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Association Between *ABCB1* Polymorphisms and Outcomes of Clopidogrel Treatment in Patients With Minor Stroke or Transient Ischemic Attack

Secondary Analysis of a Randomized Clinical Trial

Yuesong Pan, PhD; Weiqi Chen, MD, PhD; Yilong Wang, MD, PhD; Hao Li, PhD; S. Claiborne Johnston, MD, PhD; Tabassome Simon, MD, PhD; Xingquan Zhao, MD, PhD; Liping Liu, MD, PhD; David Wang, DO; Xia Meng, MD, PhD; Yongjun Wang, MD; for the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) Investigators

IMPORTANCE Genetic variants of *ABCB1* may affect intestinal absorption of clopidogrel bisulfate. However, it is unclear whether *ABCB1* polymorphisms are associated with clopidogrel efficacy for minor ischemic stroke or transient ischemic attack (TIA).

OBJECTIVES To investigate the association between *ABCB1* polymorphisms and clopidogrel efficacy for minor stroke or TIA.

DESIGN, SETTING, AND PARTICIPANTS In this prespecified secondary analysis of the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) randomized clinical trial, 3010 patients with minor stroke or TIA at 73 sites in China with experience in conducting genetic studies were included from October 1, 2009, to July 30, 2012. The analysis was conducted on March 20, 2018. Four single-nucleotide polymorphisms (*ABCB1* -154T>C [rs4148727], *ABCB1* 3435C>T [rs1045642], *CYP2C19*2* [681G>A, rs4244285], and *CYP2C19*3* [636G>A, rs4986893]) were genotyped among 2836 patients treated with clopidogrel plus aspirin (n = 1414) or aspirin alone (n = 1422). The association of *ABCB1* genetic variants (-154 TC/CC and 3435 CT/TT) with clopidogrel efficacy was evaluated in the context of *CYP2C19* status, another gene associated with clopidogrel efficacy.

INTERVENTIONS Patients in the CHANCE trial were randomized to treatment with clopidogrel combined with aspirin or to aspirin alone.

MAIN OUTCOMES AND MEASURES Primary efficacy outcome was stroke recurrence after 3 months. The safety outcome was any bleeding risk after 3 months.

RESULTS Among 2836 patients, the median age was 61.8 years (interquartile range, 54.4-71.1 years) and 1887 patients (66.5%) were male. A total of 2146 (75.7%) patients were carriers of *ABCB1* -154 TC/CC (570 [20.1%]) or 3435 CT/TT (1851 [65.3%]) genotype. Clopidogrel plus aspirin treatment was associated with reduced risk of new stroke in patients with *ABCB1* -154 TT and 3435 CC genotype (hazard ratio [HR], 0.43; 95% CI, 0.26-0.71) but not in those with *ABCB1* -154 TC/CC or 3435 CT/TT genotype (HR, 0.78; 95% CI, 0.60-1.03) compared with aspirin (P = .04 for interaction). A combined association of *ABCB1* and *CYP2C19* polymorphisms with new stroke was observed. The risk of bleeding for clopidogrel plus aspirin treatment was not associated with the *ABCB1* genotypes (2.3% and 1.3% vs 1.9% and 2.2%; P = .25 for interaction in patients with or without *ABCB1* -154 TC/CC or 3435 CT/TT genotype)

CONCLUSIONS AND RELEVANCE The *ABCB1* polymorphism was associated with the reduced efficacy of clopidogrel plus aspirin treatment compared with aspirin among patients with minor ischemic stroke or TIA. Genetic polymorphism of *ABCB1* should be considered when prescribing clopidogrel for these patients.

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Editorial
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) Investigators are listed at the end of the article.

Corresponding Author: Yongjun Wang, MD, No.119, South 4th Ring West Road, Fengtai District, Beijing, China, 100070 (yongjunwang@ncrcnd.org.cn).

Clopidogrel bisulfate combined with aspirin is a recommended treatment for patients with acute minor ischemic stroke or transient ischemic attack (TIA).[1-3] However, despite clopidogrel use, a substantial number of patients experience recurrent stroke, which may be explained at least in part by inadequate platelet inhibition.[4,5]

Clopidogrel is a prodrug that requires intestinal absorption and biotransformation to active metabolites by hepatic cytochrome P450 enzymes (CYP450). Previous studies showed that reduced function of *CYP2C19* (OMIM 124020), a gene encoding CYP450, was associated with increased adverse cardiovascular events in patients with coronary artery disease[6,7] or stroke[8-10] treated with clopidogrel. In addition, polymorphisms of the genes regulating intestinal absorption of clopidogrel, such as the gene *ABCB1* (OMIM 171050) encoding the P-glycoprotein multidrug-resistant-1 efflux transporter, might also affect clinical outcomes.[11] Several,[7,12,13] but not all,[14,15] previous studies showed an association of *ABCB1* 3435C>T polymorphisms with reduced efficacy of clopidogrel treatment in coronary artery disease. Recent studies did not detect this association in patients with ischemic stroke.[16,17] However, the sample sizes of these studies were relatively small. Therefore, the association between *ABCB1* polymorphisms and the efficacy of clopidogrel treatment in patients with stroke or TIA remains unclear.

The previous genetic secondary analysis of the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) trial showed reduced efficacy of dual therapy of clopidogrel and aspirin in carriers of the *CYP2C19* loss-of-function alleles.[10] In the present study, we further estimate the efficacy and safety of dual therapy of clopidogrel and aspirin compared with aspirin alone according to *ABCB1* genotypes in the context of *CYP2C19* status among patients in the trial.

Key Points

Question Are *ABCB1* genetic variants associated with the efficacy of clopidogrel bisulfate for minor stroke or transient ischemic attack?

Findings In this secondary analysis of a randomized clinical trial that included 2836 adults, clopidogrel plus aspirin was associated with a significant reduction in the risk of new stroke in patients with *ABCB1* -154 TT and 3435 CC genotype but not in those with *ABCB1* -154 TC/CC or 3435 CT/TT genotype compared with aspirin alone.

Meaning *ABCB1* genetic variants may be associated with the efficacy of clopidogrel for treatment of minor stroke or transient ischemic attack.

