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Post-percutaneous coronary intervention CYP2C19 genotyping in an Irish population: The potential role in identifying clopidogrel therapy-related bleeding risks

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Aims: Dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) remains the standard of care. **CYP2C19** genetic polymorphisms cause variable **clopidogrel** bioactivation. Increased function (CYP2C19*17) allele carriers (rapid metabolizers [RM] or ultrarapid metabolizers [UM]) are clopidogrel hyper-responders, hence are more susceptible to clopidogrel-related bleeding. Since current guidelines recommend against routine genotyping following PCI, data on the clinical utility of CYP2C19*17 genotype guided strategy are sparse. Our study provides real-world data on the 12-month follow-up of CYP2C19 genotyping in patients post-PCI.

Methods: This is a cohort study within an Irish population receiving 12-month DAPT following PCI. It identifies the prevalence of CYP2C19 polymorphisms within an Irish population and describes the ischaemic and bleeding outcomes after 12 months of DAPT.

Results: A total of 129 patients were included with the following CYP2C19 polymorphism prevalence: 30.2% hyper-responders (26.4% RM [1*/17*], 3.9% UM [17*/17*]) and 28.7% poor-responders (22.5% IM [1*/2*], 3.9% IM [2*/17*], 2.3% PM [2*/2*]). A total of 53 and 76 patients received clopidogrel and ticagrelor, respectively. At 12 months, total bleeding incidence within the clopidogrel group was positively correlated with CYP2C19 activity: IM/PM (0.0%), NM (15.0%) and RM/UM (25.0%). The positive relationship showed a moderate association that was statistically significant: $r_{\tau} = 0.28$, $P = 0.035$.

Conclusions: The prevalence of CYP2C19 polymorphisms in Ireland is 58.9% (30.2% CYP2C19*17, 28.7% CYP2C19*2) with an approximately one in three chance of being a clopidogrel hyper-responder. Positive correlation between bleeding and increasing CYP2C19 activity within the clopidogrel group ($n = 53$) suggests possible clinical utility of a genotype-guided strategy identifying high bleeding risk with clopidogrel in CYP2C19*17 carriers, but further studies are required.

The authors confirm that the Principal Investigator for this paper is Professor Thomas Kiernan and that he had direct clinical responsibility for patients.

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KEYWORDS

bleeding risk, clopidogrel, CYP2C19 polymorphism

1 | INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ receptor inhibitor after percutaneous coronary intervention (PCI) remains the standard of care to prevent major adverse cardiovascular events (MACE) like death, myocardial infarction and stent thrombosis.^{1,2} Clopidogrel is a thienopyridine prodrug, bioactivated by the cytochrome P450 2C19 enzyme (CYP2C19) into its pharmacologically active metabolite to exert its therapeutic effects through ADP P2Y₁₂ receptor inhibition.³ Because of its lower cost and lower risk of bleeding, it remains the most commonly prescribed P2Y₁₂ receptor inhibitor in clinical practice.⁴

Genetic polymorphisms in CYP2C19 resulting in variable clopidogrel bioactivation have been shown by several studies to have a significant impact on clinical outcomes following PCI.^{5,6} Carriers of the loss-of-function (CYP2C19*2) allele are poor responders to clopidogrel therapy and are phenotypically characterized as intermediate metabolizers (IM) or poor metabolizers (PM) depending on whether they carry one or two copies of the defective gene.⁷ IM and PM individuals have a reduced therapeutic response to clopidogrel therapy resulting in higher incidence of MACE following PCI.^{6,8} Carriers of the increased function (CYP2C19*17) allele have increased response to clopidogrel therapy and are phenotypically classified as rapid metabolizers (RM) or ultrarapid metabolizers (UM) depending on whether they carry one or two copies of the gene.⁷ An increased production of the pharmacologically active metabolite results in higher bleeding risk and lower incidence of MACE following PCI.⁹⁻¹² Interestingly, mixed carriers of one increased function (CYP2C19*17) allele and one loss-of-function (CYP2C19*2) allele are also classified as IM since there is no evidence that the increased function from the CYP2C19*17 allele compensates for the loss of function from the CYP2C19*2 allele.⁷ Significant ethnic variability of CYP2C19 allele frequencies exists.¹³ When allele frequencies of European populations were compared with Asian populations, the CYP2C19*17 allele predominated (26.5% vs 1.6%) while CYP2C19*2 alleles were fewer in comparison (14.2% vs 30.3%).¹³

While genotype-guided strategies in antiplatelet selection following PCI have demonstrated clinical utility in reducing the incidence of MACE in poor responders to clopidogrel (CYP2C19*2 allele carriers), there is less evidence for its use in reducing bleeding risk in hyper-responders to clopidogrel (CYP2C19*17 allele carriers).¹⁴⁻¹⁶ Current guidelines endorse the strategy of guided de-escalation of DAPT (switching potent P2Y₁₂ receptor inhibitor to clopidogrel), but detection of the CYP2C19*17 allele is not regarded as a factor for bleeding risk.^{17,18} Moreover, there is increasing evidence that in patients with established coronary artery disease,

What is already known about this subject

- Genetic polymorphisms in CYP2C19 result in variable clopidogrel bioactivation.
- Increased function (CYP2C19*17) allele carriers have increased risk of clopidogrel-related bleeding.
- The clinical utility of a genotype-guided strategy in identifying high bleeding risk with CYP2C19*17 postpercutaneous coronary intervention has not been proven, and data are scarce as guidelines recommend against routine genotyping.

