NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Centre for Clinical Practice

Review of Clinical Guideline (CG71) - Identification and management of familial hypercholesterolaemia

Background information

Guideline issue date: 2008

3 year review: 2011

National Collaborating Centre: National Clinical Guidelines Centre (formerly National Collaborating Centre for Primary Care)

Review recommendation

- The guideline should not be updated at this time.

Factors influencing the decision

Literature search

1. From a high-level randomised control trial (RCT) search, new evidence was identified relating to the following clinical areas within the guideline:
   - Diagnosing familial hypercholesterolaemia and identification strategies
   - Pharmacological management (monotherapy in adults and children; combined therapy in adults and children)
   - General treatment (diet)

2. No new evidence was identified in these areas which would change the direction of current guideline recommendations.

3. From initial intelligence gathering, qualitative feedback from other NICE departments, the views expressed by the Guideline Development Group, as well as the high-level RCT search, additional focused searches were also conducted for the following clinical areas:
   - Use of clinical registers as an identification strategy for familial hypercholesterolaemia *(NICE research recommendation).* Insufficient evidence was identified to warrant an update of the guideline relating to this area suggested by the research recommendation.
   - Pharmacological management: lipid-modifying drug therapy in children *(NICE research recommendation).* Insufficient evidence was identified to warrant an update of the guideline relating to this area suggested by the research recommendation:

4. Several ongoing clinical trials (publication dates unknown) were identified focusing on ezetimibe, statins and bile acid sequestrants either as monotherapy or combined therapy for familial hypercholesterolaemia; the efficacy and safety of mipomersen; low-density lipoprotein (LDL) apheresis; lomitapide for homozygous familial hypercholesterolaemia and a dietary intervention involving flaxseed.

Guideline Development Group and National Collaborating Centre perspective

5. A questionnaire was distributed to GDG members and the National Collaborating Centre (NCC) to consult them on the need for an update of the guideline. Five responses were received with respondents highlighting that since publication of the guideline more literature has become available on new therapies under development for raising high-density lipoprotein (HDL); reduction of coronary heart disease (CHD) mortality in familial hypercholesterolaemia patients treated with

statins; evidence supporting the utility of DNA testing and cascade testing in identifying patients with familial hypercholesterolaemia and novel anti-sense methods for lowering LDL-C in familial hypercholesterolaemia patients. Three RCTs related to the anti-sense drug mipomersen (an apolipoprotein B synthesis inhibitor) were identified through the high-level RCT search but this drug has not been licensed in the UK at the current time. Feedback from the questionnaire contributed towards the development of the clinical questions for the focused searches.

6. Ongoing research relevant to the guideline was highlighted by GDG members including:
   - Compilation of a national register of apheresis
   - Research to investigate the utility of identifying familial hypercholesterolaemia patients through registers of subjects at high-risk of CHD
   - Pilot study of reverse cascade testing – based on identifying children with high cholesterol levels by screening at the age of MMR immunisation
   - Research on 2whole exome sequencing of DNA samples to identify the cause of familial hypercholesterolaemia
   - Research aimed at establishing the long-term safety of statin use in children

7. The majority of questionnaire respondents felt that there is insufficient variation in current practice supported by adequate evidence at this time to warrant an update of the current guideline however, they highlighted that implementation of the guideline needs to be improved.

Implementation and post publication feedback

8. In total, 20 enquiries were received from post-publication feedback, most of which were routine. Key themes emerging from post-publication feedback were screening for familial hypercholesterolaemia,

access to DNA testing and nationwide family follow-up systems and diagnosis of familial hypercholesterolaemia. This feedback contributed towards the development of the clinical questions for focused searches described above.

9. An analysis by the NICE implementation team highlighted an audit of the NICE guideline published by the Royal College of Physicians: National Clinical Audit of the Management of Familial Hypercholesterolaemia 2009: Pilot. The results of the audit reported that 33% of patients achieved the NICE recommended reduction in LDL-C concentration of greater than 50% from baseline. In addition the majority of patients were found to be having an annual review, in line with NICE guidance.

10. In addition, qualitative feedback from the field team indicated that access to genetic testing for familial hypercholesterolaemia could be a barrier to implementation.

Relationship to other NICE guidance

NICE guidance related to CG71 can be viewed in Appendix 1.

Summary of Stakeholder Feedback

Review proposal put to consultees:
The guideline should not be updated at this time.
The guideline will be reviewed again according to current processes.

11. In total 12 stakeholders commented on the review proposal recommendation during the 2 week consultation period. The table of stakeholder comments can be viewed in Appendix 2.

12. Four stakeholders agreed and three disagreed with the review proposal. Five stakeholders did not state a definitive decision.

