Kinesin-Like Protein 6 (KIF6) Polymorphism and the Efficacy of Rosuvastatin in Primary Prevention

Paul M Ridker, MD; Jean G. MacFadyen, BA; Robert J. Glynn, ScD; Daniel I. Chasman, PhD

Background—Hypothesis-generating data raise the possibility that carriers of the kinesin-like protein 6 (KIF6) 719 arginine (Arg) allele preferentially benefit from statin therapy, and, on this basis, a commercial assay for KIF6 has been developed.

Methods and Results—In the recently completed JUPITER trial, men and women without prior cardiovascular disease or diabetes who had baseline low-density lipoprotein cholesterol <130 mg/dL and high-sensitivity C-reactive protein ≥2 mg/L were randomly allocated to rosuvastatin 20 mg daily or to placebo and followed for first major vascular events (nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, or vascular death) and for all-cause mortality. We evaluated the effect of polymorphism at rs20455 encoding the KIF6 719Arg allele on outcomes in this primary prevention trial, both among Caucasian participants and in the trial as a whole. Among 8781 Caucasian trial participants, we observed no increase in vascular event rates among carriers of the KIF6 719Arg allele as compared with noncarriers (hazard ratio, 0.91; 95% confidence interval, 0.66 to 1.26) nor any difference in percent low-density lipoprotein cholesterol reduction with rosuvastatin according to genotype (−52 versus −52 mg/dL, P=0.11). Rosuvastatin allocation was associated with an almost identical reduction in the trial primary end point among carriers (hazard ratio, 0.61; 95% confidence interval, 0.43 to 0.87) as among noncarriers (hazard ratio, 0.59; 95% confidence interval, 0.39 to 0.88) (P-interaction=0.90). Genotype had no impact on rosuvastatin efficacy in further analyses that included all-cause mortality, in analyses conducted in the total trial cohort that adjusted for race, or in analyses using generalized models of inheritance rather than recessive models.

Conclusions—In the large primary prevention JUPITER trial, rosuvastatin was equally effective at reducing cardiovascular event rates among carriers and noncarriers of the KIF6 719Arg allele. Thus, at least for rosuvastatin, there appears to be no clinical utility to screening for KIF6 genotype as a method to determine vascular risk or to predict statin efficacy.


Key Words: genetic testing ■ primary prevention ■ statins

Randomized trials consistently demonstrate that statin therapy is effective at reducing rates of first and recurrent cardiovascular events. However, as statins also have side effects and cost, there has been interest in addressing whether specific patient groups benefit to a greater or lesser degree from treatment. This concept of “personalized medicine” is particularly relevant for the development of genetic testing.

Clinical Perspective on p 317

With specific regard to statin therapy, exploratory data suggest that carriers of a common polymorphism in the kinesin-like protein 6 (KIF6) gene that leads to an arginine (Arg) substitution for tryptophan (Trp) at position 719 might preferentially benefit from statin therapy, whereas noncarriers achieve little if any event reduction.1,2 Similarly, data from acute coronary syndrome patients suggest that atorvastatin may be superior to pravastatin among KIF6 719Arg carriers but not among noncarriers.3 These data have been controversial, however, as the potential mechanism of interaction between KIF6 and statin therapy is unknown, no difference in LDL reduction with statins has been observed according to genotype, and data on KIF6 as a determinant of absolute risk have been inconsistent.4–7 Further, although commercial tests are available, there have been no formal hypothesis testing data for KIF6 in the setting of primary prevention where “personalized medicine” and concerns regarding the net risk-to-benefit ratio for statin therapy are most relevant.

To address this issue, we evaluated the KIF6 genotype in the recently completed Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial in which men and women free of cardiovascular disease and diabetes who had low-density lipoprotein cholesterol...
Table 1. Baseline Clinical Characteristics of Caucasian Participants in the JUPITER Trial According to KIF6 Genotype

