Risk estimation and the prevention of cardiovascular disease

COMMENTS RECEIVED FROM EXTERNAL REFEREES AND OTHERS

Invited reviewers:			**Declared Interests**
AA	Professor Annie Anderson	Professor of Public Heath Nutrition, University of Dundee, Dundee	None
BHFNC		British Heart Foundation National Centre, Loughborough	Kim Buxton, Assistant Director (commenting on behalf of)
CB	Professor Colin Baigent	Director, MRC Population Health Research Unit, University of Oxford, Oxford	Non-personal support from commercial healthcare companies – I was chief investigator of the SHARP trial that compared ezetimibe plus simvastatin vs placebo in patients with Chronic Kidney Disease (CKD). The trial was sponsored by the University of Oxford, and funded by a grant from Merck & Co, Inc.
MC	Ms Marissa Collins	Researcher in Health Economics, Glasgow Caledonian University, Glasgow	None
AD	Dr Andrew Docherty	Consultant Cardiologist, Wishaw General Hospital, Glasgow	None
FD	Professor Francis Dunn	Consultant, Stobhill Hospital, Glasgow	None
JE	Ms Jennifer Elliott	Specialist Nurse, Education and Research, Heart Manual Department, Astley Ainslie Hospital, Edinburgh	None
MH	Professor Mark Hamer	Chair in Exercise and Medicine, Loughborough University, Loughborough	None
AH	Professor Anthony Heagerty	Professor of Medicine, The University of Manchester, Manchester	None
AK	Dr Andrew Keen	Consultant Health Psychologist, NHS Grampian, Aberdeen	None
JL	Dr Jim Lewsey	Reader in Medical Statistics, University of Glasgow, Glasgow	None
JLo	Professor Julie Lovegrove	Director of Hugh Sinclair Unit of Human Nutrition and Deputy Director for the Institute for	Non financial interests – I am a Committee member on UK Scientific Advisory

		Cardiovascular and Metabolic Research, University of Reading, Reading.	Committee on Nutrition (SACN) and Saturated Fats Working Group for SACN.
IMac	Dr Isla Mackenzie	Clinical Reader in Clinical Pharmacology, University of Dundee and Ninewells Hospital, Dundee	Remuneration from employment – Employee of University of Dundee. Remuneration from consultancy or other fee paid work – I have received consultancy payments from MSD more than 12 months ago and AZ in the last 12 months. Non-financial interests – RCPE council member, member of FPM board, SHARP committee member and trustee, honorary secretary of SSP, former member of executive committee of BHS. Non-personal support from commercial healthcare companies, organisations – My university has received grants from several pharmaceutical companies to support research including Menarini, Ispen, Teijin, Pfizer, Novartis, Amgen.
SMcC	Dr Stephen McCabe	GP principal, Portree Medical Centre, Portree	None.
LMc	Ms Louise McCombie	Research Associate, University of Glasgow, Glasgow	Remuneration from consultancy – Counterweight Ltd.
ZM	Professor Zosia Miedzybrodzka	Professor of Medical Genetics, University of Aberdeen, Aberdeen	Remuneration from consultancy or other fee paid work - I have spoken at meetings of Scottish Lipid forum which is sponsored by a number of pharmaceutical companies. I have been in discussion with several companies regarding research funding.
OM	Mr Owen Moseley	Senior Health Economist, Healthcare Improvement Scotland,	None

		Glasgow	
MM	Professor Marie Murphy	Chair of Exercise and Health, Ulster University, Newtonabbey, Co Antrim, Northern Ireland	None
NM	Professor Nanette Mutrie	Professor of Physical Activity for Health, University of Edinburgh, Edinburgh	None
SP	Professor Stuart Pringle	Consultant Cardiologist, President Scottish Cardiac Society, Perth Royal Infirmary, Perth	Non-financial interests - I am President of the Scottish Cardiac Society which receives un-conditional educational grants in the form of sponsorships for the Spring and Autumn Meetings which are purely for education and training. The Sponsors have no influence on the contents of the meetings.
MS	Ms Marie C Shankland	Clinical Psychologist, NHS Education for Scotland, Glasgow	None
JSh	Dr John Sharp	Consultant Clinical Psychologist, Golden Jubilee National Hospital, Glasgow	None
WS	Dr William Simpson	Consultant Chemical Pathologist, NHS Grampian, Aberdeen	Remuneration from consultancy or other fee paid work – 2016: Honorarium for chairing Advisory Board for Sanofi. Non-personal support from commercial healthcare companies – Over the past five years, have eceived meeting expenses (MSD, Sanofi) and unrestricted grants to fund educational meetings (AZ, MSD, Sanofi).
JS	Dr John Stout	General Practitioner, Peterhead Health Centre, Peterhead	Remuneration from employment – received travel expenses & fees from several big pharma companies. Remuneration from consultancy – received travel expenses & fees from several big pharma companies as well as being on project boards.
VS	Dr Vivien Swanson	Reader in Health Psychology,	None

		University of Stirling, Stirling	
SW	Professor Sarah Wild	Professor of Epidemiology/Honorary Consultant in Public Health	Remuneration as holder of paid office - Other than declared job title as honorary consultant of NHS Health Board
DW	Professor David Williams	Consultant in Stroke Medicine, Royal College of Surgeons in Ireland/Beaumont Hospital, Dublin	Remuneration from consultancy or other fee paid work – I have served on the advisory board for Boehringer Ingelheim, Bayer, Daiichi Sankyo and Bristol Myers Squibb on the safe use of novel oral anticoagulants. I have also served on the advisory board for AMGEN on the use of their novel cholesterol lowering agent (PCSK9 agent).
TY	Dr Thomas Yates	Reader in Physical Activity, Sedentary Behaviour and Health, University of Leicester, Leicester.	None

Open consultation:			
AAv	Professor Alison Avenell	Clinical Chair in Health Services Research, University of Aberdeen, Aberdeen	None
Am		Amgen, Uxbridge	Dr David Catterick (commenting on behalf of) Remuneration from employment – I am a paid employee of Amgen and am making this comments on behalf of Amgen the manufacturer of evolocumab (Repatha). Shares and securities – Amgen stockholder.
AZ		Astra Zeneca, Luton	Mr Matthew Larman (commenting on behalf of) Remuneration from employment – employee of Astra Zeneca
JB	Dr Jenny Bennison	General Practitioner, Niddrie Medical Practice, Edinburgh	Remuneration from employment – Vice Chair, SIGN. Remuneration from self

			employment – GP partner at Niddrie Medical Practice, Executive Officer (Quality) RCGP Scotland. Shares and securities – various investments in ISA funds that may include some health associated companies.
IB	Dr Izabela Bodzioch	Consultant Physician, Lorn and Islands Hospital, Oban	None
JBu	Professor John Buckley	Professor of Applied Exercise Science, University Centre Shrewsbury, University of Chester	Remuneration from self employment – Movement Education Training Consultancy (METs) – providing advice and educational teaching in the area of Physical Activity and Exercise Science to associations and health service providers. Remuneration from consultancy or other fee paid work – Consultancy lecturing and advice from time to time to Office Furniture companies or exercise science equipment companies, who may also support research projects.
ND	Mrs Noreen Downes	Principal Pharmacist, SMC, Glasgow	None
IG	Dr Ian Godber	Consultant Clinical Scientist/Lead Clinician Scottish Clinical Biochemistry Managed Diagnostic Network, NHS Lanarkshire, Airdrie	None
BI		Boehringer Ingelheim	Dr Emma Forsyth (commenting on behalf of) Remuneration from employment - I work for Boehringer Ingelheim (the pharmaceutical company who makes empagliflozin) Remuneration as holder of paid office - I work for Boehringer Ingelheim (the pharmaceutical company who makes empagliflozin)

			Non-personal support from commercial healthcare companies - I work for Boehringer Ingelheim (the pharmaceutical company who makes empagliflozin)
Bin		Boehringer Ingelheim	Dr Will Spencer, Therapy Area Lead Diabetes (commenting on behalf of) No DOI.
SJ	Dr Scott Jamieson	General Practitioner, Kirriemuir Medical Practice, Kirriemuir	Non-financial interests – RCGP Scotland Council Member
EL	Dr Elspeth Lee	Health Improvement Specialist, NHS Highland, Inverness	Remuneration from employment - NHS employee - prevention work around alcohol, primarily in supporting delivery of Alcohol Brief Interventions, and meeting Scottish Government targets for ABIs (unclear if this is relevant or if just commercial work needs recording, sorry).
Sa		Sanofi, Guildford	Ms Tania Whittern (commenting on behalf of)
SMac	Dr Suzanne MacKenzie	Consultant Chemical Pathologist, NHS Ayrshire & Arran, Kilmarnock	Remuneration from consultancy or other fee paid work – received honoraria from AZ and Sanofi. Non-financial interests – Co-chair of the Scottish Lipid Forum. Non-personal support from commercial healthcare companies – The Scottish Lipid Forum has received financial support for educational activities from Sanofi, AZ, MSD, Akcea, Amgen & Mylan.
WP	Dr Werner Pretorius	Consultant Liaison Psychiatrist, Western General Hospital, Edinburgh	Remuneration from employment – I have delivered a talk on diabetes mental health for Janssen and am due to deliver similar talks for Lilly for payment.
RCPE		Royal College of Physicians, Edinburgh	Ms Lindsay Paterson (commenting on behalf of)

RCPS &G		Royal College of Physicians and Surgeons of Glasgow, Glasgow	None.
Guideline group members			
LMc	Mrs Lindsay McKechnie	Cardiac/Respiratory Dietetic Clinical Team Lead, NHS GGC, Glasgow Member of SIGN cardiac rehabilitation guideline group	None

Section	Comments received		Development group response
General			
	MC	Deprivation is a factor in CVD prevalence in section 1 but then not mentioning it again in the rest of the guideline. I wonder if a separate section on deprivation and the issues with this in targeting those in more deprived areas would be useful given incidence and prevalence is higher in this group.	*While deprivation is an independent risk factor for CVD, its impact is accounted for through the use of a risk score which incorporates a risk weighting specifically for Scotland (ASSIGN). Treatment of risk is identical across all socioeconomic groupings.* *Epidemiological evidence suggests that there is no difference in the proportion of men in Scotland (with diabetes) receiving statins for primary prevention by socioeconomic level. A greater proportion of women from deprived cohorts receive statins compared with women from affluent cohorts. In the UK, statin initiation increases very slightly with increasing deprivation.* *Jones NR, Fischbacher CM, Guthrie B, Leese G, Lindsay RS, McKnight JA, Pearson D, et al; Scottish Diabetes Research Network Epidemiology Group.* *Factors associated with statin treatment for the primary prevention of CVD in people within 2 years following diagnosis of diabetes in Scotland, 2006-2008. Diabet Med. 2014 Jun;31(6):640-6* *http://onlinelibrary.wiley.com/doi/10.1111/dme.12409/full* *O'Keeffe AG, Petersen I, Nazareth I.* *Initiation rates of statin therapy for the primary prevention of cardiovascular disease: an assessment of differences between countries of the UK and between regions within England. BMJ Open. 2015 Mar 6;5(3)* *http://bmjopen.bmj.com/content/5/3/e007207.long*
	JL	In the acknowledgements (p76) please also add Kathleen Boyd as she was also involved in supervising the work on risk estimation. "Dr Kathleen Boyd Institute of Health and Wellbeing, University of Glasgow".	*Agreed – these have been added*

		Please could you also add the Institute of Health and Wellbeing to Andrew Briggs and my addresses.	
	DW	This is a well researched and comprehensive document. It will provide a valuable resource for practicing practitioners in the field. The challenge will be trying to keep the document continually updated.	*Thank you*
	KMac	This is very comprehensive and well written. Thank you. The risk estimation tool is going to be extremely helpful. The use of risk rather than numerical targets will be a significant culture change for some.	*Thank you*
	WP	Please see additional document with comments.	*Thank you – these relate to 'Whole Food Plant Based Diet for Type 2 Diabetes' and are therefore not directly relevant for this guideline.*
	RCPE	The College agrees that this is a comprehensive, well written document which addresses the risk factors associated with vascular disease and the evidence for intervention.	*Thank you*
	BI	The Boehringer Ingelheim & Eli Lilly Diabetes Alliance (The Alliance) would like to draw the committee's attention to the recent landmark EMPA-REG OUTCOME trial in patients with type 2 diabetes which is of relevance to the document under review: *Zinman B et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28. doi: 10.1056/NEJMoa1504720. Epub 2015 Sep 17. [Link to PubMed abstract]* Having read through your guideline, I couldn't see a place where we could slot in our comments regarding empagliflozin (as there is no specific section on diabetes as a risk factor, or a category looking at secondary prevention per se) - hence my including these comments in the "general comments" section - I hope that is OK. I realise that diabetes is not covered in this guideline as it has its own dedicated SIGN guideline. This trial demonstrated that patients with type 2 diabetes at high risk for	*The general management of diabetes and glucose lowering agents are not considered in this guideline. They are covered in the revision to SIGN 116 which is currently in progress.*

		cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome (CV death, non fatal MI and non fatal CVA) and of death from any cause when the study drug was added to standard of care. The results for EMPA-REG OUTCOME confirmed a 14% relative risk reduction in the 3 Point MACE over a median follow-up period of just over 3 years. This was driven by a 38% relative risk reduction in cardiovascular death. In addition there was a 32% relative risk reduction in all-cause mortality and a 35% relative risk reduction in hospitalisation for heart failure. We would also like to point out that empagliflozin is the only oral glucose lowering agent in a completed dedicated cardiovascular trial to have demonstrated superiority in the primary composite cardiovascular endpoint. Studies involving metformin have demonstrated some cardiovascular benefit in historical studies, however, it should be noted that this was not in a prospective dedicated cardiovascular outcome trial of the design, size and robustness of EMPA-REG OUTCOME. It should also be noted that these results cannot be extrapolated across the SGLT2i class until the other class members' cardiovascular outcome trials report in the coming years and that it is empagliflozin alone that has thus far demonstrated this important effect for patients with type 2 diabetes.	
	RCPS&G	We are writing to say that we would like to express our general support for the guidance.	*Thank you*
	FD	"For '**strong'** recommendations on interventions that '**should**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more good than harm. For **'strong'** recommendations on interventions that **'should not'** be used, the guideline development	

		group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good. For '**conditiona**l' recommendations on interventions that should be '**considered**', the guideline development group is confident that the intervention will do more good than harm for **most** patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient" There seemed to be a slight mismatch between the above and the terminology use within the text. "Should be considered" seems clear enough but is there a difference between " should be offered" and "should have" which are both used within the text recommendations. In addition the word "may" and term "should be recommended for treatment" are used. It would, I feel, be good to have clarity in this regard. My own preference would be for "Should be offered" for strong recommendations and "should be considered" for conditional recommendations. This is indeed what is happening in most of the recommendations. I particularly like the term "should be offered" since it respects the patient's autonomy. May I especially commend the authors on three outstanding sections: cardiovascular risk assessment, psychological issues, and physical activity? Overall this is an excellent guideline and I would be happy to input further or expand on my comments as needed.	*Agreed. The recommendations have be harmonised, where possible, to "should be offered" for strong recommendations and "should be considered" for conditional recommendations. However, to preserve the full potential for a range of different meanings, not all recommendations may have identical wording.* *Thank you*
	JB	Excellent guideline. It will be an invaluable resource in primary care and elsewhere.	*Thank you*
	JE	Clear and understandable.	*Thank you*
	JS	Well set out. Clear & concise.	*Thank you*
	SP	This is an excellent guideline. It is comprehensive and should provide a first class "operating manual" which will be of enormous help to all	*Thank you.*

		cardiovascular professional groupings involved in heart disease treatment and prevention.	
		I wonder if the title is set in stone. The "risk estimation" part might put some people off. I think this might be relevant anyway but is particularly so when it has been decided that further work is required before deciding on fixed risk threshold, capacity to benefit measures or age-differentiated threshold. As it stands therefore it is mainly about the recommendations about prevention of cardiovascular disease rather than risk estimation. Furthermore, it is not really all cardiovascular disease. It is atherosclerotic cardiovascular disease – there are very many other cardiovascular conditions e.g. valvular, structural, cardiomyopathic, congenital, etc which are not relevant to this guideline but are still cardiovascular disease – not all spotty dogs are Dalmations.	*Disagree. Following discussion the GDG decided that the title will be retained as the guideline still contains extensive discussion of CV risk and recommendations on risk estimation and current thresholds for intervention. "Risk estimation and the Prevention of cardiovascular disease".* *There are many definitions of CVD and so the specific type of vascular damage has not been defined for the literature searches, therefore we will not include reference to a subtype of disease in the guideline title.* *The definition of CVD was not altered from the previous version of the guideline.*
		I liked the section at the beginning explaining the difference between absolute and relative risk and that is very clear. However there are frequent references to hazard ratios which is not defined at the beginning and I think is a more difficult concept as a risk over a given period of time. Mortality is 100% for all of us. If the hazard ratio is 1.20 what does that actually mean in terms of life expectancy and number of years free of heart disease? What should healthcare workers say to their patients about the benefit for a given intervention if it improves their hazard ratio? Unless I have missed it somewhere this is not clear in the guideline.	*Thank you.* *SIGN guidelines do not routinely explain the definition of statistical terms unless it is a customised term with limited familiarity.* *A mortality hazard ratio of 1.20 would define the relationship between two groups in terms of their mortality over a defined period. In this case, one group would have a 20% greater rate of death compared to the other within that period. Hazard ratio is a measure of relative risk, whereas changes in life expectancy and years free of disease are absolute measures.*
		What a pity the decision on threshold versus lifetime risk has been deferred but I can understand why it has been. I do hope a decision will be made soon which will complement this excellent guideline. Professor Sattar and his colleagues on this guideline development group are to be congratulated on bringing this Opus Magnus to such a successful conclusion.	*Noted, and agreed.*

