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Impact of the ABCD-GENE Score on Clopidogrel Clinical Effectiveness after PCI: A Multi-site, Real-world Investigation

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C.D.T., A.G.W., C.R.L., and L.H.C designed the research; C.D.T., Y.G., C.W.M., D.J.A., C.R.L., and L.H.C. analyzed the data; C.D.T., F.F., E.C.K., J.S.R., M.W., R.D.A., A.L.D., M.N.G., R.A.K., N.K., J.G.M., I.R.M., P.S., and A.L.B. performed the research; C.D.T., F.F., E.C.K., J.S.R., M.W., J.A.J., G.A.S., D.J.A., C.R.L., and L.H.C. wrote the manuscript.

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Abstract

The ABCD-GENE score was developed to identify patients at risk for diminished antiplatelet effects with clopidogrel after percutaneous coronary intervention (PCI) and utilizes **A**ge, **B**ody mass index, **C**hronic kidney disease, **D**iabetes and *CYP2C19* **GENE**tic variants. The objective of this study was to validate the ability of the ABCD-GENE score to predict risk for atherothrombotic events in a diverse, real-world population of clopidogrel-treated PCI patients who received clinical *CYP2C19* genotyping to guide antiplatelet therapy. A total of 2341 adult patients who underwent PCI, were genotyped for *CYP2C19*, and received treatment with clopidogrel across four institutions were included (mean age 64±12 years, 35% female, 20% Black). The primary outcome was major atherothrombotic events, defined as the composite of all-cause death, myocardial infarction, ischemic stroke, stent thrombosis, or revascularization for unstable angina within 12 months following PCI. Major adverse cardiovascular events (MACE), defined as the composite of cardiovascular death, myocardial infarction, ischemic stroke, or stent thrombosis, was assessed as the secondary outcome. Outcomes were compared between patients with an ABCD-GENE score ≥10 versus <10. The risk of major atherothrombotic events was higher in patients with an ABCD-GENE score ≥10 (n=505) versus <10 (n=1836; 24.6 versus 14.7 events per 100 patient-years, adjusted hazard ratio (HR), 1.66; 95% CI, 1.23–2.25; p<0.001). The risk for MACE was also higher among patients with a score ≥10 versus <10 (16.7 versus 10.1 events per 100 patient-years, adjusted HR, 1.59; 95% CI, 1.11–2.30; p=0.013). Our diverse, real-world data demonstrate diminished clopidogrel effectiveness in PCI patients with an ABCD-GENE score ≥10.

Keywords

clopidogrel; CYP2C19; precision medicine; genetic testing; percutaneous coronary intervention

Introduction

Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor is recommended after percutaneous coronary intervention (PCI) to decrease the risk of ischemic events.(1, 2) In clinical trials of patients presenting with an acute coronary syndrome (ACS), in which *CYP2C19* genotyping was not performed to guide treatment selection, prasugrel and

ticagrelor were superior to clopidogrel in reducing major atherothrombotic events and are thus preferred in this setting.(1–4) However, prasugrel and ticagrelor are associated with increased bleeding risk and higher cost compared with clopidogrel, which in addition to ticagrelor-associated dyspnea, limit their widespread use.(3–6) Thus, clopidogrel remains commonly prescribed in clinical practice, including in patients undergoing PCI following an ACS.(7, 8)

Clopidogrel is a prodrug that relies on the cytochrome P450 2C19 (CYP2C19) enzyme for biotransformation to its pharmacologically active metabolite. The wide variability in clopidogrel-induced antiplatelet effects, which in a considerable number of patients is impaired leading to high on-treatment platelet reactivity (HPR), is due to both genetic determinants(9) and clinical variables.(10–12) Importantly, HPR is a marker of increased risk of thrombotic complications in patients undergoing PCI.(10, 13) Clopidogrel effectiveness is specifically influenced by genetic variability in *CYP2C19* that contributes to wide interindividual variability in clopidogrel metabolism and inhibition of platelet aggregation.(14, 15) Approximately 30% of the U.S. population carries at least one *CYP2C19* no function allele.(16) Among clopidogrel-treated patients, no function allele carriers have lower concentrations of the active clopidogrel metabolite, higher platelet reactivity and HPR rates, and are at increased risk for cardiovascular events after PCI compared to those without a no function allele.(17, 18) In addition to *CYP2C19* genotype, clinical factors, including older age, higher body mass index (BMI), chronic kidney disease (CKD), and diabetes mellitus (DM), contribute to HPR and are associated with reduced clopidogrel effectiveness.(11, 19–23)

The ABCD-GENE (Age, Body mass index, Chronic kidney disease, and Diabetes mellitus, and *CYP2C19* GENEtic variants) score includes *CYP2C19* genotype and clinical factors independently associated with HPR among clopidogrel-treated patients following PCI.(24) The score was evaluated in two clopidogrel-treated European cohorts, with a score ≥10 predicting both HPR following elective PCI(25) and increased risk for major adverse cardiovascular events (MACE) among patients with myocardial infarction (MI), most of whom underwent PCI.(24, 26) The ABCD-GENE score was subsequently shown to identify patients at increased risk of MACE in post-hoc analyses of predominately European and Asian clinical trial participants receiving clopidogrel after PCI or ischemic stroke.(27, 28) However, validation of the ABCD-GENE score in a more diverse cohort of patients undergoing PCI in real-world clinical practice is necessary to assess the generalizability and potential clinical utility of this risk stratification tool. In addition, only the *CYP2C19*2* no function allele was considered in the evaluation of the score. While this is the most common no function allele across populations, there are other less common alleles associated with absence of CYP2C19 function, and the Association for Molecular Pathology recommends that both the *CYP2C19*2* and *CYP2C19*3* no function alleles should be included in clinical *CYP2C19* testing.(29) The objective of this analysis was to validate the association between the ABCD-GENE score and major atherothrombotic events in a diverse real-world population of clopidogrel-treated PCI patients who received clinical *CYP2C19* genotyping that included, at a minimum, the **2* and **3* alleles.

