Hepatic Metabolism and Transporter Gene Variants Enhance Response to Rosuvastatin in Patients With Acute Myocardial Infarction

The GEOSTAT-1 Study

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Background—Pharmacogenetics aims to maximize benefits and minimize risks of drug treatment. Our objectives were to examine the influence of common variants of hepatic metabolism and transporter genes on the lipid-lowering response to statin therapy.

Methods and Results—The Genetic Effects On STATins (GEOSTAT-1) Study was a genetic substudy of Secondary Prevention of Acute Coronary Events—Reduction of Cholesterol to Key European Targets (SPACE ROCKET) (a randomized, controlled trial comparing 40 mg of simvastatin and 10 mg of rosuvastatin) that recruited 601 patients after myocardial infarction. We genotyped the following functional single nucleotide polymorphisms in the genes coding for the cytochrome P450 (CYP) metabolic enzymes, CYP2C9*2 (430C>T), CYP2C9*3 (1075A>C), CYP2C19*2 (681G>A), CYP3A5*1 (6986A>G), and hepatic influx and efflux transporters SLCO1B1 (521T>C) and breast cancer resistance protein (BCRP; 421C>A). We assessed 3-month LDL cholesterol levels and the proportion of patients reaching the current LDL cholesterol target of <70 mg/dL (<1.81 mmol/L). An enhanced response to rosuvastatin was seen for patients with variant genotypes of either CYP3A5 ($P=0.006$) or BCRP ($P=0.010$). Furthermore, multivariate logistic-regression analysis revealed that patients with at least 1 variant CYP3A5 and/or BCRP allele (n=186) were more likely to achieve the LDL cholesterol target (odds ratio: 2.289; 95% CI: 1.157, 4.527; $P=0.017$; rosuvastatin 54.0% to target vs simvastatin 33.7%). There were no differences for patients with variants of CYP2C9, CYP2C19, or SLCO1B1 in comparison with their respective wild types, nor were differential effects on statin response seen for patients with the most common genotypes for CYP3A5 and BCRP (n=415; odds ratio: 1.207; 95% CI: 0.768, 1.899; $P=0.415$).

Conclusion—The LDL cholesterol target was achieved more frequently for the 1 in 3 patients with CYP3A5 and/or BCRP variant genotypes when prescribed rosuvastatin 10 mg, compared with simvastatin 40 mg.

Clinical Trial Registration—URL: http://isrctn.org. Unique identifier: ISRCTN 89508434.

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Key Words: pharmacogenetics ■ simvastatin ■ rosuvastatin ■ breast cancer resistance protein ■ CYP3A5

Following acute myocardial infarction, patients are at high risk of recurrent coronary events, making secondary prevention essential. Central to this strategy is the use of statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) and effective reduction of plasma lipids.[1] Current American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines recommend reduction of LDL

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cholesterol (LDL-C) to below 70 mg/dL (1.81 mmol/L).[2,3] However, marked individual variation in response to statins is observed in clinical practice.[4]

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Numerous single nucleotide polymorphisms (SNPs) have been described in genes encoding drug metabolism enzymes, with emerging evidence suggesting that these can influence the response to commonly used drugs such as the anticoagulant warfarin[5] and the antiplatelet agent clopidogrel.[6,7] Similarly, the role of SNPs in cell membrane transporter proteins has recently received increasing attention.[8–10] As statins have their primary site of action and metabolism within the liver, where they inhibit HMG-CoA reductase, SNPs within the cytochrome P450 (CYP) enzyme and hepatic transporter genes have the potential to play a significant role in determining statin concentration within plasma and hepatocytes and hence also clinical efficacy and tolerance to statin therapy. This has been particularly well demonstrated by the recently reported association between a common SNP in the solute carrier organic anion transporter 1B1 (SLCO1B1) hepatic uptake transporter and a highly significant increase in the incidence of musculoskeletal side effects for patients given high-dose (80 mg) simvastatin treatment.[11] Additionally, it has been suggested that a common SNP in CYP3A5 is associated with differences in LDL-C lowering achieved with selected statins.[12]

Simvastatin, being lipophilic, mainly enters and exits hepatocytes through passive diffusion. It is well documented that simvastatin is extensively metabolized by both CYP3A4 and CYP3A5. Inhibition of these CYP enzymes, not only by drugs such as erythromycin but also by consumption of grapefruit juice, is known to substantially raise plasma levels of simvastatin.[13–15] Importantly, unlike polymorphisms of CYP3A4, which are numerous but of very low frequency, there is a common polymorphism of CYP3A5, determined by a single SNP (6986A>G), which results in CYP3A5 being either present and functional (3A5*1) or entirely absent (3A5*3).[16–18] Furthermore, it is suggested that when expressed, CYP3A5 accounts for >50% of CYP3A activity and thus may be the most important determinant of genetic differences in CYP3A-dependent drug clearance and response to many medicines.[18] Present understanding of rosuvastatin pharmacokinetics is more limited. It is reported to be partially metabolized in the hepatocyte by both CYP2C9 and CYP2C19.[19] Like CYP3A5, CYP2C19 is either present and functional (CYP2C19*1) or entirely absent (CYP2C19*2) as determined by a common single SNP (681G>A).[20] However, CYP2C9 has 3 common alleles, determined by 2 SNPs. Of these, the wild-type (CYP2C9*1) is the most common and displays full enzymatic activity. CYP2C9*2 (430C>T) displays ≈12% and CYP2C9*3 (1075A>C) just 5% of wild-type activity.[21,22]

In addition to CYP metabolism, rosuvastatin concentration in the hepatocyte is also regulated by active transport. Of particular relevance are the SLCO1B1 influx transporter expressed exclusively on the basolateral membrane and the breast cancer resistance protein (BCRP), also known as ATP-binding cassette G2 (ABCG2), an efflux transporter expressed on the bile canalicular membrane. In vitro pharmacokinetic evidence strongly suggests that common nonsynonymous SNPs in the SLCO1B1 (521T>C; $Val^{174}Ala$) and BCRP (421C>A; $Gln^{141}Lys$) genes both result in markedly decreased transport function and thus could potentially play a significant role in determining rosuvastatin concentration within the hepatocyte.[23–29]

It is a continual challenge to the medical profession to seek to match individual treatments to individual patients (personalized medicine). Consequently, we studied the influence of common genetic variants of CYP enzymes (CYP2C9, CYP2C19, and CYP3A5) and hepatic uptake (SLCO1B1) and efflux (BCRP) transporters on the lipid-lowering effects of 2 statin regimens: 40 mg of simvastatin and 10 mg of rosuvastatin.