	MM	Please consider an additional section on cardiorespiratory fitness as an independent risk factor. This has a stronger evidence base that sedentary behaviour and is important given your inclusion of high intensity exercise. In addition the role of walking as a population level intervention for CVD prevention is now clear and could be featured as the cornerstone of physical activity promotion. I am happy to provide information on either of these two issues if required	*The evidence base on fitness as a risk factor is strong, but is difficult to measure in practice. There is limited evidence that it independently predicts CVD risk in isolation from other physical activity factors.* *Noted - We have included further information on walking in section 6.1.*
	BIn	The Alliance would like to draw the committee's attention to the recent landmark EMPA-REG OUTCOME trial in patients with type 2 diabetes which is of relevance to the document under review: *Zinman B et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28. doi: 10.1056/NEJMoa1504720. Epub 2015 Sep 17. [Link to PubMed abstract]* This trial demonstrated that patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome (CV death, non fatal MI and non fatal CVA) and of death from any cause when the study drug was added to standard of care. The results for EMPA-REG OUTCOME confirmed a 14% relative risk reduction in the 3 Point MACE over a median follow-up period of just over 3 years. This was driven by a 38% relative risk reduction in cardiovascular death. In addition there was a 32% relative risk reduction in all-cause mortality and a 35% relative risk reduction in hospitalisation for heart failure. Empagliflozin is the only oral glucose lowering agent in a completed dedicated cardiovascular trial to have demonstrated superiority in the primary composite cardiovascular endpoint. Studies involving metformin have demonstrated some	*The general management of diabetes and glucose lowering are not considered in this guideline. They are covered in the revision to SIGN 116 which is currently in progress.*

		cardiovascular benefit in historical studies, however, it should be noted that this was not in a prospective dedicated cardiovascular outcome trial of the design, size and robustness of EMPA-REG OUTCOME. It should be noted that these results cannot be extrapolated across the SGLT2i class until the other class members' cardiovascular outcome trials report in the coming years and that it is empagliflozin alone that has thus far demonstrated this important effect for patients with type 2 diabetes.	
	VS	Overall the draft is clearly written in a style relevant for the target audience. I did spot a few typos which I'm sure will be edited before publication.	*Thank you*
	SJ	I'd consider postponing publication until we have a CV risk assessment tool to take into account the number of life years to be gained by a therapy. The title of the whole guideline is on risk estimation and prevention and without a suitable tool, the rest of the guideline feels like window dressing.	*Noted. As it cannot be predicted if or when the work to develop a new risk tool may complete, the guideline will be published with the current thresholds for preventive treatment in place, based on the evidence included in the guideline.* *As the guideline retains recommendations for risk estimation, the title will not change.*
Section 1			
General	AA	Suggests that diet change accounts for CVD reduction but there has been no significant change in diet in the last two decades (see FSA/FSS monitoring by Barton et al). Changes in smoking should be mentioned first anyway. I'd hate anyone to get complacent about diet change. Surely preventive drug regimens more important?	*Agreed. Sentence has been modified.* *We assume this is the following paper* *"Estimation of food and nutrient intakes from food purchase data in Scotland 2001-2012. Food Standards Scotland, Wrieden and Barton, 2015)* *This shows "little progress towards meeting the [Scottish Dietary] goals over the period 2001 to 2012. This was apparent even amongst households in the least deprived areas." A comment on this finding has been added to section 5.*
1.1	MC	I think this could be restructured to be a bit clearer. I would also move paragraph 4 - "Cardiovascular disease has a multifactorial aetiology...." to before the paragraph starting "Recent estimates of disease incidence..." And I would move paragraph 5 to start after paragraph 2 and so keeping the two paragraphs which mention deprivation together - I also think this should be upfront as it is an important	*Agreed. Paragraphs have been reordered.*

		issue for CVD prevalence. Is it appropriate to use personal communication for a guideline? Also the second last paragraph is a bit confusing when talking about scoring approaches to estimate absolute risk, I would maybe trim this down and take out the scoring systems sentence as it's not clear what this is in this context.	 *The personal communication is due to citing a customised report which was carried out by ISD on behalf of SIGN but which is not specifically available in that format from their website.* *This paragraph has been retained verbatim from the previous version of the guideline.*
	FD	No change.	*Thank you*
	OM	Very minor point but should 'between 2005/6 be 2014/5' (3rd para).	*No, these data are accurate.*
	NM	I am confident that the early sections are all completed with up to date knowledge and are correctly introduced.	*Thank you*
	DW	This is well covered. While the incidence of CVD is falling the prevalence may increase due to an ageing population.	*Thank you*
	ZM	Guideline and its place welcome	*Thank you*
	WP	Essential	*Thank you*
	RCPE	The College agrees that this is a comprehensive, well written document which addresses the risk factors associated with vascular disease and the evidence for intervention.	*Thank you*
	AH	I am sure that there is a definite need for a guideline that addresses cardiovascular disease prevention measures.	*Thank you*
	JB	Clear and helpful.	*Thank you*
	SW	Remove "sex" from "Between 2005/6 and 2014/5 the age-sex standardised incidence rate for CVD has fallen by 12% in men and nearly 16% in women"	*Agreed. "Sex" has been deleted.*
	JS	Yes, old guideline outdated. Good fresh guideline.	*Thank you*
	MM	Given my area of expertise - I have limited my comments to the area of physical activity, cardiorespiratory fitness and sedentary behaviour. Given the structure of the subsequent sections I think it is important here to flag PA, fitness and SB in this section. The Framingham index may not have	 *Agreed. References to "physical activity and sedentary behaviour" have been added to this section*

		included this - but given the current evidence and the full section devoted to PA later I think it would be important to include this as a risk factor in this section	
	VS	Although this is explained later in the document, readers may find para 6 on page 5 confusing. In particular 'most CVD cases occur in the large number of individuals at lower levels of absolute risk'.	*Disagree. This is retained from the previous version of the guideline and has not been linked to confusion.*
	LMc	Ok	*Thank you*
	SJ	Could possible confusion arise in use of the word "thrombosis" where in general medical terms this commonly refers to venous thromboembolism? It is technically medically correct, but it doesn't read well and may cause momentary confusion. The second paragraph refers to the direct effect on the majority of the Scottish population. However there is no statistic to back this up. Indeed it then says it's only a fifth and that the rates are dropping. Again, it is correct it will affect most but none of the data given demonstrates that.	*Noted. No change required.* *Agreed. Although this was retained from the previous version of the guideline, without evidence it is not robust and has been revised.*
1.1.1	FD	No change.	*Thank you*
	WP	Good to see dietary advice formalised, but noticed no reference to the effects of whole food plant based diet, which has been demonstrated in population-based studies to reduce risk of obesity, diabetes and ischaemic heart disease. Work by Dean Ornish & Calwel Esselstyn has also demonstrating reversal of coronary artery disease.	*This was not a key question that was considered in this update. SIGN would need to do another systematic review on this. The guideline group has discussed the issue and believes that it is one of several dietary patterns which could be investigated, though not the most important.*
	JLo	The committee should be commended on a comprehensive report covering diverse modulators of risk.	*Thank you*
	AH	My criticism is that certainly with regard to hypertension management, the evidence has not been updated and in consequence the guideline is still behind the times.	*Disagree, we have reviewed and included meta-analyses up to the search threshold cutoffs. We have not incorporated individual primary studies as evidence, although have added a comment on the important SPRINT trial.*
	JB	Clear.	*Thank you*
	JS	Pragmatic and useful.	*Thank you*
	LMc	Ok	*Thank you*
1.2.1	FD	No change.	*Thank you*

	DW	Clear and well described.	*Thank you*
	WP	Good	*Thank you*
	JS	States current thinking & advice.	*Thank you*
	LMc	Ok	*Thank you*
	SJ	Should we define what an 'event' may include to differentiate primary and secondary prevention? Obviously MI/CVA. But would retinal arterial occlusion count? Where does PVD drift from being primary to secondary prevention?	*Agreed – "event" has been clarified.*
1.2.2	FD	No change.	*Thank you*
	DW	Appropriate target audience.	*Thank you*
	SMac	And lipidologists!!	*Agreed –added*
	WP	Primary & Secondary care – ideally public health	*Agreed – 'public health' added*
	JB	Strange order - cardiologists, dietitians, GPs. GPs do all but the initial prescriptions and often the referrals for lifestyle MX etc so I would argue we should be top of the list	*It is in alphabetical order. It is not possible to create a non-alphabetical order that will satisfy everyone.*
	JS	GPs, practice nurses, cardiologists many branches of medicine.	*Thank you*
	LMc	Ok	*Thank you*
1.3	FD	No change.	*Thank you*
	DW	Appropriate to refer as much as possible to 'absolute risk'	*Thank you*
	JB	Really clear explanation	*Thank you*
	JS	Fairly clear advice.	*Thank you*
	LMc	Ok	*Thank you*
1.3.1	MC	What is 'Absolute Risk' based on, what risk factors and/or demographic characteristics?	*While the definition in this paragraph is reasonable, we have added further details of the risk factors which traditionally constitute risk calculators.*
	FD	No change.	*Thank you*
	DW	Appropriate to refer as much as possible to 'absolute risk'	*Thank you*
	JB	Clear	*Thank you*
	JS	Good.	*Thank you*
	SP	Hazard ratios are referred to in review of the evidence - should they be defined and put in context - I am thinking particularly about some of the evidence of risk being expressed as hazard ratios - the impact on longevity and health gain over a set period may	*SIGN guidelines do not routinely explain the definition of statistical terms unless it is a customised term with limited familiarity.*

		need explained	
	LMc	Ok	*Thank you*
	SJ	Given everyone is at risk of a CVD event, I cannot see the utility in providing a relative risk... so showing any comparison to a person with 'no risk' is pointless...	*To help motivate patients, physicians may present a comparative risk for a person of the same age and sex who has no major risk factors, as well as the relative and absolute benefits of risk-reducing therapies. This allows for estimation of the total risk reduction that can be achieved by single interventions or by a combination of therapies.*
1.3.2	MC	Would be good to have a bit more explanation of what ASSIGN is and what risk factors/characteristics it considers to calculate a risk score.	*These are listed in section 1.3.1 and a cross reference to section 3 has been added.*
	FD	No change.	*Thank you*
	DW	It might be worth outlining how the ASSIGN algorithm compares with other risk tables such as Framingham.	*This is included in section 3.3*
	JB	Clear	*Thank you*
	JS	Pragmatic (accepting higher risks in Scottish population).	*Thank you*
	LMc	Ok	*Thank you*
Section 3			
3.1	FD	No change.	*Thank you*
	DW	This is covered well - no further comments.	*Thank you*
	JB	Good summary	*Thank you*
	JE	Appropriate recognition of Hypertension as a key modifiable risk factor and concept. eg global cardiac risk.	*Thank you*
	AA	Should 3.1 mention genetics (non-modifiable) as well as age and gender?	*Agreed. Genetics added and 'gender' changed to 'sex'.*
	CB	It would be helpful to make clear which risk factors are causal, since describing a risk factor as 'modifiable' is really only coherent for a causal risk factor.	*Agreed. We have added references to causality.*
	JS	Might have mentioned other conditions, eg gout, IBD, etc	*Disagree. The major risk factors are included.*
	JSh	The INTERHEART study used an exceptionally crude and flawed measure to assess the impact of 'psychosocial factors' which likely underestimates the influence of depression and to a lesser extent anxiety. The reliance on one, albeit "large N" paper, to identify risk factors	*As a selective update, this update did not seek to identify new risk factors, and we believe the major risk factors have been identified. This section includes a statement about psychosocial factors being relevant to CV risk.*

		seems somewhat reductive. A more accurate appraisal and summary of the individual risk factors could be accomplished by reviewing the specific literature associated to each. For example, there is a relatively decent literature demonstrating depression as an independent risk factor.	*Further details of the psychosocial factors linked with CVD and their magnitude are included in section 12.*
	LMc	Ok	*Thank you*
	SJ	Are there different risk factors important to a Scottish population? If they are the same we should say so, if there are data showing the important factors for the Scottish population this should be mentioned here.	*Agreed. There is evidence that CVD risk factors do not differ widely across populations (though their relative contributions to risk may). We have added a comment about this.* *Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013* *Forouzanfar, Mohammad H et al.* *The Lancet 2015;386:(10010): 2287–2323*
3.2	MC	I am not sure why a risk score calculate from a Caucasian cohort would be used on a Chinese population. I would take this sentence out. I think the suggestion is that there aren't appropriate risk measures for different ethnic groups, if this is the case I would suggest making this clearer.	*This is not the intended meaning and this sentence was retained from the previous guideline version.* *The intention is to show an example of the specificity of risk calibration. To clarify this, "For example" has been added.*
	FD	No change.	*Thank you*
	DW	This is covered well - no further comments	*Thank you*
	JB	Excellent	*Thank you*
	SW	Replace "Caucasian" with "white European"	*Agreed. Terminology has been changed*
	JS	Clear differentiation between absolute and relative and why most benefits from highest risk individuals.	*Thank you*
	LMc	Ok	*Thank you*
	SJ	It is hard to understand why CVD mortality is more important than an all-events risk tool - ASSIGN is an all-events risk score. The morbidity of CVD should be considered as much as the mortality. The reason for choosing the former should be clearer.	*This is a misunderstanding – we are saying that CVD is better than CHD as it includes stroke; no need to focus on deaths only. No change required.*
3.2.1	MC	This is clear and is a strong recommendation.	*Thank you*
	FD	No change.	*Thank you*

	DW	Excellent discussion of risk with appropriate examples	*Thank you*
	JB	Good	*Thank you*
	AA	Perhaps a comment here that in under- or overestimation all would benefit from lifestyle advice because the same risk factors are associated with development of several cancers including colorectal, breast and lung.	*Noted, however this is not directly related to cardiovascular risk.* *We have added Lifelong "pharmacological" treatment.*
	CB	There is an error that is repeated on numerous occasions throughout the document: In line 4 it is stated that 'His relative risk falls by a third...', and then similar statements follow. The use of the word 'relative' here is incorrect - his risk fell by a third, and the word 'relative' here refers to the one third reduction, not the risk. That is, there was a one third relative reduction in risk (as opposed to a a 33% absolute reduction). As written, the phrase is not meaningful. (I will draw attention to this elsewhere, but the document needs to be checked for recurrences.) In the second paragraph it does not seem appropriate to 'questionable benefits' - I would suggest deleting here.	*Agreed. Terminology has been revised here and throughout document, where appropriate.* *Agreed. Sentence has been revised to emphasise lifelong risks.*
	JS	Fairly clear.	*Thank you*
	LMc	Ok	*Thank you*
	SJ	Critically the most important part of the whole guideline and rightly holds an emphatic position in these guidelines.	*Thank you*
3.3	MC	This is where ASSIGN is explained which is useful. Suggest taking out the earlier reference to it?	*Disagree. We have added a cross reference from 1.3.2 to this section.*
	FD	No change.	*Thank you*
	DW	This is covered well - no further comments	*Thank you*
	JB	Good	*Thank you*
	SW	Suggest replace "abolished" a large social gradient with "attenuated" and "compliance" with "adherence"	*Agreed. Changes have been made.*
	JS	Fine	*Thank you*
	LMc	Ok	*Thank you*
	SJ	The other downside of ASSIGN of course being the woolly approach when a person is on antihypertensive treatment - moreover an ex-smoker	*Agreed, but there is guidance on the ASSIGN website about using pre-treatment values of BP or adding 20 mm Hg to treated SBP values.*

		where there is the need to incorporate a 'fudge factor' which feels slightly less scientific!	*Agree that the risk for former smokers is a gradient according to number of cigarettes smoked/day and time since cessation. There is information on the ASSIGN website about how to manipulate smoking data most appropriately to reflect smoking status (see http://www.assign-score.com/faqs/)*
3.4	MC	Agree about the need for further work in this area.	*Noted. This has been added to recommendations for research.*
	FD	No change.	*Thank you*
	DW	This is covered well - no further comments.	*Thank you*
	JB	Clear	*Thank you*
	CB	Paragraph 1, line 6 - what does 'less efficient' mean here? It is unclear. Paragraph 7: make clear that in the study described in ref 34, it is the RELATIVE risk of CV death that increased with younger age.	*Agreed. This sentence has been deleted.* *Agreed. We have added "relative".*
	JS	Clear	*Thank you*
	LMc	Ok	*Thank you*
	SJ	"...that this new threshold effectively placed almost all patients in England and Wales"... this was the whole problem. They weren't patients... they were people. By 'patients' we drift into labelling them as having a medical condition. A 10% risk threshold turned the general population into patients. I'd change the word 'patients' to 'people'. I would highlight that the WOSCOPS trial and PROSPER trial both used pravastatin. The section slightly deflates the reader at the end. It so eloquently argues the need for a new way to look at the concept of risk... and then says at the end we know we need to do this but can't. The last paragraph needs to be either higher up or less time spent saying why it needs to change. A huge amount of anticipation has been rested upon this new guideline and the lack of decision on how to estimate the risk will be disappointing to many. This whole concept should be the foundation stone of the new guideline and to not include this is difficult to swallow.	*Agreed. We have changed "patients" to "people".* *PROSPER is already described with pravastatin. We have clarified that WOSCOPS also used a statin.* *Noted. However, there are only two paragraphs around work to update the risk tool. Other discussion in this section emphasises the dominant role of age in CV risk, which is as relevant to those using ASSIGN as any other tool. We believe it should be retained to allow GPs in Scotland to interpret ASSIGN results in the context of a tool which does not calculate age-stratified scores.*

Section 4			
General	RCPE	In Chapter 4 the term 'optimal risk factor levels' should be clarified or amended to 'optimisation of risk factors'.	*Disagree. This term does not appear in section 4, but it appears in section 3 where it is used appropriately. The definition would be "risk factors at optimal levels to minimise CV risk" which is a much longer way to add little useful information. The GDG believes that staff working in the prevention of CVD would understand this without ambiguity.*
4.1	FD	No change.	*Thank you*
	DW	This is covered well - no further comments	*Thank you*
	JB	I would make the 'NOT' bit more prominent for those who don't need risk assessment.	*Agreed. We have formatted the word "not" to CAPS and italics.*
	JE	Appropriate recognition of JBS 3 guideline and lifetime risk	*Thank you*
	ZM	It is good to see that the importance of risk in familial hypercholesterolaemia is recognised, and that risk scoring is not recommended. I feel however that greater prominence should be given to FH and to the importance of genetic testing in risk assessment. "Family based genetic cascade testing should be used to identify individuals at risk of familial hypercholesterolaemia. Guidelines for FH identification are available at..", put in here reference to NICE guideline on this- it's being updated at present so best to check specific reference at last minute	*Thank you. This was not included as a key question and is outside the remit of this guideline therefore we are not able to add a new recommendation in favour of family-based genetic cascade testing.*
	CB	Need to make clear how 'albuminuria' is defined - do you mean micro, macro etc. The statement that stage 3 or greater CKD confers high risk appears to conflict with the text on the elderly in section 3 - many elderly people have CKD stage 3.	*Agree. Changed to "micro- or macroalbuminuria".* *Disagree. The risk is supported by evidence. The subjective issue is whether to initiate treatment in all patients at this level of risk, especially when elderly.*
	JS	Clear	*Thank you*
	JSh	Despite acknowledging 'psychosocial factors' as predictive of risk there is no recommendation that psychological or social issues be routinely assessed nor any guidance on how this could be achieved. As an absolute minimum, there should be some requirement for emotional distress to be routinely monitored.	*Agreed, however the issue of screening for psychological distress is a major topic which this guideline has not addressed.* *We have added a comment to be aware of psychosocial issues during CVD risk assessment.*