Methods

Study Participants

Details on the rationale, design, and results of the CHANCE trial (NCT00979589) have been published previously.[1,18,19] The trial protocol is given in Supplement 1. In brief, CHANCE was a randomized, double-blind, controlled clinical trial conducted at 114 hospitals in China between October 1, 2009, and July 30, 2012, that compared the efficacy of clopidogrel bisulfate (loading dose of 300 mg followed by 75 mg daily for 90 days) plus aspirin (loading dose of 75-300 mg followed by 75 mg daily for 21 days) with aspirin alone (loading dose of 75-300 mg followed by 75 mg daily for 90 days) among 5170 patients within 24 hours after onset of a minor ischemic stroke (National Institutes of Health Stroke Scale ≤3) or high-risk TIA (ABCD [age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes][2]≥4). The protocol of the CHANCE trial was approved by the ethics committee of Beijing Tiantan Hospital and all participating centers. Each participant or his or her representative provided written informed consent before being entered into the study. Data were analyzed on March 20, 2018.

Seventy-three sites with experience collecting samples for genetic studies agreed to participate in the prespecified genetic secondary analysis. All patients at these sites for whom a separate written informed consent was obtained participated in this genetic secondary analysis.

Genotyping

Details on genotyping technology were published previously.[10] Two single-nucleotide polymorphisms (SNPs) of the *ABCB1* gene (-154T>C, rs4148727 and 3435C>T, rs1045642) were genotyped in 3010 participants. Participants were classified as homozygous for the T allele (TT), heterozygous (TC), or homozygous for the C allele (CC) for *ABCB1* -154T>C SNP and homozygous for the C allele (CC), heterozygous (CT), or homozygous for the T allele (TT) for *ABCB1* 3435C>T SNP.

Because genetic variations in *CYP2C19* (*CYP2C19*2* [681G>A, rs4244285] and *CYP2C19*3* [636G>A, rs4986893]) were associated with new stroke among clopidogrel-treated patients with minor stroke or TIA,[10] we also evaluated the influence of *ABCB1* polymorphism in the context of *CYP2C19* status to understand the independent contribution of *ABCB1* polymorphism. Patients with at least 1 loss-of-function allele (*2 or *3) were classified as *CYP2C19* loss-of-function allele carriers.[10]

Genotyping of the 4 SNPs was centralized and performed using the Sequenom MassARRAY iPLEX platform (Sequenom). Genotyping success rate was greater than 94.3% among all samples genotyped for each of the 4 SNPs. The 2836 individuals with complete information for each of the 4 SNPs were included in the current analyses.

Clinical Outcomes

The definitions of the outcomes in the current analyses were identical to those in the trial.[1] The primary outcome was a new stroke (ischemic or hemorrhagic) during the 90-day follow-up period. Secondary outcomes were new vascular events (composite of ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death) and ischemic stroke at 90 days. The primary safety outcome was any bleeding. Safety outcome subtypes, including severe, moderate, and mild bleeding, defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) randomized trial criteria,[20] were also

examined. All reported efficacy and safety events were verified by a central adjudication committee that was blinded to the study group assignments.

Statistical Analysis

Continuous variables were presented as medians with interquartile ranges and categorical variables as percentages. Baseline characteristics between patients with and without genetic data were compared by Wilcoxon rank sum test for continuous variables and χ^2 test for categorical variables. Baseline characteristics for patients with and without *ABCB1* -154 TC/CC or 3435 CT/TT genotype stratified by treatment allocation were described separately. The linkage disequilibrium block and haplotype structure were measured by D′ among the 2 *ABCB1* SNPs. Hardy-Weinberg equilibrium was evaluated with a χ^2 test.

Differences in the outcome end points during the 90-day follow-up period were assessed using a Cox proportional hazards regression model, and hazard ratios (HRs) with 95% CIs were 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 event during the study were censored at termination of the trial or nonvascular death. For each model, the proportional hazards assumption was assessed by testing the interaction of treatment by time in the model. Whether the treatment effect differed in certain genotype categories was examined by testing the interactions of treatment by *ABCB1* genotype and treatment by *CYP2C19* loss-of-function allele carrier status in a multivariable Cox model. This model also included treatment group, *ABCB1* genotype, *CYP2C19* loss-of-function allele carrier status, and interaction of *ABCB1* genotype by *CYP2C19* loss-of-function allele carrier status. To exclude the influence of *CYP2C19* polymorphism, we further assessed the association of *ABCB1* polymorphism with the treatment effect among carriers and noncarriers of *CYP2C19* loss-of-function allele.

All tests were 2-sided, and $P < .05$ was considered to be statistically significant. The linkage disequilibrium block and haplotype structure were estimated using the *genetics* package version 3.5.1 in R (R Development Core Team). All other analyses were conducted with SAS, version 9.4 (SAS Institute Inc).

Results

Study Patients

A total of 3010 patients participated in the genetic substudy, of whom 2836 were successfully genotyped for all 4 SNPs (eFigure 1 in Supplement 2). Compared with the 2334 individuals without genetic data, patients included in this genetic study were less likely to have a history of ischemic stroke but more likely to have a history of congestive heart failure and a diagnosis of minor stroke rather than TIA and to be taking concomitant antihypertensive agents (eTable 1 in Supplement 2). The baseline characteristics between the clopidogrel plus aspirin and aspirin alone groups were well balanced in this genetic substudy (eTable 2 in the Supplement 2).

Among the 2836 patients with genetic data, the median (interquartile range) age was 61.8 (54.4-71.1) years, 1887 patients (66.5%) were male, 2077 (73.2%) presented with minor stroke, and 759 (26.8%) presented with TIA. In total, 2266 (79.9%) were TT homozygotes, 507 (17.9%) were TC heterozygotes, and 63 (2.2%) were CC homozygotes for *ABCB1* -154T>C. For *ABCB1*, 3435C>T, 985 (34.7%) were CC homozygotes, 1424 (50.2%) were CT heterozygotes, and 427 (15.1%) were TT homozygotes. A total of 2146 patients (75.7%) were carriers of *ABCB1* -154 TC/CC or 3435 CT/TT genotype (ie, carriers of minor allele of *ABCB1* -154T>C or *ABCB1* 3435C>T). Baseline characteristics for patients with and without *ABCB1* -154 TC/CC or 3435 CT/TT genotype stratified by treatment allocation are presented in **Table 1**.

