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No Impact of *KIF6* Genotype on Vascular Risk and Statin Response Among 18,348 Randomized Patients in the Heart Protection Study

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Objectives The aim of this study was to test the effects of the *KIF6* Trp719Arg polymorphism (rs20455) on vascular risk and response to statin therapy in 18,348 participants from the Heart Protection Study.

Background There have been claims that noncarriers of the *KIF6* 719Arg variant receive little benefit from statin therapy. Screening for this genetic variant is now being used to influence statin use.

Methods Participants received 40 mg simvastatin daily for 4 to 6 weeks before being randomly allocated 40 mg simvastatin daily or placebo for 5 years. Major coronary event was pre-defined as coronary death or nonfatal myocardial infarction, and major vascular event was pre-defined as major coronary event plus revascularization or stroke.

Results The *KIF6* genotype was not significantly associated, among placebo-allocated participants, with the risks of incident major vascular events, major coronary events, revascularizations, or strokes. Overall, 40 mg simvastatin daily produced a 42% reduction in low-density lipoprotein cholesterol, which did not differ significantly by *KIF6* 719Arg carrier status ($p = 0.51$). Proportional reductions in the risk of major vascular events with statin therapy were similar (interaction $p = 0.70$) and highly significant across *KIF6* genotypes: 23% (95% confidence interval: 16% to 29%; $p = 5.3 \times 10^{-10}$) in carriers (Arg/Arg or Trp/Arg), and 24% (95% confidence interval: 17% to 31%; $p = 4.6 \times 10^{-9}$) in noncarriers (Trp/Trp). A similar lack of interaction was observed for major coronary events, revascularizations, and strokes considered separately.

Conclusions Statin therapy significantly reduces the incidence of coronary and other major vascular events to a similar extent, irrespective of *KIF6* genotype. Consequently, the use of *KIF6* genotyping to guide statin therapy is not warranted. (Heart Protection Study; ISRCTN48489393) (J Am Coll Cardiol 2011;57:2000–7) © 2011 by the American College of Cardiology Foundation

Statins are a widely prescribed, well-tolerated, and effective approach to lowering blood concentrations of low-density lipoprotein cholesterol (LDL-C) and the risk of vascular events. Standard statin regimens typically reduce LDL-C concentrations by approximately 60 mg/dl (1.5 mmol/l) and the risks of myocardial infarction (MI), revascularization, and stroke by approximately one-third (1–3). Moreover, large-scale randomized trials have demonstrated similar proportional reductions in the risks of vascular events across a wide variety of patients (1–3). Interest in personalized medicine has resulted in efforts to identify genetic variants that influence response to medications (4,5), including statins (6–10). The effects of a few treatments have been shown to vary by genotype (11), but it is important that any claims of differential response are reliably tested to avoid patients being wrongly denied effective therapy.

Some studies have suggested that carriers of the 719Arg variant in *KIF6* (which encodes kinesin-like protein 6) might have as much as a 50% higher risk of vascular events than noncarriers (12–17). In addition, 4 randomized trials

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involving a total of 1,521 incident vascular events have generated the hypothesis that *KIF6* genotype influences vascular risk response to statin therapy (13,18,19). In those trials, noncarriers of the *KIF6* 719Arg variant seemed not to benefit significantly from statin therapy, whereas risk was reduced by between one-third and one-half among carriers. A significant interaction between *KIF6* genotype and the effect of statin therapy on vascular events was reported in the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) (adjusted p = 0.02) and WOSCOPS (West of Scotland Coronary Prevention Study) studies (adjusted p = 0.01) but not in the CARE (Cholesterol And Recurrent Events) (adjusted p = 0.39) or PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) studies (adjusted p = 0.09). A recent update from the CARE study, including nonwhites and all coronary deaths in the outcome, still showed a nonsignificant (adjusted p = 0.14) interaction (20).

The *KIF6* gene is a member of the superfamily of motor protein kinesins that are involved in intracellular transport (21,22), but the biological plausibility for vascular risk or statin response is uncertain (23). The LDL-C reduction is considered to be the main mechanism by which statins reduce vascular risk (2,3), but *KIF6* genotype does not seem to influence the LDL-C reduction produced by statin therapy (18,19). Hence, it has been suggested that any differential effect of statins on vascular risk produced by *KIF6* genotype might be acting through other mechanisms (19). These claims of a differential response to statin therapy have prompted the marketing of *KIF6* screening to assess the suitability of statins for individual patients (24). For example, it is asserted that only 10 carriers with acute coronary syndrome would require treatment with statin therapy to avoid a single coronary event, compared with 125 noncarriers (19,25). Similarly, for patients with stable coronary disease, it is claimed that the number needed to treat to prevent 1 coronary event is only 16 for carriers compared with 83 for noncarriers (26).

