Lack of Association of KIF6 Genotype With Vascular Disease and Statin Response

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Study Hypothesis

A common polymorphism in the kinesin-like protein 6 (KIF6) gene, the Trp719Arg variant, was reported in multiple exploratory studies to be associated with both vascular risk and response to statin therapy. The clinical implication of these findings was that noncarriers of the Trp719Arg variant receive little benefit from statin therapy, suggesting clinical utility for a KIF6 pharmacogenetic test to predict the suitability of statin therapy for individual patients. More recent publications have disputed the reported associations. The authors of both studies described here (Hopewell et al1 and Ridker et al2) sought to definitively confirm or reject the hypothesis that the Trp719Arg variant affects the response to statin therapy with respect to incident vascular disease.

How Was the Hypothesis Tested?

Hopewell et al1 performed a retrospective analysis of data from the Heart Protection Study (HPS), in which more than 20,000 patients with established vascular disease or risk factors for vascular disease were randomly assigned to the use of 40 mg simvastatin daily versus placebo. Genotyping of the KIF6 Trp719Arg polymorphism (also designated rs20455) was successfully performed in 18,348 HPS participants of self-reported white ethnicity, with almost equal numbers from the simvastatin arm (n=9167) and the placebo arm (n=9181). The primary outcome was incident major vascular events (defined as major coronary events, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death). The primary analysis was a comparison of event rates between the rosuvastatin and placebo arms, both in aggregate and stratified by KIF6 Trp719Arg genotype. This was performed for the self-reported Caucasian participants as well as for the entire study population.

Principal Findings

Hopewell et al1 found that there was no significant difference in the event rate between KIF6 Trp719Arg carriers and noncarriers (25.3% versus 25.7%; hazard ratio, 0.97; 95% confidence interval, 0.90 to 1.06), disputing the previous reports that the KIF6 Trp719Arg is associated with vascular risk. They also found that there was no significant difference in the reduction of vascular risk experienced by KIF6 Trp719Arg carriers with simvastatin versus placebo (hazard ratio, 0.77; 95% confidence interval, 0.71 to 0.84; P=5.3×10^-10) and experienced by KIF6 Trp719Arg noncarriers with simvastatin versus placebo (hazard ratio, 0.76; 95% confidence interval, 0.69 to 0.83; P=4.6×10^-9) (interaction P=0.70). Consistent with this finding, the two groups experienced virtually identical reductions in LDL-C levels with simvastatin (42.4% versus 42.3%). These findings fail to confirm the hypothesis that the KIF6 Trp719Arg variant affects the response to statin therapy; moreover, they unequivocally demonstrate that noncarriers of the Trp719Arg variant receive benefit from statin therapy.

Similarly, Ridker et al2 found that among Caucasian participants, there was no significant difference in the reduc-
tion of vascular risk experienced by KIF6 Trp719Arg carriers with rosuvastatin versus placebo (hazard ratio, 0.61; 95% confidence interval, 0.43 to 0.87; \( P = 0.006 \)) and experienced by KIF6 Trp719Arg noncarriers with simvastatin versus placebo (hazard ratio, 0.59; 95% confidence interval, 0.39 to 0.88; \( P = 0.009 \)) (interaction \( P = 0.90 \)). There were essentially identical reductions in LDL-C levels with rosuvastatin in carriers and noncarriers (51.7% versus 51.5%). Similar results were seen for the entire study population.

Implications
The studies of Hopewell et al\(^1\) and Ridker et al\(^2\) both soundly rejected the hypothesis that the KIF6 Trp719Arg variant affects the response to statin therapy. Moreover, they found that the Trp719Arg variant is not associated with vascular risk. It is notable that the two studies were performed with different statin drugs in different populations with different levels of vascular risk, suggesting the generalizability of the negative findings. These results stand in stark contrast to the positive findings of the earlier set of exploratory, hypothesis-generating KIF6 studies; because the HPS and JUPITER studies included significantly larger numbers of participants than any earlier study (>18 000 and >12 000, respectively, compared with <3000), they should be regarded as more definitive.

The most important message to carry away from the HPS and JUPITER studies is that noncarriers of the KIF6 Trp719Arg variant indisputably benefit from statin therapy, probably as much as carriers. This calls into question the rationale for a KIF6 pharmacogenetic test to help clinicians determine which patients should be prescribed statin therapy. On the basis of the early exploratory studies that suggested that noncarriers may not benefit from statin therapy, a commercial KIF6 test was developed and marketed to health care providers, with reportedly more than 200 000 tests performed by the time of the publication of the HPS and JUPITER studies. Guided by test results, clinicians potentially may have withheld statin therapy from patients who otherwise had clear indications for their use.

Thus, the KIF6 test is an example of a “personalized medicine” application that was introduced into practice before sufficiently large replication studies had been performed, which potentially may have been detrimental to patient care. In retrospect, it appears that the initial exploratory studies were underpowered to reliably detect a benefit of statin therapy for KIF6 W719R variant noncarriers, making it seem as if there was a difference between carriers and noncarriers. Although replication studies are now de rigeur for any genetic association study, the studies by Hopewell et al and Ridker et al show why they are mandatory when an early finding has direct clinical implications.

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Disclosures
None.
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