Received: 11 November 2021 | Revised: 31 January 2022 | Accepted: 2 February 2022

DOI: 10.1111/bcp.15282

ORIGINAL ARTICLE

Increased frequency of *CYP2C19* loss-of-function alleles in clopidogrel-treated patients with recurrent cerebral ischemia

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Aims: Clopidogrel is used as secondary prevention after cerebral ischaemia. Previous, mainly Asian, studies have shown that genetic variations in *CYP2C19* are associated with an increased risk of recurrent stroke in clopidogrel-treated patients. Evidence on the impact of this drug–gene interaction in European neurology patients is currently limited. The aim of this study is to compare the prevalence of *CYP2C19* loss-of-function (LoF) alleles in a population with recurrent cerebral ischaemia to two reference groups from the same region.

Methods: *CYP2C19*-genotyping (*2 and *3) was performed in clopidogrel-treated patients who presented with a recurrent ischaemic stroke/transient ischaemic attack (TIA). Genotype distributions were compared with two reference groups; a cohort of consecutive patients who underwent elective coronary stent implantation and a cohort of healthy Dutch volunteers.

Results: In total, 188 cases with a recurrent ischaemic event were identified, of whom 38 (20.2%) experienced an early recurrent event (24 hours to 90 days after the previous event). Among the total case group, 43.6% of the patients carried at least one *CYP2C19* LoF allele, compared with 27.6% and 24.7% in respectively the cardiology and the healthy volunteers reference groups ($P < .001$ for both comparisons). Among the cases with an early recurrent event, 55.3% of patients were carriers of at least one *CYP2C19* LoF allele ($P < .0001$).

Conclusion: In this clopidogrel-treated population with recurrent cerebral ischaemia, the frequency of *CYP2C19* LoF alleles was significantly higher than in reference groups, especially in early recurrent events. This study adds to the growing body of evidence that genotype-guided antiplatelet therapy could improve patient outcomes.

KEYWORDS
cerebral ischaemia, clopidogrel, CYP2C19, genetic variants, secondary prevention, stroke, transient ischaemic attack

1 | INTRODUCTION

The antiplatelet drug clopidogrel has been proven to reduce the occurrence of new stroke in patients with acute ischaemic stroke or transient ischaemic attack (TIA).[1] However, the efficacy in preventing recurrent ischaemia differs between individuals.[2,3] Clopidogrel is an

As no interventions were performed in this study - which was based on retrospective assessments of data from health records - no principal investigator was assigned.

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inactive prodrug which is converted by iso-enzymes of the cytochrome P450 (CYP) system to 2-oxoclopidogrel and subsequently to the active metabolite H4. This active metabolite selectively inhibits the binding of adenosine diphosphate (ADP) to the platelet P2Y12 receptor, thereby inhibiting platelet aggregation.[3] CYP2C19 plays an important role in both metabolization steps. Previous studies have shown that genetic variations in *CYP2C19* are associated with an increased risk of cardiovascular events—including death—in patients with coronary artery disease treated with clopidogrel.[4,5] In stroke research, several studies showed that in clopidogrel-treated patients with ischaemic stroke or TIA, carriers of *CYP2C19* loss-of-function (LoF) alleles were at increased risk of recurrent stroke and composite vascular events compared to non-carriers, whereas the bleeding risk was similar.[6] However, the majority of these studies were performed in East Asian countries, where the incidence of *CYP2C19* LoF alleles is considerably higher than in European populations.[7] Evidence on the impact of the *CYP2C19* genotype on the efficacy of clopidogrel in European patients with cerebrovascular disease is currently limited. The aim of this study is to explore *CYP2C19* genotype in a real-world European clopidogrel-treated population with recurrent acute ischaemic stroke or TIA.

What is already known about this subject

- In mainly East Asian studies *CYP2C19* genotype was shown to be associated with recurrent stroke in clopidogrel-treated patients.
- The drug–gene interaction also has a significant impact on the recurrence of major adverse cardiovascular events in patients with coronary artery disease.
- The influence of *CYP2C19* genotype on the efficacy of clopidogrel in a European population with cerebrovascular disease is currently limited.

