National Institute for Health and Clinical Excellence

Myocardial Infarction Secondary Prevention (Update)
Guideline Consultation Comments Table
Guideline consultation dates: Thursday 13th June 2013 – Wednesday 24th July 2013

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Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Abbott Healthcare Products Limited	1	Full	General	General	**Abbott and experts would like NICE to include** **I. GRPD data** **II. Omacor in the Drugs Section** **Omacor is clinically proven as a key drug treatment in the prevention of premature death. This is proven in robust RCTs (e.g.GISSI-P) and backed by a well-structured cohort analyses of clinical data from GPRD 2013, and clinical expert opinion.** Abbott's comments are as follows: (for further details of each of the following points please refer to the rest of this proforma) 1.Omega-3-acid-ethyl esters 90 (Omacor) is a licensed drug, not a supplement and hence recommendations on Omega-3-acid ethyl esters 90 should be discussed in section 7, Drug Therapy of CG48	Thank you for your comments. We acknowledge that there are differences in the quality of published omega-3 RCTs. This was highlighted in the GRADE tables and discussed in the 'Linking evidence to recommendation' sections. Because of differences in the quality of the studies, the guideline development group placed greater emphasis on the results from higher quality studies (such as Rauch et al) when they made their recommendations. The GDG felt that the use of omega-3-acid ethyl esters is related to diet and lifestyle factors (for example, eating oily fish) and therefore felt that this should sit within the chapter on 'Lifestyle'.

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						2. Not all Omega 3 studies included in the NICE consultation document are comparable to Omega-3-acid ethyl esters 90 (Galan 2011 ref 143, Kromhout 2010 ref 217, Matsuzaki 2009 ref 249) 3. A number of the Omega-3 studies included are not sufficiently powered to answer the review questions posed by NICE (Nilsen 2001 ref 296, Rauch 2010 ref 346) combined 4. In order to provide a balanced overview of the available clinical evidence on all-cause mortality the results of the GPRD all-cause mortality 2013 study need to be taken into consideration (Please see GPRD 2013 attachment below) 5. The current body of evidence GISSI-P (draft guideline ref 152) and more recently GPRD-2013 (see attachment below) show that 1g Omega-3-acid-ethyl esters 90 has a key role to play in reduction of sudden death in patients suffering from an MI. This is in line with DoH & NICE agenda (Department of health, NHS Outcome Framework 2012-2013 Annex 1 reducing premature mortality from major causes of death, NICE Living well for longer: preventing premature mortality http://www.nice.org.uk/media/363/21/Premature_Mortality_for_local_authorities.pdf	

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						6. The hazard ratio data for all-cause mortality reported in the recent GPRD-2013 trial (see attachment below) is in line with that reported in the GISSI-P trial, and hence the Quilici 2006 (Draft guidance ref 346) cost-effectiveness analysis based on GISSI-P, and acknowledged in CG48 2007. Indicates that the Incremental Cost-Effectiveness Ratio is likely to remain under the QALY threshold and is still valid today  Poole CD et al 2013 GPRD	
SH	Abbott Healthcare Products Limited	2	Full	General	General	Licensed Omega-3-acid ethyl ester 90 (Omacor) is a registered medicinal product in over 60 countries. Recommendations on Omega-3-acid ethyl ester 90 should be discussed in section 7, Drug Therapy. In CG87 Type 2 diabetes, Omega-3-acid ethyl ester 90 is correctly recognized as a pharmacological treatment and recommendations on this product are presented in section 1.10, management of blood lipid levels.	Thank you for your comment. Although omega-3 fatty acid capsules can be prescribed and considered a medicinal product, the GDG felt that they are more related to diet and lifestyle factors (for example, eating oily fish) and therefore felt that it should sit within the chapter on 'Lifestyle'. We have added a comment on this in the LETR "other considerations".

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						Galan 2011 (ref 143), Matsuzaki 2009 (ref 249) and Kromhout 2010 (ref 217) are not comparable to Omega-3-acid ethyl esters 90 (Omacor) the omega-3 products used are also not readily available in the U.K. A more relevant review question should therefore be introduced; **What is the clinical and cost effectiveness of prescription grade licensed Omega-3-acid ethyl esters 90 in patients with myocardial infarction?** ********** has reviewed our proforma, in his comments he stated, **"It would seem to me that it is of key importance to first establish the effectiveness (and cost-effectiveness) of Omega-3-acid-ethyl esters 90, relative to non-use of that product."**	Thank you for your comment. We acknowledge that there are differences in the dose of omega-3-acid-ethyl esters used across the studies identified, including the proportions of EPA and DHA included. However, the number of studies identified was insufficient to explore the effect of dose upon the outcomes. We have added a comment on this in the LETR "quality of evidence". The GDG felt that the weight of evidence, in particular in people treated with modern therapy following acute MI, did not support the use of omega-3 acid ethyl esters, including Omacor, particularly, given the null results provided by the Rauch trial which used prescription grade omega-3-acid ethyl esters. Additionally, no difference in all-cause mortality (using hazard ratios) in studies that treated patients with prescription grade omega-3 capsules against placebo was found.
SH	Abbott Healthcare Products	3	Full	General		**Abbott recommends the inclusion of GPRD all-cause mortality trial. All-cause mortality is listed as a critical outcome in Appendix C.1**	Thank you for your comment. Although the study by Poole et al. includes large numbers, it is a cohort study and is

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	Limited					**pg 28.**  Poole CD et al 2013 GPRD **Omega-3 Fatty Acids and Mortality Outcome in Patients With and Without Type 2 Diabetes After Myocardial Infarction: A Retrospective, Matched-Cohort Study** Authors: Poole CD; Halcox JP; Jenkins-Jones S; Carr ESM; Schifflers MG; Ray KK; Currie CJ Source: CLIN. THER.; 35/1 (40-51) /2013/ Abbott appreciate that RCTs are preferred to cohort studies, however cohort studies with hard end-points (such as death) should be considered, particularly when based on contemporary therapies. The use of cohort studies is acknowledged by the GDG, in section 6.4 of the guideline "interventions to increase uptake of and adherence to cardiac rehabilitation programmes". Various cohort studies are referred to in this section (references 158, 159 and 371). For a consistent approach we would hope that cohort studies with hard end-points	less reliable than the data provided by RCTs. Our pre-defined protocol (see Appendix C) states that RCTs will be considered in preference to cohort studies, unless no randomised evidence was identified for a particular outcome.

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						are included in this NICE review. The data in the GPRD 2013 all-cause mortality study is aligned with NHS goals to reduce premature death **NHS outcomes framework Domain 4: Preventing people from dying prematurely** **https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/151875/dh_132362.pdf.pdf** And aligned with NICE advocacy for premature death - http://www.nice.org.uk/media/363/21/Premature_Mortality_for_local_authorities.pdf ********* has reviewed our proforma, in his comments he stated "**A crucial piece of evidence in measuring the effectiveness of Omega-3-acid-ethyl esters 90 is the paper by Poole *et al*. (2013) and, as such, this should be considered, along with any other suitable evidence, by the Committee**."	
SH	Abbott Healthcare Products Limited	4	Full	General	General	**A number of the Omega-3 studies included are not sufficiently powered to answer the review questions posed by NICE** **Abbott would like to highlight the**	Thank you for your comment. The power calculation in the Rauch paper showed it required 1900 in each arm. The study included 1925 in the omega-3-acid ethyl esters arm and 1893 in the control arm.

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						underpowered nature of the Rauch 2010 (ref 346) OMEGA study. (this is not reflected in the guidance). The quality of the study should be downgraded to very low The study discussed in ref 346 was too statistically underpowered to draw any firm conclusions. The authors of the study, Rauch et al 2010 state "On the basis of the present results, the anticipated statistical power of 80% was not reached. In an a posteriori calculation, the statistical power was 44% to detect a 45% risk reduction in SCD as anticipated by the study protocol (see Methods pg 2153) and 19% for a risk reduction of 25%". The analysis and the determination of the sample size in the OMEGA study is based on that of the GISSI-P. However in the GISSI-P trial follow up was 42 months whilst the OMEGA trial follow up was only 12 months. **********was asked to review and make comments on both OMEGA study design and the presented results. His conclusion is that sample sizes of 11736 in each group would be required (12868 per group with 8.8% dropouts), in order to have an 80% chance of identifying such a difference in this 12 month follow up trial. **Abbott wish to highlight the underpowered**	However, the authors did highlight given the results that the anticipated statistical power of 80% was not reached. A comment to note this has been added was added to the 'Linking evidence to recommendation' section. Regardless of being statistically underpowered, the results in this review are meta-analysed with other papers so any limitations with power are compensated with the inclusion of other trials. And in the case where it was the only study that provided data on that outcome, a comment was added to the GRADE table regarding the lack of power.

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						nature of the Nilsen 2001 (ref 296) investigator initiated trial (This is not reflected in the guidance). The quality of the study should be downgraded to very low The study discussed in ref 296 was severely underpowered. This was acknowledged by the GDG in the 2007, CG48 full guideline page 49, **"The study was powered to measure the effects of the omega-3-acids ethyl esters only on serum lipids"** In the Nilsen 2001 study the prevalence of combined cardiac events was estimated to be around 35% for one year of observation. The hypothesis was that the treatment would reduce the outcome to 25%, this meant an absolute reduction of 10 % and a relative reduction of (1 - 0.71) x 100 = 29% as the relative risk RR = 25/35 = 0.71. For a type I error of 5% and a power of 80%, this would require 338 patients in each arm. As presented in the final publication, only 300 patients in total were recruited for this study. Hence the study was not adequately powered for the demonstration of its primary endpoint. The number of patients needed to detect a difference between the groups is calculated using the figures from the GISSI-P study: In the GISSI-P study, it has been observed that 87.4%	

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						of the patients for the Omacor group and 86.1% for the control group were without an event at the end of the study. As the sample size in each group is only 150, a 0.05 level two-sided log-rank test for equality of survival curves will only have 5% power to detect the difference between a group 1 proportion at time t of 0.874 and a group 2 proportion at time t of 0.861 (a constant hazard ratio of 0.900). This assumes no drop outs before time t. As a result, the study will not be a good test if it is important that the study have a reasonable chance of truly distinguishing between a proportion of 0.874 and 0.861.	
SH	Abbott Healthcare Products Limited	5	Full	General/ NICE version	General/ NICE version	The draft recommendation states "Do not offer or advise people to use the following to prevent another MI". Mortality (all cause, cardiac or sudden) and quality of life are listed as a critical outcome in Appendix C.1 clinical evidence reviews page 28. Prevention of another MI is not equivalent to reduction in mortality and does translate to better quality of life. Abbott wishes to flag this inconsistency. Abbott strongly believes that current body of evidence shows a statistical and clinical reduction in mortality in licensed Omega-3-acid ethyl ester 90 treated patients. (Both the GISSI-P (ref 152) and recent publication Poole 2013 GPRD all-cause mortality trial)	Thank you for your comment. Although reinfarction was not considered a critical outcome we made reference to it in the recommendation because we acknowledge that oily fish may provide other health benefits, but for the prevention of another MI the data does not support its use; the results show oily fish may increase the risk of reinfarction. We acknowledge that another MI is not equivalent to a reduction in mortality or better quality of life. And the GDG gave greater weight to these outcomes when making their decision, however

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							for this recommendation quality of life data was not available and the results on mortality were unequivocal. In contrast, the findings on reinfarction clearly showed consuming oily fish may increase the risk of reinfarction. .
SH	Abbott Healthcare Products Limited	6	Full	General	General	Abbott would like further clarification on whether the relative risk data taken from the GISSI-P (ref 152) is being calculated from the Two-way analysis or the four-way analysis. The data available from the Four-way analysis (see table 3 page 450 of the GISSI-P paper) provides a clear picture of the role of licensed Omega-3-acid ethyl esters 90 in patients with myocardial infarction as the Two-way analysis also includes a subset of patients (2830) taking vitamin E.	Thank you for your comments. We included the two-way results because it included a larger number of patients and therefore greater power to detect a difference should one exist. The 4-way analysis would have been used if the 2-way groups were not matched for Vitamin E intake or if there was an interaction between omega-3 and Vitamin E. Neither was the case, hence the larger numbers provided by the 2-way analysis were included. The paper states there was no increased benefit was apparent when the rate of the combined endpoint of death, non-fatal MI, and no-fatal stroke that was seen in patients receiving n-3PUFA plus Vitamin E was compared with the group receiving n-3 PUFA alone (1.01 (0.87 to 1.17) or with patient treated with vitamin E alone

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							(0.96 (0.83 to 1.12).
SH	Abbott Healthcare Products Limited	7	Full	General	General	Omacor is a licensed highly purified Omega-3-acid ethyl esters 90. The clinical data behind the licence is supported by 24 registration studies and more than 30 post-marketing trials. Patient exposure has been estimated at more than 1.2 million patient years since its launch (Data on file PSUR).The active molecule is licensed in over 60 countries. Prostate cancer is not listed as an expected adverse event in the Omacor summary of product characteristics. The available evidence does not support a causal association between the administration of Omacor and the risk of prostate cancer.	Thank you for your comment. We are aware that data has become available since the review within the guideline. However, the study that was highlighted was not based on people who have had an MI and therefore did not meet our inclusion criteria.
SH	Abbott Healthcare Products Limited	8	Full	21	9	**Licensed Omega-3-acid ethyl ester 90 (Omacor) is a registered medicinal product in over 60 countries. Recommendations on Omega-3-acid ethyl ester 90 should be discussed in section 7, Drug Therapy**. In CG87 Type 2 diabetes, Omega-3-acid ethyl	Thank you for your comment. We acknowledge that there are differences in the types of omega-3-acid-ethyl esters used across the studies identified, including the proportions of EPA and DHA included. However, the number of studies identified was

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						ester 90 is correctly recognized as a pharmacological treatment and recommendations on this product are presented in section 1.10, management of blood lipid levels. A more relevant review question should therefore be introduced; **What is the clinical and cost effectiveness of prescription grade licensed Omega-3-acid ethyl esters 90 in patients with myocardial infarction?** Recognition should be given to the licensed Omega-3-acid ethyl esters 90 capsule preparations comprising 840 mg eicosapentaenoic acid ethyl ester (460 mg) and docosahexaenoic acid ethyl ester (380 mg) vs. supplements or food sources. Supplements may contain as little as 21% omega-3 PUFA Omega-3-acid ethyl esters 90 is a different chemical compound to crude fish oil. A patented purification process is applied to the crude fish oil in order to achieve the high grade Omega-3-acid ethyl esters 90 medicine. Omacor consists of high levels of EPA and DHA and low levels of other fatty acids, cholesterol and environmental pollutants. The ratio of EPA and DHA in Omacor is 1.2:1 (EPA:DHA).	insufficient to explore the effect of dose upon the outcomes. The GDG felt that the weight of evidence, in particular in people treated with modern therapy following acute MI, did not support the use of omega-3 acid ethyl esters, including Omacor, particularly, given the null results provided by the Rauch trial which used prescription grade omega-3-acid ethyl esters. Additionally, no difference in all-cause mortality (using hazard ratios) in studies that treated patients with prescription grade omega-3 capsules against placebo was found.

