Original Investigation

Association Between *CYP2C19* Loss-of-Function Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients With Minor Stroke or Transient Ischemic Attack

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IMPORTANCE Data are limited regarding the association between *CYP2C19* genetic variants and clinical outcomes of patients with minor stroke or transient ischemic attack treated with clopidogrel.

OBJECTIVE To estimate the association between *CYP2C19* genetic variants and clinical outcomes of clopidogrel-treated patients with minor stroke or transient ischemic attack.

DESIGN, SETTING, AND PARTICIPANTS Three *CYP2C19* major alleles (**2*, **3*, **17*) were genotyped among 2933 Chinese patients from 73 sites who were enrolled in the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) randomized trial conducted from January 2, 2010, to March 20, 2012.

INTERVENTIONS Patients with acute minor ischemic stroke or transient ischemic attack in the trial were randomized to treatment with clopidogrel combined with aspirin or to aspirin alone.

MAIN OUTCOMES AND MEASURES The primary efficacy outcome was new stroke. The secondary efficacy outcome was a composite of new composite vascular events (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death). Bleeding was the safety outcome.

RESULTS Among 2933 patients, 1948 (66.4%) were men, with a mean age of 62.4 years. Overall, 1207 patients (41.2%) were noncarriers and 1726 patients (58.8%) were carriers of loss-of-function alleles (**2*, **3*). After day 90 follow-up, clopidogrel-aspirin reduced the rate of new stroke in the noncarriers but not in the carriers of the loss-of-function alleles ($P = .02$ for interaction; events among noncarriers, 41 [6.7%] with clopidogrel-aspirin vs 74 [12.4%] with aspirin; hazard ratio [HR], 0.51 [95% CI, 0.35-0.75]; events among carriers, 80 [9.4%] with clopidogrel-aspirin vs 94 [10.8%] with aspirin; HR, 0.93 [95% CI, 0.69 to 1.26]). Similar results were observed for the secondary composite efficacy outcome (noncarriers: 41 [6.7%] with clopidogrel-aspirin vs 75 [12.5%] with aspirin; HR, 0.50 [95% CI, 0.34-0.74]; carriers: 80 [9.4%] with clopidogrel-aspirin vs 95 [10.9%] with aspirin; HR, 0.92 [95% CI, 0.68-1.24]; $P = .02$ for interaction). The effect of treatment assignment on bleeding did not vary significantly between the carriers and the noncarriers of the loss-of-function alleles (2.3% for carriers and 2.5% for noncarriers in the clopidogrel-aspirin group vs 1.4% for carriers and 1.7% for noncarriers in the aspirin only group; $P = .78$ for interaction).

CONCLUSIONS AND RELEVANCE Among patients with minor ischemic stroke or transient ischemic attack, the use of clopidogrel plus aspirin compared with aspirin alone reduced the risk of a new stroke only in the subgroup of patients who were not carriers of the *CYP2C19* loss-of-function alleles. These findings support a role of *CYP2C19* genotype in the efficacy of this treatment.

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The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial showed that the combination of clopidogrel with aspirin compared with aspirin alone reduced the risk of stroke among patients with transient ischemic attack (TIA) or minor ischemic stroke who can be treated within 24 hours after the onset of symptoms.[1] Clopidogrel, in combination with aspirin, has become a recommended treatment option for patients with TIA or acute minor stroke.[2,3]

Clopidogrel requires conversion to an active metabolite by hepatic cytochrome p450 (CYP) isoenzymes to exert an antiplatelet effect, and polymorphisms of the *CYP2C19* gene (OMIM 124020) have been identified as strong predictors of clopidogrel nonresponsiveness.[4,5] In the clinical setting the association between *CYP2C19* loss-of-function alleles (especially the most common **2* and **3* variants) and clinical efficacy of clopidogrel has been studied extensively with discordant results.[6-8] The *CYP2C19* gain-of-function allele (**17*) is associated with increased catalytic activity,[9] and its influence on clopidogrel pharmacodynamics and clinical outcomes is unclear.[10] Very limited data are available addressing the effect of *CYP2C19* variants on clopidogrel efficacy in stroke, especially in Asian populations, in which the rates of stroke incidence[11] and mortality[12] are higher compared with white populations. The prevalence of *CYP2C19* loss-of-function variants is also high in Asian populations.[13]

In China, there are approximately 3 million new strokes every year, and approximately 30% of them are minor ischemic strokes.[14] TIA is even more common with an estimate d 23.9 million occurring in 2010, based on a Chinese national survey.[15] Understanding the relationship between *CYP2C19* variants and clinical effect of clopidogrel is critically important to optimize treatment for patients with minor stroke or TIA.