Methods

Study Design and Recruitment

GEOSTAT-1 (Genetic Effects On STATins) was a prospective genetic substudy of SPACE ROCKET (Secondary Prevention of Acute Coronary Events—Reduction of Cholesterol to Key European Targets), a UK-wide, multicenter, prospective, open-label, blinded-endpoint, randomized, controlled trial comparing the efficacy and tolerability of 40 mg of simvastatin and 10 mg of rosuvastatin (ISRCTN: 89508434; http://isrctn.org).[30]

SPACE ROCKET recruited 1263 hospital patients following acute myocardial infarction from 27 UK centers between May 2005 and March 2007. Eligibility criteria were (1) recruitment within 2 weeks of acute myocardial infarction, defined as either having primary percutaneous coronary intervention or raised biomarkers of myocardial necrosis with ≥1 of the following conditions: ischemic symptoms, development of pathological Q waves on ECG, and ECG changes suggestive of ischemia, namely ST-segment elevation or depression; (2) the need for secondary prevention with a statin (as determined by the attending clinician) and; (3) written, informed consent. Patients were ineligible if they had previous statin intolerance or known contraindications or were receiving more intensive treatment with either 80 mg of simvastatin or 80 mg of atorvastatin.

SPACE ROCKET participants were randomly allocated, by automated telephone randomization, to receive simvastatin 40 mg or rosuvastatin 10 mg for 3 months. Trial-specific blood samples were analyzed at baseline and 3 months in a central laboratory. LDL-C levels were calculated according to the Friedewald formula.[31] GEOSTAT-1 recruited SPACE ROCKET trial participants from all 27 centers between March 2006 and July 2007. All patients attending the 3-month follow-up visit were eligible, subject to their written, informed consent to GEOSTAT-1. A venous blood sample (9 mL) was taken for DNA extraction and genotyping. SPACE ROCKET and GEOSTAT-1 were both approved by the Oxford [A] research ethics committee and all participating institutions.

Genotyping

Genomic DNA was isolated from venous blood samples (9 mL) with a VersaGene DNA extraction kit (Gentra Systems, Minneapolis, Minn) according to the manufacturer's protocol. Yield and purity were determined by spectrophotometry (NanoDrop ND-1000). Genotyping of the CYP2C9*2 (430C>T; rs1799853), CYP2C9*3 (1075A>C; rs1057910), CYP2C19*2 (681G>A; rs4244285), CYP3A5*1 (6986A>G; rs776746), BCRP (421C>A; rs2231142), and SLCO1B1 (521T>C; rs4149056) functional polymorphisms was performed, according to the manufacturer's protocol, with TaqMan validated drug metabolism SNP assays (assay IDs: C__26201809_30; C__25625805_10; C__27104892_10; C__25986767_70; C__30633906_10, and C__15854163_70, respectively), with a 7900HT sequence detection system equipped with the SDS version 2.2 software suite (Applied Biosystems, Foster City, Calif). The genotyping failure rate was <0.1%. All assays were validated by either restriction fragment length polymorphism assays or direct DNA sequencing.