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						Although we recognise that where possible, meta-analyses were conducted to combine the results of studies, not differentiating dose, quality and concentration (i.e. EPA:DHA ratio) of the omega-3 products will result in potential bias.	
SH	Abbott Healthcare Products Limited	9	Full	48	42	**Abbott disagree with the draft statement "Do not offer or advise people to use the following to prevent another MI".** Mortality (all cause, cardiac or sudden) and quality of life are listed as a critical outcome in Appendix C.1 clinical evidence reviews page 28. Prevention of another MI is not equivalent to reduction in mortality and does translate to better quality of life. The statement should be reworded to reflect this inconsistency.	Thank you for your comment. Although reinfarction was not considered a critical outcome we made reference to it in the recommendation because we acknowledge that oily fish may provide other health benefits, but for the prevention of another MI the data does not support its use; the results show oily fish may increase the risk of reinfarction. We acknowledge that another MI is not equivalent to a reduction in mortality or better quality of life. And the GDG gave greater weight to these outcomes when making their decision, however for this recommendation quality of life data was not available and the results on mortality were unequivocal. In contrast, the findings on reinfarction clearly showed consuming oily fish may increase the risk of reinfarction.

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SH	Abbott Healthcare Products Limited	10	Full	52	10	**Abbott recommends Inclusion of Licensed Omega-3-acid ethyl ester 90 (Omacor) in section 7, Drug Therapy.** Licensed Omega-3-acid ethyl ester 90 (Omacor) is a registered medicinal product licensed in over 60 countries. Recommendations on Omega-3-acid ethyl ester 90 should be discussed in **section 7, Drug Therapy**. In CG87 Type 2 diabetes, Omega-3-acid ethyl ester 90 is correctly recognized as a pharmacological treatment and recommendations on this product are presented in section 1.10, management of blood lipid levels. Abbott trust that a consistent approach is applied in all NICE clinical guidelines.	Thank you for your comment. The GDG felt that the use of omega-3-acid ethyl esters is related to diet and lifestyle factors (for example, eating oily fish) and therefore felt that this should sit within the chapter on 'Lifestyle'.
SH	Abbott Healthcare Products Limited	11	Full	59	3	Recognition should be given to the licensed highly purified Omega-3-acid ethyl esters 90 capsules comprising 840 mg eicosapentaenoic acid ethyl ester (460 mg) and docosahexaenoic acid ethyl ester (380 mg) vs. supplements or food sources. Supplements may contain as little as 21% omega-3 PUFA A more relevant review question should therefore be introduced; **What is the clinical and cost effectiveness of prescription grade licenced Omega-3-acid**	Thank you for your comment. We acknowledge that there are differences in the types of omega-3-acid-ethyl esters used across the studies identified, including the proportions of EPA and DHA included. However, the number of studies identified was insufficient to explore the effect of dose upon the outcomes. The GDG felt that the weight of evidence, in particular in people

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						ethyl esters 90 in patients with myocardial infarction? Omega-3-acid ethyl esters 90 (Omacor) is a different chemical compound to crude fish oil. A patented purification process is applied to the crude fish oil in order to achieve the high grade Omega-3-acid ethyl esters 90 medicine licensed worldwide. Omacor consists of high levels of EPA and DHA and low levels of other fatty acids, cholesterol and environmental pollutants. The ratio of EPA and DHA in Omacor is 1.2:1 (EPA:DHA) Although we recognise that where possible, meta-analyses were conducted to combine the results of studies, not differentiating dose, quality and concentration (i.e. EPA:DHA ratio) of the omega-3 products will result in potential bias.	treated with modern therapy following acute MI, did not support the use of omega-3 acid ethyl esters, including Omacor, particularly, given the null results provided by the Rauch trial which used prescription grade omega-3-acid ethyl esters. Additionally, no difference in all-cause mortality (using hazard ratios) in studies that treated patients with prescription grade omega-3 capsules against placebo was found.
SH	Abbott Healthcare Products Limited	12	Full	62	4	Abbott appreciate that RCTs are preferred to cohort studies however cohort studies with hard end-points (such as death) should be considered, particularly when based on contemporary therapies The use of cohort studies is acknowledged by the GDG, in section 6.4 of the guideline "interventions to increase uptake of and adherence to cardiac rehabilitation programmes". Various cohort studies are	Thank you for your comment. Our pre-defined protocol (see Appendix C) states that RCTs will be considered in preference to cohort studies, unless no randomised evidence was identified for a particular outcome.

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						referred to in this section (references 158, 159 and 371). For a consistent approach we would hope that cohort studies with hard end-points are included in this NICE review. Recommendation of inclusion of: **Exploratory Analysis on the Use of Statins with or without n-3 PUFA and Major Events in Patients Discharged for Acute Myocardial Infarction: An Observational Retrospective Study** Authors: Macchia A; Romero M; D'Ettorre A; Tognoni G; Mariani J Source: PLOS ONE; 8/5 (e62772) /2013/. http://www.plosone.org/article/info:doi/10.1371/journal.pone.0062772  Poole CD et al 2013 GPRD	
SH	Abbott Healthcare	13	Full	62	4	**Abbott would like to highlight the underpowered nature of the Rauch 2010 (ref**	Thank you for your comment. Thank you for your comment. The

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	Products Limited					**346) OMEGA study. (This is not reflected in the full guidance).** The study discussed in ref 346 was too statistically underpowered to draw any firm conclusions. The authors of the study, Rauch et al 2010 state "On the basis of the present results, the anticipated statistical power of 80% was not reached. In an a posteriori calculation, the statistical power was 44% to detect a 45% risk reduction in SCD as anticipated by the study protocol (see Methods) and 19% for a risk reduction of 25%". **********was asked to review and make comments on the OMEGA study design and the presented results. His conclusion is that sample sizes of 11736 in each group would be neede**d (12868 per group with 8.8% dropouts), is required** in order to have an 80% chance of identifying such a difference. As per our general comment Galan 2011 (ref 143), Matsuzaki 2009 (ref 249) and Kromhout 2010 (ref 217) are not comparable to Omega-3-acid ethyl esters 90 (Omacor). Recognition should be given to the licensed highly purified Omega-3-acid ethyl esters 90 capsules comprising 840 mg eicosapentaenoic acid ethyl ester (460 mg) and docosahexaenoic acid ethyl ester (380 mg) vs. supplements or food sources.	power calculation in the Rauch paper showed it required 1900 in each arm. The study included 1925 in the omega-3-acid ethyl esters arm and 1893 in the control arm. However, the authors did highlight given the results that the anticipated statistical power of 80% was not reached. A comment to note this was added to the 'Linking evidence to recommendation' section. Regardless of being statistically underpowered, the results in this review are meta-analysed with other papers so any limitations with power are compensated with the inclusion of other trials. And in the case where it was the only study that provided data on that outcome, a comment was added to the GRADE table regarding the lack of power. With regards to the use of prescription grade omega-3-acid ethyl esters, please see our response to previous comment.

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						Supplements may contain as little as 21% omega-3 PUFA	
SH	Abbott Healthcare Products Limited	14	Full	62	5	**Abbott wish to highlight the underpowered nature of the Nilsen 2001 (ref 296) investigator initiated trial (This is not reflected in the full guidance). The quality of the study should be downgraded to very low** The study discussed in ref 296 was severely underpowered. This was acknowledged by the GDG in the 2007, CG48 full guideline page 49, **"The study was powered to measure the effects of the omega-3-acids ethyl esters only on serum lipids"** In the Nilsen 2001 study the prevalence of combined cardiac events was estimated to be around 35% for one year of observation. The hypothesis was that the treatment would reduce the outcome to 25%, this meant an absolute reduction of 10 % and a relative reduction of (1 - 0.71) x 100 = 29% as the relative risk RR = 25/35 = 0.71. For a type I error of 5% and a power of 80%, this would require 338 patients in each arm. As presented in the final publication, only 300 patients in total were recruited for this study. Hence the study was not adequately powered for the demonstration of its primary endpoint.	Thank you for your comment. Although we acknowledge that Nilsen is underpowered to detect a real difference, this limitation is compensated by conducting a meta-analysis, where the results of numerous studies are combined to provide an overall estimate of the effect. Where Nielsen was included in the meta-analysis, this study contributed a small percentage to the overall result. In cases where it contributed the most to the overall result (because no other paper reported data on that outcome) we have commented on the potential risk of bias for not reporting power calculations in the GRADE tables. Thank you for providing power calculations. However, it is unclear whether Nilsen's hypothesis was that the treatment would decrease the combined cardiac events by 25%. For this reason, it would be incorrect for us to assume that the study was underpowered based on these

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						The number of patients needed to detect a difference between the groups is calculated using the figures from the GISSI-P study: In the GISSI-P study, it has been observed that 87.4% of the patients for the Omacor group and 86.1% for the control group were without an event at the end of the study. As the sample size in each group is only 150, a 0.05 level two-sided log-rank test for equality of survival curves will only have 5% power to detect the difference between a group 1 proportion at time t of 0.874 and a group 2 proportion at time t of 0.861 (a constant hazard ratio of 0.900). This assumes no drop outs before time t. As a result, the study will not be a good test if it is important that the study have a reasonable chance of truly distinguishing between a proportion of 0.874 and 0.861.	calculations.
SH	Abbott Healthcare Products Limited	15	Full	62	12	**In order to provide a balanced overview of the available clinical evidence on all-cause mortality the results of the GPRD all-cause mortality 2013 study need to be taken into consideration** Abbott appreciate that RCTs are preferred to cohort studies however cohort studies with hard end-points (such as death) should be considered, particularly when based on contemporary therapies.	Thank you for your comment. Our pre-defined protocol (see Appendix C) states that RCTs will be considered in preference to cohort studies, unless no randomised evidence was identified for a particular outcome.

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						The use of cohort studies is acknowledged by the GDG, in section 6.4 of the guideline "interventions to increase uptake of and adherence to cardiac rehabilitation programmes". Various cohort studies are referred to in this section (references 158, 159 and 371) therefore Abbott hope a consistent approach be included in all NICE review questions Recommendation of inclusion of: **Exploratory Analysis on the Use of Statins with or without n-3 PUFA and Major Events in Patients Discharged for Acute Myocardial Infarction: An Observational Retrospective Study** Authors: Macchia A; Romero M; D'Ettorre A; Tognoni G; Mariani J Source: PLOS ONE; 8/5 (e62772) /2013/. http://www.plosone.org/article/info:doi/10.1371/journal.pone.0062772 **Omega-3 Fatty Acids and Mortality Outcome in Patients With and Without Type 2 Diabetes After Myocardial Infarction: A Retrospective, Matched-Cohort Study**	

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						Authors: Poole CD; Halcox JP; Jenkins-Jones S; Carr ESM; Schifflers MG; Ray KK; Currie CJ Source: CLIN. THER.; 35/1 (40-51) /2013/.  Poole CD et al 2013 GPRD	
SH	Abbott Healthcare Products Limited	16	Full	64	2/ Table 8	Abbott would like clarification on the references of GISSI-P trial (ref 13 and ref 152) and the number of participants provided in ref 152. The GISSI-P had 11324 participants. 6975 patients were available in the GISSI-HF trial.	Thank you for highlighting this. These numbers have been corrected.
SH	Abbott Healthcare Products Limited	17	Full	65	Table 9	Incorrect patient number provided for GISSI-P trial. The number of participants provided in ref 152 is incorrect and should read 11324. 6975 patients were available in the GISSI-HF trial	Thank you for highlighting this. These numbers have been corrected.
SH	Abbott Healthcare Products Limited	18	Full	66	Table 10	Incorrect patient number provided for GISSI-P trial. The number of participants provided in ref 152 is incorrect and should read 11324. 6975 patients were available in the GISSI-HF trial	Thank you for highlighting this. These numbers have been corrected.
SH	Abbott Healthcare Products Limited	19	Full	67	Table 11-19	Abbott would like to raise various points 1. Recognition should be given to the licensed highly purified Omega-3-acid ethyl esters 90 capsules comprising 840	Thank you for your comment. Please see individual responses to comments 3, 4, 8, 11 and 20. We included the two-way results

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						mg eicosapentaenoic acid ethyl ester (460 mg) and docosahexaenoic acid ethyl ester (380 mg) vs. supplements or food sources. Supplements may contain as little as 21% omega-3 PUFA A more accurate review question should therefore be introduced; **What is the clinical and cost effectiveness of prescription grade licenced Omega-3-acid ethyl esters 90 in patients with myocardial infarction?** 2. Underpowered studies such as Nilsen 2001 (ref 296) investigator initiated trial and Rauch 2010 is not reflected in the full guidance. The quality of the studies should be downgraded to very low 3. Inclusion of cohort studies with hard end-points (such as death) to be considered. For example Poole 2013 and Machia 2013 (Please refer to Abbotts general comments) 4. It is also not clear if the relative risk data taken from the GISSI-P (ref 152) is being calculated from the two-way analysis or the four-way analysis data. The data available in the four-way analysis (GISSI P table 3) provides a clear picture of the	because it included a larger number of patients and therefore greater power to detect a difference should one exist. The 4-way analysis would have been used if the 2-way groups were not matched for Vitamin E intake or if there was an interaction between omega-3 and Vitamin E. Neither was the case, hence the larger numbers provided by the 2-way analysis were included. The paper states there was no increased benefit was apparent when the rate of the combined endpoint of death, non-fatal MI, and no-fatal stroke that was seen in patients receiving n-3PUFA plus Vitamin E was compared with the group receiving n-3 PUFA alone (1.01 (0.87 to 1.17) or with patient treated with vitamin E alone (0.96 (0.83 to 1.12).

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						role of licensed Omega-3-acid ethyl esters 90 in patients with myocardial infarction as the two-way analysis also includes a subset of patients (2830) taking vitamin E. *********has reviewed our proforma, in his comments he stated "A crucial piece of evidence in measuring the effectiveness of Omega-3-acid-ethyl esters 90 is the paper by Poole *et al*. (2013) and, as such, this should be considered, along with any other suitable evidence, by the Committee." ******also stated that "It would seem to me that it is of key importance to first establish the effectiveness (and cost-effectiveness) of Omega-3-acid-ethyl esters 90, relative to non-use of that product."	
SH	Abbott Healthcare Products Limited	20	Full	75	15	The GDG state that newer studies reach conclusions at odds with the GISSI-P, yet these studies are too underpowered (Rauch et al 2010 ref 346 and Kromhout et al 2010 ref 217) to draw firm conclusions(please refer to general comments on the respective papers). **Abbott recommends the inclusion of robust cohort studies with hard end points such as**	Thank you for your comment. Although Rauch and Kromhout were underpowered to detect differences in some of the outcomes (because they used old data to perform the calculations when acute treatments have improved a patient's prognosis) we performed a meta-analysis and this increases the power of the conclusions

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						GPRD 2013  Poole CD et al 2013 GPRD The hazard ratio data for all-cause mortality reported in the recent GPRD-2013 trial is 0.782 if highly purified licensed Omega-3-acid ethyl esters 90 capsules is initiated within <90days. (HR of 0.680 if initiated in <14days) This in line with that reported in the GISSI-P trial table 3 four way analysis (all fatal events 0·80), and hence the Quilici 2006 cost-effectiveness analysis based on GISSI-P, and acknowledged in CG48 2007, indicates that the Incremental Cost-Effectiveness Ratio is likely to remain under the QALY threshold and is still valid today A recently published retrospective, matched-cohort study using data from nearly 700 primary care U.K. practices, from the General Practice Research Database (GPRD 2013) evaluated the impact of licensed Omega-3-acid ethyl esters 90 capsules on all-cause mortality in routine clinical practice.	since the results of different studies are combined together. In the instances where Kromhaut and Rauch were the only studies that contributed to the overall result, a comment was made in the GRADE tables regarding the lack of power and the risk of a Type II error. Although we appreciate Abbott highlighting that new studies are available, they are cohort studies and our protocol states that we were to only include RCTs since they have a lower risk of bias compared with cohort studies.

