1. Background information

Guideline issue date: 2008
3 year review: 2011
National Collaborating Centre: National Clinical Guidelines Centre (formerly National Collaborating Centre for Primary Care)

2. Consideration of the evidence

Literature search

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)

Through this stage of the process, a sufficient number of studies relevant to the following clinical areas were identified to allow assessment for proposed review decision and are summarised in Table 1 below:

- Diagnosis of familial hypercholesterolaemia
- Pharmacological management
  - Monotherapy in adults and children
  - Combination therapy in adults and children
- General treatment (diet)

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)
- Pharmacological management: lipid-modifying drug therapy in children (NICE research recommendation)

The results of the focused searches are summarised in Table 2 below. All references identified through the initial intelligence gathering, high-level RCT search and the focused searches can be viewed in Appendix 1.
Table 1: Summary of literature from high-level RCT search

<table>
<thead>
<tr>
<th>Clinical area 1: Diagnosis of familial hypercholesterolaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical question and related recommendation(s)</strong></td>
</tr>
<tr>
<td>Q: In adults and children, what is the effectiveness of the following tests to diagnose familial hypercholesterolaemia</td>
</tr>
<tr>
<td>- Biochemical assays?</td>
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<tr>
<td>- Clinical signs and symptoms?</td>
</tr>
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</table>
above?

Relevant section of the guideline:
Diagnosis of familial hypercholesterolaemia.

Recommendations:
1.1.3 and 1.1.7.

hypercholesterolaemia should include clinical signs (specifically tendon xanthoma) in addition to family history, cholesterol concentration and DNA testing.

Clinical area 2: Pharmacological management: monotherapy in adults and children

<table>
<thead>
<tr>
<th>Clinical question and related recommendation(s)</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q: What is the effectiveness in improving outcome in individuals with familial hypercholesterolaemia</td>
<td>Through the high-level RCT search 21 studies relevant to the clinical question were identified. Adults (eight studies) Ezetimibe versus placebo (three studies)</td>
<td>No new evidence was identified which would invalidate current guideline recommendations.</td>
</tr>
<tr>
<td>Relevant section of the guideline: Management (pharmacological treatment).</td>
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<tr>
<td><strong>Recommendations:</strong> Adults: 1.3.1.1 – 1.3.1.7;</td>
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</table>

- A Health Technology Assessment evaluated the clinical and cost-effectiveness of ezetimibe for patients with familial hypercholesterolaemia. A meta-analysis of studies comparing ezetimibe with placebo demonstrated significantly reduced low-density lipoprotein cholesterol (LDL-C) levels in patients treated with ezetimibe.
- A systematic review was identified which concluded that administration of ezetimibe, either as monotherapy or in combination with a statin has a minimal effect on endothelial function in the populations assessed. Another systematic review evaluating the efficacy of ezetimibe monotherapy versus placebo for treatment of familial hypercholesterolaemia concluded that this treatment leads to a significant reduction in LDL-C.

The recommendations on ezetimibe are from the NICE technology appraisal guidance 132 'Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia’ which is currently undergoing a review through technology appraisals.
Consultation on the review plans for this guidance is expected in August 2011.

**Comparisons between different statins (five studies)**

- One RCT compared the efficacy and safety of pitavastatin versus atorvastatin in patients with familial hypercholesterolaemia. Both statins reduced serum levels of total cholesterol and LDL-C. A similar RCT demonstrated no significant differences in reduction of LDL-C between pitavastatin and artovastatin groups.
- An RCT was identified which compared the efficacy of rosvastatin with atorvastatin in patients with homozygous familial hypercholesterolaemia.
- A meta-analysis concluded that statins improve arterial function and structure in patients with familial hypercholesterolaemia.
- A pooled analysis of heterozygous familial hypercholesterolemia patients treated with statins indicated in carotid atherosclerosis progression following treatment.
### Children (13 studies)

**Statins versus placebo (10 studies)**

- Four systematic reviews (including a Cochrane review) evaluated the efficacy and safety of statin use in children and adolescents with heterozygous familial hypercholesterolaemia indicating that statin monotherapy is safe and efficacious in the short-term. Similarly, an additional systematic review indicated that no long-term data on the safety and efficacy of monotherapy in children and adolescents with familial hypercholesterolaemia is available.

- One systematic review concluded that there is no conclusive evidence which provides guidance on when statin treatment should be started and target LDL-C levels in children with familial hypercholesterolaemia.

