Association between *CYP2C19* Polymorphisms and Outcomes in Cerebral Endovascular Therapy

M. Lin, M. Todaro, J. Chan, L. Churilov, W.S. Zhu, S. Ramdave, P.J. Mitchell, R.J. Dowling, P. Kwan, and B. Yan

ABSTRACT

BACKGROUND AND PURPOSE: Differing responses to clopidogrel following endovascular treatment of cerebrovascular diseases may increase the risk of vascular complications. *CYP2C19* gene polymorphisms influence clopidogrel activity. We aimed to study the clinical impact of *CYP2C19* gene polymorphisms in patients undergoing endovascular treatment.

MATERIALS AND METHODS: This was a prospective, longitudinal, observational study. Information on demographics and cerebrovascular status was collected as baseline. Clopidogrel response was tested by the VerifyNow P2Y12 assay. *CYP2C19* genotyping was undertaken by polymerase chain reaction–restriction fragment length polymorphism. Three-month follow-up data included vascular complications, mortality, and modified Rankin Scale score. Associations were investigated among *CYP2C19* genotypes, clopidogrel responsiveness, and clinical outcomes.

RESULTS: One hundred and eight participants were included. Median age was 56 years (interquartile range, 48.8–65.0 years), and 35 (32.4%) were male. Forty-four participants were classified into group 1 (homozygous *CYP2C19*1/*1*); 31, into group 2 (25 with *CYP2C19*1/*2*, two with *CYP2C19*1/*3*, three with *CYP2C19*3/*3*, one with *CYP2C19*2/*3*); 28, into group 3 (24 with *CYP2C19*1/*17*, four with *CYP2C19*17/*17*); and 5, into group 4 (*CYP2C19*2/*17*). A significantly higher proportion of participants in group 3 experienced ischemic events (9 of 28, 32.1%) compared with group 1 (5 of 44, 11.4%; $P = .04$; odds ratio, 3.7; 95% confidence interval, 1.1–12.6). There was no significant difference in clopidogrel response among the 4 genotype groups.

CONCLUSIONS: Individuals with *CYP2C19*17* may have increased risk of ischemic events following endovascular treatment, independent of clopidogrel responsiveness. Larger studies are required to confirm the influence of *CYP2C19*17* on clinical outcomes and to understand the mechanisms for increased ischemic events.

ABBREVIATIONS: IQR = interquartile range; PRU = platelet reactivity unit

Endovascular treatment of cerebrovascular diseases, for example intracranial aneurysms and large artery stenosis, involves the placement of metallic coils or stents.[1] These procedures are followed by increased thrombotic activity and platelet aggregation, resulting in ischemic complications.[2,3]

Clopidogrel is a commonly used antiplatelet drug to reduce the rate of procedure-related thrombosis.[4,5]

Clopidogrel is a prodrug and requires hepatic metabolism mediated by the cytochrome P450 2C19 (*CYP2C19*) enzyme to produce the active R-130964 constituents.[6] Active R-130964 permanently binds to P2Y12 G-protein-coupled platelet surface receptors to block the effects of adenosine diphosphate, leading to inhibition of platelet aggregation.[7]

The response to clopidogrel varies widely among individuals. Up to 66% of patients with cerebrovascular disease have a reduced response to clopidogrel,[8-11] placing them at higher risk of thrombosis,[12] while 14.9%–38% of patients are hyper-responsive to

Received February 1, 2015; accepted after revision June 4.

From the Melbourne Brain Centre (M.L., W.S.Z., B.Y.), and Departments of Radiology (P.J.M., R.J.D., B.Y.), and Neurology (M.T., P.K., B.Y.), The Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia; Department of Medicine (M.T., J.C., S.R., P.K.), University of Melbourne, Melbourne, Victoria, Australia; and Florey Institute of Neurosciences and Mental Health (L.C.), Melbourne Brain Centre, Heidelberg, Victoria, Australia.

The corresponding authors, Drs Kwan and Yan, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Our institution has received research support and grants across the years from Stryker, Covidien, MicroVention, and Codman Johnson & Johnson. No shares, money for talks, commissions, money for papers, and so forth have been received.

