision to treat.
92	SH	Southern Derbyshire CCG	5	NICE	1.1.19	12	Do we know how much risk will be underestimated in these at risk groups?	Thank you for your comment. We are unable to provide accurate figures for this and clinical judgement will be required on a decision to treat.
23	SH	British Medical Association General Practitioners Committee	10	NICE	1.1.22 1.3.17	13 21	<p>With regard to over 85s, our third comment (on page 2 of this document is particularly relevant. This age group are particularly at risk of adverse effects of statin therapy, and also have high levels of polypharmacy and co-morbidity. If they do have a cardiovascular event delayed, their shorter life-expectancy means that they will derive limited absolute benefit.</p> <p>To advocate mass-medication of an entire age group without high-quality evidence of benefit (which this guidance admits is lacking – see 2.3) could be regarded as unethical (similar to conducting a large-scale clinical trial without consent), as well as potentially harmful to individuals and wasteful for the NHS as a whole.</p> <p>Good medical care in this age group is often provided by stopping, and not starting, long-term medication, and medical intervention should concentrate on the aspects of health which affect functioning and wellbeing, rather than disease prevention. Calculating benefit in terms of</p>	Thank you for your comment. The recommendation is to consider whether treatment is appropriate and we have altered the recommendation to highlight what the patient might gain from treatment. We agree that good medical care is often provided as you describe.

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							percentage of life expectancy and not as percentage of total lifespan overstates benefits of treatment.	
266	SH	Heart UK-The Cholesterol Charity	13	NICE	1.1.28	13-14	Bullet 3 – if so consider dietetic referral	Thank you. This section of the guideline was not updated. Rec 1.1.28 includes principles for shared decisions about lifestyle modification.
267	SH	Heart UK-The Cholesterol Charity	14	NICE (& Full)	1.1.29	14	How soon? How often?	Thank you. The frequency of re-assessment should be agreed with the individual.
269	SH	Heart UK-The Cholesterol Charity	16	NICE (& Full)	1.2.2	14-15	How will NICE respond (or not) to the recent meta-analyses suggesting that saturated fat is not (or is less) relevant?	Thank you for your comment. The recent meta-analysis was not available when evidence was reviewed for this guideline but will be included if appropriate when the guideline is reviewed.
268	SH	Heart UK-The Cholesterol Charity	15	NICE	1.2.5	15	Does this imply that circumstances should include the person's financial circumstances? Diet is likely to be more expensive and raises issues of equity etcetera.	Thank you. Financial circumstances may be relevant to how a person at risk can alter their diet or other factors that contribute to CVD risk.
412	SH	Merck Sharp & Dohme	19	NICE	1.3	18 27	The whole of Section 1.3 of the draft guideline details lipid modification therapy for the primary and secondary prevention of CVD. Overall, we are concerned that other non-statin lipid modifying therapies have been markedly de-emphasised. There is a feeling in the draft guideline that atorvastatin 80 mg is the final option for patients requiring cholesterol management, or a lower dose if intolerant or contraindicated. Worryingly for the patient, the options for patients who report adverse effects on atorvastatin 80 mg is to discuss adherence, stopping the statin and trying again, reducing the dose or changing to a lower intensity group. All of these would not help lower cholesterol in patients that required intensive lipid management. There is also no effort to address patients at very high risk, or with recurrent cardiovascular events already on maximum tolerated atorvastatin dose, and hence the crucial role that combination therapy can play in	Thank you for your comment. The approach of the guideline is to recommend that people are treated with the maximum tolerated dose of statin. The GDG did not consider it appropriate to recommend drugs where evidence does not exist that they reduce clinical outcomes.

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							lowering cardiovascular risk.	
270	SH	Heart UK-The Cholesterol Charity	17	NICE (& Full)	1.3.1	18	Yes "...drugs are preferred..." but the wording undermines the advice that must be offered to all that diet and lifestyle cannot be ignored.	Thank you. This recommendation is referring to drug treatment and does not undermine importance of lifestyle modifications.
253	SH	Aneurin Bevan University Health Board (Medicines & Therapeutics Committee)	9	NICE	1.3.11	p.20	If there is to be sufficient time in a GP consultation (I note section 1.1.25 from 2008) to discuss the risks and benefits of statin treatment (taking into account additional factors such as comorbidities, potential benefits from lifestyle interventions, patient preference and life expectancy) then should not NICE consider developing a patient decision aid to support / streamline this process?	Thank you for your comment. We have discussed this with the NICE Implementation team and the NICE Medicines and Prescribing Centre who are considered developing a decision aid.
25	SH	British Medical Association General Practitioners Committee	12	NICE	1.3.11	20	Although it is correct to say that life expectancy should be taken into account when considering whether to prescribe statins, this is not quantified, and would appear to be at odds to recommend treatment on the basis of age alone in the over 85s, where life expectancy, even without other risk factors, is less than 6 years.	Thank you for your comment. The recommendation for people over 85 is a 'consider' recommendation only. The decision to prescribe needs to be made on an individual basis according to specific circumstances of each patient and their preferences.
281	SH	Heart UK-The Cholesterol Charity	28	NICE	1.3.11	20	Who is the "responsible clinician" as this is a decision to start long-term drug therapy? Is it a registered doctor or does it include nurses following a protocol?	Thank you. We have removed the word 'responsible' from this recommendation. The professional involved in prescribing of statin should ensure this takes place.
282	SH	Heart UK-The Cholesterol Charity	29	NICE (& Full)	1.3.12	20	Bullet 6: Needs to state that this replaces measurement of a fasting glucose (or random glucose) for the diagnosis of diabetes. There remains the issue not properly considered in the guideline (and omitted from the 2008 guideline and from the diabetes guidelines) of patient who have impaired fasting glycaemia or impaired glucose tolerance (but are neither normal nor diabetic). They do have a CVD risk that is at least doubled.	Thank you. The GDG adopted HbA1C in line with WHO recommendations on diagnosis of diabetes and because this requires a non-fasting sample. We have clarified this in the Full guideline. NICE have produced guidance on Preventing type 2 diabetes: risk identification and interventions for individuals at high risk and this includes general recommendations on people now labelled as 'pre-diabetes'. We have

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								added to the Full guideline that these are among the group of people where clinical judgement is required in addition to use of a risk tool.
169	SH	Pfizer Ltd	1	NICE	1.3.12	20	We are concerned that monitoring for LDL-C is not included in the list of assessments to perform before starting statin treatment? Does non-HDL cholesterol refer to LDL-C? Please could greater clarity be provided and explicit reference to LDL-C monitoring included.	Thank you. We have added information on non-HDL to the introduction to the guideline and it is discussed in the Full guideline in chapter 11.
170	SH	Pfizer Ltd	2	NICE	1.3.13	20	It is unclear why this recommendation treats statins as second line to optimisation of modifiable risk factors. The data in the ASCOT-LLA atorvastatin CV outcomes/JUPITER CV outcomes study shows that treating immediately with statins is more effective and easier to achieve a reduction in cholesterol. Modifiable risk factors should be optimised in conjunction/parallel with commencing statin treatment in order to achieve rapid cholesterol reduction and avoid losing patients to follow-up."	Thank you for your comment. We have modified the recommendations following stakeholder comment. The recommendations aim to have a balance between using lifestyle modification as main approach and not delaying statin treatment unnecessarily. The appropriate decision for an individual patient will vary according to their risk level and circumstances.
132	SH	Cornwall Council	1	NICE	1.3.13	20	"Before offering statin treatment for primary prevention, optimise the management of all other modifiable CVD risk factors if possible." There should be a clear statement specifying the time between lifestyle modification interventions and consideration of pharmacologic interventions to ensure that the former have been attempted (or not) and the impact assessed. Given the time constraints in general practice, there is a risk that, in higher risk patients, lifestyle modification interventions will either be delivered at the same time that statin is commenced, or worse, not delivered at all. The LMGs should also specify an optimal number of sessions/attendances for intervention.	Thank you for your comment. We have modified the recommendations following stakeholder comment. The recommendations aim to have a balance between using lifestyle modification as main approach and not delaying statin treatment unnecessarily. The appropriate decision for an individual patient will vary according to their risk level and circumstances. The GDG did not consider it appropriate to be specific about number of attempts at lifestyle modification.

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217	SH	NHS Sheffield CCG	5	NICE	1.3.13 1.3.14	20	1.3.13 advises offering statin therapy only after optimising all other modifiable CVD risk factors but the 1.3.14 states not to delay offering a statin after the risk assessment. There is an apparent contradiction between these 2 statements that requires clarification.	Thank you for your comment. We have now clarified wording of these recommendations.
133	SH	Cornwall Council	2	NICE	1.3.14	20	"If statin treatment is appropriate for primary prevention, offer it as soon as practicable after risk assessment " This seems to contradict 1.3.13, and does not give a chance to optimise the opportunity to undertake or support lifestyle changes	Thank you for your comment. We have modified these recommendations to make the intentions clear.
171	SH	Pfizer Ltd	3	NICE	1.3.15	21	This is the first mention of "high intensity statin treatment" Please clarify/define in the main body of the guideline what is meant by "high intensity" statin because this is not currently clear for the average reader of the guideline. A reference is made to "high intensity station treatment" in table 1 of the appendix, but it is not explained or referenced in the main document, making cross referencing difficult.	Thank you. We have added information to the introduction of the guideline and have reduced references to high intensity statins in the recommendations.
247	SH	Aneurin Bevan University Health Board (Medicines & Therapeutics Committee	3	NICE	1.3.15		I have used the QRISK2 to assess a male patient aged 60, non-smoker, systolic BP 140, non-diabetic, normal BMI, cholesterol of 5, his risk is >10%. According to the recommendation, we should start him on Atorvastatin 20mg daily for primary prevention. The cost to NHS for implementing this recommendation is enormous and also it will result in over medicating a vast number of healthy patients. For this group of patients we should concentrate our efforts in promoting healthy diet and exercise instead.	Thank you, for your comment. We have added recommendations about use of lifestyle modifications prior to statin treatment
284	SH	Heart UK- The Cholesterol Charity	31	NICE (& Full)	1.3.15	20-21	Here high-intensity statin is to be offered which covers atorvastatin 20mg-80mg, simvastatin 80mg (which probably should now never be used) and rosuvastatin 10-40mg. However 1.3.16 then states 20mg atorvastatin and says no	Thank you. We have added a recommendation about using statins of low acquisition cost.

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							more about dose escalation or other choice. Rosuvastatin of course comes into the high-intensive group but remains non-generic.	
127	SH	Department of Health	1	NICE	1.3.15 1.3.17	20-21	The draft updated guidance lowers the threshold for initiating statin therapy for primary prevention from a 20% 10-year risk to a 10% 10-year risk and the recommended statin is atorvastatin 20mg instead of simvastatin 40mg. Implementation of the updated guidance would lead to a considerable increase in prescribing of atorvastatin and may lead to supply problems until the generic market is able to respond to the updated recommendations by ramping up supply.	Thank you for your comment. The generic market has in the past responded from supplying no atorvastatin in 2011 when it was still on patent, to 8.9 million prescriptions in 2012 and 18.1 million prescriptions in 2013. We expect that the market would continue to respond to increased demand, which we anticipate will increase over the next 2 to 5 years as the recommendations are implemented when people are next assessed by their GPs.
3	SH	NHS Leeds, University of Leeds	3	NICE	1.3.15	9	May not be applicable to South Asians. Statin's main effect is on total cholesterol rather than triglycerides. Total cholesterol in South Asians is either similar or lower than in Europeans but their triglycerides are higher. Moreover, they suffer from aches and pains (? fibromyalgia) more than the Europeans. Aches and pains are the main side effects of statins and main reason for non-compliance.	Thank you. South Asians were included in the guideline as subgroup for consideration. No evidence was found for a separate recommendation.
26	SH	British Medical Association General Practitioners Committee	13	NICE	1.3.15	20	We do not agree that the threshold for statin treatment should be reduced to 10%. We do not believe that the evidence base for such widespread prescribing can be justified on the basis of available evidence, particularly the lack of evidence of improved all-cause mortality. We believe this will have the following negative effects; unsustainable workload implications for primary care, resulting in reduced access for other conditions, unnecessary treatment for those who have been miscategorised by the QRISK2 tool, increased side effects from medication. Reliance on medication may divert the patient's attention	Thank you for your comment. The recommendations are based on the clinical and cost effectiveness analysis and the GDG consider that effects on morbidity are important as well as effects on mortality.