In this study, the efficacy and safety of dual therapy of clopidogrel and aspirin compared with aspirin alone were examined according to genotype status among patients in the trial.

Key Points

Question Do variations in the *CYP2C19* gene, affecting drug metabolism, modify the benefit of clopidogrel in patients with minor stroke or transient ischemic attack?

Findings In this preplanned substudy of a randomized clinical trial that included 2933 adults, clopidogrel in addition to aspirin reduced the rate of new stroke in noncarriers of the *CYP2C19* loss-of-function alleles compared with aspirin alone (6.7% vs 12.4%, a significant difference) but not in carriers (9.4% vs 10.8%, no significant difference).

Meaning Clopidogrel may not confer additional stroke prevention compared with aspirin alone for patients with minor stroke and transient ischemic attack who are carriers of the *CYP2C19* loss-of-function alleles.

Methods

Study Population and Clinical Outcomes

The protocol and data collection were approved by ethics committees of Beijing Tiantan Hospital and all other study centers. All participants or representatives provided written informed consent before being entered into the study. The design and results of the trial have been published previously.[1] In brief, the trial was a randomized, double-blind, placebo-controlled multicenter trial conducted in China comparing clopidogrel (loading dose of 300 mg followed by 75 mg daily for 3 months) plus aspirin (loading dose of 75-300 mg followed by 75 mg daily for 21 days) vs aspirin alone (loading dose of 75-300 mg followed by 75 mg daily for 3 months) among 5170 patients with acute TIA or minor ischemic stroke within 24 hours of symptom onset.

The genetic substudy was prespecified. Seventy-three sites among 114 in the larger trial had prior experience collecting samples for genetic studies and agreed to participate in the substudy. A separate consent form was obtained from patients recruited by these 73 sites. All patients who were recruited to the parent trial also participated in this genetic substudy at these sites. The primary efficacy outcome (new stroke including both ischemic and hemorrhagic stroke) in the current analyses was the same as that in the trial.[1] The secondary efficacy outcome was the composite outcome, a new clinical vascular event (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death), and the safety outcome was any bleeding.[1] All reported efficacy and safety outcomes were confirmed by a central adjudication committee that was blinded to the study group assignments.

Genotyping

Three single-nucleotide polymorphisms (SNPs) for *CYP2C19* (National Center for Biotechnology Information [NCBI] Genome build 37.1, GenBank NG_008384), including *CYP2C19*2* (681G>A, dbSNP rs4244285), *CYP2C19*3* (636G>A, dbSNP rs4986893), and *CYP2C19*17* (−806C>T, dbSNP rs12248560), were genotyped in 3010 participants. Genotyping of the 3 SNPs was performed using the Sequenom MassARRAY iPLEX platform (Sequenom). Details on genotyping technology are presented in the Supplement. The call rate was greater than 98.5% for each of the 3 SNPs. Individuals with complete information for each of the 3 SNPs were included in the current analyses.

Patients were categorized by *CYP2C19* metabolizer status based on **2*, **3*, and **17* genotypes using the common consensus star allele nomenclature.[16] Patients with at least two **2* or **3* alleles (**2/*2*, **2/*3*, or **3/*3*) were classified as poor metabolizers, those with one **2* or **3* allele (**1/*2* or **1/*3*) were classified as intermediate metabolizers, and those without a **2*, **3*, or **17* allele (**1/*1*) were classified as extensive metabolizers. Individuals carrying at least one **17* allele (**1/*17* or **17/*17*) were classified as ultra-metabolizers. Because the clinical consequences of one **17* and a loss-of-function allele (ie, **2* or **3*) still remains unclear[17]; these individuals (**2/*17* or **3/*17*) were classified as unknown metabolizers.[18] Those with at least 1 loss-of-function allele (**2* or **3*) were classified as loss-of-function allele carriers

and those with at least 1 gain-of-function allele (*17) were classified as gain-of-function allele carriers.