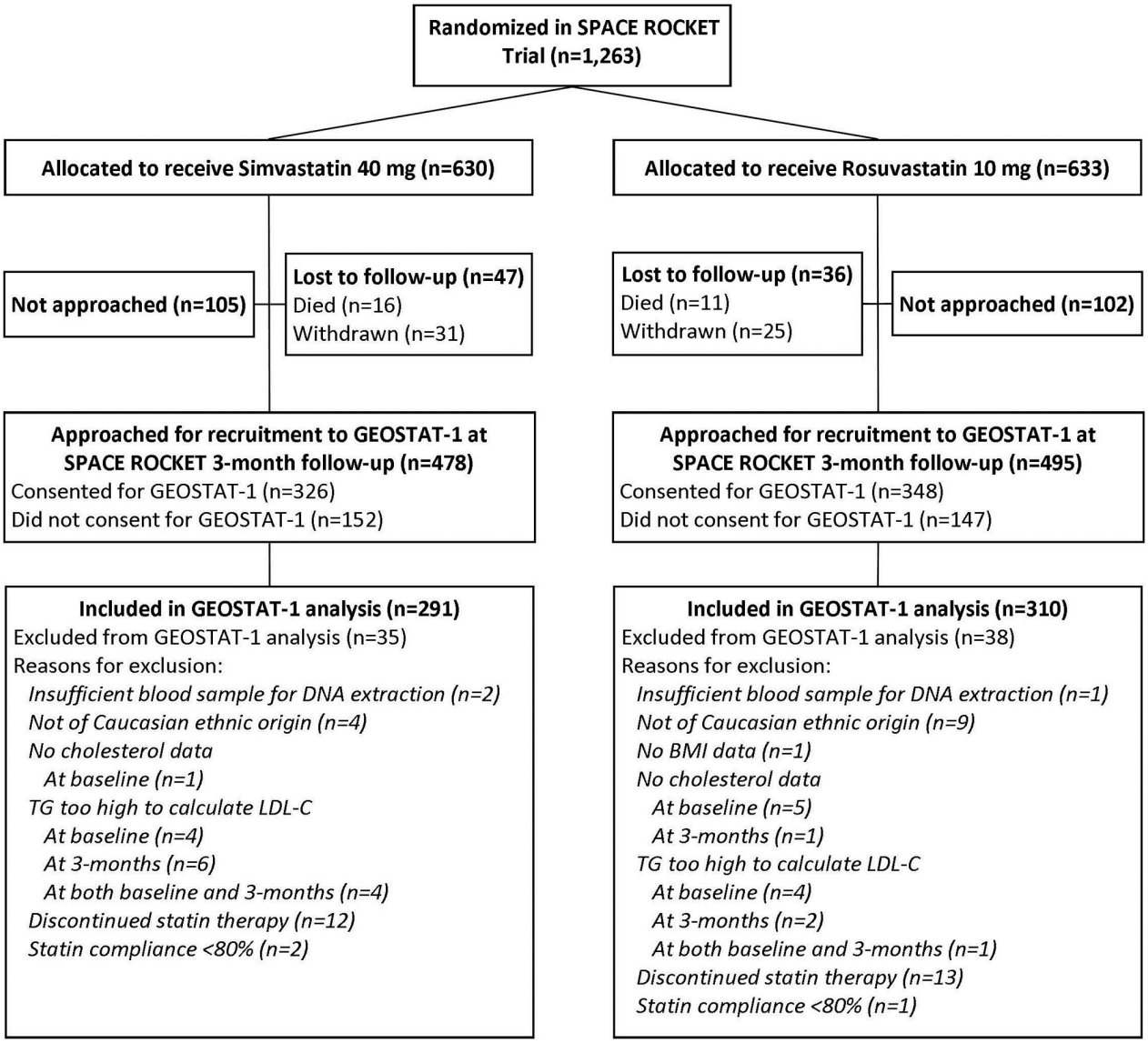

Figure 1. Flow of participants through the SPACE ROCKET trial and GEOSTAT-1. TG indicates triglycerides.

Statistical Analyses

All statistical analyses were performed with SPSS software (version 17.0, SPSS Inc, Chicago, Ill). Data were checked to ensure that all assumptions for parametric testing were met, when used. Patients were grouped according to genotype for each CYP enzyme (CYP2C9, 2C19, 3A5) and transporter (SLCO1B1 and BCRP). Because of small numbers of variant allele homozygotes, patients with either 1 or 2 copies of a variant allele were grouped together as variants. Those with 2 copies of the wild-type (most common) allele were classified as wild type.

Baseline characteristics of age, body mass index (BMI), sex, statin on admission, and lipid parameters were compared between both randomized statin and each genotype, by 2-way between-groups ANOVA or χ^2, where appropriate. To examine for differences in 3-month mean LDL-C values between each genotype group, within both simvastatin and rosuvastatin, independent-samples *t* tests were used; interactions between randomized statin and each genotype were assessed by the interaction terms of respective 2-way between-groups ANOVA. Power calculations were conducted with an online statistical power calculator.[32] To investigate the role of randomized statin in the achievement of the current ACC/AHA/ESC LDL-C–lowering target,[2,3] univariate and multivariate logistic-regression analyses were conducted. In each model, target achievement was used as the dependent variable and randomized statin as the independent variable. In the multivariate model, baseline characteristics (age, BMI, sex, LDL-C at baseline, and statin on admission) were entered simultaneously with randomized statin. *P* values <0.05 were considered statistically significant, with Bonferroni corrections applied separately to the CYP and hepatic transporter analyses of 3-month LDL-C, with probability values <0.008 and <0.013, respectively, considered statistically significant. These corrections were applied because of prior separate mechanistic hypotheses that hepatic metabolism and/or transport may affect statin efficacy. A Bonferroni correction was also applied to the LDL-C target achievement univariate logistic-regression models, with *P* values <0.017 considered statistically significant.

Results

Sample Characteristics

In total, we approached 973 SPACE ROCKET participants and 674 consented to the GEOSTAT-1 study. Of these, 73 patients were excluded from the analyses (Figure 1). Baseline characteristics for the remaining 601 patients included in the study, grouped by genotype and randomized statin, are shown in Table

Table 1. Comparison of Patients' Baseline Characteristics, Grouped by Genotype and Randomized Statin, Using 2-Way Between-Groups ANOVA or χ^2†