What this study adds

- This study identifies the prevalence of CYP2C19 genetic polymorphisms within an Irish population.
- It provides real-world data on the 12-month bleeding and ischaemic outcomes of CYP2C19 genetic polymorphisms and clopidogrel therapy.
- It identified a trend of increasing bleeding risk on clopidogrel with increasing CYP2C19 activity with peak bleeding risk with CYP2C19*17 carriers.

lifelong monotherapy with a P2Y₁₂ receptor inhibitor (instead of aspirin) after completion of DAPT provides greater protection from recurrent ischemic events without an increased risk of bleeding complications.^{19,20} With greater scope for long-term P2Y₁₂ receptor inhibitor use, the varied ischaemic and bleeding risks from clopidogrel therapy in the context of CYP2C19 genetic polymorphisms highlight the importance of a genotype-guided strategy for P2Y₁₂ receptor inhibitor selection.

Since current American and European guidelines recommend against routine genotyping following PCI, real-world data on the clinical utility of a genotype-guided strategy following PCI are limited and the clinical implications of the CYP2C19*17 allele on clopidogrel bleeding risks remain unclear.^{18,21,22} We performed a single-centre prospective cohort study in an Irish population receiving 12-month DAPT following PCI with the aim of identifying the prevalence of CYP2C19 polymorphism in an Irish population and the clinical outcomes (ischaemic and bleeding) after 12 months of DAPT (clopidogrel or ticagrelor).

2 | METHODS

2.1 | Patients and study design

Patients eligible for this study met the following inclusion criteria: (i) adult patients (age ≥ 18 years) undergoing PCI for any indication (acute coronary syndrome [ACS] or chronic coronary syndrome [CCS]) between July 2020 and January 2021, (ii) no contraindication to the guideline standard 12-month DAPT (aspirin and P2Y₁₂ receptor inhibitor) following PCI and (iii) able to provide signed written informed consent to participate in the study. All patients who underwent PCI were commenced on postprocedure DAPT. Selection of P2Y₁₂ receptor inhibitor was performed through clinical assessment of individual ischaemic and bleeding risks (ACS, complex PCI, age, prior bleeding, chronic kidney disease). Eligible patients were prospectively recruited to undergo CYP2C19 genotyping and 12-month follow-up from initial PCI (Figure 1). The CYP2C19 genotype results did not influence the initial selection of P2Y₁₂ receptor inhibitor or alter the course of the 12-month DAPT. Genotyped patients receiving clopidogrel or ticagrelor therapy were subdivided into treatment-metabolizer status phenotype groups: clopidogrel RM/UM, clopidogrel NM, clopidogrel IM/PM, ticagrelor RM/UM, ticagrelor NM and ticagrelor IM/PM. Genotyped patients were followed for 12 months following PCI to monitor the impact of CYP2C19 genetic polymorphism on ischaemic and bleeding outcomes. Patients were excluded from this study if there were (i) contraindications to 12-month DAPT (aspirin and/or clopidogrel/ticagrelor), (ii) refusal to sign written informed consent to participate in the study or (iii) serious cardiac or noncardiac

disease with expected prognosis < 1 year. The study was performed in line with the principles of the Declaration of Helsinki, and ethical approval was granted by the Research Ethics Committee of the UL Hospitals Group, Mid-West Region (reference number 113/19) prior recruitment of patients.

2.2 | CYP2C19 genotyping

CYP2C19 genotyping was performed by point-of-care DNA testing using the Spartan Cube CYP2C19 System (Spartan Bioscience, Ottawa, Ontario, Canada). This automated point-of-care DNA testing system is a validated bedside test for rapidly identifying CYP2C19 mutations (specifically the *2 and *17 alleles).²³ Each test kit is composed of a single test cartridge (containing all reagents for the test and control assays) and three buccal swabs corresponding to a patient barcode identifier. Buccal samples were collected using the three buccal swabs and inserted (without further processing) into the test cartridge. The loaded cartridge was then inserted into a bedside thermal cycling analyser which automatically performed polymerase chain reaction amplification and uploaded the detected CYP2C19 genotype results onto a network interface results library within 1 h. The test did not require processing in a central laboratory or require specialized laboratory training to perform. Doctors involved in the study were trained on how to obtain written informed consent and how to perform the point-of-care genotyping test according to the manufacturer's instructions. All included patients provided written informed consent before buccal samples were collected and analysed.