Statistical Analysis

The baseline characteristics of the patients were compared between treatment groups, with or without genotype data, and carriers and noncarriers of a *CYP2C19* loss-of-function allele. Proportions were used for categorical variables, and medians with interquartile ranges were used for continuous variables. Nonparametric Kruskal-Wallis test was used to compare group differences for nominal variables, and χ^2 tests for dichotomous variables. Differences in the rate of stroke (ischemic or hemorrhagic), the secondary composite outcome, or any bleeding during the 90-day follow-up period were assessed using Cox proportional hazards regression. Because patients who participated in the current study were a subset of those in the trial, 2 models were adopted to evaluate whether the estimates would be affected by potential divergence from the parent study: 1 unadjusted model and 1 adjusted by age, sex, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), previous or current smoker, minor stroke or TIA at randomization, time to randomization, and medical history including ischemic stroke, TIA, hypertension, diabetes, and hyperlipidemia, with pooled study centers (≥20 patients) as a random effect. Hazard ratios with 95% confidence intervals are reported. When there were multiple events of the same type, the time to the first event was used in the model. Data from patients who had no events during the study were censored at the time of study termination or nonvascular death. For each model, the proportional hazards assumption was assessed by testing the interaction between treatment and time. Whether the treatment effect differed in certain genotype categories was assessed by testing the treatment-by-genotype interaction effect with the use of Cox models adjusted by the factors mentioned previously. Similar approaches were performed in sensitivity analyses for outcome subtypes, including ischemic and hemorrhagic stroke, progressive and recurrent ischemic stroke,[19] and subtypes based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[20] including large artery atherosclerosis, small vessel occlusion, cardiogenic embolism, and other or undetermined etiology. Safety outcome subtypes, including severe, moderate, and mild bleeding, which were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria,[1,21] were also examined. All tests were 2-sided, and a *P* value of .05 was defined to indicate statistical significance. All statistical analyses were performed with SAS software (SAS Institute), version 9.4.

Results

Study Patients

A total of 3010 patients participated and 2933 of them were successfully genotyped for all the 3 SNPs (eFigure 1 in the Supplement). Compared with the trial participants without genetic data, patients included in this study were less likely to have a history of ischemic stroke, diabetes, and hyperlipidemia (eTable 1 in the Supplement). The proportion of patients with a diagnosis of acute minor stroke rather than TIA, or taking concomitant antihypertension agents was higher in the study population compared with the individuals without genetic data.

Among the 2933 participants, 1726 (58.8%) were classified as *CYP2C19* loss-of-function carriers. Patient characteristics were similar between the carriers and the noncarriers and between treatment groups within the carriers or the noncarriers (**Table 1**). In this genetic substudy population, new stroke occurred within 90 days in 8.3% (121 of 1463 patients) in the clopidogrel-aspirin group vs 11.4% (168 of 1470 patients) in the aspirin group (hazard ratio [HR], 0.71 [95% CI, 0.56-0.90]; *P* = .0045). The benefit of clopidogrel-aspirin treatment compared with aspirin alone in patients with genotype data was similar to that in the parent trial population with respect to new stroke—the primary efficacy outcome—as well as the composite efficacy outcome. The rate of any bleeding with clopidogrel-aspirin compared with aspirin in the genotyped patients was also similar to that in the total cohort in the parent trial (eTable 2 in the Supplement).[1]

Clinical Outcomes

The frequency distribution and rate of new stroke for each genotype of the three *CYP2C19* SNPs are shown in **Table 2**. Carriers of the *CYP2C19**2 allele were common, accounting for 52.5% (42.8% for GA and 9.7% for AA genotypes) of the study population, and 9.0% of the genotyped patients were *3 carriers (8.9% for GA and 0.1% for AA genotypes). Gain-of-function allele carriers (CT or TT genotype) were rare in this population. The event rates for the composite event and the safety outcome of any bleeding for each genotype of the three *CYP2C19* SNPs are listed in eTable 3 and eTable 4 in the Supplement, respectively. The minor allele frequencies for the *CYP2C19* *2, *3, and *17 alleles were 31.1%, 4.6%, and 1.0%, respectively.

Event rates for stroke, the composite secondary outcome, and bleeding varied by treatment assignment and genotype (**Figure 1**). Due to the low prevalence of *17 carriers, the number of patients with ultra or unknown metabolizer phenotypes was very small in this study population. No event was observed in the 18 patients with unknown metabolizer phenotype and only 1 ultra metabolizer treated with aspirin had a new stroke. The hazard ratio for patients with ultra or unknown metabolizer phenotypes, as well as the metabolizer phenotype by treatment interaction, were not estimated.

The effect of clopidogrel-aspirin compared with aspirin in reducing the rate of stroke was significant in the noncarriers but not in the carriers of the loss-of-function alleles (rate among noncarriers, 6.7% with clopidogrel-aspirin vs 12.4% with aspirin; HR, 0.51 [95% CI, 0.35-0.75]; rate among carriers, 9.4% with clopidogrel-aspirin vs 10.8% with aspirin; HR, 0.93 [95% CI, 0.69-1.26]; *P* = .02 for interaction). Similar results were observed for the secondary composite

Table 1. Baseline Characteristics Among Individuals With and Without *CYP2C19* Loss-of-Function Alleles Stratified by Treatment Allocation