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Trp/Trp (n = 3717)</th>
<th>Trp/Arg (n = 4023)</th>
<th>Arg/Arg (n = 1041)</th>
<th>P*</th>
<th>Trp/Arg or Arg/Arg (n = 5064)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.0 (60.0–71.0)</td>
<td>66.0 (60.0–71.0)</td>
<td>65.0 (60.0–71.0)</td>
<td>0.50</td>
<td>66.0 (60.0–71.0)</td>
<td>0.92</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1213 (32.6)</td>
<td>1317 (32.7)</td>
<td>297 (28.5)</td>
<td>0.03</td>
<td>1614 (31.9)</td>
<td>0.45</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.6 (25.5–32.0)</td>
<td>28.6 (25.5–32.1)</td>
<td>28.7 (26.1–32.4)</td>
<td>0.08</td>
<td>28.7 (25.8–32.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>134.0 (124.0–145.0)</td>
<td>134.0 (124.0–145.0)</td>
<td>135.0 (126.0–146.0)</td>
<td>0.06</td>
<td>134.0 (124.0–145.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80.0 (74.0–86.0)</td>
<td>80.0 (74.0–85.0)</td>
<td>80.0 (74.0–87.0)</td>
<td>0.46</td>
<td>80.0 (74.0–86.0)</td>
<td>0.78</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>462 (12.4)</td>
<td>556 (13.8)</td>
<td>145 (13.9)</td>
<td>0.15</td>
<td>701 (13.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>Family history of CHD, n (%)</td>
<td>506 (13.7)</td>
<td>577 (14.4)</td>
<td>133 (12.9)</td>
<td>0.37</td>
<td>710 (14.1)</td>
<td>0.59</td>
</tr>
<tr>
<td>Metabolic syndrome, n (%)</td>
<td>1480 (40.1)</td>
<td>1591 (39.9)</td>
<td>375 (36.3)</td>
<td>0.07</td>
<td>1966 (39.1)</td>
<td>0.35</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>4.1 (2.8–6.7)</td>
<td>4.1 (2.8–6.6)</td>
<td>4.0 (2.7–6.4)</td>
<td>0.79</td>
<td>4.1 (2.8–6.5)</td>
<td>0.89</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>187.0 (172.0–201.0)</td>
<td>187.0 (172.0–201.0)</td>
<td>187.0 (171.0–200.0)</td>
<td>0.69</td>
<td>187.0 (172.0–201.0)</td>
<td>0.70</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>109 (96–120)</td>
<td>110 (97–120)</td>
<td>111 (96–120)</td>
<td>0.78</td>
<td>110 (97–120)</td>
<td>0.38</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>50.0 (41.0–60.0)</td>
<td>50.0 (41.0–61.0)</td>
<td>50.0 (41.0–61.0)</td>
<td>0.45</td>
<td>50.0 (41.0–61.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>117.0 (84.0–169.0)</td>
<td>118.0 (85.0–166.0)</td>
<td>114.0 (83.0–157.0)</td>
<td>0.10</td>
<td>117.0 (84.0–164.0)</td>
<td>0.39</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>95.0 (89.0–102.0)</td>
<td>95.0 (88.0–102.0)</td>
<td>95.0 (88.0–102.0)</td>
<td>0.17</td>
<td>95.0 (88.0–102.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>HDLc, %</td>
<td>5.6 (4.5–5.8)</td>
<td>5.6 (4.5–5.8)</td>
<td>5.6 (5.4–5.9)</td>
<td>0.47</td>
<td>5.6 (5.4–5.8)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease. All values are median (interquartile range) or n (%). For hsCRP, values are based on the average of the screening and randomization visits.

*P value for generalized model of inheritance.
†P value for recessive model of inheritance.
‡CHD in a male first-degree relative before age 55 years or in a female first-degree relative before age 65 years.
§Metabolic syndrome was defined according to American Heart Association/National Heart, Lung, and Blood Institute 2005 criteria.

Methods

Details of JUPITER, a randomized, double-blind, placebo-controlled trial evaluating rosuvastatin 20 mg in the prevention of first-ever cardiovascular events among men and women free of diabetes or prior cardiovascular disease that was conducted between 2003 and 2008 in 26 countries worldwide, have been presented elsewhere. The primary eligibility criteria for JUPITER were a low level of LDLc (<130 mg/dL) and an elevated level of high-sensitivity C-reactive protein (hsCRP) (≥2 mg/L). All participants were followed prospectively for the trial primary end point (nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death) and for all-cause mortality. All components of the trial primary end point were adjudicated by an independent Endpoints Committee unaware of randomized treatment assignment. Analyses of total mortality included any reported death, regardless of whether cause of death could be ascertained from available medical records. As previously reported, after a median follow-up of 1.9 years (maximum, 5 years), rosuvastatin use was associated with a 44% reduction in the trial primary end point.

