National Institute for Health and Clinical Excellence

Lipid Modification (update)
Scope Consultation Table
13 June – 11 July 2012

Type	Stakeholder	Order No	Section No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Abbott	1	3.2.b	Section 3.2.b Current practice: Although blood cholesterol levels are mentioned specifically as a risk factor we would like to highlight that triglyceridaemia can be considered as an additional specific risk factor for CVD. High triglycerides have been shown to be an independent risk factor for coronary heart disease (Durrington , NCEP Expert Panel and Morrison), suggesting that some triglyceride-rich lipoproteins are atherogenic (NCEP Expert Panel). In addition, many studies suggest that triglyceride-rich lipoproteins are equivalent in risk to LDL-C (McBride). The review by Rankin (2008) summarises data on the role of elevated triglycerides in the pathogenesis of coronary heart disease. Several studies are discussed, which suggest that high triglyceride levels are an independent predictor of CHD events. Some recent papers discussing triglyceride levels and cardiovascular risk are summarised below. The Triglyceride Coronary Disease Consortium and Emerging Risk Factors Collaboration (2010) conducted a novel genetic analysis that studied whether high levels of triglycerides in the blood could increase the risk of CHD. The group analysed the genetic make-up of patients predisposed genetically to produce higher levels of triglycerides in the blood and they showed that these were more likely to suffer from heart disease. Three hundred and fifty thousand patients were analysed from 101 studies. The findings were consistent with a causative role of high triglycerides in the blood and the development of heart disease. Alagona (2009) reviewed the role of elevated triglycerides and low HDL	Thank you for your comment. Section 3.2.b of the scope states that cholesterol is one of the risk factors for CVD. Additional risk factors are not explicitly listed in the scope and the list is not exhaustive.

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				in residual CVD risk, remaining after statin therapy. Managed care initiatives to reduce CVD risk have, to date, focused mainly on statins, which primarily reduce LDL-C and have limited effects on TG and HDL-C at standard doses. This review looks at residual CVD risk even after statin treatment and the role of reducing TG and increasing HDL-C. It discusses the NCEP ATP III and AHA recommendations for treating TG and discusses combination therapies that may be used to for residual risk reduction. The author concluded that combination therapy may be necessary to optimally address multiple lipid abnormalities and improve patient outcomes. In the PROVE IT-TIMI 22 trial subanalysis the author examined a combination of LDL cholesterol and TG levels on CVD risk in ACS patients. During the 2-year follow-up, significantly fewer CHD events occurred in patients who had LDL cholesterol <1.81 mmol/L than in patients who had LDL cholesterol ≥ 1.81 mmol/L (HR, 0.81; P = .015). However Patients with TGs <1.69 Mmol/L, even if they had LDL cholesterol > 1.81 mmol/L, exhibited CHD event rates 15% lower than those patients who had low LDL cholesterol but high TGs. In the prospective study carried out by Fontbonne et alx, 943 men with impaired glucose tolerance or diabetes were followed up for a mean of 11 years. Univariate analysis showed that plasma triglyceride level ($p<0.006$), plasma cholesterol level ($p<0.002$) and plasma insulin level both fasting and 2-h post glucose load ($p<0.002$) were significantly higher in subjects who died from coronary heart disease compared to those who did not. In multivariate regression analysis, plasma triglyceride level was the only factor positively and significantly associated with coronary death. Lehto et alxi prospectively assessed the risk factors for CHD in patients with non-insulin dependent diabetes mellitus (NIDDM) over 7 years. 158 patients died of CHD and 256 patients had a serious CHD event. It was found that triglyceride levels >2.3 mmol/l increased the risk of CHD events by approximately 2-fold, independently of other risk factors.	

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				Considering the above, triglyceridaemia is an important risk factor that must be considered in the update of this guideline. <u>References</u> I Durrington PN Fast facts – hypertriglyceridaemia Oxford: Health Press Limited, 2000 II NCEP Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in adults. NIH Publication NO.01-3670, May 2001 III Morrison A The independent relationship between triglycerides and coronary heart disease Vasc Health Risk Management 2009;5:89-95 IV NCEP Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in adults. NIH Publication NO.01-3670, May 2001 V McBride PE Triglycerides and risk for coronary heart disease J Am Med Assoc 2009;298(3):336-338 (CVD245) VI Rankin FM Pathogenesis of CHD: the role of elevated triglycerides J Am Acad Nurse Pract 2008;20(12 suppl 2): VII Triglyceride Coronary Disease Consortium and Emerging Risk Factors Collaboration	