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						The study design is a retrospective, matched cohort study. Patients treated with licensed Omega-3-acid ethyl esters 90 capsules (Omacor) were matched in a 1:4 ratio to similar patients who had not received Omega-3 treatment after their 1st MI. A vast majority of patients received concurrent lipid lowering drugs (>84%), anti-hypertensives (>86%) and anti-platelet agents (>84%). HR for Omacor initiated <90 days was 0.782 (95%CL 0.641-0.955) P=0.0159 whilst HR of 0.68 (95%CL 0.48-0.961) P=0.0288 if initiated <14 days. (See table iv in the study) The data in the GPRD i.e. all-cause mortality of 21.8% are concordant with the 20% reduction in all-cause mortality reported in the GISSI-P trial and reinforces the data in the GISSI-P. In the GISSI-P study the Two way analysis showed a significant 10% relative decrease in risk of death, non-fatal MI and non-fatal stroke (p=0.048), and a non-significant decrease (11%, p=0.053) in risk for cardiovascular death, non-fatal MI and non-fatal stroke. Four way analysis showed a significant decrease in risk for the combined endpoint of 15% (p=0.023), and a significant decrease in risk for cardiovascular death, non-fatal MI and non-fatal stroke of 20% (p=0.008) Analysis of Omacor showed a significant	

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						decrease in mortality (20% RRR for total deaths, 30% RRR for cardiovascular deaths and 45% RRR for sudden deaths), all p<0.01	
SH	Abbott Healthcare Products Limited	21	Full	75	29	As the data in the GPRD 2013 i.e. all-cause mortality of 21.8%, HR 0.782 (95%CL 0.641-0.955) are concordant with the 0.8 relative risk (95%CL 0.67-0.94) in all-cause mortality reported in the GISSI-P trial, the Quilici 2006 study accepted in CG48 2007 is still reliable, current and should be taken into consideration.	Thank you for your comment. The paper by Quilici is based upon the data from the GISSI-P study. The GDG felt that the effect size in this study did not reflect the efficacy of Omacor in modern practice since in the GISSI-P trial, where there was a significant reduction in mortality, only 5% of patients had undergone either PCI or CABG and were not treated with statins or dual antiplatelet therapy. This is contrast to the recent study by Rauch where all patients were treated with PCI, statins and dual antiplatelet therapy and there was no benefit of omega-3 fatty acids. Thus, it appears the efficacy of omega-3 fatty acids is diminished in those who receive modern treatments. It is for this reason the economic analysis by Quilici is not relevant. This has been explained in the paragraph 'published literature' on the same page and in the cost-effectiveness section of the LETR. See below.

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							"None of the studies from the old guideline (CG48) were included in the update review because of their potentially serious limitations; in fact they are based on effectiveness evidence from the GISSI-P study which does not reflect the overall current evidence base. Studies that conducted a cost-effective analysis of omega-3 fatty acids based on the data by GISSI-P were also excluded from the review."
SH	Abbott Healthcare Products Limited	22	Full	75	34	It is not clear what is being implied in this paragraph as the margarine infused omega-3 used in Kromhout 2010 is not available OTC.	Thank you for your comment, tline 36 and 37 on page 77 have been amended to clarify that omega-3 fatty acid capsules are available over the counter, whereas supplemented margarine is not.
SH	Abbott Healthcare Products Limited	23	Full	76	Table 20	Price of Omacor is £14.24 for packs of 28 and £50.84 for packs of 100 the GDG have incorrectly priced Omacor at £14.28	Thank you for your comment, this has been amended.
SH	Abbott Healthcare Products Limited	24	Full	76	11	**In order to provide a balanced overview of the available clinical evidence on all-cause mortality the results of the GPRD all-cause mortality 2013 study need to be taken into consideration** The four studies referred to include the landmark	Thank you for your comment. This is non-RCT data and although the numbers are high, cohort studies carry a greater risk of bias compared with RCTs. For this reason only RCT data was included in this review question.

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						trial for Omega-3-acid ethyl esters 90, 1999 GISSI-P (NOTE incorrect number of patients referred to, should state 11,324)- The results of this study were confirmed in the recent GPRD study Poole CD, Halcox JP, Jenkins-Jones S et al. Clin Ther 2013; 35(1): 40-51 This study showed Omega-3-acid ethyl esters 90 effectiveness at preventing unnecessary/premature death when administered within 90 days with risk reduction in all-cause mortality of 21.8% (3.2% ARR) HR 0.782 (95%CL 0.641-0.955) and a reduction of 32% (5.2% ARR) HR 0.680 (95%CL 0.481–0.961) when administered within 14 days. Include: **Omega-3 Fatty Acids and Mortality Outcome in Patients With and Without Type 2 Diabetes After Myocardial Infarction: A Retrospective, Matched-Cohort Study** Authors: Poole CD; Halcox JP; Jenkins-Jones S; Carr ESM; Schifflers MG; Ray KK; Currie CJ Source: CLIN. THER.; 35/1 (40-51) /2013/.  Poole CD et al 2013 GPRD	

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SH	Abbott Healthcare Products Limited	25	Full	76	14	The study being referred to is Kromhout et al 2010. The dose, quality and strength of omega-3 used in this study is not comparable to licensed Omega-3-acid ethyl esters 90. However it could be noted that a secondary analysis of Kromhout 2010 (ref 217) Kromhout 2011 suggest that a low-dose supplementation of n-3 fatty acids exerts a protective effect against ventricular arrhythmia-related events in post-MI Kromhout 2011 	Thank you for your comment. We agree that the dose and quality of omega-3-acid ethyl esters is different in the Kromhout study compared with those that use capsules to provide omega-3-acid ethyl esters. We have separated the results and recommendations, where possible, to take this into account.
SH	Abbott Healthcare Products Limited	26	Full	76	17	The Nilsen et al 2001 study and the Rauch et al 2010 study are severely underpowered (as discussed in various sections of the proforma). The inclusion of these underpowered negative studies results in the low quality evidence. In order to provide a balanced overview of the	Thank you for your comment. Although we acknowledge that Nilsen is underpowered to detect a real difference, this limitation is compensated by conducting a meta-analysis, where the results of numerous studies are combined to

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						available clinical evidence on all-cause mortality the results of the GPRD all-cause mortality 2013 study need to be taken into consideration Abbott recommends the following paper for inclusion: **Omega-3 Fatty Acids and Mortality Outcome in Patients With and Without Type 2 Diabetes After Myocardial Infarction: A Retrospective, Matched-Cohort Study** Authors: Poole CD; Halcox JP; Jenkins-Jones S; Carr ESM; Schifflers MG; Ray KK; Currie CJ Source: CLIN. THER.; 35/1 (40-51) /2013/.	provide an overall estimate of the effect. Where Nielsen was included in the meta-analysis, this study contributed a small percentage to the overall result. In cases where it contributed the most to the overall result (because no other paper reported data on that outcome) we have commented on the potential risk of bias for not reporting power calculations in the GRADE tables. Thank you for providing power calculations. However, it is unclear whether Nilsen's hypothesis was that the treatment would decrease the combined cardiac events by 25%. For this reason, it would be incorrect for us to assume that the study was underpowered based on these calculations. We acknowledge that there are differences in the quality of published omega-3 RCTs. This was highlighted in the GRADE tables and discussed in the 'Linking evidence to recommendation' sections. Because of differences in the quality of the studies, the GDG placed greater emphasis on the results from higher quality studies (such as Rauch et al)

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							when they made their recommendations.
SH	Abbott Healthcare Products Limited	27	Full	76	20	**Consider to add reference to the GPRD study which confirms the benefit of early administration** and role of 1g Omega-3-acid ethyl ester 90 in the reduction in all-cause mortality in patients with a recent MI. Include: **Omega-3 Fatty Acids and Mortality Outcome in Patients With and Without Type 2 Diabetes After Myocardial Infarction: A Retrospective, Matched-Cohort Study** Authors: Poole CD; Halcox JP; Jenkins-Jones S; Carr ESM; Schifflers MG; Ray KK; Currie CJ Source: CLIN. THER.; 35/1 (40-51) /2013/.	Thank you for your comment. Although the study by Poole et al. includes large numbers, it is a cohort study and is less reliable than the data provided by RCTs. Our pre-defined protocol (see Appendix C) states that RCTs will be considered in preference to cohort studies, unless no randomised evidence was identified for a particular outcome.
SH	Abbott Healthcare Products Limited	28	Full	88	1	The draft recommendation states "Do not offer or advise people to use the following to prevent another MI". Mortality (all cause, cardiac or sudden) and quality of life are listed as a critical outcome in Appendix C.1 clinical evidence reviews page 28. Prevention of another MI is not equivalent to reduction in mortality and does translate to better quality of life. Abbott wishes to flag this inconstancy. Abbott strongly believes that current body of	Thank you for your comment, however we disagree. The guidelines' recommendations are focused on the secondary prevention of myocardial infarction. The outcomes listed in Appendix C1 are study outcomes used to inform decision making when assessing the literature and developing the recommendation.

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						evidence shows a statistical and clinical reduction in mortality in licensed Omega-3-acid ethyl ester 90 treated patients.	
SH	Agriculture and Horticulture Development Board (AHDB)	1	full	16	1.2.1	It is appreciated that the 'less meat' message was originally intended to reduce dietary intake of fat and saturated fat and may have been appropriate in the 1960s when interest arose in the Mediterranean diet and animal carcases were fattier. However, modern red meat is lower in fat and saturated fat than ever before and contains several key nutrients which may support heart health, e.g. vitamin D, selenium, B vitamins, as well as the most bioavailable sources of iron and zinc. In the UK, the fat content of carcase meat has been reduced by over 30% for pork, 15% for beef and 10% for lamb (Higgs, 2000). Fully trimmed raw beef typically contains only 5% fat, trimmed pork only 4% fat and fully trimmed raw lamb only 8%. Higgs J (2000) The changing nature of red meat: 20 years of improving nutritional quality. *Trends Food Sci Tech* 11: 85-95. Ruxton CHS, Derbyshire E, Pickard R (2013) Micronutrient challenges across the age spectrum: is there a role for red meat? *Nutr Bull* 38: 178-90.	Thank you for your comment. Recommendation 1.2.1 was not updated as part of the current guideline update, as described in Section 5 of the full guideline.
SH	Agriculture and	2	full	16	1.2.1	Processed meats tend to be high in fat, calories	Thank you for your comment.

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	Horticulture Development Board (AHDB)					and salt and may be a more appropriate target for public health advice, although it is worth remembering that meats such as Parma ham and chorizo are common features of many traditional Mediterranean cuisines. This seems to be overlooked in NICE's proposal to promote a Mediterranean-style diet. Micha R, Wallace SK, Mozaffarian D (2010) Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. Circulation 121: 2271-83.	Recommendation 1.2.1 was not updated as part of the current guideline update, as described in Section 5 of the full guideline.
SH	Agriculture and Horticulture Development Board (AHDB)	3			1.2.5	There is no evidence that moderate intakes of lean red meat, when consumed as part of a healthy balanced diet, have any negative health effects on heart health and should be excluded from a healthy diet for the secondary prevention of MI. Indeed, giving advice to patients about switching from processed and fattier cuts of meat to lean red meat would help to lower intakes of saturated fat while safeguarding intakes of B vitamins, iron, zinc and selenium – all of which are important nutrients for health, particularly in older people. Ruxton CHS (2011) The role of red meat in a balanced diet. Nurs Stand 26: 41-48. Wyness L, Weichselbaum E, O'Connor A *et al.* (2011) Red meat in the diet: An update. *Nutr*	Thank you for your comment. Recommendation 1.2.1 was not updated as part of the current guideline update, as described in Section 5 of the full guideline.

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						Bull 36: 34-77.	
SH	Astra Zeneca	1	NICE	General		The draft guidelines for secondary prevention of MI on the use of oral antiplatelets appears to be nearly exclusively focused on just one of the three NICE approved OAPs: clopidogrel. Section 2.1 of NICE states *"We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care."* It is therefore concerning that the guideline does not include some the most recent studies on NICE approved medicines relevant to this review, specifically, PLATO 2009, and does not discuss or identify research questions around the appropriate use of two other oral antiplatelets, ticagrelor and prasugrel. NICE guidelines play a significant role in ensuring the most innovative drugs are made available to NHS patients in England and Wales. Under Innovation, Health and Wealth and the NHS Standard Contract, providers are required to automatically include NICE-approved treatments on formulary and make them available to the appropriate patient population. This is to help improve the uptake of innovation in the NHS. Further, NICE has published guidance to support providers in updating local formularies accordingly.	Thank you for your comment. Recommendations on the use of prasugrel and ticagrelor can be found in NICE technology appraisal 182 and 236 respectively and therefore, evidence relating to the use of these drugs has not been reviewed. For clarity, we have now included recommendations to refer to these NICE technology appraisals in section 7.4.

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						Although the separate technology appraisal NICE TA236 recommends ticareglor for up to 12 months in ACS patients to prevent atherosclerotic events, there is minimal discussion around ticagrelor in the draft update to NICE CG48. The lack of specific inclusion of ticagrelor in draft NICE CG48 could potentially be interpreted by clinicians as guidance to use only clopidogrel as an oral antiplatelet for secondary prevention of MI. This may limit the diffusion of innovation in the NHS and ability of clinicians to offer their patients the most appropriate treatment to prevent an MI. There should be full alignment with NICE technology appraisals and clinical guidelines in order to enable clinicians to provide best practice care in line with NICE and to ensure patients are able to make fully-informed decisions on their treatment in line with the NHS Constitution. Anything less could slow the adoption and diffusion of innovation in the NHS.	
SH	Astra Zeneca	2	NICE	18	9	1.3.1 – No duration of therapy is included for any of the oral antiplatelets as stated in the final scope. The final scope available on the NICE website states that one of the key clinical issue that will be covered is:	Thank you for your comment. The duration of aspirin and clopidogrel is covered in Section 7.4. Ticagralor and prasugrel are covered by NICE technology appraisals 182 and 236. . For clarity, we have now included

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						Antiplatelet agents, including: *initiating agents after the acute phase* *duration of therapy* *duration of therapy after stenting* We could find no reference to the duration of therapy for the newer oral antiplatelets in the NICE version and therefore request that the GDG rectify this issue. We recommend that CG48 refers includes TA236's recommendation including treatment duration of up to 12 months in ACS patients.	recommendations to refer to these NICE technology appraisals in section 7.4.
SH	Astra Zeneca	3	NICE	18	9	There is no discussion about the different subgroups which ticagrelor and prasugrel are currently recommended for by NICE: Prasugrel – STEMI Ticagrelor – STEMI, NSTEMI, UA This is important additional information for NHS and raises issues around patient safety if not explicitly clarified by GDG.	Thank you for your comments. As specific recommendations on these drugs are included in TA182 and TA236, no review of this evidence has been carried out in this guideline. For clarity, we have now included recommendations to refer to these NICE technology appraisals in section 7.4.
SH	Astra Zeneca	4	NICE	26		We are concerned that the research recommendations haven't been revised since publication in 2007. We note in the final scope that it does refer to mapping and review of recommendations in relation to more recent NICE guidance and are therefore surprised that the research recommendations haven't been updated since original publication in light of this. The research recommendations do not take into	Thank you for your comment. The GDG have developed new research recommendations for the 2013 update of the guideline and these are outlined on page 57 of the full guideline document.