The linkage disequilibrium block in the 2 *ABCB1* SNPs was not constructed, and we did not show the haplotype in the 2 *ABCB1* SNPs (D′ = 0.67). The 2 *CYP2C19* genetic variants were found to be in Hardy-Weinberg equilibrium (*CYP2C19**2, $P = .87$; *CYP2C19**3, $P = .36$), whereas the 2 *ABCB1* genetic variants were found to be deviated from Hardy-Weinberg equilibrium (*ABCB1* -154T>C, $P = .001$; *ABCB1 3435C>T*, $P = .02$).

Efficacy Outcomes

Clopidogrel plus aspirin compared with aspirin was associated with a reduced rate of new stroke in patients with *ABCB1* -154 TT and 3435 CC genotype (HR, 0.43; 95% CI, 0.26-0.71; $P < .001$) but not in those with *ABCB1* -154 TC/CC or 3435 CT/TT genotype (HR, 0.78; 95% CI, 0.60-1.03; $P = .08$) ($P = .04$ for interaction) (**Table 2**). Cumulative risk of new stroke among patients with or without *ABCB1* -154 TC/CC or 3435 CT/TT genotype by treatment assignment is shown in **Figure 1**A. Separate analyses according to *CYP2C19* loss-of-function allele carrier status showed a combined association of *ABCB1* and *CYP2C19* polymorphisms with new stroke at 3 months (HR, 0.28; 95% CI, 0.12-0.63; $P = .002$ in patients with *ABCB1* -154 TT and 3435 CC genotype and without CYP2C19 loss-of-function allele) (**Figure 2**). Similar results were observed for the outcomes of composite event ($P = .04$ for interaction) and ischemic stroke ($P = .04$ for interaction) (Table 2).

For the *ABCB1* -154T>C genotype, the association of clopidogrel plus aspirin compared with aspirin with a reduced rate of new stroke was observed in TT homozygotes (7.8% vs 12.8%; HR, 0.59; 95% CI, 0.46-0.77; $P < .001$) but not in TC heterozygotes (9.7% vs 6.9%; HR, 1.42; 95% CI, 0.77-2.63; $P = .26$) or CC homozygotes (11.4% vs 17.9%; HR, 0.63; 95% CI, 0.17-2.34; $P = .49$; $P = .047$ for interaction) (eFigure 2 in the Supplement 2). Separated analyses only including noncarriers of *CYP2C19* loss-of-function allele showed similar results ($P = .049$ for interaction), whereas the clopidogrel plus aspirin group had similar rate of new stroke as the aspirin group irrespective of *ABCB1* -154T>C genotypes in carriers of *CYP2C19* loss-of-function allele ($P = .42$ for interaction) (eFigures 3 and 4 in Supplement 2). Similar results were observed for the outcomes of composite vascular event and ischemic stroke (**Table 3** and eTables 3 and 4 in Supplement 2).

For the *ABCB1* 3435C>T genotype, rates of new stroke were lower in the clopidogrel plus aspirin group than in the aspirin

Table 1. Baseline Characteristics Between Carriers and Noncarriers of *ABCB1* -154 TC/CC or 3435 CT/TT Genotype Stratified by Treatment Assignment[a]

Covariate	Carriers[b]			Noncarriers[c]		
	Total (n = 2146)	Aspirin (n = 1099)	Clopidogrel Plus Aspirin (n = 1047)	Total (n = 690)	Aspirin (n = 323)	Clopidogrel Plus Aspirin (n = 367)
Age, median (IQR), y	61.8 (54.4-71.0)	61.6 (54.3-70.5)	61.8 (54.4-71.3)	62.2 (54.8-71.5)	61.8 (53.4-72.0)	62.7 (55.4-71.3)
Male sex	1424 (66.4)	709 (64.5)	715 (68.3)	463 (67.1)	222 (68.7)	241 (65.7)
BMI, median (IQR)	24.6 (22.8-26.6)	24.7 (22.9-26.8)	24.5 (22.5-26.5)	24.4 (22.7-26.6)	24.3 (22.6-26.6)	24.4 (22.7-26.6)
Medical history						
Ischemic stroke	411 (19.2)	205 (18.7)	206 (19.7)	121 (17.5)	59 (18.3)	62 (16.9)
TIA	56 (2.6)	32 (2.9)	24 (2.3)	29 (4.2)	9 (2.8)	20 (5.5)
Myocardial infarction	36 (1.7)	21 (1.9)	15 (1.4)	11 (1.6)	7 (2.2)	4 (1.1)
Congestive heart failure	36 (1.7)	16 (1.5)	20 (1.9)	17 (2.5)	8 (2.5)	9 (2.4)
Known atrial fibrillation or flutter	34 (1.6)	17 (1.5)	17 (1.6)	16 (2.3)	9 (2.8)	7 (1.9)
Valvular heart disease	5 (0.2)	2 (0.2)	3 (0.3)	4 (0.6)	4 (1.2)	0
Hypertension	1412 (65.8)	710 (64.6)	702 (67.0)	448 (64.9)	206 (63.8)	242 (65.9)
Diabetes mellitus	424 (19.8)	221 (20.1)	203 (19.4)	148 (21.4)	67 (20.7)	81 (22.1)
Hypercholesterolemia	227 (10.6)	106 (9.6)	121 (11.6)	66 (9.6)	33 (10.2)	33 (9.0)
Current or previous smoker	933 (43.5)	464 (42.2)	469 (44.8)	287 (41.6)	136 (42.1)	151 (41.1)
Index event						
TIA	565 (26.3)	301 (27.4)	264 (25.2)	194 (28.1)	89 (27.6)	105 (28.6)
Minor stroke	1581 (73.7)	798 (72.6)	783 (74.8)	496 (71.9)	234 (72.5)	262 (71.4)
Time from symptom onset to randomization, median (IQR)	12.0 (6.5-19.5)	12.5 (6.5-19.5)	11.7 (6.0-19.4)	11.5 (6.4-18.7)	12.0 (6.5-19.0)	11.1 (6.2-18.3)
Concomitant medication						
Proton pump inhibitors	11 (0.5)	6 (0.5)	5 (0.5)	11 (1.6)	3 (0.9)	8 (2.2)
Antihypertensive agents	828 (38.8)	432 (39.4)	396 (38.2)	241 (35.1)	100 (31.1)	141 (38.5)
Antidiabetic agents	266 (12.5)	141 (12.9)	125 (12.0)	88 (12.8)	40 (12.5)	48 (13.1)
Lipid-lowing agents	927 (43.5)	461 (42.1)	466 (44.9)	273 (39.7)	120 (37.4)	153 (41.8)

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

[a] Data are presented as number (percentage) of participants unless otherwise indicated.