The HPS (Heart Protection Study) of 40 mg simvastatin daily versus placebo in over 20,000 randomized patients involved considerably more incident vascular events (n = 4,185) than the combination of all of the trials that suggested that *KIF6* genotype might influence the effects of statin therapy (1). Hence, it provides an opportunity to test this hypothesis reliably.

Methods

Study recruitment and follow-up. Details of the HPS study have been reported previously (1,27). Between 1994 and 1997, 20,536 men and women 40 to 80 years of age were recruited in the United Kingdom with ethics committee approval. Individuals were eligible provided they had blood total cholesterol concentrations of at least 135 mg/dl (3.5 mmol/l) and a previous diagnosis of coronary, cerebrovascular, or other occlusive disease of noncoronary arteries, or diabetes mellitus, or (if men at least 65 years of age) treated hypertension. At the initial screening visit, all participants provided written consent and began a "run-in" phase involving 4 weeks of placebo followed by 4 to 6 weeks of 40 mg simvastatin daily, after which compliant and eligible individuals were randomly allocated 40 mg simvastatin daily or placebo for a mean of approximately 5 years. A nonfasting blood sample was taken at screening (before starting statin therapy) and at the end of run-in (while receiving 40 mg simvastatin daily).

Abbreviations and Acronyms

CI = confidence interval
LDL-C = low-density lipoprotein cholesterol
MI = myocardial infarction
RR = risk ratio

The pre-specified outcomes of interest for assessing the effect of statin therapy in different subgroups were the first occurrence after randomization of incident major coronary events (defined as coronary death or nonfatal MI) and of incident major vascular events (defined as major coronary events, coronary or noncoronary revascularizations, or strokes) (1). Further details of outcome ascertainment and adjudication are reported elsewhere (1,27).

Genotyping assays. Extraction of deoxyribonucleic acid from stored white cells and genotyping was carried out at the Centre National de Genotypage in Evry, France. Genotypes of the *KIF6* Trp719Arg polymorphism (rs20455) were available from the Illumina 610K-Quad panel for 3,894 of 3,895 randomly selected white participants after quality control exclusions based on discrepant sex, repeat samples, poor success rate (<95%), and nonwhite ethnic origin. A further 14,454 participants of self-reported white ethnicity were successfully genotyped for this variant with a custom I.PLEX panel run on samples from 14,481 individuals. Combined, *KIF6* genotypes were available for 18,348 white participants and were consistent with Hardy-Weinberg equilibrium (p = 0.09).

Statistical methods. Differences between baseline characteristics were assessed by analysis of variance for continuous variables and by chi-square statistics for categorical variables and reported as 2-sided p values. Linear regression was used to estimate the effects of *KIF6* on LDL-C response to statin by considering the difference in $\log_e$ LDL-C levels at the screening visit before starting statin and at the randomization visit after 4 to 6 weeks on simvastatin in compliant individuals who were then randomized. Cox proportional hazard models were used to assess the association of *KIF6* with the risk of incident disease and the effects of *KIF6* on the risk response to statin. The impact of *KIF6* on outcomes was tested primarily in a dominant genetic model (p_{dom}) comparing Arg/Arg plus Trp/Arg (719Arg "carriers") versus Trp/Trp ("noncarriers"), as emphasized in the "hypothesis-generating" studies (13,18,19). The p values were also obtained for: the additive effect (p_{add}) per 719Arg allele; and genotypic effect (p_{geno}) comparing Arg/Arg versus Trp/Arg versus Trp/Trp. Analyses were performed with SAS software (version 9.1, SAS Institute, Cary, North Carolina),

and figures were generated with R software (version 2.10.1, The R foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics. The frequency of the *KIF6* 719Arg allele in the HPS study was 35% and 58% of the 18,348 genotyped participants had 719Arg "carrier" genotypes (Trp/Arg or Arg/Arg), consistent with previous studies (13,18,19). Selected characteristics at baseline did not differ materially by *KIF6* genotype (Table 1). Among simvastatin-allocated participants, compliance with study tablets (≥80% taken) ranged from 89% at the end of the first year of follow-up to 80% at the end of the fifth year, yielding an average during the study of 84% that did not differ by *KIF6* genotype (p = 0.99). Among those allocated placebo, 4% at the end of the first year of follow-up but 33% at the end of the fifth year were taking nonstudy statin therapy, yielding an average of 17% that also did not differ by *KIF6* genotype (p = 0.89). The average difference between these groups in the use of a statin was approximately 67% (84% minus 17%), and hence the "intention-to-treat" randomized comparisons assess the effects of approximately two-thirds of simvastatin-allocated participants actually taking 40 mg simvastatin daily.