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				Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies Lancet 2010;365:1634-1639 VIII Alagona 2009 Beyond LDL Cholesterol: The Role of Elevated Triglycerides and Low HDL Cholesterol in Residual CVD Risk Remaining after Stain Therapy Am J Manag Care. 2009;15:S65-S73 IX Miller M Impact of Triglyceride Levels Beyond Low-Density Lipoprotein Cholesterol after Acute Coronary Syndrome in the PROVE IT-TIMI 22 Trial J Am Coll Cardiol 2008;51:724-30 x Fontbonne A et al Diabetology 1989;32: 300-304 xi Lehto et al Diabetes 1997:46:1354-1359	
SH	Abbott	2	4.3.1.c	Section 4.3.1.c Key clinical issues that will be covered: Omega-3 fatty acids administered concomitantly with statins have shown to further reduce hypertriglyceridaemia in diabetic population compared statins alone. In a recent cross-sectional observational study[xii] of 18,663 patients with diagnosed diabetes from 50 randomly selected primary care practices it was found that 21.5% of patients did not received any lipid lowering therapy although most of them showed evidence of dyslipidaemia. Of the patients with type 2 Diabetes Mellitus that received lipid-lowering therapy, 77.1% were on statin monotherapy, however 46.5% showed TC <4 mmol/l; 42.5% LDL-C <2.0 mmol/l; 57.7% HDL-C	Thank you for your comment. The evidence for Omega-3 fatty acids and statin will be reviewed during development, in the general population and also in people with diabetes.

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				>1.0 mmol/l (male); 54.8% HDL-C >1.2 mmol/l (female); and 53.4% TG <1.7 mmol/l. The authors conclude that specific TG lowering therapies may need to be considered. Reference [xii] Feher M et al 80th European Atherosclerosis Society Congress, 2012, M4.39	
SH	AstraZeneca UK Ltd	1	General	We would like to thank NICE for the opportunity to comment on the draft scope for the Lipid Modification clinical guidelines	Thank you for your comment
SH	AstraZeneca UK Ltd	2	3.2	We note the NHS Health Check uses a risk engine for people aged 40-74 years to calculate their 10 year risk of CVD as stated in the scope. We believe that in line with the recent CTTC publication that lowering of the risk threshold should be considered and we support the lowering of the risk threshold to a 10 year risk >5-10% **Reference:** 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. Cholesterol Treatment Trialists' (CTT) Collaborators. The Lancet. 17 May 2012. doi: 10.1016/s0140-6736(12)60367-5	Thank you for your comment. The evidence on risk assessment will be reviewed as part of the development of this guideline. The cost effectiveness analysis will also establish the intervention threshold.
SH	AstraZeneca UK Ltd	3	4.1.1	We agree that women should be included as a special group within the scope of the guidelines as they are sometimes overlooked and have a greater propensity to some of the adverse events of statins	Thank you for your comment.
SH	AstraZeneca UK Ltd	4	4.3.1 f	Could clarification be given that adherence and co-enzyme Q10 will be reviewed in the context of statin-related myalgia. If so, is there an ability to consider other patient groups and their incidence of statin-related myalgia? We feel the identification of those groups with an increased pre-disposition to statin-related myalgia could improve the benefit-risk ratio of statins and a more a more cost effective approach to monitoring **References** Risk factors and drug interactions predisposing to statin-induced myopathy. Chatzizisis YS; Kosakinas KC; Misirli G et al. Drug Saf 2010: 33 (3):171-187	Thank you, we agree with your comment, and we have added an additional point to the section 4.3.1 to reflect this: "The identification of subgroups at increased risk of adverse events and strategies to improve and maintain adherence and specific interventions for individual agents, for example coenzyme

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					Q10".
SH	British Cardiovascular Society	1	4.3.1 a	The NICE update needs to consider the use of age screening (ie the sole use of an age cut-off) in selecting who should be offered statins. It has been shown, but is not widely recognised, that causal risk factors (like blood pressure and cholesterol), whilst important to reduce in the prevention of CVD, are poor at predicting who will and will not have a CVD event. Combining several causal risk factors together (using risk assessment tools like Framingham and QRISK) does not overcome this problem and adds little to a person's age (by far the dominant risk factor) in risk assessment. A person's age can be used, on its own, to generate a 10-year risk of a CVD event and has been shown to be similar in predictive accuracy to other more complicated risk assessment tools like Framingham and QRISK.[1] Age screening was first proposed in 2003 (Wald and Law, BMJ [2] using an age 55 cut-off) and was recently re-proposed (Ebrahim and Casas, Lancet 2012[3] using an age 50 cut-off) following a paper (Cholesterol Trialists (CTT) Collaborators, Lancet 2012 [4]) showing that statins were as effective in reducing CVD in individuals without vascular disease with a 5% 10-year risk of a CVD event (most people in the population over age 60) as in people with a higher CVD risk. It is in the public interest to seriously consider adopting an age-based strategy in place of Framingham-type assessment tools and this should be an explicit intention of the NICE update. An age-based approach could apply to the general population as well as people with diabetes (albeit using different age cut-offs).	Thank you, we agree with your view, and we have added 'age alone' to the list of assessment tools.

