Towards personalised medicine: HEART UK 28th Annual Conference

Towards personalised medicine was the general theme of this year's HEART UK conference, attended by 230 clinical and nursing personnel and patients and held at the University of Warwick from 2nd–4th July 2014. We report some of the meeting highlights.

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FH: improving detection in primary care

The launch of the NICE (National Institute of Health and Care Excellence) guidelines for familial hypercholesterolaemia (FH) heralded great optimism for improving detection rates in primary care.[1] Even with new research showing that FH is more common than previously thought,[2] still around 80% of patients are not recognised. Novel detection approaches are clearly needed.

Professor Nadeem Qureshi (University of Nottingham) presented preliminary findings from six GP centres taking part in FAMCHOL (Feasibility of Improving Identification of Familial Hypercholesterolaemia in General Practice: Intervention Development Study),[3] aimed at assessing the feasibility of incorporating computerised patient specific reminders for FH to improve detection rates. In a cohort of 124 patients, response rates were higher with an opportunistic screening approach (response rates of 14% versus 10% with a four-monthly mail out). Family history of premature coronary heart disease (CHD) was key to improving FH detection rates, although patient literacy may be an issue.

Dr Peter Green (NHS Medway Clinical Commissioning Group, Kent)

Dr Peter Green (NHS Medway Clinical Commissioning Group, Kent) reported on the use of a computerised audit tool (Audit+ software) to improve identification of patients at risk of FH who have not been previously screened or diagnosed. Audit triggers include an elevated cholesterol (total cholesterol >7.5 mmol/L or low-density lipoprotein [LDL] cholesterol >4.9 mmol/L), and/or family history of premature CHD. After two years, there was a substantial increase in diagnosed FH, from 0.13% (one in 750) at baseline to 0.22% (one in 450) at two years, with little change in the proportion of patients 'at risk and unscreened' (0.59% and 0.58%, respectively). Subsequently, active review of GP audit lists in the FH Nurse Advisor Programme further improved FH detection rates (to 0.26%, about one in 375), as well as decreasing the proportion of patients at risk and unscreened (0.19%). HEART UK is in discussion to ensure wider availability of the audit tool and extension of the FH Nurse Advisor Programme. The full report of the Medway audit will be published later this year.

Additionally, Dr Steve Martin (Peterborough City Hospital) highlighted simple, practical approaches such as identification of thickened Achilles tendons on examination, that may help in refining FH detection in primary care.

Novel approaches in FH management

While most patients with heterozygous FH can be successfully managed in primary care or with a shared care approach between primary and secondary care, those with a severe phenotype or with homozygous FH, need specialist management. As discussed by Dr Robert Cramb (University Hospital Birmingham), adjunctive lipoprotein apheresis can improve

LDL cholesterol reduction, in addition to current standards of care. While LDL cholesterol levels may be reduced up to 80–90% at the end of a single treatment, rebound effects due to further accumulation of LDL cholesterol necessitate repeat treatment every one to two weeks.[4] Access, affordability and practical considerations are key issues.

The approval of lomitapide, an oral inhibitor of microsomal triglyceride transfer protein, as an adjunct to a low-fat diet and other lipid-lowering treatment offers new management opportunities. Dr Jeanine Roeters van Lennep (Erasmus Medical Centre, Rotterdam, the Netherlands) discussed her clinical experience with lomitapide. She emphasised that both patients and clinicians need to be highly motivated, given that treatment involves dietary fat restriction (<20% of energy from fat) to improve gastrointestinal tolerability, regular monitoring for efficacy and liver transaminase elevation, and an annual assessment for hepatic fat accumulation. Although patient response can be variable (additional mean LDL cholesterol reduction 40–50% in clinical trials[5]), she highlighted one patient with a 67% reduction in plasma LDL-C levels (on top of current standards of care); gastrointestinal tolerability also improved during extended therapy. Treatment response did not appear to differ with/without apheresis. She concluded that while clinicians need to take account of the risk versus benefit of lomitapide, this adjunctive therapy can improve homozygous FH management.