Vascular event risk by *KIF6* genotype. The association of *KIF6* with the risk of incident vascular events in the HPS study was assessed in 9,181 placebo-allocated participants to minimize any potential influence of statin therapy. During mean follow-up of 5 years, 1,086 individuals had a major coronary event, 1,069 had a revascularization procedure, and 547 had a stroke, yielding first major vascular events among 2,335 participants. Figure 1 shows that there was no significant effect of *KIF6* genotype on the risk of major vascular events, irrespective of the modeling approach used (p_{dom} = 0.54; p_{add} = 0.46; p_{geno} = 0.76), or on any of the components of this endpoint. Adjustment for additional covariates did not alter the results materially (data not shown).

LDL-C response to statin therapy by *KIF6* genotype. Among the 18,343 genotyped participants in the HPS study with LDL-C measurements available, mean (SE) plasma LDL-C concentration at the initial screening visit ("off-statin") was 130.2 (0.23) mg/dl and did not differ by *KIF6* genotype (Table 2). After compliance with 40 mg simvastatin daily ("on-statin") during the pre-randomization run-in phase, the mean plasma LDL-C concentration in genotyped participants was 76.6 (0.18) mg/dl and again did not differ by *KIF6* genotype. Mean LDL-C concentration was reduced by 42.3% (95% confidence interval [CI]: 42.1% to 42.5%), with no impact of *KIF6* genotype on the LDL-C response to simvastatin (p_{dom} = 0.51; p_{add} = 0.50; p_{geno} = 0.79). During mean post-randomization follow-up of 5 years, there was a 30% reduction in LDL-C among participants who had been randomly allocated 40 mg simvastatin daily compared with those allocated placebo (reflecting the average difference of two-thirds in statin use), again with no impact of *KIF6* genotype (p = 0.52).

Vascular event risk response to statin by *KIF6* genotype. Among the genotyped participants in the HPS study, random allocation to 40 mg simvastatin daily reduced the relative risk of major vascular event by 23% (95% CI: 19% to 28%) (Fig. 2). The proportional reductions in the risk of major vascular events were similar, irrespective of *KIF6* genotype: 23% (95% CI: 16% to 29%) in 719Arg carriers versus 24% (95% CI: 17% to 31%) in noncarriers, with no significant interaction (p_{dom} = 0.70; p_{add} = 0.40; p_{geno} = 0.51). The previously reported "hypothesis-generating" randomized trials focused chiefly on coronary events (variously defined) (13,18,19), but the "hypothesis-testing" HPS study again found no evidence that the relative reduction in major coronary events was affected by *KIF6* genotype: 25% (95%

Table 1 Characteristics of Participants in the Heart Protection Study by *KIF6* Trp719Arg (rs20455) Genotype

Characteristic	*KIF6* 719 Genotype			p Value	
	Arg/Arg	Trp/Arg	Trp/Trp	Dominant p Value	Genotypic p Value
Patients	2,359	8,291	7,698		
Men	1,776 (75.3)	6,227 (75.1)	5,775 (75.0)	0.85	0.97
Age, yrs	63.9 (8.4)	64.0 (8.4)	64.3 (8.3)	0.04	0.09
Smoking					
Never smoked	568 (24.1)	2,062 (24.9)	1,842 (23.9)	0.23	0.36
Ex-smoker	1,466 (62.1)	5,053 (61.0)	4,748 (61.7)	0.52	0.47
Current smoker	325 (13.8)	1,176 (14.2)	1,108 (14.4)	0.57	0.75
Diabetes	662 (28.1)	2,329 (28.1)	2,166 (28.1)	0.94	0.99
Hypertension	957 (40.6)	3,408 (41.1)	3,194 (41.5)	0.49	0.71
Body mass index, kg/m^2	27.7 (4.4)	27.5 (4.3)	27.7 (4.5)	0.04	0.03
Prior disease					
Prior myocardial infarction	945 (40.1)	3,505 (42.3)	3,203 (41.6)	0.81	0.15
Other coronary heart disease	606 (25.7)	1,974 (23.8)	1,812 (23.5)	0.28	0.09
No coronary heart disease	808 (34.3)	2,812 (33.9)	2,683 (34.9)	0.22	0.46

Values are mean (SD) for continuous variables and n (%) for categorical variables. Dominant p value is test of difference between 719Arg carriers (Arg/Arg+Arg/Trp) and noncarriers (Trp/Trp). Genotypic p value is test of difference among Arg/Arg and Trp/Arg and Trp/Trp.