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						account the newer oral antiplatelet agents nor their evidence base and we strongly advise the GDG to review the research recommendations in order to improve NICE guidance and patient care in the future.	
SH	Astra Zeneca	5	NICE	18	9	While we understand that prasugrel's TA 182 is still intact, we would recommend removing prasugrel's recommendation as this technology appraisal is currently scheduled for update (ID 648). This would be consistent with the recently published NICE clinical guideline, Myocardial infarction with ST-elevation (CG167) and section 8.1.4.3 '*Publication of recommendations*' in the Guidelines Manual 2012.	Thank you for your comment, we agree and this has been amended..
SH	Astra Zeneca	6	NICE	25	16	Many patients wish to be active participants in their own healthcare, and to be involved in creating and managing their health strategy and use of services (CG138). We believe that the discharge process should take this into account and be explicitly stated in the guidelines. We believe that by actively involving patients in their own healthcare will help increased the number of patients participating in cardiac rehab.	Thank you for your comment. Recommendation 1.6.1 has been amended only to reflect changes in other recommendations and has not been updated as part of the current guideline update.
SH	Bayer plc	1	NICE	27		**Research recommendation 2.3** There is an ongoing clinical trial (PIONEER AF-PCI) (NCT01830543)[1] that has been designed to evaluate the safety of 2 different rivaroxaban treatment strategies and one Vitamin K Antagonist (VKA) treatment strategy utilizing various combinations of dual antiplatelet therapy	Thank you for your comment. This has been added to the "other considerations" in the 'Linking evidence to recommendations' section.

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						(DAPT) or low-dose aspirin (ASA) or clopidogrel (or prasugrel or ticagrelor) in subjects with atrial fibrillation who undergo Percutaneous Coronary Intervention. This study is due to complete in August 2015. (1) Janssen Scientific Affairs L. NCT01830543. A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI). July 2013. Available from: http://clinicaltrials.gov/show/NCT01830543. (Last accessed: 7/2013).	
SH	Bayer plc	2	NICE	22		**Recommendation 1.3.25** We suggest the addition of a footnote to recommendation 1.3.25 to reflect that there is a NICE TA currently in development for 'Acute coronary syndrome – rivaroxaban [ID532]'[2] which considers the use of rivaroxaban in those with acute coronary syndrome *without an additional indication for anticoagulation*. This information is included in the corresponding recommendation in the full guideline, and it is important that it is reflected in the NICE version to avoid confusion regarding the appropriate use of rivaroxaban in patients with ACS. (2) National Institue for Health and Care Excellence. Rivaroxaban for the prevention of adverse outcomes in patients after the acute	Thank you for your comment. Recommendation 1.3.25 is for people who have had an MI and who have an additional indication for anticoagulation and therefore, the GDG did not consider it appropriate to include a footnote to the NICE TA currently in development. A comment is included in the 'Linking evidence to recommendation' section for this recommendation to highlight the development of this technology appraisal.

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						management of acute coronary syndrome [ID532]. 4 July 2013. Available from: http://guidance.nice.org.uk/index.jsp?action=byId&o=13787. (Last accessed: 7/2013).	
SH	Bayer plc	3	Full	54 and 461	74	**Recommendation 74** Recommendation 74 is based on limited evidence from trials that were not designed to answer the clinical question that is being addressed. As such we suggest that the recommendation is amended to reflect that it is made in the absence of robust data to support the use of the new acting anticoagulants compared to warfarin in this population. e.g. There is currently insufficient evidence to recommend new oral anticoagulants in people who otherwise need anticoagulation and who have an MI. Consider using warfarin and discontinuing treatment with a new oral anticoagulant unless there is a specific clinical indication to continue it.	Thank you for your comment. We agree, the data on new anticoagulants were from an indirect population who did not have an indication for anticoagulants but they had either an MI or coronary heart disease. This limitation was highlighted in the section discussing the link between evidence and recommendations in the full guideline (recommendation 74 in the consultation version of the full guideline). NICE recommendations do not stipulate what evidence (or lack of evidence) helped generate the recommendation within the wording of the recommendation. The recommendation uses the word 'consider' rather than offer as a reflection of the quality of evidence. However, we agree this is important and this, as well as the consideration of the GDG in developing the recommendation, is outlined in the 'Linking evidence to recommendations' section.

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SH	Bayer plc	4	NICE	22		**Recommendation 1.3.26** Recommendation 1.3.26 is based on limited evidence from trials that were not designed to answer the clinical question that is being addressed. As such we suggest that the recommendation is amended to reflect that it is made in the absence of robust data to support the use of the new acting anticoagulants compared to warfarin in this population. e.g. There is currently insufficient evidence to recommend new oral anticoagulants in people who otherwise need anticoagulation and who have an MI. Consider using warfarin and discontinuing treatment with a new oral anticoagulant unless there is a specific clinical indication to continue it.	Thank you for your comment. It is not in line with NICE style to comment on the availability of evidence within the recommendation. The quality of evidence for this recommendation is reflected by the use of the word 'consider' rather than 'offer'. Further information about the evidence, or lack of, is available in the full guideline which discusses the quality of evidence and how the recommendation was developed.
SH	Bayer plc	5	NICE	31		**3.2 Related NICE guidance** **Under development** The on-going single technology appraisal for rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome [ID532][2] (Expected date of issue - March 2015) should be included in this section. (2) National Institue for Health and Care Excellence. Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome	Thank you for your comment, this has been added to the list of related guidance.

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						[ID532]. 4 July 2013. Available from: http://guidance.nice.org.uk/index.jsp?action=byId&o=13787. (Last accessed: 7/2013).	
SH	Bayer plc	6	Full	389		**Table 94 Summary of included studies.** **'Intervention'** In the ROCKET AF study, Aspirin **≤**100mg montherapy and thienopyridine monotherapy were allowed concomitant therapies.[3] The table incorrectly states that aspirin (***over*** 100mg/day) was allowed. It should also be made clear that an assumption has been made that the "prior MI" population are taking antiplatelet therapy as this cannot be explicitly determined from the publication, which states that "at some time during the study, 34.9% of patients in the rivaroxaban group and 36.2% of those in the warfarin group took aspirin concurrently with the assigned study drug."[3] **'Outcomes'** The table currently only lists the 'outcome' of 'major and non-major clinically relevant bleeding while on treatment', however the supplementary appendix to the publication by Patel *et al.* 2011 also presents the primary efficacy endpoint of the trial (the composite of stroke (ischemic or hemorrhagic) and systematic embolism) in this subgroup.[3] (3) Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban	Thank you for your comments. There is some uncertainty about what dose of aspirin was permitted in this trial. In the supplementary appendix the authors state that treatment with >100mg and ≤ 100mg of aspirin was allowed (page10). It also states on page 11 that up to 100mg was allowed. This uncertainty was mentioned in the GRADE table 98 and summary table 94. It is unclear how many from post MI patients were taking aspirin and/or thienopyridine for that matter since they too were permitted for patients undergoing cardiovascular interventions. This uncertainty was mentioned in the GRADE table 98 and summary table 94. The data presented on post MI subgroups included Fig 3. ITT to site notification, Fig 4. safety on treatment and Fig 5 major and non-major clinically relevant bleeding. Of these bleeding was the only relevant outcome.

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						versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011 Sep 8;365(10):883-91.	Composite outcomes were not reported if single outcomes were available.
SH	Bayer plc	7	Full	396		**Rivaroxaban plus aspirin plus theinopyridine versus aspirin plus theinopyridine** The included study is listed as Mega 2012[255] ATLAS ACS TIMI 46. However the correct citation for ATLAS ACS TIMI 46 is Mega 2009.[255] Mega 2012 relates to the publication from the phase III ATLAS ACS TIMI 51 trial, which is listed as reference 256. Whilst the trial mentioned in this table is described as the phase II ATLAS TIMI 46 trial, the data extracted appears to be from the phase III ATLAS ACS TIMI 51 trial. Both the ATLAS TIMI 46 phase II trial, and the ATLAS TIMI 51 phase III trial should be included in this table.	Thank you for highlighting this. The reference for ATLAS ACS TIMI 51 has been corrected, in addition to the description of this study in Table 94 and Table 100. Data on the risk of bleeding was added from ATLAS TIMI 46.
SH	Bayer plc	8	Full	402		The numbers of patients presented in this table appear to differ slightly from those in the publication by Patel *et al.* 2011[3] It should be noted that the reported rates for major and non-major clinically relevant bleeding in the prior MI sub-group are from the "on-treatment" population; however the baseline characteristics reported are for the ITT population.[3] (3) Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban	Thank you for your comment. There is a discrepancy between the number of patients who had a prior MI provided in the baseline (ITT) characteristics table (Table 1), versus those reported in Figure 3 and 4 in the appendix (presumably available case analysis numbers). Unfortunately in Fig 5 for major and minor bleeding there was no denominator provided for those who had an MI so the ITT numbers

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						versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011 Sep 8;365(10):883-91.	provided in Table 1 were used.
SH	Bayer plc	9	Full	402		**Table 98: GRADE profile: rivaroxaban versus warfarin** The table currently only lists the 'outcome' of 'major and non-major clinically relevant bleeding while on treatment', however the supplementary appendix to the publication by Patel *et al.* 2011 also presents the primary efficacy endpoint of the trial (the composite of stroke (ischemic or hemorrhagic) and systematic embolism) in the prior MI subgroup.[3] (3) Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011 Sep 8;365(10):883-91.	Thank you for your comment. The data presented on post MI subgroups included Fig 3. ITT to site notification, Fig 4. safety on treatment and Fig 5 major and non-major clinically relevant bleeding. Of these bleeding was the only relevant outcome. Composite outcomes were not reported if single outcomes were available**.**
SH	Bayer plc	10	Full	407		**Table 100: GRADE profile: triple therapy versus dual therapy** The results presented for rivaroxaban in this table are referenced to citation 255 (ATLAS TIMI 46) however the data appears to be from the ATLAS TIMI 51 trial (citation 256).	Thank you this has been corrected.
SH	Bayer plc	11	Full	429	12	**Rivaroxaban plus aspirin versus warfarin plus aspirin** The supplementary appendix to the publication by Patel *et al.* 2011 also presents the primary efficacy endpoint of the trial (the composite of	Thank you for your comment. The data presented on post MI subgroups included Fig 3. ITT to site notification, Fig 4. safety on treatment and Fig 5 major and non-major clinically relevant

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						stroke (ischemic or hemorrhagic) and systematic embolism) in the subgroup who have had a prior MI.[3] (3) Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011 Sep 8;365(10):883-91.	bleeding. Of these bleeding was the only relevant outcome. Composite outcomes were not reported if single outcomes were available**.**
SH	Bayer plc	12	Full	430	34	The full guideline states that "one RCT with 10,227 people showed that low dose rivaroxaban plus dual antiplatelet therapy is equally effective as dual antiplatelet therapy on the risk of all-cause mortality [Very low quality evidence]" However in accordance with the forest plots presented in appendix I (Figure 218), the statement should read: "One RCT with 10,227 people showed that low dose rivaroxaban plus dual antiplatelet therapy is more effective than dual antiplatelet therapy on the risk of all-cause mortality [Very low quality evidence]."	Thank you for your comment, this has been amended.
SH	Bayer plc	13	Full	430	**37**	The full guideline states that "one RCT with 10,228 people showed that moderate dose rivaroxaban plus dual therapy increase the risk of all-cause mortality more than dual therapy alone, but there was considerable uncertainty [Low quality evidence]." However in accordance with the forest plots	Thank you for your comment, this has been amended.

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						presented in appendix I (Figure 218), the statement should read: "One RCT with 10,228 people showed that moderate dose rivaroxaban plus dual therapy is equally effective as dual antiplatelet therapy on the risk of all-cause mortality, but there was considerable uncertainty [Low quality evidence]."	
SH	Bayer plc	14	Full	433	1	The full guideline states that "one RCT with 10,228 people suggested that moderate dose rivaroxaban plus dual therapy increase the risk of stroke more than dual antiplatelet therapy alone, but there was some uncertainty [Very low quality evidence]." However in accordance with the forest plots presented in appendix I (Figure 222), the statement should read: "One RCT with 10,228 people suggested that moderate dose rivaroxaban plus dual therapy has no effect on the risk of stroke compared with dual antiplatelet therapy alone."	Changes were made in response to earlier comment. Evidence statement has been corrected to: One RCT with 10,228 people showed that 10mg/day dose rivaroxaban plus dual antiplatelet therapy is equally effective as dual antiplatelet therapy alone on the risk of all-cause mortality, but there was some uncertainty [Low quality evidence].
SH	Bayer plc	15	Full	460		**Trade-off between clinical benefits and harms** In the ATLAS TIMI 51 trial, rivaroxaban plus dual antiplatelet therapy increased rather than reduced the risk of bleeding.	Thank you for your comment, this has been amended.
SH	Bayer plc	16	Full	460		**Trade-off between clinical benefits and harms** The text in this section relating to rivaroxaban discusses "high dose" and "low dose". We	Thank you for your comment. The low and high dose label for rivaroxaban has been removed from the guideline and replaced with the actual dose.

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						suggest that the actual doses used in the ATLAS TIMI 51 trial are described e.g. twice-daily 5-mg dose and twice-daily 2.5-mg dose as these are not the doses licensed for people with an on-going requirement of anticoagulation, which are higher at 15 or 20 mg per day, and we feel that the use of "high dose" in this context may be confusing and could have implications for patient safety.	
SH	Bayer plc	17	Full	460		**Trade-off between clinical benefits and harms** This section includes the statement *"there was an increase for rivaroxaban plus dual antiplatelet in the risk of bleeding when compared with warfarin plus antiplatelet"* It is not clear which trial this based on. Neither the publication of the ROCKET-AF trial[3] nor the ATLAS TIMI 51 trial[4] report results for rivaroxaban plus *dual* antiplatelet versus warfarin plus antiplatelet. (3) Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011 Sep 8;365(10):883-91. (4) Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012 Jan 5;366(1):9-19.	Thank you for your comment. This has been changed to say antiplatelet, not dual antiplatelet.