Cytochrome P450 enzymes	Simvastatin		Rosuvastatin		Significant Difference
CYP2C9 (n=600)	WT (n=170)	Var[a] (n=120)	WT (n=200)	Var[b] (n=110)	
Characteristic					
Age, mean (SD), y	61.72 (9.92)	62.64 (11.28)	62.39 (11.00)	61.25 (10.21)	
BMI, mean (SD), kg/m^2	27.72 (4.42)	27.69 (4.30)	27.78 (4.29)	28.98 (5.48)	
Male, n (%)	143 (84.1)	96 (80.0)	157 (78.5)	93 (84.5)	
Statin on admission, n (%)	36 (21.1)	33 (27.5)	46 (23.0)	27 (24.5)	
Cholesterol, mean (SD), mg/dL					
Total	176.38 (37.70)	175.61 (40.24)	176.58 (42.31)	173.04 (39.87)	
LDL	105.86 (32.99)	104.44 (34.13)	107.12 (37.86)	102.42 (34.62)	
HDL	42.08 (12.24)	41.02 (10.01)	40.52 (9.70)	40.68 (9.38)	
Triglycerides	149.87 (64.10)	158.62 (64.06)	153.10 (62.44)	156.48 (62.38)	
CYP2C19 (n=601)	WT (n=225)	Var[c] (n=66)	WT (n=214)	Var[d] (n=96)	
Characteristic					
Age, mean (SD), y	61.59 (10.59)	63.90 (9.98)	62.12 (10.39)	61.68 (11.49)	
BMI, mean (SD), kg/m^2	27.70 (4.25)	27.72 (4.75)	28.15 (4.73)	28.31 (4.90)	
Male, n (%)	186 (82.7)	54 (81.8)	171 (79.9)	79 (82.3)	
Statin on admission; n (%)	61 (27.1)	8 (12.1)	50 (23.4)	23 (24.0)	‡
Cholesterol, mean (SD), mg/dL					
Total	177.54 (38.90)	170.59 (37.70)	176.90 (41.54)	171.81 (41.19)	
LDL	106.79 (34.03)	99.68 (30.77)	106.05 (37.07)	104.13 (36.18)	
HDL	41.42 (11.16)	42.35 (12.02)	41.21 (9.09)	39.17 (10.48)	
Triglycerides	154.30 (62.71)	150.84 (68.68)	155.86 (60.63)	150.81 (66.20)	
CYP3A5 (n=601)	WT (n=256)	Var[e] (n=35)	WT (n=271)	Var[f] (n=39)	
Characteristic					
Age, mean (SD), y	62.74 (10.46)	57.55 (9.59)	61.25 (10.75)	67.07 (9.20)	‡
BMI, mean (SD), kg/m^2	27.88 (4.34)	26.45 (4.30)	28.17 (4.54)	28.45 (6.23)	‡
Male, n (%)	212 (82.8)	28 (80.0)	219 (80.8)	31 (79.5)	
Statin on admission, n (%)	66 (25.8)	3 (8.6)	58 (21.4)	15 (38.5)	‡
Cholesterol, mean (SD), mg/dL					
Total	174.39 (39.12)	187.42 (33.62)	176.61 (41.74)	166.42 (38.55)	‡
LDL	103.58 (33.59)	116.82 (29.85)	106.67 (36.76)	97.02 (36.04)	‡
HDL	41.40 (11.27)	43.35 (11.92)	40.56 (9.47)	40.69 (10.40)	
Triglycerides	155.04 (63.19)	142.35 (69.66)	154.59 (62.82)	152.26 (59.68)	
Hepatic transporters					
SLCO1B1 521 (n=601)	WT (n=200)	Var[g] (n=91)	WT (n=231)	Var[h] (n=79)	
Characteristic					
Age, mean (SD), y	61.23 (10.22)	64.07 (10.83)	61.46 (10.71)	63.50 (10.71)	‡
BMI, mean (SD), kg/m^2	27.68 (4.38)	27.77 (4.32)	28.09 (4.76)	28.52 (4.81)	
Male, n (%)	168 (84.0)	72 (79.1)	190 (82.3)	60 (75.9)	
Statin on admission; n (%)	47 (23.5)	22 (24.2)	53 (22.9)	20 (25.3)	
Cholesterol, mean (SD), mg/dL					
Total	174.65 (39.60)	178.84 (36.62)	173.61 (41.21)	180.34 (41.92)	
LDL	104.48 (33.95)	106.71 (32.29)	104.13 (37.01)	109.33 (35.93)	
HDL	41.60 (11.96)	41.71 (9.94)	40.82 (9.66)	39.88 (9.33)	
Triglycerides	150.84 (65.55)	159.39 (60.42)	151.06 (61.16)	163.77 (65.15)	

(*Continued*)

Table 1. Continued

BCRP 421 (n=601)	WT (n=231)	Var[i] (n=60)	WT (n=239)	Var[j] (n=71)
Characteristic				
Age, mean (SD), y	62.07 (10.38)	62.29 (10.94)	61.51 (10.92)	63.56 (9.97)
BMI, mean (SD), kg/m^2	27.80 (4.50)	27.37 (3.75)	28.37 (4.74)	27.63 (4.86)
Male, n (%)	196 (84.8)	44 (73.3)	191 (79.9)	59 (83.1)
Statin on admission, n (%)	56 (24.2)	13 (21.7)	59 (24.7)	14 (19.7)
Cholesterol, mean (SD), mg/dL				
Total	176.60 (39.18)	173.49 (36.90)	176.22 (41.86)	172.33 (40.11)
LDL	105.42 (33.56)	104.25 (33.04)	106.14 (37.39)	103.16 (34.69)
HDL	41.82 (11.85)	40.93 (9.22)	40.81 (9.84)	39.81 (8.62)
Triglycerides	154.66 (66.43)	149.12 (53.96)	154.03 (63.00)	155.18 (60.50)

WT indicates wild type; Var, variant.

†Continuous variables were compared with 2-way between-groups ANOVA and categorical variables by χ^2.

‡Significant result obtained on analysis ($P<0.05$).

Distribution of variants: [a], *1/*2=65, *1/*3=35, *2/*2=11, *2/*3=5, *3/*3=4; [b], *1/*2=72, *1/*3=27, *2/*2=4, *2/*3=6, *3/*3=1; [c], *1/*2=60, *2/*2=6; [d], *1/*2=86, *2/*2=10; [e], *1/*1=1, *1/*3=34; [f], *1/*1=0, *1/*3=39; [g], TC=82, CC=9; [h], TC=72, CC=7; [i], CA=54, AA=6; [j], CA=67, AA=4.

1. As a result of random allocation of patients to each treatment group, there were no statistically significant differences for the vast majority of baseline characteristics. By way of exception to this observation, we noted some interrelated variables that did differ significantly at baseline. For example, in the randomized statin/CYP3A5 groups, there were differences in age and BMI at randomization, number of patients on a statin at admission, and baseline total cholesterol and LDL-C concentrations. Differences in prior statin use were seen to associate positively with age and inversely with total and LDL-C. Baseline characteristics for SPACE ROCKET (n=1263) and GEOSTAT-1 (n=601) participants, grouped by randomized statin, are shown in supplemental Table I (online-only Data Supplement). Allele and genotype frequencies are shown in supplemental Tables II and III. All variants were in Hardy-Weinberg equilibrium.

LDL-C Concentration at 3 Months

To investigate the effect of each variant allele on the cholesterol-lowering abilities of simvastatin 40 mg and rosuvastatin 10 mg, a series of independent samples *t* tests were conducted. These compared the 3-month mean LDL-C for each genotype, according to statin (Table 2).