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							away from addressing other modifiable risk factors. The cohort will have an annual risk of an event (not death) of less than 2%, most people would not regard this as a high risk, and of course for many it will be below average for their age and gender. At low levels of risk the impact of frequent-mild or serious-rare adverse effects become more important, and the number-needed-to-treat figures become unacceptably large. The implications of prescribing to so many healthy people are so great that this should only be done in the presence of incontestable evidence of benefit, which is currently not available.	
134	SH	Cornwall Council	3	NICE	1.3.15	20	Under the current NHS Health Check pathway anyone with QRisk $\geq 20\%$ is moved out of the programme for ongoing PC management with no path for review and return to the programme if their QRisk is reduced to below 20%. With a 10% threshold this will have implications for the NHS Health Check pathway	Thank you for this information which we will share with the NICE Implementation team.
283	SH	Heart UK- The Cholesterol Charity	30	NICE	1.3.15	20	It is understood that JBS3, which is expected to be published on 26 th March, will recommend lifetime risk. This may lead to confusion.	Thank you for your comment. JBS3 recommends drug treatment on the basis of 10year risk.
286	SH	Heart UK- The Cholesterol Charity	33	NICE	1.3.15	20	At the first main mentions of "high-intensity" statin there should be a reference to the Table appendix and page number	Thank you for your comment. We have removed reference to 'high-intensity statins' in many of the recommendations and do provide direction to the table at first mention.
218	SH	NHS Sheffield CCG	6	NICE	1.3.15	20	We welcome the recommendation to use QRISK assessment tool.	Thank you for your comment.
219	SH	NHS Sheffield CCG	7	NICE	1.3.15	20	'Offer high intensity statin treatment to those with a 10% or greater 10 year risk of developing CVD.' The lowering of the CVD threshold from 20% to 10% has implications for the number of people eligible and therefore the cost of treatment. We have calculated that this will add approximately an extra £900,000 to the primary care drugs	Thank you for your comment. We cannot comment on the accuracy of your calculations as we do not know the number of potentially eligible patients in Sheffield, but note that costs for

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							<p>cost across Sheffield, if all eligible patients were treated. Our current number of patients receiving statins for primary prevention is in line with the population estimate of the number with a 20% risk, indicating a high level of implementation. Whilst the NICE health economic analysis of the cost per QALY indicates this is cost effective, the benefit for an individual is limited. The majority of patients at low risk who receive a statin will derive no benefit from them. This can therefore be considered a public health measure to reduce the level of CV disease in the population and will only be successful if large numbers of patients agree to take the statin. It is not clear that the threshold cost per QALY for this type of intervention is the same as for the technology appraisals. We query whether this represents value for money for the CCG as this increase in statin spend will need to be found from within the existing budget.</p> <p>Lowering the threshold for treatment with statins may result in a reliance on medical treatment and less emphasis on lifestyle measures to reduce cholesterol in those in the 10 to 20% 10 year CV risk group.</p>	<p>atorvastatin have decreased several times in the past year.</p> <p>We also note that, although providing preventative treatment to an increased number of people will clearly increase up-front costs, there will also be savings in the future costs of treating CVD, though we acknowledge that these will take several years to take effect.</p> <p>We agree that any preventative health intervention can be considered in a sense to be a public health measure, but this does not mean that this would only be successful if large numbers of patients agree to take statins. Unlike public health measures regarding infectious disease such as vaccination, there is no effect on other people from taking statins – the whole benefit is to the person taking the statin. Therefore, if a small number of additional people take statins there will be a small total benefit to the population, and if a large number take statins there will be a larger benefit – this benefit would be entirely proportional to the number of people (at the same risk level) who take statins, and hence the cost effectiveness is the same regardless of the number of people involved. The benefit to each individual is small, but it is irrespective of how many other people take statins. As the benefit is a reduction in risk of CVD then indeed only some people will actually avoid a</p>

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								<p>CV event or death as a result of taking statins (and we will not know, even in retrospect, which individuals they were). That is the effect of any intervention which lowers risk but does not entirely prevent illness, whether it is a change in diet or exercise, the use of drugs to lower blood pressure, or indeed the use of statins for secondary prevention and in those at very high risk. We have included information on numbers needed to treat in the guideline, and encourage clinicians to discuss with their patients the quantity of benefit to them as an individual as part of their discussion to help them to decide whether to take statins.</p> <p>We are not sure if by your comment you mean that it is not clear whether the threshold cost per QALY for this type of intervention is in fact the same under current NICE policy, or whether it should be the same. The situation is that the NICE cost-effectiveness threshold is the same for all types of intervention, on the basis that it is important that all health interventions are considered equally against each other. We see no reason why the threshold should be different for preventative interventions rather than treatments. Spending money on statins for primary prevention according to these recommendations (bearing in mind the decreases expected in costs of future CVD care) thus provides equally good value for money for the CCG as many</p>

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								<p>other treatments recommended by NICE, all judged against the same threshold.</p> <p>We would be concerned if any GP saw this guideline as an excuse to 'rely' on medical treatment alone and not to address lifestyle measures. This guideline includes recommendations on both lifestyle measures and statins, and both sections should be read and applied. We strongly encourage GPs to work with their patients to make lifestyle changes to reduce their cholesterol levels.</p>
187	SH	Erewash CCG	7	NICE	1.3.15	20 and general	<p>What direct evidence do you have that looked at high intensity statins in primary prevention with outcome data for reducing CV morbidity and/or mortality? (with the exception of simva 80mg)</p> <p>What happened to simvastatin 40mg that was used in the landmark HPS study?</p> <p>We assume that some of the changes around primary prevention are driven by the Cholesterol treatment trialist collaboration publication in 2012</p> <p>Points we wish to raise in relation to this if correct</p> <ol style="list-style-type: none"> 1. Why didn't the CTT meta-analysis consider the side effects of statins on serious adverse events? 2. Why if statins are safe, so many warnings and issues around simvastatin 80mg and why was cerivastatin withdrawn? 	<p>Thank you for your comment. We would like to emphasize that recommendations are based on both clinical and cost effectiveness.</p> <p>Studies in primary prevention with high intensity statins include Crouse 2007 (METEOR) and Ridker 2008 (JUPITER). The HPS study (Meade 1999) is also included in our clinical evidence review. Please see chapter 11 of the full guidelines.</p> <p>We did not base our recommendations on the CTT meta-analysis, but we carried out our own meta-analysis of 51 RCTs (34 of statins versus placebo and 17 of head-to-head comparison of different statins). Please see full details in chapter 11 of the full guideline.</p>
94	SH	Southern Derbyshire		NICE	1.3.15	20 and general	What direct evidence do you have that looked at high intensity statins in primary prevention with outcome data	Thank you for your comment. We would like to emphasize that recommendations

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		CCG	7			I	<p>for reducing CV morbidity and/or mortality? (with the exception of simva 80mg)</p> <p>What happened to simvastatin 40mg that was used in the landmark HPS study?</p> <p>We assume that some of the changes around primary prevention are driven by the Cholesterol treatment trialist collaboration publication in 2012</p> <p>Points we wish to raise in relation to this if correct</p> <ol style="list-style-type: none"> 3. Why didn't the CTT meta-analysis consider the side effects of statins on serious adverse events? 4. Why if statins are safe, so many warnings and issues around simvastatin 80mg and why was cerivastatin withdrawn? 	<p>are based on both clinical and cost effectiveness.</p> <p>Studies in primary prevention with high intensity statins include Crouse 2007 (METEOR) and Ridker 2008 (JUPITER). The HPS study (Meade 1999) is also include in our clinical evidence review. Please see chapter 11 of the full guidelines.</p> <p>We did not base our recommendations on the CTT meta-analysis, but we carried out our own meta-analysis of 51 RCTs (34 of statins versus placebo and 17 of head-to-head comparison of different statins). Please see full details in chapter 11 of the full guideline.</p>
220	SH	NHS Sheffield CCG	8	NICE	1.3.16	21	<p>'Offer atorvastatin 20mg for the primary prevention of CVD.' The recommendation for the use of a high intensity statin for primary prevention does not come directly from the clinical trials. We are aware that benefit of a high intensity stain for primary prevention is demonstrated from interpolation of the individual data from the clinical trials by the Cholesterol Treatment Trialist's (CTT) collaborators. However, this does seem to be in line with statement 1.3.1 where it states that drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality. There is no primary prevention study that uses 20mg atorvastatin dose. The CTT analysis in primary prevention has been criticised on a number of levels, including that one of the main drivers of the significant event reductions is the revascularisation data, which is subject to physician bias.</p>	<p>The recommendation was based on the clinical and cost effectiveness evidence we reviewed, and not on the analysis by CTT. We acknowledge that there is no primary prevention trial assessing atorvastatin 20 mg.</p>
398	SH	Merck Sharp & Dohme	5	NICE	1.3.16	21	<p>MSD agrees with atorvastatin 20 mg as a starting dose for the primary prevention of CVD. However, for consistency with the sections for established CVD (section 1.3.18) and</p>	<p>Thank you for your comment. It would not be consistent to introduce recommendation of other</p>

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							<p>type 2 diabetes (section 1.3.24), coupled with the recognition that atorvastatin 20 mg might not be appropriate for all patients, we recommend that section 1.3.16 be changed to (bold indicates new text):</p> <p><i>Offer atorvastatin 20 mg for the primary prevention of CVD. If any of the following apply use a lower dose of atorvastatin, a lower intensity statin or discuss other pharmacological therapies for lipid modification, including those recommended by NICE:</i></p> <ul style="list-style-type: none"> • potential drug interactions • risk of adverse effects • patient preference [new 2014] 	pharmacological therapies for lipid modification in this recommendation, as they are not recommended in 1.3.18 or 1.3.24 either. Other lipid-modifying therapies are discussed in Chapters 12–16 and should be considered in line with recommendations 1.3.46–1.3.52 and 1.3.1.
285	SH	Heart UK- The Cholesterol Charity	32	NICE (& Full)	1.3.17	21	What one may be considering here is likely life expectancy for each individual balanced against co-morbidities, concurrent medication, patient wishes etcetera.	Thank you.
221	SH	NHS Sheffield CCG	9	NICE	1.3.17	21	Treatment in the over 85 years old is a “consider” recommendations. It is advised that assessment and treatment is guided by the benefits and treatment and informed preference. As there is a lack of data in the over 85 years, it will be difficult for GPs to communicate the benefits and risks to older patients in line with recommendation 1.1.27.	Thank you for your comment. We have added more detail to this recommendation to indicate that the benefit may lie in reduction of non-fatal myocardial infarction.
399	SH	Merck Sharp & Dohme	6	NICE	1.3.18 1.3.24	21 to 22	<p><u>For people with established CVD and type 2 diabetes, a start dose of atorvastatin 80 mg may not be appropriate</u></p> <p>While MSD agrees with starting all patients with ACS on atorvastatin 80 mg, due to their very high risk of a subsequent CV event, atorvastatin 80 mg as the initial</p>	Thank you for your comment. We have altered the recommendations following stakeholder comments to initiate treatment with atorvastatin 20mg for people with Type 2 diabetes. Treatment can be titrated to 80mg according to tolerability.

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							<p>treatment is inappropriate for people with established CVD or type 2 diabetes. There are three main areas of concern with respect to this:</p> <ol style="list-style-type: none"> 1. low usage and reticence of atorvastatin 80 mg among GPs (comment 7). 2. atorvastatin 80 mg is not appropriate to use in a significant proportion of people due to a greater risk of adverse events (comments 8 and 9). 3. the methodological approach used for and the uncertainty associated with the de novo clinical and cost-effectiveness analyses produced for this guideline update (comments 10 to 17). <p>We recommend the following changes to the recommendations in the guideline (bold text highlights changes:</p> <p>Section 1.3.18 <i>Start treatment in people with established CVD with atorvastatin 40 mg and increase dose to atorvastatin 80 mg if tolerated, and a greater reduction in non-HDL or LDL cholesterol is required. If any of the following apply use a lower dose of atorvastatin or discuss other pharmacological therapies for lipid modification, including those recommended by NICE:</i></p> <ul style="list-style-type: none"> • <i>potential drug interactions</i> • <i>risk of adverse effects</i> • <i>patient preference. [new 2014]</i> <p>Section 1.3.20 <i>If a person has acute coronary syndrome, do not delay statin treatment, and start with atorvastatin 80 mg. Take a lipid sample on admission and about 3 months after the start of treatment. [2014]</i></p>	<p>The GDG did not consider it appropriate to change the recommendations for people treated for secondary prevention as their experience is that atorvastatin is tolerated when used in ACS and the recommendations allow lower doses of atorvastatin if there is high risk of adverse effects.</p>

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							<p>Section 1.3.24 <i>When offering statin treatment for the prevention of CVD in people with type 2 diabetes, start with atorvastatin 40 mg and increase dose to atorvastatin 80 mg if tolerated, and a greater reduction in non-HDL or LDL cholesterol is required. If any of the following apply use a lower dose of atorvastatin or discuss other pharmacological therapies for lipid modification, including those recommended by NICE:</i></p> <ul style="list-style-type: none"> • potential drug interactions • risk of adverse effects • patient preference. [new 2014] <p>See comments 2 and 4 for our response on the use of non-HDL cholesterol and appropriateness of using objective targets levels.</p>	
404	SH	Merck Sharp & Dohme	11	NICE	1.3.18 1.3.24	21 to 22	<p><u>The clinical effectiveness (on CV outcomes) and cost-effectiveness of atorvastatin 80 mg versus atorvastatin 20 mg and 40 mg is uncertain</u></p> <p>Atorvastatin 80 mg has been shown to reduce cardiovascular events compared with atorvastatin 10 mg in patients with stable coronary disease in the TNT study (La Rosa, 2005). Although there is good evidence for incremental CV risk reduction with more intensive LDL-c lowering therapies, there are no head-to-head RCT's that have specifically compared the clinical effectiveness of atorvastatin 80 mg with either atorvastatin 40 mg or atorvastatin 20 mg at reducing cardiovascular events (see table 40, Full Clinical Guideline). This has been recognised by the GDG in the draft guideline ("it was not possible to establish the relative effectiveness of atorvastatin 20 mg, 40 mg and 80 mg using trial data", Section 2.5) and a research question highlighting the</p>	<p>Thank you for your comment. Where there is an absence of perfect evidence NICE methods state that the GDG should make a decision based on the evidence that is available and their clinical experience where necessary. There are many studies showing that increasing doses of the same statin lead to increased reductions in CV events and death, and there is no reason to believe this is different for atorvastatin and that the effectiveness of atorvastatin 20 mg and 40 mg are not intermediate to atorvastatin 10 mg and 80 mg (atorvastatin 80 mg shows a 14% reduction in all-cause mortality, a 38% reduction in CV mortality, and a 21% reduction in non-fatal MI compared to</p>