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SH	Bayer plc	18	Full	460		**Trade-off between clinical benefits and harms** It is not clear that the two paragraphs relating to rivaroxaban in this section are related to two different trials including different populations and investigating different doses of rivaroxaban.	Thank you for your comment. This has now been clarified.
SH	Bayer plc	19	Full	460		**Economic considerations** The conclusion that *"these drugs are unlikely to be cost effective"* does not appear to be substantiated by any evidence. Rivaroxaban has been appraised by NICE for stroke prevention in atrial fibrillation, as well as for the treatment and secondary prevention of DVT and PE, and has been found to be a cost effective option for patients requiring long term anticoagulation. Of note, whilst the drug cost of warfarin is very low, management of a patient taking warfarin is associated with regular, costly visits for INR monitoring and this should be taken into consideration in any assessment of cost effectiveness.	Thank you for your comment. We have amended the sentence to clarify that 'these drugs are unlikely to be cost effective when used in combination with dual antiplatelet therapy in people who have had an MI as they are associated with an increase in risk of bleeding and no sufficient evidence was found on their additional effectiveness compared to dual antiplatelet therapy alone'. The cost of INR monitoring for warfarin treatment was considered by the GDG when making this recommendation.
SH	Bayer plc	20	Full	461		**Relative values of different outcomes** The text relating to the GDG discussions suggests that they were considering the appropriateness of "adding new acting anticoagulants to triple therapy"; we suggest that this should be "adding new acting anticoagulants to *dual* therapy."	Thank you for highlighting this. This has been corrected In the 'Linking evidence to recommendations' section for recommendation 77 and 78.
SH	Bayer plc	21	Full	461		**Recommendation 74**	Thank you for your comment. This

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						The current wording of recommendation 74 does not make it clear that the recommendation is based on the consideration of the appropriateness of adding new acting anticoagulants to *dual* therapy, which is what is implied under "relative values of different outcomes". At some time during the ROCKET-AF study, 34.9% of patients in the rivaroxaban group and 36.2% of those in the warfarin group took aspirin concurrently with the assigned study drug,[3] therefore unless there is a high risk of bleeding, rivaroxaban can be considered with aspirin alone. (3) Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011 Sep 8;365(10):883-91.	recommendation relates to people who need anticoagulation and therefore, who require the full dose for anticoagulation (for example, for AF). It is a limitation of the ROCKET-AF study that it is unclear what percentage of the post MI subgroup was taking concomitant antiplatelet therapy. In the section discussing the link between evidence and recommendations in the full version of the guideline we highlighted this, in addition to the possibility that these patients were on dual-antiplatelet therapy given the description in the methods. "From the larger trial sample 34-36% were taking aspirin but patients could also be on dual-antiplatelet therapy (aspirin and a thienopyridine) if they were undergoing a cardiovascular intervention." ; Given the the post MI subgroup included in this review, it is very likely that these patients were taking additional therapy."
SH	Bayer plc	22	Full	462		**Economic considerations** The conclusion that *"these drugs are unlikely to be cost effective"* does not appear to be substantiated by any evidence. Rivaroxaban has been appraised by NICE for stroke prevention in	Thank you for your comment. We have amended the sentence to clarify that 'these drugs are unlikely to be cost effective when used in combination with dual antiplatelet therapy in people who have had an MI as they are

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						atrial fibrillation, as well as for the treatment and secondary prevention of DVT and PE, and has been found to be a cost effective option for patients requiring long term anticoagulation. Of note, whilst the drug cost of warfarin is very low, management of a patient taking warfarin is associated with regular, costly visits for INR monitoring and this should be taken into consideration in any assessment of cost effectiveness.	associated with an increase in risk of bleeding and no sufficient evidence was found on their additional effectiveness compared to dual antiplatelet therapy alone'.
SH	Bayer plc	23	Full	462		**Other considerations** We would also recommend adding a note to "other considerations" to state that there is an ongoing clinical trial (PIONEER AF-PCI) (NCT01830543)[1] that has been designed to evaluate the safety of 2 different rivaroxaban treatment strategies and one Vitamin K Antagonist (VKA) treatment strategy utilizing various combinations of dual antiplatelet therapy (DAPT) or low-dose aspirin (ASA) or clopidogrel (or prasugrel or ticagrelor) in subjects with atrial fibrillation who undergo Percutaneous Coronary Intervention This study is due to complete in August 2015. (1) Janssen Scientific Affairs L. NCT01830543. A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI).	Thank you for your comment. This has been added to the "other considerations" in the 'Linking evidence to recommendations' section.

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						July 2013. Available from: http://clinicaltrials.gov/show/NCT01830543. (Last accessed: 7/2013).	
SH	Bayer plc	24	Full	463		**Economic considerations** Reference to the new oral anticoagulants is not relevant to recommendation 75.	Thank you for your comment. We have amended this.
SH	Bayer plc	25	Full	600		Citation 317 appears to relate to the incorrect publication, we believe it should be Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91. doi: 10.1056/NEJMoa1009638. Epub 2011 Aug 10. As correctly cited in appendix G.	Thank you for highlighting this. This has been corrected.
SH	Bayer plc	26	Appendix G	533		The publication cited in this table is for the ATLAS TIMI 46 trial, however the data appears to be from the ATLAS ACS TIMI 51 trial (Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C et al. Rivaroxaban in patients with a recent acute coronary syndrome. New England Journal of Medicine. 2012; 366(1):9-19.) Both the ATLAS TIMI 46 phase II trial, and the ATLAS TIMI 51 phase III trial should be included in this appendix.	Thank you for your comment, this has been amended.
SH	British Association for	1	Full	17	34	Superior rates of adherence to home based cardiac rehabilitation, have been reported,[1]	Thank you for your comment. We agree and the guideline update

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	Cardiovascular Prevention and Rehabilitation (BACPR)					and offering patients a choice of rehabilitation would be expected to improve the current low uptake,[2] especially in older patients, the socially deprived, ethnic minorities, and those from rural areas who might have practical problems in accessing centre based facilities, in whom poor rates of uptake and adherence have been reported.[3] [1] Dalal HM, Evans PH. Achieving national service framework standards for cardiac rehabilitation and secondary prevention. BMJ 2003;326:481-4. [2] Wingham J, Dalal HM, Sweeney KG, Evans PH. Listening to patients: choice in cardiac rehabilitation. Eur J Cardiovasc Nurs 2006;5:289-94 [3]Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, et al. Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups. Health Technol Assess 2004;8:iii-iv,ix-x,1-152.	includes a recommendation (1.1.19) highlighting that people who have had an MI should be offered a cardiac rehabilitation programme in a choice of venues.
SH	British Association for Cardiovascular	2	Full	109	2	Patients' preference has been hypothesised to have an impact on uptake and adherence to home	Thank you for your comment. For this review on barriers and facilitators to cardiac rehabilitation

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	Prevention and Rehabilitation (BACPR)					based cardiac rehabilitation, and evidence suggests that white patients who work full time or part time and feel they have limited time are more likely to have a preference for home based cardiac rehabilitation.[5] The Cornwall heart attack rehabilitation management study (CHARMS) [6] used a comprehensive cohort design, which incorporated an element of preference—by which patients could choose between home based and hospital based cardiac rehabilitation—in addition to the randomised element of home based and centre based allocation. The authors reported that all of the primary and secondary outcomes were similar between the randomised allocation to home and hospital based rehabilitation, compared to allocation according to patient preference. This trial therefore does not support the hypothesis of patient preference as a driver of patient outcome and adherence. [5] Grace S, McDonald J, Fishman D, Caruso V. Patient preferences for home-based versus hospital-based cardiac rehabilitation. J Cardiopulm Rehabil 2005;25:24-9.	programmes we included relevant papers until we reached a point of saturation, that is. when we felt that enough papers supported a particular outcome. Seven papers reported location and transport difficulties as a reason why patients found it difficult to attend and that people preferred a community based venue. As such, not every available paper on this topic was included in the review. In addition, any paper published prior to 2006 was not included since it was felt the patient's insight would not reflect current practice/facilities. On balance the GDG thought that offering a choice of venues was the best way to get the widest group of people to engage with the rehabilitation program.

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						[6] Dalal HM, Evans PH, Campbell JL, Taylor RS, Watt A, Read KL, et al. Home-based versus hospital-based rehabilitation after myocardial infarction: a randomized trial with preference arms—Cornwall heart attack rehabilitation management study (CHARMS). Int J Cardiol 2007;119:202-11.	
SH	British Association for Cardiovascular Prevention and Rehabilitation (BACPR)	3	Full	109	38	An important UK qualitative study involving patient choice has not been reviewed. This study adds information about the factors that influence the choice patients make about their rehabilitation programme. Home based rehabilitation is influenced by a desire for the rehabilitation to fit with life, being self-disciplined, disliking groups and travel or transport problems. Hospital based rehabilitation is influenced by the desire for supervision during exercise, a lack of self-discipline, camaraderie of a group and would make an effort to attend. Some participants expressed that if there was not the option of an alternative form of rehabilitation that they would not have completed a rehabilitation programme. The recommendation is that there should be a choice of cardiac rehabilitation and that understanding the factors that influence patient's choices may help professionals guide them to the most appropriate cardiac rehabilitation method.	Thank you for your comment. We have recommended that cardiac rehabilitation is available in a choice of venues.

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						[2] Wingham J, Dalal HM, Sweeney KG, Evans PH. Listening to patients: choice in cardiac rehabilitation. Eur J Cardiovasc Nurs 2006;5:289-94	
SH	British Association for Cardiovascular Prevention and Rehabilitation (BACPR)	4	Full	100	4	A recent Cochrane review of 12 RCTs that included three UK trials of home vs. centre based cardiac rehabilitation in post MI patients has not been reviewed. Table 7 in the paper gives a Summary of adherence at follow-up in home and centre based settings. Overall adherence in all the UK based studies was similar between centre and home based groups, although one Italian study reported superior adherence in the home based participants. An accompanying BMJ editorial said 'Uptake of hospital based programmes is consistently lower in groups most in need of support for risk factor reduction, including women, elderly people, people in different ethnic groups, and people of low socioeconomic status. Ensuring access to centre based services is more challenging in large countries. Even in high income countries with universal and free access to cardiac rehabilitation, such as Australia and Canada, rural populations have limited access to centre based programmes. Home based programmes overcome many of the most common barriers to participation in these	Thank you for your comment. The Cochrane review only reported the number of patients who completed a cardiac rehabilitation programme, not how many began or adhered to the programme, which were considered by the GDG to be more important in terms of gaining benefit from the cardiac rehabilitation programme, so we did not incorporate the Cochrane review. Our search strategy was also from 2006 onwards, as evidence published from this date was deemed to be more applicable to current clinical practice, so any papers published prior to this date were not considered. There was one paper by Dalal 2007 in the Cochrane review that included post MI patients and reported on adherence; therefore it has been added to the review. Inclusion of this paper did not make any difference to the conclusion.

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						populations and settings.' Clark went on to say 'The findings emphasise the importance of patient choice in determining the services offered. Giving patients choice about the type of programme they will receive increases access to services and leads to health benefits even in patients who have previously decided not to use centre based programmes'.[8] 1 [7] Dalal HM, Zawada A, Jolly K, Moxham T, Taylor RS. Home based versus centre based cardiac rehabiltiation: Cochrane systematic review and meta-analysis. BMJ 2010; 340:b5631. [8] Clark A. Home based cardiac rehabilitation BMJ 2010;340:b5631	
SH	British Association for Cardiovascular Prevention and Rehabilitation (BACPR)	5	Full	107	10	Two more recent, UK base RCTs give more up to date information on comparative cost effectiveness of centre and home based cardiac rehabilitation. It would be useful to include health economic information from these studies.[9,10] [9]Taylor RS, Watt A, Dalal HM, Evans PH, Campbell JL, Read KL, et al. Home-based cardiac rehabilitation versus hospital-based rehabilitation: a cost effectiveness analysis. Int J	Thank you for your comment. The guideline that your comment refers to is about the cost-effectiveness of comprehensive cardiac rehabilitation and this section was not updated as explained in section 6.1 'Sections not updated in this chapter'. The study by Taylor et al (2007) was about home vs hospital-based rehabilitation which was not a question which was considered

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						Cardiol 2007;119: 196-201. [10] Jolly K, Lip GYH, Taylor RS, Raftery J, Mant J, Lane D et al. The Birmingham rehabilitation uptake maximisation study (BRUM): Heart. 2009; 95(1):36-42	for update in the current update of the guideline. The study by Jolly et al (2009) was included in section 6.4.1.2 which is about interventions designed to increase uptake of and adherence to cardiac rehabilitation programmes.
SH	British Association for Cardiovascular Prevention and Rehabilitation (BACPR)	6	Full	130	26	A model from Cornwall demonstrates how the uptake of cardiac rehabilitation and secondary prevention post MI was improved through collaborative working between primary and secondary care. Integration of rehabilitation services with secondary prevention clinics in primary care helped to achieve the national service framework targets for cardiac rehabilitation.[1] There is a call for better organisation of services across sectors, so 'care can be more readily integrated, systematised and individualised' [11] [1] Dalal HM, Evans PH. Achieving national service framework standards for cardiac rehabilitation and secondary prevention. BMJ 2003; 326:481-4. [11]Redfern J, Maiorana A, Neubeck L, et al. Achieving coordinated secondary prevention of coronary heart disease for all in need (SPAN). Int J Cardiol 2011; 146:1–3.	Thank you for your comment. We agree that the improved organisation of care is important and we have developed recommendations to support this concept (see recommendation 1.1.12 and 1.3.2).
SH	British	7	Full	6	44	6.5.2: Edinburgh Heart Manual needs to change	Thank you for your comment, this has

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	Association for Cardiovascular Prevention and Rehabilitation (BACPR)					to 'Heart Manual' This also applies to: Page 51: Page 206: Section 6.5.2 Lines 1,2, 5, 16, 17, 20 Page 207: Section 6.5.7.1 Line 33	been updated.
SH	British Association for Cardiovascular Prevention and Rehabilitation (BACPR)	8	Full	51	11	http://www.cardiacrehabilitation.org.uk/heart_manual/heartmanual.htm) needs to change to: www.theheartmanual.com This also applies to page 208 Line 2	Thank you for your comment, this has been updated.
SH	British Cardiovascular Society	1	Full	20	14	The omission of management in diabetic patients should be re-considered. Diabetes has several implications relevant to these guidelines, cardiovascular risk in diabetics post MI is higher than in non-diabetics, and up to 30% of patients suffering from acute MI have diabetes. NICE guidance on the management of diabetes does not cover secondary prevention post MI. Specifically diabetes affects revascularisation strategy (CABG, stent choice), antiplatelet choice (prasugrel guidance), prescription in those with LVSD (eplerenone advised even if no symptoms/signs heart failure), target BP, dietary and lifestyle advice. In addition reference to the NICE guidance on hyperglycaemia CG130, and PH38 guidance on those at risk of diabetes- but without known diabetes is highly relevant	Thank you for your comment. The scope of this update did not include the management of people with diabetes as a specific subgroup. The reason for this is stated in the original guideline CG48, in section 2.5.2 "Areas outside the remit of the guideline": "… The guideline does not cover the additional management of diabetes and glycaemic control in patients who have had an MI, as this is more appropriately placed in the revisions of the diabetes guidelines." The update refers to these revisions.