[b] Carriers were defined as patients with *ABCB1* -154 TC/CC or 3435 CT/TT genotype.

[c] Noncarriers were defined as patients with *ABCB1* -154 TT and 3435 CC genotypes.

group irrespective of *ABCB1* 3435C>T polymorphism (rate among CC homozygotes, 7.9% vs 12.5%; HR, 0.62; 95% CI, 0.41-0.92; *P* = .02; rate among CT heterozygotes, 8.8% vs 11.7%; HR, 0.75; 95% CI, 0.54-1.04; *P* = .08; rate among TT homozygotes, 7.1% vs 11.3%; HR, 0.62; 95% CI, 0.33-1.17; *P* = .14; *P* = .78 for interaction) (eFigure 2 in Supplement 2). The *ABCB1* 3435C>T genotype was not associated with modified efficacy of clopidogrel plus aspirin treatment in carriers or in noncarriers of *CYP2C19* loss-of-function allele (*P* = .70 for interaction in carriers; and *P* = .94 for interaction in noncarriers) (eFigures 3 and 4 in Supplement 2). Similar results were observed as those for the outcomes of composite event and ischemic stroke (eTables 5-7 in Supplement 2).

Safety Outcomes

Patients with or without *ABCB1* -154 TC/CC or 3435 CT/TT genotype in the clopidogrel plus aspirin group and the aspirin group had a similar rate of any bleeding (2.3% and 1.3% vs 1.9% and 2.2%; *P* = .25 for interaction) (Figure 1B and Table 2). The rate of any bleeding did not differ in separate analyses according to *CYP2C19* loss-of-function allele carrier status (1.8% and 1.4% vs 1.4% and 2.1%, *P* = .55 for interaction in carriers; 3.0% and 1.1% vs 2.5% and 2.3%, *P* = .30 for interaction in noncarriers of *CYP2C19* loss-of-function allele) (Figure 2).

The rate of any bleeding did not differ between patients in the clopidogrel plus aspirin group and those in the aspirin group irrespective of *ABCB1* -154T>C genotype (1.7% and 1.1% vs 2.3% and 1.6%; *P* = .76 for interaction) (Table 3) and regardless of carrying or not carrying *CYP2C19* loss-of-function allele (1.1% and 1.7% vs 1.9% and 1.5%; *P* = .59 for interaction in carriers; 2.6% and 0.0% vs 3.0% and 1.7%; *P* = .99 for interaction in noncarriers) (eTables 3 and 4 in Supplement 2).

Although the clopidogrel plus aspirin group had a higher rate of mild bleeding than the aspirin group in *ABCB1* 3435 CT/TT genotypes (1.7% vs 0.6%; *P* = .04), the interaction of treatment by *ABCB1* 3435C>T genotype was not significant (*P* = .16 for interaction) (eTable 5 in Supplement 2). The clopidogrel plus aspirin group had a similar rate of any bleeding compared with the aspirin group irrespective of *ABCB1* 3435C>T genotype in carriers and noncarriers of *CYP2C19* loss-of-function allele (*P* = .30 for interaction in carriers; *P* = .51 for interaction in noncarriers) (eTables 6 and 7 in Supplement 2).

Table 2. Association of Clopidogrel Plus Aspirin vs Aspirin Alone With Clinical Outcome Stratified by *ABCB1* Genotypes

Outcome	*ABCB1*-154 TC/CC or 3435 CT/TT					*ABCB1*-154 TT and 3435 CC				
	No. (%)					No. (%)				
	Total (n = 2146)	Aspirin (n = 1099)	Clopidogrel Plus Aspirin (n = 1047)	HR (95% CI)	*P* Value	Total (n = 690)	Aspirin (n = 323)	Clopidogrel Plus Aspirin (n = 367)	HR (95% CI)	*P* Value	*P* Value for Interaction
Stroke	214 (10.0)	122 (11.1)	92 (8.8)	0.78 (0.60-1.03)	.08	71 (10.3)	47 (14.6)	24 (6.5)	0.43 (0.26-0.71)	<.001	.04
Composite event[a]	215 (10.0)	123 (11.2)	92 (8.8)	0.78 (0.59-1.02)	.07	72 (10.4)	48 (14.9)	24 (6.5)	0.42 (0.26-0.69)	<.001	.04
Ischemic stroke	211 (9.8)	121 (11.0)	90 (8.6)	0.77 (0.59-1.02)	.07	69 (10.0)	46 (14.2)	23 (6.3)	0.42 (0.26-0.70)	<.001	.04
Bleeding[b]											
Severe	0	0	0	NE	NA	0	0	0	NE	NA	NA
Moderate	1 (0.1)	0	1 (0.1)	NE	NA	0	0	0	NE	NA	NA
Mild	21 (1.0)	6 (0.6)	15 (1.4)	2.60 (1.01-6.70)	.048	5 (0.7)	3 (0.9)	2 (0.5)	0.55 (0.09-3.31)	.52	.15
Any	38 (1.8)	14 (1.3)	24 (2.3)	1.71 (0.88-3.33)	.11	14 (2.0)	7 (2.2)	7 (1.9)	0.87 (0.30-2.48)	.79	.25

Abbreviations: HR, hazard ratio; NA, not applicable; NE, not estimable.

