Lipoprotein(a) is a causal risk factor for coronary artery disease

**WHAT WAS KNOWN**
- Lipoprotein(a) is a unique type of low-density lipoprotein particle where an apolipoprotein(a) molecule is covalently bound to apolipoprotein B.
- Levels of these cholesterol-rich Lp(a) particles are highly heritable and a risk factor for coronary artery disease (CAD).
- The kringle domain of the apolipoprotein(a) molecule shows striking copy-number variation (CNV) and isoform size is negatively correlated with Lp(a) levels.
- Isoform assays are technically challenging, expensive and with limited resolution which limits their application in large-scale epidemiological studies.
- The genetic determinants of Lp(a) levels and of isoform size were incompletely understood, as was their causal relevance for CAD.

**WHAT THIS ADDS**
- We identified two SNPs that individually and when combined into an apolipoprotein(a) genotype score, showed strong associations to CAD risk and Lp(a) levels.
- The SNPs tagged short (low copy number) isoform alleles that jointly confer a 50% increase in CAD risk to one-sixth of the population.
- The pattern of SNP associations to Lp(a) levels and CAD risk was consistent with a causal relationship between biomarker and disease.
- The genotype score has subsequently revealed novel risk associations with ischemic stroke, peripheral vascular disease and aortic aneurysms.
- The study refocused attention on Lp(a) as an emerging risk factor and validates Lp(a) as a novel drug target for CAD prevention.

**WHAT WE DID**
- Patients with premature CAD and ancestry-matched controls were assembled from four European countries (Germany, Italy, Sweden and UK) through the PROCARDIS collaboration.
- Lp(a) levels were measured in patients and controls and apolipoprotein(a) isoform sizes were estimated using proteomic (immunoblot) and genomic (qPCR) methods.
- Fifty-thousand single nucleotide polymorphisms (SNPs) were genotyped to systematically scan for CAD associations in two-thousand candidate genes across the genome.

**REFERENCES**
Genetic variants associated with Lp(a) lipoprotein level and coronary disease.