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				Therefore the Scope document should be amended in section 4.3.1 as follows: (1) "people without diabetes – for example QRISK and Framingham risk assessment tools…" should be changed to "people without diabetes – for example Age alone, QRISK and Framingham risk assessment tools" (2) "people with diabetes – for example UKPDS Risk Engine, Epic – Norfolk Cambridge diabetes, FinRisk Tools…should be changed to "people with diabetes – for example Age alone, UKPDS Risk Engine, Epic –Norfolk Cambridge diabetes, FinRisk Tools. Refs: 1. Wald NJ, Simmonds M, Morris JK. Screening for future cardiovascular risk using age alone compared with multiple risk factors and age. PLOS ONE 6(5):e18742.doi:10.1371/journal.pone.0018742 2. 1. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;**326**:1419-23 3. Ebrahim S, Casas JP Statins for all by the age of 50 years? Lancet 2012 DOI:10.1016/S0140-6736(12)60367-5 4. Cholesterol Treatment Trialists (CTT) Collaborators. 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 2012, DOI: 10.1016/S0140-6736(12)60367-5	
SH	Department of Health	1	General	The Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment
SH	McNeil Nutritionals	1	5.3.2	**Clinical effectiveness of low fat diets for primary prevention** As noted in the European Guidelines on Cardiovascular Disease	Thank you, your comment refers to the published clinical guideline CG67 on Lipid modification, and

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				Prevention in Clinical Practice (version 2012) the effect of consumption of foods with added plant stanols and sterols on lowering cholesterol is additional to that obtained with a low-fat diet (1). Indeed, several placebo controlled clinical trials show that consuming plant stanols as part of a diet low in saturated fat (saturated fat intake equal to or less than 10% of total energy intake) results in significantly greater reduction in cholesterol lowering than consuming a low saturated fat diet alone (2-6). For example, Athyros et al (2011) recently showed in a placebo controlled study that a low saturated fat diet with added plant stanols led to an 18% reduction in LDL cholesterol compared to 5% reduction on a comparable low saturated fat diet alone. The benefits of low (saturated) fat diets with added plant stanols and sterols should be considered given that such a dietary change is relatively simple to implement and could impact significantly on an individual's ability to reach their cholesterol goals. 1. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). European Heart Journal doi:10.1093/eurheart/ehs092 2. Andersson, A.; Karlström, B.; Mohsen, R. and Vessby, B., 1999. Cholesterol-lowering effects of a stanol ester-containing low-fat margarine used in conjunction with a strict lipid-lowering diet. *Eur. Heart J.* 1, S80-S90. 3. Athyros, V.G.; Kakafika, A.I.; Papageorgiou, A.A.; Tziomalos, K.; Peletidou, A.; Vosikis, C.; Karagiannis, A. and Mikhailidis, D.P., 2011. Effect of a plant stanol ester-containing spread, placebo spread, or Mediterranean diet on estimated cardiovascular risk and lipid, inflammatory and haemostatic factors. *Nutr. Metab. Cardiovasc. Dis.* 20, 213-221. 4. Hallikainen, M.A. and Uusitupa, M.I.J., 1999. Effects of 2 low-fat	not to the draft scope for the update of the guideline. It is part of our scope to review the evidence for stanols and sterols and update this section of the guideline. We will conduct a systematic review of the literature about stanols and sterols.