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

[b] Bleeding events were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries randomized trial criteria.

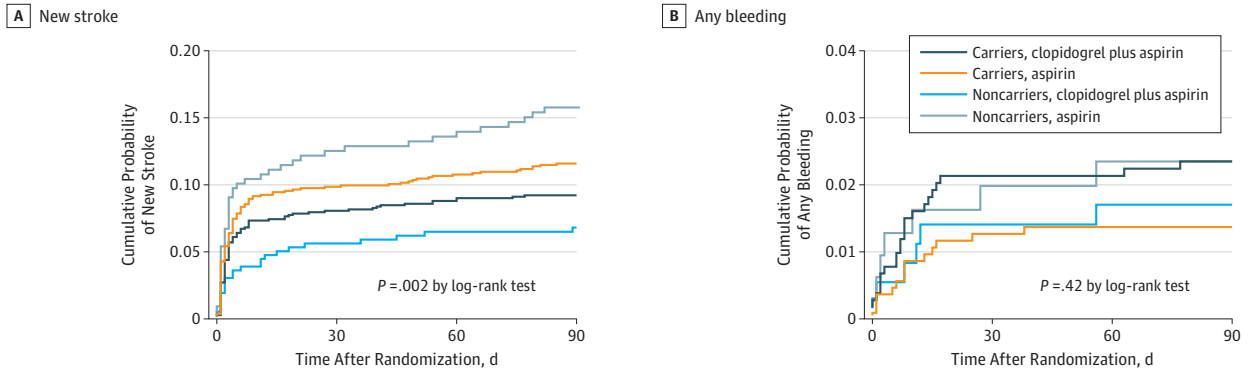
Discussion

A number of factors affect the clinical response to clopidogrel, including genetic variants such as in the *CYP2C19* gene. The present analysis found that the *ABCB1* polymorphism was associated with the efficacy of clopidogrel plus aspirin treatment compared with aspirin alone in patients with acute minor stroke or TIA. The *ABCB1* -154TC/CC genotypes were associated with less protection from new stroke with clopidogrel only in noncarriers of the *CYP2C19* loss-of-function allele compared with the *ABCB1* -154TT genotype. However, the *ABCB1* 3435C>T polymorphism was not associated with the efficacy of clopidogrel plus aspirin treatment irrespective of *CYP2C19* loss-of-function allele carrier status. The risk of bleeding for clopidogrel plus aspirin treatment compared with aspirin alone was not associated with *ABCB1* genotype.

There are limited data available addressing the association of *ABCB1* polymorphism with clopidogrel efficacy in stroke. Two recent studies with small sample sizes reported no association between *ABCB1* polymorphisms and clinical response to clopidogrel treatment.[16,17] Su et al[16] reported that *ABCB1* 3435C>T was not associated with clopidogrel response according to platelet aggregation in clopidogrel-treated Chinese patients with ischemic stroke. Li et al[17] found that the *ABCB1* -129T>C (rs3213619), 1236C>T (rs1128503), and 3435C>T SNPs were not associated with clopidogrel response and recurrent ischemic events in 268 Chinese patients with extracranial or intracranial stenting. Furthermore, Kim et al[21] found that the *ABCB1* 3′UTR A>G (rs3842) SNP, but not the *ABCB1* -154T>C SNP, was associated with the development of ischemic stroke in a Korean population in a case-control study that enrolled 121 participants with ischemic stroke and 291 control participants. However, the generalization of these studies was limited by their small sample sizes and limited statistical power. Compared with previous studies, our study had a larger sample size and evaluated the association of *ABCB1* polymorphism with clopidogrel efficacy in the context of *CYP2C19* status. Some but not all previous studies showed that the *CYP2C19* and *ABCB1* polymorphisms had a combined association with adverse clinical outcomes in patients with acute coronary syndromes undergoing percutaneous coronary intervention.[12,22] We observed similar combined associations of *CYP2C19* and *ABCB1* polymorphisms with stroke recurrence in patients with stroke or TIA in this study. Furthermore, our study observed a higher rate of mild bleeding in the clopidogrel plus aspirin group compared with the aspirin group in the *ABCB1* 3435 CT/TT genotypes. The mechanism is unclear and potentially owing to a small sample size. In addition, this study included a randomized control group (patients treated with aspirin alone) to evaluate the association of *ABCB1* polymorphism with the efficacy of clopidogrel, whereas previous studies were conducted exclusively in patients treated with clopidogrel (with or without aspirin); our method allowed us to avoid potential confounding.[23]

The frequency of carriers of *ABCB1* -154 TC/CC or 3435 CT/TT genotype in this study was 75.7%, similar to that reported in other Chinese,[16,24] Mexican[24] and Native American

Figure 1. Risk of Stroke and Any Bleeding for Carriers and Noncarriers of *ABCB1* -154 TC/CC or 3435 CT/TT Genotype by Treatment Assignment



No. at risk

Carriers, clopidogrel plus aspirin	1047	957	950	803
Carriers, aspirin	1099	990	981	816
Noncarriers, clopidogrel plus aspirin	367	345	342	289
Noncarriers, aspirin	323	282	279	236

No. at risk

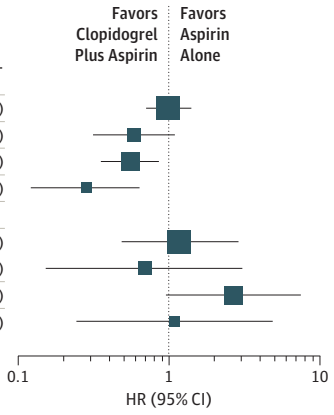
Carriers, clopidogrel plus aspirin	1047	937	930	787
Carriers, aspirin	1099	979	969	808
Noncarriers, clopidogrel plus aspirin	367	342	338	287
Noncarriers, aspirin	323	278	274	233

A, Probability of new stroke from randomization throughout 90-day follow-up in carriers vs noncarriers treated with clopidogrel plus aspirin and aspirin alone.

B, Probability of any bleeding from randomization throughout 90-day follow-up in carriers vs noncarriers treated with clopidogrel plus aspirin and aspirin alone.