Methods

Study Population

The study population included patients who were ≥18 years of age, underwent elective or emergent PCI, received $P2Y_{12}$ inhibitor therapy, and were genotyped clinically for *CYP2C19*, as previously described.(30, 31) Four institutions (University of Florida, Gainesville; University of Florida, Jacksonville; University of North Carolina, Chapel Hill; University of Maryland, Baltimore) contributed data for 3,688 patients meeting these criteria, of whom, 2,341 were treated with clopidogrel. Data collection was approved by the Institutional Review Board at each site.

CYP2C19 genotype was determined in a College of American Pathologists (CAP)-accredited and Clinical Laboratory Improvement Amendments (CLIA)-licensed laboratory at each institution, and results were reported in the electronic health record, as previously described.(32–34) All sites interrogated the *CYP2C19*2, *3*, and **17* alleles, with two of four sites testing for additional rare no function alleles (Table S1). Patients carrying a no function allele were assigned the CYP2C19 poor (PM; two no function alleles) or intermediate (IM; one no function allele) metabolizer phenotype, consistent with Clinical Pharmacogenetics Implementation Consortium guidelines.(16) At each institution, alternative antiplatelet therapy with prasugrel or ticagrelor was recommended for CYP2C19 IMs and PMs, in the absence of contraindications, whereas no prescribing recommendations were made for those without a no function allele.(34) The ultimate prescribing decision was left to the clinician's discretion, and approximately 45% of IMs and PMs were treated with clopidogrel across sites.(30, 31)

Data abstraction

Data were manually abstracted from the electronic health record at each site using a common data collection form, as previously described.(35) Data for eligible patients were abstracted through review of patient encounters or phone interviews, starting with the hospitalization for the index PCI (defined as the PCI performed in association with *CYP2C19* genotyping) and including subsequent outpatient encounters and hospitalizations. Patients were followed longitudinally until an outcome of interest occurred, clopidogrel was discontinued, or the prespecified follow-up time of 12 months post-PCI was achieved, whichever occurred first. Patients were included regardless of length of follow-up. Ischemic events were identified from provider-reported diagnoses at each encounter or clinical notes in the event of death. Data collection procedures were approved by the institutional review board at each institution.

Study Endpoints

The primary outcome was major atherothrombotic events, defined as the composite of all-cause death, MI, ischemic stroke, stent thrombosis, or revascularization for unstable angina within 12 months following the index PCI. MACE, defined as the composite of cardiovascular death, MI, ischemic stroke, or stent thrombosis, within 12 months post-PCI was assessed as the secondary outcome. All events were independently reviewed and verified by an interventional cardiologist.

Data Analysis

Data were curated and aggregated at the University of Florida, Gainesville. The ABCD-GENE score was calculated from information at the time of index PCI, with four points assigned for age >75 years, four points for body mass index >30 kg/m^2, three points for CKD (defined as an estimated glomerular filtration rate of <60 ml/min/1.73m^2), three points for DM, six points for IMs, and 24 points for PMs.(24)

Patient characteristics and event rates (per 100 patient-years) for the primary and secondary endpoints were compared between clopidogrel-treated patients with an ABCD-GENE score ≥10 versus <10 using the chi-square test or two-sample t-test as appropriate.(24) Unadjusted hazard ratios (HR) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression. Multivariable Cox regression was used to estimate the risk for major atherothrombotic events and MACE, and adjusted HRs and 95% CIs were calculated. The adjusted model included sex, smoking status, index PCI indication (i.e., MI versus unstable angina or elective PCI), PCI strategy (i.e., stent vs percutaneous transluminal coronary angioplasty), and institution.

An exploratory analysis arose based on the observation that 159 patients with an ABCD-GENE score <10 were CYP2C19 IMs. Given known effects of IM status in reducing antiplatelet effects and clinical effectiveness of clopidogrel,(16) the ABCD-GENE score <10 group was stratified into IMs and non-IMs. Median scores were compared between IMs versus non-IMs with a score <10 using the Mann-Whitney U test. The risk for major atherothrombotic events and MACE among CYP2C19 IMs and non-IMs with an ABCD-GENE score <10, compared with the ≥10 group, was evaluated using multivariable Cox regression as described in the primary analysis. Similarly, based on the observation that 216 patients with a score ≥10 did not have a *CYP2C19* no function allele, as a second exploratory analysis, we compared risk for major atherothrombotic events and MACE between CYP2C19 IM/PMs versus non-IM/PMs with a score ≥10.

