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.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00239681.

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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.

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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
Baseline Characteristic                        | Trp/Trp (n = 3717) | Trp/Arg (n = 4023) | Arg/Arg (n = 1041) | P*       | Trp/Arg or Arg/Arg (n = 5064) | P†       |
---|---|---|---|---|---|---|
Age, y                          | 66.0 (60.0–71.0) | 66.0 (60.0–71.0) | 65.0 (60.0–71.0) | 0.50 | 66.0 (60.0–71.0) | 0.92 |
Female, n (%)                    | 1213 (32.6) | 1317 (32.7) | 297 (28.5) | 0.03 | 1614 (31.9) | 0.45 |
Body mass index, kg/m²           | 28.6 (25.5–32.0) | 28.6 (25.5–32.1) | 28.7 (26.1–32.4) | 0.08 | 28.7 (25.8–32.2) | 0.10 |
Blood pressure, mm Hg            | Systolic 134.0 (124.0–145.0) | 134.0 (124.0–145.0) | 135.0 (126.0–146.0) | 0.06 | 134.0 (124.0–145.0) | 0.54 |
                                      Diastolic 80.0 (74.0–86.0) | 80.0 (74.0–85.0) | 80.0 (74.0–87.0) | 0.46 | 80.0 (74.0–86.0) | 0.78 |
Current smoking, n (%)           | 462 (12.4) | 556 (13.8) | 145 (13.9) | 0.15 | 701 (13.8) | 0.05 |
Family history of premature CHD, n (%) | 506 (13.7) | 577 (14.4) | 145 (13.9) | 0.15 | 701 (14.1) | 0.05 |
Metabolic syndrome,§ n (%)       | 1480 (40.1) | 1591 (39.9) | 375 (36.3) | 0.07 | 1966 (39.1) | 0.35 |
hsCRP, mg/L                      | 4.1 (2.8–6.7) | 4.1 (2.8–6.6) | 4.0 (2.7–6.4) | 0.79 | 4.1 (2.8–6.5) | 0.89 |
Total cholesterol, mg/dL         | 187.0 (172.0–201.0) | 187.0 (172.0–201.0) | 187.0 (171.0–200.0) | 0.69 | 187.0 (172.0–201.0) | 0.70 |
LDLC, mg/dL                     | 109 (96–120) | 110 (97–120) | 111 (96–120) | 0.78 | 110 (97–120) | 0.38 |
HDLC, mg/dL                     | 50.0 (41.0–60.0) | 50.0 (41.0–61.0) | 50.0 (41.0–61.0) | 0.45 | 50.0 (41.0–61.0) | 0.83 |
Triglycerides, mg/dL             | 117.0 (84.0–169.0) | 118.0 (85.0–166.0) | 114.0 (83.0–157.0) | 0.10 | 117.0 (84.0–164.0) | 0.39 |
Glucose, mg/dL                  | 95.0 (89.0–102.0) | 95.0 (88.0–102.0) | 95.0 (88.0–102.0) | 0.17 | 95.0 (88.0–102.0) | 0.06 |
HbA1c, %                        | 5.6 (5.4–5.8) | 5.6 (5.4–5.8) | 5.6 (5.4–5.9) | 0.47 | 5.6 (5.4–5.8) | 0.65 |

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.
§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 LDL <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.