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							<p>clinical effectiveness of these atorvastatin doses has been included. Given that there is considerable uncertainty on the relative effectiveness of atorvastatin 80 mg versus 40 mg and 20 mg at reducing CV events (and therefore cost-effectiveness), it is not appropriate for the GDG to recommend the 80 mg dose over the 40 mg or 20 mg dose in people with established CVD or type 2 diabetes.</p> <p>Within this guideline update, the GDG looked at assessing the clinical and cost- effectiveness across the low-, medium- and high-intensity statins groups. While they have demonstrated that “high intensity statin treatment using atorvastatin 20 mg, 40 mg or 80 mg is cost-effective compared to medium and low intensity statin treatment and compared to no treatment for people who have CVD”, they have failed to demonstrate a sufficiently robust analysis that demonstrates that atorvastatin 80 mg is more cost-effective than atorvastatin 40 mg and 20 mg in people with CVD or for people with type 2 diabetes. The GDG and NCCPC have applied a crude method to estimate the level of incremental benefit in CV event reduction that would be required for atorvastatin 80 mg to be cost-effective, and adopted a subjective approach to recommend that statin therapy for secondary prevention should be initiated with atorvastatin 80 mg. This may not be in the best interest of patients, and is inconsistent with the approach adopted in NICE technology appraisals.</p> <p>NICE’s Guide to the methods of technology appraisal (NICE, 2013) states that there are two recommended options for the reference case when no head-to-head data are available from an RCT for the intervention and comparators of interest:</p> <ul style="list-style-type: none"> The use of an network meta-analysis to synthesis clinical effectiveness estimates (Section 5.2.12, NICE Guide to methods of technology appraisal, 2013) 	<p>atorvastatin 10 mg (stroke not reported)).</p> <p>The GDG hence concluded that, while the magnitude of the difference in effectiveness is uncertain, it is certainly reasonable to assume that atorvastatin 80 mg will be more clinically effective than atorvastatin 20 mg, and this is likely to be considerably greater than an increase of 2% relative effectiveness. Nevertheless, it would be helpful for future guidance, especially for primary prevention, to quantify the degree of increased effectiveness shown by atorvastatin 40 mg and 80 mg compared to atorvastatin 20 mg, and so the GDG has also made a research recommendation.</p> <p>Section 5.2.12 of the Guide to the methods of technology appraisal states: “Data from head-to-head RCTs should be presented in the reference-case analysis. When technologies are being compared that have not been evaluated within a single RCT, data from a series of pairwise head-to-head RCTs should be presented together with a network meta-analysis if appropriate”, such an NMA being presented in addition to the reference case analysis. It is the GDG’s opinion that an NMA was not appropriate in this case due to the heterogeneity of the studies that would be included in such an NMA. However, an NMA has been carried out in a recent review in this</p>

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							<p>Please insert each new comment in a new row.</p> <ul style="list-style-type: none"> alternatively, the use of surrogate endpoints to infer treatment effect of the final endpoint (section 5.7.5, NICE Guide to methods of technology appraisal, 2013) <p>While there is evidence demonstrating the relationship between LDL-c and CV event reduction (CTT Collaboration et al., 2010), the GDG has dismissed the relevance of the second option, as stated in the Full Guideline: <i>"The GDG did not consider that the use of a surrogate outcome – evidence of LDL-cholesterol lowering – was sufficient to make a recommendation for statin treatment"</i>.</p> <p>In an effort to use the most appropriate way of evaluating the comparative clinical effectiveness of therapies where no head-to-head data exists, there is no indication that the GDG has evaluated the feasibility to conduct, or conducted an indirect comparison between atorvastatin 80 mg, atorvastatin 40 mg and atorvastatin 20 mg.</p> <p>The GDG has identified the following studies that were conducted versus placebo that could potentially be used in an indirect comparison between atorvastatin 80 mg and 20 mg. The following summary is based on Table 39 from the Full Guideline:</p> <ul style="list-style-type: none"> Amarenco et al. 2006, (SPARCL), Atorvastatin 80 mg versus placebo Athyros et al. 2002, (GREACE), Atorvastatin 20 mg versus placebo Koren et al. 2004 (ALLIANCE), Atorvastatin 80 mg versus placebo <p>GREACE and ALLIANCE were both conducted in patients with established coronary heart disease. The risk ratios (as reported in the Appendices, Section I.4.3) for non-fatal MI, were 0.41 (95% CI: 0.25-0.68) for atorvastatin 20 mg</p>	<p>Please respond to each comment</p> <p>area including similar trials to our clinical review (Ribeiro 2013 Int J Card 166:431-439). We have carried out a sensitivity analysis substituting the risk ratios produced by this NMA into our model, and this did not affect the cost effectiveness of our recommendations.</p> <p>Section 5.7.5 does not say that surrogate end points should be used, but explains the conditions that should be met for surrogate end points to be considered. It states that surrogate end points can only be used where there is evidence for the relationship between the surrogate end point and the final end point. There is no such evidence specifically relating to atorvastatin 20 mg or 40 mg. While there is evidence of the association between cholesterol reduction in statins in general and final end points, this is not derived from studies seeking to investigate this relationship, but from studies of which both of these were reported as outcomes. In any case, the progressive reductions in LDL cholesterol shown by increasing doses of atorvastatin are entirely in line with the increasing effectiveness of doses of atorvastatin at reducing final end points, as assumed by the GDG.</p> <p>The GDG chose to group all statins into 3 intensity groups and evaluate effectiveness between and not within these groups due to the small number of</p>

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							<p>Please insert each new comment in a new row.</p> <p>versus placebo in GREACE and 0.56 (95% CI: 0.40-0.77) for atorvastatin 80 mg versus placebo in ALLIANCE. While the risk ratios CV mortality, were 0.53 (95% CI: 0.31-0.90) for atorvastatin 20 mg versus placebo in GREACE and 0.71 (95% CI: 0.48-1.04) for atorvastatin 80 mg versus placebo in ALLIANCE. Based on inference, it appears that atorvastatin 80 mg may not offer greater reduction in CV events than lower doses of atorvastatin. This demonstrates that there is significant level of uncertainty around the GDG's belief that the additional reduction in CV events caused by atorvastatin 80 mg compared to 20 mg is "likely to be large enough to cause atorvastatin 80 mg to be cost-effective compared with atorvastatin 20 mg" (section 11.8.1, Full Guideline). The cost-effectiveness of atorvastatin 80 mg versus 20 mg is clearly uncertain – and therefore there is even greater considerable uncertainty if atorvastatin 80 mg is cost-effective over the lower dose 40 mg. Without further analysis and/or data, the GDG cannot determine with sufficient certainty that atorvastatin 80 mg is cost-effective versus atorvastatin 40 mg or atorvastatin 20 mg – and therefore, it is not appropriate to make a recommendation in sections 1.3.18 and 1.3.24 for initiating people with CVD or type 2 diabetes on atorvastatin 80 mg.</p> <p><u>References</u></p> <ul style="list-style-type: none"> - La Rosa JC et al. (2005) Intensive lipid lowering with atorvastatin in patients with stable coronary disease. <i>N Engl J Med</i> 352(14): 1425-1435. - NICE. (2013) Guide to the methods of technology appraisal. [online] Available from: http://www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyAppraisal2013.pdf (accessed March 17th 2014). - Cholesterol Treatment Trialists' (CTT) Collaboration1, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, 	<p>Please respond to each comment</p> <p>studies involving most statin doses and the heterogeneous populations in which they have been carried out. We have hence not compared individual studies for individual doses against each other, as these give inconsistent results. Careful choosing of individual studies could be used to show that almost any statin dose is more or less effective than any other on certain outcomes, but we do not think this is helpful. By instead combining evidence into 3 large groups clear patterns are found in effectiveness. Within each group other methods and assumptions have to be used, as explained above.</p>

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							<p>Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. <i>Lancet</i>. 2010 Nov 13;376(9753):1670-81</p> <ul style="list-style-type: none"> - Amarenco et al. (2006) High-dose atorvastatin after stroke or transient ischemic attack. <i>N Engl J Med</i> 355(6): 549-559. - Athyros VG et al. (2002) Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. <i>Curr Med Res Opin</i> 18(4): 220-228. - Koren MJ, Hunninghake DB; ALLIANCE Investigators. (2004) Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the alliance study. <i>J Am Coll Cardiol</i> 44(9): 1772-1779. 	
248	SH	Aneurin Bevan University Health Board (Medicines & Therapeutics Committee)	4	NICE	1.3.18		Many patients i see are concerned about the side effects of the statins they take. The use of significantly higher doses of statins, resulting in more side effects, may result in many more patients stopping, or quietly not take the statin prescribed. (Effectively reviewing and supporting such high populations of patients on statins so this doesn't happen will be very difficult in practice.)	Thank you for your comment. Following stakeholder comments we have performed additional sensitivity analyses to include additional consultations and the possibility that people may suffer increased side effects. Statins remain cost effective at a 10% threshold of 10 year CVD risk.
222	SH	NHS Sheffield CCG	10	NICE	1.3.18	21	Atorvastatin 80mg is recommended as the starting treatment for all patients with established CVD. This is in contrast with CG67 where only those with ACS were recommended to treat with a high intensity statin. Evidence of benefit from clinical trials of high intensity statins is limited to patients with stable CHD and ACS and not all trials show benefit. There are no studies comparing high intensity statins v low intensity statins post stroke or for patients with peripheral arterial disease.	Thank you for your comment. This guideline updates and replaces CG67. More discussion and explanation on how the GDG interpreted the evidence and formulated the recommendations are in the evidence to recommendation sections of the full guideline, section 11.8.

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287	SH	Heart UK- The Cholesterol Charity	34	NICE	1.3.19	21	"...in secondary prevention to manage OTHER modifiable risk factors.	Thank you for this suggestion.
288	SH	Heart UK- The Cholesterol Charity	35	NICE	1.3.21	21	Same comment about what statin and dose to use as for 1.3.15	Thank you for your comment.
289	SH	Heart UK- The Cholesterol Charity	36	NICE	1.3.21	21	Does this recommendation in type 1 diabetes relate to adults only? We recommend specifying age.	Thank you for your comment. Yes, the whole guideline is for adults only
223	SH	NHS Sheffield CCG	11	NICE	1.3.21	21	Patients with Type 1 diabetes – is there an age from which statin therapy should be offered for primary prevention?	Thank you for your comment. We have reworded the recommendations for primary prevention in people with type 1 diabetes to clarify this.
422	SH	The Royal College of Pathologists	8	NICE	1.3.21	21	Does this recommendation in type 1 diabetes relate to adults only? We recommend that a lower age is specified.	Thank you for your comment. Yes, the whole guideline is for adults only
290	SH	Heart UK- The Cholesterol Charity	37	NICE	1.3.22	22	We now have "...start with atorvastatin 20mg." Agreed, BUT this implies subsequent dose escalation, however there is no discussion as to how, why, when, to do this. The limited, best data for type 1 diabetes is not for atorvastatin but is the 700 or so individuals on insulin in HPS (but not stratified to treatment or placebo, and not necessarily type 1 diabetes).	Thank you for your comment. We have one general recommendation 1.3.38 indicating follow up of people treated with statins.
291	SH	Heart UK- The Cholesterol Charity	38	NICE	1.3.22	22	The GDG considered that CVD risk in type 1 diabetes is at least that present in type 2 (full guideline, page 183), hence Atorvastatin dose offered should be the same.	Thank you for your comment. We have reviewed the recommendations and now Atorvastatin 20 mg is offered to people type 1 and type 2 diabetes.
423	SH	The Royal College of Pathologists	9	NICE	1.3.22	22	The GDG considered that CVD risk in type 1 diabetes is at least that present in type 2 (full guideline, page 183), hence Atorvastatin dose offered should be the same.	Thank you for your comment. We have reviewed the recommendations and now Atorvastatin 20 mg is offered to people type 1 and type 2 diabetes.