13. Those stakeholders that disagreed with the review proposal commented that:
    - A major obstacle to the implementation of the NICE familial hypercholesterolaemia Guideline CG71 in England is the identification of familial hypercholesterolaemia index cases in primary care using the Simon Broome criteria and highlighted a genetic testing strategy using the Lipochip system. Currently, however, there is an in progress Diagnostic technology guidance: Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia with an estimated publication date of January 2012.
    - There should be more emphasis on reducing cardiovascular risk rather than just reducing cholesterol. However, the guideline scope indicates that the management of adults and children with homozygous and heterozygous familial hypercholesterolaemia guideline addresses, as appropriate, lipid modification, cardiovascular risk reduction and assessment of the degree of atherosclerosis.
    - The paediatric guidance in this guideline is incomplete. However, the guideline scope indicates that the populations covered in the guideline are adults and children with heterozygous familial hypercholesterolaemia and adults and children with homozygous familial hypercholesterolaemia. These populations were used when conducting the in-house review of this guideline.

14. During consultation, stakeholders suggested new areas to consider in a future update of the guideline including:
    - Addition of the familial hypercholesterolaemia registers for paediatrics and lipoprotein apheresis

Anti-discrimination and equalities considerations

15. No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation. The original scope contains recommendations for case identification, diagnostic testing and the management of heterozygous familial hypercholesterolaemia in adults and children in primary, secondary and tertiary care settings and tertiary care for homozygous familial hypercholesterolaemia in all age groups.

Conclusion

16. No new evidence was identified which would invalidate or change the direction of current guideline recommendations. However, GDG members highlighted relevant ongoing research which is likely to inform future reviews of the guideline. In addition, technology appraisal guidance 132 'Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia' is currently scheduled to undergo a review in October 2011. A decision to update this technology appraisal in the future may have an impact on the guideline recommendations and would need to be taken into consideration.

17. The Familial hypercholesterolaemia guideline should not be updated at this time.

Relationship to quality standards

18. This topic is not currently being considered for inclusion in the scope of a quality standard.

19. This topic is currently being considered as one of the proposed core library of topics.

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Centre for Clinical Practice
August 2011

Appendix 1

The following NICE guidance is related to CG71:

Guidance	Review date
TA39: Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation, 2002.	This guidance has been replaced by PH10: Smoking cessation services, 2008.
CG30: Long acting reversible contraception: the effective and appropriate use of long-acting reversible contraception, 2005.	Reviewed for update January 2011. Review recommendation was not to update the guideline at this time.
CG43: Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children, 2006.	Due to be reviewed for update in 2011 – review decision date December 2011.
TA94: Statins for the prevention of cardiovascular events in people at increased risk of developing cardiovascular disease or those with established cardiovascular disease, 2006.	Currently under consultation.
PH1: Brief interventions and referral for smoking cessation in primary care and other settings, 2006.	Guidance was reviewed in March 2010 and it was decided not to update at this stage. Next review date is March 2012.
TA123: Varenicline for smoking cessation, 2007.	Guidance was placed on static list in January 2011.
TA132: Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia, 2007.	Consultation on the review plans for this guidance is expected in October 2011.

CG48: Secondary prevention in primary and secondary care for patients following a myocardial infarction, 2007.	Guideline was reviewed in January 2011 and will undergo an update.
CG67: Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease, 2008.	Currently under review – review decision date July 2011.
Related NICE guidance in progress	
Diagnostic technology guidance: Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia.	In progress. Expected publication date: January 2012.

Appendix 2

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Familial Hypercholesterolaemia Guideline Review Consultation Comments Table

27 June - 10 July 2011

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
HEART UK		HEART UK distributed the review to its Familial Hypercholesterolaemia Guideline Implementation Team and received no substantive comments on the review.			Thank you for your comment.
HEART UK		HEART UK distributed the review to its Familial Hypercholesterolaemia Guideline Implementation Team and received the following comment on the review: A major obstacle to the implementation of the NICE FH Guideline CG71 in England is the identification of FH index cases in primary care using the Simon Broome criteria. The criteria have been criticised by GPs as lacking specificity and if the recommendations of CG71 were followed, the result would be an unacceptably high number of unnecessary referrals of patients with total cholesterol>7.5 and or LDL-cholesterol >4.9 to secondary care for confirmation/exclusion of the diagnosis and genetic testing. The cost to primary care budgets would be prohibitive at a time when			Thank you for your comment. There is an in progress Diagnostic technology guidance: Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia with an estimated publication date of January 2012. Diagnosis of FH and the Simon Broome criteria will be assessed in the next review of this guideline.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
		efforts are being made to divert resources away from ambulatory secondary care and capacity of specialist clinics in many parts of the country could not cope with this demand. This problem is not unique to the UK and we wish to draw the attention of the CDG to an alternative model of service provision which has been developed for predominantly rural areas of Spain where there are few specialist clinics. Dr Rodrigo Alonso and colleagues of the Fundación Hipercolesterolemia Familiar (Spanish counterpart organisation to HEART UK) have introduced a primary care based genetic testing strategy in the province of Castilla-Leon in central Spain, administered by primary care doctors. They used Dutch MedPed points based scoring system for diagnosis of FH which was built into the genetic testing request form to decide whether the genetic test should be performed (translation attached). Those screened and found to have a score of 6 points or greater are considered to have probable FH and to be eligible for testing which is performed non-invasively using saliva samples. The Progenika Lipochip system was used and in response to a request from HEART UK they have supplied a brief summary of the data obtained so far, which are as yet unpublished, with permission to forward as evidence to NICE (see attached PowerPoint slide – **this has been removed for publication of the recommendation**). The detection rate among 622 people screened as possibly affected index cases			