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				stanol ester-containing margarines on serum cholesterol concentrations as part of a low-fat diet in hypercholesterolemic subjects. *Am. J. Clin. Nutr.* 69, 403-410. 5. Hallikainen, M.A.; Sarkkinen, E.S.; Gylling, H.; Erkkila, A.T. and Uusitupa, M.I., 2000. Comparison of the effects of plant sterol ester and plant stanol ester-enriched margarines in lowering serum cholesterol concentrations in hypercholesterolaemic subjects on a low-fat diet. *Eur. J. Clin. Nutr.* 54, 715-725. 6. Jones, R.J.; Raeini-Sarjaz, M.; Ntanios, F.Y.; Vanstone, C.A.; Feng, J.Y. and Parsons, W.E., 2000. Modulation of plasma lipid levels and cholesterol kinetics by phytosterol versus phytostanol esters. *J. Lipid Res.* 41, 697-705.	
SH	McNeil Nutritionals	2	5.4	**Plant stanols and sterols** Dietary approaches to reducing the burden of CVD risk involving foods with added plant stanols/sterols have recently been evaluated in Europe by the European Food Safety Authority and subsequently, health claims related to plant stanol and sterol consumption have been approved. These independent scientific assessments have been completed as part of the mandatory health claim evaluations process for disease risk reduction claims related to foods. Thus, as in the case of fruit and vegetables (Guideline-5.3.6/5.3.7) where DOH guidelines are outlined in the absence of randomised controlled trials, this section of the guideline should reflect the authorative scientific opinions relating to plant stanols and sterols published by the European Food Safety Authority. To date, five separate evaluations in relation to the cholesterol lowering effect of dietary plant stanols and sterols, at intakes ranging from 1.5 to 3g/d, have been conducted and resulted in positive opinions. Foods with added plant stanols and sterols can bear the health claim ***'to lower/reduce blood***	Thank you, your comment refers to the published clinical guideline CG67 on Lipid modification, and not to the draft scope for the update of the guideline. It is part of our scope to review the evidence for stanols and sterols and update this section of the guideline. We will conduct a systematic review of the literature about stanols and sterols.

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				cholesterol' and state ***'High cholesterol is a risk factor in the development of coronary heart disease'.*** Consumption of foods with added plant stanols and sterols have been proven to reduce cholesterol in various populations within 2 to 3 weeks. Efficacy (7-10% lowering of LDL cholesterol with intakes from 1.5-2.4g/d; 11.3/11.4% with intake in region of 3g/d) is sustained as long as consumption is maintained (1-6). Furthermore, as noted in the recently published European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (version 2012), the effect of consumption of foods with added plant stanols and sterols on lowering cholesterol is additional to that obtained with the use of statins which is particularly relevant given the prevalence of failure to reach cholesterol goals/targets (7). 1. European Commission. Official Journal of European Communities 2010a. Commission Regulation (EU) No 376/2010 of 3 May 2010. 2. European Commission. Official Journal of European Communities 2010a. Commission Regulation (EU) No 384/2010 of 5 May 2010. 3. European Commission. Official Journal of European Communities 2010a. Commission Regulation (EU) No 983 /2009 of 21/october 2009. 4. European Commission. Official Journal of European Communities 2010a. Commission Regulation (EU) No 432/2012 of 16 May 2012. 5. EFSA (2012), 10 (5) 2692 Plant Stanol Esters and Blood Cholesterol .Scientific Opinion of the NDA Panel - Published: 16 May 2012 6. EFSA (2012), 10 (5) 2693 Plant Sterols and Stanols and Blood	

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				Cholesterol . Scientific Opinion of the NDA Panel - Published: 16 May 2012. 7. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). European Heart Journal doi:10.1093/eurheart/ehs092.	
SH	Medicines and Healthcare products Regulatory Agency	1	3.1 b	It may be possible to show more recent mortality figures than the 2005–6 ones. The British Heart Foundation's *Coronary heart disease statistics* 2010 edition includes 2008 figures for deaths by all diseases of the circulatory system (190,857)	Thank you for your comment. The scope has been amended with these more recent figures.
SH	Medicines and Healthcare products Regulatory Agency	2	4.1.1	The guideline will cover adults with type 1 and type 2 diabetes but section 4.3.2 excludes those with prediabetes. Clinicians may value guidance on statin treatment in this group of individuals, particularly in view of concerns about an association between statins and new-onset diabetes (see comment 3, below).	Thank you for your comment. People with pre-diabetes are not included as a separate subgroup, but they will be considered in relation to their risk of cardiovascular disease related to lipids. We have now amended the wording of the 'Clinical issues that will not be covered' section to make this clear.
SH	Medicines and Healthcare products Regulatory Agency	3	4.3.1	Under Key clinical issues to be covered, you may wish to consider including recommendations for monitoring blood glucose, since an association has been found between statin use and new-onset diabetes in patients already at risk of diabetes; summaries of product characteristics will in future include the following warning: "Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of	Thank you, we agree with your suggestion, and we have explicitly added 'monitoring glycaemia' to the scope.

