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Lessons from the trials

Is there a role for genetic risk assessment in the treatment of dyslipidemia in primary and secondary prevention of coronary heart disease?

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ABSTRACT

Genetic variants have been associated with the risk of coronary heart disease (CHD). Mega et al studied the association of a genetic risk score based on 27 genetic variants with incidents of recurrent CHD, adjusting for traditional risk factors using data from a community based study and 4 randomized controlled trials of both primary and secondary prevention with statin therapy. When individuals were divided into low, intermediate and high genetic risk categories, a significant gradient in risk of incident and recurrent CHD was shown.

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INTRODUCTION

The risk of developing coronary heart disease (CHD) depends on several factors that are related to both lifestyle and genetics. Heritable factors account for 30–60% of coronary artery disease development. Recent genome-wide association studies have identified around 50 chromosomal loci that are robustly associated with CHD.¹ Mega et al studied whether the developing of genetic risk score (27 genetic variants associated with CHD) will help in risk stratifying patients receiving statin therapy in both primary and secondary prevention.²

THE STUDY

The investigators analyzed data from the following studies:

- **The primary prevention population:** The Malmo Diet and Cancer Study (MDCS), JUPITER, and ASCOT studies, where genetic samples were available from 27817, 8749 and 6978 people consecutively.
- **The secondary prevention population:** CARE, and PROVE IT-TIMI 22, where genetic samples were available in 2878 and 1999 individuals consecutively.

The genetic risk score was derived on the basis of 27 SNPs that were significantly associated with coronary artery disease at genome-wide level in previous analyses. Each individual participant received a score equal to the sum of the numbers of risk alleles for each SNP weighted by the log of the odds ratio reported with the SNP in the original report.

The outcome of interest was coronary heart disease. The investigators used the Cox proportional hazard models to assess the risk of coronary heart disease for each quintile of genetic risk, in which they used the first quintile as a reference group. Additionally, the risk categories 'low' [quintile 1], 'intermediate' [quintile 2-4], and 'high' [quintile 5] and per 1 SD were calculated. These analyses were done on the participants in MDCS, and in the placebo or low-intensity statin treatment groups of the applicable trials.

RESULTS

Higher genetic risk scores were associated with a raised risk of coronary heart disease, independent of established clinical predictors. Specifically, when evaluating participants in low, intermediate, and high genetic risk categories, a gradient of risk coronary heart disease was evident in the studies (See Table 1).

Baseline LDL cholesterol and HDL cholesterol levels were similar across genetic risk score categories within each trial, as were the absolute and the percentage changes with statin therapy. Analyses were done to investigate the clinical benefit of statin therapy across the genetic risk score. The relative risk reductions were 34% in low, 32% in the intermediate, and 50% in high genetic risk score categories in the primary prevention trials, and 3% in low, 28% in intermediate, and 47% in high genetic risk score categories in the secondary prevention trials. When the data were combined, the gradient of relative risk reductions with statin therapy across low, intermediate, and high genetic risk score categories were 13%, 29%, and 48%, respectively (p value for trend = 0.02777).

Similarly, in terms of the absolute risk reductions, a graded increase in the benefit of statin therapy across the genetic risk score categories was evident in both the primary and secondary prevention trials. Correspondingly, the number needed to treat to reduce coronary heart disease events in 10 years with statin therapy in primary prevention differed depending on genetic risk score; 66 for low genetic risk score, 42 for intermediate risk and 25 for those individuals with high risk score.

DISCUSSION

The current study demonstrated that combining the 27- genetic variants that were individually associated with the risk of coronary heart disease into a risk score could identify people at increased risk of CHD events, including incident CHD in primary prevention populations and recurrent CHD events in secondary prevention populations. Furthermore, observation from the four statin trials suggests that individuals with a high genetic risk score have both a greater absolute and relative benefit from statins and the benefit is larger among high when compared to the intermediate risk group.

The investigators outlined the limitations of the study including, first data from several studies were used in the analysis, and each data has its own criteria, treatment allocation, and duration of

follow-up. Second, the numbers needed to treat were calculated by extrapolation of the effect of statin therapy during a 10-year period, and treatment effect could vary overtime. Third, these analyses were done within completed clinical trials, and the genetic risk score was not used specifically as an enrollment criterion, moreover the analyses were conducted in statin trials that yielded positive outcomes only. Fourth, although the investigators focused on genetic variants that were associated with the risk of CHD. Other variants have been described that are associated with LDL cholesterol levels. Finally, the gradient of the relative risk reduction across genetic risk score categories in the study was unexpected.

In an accompanying editorial by Schunkert and Samani,¹ they commented that the study by Mega et al² illustrates the expanding clinical use of genetic discoveries in CHD, from identifying new therapeutic targets to prioritizing (or de-prioritizing) existing targets for medical intervention to now potentially providing a valuable algorithm for improved precision in prediction of event rates and responses to treatment. They did suggest that this genetic risk score will need further careful evaluation, including testing the genetic score in the context of scores that are presently recommended^{3,4} to see how this score modulates risk calibration and discrimination provided by those established scores. Additionally, the cost-effectiveness of incorporating this genetic risk score assessment will need to be established.¹

WHAT WE HAVE LEARNED?

The genetic risk score identified individuals at increased risk of CHD across primary and secondary prevention populations. Furthermore, people with high-risk scores had the largest relative and absolute risk reductions with statin therapy.

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