When randomized to rosuvastatin, patients in the CYP3A5 and BCRP variant groups obtained significantly lower mean

Table 2. *t* Tests Comparing Mean 3-Month LDL-C Levels, According to Genotype and Randomized Statin

	LDL-C Values per Genotype Group			
	WT	Var	Mean Difference‡	*P*
CYP enzyme genes per randomized statin				
Simvastatin (n=291)				
CYP2C9	78.86 (27.26) (n=170)	79.21 (22.42) (n=120)[a]	−0.36 (−6.31, 5.59)	0.905
CYP2C19	79.95 (25.95) (n=225)	75.64 (22.79) (n=66)[b]	4.31 (−2.65, 11.27)	0.224
CYP3A5	78.59 (26.49) (n=256)	81.74 (13.62) (n=35)[c]	3.15 (−2.50, 8.80)	0.270
Rosuvastatin (n=310)				
CYP2C9	74.38 (23.92) (n=200)	73.39 (20.74) (n=110)[d]	0.99 (−4.34, 6.32)	0.716
CYP2C19	74.86 (22.89) (n=214)	72.19 (22.65) (n=96)[e]	2.66 (−2.85, 8.18)	0.343
CYP3A5	75.38 (23.05) (n=271)	64.65 (18.83) (n=39)[f]	10.74 (3.13, 18.34)	0.006†
Hepatic transporter genes per randomized statin				
Simvastatin (n=291)				
SLCO1B1	79.52 (25.36) (n=200)	77.77 (25.25) (n=91)[g]	1.75 (−4.56, 8.05)	0.586
BCRP	78.49 (25.18) (n=231)	80.82 (25.85) (n=60)[h]	−2.33 (−9.55, 4.89)	0.525
Rosuvastatin (n=310)				
SLCO1B1	73.24 (23.41) (n=231)	76.34 (20.85) (n=79)[i]	−3.10 (−8.95, 2.75)	0.298
BCRP	75.85 (23.37) (n=239)	67.92 (19.80) (n=71)[j]	7.93 (1.91, 13.94)	0.010*

*$P<0.013$ and therefore statistically significant after correction for multiple testing.

†$P<0.008$ and therefore statistically significant after correction for multiple testing.

‡Positive values represent lower LDL-C levels in the variant-allele group, and values in brackets represent 95% CIs.

Distribution of variants: [a], *1/*2=65, *1/*3=35, *2/*2=11, *2/*3=5, *3/*3=4; [b], *1/*2=60, *2/*2=6; [c], *1/*1=1, *1/*3=34; [d], *1/*2=72, *1/*3=27, *2/*2=4, *2/*3=6, *3/*3=1; [e], *1/*2=86, *2/*2=10; [f], *1/*1=0, *1/*3=39; [g], TC=82, CC=9; [h], CA=54, AA=6; [i], TC=72, CC=7; [j], CA=67, AA=4.

Table 3. Univariate and Multivariate Logistic-Regression Models Predicting Achievement of LDL-C Target

Models and Predictors	OR	95% CI for OR Lower	Upper	*P*
Univariate model (all patients; n=601)				
Randomized statin (rosuvastatin)	1.376	0.996	1.902	0.053
Univariate model (WT-allele carriers; n=415)				
Randomized statin (rosuvastatin)	1.098	0.745	1.619	0.635
Univariate model (variant-allele carriers; n=186)				
Randomized statin (rosuvastatin)	2.307	1.272	4.185	0.006
Variate model (variant-allele carriers; n=186)				
Randomized statin (rosuvastatin)	2.289	1.157	4.527	0.017
LDL-C at baseline (per 10 mg/dL)	0.732	0.648	0.826	<0.0005
Statin on admission (yes)	0.307	0.129	0.731	0.008
Age	1.022	0.987	1.059	0.217
BMI	1.000	0.931	1.073	0.990
Sex (female)	1.266	0.566	2.833	0.566

OR indicates odds ratio; WT, wild-type.

Variant-allele carriers included patients carrying at least 1 CYP3A5*1 and/or BCRP 421A allele.

3-month LDL-C concentrations than did those in the wild-type groups (10.74 mg/dL, $P=0.006$ and 7.93 mg/dL, $P=0.010$, respectively). The robustness of these observations was demonstrated by multivariate linear-regression analyses performed with genotype adjusted for baseline LDL-C (CYP3A5, $P=0.022$ and BCRP, $P=0.006$). Such differences, with respect to CYP3A5 and BCRP variant groups, were not present in those patients randomized to simvastatin ($P=0.270$ and $P=0.525$, respectively). Furthermore, there were no significant differences in mean 3-month LDL-C concentrations between wild-type (most common allele) and variant groups for CYP2C9, CYP2C19, and SLCO1B1 genotypes, when randomized to either statin (Table 2). These analyses had between 71.7% and 96.6% power to detect a 10% mean difference (supplemental Table IV). Finally, formal tests for statin and genotype interactions revealed significant interactions among BCRP ($P=0.031$) and CYP3A5 ($P=0.020$) genotypes, but not CYP2C9 ($P=0.740$), CYP2C19 ($P=0.714$), and SLCO1B1 ($P=0.268$) genotypes.

LDL-C Target Achievement

To investigate the role of CYP3A5 and BCRP genotype and randomized statin in the achievement of the current ACC/AHA/ESC LDL-C target,[2,3] univariate logistic-regression analyses were conducted for (1) all patients, (2) those wild type for both genes, and (3) those carrying at least 1 variant allele (CYP3A5*1 and/or BCRP 421A; Table 3). Each model used achievement of the LDL-C target (<70 mg/dL; <1.81 mmol/L) as the dependent variable (target missed=0; target achieved=1) and randomized statin as the independent variable.