		Table 2 could be adapted to include psychiatric history and social support within the clinical history for cardiovascular risk assessment.	
	LMc	Ok; not sure why weight is not included	*This is included in section 4.2.2*
	IB	Previous cardiovascular event - angina included - whereas if not documented on imaging should not be considered as previous cardiovascular event. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. (2016 European Guidelines on cardiovascular disease prevention in clinical practice - page 2330)	*Agreed. We have changed to "established CVD (including previous AMI, ACS, angina, coronary revascularisation and other revascularisation procedures, stroke and TIA, aortic aneurysm, PAD and those with significant plaque on coronary angiography or carotid ultrasound.)"*
	SJ	I wouldn't say all adults >40 should have an assessment of risk - it's not rigid. Maybe a GP and an individual should consider if they wish to assess their risk after discussion regarding the merits of doing such screening. There is no evidenced high quality data referenced showing that screening all adults >40 will improve life-expectancy.	*Agreed. We have changed text to "should be offered risk assessment" rather than mandating this.*
4.2	FD	No change.	*Thank you*
	DW	This is covered well - no further comments	*Thank you*
	JS	Fair	*Thank you*
	MM	I feel strongly that an assessment of physical activity (PA) should be included in Table 2. Items to include in a clinical history for cardiovascular risk assessment. We now have validated tools for assessing PA in a clinical setting e.g. GPAQ and IPAQ and know that the clinician asking about PA is powerful for altering behaviour. Moreover recommending clinicians to ask about PA would also drive the medical education curricula to include PA. This is increasing in most developed countries - and I understand Scotland is one of the UK countries leading the way in this regard. It is more difficult, but not impossible, to assess cardiorespiratory fitness in a	*Noted, however we don't know the direct association between formal measurement of PA and effects on CV risk.* *We broadly agree. We have added text under table 2, similar to the weight box from table 3, indicating that PA is not a risk factor included in the ASSIGN algorithm, but can help to prioritise intervention in those who are not meeting current targets.* *Agreed.*

		clinical setting. The assessment of sedentary behaviour is also possible - however given the strength of available evidence for the association of SB and CVD risk - this is not yet justified.	*Agreed.*
	LMc	Ok	*Thank you*
4.2.1	FD	No change.	*Thank you*
	DW	This is covered well - no further comments	*Thank you*
	LMc	Ok	*Thank you*
4.2.2	FD	"Systolic blood pressure should be measured according to the NICE/British Hypertension Society (BHS) guideline.[39] The mean systolic pressure measured over two separate occasions should be used to calculate risk. In individuals taking antihypertensive medication, if there is no option to record the fact of this treatment, most recently recorded pretreatment value should be adopted " I had to read the above section a few times and feel it should be made more clear what exactly is to be used in calculations.	*Agreed. We have deleted "if there is no option to record the fact of this treatment...."*
	DW	Consider adding Hip-Waist Ratio?	*Disagree. This is of limited benefit above BMI and is far less reproducible.*
	IG	Draft guidance would have a massive impact on the number of $HbA1_c$ tests carried out within Scotland. The NHS Lanarkshire Diabetes MCN published guidance on a pragmatic approach to the diagnosis of diabetes, incorporating the use of HbA1c as a diagnostic test, in 2010 (updated in 2014). This followed the WHO position statement on the use of HbA1c for diagnosis in 2009. Fasting Blood Glucose remains the test of choice in symptomatic and high risk asymptomatic populations in the first instance, followed by an HbA1c in the event of an abnormal result. HbA1c should not be requested as a screening test for Diabetes. An Oral Glucose Tolerance Test remains the diagnostic tool of choice in pregnancy, haemoglobinopathy or where there is increased red cell turnover. The diagnosis of diabetes in asymptomatic individuals should be based on the presence of two abnormal results and	*Noted. We have amended this section to emphasise that screening for diabetes may be achieved using a range of methods. We have cross referred to SIGN 116.*

		can include random or fasting blood glucose and HbA1c. HbA1c remains the test of choice in monitoring the control of established diabetes and should be performed at least annually in this group of people. Most treatments for Type 2 Diabetes can take 6 months to show their maximum therapeutic response hence HbA1c monitoring of treatment should generally be requested no more than twice per year. More frequent monitoring may be required in Type 1 Diabetes.	
	JLo	It was stated that 'weight and body mass index' should be measured when assessing cardiovascular risk. Was consideration given to the measurement of waist circumference as an additional measure, due to its utility in identification of cardio-metabolic risk?	*It was considered, but was removed from a previous version of the guideline. Difficulties in accurately measuring waist size may detract from its practical utility.*
	WS	Table 3, cholesterol: Mention should be made, as for blood pressure in the first line of this table, of the requirement to consider current treatment. Triglyceride should also be measured in the initial random sample; otherwise the accuracy of the HDL-cholesterol cannot be assured (if triglyceride is raised, calculated LDL is inaccurate, however HDL-C is also inaccurate if the triglyceride is markedly raised). Fasting for lipid analysis is always required if that patient's triglyceride had previously been raised. Cholesterol may fall significantly during the acute phase response, so it should only be measured as part of risk assessment in patients who are well. It is unreliable if patients are unwell for any reason.	*Disagree. It is not routinely recommended that individuals already on optimal lipid-lowering treatment are considered for risk estimation and there is no simple rule of thumb to alter "on treatment" lipid results as there is for blood pressure.* *Agreed. We have added triglyceride measurement into this table.* *Disagree. It depends on the definition of "raised"; for marked elevation then we agree; but for modest elevations there is unlikely to be much gain and risk estimation may be better unfasted* *Agreed, however this is more detail than required for this summary box and applies only to a minority of patients.*
	JB	Make the need to record pretreatment blood pressure more obvious	*Agreed, the table now states "In individuals taking antihypertensive medication the most recently recorded pretreatment value should be adopted."*
	SW	Statement that diabetes confers a doubling of risk of CVD is inconsistent with rate ratio of 1.55 given in table 7	*Disagree. Table 7 is for bleeding risks rather than CVD risk. The table title has been clarified.*

		in section 9.2 (and contemporary Scottish data recently submitted for publication). Worth noting that relative risks are higher for type 1 than type 2 diabetes. Should also indicate that WHO recommendations are that two positive results for HbA1c (as well as glucose) are required to diagnose diabetes in people without symptoms.	*Agreed, though we are not differentiating type 1 and 2 diabetes for risk estimation.* *We have revised the section on diabetes to suggest any validated tool may be used for diagnosis.*
	JE	Nice and clear parameters	*Thank you*
	AA	Re prerecorded pretreatment value. How relevant is this is in a women with hypertension diagnosed at 50 well controlled for 15 years?	*Advice from the ASSIGN website is to use the most recent pretreatment value or add 20 mm Hg to the SBP value. We acknowledge that for some individuals, this may be less accurate than others.*
	CB	Diabetes, first paragraph, line 5: 'not recommended' would be better replaced by 'not necessary' Might it be sensible to have a separate box for 'pre-diabetes' to contain the second diabetes paragraph? Rheumatoid arthritis: typo in QRESEARCH. Renal function: GFR should be eGFR. Not all patients with CKD are at increased risk - eg, what about the young?	*Disagree. We do not recommend risk estimation of people with diabetes, so we do not endorse leaving the option.* *This para has been revised.* *Noted – now edited* *Agreed – now edited* *We don't know. CKD confers increased risk irrespective of age. The interaction between age and other vascular risk factors may lead even younger patients to be at increased risk compared with non-CKD peers.*
	JS	Important	*Agreed*
	JSh	How are the 'psychosocial factors', recognised earlier within the document as predictive of risk, measured? Minimum should be: • depression (e.g., PHQ-9) • anxiety (e.g., GAD-7) • social support	*See above. This was not included as a key question for this update.*
	AAv	The cost of measuring HbA1c is around 10–20 times that of fasting glucose. In Grampian very recent guidance indicates that fasting glucose remains the first line test, as we have no assurance from the Health Board to support the costs of HbA1c for first line testing. This is likely to be the case for many other areas of Scotland. There is certainly	*Noted. We have revised the diabetes paragraph to suggest use of a validated tool, rather than specify a single method.*

		no supported national policy in Scotland to use HbA1c for first line testing, due to financial constraints. So this section needs rewording to reflect local policies and that HbA1c can be used according to such local policies.	
	LMc	Ok	*Thank you*
4.3	FD	No change.	*Thank you*
	DW	Well discussed	*Thank you*
	CB	Paragraph 2 is very unclear - are you referring to regression dilution?	*Agreed, sentence has been deleted.*
	JS	Clear	*Thank you*
	LMc	Ok	*Thank you*
	SJ	The practical application of using these tools in an ethnically diverse population is very difficult when the IT cannot easily support the transitions to find a pre-treatment BP, to take into account ethnic background and their smoking or ex-smoking status... the utility if we are going to use this in all patients >age 40 must be improved for the time allowed.	*Noted.*
4.4	FD	No change.	*Thank you*
	DW	This is covered well - no further comments. My only question is whether a prior history of stroke/TIA would also qualify an individual as high risk?	*Yes, this is clear from section 4.1*
	TY	Given patients and clinicians may only read the recommendations rather than the supporting text, it would be helpful to have a specific recommendation around the type of risk score used. The text supports recommending ASSIGN	*We did not review evidence for the discrimination or prediction of different risk tools. This would require both economic and scientific performance analyses which were not available. Further, the guideline was updated in the context of ongoing work to develop a new risk tool for Scotland.*
	CB	There are inconsistencies in the section: be clear what albuminuria means, and avoid using it in conjunction with proteinuria.	*We have changed the references in association with diabetes to "micro or macroalbuminuria", however the reference in association with CKD refers to any albuminuria as noted in the text.*
	JS	Clear	*Thank you*
	LMc	Ok	*Thank you*
	SJ	If a patient is already on lipid-lowering therapy, then we need to be clearer that we don't want to just monitor risk factors annually. It is 'fire and forget' regarding the lipid-lowering therapy, but we should be actively supporting modifiable risk factor changes - not	*Agree we have revised the good practice point.* *"Consider annual review to discuss lifestyle modification, medicines and address CVD risk factors. Frequency of review may be adapted to the*

		just 'monitoring'...	*individual."* *NICE recommends annual review of lipid lowering and blood pressure medication*
	BHFNC	Whilst physical activity is not included in any of the existing risk estimation tools, given that physical activity is an independent risk factor for cardiovascular disease I would like to suggest that it is included as one of the other risk factors that should be taken into account when assessing and managing a person's overall CVD risk. I would therefore recommend that physical activity is included in ***section 4.4. How to determine cardiovascular risk*** and I would recommend that the Scottish Physical Activity Questionnaire is recommended in the guidelines as a valid tool to assess physical activity.	*Agreed – this has been added after table 2. See above* *Agreed – this has been added to the final GPP* *We have not reviewed the optimal method of PA assessment.*
Section 5			
General	SMcC	Sugar and refined carbohydrates - I find it astonishing that there is no mention of sugar and refined carbs in the diet section when it is clear that this is what is driving our current epidemic of obesity and type 2 diabetes. Now 10% of children entering school at 5 years of age are obese. This is storing up huge potential cardiovascular risks for the future and is absolutely nothing to do with cholesterol consumption or dietary consumption of fat - yet we are still majoring on those.	*We have not covered this as a KQ. The guideline has focused on fat modification in the diet, dietary patterns which reduce CVD outcomes and weight loss.* *We believe that it is far from clear that sugar is <u>driving</u> the obesity epidemic, although it may be one component. We don't believe there is RCT evidence on interventions to modify sugar consumption on CVD risk.*
	WP	It is well worth consider the evidence on whole food plant based diets reducing risk of obesity, T2DM & IHD. I've forwarded a summary to SIGN as I've researched the optimal diet to manage and reverse T2DM in my diabetes mental health role where I get referred people who overeat unhealthy foods.	*Thank you. This was not included in the key questions considered. The information provided is specific to whole food diets in people with type 2 diabetes only and therefore does not reflect either the interventions or population which are most directly relevant to this guideline.*
	DW	This is covered well - no further comments	*Thank you*
	RCPE	SIGN may wish to promote the adoption of a "Mediterranean style" diet in the guideline. It is cheap to buy and does not cost the NHS anything. As the evidence in favour of the diet is very strong, and there is also adherence evidence, it may be worthwhile featuring this ahead of	*Thank you. This is already one of our recommendations (see section 5.5).*

		individual dietary factors.	
	JLo	A combination of nutrient (saturated fat) and food base (fruits and vegetables, nuts, soya) recommendations are outlined, but it is unclear how these were chosen over other possible inclusions.	*These were included in the previous version of the guideline and chosen by the GDG to inform the key questions of the guideline.*
		The use of food-based recommendations are useful for better translation of guidance for greater efficacy, although minimum and/or maximum intakes may provide further utility.	*We have provided food-based recommendations for all the nutrients which received recommendations*
		As stated in the introductory paragraph '…randomised controlled trials of diet …….. are more difficult to conduct than those of drugs or supplements' and the lack of studies with mortality as an outcome measure can seriously limit the evidence for direct causal effects. It is therefore an important consideration as to whether dietary recommendations should be based on hard endpoint data only (which may never be available for certain nutrients and foods), or whether consistent effects on established biomarkers of CVD risk, such as serum LDL cholesterol reduction, can be sufficient for recommendations. The strength of evidence linking decreased serum LDL cholesterol to reduced CHD mortality is strong and consistent (as described in section 10.3), yet within the report specific recommendations are not always given when significant LDL-cholesterol reductions are observed. Further comment on which criteria were used to inform decisions on recommendations would be helpful.	*The literature review was limited to RCTs with CV, LDL-cholesterol or blood pressure outcomes with a minimum of one year duration. As the questions related to interventions only, observational studies were excluded. Although RCTs are limited in some areas of dietary interventions, there is no a priori reason why they could not be conducted, therefore we do not lower our threshold for evidence inclusion to compensate for a lack of availability.* *Disagree. The PICO key questions are listed in appendix 1.*
		<u>Total fat</u> Was consideration given to the quantity of fat in the diet? This would be worthy of consideration, particularly in light of the evidence on saturated fat reduction and its replacement macronutrient (see below).	*This was considered. There was no evidence that total fat in the diet affected outcomes. Only saturated fat reduction was protective of CV risk but did not influence total mortality or CV mortality. This has been further clarified (see title of 5.1.1)*
		<u>Carbohydrates</u> The evidence for replacement of saturated fat with total carbohydrate shows limited benefit to CHD mortality	*Complex carbohydrate intake has not been related with change in CVD risk in evidence from RCTs. This guideline supports the use of the current DRV and SACN reports and did not consider all*

		as discussed below, although there is evidence that this may be dependent on carbohydrate type, with wholegrain being associated with reductions in risk of CHD (eg Li Y et al., 2015). Carbohydrates are not covered in these guidelines and inclusion of advice on carbohydrates, particularly dietary fibre and sugars is recommended. <u>Dietary fibre</u> Inclusion of recommendations for dietary fibres and wholegrain is important. There is consistent evidence from systematic reviews and meta-analyses (eg Threapleton et al., 2013a and 2013b) that indicate a higher consumption of dietary fibre is associated with a reduced incidence of cardiovascular disease (RR 0.91, 95% CI 0.88, 0.94 for each 7g/day increase; p<0.001); a reduced incidence of coronary events (RR 0.91, 95% CI 0.87, 0.94 for each 7g/day increase; p<0.001); reduced incidence of haemorrhagic plus ischemic stroke (RR 0.93, 95% CI 0.88, 0.98 for each 7 g/day increase; p=0.002). Furthermore, a systematic review and meta-analysis performed as part of the SACN Carbohydrate and Health Report (SACN, 2015. Section 8.18) showed a reduced incidence of type 2 diabetes (RR 0.94, 95% CI 0.90, 0.97 for each 7 g/day increase; p=0.001). Evidence for the effects of dietary fibre and wholegrain on cardiovascular endpoints is therefore strong within a mixed population. SACN report Carbohydrate and Health Report (2015). (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/445503/SACN_Carbohydrates_and_Health.pdf *Threapleton DE, Greenwood DC, Evans CE, Cleghorn CL, Nykjaer C, Woodhead C, Cade JE, Gale CP & Burley VJ (2013a) Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. BMJ 347, f6879.* *Threapleton DE, Greenwood DC,*	*aspects of diet.* *Fibre was not specifically included as a variable in the key questions and therefore has not been considered in this review. Furthermore, the suggested study is a systematic review of observational studies and not relevant to questions on the efficacy of interventions.*