Covariate	Carrier[a]			Noncarrier[b]		
	Total (n = 1726)	Aspirin (n = 872)	Clopidogrel-Aspirin (n = 854)	Total (n = 1207)	Aspirin (n = 598)	Clopidogrel-Aspirin (n = 609)
Age, median (IQR), y	62.3 (54.5-71.2)	62.3 (54.6-71.1)	62.2 (54.4-71.2)	62.5 (55.0-71.2)	62.2 (54.5-70.6)	63.1 (55.5-71.5)
Male, No. (%)	1164 (67.4)	578 (66.3)	586 (68.6)	784 (65.0)	387 (64.7)	397 (65.2)
BMI, median (IQR)	24.5 (22.8-26.5)	24.6 (22.9-26.7)	24.4 (22.6-26.3)	24.5 (22.5-26.6)	24.5 (22.5-26.6)	24.5 (22.5-26.4)
Medical history, No. (%)						
Ischemic stroke	329 (19.1)	161 (18.5)	168 (19.7)	224 (18.6)	110 (18.4)	114 (18.7)
TIA	48 (2.8)	23 (2.6)	25 (2.9)	42 (3.5)	21 (3.5)	21 (3.4)
Myocardial infarction	35 (2.0)	24 (2.8)	11 (1.3)	16 (1.3)	7 (1.2)	9 (1.5)
Congestive heart failure	24 (1.4)	11 (1.3)	13 (1.5)	25 (2.1)	12 (2.0)	13 (2.1)
Known atrial fibrillation or flutter	22 (1.3)	11 (1.3)	11 (1.3)	26 (2.2)	12 (2.0)	14 (2.3)
Valvular heart disease	4 (0.2)	2 (0.2)	2 (0.2)	4 (0.3)	3 (0.5)	1 (0.2)
Hypertension	1136 (65.8)	567 (65.0)	569 (66.6)	787 (65.2)	386 (64.5)	401 (65.8)
Diabetes mellitus	352 (20.4)	182 (20.9)	170 (19.9)	228 (18.9)	114 (19.1)	114 (18.7)
Hypercholesterolemia	191 (11.1)	94 (10.8)	97 (11.4)	111 (9.2)	55 (9.2)	56 (9.2)
Current or previous smoker, No. (%)	748 (43.3)	368 (42.2)	380 (44.5)	496 (41.1)	241 (40.3)	255 (41.9)
Index event, No (%)						
TIA	458 (26.5)	239 (27.4)	219 (25.6)	326 (27.0)	163 (27.3)	163 (26.8)
Minor stroke	1268 (73.5)	633 (72.6)	635 (74.4)	881 (73.0)	435 (72.7)	446 (73.2)
Time from symptom onset to randomization, median (IQR)	11.5 (6.0-19.0)	12.5 (6.5-20.0)	11.7 (6.5-19.0)	12.0 (6.5-19.5)	12.0 (6.5-19.0)	10.5 (6.0-19.0)
Concomitant medication, No. (%)						
Proton pump inhibitors	10 (0.6)	5 (0.6)	5 (0.6)	10 (0.8)	4 (0.7)	6 (1.0)
Antihypertensive agents	653 (37.8)	328 (37.6)	325 (38.1)	452 (37.4)	222 (37.1)	230 (37.8)
Antidiabetes agents	203 (11.8)	103 (11.8)	100 (11.7)	160 (13.3)	81 (13.5)	79 (13.0)
Lipid-lowering agents	754 (43.7)	369 (42.3)	385 (45.1)	496 (41.1)	238 (39.8)	258 (42.4)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; TIA, transient ischemic attack.

[a] Loss-of-function allele carriers were defined as patients with at least one *CYP2C19* loss-of-function allele (ie, **2* or **3*): **1/*2*, **1/*3*, **2/*2*, **2/*3*, **3/*3*, **2/*17*, or **3/*17*.

[b] Loss-of-function noncarriers were defined as patients with no *CYP2C19* loss-of-function allele: **1/*1*, **1/*17*, or **17/*17*.

Table 2. Distribution and Event Rates of New Stroke by Genotype for Each of the Three *CYP2C19* SNPs