In the model including all patients (Table 3), randomized statin demonstrated a nonsignificant trend as a predictor of target achievement. Randomized statin did play a significant role in predicting target achievement in the model including only those patients carrying at least 1 variant allele (Table 3). An odds ratio of 2.3 suggested that those randomized to rosuvastatin were much more likely to achieve target than those randomized to simvastatin; a Nagelkerke R^2 suggested that randomized statin explained 5.5% of the variance in target achievement. Randomized statin did not play a significant role in predicting target achievement in the model including only those patients who were wild type for both genotypes (Table 3; Nagelkerke $R^2=0.1\%$). In a logistic-regression model that included all patients, a significant statin and combined genotype (BCRP/CYP3A5) interaction was demonstrated ($P=0.041$).

A multivariate logistic-regression analysis was performed to assess whether the predictive effect of randomized statin on achievement of cholesterol target in patients with at least 1 variant allele was independent of potentially confounding factors. Baseline characteristics added to the model were age, BMI, sex, LDL-C at baseline, and use of statin on admission. Achievement of LDL-C target was used as the dependent variable (target missed=0; target achieved=1). Overall, the model was statistically significant, χ^2 (6, n=186) =45.44, $P<0.0005$, indicating that it was able to distinguish between patients achieving and not achieving target. The model was able to explain between 21.7% (Cox and Snell R^2) and 29.0% (Nagelkerke R^2) of the variance in target achievement and correctly classified 69.9% of cases, with a sensitivity of 63.9% and specificity of 74.8%. A receiver operator curve analysis to further assess the goodness of fit of the model had an area under the curve of 0.775 (95% CI: 0.708 to 0.841).

Table 3 shows odds ratios and their 95% CIs for the individual predictors in the model. Patients randomized to rosuvastatin were 2.3 times more likely to achieve target than those randomized to simvastatin. LDL-C at baseline and statin on admission also made independent statistically significant contributions to the model. The odds ratios suggest that for every 10 mg/dL increase in LDL-C at baseline, patients are 1.4 times less likely to achieve target. Additionally, those who were already receiving statin therapy were 3.3 times less likely to achieve target. Age, BMI, and sex did not make statistically significant contributions to this model. Supplemental Table V shows target achievement among each genotype and statin group. Notably, within the group of patients with at least 1 variant CYP3A5 or BCRP allele, 54.0% of those randomized to rosuvastatin achieved the LDL-C target (<70 mg/dL; <1.81 mmol/L) compared with 33.7% of those randomized to simvastatin. The differences in 3-month LDL-C levels for each genotype group, according to randomized statin, are illustrated in Figure 2.

Discussion

Our study highlights that there is a variation in individual responses to different statins, and therefore, "one size does not fit all." Key factors in this variation are the genetic determinants of statin metabolism and transport within the liver. We have observed that patients with at least 1 variant CYP3A5 and/or

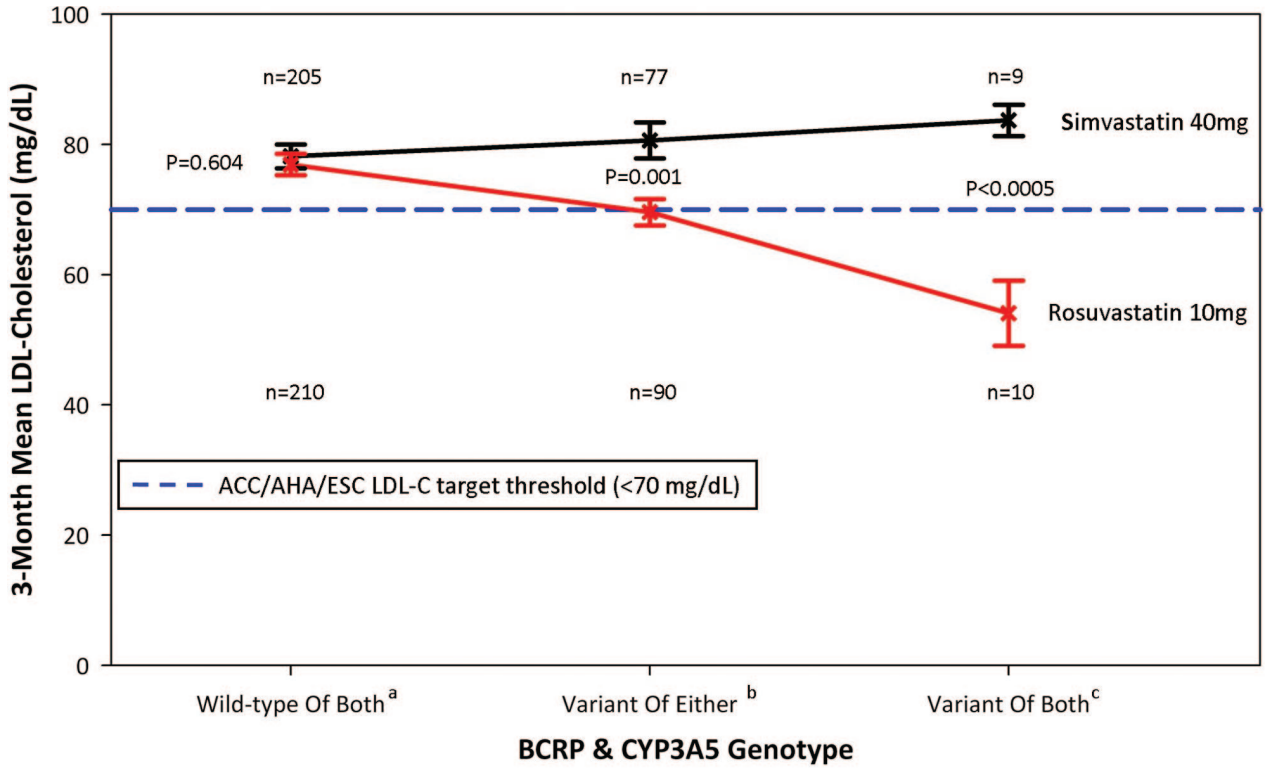

Figure 2. Mean 3-month LDL-C levels for patients randomized to simvastatin or rosuvastatin, according to BCRP and CYP3A5 genotype. [a]BCRP 421CC and CYP3A5 *3/*3 genotype only; [b]BCRP 421AA or 421CA or CYP3A5 *1/*1 or *1/*3 genotypes; [c]BCRP 421AA or 421CA and CYP3A5 *1/*1 or *1/*3 genotypes. Error bars represent ±1 SE. Probability values generated from independent samples *t* tests comparing simvastatin (40 mg) vs rosuvastatin (10 mg) within each genotype group.