		Evans CE, Cleghorn CL, Nykjaer C, Woodhead C, Cade JE, Gale CP & Burley VJ (2013b) Dietary fiber intake and risk of first stroke: a systematic review and meta-analysis. Stroke 44, 1360-1368.	
	JB	Good introductory section.	*Thank you*
	JS	Maybe more could be mentioned about worst fats/hydrogenated & healthier fats	*We have renamed the first subsection to show the role of total fats and already have sections on saturated fats, fish oils and Mediterranean diets (which are high in MUFA, in the dietary patterns section), which together give an overview of the effects of different fat types on CVD outcomes.*
	MM	As in many such guidelines there appears to be a level of detail in the dietary guidance well above that afforded to PA and cardiorespiratory fitness. Although I am not a diet expert- it seems that the discrepancy is not justified by either the strength or the volume of the evidence.	*Evidence in the diet section was restricted to RCTs only, whereas the PA section had observational evidence.* *There are more high-quality, long-term RCTs available for dietary interventions than PA.*
	LMc	Ok	*Thank you*
5.1.1	DW	This is covered well - no further comments	*Thank you*
	SMac	Could this section be expanded to explain why if refutes the 'saturated fat myth?'	*We have presented Cochrane review data showing effects of saturated fat reduction on CVD events (reduction in risk) and mortality/CVD mortality (no significant reduction). Evidence suggests that saturated fat reduction reduces CVD events by 14%.*
	JLo	In this section it is recommended that 'diets low in saturated fats should be recommended to all for the reduction of cardiovascular risk', a Cochrane review is described, but the reference is not quoted in the text. To contextualise this recommendation and to make it more practical, it would be helpful to consider giving more specific advice regarding what should replace saturated fats for optimum effect. There is consistent evidence from prospective cohort studies *(eg Jakobsen et al. 2009; Farvid et al. 2014; Micha, R. and D. Mozaffarian 2010)* and RCTs *(eg Hooper, L., et al. 2015; Micha, R. and D. Mozaffarian. 2010; Mozaffarian et al 2010),* that replacing saturated fat with PUFA reduces CHD	*Agreed. The reference has been added.* *Noted, however cohort studies were not eligible to answer the question on interventions.* *The 2012 Hooper Cochrane review is included as evidence in this guideline. The newer version postdated our searches, but would not alter*

		mortality and risk factors, whereas replacement with carbohydrate has minimal benefit *(eg Jakobsen et al. 2009; Farvid et al. 2014; Micha, R. and D. Mozaffarian 2010).*	*conclusions.*
		Evidence for benefit from saturated fat replacement with MUFA is limited for mortality outcomes *(eg Hooper, L., et al. 2015)*, yet evidence for benefit on risk factors, including lipids, is strong for replacement of saturated fats with both PUFA and MUFA *(eg Li Y et al., 2015; Micha, R. and D. Mozaffarian. 2010; Mensink et al., 2003)*. These, and other data, could inform more specific advice on what should replace dietary saturated fats for optimum benefit.	*This systematic review (Micha and Mozaffarian, 2010) examined replacement of SF with PUFA. It suggested that inclusion of PUFA reduced CHD events. However, it is unclear whether SF reduction or increased PUFA was responsible for the change. The Cochrane review provides evidence to reduce SFA.*
		Del Gobbo et al., (2015) Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. Am J Clin Nutr. 2015 Dec;102(6):1347-56	*This review only included studies below our one year follow up threshold for inclusion (max duration 26 weeks).*
		Farvid, M. S., et al. (2014). Dietary linoleic acid and risk of coronary heart disease: A systematic review and meta-analysis of prospective cohort studies Circulation 130(18): 1568-1578.	*This is an observational study and therefore excluded.*
		Hooper, L., et al. (2015). Reduction in saturated fat intake for cardiovascular disease The Cochrane database of systematic reviews 6	*We have cited Hooper 2012, and the newer version does not alter conclusions.*
		Jakobsen, U., et al. (2009). Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. Am J Clin Nutr. 89(5)	*This is an observational study and therefore excluded.*
		Li y et al. (2015). Saturated Fats Compared With Unsaturated Fats and Sources of Carbohydrates in Relation to Risk of Coronary Heart Disease: A Prospective Cohort Study. J Am Coll Cardiol. 6;66(14):1538-48	*This is an observational study and therefore excluded.*
		Mensink et al., (2003) Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr. 2003 May;77(5):1146-55	*This study is relevant, but will not change advice as it is consistent with more recent Hooper 2012 Cochrane review.*
		Micha, R. and D. Mozaffarian (2010). Saturated fat and cardiometabolic risk	*See above*

		factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence. Lipids 45(10): 893-905. *Mozaffarian et al (2010). Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS Med. 2010 Mar 23;7(3):e1000252*	*See above. The two reviews by Mozaffarian et al report the same impact of increased PUFA and reduced SFA on CHD mortality.*
	TY	The recommendation seems generic and lack specific guidance. For example: To what level should saturated fat be restricted per day? To what level should salt be reduced? Etc There does not seem to be any recommendations on the most effective dietary strategy of all - low calorie? Whilst dietary composition is important, hypocaloric diets of whatever variety have the strongest effect on health through weight loss. Should this be mentioned and/or linked to the weight loss section?	*Agreed.* *We have added a GPP around saturated fat intake. The salt limit is included in section 5.2 (6 g/day).* *We did not specifically include this as a key question, however the effects of weight loss on CVD risk are covered in section 5.7*
	CB	Avoid citing RRs for total mortality - emphasis should be on vascular mortality, since this is more sensitive and generalisable.	*Noted, however vascular mortality is not always reported in studies.*
	JS	Ok	*Thank you*
	LMc	Ok	*Thank you*
5.1.2	DW	This is covered well - no further comments	*Thank you*
	JE	Clear message	*Thank you*
	JS	Would be beneficial if could be disseminated to whole population the importance of eating fish	*No clear evidence that omega-3 supplementation reduces risk. Observational data that biomarkers of omega-3 PUFAs are associated with moderately lower incidence of fatal CHD. On balance, no evidence to change current dietary guidelines – 2 portions of fish, including one portion of fatty fish.*
	LMc	Ok	*Thank you*
	SJ	The guideline should take the further step in clearly stating that (consistent with SMC guidance of Nov 2002) Omega-3 Acid Ethyl esters should therefore not be prescribed on the NHS in Scotland. They are an unnecessary expense... In the same way we are clear subsequently about antioxidant vitamin supplementation.	*Agreed. A recommendation has been added which reinforces SMC findings.* *SMC has published two pieces of advice about omega-3 acid ethyl esters on the same date (Nov 2002).* *In one, this product is acceptable for general use within NHSScotland as an additional treatment for the secondary prevention of myocardial infarction.*

			In the other it is not recommended for use within the NHS in Scotland for hypertriglyceridaemia based on the lack of long-term data to indicate that reductions in triglyceride levels provide real benefit in terms of reducing cardiovascular events, on a lack of evidence of increased patient acceptability of the product, and lack of a pharmacoeconomic case for the drug.
5.2	MC	If updated at some point, it might be useful to increase the scope of this section to include more economic evaluations in reducing dietary salt and the papers which have modelled the outcomes of this over a longer time horizon.	*Noted. Thank you.*
	DW	Consider recent evidence suggesting low salt intake could be potential harmful (PURE investigators).	*As noted in section 1.2.3, this section was not updated.*
	JS	Didn't seem to mention that genotype for salt intake important? (although no current way of identifying this)	*As noted in section 1.2.3, this section was not updated.*
	LMc	Ok	*Thank you*
5.3	MC	If this is updated at some point, it might be useful to look at deprivation in this section as this is a factor in people achieving the recommended daily intake of fruit and veg.	*Noted. Thank you.*
	DW	This is covered well - no further comments.	*Thank you*
	JLo	It is stated that 'diets rich in fruit and vegetables tend also to be low in fat', however there are a number of dietary habits that are related to higher fruit and vegetable consumption and it unclear why 'low fat' is highlighted, particularly in light of the evidence that saturated fat replacement with carbohydrates has minimal benefit to CVD risk. However, a comment relating to possible confounding due to associated dietary patterns would seem appropriate.	*As noted in section 1.2.3, this section was not updated, however the second sentence will be deleted for clarity.*
	AA	Fruits and vegetables. My understanding is that increases from baseline will be helpful apart from absolute intake – could this be checked please	*As noted in section 1.2.3, this section was not updated.*
	CB	Another example of an incorrect use of 'relative' - see line 6, where it is stated that there was a 15% reduced relative risk of CHD. The word 'relative' should be deleted - there was	*Thank you – this has been corrected*

		a 15% reduced risk, or a 15% relative reduction in risk - the word 'relative' should refer to the reduction, not the risk (in order to make clear the meaning of the % change - relative or absolute). This error is repeated frequently throughout the guideline.	
	JS	Ok	*Thank you*
	LMc	Ok	*Thank you*
5.4.1	JLo	Is the recommendation specific to 'antioxidant' vitamin supplementation or all vitamin supplements including vitamin D?	*We didn't consider Vitamin D. Only antioxidant vitamin supplements*
	JS	Ok	*Thank you*
	LMc	Ok	*Thank you*
5.4.2	CB	Typo in recommendation: homocysteine, not homocystine.	*Agreed – now corrected.*
	JS	Ok	*Thank you*
	LMc	Ok	*Thank you*
5.4.3	DW	This is covered well - no further comments	*Thank you*
	JLo	It is accepted that data is lacking on the long-term effects of stanols and sterols on CVD mortality, however, it is stated that 'there is no evidence on whether these reductions in cholesterol translate in the longer term into reduction in CVD…'. This statement implies that doubt exists for the benefit of consistent reduction in serum LDL cholesterol, on CVD. If this was not the intension, then perhaps this could be reworded for clarity.	*Trials were short term, and we don't have evidence to show that compliance would be maintained in the longer term or that cholesterol lowering would extend long term. We have reworded to make this clearer.*
		Further evidence that could be considered is the dose response study by Musa-Veloso K. 2011. Moreover, there is evidence that use of stanols and sterols as an adjunct to statin therapy has clinical benefit, and would seem of relevance in this report. Scholle JM et al. 2009 found that the use of plant sterols/stanols in combination with statin therapy significantly lowered total cholesterol (WMD, -14.01 mg/dL [95% CI, -18.66 to -9.37], p < 0.0001) and LDL cholesterol (WMD, -13.26 mg/dL [95% CI, -17.34 to -9.18], p < 0.0001) but not HDL cholesterol or triglycerides. *Musa-Veloso K et al (2011). A comparison of the LDL-cholesterol*	*Not relevant to KQ as the stanols were used in combination with statin therapy* *This study reports interactions between medication and dietary intakes. We are examining the role of diet interventions alone in this section.*

		lowering efficacy of plant stanols and plant sterols over a continuous dose range: results of a meta-analysis of randomized, placebo-controlled trials. Prostag Leukotriene Essential Fatty Acids 2011;85:9-28 *Scholle JM et al. (2009) The effect of adding plant sterols or stanols to statin therapy in hypercholesterolemic patients: systematic review and meta-analysis. J Am Coll Nutr. 2009 Oct;28(5):517-24*	
	JS	Ok	*Thank you*
	LMc	Ok	*Thank you*
5.4.4	JLo	As stated in SIGN, data on mortality is limited, however the lack of recommendation in this section is in contrast to that given in 5.5 Dietary Patterns, where recommendations 'on adopting a Mediterranean diet supplemented with….. nuts..' is given. Perhaps these recommendations could be taken together to prevent mixed messages. A recent systematic review and meta-analysis of 61 RCT reported that nut intake (per serving/d) lowered total cholesterol (-4.7 mg/dL; 95% CI: -5.3, -4.0 mg/dL), LDL cholesterol (-4.8 mg/dL; 95% CI: -5.5, -4.2 mg/dL), ApoB (-3.7 mg/dL; 95% CI: -5.2, -2.3 mg/dL), and triglycerides (-2.2 mg/dL; 95% CI: -3.8, -0.5 mg/dL) (Del Gobbo et al., 2015). These reported reductions in lipids and the data from PREDIMED taken together could be presented in a revised recommendation. *Del Gobbo et al., (2015) Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. Am J Clin Nutr. 2015 Dec;102(6):1347-56*	*As noted in section 1.2.3, this section was not updated. Furthermore, the data in this study are only applicable to a maximum period of 23 weeks, and therefore excluded as falling below our threshold of one year follow up.*
	JS	Ok	*Thank you*
	LMc	Ok	*Thank you*
5.4.5	JLo	Similar comments to the previous food-based recommendations in relation to LDL-cholesterol reductions and confidence in benefit.	*As noted in section 1.2.3, this section was not updated.*
	JS	Ok	*Thank you*
	LMc	Ok	*Thank you*
5.5	MC	It is easy to suggest adopting a	*It is unclear whether the reviewer is*

		Mediterranean diet but again deprivation isn't considered in this section which, particularly for Scotland, is something we need to think more of.	*suggesting the impact of deprivation on CV risk as mediated through the diet, or the difficulty in incorporating a Mediterranean diet for more deprived population subgroups. If the latter, this may be an issue more related to implementation than establishing efficacy.* *We agree cost of food and cooking skills are useful considerations as to how practical a med style diet is. Implementation issues while outwith this remit, can be assisted using the Eat Well guidance which we have incorporated.*
	DW	This is covered well - no further comments	*Thank you*
	LMc	To help support the education and adherence to a Mediterranean type diet it is appropriate to utilise the Eat Well Guidance, a resource for patient education as this is readily available and well utilised by health professionals to across Scotland. This can be supported by more specific advice about adhering to a Mediterranean type diet on an individual patient basis	*We agree that the current Eat Well guidance could have value in assisting with implementation of dietary change.* *We have added the Eat Well guide as an annex.*
	WP	When HbA1c increased by 1% point, the risk of cardiovascular disease in patients with diabetes increased by 20% over a decade (Selvin et al., 2004). Diets high in vegetables, beans, fruits and nuts and very low in animal protein are best at preventing and reversing coronary artery disease (Gardner et al., 2005; Tucker et al., 2005; Campbell et al., 1998). Fifty heart attack survivors were placed on a special diet low in animal protein and saturated fat in 1946 (Morrison 1960). After eight years 28 (56%) of the diet group were alive compared to 12 (24%) of the control group. After 12 years 19 (38%) of the diet group survived compared to none of the controls. Ornish demonstrated that blocked coronary arteries were visibly opening up on angiogram in 82% of 28 participants following a low fat, vegetarian diet as well as regular exercise and stress management (without the use of cholesterol-lowering drugs) over one year (Ornish, 1990 & 1998). Those on the vegetarian diet achieved a 91% reduction in angina frequency, arterial	*These studies predate the search period. Also advances in medical management, make these findings inappropriate.* *The regimens described here are shorter in duration than a year, and also some involved residential interventions, which are not applicable widely.*

		blockages diminishes by over 4%, while angina increased by 161% in the control group. Their average cholesterol fell from 227mg/dl to 172 mg/dl (5.88 to 4.45 mmol/l) and LDL cholesterol from 152 mg/dl to 95 mg/dl (3.94 to 2.46 mmol/l - an average of 40%) and they lost on average 10 kg in the first year. Esselstyn (1999) studied patients with advanced coronary heart disease placed on a low fat vegan diet. This group of patients who had suffered a combined 49 cardiac events over eight years and who had average cholesterol of 246 mg/dl (6.37 mmol/l) were place on a whole food plant based diet. They achieved weight loss and reduced cholesterol levels and cholesterol lowering medication was only prescribed in those whose levels did not normalise on diet alone. Over the following 11 years there were no cardiac events in patients who followed the program and average cholesterol was 132 mg/dl (3.42 mmol/l). Angiograms showed that 70% of patients had experienced (on average 7%) opening of blocked arteries (Esselstyn 1998). Seventeen years into the study all but one patient following the diet were still alive. The same dietary change reduced blood pressure by reducing blood viscosity and by increasing potassium (Berkow & Barnard, 2005), while the average person who adopted a vegetarian diet lost 10% of their body weight. Cultures that have lower CHD rates eat less saturated fat and animal protein and more fruit and vegetables (Jolliffe 1959). When people from such cultures migrated to cultures with high saturated fat and animal protein intake, their risk of coronary heart disease and stroke increased, as demonstrated by Japanese men who moved to the USA (Kato 1973). The importance of animal protein in CHD was overlooked and fat became the focus. Eating more plant (instead of animal) protein has a bigger impact on lowering cholesterol than reducing saturated fat or cholesterol intake (Sirtori 1983).	*Noted. The use of a vegan diet does not fulfil the current UK dietary requirements. They are not appropriate for wide scale application.* *See above*
	JLo	Has the committee considered the potential benefits of other dietary patterns including the DASH diets and	*The search was limited to diets reporting with the following interventions:*

		Portfolio diets? It would be helpful to define what is meant by 'Mediterranean diet' as many groups interpret this differently. Furthermore, perhaps it should be stipulated that the recommendation on 'nuts' should be 'unsalted nuts' which were used in PREDIMED. Salted varieties of nuts are consumed more commonly in Scotland than Spain, and the addition of 'unsalted nuts' would give a clearer recommendation. The recommendation to add 'extra virgin olive oil' also relates to the dietary fat recommendations, in which the substitution of saturated fats with unsaturated fat sources is beneficial and could be considered together.	• *Mediterranean diet,* • *Low GI/GL* • *Low carbohydrate* *Agreed – the Eat Well guide has been incorporated which describes the optimal components of a healthy diet and their relative contributions.* *Noted. Thank you.*
	TY	There is a wealth of epidemiological evidence looking at the cardiovascular benefits of prudent vs non-prudent diets that go beyond olive oil and nuts (i.e. whole grains, legumes etc. vs diets high in red/processed meats, high fat dairy procts, fried food, etc). Was this wider evidence around patterns considered? It seems a shame not to present the wider evidence on this with accompanying recommendations.	*The search was limited to diets as noted above.* *The evidence considered was limited to RCTs, or linked cohort studies. Epidemiological studies would not be appropriate for dietary interventions.*
	AA	Diet – should read Mediterranean diet pattern not Mediterranean diet (Scottish diet could follow that pattern not necc exactly same ingredients). Supplemented with extra virgin oil is a bit non–specific (is it a teaspoon per week? per day? per meal or what did the trials actually show and were these dependent on base line values? This recommendation is meaningless without specifics. It also need some comment on caloric value (or not).	*Agreed – changes have been made throughout the section.* *This was not a dose response study so we will not recommend volumes of oil. In the trial, participants consumed around 30 g/day EVOO per person and 30 g mixed unsalted nuts.* *No calorie restriction was imposed in the trial. Total calorie intake reduced in all trial arms (EVOO, Nuts, and control).*
	JS	Ok	*Thank you*
	LMc	Ok	*Thank you*
	SJ	Reading all the evidence given, I don't think the conclusion is fairly that a Mediterranean diet will reduce CV risk. Subgroup analysis of higher risk groups, looking at secondary outcome gains to then make a conclusion doesn't sit right... I don't think the evidence is nearly as conclusive as	*Disagree.* *The primary outcome of the PREDIMED trial was a reduction of around 30% in MI, stroke and death from CVD in those eating a Mediterranean diet pattern compared with those on a low-fat diet. All of those recruited were at high risk of*

		the recommendation states...	*CVD.* *These patients were overweight/obese which represents ~2/3 of the Scottish population. Recommendation does state 'recommended for adults at high risk of CVD'.*
5.6	DW	This is covered well - no further comments	*Thank you*
	AA	Suggest that following: "Randomised trials have shown that dietary advice can have effects on self-reported dietary intake and objective risk factors. Most evidence on beneficial effects is for patients with cardiovascular disease." is replaced with: "Randomised trials have shown that dietary advice effects self-reported dietary intake AS WELL AS objective risk factors. Most evidence on beneficial effects is for patients with a diagnosis of cardiovascular disease rather than those estimated to be at higher risk" ???	*Thank you. As noted in section 1.2.3, this section was not updated. However, this is a minor clarification of the grammar and clarity of the sentence and has been made.*
	JS	Ok	*Thank you*
	LMc	Ok	*Thank you*
5.6.1	DW	This is covered well - no further comments	*Thank you*
	AA	Self-help resources versus dietitians – has the evidence allowed for SES background?	*This was not taken into account. As noted in section 1.2.3, this section was not updated.*
	JS	A bit of a can of worms	*Noted*
	LMc	Ok	*Thank you*
5.6.2	DW	This is covered well - no further comments	*Thank you*
	JB	Worth mentioning work on brief intervention advice for alcohol and smoking?	*Thank you. As noted in section 1.2.3, this section was not updated.*
	AA	No mention of behavioural change techniques (e.g. goal setting, self-monitoring etc). Implementation theory now strongly recommends these approaches (see work by Susan Michie et al)	*Thank you. As noted in section 1.2.3, this section was not updated.*
	JS	Ok	*Thank you*
	LMc	Ok	*Thank you*
5.7	MC	States that individuals who are overweight or obese should be targeted with interventions designed to reduce weight. If this guideline may	*A separate patient version of the guideline will be produced and may incorporate this information.*