Please address correspondence to Patrick Kwan, MD, PhD, Department of Neurology, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia; e-mail: kwanp@unimelb.edu.au; and Bernard Yan, MD, Department of Neurology, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia; e-mail: bernard.yan@mh.org.au

Evidence-Based Medicine Level 2.

http://dx.doi.org/10.3174/ajnr.A4481

clopidogrel.[13,14] Differing responses to clopidogrel may be related to *CYP2C19* gene polymorphisms.[6,9] Of particular clinical importance are the *CYP2C19*2* and *CYP2C19*3* alleles, more commonly seen in Asian descent than African and Caucasian descent, which reduce enzyme activity and have been associated with an increased incidence of stent thrombosis in coronary intervention studies.[8,12] In contrast, *CYP2C19*17* may increase hemorrhagic complications,[14] but its impact on ischemic events and clinical outcome has not been definitively clarified.[14,15]

The influence of *CYP2C19* polymorphisms on outcomes to clopidogrel treatment has been poorly studied in patients with cerebrovascular disease compared with cardiovascular disease. Results from studies in coronary artery disease cannot be readily extrapolated to cerebrovascular disease owing to their different pathophysiology. Coronary artery studies focus mainly on clopidogrel hyporesponsiveness and ischemia as phenotypic outcomes because hemorrhagic complications are rare.[16] However, both ischemia and hemorrhage are considerable risks for patients undergoing endovascular neurointervention.[17]

We prospectively investigated the relationship among common *CYP2C19* variants, clopidogrel response, and clinical outcomes in patients following neurointerventional procedures. We hypothesized that *CYP2C19* variants were associated with clinical outcomes.

MATERIALS AND METHODS

Subjects

This was a prospective cohort study. Consecutive patients who underwent elective neurointervention for intracranial aneurysms or intracranial stenosis were prospectively recruited from The Royal Melbourne Hospital. The neurointervention procedures included simple coiling, balloon-assisted coiling, stent-assisted coiling, balloon and stent-assisted coiling, and Pipeline Embolization Device (Covidien, Irvine, California) flow-diversion stent placement of intracranial aneurysms and intracranial stenosis.

Inclusion criteria were the following: age older than 18 years, imaging evidence of intracranial aneurysms or intracranial stenosis intended for neurointervention, and ongoing use of clopidogrel on recruitment. Participants were excluded if there was significant coagulopathy, such as hemophilia, or other terminal medical comorbidities. All participants provided written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Royal Melbourne Hospital Human Research and Ethics Committee (HREC 2006.155).

Baseline demographic information for each participant included the following: age, sex, ethnicity (African, Asian, Caucasian), cerebrovascular risk factors (smoking history, diabetes, hypertension, hypercholesterolemia, atrial fibrillation, and peripheral vascular disease), size and location of the aneurysms, and indication for the procedure (stent placement or coiling of aneurysm or stenosis). All participants were prescribed clopidogrel, 75 mg/day, and aspirin, 150 mg/day, for at least 3 days before the procedures. Concomitant use of heparin, warfarin, and proton-pump inhibitors was noted.

Ex Vivo Clopidogrel Response Testing

Arterial blood samples were collected perioperatively through the angiographic puncture site of the femoral artery. Samples collected in sodium citrate tubes were rested at room temperature (25°C) for 30 minutes to 4 hours. After resting, the samples were tested for clopidogrel responsiveness by using the VerifyNow P2Y12 assay (Accumetrics, San Diego, California) in accordance with the manufacturer's instructions. The assay produces a value for inhibition of platelet activity in a percentage (percentage inhibition). This value indicates the level of active clopidogrel metabolite-P2Y12 receptor interaction, which inhibits platelet aggregation.[18] According to the manufacturer's manual, percentage inhibition is derived by the VerifyNow P2Y12 assay from the platelet reactivity unit (PRU) and baseline platelet thrombosis activity (BASE). The formula used to calculate percentage inhibition is Percentage Inhibition = (BASE − PRU) × 100/BASE.

CYP2C19 Genotyping

For each patient, a second blood sample was collected, from which genomic DNA was extracted by using the Gentra Puregene Blood Kit (Qiagen, Hilden, Germany) and suspended in DNA Hydration Solution (Qiagen).

