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CONFERENCE SUMMARIES

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Dyslipidaemia: integration between primary and secondary care

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It is the implementation of guidelines, not the guidelines themselves, that change clinical practice. This session examined some of the issues that were faced when interpreting national guidelines for local implementation. Local guidelines for the use of lipid lowering drugs have been in place and regularly updated for more than 10 years and were recently reviewed to incorporate the recommendations in the National Institute for Health and Clinical Excellence (NICE) lipid modification guideline[1] and the relevant section of the NICE type 2 diabetes guideline.[2] The process formed the basis of this talk.

Lipid lowering drugs impact on practice in primary care and in a range of specialty areas. Membership of the local guideline development group reflected this with colleagues from primary care and a wide range of specialties, including those perhaps less likely to be represented, such as from mental health services and rheumatology. Integration and a common agreed approach across primary and secondary care aims to avoid confusion and inconsistency.

The local guideline identified three main groups: those with vascular disease, those with diabetes, and those with neither of these conditions, ie primary prevention. In addition, the guideline included additional notes to supplement the recommendations.

Some recommendations are routine and were unchanged from previous iterations of the guideline. All patients with vascular disease have a lipid profile and liver function tests measured, and any secondary causes identified at baseline and, in the absence of contra-indications, are treated with a statin. In the absence of a recent acute coronary syndrome, simvastatin 40 mg od is first line treatment, with further titration being considered if total cholesterol remains above 4 mmol/l, and low-density lipoprotein (LDL) cholesterol above 2 mmol/l. This is consistent with the NICE lipid modification guideline. Recognising the importance of management directed at atherogenic components of the lipid profile and, in the spirit of considering some of the practical barriers to guideline implementation, a corresponding threshold

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for non-high-density lipoprotein (non-HDL) cholesterol is also included in the local guideline that can be used if a fasting sample cannot be easily obtained from which to calculate LDL cholesterol. In considering titration from simvastatin 40 mg od to a more potent statin, the local guideline group reviewed the evidence for clinical and cost effectiveness and the risk of adverse effects. There is a modest additional cholesterol lowering with simvastatin 80 mg od compared to simvastatin 40 mg od.[3] The full version of the NICE lipid modification guideline reported that in patients without a recent acute coronary syndrome, one step titration to simvastatin 80 mg od was cost effective, but a two- step titration, which included atorvastatin 80 mg od, was not.[4] Following publication of the NICE lipid modification guideline the investigators for the SEARCH trial had presented a higher risk of myopathy with simvastatin 80 mg od compared to simvastatin 20 mg od.[5] Consequently, the local guideline emphasises the importance of considering the risks and benefits before titrating to simvastatin 80 mg od. The more recently published Medicines and Healthcare products Regulatory Agency (MHRA) drug alert has subsequently reiterated this.[6] In view of the evidence that a second titration to atorvastatin 80 mg od was not cost effective, this is not routinely recommended in all patients.

However, the NICE lipid modification guideline does not include recommendations for patients with diabetes, and the full version of the NICE type 2 diabetes guideline reported that a second titration in patients with type 2 diabetes and cardiovascular disease is cost effective.[7] This reflected the higher observed risk of vascular events in patients with type 2 diabetes compared to those without. The local guideline group recognised that this is the case. They also felt that there are other patients without type 2 diabetes who could be considered to be at a higher cardiovascular disease risk than had been allowed for in the economic modelling for the NICE lipid modification guideline, and in which case treatment with atorvastatin 80 mg od might also be cost effective in this group. The observed baseline risk in patients with type 2 diabetes in the economic model in the full version of the NICE type 2 diabetes guideline was increased by a factor of 1.9. In a sensitivity analysis, if the observed risk is increased by a factor of at least 1.6 a two-step titration to a total target cholesterol of 4 mmol/l was cost effective.

Consequently, the local guideline aimed to identify a group of patients without diabetes who were likely to have an increased risk and in whom titration to atorvastatin 80 mg od would be considered if the lipid parameters remained above target. The REACH registry[8] examined the risk of cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke and hospitalisation in stable patients recruited from an outpatient clinic and found that at one year there was an increasing risk of an event, as the number of arterial locations affected (coronary, carotid and peripheral arterial disease) increased. The local guideline drew on this to recommend that in stable patients with vascular disease in more than one arterial location, treatment with atorvastatin 80 mg od, should be considered if lipid parameters remained above target.