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				hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI > 30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines."	
SH	Merck Sharp & Dohme Ltd	1	4.1.1	We agree with the proposal to describe lipid management in patients with chronic kidney disease and diabetes (type 1 and 2) in the update to CG67, rather than across the separate guidelines.	Thank you for your comment.
SH	Merck Sharp & Dohme Ltd	2	4.3.1 b	"Treating to a target lipid level" is specified as one of the lipid modification strategies, in primary and secondary prevention. A tightly linked measure (TLM) for 'Diabetes: Lipid management' is currently under development for potential inclusion in the 2013/14 QOF indicator set. If recommended (recommendation is anticipated at the December QOF Advisory Committee Meeting), the TLM will incentivise the management of total cholesterol to ≤ 4.0 mmol/l, through a series of stages. Whilst still in development, we suggest it would be beneficial to consider any relevant updates to the QOF indicators in the development of the guideline.	Thank you for your comment. We will work closely with our colleagues in the NICE QOF Indicator Programme to keep them informed of the guideline recommendations.
SH	Merck Sharp & Dohme Ltd	3	4.3.1 c	We suggest that under the sub-heading "second line treatments", ezetimibe should also be listed, along with a cross reference to the prevailing recommendations of the technology appraisal (TA132).	Thank you for your comment. This section in the scope is listing the areas that are included in the update. TA132 is listed under Related NICE guidance in section 5.1.2 using standard NICE format.
SH	Merck Sharp	4	4.4	As per our comments on the proposed 2013/14 QOF TLM for 'Diabetes:	Thank you for your comment.

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	& Dohme Ltd			Lipid management', we suggest "Attainment of cholesterol targets' could be included within the list of main outcomes.	The outcomes listed are not an exhaustive list and other outcomes will be decided by the GDG. The guideline is for the primary and secondary prevention of cardiovascular disease and morbidity and mortality will be the preferred outcomes as in CG67.
SH	North of England Cardiovascular Network	1	4.3.1	Even though ezetimibe has its own guidance, I would have expected it to be included in scope for lipid modification guidance	Thank you for your comment. We refer to technology appraisal in the Related NICE guidance section of the scope, section 5.1.2. Following consultation with stakeholders, it has been determined that TA132 (Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia) does not meet criteria for updating in the context of a clinical guideline.
SH	Roche Products Ltd.	1	4.1.1	Roche supports the stakeholder feedback to include people with severe mental illness as a potential sub-group. We recognize that recommendations may be limited by the availability of evidence, however, independent association between mental health and CVD merits exploration.	Thank you, we agree with your suggestion and we have added 'people with serious mental illness' as a special group.
SH	Roche Products Ltd.	2	4.3.1 a	Roche supports the stakeholder feedback that the GDG 'does not have to recommend one or more tools' and we are satisfied that NICE will allow the selection of the most appropriate tool as defined by criteria outlined in the guideline.	Thank you for your comment

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SH	Roche Products Ltd.	3	4.3.1 b	Roche would suggest modifying the wording '…treating to a target lipid level' to 'treating to a target metabolic profile' to account for different ways of assessing effects or defining lipid targets. Moreover targets may refer to absolute or relative numbers in this area or both, making the inclusion of lipid ratios more important.	Thank you for your comment. We believe that 'treating to a target lipid level' is an accurate definition for the scope; metabolic profile would be a too broad definition. The decision on whether to use absolute or relative numbers will be taken by the GDG during the development of the guideline.
SH	Roche Products Ltd.	4	4.3.1 c	We recognize that the omission of ezetimibe from this guideline is correct due to its inclusion in the NICE HTA programme. We would suggest that 'fibrates' be expanded to the broader class of drug 'ppar alpha agonists'. Furthermore, we would support the addition of 'pioglitazone' as a second line treatment.	Thank you for your comment. To our knowledge, all the licensed 'ppar alpha agonists' for use in lipid modification are fibrates. Pioglitazone is not generally considered as a lipid modification treatment or a second line treatment as an alternative to statins or the other second line agents.
SH	Roche Products Ltd.	5	4.3.2	Roche would support the stakeholder feedback to include pre-diabetes and metabolic syndrome patients in this clinical guideline. While we acknowledge the development of the NICE public health guidance on preventing type 2 diabetes may have some overlap, we feel the inclusion of these patients would be relevant to this guideline.	Thank you for your comment. People with pre-diabetes and metabolic syndrome are not included as a separate subgroup, but they will be considered in relation to their risk of cardiovascular disease related to lipids. We have now amended the wording of the 'Clinical issues that will not be covered' section to make this clear.