Genotyping for *CYP2C19*2*, **3*, and **17* was performed by using polymerase chain reaction–restriction fragment length polymorphism as previously described (**2* and **3*[19]; **17*[20]). Each polymerase chain reaction contained GoTaq Hot Start Mastermix (Promega, Madison, Wisconsin; 400-μmol/L deoxyadenosine triphosphate, 400-μmol/L deoxyguanosine triphosphate, 400-μmol/L deoxycytidine triphosphate, 400-μmol/L deoxythymidine triphosphate, and 4-mmol/L magnesium chloride), 20-μM forward and reverse primers, nuclease-free water, and 50-ng DNA for **2* and **17* and 100-ng DNA for **3*.

For *CYP2C19*2*, the 169-bp polymerase chain reaction product was digested by 200-U SmaI (New England Biolabs, Ipswich, Massachusetts) at 25°C overnight. The *CYP2C19 *1* (wild type) yields a 120- and 49-bp product, whereas the *CYP2C19*2* (681 G>A) variant is resistant to digestion.[19]

The 636 G>A region for *CYP2C19*3* identification was analyzed by digesting the 329-bp polymerase chain reaction product with 16-U BamHI (New England Biolabs) at 37°C for 2 hours. The *CYP2C19*1* yields a 233- and 96-bp product, while the *CYP2C19*3* variant was resistant to digestion.[19]

For the *CYP2C19*17* variant, the 470-bp polymerase chain reaction product (containing the 806 C>T region) was digested with 40-U SfaNI (New England Biolabs) at 37°C for 3 hours followed by enzyme inactivation at 65°C for 20 minutes. *CYP2C19*1* yielded 3 products of 183, 142, and 113 bp. The *CYP2C19*17* variant yielded 3 products of 217, 142, and 113 bp after digestion.[20] The digested patterns for each genotype were separated on a 3% gel by electrophoresis.

To investigate the potential effect of different types of *CYP2C19* polymorphisms, we classified the participants into 4 mutually exclusive genotype groups based on their expected phenotypic behavior.

Clinical Outcomes

A neurologist (B.Y.) specializing in cerebrovascular disease assessed the participants at 3 months after the procedure. Participants who were unable to attend clinics were contacted by telephone.

Clinical end points included cerebral ischemic events and intracerebral hemorrhage periprocedurally and at 3 months postprocedure, and 3-month postprocedural modified Rankin Scale score and mortality. Periprocedural complications included intraoperative clot formations. Three-month ischemic end points included transient ischemic attack (TIA) and symptomatic and asymptomatic (without symptoms but evident on repeat imaging) ischemic stroke. TIA was defined by an acute neurologic deficit that resolved within 1 hour without evidence of ischemia on neuroimaging. Ischemic stroke was defined by an acute neurologic deficit with evidence of ischemia on neuroimaging, without hemorrhage. Hemorrhagic complications included intracranial hemorrhages and any hemorrhage outside the cranium. Major hemorrhagic complications were defined if the participant required surgical intervention. Brain CT and angiography were performed as clinically indicated to identify vascular events.

The modified Rankin Scale score is a 6-scale score used to describe functional status. mRS 0–1 is generally regarded as good functional outcome, and mRS 2–6, poor functional outcome.[21]

Statistical Analysis

Group 1 comprised wild type carriers (*CYP2C19*1/*1*), who also acted as the control group. Group 2 comprised participants who carried *CYP2C19*2* or *CYP2C19*3* (presumed hypofunctioning alleles) in the absence of *CYP2C19*17* (presumed hyperfunctioning allele). Group 3 comprised participants with *CYP2C19*17* in the absence of *CYP2C19*2* and *CYP2C19*3*. Group 4 comprised *CYP2C19*2/*17* individuals (combination of hypo- and hyperfunctioning alleles). Group 1 was used as a reference group (because *CYP2C19*1* is known to be the wild type variant) to facilitate the estimation of the effect of the inheritance of other polymorphisms on individual clopidogrel response and clinical outcome compared with the wild type.