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402	SH	Merck Sharp & Dohme	9	NICE	1.3.23 1.3.24	22	<p><u>Primary prevention of CVD for people with type 2 diabetes</u></p> <p>We are concerned that the recommendation to initiate people with type 2 diabetes, who have a 10% or greater 10-year risk of developing CVD, with atorvastatin 80 mg. Such a high dose of atorvastatin might not be appropriate in a significant proportion of this population (Diabetes UK Stats, 2010).</p> <ul style="list-style-type: none"> Those people with comorbidities for type 2 diabetes and CKD is over 900,000 in England (33% prevalence; Diabetes UK stats, 2010). <p>As recognised in the section for people with chronic kidney disease (CKD), a lower dose of atorvastatin (20 mg) is recommended as the start dose for people with stage 1 to 5 CKD. For those people with stage 1-3 CKD, a dose increase is recommended if a greater than 40% reduction in non-HDL cholesterol has not been achieved. In the full guideline, it is stated that the lower dose of atorvastatin is recommended as "There is concern that people with more severe CKD are at greater risk of adverse events as a result of taking high doses of statins than people without CKD, and there are some restrictions in SPCs for this population". In the SPC, atorvastatin should be prescribed with caution in patients with renal impairment, and additional testing is required prior to starting treatment.</p> <p>Type 2 diabetes is a chronic and progressive disease, where patients are at increased risk of developing macrovascular and microvascular complications. At least one third of people with type 2 diabetes are expected to develop CKD (Diabetes UK stats, 2010). CKD is also a progressive disease and for those people on high-dose atorvastatin, regular monitoring of their renal function is</p>	<p>Thank you for your comment. We have revised the recommendations for primary prevention of CVD for people with type 2 diabetes to recommend atorvastatin 20 mg.</p> <p>References</p> <ul style="list-style-type: none"> Diabetes UK Stats. (2010) Key statistics on diabetes. [online] Available at: http://www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf (accessed March 25th 2014). <p>Non RCT (This is a diabetes report in the UK)</p> <ul style="list-style-type: none"> Health & Social Care Information centre. Quality and Outcomes Framework – 2012 -13: England level, Prevalence tables. [online] Available at: http://www.hscic.gov.uk/catalogue/PUB12262 (accessed March 17th 2014). <p>Non RCT (Quality and Outcomes Framework)</p> <ul style="list-style-type: none"> SHARP. (2011) The Effects of Lowering LDL Cholesterol with Simvastatin plus Ezetimibe in Patients with Chronic Kidney Disease (Study of Heart and Renal Protection): a Randomized Placebo-Controlled Trial. <i>Lancet</i> 377: 2181-

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							<p>critical to ensure that the prescribed dose of atorvastatin is adjusted accordingly to avoid exposure to unnecessarily high doses of statin and a greater risk of adverse events. In 2012-13, there were over 2.7 million people with diabetes in England (QoF, 2013). Assuming one third of these patients have or will develop CKD, this equates to over 900,000 people with type 2 diabetes where there should be cautious use of and regular monitoring with atorvastatin 80 mg due to the risk of adverse events.</p> <p>It is also worth noting the SHARP study that evaluated using a combination of low dose simvastatin and ezetimibe to reduce CV risk in patients with moderate to severe CKD (SHARP, 2011). This combination treatment is a particularly good option for CKD patients as it avoids the possibility of side-effects with high statin doses, and should be considered if further reduction of non-HDL-c is required in CKD patients. It is the only therapy for which robust, positive CV outcomes data exists for CKD patients.</p> <ul style="list-style-type: none"> At least 30% of people on statins could be at risk of drug-drug interactions (Bakhai et al., 2012) and adverse events <p>Furthermore, the current draft recommendations recognise that atorvastatin 80 mg may not be appropriate if there are potential drug-drug interactions. The GDG needs to recognise that there is a significant number of patients covered by this guideline that will have co-morbidities, on multiple treatments and are therefore at a significant risk of drug-drug interactions. For example, the use of concomitant medications that inhibit the CYP3A4 enzyme can increase the concentration of statins and increase the risk of adverse events (Borttorff, 2006; Omar et al. 2001; Cziraky et al., 2006; Acharjee et al., 2008). A study in the General Practice Research Database showed that almost</p>	<p>2192.</p> <p>This RCT simvastatin plus ezetimibe versus placebo. Ezetimibe is excluded from our review, please refer to the NICE Ezetimibe Technology Appraisal; http://guidance.nice.org.uk/TA132.</p> <ul style="list-style-type: none"> Bottomorff MB. (2006) Statin safety and drug interactions: clinical implications. <i>Am J Cardiol</i> 97(suppl): 27C–31C. <p>Non-RCT</p> <ul style="list-style-type: none"> Omar MA, Wilson JP, Cox TS. (2001) Rhabdomyolysis and HMG-CoA reductase inhibitors. <i>Ann Pharmacother</i> 35: 1096–1107. <p>Non-RCT</p> <ul style="list-style-type: none"> Cziraky MJ, Willey VJ, McKenney JM, et al. (2006) Statin safety: an assessment using an administrative claims database. <i>Am J Cardiol</i> 97(suppl): 61C–68C. <p>Non-RCT (observational study)</p> <ul style="list-style-type: none"> Acharjee S, Welty FK. (2008) Atorvastatin and cardiovascular risk in the elderly-patient considerations. <i>Clin Interv Aging</i> 3(2): 299–314.

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192	SH	Erewash CCG	12	NICE	1.3.24	Page 2	All type 2 diabetics once identified as at risk using UKPDs are then treated like secondary prevention. Wouldn't an age cut off at 40 been more pragmatic for implementing? And why screen as primary to treat as secondary prevention?	Thank you for your comment. Following consultation, the GDG have reviewed the recommendations and the use of QRISK2 is recommended for assessing CV risk in people with type 2 diabetes. We have altered the recommendations to start treatment at atorvastatin 20mg
99	SH	Southern Derbyshire CCG	12	NICE	1.3.24	Page 2	All type 2 diabetics once identified as at risk using UKPDs are then treated like secondary prevention. Wouldn't an age cut off at 40 been more pragmatic for implementing? And why screen as primary to treat as secondary prevention?	Thank you for your comment. Following consultation, the GDG have reviewed the recommendations and the use of QRISK2 is recommended for assessing CV risk in people with type 2 diabetes. We have altered the recommendations to start treatment at atorvastatin 20mg
292	SH	Heart UK- The Cholesterol Charity	39	NICE	1.3.24	22	Why atorvastatin 80mg in type 2 diabetes and 20mg in type 1 diabetes? The best type 2 diabetes is of course with atorvastatin 10mg and not 20 or 80mg (CARDS trial).	Thank you for your comment. Following stakeholder comments we have altered these recommendations and now recommend atorvastatin 20mg for people with Type 1 and Type 2 diabetes.
411	SH	Merck Sharp & Dohme	18	NICE	1.3.25 1.3.28	22 to 23	MSD agrees with the initiation of atorvastatin 20 mg for people with CKD, with the reasons detailed in the full guideline: "There is concern that people with more severe	Thank you for your comment

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							CKD are at greater risk of adverse events as a result of taking high doses of statins than people without CKD, and there are some restrictions in SPCs for this population".	
188	SH	Erewash CCG	8	NICE	1.3.25 1.3.28		Practical issues on how to implementation in primary care for CKD <ul style="list-style-type: none"> • CKD 1&2- QRISK assess and if >10% risk use atorva 20mg • CKD 1&2 with CVD- don't risk assess use atorva 20mg increase with 40% target • CKD 3- don't risk assess use atorva 20mg increase with 40% target • CKD 4 or greater (only CKD 5 left!?) atorva 20mg agreeing higher doses with renal consultant 	Thank you for your comment. The recommendations about statin therapy in people with CKD have been amended to increase clarity and to recognise the classification of CKD recommended in the NICE CKD guideline.
95	SH	Southern Derbyshire CCG	8	NICE	1.3.25 1.3.28		Practical issues on how to implementation in primary care for CKD <ul style="list-style-type: none"> • CKD 1&2- QRISK assess and if >10% risk use atorva 20mg • CKD 1&2 with CVD- don't risk assess use atorva 20mg increase with 40% target • CKD 3- don't risk assess use atorva 20mg increase with 40% target • CKD 4 or greater (only CKD 5 left!?) atorva 20mg agreeing higher doses with renal consultant 	Thank you for your comment. The recommendations about statin therapy in people with CKD have been amended to increase clarity and to recognise the classification of CKD recommended in the NICE CKD guideline.
293	SH	Heart UK- The Cholesterol Charity	40	NICE	1.3.25	22	This says treat CKD1 or CKD2 as primary prevention, BUT paragraph 1.1.19 points out that these people will have an under-estimated risk. Therefore, by how much should one increase the QRISK2 calculated risk?	Thank you for your comment. "People with stage 1 or 2 CKD" has now been removed from recommendation 1.1.18.
27	SH	British Medical Association General Practitioners Committee	14	NICE	1.3.26	22	Many people who have CVD also have CKD stage 1 or 2. If this group are to be treated differently from the general population as specified in 1.3.18 then that paragraph should specifically mention their exclusion.	Thank you for your comment. The recommendations about statin therapy in people with CKD have been amended..
294	SH	Heart UK- The	41	NICE	1.3.26	22	OK, increase if >40% drop in non-HDL-C not achieved, but is this to 40mg or 80mg atorvastatin (or to rosuvastatin 20	Thank you. The guideline is not recommending the use of rosuvastatin

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		Cholesterol Charity					<p>or 40mg)?</p> <p>What if >40% still not achieved (as may well not be as the extra LDL-C lowering (& non-HDL-C lowering) will only be 5-10%.</p> <p>Should ezetimibe be added?</p> <p>The protocol outlined in the draft guideline does not follow through the follow-up. As currently set up there is no follow up measurements for most people, or just one follow up.</p> <p>There are quite substantial day to day variations in measurement.</p>	<p>and a recommendation has been added to say to use statins of low acquisition cost.</p> <p>40% reduction in non-HDL is a guide to treatment and is not a target that people should achieve. The GDG agree that day to day variations in cholesterol measurement add to the reasons not to use targets.</p> <p>It is up to the individual healthcare professional and patient to agree further follow up according to requirement to increase statin and discuss side effects.</p> <p>We have added a recommendation for annual review once people are stable. Ezetimibe is outside the scope of this guideline update, please refer to the NICE Ezetimibe Technology Appraisal; http://guidance.nice.org.uk/TA132.</p>
295	SH	Heart UK- The Cholesterol Charity	42	NICE	1.3.26	22	CKD stages 1 and 2 would not be regarded as severe and do not carry SPC restrictions. Patients with CVD should therefore be treated as those without CKD.	Thank you for your comment. The recommendations about statin therapy in people with CKD have been amended to increase clarity and to recognise the classification of CKD recommended in the NICE CKD guideline.
424	SH	The Royal College of Pathologists	10	NICE	1.3.26	22	CKD stages 1 and 2 would not be regarded as severe and do not carry SPC restrictions. Patients with CVD should therefore be treated as those without CKD.	Thank you for your comment. The recommendations about statin therapy in people with CKD have been amended to increase clarity and to recognise the classification of CKD recommended in the NICE CKD guideline.
145	SH	Greater Manchester	2	NICE	1.3.27	23	It is not clearly stated if the treatment would be primary or secondary prevention. Presumably secondary prevention	Thank you for your comment. The recommendations about statin therapy in

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		Commissioning Support Unit GMCSU					as mentions reducing raised cholesterol. If so, what are the recommendations for primary prevention for people with CKD stage 3&4?	people with CKD have been amended to increase clarity and to recognise the classification of CKD recommended in the NICE CKD guideline.
296	SH	Heart UK- The Cholesterol Charity	43	NICE	1.3.27	23	As for 1.3.26 Secondly, while 1.3.26 is about CKD1-2 with CVD, is 1.3.27 for CKD3 with CVD, or also for those with CKD3 without CVD?	Thank you for your comment. The recommendations about statin therapy in people with CKD have been amended to increase clarity and to recognise the classification of CKD recommended in the NICE CKD guideline.
147	SH	Greater Manchester Commissioning Support Unit GMCSU	4	NICE	1.3.28	23	Not clearly stated if refers to primary or secondary prevention.	Thank you for your comment. The recommendations about statin therapy in people with CKD have been amended to increase clarity and to recognise the classification of CKD recommended in the NICE CKD guideline.
189	SH	Erewash CCG	9	NICE	1.3.29	23	Why is there a 3 month follow up? It's not clear if this relates to primary or secondary prevention. Please clarify in relation to primary prevention as it appears it's a 40% reduction LDLc in all patients being treated.	Thank you. This applies to all and a 40% reduction in non- HDL also applies to all.
96	SH	Southern Derbyshire CCG	9	NICE	1.3.29	23	Why is there a 3 month follow up? It's not clear if this relates to primary or secondary prevention. Please clarify in relation to primary prevention as it appears it's a 40% reduction LDLc in all patients being treated.	Thank you. This applies to all and a 40% reduction in non- HDL also applies to all.
151	SH	Greater Manchester Commissioning Support Unit GMCSU	8	NICE	1.3.29	23	Suggests that best timing of dose should be night – not applicable to atorvastatin (new recommended treatment of choice). Nor applicable to rosuvastatin. The statins which should be taken in the evening are: simvastatin, fluvastatin. Pravastatin should be taken preferably in the evening.	Thank you for your comment. The part about taking the statin at night has been removed from the recommendation.
297	SH	Heart UK- The Cholesterol Charity	44	NICE	1.3.29	23	In primary prevention or chronic CVD lipid measurement after initiation of statin treatment should be after 1 month (at which time LFTs can also be performed), rather than waiting for 3 months, so that dose optimisation is not	Thank you for your comment. The recommendations are for treatment with high intensity statins so all patients are likely to benefit. Review up to 3 months

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							delayed. If > 40% reduction in non-HDL cholesterol then repeat both after 12 months and then lipids annually to improve compliance.	was recommended in CG67 and the GDG did not consider it appropriate to change this as they considered it more feasible in routine practice than one month.
298	SH	Heart UK- The Cholesterol Charity	45	NICE	1.3.29	23	Timing of dose is not relevant for high intensity statins, the best result coming from maximal compliance ie when the patient is most likely to take the medication. (NB 80 mg Simvastatin, whilst categorised as a high intensity statin, is not recommended for use because of an increased incidence of muscular side effects).	Thank you. This was an error and has been removed from the recommendation.
224	SH	NHS Sheffield CCG	12	NICE	1.3.29	23	A target of 40% reduction in non-HDL cholesterol is recommended. This presumably covers both primary and secondary prevention. This was not a target in the clinical trials and treatment to target guidelines are not supported by direct evidence from trials (BMJ 2010;341:c3531). There is the risk that including a target will lead to over treatment with more expensive statins such as rosuvastatin or combination therapy with ezetimibe.	Thank you for your comment. This is not a target but a guide to treatment as individual patients will respond differently to medicines
436	SH	Royal College of Nursing	3	NICE	1.3.29	23	The guidance suggests actions to be taken if the non HDL level has not reduced by >40%. However it does not give advice for what to do if the patient is adherent to taking the drugs and lifestyle changes and is already taking atorvastatin 80mg. Should the statin be changed to rosuvastatin? Should the patient be referred to a specialist at this stage? Advice on this would be helpful for healthcare professionals and patients.	<p>Thank you. The guideline is not recommending the use of rosuvastatin and a recommendation has been added to say to use statins of low acquisition cost.</p> <p>40% reduction in non-HDL is a guide to treatment and is not a target that people should achieve. The GDG agree that day to day variations in cholesterol measurement add to the reasons not to use targets.</p> <p>It is up to the individual healthcare professional and patient to agree further follow up according to requirement to</p>