Kaplan-Meier analyses were used to depict the cumulative incidence of major atherothrombotic events and MACE by ABCD-GENE score group during the 12-month follow-up period. $P<0.05$ was considered statistically significant. All statistical analyses were performed using R statistical software (version 4.1).(36)

Results

Patient Characteristics

Characteristics of the 2,341 patients included in the analysis are shown in Table 1. All were treated with clopidogrel at the time of event or last follow-up. Mean (SD) age was 64±12 years, 817 (35%) were female, 470 (20%) were Black or African American, and 1601 (68%) had an ACS indication for PCI. A total of 448 (19%) patients were no function allele carriers (18% IMs, 1% PMs), and 505 (22%) had an ABCD-GENE score ≥10. Among CYP2C19 IMs, six (1%) had a diplotype that did not include the *CYP2C19*2* allele (**1/*3*, **1/*4*, **1/*8* [n=2], **6/*17*, and **8/*17*).

Apart from the expected differences in ABCD-GENE score components, there also were significant differences in sex, smoking status, PCI strategy (i.e., any stent type versus percutaneous transluminal coronary angioplasty), medical history, and anticoagulant use between clopidogrel-treated patients with an ABCD-GENE score ≥10 versus <10 (Table 1). All clinical components of the ABCD-GENE score were more prevalent in the ≥10 versus the <10 group (Table 2). Among those with an ABCD-GENE score ≥10, 269 (53%) and 20 (4%) patients were CYP2C19 IMs and PMs compared with 159 (9%) and 0 patients with a score <10, respectively (Table 2).

Clinical outcomes

Median [IQR] follow-up time after PCI was 229 [37–346] days for patients with an ABCD-GENE score <10 and 182 [29–330] days in those with a score ≥10. The rate of major atherothrombotic events was higher in patients with an ABCD-GENE score ≥10 versus <10 (24.6 versus 14.7 per 100 patient-years; adjusted hazard ratio [HR], 1.66; 95% CI, 1.23 – 2.25; p<0.001) (Table 3, Figure 1A). Patients with an ABCD-GENE score ≥10 also had a higher rate of MACE compared to patients with a score <10 (event rate 16.7 versus 10.1 per 100 patient-years; adjusted HR, 1.59; 95% CI, 1.11 – 2.30; p=0.013) (Table 3, Figure 1B).

Characteristics of patients with an ABCD-GENE score <10 stratified by IM status are shown in Table S2. Median [IQR] ABCD-GENE score was greater among CYP2C19 IMs versus non-IMs with a score <10 (6 [IQR, 6–9] versus 4 [IQR, 0–7]; p<0.001). Kaplan-Meier curves for major atherothrombotic events are depicted for patients with an ABCD-GENE score ≥10 and <10, stratified by CYP2C19 IM status, in Figure 2. The major atherothrombotic event rate was lower among non-IMs with an ABCD-GENE score <10 versus patients with a score ≥10 (adjusted HR, 0.58; 95% CI, 0.43–0.79; p<0.001). In contrast, there was no significant difference in the major atherothrombotic event rate between IMs with a score <10 and patients with a score ≥10 (adjusted HR, 1.03; 95% CI, 0.59–1.81; p=0.917) (Table 4). Similar results were observed for MACE among non-IMs with a score <10 (adjusted HR, 0.61; 95% CI, 0.42–0.88; p=0.008) and IMs with a score <10 (adjusted HR, 0.97; 95% CI, 0.48–1.95; p=0.925) compared to those with a score ≥10 (Table 4; Figure S1). In the subset of patients with an ABCD-GENE score ≥10 (n=505), major atherothrombotic event and MACE rates were not significantly different between IM/PMs versus non-IM/PMs (Table S3).

Discussion

The ABCD-GENE score is a recently developed tool that integrates clinical factors and *CYP2C19* genotype to identify PCI patients at risk for diminished clopidogrel antiplatelet effects and clinical effectiveness.(24) The score was originally derived using platelet reactivity data from a randomized, controlled trial(37) and associated with clinical outcomes in two European registries, POPULAR (Do Platelet Function Assays Predict Clinical Outcomes in Clopidogrel-Pretreated Patients Undergoing Elective PCI)(25) and FAST-MI (French Registry of Acute ST-Elevation and Non–ST-Elevation Myocardial Infarction),(26) which were conducted in the Netherlands and France, respectively. An ABCD-GENE score ≥10 was associated with diminished clopidogrel response and increased risk of

MACE versus a score <10.(24) The score was further evaluated in Asian patients for its association with HPR with clopidogrel after PCI and its association with recurrent stroke with clopidogrel plus aspirin versus aspirin alone following minor stroke or transient ischemic attack.(28, 38) Most recently, the predictive value of the ABCD-GENE score in identifying patients at increased risk of ischemic events was shown in a post-hoc analysis of data from predominately White or Asian participants in a clinical trial of genotype-guided therapy after PCI.(27) Similar to findings from European registries and post-hoc analysis of clinical trial data, we found that the risk of major atherothrombotic events and MACE was approximately 1.6-fold higher in clopidogrel-treated PCI patients with an ABCD-GENE score ≥10 compared to those with a score <10 in a diverse, real-world clinical setting. Moreover, the increased risk for MACE observed herein among those with an ABCD-GENE score ≥10 versus <10 (adjusted HR, 1.59; 95% CI, 1.11 – 2.30) was comparable to the risk for MACE reported in the FAST-MI registry (adjusted HR, 1.48; 95% CI, 1.16 – 1.90).(24)