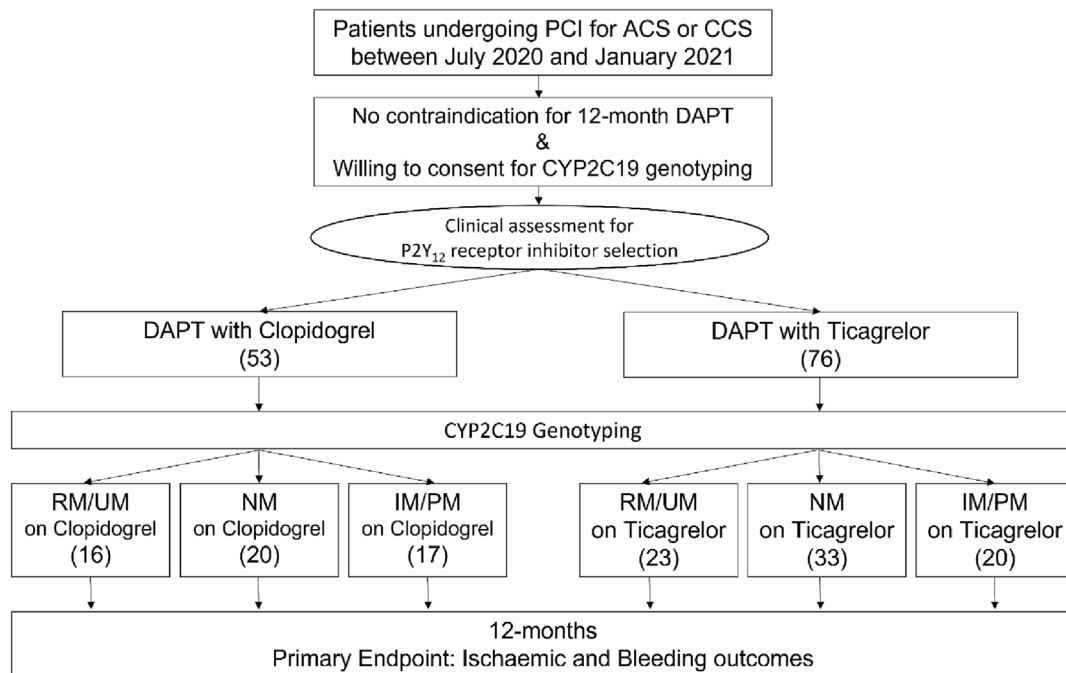


FIGURE 1 Study flow diagram. ACS, acute coronary syndrome; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; RM, rapid metabolizer; UM, ultra metabolizer; NM, normal metabolizer; IM, intermediate metabolizer; PCI, percutaneous coronary intervention; PM, poor metabolizer.

2.3 | Patient follow-up and outcomes

All included patients were scheduled follow-up in clinic at 6 weeks, 4 months and 12 months following PCI. Patients were screened for ischaemic or bleeding events during clinic visits by assessing clinical symptoms of cardio/cerebrovascular ischaemia and bleeding events experienced. Bleeding events were further screened and quantified by measuring haemoglobin levels during the clinic visit. All included patients were screened for any hospital admission occurring within 12 months of initial PCI. Patients who required hospital admission had their inpatient hospital records reviewed for any ischaemic or bleeding events that had taken place. All missed outpatient clinic appointments during the COVID-19 pandemic were followed up with a telephone call to assess self-reported symptoms of cardio/cerebrovascular ischaemia and bleeding events experienced.

The primary outcomes were ischaemic and bleeding outcomes. Ischaemic outcomes were a composite of MACE including noncardiovascular death, cardiovascular death, ACS, stroke, stent thrombosis, urgent revascularization within 12 months of initial PCI and in-stent restenosis (ISR). Bleeding outcomes were assessed and defined according to the thrombolysis in myocardial infarction (TIMI) bleeding criteria and were classified as TIMI major, minor or minimal bleeding.²⁴ All clinical events were assessed and validated by two doctors who were blinded to treatment allocation (clopidogrel vs ticagrelor) and CYP2C19 genotype.

2.4 | Statistical analyses

All calculations and statistical analysis were performed using SPSS software, version 27 (IBM Corporation, Armonk, NY, USA). $P < .05$ was considered statistically significant. Descriptive statistics were expressed as mean \pm standard deviation. Statistical comparison of the baseline categorical and qualitative variables between the clopidogrel and ticagrelor groups was performed using Fisher's exact test. Differences in baseline categorical and qualitative variables between the metaboliser status of the clopidogrel and ticagrelor groups were statistically analysed using a nonparametric univariate test (Kruskal-Wallis test). The trends of ischaemic and bleeding outcomes according to CYP2C19 activity based on the metaboliser status of the clopidogrel and ticagrelor groups were statistically analysed using a nonparametric, rank-based trend test (Jonckheere-Terpstra test). To estimate the size of the effect of the correlation between CYP2C19 activity and bleeding within the clopidogrel group, a nonparametric measure of correlation for ranked variables was used (Kendall's tau $[\tau]$ correlation coefficient).

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to

PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019 a,b).^{25,26}

3 | RESULTS

3.1 | Baseline patient characteristics

Of the adult patients undergoing PCI for any indication between July 2020 and January 2021, a total of 129 patients met the inclusion criteria and were included in this study. All 129 patients received postprocedure DAPT (aspirin and P2Y₁₂ receptor inhibitor) for 12 months and were genotyped for CYP2C19 mutations. The baseline characteristics of all included patients are shown in Table 1. The mean age of included patients was 63.8 ± 10.4 years with the majority being male (76.7%) and undergoing PCI for ACS indication (76.7%). After clinical evaluation of individual ischaemic and bleeding risks (independent of CYP2C19 genotype) following PCI, 53 patients received clopidogrel and 76 patients received ticagrelor in combination with aspirin as part of 12-month DAPT. Comparison of the baseline characteristics of patients receiving clopidogrel and ticagrelor DAPT is shown in Table 1. When a clinical assessment strategy was used for P2Y₁₂ receptor inhibitor selection, patients receiving clopidogrel were more likely to be comorbid with hypertension (69.8% vs 52.6%, $P = 0.037$), affected by previous stroke (9.4% vs 1.3%, $P = 0.042$), discharged on an oral anticoagulant (9.4% vs 0.0%, $P = 0.01$) and have CCS as the indication for PCI (35.8% vs 14.5%, $P = 0.005$). Patients receiving ticagrelor were more likely to have ACS (85.5% vs 64.2%, $P = 0.006$) and ST-elevated myocardial infarction (52.6% vs 13.2%, $P = <0.0001$) as the indication for PCI, and were more likely to be discharged on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (85.5% vs 64.2%, $P = 0.005$) and beta-blockers (89.5% vs 71.7%, $P = 0.009$).