Table 2. Change in LDLC, HDLC, Triglycerides, and hsCRP With Rosuvastatin Among Caucasian Participants in the JUPITER Trial According to KIF6 Genotype

<table>
<thead>
<tr>
<th>Genotype*</th>
<th>Trp/Trp</th>
<th>Trp/Arg</th>
<th>Arg/Arg</th>
<th>P†</th>
<th>Trp/Arg or Arg/Arg</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LDLC, mg/dL</td>
<td>109.0 (95.0–119.0)</td>
<td>110.0 (98.0–120.0)</td>
<td>110.0 (95.0–119.0)</td>
<td>0.01</td>
<td>110.0 (97.0–120.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>On-treatment LDLC, mg/dL</td>
<td>52.0 (42.0–63.0)</td>
<td>52.0 (42.0–64.5)</td>
<td>51.0 (42.0–63.0)</td>
<td>0.08</td>
<td>52.0 (42.0–64.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>% Change in LDLC</td>
<td>−51.5 (−59.0 to −40.0)</td>
<td>−51.4 (−60.2 to −41.2)</td>
<td>−51.8 (−59.4 to −41.3)</td>
<td>0.25</td>
<td>−51.7 (−60.0 to −41.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>Baseline HDLC, mg/dL</td>
<td>49.0 (40.0–59.0)</td>
<td>49.0 (40.1–60.0)</td>
<td>50.0 (42.0–61.0)</td>
<td>0.09</td>
<td>50.0 (41.0–60.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>On-treatment HDLC, mg/dL</td>
<td>53.0 (44.0–64.0)</td>
<td>53.0 (44.0–65.0)</td>
<td>52.0 (44.0–66.0)</td>
<td>0.72</td>
<td>53.0 (44.0–65.0)</td>
<td>0.44</td>
</tr>
<tr>
<td>% Change in HDLC</td>
<td>−7.4 (−19.1–17.9)</td>
<td>−6.3 (−22.2–16.7)</td>
<td>−5.6 (−3.7–17.6)</td>
<td>0.14</td>
<td>−6.2 (−2.3–16.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Baseline triglyceride, mg/dL</td>
<td>118.0 (86.0–172.0)</td>
<td>118.0 (84.0–166.0)</td>
<td>110.0 (83.0–167.0)</td>
<td>0.14</td>
<td>117.0 (84.0–166.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>On-treatment triglyceride, mg/dL</td>
<td>98.0 (74.0–136.0)</td>
<td>97.0 (73.0–133.0)</td>
<td>100.0 (71.5–135.0)</td>
<td>0.39</td>
<td>97.0 (73.0–134.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>% Change in triglyceride, mg/dL</td>
<td>−17.5 (−34.3–2.7)</td>
<td>−16.3 (−33.9–3.8)</td>
<td>−14.3 (−32.5–8.5)</td>
<td>0.08</td>
<td>−15.9 (−33.7–4.7)</td>
<td>0.13</td>
</tr>
<tr>
<td>Baseline hsCRP, mg/L</td>
<td>4.1 (2.8–6.7)</td>
<td>4.0 (2.7–6.3)</td>
<td>4.0 (2.7–6.4)</td>
<td>0.50</td>
<td>4.0 (2.7–6.4)</td>
<td>0.29</td>
</tr>
<tr>
<td>On-treatment hsCRP, mg/L</td>
<td>2.0 (1.2–3.7)</td>
<td>2.0 (1.2–3.9)</td>
<td>1.9 (1.1–3.6)</td>
<td>0.64</td>
<td>2.0 (1.2–3.8)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Values are median (interquartile range).
*Among those compliant at 12 months.
†P value for generalized model of inheritance.
‡P value for recessive model of inheritance.
As anticipated and consistent with prior data, the carrier rate for the \textit{KIF6} 719Arg allele was higher among self-reported black participants (97\%) than among self-reported Hispanic (58\%) or Caucasian participants (58\%). Thus, as specified on an a priori basis to avoid issues of population stratification, we conducted our initial analysis among Caucasian participants only. Table 1 presents baseline clinical characteristics of these individuals according to genotype. As shown, there were no substantive differences according to genotype for any of the major cardiovascular risk factors at study entry.