Our findings help increase the generalizability of the ABCD-GENE score given the real-world study population who underwent emergent or elective PCI; had a high comorbidity burden, especially in regard to prevalence of obesity, CKD, DM, and history of MI,(26) and were diverse in ancestry. The population reported herein was from the United States, and 20% were Black or African American. Further, the patients included in our analysis received *CYP2C19* testing as part of their clinical care to help guide post-PCI antiplatelet therapy and thus represent patients in whom the score would be applied to in practice. All patients in the current analysis were genotyped for both the *CYP2C19*2* and **3* no function alleles at a minimum, as recommended per current guidelines; although detection of the **3* and other no function alleles only resulted in 1% of additional patients classified as IM or PM. These data add to the evidence of ABCD-GENE score associations with outcomes during clopidogrel treatment after PCI and demonstrate diminished clopidogrel effectiveness in a real-world population of PCI patients with a score ≥10.(24, 28)

Given evidence that *CYP2C19* genotype influences the effectiveness of clopidogrel, but not prasugrel or ticagrelor, pharmacogenetic guidelines recommend prasugrel or ticagrelor for CYP2C19 IMs and PMs in the absence of contraindications.(16) Similarly, the Food and Drug Administration-approved clopidogrel labeling recommends alternative therapy in PMs, with recommendations for alternative therapy expanded to IMs in their Table of Pharmacogenetic Associations.(39, 40) Clinical trials and observational studies have examined outcomes with guided approaches to the selection of $P2Y_{12}$ inhibitor therapy, using either genetic or platelet function testing.(35, 41–43) Recent large-scale meta-analyses of these data have shown improved outcomes, including better safety and efficacy profiles, with a guided approach to $P2Y_{12}$ inhibitor therapy selection compared with a non-guided approach.(44, 45) Importantly, outcomes varied depending on whether $P2Y_{12}$ inhibitor therapy was escalated from clopidogrel to alternative therapy with prasugrel or ticagrelor in no function allele carriers or de-escalated from prasugrel or ticagrelor to clopidogrel in patients without a no function allele. Compared to a non-guided treatment approach, an escalation approach was associated with a reduction in ischemic events without any increase in bleeding, while a de-escalation approach was associated with a reduction in bleeding, without any increase in ischemic events.(45) These findings suggest a guided approach

can be used to better balance the risks and benefits of $P2Y_{12}$ inhibitors and facilitate the selection of antiplatelet therapy post-PCI.

Importantly, *CYP2C19* genotype is only one factor explaining the inter-patient variability in clopidogrel response.(9) Advanced age, obesity, CKD, and DM have also been associated with diminished antiplatelet effects of clopidogrel. Specifically, the SENIOR-PLATELET study showed that clopidogrel-treated patients age 75 years or older were more likely to have high residual platelet reactivity compared with patients younger than 75 years.(23) Similarly, elevated BMI has been associated with an attenuated clopidogrel response.(22, 46, 47) A meta-analysis of clopidogrel-treated patients determined that patients with CKD were more likely to develop HPR and were at increased risk for cardiovascular events compared to patients without CKD.(19) Diabetes is also associated with significantly reduced clopidogrel active metabolite formation and increased platelet reactivity.(20, 21) Although the mechanism underlying these effects remains unclear, suppression of hepatic CYP2C expression and activity in the setting of chronic inflammatory conditions (such as advanced age, obesity, CKD, and diabetes) could contribute to reduced clopidogrel active metabolite formation.(48–50) The ABCD-GENE score combines these independent risk factors for clopidogrel non-response. With the increasing uptake of *CYP2C19* testing in clinical practice,(34) the ABCD-GENE score represents a feasible means of more precisely predicting clopidogrel response following PCI.

While all patients in our cohort were genotyped clinically, and prasugrel or ticagrelor was recommended in patients with a no function allele, 19% of no function allele carriers (IM, 18%; PM, 1%) remained on clopidogrel. Most of these patients were IMs, suggesting that physicians may be less likely to heed recommendations to avoid clopidogrel in IMs compared to PMs, perhaps because the clopidogrel labeling only addresses PMs. In an exploratory analysis from this project that focused on the 159 CYP2C19 IMs with an ABCD-GENE score <10, the risk for major atherothrombotic events and MACE was not different between IMs with an ABCD-GENE score <10 and anyone with a score ≥10. These data suggest that patients with a no function allele are at increased risk for ischemic events with clopidogrel even if their ABCD-GENE score is <10. A previous analysis showed that when the ABCD-GENE score is considered as a continuous variable, each one-point increase in the score increases the relative risk of MACE by approximately 4%.(24) The actual score was higher in the IM group, and we cannot rule out that this contributed to our findings. In addition, an exploratory analysis within the 505 patients with a score ≥10 showed that major atherothrombotic and MACE event rates were not significantly different between CYP2C19 IM/PMs versus non-IM/PMs, suggesting that patients without a no function allele are at increased risk for ischemic events with clopidogrel if their ABCD-GENE score is ≥10. Taken together, data from the current analysis add to the ABCD-GENE score literature and suggest that patients with at least one no function allele or an ABCD-GENE score ≥10 are at elevated risk of diminished clopidogrel clinical effectiveness. Given this and the small sample size, these data should be interpreted with caution, and further study of clopidogrel response among IMs with a score <10 and among non-IM/PMs with a score ≥10 is warranted.