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								increase statin and discuss side effects. We have added a recommendation for annual review once people are stable.)
425	SH	The Royal College of Pathologists	11	NICE	1.3.29	23	In primary prevention or chronic CVD lipid measurement after initiation of statin treatment should be after 1 month (at which time LFT's can also be performed), rather than waiting for 3 months, so that dose optimisation is not delayed. If > 40% reduction in non-HDL cholesterol then repeat both after 12 months and then lipids annually to improve compliance.	Thank you for your comment. The recommendations are for treatment with high intensity statins so all patients are likely to benefit. Review up to 3 months was recommended in CG67 and the GDG did not consider it appropriate to change this as they considered it more feasible in routine practice than one month.)
426	SH	The Royal College of Pathologists	12	NICE	1.3.29	23	Timing of dose is not relevant for high intensity statins, the best result coming from maximal compliance ie when the patient is most likely to take the medication. (NB 80 mg Simvastatin, whilst categorised as a high intensity statin, is not recommended for use because of an increased incidence of muscular side effects).	Thank you. This was an error and has been removed from the recommendation.)
172	SH	Pfizer Ltd	4	NICE	1.3.29	23	Could there be clarity around why monitoring for LDL-C is not included in the list of assessments to perform before starting statin treatment? Does non-HDL cholesterol refer to LDL-C?	Thank you for your comment. We have explained the difference between non-HDL cholesterol and LDL cholesterol in the introduction to the NICE guideline.
2	SH	NHS Leeds, University of Leeds	2	NICE	1.3.3	9	As a non-fasting lipid sample is being taken the triglycerides results should be interpreted together with blood glucose and/or HBA1c	Thank you for your comment which is in keeping with our recommendations.
186	SH	Erewash CCG	6	NICE	1.3.3	18	Lipid tests- should this be changed to at least 2 lipid samples to account for variability (we recall that this variation can be as much as 16% in the literature)	Thank you. The GDG discussed this but considered that more than 2 tests are required if one wishes to account for variability and that the limitations of individual tests should be understood and accepted. Non- HDL treatments are not targets and are intended as a guide to treatment only.
93	SH	Southern Derbyshire		NICE	1.3.3	18	Lipid tests- should this be changed to at least 2 lipid samples to account for variability (we recall that this	Thank you. The GDG discussed this but considered that more than 2 tests are

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		CCG	6				variation can be as much as 16% in the literature)	required if one wishes to account for variability and that the limitations of individual tests should be understood and accepted. Non-HDL treatments are not targets and are intended as a guide to treatment only.
272	SH	Heart UK- The Cholesterol Charity	19	NICE	1.3.3	18	A single sample for lipid measurement is insufficient information on which to initiate medication for primary prevention (in a similar way to treating high blood pressure after 1 measurement). We recommend; ...at least 2 lipid samples should be taken, one of which must be a full lipid profile.	Thank you. The GDG discussed this but considered that more than 2 tests are required if one wishes to account for variability and that the limitations of individual tests should be understood and accepted. Non-HDL treatments are not targets and are intended as a guide to treatment only.
216	SH	NHS Sheffield CCG	4	NICE	1.3.3	18	The GDG recommends use of non-HDL cholesterol. This is not currently measured in primary care. The stated benefit of this parameter is that it does not require a fasting sample. None of the statin studies used this measure to select subjects for inclusion or to monitor the effectiveness of the treatment.	Thank you for your comment. Non-HDL can be reported by the laboratory without the use of a fasting sample. The NICE implementation team are aware of the need to highlight the use of non-HDL to laboratory and clinicians.
416	SH	The Royal College of Pathologists	2	NICE	1.3.3	18	A single sample for lipid measurement is insufficient information on which to initiate medication for primary prevention (in a similar way to treating high blood pressure after 1 measurement). We recommend; ...at least 2 lipid samples should be taken, one of which must be a full lipid profile.	Thank you for your comment. Treatment is being recommended on the basis of overall cardiovascular risk and not on lipid levels.
299	SH	Heart UK- The Cholesterol Charity	46	NICE	1.3.31	23	If changing to a lower intensity statin the initial dose should be no more than that which caused adverse effects.	Thank you for your comment. The dose of the new statin at a lower intensity has not been specified, and the physician will use their clinical knowledge and judgement to advise the patient on a new dose.
300	SH	Heart UK- The Cholesterol	47	NICE	1.3.31	23	Agreed – but does this recommend including non-generic statin in the possible treatments?	Thank you for your comment. Statins (and doses) included in this guideline are listed in Appendix B.

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		Charity						
427	SH	The Royal College of Pathologists	13	NICE	1.3.31	23	If changing to a lower intensity statin the initial dose should be no more than that which caused adverse effects.	Thank you for your comment. The dose of the new statin at a lower intensity has not been specified, and the physician will use their clinical knowledge and judgement to advise the patient on a new dose.
413	SH	Merck Sharp & Dohme	20	NICE	1.3.31	23	<p>This section details the strategies for patients who report adverse events when taking high-intensity statins. These are to discuss stopping the statin and trying again, reducing the dose, or changing to a lower intensity group. While we agree that any statin dose reduces CVD risk, worryingly, for patients that require more intensive lipid management (e.g. comorbid CVD & diabetes) these options only offer modest or no cholesterol reduction towards previous recommended levels (e.g. comorbid CVD & diabetes recommended level of TC 4 mmol/l). We recommend that an additional bullet should be added at the end of section 1.3.31 to discuss other non-statin options:</p> <ul style="list-style-type: none"> <i>discuss other pharmacological therapies for lipid modification, including those recommended by NICE</i> 	Thank you for your comment. Other pharmacological therapies are discussed in Chapters 12–16 and should be considered in line with recommendations 1.3.46–1.3.52 and 1.3.1.
301	SH	Heart UK- The Cholesterol Charity	48	NICE	1.3.32	24	Specialist advice should also be sought for such high risk patients who do not achieve a non-HDLC reduction of 40% on maximally tolerated statin treatment.	Thank you for your comment. Options on what to do if 40% reduction on non-HDL cholesterol are given in recommendation 1.3.28.
428	SH	The Royal College of Pathologists	14	NICE	1.3.32	24	Specialist advice should also be sought for such high risk patients who do not achieve a non-HDLC reduction of 40% on maximally tolerated statin treatment.	Thank you for your comment. Options on what to do if 40% reduction on non-HDL cholesterol are given in recommendation 1.3.28.
246	SH	Aneurin Bevan University Health Board	2	NICE	1.3.33		If patients are satisfactorily managed on Simvastatin there is no good patients orientated outcome data to support the change to a 'higher intensity' statin.	Thank you for your comment, we have now amended the wording of this recommendation.

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		(Medicines & Therapeutics Committee)						
173	SH	Pfizer Ltd	5	NICE	1.3.33	24	As with high intensity statin treatment in section 1.3.15, this section includes the (above) first mention of low and medium intensity statins. We suggest that it would be appropriate to define what is meant by low, medium high intensity statins in the main body of the guideline, rather than refer only to table 1 in the appendix.	Thank you for your comment. We have added a definition of the three statin intensities in the introduction of the NICE guideline.
271	SH	Heart UK- The Cholesterol Charity	18	NICE (& Full)	1.3.3	18	Agreed, but needs reference to section numbers as to what to do if non-fasting triglycerides are markedly raised.	Thank you for your comment. The three recommendations about what to do if triglyceride concentration is elevated are within the same section "Lipid measurement and referral" therefore we do not believe a cross reference to these would be particularly helpful.
225	SH	NHS Sheffield CCG	13	NICE	1.3.33	24	Use of proportion of patients taking high intensity statins for secondary prevention as an audit measure. The current audit measure uses a cholesterol level of 5mmol/l to assess management of patients. Changing this to simply having a high intensity statin on a repeat prescription list may exclude patients whose cholesterol is well controlled on a lower intensity statin and lifestyle measures. If the QoF measure is changed in line with this it may also increase the number of exceptions as people who do not wish to take the higher dose or who have side-effects will be excepted. The requirement for measurement of an annual cholesterol level for QoF helps to pick up patients who are not compliant with their medication, not always ascertained from a medication review.	Thank you for your comment. We have removed the recommendation on audit for the reasons you describe. We have added a recommendation for annual review and suggested that a measurement of cholesterol may be useful in this review.
302	SH	Heart UK- The Cholesterol Charity	49	NICE	1.3.34	24	It would be useful to retain, for audit purposes, the use of cholesterol levels in patients with established CVD (ie section 1.4.25 from the old Guideline), rather than moving to the proportion of people taking high intensity statins for secondary prevention. The continued use of cholesterol	Thank you for your comment. We have removed the recommendation on audit as we considered patients may already be stable on lower intensity statins and not wish to change. We disagree that the

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							levels is more focussed on the needs of each patient as they present, rather than the more universal blanket approach of whether high intensity statins are being used.	use of cholesterol levels is more focussed on the need of individual patient.
395	SH	Merck Sharp & Dohme	2	NICE	1.3.34	24	<p><u>Numerical targets for non-HDL-c should be included in the guideline</u></p> <p>MSD agrees with the replacement of LDL-c by non-HDL-c in recognition that non-HDL-c has been shown to perform better on risk prediction compared to LDL-c. However, the draft guideline under consultation provides no clarification on:</p> <ul style="list-style-type: none"> - what non-HDL-c is - how non-HDL-c is calculated - how does non-HDL-c relate to LDL-c (most well-known marker among HCPs and patients) and - how well treatment should be applied. <p>It is noted that section 1.4.25 from the 2008 guideline is replaced with section 1.3.34 in the draft guideline, which is more of a 'fire and forget' approach with no clarification on patient follow up and/or a treatment aim in high risk secondary prevention patients. While the GDG has reasoned that as atorvastatin 80 mg was found to be cost-effective, and patients would be on the highest available dose of statin, a proportion approach would be appropriate rather than specific targets, the GDG has dismissed evidence on impact of fire and forget strategy on patient adherence and thereby potential outcome. MSD is concerned that this may adversely impact best patient healthcare management.</p> <p>The ESC/EAS guidelines, based on Class 1, Level A evidence, recommend an LDL-c goal of 2 mmol/l in those with known CVD, Type 2 or 1 diabetes with target organ damage, moderate to severe CKD or a score level of >10% (same score level as identified in this guideline).</p>	<p>Thank you for your comment. The recommendations are made in line with the RCTs and use evidence from trials on effect on hard endpoints. The GDG considered that the aim should be to ensure people are taking the maximum tolerated dose of statin rather than aim for a specific lipid level that many will not achieve.</p> <p>We have removed the recommendation on audit as we considered patients may already be stable on lower intensity statins and not wish to change.</p>

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							<p>This is similar to what was recommended in CG67 (2008).</p> <p>The recently released consensus from JBSIII guidelines is consistent with NICE in replacing LDL-c by non-HDL-c in both clinical practice and clinical trials. However, JBSIII continues to recommend a treatment aim on a non-HDL-c lowering to achieve <2.5 mmol/l (corresponding to an LDL-c level of <1.8mmol/l) in patients with acute coronary syndrome and to a level corresponding to LDL-c <2 mmol/l in patients at high risk of CVD (established CVD, Type 2 DM, CKD 3-5). CVD outcome trials which have tested the 'lower the better' LDL-c hypothesis have shown benefit down to levels as low as <1.8 mmol/l, which is recommended in national and international guidelines (ESC/EAS and JBSIII).</p> <p>The need for targets and follow-up in secondary prevention were recognised by NICE in CG67 Section 1.4.25 (2008), and in recognition that more than a half of patients will not achieve a total cholesterol of less than 4 mmol/l or an LDL cholesterol of less than 2 mmol/l, an 'audit' level of total cholesterol of 5 mmol/litre was recommended to assess progress in populations or groups of people with CVD (NICE CG67, 2008). We are very concerned by the removal of targets from the draft guideline (the only measure being for a 40% reduction in non-HDL-c recommended for primary prevention). As MSD are recommending starting people with established CVD with atorvastatin 40 mg, we believe regular non-HDL-c testing and cholesterol targets should be incorporated into the draft guideline, with an appropriate 'audit' level of 3.3 mmol/L for non-HDL-c (2.6 mmol/L for CHD and diabetes patients).</p> <p>Since the first guideline on lipid modification, and the use of recommended cholesterol levels adopted from the NICE</p>	