| Baseline Characteristic | Trp/Trp (n = 3717) | Trp/Arg (n = 4023) | Arg/Arg (n = 1041) | P*       | Trp/Arg or Arg/Arg (n = 5064) | P†       |
---|---|---|---|---|---|---|
Baseline LDL, mg/dL        | 109.0 (95.0–119.0) | 110.0 (98.0–120.0) | 110.0 (95.0–119.0) | 0.01 | 110.0 (97.0–120.0) | 0.01 |
On-treatment LDL, mg/dL    | 52.0 (42.0–63.0) | 52.0 (42.0–64.5) | 51.0 (42.0–63.0) | 0.08 | 52.0 (42.0–64.0) | 0.83 |
% Change in LDL            | −51.5 (−59.0 to −40.0) | −51.4 (−60.2 to −41.2) | −51.8 (−59.4 to −41.3) | 0.25 | −51.7 (−60.0 to −41.3) | 0.11 |
Baseline HDLC, mg/dL       | 49.0 (40.0–59.0) | 49.0 (41.0–60.0) | 50.0 (42.0–61.0) | 0.09 | 50.0 (41.0–60.5) | 0.05 |
On-treatment HDLC, mg/dL   | 53.0 (44.0–64.0) | 53.0 (44.0–65.0) | 52.0 (44.0–66.0) | 0.72 | 53.0 (44.0–65.0) | 0.44 |
% Change in HDLC           | 7.4 (−1.9–17.9) | 6.3 (−2.2–16.7) | 5.6 (−3.7–17.6) | 0.14 | 6.2 (−2.3–16.7) | 0.07 |
Baseline triglyceride, mg/dL| 118.0 (86.0–172.0) | 118.0 (84.0–166.0) | 110.0 (83.0–167.0) | 0.14 | 117.0 (84.0–166.0) | 0.08 |
On-treatment triglyceride, mg/dL | 98.0 (74.0–136.0) | 97.0 (73.0–133.0) | 100.0 (71.5–135.0) | 0.39 | 97.0 (73.0–134.0) | 0.27 |
% Change in triglyceride, mg/dL | −17.5 (−34.3–2.7) | −16.3 (−33.9–3.8) | −14.3 (−32.5–8.5) | 0.08 | −15.9 (−33.7–4.7) | 0.13 |
Baseline hsCRP, mg/L        | 4.1 (2.8–6.7) | 4.0 (2.7–6.3) | 4.0 (2.7–6.4) | 0.50 | 4.0 (2.7–6.4) | 0.29 |
On-treatment hsCRP, mg/L    | 2.0 (1.2–3.7) | 2.0 (1.2–3.9) | 1.9 (1.1–3.6) | 0.64 | 2.0 (1.2–3.8) | 0.97 |
% Change in hsCRP           | −52.9 (−69.3 to −22.2) | −48.9 (−68.7 to −20.0) | −54.3 (−73.3 to −21.9) | 0.07 | −50.0 (−69.8 to −20.5) | 0.42 |

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.
a 54% reduction in myocardial infarction, a 48% reduction in stroke, a 46% reduction in revascularization, a 43% reduction in venous thromboembolism, and a 20% reduction in total mortality.8,10

As part of the JUPITER protocol, 12,648 participants provided consent for genetic analyses, had DNA available for genotyping, and had successful evaluation of the KIF6 polymorphism (rs20455) as part of a genome-wide scan conducted using the Illumina 1 mol/L OmniQuad platform. Briefly, raw genotype intensity data were reduced to genotype calls using the Illumina Genome Studio (v. 1.6.2) software (Illumina, San Diego, CA). Single-nucleotide polymorphism clusters were initially defined automatically, but single-nucleotide polymorphisms identified for poor clustering on the basis of the ABrMean (intensity) parameter, cluster separation measures, deviation from Hardy-Weinberg equilibrium, or call frequency were retained in the final data if the updated clusters met quality standards and the genotyping was successful in ≈98.5% of the samples. Of these, 12,648 trial participants, 8,781 (69%) self-reported ethnicity as Caucasian and had this confirmed by an analysis of panels of other ancestry informative polymorphisms. Using post hoc identity by descent estimates of inheritance, we found 16 individuals in our study who appeared to have a sibling included in the cohort.

On an a priori basis, and as done in all of the hypothesis-generating studies,1,2 primary comparisons were made between carriers of the KIF6 719Arg allele (Arg/Arg homozygotes and Arg/Trp heterozygotes) and noncarriers of the KIF6 719Arg allele (Trp/Trp homozygotes). In addition to this recessive model of inheritance, additional analyses were conducted using generalized models of inheritance using unordered comparisons across the 3 genotype groups (Trp/Trp, Trp/Arg, Arg/Arg). Initial analyses compared distributions of baseline cardiovascular risk factors between carriers and noncarriers (secondarily across the 3 groups formed by the number of Arg alleles) via a χ² test for discrete characteristics or a Wilcoxon rank-sum test for continuous characteristics (secondarily by a Kruskal-Wallis test for 3 groups). Analyses of the impact of KIF6 on rosuvastatin treatment compared percent changes in LDL and HDL cholesterol, triglycerides, and hsCRP between 2040 carriers and 1513 noncarriers of the Arg allele among Caucasian subjects who appeared to have a sibling included in the cohort. As shown, there were no substantive differences according to genotype for any of the major cardiovascular risk factors at study entry.