3.2 | CYP2C19 genotypes and metabolizer status

Within the Irish cohort of 129 patients, the following CYP2C19 genotypes were identified (Table 2): 39 (30.2%) patients were hyper-responders (26.4% RM [1*/17*], 3.9% UM [17*/17*]), 53 (41.1%) patients were normal-responders (41.1% NM [1*/1*]) and 37 (28.7%) patients were poor-responders (22.5% IM [1*/2*], 3.9% IM [2*/17*], 2.3% PM [2*/2*]). The following treatment-metabolizer status phenotype groups were identified within the genotyped cohort: 16 (12.4%) clopidogrel RM/UM, 20 (15.5%) clopidogrel NM, 17 (13.2%) clopidogrel IM/PM, 23 (17.8%) ticagrelor RM/UM, 33 (25.6%) ticagrelor NM and 20 (15.5%) ticagrelor IM/PM.

3.3 | 12-month outcomes of clopidogrel and ticagrelor therapy according to metabolizer status

The baseline characteristics and 12-month ischaemic and bleeding outcomes of the treatment-metabolizer status phenotype groups are

TABLE 1 Baseline patient characteristics and comparison between clopidogrel and ticagrelor therapy.

| Characteristic | All (%) (n = 129) | Clopidogrel (%) (n = 53) | Ticagrelor (%) (n = 76) | P value |
|----------------------------|-------------------|--------------------------|-------------------------|---------|
| Patient demographic | | | | |
| • Mean age (years) | 63.8 ± 10.4 | 66.5 ± 9.8 | 61.9 ± 10.3 | 0.721 |
| • Male | 99 (76.7) | 38 (71.7) | 61 (80.3) | 0.178 |
| Baseline comorbidities | | | | |
| • BMI (kg/m ²) | 29.7 ± 6.1 | 30.3 ± 5.9 | 29.3 ± 6.2 | 0.389 |
| • Hypertension | 77 (59.7) | 37 (69.8) | 40 (52.6) | 0.037 |
| • Dyslipidaemia | 72 (55.8) | 32 (60.4) | 40 (52.6) | 0.245 |
| • Diabetes | 24 (18.6) | 11 (20.8) | 13 (17.1) | 0.382 |
| • Active smoker | 57 (44.2) | 22 (41.5) | 35 (46.1) | 0.371 |
| • Family Hx CAD | 60 (46.5) | 26 (49.1) | 34 (44.7) | 0.380 |
| • Prior MI | 17 (13.2) | 5 (9.4) | 12 (15.8) | 0.218 |
| • Prior PCI | 32 (24.8) | 14 (26.4) | 18 (23.7) | 0.440 |
| • Prior CABG | 10 (7.8) | 6 (11.3) | 4 (5.3) | 0.176 |
| • CCF | 4 (3.1) | 2 (3.8) | 2 (2.6) | 0.545 |
| • Prior stroke | 6 (4.7) | 5 (9.4) | 1 (1.3) | 0.042 |
| • PAD | 4 (3.1) | 2 (3.8) | 2 (2.6) | 0.545 |
| • Prior bleeding | 4 (3.1) | 3 (5.7) | 1 (1.3) | 0.188 |
| Presentation | | | | |
| • ACS | 99 (76.7) | 34 (64.2) | 65 (85.5) | 0.006 |
| ◦ STEMI | 47 (36.4) | 7 (13.2) | 40 (52.6) | <0.0001 |
| ◦ NSTEMI | 36 (27.9) | 18 (34.0) | 18 (23.7) | 0.140 |
| ◦ UA | 16 (12.4) | 9 (17.0) | 7 (9.2) | 0.148 |
| • CCS | 30 (23.3) | 19 (35.8) | 11 (14.5) | 0.005 |
| Discharge medication | | | | |
| • Aspirin | 129 (100.0) | 53 (100.0) | 76 (100.0) | - |
| • Anticoagulation | 5 (3.9) | 5 (9.4) | 0 (0.0) | 0.010 |
| • Statin | 125 (96.9) | 50 (94.3) | 75 (98.7) | 0.188 |
| • ACEi/ARB | 99 (76.7) | 34 (64.2) | 65 (85.5) | 0.005 |
| • Beta-blocker | 106 (82.2) | 38 (71.7) | 68 (89.5) | 0.009 |
| • PPI | 103 (79.8) | 46 (86.8) | 57 (75.0) | 0.076 |

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass graft; CCF, congestive cardiac failure; CCS, chronic coronary syndrome; NSTEMI, non ST-elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; STEMI, ST-elevated myocardial infarction; UA, unstable angina.

