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EAS Updates

Highlights from the 87th EAS congress, 26–29th May 2019

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1. News from the EAS FHSC global registry

The EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC) Registry is an important example of the Society's global position in atherosclerosis research. To date, nearly 60,000 FH cases – including over 7000 children with FH - have been enrolled in the Registry by 68 countries. Recent news from the EAS FHSC Registry has highlighted the extent of unmet needs in FH research and care [1], emphasising the importance of this initiative. Professor Kausik Ray (Imperial College, London, UK), who leads the Registry, overviewed new insights from individual lead investigators, including findings from the ELSA-Brazil study showing differences in FH prevalence according to ethnicity [2]; the DIAMOND-FH study in Switzerland showing how low-density lipoprotein cholesterol (LDL-C) levels are influenced by age in people with FH- causing variants in the *APOB* gene [3]; the impact of universal screening of children on cascade screening for FH in Slovenia [4]; as well as data from Serbia, Slovakia, Uzbekistan and South Africa [5–8], amongst others, highlighting the issue of undertreatment of FH. In addition, findings from Vietnam emphasised the need for education of FH patients to ensure uptake of statin treatment [9].

A key outcome from participation in the FHSC Registry is that many countries have now initiated their own FH registries. These include the CaReHigh Registry in Germany, the A-HIT1 and A-HIT2 Registries in Turkey, and the FH Canada national registry [10–12]. Some of the FH Lead Investigators discuss the status of FH care and new initiatives in FH that have been a direct consequence of participation in the FHSC Registry.

- Professor Winfried März (University of Heidelberg, Germany and University of Graz, Austria) discusses the CaReHigh FH Registry in Germany
- Dr Meral Kayikcioglu (Ege University, İzmir, Turkey) discusses FH initiatives in Turkey
- Professor Maciej Banach (Medical University of Lodz, Lodz, Poland) discusses the status of FH care in Poland

Going forward, the mission of the FHSC Registry is to ensure that the World Health Organisation recognises the importance of early detection of cholesterol, with the ultimate aim of establishing a global policy for universal screening for FH. Collaboration with the patient representative network, FH Europe, as well as the International Atherosclerosis Society and the World Heart Federation, are key to achieving this.

2. Late Breaking Sessions highlight FH and novel therapies

FH was also a focus of presentations in the Late Breaking Sessions, relating to both detection and treatment. In an analysis of more than 1.7 million patient records, individuals who were likely to have FH based on cholesterol and family history of premature cardiovascular disease but were not diagnosed as FH, were twice as likely to die earlier than individuals with an FH diagnosis [13]. Despite the limitations of a retrospective design, these findings provide compelling support for screening to identify and treat individuals with FH early and thus improve long-term health outcomes. Additionally, a novel 4S (Scandinavian Simvastatin Survival Study) analysis showed greater benefit from statin treatment in the secondary prevention setting among those individuals with a likely genetic vulnerability to high cholesterol levels [14]. Researchers stratified data according to LDL-C level (< 4.9 mmol/L or ≥ 4.9mmol/L), and the presence of premature coronary artery disease (CAD) (i.e. onset < 55 years in men and < 60 years in women) in the patient, his/her sibling, or both. The combination of

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high LDL-C and premature CAD in the patient and siblings was considered suggestive of an 'FH phenotype'. In these individuals, treatment with simvastatin was associated with over 80% reduction in the risk for all-cause death, and over 50% reduction in major CAD events.

Results from the ORION-2 study with inclisiran, an RNA interference agent targeting PCSK9 (proprotein convertase subtilisin/kexin type 9), provided proof-of-concept support for further investigation of inclisiran in patients with homozygous FH due to two alleles in the *LDLR* gene [15]. Administration of two doses of inclisiran 300 mg (day 1 and day 90) was effective in three patients with LDL-C reductions averaging 30%, similar to results seen in the TESLA study with the PCSK9 monoclonal antibody evolocumab [16]. As a caveat, however, homozygous FH patients must have *LDLR* mutations with residual LDL receptor activity, as has been previously shown for the PCSK9 monoclonal antibody therapy [16]; the treatment is not effective in those with null *LDLR* mutations.

