



Could genetics be the answer?

Atherosclerotic coronary artery disease is responsible for millions of deaths worldwide on a yearly basis.

Statin therapy reduces the risk of a first myocardial infarction. There is a relative risk reduction of about 20% for every 1 mmol/L reduction of LDL-cholesterol and this effect of statins has been shown in virtually every subgroup of patients as demonstrated by clinical measures or biochemical measures.

The question is, if it can be shown that there is a specific subgroup of patients that may benefit more from statin therapy, it could have a large influence on the decision on who to treat with statins. Could genetic determination be the answer?

During very large genome-wide association studies and subsequent meta-analyses, it was demonstrated that there are > 150 common single nucleotide polymorphisms (SNPs) that are robustly associated with cardiovascular disease, coronary artery disease and cardiovascular traits such as coronary calcification. Many of these loci are involved in lipid metabolism. Together these SNPs explain about 10.6% of cardiovascular heritability. There is now a genetic risk score (GRS) that has been developed for which SNPs at independent loci are combined and they are then weighted according to the effect sizes as it was published in the research articles. This GRS can then be added to the current clinical risk scores in use, such as the Framingham Risk Score to increase our ability to determine an individual's overall cardiovascular risk estimate.

In two previous studies it was shown that in those patients who had the highest GRS, the effect of statin therapy was significantly more beneficial with a larger relative risk reduction as compared to patients with much smaller GRS results. This difference in beneficial clinical cardiovascular outcomes occurred despite patients having the same or similar reduction in LDL-cholesterol levels. For a given reduction in LDL level the outcome differed according to the size of their genetic risk score: the larger the GRS the larger the relative risk reduction. These two trials were: ASCOT-LLA (Anglo-Scandinavian Cardiac outcomes Trial-Lipid Lowering Arm) and the JUPITER trial (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin).

In a recent study using data from a previously done primary prevention study using statin therapy, the WOSCOPS study (West of Scotland Coronary Prevention Study) of more than 4 000 participants and using data from two observation studies, the CARDIA (Coronary Artery Risk Development in Young Adults) and the BIOLMAGE study, the genetic risk scores were calculated. The GRS were calculated for each individual derived from 57 common DNA sequence variants previously associated with coronary heart disease.

In patients with a high GRS the relative risk reduction of fatal and non-fatal coronary artery disease was 44% (95%CI: 22-60) as compared to patients with lower and low GRS in whom the relative risk reduction was 24% (95%CI: 8-37%) despite having the same (or similar) reduction in LDL-cholesterol levels.

Pooling data from WOSCOPS, ASCOT-LLA and JUPITER in primary prevention using statins, the relative risk reduction was 46% in the high genetic risk score group and 26% in the other groups with lower genetic risk scores. Across all three studies, the absolute risk reduction was 3.6% in the high genetic risk score group as compared to 1.3% in the groups with lower genetic risk scores (NNT correspondingly 28 vs 77). Those patients with high genetic risk scores also had higher risk of coronary artery calcifications and more carotid plaques.

Conclusions

- 1** Those patients with higher genetic risk scores derive more benefit from statin therapy for primary prevention.
- 2** The benefit of statins for primary prevention of a first myocardial infarction is much larger as a relative risk reduction as well as an absolute risk reduction with corresponding NNT.
- 3** Using these 57 SNPs in a polygenic risk score can identify individuals who are at a greater risk to develop atherosclerotic coronary artery disease and these patients then may be targeted to receive much more intense therapy.
- 4** In future, it is hoped that a most accurate panel of SNPs can be identified to predict future risk of atherosclerotic disease in all ethnic groups.

References are available on request. **SE**



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