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More insights to inform trials of novel agents targeting high lipoprotein(a)

Maastricht, 27 May, 2019 – Treatment with anti-platelet or anti-thrombin therapies is unlikely to reduce the increased risk of cardiovascular disease, such as heart attacks and strokes, that is linked with high lipoprotein(a) levels. That is the conclusion of a new study based on data from 480,000 people of European descent in the UK Biobank.

There is strong evidence that high plasma levels of lipoprotein(a) are a causal risk factor for cardiovascular disease. The European Atherosclerosis Society Consensus Panel has previously recommended screening for elevated lipoprotein(a) in individuals at intermediate, high, or very high cardiovascular risk, and suggested a desirable plasma concentration of less than 50 mg/dL. These recommendations are also included in current European lipid guidelines for prevention of cardiovascular disease.

Traditionally, it has been thought that the increase in cardiovascular risk associated with high lipoprotein(a) levels is due to both proatherogenic and prothrombotic effects. However, it is difficult to separate these effects. With ongoing trials of novel potent lipoprotein(a) lowering therapies, researchers from the Universitätsklinikum Leipzig, Germany and the Centre for Naturally Randomized Trials, University of Cambridge, UK investigated whether lipoprotein(a) has a clinically significant prothrombotic effect.

The researchers used data from the UK Biobank, including 375,000 people with lipoprotein(a) levels measured using a single assay (isoform insensitive). This is important as lipoprotein(a) levels can vary across different assays. According to Professor Brian Ference (University of Cambridge, UK): ‘This is by far the largest study ever where everyone had lipoprotein(a) measured with the same assay.’ In these people, the median lipoprotein(a) level was 20.1 nmol/L; the 80th percentile was 80.9 nmol/L, the 90th percentile was 131.2 nmol/L and the 95th percentile was 158.3 nmol/L.

Importantly, high lipoprotein(a) levels did not appear to lead to a clinically meaningful increase in the risk of thrombotic events such as deep vein thrombosis or pulmonary embolism. In addition, the effect of lipoprotein(a) on the risk of cardiovascular events did not differ among
people with and without a variant in the gene encoding guanylate cyclase soluble subunit alpha-3 (GUCY1A3), which mediates nitric oxide signalling and thus has a key role regulating vascular tone and platelet activation. This genetic variant mimics the effect of an anti-platelet agent. Furthermore, the effect of lipoprotein(a) on the risk of cardiovascular events did not differ among people with and without genetic variants in the Factor II (prothrombin) and Factor 5 genes, which when combined into a genetic score mimics the effect of an antithrombin therapy. Together, these results suggest that lipoprotein(a) does not have a clinically meaningful prothrombotic effect for most people.

Commenting on these results, Professor Ference said: ‘Antiplatelet and antithrombin therapies are part of the routine evidence-based management of patients at high and very high risk of cardiovascular events. Given current understanding of the biology of lipoprotein(a), a key question is whether these treatments are likely to influence cardiovascular risk associated with high lipoprotein(a) levels. This could be an important factor in the design of cardiovascular outcome trials testing the effects of novel treatments to lower lipoprotein(a) levels because such trials are likely to enrol patients with cardiovascular disease who are also receiving an antiplatelet therapy. Based on the results of our analysis, in which lipoprotein(a) levels were measured with the same sensitive assay, concomitant antiplatelet therapy should not have any effect on the amount that lipoprotein(a) must be reduced to achieve clinically meaningful benefit in a short-term trial.’

Workshop: Cardiovascular risk assessment from epidemiology to genetics
Monday 27 May, 15:45 – 17:15, Willem Erkelens


Contact:
Local Press agency: MEDCON International
info@medconinternational.com

EAS Administration Executive
Dr. Carmel Hayes
+46768 61 00 51
Email: office@eas-society.org

For contacting speakers:
Please come to the EAS2019 Faculty desk in the Registration area or email to our Congress organiser Kenes Group
Timi Simantov
E-mail: tsimantov@kenes.com
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