Distribution of age and clopidogrel response among the 4 genotype groups was examined by using the Kruskal-Wallis test equality-of-population rank test. Imbalances in the proportion of vascular risk factors in the 4 genotype groups were tested by the Fisher exact test. Logistic regression analysis was used to investigate the association between the group membership and the categoric outcomes (ischemia, hemorrhage, good functional outcome [mRS 0–1]). The effect sizes for each outcome were estimated as odds ratios by using group 1 as a reference.

The statistical analyses were conducted by using STATA, Version 13 IC (StataCorp, College Station, Texas) and SPSS, Version 19 software (IBM, Armonk, New York). Due to the exploratory nature of this study, no adjustment for multiplicity of comparisons was made, and the value of $P = .05$ was the threshold for statistical significance for all the comparisons.

RESULTS

Baseline Characteristics

A total of 108 participants recruited from 2010 to 2013 were included in this study. Among them, 93 (86.1%) underwent endovascular treatment for unruptured aneurysms; 13, (12.0%) for intracranial stenosis; and 2 (1.9%), for venous sinus stenosis. Eleven (10.2%) participants underwent coiling alone, 26 (24.1%) underwent balloon-assisted coiling, and 13 (12.0%) underwent concurrent stent placement and coiling, while 7 (6.5%) required balloon-assisted stent placement and coiling. The median age was 56 years (interquartile range [IQR], 48.8–65.0), and 35 participants (32.4%) were men. Most (91.7%) were of white descent.

Table 1: Clopidogrel response by genotype groups[a]

	Group 1 (*n* = 38)	Group 2 (*n* = 25)	Group 3 (*n* = 25)	Group 4 (*n* = 5)	Fisher Exact Test, *P* Value
Percentage inhibition[b]					
Median	37.5	17.0	30.0	30.0	.32
IQR	17.0–70.0	6.0–47.0	12.0–47.0	24.0–54.0	

[a] Group 1: *CYP2C19*1/*1*; Group 2: *CYP2C19*1/*2,*1/*3, *2/*2, *2/*3*; Group 3: *CYP2C19*1/*17,*17/*17*; Group 4: *CYP2C19*2/*17*.
[b] Percentage inhibition = (BASE − PRU) × 100/BASE.

There was no significant difference in the age distribution among the 4 groups (Kruskal-Wallis, $P = .93$). There was also no significant difference in the distribution of sex in the genotype groups (Fisher exact test, $P = .06$). No significant difference was found among the 4 genotype groups for cerebrovascular risk factors, such as history of cerebrovascular disease (transient ischemic attack, ischemic and hemorrhagic stroke), cigarette smoking, diabetes, hypertension, hypercholesterolemia, and atrial fibrillation or peripheral vascular disease (Fisher exact test $P = .13$, $P = .73$, $P = .72$, $P = .61$, $P = .96$, $P = .91$, $P = .12$, respectively).

CYP2C19 *Genotypes*

On the basis of the *CYP2C19* genotypes, 44 participants were classified into group 1 (homozygous *CYP2C19*1/*1*); 31, into group 2 (25 with *CYP2C19*1/*2*, two with *CYP2C19*1/*3*, three with *CYP2C19*3/*3*, one with *CYP2C19*2/*3*; none had *CYP2C19*2/*2*). Twenty-eight were classified into group 3 (24 with *CYP2C19*1/*17*, four with *CYP2C19*17/*17*); and 5, into group 4 (*CYP2C19*2/*17*; none had *CYP2C19*3/*17*). There was no significant difference in the distribution of age, sex, and other cerebrovascular risk factors among the 4 *CYP2C19* genotype groups.

CYP2C19 *Genotypes and Outcomes*

At 3 months postprocedure, 18 of 108 (16.7%) participants had experienced ischemic events, 16 (14.8%) had hemorrhagic complications (5 major and 11 minor), and 4 (3.7%) had complications of both a hemorrhagic and ischemic nature. Two of the ischemic complications occurred in the periprocedural period. Ninety-nine of 108 (91.7%) participants had good functional outcome at 3 months. One participant, who carried *CYP2C19*1/*1*, died (Tables 1 and 2).