This study is not without limitations. Notably, the pharmacodynamic outcome, HPR, was not assessed in our study, and thus we could not examine the ability of the ABCD-GENE score to predict HPR with clopidogrel in our population or determine whether HPR mediated the observed increased risk for ischemic events in patients with a score ≥10. Both the primary outcome and the more restrictive MACE definition were consistent with the results published in the original ABCD-GENE score manuscript,(24) which increased confidence in the validity of the current results using real-world data. In addition, data on the severity and duration of various comorbid conditions, such as diabetes and hyperlipidemia, and laboratory parameters, such as glucose, cholesterol, C-reactive protein, and liver enzymes were not collected, and the potential impact on ischemic outcomes was not evaluated. Finally, events were identified based on electronic health record review, and events that occurred in other health systems may have been missed.

In summary, our real-world outcomes data extend the association between the ABCD-GENE score and cardiovascular events with clopidogrel treatment to a diverse, real-world U.S. population who underwent PCI and received clinical *CYP2C19* genotyping. Within this population, an ABCD-GENE score ≥10 was associated with an increased risk for atherothrombotic events compared with a score <10. Our data suggest the ABCD-GENE score may be used in patients undergoing PCI to identify poor responders to clopidogrel. Whether treatment with an alternative $P2Y_{12}$ inhibitor would improve outcomes in patients with a high score remains to be determined. Given the significant body of evidence on factors contributing to poor clopidogrel response informing recent advances in guided selection of DAPT for patients undergoing PCI, the ABCD-GENE score represents a practical approach to integrate both clinical and genetic predictors of clopidogrel non-response to identify those patients at risk for diminished clopidogrel clinical effectiveness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest:

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Study Highlights

What is the current knowledge on the topic?

The ABCD-GENE score was developed using platelet function data and includes five independent predictors of high on-treatment platelet reactivity to predict clopidogrel non-response after percutaneous coronary intervention (PCI). While the score is predictive of clopidogrel non-response in predominately European and Asian patients and clinical trial participants, its ability to predict outcomes in a diverse, high-risk, real-world population is unknown.

What question did this study address?

The objective of this study was to validate the association between the ABCD-GENE score and risk for major atherothrombotic events in a diverse real-world population of clopidogrel-treated PCI patients.

What does this study add to our knowledge?

These data extend the association between an ABCD-GENE score ≥10 and increased risk for adverse atherothrombotic events among patients receiving clopidogrel after PCI to a diverse real-world population.

How might this change clinical pharmacology or translational science?

These data support use of the ABCD-GENE score for patients undergoing PCI to more precisely predict risk for poor response to clopidogrel.

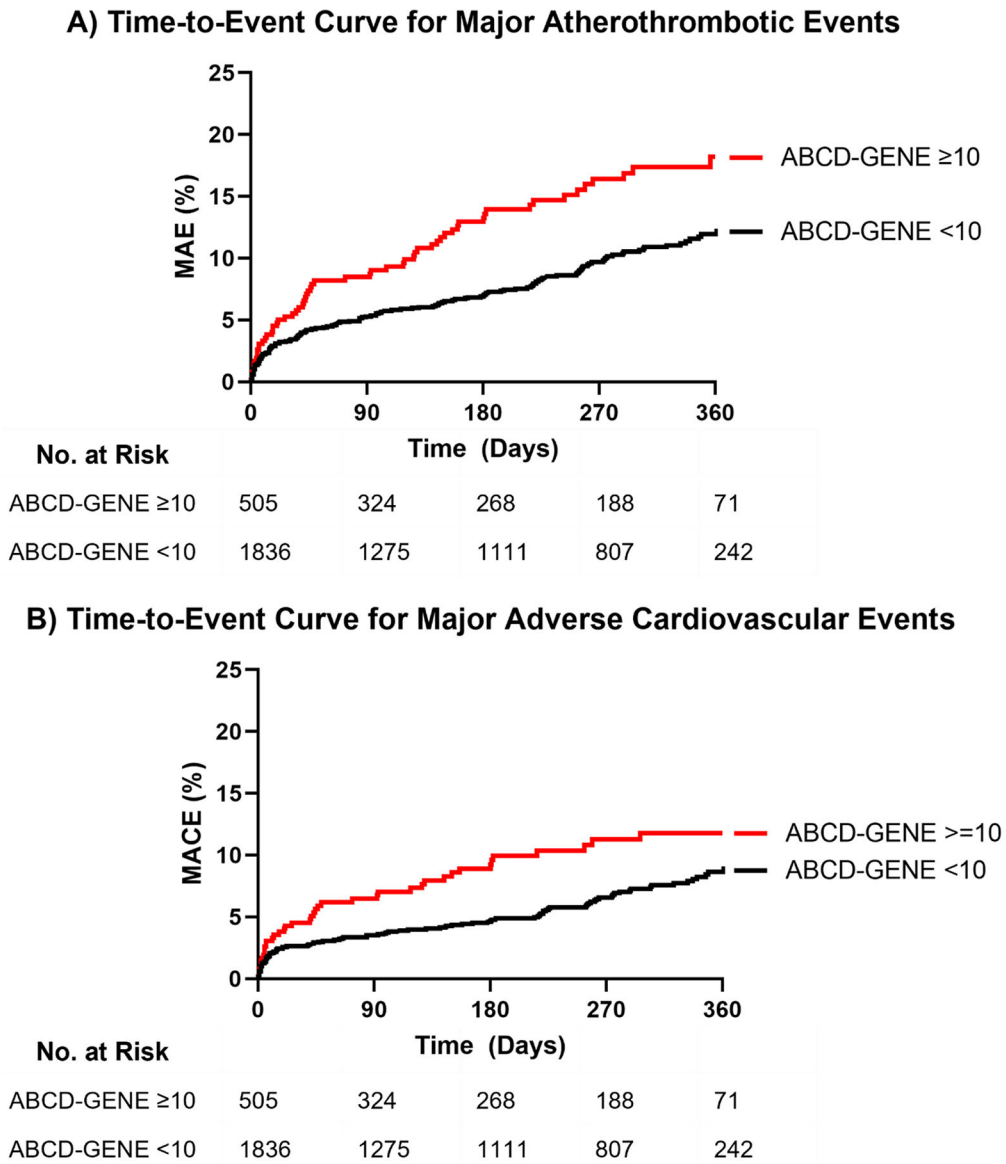

Figure 1. Time-to-Event Curves for Atherothrombotic Events.