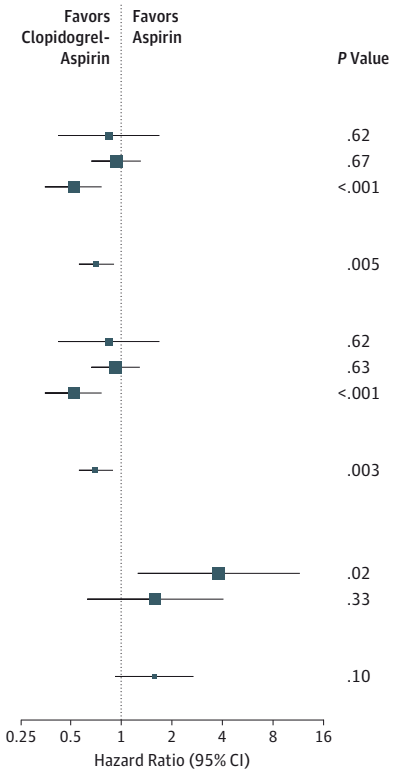
	Overall, No. (%)		Aspirin, No. (%)		Clopidogrel-Aspirin, No. (%)	
	Frequency (N = 2933)	Event Rate	Frequency (n = 1470)	Event Rate	Frequency (n = 1463)	Event Rate
*CYP2C19*2* (681G>A)						
GG	1392 (47.5)	131 (9.4)	692 (47.1)	82 (11.8)	700 (47.9)	49 (7.0)
GA	1255 (42.8)	130 (10.4)	636 (43.3)	72 (11.3)	619 (42.3)	58 (9.4)
AA	286 (9.7)	28 (9.8)	142 (9.6)	14 (9.9)	144 (9.8)	14 (9.7)
*CYP2C19*3* (636G>A)						
GG	2669 (91.0)	266 (10.0)	1334 (90.7)	156 (11.7)	1335 (91.3)	110 (8.2)
GA	260 (8.9)	22 (8.5)	132 (9.0)	11 (8.3)	128 (8.7)	11 (8.6)
AA	4 (0.1)	1 (25.0)	4 (0.3)	1 (25.0)	0	NE
*CYP2C19*17* (−806C>T)						
CC	2875 (98.0)	288 (10.0)	1442 (98.1)	167 (11.6)	1433 (98.0)	121 (8.4)
CT	58 (2.0)	1 (1.7)	28 (1.9)	1 (3.6)	30 (2.0)	0 (0)

Abbreviation: NE, not estimable.

efficacy outcome (**Table 3**). Treatment assignment was not associated with bleeding in either carriers or noncarriers and did not differ between the carriers and the noncarriers (P = .78 for interaction, Table 3). Similar results were obtained from the unadjusted and adjusted models, and therefore only the results from the unadjusted model are

Figure 1. Clopidogrel-Aspirin vs Aspirin on Clinical Outcome Stratified by Metabolizer Phenotype

Outcome and Metabolizer Phenotype	Aspirin: No. of Patients With Events/Total Patients (%)	Clopidogrel-Aspirin: No. of Patients With Events/Total Patients (%)	Hazard Ratio (95% CI)	*P* Value
Stroke				
Metabolizer phenotype				
Poor	19/188 (10.1)	17/181 (9.4)	0.84 (0.42-1.69)	.62
Intermediate	75/675 (11.1)	63/664 (9.5)	0.93 (0.66-1.30)	.67
Extensive	73/579 (12.6)	41/588 (7.0)	0.52 (0.35-0.76)	<.001
Ultra	1/19 (5.3)	0/21 (0.0)	NE	
Unknown	0/9 (0.0)	0/9 (0.0)	NE	
Total	168 (11.4)	121 (8.3)	0.71 (0.56-0.90)	.005
Composite event				
Metabolizer phenotype				
Poor	19/188 (10.1)	17/181 (9.4)	0.84 (0.42-1.69)	.62
Intermediate	76/675 (11.3)	63/664 (9.5)	0.92 (0.66-1.29)	.63
Extensive	73/579 (12.6)	41/588 (7.0)	0.52 (0.35-0.76)	<.001
Ultra	2/19 (10.5)	0/21 (0.0)	NE	
Unknown	0/9 (0.0)	0/9 (0.0)	NE	
Total	170 (11.6)	121 (8.3)	0.70 (0.56-0.89)	.003
Bleeding				
Metabolizer phenotype				
Poor	4/188 (2.1)	2/181 (1.1)	NE	
Intermediate	8/675 (1.2)	18/664 (2.7)	3.80 (1.25-11.55)	.02
Extensive	9/579 (1.6)	15/588 (2.6)	1.59 (0.62-4.07)	.33
Ultra	1/19 (5.3)	0/21 (0.0)	NE	
Unknown	0/9 (0.0)	0/9 (0.0)	NE	
Total	22 (1.5)	35 (2.4)	1.57 (0.92-2.68)	.10



NE indicates not estimable. Patients with two **2* or **3* alleles (ie, **2/*2*, **2/*3*, or **3/*3*) were classified as having the poor metabolizer phenotype, those with one **2* or **3* allele (ie, **1/*2* or **1/*3*) were classified as having the intermediate metabolizer phenotype, those without a **2*, **3*, or **17* allele (ie, **1/*1*) were classified as having the extensive metabolizer phenotype, those with a single **17* allele (ie, **1/*17*) and **17* homozygotes were classified as having the ultra metabolizer phenotype. Composite event was defined as a new clinical vascular event, including ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death. The size of the data markers indicate the sample size of the subgroup.

presented. The corresponding cumulative risk curves demonstrated findings consistent with the analyses using Cox models and showed that most events occurred in the first few days (**Figure 2**).