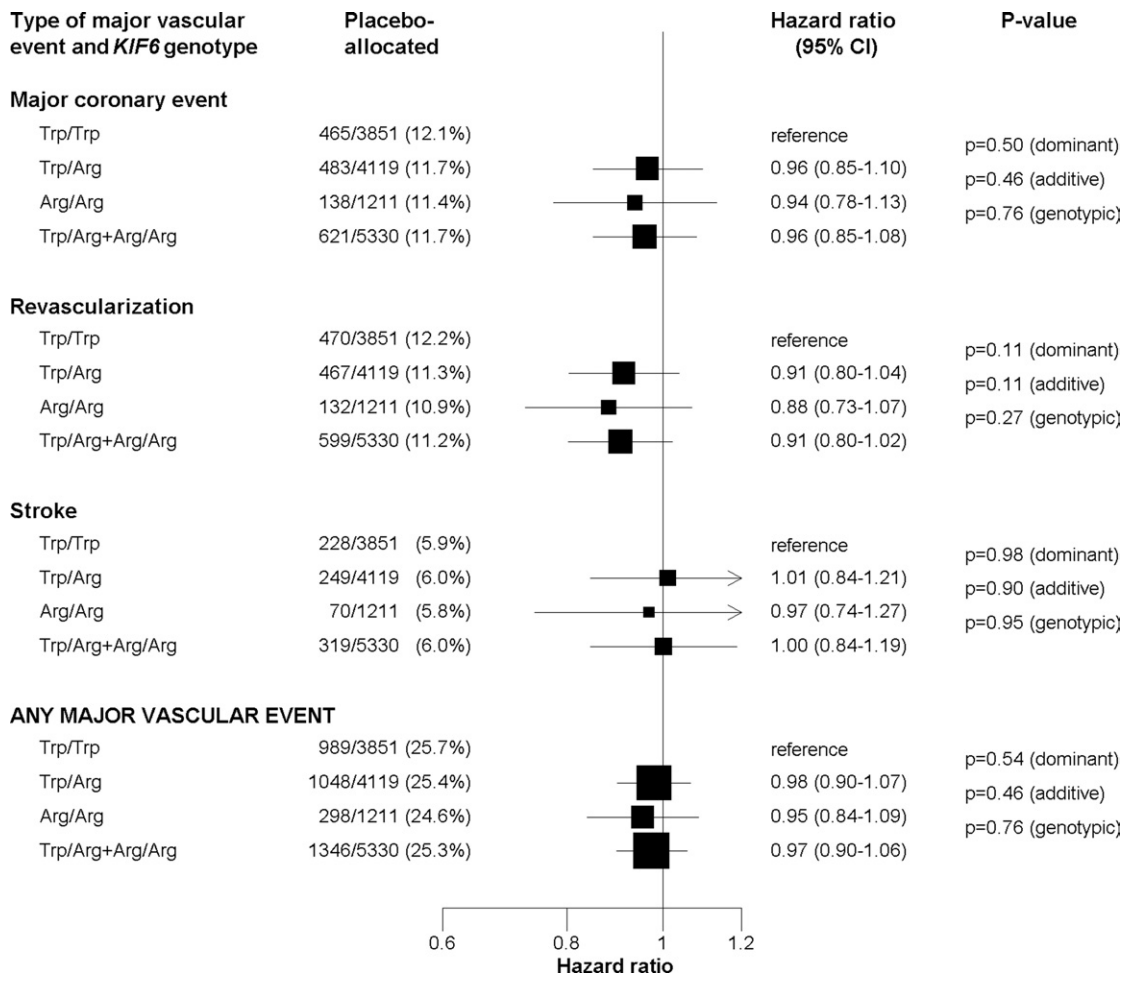

Figure 1 **Association of *KIF6* Genotype With Major Vascular Events Among Placebo-Allocated Participants**

Hazard ratios for each genotype are indicated by **squares** (size inversely proportional to variance) with **horizontal lines** indicating 95% confidence intervals (CIs).