shown in Tables 3 and 4. The incidence of total ischaemic outcomes observed within the clopidogrel group was consistent across all metabolizer status phenotype groups (range 6.3–15.0%), with ISR being the most common ischaemic complication. There was no observable trend in ischaemic outcomes with increasing CYP2C19 activity (IM/PM [11.8%], NM [15.0%], RM/UM [6.3%], $P = 0.633$). Detected within the clopidogrel group was an observable trend of increasing total bleeding incidence with increasing CYP2C19 activity (IM/PM [0.0%], NM [15.0%], RM/UM [25.0%], $P = 0.035$). The positive relationship between total bleeding incidence and CYP2C19 activity showed a moderate association that was statistically significant: $r_{\tau} = 0.28$, $P = 0.035$. The incidence of total ischaemic outcomes observed within the ticagrelor group was consistent across all metabolizer status phenotype groups (range 5.0–9.1%), with stroke being

the most common ischaemic complication. The incidence of total bleeding outcomes observed within the ticagrelor group was also consistent across all metabolizer status phenotype groups (range 4.3–6.1%). There were no observable trends in ischaemic (IM/PM [5.0%], NM [9.1%], RM/UM [8.7%], $P = 0.672$) or bleeding (IM/PM [5.0%], NM [6.1%], RM/UM [4.3%], $P = 0.911$) outcomes with increasing CYP2C19 activity within the ticagrelor group. There were no significant differences in baseline characteristics within the clopidogrel group. Although a statistically significantly lower use of beta-blockers was detected within the ticagrelor NM group when compared with ticagrelor RM/UM and ticagrelor IM/PM groups ($P = 0.027$), it had no significant impact on clinical outcomes. There were no significant differences in the other baseline characteristics within the ticagrelor group.

TABLE 2 CYP2C19 genotypes and metabolizer status.

| Characteristic | All (%) (n = 129) | Clopidogrel (%) (n = 53) | Ticagrelor (%) (n = 76) |
|---|-------------------|--------------------------|-------------------------|
| CYP2C19 genotypes | | | |
| • 1*/17* (RM) | 34 (26.4) | 13 (24.5) | 21 (27.6) |
| • 17*/17* (UM) | 5 (3.9) | 3 (5.7) | 2 (2.6) |
| • 1*/1* (NM) | 53 (41.1) | 20 (37.7) | 33 (43.4) |
| • 1*/2* (IM) | 29 (22.5) | 13 (24.5) | 16 (21.1) |
| • 2*/17* (IM) | 5 (3.9) | 3 (5.7) | 2 (2.6) |
| • 2*/2* (PM) | 3 (2.3) | 1 (1.9) | 2 (2.6) |
| Metabolizer status | | | |
| • Rapid/ultra metabolizer (RM/UM) | 39 (30.2) | 16 (30.2) | 23 (30.3) |
| • Normal metabolizer (NM) | 53 (41.1) | 20 (37.7) | 33 (43.4) |
| • Intermediate/poor metabolizer (IM/PM) | 37 (28.7) | 17 (32.1) | 20 (26.3) |

Abbreviations: IM, intermediate metabolizers; NM, normal metabolizers; PM, poor metabolizers; RM, rapid metabolizers; UM, ultrarapid metabolizers.

4 | DISCUSSION

Our study provides real-world data on the use of point-of-care CYP2C19 genotyping following PCI within an Irish population. Our results demonstrate a high prevalence of CYP2C19 polymorphisms within an Irish population with an overall 58.9% chance of carrying either an increased function (CYP2C19*17) allele or loss-of-function (CYP2C19*2) allele. When comparing the CYP2C19 allele frequency of our Irish cohort with the consolidated European population demonstrated in a previous review, our Irish cohort follows the European trend of having a predominance for the CYP2C19*17 allele (Irish 30.2%, European 26.5%) but differs in having a higher frequency of the CYP2C19*2 allele (Irish 28.7%, European 14.2%).¹³ The high proportion of CYP2C19 polymorphisms within our Irish cohort suggests that Irish patients receiving DAPT after PCI are more likely to experience variable clopidogrel bioactivation, possibly resulting in higher or lower ischaemic or bleeding risks depending on the corresponding metabolizer status phenotype.

When clinical evaluation alone (of ischaemic and bleeding risks) was used to determine treatment allocation of DAPT (clopidogrel or ticagrelor), patients receiving clopidogrel therapy were significantly more likely to possess characteristics associated with higher bleeding risks: hypertension (69.8% vs 52.6%, $P = 0.037$), previous stroke (9.4% vs 1.3%, $P = 0.042$) and discharged on an oral anticoagulant (9.4% vs 0.0%, $P = 0.01$).^{25,27} This demonstrates that treatment allocation to clopidogrel therapy in our study is consistent with the current consensus that patients with identified higher bleeding risks should receive clopidogrel in place of a potent P2Y₁₂ receptor inhibitor.^{17,18}

We detected a trend of increasing total bleeding incidence with increasing CYP2C19 activity within the clopidogrel group that was statistically significant: IM/PM (0.0%), NM (15.0%), RM/UM (25.0%), $P = 0.035$. Our trend reflects the impact of variable CYP2C19 activity (based on corresponding genotypes) on clopidogrel bioactivation and activity. Carriers of the CYP2C19*17 allele (RM/UM) have higher bleeding risks due to increased pharmacologically active metabolite, while carriers of the CYP2C19*2 allele (IM/PM) are less prone to

bleeding due to reduced bioactivation of clopidogrel.^{6,8-12} Since ticagrelor is not bioactivated by CYP2C19, this trend of increasing bleeding with CYP2C19 activity was not replicated in the ticagrelor group (IM/PM [5.0%], NM [6.1%], RM/UM [4.3%], $P = 0.911$). Considering the current consensus recommends clopidogrel therapy for patients identified with high-bleeding-risk, patients with clinically identified high-bleeding-risk may be unknowingly subjected to even further increase in bleeding risk when prescribed clopidogrel and concomitantly a CYP2C19*17 carrier. Based on the high prevalence of CYP2C19*17 allele within our Irish cohort (approximately one in three chance of being a clopidogrel hyper-responder), CYP2C19 genotyping within an Irish population may have clinical utility in identifying CYP2C19*17 carriers who are at increased risk of clopidogrel-related bleeding.