Similar trends were observed for outcome subtypes including progressive and recurrent ischemic stroke, large artery atherosclerosis, and small vessel occlusion as shown in eTable 5 in the Supplement, and the finding for progressive ischemic stroke was statistically significant ($P = .04$ for interaction effect). There were 20 out of 2933 patients who had concomitant usage of proton pump inhibitors with high events rates compared with those without proton pump inhibitor usage (eTable 6 in the Supplement).

Secondary Analysis

The association between *CYP2C19* loss-of-function carrier status with the clinical outcomes was tested in patients who received clopidogrel-aspirin dual treatment or aspirin only separately. The event rates for both stroke and the composite outcome (rates were same as for stroke) were higher in carriers compared with noncarriers (9.4% for carriers vs 6.7% for noncarriers; HR, 1.46 [95% CI, 1.05-2.13]; $P = .047$) receiving clopidogrel-aspirin treatment. No difference in either stroke (10.8% for carriers vs 12.4% for noncarriers; HR, 0.86 [95% CI, 0.66-1.17]; $P = .34$) or the composite outcome (10.9% for carriers vs 12.5% for noncarriers; HR, 0.86 [95% CI, 0.63-1.16]; $P = .32$) between carriers and noncarriers were observed in aspirin-treated group. The rate of any bleeding did not vary between carriers and noncarriers from either clopidogrel-aspirin-treated group (2.3% for carriers vs 2.5% for noncarriers; HR, 0.99 [95% CI, 0.51-1.94]; $P = .98$) or the group treated with aspirin only (1.4% for carriers vs 1.7% for noncarriers; HR, 0.92 [95% CI, 0.39-2.17]; $P = .86$).

Discussion

In this substudy, the *CYP2C19* loss-of-function carrier genotypes were associated with less protection from subsequent stroke and composite vascular events for patients with acute minor stroke or TIA treated with clopidogrel and aspirin compared with noncarrier status. The differences in response to therapy were largely driven by that within the noncarriers. Increased risk for stroke and composite vascular events was observed in carriers compared with noncarriers of *CYP2C19* loss-of-function alleles in patients treated with clopidogrel-

Table 3. Effect of Clopidogrel-Aspirin Compared With Aspirin on Clinical Outcome Stratified by *CYP2C19* Loss-of-Function Carrier Status

	Carriers[a]					Noncarriers[b]					
	No. (%)					No. (%)					
Outcome	Total (n = 1726)	Aspirin (n = 872)	Clopidogrel-Aspirin (n = 854)	Hazard Ratio (95% CI)	*P* Value	Total (n = 1207)	Aspirin (n = 598)	Clopidogrel-Aspirin (n = 609)	Hazard Ratio (95% CI)	*P* Value	*P* Value for Interaction
Stroke	174 (10.1)	94 (10.8)	80 (9.4)	0.93 (0.69-1.26)	.64	115 (9.5)	74 (12.4)	41 (6.7)	0.51 (0.35-0.75)	<.01	.02
Composite event[c]	175 (10.1)	95 (10.9)	80 (9.4)	0.92 (0.68-1.24)	.59	116 (9.6)	75 (12.5)	41 (6.7)	0.50 (0.34-0.74)	<.01	.02
Ischemic stroke	171 (9.9)	93 (10.7)	78 (9.1)	0.85 (0.63-1.15)	.29	113 (9.4)	74 (12.4)	39 (6.4)	0.51 (0.34-0.75)	<.01	.03
Bleeding[d]											
Severe	1 (0.1)	0 (0.0)	1 (0.1)	NE		1 (0.1)	1 (0.2)	0 (0.0)	NE		
Moderate	2 (0.1)	0 (0.0)	2 (0.2)	NE		0 (0.0)	0 (0.0)	0 (0.0)	NE		
Mild	10 (0.6)	2 (0.2)	8 (0.9)	4.05 (0.86-19.05)	.08	16 (1.3)	7 (1.2)	9 (1.5)	1.23 (0.46-3.29)	.69	.20
Any bleeding	32 (1.9)	12 (1.4)	20 (2.3)	1.65 (0.80-3.40)	.17	25 (2.1)	10 (1.7)	15 (2.5)	1.42 (0.64-3.15)	.39	.78

Abbreviation: NE, not estimable.