CI: 16% to 34%) in 719Arg carriers versus 28% (95% CI: 18% to 38%) in noncarriers. Likewise, there was no evidence of any differential effect of simvastatin by *KIF6* genotype on the need for revascularization or risk of stroke considered separately (after allowance for the number of comparisons). Adjustment for additional covariates did not alter the results materially (data not shown).

Comparisons with previous trials of statin response by *KIF6* genotype. Figure 3 compares the observed effects of statin therapy on vascular events by *KIF6* genotype in

Table 2 **Pre-Randomization LDL-C and LDL-C Response to Simvastatin in the Heart Protection Study by *KIF6* Trp719Arg (rs20455) Genotype**

KIF6 Genotype	n	LDL-C (mg/dl) Mean (SE)		LDL-C Reduction % (95% CI)	p Value for Interaction (Statin × Genotype)*
		Off-Statin	On-Statin		
719 Trp/Trp	7,696	130.2 (0.36)	76.6 (0.28)	42.3 (42.0–42.6)	
719 Trp/Arg	8,290	130.2 (0.34)	76.6 (0.27)	42.4 (42.1–42.7)	0.51 (dominant)
719 Arg/Arg	2,357	130.5 (0.64)	76.8 (0.51)	42.4 (41.8–42.9)	0.50 (additive)
719 Arg carriers	10,647	130.2 (0.30)	76.6 (0.24)	42.4 (42.1–42.6)	0.79 (genotypic)
Overall	18,343	130.2 (0.23)	76.6 (0.18)	42.3 (42.1–42.5)	

Off-statin measurements are taken at screening; on-statin measurements are taken after 4 to 6 weeks of pre-randomization treatment with 40 mg simvastatin daily. *The p value from model adjusted for age, age^2, sex, and age × sex interaction.

LDL-C = low-density lipoprotein cholesterol.