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
		with a Dutch Score of 6 points or greater was an impressive 44%. This compares favourably with detection rates in the DNA testing pilot study in 5 UK centres (Taylor et al 2010) and those reported from other secondary care strategies based on specialist clinics in Wales, Scotland and Northern Ireland. We would recommend that the GDG 1. Consider the potential for the use of the Dutch scoring system as an alternative means of identifying index cases and 2. Undertake an analysis of the cost effectiveness of the primary care based model for genetic testing as used in Spain.			
UK Clinical Pharmacy Association (UKCPA)		We have no comments to make on this consultation.			Thank you for your comment.
AstraZeneca	Agree with proposal not to update	AstraZeneca agrees that the update of these guidelines is not a priority.			Thank you for your comment.
MSD Ltd	We agree with the Review Recommendation that the				Thank you for your comment.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
	guideline should not be updated at this time.				
Black Country Cancer and Cardiac Network	Agree	We would like to see a strong recommendation for the inclusion of a systematic national screening database to support widespread genetic cascade testing throughout England	Although this is referred to in the review document it should be recognised that failure to have this at national level is hampering implementation	Piecemeal developments will certainly create inequalities in areas that do not provide a service.	Thank you for your comment. This relates to implementation of the guideline. Implementation support is provided by NICE to facilitate implementation of the guideline and we will pass on your comments.
Greater Manchester and Cheshire Cardiac and Stroke Network	Agree with the proposal to be reviewed & updated	The importance of familial hypercholesterolaemia is that it raises the risk of cardiovascular disease. So if the TC:HDL level is brought down to a reasonable level, there should not be increasingly heroic attempts to reduce cholesterol but other cost-effective measures should be used to reduce cardiovascular risk eg reducing blood pressure even in those who are normotensive (http://www.bmj.com/content/338/bmj.b1665.full) if there ten year cardiovascular risk exceeds 20%. If the need for more emphasis on reducing cardiovascular risk rather than just reducing cholesterol would, even on its own, justify a review.			Thank you for your comment. The guideline scope indicates that the management of adults and children with homozygous and heterozygous FH guideline addresses, as appropriate, lipid modification, cardiovascular risk reduction and assessment of the degree of atherosclerosis.
Department of Health		I wish to confirm that the Department of Health has no substantive comments to make regarding this consultation			Thank you for your comment.
Pfizer Limited	We agree the	We are not aware of new data, which warrants a guideline change at this time.			Thank you for your comment.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
	guideline should not be updated now				
Royal College of Paediatrics and Child Health	Disagree	The College notes that the paediatric guidance in this guideline is incomplete, confusing and unhelpful.	Paediatric guidance should include children under the age of 10 as well and this is currently not clear.	The costing analysis is based on screening for the common European mutations and does not take into account that in areas with large ethnic diversity (e.g. Birmingham) more extended testing will be needed as common mutations are not known for ethnic minority groups.	The guideline scope indicates that the populations covered in the guideline are: • Adults and children with heterozygous FH. • Adults and children with homozygous FH. These populations were used when conducting the in-house review of this guideline.
Royal College of Paediatrics and Child Health		We think that the Simon Broome criteria for paediatrics should be added.			Thank you for your comment. The guideline indicates that the Simon Broome criteria can be used to diagnose FH in children aged under 16 years of age.
Royal College of Paediatrics and Child Health		The terminology child friendly should be better described. Provision of paediatric trained professionals is essential, as current guidance does not offer sufficient protection especially when dealing with concerns regarding child protection.			Thank you for your comment. This is outwith the scope of this guideline which covers case identification, diagnostic testing and the management of

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
					heterozygous familial hypercholesterolaemia in adults and children in primary, secondary and tertiary care settings and tertiary care for homozygous familial hypercholesterolaemia in all age groups.
Royal College of Physicians	Agree	We would support the continued use of CG71 and do not believe that it requires further modification at this stage. We would however draw attention to the paragraphs on implementation on pages 20 and 21. We believe that there is clear evidence of cost benefit from molecular cascade testing as evaluated to date and the cost per QALY is around a fifth of the NICE cut of £30,000. It is very disappointing that the funding has not been forthcoming from the commissioners in this regard.			Thank you for your comment. This relates to implementation of the guideline. Implementation support is provided by NICE to facilitate implementation of the guideline and we will pass on your comments.
GDG member		There are two new FH registers, one for paediatrics, and one for lipoprotein apheresis. Both were requested by NICE guidelines. Hosted by RCP. Not much to include, but useful. Can be accessed through HEART UK: https://audit.rcplondon.ac.uk/lpapheresis			Thank you for your comment. These familial hypercholesterolaemia registers will be monitored and assessed in the next review.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
Sanofi-aventis		Please note that Sanofi have no comments at this time.			Thank you for your comment.