What this study adds

- The frequency of *CYP2C19* loss-of-function alleles is increased in patients with recurrent stroke in a real-world European population.
- The group of patients with an early recurrent ischaemic event consisted of more than twice as many CYP2C19 intermediate and poor metabolizers than in the two reference groups.
- This study adds to the growing body of evidence that genotype-guided antiplatelet therapy could improve outcomes in populations with cerebrovascular disease.

2 | METHODS

2.1 | Study population

Consecutive patients who received clopidogrel 75 mg once daily as secondary prevention after an ischaemic stroke or TIA, with a recurrent ischaemic stroke or TIA and for whom *CYP2C19*-genotyping was performed, were defined as cases. These patients were either admitted to or presented at the outpatient clinic of the St. Antonius Hospital Nieuwegein in the Netherlands, between February 2018 and February 2020. A recurrent event was defined as a new acute neurological event with symptoms occurring at least 24 hours after the last stroke/TIA. An *early* recurrent event was defined as a new ischaemic event between 24 hours and 90 days after the previous stroke/TIA. The diagnosis and further details concerning the aetiology of the events of all included cases were evaluated retrospectively by two independent experts. The ethnicity of the population in and around the city of Nieuwegein is predominantly Caucasian (> 85%).[8]

The first reference group consisted of consecutive patients who underwent elective coronary stent implantation in the St. Antonius Hospital Nieuwegein between December 2005 and December 2007.[9] A large group of Dutch healthy volunteers was defined as the second reference group.[10]

2.2 | CYP2C19 genotyping

From all subjects, genomic DNA was isolated from venous EDTA-anticoagulated blood. The LoF alleles *CYP2C19*2* (G681A, rs4244285) and *CYP2C19*3* (G636A, rs4986893) were determined by real-time polymerase chain reaction using the StepOnePlus™ Real-Time PCR system (Applied Biosystems, Waltham, MA, USA), pre-validated Drug Metabolism TaqMan Genotyping Assays (for CYP2C19*2 Assay ID C__25986767_70 and for CYP2C19*3 Assay ID C__27861809_10) and TaqMan GTXpress Master Mix (Thermo Fisher Scientific, Waltham, MA, USA), according to the manufacturer's instructions.

2.3 | Statistical analysis

The Kolmogorov–Smirnov test was used to check for normal distribution of continuous data. Continuous data, except the time since last ischaemic stroke, were normally distributed. Normally distributed data were presented as mean (± standard deviation [SD]). Continuous data not meeting the criteria for normal distribution were expressed as median [interquartile range (IQR)]. The genotype distributions were tested for Hardy–Weinberg equilibrium using the chi-square test. A two-sided *P*-value of <.05 was considered to be statistically significant.

Differences in *CYP2C19* genotype distributions between the case and reference groups were analysed with the chi-square test for categorical variables. Statistical analysis was performed with SPSS software (version 25.0; IBM, Armonk, NY, USA).

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3 | RESULTS

3.1 | Patient characteristics

In total, 188 cases with a recurrent ischaemic stroke or TIA while using clopidogrel 75 mg/day in whom *CYP2C19* genotyping was performed were identified. Of these, 38 cases (20.2%) suffered from an early recurrent event (between 24 hours and 90 days after the previous event). The mean (± SD) age was 72.4 ± 8.8 years and 109 (58.0%) of the cases were male. The majority of cases presented with an ischaemic stroke (56.9%), the remaining 43.1% with a TIA. Table 1 summarizes the characteristics of the cases.

3.2 | *CYP2C19* genotype distribution

No significant deviations from Hardy–Weinberg equilibrium were observed. When the two reference groups were compared, there were no statistically significant differences between genotype and LoF allele carrier *vs* noncarrier frequencies between these groups ($P = .77$ and $P = .47$, respectively).