- A meta-analysis was identified which assessed the effect of statins, in comparison with placebo, on the lipid profile of children and adolescents with familial hypercholesterolaemia. The meta-analysis concluded that statins are an efficacious treatment of familial hypercholesterolaemia.
hypercholesterolaemia in children.

- One RCT compared the efficacy of rosuvastatin versus placebo in children with familial hypercholesterolaemia. The results indicated that rosuvastatin lowered LDL-C compared with placebo.
- An RCT comparing pravastatin with placebo in children with familial hypercholesterolaemia indicated no adverse effects following treatment. Another RCT was identified which evaluated lipoprotein-associated phospholipase A(2) (LP-PLA(2)) levels in children with heterozygous familial hypercholesterolaemia treated with pravastatin or placebo. After two years of treatment, LP-PLA(2) levels were significantly lower in the pravastatin treated group compared with placebo.

**Resins versus placebo (three studies)**

- A systematic review was identified which evaluated the efficacy and safety of bile acid sequestrants in children and adolescents with familial hypercholesterolaemia.
- An RCT evaluated the efficacy of colesevelam hydrochloride (a bile acid sequestrant) in patients aged between 10-17 years old with heterozygous familial hypercholesterolaemia. The results of the study indicated that colesevelam monotherapy led to a reduction in LDL-C levels. Comparable results were reported in another RCT.

In summary, the identified evidence supports the guideline recommendations relating to the use of statins which state that statins should be the initial treatment for all adults with familial hypercholesterolaemia. In addition, the evidence indicates the efficacy of ezetimibe in reducing LDL-C levels in adults with familial hypercholesterolaemia which supports the guideline recommendation that states ezetimibe monotherapy is an option for treatment of adults with heterozygous-familial hypercholesterolaemia who are intolerant to statin therapy. The recommendations on ezetimibe are from the NICE technology appraisal guidance 132 ‘Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia’ which is currently undergoing a review through technology appraisals.
Consultation on the review plans for this guidance is expected in August 2011. In terms of studies in children with familial hypercholesterolaemia, the identified evidence indicated that bile acid sequestrants reduce LDL-C levels which supports the guideline recommendations that healthcare professionals should consider offering children and young people intolerant of statins other lipid-modifying drug therapies capable of reducing LDL-C concentration (such as bile acid sequestrants. In addition, the evidence identified supports the use of statin monotherapy in children and adolescents with familial hypercholesterolaemia.

| Clinical area 3: Pharmacological management: combination therapy in adults and children |
|---|---|---|
| **Clinical question and related recommendation(s)** | **Summary of evidence** | **Relevance to guideline recommendations** |
| Q: What is the effectiveness of the following adjunctive pharmacotherapy with statins in individuals? | Through the high-level RCT search five studies relevant to the clinical question were identified. | No new evidence was identified which would invalidate current guideline recommendations. |
| Adults (four studies) | Statins and resins (one study) |  |

CG71: Familial Hypercholesterolaemia, review proposal consultation document
with familial hypercholesterolaemia:
- Stains and resins
- Statins and niacin
- Statins and fibrates
- Statins and fish oils
- Statins and resins with nicotinic acid
- Statins and ezetimibe

Relevant section of the guideline:
Management (pharmacological treatment).

- One RCT was identified which assessed the efficacy and tolerability of a bile acid sequestrant versus placebo when added to combination treatment with statin plus ezetimibe in patients with familial hypercholesterolaemia. The results indicated that the bile acid sequestrant in combination with a statin plus ezetimibe improved LDL-C concentrations compared with placebo.

Statins and niacin (one study)
- One RCT evaluated the safety and efficacy of ezetimibe/simvastatin in combination with niacin in patients with familial hyperlipidaemia. The results indicated a significant reduction in LDL-C, triglycerides and apolipoprotein B in the group receiving the combination therapy.

Statins and ezetimibe (one study)
- One RCT was identified which compared statin plus placebo versus statin plus ezetimibe in patients with familial hypercholesterolaemia. No significant difference in intima-media thickness was observed between the two groups.
### Recommendations:

1.3.1.8 and 1.3.1.15-1.3.1.18.

**Cost-effectiveness of high-intensity statins versus low-intensity statins in the management of familial hypercholesterolaemia (one study)**

- One study was identified which used modelling techniques to determine the cost-effectiveness of high-intensity versus low-intensity statins for treatment of familial hypercholesterolaemia. The model indicated that high-intensity statins are cost-effective for treatment of patients with familial hypercholesterolaemia between 20 and 59 years of age.