A significantly higher proportion of participants in group 3 (*CYP2C19*1/*17* or **17/*17*) experienced ischemic events (9 of 28, 32.1%) compared with group 1 (*CYP2C19*1/*1*) individuals (5 of 44, 11.4%; $P = .04$; odds ratio, 3.7; 95% confidence interval, 1.1–12.6). The difference remained significant after adjustment for age ($P = .03$; OR, 4.0; 95% CI, 1.1–14.3) and ex vivo clopidogrel response ($P = .04$; OR, 4.5; 95% CI, 1.1–17.9). No significant differences between group 1 (5 of 44, 11.4%) and the other genotype groups, groups 2 (3 of 25, 9.7%) and 4 (1 of 5, 20%), were identified in the incidence of ischemia. Other adjustments for sex, history of cerebrovascular disease, and peripheral vascular disease did not have a significant influence on the results.

Table 2: Postprocedural clinical outcomes by genotype groups[a]

	Group 1 (n = 44)	Group 2 (n = 31)	Group 3 (n = 28)	Group 4 (n = 5)	Fisher Exact Test, P Value
Ischemic complication (No.) (%)	5 (11.4)	3 (9.7)	9 (32.1)	1 (20.0)	.08
Hemorrhagic complication (No.) (%)	8 (18.2)	1 (3.2)	5 (17.9)	2 (40.0)	.06
mRS ≥2 (No.) (%)	5 (11.4)	1 (3.2)	2 (7.1)	1 (20.0)	.35

[a] Group 1: *CYP2C19*1/*1*; Group 2: *CYP2C19*1/*2,*1/*3, *2/*2, *2/*3*; Group 3: *CYP2C19*1/*17,*17/*17*; Group 4: *CYP2C19*2/*17*.

No significant differences between group 1 and the other genotype groups were identified in the incidence of hemorrhage. Age is a known influencing factor on mRS. However, there was no significant difference in age-adjusted mRS between group 1 and the other genotype groups.

CYP2C19 *Genotypes and Ex Vivo Clopidogrel Response*

Clopidogrel response was available in 93 participants. Of these participants, 38 of 44 (86.4%) were from group 1; 25 of 31 (80.1%), from group 2; 25 of 28 (89.3%), from group 3; and 5 of 5 (100%), from group 4. The median clopidogrel response was 37.5% inhibition (IQR, 12.0%–70.0%) for group 1, 17.0% (IQR, 6.0%–47.0%) for group 2, 30.0% (IQR, 12.0%–47.0%) for group 3, and 30.0% (IQR, 24.0%–54.0%) for group 4. Overall, there was no significant difference in clopidogrel response in terms of percentage inhibition among the 4 genotype groups (Kruskal-Wallis, $P = .32$). There was no significant difference in percentage inhibition among patients with no complications (26.0%; IQR, 12.0%–53.0%) compared with ischemic events (30.6%; IQR, 2.75%–51.0%; $P = .5$) and hemorrhagic events (47.9%; IQR, 31.5%–70.8%; $P = .9$).

PRU values were also compared between the genotype groups 2, 3, and 4 and group 1. The median PRU between group 1 and group 2 was not significant (237; IQR, 105–291 versus 261; IQR, 184–316; $P = .78$). Similarly, no significance was found between group 1 and group 4 (237; IQR, 105–291 versus 246; IQR, 195–281; $P = .88$). There appeared to be a significant difference between the median PRUs of group 1 and group 3 (237; IQR, 105–291 versus 232; IQR, 209–245; $P = .03$).

Ex Vivo Clopidogrel Response and Clinical Outcomes

Among the 93 participants with clopidogrel-response testing, 16 (17.2%) experienced ischemic events. There was no significant difference between the median clopidogrel response of participants who developed ischemic events ([$n = 16$] 15.5%; IQR, 2.5%–55.0%) compared with participants without ischemic events ([$n = 77$] 30.0%; IQR, 13.0%–65.0%) ($P = .3$).

Of the 93 participants with clopidogrel-response results, 14 (15.1%) experienced hemorrhagic events. The median clopidogrel response of participants who experienced hemorrhagic events was significantly higher ([$n = 14$] 46.0%; IQR, 30.0%–72.0%) compared with those who did not experience hemorrhages ([$n = 22$] 22.0%; IQR, 1.0%–53.0%) ($P = .03$).