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						including screening for diabetes and the management of blood glucose concentration following MI.	
SH	British Cardiovascular Society	2	Full	188-190	all	The panel should reconsider offering cardiac rehabilitation to all in there own home. An effective exercise program (an essential part of cardiac rehabilitation) can not be adequately delivered in the patient's home. If home is offered and accepted as the site for cardiac rehabilitation then many patients who would have been prepared to travel may opt for this, undermining both the effectiveness and cost effectiveness of cardiac rehabilitation. There would be considerable logistic difficulties to a home based service particularly in geographically wide / rural regions. Therefore the panel may consider offering cardiac rehabilitation at home only in exceptional circumstances – for instance in the setting of significant co-morbidity / mobility problems. Offering cardiac rehab at home might contribute to increased cardiac rehab uptake rates which in itself is important to encourage smoking cessation, healthy living, etc, but home rehab should not be at the *expense* of the excercies component of cardiac rehab.	Thank you for your comment however we disagree. We did not review the evidence on the effectiveness of cardiac rehabilitation programmes in different settings (for example, home based or hospital based) however the evidence identified supports an increase in the uptake and adherence to cardiac rehabilitation programmes when this is offered in a range of settings.
SH	British Cardiovascular Society	3	Full Full	53 438	4-11	Guidance on STEMI CG167 and NSTEMI CG94 and technology appraisals on prasugrel and ticagrelor, recommend prasugrel as an option in the setting of primary PCI stent thrombosis on clopidogrel and diabetes and ticagrelor as an	Thank you for your comment. Recommendations on the use of prasugrel and ticagrelor can be found in NICE technology appraisal 182 and 236 respectively and therefore,

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						option following cardiology review in all ACS patients. To give only the option of clopidogrel in this guidance conflicts with the above guidance. Prasugrel and Ticagrelor should be included as options – usually a continuation of the acute treatment	evidence relating to the use of these drugs has not been reviewed. For clarity, we have now included recommendations to refer to these NICE technology appraisals in section 7.4.
SH	British Cardiovascular Society	4	Full	318	9	It is not clear why an assessment of the PLATO, TRITON and CURRENT OASIS 7 trials comparing clopidogrel to ticagrelor, prasugrel and double dose clopidogrel respectively are not discussed in this section – as stated in point 3 this potentially conflicts with other NICE guidance. There are certainly questions over duration of treatment with respect to prasugrel and ticagrelor that could be addressed here, even if a decision on which antiplatelet to use in covered in other guidance.	Thank you for your comment. The current guideline update has reviewed evidence only on the duration of clopidogrel. Recommendations on the duration of ticagrelor and prasugrel can be found in NICE technology appraisals 182 and 236. For clarity, we have now included recommendations to refer to these NICE technology appraisals in section 7.4.
SH	British Cardiovascular Society	5	Full	463		Consideration of patients who are already on aspirin and prasugrel or ticagrelor and are found to need oral anticoagulation should be further addressed. The options of changing from DAPT with prasugrel/ticagrelor to clopidogrel and warfarin either immediately or after a defined period (eg 1-3 months) should be considered by the panel.	Thank you for your comment. The group discussed a variety of approaches to the issue of anticoagulation in patients needing antiplatelet therapy after MI, but elected to make only recommendations where the group felt the evidence, both direct and indirect was stronger, recognising that the recommendations could not cover all the options of timing and choice of agent that are possible. Recommendation 1.3.27 highlights that these drugs should not be used routinely and therefore, acknowledges

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							that there are situations in which this combination may be used.
SH	British Cardiovascular Society	6	Full Full	53 449	11	Assessment of bleeding risk in relation to cardiovascular risk is critical to decide on treatment strategy. This should be done during hospital admission (or at the time of first contact) in addition to being repeated at the follow-up visit so that the management plan can be formulated at the start of treatment. Specific scores such as GRACE, HAS-BLED should be mentioned.	Thank you for your comment. We agree, assessment of bleeding risk should be carried out and this is captured in recommendation 1.3.3. However, hospital admission is outside the remit of the scope of the current guideline, which focuses upon secondary prevention, rather than acute management following hospital admission. Recommendations on the acute management of NSTEMI and STEMI can be found in NICE clinical guideline CG167 'Myocardial infarction with ST-segment elevation' and CG94 'Unstable angina and NSTEMI'. We have not recommended any bleeding risk score since the different tools were not reviewed as it was outside the remit of the current guideline update.
SH	British Cardiovascular Society	7	Full	53	23-24	As per the European guidance for STEMI 2012 a proton pump inhibitor should be considered in patients at risk of gastrointestinal bleeding (this group not only includes those with dyspepsia)	Thank you for your comment. Recommendation 1.3.14 and 1.3.15 were not updated as part of the current guideline update.
SH	British Cardiovascular Society	8	Full Full	55 554	7 3	Eplerenone should also be given to patients with LVSD and diabetes (even if no signs/symptoms of heart failure).	Thank you for your comment however, the section on Aldosterone antagonists was not updated as part of the current guideline update, as outlined in

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							Section 5**.**
SH	British Cardiovascular Society	9	Full Full	554 54	3 17	One of the aims of this guidance is to advise rapid uptitration of ACE inhibitors to target dose (page 307) – in patients co-prescribed eplerenone this is likely to increase the incidence of hyperkalaemia compared to the current situation where uptitration is not performed well. This means that this guidance for monitoring potassium levels needs to be strongly emphasised. The guidance suggests 48hrs, 1 week, 1 months, 3 months then every 3 months – this will occur in those followed up in heart failure clinics, but many of such patients will not be so firm arrangements for such patients must be made to avoid undetected and potentially dangerous hyperkalaemia. This is more likely in those with renal dysfunction and those with potassium levels at the upper limit of normal. Sensible cautions should be applied and contraindications to epleronone +/- ACE inhibitors, for example, serum creatinine concentration >150 micromol/L, should be specified.	Thank you for your comment. Guidance on monitoring people who are prescribed ACE inhibitors or aldosterone antagonists is provided in Section 7.11. Providing more specific information on monitoring of people on secondary prevention was not within the scope of the current guideline update.
SH	British Cardiovascular Society	10	Full	310		Consider rewording recommendation to 'Offer people who are intolerant to ACE inhibitors an ARB after an MI'	Thank you for your comment. The GDG felt that on balance the recommendation was clearer as it currently stands and therefore no amendment was made.
SH	British Cardiovascular Society	11	Full	445		The PLATO trial showed a mortality benefit in medically managed ACS patients (substudy BMJ 2011). Consideration of ticagrelor in this	Thank you for your comment. Recommendations on the duration of ticagrelor and prasugrel can be found

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						subgroup is therefore needed.	in NICE technology appraisals 182 and 236. For clarity, we have now included recommendations to refer to these NICE technology appraisals in section 7.4.
SH	British Cardiovascular Society	12	Full	453		In medically managed patients, the PLATO trial suggested that intense DAPT with ticagrelor and aspirin saves lives compared to clopidogrel + aspirin. There is therefore a concern that in such patients who need anticoagulation, antiplatelet cover with aspirin alone may expose some patients to an excess cardiovascular risk. Whilst ticagrelor cannot be recommended in conjunction with warfarin, would the panel consider clopidogrel and warfarin an option? The latter combination has little excess bleeding risk compared to aspirin and warfarin and has more potent antiplatelet cover. In reality, the medically managed group are heterogenous and so treatment decisions need to be individualized based on cardiovascular and bleeding risks. So, for medically managed patients who require anticoagulation, would the panel consider both aspirin/ warfarin and clopidogrel/warfarin combinations to be potential options?	Thank you for your comment. As you acknowledge, the recommendations in section 7.4.6 relate to people who have a pre-existing indication for anticoagulation and who have an MI. The combination of warfarin and clopidogrel is recommended for those people who have had an MI who have undergone primary PCI and for individuals who have a sensitivity to aspirin. The GDG felt there was insufficient evidence to recommend this treatment option for the medically managed population, in general. However, the recommendations do emphasise that bleeding, cardiovascular and thromboembolic risks should be taken into consideration when considering an individual's treatment.
SH	British Cardiovascular Society	13	Full Full	558 52	11-15 34	Identification of patients with significant LV dysfunction is critical post MI with timely referral to heart failure services giving patients with	Thank you for your comments. Whilst we agree that the timing of assessing LV function is critical for people who

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						significant LV dysfunction the best chance of a good outcome. Following acute treatment (revascularisation and drug therapy) LV function may significantly improve but also, despite appropriate treatment, may significantly deteriorate in up to 30% of patients due to adverse remodelling. These patients may remain asymptomatic during this phase. Therefore assessment of LV function needs to be performed both acutely and repeated during follow-up to pick up such patients. Whilst assessment of LV function on more than 1 occasion may be considered excessive for all patients, the panel should consider which groups of patients with larger infarcts should be re-assessed; and also which patients should be referred and at what time to heart failure services. These issues are not covered in the NICE guidelines for chronic heart failure CG108. Patients with LVEF<30% at 6 weeks post MI should be referred for an ICD.	have had an MI, and how to identify who should be assessed both acutely and during follow-up, these areas are outside the scope of the current guideline update. However, the recommendations on the use of defibrillators, beta-blockers, aldosterone antagonists, calcium channel blockers, do distinguish between those who do and do not have LV dysfunction. Additionally, recommendation 1.3. 4 provides guidance on how to identify left ventricular dysfunction.
SH	British Cardiovascular Society	14	Full	318		Due to differing risks and consequences of stent thrombosis in different patients, the cardiology team involved in a patients' coronary angioplasty should be involved in decisions involving potential changes in antithrombotic therapy particularly within 6 months of PCI.	Thank you for your comment. We agree that assessment of patients needs to take place and we have recommended that all people who have an MI are offered an assessment of bleeding risk and left ventricular function (see recommendation 1.3.3 and 1.3.4).
SH	British Heart Foundation	1	NICE	General		The British Heart Foundation is the nation's heart charity. We welcome the opportunity to	Thank you for your comment.

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						respond to this consultation.	
SH	British Heart Foundation	2	NICE	General		We welcome the recommendations that NICE has suggested to update this guideline. We believe that these changes will help improve the care received by those that have survived a heart attack.	Thank you for your comment.
SH	British Heart Foundation	3	NICE	General		In particular, we welcome the increased emphasis in the guideline on the provision of appropriate, personalised rehabilitation after an event. Cardiac rehabilitation is an example of effective secondary prevention for people living with heart disease. These programmes offer lifestyle advice and support to help people manage their own condition and to prevent a further major heart event.	Thank you for your comment, we agree.
SH	British Heart Foundation	4	NICE	16	1.2.2	We have noted the recommendation that eating oily fish should not be routinely recommended for the sole purpose of preventing another heart attack. We will amend our own guidance accordingly in light of this change from the previous guideline.	Thank you for your comment.
SH	British Medical Association	1	NICE version	General		Although a lot of what is recommended in this guideline is aimed at early lifestyle modification and referral into rehabilitation programmes, and as such will be secondary-care initiated, it is also of relevance for GPs. The review recognises the importance of a clear discharge summary including, for the first time, recommendations about the target doses for ACE inhibitors and Beta Blockers. This will be	Thank you for your comment.

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						useful as at present, it many patients are discharged on small doses with no indication to the GP or the patient that they should be increased. In summary, this is a useful review and it is welcomed.	
SH	British Medical Association	2		1.3.29	22	Although the recommendation to continue beta blockers beyond a year acknowledges that the research on this is not yet complete, it does provide some reassurance for patients who wish to stop because of undesirable side effects.	Thank you for your comment, we agree.
SH	Department of Health	1	General			I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.
SH	Eli Lilly and Company Limited	1	NICE	18	1.3.1	Thank you for providing Lilly with the opportunity to review and comment on this draft guideline. We agree with the recommendation that dual antiplatelet therapy be offered to all patients who have had an acute M.I. We also agree that prasugrel is offered as a treatment option in combination with aspirin.	Thank you for your comment.
SH	Eli Lilly and Company Limited	2	NICE	19	1.3.12	It is our understanding that this heading refers to the duration of antiplatelet therapy. We believe that this heading should be more specific e.g. Duration of antiplatelet therapy. The addition of a statement directing readers to guidance for prasugrel (TA182) and ticagrelor (TA236), which gives information on treatment duration, would be helpful here.	Thank you for your comment. Section 7.4 refers to a number of elements of antiplatelet therapy, including the duration of therapy, such as use of aspirin. Recommendations on the use of prasugrel and ticagrelor can be found in NICE technology appraisal 182 and 236. For clarity, we have now included recommendations to refer to

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							these NICE technology appraisals in section 7.4.
SH	Eli Lilly and Company Limited	3	FULL	323	7.4.5	We believe that the statement on page 323 which states, *"This chapter considers evidence relating to clopidogrel only as recommendations on treatment with prasugrel and ticagrelor can be found in TA182 'Acute coronary syndromes – prasugrel' and TA236 'Acute coronary syndromes – ticagrelor'."* should be moved to the beginning of the chapter 7.4. This upfront statement would make it clear that the remainder of the chapter focuses only on the antiplatelet treatment option, clopidogrel.	Thank you for your comment. Recommendations on the duration of ticagrelor and prasugrel can be found in NICE technology appraisals 182 and 236. For clarity, we have now included recommendations to refer to these NICE technology appraisals in section 7.4.
SH	Isle of Wight Clinical Commissioning Group	1	NICE	16	12	Omega- 3 fatty acid capsules (Omacor) is a drug rather than a food or food supplement hence should be a consideration under drugs rather than foods (diet)	Thank you for your comment. The GDG felt that the use of omega-3-acid ethyl esters is related to diet and lifestyle factors (for example, eating oily fish) and therefore felt that this should sit within the chapter on 'Lifestyle'.
SH	Isle of Wight Clinical Commissioning Group	2	NICE	16	12	Omacor 1g/day, have shown a significant reduction of a combined endpoint including all-cause death. Preventing premature death is in line with DoH addenda.	Thank you for your comment. The GDG felt that in the context of modern treatment of myocardial infarction, omega-3-acid ethyl esters (Omacor) do not have a significant effect and therefore, did not recommend the use of these agents.