A) Major atherothrombotic events (MAE), defined as the first occurrence of death, myocardial infarction (MI), ischemic stroke, stent thrombosis (ST), or unstable angina requiring revascularization at 1-year post-PCI. Adjusted hazard ratio (HR) 1.66 (95% CI, 1.23 – 2.25), p<0.001. B) Major adverse cardiovascular events (MACE), defined as the first occurrence of cardiovascular death, MI, ST, or ischemic stroke at 1-year post-PCI. Adjusted HR 1.59 (95% CI, 1.11 – 2.30), p=0.013. The tails of the Kaplan-Meier curves in Panels A and B were truncated at 360 days post-PCI, after which time less than 10% of each stratum were available for follow-up. In Panel A, n=4 events were observed in the ABCD-GENE score <10 group after day 360, when only 71 (4% of patients with a score <10) patients were still in follow-up. In Panel B, n=1 event occurred after day 360 in the ABCD-GENE score <10 group. No cardiovascular events occurred after day 360 for the ABCD-GENE score ≥10 group when 16 (3%) patients were available for follow-up.

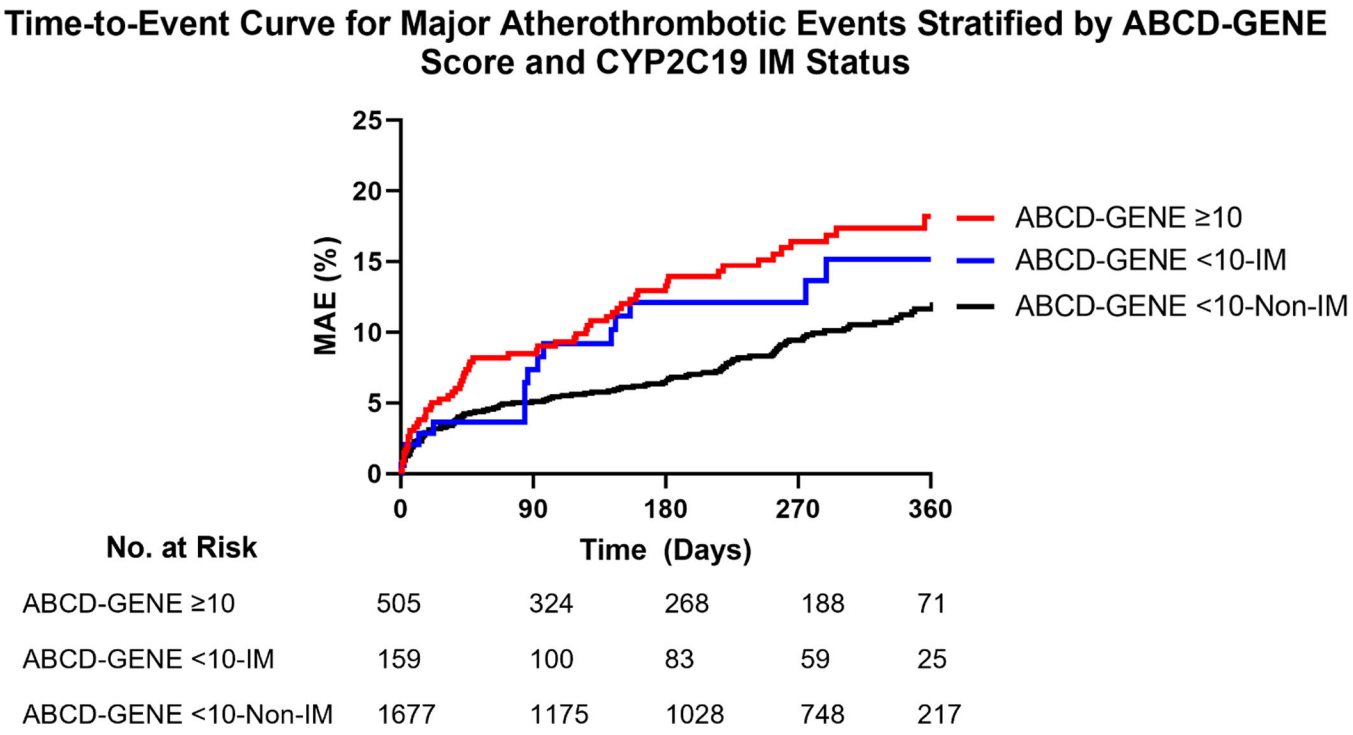

Figure 2. Time-to-Event Curve for Major Atherothrombotic Events Stratified by ABCD-GENE Score and CYP2C19 IM Status.