There was no significance between the median PRU values for the ischemic-versus-nonischemic participants (253; IQR, 151.75–313.75 versus 244; IQR, 172–295; $P = .44$). Similarly, the median PRU evaluation was made for hemorrhagic-versus-nonhemorrhagic participants (211; IQR, 100–242 versus 249; IQR, 172.5–306.5; $P = .60$). These results showed no statistical significance.

DISCUSSION

Clopidogrel is a common antiplatelet prescribed to prevent secondary ischemia for patients with cerebrovascular conditions treated by endovascular techniques. However, variations in clopidogrel response associated with *CYP2C19* polymorphisms may have a negative impact on treatment results.

Our investigation suggests increased risk of ischemic events in individuals carrying the *CYP2C19*17* allele (group 3) compared with homozygous *CYP2C19*1/*1* wild type carriers (group 1). *CYP2C19*17* is generally thought to be hyperfunctioning[20]; this feature should suggest an increased risk of hemorrhage. However, our study shows *CYP2C19*17* to be significantly associated with ischemic events, despite no significant association with platelet activity. This novel finding is unexpected and leads us to suspect involvement of other pathways in the association between the *CYP2C19* gene and clinical outcomes. Our study did not obtain data from imaging sources to interpret clinical outcomes but, instead, defined ischemic events evidenced by stroke or transient ischemic attacks in clinical follow-up only.

Correlation between *CYP2C19*17* and secondary ischemic events following endovascular treatment of cerebrovascular disease has not been reported previously, to our knowledge. However, studies investigating the phenotypic effects of *CYP2C19*17* are limited, and the influence of this polymorphism on the activity of clopidogrel, and hence clinical outcomes, remains controversial. Although a recent study in patients with myocardial infarction has suggested a significantly increased incidence of bleeding events and 1-year mortality rate among *CYP2C19*17* carriers,[15] others have found that *CYP2C19*17* has minimal influence on clopidogrel response.[21] The lack of association between *CYP2C19*17* and the ex vivo clopidogrel response in the present study, along with conflicting findings in previous studies, suggests that the polymorphism may influence clinical outcomes via mechanisms independent of measured clopidogrel response in this patient population. This influence has not been previously investigated and deserves further exploration in future studies.

Compared with *CYP2C19*17*, *CYP2C19*2* and *CYP2C19*3* are well-documented as hypofunctioning alleles in healthy subjects and patients with coronary artery and cerebrovascular diseases.[9,12,22-24] These alleles have also been reported to be significantly associated with subacute stent thrombosis and myocardial infarction following percutaneous coronary intervention.[8,25] This correlation is understood to be a leading cause for increased risk of ischemic complications.[26] Our results did not find *CYP2C19*2* or *CYP2C19*3* to be significantly associated with clinical outcome and clopidogrel response. However, the trends indicated in our results are reflective of those in previous literature.

In this study, *CYP2C19* polymorphism was not associated significantly with mRS, a commonly used functional outcome in interventional studies of cerebrovascular disease. The inclusion of primarily participants undergoing elective procedures may explain the small number of poor functional outcomes recorded, with mRS ≥2 recorded in only 8.5% (7 of 106). This low incidence

of poor clinical outcome limited our ability to draw conclusions concerning the influence of *CYP2C19* genotypes on functional outcomes. Further studies to validate the association between *CYP2C19* polymorphisms and functional outcomes are needed because cerebrovascular complications (ischemia and hemorrhage) are major contributors of morbidity.

Our results did not show a significant association between clopidogrel response and *CYP2C19* polymorphisms and clinical outcome. Point-of-care clopidogrel response testing platforms such as the VerifyNow P2Y12 assay could add clinical benefits for patients receiving endovascular neurointervention, provided that standardized values predicting response (ischemia and hemorrhage) can be defined. However, there is currently no standard definition for VerifyNow P2Y12 assay values. Values assigned to define clopidogrel hyporesponsiveness in previous studies vary widely between 15%[18] and 40%,[27] though the cutoff value of 20% is commonly used.[10,28] Likewise, there is no standard VerifyNow P2Y12 value to define clopidogrel hyperresponsiveness. The rare occurrence of hemorrhagic complications in coronary artery disease may have resulted in limited research being conducted on clopidogrel hyper-responsiveness. PRU values are also useful in defining clopidogrel responsiveness. However, the PRU values were not found to be statistically significant for the clinical outcomes of our study, ischemia and hemorrhage, compared to no complications. Similarly, no significance was found in PRU values of *CYP2C19*2* and *CYP2C19*3* compared with the wild type. However, the PRU values in *CYP2C19*17* carriers were significantly lower compared with the wild type. The influence of *CYP2C19*17* on platelet reactivity is an area that requires more research.