Dr Robert Cramb presented an algorithm positioning lomitapide after optimised LDL cholesterol apheresis in patients not at target. Clinical trial data show that up to 55% of patients achieve the European Atherosclerosis Society (EAS) target for homozygous FH of <2.5 mmol/L with lomitapide.[6] In April 2015, homozygous FH is to be funded by a highly specialised service (adult specialised cardiac services); until then funding remains the responsibility of individual clinical commissioning groups.

Polypill: a population approach to personalised medicine

Dr David Wald (Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine, London) made the case for a population approach to tailored therapy using the polypill, incorporating inexpensive treatments for hypercholesterolaemia and high blood pressure, in the primary prevention setting. He argued that rather than focus on arbitrary cut-offs for cholesterol and blood pressure, as age is the major factor influencing risk for cardiovascular disease (CVD), the polypill should be prescribed to all individuals aged ≥50 years without CVD. Such an approach is supported by clinical trial evidence, which demonstrated reductions of 11–12% in blood pressure and 39% in LDL cholesterol.[7] These treatment benefits would be expected to translate to substantial reduction in CVD event rates in the long-term and offer cost advantages to current approaches to CVD prevention.

Looking to the future?

Novel management approaches, focusing both on other lipoproteins and novel treatments, were also discussed. The case for considering lipoprotein(a) [Lp(a)] in high-risk patients was made by Professor Borge Nordestgaard (Herlev Hospital, Copenhagen University Hospital, Denmark). The EAS Consensus Panel Position Statement clearly supports elevated Lp(a) as a cardiovascular (CV) risk factor, independent of LDL cholesterol or other lipids.[8] Supportive data show that Lp(a) may exert pro-atherogenic, pro-thrombotic and antifibrinolytic effects which enhance atherothrombosis; new data linking Lp(a) with aortic valve stenosis also suggest a potential role in wound healing. The EAS recommends measuring Lp(a) once in individuals with or at intermediate to high risk of CVD, with a strong family history of premature CVD or elevated Lp(a), with FH, recurrent CVD despite statin treatment, aortic valve stenosis or calcification, or with ≥3% 10-year risk of fatal CVD based on SCORE.[8] The desirable level is <80th percentile (~50 mg/dL).[8] Lp(a) is a secondary priority after LDL-C reduction; current therapeutic options are limited, although novel approaches which specifically target Lp(a) are under investigation.

Non-alcoholic fatty liver disease (NAFLD), escalating rapidly in line with increasing obesity, poses a major issue for public health, especially given its association with CV complications. As discussed by Professor Bart Staels (University Lille 2, INSERM U1011, Pasteur Institute, Lille, France), treatments targeting peroxisome proliferator-activating receptors (PPAR) may offer new potential. PPARα ligands (fibrates), already established in the setting of atherogenic dyslipidaemia (elevated triglycerides and low high-density lipoprotein [HDL] cholesterol), also reduce vascular inflammation and hepatic fat accumulation. Novel selective PPARαα modulators (SPPARMs) such as K-877, with improved selectivity and potency compared with fibrates, may offer benefit, as indicated by improvement in lipid metabolism.[9] An alternative approach is GFT505, a dual PPARα/δ agonist with preferential activity on PPARα. In clinical trials, treatment with GFT505 was associated with significant reduction in levels of liver enzymes;[10] a phase IIb trial is investigating GFT505 in the setting of non-alcoholic hepatic steatosis (NASH).

