Lp(a)… How does it fit with FH

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The molecular mass polymorphism of apo(a) is the major determinant of Lp(a) concentration. Nonetheless, the inheritance of the definite HeFH phenotype typically doubles its levels compared to unaffected first degree relatives. In such patients expression of *APOE4* can further increase Lp(a). Lp(a) identifies particularly high atherosclerotic cardiovascular disease (ASCVD) risk in definite HeFH. However, Lp(a) measurement can also have a role in the management of people investigated for possible HeFH, who prove to be negative for FH-causing mutations. It predicts ASCVD risk not only in monogenic, but also in polygenic hypercholesterolaemia. Its levels are frequently raised when there is a family history of early-onset ASCVD, as is typical of people in whom the diagnosis of HeFH is investigated. Levels >180 mg/dL (430 nmol/L) (around the 99 to 99.5 percentile for the general population ie 1in 100 to 200), are stated in the European guidelines to indicate an ASCVD risk equivalent to HeFH. Thus high Lp(a) can militate in favour of more intense treatment at an earlier age than might be indicated by multifactorial risk engines even in FH-causing mutation- negative patients. RCT evidence for treatment of Lp(a) *per se* is lacking, although sub-analysis of trial results suggest that PCSK9 inhibition may decrease ASCVD incidence most effectively when Lp(a) is initially high. It is, however, well established that Lp(a) confers higher ASCVD risk when LDL cholesterol is also raised. Therefore our current strategy when high Lp(a) and LDL cholesterol co-exist must be to adopt lower LDL cholesterol therapeutic goals at an earlier age.

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Paul Durrington retired from his substantive post as Professor of Medicine at the University of Manchester in 2009 and retired as Consultant Physician at Manchester Royal Infirmary, UK in 2012. He continues to work in the Cardiovascular Research Group of the University of Manchester as Honorary Professor of Medicine and to publish regularly. He graduated in physiology and medicine at the University of Bristol and trained in general internal medicine, diabetes mellitus and metabolic disorders. From 1979-80, he worked at the University of California, San Diego, USA, as a travelling fellow of the British Heart Foundation and American Heart Association. His research interests centre on disorders of lipoprotein metabolism, atherogenic modification of lipoproteins, insulin resistance and diabetes. He was Chairman of the British Hyperlipidaemia Association (1992-1995), a member of the British Heart Foundation Project Grants Committee (1997-2000), Director of Research and Development at the Central Manchester Healthcare Trust (1997-2001) and a member of the European Science Foundation Genetics and Epidemiology of Atherosclerosis International Review panel (2005). From 2008 to 2012 he led the Greater Manchester Vascular Research Network. He was a member of the European Cardiac Society Task Force on Dyslipidaemia (2009-2015) and is from time to time a consultant to the National Institute of Health and Care Excellence (NICE) and an editor of Current Opinion in Lipidology. In 2010 he gave the Myant Lecture to HEART UK. Currently, he chairs of the Steering Committee of the National Institute of Health Research funded HealthTechnology Assessment

Project:15/134/02 – 'Evaluating alternative protocols for identifying and managing patients with familial hypercholesterolaemia: cost-effectiveness analysis with qualitative study'. In 2001 he was elected to the Fellowship of the Academy of Medical Sciences for his work on diabetic dyslipidaemia and on HDL metabolism. He is author of over 400 original papers and other publications including *Hyperlipidaemia: Diagnosis and Management* 3rd Edition (2007, London: Hodder Arnold) and with Allan Sniderman *Hyperlipidemia* 6th Edition (2020, Oxford: Karger Press).