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SH	Roche Products Ltd.	6	General	We note the discussion on the possible change of risk threshold and the subsequent necessary modification to the NHS Health Checks policy this would imply. To uphold the principle of evidence and clinical practice based guidelines, we would support the review of this threshold.	Thank you for your comment
SH	Royal Berkshire NHS Foundation Trust	1	4.3.1 a	Our comments are as follows: When choosing the most appropriate risk tool system to estimate an individual's absolute risk of developing CVD, this should take into account that patient's with raised triglycerides and low HDL might have Familial Combined Hyperlipidaemia (FCH). I am aware that the guideline does not include people with genetic disorders that increase CVD risk but I am concerned with the fact that, in patients with FCH, the CVD calculation may underestimate risk and GPs will be falsely reassured by this. Hence, I think that if fasting triglycerides are raised, a recommendation to measure Apolipoprotein B may be necessary to correctly assess CVD risk and to diagnose FCH. The 2009 Canadian Cardiovascular Society guidelines include Apolipoprotein B in the risk assessment. I currently advise GPs in the West Berkshire area to measure Apolipoprotein B when triglycerides are raised and a high number of patients with FCH are being detected.	Thank you for your comment. The guideline will not cover people with genetic disorders that increase CVD risk, however, we understand your view and we have added familial lipids disorders as a possible criteria for referral to specialist assessment and management for people found to have lipid disorders (Scope section 4.3.1.h)
SH	Royal Brompton & Harefield NHS Foundation Trust	1	4.3.1 c	Assessment of clinical and cost effectiveness of pharmacological intervention for secondary prevention should take into account the severity of disease as there are patients with mild CVD and those with severe, aggressive diffuse disease including those who have had multiple coronary and surgical interventions.	Thank you for your comment. We will consider whether we can make different recommendations for the population who require secondary prevention according to the clinical and cost effectiveness analysis.
SH	Royal Brompton & Harefield NHS Foundation	2	4.3.1 e	Assessment and monitoring of blood lipids: which fractions of blood lipids should be measured including lipoprotein (a). When and for how long should monitoring of liver function test and creatine kinase continue?	Thank you for your comment. During the development phase of the guideline we will look at the clinical evidence to answer the

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	Trust				questions you formulated.
SH	Royal Brompton & Harefield NHS Foundation Trust	3	4.3.1 g	In clinical practice, statin intolerance is one of the main reasons for referral to specialist assessment and management.	Thank you for your comment
SH	Royal College of General Practitioners	1	4.1.3	point 4.1.3 a) the implication that QRisk cannot be used in people with diabetes is incorrect. It can be used in people with diabetes and can be considered for use in people with diabetes	Thank you, we agree with your comment and we have amended the scope to reflect this.
SH	Royal College of General Practitioners	2	4.1.3	point 4.1.3 b) treating individuals who already have established cardiovascular disease with the highest tolerated statin dose should be considered as a clinical strategy – it avoids the artificial construction of targets and highlights patient utility	Thank you for your comment. We agree with your view, and treating with the highest tolerated statin dose might be the recommended strategy depending on the result of clinical and cost effectiveness review. We have altered the scope to say 'for example fixed dose or treating to a target lipid level' to clarify this.
SH	Royal College of General Practitioners	3	4.4	Point 4.4 The GDG should consider that any new drug for lipid modification for **primary prevention** should have evidence of reduction **in total mortality** as well as cardiovascular mortality. Outcomes including non-fatal cardiovascular events (which often include	Thank you for your comment. We will take your observations into account when developing the clinical questions and protocols for the guideline.

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				operative procedures and silent infarction (half of all infarcts are silent) - are **not** a sufficient basis on which to recommend treatment for lipid modification in people who have **not** previously had a CVD event.	
SH	Royal College of General Practitioners	4	4.3.1	It might also be recommended that AST/ALT liver function tests are NOT routinely required for the monitoring of adverse events in people taking statins – our local lab charges £45 for a bundle of liver function tests and does not separate out which one. Unless there is prior evidence of liver disease there is no evidence that routine monitoring is useful and it is a large unnecessary expense with more spent on LFTs as on the annual cost of simvastatin!!	Thank you for your comment, we have added liver function test to the scope as a way of monitoring lipid-lowering treatment.
SH	Royal College of Nursing	1	General	The Royal College of Nursing welcomes proposals to update this guideline. It is timely. There have been changes in the targets and management of lipids in the past few years.	Thank you for your comment
SH	Royal College of Nursing	2	4.3.1 c	Cholesterol absorption inhibitors have not been included in this section so need to be added.	Thank you for your comment. To our knowledge, the only cholesterol absorption inhibitor is Ezetimibe. This section in the scope is listing the areas that are included in the update. TA132 is listed under Related NICE guidance in section 5.1.2 using standard NICE format. Following consultation, it has been determined that TA132 (Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia) does not meet criteria for updating in the