The findings from our study are supported by results from recent studies which also demonstrate increased bleeding risk in CYP2C19*17 allele carriers. Ali et al investigated the impact of CYP2C19 polymorphisms on bleeding outcomes within an Arab population ($n = 254$) receiving clopidogrel therapy after PCI and demonstrated a similar trend of increasing total bleeding incidence with increasing CYP2C19 activity: IM/PM (0.0%), NM (1.7%), RM/UM (25.0%).¹¹ The risk of experiencing a bleeding event was significantly higher when RM/UM was compared with NM (hazard ratio [HR] 18.83, 95% CI 4.24-83.67, $P < 0.0001$).¹¹ Extending the relevance of this phenomenon beyond clopidogrel therapy after PCI, increased bleeding outcomes were also observed in CYP2C19*17 allele carriers receiving clopidogrel therapy after percutaneous neurointervention procedures. Saiz-Rodríguez et al investigated the impact of CYP2C19 polymorphisms on bleeding outcomes within a population receiving clopidogrel therapy after neurointervention ($n = 123$) and demonstrated a similar trend of increasing total bleeding incidence with increasing CYP2C19 activity that is statistically significant: IM/PM (0.0%), NM (3.8%), RM/UM (13.2%), $P = 0.041$.¹²

Despite multiple studies demonstrating the positive relationship between CYP2C19*17 allele and clopidogrel-related bleeding risks, the data from a large observational study show conflicting evidence.

TABLE 3 Comparison of baseline patient characteristics and 12-month ischaemic and bleeding outcomes of clopidogrel therapy between metabolizer status.

| Characteristic | RM/UM clopidogrel (%) (n = 16) | NM clopidogrel (%) (n = 20) | IM/PM clopidogrel (%) (n = 17) | P value |
|-------------------------------|--------------------------------|-----------------------------|--------------------------------|---------|
| Patient demographic | | | | |
| • Mean age (years) | 65.6 ± 8.9 | 66.8 ± 10.0 | 67.1 ± 10.5 | 0.891 |
| • Male | 11 (68.8) | 17 (85.0) | 10 (58.8) | 0.208 |
| Baseline comorbidities | | | | |
| • BMI (kg/m ²) | 32.2 ± 5.8 | 28.8 ± 6.2 | 30.4 ± 5.3 | 0.171 |
| • Hypertension | 11 (68.8) | 16 (80.0) | 10 (58.8) | 0.381 |
| • Dyslipidaemia | 7 (43.8) | 14 (70.0) | 11 (64.7) | 0.259 |
| • Diabetes | 6 (37.5) | 1 (5.0) | 4 (23.5) | 0.057 |
| • Active smoker | 6 (37.5) | 11 (55.0) | 5 (29.4) | 0.275 |
| • Family Hx CAD | 8 (50.0) | 13 (65.0) | 5 (29.4) | 0.101 |
| • Prior MI | 3 (18.8) | 1 (5.0) | 1 (5.9) | 0.318 |
| • Prior PCI | 5 (31.3) | 4 (20.0) | 5 (29.4) | 0.711 |
| • Prior CABG | 2 (12.5) | 2 (10.0) | 2 (11.8) | 0.971 |
| • CCF | 1 (6.3) | 0 (0.0) | 1 (5.9) | 0.538 |
| • Prior stroke | 3 (18.8) | 1 (5.0) | 1 (5.9) | 0.318 |
| • PAD | 2 (12.5) | 0 (0.0) | 0 (0.0) | 0.095 |
| • Prior bleeding | 2 (12.5) | 1 (5.0) | 0 (0.0) | 0.302 |
| Presentation | | | | |
| • ACS | 9 (56.3) | 13 (65.0) | 12 (70.6) | 0.693 |
| ◦ STEMI | 1 (6.3) | 4 (20.0) | 2 (11.8) | 0.476 |
| ◦ NSTEMI | 7 (43.8) | 6 (30.0) | 5 (29.4) | 0.618 |
| ◦ UA | 1 (6.3) | 3 (15.0) | 5 (29.4) | 0.205 |
| • CCS | 7 (43.8) | 7 (35.0) | 5 (29.4) | 0.693 |
| Discharge medication | | | | |
| • Aspirin | 16 (100.0) | 20 (100.0) | 17 (100.0) | 0.346 |
| • Anticoagulation | 0 (0.0) | 4 (20.0) | 1 (5.9) | 0.108 |
| • Statin | 14 (87.5) | 20 (100.0) | 16 (94.1) | 0.279 |
| • ACEi/ARB | 9 (56.3) | 14 (70.0) | 11 (64.7) | 0.698 |
| • Beta-blocker | 12 (75.9) | 15 (75.0) | 11 (64.7) | 0.744 |
| • PPI | 13 (81.3) | 19 (95.0) | 14 (82.4) | 0.394 |
| Ischaemic outcomes | | | | |
| • Total events | 1 (6.3) | 3 (15.0) | 2 (11.8) | 0.633 |
| ◦ Noncardiovascular death | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1.0 |
| ◦ Cardiovascular death | 1 (6.3) | 0 (0.0) | 0 (0.0) | 0.199 |
| ◦ ACS | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1.0 |
| ◦ Stroke | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.972 |
| ◦ ST | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1.0 |
| ◦ Urgent revascularization | 0 (0.0) | 1 (5.0) | 0 (0.0) | 1.0 |
| ◦ ISR | 0 (0.0) | 2 (10.0) | 2 (11.8) | 0.211 |
| Bleeding outcomes | | | | |
| • Total events | 4 (25.0) | 3 (15.0) | 0 (0.0) | 0.035 |
| ◦ TIMI minimal | 2 (12.5) | 0 (0.0) | 0 (0.0) | 0.346 |
| ◦ TIMI minor | 1 (6.3) | 2 (10.0) | 0 (0.0) | 0.425 |
| ◦ TIMI major | 1 (6.3) | 1 (5.0) | 0 (0.0) | 0.067 |