[a] Loss-of-function allele carriers were defined as patients with at least one *CYP2C19* loss-of-function allele (ie, **2* or **3*): **1/*2*, **1/*3*, **2/*2*, **2/*3*, **3/*3*, **2/*17*, or **3/*17*.

[b] Loss-of-function noncarriers were defined as patients with no *CYP2C19* loss-of-function allele: **1/*1*, **1/*17*, or **17/*17*.

[c] Composite event was defined as a new clinical vascular event, including ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death.

[d] Bleeding events were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria as follows: severe bleeding was defined as fatal or intracranial hemorrhage or other hemorrhage causing hemodynamic compromise that required blood or fluid replacement, inotropic support, or surgical intervention; moderate bleeding as bleeding that required transfusion of blood but did not lead to hemodynamic compromise requiring intervention; and mild bleeding as bleeding not requiring transfusion and not causing hemodynamic compromise (eg, subcutaneous bleeding, mild hematomas, and oozing from puncture sites).

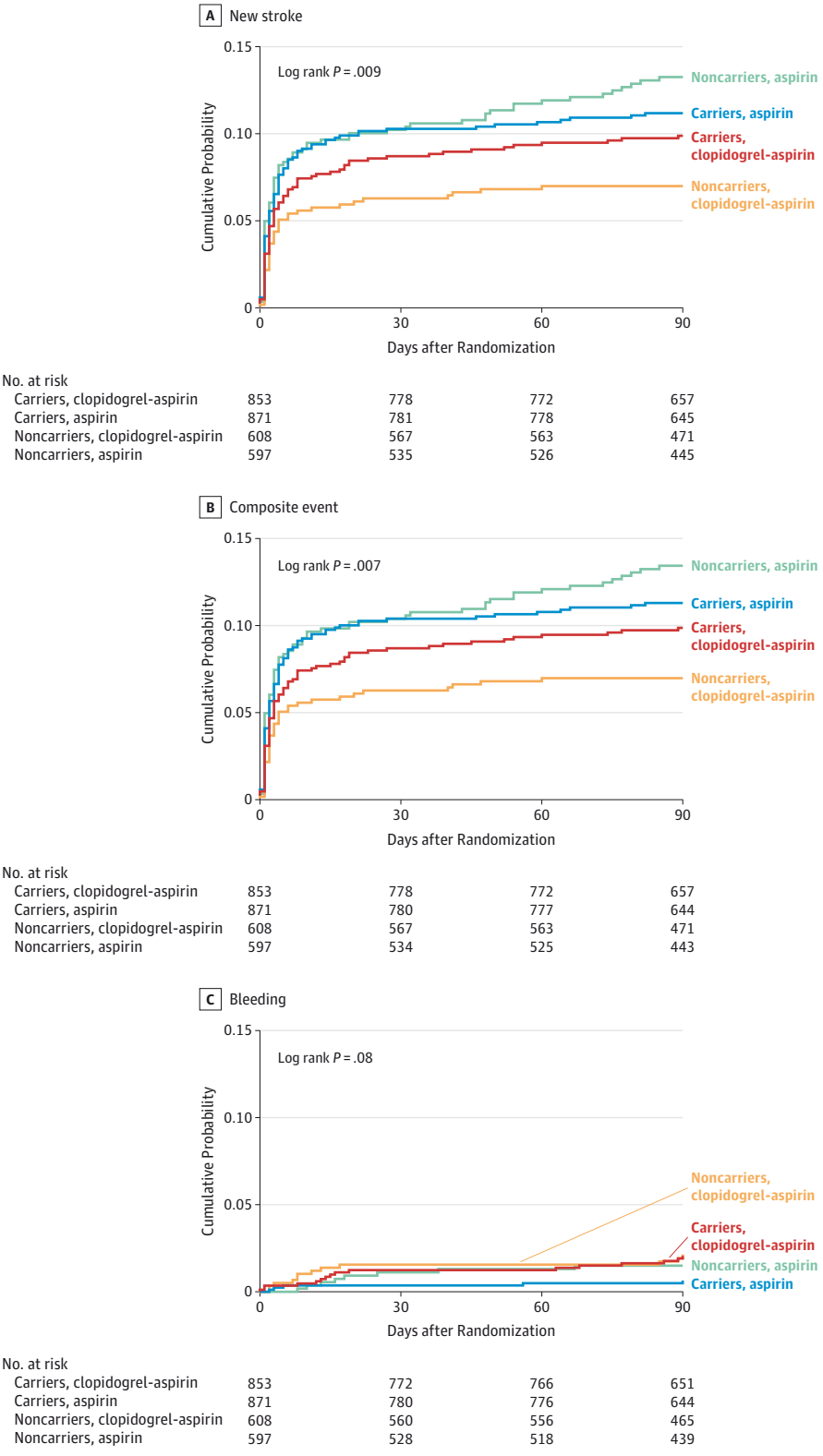
aspirin. The risk of any bleeding for clopidogrel-aspirin treatment compared with aspirin was not modified by the loss-of-function genotype.