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SH	Isle of Wight Clinical Commissioning Group	3	NICE	16	12	The use of Omega- 3 fatty acid capsules has been considered cost-effective by NICE	Thank you for your comment. The cost effectiveness data in CG48 was based upon the data from the GISSI-P trial. The GDG felt that in the context of modern treatment of myocardial infarction, Omacor does not have a significant effect and as such, cost effectiveness was not calculated on the basis of the relevant data.
SH	Isle of Wight Clinical Commissioning Group	4	NICE	16	12	There is no differentiation between Omacor and omega-3 studies which may be of different strength/potency.	Thank you for your comment. We acknowledge that there are differences in the types of omega-3-acid-ethyl esters used across the studies identified, including the proportions of EPA and DHA included. However, the number of studies identified was insufficient to explore the effect of dose upon the outcomes. The GDG felt that the weight of evidence, in particular in people treated with modern therapy following acute MI, did not support the use of omega-3 acid ethyl esters, including Omacor, particularly, given the null results provided by the Rauch trial which used prescription grade omega-3-acid ethyl esters. Additionally, no difference in all-cause mortality (using hazard ratios) in studies that treated patients with prescription grade omega-3 capsules

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							against placebo was found.
SH	Isle of Wight Clinical Commissioning Group	5	NICE	16	12	GISSI-P & GRPD should not be compared to a number of other Omega-3 studies because of differences in robustness, GPRD backing GISSI-P data and the specific benefit seen with Omacor with early treatment rather than generally as per the Omega-3 studies.	Thank you for your comment. We acknowledge that there are differences in the quality of published omega-3 RCTs. This was highlighted in the GRADE tables and discussed in the 'Linking evidence to recommendation' sections. Because of differences in the quality of the studies, the guideline development group placed greater emphasis on the results from higher quality studies (such as Rauch et al) when they made their recommendations.
SH	Merck Sharp & Dohme	1	NICE	18		Section 1.3.1: Although this section is marked [2007, amended 2013], we request the following comment be taken into consideration: The original version of CG48 was published in May 2007. The wording of section 1.3.1 in the draft updated guideline remains largely unchanged compared with the original version, with statins listed as one class of drugs which should be offered to patients who have had an acute MI. It is important to note that for some patients, statins may be an inappropriate or contraindicated class of drug; for such patients,	Thank you for your comment. Recommendation 1.3.1 was only amended to reflect changes to the updated recommendations. The section on 'Lipid modification' was not updated in the current guideline update.

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						alternative lipid modifying therapies (e.g. ezetimibe) have been recommended by NICE in the interim period since publication of CG48 in May 2007 (TA132[1] for ezetimibe was published in November 2007). The draft guideline does not seem to account for this guidance. We suggest that section 1.3.1 should state "statins **or other appropriate lipid modifying therapies"** should be offered to all patients who have had an acute MI. This would ensure consistency with the available NICE guidance, and section 1.3.41 of this update (see comment below). Ref 1: NICE (2007) TA132 Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. Available at: http://publications.nice.org.uk/ezetimibe-for-the-treatment-of-primary-heterozygous-familial-and-non-familial-ta132	
SH	Merck Sharp & Dohme	2	NICE	18		Section 1.3.2: This section specifies that patients should have a clear management plan that includes monitoring of blood pressure and monitoring of renal function. However the draft guideline does not specify recommended target levels for blood pressure and renal function for the patient population covered by CG48. Additionally, no mention is made of the	Thank you for your comment. Target levels for blood pressure and renal function are not within the remit of the current guideline update, which focuses on secondary prevention following a myocardial infarction. Monitoring lipid-lowering treatment is being covered by the update of NICE

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						importance of monitoring lipid levels (vs. clinical target levels) as part of the patient's management plan.	clinical guideline 67 'Lipid modification', currently in development.
SH	Merck Sharp & Dohme	3	NICE	19		Sections 1.3.12 – 1.3.18 (Antiplatelet therapy): Within these sections, the only antiplatelet therapy referred to by name is clopidogrel. This is despite section 1.3.1 referring to both prasugrel and ticagrelor as alternative options to clopidogrel. For consistency, and to ensure clarity of recommendations to users of the guideline, we suggest it would be appropriate for sections 1.3.12 - 1.3.18 to reflect all therapy options recommended by NICE for use in combination with aspirin as dual antiplatelet therapy.	Thank you for your comment. This section refers to a number of elements of antiplatelet therapy, including the duration of therapy, such as use of aspirin. Recommendations on the use of prasugrel and ticagrelor can be found in NICE technology appraisal 182 and 236. For clarity, we have now included recommendations to refer to these NICE technology appraisals in section 7.4.
SH	Merck Sharp & Dohme	4	NICE	24		Recommendation 1.3.41 includes reference to NICE CG67 (Lipid modification). Publication of the updated version of CG48 is due in November 2013. However, CG67 is also undergoing a planned review, and is not due to publish until July 2014. It will be important to consider how to most appropriately cross-reference to the latest available NICE recommendations, to ensure users to the updated acute MI guideline are not mistakenly referred to out-of date materials.	Thank you for your comment. We are aware that NICE clinical guideline 67 is currently being updated and when the updated guideline is published, the NICE website will clearly link to the updated version of the guideline.

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SH	Merck Sharp & Dohme	5	NICE	24		Section 1.3.41: Although this section is marked [2007], we would request the following comment be taken into consideration: The first greyed out box in this section states statin therapy is recommended for adults with clinical evidence of cardiovascular disease (with reference to TA94 and CG67). Yet the second greyed out box directly below the first refers to the use of "statins and other lipid lowering agents". As stated in our previous comment, there are some patients for whom the use of statins may be inappropriate or contraindicated. Consequently we suggest that for consistency between the two boxes in this section, the wording in the first box should be amended to "statin or other lipid lowering agent therapy".	Thank you for your comment. The section on 'Lipid modification' was not updated in the current guideline update and recommendations on the use of lipid lowering agents will be covered by the update of NICE clinical guideline 67 'Lipid modification'.
SH	Merck Sharp & Dohme	6	NICE	24		Section 1.3.41: Following on from the above comment, the second greyed out box in this section refers to recommendations on the use of statins and other lipid lowering agents being available in NICE CG67 and TA94. MSD suggests that this box should also reference TA132[1] which provides NICE's recommendations on the use of ezetimibe as a lipid-lowering therapy for patients with primary hypercholesterolaemia. Ref 1: NICE (2007) TA132 Ezetimibe for the treatment of primary (heterozygous-familial and	Thank you for your comment. The section on 'Lipid modification' was not updated in the current guideline update and recommendations on the use of lipid lowering agents will be covered by the update of NICE clinical guideline 67 'Lipid modification'.

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						non-familial) hypercholesterolaemia. Available at: http://publications.nice.org.uk/ezetimibe-for-the-treatment-of-primary-heterozygous-familial-and-non-familial-ta132	
SH	Merck Sharp & Dohme	7	NICE	30		Section 3.2: The section on related NICE guidance should include TA132[1] (Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia). Ref 1: NICE (2007) TA132 Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. Available at: http://publications.nice.org.uk/ezetimibe-for-the-treatment-of-primary-heterozygous-familial-and-non-familial-ta132	Thank you for your comment, this has been added to the list of related guidance.
SH	Pfizer Ltd	1	Full	57	8	Pfizer believe the guideline would be strengthened by the additional reference to the REMINDER trial. REMINDER trial, a double-blind, randomized, placebo-controlled trial evaluating the safety and efficacy of early treatment with eplerenone in patients with acute MI. Patients were identified during ER or ambulance evaluation and diagnosis of acute STEMI in the	Thank you for your comment. The recommendations on the use of aldosterone antagonists have not been updated as part of the current guideline update.

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						absence of heart failure. Those who agreed to participate were randomized and given an initial dose of either eplerenone or placebo within 12 to 24 hours of the initial onset of symptoms of an acute MI. Eplerenone once-daily dosing of 25 or 50 mg/day was based on serum potassium and eGFR levels. Most patients (88.6 percent) received the 50-mg dose. Patients in both arms of the trial also received standard medical care for acute STEMI. A total of 1,012 patients were randomized, 506 to each arm. The primary endpoint was a composite of cardiovascular mortality, ventricular arrhythmia, clinical or subclinical heart failure as determined by left ventricle ejection fraction (LVEF) below 40 percent or elevated brain natriuretic peptide (BNP)/NT-proBNP one month or longer after enrollment. After a mean follow-up of 10.5 months, 93 patients (18.4 percent) in the eplerenone group had reached the primary endpoint versus 150 patients (29.6 percent) in the placebo group. Eplerenone had an overall hazard ratio of 0.57 ($p<0.0001$) for the primary endpoint. After the same follow-up period, a high BNP/NT-proBNP level was seen in 18 patients (16 percent) in the eplerenone group compared to the 131 patients (25.9 percent) in the placebo group. The eplerenone hazard ratio for high	

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						BNP/NT-proBNP was 0.58 (>0.0002). Adverse event rates were similar in both groups. Serum potassium levels exceeded 5.5 mmol/L in 5.6 percent of the eplerenone group and 3.2 percent of the placebo group (p=0.09) and were below 3.5 mmol/L in 1.4 percent of the eplerenone group and 5.6 percent of the placebo group (p=0.0002). *American College of Cardiology* *SAN FRANCISCO (March 10, 2013)* *http://www.cardiosource.org/News-Media/Media-Center/News-Releases/2013/03/REMINDER-Trial.aspx*	
SH	Pfizer Ltd	2	Full	98-99	37-39; 1-6	Pfizer welcomes the cross-referral made to NICE public health (PH) guidance 1 and 10 on smoking cessation. In addition to the PH1 and PH10 guidance, the guideline may also wish to cross-refer to the forthcoming NICE smoking cessation quality standard as this is due to be published in August 2013, i.e. prior to the publication of this guideline (November 2013) according to the current timeline on the NICE website. In particular, quality statements 1-4, and 6 as set out in the draft smoking cessation quality standard will be highly pertinent to the guideline and will reinforce and update the current smoking cessation guidance referred to from PH1 and PH10.	Thank you for your comment. Section 5.5 has not been updated as part of the current guideline update, as outlined in Section 5.

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						Link to draft smoking cessation quality standard: http://www.nice.org.uk/guidance/index.jsp?action=download&o=63077	
SH	Roche Diagnostics	1	Full	319	5	We acknowledge the fact that the GDG may not have had the scope to cover a comparison of the dual antiplatelet therapy (APT) options (clopidogrel, prasugrel or ticagrelor) for the secondary prevention of MI, given this very extensive and comprehensive work. However, the guideline may benefit from a more detailed discussion of differences between the therapy options as the majority of patients in the NHS receive APT after PCI. It could be acknowledged that patients who are poor CYP2C19 metabolisers may not respond to clopidogrel (i.e. show high on-treatment platelet reactivity) with associated increased risk of cardiovascular events (SPC clopidogrel, Sanofi, 2013) and that the alternatives prasugrel or ticagrelor may be associated with higher bleeding risk. We like to highlight that platelet function testing allows the identification of patients with high on-treatment platelet reactivity on clopidogrel (Bonello, L. *et al. J Am Coll Cardiol* 2010;56(12):919-33). PFT is supported by a recommendation from the American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions Guideline for	Thank you for your comment. . Recommendations on the ticagrelor and prasugrel can be found in NICE technology appraisals 182 and 236. For clarity, we have now included recommendations to refer to these NICE technology appraisals in section 7.4. Platelet function testing was not identified during the scoping phase as an area that should be included in the guideline update.

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						Percutaneous Coronary Intervention (Levine, G.N. *et al.* (2011). *Circulation* 2011;124(23)*:*2574-609).	
SH	Roche Products	1	General			We feel this is a very well written document and I can confirm that Roche does not have any comments to make on this guideline.	Thank you for your comment.
SH	Royal College of Nursing	1	General	General		The Royal College of Nursing welcome the update of this guideline. It is timely and comprehensive.	Thank you for your comment.
SH	Royal College of Nursing	2	Full			Very good guideline and easy to read. One area of practice that would improve things in many centres is to have the episode of care centralised to one computer programme. This would provide collateral information, especially to clinicians at follow up clinics on the level of rehabilitation entered into and any progress made.	Thank you for your comment. We agree.
SH	Royal College of Nursing	3	full			The current IT systems used in many centres have a separate physiotherapy data base for exercise programmes. We are aware that this is in the process of being changed at some centres but we are also aware that some other centres are facing similar issues. A guideline such as this would help secure such progress and encourage more harmonised working with multiple disciplinary teams. The additional benefit from such a change would be for example, for an instant booking to be made	Thank you for your comment.

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						for the exercise programme at the point of discharge from hospital.	
SH	Royal College of Physicians	1	General			The RCP has had sight of and wishes to endorse the comments submitted by the British Cardiovascular Society on the above guideline.	Thank you for your comment.
SH	Sheffield NHS Teaching Hospitals Foundation Trust	1	Full	44	Algorithm A	This algorithm is outdated since it highlights the use of aspirin and clopidogrel whereas ESC guidelines recommend clopidogrel only as second line therapy to ticagrelor or, when appropriate, prasugrel	Thank you for your comment. The algorithm summarises the recommendations presented within the current guideline (update of CG48) and does not reflect recommendations in other guidelines. Recommendations on the use of prasugrel and ticagrelor can be found in NICE technology appraisal 182 and 236 respectively and therefore, evidence relating to the use of these drugs has not been reviewed. For clarity, we have now included recommendations to refer to these NICE technology appraisals in section 7.4.
SH	Sheffield NHS Teaching Hospitals Foundation Trust	2	Full	48	21-24	This advice is outdated since it highlights the use of aspirin and clopidogrel whereas ESC guidelines recommend clopidogrel only as second line therapy to ticagrelor for NSTE ACS regardless of management strategy	Thank you for your comment. Recommendations on the use of prasugrel and ticagrelor can be found in NICE technology appraisal 182 and 236 respectively. For clarity, we have now included recommendations to refer to these NICE technology appraisals in section 7.4.
SH	Sheffield NHS	3	Full	48	25-28	This advice is outdated since it highlights the	Thank you for your comment.

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	Teaching Hospitals Foundation Trust					use of aspirin and clopidogrel whereas ESC guidelines recommend clopidogrel only as second line therapy to ticagrelor or prasugrel for STEMI managed with primary PCI which represents the majority of patients in the UK	Recommendations on the use of prasugrel and ticagrelor can be found in NICE technology appraisal 182 and 236 respectively and therefore, evidence relating to the use of these drugs has not been reviewed. For clarity, we have now included recommendations to refer to these NICE technology appraisals in section 7.4.
SH	Sheffield NHS Teaching Hospitals Foundation Trust	4	Full	53	4-5	This advice is outdated since it highlights the use of aspirin and clopidogrel whereas ESC guidelines recommend clopidogrel only as second line therapy to ticagrelor for NSTE ACS regardless of management strategy	Thank you for your comment. Recommendations on the use of prasugrel and ticagrelor can be found in NICE technology appraisal 182 and 236 respectively and therefore, evidence relating to the use of these drugs has not been reviewed. For clarity, we have now included recommendations to refer to these NICE technology appraisals in section 7.4.
SH	Sheffield NHS Teaching Hospitals Foundation Trust	5	Full	53	10	This advice is outdated since it highlights the use of clopidogrel in patients undergoing CABG whereas ticagrelor was shown to reduce mortality compared to clopidogrel in patients undergoing CABG following ACS, including STEMI	Thank you for your comment. An additional recommendation in section 7.4 has now been included to highlight that for people who have had CABG, following a STEMI, a second antiplatelet agent should be continued for up to 12 months.
SH	Sheffield NHS Teaching Hospitals	6	Full	54	25-26	This recommendation is contrary to ESC NSTE ACS 2011 guidelines which do not recommend beta blockers in patients with normal LV systolic	Thank you for your comment. The Guideline group discussed the role of beta blockers and felt that it was

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	Foundation Trust					function following MI. There is no convincing evidence to support the recommendation for beta blockers in these patients.	appropriate to soften the recommendation for long term betablockade in all people who have had an MI as stated in the original guideline. However, the GDG felt overall that the evidence was not strong enough to recommend the abandonment of betablockade entirely in patients with normal LV function. The group did highlight this as an area needing further research.
SH	Sheffield NHS Teaching Hospitals Foundation Trust	7	Full	318-450 (Section 7.4.1 to 7.4.8)		These sections are outdated and therefore of limited practical value for patients with acute coronary syndrome who do not require oral anticoagulation since they are focussed on clopidogrel, which is now recommended by the European Society of Cardiology as second-line therapy only in NSTEMI and PCI-managed STEMI, in view of the evidence of superior outcomes with ticagrelor and, in some patients groups, prasugrel.	Thank you for your comment. .The current guideline update has reviewed evidence only on clopidogrel. Recommendations on ticagrelor and prasugrel can be found in NICE technology appraisals 182 and 236. For clarity, we have now included recommendations to refer to these NICE technology appraisals in section 7.4.
SH	The British Dietetic Association	1	Full	49	14	One reviewer questioned why patients ("overweight or obese") post MI are advised to lose weight when there is no evidence available to back this up - when compared to the evidence presented for Omega 3, diet, medications Indeed, the NICE Obesity Guidance presents no	Thank you for your comment. Recommendation 1.2.14 was not updated as part of the current guideline update, as described in Section 5 of the full guideline.

