Genetically-Mediated Vascular Endothelial Cell Dysfunction and its Dependence on Serum LDL Cholesterol Levels for the Development of Coronary Artery Atherosclerosis: Genetic Insights from the UKBB and FOURIER Trial

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BACKGROUND

• Coronary atherosclerosis develops from cholesterol entering the vessel wall through abnormal endothelial cells
• Whether EC dysfunction contributes to atherosclerosis in the absence of sufficient circulating cholesterol is unknown

METHODS

• We analyzed 348,967 primary prevention patients from the UK Biobank and 14,298 secondary prevention patients from the FOURIER trial
• Using the latest CAD GWAS, we created a PRS for both EC-mediated CAD and LDL-mediated CAD to determine how each predicted risk
• Actual LDL-C values were used to see how EC PRS predicted CAD risk as a function of baseline LDL-C in both cohorts
• Endpoints included the development of CAD in the UK Biobank and major vascular events in FOURIER

Figure 1) The risk of developing CAD is greatest when both LDL and endothelial cell pathways are involved

RESULTS

• Among 241 genome-wide significant SNPs associated w/ CAD, we identified 45 loci w/ known effects on LDL metabolism & 35 on EC fxn
• In the UKBB, the EC and LDL PRS each predicted development of CAD to a similar degree, with HRs of 1.24 [1.21-1.26] and 1.27 [1.25-1.30]
• When assessed in combination, the risk prediction of the EC and LDL PRS appeared to be additive, such that there was a nearly 5-fold gradient of risk across risk groups (p<0.001, Figure 1)
• Using actual LDL-C values in UKBB, we found that the risk associated with elevated EC PRS was dependent on higher LDL-C, such that the association was strongest when LDL-C was >140 mg/dl and no association was seen when LDL-C was <60 mg/dl (p=0.004, Figure 2)

Figure 2) Endothelial cell mediated risk of CAD is dependent on the concentration of LDL-C in primary prevention

• In FOURIER, the EC PRS also predicted risk of major vascular events in the placebo arm, where the mean LDL-C was 90 mg/dl (p<0.001), but not in the treatment arm (mean LDL-C 30 mg/dl, p=0.49) (Figure 3)
• As such, individuals with high EC PRS derived the greatest benefit from aggressive LDL-C lowering with evolocumab

Figure 3) Endothelial cell mediated risk of CAD is dependent on the concentration of LDL-C in secondary prevention

CONCLUSIONS

• Genetically-mediated EC dysfunction is a strong, independent risk factor for the development of CAD
• However, very low levels of serum cholesterol, achieved either naturally or pharmaceutically, appears to offset the risk of genetically-mediated vascular EC dysfunction

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