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					context of a clinical guideline. NICE has therefore decided it will be updated as a technology appraisal.
SH	Royal College of Nursing	3	4.3.1 e	The frequency of monitoring of cholesterol levels should be included.	Thank you for your comment. This will be considered during the development phase of the guideline.
SH	Royal College of Paediatrics and Child Health	1	General	The Royal College of Paediatrics and Child Health...have not received any responses to comment on this scope.	Thank you for your comment.
SH	Royal College of Psychiatrists	1	General	NICE need to be reminded that adverse events that need to be considered include Mental Health issues (such as a reported increase in suicidal ideation in people on lipid lowering drugs).	Thank you for your comment. 'People with serious mental illness' have now been added to the scope as a special group that will be considered.
SH	Royal Pharmaceutical Society	1	general	The Royal Pharmaceutical Society is disappointed that the role of the community pharmacist will not be covered in these guidelines. The scope omits information on how the community pharmacist can assist in the management of cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease. As the first point of contact for many potentially at-risk patients, we believe community pharmacists to be appropriate implementors of the vascular risk assessment and identification programmes. Pharmacists are adept in identifying alarm symptoms that warrant the patient being referred to their GP, and are on hand to provide appropriate	Thank you for your comment. We acknowledge the important role that community pharmacists play in vascular risk assessment and in providing advice to patients. NICE clinical guidelines do not generally make recommendations about who should deliver a service as this needs to be decided according to local circumstances and professional competencies.

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				lifestyle advice to help patients manage their condition and to prevent adverse complications. Equally, community pharmacists can offer patients medication use reviews (MURs) and additional advanced services (e.g. New Medicine Service), which provide an opportunity to assess medicine adherence. As experts in medicine, pharmacists can offer advice on how to take medicine, raise patients' awareness of possible side effects and cautions, and where appropriate, reinforce information and increase understanding of the patient's condition and therapy, to meet their specific needs. Many pharmacists have also played a critical role in the provision of the NHS Health Check service which has improved patient access to CVD screening, advice and information, brief interventions and provided a system of recall and referral.	
SH	Unilever UK/Ire	1	1.3.6	Our comments are as follows, we are concerned by the potential opportunity for misinterpretation of the plant stanols and sterol recommendation. In isolation from any other information about plant sterols and stanols in this section, the wording does not draw distinction between the primary prevention of CVD and raised cholesterol, which could lead healthcare professionals to conclude that plant sterols and stanols simply should not be recommended for either. Research recently conducted by Opinion Health about the interpretation of this set of NICE Guidelines amongst 150 GPs and nurses [1] reinforces this concern. Consistent with the Guidelines, only 30.7% stated they would recommend plant sterols and stanols for the primary prevention of CVD. However, when asked in relation to lowering cholesterol, only 42% reported that they would recommend plant sterols or stanols. Of those	Thank you, your comment refers to the published NICE guideline CG67 on Lipid modification, and not to the draft scope for the update of the guideline. It is part of our scope to review the evidence for stanols and sterols and update this section of the guideline. We will conduct a systematic review of the literature about stanols and sterols. The remit for the guideline is the primary and secondary prevention of

[1] Opinion Health Survey of 150 GPs and nurses, 4th July 2012

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				that said they would not recommend, 47% stated this was because NICE Guidelines did not recommend their use, which clearly demonstrates the potential for misinterpretation, given no such direction has been explicitly given. The influence of the NICE Guidelines is far reaching and the statement not to routinely recommend plant sterols and stanols, is quoted, often out of context, on a number of third party websites including www.patient.co.uk and www.bhf.org.uk. In addition, the research also highlights the possible confusion around the term 'primary prevention of CVD'. When asked to rate a number of risk factors on a scale of one to five, where one is a low risk and five is a high risk, 89%[2] of our sample of 150 GPs and nurses rated raised cholesterol the highest scores of four or five. We therefore would ask that the recommendation is changed to include the additional end point that plant sterols and stanols are beneficial for lowering cholesterol. [1] Opinion Health Survey of 150 GPs and nurses, 4th July 2012 [2] Opinion Health Survey of 150 GPs and nurses, 4th July 2012	cardiovascular disease and the preference in making recommendations for the NHS is reduction in morbidity and mortality rather than lowering cholesterol.
SH	Unilever UK/Ire	2	4.2	Our comments are as follows, the wording of this section; *'Plant sterols and stanols have been shown to reduce cholesterol levels, but it is not known whether the consumption of plant sterols as part of a low-fat diet will provide worthwhile additional benefit and whether they reduce CVD events.'*	Thank you, your comment refers to the published NICE guideline CG67 on Lipid modification, and not to the draft scope for the update of the guideline.