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						evidence of a comparable standard (RCTs) either (for any population group). If the emphasis is on available evidence then line 14 should be removed Interestingly European Guidance on Clinical Practice highlights the paradox regarding this issue …see copied extract below ***4.6.4 The obesity paradox in established coronary artery disease*** ***If, at the population level, obesity is associated with an increased risk of CVD incidence and mortality, among those with established coronary artery disease, the evidence is contradictory. Systematic reviews of patients with coronary artery disease or undergoing PCI have suggested an 'obesity paradox' whereby obesity appears protective against an adverse prognosis.366 – 369*** **European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)** **European Heart Journal (2012) 33, 1635–1701** **doi:10.1093/eurheartj/ehs092**	
SH	The British	2	Full	62	11-15	There are considerable limitations of depending	Thank you for your comment. We

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	Dietetic Association					solely on RCTs for dietary issues. As explained clearly by Truswell, this approach is more suited to drug trials. (Ref: Truswell AS (2005) Some problems with Cochrane reviews of diet and chronic disease. European Journal of Clinical Nutrition (2005) 59, Suppl 1, S150-154) It was also felt that there was a need for NICE to adopt a uniform approach. Other sources of evidence are used in other sections and feel that to be consistent that information derived from RCTs can be used as the starting point for discussion but that other sources of information e.g. from cohort studies, good quality cross-over trials, epidemiological data should also be considered and discussed.	acknowledged the limitations of using RCTs to study the effectiveness of lifestyle interventions and these are outlined on page 62. In this discussion, we also highlight how RCTs are used in preference to cohort studies since one of the main advantages in this review is that they rely less on re-call bias of omega-3 or fish intake, and since patients are randomised they reduce the likelihood of other unmeasured confounders influencing the outcome. Throughout the guideline we have used cohort studies if no RCT evidence or low quality RCT evidence is available. We used cohort studies when identifying barriers to uptake and adherence to cardiac rehabilitation programs as the RCT is an inappropriate study design to answer this review question.
SH	The British Dietetic Association	3	Full	62	14	"RCTs are less reliant on self-reporting of omega-3 fatty acid intake" We presume this is because of the use of omega-3 capsules – but does this automatically make the results more reliable? There is an arguement that all trials carried out	While we agree that there are limitations with the use of RCTs for lifestyle interventions, we do feel one of the main advantages they have in this review over cohort studies is that they have a reduced risk of recall bias i.e. in an RCT a person can more easily calculate their omega-3 intake.

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						to date on fish oil supplements are invalidated by the fact that dietary sodium and potassium intake was not controlled as fish are an important source of potassium but fish oil contains none. BMJ Vol 332 15 April 2006 "Risks and benefits of omega-3 fats Summary of responses" Surely whether the results are reliable or not is much more complex that simply whether it was a RCT or not.	Recall bias can include fish and capsule intake that is why we say on page 62 "RCTs are less reliant on self-reporting of omega-3 fatty acid intake", meaning both the capsules and fish.We agree that a study's reliability extends beyond whether it is an RCT or not and the limitations of the studies included in the review are described in the relevant GRADE tables. Thank you for your comments on the role of sodium and potassium intake. However, assessing the role of sodium and potassium intake was not within the scope of the guideline update. Any effect sodium and potassium may have should be controlled for in the studies since the patients were randomised to the treatment groups and any background effects should be randomly distributed.
SH	The British Dietetic Association	4	Full	62	15	There is an assumption that non-measured confounders should be randomly distributed in RCTs but again this will depend on current knowledge e.g. prior to wide use of statins, we were not aware that this would impact on the effect of omega-3 supplementation.	Thank you for your comments. No study can measure all possible confounders and there are no doubt numerous unknown confounders that may influence the results. But compared with cohort studies RCTs are less likely to be influenced by known and unknown confounders such

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						There are likely to be many aspects that haven't been adequately controlled and randomly distributed between the 2 groups therefore it would be helpful to consider other sources of information. Also several studies have stressed the need to consider the balance of omega-6 to omega-3 fats in the diet as they compete for the same rate-limiting enzymes. Owing to dependence on RCT evidence alone in this particular section of the guidelines, this aspect is ignored e.g. numerous articles illustrating the importance of this aspect are given in "Excess omega-6 fats thwart health benefits from omega-3 fats" E. F Tribole Rapid response published 27/3/2006 to Risks and benefits of omega-3 fats" BMJ 2006;332:752-60 (1 April)	as statins and omega-6 since the patients are randomised and background factors should be distributed equally amongst the groups, therefore leaving the intervention of omega-3-acid ethyl esters as the main difference between the groups and dominate moderator of the outcomes. Given that non-RCTs are less reliable, data from RCTs were only included for this review question.
SH	University of Hertfordshire	1	FULL	General		We welcome the inclusion of a Mediterranean-style diet in the NICE guidelines for the secondary prevention of myocardial infarction. However, we believe that the current descriptor of this diet, as given in section 1.2.1 of the Draft Guideline document, is inadequate in terms of either the dietary recommendations given in the	Thank you for your comment. Recommendation 1.2.1was not updated as part of the current guideline update, as described in Section 5 of the full guideline.

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						main clinical study cited (the Lyon heart study) or by the more widely accepted definition of a Mediterranean diet, and should be replaced with a more accurate descriptor (see below). Since recent evidence demonstrates that primary prevention of cardiovascular disease by a Mediterranean diet is even more impressive (eg Predimed study), an accurate description of this diet will be very important for any future review by NICE. Based on the Lyon heart study, we recommend replacing Advise people to eat a Mediterranean-style diet (more bread, fruit, vegetables and fish; less meat; and replace butter and cheese with products based on plant oils) Advise people to eat a Mediterranean-style diet (more bread, cereals, legumes, fruit, vegetables and fish; less meat; replace butter and cream with rapeseed or olive oil-based margarine; use olive or rapeseed oil for salad and food preparation). Evidence The dietary instructions for the Lyon heart study include consumption of legumes and rapeseed and olive oils [1, 2]. None of these are mentioned in the current descriptor in the Draft Guideline document, although all have been	

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						shown to have cardioprotective benefits. The Draft Guideline document recommendation to "replace butter and cheese with products based on plant oils" is misleading. Firstly, it ignores the specific advice given in the Lyon study to use rapeseed oil-based margarine. Rapeseed oil is especially rich in alpha-linolenic acid (ALA), and subsequent analysis of the Lyon study indicated that ALA was very important for the health outcomes. Using the term "plant oils" is likely to result in the consumption of more common vegetable oils in the UK, eg sunflower oil which is very low in ALA. Secondly, the original advice given in the Lyon study was to replace butter and cream, not cheese. Cheese consumption was not different between the experimental and control groups in the Lyon study. However, it is noteworthy that Mediterranean cheeses are commonly made from sheep and goat milk which are rich in medium chain fatty acids (that do not raise cholesterol levels). The dietary advice for the Lyon heart study also included using olive and rapeseed oil for salad and food preparation. Leaving out olive oil from the descriptor ignores the large body of evidence for its cardioprotective effects (especially virgin olive oil). Tree nuts (not mentioned in the Lyon study) are also commonly included in the Mediterranean diet and data from the Predimed primary prevention intervention trial strongly supports the cardioprotective effects of these	

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						nuts [3]. References 1. de Lorgeril M and Salen P (2006) The Mediterranean-style diet for the prevention of cardiovascular diseases Pub Health Nut 9 (1A): 118-123 2. de Lorgeril M and Renaud S (1994) Mediterranean alphalinolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet 343: 1454–1459 3. Estruch R et al (2013) Primary Prevention of Cardiovascular Disease with a Mediterranean Diet New Eng J Med 368: 1279-1290	

These organisations were approached but did not respond:
Action Heart
Aintree University Hospital NHS Foundation Trust
Alere
Allocate Software PLC
Amgen UK
AMORE health Ltd
AMORE Studies Group
Anglia Stroke and Heart Network
Arrhythmia Alliance
Association of Anaesthetists of Great Britain and Ireland
Association of British Clinical Diabetologists
Association of British Insurers
Association of Chartered Physiotherapists in Cardiac Rehabilitation
Association of Clinical Pathologists
Atrial Fibrillation Association
Barnet and Chase Farm Hospitals NHS Trust

Barnsley Hospital NHS Foundation Trust
Boots
Boston Scientific
Bradford District Care Trust
Brahms UK Limited Thermo Fisher Scientific
Bristol Myers Squibb Pharmaceuticals Ltd
British Association for Nursing in Cardiovascular Care
British Association of Critical Care Nurses
British Cardiovascular Intervention Society
British Medical Journal
British National Formulary
British Nuclear Cardiology Society
British Psychological Society
Cambridge University Hospitals NHS Foundation Trust
Camden Link
Capsulation PPS
Capsulation PPS
Cardiac and Stroke Networks in Lancashire & Cumbria
Care Quality Commission (CQC)
Chartered Society of Physiotherapy
Clarity Informatics Ltd
Coventry and Warwickshire Cardiac Network
Covidien Ltd.
Croydon Clinical Commissioning Group
Croydon Health Services NHS Trust
Croydon University Hospital
Daiichi Sankyo UK
Department for Work and Pensions
Department of Health, Social Services and Public Safety Northern Ireland
Dorset Primary Care Trust
East and North Hertfordshire NHS Trust
East Kent Hospitals University NHS Foundation Trust
East Midlands Ambulance Service NHS
Education for Health
Faculty of Intensive Care Medicine
Faculty of Sexual and Reproductive Healthcare
Faculty of Sport and Exercise Medicine
Five Boroughs Partnership NHS Trust

G&N Medical Ltd
Gloucestershire Hospitals NHS Foundation Trust
Hammersmith and Fulham Primary Care Trust
Health Quality Improvement Partnership
Healthcare Improvement Scotland
Heart Care Partnership
Heart To Heart Psychotherapy Outreach Clinic
HEART UK
Herts Valleys Clinical Commissioning Group
Hindu Council UK
Hockley Medical Practice
Humber NHS Foundation Trust
Independent Healthcare Advisory Services
Inner North West London PCTs
Institute Metabolic Science
Institute of Biomedical Science
Integrity Care Services Ltd.
Kidney Alliance
Lancashire Care NHS Foundation Trust
Leeds Community Healthcare NHS Trust
Liverpool Heart and Chest Hospital NHS Trust HQ
Liverpool Primary Care Trust
Luton and Dunstable Hospital NHS Trust
Maquet UK Ltd
Medicines and Healthcare products Regulatory Agency
Medicines Company, The
Ministry of Defence
National Association of Primary Care
National Clinical Guideline Centre
National Collaborating Centre for Cancer
National Collaborating Centre for Mental Health
National Collaborating Centre for Women's and Children's Health
National Institute for Health Research Health Technology Assessment Programme
National Patient Safety Agency
National Public Health Service for Wales
National Treatment Agency for Substance Misuse
NDR UK
NHS Barnsley Clinical Commissioning Group

NHS Connecting for Health
NHS County Durham and Darlington
NHS Direct
NHS England
NHS Greater Manchester Commissioning Support Unit
NHS Halton CCG
NHS Improvement
NHS Luton CCG
NHS Plus
NHS Sheffield
NHS South Cheshire CCG
NHS Wakefield CCG
NHS Warwickshire North CCG
NHS Warwickshire Primary Care Trust
NHS West Hampshire CCG
North Trent Network of Cardiac Care
Northern Ireland Chest Heart and Stroke
Nottingham City Council
Oxford Health NHS Foundation Trust
Papworth Hospital NHS Foundation Trust
Peninsula Heart & Stroke Network
Pharmametrics GmbH
Primary Care Cardiovascular Society
Primary Care Pharmacists Association
Primrose Bank Medical Centre
Public Health Agency
Public Health Wales NHS Trust
Queen Elizabeth Hospital King's Lynn NHS Trust
Randox Laboratories Limited
Royal Berkshire NHS Foundation Trust
Royal Brompton Hospital & Harefield NHS Trust
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of General Practitioners in Wales
Royal College of Midwives
Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health
Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition

Royal College of Pathologists
Royal College of Physicians and Surgeons of Glasgow
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons of England
Royal Pharmaceutical Society
Royal Society of Medicine
Sanofi
Sanofi Pasteur MSD Ltd
Scottish Intercollegiate Guidelines Network
Shropshire and Staffordshire Cardiac Network
SNDRi
Social Care Institute for Excellence
Solvay
South Asian Health Foundation
South London & Maudsley NHS Trust
South London Cardiac and Stroke Network
South London Cardiovascular and Stroke Network
South Warwickshire NHS Foundation Trust
South West Yorkshire Partnership NHS Foundation Trust
Southport and Ormskirk Hospital NHS Trust
St John Ambulance
St Mary's Hospital
Staffordshire and Stoke on trent NHS Partnerships
Surrey Heart & Stroke Network
Teva UK
The Association for Clinical Biochemistry & Laboratory Medicine
The British In Vitro Diagnostics Association
The For All Healthy Living Centre
The Patients Association
The Rotherham NHS Foundation Trust
Torbay and Southern Devon Health and Care NHS Trus
UK Clinical Pharmacy Association
University Hospital Birmingham NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
University Hospitals Birmingham
University of Nottingham
Verathon Medical UK Limited

Walsall Local Involvement Network
Warwickshire County Council
Welsh Government
West Sussex Public Health
Western Cheshire Primary Care Trust
Western Sussex Hospitals NHS Trust
Westminster Local Involvement Network
York Hospitals NHS Foundation Trust
Yorkshire and Humber Strategic Clinical Networks