<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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>103</td>
<td>99</td>
<td>32</td>
<td>131</td>
</tr>
<tr>
<td>Placebo event rate</td>
<td>1.50</td>
<td>1.28</td>
<td>1.71</td>
<td>1.37</td>
</tr>
<tr>
<td>Rosuvastatin event rate</td>
<td>0.88</td>
<td>0.80</td>
<td>0.93</td>
<td>0.83</td>
</tr>
<tr>
<td>HR</td>
<td>0.59</td>
<td>0.62</td>
<td>0.56</td>
<td>0.61</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.39–0.88)</td>
<td>(0.42–0.94)</td>
<td>(0.27–1.15)</td>
<td>(0.43–0.87)</td>
</tr>
<tr>
<td>P</td>
<td>0.009</td>
<td>0.023</td>
<td>0.11</td>
<td>0.006</td>
</tr>
<tr>
<td>P-interaction for a differential drug effect by genotype (recessive model)=0.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point+ total mortality</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>154</td>
<td>163</td>
<td>48</td>
<td>211</td>
</tr>
<tr>
<td>Placebo event rate</td>
<td>2.20</td>
<td>2.02</td>
<td>2.44</td>
<td>2.11</td>
</tr>
<tr>
<td>Rosuvastatin event rate</td>
<td>1.35</td>
<td>1.42</td>
<td>1.52</td>
<td>1.44</td>
</tr>
<tr>
<td>HR</td>
<td>0.62</td>
<td>0.70</td>
<td>0.69</td>
<td>0.69</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.45–0.85)</td>
<td>(0.51–0.96)</td>
<td>(0.36–1.15)</td>
<td>(0.52–0.90)</td>
</tr>
<tr>
<td>P</td>
<td>0.003</td>
<td>0.025</td>
<td>0.14</td>
<td>0.007</td>
</tr>
<tr>
<td>P-interaction for a differential drug effect by genotype (recessive model)=0.62</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>P-interaction for a differential drug effect by genotype (generalized model)=0.75</td>
<td></td>
<td></td>
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</tbody>
</table>

Rates are per 100 person-years.

The Primary JUPITER end point was nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina or coronary revascularization, or cardiovascular death.

P values in each column reflect tests for significance between rosuvastatin and placebo within a given genotype group.

P values for interaction reflect the test for significance of a drug effect across the genotype groups, using either recessive or generalized models.

Secondary analyses were performed using the additional end point of all-cause mortality. All analyses were then repeated in the total study population, adjusting for race. Additionally, all analyses were repeated with further adjustment for sex, obesity, metabolic syndrome, LDL, and HDL cholesterol. All probability values reported are 2-sided; all confidence intervals computed at the 95% level, and all analyses conducted using SAS version 9.1.

The JUPITER trial protocol was designed and written by the study chair (P.M.R.) and approved by the local institutional review board at each participating center. The JUPITER trial and its genotyping were financially supported by Astra-Zeneca; additional funds to support analyses of KIF6 were provided by Celera. Neither of these sponsors played a role in the conduct of these analyses, in the drafting of this manuscript, or in the decision to submit these analyses for publication.

Results

As anticipated and consistent with prior data,9 the carrier rate for the 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.
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 \textit{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 \textit{KIF6} 719 Arg 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 \textit{KIF6} genotyping. As shown in Table 4, observations regarding the \textit{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 \textit{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 \textit{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 \textit{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 \textit{KIF6} as a potential candidate gene and thus was hypothesis testing, the prior data from CARE and WOSCOPS identified \textit{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 \textit{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 \textit{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 \textit{KIF6} and vascular risk from the Ottawa Heart Study, the Welcome Trust Case Control Consortium, and a recent meta-analysis,\textsuperscript{1-6} 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 \textit{KIF6} among those taking statin therapy; in an analysis limited to those allocated to active statin therapy. Taken together, the accumulating data for \textit{KIF6} underscore the importance of external replication for findings of potential clinical relevance in the emerging field of pharmacogenetics.

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**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. 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 kinesin-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 rosvuastatin 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 reduction with rosvuastatin according to genotype. Further, rosvuastatin was associated with an almost identical reduction in the trial primary end point among carriers as among noncarriers. Thus, at least for rosvuastatin, there appears to be no clinical utility to screening for KIF6 genotype as a method to determine vascular risk or to predict statin efficacy.
Kinesin-Like Protein 6 (KIF6) Polymorphism and the Efficacy of Rosuvastatin in Primary Prevention
Paul M Ridker, Jean G. MacFadyen, Robert J. Glynn and Daniel I. Chasman

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