[2] Opinion Health Survey of 150 GPs and nurses, 4th July 2012

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				underplays the robust body of clinical evidence that conclude the cholesterol lowering benefits that can be derived by taking plant sterols and stanols as part of a healthy diet and lifestyle. Research recently conducted about the interpretation of this set of NICE Guidelines amongst 150 GPs and nurses[3] revealed that 84.15% attributed their inability to recommend plant sterols or stanols for the lowering of cholesterol to the insufficient clinical evidence to show they work. Yet the cholesterol-lowering efficacy of plant sterols is proven and undisputed with over 120 studies showing that plant sterols and stanols significantly lower cholesterol. A daily intake of 2g plant sterols or stanols results on average in a 10% cholesterol lowering. There is a sustained LDL-cholesterol lowering effect with long-term use. Several clinical trials have also evaluated the cholesterol-lowering efficacy of plant sterols and stanols on top of a healthy diet and concluded that the cholesterol-lowering effect of plant sterols and stanols is additive to that of a healthy diet. The overall reduction in LDL-cholesterol that can be achieved from the combination of these two dietary approaches can be expected to be in the range of 10-15% and even more.[4] Further more, in May 2012, EFSA's expert panel upon reviewing the scientific evidence positively concluded that: 'plant sterols and stanol	The remit for the guideline is the primary and secondary prevention of cardiovascular disease and when making recommendations for the NHS our preference is for effects on morbidity and mortality rather than on cholesterol lowering effects.

[3] Opinion Health Survey of 150 Healthcare Professionals, 4th July 2012

[4] Katan MB, Grundy SM, Jones P, Law M, Miettinen T, Paoletti R for the Stresa Workshop Participants. Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. Mayo Clin Proc 2003; 78:965-978.

[5] Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies

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				esters at a daily intake of 3g (range 2.6 - 3.4g) lower LDL-cholesterol by 11.3 % (95% CI: 10.0 – 12.5).' [5] We therefore would ask that this section is reworded to communicate the following: 'There is a strong body of evidence that shows consumption of plant sterols and stanols as part of a low-fat diet can significantly reduce cholesterol and even have an additive effect to a healthy diet. High cholesterol is a key modifiable risk factor for the development of CVD.' [1] Opinion Health Survey of 150 Healthcare Professionals, 4th July 2012 [4] Katan MB, Grundy SM, Jones P, Law M, Miettinen T, Paoletti R for the Stresa Workshop Participants. Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. Mayo Clin Proc 2003; 78:965-978. [5] Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies	
SH	University of Nottingham	1	4.3.1	QRISK2 has been developed for use in patient with diabetes as well as patients without diabetes. It has a variable for type 2 diabetes which allows this distinction. QRISK should therefore be included in (a) and also in (b) for people with diabetes	Thank you, we agree with your view and we have added QRISK to the list of assessment tools for people with and without diabetes.
SH	University of Nottingham	2	4.3.1	There is no reference associated with The epic-norfolk Cambridge diabetes score ios this the work by Rhaman etc al If so, then this is a score which predicts risk of diabetes in patients without diabetes. http://fampra.oxfordjournals.org/content/25/3/191.abstract There has been a paper in 2010 to test whether the Cambridge diabetes score can predict risk of CVD in patients aged 40-74 FREE of diabetes and CVD at baseline. This study which was published in the BJGP	Thank you for your comment, we have now removed the epic-Norfolk Cambridge diabetes score from the list of assessment tools in the scope.

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				although the validation results were worse than Framingham. For example, the ROC for the Cambridge risk score was 0.72 compared with 0.77 for Framingham. http://www.ingentaconnect.com/content/rcgp/bjgp/2010/00000060/00000577/art00002 This BJGP paper did not look at CVD risk in patients WITH diabetes so does not appear relevant here.	
SH	University of Nottingham	3	4.4 d	Please note the publication of QRISK lifetime in the BMJ http://www.bmj.com/content/341/bmj.c6624.full	Thank you for your comment.