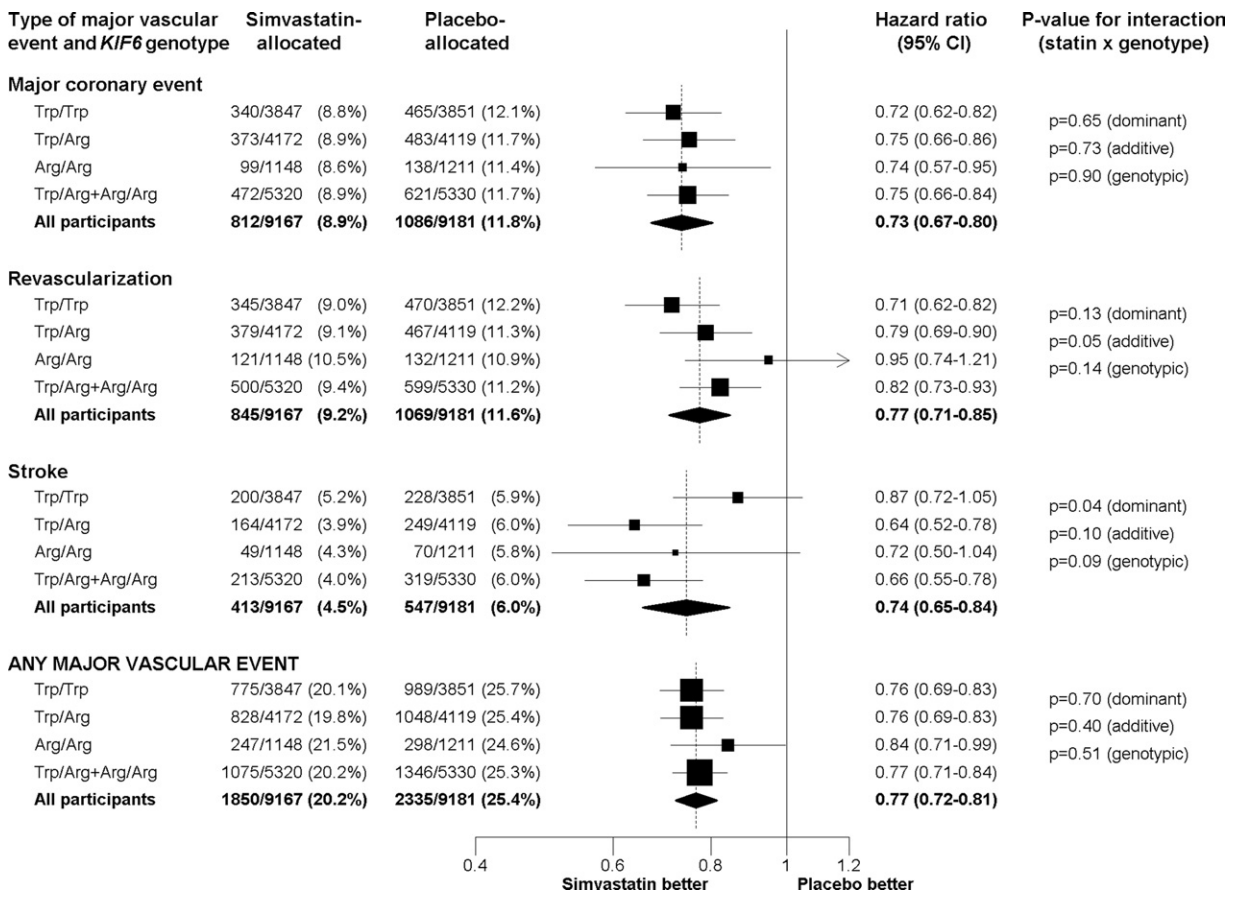

Figure 2 **Effects of Simvastatin on Major Vascular Events by *KIF6* Genotype**

Conventions as for Figure 1. Hazard ratios and 95% confidence intervals (CIs) for all participants combined are indicated by **diamonds**.

the "hypothesis-generating" trials (13,18,19) and in the present analysis of "hypothesis-testing" HPS (which involved approximately 3 times as many vascular events as in all of the previous trials combined). In the "hypothesis-generating" trials, the statin benefits seemed to be greater in *KIF6* carriers (weighted carrier to noncarrier ratio of RRs: 0.64; 95% CI: 0.51 to 0.79), but this trend chiefly reflects differences between the carrier versus noncarrier vascular event rates in the control arm rather than differences among participants allocated statin. By contrast, in the HPS study, vascular event rates were very similar in carriers and noncarriers, both among those allocated placebo (25.3% and 25.7%, respectively) and among those allocated simvastatin (20.2% and 20.1%, respectively). Consequently, the relative reduction in risk with allocation to simvastatin in the HPS study was similar, irrespective of genotype (carrier to noncarrier ratio of RRs: 1.02) and, given the large numbers of events on which this test of the hypothesis is based, was not consistent with there being much difference in the size of the risk reduction (95% CI: 0.91 to 1.16).

Discussion

The present large-scale test using the HPS randomized trial does not confirm the hypothesis that *KIF6* genotype is importantly relevant either to the overall risk of vascular events or to the effects of statin therapy on vascular risk.

The most extreme associations of *KIF6* carrier status with risk of incident vascular events were reported in the placebo groups of the CARE (RR: 1.57; 95% CI: 1.10 to 2.25) and WOSCOPS (RR: 1.59; 95% CI: 1.18 to 2.14) studies based on 142 and 276 coronary disease cases, respectively (13). These initial "hypothesis-generating" analyses involved testing 35 genetic polymorphisms for risk associations and placing data-dependent emphasis on the most extreme risk association in further analyses, which was for *KIF6*. By contrast, no significant associations were observed in the placebo group of the PROSPER study overall (adjusted RR: 1.06; 95% CI: 0.86 to 1.30) (18) based on 379 coronary disease cases or in the HPS study (RR: 0.97; 95% CI: 0.90 to 1.06) based on 2,335 coronary or other vascular disease cases. Studies among people with pre-existing vascular disease (such as in these trials) might not be optimal for