**Children (one study)**

An RCT was identified which concluded that coadministration of ezetimibe with simvastatin provided higher LDL-C reduction compared with simvastatin alone in adolescents with heterozygous familial hypercholesterolaemia studied up to 53 weeks. In addition, all treatments were well tolerated.

In summary, the identified evidence supports the evidence summary...
presented in the guideline which concluded that combination therapy in adults is superior to monotherapy in the treatment of familial hypercholesterolaemia individuals to lower LDL-C and that high-intensity statins are cost-effective for the treatment of patients under 60 years of age. One study was identified relating to combination therapy in adolescents however, additional RCTs are required to generate an evidence base for this intervention in the future.

### Clinical area 4: General treatment (diet)

<table>
<thead>
<tr>
<th>Clinical question and related recommendation(s)</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
</tr>
</thead>
</table>
| Q: What is the effectiveness of dietary interventions to improve outcome in:  
  - Adults | Through the high-level RCT search three studies relevant to the clinical question were identified:  
  - A Cochrane systematic review was unable to conclude about the effectiveness of a cholesterol-lowering diet, or any of the other dietary interventions suggested for familial hypercholesterolaemia, | No new evidence was identified which would invalidate current guideline recommendations. |
<table>
<thead>
<tr>
<th>Relevant section of the guideline: General treatment (diet).</th>
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</thead>
<tbody>
<tr>
<td>Recommendation(s): 1.3.2.2 – 1.3.2.7.</td>
</tr>
</tbody>
</table>

- Children and young people with familial hypercholesterolaemia?

- A study was identified which describes the protocol for the PRO-FIT project which will provide information about the effects and implementation of a healthy lifestyle intervention for individuals with familial hypercholesterolaemia.

- In addition, a randomised dietary intervention study was identified which tested the effect of foods rich in plant sterols on LDL-C in patients with familial hypercholesterolaemia. The results indicated that plasma sitosterol/cholesterol ratio was higher during plant sterol-rich periods than during the low plant sterols periods.

In summary, insufficient consistent evidence was identified focusing on the effectiveness of dietary interventions in improving outcomes in people with familial hypercholesterolaemia. As such, no new evidence was identified which would invalidate the current guideline recommendations which states that healthcare professionals should advise people with familial hypercholesterolaemia to eat five portions of fruit and vegetables and two portions of fish a week in addition to...
<table>
<thead>
<tr>
<th>consuming a diet in which:</th>
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<tbody>
<tr>
<td>• Total fat intake is 30% or less of total energy intake</td>
</tr>
<tr>
<td>• Saturated fats are 10% or less of total energy intake</td>
</tr>
<tr>
<td>• Intake of dietary cholesterol is less than 300 mg/day</td>
</tr>
<tr>
<td>• Saturated fats are replaced by increasing the intake of monounsaturated and polyunsaturated fats</td>
</tr>
</tbody>
</table>
Table 2: Summary of literature from focused searches

<table>
<thead>
<tr>
<th>Clinical question and related recommendation(s)</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q: What are the clinical and cost-effectiveness of identifying a person with familial hypercholesterolaemia (defined by DNA testing) from GP registers and from secondary care registers?</td>
<td>Through the high-level RCT search two studies relevant to the clinical question were identified. An observational study was identified which evaluated the efficacy of combined computer and note-based searching in primary care settings as a method of identifying index cases of familial hypercholesterolaemia. The study concluded that there is potential for this method to be used for identification of new cases of familial hypercholesterolaemia in primary care. In addition, a review article was identified which discussed potential strategies for identification of people with familial hypercholesterolaemia. Approaches suggested included notes searching in primary care and</td>
<td>Insufficient evidence was identified to warrant an update of the guideline relating to the area suggested by the research recommendation.</td>
</tr>
</tbody>
</table>

CG71: Familial Hypercholesterolaemia, review proposal consultation document

27th June – 10th July 2011 16 of 30
Identification strategies:
identification using clinical registers.

Recommendation:
NICE research recommendation.

Identification of cases from national registers of people with documented chronic heart disease.

In summary, there is insufficient evidence at this time to determine the clinical and cost-effectiveness of identifying a person with familial hypercholesterolaemia from GP registers and secondary care registers although one small study indicates the potential of this method.

Intelligence from the Guideline Development Group (GDG) highlighted that research is ongoing in this area and may address this clinical question in a future review of this guideline.