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							<p>guideline (CG67) by the QOF, the improvement in the outcomes for patients with CVD should be applauded (e.g. mortality rates for patients under 75 with CVD have reduced by 40% between 2001 and 2010 [CVD Outcomes 2013]). According to the EUROASPIRE survey, the UK had one of the worst performances on cholesterol management in Europe, which improved during the period that cholesterol targets were recommended and incentivised (EUROASPIRE II 2001; EUROASPIRE III 2009). This improvement in CVD outcomes is now at risk by the removal of targets in the draft guideline. In addition to this there is a wealth of evidence that shows the relationship between non-HDL-c lowering and cardiovascular risk reduction, indicating that across lipid-modifying drugs there is a 1:1 relationship between percent non-HDL-c lowering and CHD reduction (Robinson 2009; Cui 2001). By using atorvastatin 80 mg in patients there is no individualised approach to assess the patient, the tolerance and safety of the regimen, and treat to a more aggressive cholesterol level if appropriate (e.g. people with diabetes or comorbid CVD and diabetes).</p> <p>In summary, regular non-HDL-c testing with appropriate targets are crucial to the patient and health care professional to monitor the progress and assess cardiovascular risk. Treatment decisions should be made by focusing on individual patients, not a population approach. For the reasons outlined, removing cholesterol targets from the guideline is not consistent with good patient-centred care and other national and international guidelines.</p> <p><u>References</u></p> <p>- NICE CG67. (2008) Lipid modification. [online] available from: http://www.nice.org.uk/nicemedia/live/11982/40689/40</p>	

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							<p>Please insert each new comment in a new row.</p> <p>689.pdf accessed March 25th 2014.</p> <ul style="list-style-type: none"> - Cardiovascular Disease Outcomes Strategy (2013). [online] Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/214895/9387-2900853-CVD-Outcomes_web1.pdf (accessed January 24th 2014). - EUROASPIRE II Study Group. (2001) Lifestyle and Risk Factor Management and Use of Drug Therapies in Coronary Patients from 15 Countries. <i>European Heart Journal</i> 22: 554-572. - Kotseva K, Wood D, Backer GD, Bacquer DD, Pyörälä K, Keil U. (2009) EUROASPIRE III: A Survey on the Lifestyle, Risk Factors and Use of Cardioprotective Drug Therapies in Coronary Patients from 22 European Countries. <i>European Journal of Cardiovascular Prevention and Rehabilitation</i>. DOI: 10.1097/HJR.0b013e3283294b1d. - Robinson JG, Wang S, Smith BJ, Jacobson TA. (2009) Meta-Analysis of the Relationship Between Non-High-Density Lipoprotein Cholesterol and Coronary Heart Disease Risk. <i>Journal of the American College of Cardiology</i> 53(4): 316-322. - Cui Y, Blumenthal RS, Flaws JA, Whiteman MK, Langenberg P, Bachorik PS, Bush TL. (2001) Non-High-Density Lipoprotein Cholesterol Level as a Predictor of Cardiovascular Disease Mortality. <i>Arch Intern Med</i> 161: 1413-1419. 	Please respond to each comment
154	SH	Greater Manchester Commissioning Support Unit GMCSU	11	NICE	1.3.35	24	<p>Should be 'vitamin E' not 'vitamin D'. What is the relevance to the guideline? Is it important to put it in the shorter NICE guideline?</p>	<p>Thank you for your comment. The interventions considered for the adherence to statin therapy review are either coenzyme-Q10 or Vitamin D (not vitamin E), as described in the review protocol (see appendix C, section C.10). The Caso 2007 paper compares coenzyme-Q10 (intervention group) with</p>

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								vitamin E (control group). We have now amended the table to clarify this.
305	SH	Heart UK-The Cholesterol Charity	52	NICE	1.3.36	24	<p>Grapefruit juice needs to be taken in some quantity.</p> <p>The wording tends to suggest that “some foods” including “grapefruit juice” interfere with statins.</p> <p>In fact grapefruit juice increases rather than decreases the effects of the statin by interfering with clearance rather than with activity – better wording would help here.</p>	Thank you for your comment, we have formulated the recommendation following the Summary of Product Characteristics for statins, and the GDG believe the recommendation is sufficient.
306	SH	Heart UK-The Cholesterol Charity	53	NICE	1.3.37	24	<p>Wording is difficult here</p> <p>Better would be “...interactions or during treatment of intercurrent illnesses...”</p>	Thank you for your comment, but the GDG believe the current wording is clear and the recommendation is easy to understand.
303	SH	Heart UK-The Cholesterol Charity	50	NICE	1.3.38	24	<p>Definition of elevated CK is required; Recommend > 5 x ULN.</p>	Thank you. We have added more detail to indicate the levels of CK at which statins should not be used.
429	SH	The Royal College of Pathologists	15	NICE	1.3.38	24	<p>Definition of elevated CK is required; Recommend > 5 x ULN.</p>	Thank you. We have added more detail to indicate the levels of CK at which statins should not be used.
307	SH	Heart UK-The Cholesterol Charity	54	NICE	1.3.45	25	<p>Not just “in pregnancy”</p> <p>The advice is to “stop statins from conception planning until the end of breast feeding”</p>	Thank you, we agree with your comment, the recommendation has been amended accordingly.
308	SH	Heart UK-The Cholesterol Charity	55	NICE	1.3.48	26	<p>Bile acid sequestrants should be available to be offered by lipid specialists.</p>	Thank you for your comment, we believe this is covered in recommendation: 1.3.41 Seek specialist advice about options for treating people at high risk of CVD such as those with CKD, type 1 diabetes, type 2 diabetes or genetic dyslipidaemias, and those with established CVD, who are intolerant to 3 different statins. Advice can be sought for example, by telephone, virtual clinic

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								or referral.
430	SH	The Royal College of Pathologists	16	NICE	1.3.48	26	Bile acid sequestrants should be available to be offered by lipid specialists.	Thank you for your comment, we believe this is covered in recommendation: 1.3.41 Seek specialist advice about options for treating people at high risk of CVD such as those with CKD, type 1 diabetes, type 2 diabetes or genetic dyslipidaemias, and those with established CVD, who are intolerant to 3 different statins. Advice can be sought for example, by telephone, virtual clinic or referral.
273	SH	Heart UK- The Cholesterol Charity	20	NICE	1.3.5	18	Common secondary causes of dyslipidaemia should be excluded before starting medication for primary prevention, as well as before referring for specialist advice	Thank you, we agree with your comment. Recommendation 1.3.13 includes the following "Before starting statin treatment perform baseline blood tests and clinical assessment, and treat comorbidities and secondary causes of dyslipidaemia."
417	SH	The Royal College of Pathologists	3	NICE	1.3.5	18	Common secondary causes of dyslipidaemia should be excluded before starting medication for primary prevention, as well as before referring for specialist advice	Thank you, we agree with your comment. Recommendation 1.3.13 includes the following "Before starting statin treatment perform baseline blood tests and clinical assessment, and treat comorbidities and secondary causes of dyslipidaemia."
311	SH	Heart UK- The Cholesterol Charity	58	NICE	1.3.50	27	The evidence suggests that the benefits of N-3 supplements could vary according to the specific nature of the underlying disease process and the dose/formulation of the supplement.	Thank you for your comment. The evidence considered in this guideline indicates that there is no benefit in using omega 3 fatty acids supplement.
312	SH	Heart UK- The Cholesterol Charity	59	NICE	1.3.51	27	Combination therapy should be available to be offered by lipid specialists.	Thank you for your comment, we believe this is covered in recommendation: 1.3.41 Seek specialist advice about options for treating people at high risk of CVD such as those with CKD, type 1 diabetes, type 2 diabetes or genetic dyslipidaemias, and those with established CVD, who are intolerant to 3

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								different statins. Advice can be sought for example, by telephone, virtual clinic or referral.
313	SH	Heart UK- The Cholesterol Charity	60	NICE	1.3.51	27	There are individuals who have a poorer response to a statin because of their rates of cholesterol reabsorption. Here ezetimibe addition may be more than averagely effective. Where a patient is intolerant of ezetimibe (and there are some) then a resin with a statin can be quite effective.	Thank you for your comment. Ezetimibe is outside the scope of this guideline, please refer to the NICE Ezetimibe Technology Appraisal; http://guidance.nice.org.uk/TA132 . The GDG have formulated recommendations about referral to specialist care if statin therapy is ineffective.
431	SH	The Royal College of Pathologists	17	NICE	1.3.51	27	Combination therapy should be available to be offered by lipid specialists.	Thank you for your comment, we believe this is covered in recommendation: 1.3.41 Seek specialist advice about options for treating people at high risk of CVD such as those with CKD, type 1 diabetes, type 2 diabetes or genetic dyslipidaemias, and those with established CVD, who are intolerant to 3 different statins. Advice can be sought for example, by telephone, virtual clinic or referral.
155	SH	Greater Manchester Commissioning Support Unit GMCSU	12	NICE	1.3.52	27	Should clearly state that this applies to both primary and secondary prevention (i.e. this might be not clear to people using this guideline for first time and not familiar with previous version(s).	Thank you for your comment. We have clarified which recommendations are for primary and secondary prevention.
314	SH	Heart UK- The Cholesterol Charity	61	NICE	1.3.52	27	It would be appropriate to state here the specific indications for which TA132 recommends ezetimibe. The indication for ezetimibe may change if hard RCT outcome data becomes available	Thank you for your comment. As you indicate the indications for ezetimibe might change so inserting specific recommendations from Technology Appraisal132 might be misleading as this is likely to be updated before the next update of this guideline.
193	SH	Erewash	13	NICE	1.3.52	Page	Ezetimibe.	Thank you for your comment. This is

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		CCG				27	<p>Whilst FH is outside of this guideline it is still permitted as per TA if statin intolerant in <u>this</u> CG. Please clarify its role outside of TA and relevance to this CG.</p> <p>This drug still has no patient orientated outcome data. A statement to say it has no place in primary or secondary prevention would be helpful. To include it – please complete an assessment.</p>	<p>outside the area of our scope, please refer to the NICE Ezetimibe Technology Appraisal; http://guidance.nice.org.uk/TA132.</p>
100	SH	Southern Derbyshire CCG	13	NICE	1.3.52	Page 27	<p>Ezetimibe.</p> <p>Whilst FH is outside of this guideline it is still permitted as per TA if statin intolerant in <u>this</u> CG. Please clarify its role outside of TA and relevance to this CG.</p> <p>This drug still has no patient orientated outcome data. A statement to say it has no place in primary or secondary prevention would be helpful. To include it – please complete an assessment.</p>	<p>Thank you for your comment. This is outside the area of our scope, please refer to the NICE Ezetimibe Technology Appraisal; http://guidance.nice.org.uk/TA132.</p>
414	SH	Merck Sharp & Dohme	21	NICE	1.3.52	27	<p>Whilst we understand that this point has not changed since 2008, and not available for comment, we would like to make a comment on the positioning of ezetimibe. After statin therapy, the guideline discusses treatment options nicotinic acid, bile sequestrants, and omega-3 fatty acid compounds with recommendations to 'do not offer for the prevention of CVD'. With the clear positioning of ezetimibe in relation to statins in TA132, we recommend that section 1.3.52 should be moved to directly after the section on 'statins for the prevention of CVD', before discussing fibrates and those not recommended.</p>	<p>Thank you for your comment. The order of the recommendations does not affect their content. The recommendations are placed in this order as the evidence reviews conducted for this guideline are ordered consecutively first, and cross-referrals to other NICE guidance are placed following those.</p>
250	SH	Aneurin Bevan University Health Board (Medicines &	6	NICE	1.3.6		<p>some of the precise advice - eg 1.3.6 is helpful for everyday practice.</p>	<p>Thank you for your comment.</p>

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		Therapeutics Committee						
274	SH	Heart UK-The Cholesterol Charity	21	NICE	1.3.6	18	Total cholesterol of > 7.5 relates to adults, for < 16yo is > 6.7 mmol/L. Recommend both are included.	Thank you for your comment. This guideline includes adults only.
275	SH	Heart UK-The Cholesterol Charity	22	NICE	1.3.6	18	Where Familial Hypercholesterolaemia is being considered a full fasting lipid profile should be performed in order that a fasting triglyceride is analysed and calculated LDL cholesterol reported.	Thank you for your comment. The guideline is not indicating how FH should be diagnosed but where it should be considered and reference made to the FH guideline (http://publications.nice.org.uk/identification-and-management-of-familial-hypercholesterolaemia-cg71).
276	SH	Heart UK-The Cholesterol Charity	23	NICE (& Full)	1.3.6	18	Bullet 2: Needs definition of "premature" within or close to this paragraph	Thank you for your comment. The GDG believe that the meaning of 'premature' is widely known, and it would also be difficult to agree an age cut-off for a premature coronary heart disease.
418	SH	The Royal College of Pathologists	4	NICE	1.3.6	18	Total cholesterol of > 7.5 relates to adults, for < 16yo is > 6.7 mmol/L. Recommend both are included.	Thank you for your comment. This guideline includes adults only.
419	SH	The Royal College of Pathologists	5	NICE	1.3.6	18	Where Familial Hypercholesterolaemia is being considered a full fasting lipid profile should be performed in order that a fasting triglyceride is analysed and calculated LDL cholesterol reported.	Thank you for your comment. The guideline is not indicating how FH should be diagnosed but where it should be considered and reference made to the FH guideline (There is separate NICE guidance for people with FH; http://publications.nice.org.uk/identification-and-management-of-familial-hypercholesterolaemia-cg71).
197	SH	Erewash CCG	17	NICE	1.1.9 1.3.21	Page 9 21	Please can you elaborate on the evidence for treating type 1 diabetic as secondary prevention?	Thank you for your comment. Following stakeholder consultation we have altered this recommendation.