Major atherothrombotic events (MAE), defined as the first occurrence of death, myocardial infarction, ischemic stroke, stent thrombosis, or unstable angina requiring revascularization at 1-year post-PCI. Adjusted hazard ratio (HR) for ABCD-GENE score <10-Non-IM versus ≥10 = 0.58 (95% CI, 0.43–0.79), p<0.001. Adjusted HR for ABCD-GENE score <10-IM versus ≥10 = 1.03 (95% CI, 0.59–1.81), p=0.917. IM: CYP2C19 intermediate metabolizer. The tails of the Kaplan-Meier curve were truncated at 360 days post-PCI, after which time less than 10% of each stratum were available for follow-up. In the ABCD-GENE <10-Non-IM group, n=4 events were observed after day 360, when only 64 patients (4%) were still in follow-up. No MAE occurred after day 360 for the ABCD-GENE score ≥10 or score <10-IM groups when 16 (3%) and 7 (4%) patients were available for follow-up, respectively.

Table 1.

Patient Characteristics at the Time of Index Percutaneous Coronary Intervention

	Full Cohort (n=2341)	ABCD-GENE Score <10 (n=1836)	ABCD-GENE Score ≥10 (n=505)	p value for comparison of ABCD-GENE score <10 vs ≥10
Age, years	64.2 ± 12.0	63.1 ± 11.7	68.2 ± 12.1	<0.001
Female sex	817 (34.9)	609 (33.2)	208 (41.2)	0.001
Race				
White	1733 (74.0)	1357 (73.9)	376 (74.5)	0.968
Black or African American	470 (20.1)	370 (20.2)	100 (19.8)	
Other or Unknown Race[c]	138 (5.9)	109 (5.9)	29 (5.7)	
BMI, kg/m ^{2}	29.9 ± 6.6	28.9 ± 6.1	33.6 ± 7.0	<0.001
Current smoker	672 (28.7)	579 (31.5)	93 (18.4)	<0.001
PCI Indication [a]				
STEMI	401 (17.1)	342 (18.6)	59 (11.7)	0.17
NSTEMI	661 (28.2)	505 (27.5)	156 (30.9)	
UA	539 (23.0)	408 (22.2)	131 (25.9)	
Stable CAD/Elective	740 (31.6)	581 (31.6)	159 (31.5)	
PCI Strategy [b]				
Drug-eluting stent	2009 (85.8)	1587 (86.4)	422 (83.6)	<0.001
Bare metal stent	261 (11.1)	210 (11.4)	51 (10.1)	
PTCA	71 (3.0)	39 (2.1)	32 (6.3)	
Medical history				
Hypertension	1953 (83.4)	1490 (81.2)	463 (91.7)	<0.001
Dyslipidemia	1540 (65.8)	1167 (63.6)	373 (73.9)	<0.001
Prior MI	616 (26.3)	467 (25.4)	149 (29.5)	0.075
Prior Revascularization	1065 (45.5)	797 (43.4)	268 (53.1)	<0.001
Prior Stent	721 (30.8)	539 (29.4)	182 (36.0)	0.005
Prior CABG	277 (11.8)	204 (11.1)	73 (14.5)	0.047
Prior PTCA	67 (2.9)	54 (2.9)	13 (2.6)	0.774
Stroke/TIA	287 (12.3)	218 (11.9)	69 (13.7)	0.313
PVD	232 (9.9)	176 (9.6)	56 (11.1)	0.359
Heart failure	387 (16.5)	273 (14.9)	114 (22.6)	<0.001
Atrial fibrillation	254 (10.9)	178 (9.7)	76 (15.0)	0.001
Gastrointestinal or intracranial hemorrhage	68 (2.9)	44 (2.4)	24 (4.8)	0.008
Cancer	120 (5.1)	99 (5.4)	21 (4.2)	0.318
Discharge medication				
Aspirin	2288 (97.7)	1799 (98.0)	489 (96.8)	0.17
Statin	2185 (93.3)	1717 (93.5)	468 (92.7)	0.566

	Full Cohort (n=2341)	ABCD-GENE Score <10 (n=1836)	ABCD-GENE Score ≥10 (n=505)	p value for comparison of ABCD-GENE score <10 vs ≥10
β-blocker	2007 (85.7)	1575 (85.8)	432 (85.5)	0.948
ACE inhibitor or ARB	1555 (66.4)	1213 (66.1)	342 (67.7)	0.519
ARA	99 (4.2)	77 (4.2)	22 (4.4)	0.971
Anticoagulant	264 (11.3)	176 (9.6)	88 (17.4)	<0.001
PPI	763 (32.6)	595 (32.4)	168 (33.3)	0.755

[a] p value for comparison of primary PCI indication categories (i.e., myocardial infarction [STEMI/NSTEMI] vs. unstable angina or Stable CAD/ Elective) between groups.

[b] p value for comparison of PCI strategy (i.e., any stent type vs. PTCA) between groups.

[C] Detailed breakdown includes patients of the following ancestries: American Indian or Alaska Native (n=29), Asian (n=14), mixed ancestry (n=2), Native Hawaiian or Other Pacific Islander (n=2), or unknown (n=91).

Data are presented as number (%) or mean ± SD.

ACE, angiotensin converting enzyme; ARA, aldosterone receptor antagonist; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; IM, CYP2C19 intermediate metabolizer; MI, myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack

Table 2.