Clinical area 2: Pharmacological management: lipid-modifying drug therapy in children

<table>
<thead>
<tr>
<th>Clinical question and related recommendation(s)</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q: What is the clinical effectiveness and safety of differing doses of lipid-modifying therapy</td>
<td>The aim of this clinical question is to determine if there is evidence to establish target serum LDL-C concentration in treated children with familial hypercholesterolaemia receiving lipid-modifying therapy.</td>
<td>Insufficient evidence was identified to warrant an update of the guideline relating to the area suggested</td>
</tr>
</tbody>
</table>
in children with familial hypercholesterolaemia?

Relevant section of the guideline:
Pharmacological management: lipid-modifying drug therapy in children

Recommendation:
NICE research recommendation.

| Through the focused search one study (a follow-up of a placebo-controlled study) relevant to the clinical question was identified. The aim of this study was to determine whether there is a relation between the age of initiation of statin treatment and carotid intima-media thickness (IMT) in 8-18 year old patients with familial hypercholesterolaemia. The study indicated that early initiation of statin treatment in patients with familial hypercholesterolaemia delays the progression of carotid IMT. However, further research is required to assess at which age abnormalities can be seen in children to determine an LDL-C concentration below which carotid IMT is normal and where thickening is absent, and above which it is abnormal and where thickening is observed. | by the research recommendation. |
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

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.

One GDG member highlighted that there has been increased publicity about the potential adverse effects of statins. Similarly, the Medicines and healthcare product regulatory agency (MHRA) issued advice in May 2011 that patients should be advised of the increased risk of myopathy with simvastatin 80mg. The NICE technology appraisal guidance 94 ‘Statins for the prevention of cardiovascular events in patients at increased risk of developing
cardiovascular disease or those with established cardiovascular disease’ is currently on the static list.

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 whole 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

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**

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.

An analysis by the NICE implementation team highlighted an audit of the NICE guideline published by the Royal College of Physicians: National Clinical CG71: Familial Hypercholesterolaemia, review proposal consultation document
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.

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**

The following NICE guidance is related to CG71:

<table>
<thead>
<tr>
<th>Guidance</th>
<th>Review date</th>
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<tbody>
<tr>
<td>TA39: Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation, 2002.</td>
<td>This guidance has been replaced by PH10: Smoking cessation services, 2008.</td>
</tr>
<tr>
<td>CG30: Long acting reversible contraception: the effective and appropriate use of long-acting reversible contraception, 2005.</td>
<td>Reviewed for update January 2011. Review recommendation was not to update the guideline at this time.</td>
</tr>
<tr>
<td>TA94: Statins for the prevention of cardiovascular events in people at increased risk of developing cardiovascular disease or those with</td>
<td>This guidance is currently on the static list.</td>
</tr>
<tr>
<td>CG71: Familial Hypercholesterolaemia, review proposal consultation document</td>
<td>27th June – 10th July 2011</td>
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<td><strong>established cardiovascular disease, 2006.</strong></td>
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<tr>
<td><strong>PH1: Brief interventions and referral for smoking cessation in primary care and other settings, 2006.</strong></td>
<td>Guidance was reviewed in March 2010 and it was decided not to update at this stage. Next review date is March 2012.</td>
</tr>
<tr>
<td><strong>TA123: Varenicline for smoking cessation, 2007.</strong></td>
<td>Guidance was placed on static list in January 2011.</td>
</tr>
<tr>
<td><strong>TA132: Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia, 2007.</strong></td>
<td>Currently undergoing a review through technology appraisals. Consultation on the review plans for this guidance is expected in August 2011.</td>
</tr>
<tr>
<td><strong>CG48: Secondary prevention in primary and secondary care for patients following a myocardial infarction, 2007.</strong></td>
<td>Guideline was reviewed in January 2011 and will undergo an update.</td>
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<tr>
<td><strong>Related NICE guidance in progress</strong></td>
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<tr>
<td>Diagnostic technology guidance: Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia.</td>
<td>In progress.</td>
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<td>Expected publication date: January 2012.</td>
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</tbody>
</table>

**Anti-discrimination and equalities considerations**

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 CG71: Familial Hypercholesterolaemia, review proposal consultation document.
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**

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, the review of technology appraisal guidance 132 ‘Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia’ is currently ongoing whilst technology appraisal guidance 94 ‘Statins for the prevention of cardiovascular events in patients at increased risk of developing cardiovascular disease or those with established cardiovascular disease’ is currently on the static list. A decision to update these technology appraisals in the future may have an impact on the guideline recommendations and would need to be taken into consideration.

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

**3. Review recommendation**

The guideline should not be updated at this time.

Centre for Clinical Practice
27.06.11
Appendix 1


CG71: Familial Hypercholesterolaemia, review proposal consultation document


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