Antisense and gene silencing therapies may help to address outstanding challenges in dyslipidaemia management. As discussed by Dr Mike Khan (University of Warwick, Biomedical Research Institute, Coventry), these offer advantages over current pharmacotherapeutic approaches by reducing the development of a 'lead' agent, and improving the specificity of effect and predictability of adverse events, although the key hurdle is in functional delivery of the agent. Current antisense agents in development focus on genetically validated targets, such as apolipoprotein (apo)CIII and Lp(a). However, gene silencing (siRNA) approaches offer a number of additional benefits, including lower dose and immunogenicity; current targets include pro-protein convertase subtilisin/kexin type 9 (PCSK9), apoCIII and apoB.

Guidelines and treatments under scrutiny

Professor Tony Wierzbicki (Guy's and St. Thomas' Hospitals, London) overviewed contentious issues relating to recent lipid guidelines. FH was very much a focus, given recent publications from the EAS, US National Lipid Association and International FH Foundation; the latter two have suggested the need for world standards for diagnosis and management. However, so far there is no evidence to support LDL cholesterol targets specifically in FH.

With respect to general CVD guidelines, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of blood cholesterol caused great consternation by shifting the focus from lipid targets to intensity of statin therapy, based on a novel risk calculation system.[11] However, consistent with other guideline groups, there is recognition that LDL cholesterol is the priority for intervention. Moreover, as highlighted by Professor Wierzbicki, the only statin study to date to have specifically tested a treat-to-target approach is 4S (Scandinavian Simvastatin Survival Study). The recent Joint British Societies guidelines (JBS3)[12] have changed the focus from calculation of 10-year CVD risk to lifetime-based risk, which may well offer greater benefit and cost-effectiveness. Updated NICE guidelines for the assessment and management of hyperlipidaemia were published this July.

With lowering of risk thresholds for consideration of statin therapy, as proposed in draft NICE guidance, there has been ongoing debate of the potential risk versus the benefit of statins, fuelled to a large extent by the media. Dr David Preiss (University of Glasgow and BHF Glasgow Cardiovascular Research Centre) overviewed the evidence to date. Undoubtedly, statin treatment is associated with a small increased risk (11–12%) of new-onset diabetes, although this is far outweighed by the CV benefits in medium to high-risk patients.[13] The evidence is more nebulous for other effects, including effects on cognition, fatigue or change in body weight; the last may warrant further study.

HDL: where are we now?

HDL cholesterol has been under attack with the failure of recent trials, including AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) and HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events), with niacin,[14,15] and the termination of dalcetrapib, the second cholesteryl ester transfer protein inhibitor.[16] But, as overviewed in the Myant Lecture by Professor Arnold von Eckardstein (Institute of Clinical Chemistry, University Hospital of Zurich and University of Zurich, Switzerland), HDL cholesterol and HDL are different measures. While low HDL cholesterol is undoubtedly a risk factor for CVD, it is a poor surrogate for HDL, due to the heterogeneity of the HDL particle population, in terms of size, molecular composition, structure and function.

Trial design is also at fault; neither HPS2-THRIVE nor trials with dalcetrapib specifically selected patients with low plasma HDL cholesterol levels. Furthermore, the many molecules (both lipids and proteins) associated with HDL exert both distinct and overlapping activities, which may be compromised by inflammatory conditions, such as acute coronary syndromes. Professor Eckardstein concluded that a better understanding of HDL metabolism and structure-function-relationships is key to exploiting HDL and its associated components as potential targets for anti-atherosclerotic therapies.

Back to basics: diet

Finally, dietary fat and CVD was another hot topic, fuelled by recent media attention (*Times 2*, 2nd July 2014: 'Why we can all eat fat again'). As discussed by Professor Tom Sanders (Kings College London), consideration of the type of fat is crucial. Consistent with guidelines, individuals should aim to reduce and modify fat intake, replacing saturated fat with polyunsaturated or monosaturated fats, and eliminating trans fats. The key question is how best to engage individuals to ensure uptake of these changes and persistence long-term

Diary date

Next year's HEART UK 29th Annual Conference 'Lipids in the community' will take place on 16th–18th September 2015 at The Royal College of Surgeons of England, London. For updates visit http://www.heartuk.org.uk/

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