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The Monday Report: Genomic medicine, CETP inhibition and sex differences in CVD

Monday's Plenary session ranged from recent elucidation of the ABCG5/G8 membrane transporters that play a key role in maintaining sterol balance, to the possibilities that genomic medicine offers for improving diagnosis and clinical management of atherosclerotic cardiovascular disease. **Professor Helen Hobbs (University of Texas Southwestern Medical Center, Dallas, Texas, USA)** overviewed very recent work that has led to structural characterization of the G5/G8 heterodimer.¹ This work provides a framework for understanding sterol transport, and the impact of mutations in ABCG5/G8 on coronary artery disease risk.

Genomic medicine: now and the future

Atherosclerosis is undoubtedly a complex process involving a very large number of genetic loci influencing different pathways. **Professor Heribert Schunkert (Deutsches Herzzentrum München, Technische Universität München, Germany)** commented that genome-wide association studies (GWAS) have provided a critical tool for elucidating common variants with effects on coronary heart disease (CHD) risk, with implications for both established and novel treatment targets. Given that the effect sizes of individual alleles are small, the development of genetic risk scores based on multiple genetic loci offers the possibility of translating discoveries from GWAS to tools for the clinic, allowing the possibility of stratifying therapies to individuals most at risk, and therefore most likely to gain from the intervention. **Dr. Terri Manolio (National Human Genome Research Institute, Rockville, USA)** overviewed how the application of genomic information about an individual can be used in diagnosis and therapy. In a recent report,² the use of CHD risk estimates that incorporated genetic risk and clinical information improved LDL cholesterol lowering beyond that based on conventional risk factors alone. Such applications have important implications on a population level, with policy implications for clinical use. Clearly to optimize their use, structured collaborations across institutions, implementation using a common infrastructure, and common clinical decision support tools including point-of-care educational materials, are all critical. Dr. Manolio overviewed projects in the USA that are adopting these approaches. As she concluded: '*Genotyping is the future; we need to ensure best use of the information with collaborative approaches.*'

ACCENTUATE: CETP inhibition on the rails?

Monday also provided new insights into novel therapies. A report from the ACCENTUATE trial,³ which evaluated the effects of the cholesteryl ester transfer protein (CETP) inhibitor evacetrapib on atherogenic lipoproteins, was of key interest in the light of recent termination of the cardiovascular outcomes trial ACCELERATE due to futility. ACCENTUATE was conducted to compare the effects of different therapeutic strategies in 366 high risk patients (pre-existing atherosclerotic cardiovascular disease or diabetes), treated with atorvastatin 40 mg daily for at least 30 days (mean baseline LDL cholesterol 83 mg/dl). Patients were randomized to either doubling the dose of atorvastatin to 80 mg daily, adding ezetimibe 10 mg daily or adding evacetrapib 130 mg daily.³ The duration of treatment was 90 days. The primary endpoint, the percent reduction in LDL cholesterol, was significantly greater with evacetrapib (33% versus 27% with ezetimibe, $p=0.045$; or doubling the dose of atorvastatin, 33% versus 6%, $p<0.001$), despite a somewhat modest effect on apolipoprotein (apo) B (decrease by 23% versus 18.8% with ezetimibe and 6.5% with atorvastatin 80 mg daily). Evacetrapib treatment also led to a

robust increase in high-density lipoprotein cholesterol (by 125%). Effects on LDL and HDL cholesterol were entirely consistent with the profile of lipid modifying previously shown for evacetrapib. Interestingly, however, evacetrapib was also associated with increases in apoCIII (by 50%) and apoE (by 28%). Indeed, there was strong correlation between HDL cholesterol and apoCIII and apoE, although HDL functionality studies showed no impact on cholesterol efflux capacity. There was no evidence to suggest possible 'off-target' effects of evacetrapib in either ACCENTUATE or ACCELERATE.

Given that evacetrapib is now the third CETP inhibitor to have been discontinued, lead author **Professor Steve Nicholls (University of Adelaide, Adelaide, Australia)** questioned whether CETP inhibition is still a viable therapeutic strategy. *'These findings continue to challenge the hope that CETP inhibition might successfully address residual cardiovascular risk.'* However, he did acknowledge that REVEAL, the cardiovascular outcomes study with anacetrapib, continues. Clearly more information is needed on effects of CETP inhibition on other functional properties of HDL beyond cholesterol efflux, on atherogenic lipoproteins, as well as information relating to the effect of treatment on the atherosclerotic plaque. For further discussion of ACCENTUATE and CETP inhibition check the interview with Professor Nicholls on the EAS website.

Cardiovascular risk: is it the same in men and women?

The joint European Society of Cardiology/EAS session focused on this key question. While findings from the EUROASPIRE survey⁴ highlight differences in the prevalence of risk factors between the sexes, notably smoking, hypertension (more prevalent in men) and obesity (more prevalent in women), clinical practice does not sufficiently taken gender into consideration. Moreover, despite the general conception that premenopausal women are at lower risk of coronary heart disease risk than men, it should be recognized that this 'protective' effect is countered by the onset of the menopause. Importantly, clinicians need to recognize that CVD is the main cause of death in women in all countries of Europe.⁵

As highlighted by **Professor Eva Bossano Prescott (Bispebjerg Hospital, Denmark)**, questions remain regarding differences in the clinical manifestations of CHD in men and women, especially with respect to angina (more common in women) and epicardial disease (more common in men). This different clinical profile between the sexes underscores the need for better non-invasive markers and biomarkers to evaluate these differences. **Professor Georgios Kararigas (Center for Cardiovascular Research and German Center for Cardiovascular Research, Charite University Hospital, Berlin, Germany)**, also made the case for further work at the molecular level to investigate differences in propensity for CHD in men and women. He cited evidence that women with heart failure have better prognosis than men, with protective effects thought to be due to the oestrogen receptor β . Basic research suggests the functional relevance of these receptors in regulating calcium metabolism in a sex-specific manner. Experimental studies also suggest that the proteomic response of the heart to pressure overload is modulated by oestrogen receptors, which may underlie the sex differences in clinical manifestations. Additionally, here are differences in maladaptive left ventricular remodeling between the sexes which impacts survival. These research directions may ultimately lead to the development of more appropriate and personalized clinical care for men and women; an overlooked priority still in the 21st century.

References

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