The Late Breaking Sessions also provided insights into other novel therapies. Phase 2 data for an adnectin PCSK9 inhibitor, LIB003, showed sustained LDL-C reductions at 12 weeks of more than 70% with a 300 mg dose given subcutaneously every 4 weeks. Treatment with LIB003 also appeared to be well tolerated, supporting ongoing development of this agent in phase 3 trials [17]. Furthermore, results of a phase 3 trial in high cardiovascular risk patients (65% on a statin) showed that a fixed combination of bempedoic acid and ezetimibe, two nonstatin therapies with complementary modes of actions, led to an LDL-C reduction of 38% (placebo-corrected), significantly greater than with either agent alone [18]. These findings suggest potential for this oral combination therapy in patients with statin intolerance, a group whose therapeutic options are limited.

3. News from the plenaries

The first Plenary Session focused on metabolic dysfunction, with discussion of potential targets for therapeutic intervention. This covered olfactory receptors in macrophages in vascular tissue, mitochondria-derived oxidative stress, shown to play a key role in cardiovascular ageing, as well as *PNPLA3* (palatin-like phospholipase domain-containing 3) expression. Previous studies had indicated that a missense mutation in this gene (*PNPLA3-148 M*), influenced the propensity for hepatic fat accumulation and susceptibility for more severe liver damage, and this was exacerbated by concomitant adiposity [19,20]. Understanding the underlying mechanisms, involving disruption of ubiquitylation and proteasomal degradation of PNPLA3, resulting in impaired mobilisation of triglycerides from lipid droplets [21], suggests new therapeutic strategies aimed at preventing progressive fatty liver disease, now the most prevalent cause of chronic liver disease worldwide.

In the second Plenary Session, strategies aimed at improving cardiovascular risk estimation were considered. Professor Chris Packard (University of Glasgow, UK) suggested a new paradigm for cardiovascular disease prevention specifically focused on younger adults in the primary prevention setting. Integral to this was a framework of biomarkers, categorised according to their utility as causal (with LDL-C as the benchmark), systems biomarkers not necessarily directly involved in atherogenesis (e.g. C-reactive protein), or those relevant to disease progression such as high-sensitivity troponin T and I and NT-proB-type Natriuretic Peptide. Genetic risk was also an important component to be taken into consideration, especially that relating to common small-effect variants, likely to have a profound impact on risk at the population level. The current approach for global risk estimation in Europe, SCORE, has limitations. Ongoing revisions include extension of the upper age limit to 70 years, and setting the cholesterol range from 4 to 7 mmol/L (values above this would indicate an inherited hypercholesterolemia and therefore high risk). Further revision should aim to consider the duration of exposure to risk factors, as well as environmental factors and the impact of prognostic changes in the microbiome that may affect cardiovascular risk estimation.

A Joint Session of the European Society of Cardiology (ESC) and the EAS focused on the role of noninvasive imaging in risk estimation. Professor Valentin Fuster (Mount Sinai Heart, New York, USA) emphasised that preventive strategies should be directed to promoting cardiovascular health. He specifically focused on noninvasive imaging aimed at detecting early arterial inflammation, as well as integrative approaches combining imaging with genomic screening in early life. ESC President Professor Jeroen Bax (University of Leiden, the Netherlands) gave a glimpse of the future, in proposing that integrative machine learning will become the norm for imaging in the future.