BCRP allele, who were randomized to rosuvastatin (10 mg), were 2.3 times more likely to achieve the current LDL-C target than those randomized to simvastatin (40 mg).

There was no statistically significant variation in response to simvastatin (40 mg) based on the presence or absence of the variant CYP3A5 allele (3A5*1), and we were therefore unable to confirm previously reported differences relating to 46 white subjects receiving simvastatin, lovastatin, or atorvastatin.[12] Our observations are in agreement with a second limited evaluation of simvastatin (20 mg) and this gene variant.[33] As our investigation is an order of magnitude larger than either of those studies and had 91.7% power to detect a clinically relevant mean difference (10%) in 3-month LDL-C, we consider our findings to be robust. Similarly, we found no variation in response to rosuvastatin based on CYP2C9 or CYP2C19 genotype, suggesting that neither enzyme plays a clinically significant role in the metabolism of rosuvastatin. This is in keeping with a previous study examining the metabolism, excretion, and pharmacokinetics of rosuvastatin in healthy adult, male volunteers.[19]

To varying degrees, all statins are substrates of the SLCO1B1 influx transporter.[34] However, the effects of the SLCO1B1 (521T>C; $Val^{174}Ala$) polymorphism differ between statins. For example, the 521C allele is strongly associated with simvastatin-induced myopathy, thought to be due to reduced hepatic uptake of active simvastatin acid, causing accumulation of simvastatin acid in plasma.[11] In a case-control analysis of 85 definite or incipient myopathy cases and 90 controls, >60% of the myopathy cases could be attributed to the 521C allele, and the odds ratio for myopathy was 4.5 per copy of the 521C allele. Rather surprisingly, considering reduced hepatic uptake, in the replication cohort (Heart Protection Study, 20 536 patients), those patients taking 40 mg of simvastatin daily and possessing the 521C allele had only a slight reduction in the cholesterol-lowering efficacy of simvastatin (≈1%).[11] This may reflect the fact that simvastatin is administered in a lactone form, which, being lipophilic, mainly enters hepatocytes through passive diffusion. In keeping with these observations, we found no association in our study of the 521C allele with reduced efficacy of simvastatin.

Hepatic clearance accounts for >70% of total plasma clearance of rosuvastatin and, as it is administered in an acid form (hydrophilic), its uptake into hepatocytes is regulated by active transport. Two independent pharmacokinetic studies in humans have both reported that subjects who were carriers of 2 SLCO1B1 521C alleles had higher peak plasma concentrations of rosuvastatin. There were also larger average areas under the plasma concentration–time curves. These studies were conducted after administration of a single 10 mg dose of rosuvastatin.[35,36] Although there are currently no clinical reports on the effects of the 521C allele on the efficacy of rosuvastatin to lower LDL-C levels, extrapolation of the aforementioned pharmacokinetic studies would point to a reduced response. In keeping with this hypothesis, we did observe a trend toward reduced efficacy of rosuvastatin in carriers of the 521C allele, but this did not reach statistical significance (Table 2).

In contrast, a significant difference was observed in the 3-month cholesterol levels achieved in patients with at least 1 variant CYP3A5 allele (*1/*1 or *1/*3), compared with individuals carrying wild-type alleles, when randomized to receive 10 mg of rosuvastatin (Table 2). This suggests that rosuvastatin may be modified by the CYP3A5 enzyme and that the metabolite either has increased ability to inhibit HMG-CoA reductase or is of a similar inhibitory activity but less readily excreted from the hepatocyte. It has previously been reported that unlike the acid form of rosuvastatin, the lactone form is a good substrate of the CYP3A4/3A5 enzymes,[37,38] and that itraconazole, an inhibitor of CYP3A4, leads to modest increases in rosuvastatin plasma concentrations.[39] Furthermore, atorvastatin, a closely related molecule, has previously been reported to undergo modification by the CYP3A4/3A5 enzymes and yet still retain HMG-CoA reductase inhibitory activity.[40,41] The alternative explanation is that the differences in LDL-C seen at 3 months may be solely due to random differences at baseline. However, and importantly, after adjustment for baseline LDL-C with linear-regression analysis, the effect remained statistically significant ($P=0.022$).

The difference in response to rosuvastatin 10 mg in patients with 1 or more poorly functional, variant BCRP (421A) alleles is unlikely to be explained by baseline patient characteristics, which were well matched between groups (Table 1). After adjustment for baseline LDL-C with linear-regression analysis, the effect remained statistically significant ($P=0.006$). Importantly, there is strong in vitro evidence to support the biological relevance of our findings: pharmacokinetic studies have shown that the BCRP 421C>A SNP results in decreased transport function[25–27] and other reports suggest that the BCRP is the main efflux transporter of rosuvastatin from hepatocytes.[42] Therefore, decreased efflux of rosuvastatin from hepatocytes, leading to higher concentrations and thus more effective HMG-CoA reductase inhibition, represents a plausible mechanism for the contrasting efficacy of rosuvastatin in patients with alternate genotypes.