Figure 2. Risk of Stroke and Any Bleeding for Carriers and Noncarriers of *ABCB1* -154 TC/CC or 3435 CT/TT Genotype by *CYP2C19* Loss-of-Function (LOF) Allele Carrier Status and Treatment Assignment

Outcome	*ABCB1* Genotype	Aspirin Alone No./Total No. (%)	Clopidogrel Plus Aspirin No./Total No. (%)	Hazard Ratio (95% CI)	*P* Value	*P* Value for Interaction
New stroke						
Carriers of LOF	-154 TC/CC or 3435 CT/TT	66/652 (10.01)	62/620 (10.0)	0.99 (0.70-1.40)	.95	.15
	-154 TT and 3435 CC	25/195 (12.8)	16/209 (7.7)	0.58 (0.31-1.09)	.09	
Noncarriers of LOF	-154 TC/CC or 3435 CT/TT	56/447 (12.5)	30/427 (7.0)	0.55 (0.35-0.85)	.008	.16
	-154 TT and 3435 CC	22/128 (17.2)	8/158 (5.1)	0.28 (0.12-0.63)	.002	
Any bleeding						
Carriers of LOF	-154 TC/CC or 3435 CT/TT	9/652 (1.4)	11/620 (1.8)	1.17 (0.48-2.88)	.73	.55
	-154 TT and 3435 CC	4/195 (2.1)	3/209 (1.4)	0.69 (0.15-3.06)	.62	
Noncarriers of LOF	-154 TC/CC or 3435 CT/TT	5/447 (1.1)	13/427 (3.0)	2.67 (0.95-7.49)	.06	.30
	-154 TT and 3435 CC	3/128 (2.3)	4/158 (2.5)	1.08 (0.24-4.87)	.92	



Squares indicate point estimation and size of the squares indicate sample size. Error bars indicate 95% CIs.

populations[24,25] and higher than that in persons of European (66.5%) and African (52.5%) descent.[25] The *ABCB1* -154 TC/CC or 3435 CT/TT genotype may be associated with higher P-glycoprotein expression and thus an enhanced intestinal efflux, possibly of clopidogrel.[11,21] This study provided evidence that besides *CYP2C19*, the genetic polymorphism of *ABCB1* encoding the P-glycoprotein, which plays an important role in intestinal absorption of clopidogrel, should also be considered when prescribing clopidogrel for patients with minor ischemic stroke and TIA. Genetic testing may allow clinicians to personalize antiplatelet therapy; however, its cost-effectiveness needs further investigation. Varying the dose of clopidogrel or shifting to new antiplatelet agents (eg, prasugrel) based on genetic results may be another alternative but also needs to be further evaluated.[10] Future research may focus on the cost-effectiveness of genetic testing in clinical practice and evaluation of efficacy of alternatives for those with *ABCB1* -154TC/CC genotypes.

Limitations

Our study has several limitations. First, enrollment in the CHANCE trial was restricted to Chinese patients. Given the variability in genetic variants across races/ethnicities, further evaluation is required before applying these results to non-Asian populations. More pharmacogenomic data in a Western population are expected from the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial,[26] which evaluated the efficacy and safety of clopidogrel plus aspirin vs aspirin alone in patients with minor stroke and TIA within 12 hours. Second, because the baseline data of stroke mecha-

Table 3. Association of Clopidogrel Plus Aspirin vs Aspirin Alone With Clinical Outcome Stratified by *ABCB1* –154T>C Genotypes

Outcome	*ABCB1*-154 TC/CC					*ABCB1*-154 TT					
	No. (%)					No. (%)					
	Total (n = 570)	Aspirin (n = 276)	Clopidogrel Plus Aspirin (n = 294)	HR (95% CI)	*P* Value	Total (n = 2266)	Aspirin (n = 1146)	Clopidogrel Plus Aspirin (n = 1120)	HR (95% CI)	*P* Value	*P* Value for Interaction
Stroke	51 (8.9)	22 (8.0)	29 (9.9)	1.25 (0.72-2.17)	.44	234 (10.3)	147 (12.8)	87 (7.8)	0.59 (0.46-0.77)	<.001	.02
Composite event[a]	52 (9.1)	23 (8.3)	29 (9.9)	1.19 (0.69-2.06)	.53	235 (10.4)	148 (12.9)	87 (7.8)	0.59 (0.45-0.77)	<.001	.02
Ischemic stroke	51 (8.9)	22 (8.0)	29 (9.9)	1.25 (0.72-2.17)	.44	229 (10.1)	145 (12.6)	84 (7.5)	0.58 (0.44-0.76)	<.001	.02
Bleeding[b]											
Severe	0	0	0	NE	NA	0	0	0	NE	NA	NA
Moderate	0	0	0	NE	NA	1 (0.0)	0	1 (0.1)	NE	NA	NA
Mild	3 (0.5)	0	3 (1.0)	NE	NA	23 (1.0)	9 (0.8)	14 (1.3)	1.54 (0.67-3.55)	.31	.99
Any bleeding	8 (1.4)	3 (1.1)	5 (1.7)	1.58 (0.38-6.59)	.53	44 (1.9)	18 (1.6)	26 (2.3)	1.39 (0.76-2.55)	.29	.76

Abbreviations: HR, hazard ratio; NA, not applicable; NE, not estimable.

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

[b] Bleeding events were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries randomized trial criteria.

nisms were not available in the CHANCE trial, it was impossible to assess the influence of stroke mechanisms on the pharmacogenetic effect of *ABCB1* in this study. Third, the event rates for bleeding were low in this population, which may limit statistical power to detect the association with the safety outcome. Fourth, caution is needed when explaining the results because the 2 *ABCB1* genetic variants were deviated from Hardy-Weinberg equilibrium.

Conclusions

Among patients with minor ischemic stroke or TIA, the *ABCB1* polymorphism was found to be associated with reduced efficacy of clopidogrel plus aspirin treatment compared with aspirin alone in this study. However, further validations are needed in other studies with large sample sizes.