Prevalence of the clinical and genetic components of the ABCD-GENE score for clopidogrel-treated patients

	Full cohort (n=2341)	ABCD-GENE <10 (n=1836)	ABCD-GENE ≥10 (n=505)	p value for comparison of ABCD-GENE score <10 vs ≥10
ABCD-GENE Score	6 [3 – 8]	4 [3 – 7]	11 [10 – 13]	<0.001
Age >75 years	412 (18%)	239 (13%)	173 (34%)	<0.001
BMI >30 kg/m^2	1051 (45%)	658 (36%)	393 (78%)	<0.001
CKD	670 (29%)	353 (19%)	317 (63%)	<0.001
Diabetes	987 (42%)	641 (35%)	346 (69%)	<0.001
CYP2C19 **Gene**tic Test				
2 LOF alleles (PM)	20 (1%)	0	20 (4%)	<0.001[a]
1 LOF allele (IM)	428 (18%)	159 (9%)	269 (53%)	
0 LOF alleles (NM, RM, UM)	1893 (81%)	1677 (91%)	216 (43%)	

[a] p value for comparison of ≥1 LOF alleles vs 0 LOF alleles between groups.

Data are presented as median [IQR] or number (%).

BMI, body mass index; CKD, chronic kidney disease defined as an estimated glomerular filtration rate of < 60 ml/min/1.73m^2; IM, CYP2C19 intermediate metabolizer; NM, CYP2C19 normal metabolizer; PM, CYP2C19 poor metabolizer; RM, CYP2C19 rapid metabolizer; UM, CYP2C19 ultra-rapid metabolizer; LOF, loss-of-function.

Table 3.

Association of ABCD-GENE Score with Ischemic Outcomes within 1-Year After Percutaneous Coronary Intervention

	No. of events	Event rate per 100 person-years	Unadjusted HR	Adjusted HR[a]
Major atherothrombotic events				
ABCD-GENE score <10 (n=1836)	150	14.7 (95% CI, 12.3 – 17.0)	Reference	Reference
ABCD-GENE score ≥10 (n=505)	62	24.6 (95% CI, 18.5 – 30.8)	1.63 (95% CI, 1.21 – 2.19) p=0.001	1.66 (95% CI, 1.23 – 2.25) p<0.001
MACE				
ABCD-GENE score <10 (n=1836)	103	10.1 (95% CI, 8.1 – 12.0)	Reference	Reference
ABCD-GENE score ≥10 (n=505)	42	16.7 (95% CI, 11.6 – 21.7)	1.60 (95% CI, 1.12 – 2.29) p=0.011	1.59 (95% CI, 1.11 – 2.30) p=0.013

[a]Model adjusted for: sex, smoking status, percutaneous coronary intervention (PCI) indication (i.e., MI vs. UA or elective PCI), PCI strategy (i.e., stent versus percutaneous transluminal coronary angioplasty), and institution

ABCD-GENE (Age, oBesity, Chronic kidney disease, Diabetes, *CYP2C19* GENEtic variants) score; MACE, major adverse cardiovascular events. Major atherothrombotic events defined as the composite of death, myocardial infarction (MI), ischemic stroke, stent thrombosis (ST), or unstable (UA) requiring revascularization. MACE defined as the composite of cardiovascular death, MI, ST, or ischemic stroke.

Table 4.

Association Between ABCD-GENE Score and Major Atherothrombotic Events with CYP2C19 Intermediate Metabolizers (IMs) and non-IMs within 1-Year After Percutaneous Coronary Intervention

	No. of events	Event rate per 100 person-years	Unadjusted HR	Adjusted HR[a]
Major atherothrombotic events				
ABCD-GENE score ≥10 (n=505)	62	24.6 (95% CI, 18.5 – 30.8)	Reference	Reference
ABCD-GENE score <10: IMs (n=159)	16	20.1 (95% CI, 10.3 – 30.0)	0.82 (95% CI, 0.47–1.42) P=0.482	1.03 (95% CI, 0.59–1.81) P=0.917
ABCD-GENE score <10: Non-IMs (n=1677)	134	14.2 (95% CI, 11.8 – 16.6)	0.60 (95% CI, 0.44–0.81) P<0.001	0.58 (95% CI, 0.43–0.79) P<0.001
MACE				
ABCD-GENE score ≥10 (n=505)	42	16.7 (95% CI, 11.6 – 21.7)	Reference	Reference
ABCD-GENE score <10: IMs (n=159)	10	12.6 (95% CI, 4.8 – 20.4)	0.76 (95% CI, 0.38–1.51) P=0.431	0.97 (95% CI, 0.48–1.95) P=0.925
ABCD-GENE score <10: Non-IMs (n=1677)	93	9.9 (95% CI, 7.9 – 11.9)	0.61 (95% CI, 0.43–0.88) P=0.009	0.61 (95% CI, 0.42–0.88) P=0.008

[a]Model adjusted for: sex, smoking status, percutaneous coronary intervention (PCI) indication (i.e., MI vs. UA or elective PCI), PCI strategy (i.e., stent versus percutaneous transluminal coronary angioplasty), and institution

ABCD-GENE (Age, oBesity, Chronic kidney disease, Diabetes, *CYP2C19* GENEtic variants); IM: CYP2C19 intermediate metabolizer; MACE, major adverse cardiovascular events. Non-CYP2C19 IMs consists of CYP2C19: normal, rapid, and ultra-rapid metabolizers. Major atherothrombotic events defined as the composite of death, myocardial infarction (MI), ischemic stroke, stent thrombosis (ST), or unstable angina (UA) requiring revascularization. MACE defined as the composite of cardiovascular death, MI, ST, or ischemic stroke.