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104	SH	Southern Derbyshire CCG	17	NICE	1.1.9 1.3.21	Page 9 21	Please can you elaborate on the evidence for treating type 1 diabetic as secondary prevention?	Thank you for your comment. Following stakeholder consultation we have altered this recommendation.
320	SH	Heart UK- The Cholesterol Charity	67	NICE (& Full)	1.3.7 & elsewhere	Page 38 and previously	<p>Non HDL-C values of 7.5-9.0, even when lowered by 40% still leave non-HDL-C values of 4.5-5.4mmol/l which would equate to LDL-C values of 3.5-4.5 mmol/l</p> <p>The RCT evidence overwhelmingly shows benefit of lowering LDL-C (and therefore by implication non-HDL-C) to much lower levels – i.e. LDL-C to 1.7mmol/l</p> <p>It is accepted that the RCTs are not true treat to target (except GREACE), but the evidence is still strong.</p>	<p>Thank you for your comment. The recommendations are made in line with the RCTs and use evidence from trials on effect on hard endpoints. The GDG considered that the aim should be to ensure people are taking the maximum tolerated dose of statin rather than aim for a specific lipid level that many will not achieve.</p> <p>The guideline recommends that people with non-HDL levels of >7.5 should be assessed for inherited lipid disorders and would fall outside the scope of this guideline.</p>
277	SH	Heart UK- The Cholesterol Charity	24	NICE (& Full)	1.3.8	19	<p>Such a patient with triglycerides >20 mmol/l may not need immediate lipid specialist review, but if due to poor control of diabetes they probably do need specialist diabetes review.</p> <p>The acute pancreatitis risk is present for all of these patients and not just where the triglycerides are due to conditions other than alcohol or diabetes. There is very often a mix of secondary causes with or without a primary genetic cause/predisposition</p>	Thank you for your comment. The recommendation does not state which specialist should see these patients and expect that this will depend on local arrangements.
278	SH	Heart UK- The Cholesterol Charity	25	NICE	1.3.8	19	To facilitate appropriate review of people with a triglyceride > 20 mmol/L definition of excess alcohol or poor glycaemic control would be helpful.	Thank you. The GDG did not consider it possible to be this specific.
420	SH	The Royal College of Pathologists	6	NICE	1.3.8	19	To facilitate appropriate review of people with a triglyceride > 20 mmol/L definition of excess alcohol or poor glycaemic control would be helpful.	Thank you. The GDG did not consider it possible to be this specific.

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24	SH	British Medical Association General Practitioners Committee	11	NICE	1.3.9	19	No evidence is offered for having to perform the repeat triglyceride test within 2 weeks	Thank you. This is a consensus recommendation based on the risks associated with high triglyceride levels
279	SH	Heart UK- The Cholesterol Charity	26	NICE	1.3.9	19	Repeated triglyceride measurement as a fasting sample does not require leaving for 5 days and could more simply be stated as "within 2 weeks".	Thank you for your suggestion. The GDG considered that since TG levels can be influenced by e.g. diet and alcohol intake some delay before repeating TG level was appropriate and agreed that 5 days was a reasonable period.
280	SH	Heart UK- The Cholesterol Charity	27	NICE	1.3.9	19	Bullet 3: "...Seek specialist advice if the triglyceride remains elevated..." – does this mean >20, between 10 & 20, between 4.5 & 9.9, or 2-4.5 mmol/l?	Thank you for your comment. We have clarified that this is above 10mmol/l.
421	SH	The Royal College of Pathologists	7	NICE	1.3.9	19	Repeated triglyceride measurement as a fasting sample does not require leaving for 5 days and could more simply be stated as "within 2 weeks".	Thank you for your suggestion. The GDG considered that since TG levels can be influenced by e.g. diet and alcohol intake some delay before repeating TG level was appropriate and agreed that 5 days was a reasonable period.
158	SH	Greater Manchester Commissioning Support Unit GMCSU	15	NICE	1.4.23		In the replacement section 'comorbidities' added to list of criteria allowing to lower dose of atorvastatin but do not appear on page 21 in section 1.3.18.	Thank you for your comment. The table on page 44 (recommendations to be deleted) has been removed from the final version of the guideline, as per NICE process.
159	SH	Greater Manchester Commissioning Support Unit GMCSU	16	NICE	1.4.24	44	In the replacement section 'comorbidities' added to list of criteria allowing to lower dose of atorvastatin but do not appear on page 21 in section 1.3.18 (as above).	Thank you for your comment. The table on page 44 (recommendations to be deleted) has been removed from the final version of the guideline, as per NICE process.
1	SH	NHS Leeds, University of Leeds	1	NICE	1.8.8	9	QRISK2 uses body mass index (height and weight). South Asians are shorter and weigh less compared to Europeans; therefore it will underestimate risk in South Asians. South Asians also have decreased prevalence of	Thank you for your comment. In addition to BMI, QRISK2 takes also into account ethnicity (including Indian, Pakistani, Bangladeshi, or Other Asian), therefore

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							atrial fibrillation and smoking than Europeans.	we do not believe that overall QRISK2 underestimates risk in this population.
315	SH	Heart UK- The Cholesterol Charity	62	NICE	2.1	28	There is no review of evidence for the use of deprivation data. How far down the postcode is used in QRISK2? How much is based on the surgery's postcode? How much actual individual patient deprivation data is used in QRISK2.	Thank you we agree your comment. The validation studies on QRISK2 we have included in the review assess the tool as a whole, and not its components in isolation. The purpose of this research recommendation is to compare the age-alone strategy with structured multi-factorial risk assessment to identify people at high risk. Please see appendix N.1 for more detailed information on this research recommendation.
245	SH	Aneurin Bevan University Health Board (Medicines & Therapeutics Committee)	1	NICE	2.3		However, there is no evidence to validate the CVD benefits and side effects of statin therapy in this age group of >85 yrs. It is not evidence based. Also no robust risk/ benefit assessment for this age group has been done.	Thank you, we agree with your comment. The GDG have indeed written this research recommendation to conduct a research trial on the efficacy and safety on statin therapy in older people. Please see appendix N.3 for more detailed information on this research recommendation.
249	SH	Aneurin Bevan University Health Board (Medicines & Therapeutics Committee)	5	NICE	2.3		have the risks of prescribing statins to the elderly been taken in to account? This statement is at odds with current moves to reduce the burden of medicines for the elderly.	Thank you, we agree with your comment. The GDG have indeed written this research recommendation to conduct a research trial on the efficacy and safety on statin therapy in older people. Please see appendix N.3 for more detailed information on this research recommendation.
251	SH	Aneurin Bevan University Health Board (Medicines & Therapeutics Committee)	7	NICE	2.3		I've read the first draft guidance you sent me (which didn't contain the evidence to recommendation details) and from that I'm very much in agreement with Dr Tom Lau about the lack of evidence for treating 85+ year olds and about treating anyone with a risk >10% with high intensity statins.	Thank you, we agree with your comment. The GDG have indeed written this research recommendation to conduct a research trial on the efficacy and safety on statin therapy in older people.

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		Therapeutics Committee						Please see appendix N.3 for more detailed information on this research recommendation.
316	SH	Heart UK- The Cholesterol Charity	63	NICE	2.3	29	This research recommendation is supported. Item 1.1.2 highlights age 40-74 and item 1.1.22 considers all aged 85 or older to be at increased risk and item 1.3.17 that they are considered for treatment. Those between 75 and 85 are therefore at potential risk of being missed. A more equitable recommendation, until evidence is available, would be to consider all those above 74 to be at high risk and considered for treatment.	Thank you for your comment. Recommendation 1.1.2 is a recommendation from previous guideline that was not updated. The recommendation was about stratifying people at risk and was for people aged 40-74 as that was the age range covered by the risk tools available at that time. We have removed this age range from this recommendation and maintained the recommendation
432	SH	The Royal College of Pathologists	18	NICE	2.3	29	This research recommendation is supported. Item 1.1.2 highlights age 40-74 and item 1.1.22 considers all aged 85 or older to be at increased risk and item 1.3.17 that they are considered for treatment. Those between 75 and 85 are therefore at potential risk of being missed. A more equitable recommendation, until evidence is available, would be to consider all those above 74 to be at high risk and considered for treatment.	Thank you for your comment. Recommendation 1.1.2 was not updated and a discrepancy arose. We have amended this recommendation as QRISK2 includes people up to age 84 so these people can be risk assessed.
317	SH	Heart UK- The Cholesterol Charity	64	NICE	2.4	29	As before the word should be "sex" and not "gender".	Thank you for alerting us to this
153	SH	Greater Manchester Commissioning Support Unit GMCSU	10	Appendices	C.10	40	States 'vitamin D'. Should be 'vitamin E'. Consequently all errors will need amending.	Thank you for your comment. The interventions considered for the adherence to statin therapy review are either coenzyme Q ₁₀ or Vitamin D (not vitamin E),
408	SH	Merck Sharp & Dohme	15	Appendix	L.3.1.3	568	<u>Methodology used for threshold analysis</u> The methodology used for the threshold analysis to	Thank you for your comment. In the threshold analysis conducted by the NCGC the effectiveness of non-CV death

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							<p>estimate the level of additional reduction in the risk of CV events that would be required to make higher doses of atorvastatin more cost-effective than lower doses does not evaluate this adequately, and is not consistent with NICE's reference case. As part of the analysis, the NCCPC has assumed that increasing the dose of atorvastatin, corresponds to the same relative risk reduction for each CV event endpoints. However, the risk ratios used in the cost-effectiveness model for low-, medium- and high-intensity shows that the relative risk reduction for some endpoints, such as non-fatal stroke, non-CV death, does not change as the intensity of the statin is increased (Figure 53 & 58, Appendix I). Should the NCCPC continue to rely on the threshold analysis, it should evaluate the increase in CV event reduction required for those endpoints, such as MI, where a dose-dependent relationship has been investigated and shown. Furthermore, the threshold analysis does not fully take into account any potential differences in adverse events or discontinuation rates.</p>	<p>is not altered. The effectiveness of stroke is reduced relatively in line with other outcomes, however the inconsistent reductions in stroke event rates between different statin intensities is explored in additional sensitivity analyses (which show that cost effectiveness is not affected by altering the stroke rates). As the largest reductions from statin therapy are to MI (with angina and PAD) and CV mortality, the relative increased reduction in these contribute much more than change in stroke rate. If stroke (and TIA) rate is held constant then the result of the analysis is unchanged.</p> <p>We acknowledge that adverse events are not taken into account in this threshold analysis. In reality we would expect a larger net benefit from atorvastatin 80 mg, which would more than compensate from any increase in adverse events. Discontinuation rates are discussed in relation to the scenario analysis in Section L.2.3.7. We have no evidence that atorvastatin 80 mg is likely to have higher discontinuation rates compared to atorvastatin 20 mg, particularly when the first option in response to any adverse event would be to suggest decreasing the dose to 40 mg or 20 mg of atorvastatin.</p>
405	SH	Merck Sharp & Dohme	12	Appendix	L.2.5.2	564	<p><u>Discontinuation rates</u></p> <p>Discontinuation rates have been shown to be higher for atorvastatin 80 mg compared with moderate statin doses</p>	<p>Thank you for your comment. Davidson and Robinson show that atorvastatin 80 mg is associated with higher discontinuation rates in studies</p>

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							<p>(Davidson et al., 2007). This dose dependent effect has been taken into account in the cost-effectiveness analysis of low-, medium- and high-intensity statins. It was assumed that for those on high intensity treatment, 5% would cease taking statins and 5% would change to medium intensity statin, while for those on medium intensity statins, 2% would cease taking statins and 2% would change to low intensity statin. However, for the crude cost-effectiveness analysis that was undertaken between the atorvastatin doses, higher discontinuation rates for atorvastatin 80 mg than 40 mg and 20 mg doses was not considered and included in the modelling.</p> <p><u>References</u></p> <ul style="list-style-type: none"> - Davidson MH and Robinson JG. (2007) Safety of Aggressive Lipid Management. <i>Journal of the American College of Cardiology</i> 49: 1753-1762. 	<p>comparing it to medium-intensity statins (atorvastatin 10 mg or simvastatin 20–40 mg) but they do not compare rates of discontinuation for atorvastatin 80 mg to those for atorvastatin 20 mg or 40 mg. We have no evidence that atorvastatin 80 mg is likely to have higher discontinuation rates compared to atorvastatin 20 mg, particularly when the first option in response to any adverse event would be to suggest decreasing the dose to 40 mg or 20 mg of atorvastatin.</p>
409	SH	Merck Sharp & Dohme	16	Appendix	L.2.3.7	562	<p><u>Modelling new onset of diabetes in cost-effectiveness model</u></p> <p>The earlier onset of diabetes associated with statins was modelled as an adverse event in the cost-effectiveness analysis conducted by the NCCPC. There are two limitations of this approach. Firstly, they only modelled this adverse event by considering the 1st 4 years of diabetes treatment costs. However, the impact of earlier onset of diabetes on long-term complications (i.e. macrovascular and microvascular) associated diabetes has not been considered. Secondly, the NCCPC's cost-effectiveness analyses have not fully considered the evidence that demonstrates the risk for the onset of diabetes is dose-dependent. A meta-analysis of five outcome studies (including three atorvastatin 80 mg RCTs, PROVE-IT-TIMI 22, TNT and IDEAL) conducted by Preiss <i>et al.</i>, 2011 demonstrated that intensive-dose statin therapy (defined</p>	<p>Thank you for your comment. We have considered the Preiss meta-analysis and have now modified our model so that the risk of diabetes onset is dependent on the intensity of the statin. (This did not affect the cost effectiveness of high-intensity statins.)</p> <p>The GDG has confirmed its view that additional cases of diabetes seen in medium-term clinical trials are most likely to represent cases of diabetes developed earlier than would have been the case without statins, and so the base case economic modelling still includes 4 years of diabetes treatment costs as the most likely impact. However, we have added an additional sensitivity analysis to</p>

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							<p>as simvastatin or atorvastatin 80 mg) was associated with a 12% higher risk for new-onset diabetes compared to moderate dosing. As such, in the cost-effectiveness analysis comparing low-, medium- and high-intensity statin and atorvastatin 80 mg to atorvastatin 40 mg and 20 mg, the differences in risk of new-onset diabetes, as well as the impact of long-term complications associated diabetes, needs to be modelled and considered by the GDG in making recommendations.</p> <p><u>References</u></p> <ul style="list-style-type: none"> - Preiss D, Seshasai SR, Welsh P, et al. (2011) Risk of incident diabetes with intensive dose compared with moderate-dose statin therapy: a meta-analysis. <i>JAMA</i> 305:2556–2564. 	consider the impact of adding full lifetime additional costs of diabetes treatment if 25%, or even 100%, of those with new-onset diabetes did in fact have diabetes which would not otherwise have occurred at all without statin treatment, instead of just being brought forward. High-intensity statins were still cost effective in both the 25% and 100% analyses.
335	SH	Association of British Clinical Diabetologists, Diabetes UK	10	NICE, Appendix A	1.4.23	44	<p>States 'start statin treatment in people with...type 1 diabetes or type 2 diabetes with atorvastatin 80 mg '.</p> <p>There is no suggestion in main body of text of 80 mg atorvastatin as start dose for type 1, rather 20 mg is stated</p>	Thank you for your comment. The recommendation for type 1 diabetes is indeed to start with atorvastatin 20mg. Please note that most of Appendix A has been deleted after stakeholders consultation, as per NICE process.