There is in vivo clinical support for the BCRP 421C>A SNP effect on rosuvastatin efficacy. First, in addition to being expressed on the bile canalicular membrane, BCRP is also highly expressed at the apical membrane of small intestinal enterocytes, where it functions as a physiological barrier, as it limits the absorption of its substrates from the gut.[43] Recently, 2 independent in vivo pharmacokinetic studies both reported that subjects who were carriers of 1 BCRP A allele displayed higher peak plasma concentrations of rosuvastatin and larger average areas under the plasma concentration–time curves; the effects were even greater for subjects carrying 2 A alleles.[44,45] Second, in a recent study of 191 Chinese patients with primary hypercholesterolemia receiving rosuvastatin (10 mg) for at least 4 weeks, patients who were homozygous for the BCRP (421A) allele showed greater reductions in LDL-C (56.9±2.2%) than those homozygous for the BCRP (421C) allele (50.5±1.1%), with heterozygous individuals having intermediate values (52.6±1.5%).[46]

The aforementioned studies therefore suggest that the biological mechanisms underlying our present clinical observations might be a combination of increased plasma concentrations of rosuvastatin and decreased efflux of rosuvastatin from hepatocytes in carriers of the A allele. Theoretically, this might also increase the risk of hepatotoxicity, which we assessed by comparing the 3-month mean plasma levels of alanine transaminase, a very sensitive marker of hepatocellular insufficiency. We observed no difference ($P=0.484$) between patients with 2 wild-type BCRP 421C alleles (31.21 IU/L; n=238) and those with either 1 or 2 variant BCRP 421A alleles (29.82 IU/L; n=71). However, this does not exclude the possibility of such an effect at higher doses of rosuvastatin.

By constructing a multivariate logistic-regression model for patients with 1 or more variant CYP3A5 and/or BCRP alleles (CYP3A5*1 and/or BCRP 421A; 31% of patients), we have described the clinical factors that predict the likelihood of achieving the current ACC/AHA/ESC LDL-C target. Overall, our algorithm demonstrated that patients carrying 1 or more variant alleles were 2.3 times more likely to reach the LDL-C target when randomized to 10 mg of rosuvastatin compared with 40 mg of simvastatin. The most powerful predictor overall was baseline LDL-C, an observation that would be readily anticipated. Another expected predictive factor was the use of statin therapy before admission. However, perhaps surprisingly, it was patients already on statin therapy at admission who were least likely to achieve the target LDL-C at 3 months. This group may represent a subset of patients with an increased tendency to statin resistance, who might also be expected to derive greater benefit from a more aggressive cholesterol-lowering regimen.

Strengthened by being conducted, prospectively, in the setting of a randomized, controlled trial, our study is nevertheless limited by inclusion of only whites, who are known to have much lower frequencies of the variant CYP3A5*1 and BRCP 421A alleles than people originating from Asia.[47] This was not a result of application of initial selection criteria relating to ethnicity but reflects patients otherwise eligible and willing to take part in the main SPACE ROCKET trial. One might predict our observations to be of even greater relevance to individuals with Asian ancestry. This may also explain the higher blood levels of rosuvastatin that have been observed among this group of patients,[48] which led to the reduction in the recommended starting dose of rosuvastatin among Asians.[49]

We believe it is important to highlight that we conducted our analyses on the basis of 3-month LDL-C measurements and not percentage change from baseline for 2 important reasons. First, in the contexts of both acute myocardial infarction and cardiac catheterization or percutaneous coronary intervention, lipid measurements have been shown to be unstable and subject to high levels of intra- and interindividual variation over time.[50–52] Therefore, because of differences in the time from event to blood sampling among participants, the baseline cholesterol levels obtained may not represent a true reflection of an individual's stable cholesterol levels; this was demonstrated in the parent SPACE ROCKET trial.[30] Second, and of more relevance, is the fact that it is the posttreatment cholesterol level that has the greatest clinical significance, and it is on these levels that current treatment targets are based. Nevertheless, our findings require further

validation in both the current and also alternative clinical settings. Furthermore, use of different statin doses and study of other ethnic groups should be explored to provide confirmation and assess generalizability.

Data such as those published by the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) investigators suggest that targeted and timely determination of each patient's genetic profile might help to explain, and hence avoid, rare adverse events such as statin-induced myopathy.[11] However, the greatest value in being able to optimize statin response is likely to be in the number of major cardiovascular events that might be effectively avoided[53] in a manner that is also cost-effective. The SPACE ROCKET trial demonstrated no effect of statin selection for higher cholesterol targets that are now obsolete; there were, however, significant benefits in favor of rosuvastatin (10 mg) when assessing currently recommended ACC/AHA/ESC LDL-C targets.[30] In GEOSTAT-1, we have demonstrated that these results can be attributed to the 1 in 3 patients with CYP3A5 and/or BCRP variant genotypes. We believe that genetic profiling of patients will, in the future, form an important part of the clinical process of optimal statin selection and dosing.

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Disclosures

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CLINICAL PERSPECTIVE

The Genetic Effects On STATins Study (GEOSTAT-1) highlights the variation in individual response to different statins. Patients with at least 1 variant copy of the genes that code for the liver enzyme CYP3A5 and/or the liver transporter breast cancer resistance protein (BCRP) were 2.3 times more likely to achieve the current LDL cholesterol target after myocardial infarction of 70 mg/dL, when prescribed rosuvastatin 10 mg compared with simvastatin 40 mg. This is consistent with recently published studies in which much higher rosuvastatin (and also atorvastatin) blood levels were observed in individuals with 1 or more variant copies of the breast cancer resistance protein gene variant. A potential clinical value of these findings might be the ability to use genetic information to optimize selection of statin subtype and dose to better avoid rare side effects that can occur with use of a higher statin dose. Such considerations would have particular relevance for the treatment of Asian patients, who are known to have a greater frequency of the breast cancer resistance protein gene variant and also higher blood concentrations after treatment with rosuvastatin. Awareness of a patient's genetic profile would also be expected to render safer and also more effective the use of rosuvastatin 20 mg in the clinical context of primary prevention of major cardiovascular events (as studied in the Justification for the Use of statins in Primary prevention Trial Evaluating Rosuvastatin [JUPITER] trial) and also the use of rosuvastatin 40 mg for reversal of coronary atheromatous plaque size (as demonstrated in the A STudy to Evaluate the effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden [ASTEROID] trial).