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCF, congestive cardiac failure; CCS, chronic coronary syndrome; IM, intermediate metabolizers; ISR, in-stent restenosis; MI, myocardial infarction; NM, normal metabolizers; NSTEMI, non ST-elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PM, poor metabolizers; PPI, proton pump inhibitor; RM, rapid metabolizers; ST, stent thrombosis; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; UA, unstable angina; UM, ultrarapid metabolizers.

TABLE 4 Comparison of baseline patient characteristics and 12-month ischaemic and bleeding outcomes of ticagrelor therapy between metabolizer status.

| Characteristic | RM/UM ticagrelor (%) (n = 23) | NM ticagrelor (%) (n = 33) | IM/PM ticagrelor (%) (n = 20) | P value |
|-------------------------------|-------------------------------|----------------------------|-------------------------------|---------|
| Patient demographic | | | | |
| • Mean age (years) | 63.5 ± 11.4 | 62.0 ± 9.5 | 60.0 ± 10.7 | 0.604 |
| • Male | 17 (73.9) | 28 (84.8) | 16 (80.0) | 0.603 |
| Baseline comorbidities | | | | |
| • BMI (kg/m ²) | 29.7 ± 7.6 | 28.0 ± 4.9 | 31.0 ± 6.2 | 0.162 |
| • Hypertension | 15 (65.2) | 16 (48.5) | 9 (45.0) | 0.345 |
| • Dyslipidaemia | 8 (34.8) | 21 (63.6) | 11 (55.0) | 0.104 |
| • Diabetes | 4 (17.4) | 5 (15.2) | 4 (20.0) | 0.902 |
| • Active smoke | 11 (47.8) | 11 (33.3) | 13 (65.0) | 0.082 |
| • Family Hx CA | 8 (34.8) | 15 (45.5) | 11 (55.0) | 0.415 |
| • Prior MI | 3 (13.0) | 7 (21.2) | 2 (10.0) | 0.510 |
| • Prior PCI | 4 (17.4) | 11 (33.3) | 3 (15.0) | 0.223 |
| • Prior CABG | 2 (8.7) | 2 (6.1) | 0 (0.0) | 0.433 |
| • CCF | 1 (4.3) | 0 (0.0) | 1 (5.0) | 0.455 |
| • Prior stroke | 0 (0.0) | 0 (0.0) | 1 (5.0) | 0.247 |
| • PAD | 0 (0.0) | 1 (3.0) | 1 (5.0) | 0.587 |
| • Prior bleeding | 0 (0.0) | 0 (0.0) | 1 (5.0) | 0.247 |
| Presentation | | | | |
| • ACS | 20 (87.0) | 29 (87.9) | 16 (80.0) | 0.715 |
| ◦ STEMI | 11 (47.8) | 16 (48.5) | 13 (65.0) | 0.439 |
| ◦ NSTEMI | 8 (34.8) | 9 (27.3) | 1 (5.0) | 0.061 |
| ◦ UA | 1 (4.3) | 4 (12.1) | 2 (10.0) | 0.611 |
| • CCS | 3 (13.0) | 4 (12.1) | 4 (20.0) | 0.715 |
| Discharge medication | | | | |
| • Aspirin | 23 (100.0) | 33 (100.0) | 20 (100.0) | 0.229 |
| • Anticoagulation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1.0 |
| • Statin | 22 (95.7) | 33 (100.0) | 20 (100.0) | 0.316 |
| • ACEi/ARB | 20 (87.0) | 29 (87.9) | 16 (80.0) | 0.715 |
| • Beta-blocker | 22 (95.7) | 26 (78.8) | 20 (100.0) | 0.027 |
| • PPI | 17 (73.9) | 25 (75.8) | 15 (75.0) | 0.988 |
| Ischaemic Outcomes | | | | |
| • Total events | 2 (8.7) | 3 (9.1) | 1 (5.0) | 0.672 |
| ◦ Noncardiovascular death | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1.0 |
| ◦ Cardiovascular death | 1 (4.3) | 0 (0.0) | 0 (0.0) | 0.196 |
| ◦ ACS | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1.0 |
| ◦ Stroke | 1 (4.3) | 1 (3.0) | 1 (5.0) | 0.932 |
| ◦ ST | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1.0 |
| ◦ Urgent revascularization | 0 (0.0) | 1 (3.0) | 0 (0.0) | 0.942 |
| ◦ ISR | 0 (0.0) | 1 (3.0) | 0 (0.0) | 0.942 |
| Bleeding outcomes | | | | |
| • Total events | 1 (4.3) | 2 (6.1) | 1 (5.0) | 0.911 |
| ◦ TIMI minimal | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.942 |
| ◦ TIMI Minor | 1 (4.3) | 1 (3.0) | 0 (0.0) | 0.385 |
| ◦ TIMI major | 0 (0.0) | 1 (3.0) | 1 (5.0) | 0.172 |