### Results

As anticipated and consistent with prior data,\(^9\) the carrier rate for the \textit{KIF6} 719Arg allele was higher among self-reported black participants (97\%) than among self-reported Hispanic (58\%) or Caucasian participants (58\%). Thus, as specified on an a priori basis to avoid issues of population stratification, we conducted our initial analysis among Caucasian participants only. Table 1 presents baseline clinical characteristics of these individuals according to genotype. As shown, there were no substantive differences according to genotype for any of the major cardiovascular risk factors at study entry.

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### Table 3. Efficacy of Rosuvastatin on Trial Outcomes According to \textit{KIF6} Genotype Among Caucasian Participants in the JUPITER Trial Who Provided Consent for Genetic Analyses

<table>
<thead>
<tr>
<th>End Point</th>
<th>Trp/Trp (n=3717)</th>
<th>Trp/Arg (n=4023)</th>
<th>Arg/Arg (n=1041)</th>
<th>Trp/Arg or Arg/Arg (n=5064)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point*</td>
<td>n</td>
<td>103</td>
<td>99</td>
<td>32</td>
</tr>
<tr>
<td>Placebo event rate</td>
<td>HR</td>
<td>0.59</td>
<td>0.62</td>
<td>0.56</td>
</tr>
<tr>
<td>Rosuvastatin event rate</td>
<td>95% CI</td>
<td>(0.39–0.88)</td>
<td>(0.42–0.94)</td>
<td>(0.27–1.15)</td>
</tr>
<tr>
<td>P</td>
<td>0.009</td>
<td>0.023</td>
<td>0.11</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*p-interaction for a differential drug effect by genotype (recessive model)=0.90*
Baseline and on-treatment levels of LDLC were similar in all genotype groups such that a 52% reduction in LDLC was observed among both carriers and noncarriers of the KIF6 719Arg allele. Similarly, no clinically meaningful differences in baseline or on-treatment levels of HDLC, triglycerides, or hsCRP were observed according to genotype (Table 2).

Among Caucasians, rates of incident cardiovascular events were similar among carriers and noncarriers of the KIF6 719Arg allele; for the trial primary end point, the hazard ratio (HR) for carriers as compared with noncarriers among those allocated to placebo was 0.91 (95% confidence interval [CI], 0.66 to 1.26) (Table 3). In models not assuming a recessive pattern of inheritance, the HRs for developing the trial primary end point for the 3 genotype groups were 1.0, 0.85, and 1.3 with no significant effect on a per allele additive basis (HR per Arg allele, 1.0; 95% CI, 0.79 to 1.27; P=0.99). Comparable HRs for developing the trial primary end point as well as total mortality for the 3 respective genotypes were 1.0, 0.92, and 1.10, again with no significant effect on a per allele additive basis (HR per Arg allele, 1.0; 95% CI, 0.83 to 1.23; P=0.93).

As also shown in Table 3 and in the Figure, among the Caucasians, rosuvastatin allocation was associated with an almost identical reduction in the trial primary end point among carriers (HR, 0.61; 95% CI, 0.43 to 0.87) as among noncarriers (HR, 0.59; 95% CI, 0.39 to 0.88); the probability value for the test of interaction between drug effect and genotype assuming a recessive pattern of inheritance was 0.90. In comparable analyses using a generalized model of inheritance, the probability value for the test of interaction between drug effect and genotype was 0.99. These effects were similar in analyses that additionally included total mortality.

We repeated these analyses for all members of the JUPITER trial cohort who provided genetic consent and had adequate DNA available for KIF6 genotyping. As shown in Table 4, observations regarding the KIF6 genotype and outcomes for the total JUPITER cohort were virtually identical to that observed in the prespecified subgroup of Caucasian participants. Specifically, after adjusting for race, for the trial primary end point we found no evidence of a statistically significant difference in event reduction with rosuvastatin according to carrier status (P-interaction for the total cohort using a recessive model=0.71, P-interaction using a generalized inheritance model=0.45). Similarly, for the end point that also included total mortality, the probability values for interaction using recessive and generalized models were 0.42 and 0.27, respectively.

None of these effects were altered in analyses that further adjusted for the small differences in sex, obesity, or metabolic syndrome observed at baseline between the genotype groups, or after additional control for LDL and HDL cholesterol.

**Discussion**

In the randomized JUPITER primary prevention trial evaluating rosuvastatin 20 mg and placebo, carriers of the KIF6 719Arg allele did not have a higher frequency of vascular events nor a substantive difference in lipid or hsCRP reduction when compared with noncarriers. Further, we observed that rosuvastatin was equally effective at reducing incident vascular events among those with and without the KIF6
patients, at least in theory these entry criterion and trial differences might explain apparent differences in outcome.