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Author Affiliations: Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China (Pan, Chen, Y. Wang, Li, Zhao, Liu, Meng, Y. Wang); China National Clinical Research Center for Neurological Diseases, Beijing, China (Pan, Chen, Y. Wang, Li, Zhao, Liu, Meng, Y. Wang); Center of Stroke, Beijing Institute for Brain Disorders, Beijing, China (Pan, Chen, Y. Wang, Li, Zhao, Liu, Meng, Y. Wang); Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease, Beijing, China (Pan, Chen, Y. Wang, Li, Zhao, Liu, Meng, Y. Wang); Dean's Office, Dell Medical School, University of Texas at Austin, Austin, Texas (Johnston); Department of Clinical Pharmacology and Clinical Research Platform of East of Paris (URCEST-CRC-CRB), Assistance Publique–Hôpitaux de Paris, Paris, France (Simon); Department of Clinical Pharmacology, Sorbonne Université, Paris, France (Simon); FACT (French Alliance for Cardiovascular Clinical Trials), Paris, France (Simon); Illinois Neurological Institute Stroke Network, OSF Healthcare System, Peoria, Illinois (D. Wang); Department of Neurology, University of Illinois College of Medicine at Peoria, Peoria, Illinois (D. Wang).

Author Contributions: Dr Yongjun Wang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Pan, Chen, Yilong Wang, Li, Zhao, Liu, Yongjun Wang.
Acquisition, analysis, or interpretation of data: Johnston, Simon, D. Wang, Meng, Yongjun Wang.
Drafting of the manuscript: Pan, D. Wang.
Critical revision of the manuscript for important intellectual content: Chen, Yilong Wang, Li, Johnston, Simon, Zhao, Liu, Meng, Yongjun Wang.
Statistical analysis: Pan.
Obtained funding: Zhao, Yongjun Wang.
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Supervision: Chen, Yilong Wang, Li, Johnston, Zhao, Liu, D. Wang, Yongjun Wang.

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Group Members: Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) Investigators: Beijing Tiantan Hospital, Beijing, China: Yongjun Wang, MD; Yilong Wang, MD, PhD; Xingquan Zhao, MD, PhD; Dell Medical School, University of Texas at Austin, Austin: S. Claiborne Johnston, MD, PhD; Taizhou First People's Hospital, Taizhou, China: Zhimin Wang, MD; Taiyuan Iron And Steel (Group) Co., Ltd., General Hospital, Taiyuan, China: Haiqin Xia, MD; Penglai People's Hospital, Yantai, China: Guiru Zhang, MD; The Third People's Hospital of Datong, Datong, China: Xudong Ren, MD; The Fourth Central Hospital of Tianjin, Tianjin, China: Chunling Ji, MD; The Second Hospital of Hebei Medical University, Shijiazhuang, China: Guohua Zhang, MD; The First Hospital of Fangshan District, Beijing, China: Jianhua Li, MD; Beijing Puren Hospital, Beijing, China: Bohua Lu, MD; Tianjin Ninghe District Hospital, Tianjin, China: Liping Wang, MD; The People's Hospital of Zhengzhou, Zhengzhou, China: Shutao Feng, MD; Affiliated Hospital of North China Coal Medical College, Tangshan, China: Dali Wang, MD; Zhejiang Zhoushan Hospital, Zhoushan, China: WeiguoTang, MD, PhD; HanDan Central Hospital, Handan, China: Juntao Li, MD; Zhecheng People's Hospital, Zhecheng, China: Hongtian Zhang, MD; Shanxi Medical University