		also be accessed by patients, should the types of interventions that may be available be outlined in this section or is that outwith the scope of the guidance?	
	DW	This is covered well - no further comments	*Thank you*
	AA	Body weight. There is some modest evidence on self-monitoring of body weight as useful for weight maintenance – might this be useful here?	*Noted, thank you.*
	CB	Para 2, typo: 'lead' should be 'led'	*Agreed – now corrected.*
	JS	Ok	*Thank you*
	VS	Longer-term maintenance of weight loss is important for CV risk reduction. Behavioural interventions focusing on both weight loss and physical activity, based on evidence-based behaviour change techniques (BCTs) are important for weight loss maintenance. Dombrowski et al, BMJ 2014;348:g2646	*We agree that changing behaviour is important: However, this section was focused on health outcomes resulting from weight loss rather than the most effective approaches to achieve weight loss.*
	LMc	Would support completely the need for annual weighing to be included for all patients. The discussion around target weight perhaps should give some context around what 'maintain' means? NICE for example states reverting back to rate of background weight gain of the population. This to be included please.	*Thank you.* *There is no discussion of target weight.* *Noted. This was not included as a key question and this evidence has not been reviewed.*
5.8	DW	This is covered well - no further comments	*Thank you*
	SMac	There is still no funding in place in Scottish labs to support diabetes screening/diagnosis with HBA1c and it is therefore discouraged in many Health Board areas.	*Noted.*
	JS	Ok	*Thank you*
Section 6			
General	DW	This is covered well - no further comments	*Thank you*
	RCPE	Recommendations, eg. for physical activity, should have the potential benefit clearly described as well as mention of any significant potential risks (there are some risks to intense and endurance exercise, for example atrial fibrillation).	*We have specifically addressed risks of vigorous and high intensity exercise in section 6.2.3. Risk of AF with exercise is very low in the general population but we can't specifically mention risk of all rare outcomes.*
	JB	'mental illness' could this be	*Following guidance from*

		reworded, it sounds pejorative?	*http://www.time-to-change.org.uk/news-media/media-advisory-service/help-journalists/mind-your-language we have amended this to "mental health problems".*
	JS	Ok	*Thank you*
	MM	This section is clear but lack a sub-section on cardiorespiratory fitness (sometimes referred to as physical fitness but this is incorrect as PF includes muscular strength and endurance which is not as strongly or consistently associated with CVD outcomes as CR fitness). In my view is a serious omission given the strength of the evidence for an independent effect of CR fitness on CVD morbidity and mortality. The strength (volume and quality) of evidence is much greater for CR fitness than for sedentary behaviour and although the latter is an emerging risk factor worthy of inclusion - not including CR fitness is ignoring an well-established risk factor independent of physical activity.	*Agreed. Although this was not included in the key questions, we have added a statement to clarify the risk. "There is also evidence that cardiorespiratory fitness (i.e. the ability of the body to use oxygen to do physical work, which is improved by increasing physical activity) is a risk factor for CVD" Kodama et al (2009), Celis-Morales (2016).*
	JBu	Generally it looks good but clear definition of the nuances needs addressing Often Physical Activity is noted as the risk factor, when in fact we should clearly state that the Risk factor is "Physical Inactivity". Please note this is what the WHO refer to in their 25 x 25 Programme (see additional document) There are indeed three risk independent sub-factors which you have mentioned inherently but not very explicitly. It should state: There are 3 elements related to physical inactivity risk 1. Individuals who expend less than 1500 kcal/week in PA above their basal metabolic rate – as measured through the target of 150 mins MVPA 2. Individuals whose aerobic fitness is <30ml/kg/min (<9 METs) 3. Individuals (whether active or inactive) who spend >7 hours per day sitting during their waking hours	*Agreed. This term has been revised in the heading to section 6.2.1* *Noted. It is not clear where these "definitions" have been sourced from. We have discussed these elements throughout the section.* *We have added further discussion of cardiorespiratory fitness.* *We have considered the evidence here, the threshold is not clear cut, but sedentary is mentioned*

		Other than this the core of information seems appropriate	
6.1	NM	All fine here.	*Thank you*
	DW	This is covered well - no further comments	*Thank you*
	JS	Good	*Thank you*
	MM	Physical activity has 4 dimensions not 3. Type of PA has been omitted and may be important given that certain modes of exercise may be more suitable for individuals with pre-existing CVD (e.g. hypertension) or other co-morbidities. This distinction of type of PA is, in my view - on a par with the consideration of different dietary components and so merits some description	*Noted, however this statement is drawn from a reference which supports the three dimensions. We have added a comment to highlight the relevance of type of PA.*
6.2.1	NM	Clearly written.	*Thank you*
	DW	This is covered well - no further comments	*Thank you*
	MH	I was surprised that recent meta-analyses were not described more and cited. for example, Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. JAMA Intern Med. 2015;175(6):959-967.	*Thank you. As noted in section 1.2.3, this section was not updated.*
	JS	Ok	*Thank you*
	MM	Well explained - but Cardiorespiratory fitness is also an independent risk factor and so should be included in a separate sub-section	*Agreed. A new paragraph has been added, though not in a new subsection.*
6.2.2	NM	Good connection to current practice.	*Thank you*
	DW	This is covered well - no further comments	*Thank you*
	JB	Good clear table	*Thank you*
	TY	It may be helpful to have a stronger emphasis on the dose response nature of both physical activity and fitness (i.e. to secure the message that the more that is done, the greater the benefit).	*This comment does not specify which relationship is being referred to. We presume it is the relation between frequency or intensity of physical activity and risk of CVD. This is clearly stated in section 6.2.2, para 3. On the other hand, the lack of evidence for a relationship between duration, intensity or frequency of exercise and blood lipid response is noted in 6.2.5.*
	MH	See above. Arem refers to L-shaped association.	*Noted. No new evidence was considered for this section.*

	JE	Good to have inclusion of high intensity/vigorous activity for those able to do so. Clear guidance on PA targets for health and message regarding risk of sedentary behaviour acknowledged.	*Thank you*
	CB	Para 2, last line: state what period of time the 2.6% increase in risk occurred over.	*This paragraph was retained verbatim from the previous version of the guideline. We have clarified the relevant section. (2.6% reduction in incidence of CHD across 2–4 years of follow up).*
	JS	Ok	*Thank you*
	BHFNC	I agree with the statement regarding the inconsistencies in the evidence regarding the amount, frequency, intensity and type of physical activity required to achieve health benefits. However I think this section should emphasise that the evidence consistently identifies that an overall weekly volume of 150 minutes of moderate intensity activity as being associated with substantial health benefits. Reference: US Department of Health and Human Services 2008 Physical Activity Guidelines Advisory Committee Report. UK CMOs physical activity guidelines (2011) Start Active, Stay Active.	*We do recommend this amount of PA in section 6.2.4*
6.2.3	NM	Fine - but perhaps more should be made of the ability of people to sustain activity levels. It is more likely that activity is sustained via moderate levels of activity. Vigorous levels tend to reduce over time. Also maybe more needs to be said about the mode of activity. While it is true from evidence that any mode is good, it is more likely that people can start and sustain walking as a mode. I have a slight concern over the use of the term 'out of breath' to indicate faster breathing. In my experience this can put people off especially if they have asthma. This is exactly the feeling they do not want. Suggest change to 'breathing faster than normal'.	*We don't have good RCT data to show that sustainability is greater with moderate levels of PA. Data from patients with heart failure suggest that dropout was lower with increasing intensity.* *We have added a statement earlier to note that type of PA may be important, as with frequency, intensity and duration.* *Agreed. We have changed this wording.*
	DW	This is covered well - no further comments	*Thank you*
	TY	The report rightly points out that vigorous exercise is more likely to	*Agreed – see above. Paragraph added regarding the relationship between*

		improve fitness. It would be helpful to then have a brief paragraph stating the evidence linking fitness to CVD. This is important because fitness is a highly powerful predictor of CVD mortality and morbidity in a linear dose-repose fashion, for example see [Kodama et al]. Indeed fitness is more strongly predictive of CVD than either PA or sedentary time alone. This will help demonstrated that increased fitness is an important outcome of any PA intervention. *Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a metaanalysis. JAMA. 2009 May 20;301(19):2024-35.*	*cardiorespiratory fitness and CVD risk.*
	JS	Ok & important	*Thank you*
6.2.4	NM	Excellent to see this section added and I believe conclusions are correct for this stage of the evidence.	*Thank you*
	DW	This is covered well - no further comments	*Thank you*
	TY	It may be helpful to give the definition of sedentary behaviour. It should be recognized that many studies have demonstrated acute benefits of regularly breaking sedentary behaviour on CVD risk markers, particularly glucose [Dempsey et al] & insulin, but also FFAs and lipids. Thus there is experimental evidence to support the potential benefits of breaking prolonged sedentary behaviour. *Dempsey, Paddy C., et al. "Sitting Less and Moving More: Improved Glycaemic Control for Type 2 Diabetes Prevention and Management." Current Diabetes Reports 16.11 (2016): 114.*	*This is already included in section 6.1* *Noted. We have mentioned some mechanistic data, however most of these trials are very short term.*
	MH	I think the recent Lancet paper by Ekelund et al should be cited that suggests risks of excess sitting can be attenuated by ~1 hr per day MVPA. Thus the associations of sedentary are not independent of PA.	*Agreed – we have cited this. It was not published at the time of consultation.*
	JS	Good	*Thank you*

	MM	The nature of the available evidence in this area may not be strong enough to confirm SB as a risk factor. The term 'emerging' might be a more accurate description	*We have reflected the nature of the evidence in our text, and avoided using the term 'risk factor'.*
	SJ	No evidence was provided showing the benefits to children doing moderate to vigorous-intensity physical activity for at least 60 mins+/day. This is quite a recommendation and should be more robustly substantiated.	*The evidence is linked in the guideline. It is National guidance for physical activity and includes children and adults.*
	BHFNC	It is welcoming to see the inclusion of sedentary behaviour in this guideline. To aid understanding of this concept I would recommend a definition of sedentary behaviour is included within this section or in an appendix or glossary. Please refer to the following reference for the definition that is used by the Sedentary Behaviour Research Network. Reference: Sedentary Behaviour Research Network. 2012. Standardized use of the terms "sedentary" and "sedentary behaviours". Appl Physiol Nutr Metab. **37**: 540–542. **Recommendations (page 25):** 1. For consistency I would recommend that the description of moderate intensity physical activity is taken from the CMO's UK physical activity guidelines. 2. Not everyone will have the opportunity to incorporate occupational activity into their target 150 minutes of moderate intensity physical activity, therefore I would recommend that the wording of this statement is amended to reflect that physical activity can be accumulated from both occupational and/or leisure time activity.	*Sedentary behaviour was defined in section 6.1 as follows* *"Sedentary behaviour is any waking behaviour characterised by an energy expenditure ≤1.5 METs while in a sitting or reclining posture."* *Noted, however this full description is too long to include in a recommendation.* "A moderate intensity physical activity requires an amount of effort and noticeably accelerates the heart rate, e.g. brisk walking, housework and domestic chores. On an absolute scale, moderate intensity is defined as physical activity that is between 3 and 6 METs" *We have already included a table which shows the absolute intensity of physical activity so this is not needed here.* *Agreed – wording amended to "may include".*

		3. I would recommend this statement is prefaced with 'All' individuals should be advised to minimise the amount of time spent being sedentary (ie. sitting or lying down) over extended periods.	*Disagree. There are subgroups of individuals who are not able to comply or have mobility problems.*
6.2.5	DW	This is covered well - no further comments	*Thank you*
	TY	Lack specific guidance on the amount (eg 150 mins per week etc) but this might be beyond the scope of this update.	*The amount of physical activity is specifically mentioned in section 6.2.4*
	MH	Other key risk factors not cited include inflammatory markers and blood glucose control	*As noted in section 1.2.3, this section was not updated.*
	CB	It does not make sense to talk about 'commonly observed' changes in the context of a small mean difference, since increases will be slightly more common than decreases - there is a need to refer to the group mean changes in LDL, TG and TC.	*As noted in section 1.2.3, this section was not updated.*
	JS	Good	*Thank you*
	JSh	No mention here of the beneficial effect of physical exercise on depression which is acknowledged as a key risk factor.	*As noted in section 1.2.3, this section was not updated.*
	VS	This section does not highlight the effect of physical activity on weight loss maintenance (see above)	*As noted in section 1.2.3, this section was not updated.*
	BHFNC	The inclusion of a section on the effects of physical activity on other key risk factors is very welcomed as we know the evidence indicates that physical activity has both an independent and interactive effect on cardiovascular disease risk. Whilst it is recognised that it is beyond the scope of this guideline to review all the evidence on physical activity and other health outcomes the inclusion of a summary of the evidence on the other clinical factors that have been specifically referenced in this document would be welcomed (reference page 14). The evidence on the role of physical activity in the prevention and management of diabetes and the management of rheumatoid arthritis is now well established. In addition there is a wealth of evidence regarding the benefits of physical activity for	*As noted in section 1.2.3, this section was not updated.*

		psychological wellbeing. Please refer to the US Department of Health and Human Services report as cited above.	
Section 7			
7.1	DW	This is covered well - no further comments	*Thank you*
	JS	Ok	*Thank you*
7.1.1	DW	This is covered well - no further comments	*Thank you*
	CB	It would be preferable to refer to the Million Women's Study of smoking in women - see Lancet 2013, 381: 133-41. This is now the definitive study on the topic of smoking risks in women.	*Agreed. A sentence has been added to include this study.*
	JS	Ok	*Thank you*
7.1.2	DW	This is covered well - no further comments	*Thank you*
	CB	Paras 2 and 3, misuse of the word 'relative' in statements on 'increase in relative risk' - delete 'relative' - see earlier explanation.	*This section was not updated.*
	JS	Ok	*Thank you*
7.2.1	DW	This is covered well - no further comments	*Thank you*
	JB	No discussion about *who* should do the smoking cessation interventions	*This was not part of the key questions, but it also depends on the specific interventions used.*
	JS	Ok	*Thank you*
	AD	What is the best model/service provision for smoking cessation? see www.http://ottawamodel.ottawaheart.ca Andrew Pipe Ottawa model for smoking cessation	*As noted in section 7.2.1 varenicline or combination nicotine replacement therapy should be offered alone or as part of a smoking cessation programme to augment professional advice and increase long-term abstinence rates.*
	VS	This section is mainly focused on the role of pharmacological interventions for smoking cessation. Alongside medication and advice from health professionals, individualised motivational and behavioural support is as important for effective smoking cessation (Aveyard, P, Raw, M, 2012. Improving smoking cessation approaches at the individual level. Tobacco Control 2012;21:252-257 doi:10.1136/tobaccocontrol-2011-50348).	*Noted. The key question linked to this section only investigated a new pharmacological agent which was not available when the previous guideline was published.*

		Psychologists have used taxonomies of behaviour change techniques to identify individual components which are effective in different contexts. This helps to individualise interventions to target specific groups and deliver more effective care, and provide a basis for focused training health professionals in relevant competencies. *(Michie S, Churchill S, West R, Identifying evidence-based competences required to deliver behavioural support for smoking cessation. Ann Behav Med 2011;41:59–70).*	*We broadly agree with this point and have recommended the use of smoking cessation programmes which will incorporate behavioural interventions.*
7.2.2	JE	Useful to see this section given the large numbers of people who are using them. No word of caution however given the fact they are not regulated yet?	*The caution is implicit in the current text.*
	JS	Ok	*Thank you*
7.2.3	DW	This is covered well - no further comments	*Thank you*
	JS	Ok	*Thank you*
Section 8			
8.1	DW	This is covered well - no further comments	*Thank you*
	EL	P. 34 Would it have more impact to say “drinks poured at home are often larger than pub measures? P. 34 In the table against wine, would it be useful to mention the volumes of the small medium and large glass sizes, likely to be used in pubs? Can the final paragraph in 8.1 be updated to reflect the August 2016 update to guidance since the quoted percentages, and which is included in subsequent advice in the guideline?	*Agreed – wording has been revised* *This is covered in Annex 4.* *Agreed. Figures have been updated to 2016 SHS.*
	WS	Table 6. It may be prudent to give equivalent units for beer /lager in terms of mls (and typical cans) as well as pints.	*Additional information already provided in Annex 4. No change required.*
	JE	Is it helpful to include " 23% of men and 17% of women report drinking at harmful or hazardous levels (defined as more than 21 units of alcohol consumed per week for men and more than 14 units per week for women)" especially when the message is about men and women both sticking to 14 units per week as a	*Agreed. This has been updated.*

		maximum number of units consumed? This may be confusing? The recent Joint UK medical officer consultation deliberately only mentioned the 14 unit per week figure and not even the daily limit of 2 per day to avoid confusion.	
	AA	Update reported alcohol intake in line with CMO's 2016 recommendation (Scottish Health Survey Staff need to get this message!!)	*Agreed. See above.*
	JS	Ok	*Thank you*
8.1.1	DW	This is covered well - no further comments	*Thank you*
	EL	Good to have the inclusion of the reasons to challenge to the many claims of protective factors of drinking alcohol.	*Thank you*
	AA	Might be better to highlight cancers where relatively low amounts of alcohol are associated with greater risk e.g. breast, colorectal cancer. The others given are associated with higher intakes. 'Drink free days' doesn't sound correct … days free of alcoholic drinks. The recommendation is carefully worded and sounds appropriate – well done!	*Noted, although the key question we considered did not include cancer outcomes. See section 8.1 which notes "The effects of alcohol on other long-term conditions, for example, mental health, liver disease and cancer are not considered in this guideline but should be taken in to account when providing advice in a clinical setting."* *Disagree. This wording is directly lifted from the Joint CMO report on alcohol.*
	JS	Ok	*Thank you*
8.1.2	MC	Is there anything specific to Scotland on the use of brief interventions? That would be interesting to find out.	*This section was not updated. We agree it would be interesting.*
	DW	This is covered well - no further comments	*Thank you*
	EL	Any scope to highlight training/support to deliver ABIs from Health Scotland and territorial boards to ensure clinical staff using the guideline know how to act on this section?	*This section was not updated, therefore we have not identified the available evidence base in this area.*
	JS	Ok	*Thank you*
Section 9			
9.1	DW	This is covered well - no further comments although the combination of aspirin and dipyridamole is poorly tolerated by patients.	*Thank you. Noted*
	AZ	Within this section it is stated, 'A P2Y12 receptor antagonist is recommended in combination with aspirin in patients with proven	*Noted. We have already included a statement about combination therapy with aspirin and P2Y12 receptor antagonists and cross referred to SIGN*