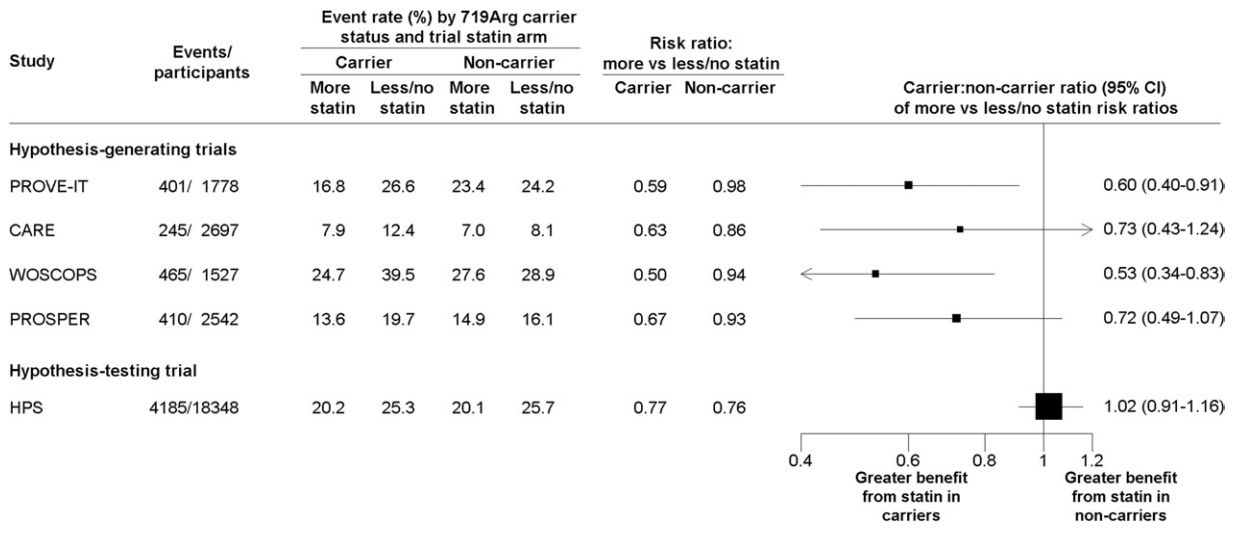

Figure 3 **Effects of Statin Therapy on Vascular Events by *KIF6* Genotype in the "Hypothesis-Generating" and "Hypothesis-Testing" Trials**

Carrier versus noncarrier ratios of risk ratios for the effects of statin therapy in each trial are indicated by **squares** (size inversely proportional to variance) with **horizontal lines** indicating 95% confidence intervals (CIs). For comparability, all risk ratios are based on unadjusted analyses (estimated, if not cited in the related publications, from the available data). Treatment comparisons: 40 mg pravastatin daily versus placebo in the CARE (Cholesterol And Recurrent Events), WOSCOPS (West of Scotland Coronary Prevention Study), and PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) studies; 80 mg atorvastatin daily versus 40 mg pravastatin daily in the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) study; and 40 mg simvastatin daily versus placebo in the HPS (Heart Protection Study). Vascular event outcomes: fatal or nonfatal myocardial infarction (MI) in the CARE study; any coronary death, nonfatal MI, or coronary revascularization in the WOSCOPS and PROSPER studies; death from any cause, nonfatal MI, unstable angina, coronary revascularization, or stroke in the PROVE-IT trial; and coronary death, nonfatal MI, coronary or noncoronary revascularization, or stroke in the HPS study. Data for PROSPER are for patients with prior vascular disease.

detecting genetic associations with vascular risk, because the underlying effect might be attenuated. Moderate associations of *KIF6* genotype with the risk of vascular events in people of white ethnic origin have been reported by some population-based observational studies (12,16,17). However, the Ottawa Heart Study and a recent meta-analysis of 19 case-control studies involving 17,000 coronary disease cases found no association between *KIF6* carrier status and the risk of coronary disease (28,29). Furthermore, large scale genome-wide association studies involving several thousand disease cases have also failed to report an association of *KIF6* with major coronary events (30–34). Nor have associations of *KIF6* with stroke been reliably demonstrated (15,35,36).

The lipid-lowering effects of statin therapy do not seem to be materially influenced by *KIF6* genotype. For example, it was not previously found to be associated with pretreatment cholesterol concentrations or with lipid response to statin therapy among approximately 20,000 and 6,000 individuals, respectively, in genome-wide scans followed by replication studies (37,38). The effects of *KIF6* genotype on cholesterol concentrations have not been reported for the CARE and WOSCOPS placebo-controlled trials of 40 mg pravastatin daily (13,20). Among 5,752 patients in the PROSPER study, however, no significant differences were observed between *KIF6* carriers and noncarriers in baseline cholesterol concentrations or in the LDL-C reductions produced by 40 mg pravastatin daily (18). Similarly, among 1,778 patients in the PROVE-IT study, *KIF6* genotype did not seem to have any material effect on cholesterol concentrations (19). These findings are consistent with the results among 18,343 genotyped participants in the HPS study, where actual use of 40 mg simvastatin daily for 4 to 6 weeks produced a 42% LDL-C reduction, while two-thirds compliance to the random allocation of 40 mg simvastatin daily versus placebo for 5 years produced an average 30% LDL-C reduction, irrespective of *KIF6* genotype. It has been suggested that the apparent lack of effect of statin therapy on vascular events in some trials among *KIF6* noncarriers, despite LDL-C being lowered to a similar extent as among carriers, provides evidence that the benefits of statin therapy are independent of LDL-C lowering effects (i.e., pleiotropic mechanisms) (19). Consequently, if a lack of effect of statin therapy on vascular events among *KIF6* 719Arg noncarriers had been reliably demonstrated, it would have had important biological as well as therapeutic implications.