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These organisations were approached but did not respond:

**AbbVie
Adverse Psychiatric Reactions Information Link
Aegerion Pharmaceuticals Limited
Aintree University Hospital NHS Foundation Trust
Alder Hey Children's NHS Foundation Trust
Allocate Software PLC
Alpro UK Ltd
Amgen UK
AMORE health Ltd
AMORE Studies Group
Anglia Stroke and Heart Network
Association of Anaesthetists of Great Britain and Ireland
Association of British Healthcare Industries
Association of British Insurers
Association of Children's Diabetes Clinicians
Association of Clinical Pathologists
Avon, Gloucestershire and Wiltshire Strategic Health Authority
Barnsley Primary Care Trust
Baxter Healthcare
BBOLMC
Bedfordshire Primary Care Trust
Betsi Cadwaladr University Health Board
Birmingham & Brunel Consortium
Birmingham, Sandwell and Solihull Cardiac and Stroke Network
Blood Pressure UK
Boehringer Ingelheim
Bolton Primary Care Trust
Boots
Bradford District Care Trust
Breakspear Medical Group Ltd**

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Bristol-Myers Squibb Pharmaceuticals Ltd
 British Association for Nursing in Cardiovascular Care
 British Association for Sexual Health and HIV
 British Association of Stroke Physicians
 British Cardiac Patients Association
 British Cardiovascular Society
 British Geriatrics Society
 British Heart Foundation
 British Hypertension Society
 British Medical Journal
 British National Formulary
 British Nuclear Cardiology Society
 British Nutrition Foundation
 British Psychological Society
 British Red Cross
 British Society of Paediatric Gastroenterology Hepatology and Nutrition
 Buckinghamshire Primary Care Trust
 BUPA Foundation
 Calderdale Primary Care Trust
 Cambridge University Hospitals NHS Foundation Trust
 Camden Link
 Capsulation PPS
 Capsulation PPS
 Cardiac and Stroke Networks in Lancashire & Cumbria
 Care Quality Commission (CQC)
 Central London Community Health Care NHS Trust
 Central London Community Health Care NHS Trust
 Cheshire and Merseyside Cardiac Network
 Chesterfield Primary Care Trust
 Children living with Inherited Metabolic Diseases
 CHKS Ltd
 CIS' ters
 City and Hackney Teaching Primary Care Trust
 Clarity Informatics Ltd
 Clinical Trial Service Unit
 Coast to Coast Cardiac Network
 Co-operative Pharmacy Association
 Countess of Chester Hospital NHS Foundation Trust
 Coventry and Warwickshire Cardiac Network

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Croydon Clinical Commissioning Group
 Croydon Health Services NHS Trust
 Croydon Primary Care Trust
 Croydon University Hospital
 Cumbria and Lancashire Cardiac and Stroke Network
 Cybex Ventures
 David Lewis Centre, The
 Department of Health, Social Services and Public Safety - Northern Ireland
 Dept of Primary Health Care Sciences, University of Oxford
 Derbyshire County Primary Care Trust
 Derbyshire Mental Health Services NHS Trust
 Diabetes UK
 Division of Public Health & Primary Health Care
 Dorset Primary Care Trust
 Dudley Primary Care Trust
 East and North Hertfordshire NHS Trust
 East Kent Hospitals University NHS Foundation Trust
 Education for Health
 EMIS
 Essex Cardiac & Stroke Network
 Ethical Medicines Industry Group
 Faculty of Public Health
 Faculty of Sport and Exercise Medicine
 Fellowship of Postgraduate Medicine
 Five Boroughs Partnership NHS Trust
 Fresenius Kabi Ltd
 Genzyme Therapeutics
 Great Western Hospitals NHS Foundation Trust
 Greater Manchester and Cheshire Cardiac and Stroke Network
 Guerbet Laboratories Ltd
 Guy's and St Thomas' NHS Foundation Trust
 Hammersmith and Fulham Primary Care Trust
 Harrogate and District NHS Foundation Trust
 Health & Social Care Information Centre
 Health and Care Professions Council
 Healthcare Improvement Scotland
 Healthcare Infection Society
 Healthcare Quality Improvement Partnership
 Healthwatch East Sussex

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Heart of Birmingham Teaching Primary Care Trust
 Heart of England NHS Foundation Trust
 HEART UK
 Herts Valleys Clinical Commissioning Group
 Hockley Medical Practice
 Humber NHS Foundation Trust
 Inner North West London PCTs
 Institute of Biomedical Science
 James Paget University Hospitals NHS Foundation Trust
 KasTech Ltd
 Kent Cardiac Network
 Kimal PLC
 L.IN.C.Medical
 Lancashire Care NHS Foundation Trust
 Leeds Community Healthcare NHS Trust
 Leeds North Clinical Commissioning Group
 Leeds Primary Care Trust (aka NHS Leeds)
 Leeds South and East Clinical Commissioning Group
 Leicestershire, Northamptonshire and Rutland Cancer Network
 Lilly UK
 Lincolnshire Teaching Primary Care Trust
 Liverpool Primary Care Trust
 Lloyds Pharmacy
 Local Government Association
 London Medical
 Luton and Dunstable Hospital NHS Trust
 Maidstone and Tunbridge Wells NHS Trust
 McNeil Nutritionals Ltd
 Medicines and Healthcare products Regulatory Agency
 Mid Staffordshire NHS Foundation Trust
 Ministry of Defence (MOD)
 MRC Human Nutrition Research
 MSD Ltd
 National Association of Primary Care
 National Collaborating Centre for Cancer
 National Collaborating Centre for Mental Health
 National Collaborating Centre for Women's and Children's Health
 National Deaf Children's Society
 National Institute for Health Research Health Technology Assessment Programme

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National Institute for Health Research
National Obesity Forum
National Patient Safety Agency
National Prescribing Centre
National Public Health Service for Wales
Newcastle upon Tyne Hospitals NHS Foundation Trust
NHS Barnsley Clinical Commissioning Group
NHS Birmingham South and Central CCG
NHS Bournemouth and Poole
NHS Bristol
NHS Bromley
NHS Clinical Knowledge Summaries
NHS Connecting for Health
NHS County Durham and Darlington
NHS Cumbria Clinical Commissioning Group
NHS Derbyshire county
NHS Direct
NHS England - Greater Manchester
NHS Fylde & Wyre CCG
NHS Halton CCG
NHS Health at Work
NHS Improvement
NHS Kensington and Chelsea
NHS Kirklees
NHS Luton CCG
NHS Manchester
NHS Medway Clinical Commissioning Group
NHS Newcastle
NHS North Lancs
NHS Nottingham City
NHS Nottinghamshire County
NHS Plus
NHS Plymouth
NHS Portsmouth Clinical Commissioning Group
NHS South Central vascular Network
NHS South Cheshire CCG
NHS Southern Derbyshire CCG
NHS Sussex
NHS Sutton and Merton

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NHS Trafford
NHS Wakefield CCG
NHS Warwickshire North CCG
NHS Warwickshire Primary Care Trust
NHS West Kent
NHS West Lancashire CCG
NHS West Suffolk CCG
North Cheshire Hospitals NHS Trust
North East Lincolnshire Care Trust Plus
North East Yorkshire and Northern Lincolnshire Cardiac & Stroke Network
North of England Cardiovascular Network
North of England Commissioning Support
North Trent Network of Cardiac Care
North West London Cardiac Network
North West London Hospitals NHS Trust
North West London Perinatal Network
North Yorkshire & York Primary Care Trust
Nottingham City Council
Nottingham City Hospital
Novartis Pharmaceuticals
Numares Group
Nutrition and Diet Resources UK
Nutrition Society
Oxfordshire Clinical Commissioning Group
Oxfordshire Primary Care Trust
Papworth Hospital NHS Foundation Trust
Peninsula Clinical Managed Cardiac Network
Peninsula Heart & Stroke Network
PERIGON Healthcare Ltd
PharmaPlus Ltd
PHE Alcohol and Drugs, Health & Wellbeing Directorate
Powys Local Health Board
PrescQIPP NHS Programme
Primary Care Cardiovascular Society
Primary Care Dermatology Society
Primary Care Diabetes Society
Primary Care Pharmacists Association
Primrose Bank Medical Centre
Programme development Group in Maternal and Child Nutrition

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Public Health Wales NHS Trust
 Queen Elizabeth Hospital King's Lynn NHS Trust
 Randox Laboratories Limited
 Renal Association
 Roche Diagnostics
 Rotherham Primary Care Trust
 Royal Berkshire NHS Foundation Trust
 Royal Brompton Hospital & Harefield NHS Trust
 Royal College of Anaesthetists
 Royal College of General Practitioners in Wales
 Royal College of Midwives
 Royal College of Midwives
 Royal College of Obstetricians and Gynaecologists
 Royal College of Paediatrics and Child Health
 Royal College of Paediatrics and Child Health , Gastroenterology, Hepatology and Nutrition
 Royal College of Physicians of Edinburgh
 Royal College of Psychiatrists
 Royal College of Radiologists
 Royal College of Surgeons of England
 Royal Surrey County Hospital NHS Trust
 Royal United Hospital Bath NHS Trust
 Sandwell Primary Care Trust
 School of Health and Population Sciences
 Scottish Intercollegiate Guidelines Network
 Sheffield Primary Care Trust
 Sheffield Teaching Hospitals NHS Foundation Trust
 Shropshire and Staffordshire Cardiac Network
 Simon Broome committee of HEART UK
 SNDRi
 Social Care Institute for Excellence
 Society for Academic Primary Care
 Society for Endocrinology
 Society of District General Hospital Nephrologists
 Society Of Vascular Nurses
 Solihull NHS Primary Care Trust
 Solvay
 Somerset Primary Care Trust
 South Asian Health Foundation
 South Central Cardiovascular Network

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South East Staffordshire and Seisdon Penninsula CCG
South London & Maudsley NHS Trust
South Staffordshire Primary Care Trust
South West London Cardiac & Stroke Network
South West Yorkshire Partnership NHS Foundation Trust
Southport and Ormskirk Hospital NHS Trust
St Mary's Hospital
Staffordshire and Stoke on Trent Partnership NHS Trust
Stockport Clinical Commissioning Group
Stockport Primary Care Trust
Sussex Heart Network
Tameside Hospital NHS Foundation Trust
TCR
Teva UK
The Association for Clinical Biochemistry & Laboratory Medicine
The Association of the British Pharmaceutical Industry
The National Association of Assistants in Surgical Practice
The Natural Ketosis Company
The Neurological Alliance
The Patients Association
The Phoenix Partnership
The Princess Alexandra Hospital NHS Trust
The Rotherham NHS Foundation Trust
The Stroke Association
Trent Cardiac Network
UK Clinical Pharmacy Association
UK Health Forum
UK Specialised Services Public Health Network
Unilever UK Ltd
United Kingdom National External Quality Assessment Service
University College London Hospital NHS Foundation Trust
University Hospital Aintree
University Hospital Birmingham NHS Foundation Trust
University Hospitals Birmingham
University of East Anglia
University of Nottingham
Walsall Local Involvement Network
Warrington Primary Care Trust
Welsh Endocrine and Diabetes Society

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Welsh Government
West London Mental Health NHS Trust
West Surrey Cardiac Network
West Sussex Public Health
West Yorkshire Cardiac Network
Western Cheshire Primary Care Trust
Western Sussex Hospitals NHS Trust
Wigan Borough Clinical Commissioning Group
Wiltshire Primary Care Trust
Wirral Primary Care Trust
Worcestershire Health and Care NHS Trust
York Hospitals NHS Foundation Trust
Yorkshire and Humber Strategic Clinical Networks

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