		Troponin-positive acute coronary syndrome for six months following the acute event.' However SIGN 148 states in its Key Recommendations section, 2.2, page 6 that 'In the presence of ischaemic electrocardiographic changes or elevation of cardiac troponin, patients with an acute coronary syndrome should be treated immediately with both aspirin (300 mg loading dose) and ticagrelor (180 mg loading dose).' Therefore, it is our view that the wording within 9.1 should be changed to reflect this recommendation within SIGN 148. We feel that this is important to allow consistent prescribing and ensure patient safety across Scotland.	*148. The specific choice of antiplatelet agent will be determined by the clinician with respect to the patient's individual characteristics.* *The GDG notes that this comment is submitted from the manufacturer of ticagrelor.* *No change required.*
		Following on from this section, there is a sentence that states, 'Clopidogrel is more expensive than aspirin and should be used if aspirin causes side effects.' We are concerned that this sentence occurs immediately after a section detailing appropriate dual antiplatelet prescribing following an acute coronary syndrome event. We believe this could be misinterpreted and has the potential to result in prescriptions of, for example, ticagrelor plus clopidogrel in aspirin intolerant acute coronary syndrome patients. Our view is that to ensure patient safety, this sentence should not be placed immediately after a sentence detailing acute coronary syndrome antiplatelet regimens. Generally, we believe there should be clearer separation, highlighting the differences of antiplatelet prescribing between primary and secondary prevention of CVD patients.	*Agreed. Sentence on cost of clopidogrel has been deleted and statement about use in ACS moved.*
		If within the scope of the publication search criteria for this guideline, we feel that the following study should be considered for inclusion: Bonaca MP et al. N Engl J Med 2015;372:1791–1800. This study, PEGASUS TIMI-54, randomised patients who had previously experienced a myocardial infarction between one and three years after this index event. They were randomised to either the current standard of care, low dose aspirin plus placebo, or 60mg ticagrelor plus low dose aspirin or 90mg ticagrelor plus low dose aspirin. Following this	*The guideline has not reviewed the evidence for antiplatelet therapy for secondary prevention of CVD, however we have extended the sentence about SIGN 148 to highlight that longer therapy may be considered in specific patients.*

		publication, there is now a license for 60mg ticagrelor1 with low dose aspirin in patients with a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event. We believe it is important for a guideline focusing on the prevention of cardiovascular disease to highlight that up to 3 years of extended dual antiplatelet therapy with 60mg ticagrelor and low dose aspirin could be suitable for some patients and currently is a licensed option across Europe. This inclusion would be aligned with SIGN 148, which, in relation to dual antiplatelet duration, states in the Key Recommendations section 2.4 page 6 'Longer durations may be used where the risks of atherothrombotic events outweigh the risk of bleeding.' Also, in August 2016, NICE issued an appraisal consultation document2 containing the draft recommendation for the long term use of ticagrelor 60 mg (in combination with aspirin) in patients who are at increased risk of atherothrombotic events. The final appraisal decision is expected to be published on the NICE website in late October 2016 (https://www.nice.org.uk/guidance/indevelopment/gidta10016/documents). *Brilique 60 mg Summary of product characteristics* *https://www.medicines.org.uk/emc/medicine/23935/SPC/Brilique+90+mg+film+coated+tablets/* *NICE 'Ticagrelor for preventing atherothrombotic events after myocardial infarction' appraisal consultation document.* *https://www.nice.org.uk/guidance/GID-TA10016/documents/appraisal-consultation-document*	*Agreed*
	CB	Para 4: final line - make clear that this refers to monotherapy.	*Agreed. This sentence has been revised.*
	JS	Ok	*Thank you*
	AD	In secondary prevention of cerebrovascular disease, why is clopidogrel not recommended over Aspirin + Dipyridamole given the head-to-head trial by Yusuf S et al	*This section was not updated, however SIGN 108 recommends aspirin + dipyridamole with clopidogrel as an alternative.* *We have reviewed this RCT and note*

		PROFESS. N Engl J Med. 2008 Sep 18;359(12):1238-51	*that the PROFESS trial showed no net difference in recurrent stroke rates between aspirin + dipyridamole and clopidogrel but discontinuation due to adverse effects was higher in the dipyridamole arm.* *We have revised this recommendation to say clopidogrel is an alternative treatment (not just when aspirin contraindicated).*
9.2	DW	This is covered well - no further comments	*Thank you*
	CB	Table 7 is misattributed - it comes from the Antithrombotic Trialists' Collaboration Lancet 2009 paper (ref 191), where it is Table 3, p1856. In the text the results of ref 194 are conflated with the ATT results. Ref 195 should not be interpreted as showing that the risk of haemorrhagic stroke was only increased in men - suggest deleting this sentence.	*Noted, however, the table is cited in association with the Sutcliffe Health Technology Assessment which, itself, includes multiple sources of evidence including the ATT study where these data originate.* *We disagree. The results of each source of evidence is clearly shown for the separate statements. The ATT results are included within the Sutcliffe HTA, but we feel this is adequately described in the text.* *We agree that this reference does not prove that haemorrhagic stroke is only increased in men, however the available data suggests increases in both sexes which only reach statistical significance in men. Therefore we have deleted the sentence "Further analysis suggests the increase in haemorrhagic stroke was statistically significant only in men".*
	JS	Ok	*Thank you*
9.3	DW	This is covered well - no further comments	*Thank you*
	SW	Should replace "diabetics" with "people with diabetes"(and could also replace "patients with diabetes" too)	*Agreed – these revisions have been made.*
	JS	Ok	*Thank you*
9.4	DW	This is covered well - no further comments	*Thank you*
	CB	The text is not evidence-based. See the ATT paper ref 191, Fig 2. There is no significant heterogeneity of RRs by SBP or DBP, which includes categories of SBP > or = 160 mm Hg, and DBP >90 MM Hg.	*Noted. We do not understand which part of this section is being questioned. The data presented broadly match those of the reviewer.*
	JS	Ok	*Thank you*
	AD	Aspirin not recommended in	*The Cochrane review which we use to*

		hypertension - not even in those >55yrs (see HOT study ref 286 within document). Are there groups of hypertensive patients who may benefit from the addition of Aspirin because of age or co-morbidity? e.g. J Am Coll Cardiol 2010;56:956–65	*support the recommendation not to use aspirin for primary prevention included the HOT trial.* *We agree that individual patients may have combinations of risk factors, such as age or comorbidity which may confer higher CVD risk. However this recommendation applies to a population rather than subgroups within that population.*
9.5	DW	This is covered well - no further comments	*Thank you*
	JS	Ok	*Thank you*
Section 10			
	RCPE	In Chapter 10 it is not always clear whether the risk reductions are relative or absolute. Additionally, most of the risk scores take into account age, and so a non-smoker aged 80 with high cholesterol may have a higher risk score that a smoker aged 35. There needs to be a cautionary message about the influence of age in risk scores.	*Noted. We have checked all risk reductions and clarified where required.* *See section 3.4*
10.1	DW	This is covered well - no further comments	*Thank you*
	JS	Ok	*Thank you*
10.2	SMcC	When to check lipids on those on maximum (or maximum tolerated) doses of statin?	*This was not included in the remit of the guideline, NICE recommends measuring at 3 months after initiation of treatment and to take action if a greater than 40% reduction in non-HDL cholesterol is not achieved*
	DW	This is covered well - no further comments	*Thank you*
	WS	(see comments on section 4.2.2; HDL cholesterol accuracy is compromised in the presence of high triglyceride levels, whether fasting or not. It would therefore be prudent to recommend continuing to check a full lipid profile including triglyceride (the additional cost of routinely including triglyceride is low, often less than one pence, per sample. The cost of acting on an unsuspectedly inaccurate result is potentially huge by comparison). If triglyceride is raised in a patient's non-fasting sample, then it would be prudent for that patient to continue to fast overnight before taking samples for lipids. Also, lipid measurements for risk	*Agreed. We have added a note to include trigs in risk estimation in section 4.2.2.* *Debatable about retesting given high trigs; Emerging Risk Factors Collaboration suggests that fasting and non-fasting give equivalent data but presumably this lacks decent data on those with high trigs (however defined).* *Agreed. We have added this to this*

		estimation should only be made in patients with no evidence of intercurrent illness. Ideally, abbreviations of these points could be incorporated in the 'good practice' points at the end of section 10.4.2	*section and to section 4.2.2*
	JB	Good, pragmatic	*Thank you*
	JS	Ok	*Thank you*
10.3	DW	This is covered well - no further comments	*Thank you*
	WS	The statement starting line 4 "Statin ... 20-25% per 1 mmol/L ... in numerous RCTs" is factually incorrect. No RCT has shown a defined benefit per defined reduction of LDL-C; this has only been assumed by oft-quoted meta-analyses (which have been dominated by results of the 4S trial, one of the few where the active treatment reduced LDL by anything other than 1 mmol/l on average)	*Agreed. We have revised this to "...reduction in LDL cholesterol in* meta-analyses *of RCTs..."*
	DS	Ok (no mention of pleotrophic effects: if indeed important?)	*Not needed. No clear evidence of existence of pleiotrophic effects.*
10.4.1	DW	This is covered well - no further comments	*Thank you*
	CB	This section mixes evidence on effects of LDL cholesterol lowering on CV outcomes and lipid parameters - the topic of this section is surely effects on LDL cholesterol. Suggest reorganising. In para 2, define clinical events (in the context of the CTT, major vascular events - ie, MI or CHD death, stroke or coronary revascularisation). Note that here, and elsewhere, the use of absolute event rates in trials is potentially misleading - it needs to be made clear that trial selection may influence the rates and so the potential benefits or hazards when the trials are applied in current practice may be different.	*Good point, agreed. We have added a new subsection "Effect of statins on cardiovascular end points" and transferred some of this material.* *We accept this, however it is a truism for the entire guideline wherever we quote absolute event rates. We have added a comment into the definitions section (1.3.1).*
	JS	Ok	*Thank you*
10.4.2	SMcC	We, as GPs need clear guidance on when to start and, more importantly, when to stop statins - but we must not got down the route of "blunderbuss" therapy as NICE seem to have done. Current NICE guidance, when applied rigidly, would have every man in the country aged 52 and over on a statin - almost "statins in the water" territory. We must stick with a properly targeted	*Noted.* *This is really about the issue of risk estimation to allocate statins (which we hope will be more adequately addressed subsequently).*

		approach to statin use. We must be given clear guidance on numbers needed to treat (NNT) and number needed to harm (NNH) for statins and, indeed, for all the drugs we might wish to use in cardiovascular prevention/treatment.	*We have generally not cited NNH or NNT for all effects throughout this guideline and are concerned that using it in this section may lead to a "number-based", rather than person-centred approach to managing risk. However, we have added a paragraph to the section on safety explaining the absolute size of the benefits and harms associated with statins using real events avoided / caused and a new subsection (10.4.7) which has converted absolute risk differences to NNT and NNH for statin therapy.*
	DW	This is covered well - no further comments	*Thank you*
	ZM	A comment on value of statins from an early age in FH could be inserted here to emphasise the importance of early intervention in this v high risk subset.	*Disagree. See 10.5.2 where this is covered fully.*
	WS	Table 10. The figures in this table are at odds with those in table 9 (LDL lowering) and the following paragraph (CVD risk reduction). The value of this table is doubtful in any case as it is based on modelling rather than observation. The paragraph "A further meta-analysis..." possibly misrepresents reference 213; the draft states "... mortality was significantly reduced with higher potency statins (but not lower potency...", whereas the referenced paper concludes "Neither metaregression nor stratified analyses suggested statistically significant differences in efficacy between high- and low-potency statins..."	*Disagree – these tables represent different data. Table 9 shows % LDL reduction (based on meta-analysis of 164 trials) where Table 10 shows absolute LDL-c reduction (based entirely on Table 9 data) based on baseline LDL-c of 2 and 4 mmol/L plus CVD risk reduction.* *We agree that the formatting was unclear so have improved this. We feel it is appropriate to base the CVD benefit on the CTT meta-analyses.* *Agreed. Paragraph has been revised. The reviewer rightly indicates that there was no evidence of a difference in efficacy between statin intensities in this paper, however the NICE guideline does show some differences which are also now cited in 10.4.3 and 10.4.4*
	TY	For ease of use it would be helpful to remind the reader what is meant by high risk in this and other recommendations: such as 'Adults wo are assessed at high risk (CVD risk 20% or greater) ....."	*Agreed in theory, though this is a question of logistics around including a long list of categories of risk in each recommendation. See section 4.1 for clear explanation of those estimated to be at high risk or automatically eligible for preventive treatment.*
	CB	In para 4, the RRRs from ref 211 are heavily influenced by JUPITER, which stopped early, and they may as a	*Noted. Like all meta-analyses, this one has weighted the included trials to determine a pooled result.*

		consequence be an overestimate of the truth.	*A caveat around magnitude of effect size has been added.*
	JS	Ok	*Thank you*
10.4.3	FD	Not sure about Atorvastatin 80 mg as a starting dose. We are dealing with an increasingly elderly population and overall I feel that 40 mg would provide the great majority of the benefit at less of a risk. I would add my comment on the dose of Atrovastatin that the subsequent comments on the dose in the elderly does ease my concerns a bit but I still feel the evidence is not strong enough to justify the 80mg dose. I understand a number of other colleagues agree with this position.	*Noted. No evidence to support or refute this. The recommendation already includes instructions to engage in "an informed discussion of risks and benefits". Evidence is presented to show the efficacy, cost effectiveness and safety of Atorvastatin 80 mg with respect to other drugs and doses.*
	DW	This is covered well - no further comments	*Thank you*
	SMac	Non-HDL-cholesterol is not routinely available currently from most Scottish labs.	*While not directly reported, this can be easily calculated as TC-HDL. We understand that Scottish labs will report this increasingly in future and hope that this recommendation encourages this transition.*
	CB	Para 1, line 4: note that an annual event rate of 5.6% may be a substantial overestimate of the magnitude of the event rate that would be observed in an equivalent patient today. Para 2, line 1: delete 'relative' - there is no such thing as a 'reduction in the relative risk' - only a relative reduction of X% in the risk. Penultimate paragraph, final sentence is unclear.	*Noted. The point is that the secondary prevention population is at much higher risk than the primary prevention population. We are aware of a secular decline in event rates. A short statement has been added to clarify this.* *Agreed – this has been changed.* *Agreed - this has been revised.*
	JS	Ok	*Thank you*
10.4.4	DW	This is covered well - no further comments	*Thank you*
	WS	Paragraph 2 is ambiguous: "... four additional cases ..." and "... one additional case ..." are alluded to, but basal rates are not stated, so the significance of the additional cases is unknown. Paragraph 4: I assume that the reference to the BNF (ref 151) is with regard to the recommendation of contraception, and not the reporting of congenital abnormalities as suggested by the wording of the paragraph.	*Agreed. Extra information has been added to aid interpretation.* *Agreed - We have moved the position of the reference number to before the statement on congenital abnormalities.*

		Penultimate paragraph: I would suggest greater care with the wording of this paragraph; whilst statins increase the chances of being diagnosed with diabetes, it is important to state that they do not increase the risk of the unfavourable outcomes traditionally associated with diabetes.	*There is no evidence of DM-related harms (though no trial could ever demonstrate this reliably). We have added a statement to cover this.*
	CB	A better reference for the statements on cancer would be the CTT cancer paper - see PLoS ONE 7(1): e29849. doi:10.1371/journal.pone.0029849 It would also be sensible to refer to Collins et al, Lancet 2016 eptember 8, http://dx.doi.org/10.1016/ S0140-6736(16)31357-5	*Noted. This reference incorporates the same evidence as the study cited. No change required.* *This is referred to in 10.4.5, 10.4.6 and 10.4.7*
	JS	Ok	*Thank you*
10.4.5	DW	This is covered well - no further comments	*Thank you*
	WS	Recommendation 1: "...significant creatinine kinase..." should read "...significant creatine kinase..."	*Agreed. Typo now corrected.*
	JB	Really useful	*Thank you*
	JS	Ok	*Thank you*
10.5.1	DW	This is covered well - no further comments	*Thank you*
	SW	Statement that diabetes confers a doubling of risk of CVD is inconsistent with rate ratio of 1.55 given in table 7 in section 9.2 (and contemporary Scottish data recently submitted for publication).	*Disagree. Table 7 contains data on bleeding risk. We have clarified the table title.*
	CB	Para 2, line 2, delete 'relative'	*Agreed and removed.*
	JS	Ok	*Thank you*
10.5.2	DW	This is covered well - no further comments	*Thank you*
	ZM	This is well written but should include comment on early intervention, preferably by age of 10.	*We did not investigate the age of treatment; however we have included a general threshold of 12 years with the possibility of starting treatment younger if warranted, under specialist supervision.*
	WS	Final paragraph: "... is not considered adequate..." - no definition of 'adequate' is offered.	*Agreed. We have added in NICE's definition of 'adequate' response.*
	Sa	"Subjects with familial hypercholesterolaemia based on clinical or genetic evidence … not considered adequate on maximally tolerated statin therapy, or for	*At the time of writing, no meta-analyses of PCSK9 use in people with FH was available. The SIGN literature searches were limited to systematic reviews and meta-analyses only. We have updated*

		monotherapy where statins are contraindicated." The SMC recently accepted the PCSK9 inhibitor alirocumab for restricted use in NHS Scotland, including the treatment of patients with familial hypercholesterolaemia (SMC No. (1147/16)). We recommend that this SIGN Guideline refers to this recent technology appraisal. The Guideline may want to refer to the clinical and cost-effectiveness evidence for this population that supported this submission: The FH I, FH II and HIGH FH studies were conducted in patients with heterozygous hypercholesterolaemia (HeFH). Diagnosis was either by genotyping or clinical criteria (Simon Broome criteria or World Health Organization/Dutch Lipid Network criteria with a score of >8 points). In FH I and FH II, patients were eligible if they had LDL-C levels greater than the current guidelines for primary (≥2.6mmol/L) or secondary (≥1.8mmol/) prevention, as appropriate. In HIGH FH, patients were eligible if their LDL-C levels were ≥4.1mmol/L. All patients were receiving maximally tolerated stable statin therapy with or without other lipid-lowering therapy. The primary outcome and secondary outcomes related to changes in calculated LDL-C for these studies are presented in Table 1. The mean percentage changes from baseline to week 24 for the other secondary outcome lipid variables were numerically or statistically significantly better in the alirocumab group versus the placebo group. Table 1. Primary outcome and selected secondary outcomes for FH I, FH II and HIGH FH FH I (N=485) FH II (N=247) HIGH FH (N=106) Baseline LDL-C, mmol/L (SD) 3.7 (1.3) 3.5 (1.1) 5.1 (1.4) Mean % change from baseline in calculated LDL-C at week 24 versus placebo -58% -51% -39%	*this section to add meta-analysis evidence published up to April 2017 and the results of the only CV outcome trial to be published on a PCSK9 inhibitor.*

		p value p<0.0001 p<0.0001 p<0.0001 Mean absolute change from baseline in calculated LDL-C at week 24 versus placebo, mmol/L -2.2 -1.8 -1.9 Mean % change in calculated LDL-C from baseline to week 52 versus placebo -56% -59% -39%. Difference in the proportion of patients in the alirocumab and placebo groups achieving calculated LDL-C <1.8mmol/L at week 24 59% 67% 30% SD: standard deviation The SMC assessed the cost-effectiveness of alirocumab for the treatment of adults with heterozygous familial hypercholesterolaemia in addition to appropriate dietary measures. Alirocumab, either in combination with statins or statins and other lipid-lowering therapies or, alone or in combination with other lipid-lowering therapies due to intolerance or contraindication to statins, was found to be a cost-effective treatment option and therefore was accepted for restricted use within NHS Scotland in 8 July 2016 in the following patients at high cardiovascular risk: 1. Patients with heterozygous familial hypercholesterolaemia (HeFH) and LDLC ≥ 5.0mmol/L, for primary prevention of cardiovascular events 2. Patients with HeFH and LDL-C ≥ 3.5mmol/L, for secondary prevention of cardiovascular events "Individuals with familial hypercholesterolaemia should be offered statin therapy regardless of calculated cardiovascular risk and may be considered for combination therapy with ezetimibe where LDL-cholesterol lowering is inadequate on maximally tolerated statin therapy, or for monotherapy where statins are contraindicated." Alirocumab is recommended for restricted use within the NHS Scotland, therefore the above	*We have also added the SMC advice for alirocumab and evolocumab in section 10.6.5 and section 14.4.*