As shown in Table 2, 43.6% of the cases carried at least one *CYP2C19* LoF allele (*CYP2C19*2* or **3*), compared with 27.6% and 24.7% in respectively the cardiology reference group and the healthy reference group (for both comparisons $P < .01$). The prevalence of CYP2C19 poor metabolizers in the case group was approximately twice as high as in both reference groups (5.3% *vs* 3.3% and 2.6%, respectively). Only one patient in the case group was carrier of a *CYP2C19*3* LoF allele.

When cases were divided according to the type of ischaemic event, genotype frequencies were similar in both groups; in the stroke subgroup, 43% of the patients were *CYP2C19* LoF allele carriers and in the TIA subgroup 44%.

The prevalence of *CYP2C19* LoF alleles was even higher in cases with an *early* recurrent ischaemic event. More than 55% of these cases carried at least one *CYP2C19* LoF allele (Table 2), twice the prevalence of the *CYP2C19* LoF carriers in the reference groups (for both comparisons $P < .0001$). In analyses of the TIA and stroke subgroups, the distribution of *CYP2C19* LoF alleles in cases with an early recurrent ischaemic event remained similar. Subanalyses according to stroke aetiology (TOAST classification),[11] stroke severity (NIHSS) and the use of (es)omeprazole or anticoagulants did not change these findings.

TABLE 1 Baseline characteristics of the study population

Variable	Noncarriers *CYP2C19* LoF allele(s) ($n = 106$)	Carriers *CYP2C19* LoF allele(s) ($n = 82$)
Age (years)	74.8 ± 10.7	69.1 ± 12.0[a]
Gender (male)	66 (62.2)	43 (52.4)
BMI (kg/m^2)	26.9 ± 3.7	27.5 ± 5.4
Diabetes mellitus	25 (23.6)	17 (20.7)
Smoking, present	19 (17.9)	19 (23.2)
Ischaemic stroke type		
Stroke	61 (57.5)	46 (56.1)
TIA	45 (42.5)	36 (43.9)
Ischaemic stroke subtype (TOAST classification)		
Large-artery atherosclerosis	21 (19.8)	15 (18.3)
Cardioembolism	6 (5.7)	4 (4.9)
Small-vessel occlusion	22 (20.8)	11 (13.4)
Stroke of other determined aetiology	5 (4.7)	3 (3.7)
Stroke of undetermined aetiology	52 (49.1)	49 (59.8)
NIHSS at presentation	2.5 ± 3.9	2.8 ± 4.3
Time since last ischaemic stroke (months)	19.0 [42]	13.5 [39]
Time since last ischaemic stroke ≤ 3 months	17 (16.0)	21 (25.6)
First recurrence	65 (61.3)	51 (62.2)
Hypertension	75 (70.8)	55 (67.1)
Hypercholesterolaemia	89 (84.0)	68 (82.9)
Atrial fibrillation	7 (6.6)	8 (9.8)
Other CV disease	11 (10.4)	8 (9.8)
Concomitant medication		
(Es)omeprazole	10 (9.4)	2 (2.4)
Other PPI	44 (41.5)	37 (45.1)
Acetylsalicylic acid	9 (8.5)	12 (14.6)
Other anticoagulant	2 (1.9)	2 (2.4)

Data presented are mean ± SD, median [interquartile range] or number of patients (percentage). BMI: body mass index, TIA: transient ischaemic attack, CV: cardiovascular, PPI: proton pump inhibitor;
[a]$P = .001$, for all other comparisons: $P > .05$.

4 | DISCUSSION

In this real-world study, we determined the frequency of *CYP2C19* LoF carriers in clopidogrel-treated patients with recurrence of cerebral ischaemic events. We found that 43.6% of patients who suffered from a recurrent ischaemic event were CYP2C19 intermediate or poor metabolizers. This percentage is markedly higher than the percentages observed in the two reference groups from the same geographical region. The impact of *CYP2C19* genotype was most profound in patients with an *early* recurrent ischaemic event, defined as an event occurring between 24 hours and 90 days after the previous stroke/TIA. This subgroup consisted of more than twice as many CYP2C19 intermediate and poor metabolizers than the reference groups. This is in line with our expectations; when clopidogrel's active metabolite is inadequately formed, an instant risk of therapy failure—resulting in recurrent ischaemic events—occurs.