The NICE lipid modification guideline also recommends that all patients with acute coronary syndrome/MI should have a high intensity statin started early after the event, and reported that treatment with both simvastatin 80 mg od and atorvastatin 80 mg od is cost effective. Again the local guideline group anticipated that simvastatin 80 mg od was likely to be associated with more adverse effects than atorvastatin 80 mg od and also noted that trials which included treatment with simvastatin 80 mg od had included a run-in period,[5] or a period of treatment with a lower dose initially,[9] unlike trials with atorvastatin 80 mg od.[10] Taking all this into account the local guideline group recommended atorvastatin 80 mg od in preference to simvastatin 80 mg od. It was, however, recognised that the cost impact with atorvastatin 80 mg od was higher. This was discussed with, and endorsed by, medicines management in the commissioning organisation who also agreed that GP practices would not be criticised for continuing to prescribe non-generic statins, rather than generic statins, for this indication.

The presentation also summarised the recommendations for patients with diabetes which are consistent with those in the NICE guidelines, including the recommendation to combine a statin and fibrate in patients with type 2 diabetes and hypertriglyceridaemia. An accurate measure of triglycerides requires a fasting blood sample and triglycerides above 10 mmol/l should be considered for urgent management in view of the risk of pancreatitis, and such patients will generally require referral to secondary care. The importance of identifying and addressing secondary causes, including lifestyle factors and poor glycaemic control, was emphasised and the local guideline recommended that in the absence of requiring urgent intervention, lifestyle changes should be encouraged and implemented for six months before considering combination treatment. It was noted that in the full version of the NICE type 2 diabetes guideline, the NICE guideline development group had been cognisant that there was less evidence from which to make recommendations for combination treatment, and the presentation being made summarised the results of the more recently published ACCORD study.[11] This study had examined the impact of combined treatment with statin and fibrate compared to statin monotherapy in patients with type 2 diabetes at high risk of vascular events. Patients taking open label simvastatin were randomised to fenofibrate or placebo and there was no difference in the primary outcome of cardiovascular death, non-fatal MI or non-fatal stroke between the two arms (annual rate 2.2% in the fenofibrate group and 2.4% in the placebo group (hazard ratio in the fenofibrate group, 0.92; 95% confidence interval 0.79 to 1.08; $p=0.32$)). The study did not support the routine use of the combination of fenofibrate and simvastatin. However, it was noted that the recruitment criteria required that patients had a fasting triglyceride level less than 8.5 mmol/l if not treated with a statin or less than 4.5 mmol/l if treated with a statin and average triglyceride level at baseline had been 1.8 mmol/l. In a prespecified subgroup analysis of the ACCORD study there was heterogeneity in treatment effect according to lipid subgroups with a possible benefit for patients with both a high baseline

triglyceride level and low baseline level of HDL cholesterol. The local guideline, consistent with the NICE type 2 diabetes guideline, has recommended combination treatment only if triglycerides are raised.

The local guideline recognises that the combination of fibrates and statins is associated with a higher risk of adverse effects, compared to treatment with either drug alone, and this should be taken into account in individual patients. High dose statin in combination with a fibrate was not generally recommended unless advised from specialist care.

The local recommendations for primary prevention are consistent with those in the NICE lipid modification guideline – managing cardiovascular risk, not just cholesterol, and recommending simvastatin 40 mg od in patients with a 10-year cardiovascular disease risk of 20% or more, with no routine titration. However, unlike the NICE guideline it was recommended that a lipid profile be measured after three months. Many patients want to know that the statin is making a difference to their cholesterol and any problems with concordance can be identified.

Lastly, the importance of identifying patients with severe hypercholesterolaemia who might have familial hypercholesterolaemia (FH) was discussed. FH should be considered when the total cholesterol is >7.5 mmol/l, and/or LDL cholesterol >4.9 mmol/l.[12] However, every GP practice has a large number of such patients and automatic referral to a lipid clinic is impractical, necessitating an initial triage in primary care. A flowchart had been developed locally which emphasises the importance of identifying and addressing secondary causes, and which incorporates recommendations to refer patients with possible or definite FH from Simon Broome criteria to the lipid clinic. It also identifies those with the most severely abnormal lipid profiles for referral, even in the absence of fulfilling the Simon Broome criteria.

Acknowledgement

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