		recommendations should be updated to reflect this. In particular, following the review from the SMC of alirocumab for the treatment of adults with heterozygous familial hypercholesterolaemia, alirocumab is recommended for restricted use within NHS Scotland in the following patients at high cardiovascular risk: 1. Patients with heterozygous familial hypercholesterolaemia (HeFH) and LDLC ≥ 5.0mmol/L, for primary prevention of cardiovascular events 2. Patients with HeFH and LDL-C ≥3.5mmol/L, for secondary prevention of cardiovascular events *Scottish Medicines Consortium (SMC). (2016) alirocumab 75mg and 150mg solution for injection in prefilled pen (Praluent®) SMCNo. (1147/16).*	
	JS	Ok	*Thank you*
10.5.3	DW	This is covered well - no further comments	*Thank you*
	JS	Ok	*Thank you*
10.5.4	DW	This is covered well - no further comments	*Thank you*
	JB	Useful	*Thank you*
	CB	Para 3: ref 235 refers to a trial of just 893 people, so not powered to examine clinical outcomes, so quoting effects on total mortality is inappropriate. (Note: the effect on vascular mortality, 4 vs 10, was not significant, but total mortality is significant only due to 2 vs 8 nonvascular deaths - and we know that this result on nonvascular mortality is not real.) Para 4 seems to belong in the one on safety - or delete it altogether. It has nothing to do with the elderly.	*Agreed. Paragraph has been deleted.* *Noted, however this is the only study identified with an elderly population involving statin cessation. We have added an introductory sentence to show that the evidence in this area is insufficient and this trial represents the only data available.* *We have also removed the final sentence with cost savings.*
	JS	Ok	*Thank you*
10.5.5	DW	This is covered well - no further	*Thank you*

		comments	
	SW	Need to add "relative" in concluding sentence ie "Therefore, the available evidence shows no difference in the relative effectiveness of statin therapy in men and women"	*Agreed. Added.*
	JS	Ok	*Thank you*
10.5.6	FD	What is the conclusion here?	*A conclusion has been added (largely based on the recent CTT meta-analysis by Herrington et al, suggested by another reviewer).*
	DW	This is covered well - no further comments	*Thank you*
	WS	Table 11: It is not clear whether this is real data or data adjusted to 'per mmol/L LDL lowering'	*These data were not adjusted by LDL reduction. But control rate is median control group rate across the studies, and treatment group rate calculated by relative risk reduction. Table title now clarified.*
	CB	A better reference here would be the one produced by the CTT, which had access to individual patient data, from Lancet Diabetes Endocrinol 2016; 4:829–39.	*Agreed. This paragraph has been revised to include this reference which was published after the date of our searches.*
	JS	Ok	*Thank you*
10.6	DW	This is covered well - no further comments	*Thank you*
	WS	The reference provided (210) is a meta-analysis of 58 trials of lipid lowering 'by any means', not 'by means other than statins' as stated in the draft. Indeed, the reference is mainly with regard to statin therapy.	*Agreed. We have provided a more appropriate reference from the era prior to the advent of statins.*
	JS	Ok	*Thank you*
10.6.1	DW	This is covered well - no further comments	*Thank you*
	JS	Ok	*Thank you*
10.6.2	DW	This is covered well - no further comments	*Thank you*
	CB	In the recommendation it is stated that ezetimibe and bile acid sequestrants should only be considered for primary prevention in patients for whom statins are c/i or in patients with FH, but what about patients who have not yet had an event but have a high risk equivalent condition eg diabetes or CKD?	*We think that this recommendation is reasonable based on the cost of ezetimibe (for modest LDL-c reduction) and the poor tolerance of bile acid sequestrant therapy. Therefore we feel that it is most important that clinicians focus on statin therapy for primary prevention.* *We have also cross referred to section 10.5.2 to remind the reader of the recommendation for patients with FH.*
	JS	Ok	*Thank you*

10.6.3	DW	This is covered well - no further comments	*Thank you*
	WS	Should the long term follow up of the BIP trial be considered here? (Cardiovasc Diabetol. 2016 Jan 22;15:11)	*This study was published after the literature search deadlines and was a longitudinal cohort study based on an initial RCT which we did not consider.*
	JS	Ok	*Thank you*
10.6.4	DW	This is covered well - no further comments	*Thank you*
	JS	Ok	*Thank you*
10.6.5	DW	This is covered well - no further comments	*Thank you*
	ND	The current text states that "These agents are now licensed but not yet available for clinical use in Scotland pending long-term outcome data and consideration of cost effectiveness". Can I advise that alirocumab has now been accepted for restricted use by SMC (see website). In addition, SMC has received a resubmission for evolocumab and advice is due to be published early 2017. It may be more appropriate to refer to the SMC advice for both agents in this class if the timelines for publication of the CV risk guideline allows this. I recognise that there is still a knowledge gap with respect to long term outcome data.	*The text has been revised to reflect current SMC advice.*
	Am	To ensure this guideline update is informed by the most current information please be advised of the recent important Phase III clinical trial data for evolocumab: GAUSS-3 The Phase III GAUSS-3 trial identified patients with high cholesterol who could not tolerate statins due to muscle-related adverse events and compared the efficacy of evolocumab 420 mg once monthly with ezetimibe in reducing LDL-C levels from baseline in this patient population (n=218).1 Co-primary endpoints were the mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels and from baseline to week 24 levels.(Nissen et al) The use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C levels after 24 weeks (-52.8% with evolocumab vs -16.7% with ezetimibe,	*Noted.*

		p<0.001). (Nissen et al) Similar significant reductions were observed in LDL-C levels for the mean of weeks 22 and 24 (-54.5% with evolocumab vs -16.7% with ezetimibe, p<0.001). (Nissen et al) No notable side effects occurred in GAUSS-3 and there were no new safety findings when compared with previous clinical studies with evolocumab. GAUSS3 therefore represents the first major clinical trial to include a blinded, placebo-controlled “statin rechallenge” in patients with a history of muscle-related side effects. Evolocumab is the only PCSK9 inhibitor that was evaluated in patients who were confirmed as suffering from statin-intolerance and although GAUSS-3 was modest in size, its positive results demonstrated that evolocumab is atreatment option for statin intolerant patients who have not been able to adequately lower their LDL cholesterol through diet and statins alone. GLAGOV The Phase III GLAGOV trial evaluated the effect of evolocumab 420 mg once monthly on coronary artery disease (CAD) in 968 patients receiving maximally tolerated statin therapy. The primary efficacy end point is the change in percent atheroma volume (PAV) by serial coronary intravascular ultrasound (IVUS) imaging, performed at baseline and at the end of a 78-week treatment period. Secondary end points include the percentage of patients demonstrating PAV regression (defined as any reduction from baseline), the nominal change in total atheroma volume (TAV) by IVUS imaging from baseline to 78 weeks, and the percentage of patients demonstrating TAV regression (defined as any reduction from baseline). (Puri et al) Although the results of GLAGOV have not been fully published yet, Amgen announced positive top-line results from GLAGOV in September 2016, confirming that GLAGOV met his primary and secondary endpoints. No new safety concerns were identified and the incidence of treatment-emergent adverse events was comparable between both groups.	

		This positive announcement indicates that evolocumab reduces atherosclerotic plaque build-up in the coronary arteries of patients already treated with optimised statin therapy. Detailed results from the trial will provide important mechanistic data supporting the use of evolocumab in this patient population and will be available in November 2016. Evolocumab is therefore currently the only PCSK9 inhibitor that has been shown to impact plaque build-up in an imaging study and these positive data are therefore unique to evolocumab. *Nissen SE et al. JAMA. 2016;315:1580-90* *Puri R et al. Am Heart J. 2016;176:83-92* We would like to make SIGN aware that it is expected that top-line results of the Phase III FOURIER outcomes trial will be available early in 2017 and that full results will be presented at American College of Cardiology conference in March 2017 (Washington; 17-19 March 2017) along with a simultaneous publication. We would therefore propose that the timelines for finalisation of this guideline update fully consider the imminent publication of this pivotal clinical trial data such that it reflects the most up-to-date information on the impact of PCSK9 inhibitors on the reduction of cardiovascular events. If the guideline update is published ahead of this data becoming available we would then propose that provision is made for the guideline to undergo a targeted rapid update to address this. The Phase III FOURIER trial compares the effect of evolocumab with placebo in 27,564 patients on an optimised statin regimen who have had a myocardial infarction (MI), an ischemic stroke, or symptomatic peripheral artery disease. (Sabatine) Evolocumab-treated patients received either evolocumab 140 mg biweekly or 420 mg every month. The primary end point is major cardiovascular events defined as the composite of cardiovascular death, MI, stroke, hospitalisation for unstable angina, or	*The FOURIER trial has been cited.*

		coronary revascularisation. The key secondary end point is the composite of cardiovascular death, MI, or stroke. FOURIER will provide robust dataset to examine the relationship between achieved LDL-C and cardiovascular outcomes. It will also provide important safety data for two related issues: long-term administration of evolocumab and achievement of very low LDL-C levels. *Sabatine MS et al. Am Heart J. 2016;173:94-101* It should be noted that on 22 May 2015, the Committee for Medicinal Products for Human Use (CHMP) recommended a positive opinion for the marketing authorisation (MA) for evolocumab intended for adult patients with hypercholesterolaemia and mixed dyslipidaemia, and adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia (HoFH). The European Commission approved the MA for evolocumab in all European Union Member States on 17 July 2015. As such evolocumab (Repatha®) is the only PCSK9 that is indicated in adults and adolescents aged 12 years and over with HoFH in combination with other lipid-lowering therapies. We believe this is an important point of clarification as in patients with HoFH, LDL-C levels are 6- to 10 fold higher than normal and the rates of early-onset CVD and premature CHD events are extremely high. (Goldberg et al) Although not considered by NICE for use in HoFH patients, evolocumab will be commissioned in HoFH patients by NHS England (September 2016). In addition evolocumab has also recently been recommended as an option for use within NHS Wales for the treatment of adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies (July 2016). Alirocumab (Praluent®) is not licensed for use in HoFH patients and there are no additional recommendations for alirocumab in HoFH patients.	

		Goldberg AC, Hopkins PN, Toth PP et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011;5:S1-8. Please note that evolocumab (Repatha®) is currently being considered by the Scottish Medicines Consortium (SMC) for use in NHS Scotland. The submission to the SMC has been scheduled for the New Drugs Committee (NDC) meeting on Tuesday 29 November 2016, with draft advice from NDC being submitted to the Scottish Medicines Consortium (SMC) for a final decision on Tuesday 10 January 2017. Advice will then be issued in confidence to NHS Boards and ADTCs across Scotland on Friday 13 January 2017 and published on the SMC website on the afternoon of Monday 13 February 2017. https://www.scottishmedicines.org.uk/SMC_Advice/Forthcoming_Submissions/evolocumab_Repatha We would therefore propose that the timelines for finalisation of this guideline update fully consider the current status of this appraisal by the SMC to ensure when published it reflects the most up-to-date guidance information in Scotland.	
	KMac	Alirocumab has been approved by SMC and Evolocumab will be considered by SMC soon.	*Evidence for the lipid-lowering efficacy of these drugs has been added and a new recommendation included.*
	WS	Final paragraph: Requires updating to reflect decision by SMC.	*See above*
	Sa	"A meta-analysis of short-term studies using different dosing regimens of evolocumab and alirocumab showed reductions in LDL cholesterol of more than 50% compared to placebo without significant increase in adverse events." For the sake of clarity we would recommend rephrasing the above as follows: A meta-analysis of short-term studies	*See above*

		using different dosing regimens of evolocumab and alirocumab showed reductions in LDL cholesterol of more than 50% from baseline compared to placebo without significant increase in adverse events. "It is anticipated that this group of agents may have a role in patients with familial lipid disorders, in high-risk patients intolerant of statins, and in achieving lower cholesterol levels than hitherto attainable in patients with established disease. These agents are now licensed but not yet available for clinical use in Scotland pending long-term outcome data and consideration of cost effectiveness." Alirocumab is now accepted for restricted use in Scotland. The SMC assessed the cost-effectiveness of alirocumab for the treatment of adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, in addition to appropriate dietary measures (SMC). Alirocumab, either in combination with statins or statins and other lipid-lowering therapies or, alone or in combination with other lipid-lowering therapies due to intolerance or contraindication to statins, was found to be a cost-effective treatment option and therefore was accepted for restricted use within NHS Scotland in 8 July 2016 in the following patients at high cardiovascular risk: 1. Patients with heterozygous familial hypercholesterolaemia (HeFH) and LDLC ≥5.0mmol/L, for primary prevention of cardiovascular events 2. Patients with HeFH and LDLC ≥3.5mmol/L, for secondary prevention of cardiovascular events 3. Patients at high risk due to previous cardiovascular events and LDLC ≥4.0mmol/L (2) 4. Patients with recurrent/polyvascular disease and LDLC ≥3.5mmol/L (3) The SMC clinical experts considered evidence regarding the relationship of LDL-C reduction to future reduction of	

		cardiovascular (CV) events using the Cholesterol Treatment Trialists' (CTT) metaanalysis (Baigent et al) to model the size of reduction in CV events for a given change in LDL-C as CV outcomes data are not yet available for alirocumab or any PCSK9 product. In addition, although not powered or designed to demonstrate outcomes, a post-hoc safety analysis of the ODYSSEY LONG TERM safety study of alirocumab (data up to 78 weeks) as add-on therapy to stable, maximally tolerated, daily statin therapy with or without other lipid modifying therapy, showed a significantly lower rate of major adverse cardiovascular events (MACE) in the alirocumab arm (1.7% versus 3.3%, HR = 0.52 [CI:0.31 – 0.90]) (5). 1. "Ezetimibe and bile acid sequestrant therapy should only be considered for primary prevention in patients at elevated CVD risk in whom statin therapy is contraindicated, and in patients with familial hypercholesterolaemia. 2. Ezetimibe and bile acid sequestrant therapy may be considered for secondary prevention in combination with maximum tolerated statin therapy if LDL cholesterol is considered to be inadequately controlled. 3. Individuals with: a. CVD or who are at high cardiovascular risk, and b. hypertriglyceridaemia (>1.7 mmol/L), and/or c. low high density lipoprotein cholesterol level (<1 mmol/L in men, or <1.2 mmol/L in women) may be considered for treatment with a fibrate. 4. Nicotinic acid is not recommended for cardiovascular risk reduction in any group." Alirocumab is recommended for restricted use within the NHS Scotland, therefore the above	

		recommendations should be updated to reflect this. In particular, following the review from the SMC of alirocumab for the treatment of adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, alirocumab is recommended for restricted use within NHS Scotland in the following patients at high cardiovascular risk: 1. Patients with heterozygous familial hypercholesterolaemia (HeFH) and LDLC ≥5.0mmol/L, for primary prevention of cardiovascular events 2. Patients with HeFH and LDLC ≥3.5mmol/L, for secondary prevention of cardiovascular events 3. Patients at high risk due to previous cardiovascular events and LDLC ≥4.0mmol/L (2) 4. Patients with recurrent/polyvascular disease and LDLC ≥3.5mmol/L (3) FOOTNOTES/REFERENCES 1 Scottish Medicines Consortium (SMC). (2016) alirocumab 75mg and 150mg solution for injection in prefilled pen (Praluent®) SMC No. (1147/16) 2 The 'patients at high risk' group included those with a history of acute coronary syndrome (ACS, myocardial infarction or unstable angina), coronary revascularisation and other arterial revascularisation procedures or other coronary heart disease, ischaemic stroke and peripheral artery disease. 3 'Patients with recurrent/polyvascular disease' included those with recurrent incidences of CV events (more than one previous event) or evidence of disease in multiple vascular beds. 4 Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-81. 5 National institute for health and care excellence (NICE) (2016) Single technology appraisal: Alirocumab for treating primary	

		hypercholesterolaemia and mixed dyslipidaemia [ID779]	
	JS	Ok	*Thank you*
	AD	Proprotein convertase subtilisin/kexin type 9 Advice needs to be updated to reflect SMC advice on Alirocumab - particularly in the context of familial hypercholesterolaemia. What is the clinical importance of poly-vascular disease in predicting risk? see REACH Registry by Steg PG et al	*See above*
10.7	DW	This is covered well - no further comments	*Thank you*
	Sa	This section on treating patients with combined dyslipidaemia has omitted the use of PCSK9 inhibitors and in particular alirocumab which as part of the phase 3 trial programme included patients with dyslipidaemia and this is reflected in the licence indication. Alirocumab is indicated in adults with mixed dyslipidaemia, as an adjunct to diet: • in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of statin (when used as recommended by treatment guidelines) or, • alone or in combination with other lipid-lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated The effect of this technology on cardiovascular morbidity and mortality has not yet been determined. *Sanofi. alirocumab (Praluent®) solution for injection in prefilled pen. www.medicines.org.uk Last updated 3 August 2016.*	*The SMC advice for PCSK9 inhibitors has been added to this section with a new recommendation.*
	SW	This is probably a more general point that is particularly pertinent to this section but in my opinion it's important to clarify that drug treatments should always be offered alongside reinforcement of lifestyle advice. This may have been stated previously and, if so, I apologise for missing it.	*True especially as mixed dyslipidaemia often related to lifestyle. A good practice point has been added to emphasise this point while separate sections on diet, physical activity and smoking provide recommendations on lifestyle modifications generally.*
	JS	Ok	*Thank you*
	AD	Reconsider if there is sufficient	*This was not a recommendation, it is a*

		strength of evidence to make the recommendation that combination therapy with a statin and fibrate may be required for combined dislipidaemia	*GPP carried over verbatim from SIGN 97.* *The text has been weakened to state that combined therapy may be 'considered'. In the context of subgroup findings from trials (ie patients with high trigs and low HDL-c), this seems a reasonable position.*
Section 11			
General	IMac	Has enough account been taken of the findings of SPRINT, PATHWAY-2, PATHWAY-3, and PATHWAY-1 (only in abstract to date so perhaps not possible to include, ACCELERATE?	*PATHWAY 1,2 & 3 studies relate to optimising treatment of hypertension. This was not specifically reviewed by SIGN. However, the existing BHS/NICE guideline referred to in our document is broadly compatible with the main conclusions of these studies.* *ACCELERATE was a trial of evacetrapib for lowering HDL-c. It was stopped early in 2016 due to futility and the drug development programme abandoned, so is of no relevance here.* *See AH comment below.*
	DW	This is covered well, including the advice given to patients with a history of stroke. - no further comments. My overall comments is that the data from the SPRINT trial should be included and discussed	*See above*
	AH	There is little controversial here apart from the hypertension advice which I frankly believe needs to be reconsidered urgently. There are new trials that have been recently been published (SPS3, ACCORD, HOPE-3 and SPRINT). Some of these did not achieve conventional levels of significance but others did and all of these trials suggest that the target for acceptable blood pressure control should be reduced. If this is to be considered a most recent guideline it will be superseded within six months by American guidelines which are going to reduce the target for acceptable blood pressure control and therefore render these guidelines obsolete from this perspective. At the very least if these guidelines do not wish to change the target they should consider the evidence, the meta-analyses that have recently been published that support a reduction in target levels, and give justification for maintaining current target criteria.	*ACCORD-2 is referred to in Section 11.2.1* *The guideline cites the Wie et al meta-analysis which incorporates SPS3, ACCORD and HOPE-3. We are aware of the SPRINT trial, however it was published after the literature review and therefore not considered in meta-analyses. A comment has been added to section 11.2 to explain this.*