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TABLE 2 *CYP2C19* genotype distribution. Reference group 1: cardiology patients. Reference group 2: healthy subjects

	Cases		Reference group 1			Reference group 2		
CYP2C19 phenotype/genotype	Total ($n = 188$)	Early recurrent event ($n = 38$)	Total ($n = 725$)	*P*-value (total cases)	*P*-value (early recurrent events)	Total ($n = 745$)	*P*-value (total cases)	*P*-value (early recurrent events)
Extensive metabolizers *CYP2C19*1/*1*	106 (56.4)	17 (44.7)	525 (72.4)			561 (75.3)		
Intermediate metabolizers *CYP2C19*1/*2* *CYP2C19*1/*3*[a]	72 (38.3)	20 (52.6)	176 (24.3)	0.002	< .0001	165 (22.1)	< .0001	< .0001
Poor metabolizers *CYP2C19*2/*2*	10 (5.3)	1 (2.6)	24 (3.3)			19 (2.6)		
Carriers *CYP2C19* LoF allele	82 (43.6)	21 (55.3)	200 (27.6)	< .0001	< .0001	184 (24.7)	< .0001	< .0001
Noncarriers *CYP2C19* LoF allele	106 (56.4)	17 (44.7)	525 (72.4)			561 (75.3)		

[a]In the case group, one subject carrying a *CYP2C19*3* allele (*CYP2C19*1/*3*) was found.

These findings suggest that *CYP2C19* genotype is a strong predictor of clopidogrel's efficacy in reducing the risk of recurrent events in European patients with a history of TIA/ischaemic stroke. These results are consistent with recent, mainly East Asian studies in which the incidence of recurrent stroke was found to be approximately twice as high in CYP2C19 intermediate and poor metabolizers compared to extensive metabolizers.[6] However, there is a large difference in *CYP2C19* genotype distribution between the Asian population (50–60% carriers of a *CYP2C19* LoF allele) and the European population (25–28% carriers of a *CYP2C19* LoF allele) and the Asian population has a higher incidence of intracranial-artery stenosis than non-Asian populations.[7] Therefore the results in the Asian studies are not automatically generalizable to a Western population.

Our findings can also be correlated to extensive research from the field of cardiology; presence of *CYP2C19* LoF alleles in Western populations with acute coronary syndromes (ACS) and/or undergoing percutaneous coronary interventions (PCI) is associated with a higher risk of in-stent thrombosis, recurrent cardiovascular events and death.[12]

Recently, results from the genetic substudy of the POINT trial[13] were published, in which no interaction by *CYP2C19* genotype for major ischaemia or stroke was observed. As the authors acknowledged, their study had very limited statistical power of 50% due to the low prevalence of LoF allele carriers. This could explain why a genotype–phenotype interaction could not be detected. Moreover, the clopidogrel loading dose in this trial was 600 mg instead of 300 mg, which could have negated any significant effect of LoF alleles on (early) ischaemic events.

Based on the impact of this drug–gene interaction, genotype-guided therapy is increasingly applied in clinical practice and has been included in several international guidelines.[14,15] Several cost-effectiveness analyses for PCI patients suggest genotype-guided therapy to be cost-effective, also for European intermediate and poor metabolizer frequencies.[16]

It is recommended that in ischaemic stroke/TIA care, CYP2C19 intermediate metabolizers are treated with a higher maintenance dose of 150 mg clopidogrel/day.[15] In CYP2C19 poor metabolizers, however, high dose clopidogrel will not achieve adequate plasma concentrations of clopidogrel's active metabolite. In that case, alternative platelet aggregation inhibitors are proposed.[15] The combination of aspirin and dipyridamole is considered to be noninferior to clopidogrel monotherapy.[17] However, the use of dipyridamole is hampered by the high incidence of severe headache. Genetic variations in *CYP2C19* do not decrease the efficacy of P2Y12 inhibitors prasugrel and ticagrelor. However, prasugrel is contraindicated in patients with previous TIA or stroke because of an increased risk of haemorrhagic complications.[18] In the SOCRATES trial, ticagrelor was not found to be superior to aspirin in the prevention of major vascular events in patients with nonsevere ischaemic stroke or high-risk TIA.[19] Recently, ticagrelor on top of aspirin was found to beneficial in preventing stroke or death within 30 days but was also associated with an increased risk of severe bleeding.[20] Therefore, further

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research is needed to identify a suitable alternative for CYP2C19 poor metabolizers in stroke management.