Large-scale meta-analyses of randomized trials have shown that statin therapy reduces not only the risk of coronary death and nonfatal MI but also the need for revascularization procedures and the risk of ischemic stroke (2,3). Previously reported trials of the effects of *KIF6* genotype on statin response have assessed different vascular outcomes: the CARE study used the composite of fatal or nonfatal MI (13) (expanded subsequently to include all coronary deaths [20]); the WOSCOPS and PROSPER studies used the composite of any coronary death, nonfatal

MI, or coronary revascularization (13,18); and the PROVE-IT study used the composite of death from any cause or major cardiovascular event (which included MI, unstable angina, coronary revascularization, and stroke) (19). The extreme statistical significance of the reduction in any major vascular event ($p = 2.3 \times 10^{-17}$) in the HPS study and the large number of events (n = 4,185) on which it was based (1) allowed particularly reliable assessment of the effects of statin treatment in different circumstances. Consequently, this "hypothesis-testing" analysis in the HPS study has been able to demonstrate not only that statin therapy produces similar proportional reductions in the risk of major vascular events among *KIF6* carriers and noncarriers (23% and 24%, respectively) but also that these benefits are highly significant both among carriers (95% CI: 16% to 29%; $p = 5.3 \times 10^{-10}$) and, by contrast with the "hypothesis-generating" trials, among noncarriers (95% CI: 17% to 31%; $p = 4.6 \times 10^{-9}$) (Fig. 2). Moreover, the findings were similar in the HPS study when such analyses were conducted separately for major coronary events or for other major vascular events. The CARE, WOSCOPS, and PROSPER studies tested pravastatin (which is not now widely used), and the PROVE-IT study compared atorvastatin versus pravastatin, whereas the HPS study tested simvastatin. One cannot exclude the possibility, although unlikely, that the type of statin might be important for *KIF6* interaction. But, in the large-scale meta-analyses of randomized trials of statin therapy, the relative reductions in major vascular events were proportional to the absolute reductions in LDL-C (irrespective of the statin used) and were similar in all of the subgroups considered (2,3). Therefore, it seems most probable that the apparent *KIF6* interaction in the "hypothesis-generating" trials is due chiefly (if not entirely) to selective emphasis on data-derived findings based on relatively small numbers of events.

During the HPS study, an average of approximately one-sixth of participants allocated 40 mg simvastatin daily stopped taking statin therapy, and approximately one-sixth of placebo-allocated participants started taking a statin. Therefore, the observed average difference in LDL-C of approximately 40 mg/dl (1 mmol/l) between simvastatin-allocated and placebo-allocated participants represents only approximately two-thirds of the LDL-C difference produced by actual use of 40 mg simvastatin daily. Similarly, the reduction of approximately one-quarter in major vascular events in the intention-to-treat comparison is likely to represent only approximately two-thirds of the risk reduction produced by full compliance with this statin regimen. Hence, actual use of 40 mg simvastatin daily would be expected to lower LDL-C by approximately 60 mg/dl (1.5 mmol/l) in this population and reduce the rates of major vascular events by approximately one-third, irrespective of *KIF6* genotype. Such noncompliance could not, however, plausibly result in a positive bias whereby benefit would be falsely observed among noncarriers despite a real lack of benefit.

Conclusions

The *KIF6* 719Arg noncarrier genotype is relatively common (approximately 40% of all whites are noncarriers), and hence, concluding falsely that noncarriers will not benefit from statin therapy might lead to a very large number of unnecessary vascular events and deaths. The results of the HPS study demonstrate unequivocally that statin therapy produces substantial beneficial effects on coronary and other major vascular events, irrespective of whether an individual is a *KIF6* 719Arg carrier or noncarrier. Consequently, testing for *KIF6* genetic variants is not warranted for guiding the use of statin therapy (or other interventions aimed at lowering cardiovascular risk).

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Key Words: *KIF6* ■ pharmacogenetics ■ statin response ■ vascular risk.