	JB	Very full and helpful section	*Thank you*
	JS	Ok	*Thank you*
	MM	Should this section not include information on the importance of the correct exercise or physical activity prescription for patients with uncontrolled hypertension?	*This was not specifically examined by SIGN on this occasion. The key questions were limited to antihypertensive drug therapy.*
11.1.1	FD	I would have thought the recommendation should be stronger than 'considered' for treatment.	*Agree. We have change this to "should be offered".*
	DW	This is covered well, including the advice given to patients with a history of stroke. -no further comments. My overall comments is that the data from the SPRINT trial should be included and discussed	*See above*
	JS	Ok	*Thank you*
11.1.2	FD	It is not clear if this refers to both baseline normotensive and hypertensive patients.	*Agreed. We have revised the recommendation to "irrespective of baseline BP" to "even at levels of baseline BP which are considered conventionally normotensive".*
	DW	This is covered well, including the advice given to patients with a history of stroke - no further comments. My overall comments is that the data from the SPRINT trial should be included and discussed	*See above and section 11.2*
	JS	Ok	*Thank you*
11.1.3	DW	This is covered well, including the advice given to patients with a history of stroke - no further comments. My overall comments is that the data from the SPRINT trial should be included and discussed	*See above and section 11.2*
	JS	Ok	*Thank you*
11.2	IMac	As above - SPRINT important	*See above*
	DW	This is covered well, including the advice given to patients with a history of stroke - no further comments. My overall comments is that the data from the SPRINT trial should be included and discussed	*See above and section 11.2*
	JS	Ok	*Thank you*
11.2.1	DW	Well covered	*Thank you*
	JS	Ok	*Thank you*
11.2.2	DW	Well covered	*Thank you*
	JS	Ok	*Thank you*
11.2.3	DW	Well covered	*Thank you*

	JS	Ok	*Thank you*
11.3	DW	Well covered	*Thank you*
	JS	Ok	*Thank you*
11.3.1	DW	Clearly discussed and well evidenced	*Thank you*
	JS	Ok	*Thank you*
11.4	DW	Well covered	*Thank you*
	JS	Ok	*Thank you*
Section 12			
12.1.1	AK	I think the layout of this seems a bit confused, and I'm not sure anxiety, depression and so on should be subsumed under a heading "stress". I don't know many who would think depression is a component of stress as stated on page 66. In view of your questions highlighted on page 89, I think it would make more sense to separate this in to three subsections, namely, 1) depression, 2) anxiety, and 3) stress. The first of these doesn't appear in your question list but as a topic of great interest to researchers over the years, I am assuming that it exists within the current guideline. I feel the evidence of whether anxiety, stress and depression are risk factors for cardiovascular disease and events is more equivocal that stated. For example, Jansky et al (2010) reported 37 year follow-up results of over 49,000 Swedish men and found a diagnosis of anxiety not depression predicted MI events. Some relevant other papers include: *Janszky I, Ahnve S, Lundberg I, Hemmingsson T. Earlyonset depression, anxiety, and risk of subsequent coronary heart disease: 37 year follow up of 49,321 young Swedish men. J Am Coll Cardiol 2010; 56: 31–37.* *Nabi H, Hall M, Koskenvuo M, SinghManoux A, Oksanen T, Suominen S, Kivimäki M, Vahtera J. Psychological and somatic symptoms of anxiety and risk of coronary heart disease: the health and social support prospective cohort study. Biol Psychiatry 2010; 67: 378–385.* *Roest AM, Zuidersma M, de Jonge P. Myocardial infarction and generalised anxiety disorder: 10year follow up. Br J Psychiatry 2012; 200: 324–329.*	*Agreed that the heading 'stress' may be unhelpful. We have removed this subheading. We have also changed the section title to "Psychological wellbeing" which matches the title in the cardiac rehab guideline.* *Disagree. Depression was not included in the key questions used in the selective update as it was adequately addressed by the previous guideline. This section is a composite of material retained from SIGN 97 and newer material derived from the questions published in the updated version, therefore the content does not only reflect the listed questions.* *Thank you. This evidence is inconsistent. Some conclude that anxiety is not an independent risk factor for CHD. Other studies suggest that it may be.* *Jansky et al, Nabi et al and Roest et al 2012 are all observational studies and therefore not considered in this literature search, which was restricted to systematic reviews only.*

		Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. J Am Coll Cardiol 2010; 56: 38–46. *Batelaan NM, Seldenrijk A, Bot M, van Balkom AJLM, Penninx BWJH. Anxiety and new onset of cardiovascular disease: critical review and meta-analysis. Bri J Psychiatry 2016, 208: 223-231.*	*Roest et al 2010 was identified but excluded on quality grounds.* *We have appraised and added Batelaan et al.* *We did not include depression in the literature searches for this update as there is an existing recommendation to take it into account when assessing risk.*
	DW	Well discussed	*Thank you*
	MH	There is robust evidence demonstrating that individuals with greater cardiovascular responses to laboratory-induced mental stressors subsequently have an increased risk of elevated blood pressure, hypertension, left ventricular mass, subclinical atherosclerosis, and clinical cardiac events. *Chida and Steptoe, Hypertension 2010;55: 1026-32*	*Noted. We are not convinced this reflects anxiety in natural settings.*
	JS	Ok	*Thank you*
	JSh	The recommendation states "Depression and social isolation or lack of quality social support are risk factors for the development of and prognosis of coronary heart disease and should be taken in to account when assessing individual risk" yet this very document fails to recommend this within section 4.	*Agreed. This has been added after table 2 in section 4.*
	VS	As discussed in the draft, because of a lack of clear definition, research on the association between 'stress' and CHD, and determination of causality is inconclusive. The statement: 'While stress is a commonly-used term it has no precise definition and cannot be readily measured' would read better as: 'stress is a commonly-used global term which has different interpretations, and as such, accurate measurement is problematic'. It might be helpful to frame stress in terms of 'stressors' or causes (eg acute and chronic life events, psychosocial work characteristics, social isolation or lack of social support). Depression, anxiety and panic attacks are psychological consequences or outcomes of stressors. Both stressors and outcomes are therefore potentially	*Agreed. This section was mostly not updated from the previous guideline. We will revise the text of the opening paragraph to: "Stress is perceived by the majority of cardiac patients to have been an important cause of their heart disease. This belief is also common among the general public, and confusion exists among health professionals as to its role in the development of and outcome with CHD. Stress is a commonly-used global term which has different interpretations making accurate measurement problematic. Social isolation or lack of social support; work stress; and acute and chronic life events can serve as stressors, with resulting psychological outcomes such as depression and anxiety."*

		associated with increased risk of CHD.	
12.2.1	AK	This section doesn't seem to reflect the question detailed on page 89 "Is there evidence that interventions to alleviate anxiety and depression influence cardiovascular risk?" Again at times, this section seems a bit confusing to readers, or me at least.	*This section is a composite of material retained from SIGN 97 and newer material derived from the questions published in the updated version.*
		Whilst in the UK some healthcare providers do design psychological services in a stepped care fashion, most notably IAPT in England, a systematic review in 2015 found no evidence this delivers more effective outcomes or is more cost-effective.	*The reference to stepped care model was from the NICE depression guideline and was not further evaluated. As stepped care was not systematically reviewed and there is no recommendation for it, we would not propose to review this evidence.*
		van Straten, Annemieke, et al. "Stepped care treatment delivery for depression: a systematic review and meta-analysis." Psych Med 2015; 45: 231-246.	
		The answer to the question above appears to be no. Certainly that is entirely in-keeping with recent systematic reviews of treating depression across LTCs.	
		I'm not sure why the rest of the material is presented because it doesn't seem to reflect the questions SIGN posed. In view of the fact that anxiety and depression are common in those with CVD, it seems sensible to point out that psychological and other treatments can be successful. I certainly agree that there is much evidence that both anxiety and depression will compound markedly the disease burden and negatively impact on quality of life.	*See above – the key questions listed are the newer questions added for the selective update and do not comprise the full set used in the previous version of the guideline.*
		It might be wiser to simply encourage readers to look for the clinical guidelines on these topics and it makes no obvious sense to refer only to depression. The NICE guidance on treating depression in those with LTCs was checked relatively recently (2015).	*The previous guideline identified depression, lack of social support and social isolation as independent risk factors for CVD, among the psychosocial factors considered.* *We have cross referenced to the NICE guideline suggested.*
		To indicate explicitly that people with certain kinds of problems should see a specific professional, there must be an evidence base to indicate superiority of outcomes. As far as I know, there is no evidence that clinical psychologists have better	*Agreed. We have deleted the phrase "patients who are resistant to change". The GPP has been revised to align with the NES Matrix – A guide to delivering evidence-based psychological therapies in Scotland.*

		outcomes than other professionals (page 68). Moreover, this approach is out of keeping with the style of rest of the document. For example, there is no indication that people need to see a fully qualified medical practitioner for SSRIs (page 69) or indeed which specific healthcare professionals are best suited to deliver the care highlighted elsewhere in the guideline update.	
	NM	It would be good have physical activity mentioned here again. Solid evidence for improved mood and for both prevention and treatment of depression.	*Disagree. This section covers the impact of psychological distress on cardiovascular risk.*
	DW	Well discussed	*Thank you*
	JS	Ok	*Thank you*
	MS	In the section I wondered if it would be helpful to consider the NICE Guideline CG91. In the Matrix tables 2015 we gave the following advice:- Overarching recommendation for healthcare professionals NICE Guideline CG91 'Depression in adults with a Chronic Physical Health Problem' recommends that practitioners should be aware of the elevated risk of common mental health disorders and comorbid psychological difficulties, particularly depression, in people with a Chronic Health Problem, underlying the guidance on effective case identification and recognition, and on risk assessment and monitoring for this patient group. Where low or high intensity psychosocial interventions (excluding self-management) are recommended for the treatment of common mental health problems, follow the recommendations for intervention delivery set out in NICE guidelines CG91 and CG90, or the relevant NICE anxiety disorder guideline, unless otherwise stated. NICE guideline recommendations for depression and anxiety disorders can also be cross-referenced in the NES (2015) Psychological Therapies Matrix3.	*Noted. We have added a cross reference to NICE guidelines 90 and 91, as this SIGN guideline will apply to people with and without a comorbid chronic disease, as the primary prevention population are at risk of disease.*
	VS	The statement: 'The stepped-care model which organises the provision	*We have reworded to "least intrusive, but most effective, intervention….."*

		of services in a structured manner and emphasises offering the least intrusive, most effective intervention first..' is misleading as it suggests that lower intensity interventions are more effective overall than those of higher intensity. Reference to 'intrusive' intervention is also rather misleading. The point is that lower intensity interventions target less complex / intense problems. There is no reference to or evaluation of 'third wave' therapies including ACT or mindfulness (eg. MBSR-Mindfulness based stress reduction) approaches in this section. The evidence base is relatively new, and not very strong, but there is some evidence for efficacy of ACT in comparison with CBT for psychological distress (e.g. Ost, L, (2014) The efficacy of Acceptance and Commitment Therapy: An updated systematic review and meta-analysis. Behaviour Research and Therapy, 1-17.) MBSR has also been used to treat anxiety and depression, including in CHD patients (e.g. Parswani et al 2013). I think it is relevant here as many patients will be aware of these interventions which are increasingly available, and may seek guidance regarding their efficacy.	*There are a number of different therapeutic approaches emerging, including third wave therapies such as ACT, but study numbers are low and evidence is limited currently.* *The systematic review by Ost is not relevant to the key question. It pooled RCTs of any population receiving ACT. These were heterogeneous, although none specified patients with CVD. They included patients with psychiatric disorders, somatic disorders or stress in work.* *The literature search has been limited to systematic reviews only, therefore the RCT by Parswani et al was not considered. Furthermore, this is a small study with no CVD outcomes.*
12.2.2	MM	Some cross-referencing to the role of exercise on depression seems warranted given the current evidence	*This was not included in the key questions.*
Section 13			
General	SMcC	I have campaigned for many years to have relative risk reductions removed from medical papers and guidelines and have absolute risk reductions instead. Relative risk reductions mean a lot to researchers but are mis-leading for patients and the public. So, for example, if a drug reduces the risk of something from 10 in 10,000 to 7 in 10,000 that's a relative risk reduction of 30% which sounds fantastic. But it's already a rare event and, in reality, we have only reduced its absolute likelihood by 0.03% which is effectively nothing at all. We must put all risks in context to allow clinicians and patients to make truly informed choices. So something	*We agree, however this is not relevant to this section. Use of absolute risk in isolation may be misinterpreted unless the baseline risk of the trial participants is described. Where possible, we use a combination of absolute and relative risk throughout the guideline.* *While we agree that this may be a persuasive approach, it is difficult to validate these risks systematically. Risks*

		like a "micromort" table that compares medical risks to non-medical risks (e.g. diving, cycling, etc.) will give patients the kind of tools they need to make truly informed choices about the therapy they are being offered. As clinicians we need to be given the tools to allow us to take a truly consensual approach to treating out patients. SIGN could/should develop a standard "risk comparisons" table to put into all their guidelines.	*of routine daily activities carried out consciously (eg cycling) may not be appropriate to compare to lifetime risk estimates for chronic diseases which are sampled from population cohorts.*
	DW	Comprehensive	*Thank you*
	JS	Ok	*Thank you*
	VS	It would be helpful here to stress the importance of practitioner skills in communication and behaviour change, shared decision making and shared care planning (adopting a 'Realistic Medicine' approach as per the recent (2016) CMO Report).	*Noted. However, this section is information for provision to patients, rather than healthcare professional training.*
13.1	DW	Comprehensive	*Thank you*
	ZM	This could reference NICE and European Atherosclerosis Society familial hypercholesterolaemia guidance if it does not do so, also HEART UK and BHF patient information.	*These organisations provide material mainly targeted at healthcare professionals.* *The BHF is already listed in this section. We have added Heart UK.*
	EL	ABI training available from Health Scotland and Territorial Boards to ensure clinical staff using the guideline know how to access this?	*We do not understand this comment. Health Scotland provides information to policy and decision makers to take action to reduce health inequalities. Its advice is not directly relevant to this section.*
	WS	Consider including HEART UK as a useful source of further information. Also consider referring to the JBS risk calculator as a user-friendly tool to help patients understand the nature of cardiovascular risk factor modification.	*We have added Heart UK.* *This section already includes the suggestion "explain the individual's specific levels of risk using terminology and visual tools appropriate to the patient." We do not endorse other risk calculators than ASSIGN.*
	SW	The following websites may be helpful for some people: https://www.livingitup.scot/ - to support health, wellbeing and self-management for the over 50s http://www.mydiabetesmyway.scot.nhs.uk/ - for people with diabetes	*Thank you. We feel that the "Living it up" website is not typical of the other organisations listed in this section in that it does not provide verified information, but is a portal for communicating patient stories. While we generally endorse both this site and My Diabetes My Way, the function of the latter is to provide access for individual patients to personalised health records, rather than provide specific advice. We feel that there is no additional information provided by this*

			site compared with Diabetes UK, which is already listed.
	JS	Ok	*Thank you*
13.2	DW	Comprehensive	*Thank you*
	JS	Ok	*Thank you*
Section 14			
General	DW	No further comment	*Thank you*
	JS	Ok	*Thank you*
14.1	DW	No further comment	*Thank you*
	JS	Ok	*Thank you*
14.2	DW	No further comment	*Thank you*
	JS	Ok	*Thank you*
14.3	DW	No further comment	*Thank you*
	JS	Ok	*Thank you*
14.4	DW	No further comment	*Thank you*
	Sa	Alirocumab is recommended for restricted use within the NHS Scotland, therefore the above recommendations should be updated to reflect this. The SMC advice is for alirocumab either in combination with statins or statins and other lipid-owering therapies or, alone or in combination with other lipid-lowering therapies due to intolerance or contraindication to statins, in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet. Alirocumab is recommended for specialist use only in patients at high cardiovascular risk as follows: 1. Patients with heterozygous familial hypercholesterolaemia (HeFH) and LDLC ≥5.0mmol/L, for primary prevention of cardiovascular events 2. Patients with HeFH and LDLC ≥3.5mmol/L, for secondary prevention of cardiovascular events 3. Patients at high risk due to previous cardiovascular events and LDLC ≥4.0mmol/L (1) 4. Patients with recurrent/polyvascular disease and LDLC ≥3.5mmol/L (2)	*Agreed. We have added this.*

		FOOTNOTES 1 The ‘patients at high risk’ group included those with a history of acute coronary syndrome (ACS, myocardial infarction or unstable angina), coronary revascularisation and other arterial revascularisation procedures or other coronary heart disease, ischaemic strokeand peripheral artery disease. 2 ‘Patients with recurrent/polyvascular disease’ included those with recurrent incidences of CV events (more than one previous event) or evidence of disease in multiple vascular beds.	
	JS	Ok	*Thank you*
Section 15			
15.1	DW	No further comment	*Thank you*
	JS	? seems ok	*Thank you*
15.1.1	DW	No further comment	*Thank you*
	JS	Ok	*Thank you*
15.1.2	DW	No further comment	*Thank you*
	JS	Ok	*Thank you*
15.2	JS	Ok	*Thank you*
Annexes			
	JB	Annex 2 – useful	*Thank you*
	MH	Might be useful to also include step count for easier interpretation. Kozy Keadle's guidelines for example; Sit less; avoid taking <5,000 steps/d Walk more; take >7500 steps/d	*Disagree. We feel that the messages around physical activity are well described, and draw attention to the included Annex 3*
	JS	Annex 1 – ok	*Thank you*
	JS	Annex 2 - ok	*Thank you*