The findings in our study were novel. However, the mechanism by which *CYP2C19*17* influenced clinical outcomes remains undefined because we did not find a significant correlation between the *CYP2C19*17* genotype and platelet activity. The main limitation of the present study was the small sample size, and the elective nature of the endovascular treatments was likely a contributing factor to low rates of poor functional outcomes.

CONCLUSIONS

Our results suggest an increased risk of ischemic events in carriers of *CYP2C19*17* who undergo neurointervention. Further research to validate the association and to understand the underlying biologic mechanisms is warranted.

Disclosures: Patrick Kwan—*UNRELATED*: *Grants/Grants Pending*: UCB (research grants)*; *Payment for Lectures (including service on Speakers Bureaus)*: Eisai, GlaxoSmithKline, UCB, *Comments*: lecture fees; *OTHER RELATIONSHIPS*: He received research grants from the National Health and Medical Research Council of Australia, Australian Research Council, Hong Kong Research Grants Council, and Health and Medical Research Fund. He and his institution also received speaker's or consultancy fees and/or research grants from Eisai, GlaxoSmithKline, and UCB. Bernard Yan—*UNRELATED*: research and educational grants from Bayer, Codman (Johnson & Johnson); *Payment for Lectures (including service on Speakers Bureaus)*: Stryker, bioCSL, and Boehringer Ingelheim. *Money paid to the institution.

REFERENCES

1. Molyneux A, Kerr R, Stratton I, et al; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. **International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial.** *Lancet* 2002;360:1267–74 CrossRef Medline
2. Lee DH, Kim HS, Kim SM, et al. **Change of platelet reactivity to antiplatelet therapy after stenting procedure for cerebral artery stenosis: VerifyNow antiplatelet assay before and after stenting.** *Neurointervention* 2012;7:23–26 CrossRef Medline
3. Zhang QY, Li Y, Guan SY, et al. **Incidence and predictors of definite stent thrombosis after coronary stent implantation.** *Chin Med J (Engl)* 2012;125:1547–51 Medline
4. Yamada NK, Cross DT 3rd, Pilgram TK, et al. **Effect of antiplatelet therapy on thromboembolic complications of elective coil embolization of cerebral aneurysms.** *AJNR Am J Neuroradiol* 2007;28:1778–82 CrossRef Medline
5. Kang HS, Han MH, Kwon BJ, et al. **Is clopidogrel premedication useful to reduce thromboembolic events during coil embolization for unruptured intracranial aneurysms?** *Neurosurgery* 2010;67:1371–76; discussion 1376 CrossRef Medline
6. Kazui M, Nishiya Y, Ishizuka T, et al. **Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite.** *Drug Metab Dispos* 2010;38:92–99 CrossRef Medline
7. Grau AJ, Reiners S, Lichy C, et al. **Platelet function under aspirin, clopidogrel, and both after ischemic stroke: a case-crossover study.** *Stroke* 2003;34:849–54 CrossRef Medline
8. Collet JP, Hulot JS, Pena A, et al. **Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study.** *Lancet* 2009;373:309–17 CrossRef Medline
9. Brandt JT, Close SL, Iturria SJ, et al. **Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel.** *J Thromb Haemost* 2007;5:2429–36 CrossRef Medline
10. Rho GJ, Shin WR, Kong TS, et al. **Significance of clopidogrel resistance related to the stent-assisted angioplasty in patients with atherosclerotic cerebrovascular disease.** *J Korean Neurosurg Soc* 2011;50:40–44 CrossRef Medline
11. Pandya DJ, Fitzsimmons BF, Wolfe TJ, et al. **Measurement of antiplatelet inhibition during neurointerventional procedures: the effect of antithrombotic duration and loading dose.** *J Neuroimaging* 2010;20:64–69 CrossRef Medline
12. Shuldiner AR, O'Connell JR, Bliden KP, et al. **Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy.** *JAMA* 2009;302:849–57 CrossRef Medline
13. Goh C, Churilov L, Mitchell P, et al. **Clopidogrel hyper-response and bleeding risk in neurointerventional procedures.** *AJNR Am J Neuroradiol* 2013;34:721–26 CrossRef Medline
14. Sibbing D, Koch W, Gebhard D, et al. **Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement.** *Circulation* 2010;121:512–18 CrossRef Medline
15. Cresci S, Depta JP, Lenzini PA, et al. **Cytochrome P450 gene variants, race, and mortality among clopidogrel-treated patients after acute myocardial infarction.** *Circ Cardiovasc Genet* 2014;7:277–86 CrossRef Medline
16. Dias V, Cabral S, Gomes C, et al. **Intramyocardial dissecting haematoma: a rare complication of acute myocardial infarction.** *Eur J Echocardiogr* 2009;10:585–87 CrossRef Medline
17. Darweesh SK, Leening MJ, Akoudad S, et al. **Clopidogrel use is associated with an increased prevalence of cerebral microbleeds in a stroke-free population: the Rotterdam study.** *J Am Heart Assoc* 2013;2:e000359 CrossRef Medline
18. Godino C, Mendolicchio L, Figini F, et al. **Comparison of VerifyNow-P2Y12 test and Flow Cytometry for monitoring individual platelet response to clopidogrel: what is the cut-off value for identifying patients who are low responders to clopidogrel therapy?** *Thromb J* 2009;7:4 CrossRef Medline
19. De Morais SM, Wilkinson GR, Blaisdell J, et al. **Identification of a new**