There are some limitations to this study. Firstly, in this observational study, we did not take into account other patient characteristics and environmental factors, such as obesity, smoking behaviour or other medications, that may have an effect on platelet aggregation or other risk factors that may have contributed to the recurrence of stroke. For example, the use of (es)omeprazole is associated with clopidogrel resistance.[21] However, exclusion of the users of (es)omeprazole (6.4% of the patients) from our analyses did not change the findings. Also, the subgroups were too small to explore possible associations between stroke characteristics and genotype. We hypothesized that stroke aetiology also might determine the strength of association, since clopidogrel is insufficient prophylaxis for recurrent cardiac embolisms regardless of *CYP2C19* genotype. However, our subanalyses did not yield a significant association, due to the small sample size of the subgroups.

Secondly, we did not determine the *CYP2C19*17* genetic variation; therefore, we were not able to define CYP2C19 ultrarapid metabolizers. However, this phenotype has not been found to be clinically relevant for the efficacy/safety of clopidogrel.[22] If patients with one LoF allele (**2* or **3*) also carry a **17* allele, those patients are classified as CYP2C19 intermediate metabolizers. Therefore, in our opinion it is justified to report genotype frequencies without the knowledge of **17*. In addition, in the case group, only one patient was carrier of a *CYP2C19*3* LoF allele; all other LoF carriers carried at least one *CYP2C19*2* allele. As the allele frequency of *CYP2C19*3* in Europeans is only 0.02%, this was expected.[23]

Furthermore, no detailed information on the ethnicity of the patients with recurrent stroke/TIA was available. The ethnic background of residents in/around the city of Nieuwegein is primarily Caucasian, but it cannot be ruled out that in the case group more patients of Asian ancestry (with a higher *CYP2C19* LoF allele frequency) were present than expected in the general population in this region.

Lastly, the design of the present study is less robust than, for instance, a prospective follow-up study or a case–control study. We aimed to make the comparison of genotype frequencies more robust by using two independent reference groups. The first reference group consisted of *consecutive* patients undergoing PCI in the same hospital in Nieuwegein as the cases. Of note, some patients in this group underwent stenting for a recurrent myocardial infarction whilst clopidogrel-treated. Consequently, the frequency of LoF *CYP2C19* alleles in this first reference group might be higher than in the general population. To represent the general population, we included a second reference group, consisting of healthy volunteers in the Netherlands. Since the LoF allele frequencies of the second reference group did not differ from the first reference group, possible selection bias due to this concern is dismissed.

In conclusion, we have shown that the frequency of *CYP2C19* LoF alleles is increased in patients with recurrent stroke in a real-world European population. This study adds to the growing body of evidence that genotype-guided antiplatelet therapy could improve outcomes in populations with cerebrovascular disease.

ACKNOWLEDGEMENTS

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

COMPETING INTERESTS

The authors report there are no conflicts of interest to declare.

CONTRIBUTORS

A.H., M.B. and P.H. conceived the study. A.H., C.M. and L.O. researched the literature. A.H. developed the study protocol and gained ethical approval. C.M. and L.O. collected patient data and performed data analysis. A.H., C.M. and L.O. wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version.

INFORMED CONSENT

Written consent was waived by the ethics committee MEC-United as the study is retrospective observational, only available data was used and no patient interventions were required.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Minderhoud C, Otten LS, Hilkens PHE, van den Broek MPH, Harmsze AM. Increased frequency of *CYP2C19* loss-of-function alleles in clopidogrel-treated patients with recurrent cerebral ischemia. *Br J Clin Pharmacol*. 2022;88(7):3335-3340. doi:10.1111/bcp.15282

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