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCF, congestive cardiac failure; CCS, chronic coronary syndrome; IM, intermediate metabolizers; ISR, MI, myocardial infarction; NM, normal metabolizers; NSTEMI, non ST-elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PM, poor metabolizers; PPI, proton pump inhibitor; RM, rapid metabolizers; ST; STEMI, ST-elevated myocardial infarction; TIMI; UA, unstable angina; UM, ultrarapid metabolizers.

Lee et al demonstrated within a large study population ($n = 3342$) that no significant difference in actionable bleeding outcomes exists when RM/UM is compared with NM (HR 1.34, 95% CI 0.83-2.17, $P = 0.224$).⁸ As the largest observational study, the conflicting evidence certainly questions the prospects of a genotype-guided strategy being used for bleeding risk assessment. Considering the low bleeding event rates observed when the Global Strategies for Opening Occluded Coronary Arteries bleeding criteria were used to clinically define significant bleeding in this study, RM/UM still had the highest rate of clinically significant bleeding, with the author suggesting that the study was underpowered to detect differences between the phenotypes when the overall bleeding incidence was low.^{8,27} These limitations demonstrate ongoing ambiguity in the true potential of a genotype-guided strategy being used for bleeding risk assessment by detecting the CYP2C19*17 allele.

Current de-escalation strategies of switching potent P2Y₁₂ receptor inhibitors to clopidogrel are based on clinical assessment, platelet function testing and CYP2C19 genotyping that considers only the CYP2C19*2 allele.^{17,18} With increasing scope for long-term P2Y₁₂ receptor inhibitor monotherapy from emerging meta-analyses, the use of CYP2C19 genotyping for CYP2C19*17 allele detection may play a role in reducing bleeding events by identifying a genetic predisposition to clopidogrel-related bleeding. The prospect of reducing bleeding events through this approach is amplified within an Irish population where the chance of being a clopidogrel hyper-responder is demonstrated as approximately one in three in our study. While a genotype-guided strategy for the CYP2C19*17 allele may provide an additional layer of bleeding risk assessment to guide the physician in antiplatelet selection, further investigations are needed to demonstrate its effectiveness as a tool for bleeding risk assessment.

4.1 | Limitations

There are several limitations to this study that must be mentioned. First and foremost, the sample size for our clopidogrel group was very small ($n = 53$), thus impacting the internal validity of our study and increasing the difficulty of determining if the trend of increased bleeding with increasing CYP2C19 activity is truly due to polymorphisms or chance. Ours was a single-centre study within the mid-west of Ireland which involved only people of Irish ethnic origin. With CYP2C19 polymorphisms having significant ethnic variability, allele frequency results may not be generalizable to more cosmopolitan areas of Ireland where ethnic diversity is greater. These limitations would therefore require larger, multicentre studies to be conducted to evaluate if a genotype strategy for the CYP2C19*17 allele may have clinical utility in identifying high bleeding risk within an Irish population.

5 | CONCLUSION

We demonstrated that the prevalence of CYP2C19 polymorphisms (CYP2C19*2 or CYP2C19*17) is 58.9% within an Irish population. The

chance of being a hyper-responder (RM/UM) to clopidogrel therapy was 30.2% or approximately one in three. When clinical evaluation alone was used to determine treatment allocation of DAPT (clopidogrel or ticagrelor), patients receiving clopidogrel therapy were more likely to possess characteristics associated with higher bleeding risks. A trend of increasing total bleeding incidence with increasing CYP2C19 activity within the clopidogrel group was detected: IM/PM (0.0%), NM (15.0%), RM/UM (25.0%). This positive relationship showed a moderate association that was statistically significant: $r_t = 0.28$, $P = 0.035$. Considering the high prevalence of CYP2C19 polymorphisms within an Irish population and the increased propensity for clopidogrel-related bleeding in CYP2C19*17 allele carriers, a genotype-guided strategy for the CYP2C19*17 allele may have clinical utility in identifying high bleeding risk within an Irish population but further studies are needed to evaluate this.

AUTHOR CONTRIBUTIONS

All authors contributed to the study design, interpretation of the findings, revision of the manuscript and approved the final version of the manuscript. Bing Wei Thaddeus Soh, Ronan Cusack and Max Waters acquired and analysed the data. Bing Wei Thaddeus Soh performed the statistical analysis and drafted the initial manuscript. Thomas Kiernan provided oversight for all aspects of the study.

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COMPETING INTERESTS

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data from our study are available from the corresponding author upon reasonable request.

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