Third, the possibility that the earlier findings were reflective of the play of chance needs consideration; a formal test for interaction of the effects of the KIF6 genotype on pravastatin efficacy was modestly significant in the WOSCOPS analysis but not in CARE or PROSPER. Further, unlike our study, which focused on KIF6 as a potential candidate gene and thus was hypothesis testing, the prior data from CARE and WOSCOPS identified KIF6 as a potential genetic effect modifier as part of a study evaluating many genetic polymorphisms. As such, the prior data must appropriately be considered as hypothesis generating and in theory could have reflected a difference in event rates among those allocated to placebo as much as a difference in event rates among those allocated to active statin therapy. Taken together, the accumulating data for KIF6 underscore the importance of external replication for findings of potential clinical relevance in the emerging field of pharmacogenetics.

As in any null study, a potential limitation of our analysis is the ability to detect true effects. In this regard, we observed considerable precision in our estimates of both absolute vascular risk and on the relative effects within those allocated to rosuvastatin and can thus exclude with confidence a wide range of clinically relevant effects. For example, although early work suggested that carriers of the KIF6 719Arg allele might have an increased risk of vascular events, carriers in our study had no such effect (HR, 0.91), with an upper-bound of the 95% CI of 1.26. Our null data are also consistent with recent null data on KIF6 and vascular risk from the Ottawa Heart Study, the Welcome Trust Case Control Consortium, and a recent meta-analysis, all of which suggest that the original estimates were overly optimistic. Similarly, we also had considerable precision with respect to our ability to describe true differences for KIF6 among those taking statin therapy; in an analysis limited to those allocated to rosuvastatin where 116 hard vascular end points accrued, the HR for carriers as compared with noncarriers was 1.01 (95% CI, 0.69 to 1.5) suggesting again that clinically relevant differences are unlikely to have been missed. Finally, our null data on LDLC reduction is fully consistent with prior studies in this arena. Although it has previously been suggested on this basis that the potential effect of KIF6 is therefore mediated through non-LDL effects of statin therapy, we also found no evidence of effect modification in our data for hscRP reduction according to genotype. We believe this to be a clinically important null finding as both LDLC and hsCRP have previously been shown to independently associate with reduced vascular event rates within both the JUPITER and PROVE IT trials.

In sum, in this hypothesis-testing evaluation, we observed virtually identical effects of rosuvastatin on event reduction among carriers and noncarriers of the KIF6 719Arg allele. As such, these prospective data from the JUPITER trial do not support the use of KIF6 genotyping as a method to determine absolute vascular risk nor relative statin efficacy.

### Sources of Funding

JUPITER was an investigator-initiated trial funded by Astra-Zeneca. Genotyping in the JUPITER trial was funded primarily by Astra-Zeneca with additional support from Celera, Inc.
Disclosures

Dr Ridker is listed as a coinventor on patents held by the Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease that have been licensed to Siemens and AstraZeneca and has served as a consultant to AstraZeneca. Drs Ridker and Chasman are coinventors on a patent not related to KIF6 that has been licensed to Celera.

References


CLINICAL PERSPECTIVE

Hypothesis-generating data raise the possibility that carriers of the kinesis-like protein 6 (KIF6) 719Arg allele preferentially benefit from statin therapy and on this basis a commercial assay for KIF6 is now being marketed. However, there have been no formal hypothesis testing data for KIF6 in the setting of primary prevention where “personalized medicine” and concerns regarding the net risk-to-benefit ratio for statin therapy are most relevant. We therefore evaluated the KIF6 genotype in the recently completed JUPITER trial, in which men and women free of cardiovascular disease were randomly allocated to rosuvastatin or placebo and followed for incident vascular events. Among 8781 Caucasian trial participants followed for up to 5 years, we observed no increase in vascular event rates among carriers of the KIF6 719Arg allele nor any difference in percent LDL cholesterol reduction with rosuvastatin according to genotype. Further, rosuvastatin was associated with an almost identical reduction in the trial primary end point among carriers as among noncarriers. Thus, at least for rosuvastatin, there appears to be no clinical utility to screening for KIF6 genotype as a method to determine vascular risk or to predict statin efficacy.
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