There are limited data available addressing the association of *CYP2C19* variants with clopidogrel efficacy in stroke. Three recent small studies reported an association between *CYP2C19*2* loss-of-function allele and elevated risk of poor outcome in patients receiving clopidogrel.[22-24] In a group of 176 white patients with small subcortical stroke who received clopidogrel and aspirin, *CYP2C19*2* loss-of-function allele was associated with increased risk of stroke compared with extensive or ultrarapid (**17*) metabolizer phenotypes.[23] No such association was observed in either African American or Spanish patients. Sun and colleagues[24] observed an increased risk of a composite of vascular events (including vascular death, nonfatal ischemic stroke, and nonfatal myocardial infarction) during 3-month follow-up in carriers compared with noncarriers of *CYP2C19*2* or *CYP2C19*3* alleles in a cohort of 625 consecutive patients with ischemic stroke receiving clopidogrel. No association between bleeding and carrier status was observed in either of the 2 studies.[23,24] The results from the clopidogrel-aspirin-treated group support both of their findings. Jia and colleagues[22] and Yang and colleagues.[25] reported an association between *CYP2C19* loss-of-function allele (**2* or **3*) and elevated adenosine-diphosphate-induced platelet aggregation in stroke patients with clopidogrel treatment. Compared with previous studies, this study population is larger with increased power and precision. This study included a randomized control group (patients treated with aspirin only) to evaluate the effect of genotype status on clopidogrel efficacy whereas the prior studies were conducted exclusively in patients with clopidogrel treatment (with or without aspirin). Including a randomized control group allowed us to avoid pleiotropic effect-of-function alleles and other potential confounding.[18]

The frequency of *CYP2C19* loss-of-function alleles in this study was 58.8% (1726 of 2933 patients), similar to that which has been reported in other East Asian populations,[24,26] and higher than that in other populations, where it has ranged from 18% in Mexicans to 33% in African Americans.[13,17,27] This study provided evidence supporting genetic testing that may allow clinicians to personalize antiplatelet therapy, especially in East Asian patient populations for whom the prevalence of *CYP2C19* loss-of-function allele is high. However, clopidogrel is currently the only approved antiplatelet agent adjunct to aspirin after stroke or TIA, so there is no existing alternative in the acute period. Varying the dose of clopidogrel or shifting to new antiplatelet agents (eg, prasugrel) based on genetic results may be alternatives but have not been adequately evaluated.[28]

There were several limitations in this study. Because the baseline data were not available for study participants, it was not possible to assess the effect of stroke mechanisms on the pharmacogenetic effect of *CYP2C19* observed in this study. Aspirin resistance is well documented.[29] Because aspirin aggregability function was not tested in this study, it remains possible that more aspirin-resistant patients were randomly included in the *CYP2C19* loss-of-function carriers, and therefore influenced the patients' outcomes in this group. The event rates for bleeding were very low in this population; therefore the statistic power was limited to detect any association with this safety outcome. In addition, this study was

Figure 2. Cumulative Probability of Stroke, Composite Event, and Bleeding According to Loss-of-Function Allele Carrier Status



Loss-of-function allele carriers were defined as patients with at least 1 loss-of-function allele (ie, **2* or **3*): **1/*2*, **1/*3*, **2/*2*, **2/*3*, **3/*3*, **2/*17*, or **3/*17*; loss-of-function allele noncarriers were defined as patients with no loss-of-function allele: **1/*1*, **1/*17*, or **17/*17*. Composite event was defined as a new clinical vascular event, including ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death.

conducted exclusively among Chinese patients, therefore the results may not apply to other settings.

The ongoing Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial, sponsored by the

National Institutes of Health, which is similar to this trial, is currently enrolling patients at sites primarily in North America and Europe. The POINT trial is assessing a higher loading dose of clopidogrel (600 mg) and a narrower time window (treatment within 12 hours after symptom onset).[30] It will be important to compare the association of *CYP2C19* variants with efficacy of clopidogrel in a different population before applying these results to non-Asian populations, particularly given the variability in results of cardiovascular studies.

Conclusions

Among patients with minor ischemic stroke or transient ischemic attack, the use of clopidogrel plus aspirin compared with aspirin alone reduced the risk of a new stroke only in the subgroup of patients who were not carriers of the *CYP2C19* loss-of-function alleles. These findings support a role of *CYP2C19* genotype in the efficacy of this treatment.

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