genetic defect responsible for the polymorphism of (S)-mephenytoin metabolism in Japanese. *Mol Pharmacol* 1994;46:594–98 Medline
20. Rudberg I, Mohebi B, Hermann M, et al. **Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients.** *Clin Pharmacol Ther* 2008;83:322–27 CrossRef Medline
21. Huang Y, Guo JW; Project Group for Demonstration Study of Syndrome Differentiation Protocol and Effect Evaluation of Acute Ischemic Stroke. **Outcome and safety assessment of an herbal medicine treatment protocol for yin pattern of acute ischemic stroke.** *Zhong Xi Yi Jie He Xue Bao* 2010;8:417–26 CrossRef Medline
22. Geisler T, Schaeffeler E, Dippon J, et al. **CYP2C19 and nongenetic factors predict poor responsiveness to clopidogrel loading dose after coronary stent implantation.** *Pharmacogenomics* 2008;9:1251–59 CrossRef Medline
23. Lee JB, Lee KA, Lee KY. **Cytochrome P450 2C19 polymorphism is associated with reduced clopidogrel response in cerebrovascular disease.** *Yonsei Med J* 2011;52:734–38 CrossRef Medline
24. Hulot JS, Bura A, Villard E, et al. **Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects.** *Blood* 2006;108:2244–47 CrossRef Medline
25. Harmsze AM, van Werkum JW, Ten Berg JM, et al. **CYP2C19*2 and CYP2C9*3 alleles are associated with stent thrombosis: a case-control study.** *Eur Heart J* 2010;31:3046–53 CrossRef Medline
26. Ryu DS, Hong CK, Sim YS, et al. **Anti-platelet drug resistance in the prediction of thromboembolic complications after neurointervention.** *J Korean Neurosurg Soc* 2010;48:319–24 CrossRef Medline
27. Prabhakaran S, Wells KR, Lee VH, et al. **Prevalence and risk factors for aspirin and clopidogrel resistance in cerebrovascular stenting.** *AJNR Am J Neuroradiol* 2008;29:281–85 CrossRef Medline
28. Nordeen JD, Patel AV, Darracott RM, et al. **Clopidogrel resistance by P2Y12 platelet function testing in patients undergoing neuroendovascular procedures: incidence of ischemic and hemorrhagic complications.** *J Vasc Interv Neurol* 2013;6:26–34 Medline