Finally, in the third Plenary Session the focus returned to novel therapeutic strategies for cardiovascular disease prevention. Professor Matthias Nahrendorf (Harvard Medical School, Boston, USA) made the case for immunomodulation aimed at targets beyond the arterial vessel wall as the next game changer for preventive strategies. Specifically, he focused on the role of monocytes/macrophages in the repair process in the acute period following myocardial infarction, as well as in facilitating conduction at the atrioventricular node [22,23]. The remaining plenary lectures focused on lipoprotein targets beyond LDL. Novel approaches targeting elevated triglycerides, a marker for triglyceride-rich lipoproteins and their remnants, may offer benefit given emerging evidence for the causality of remnants in cardiovascular disease; however, discordance between the magnitude of reduction in triglycerides and apolipoprotein B reduction observed in clinical trials with some of these agents, suggests the need for caution. And lastly, the role of high-density lipoprotein (HDL) cannot be disregarded, with accumulating evidence for the complexity of HDL metabolism, and changes in the atheroprotective capacity of HDL particles in the setting of insulin resistant conditions such as type 2 diabetes mellitus.

4. Lipoprotein(a) in the news

As at last year's congress in Lisbon, there were important insights regarding the magnitude of lipoprotein(a) [Lp(a)] reduction required to reduce the risk of cardiovascular risk in clinical trials, against a background of well-controlled LDL-C levels. An analysis from the UK Biobank [24], including 375,000 people with Lp(a) measured using a single isoform insensitive assay, showed that reduction in Lp(a) levels by 160–180 nmol/L, corresponding to about 86 mg/dL (range 75–104 mg/d), would provide the same effect on lifetime risk of major cardiovascular events as 1 mmol/L lowering of LDL-C levels. Importantly, this magnitude of reduction was the same among men and women. In addition, Lp(a) did not appear to have a clinically meaningful prothrombotic effect for most people, as shown in individuals with and without a variant in the gene encoding guanylate cyclase soluble subunit alpha-3 (GUCY1A3), and in those with and without genetic variants in the Factor II (prothrombin) and Factor 5 genes. On the basis of these findings, the researchers concluded that concomitant antiplatelet therapy should not have any effect on the amount that Lp(a) must be reduced to achieve clinically meaningful benefit in a short-term trial.

- Professor Brian Ference (Centre for Naturally Randomized Trials, University of Cambridge, UK) and Dr Julius Katzmann (Universitätsklinikum Leipzig, Germany)

There were also insights from the Copenhagen studies showing that high Lp(a) was associated with observational and genetic risk of ischaemic stroke [25]. In observational analyses, a 50 mg/dL (105 nmol/L) higher Lp(a) level was associated with about 20% increase in the risk of ischaemic stroke, of similar magnitude to that reported for genetic causal risk. Another study involving up to 30-year follow-up of 2813 children suggested that Lp(a) levels fluctuate substantially over time, and therefore Lp(a) may need to be measured more than once when screening for elevated Lp(a) for risk estimation [26].

- Dr. Pia Kamstrup (Herlev and Gentofte Hospital, Copenhagen University Hospital, Denmark) discusses recent data from the Cop0enhagen studies showing an association between lipoprotein(a) and ischaemic stroke.

A lively seminar debated whether to treat elevated Lp(a) or not. Despite raising issues with statistical inferences from post hoc analyses of clinical trials, both Professor Brian Ference (Centre for Naturally Randomized Trials, University of Cambridge, UK) and Professor Sam Tsimikas (University of California San Diego, USA) agreed that the totality of evidence supports a high Lp(a) level as an extraordinarily strong cardiovascular risk factor and emphasised the importance of screening for elevated Lp(a). With the advent of novel therapies specifically directed to Lp(a), the design of trials aimed at testing whether lowering Lp(a) levels reduces cardiovascular events is critical. In particular, it is essential that these trials enrol patients with sufficiently elevated Lp(a) levels that allow for clinically meaningful reduction in Lp(a). This question has driven research presented at EAS Congresses in Maastricht and Lisbon.

Obviously, the 87th EAS Congress Maastricht offered more innovative research and pertinent discussions than summarised in this report. The future for research into atherosclerotic cardiovascular disease in Europe, whether in basic science or clinical trials, bodes well. And the EAS continues to be at the forefront of research, education and collaboration aimed at preventing the clinical sequelae of cardiovascular disease.

Conflicts of interest

The author declared she does not have anything to disclose regarding conflict of interest with respect to this manuscript.

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