Second Hospital, Taiyuan, China: Guanglai Li, MD; Baotou Central Hospital, Baotou, China: Baojun Wang, MD, PhD; The General Hospital of Changjiang River Shipping, Wuhan, China: Yuhua Chen, MD; Dalian Economic And Technological Development Zone Hospital, Dalian, China: Ying Lian, MD; First Neurology Department, Affiliated Hospital of North China Coal Medical College, Tangshan, China: Bin Liu, MD; The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China: Junfang Teng, MD; First Affiliated Hospital of Liaoning Medical University, Jinzhou, China: Rubo Sui, MD; Lianyungang Municipal Hospital of TCM, Lianyungang, China: Lejun Li, MD; Central Hospital In Qiu County, Handan, China: Zhiling Yuan, MD; Tianjin First Center Hospital, Tianjin, China: Dawei Zang, MD; Renmin Hospital of Wuhan University, Wuhan, China: Zuneng Lu, MD; Qingdao Central Hospital, Qingdao, China: Li Sun, MD; Baogang Hospital, Baotou, China: Dong Wang, MD; Changzhi City People's Hospital of Shanxi Province, Changzhi, China: Liying Hou, MD; Harrison International Peace Hospital, Hengshui, China: Dongcai Yuan, MD; People's Hospital of Linzi District, Zibo, China: Yongliang Cao, MD; Yantai Mountain Hospital, Yantai, China: Hui Li, MD; Beijing Pinggu District Hospital, Beijing, China: Xiuge Tan, MD; Taiyuan Central Hospital, Taiyuan, China: Huicong Wang, MD; Chengde Central Hospital, Chengde, China: Haisong Du, MD; Shijiazhuang Central Hospital, Shijiazhuang, China: Mingyi Liu, MD; First Neurology Department, Dalian Municipal Central Hospital, Dalian, China: Suping Wang, MD; Xi'an 141 Hospital, Xi'an, China: Qiuwu Liu, MD; Chengdu Third Municipal People's Hospital, Chengdu, China: Zhong Zhang, MD; Affiliated Hospital of Chifeng University, Chifeng, China: Qifu Cui, MD; Zhengzhou Central Hospital, Zhengzhou, China: Runqing Wang, MD; Lihuili Hospital Medical Center, Ningbo, China: Jialin Zhao, MD; Henan Provincial People's Hospital, Zhengzhou, China: Jiewen Zhang, MD; Jinzhong City Second Hospital, Jinzhong, China: Jianping Zhao, MD; Beijing Anzhen Hospital, Capital Medical University, Beijing, China: Qi Bi, MD, PhD; Beijing Huairou District Chinese Medicine Hospital, Beijing, China: Xiyou Qi, MD; Hebei Medical University Third Hospital, Shijiazhuang, China: Junyan Liu, MD; First Affiliated Hospital Shanxi Medical University, Taiyuan, China: Changxin Li, MD; Hebei Provincial People's Hospital, Shijiazhuang, China: Ling Li, MD; Guangzhou First Municipal Peoples Hospital, Guangzhou, China: Xiaoping Pan, MD; Central Hospital In Cangzhou, Cangzhou, China: Junling Zhang, MD; The Chinese People's Armed Police Force Medical School Affiliated Hospital, Tianjin, China: Derang Jiao, MD; Zhejiang Wenzhou Medical College First Affiliated Hospital, Wenzhou, China: Zhao Han, MD; Jilin Central Hospital, Jilin, China: Dawei Qian, MD; Anhui Maanshan Central Hospital, Maanshan, China: Jin Xiao, MD; Beijing Aviation Industry Central Hospital, Beijing, China: Yan Xing, MD; Luhe Hospital, Beijing, China: Huishan Du, MD; Beijing Fuxing Hospital, Capital Medical University, Beijing, China: Guang Huang, MD; The 306th Hospital of P.L.A, Beijing, China: Yongqiang Cui, MD; The First Affiliated Hospital of Tianjin University of Chinese Medicine, Tianjin, China: Yan Li, MD; Baiqiuen International Peace Hospital of People's Liberation Army, Shijiazhuang, China: Lianyuan Feng, MD; Fourth Affiliated Hospital of China Medical University, Shenyang, China: Lianbo Gao, MD; Xiangya Hospital Central-South University, Xiangya, China: Bo Xiao, MD; Tangshan Worker's Hospital, Tangshan, China: Yibin Cao, MD; The 1st Hospital in Handan, Handan, China: Yiping Wu, MD; Yangquan Coal (Group) Co., Ltd. General Hospital, Yangquan, China: Jinfeng Liu, MD; Tianjin Tianhe Hospital, Tianjin, China: Zhiming Zhang, MD; Nantong First People's Hospital, Nantong, China: Zhengxie Dong, MD; The 1st Hospital of Zhangjiakou City, Zhangjiakou, China: Limin Wang, MD; West China Hospital, Chengdu, China: Li He, MD, PhD; The Second Affiliated Hospital of Shandong University of TCM, Jinan, China: Xinchen Wang, MD; Fenyang Hospital of Shanxi Province, Fenyang, China: Xueying Guo, MD; Zhejiang Zhoushan Putuo District People's Hospital, Zhoushan, China: Ming Wang, MD; Xiyuan Hospital of China Academy of Chinese Traditional Medicine, Beijing, China: Xiaosha Wang, MD; No.2 People's Hospital East in Lianyungang City, Lianyungang, China: Jiandong Jiang, MD; Affiliated Hospital of Qingdao University Medical College, Qingdao, China: Renliang Zhao, MD, PhD; Qilu Hospital of Shandong University, Jinan, China: Shengnian Zhou, MD, PhD; Zibo Hospital of Traditional Chinese Medicine, Zibo, China: HaoHu, MD; Beijing Shijitan Hospital, Beijing, China: Maolin He, MD, PhD; Beijing Haidian Hospital, Beijing, China: Fengchun Yu, MD; Beijing Shunyi District Hospital, Beijing, China: Quping Ouyang, MD; Dalian Third Municipal Hospital, Dalian, China: Jingbo Zhang, MD; The First Affliated Hospital of Jinan University, Guangzhou, China: Anding Xu, MD, PhD; Navy Genaral Hospital of P.L.A, Beijing, China: Xiaokun Qi, MD; Beijing Second Artillery General Hospital, Beijing, China: Lei Wang, MD; Beijing Daxing District Hospital, Beijing, China: Fuming Shi, MD; Sichuan Province People's Hospital, Chengdu, China: Fuqiang Guo, MD; Dalian Municipal Central Hospital, Dalian, China: Jianfeng Wang, MD; The Second Hospital in Baoding, Baoding, China: Fengli Zhao, MD; The Hospital Combine Traditional Chinese and Western Medicine in Cangzhou, Cangzhou, China: Ronghua Dou, MD; The 309th Hospital Of P.L.A, Beijing, China: Dongning Wei, MD; Liangxiang Hospital Of Fangshan District, Beijing, China: Qingwei Meng, MD; HuaXin Hospital First Hospital of Tsinghua University, Beijing, China: Yilu Xia, MD; Tianjin Huanhu Hospital, Tianjin, China, ShiminWang, MD; Shijiazhuang First Hospital, Shijiazhuang, China: Zhangcang Xue, MD; The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China: Yuming Xu, MD, PhD; Xinzhou City People's Hospital, Xinzhou, China: Liping Ma, MD; Sichuan Province People's Hospital of Deyang City, Deyang, China: Chun Wang, MD; First Hospital, Jilin University, Jilin, China: Jiang Wu, MD; Shandong Provincial Hospital, Jinan, China: Yifeng Du, MD; Fujian Province Hospital, Fuzhou, China: Yinzhou Wang, MD; Liaoyang City Third People's Hospital, Liaoyang, China: Lijun Xiao, MD; Handan City Center Hospital, Handan, China: Fucong Song, MD; Beijing Chaoyang Hospital, Capital Medical University, Beijing, China: Wenli Hu, MD; Beijing University of Chinese Medicine East Hospital, Beijing, China: Zhigang Chen, MD; Hebei Medical University Fourth Hospital, Shijiazhuang, China: Qingrui Liu, MD; The Fourth Affiliated Hospital of Soochow University, Suzhou, China: Jiemin Zhang, MD; Zhejiang University of Chinese Medicine Affiliated First Hospital, Hangzhou, China: Mei Chen, MD; Affiliated Hospital of Kailuan Company Ltd, Tangshan, China, Xiaodong Yuan, MD; Affiliated Hospital of Weifang Medical University, Weifang, China: Zhihui Liu, MD; The First Hospital of Harbin Medical University, Harbin, China: Guozhong Li, MD; Dalian Friendship Hospital, Dalian, China: Xiaohong Li, MD; Tianjin Dagang Hospital, Tianjin, China: Tingchen Tian, MD.

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