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# Precision medicine for antithrombotic therapy in patients after percutaneous coronary interventions

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# Precision medicine for antithrombotic therapy in patients after percutaneous coronary interventions

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# Editorial: Precision medicine for antithrombotic therapy in patients after percutaneous coronary interventions

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Editorial on the Research Topic
Precision medicine for antithrombotic therapy in patients after percutaneous coronary interventions

Precision medicine is an innovative medical model aiming at providing the right treatment to the right patient at the right time (1). After percutaneous coronary interventions (PCI), antiplatelet therapy plays a key role in preventing thrombotic events such as stent thrombosis or myocardial infarction, but is inevitably associated with increased bleeding (2). Given the inter-patient variability in response to antiplatelet therapy, a multi-factorial approach that accounts for clinical, procedural, and genetic factors is necessary for attaining an optimal balance between ischemic and hemorrhagic events. A precise, individualized, strategy is needed as opposed to a standard "one-size-fits all" approach (1). In this Special Issue of Frontiers in Cardiovascular Medicine, the authors provide relevant evidence on the impact of different antiplatelet treatment regimens on outcomes and on the different response that these regimens may display in specific subgroup of patients.

Antiplatelet therapy may be either intensified/prolonged or de-escalated/shortened to achieve an optimal trade-off between ischemic and bleeding events according to the individual patient characteristics (2, 3). In their original contribution, Kwan Young Lee et al. sought to explore the effectiveness of extended (>24 months) dual antiplatelet therapy (DAPT) in high ischemic risk acute coronary syndrome (ACS) patients undergoing PCI who had no major bleeding after at least 1 year of DAPT. Ischemic risk was defined according to the PEGASUS-TIMI 54 criteria. They found extended DAPT was associated with a lower risk of mortality without increasing the risk of major bleeding among 2 years survivors after ACS who met the PEGASUS criteria and had no major bleeding events before 24 months. Similar results were also observed in the report from the Korean nationwide registry including 273,670 Korean PCI patients by Seung-Jung Lee et al. that suggests prolonged (1–3 years) DAPT may be particularly beneficial in diabetic patients. The further contribution by Ana Lucrecia Marcano et al. explore the pathophysiological mechanisms at the basis of these clinical findings in diabetes mellitus (DM) patients. In their pharmacodynamic, crossover,

study randomizing Mediterranean patients with DM to either ticagrelor ($n = 20$) or clopidogrel ($n = 20$), the authors found that ticagrelor was associated with greater platelet inhibition after a loading dose and at 1 week, compared with clopidogrel. These finding are in line with previous reports (4). Collectively, evidence from these studies support an intensified/prolonged antithrombotic regimen may be particularly useful in high-ischemic risk patients, particularly if not at high risk for bleeding (5).

The ever growing understanding of the prognostic impact of bleeding events, the availability of less thrombogenic stent platforms and the notion that the ischemic risk is highest during the first 1–3 months after PCI/ACS, have fueled interest in implementing the so-called "de-escalation" strategies (6, 7). A comprehensive appraisal of these strategies is provided in the review article by Marie Muthspiel et al. while the network meta-analysis by Oumaima El Alaoui El Abdallaoui et al. allows for a direct and indirect comparison between different de-escalation strategies among 42,511 patients from 10 randomized controlled trials (RCTs). Their findings suggest both a strategy of de-escalation of $P2Y_{12}$ inhibitor intensity and a strategy of $P2Y_{12}$ inhibitor monotherapy may be associated with better outcomes compared to standard DAPT among ACS patients undergoing PCI. Moreover, they speculate that the former strategy may be more effective in reducing ischemic events while the latter strategy may be more effective in reducing bleeding, compared to standard DAPT.

The individual response to specific antiplatelet agents may be affected by clinical variables but also by sex-related, genetic, and demographics characteristics (1). The increasing awareness of the different response to antithrombotic agents woman may exhibit as opposed to men has been subject of growing interest (8). Indeed, females are often underrepresented in RCTs and the so called "Yentl syndrome" identifies the issues related to the paucity of evidence focusing on the subgroup of woman (8). To this extent, Laborante et al. provide a comprehensive summary of the evidence on gender-differences in antithrombotic therapy in ischemic heart disease, discussing the future perspectives for tackling the Yentl syndrome. Demographic characteristics, especially those concerning the different ischemic and bleeding risks across Asian versus Non-Asian patients, are one of the leading confounding factors in the appraisal of RCTs on antithrombotic therapy (1). Indeed, Asian patients display an increased risk of bleeding and a reduced risk of ischemic events compared with non-Asian patients, limiting the application of the evidence from RCTs between these populations (9). The response to specific $P2Y_{12}$ inhibitors, in particular clopidogrel, may be predicted according to the genotype responsible for the transcription of the enzyme that leads to clopidogrel metabolism, the cytochrome (CYP) C219 (10). In fact, the presence of CYP2C19 "loss-of-function" (LoF) alleles is associated with reduced generation of clopidogrel's active metabolite, high platelet reactivity and increased rates of thrombotic complications (11). However, the prevalence of CYP2C19 LoF alleles is significantly affected by ethnicity (10). Interestingly, Asian patients present increased bleeding and lower ischemic risks compared with other ethnicities despite the higher prevalence of CYP2C19 LoF alleles compared to the general population, contributing to the so called "Asian Paradox" (9). Studies like that by Yu-Wei Chen et al. exploring the impact on outcomes of CYP2C19 LoF in 999 East Asian patients with ACS undergoing PCI, have the important role of supporting the clinical impact of this genetic phenotype across difference ethnicities, despite the inherent differences in bleeding and ischemic risks between these populations (9). To this extent, it is of great interest the review article from Anh B Nguyen et al. discussing the race and ethnicity disparities in outcome studies of CYP2C19 genotype-guided antiplatelet therapy.

Finally, the management of antithrombotic therapy in patients with atrial fibrillation and concomitant ACS or PCI still represents a clinical conundrum (12). In this setting, it is of utmost importance the adequate selection of patients that may benefit the most from different antithrombotic regimens, given that the association between anticoagulants and antiplatelet leads to a particularly high risk of bleeding (13, 14). The study by Zhitong Li et al. adds important information on the additive role of atrial cardiomyopathy, assessed by B-type natriuretic peptide, P-wave terminal force in ECG lead V1, and left atrium diameter, on top of the standard $CHA_2DS_2$-VASc score for the prediction of the risk of cerebrovascular events in ACS patients.

## Author contributions

MG has drafted the manuscript. All the authors have read and approved the final version of the manuscript.

## Conflict of interest

MG declares that he has received consulting fees or honoraria from Terumo, outside the present work. FC declares that he has received consulting fees or honoraria from Astra Zeneca, and Chiesi Farmaceutici, outside the present work. DJA declares that he has received consulting fees or honoraria from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, Novartis, PhaseBio, PLx Pharma, Pfizer, Sanofi and Ventura, outside the present work. DA also declares that his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, Renal Guard Solutions and Scott R. MacKenzie Foundation.

## Publisher's note

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# Prolonged dual antiplatelet therapy after drug-eluting stent implantation in patients with diabetes mellitus: A nationwide retrospective cohort study

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**Background:** Optimal duration of dual antiplatelet therapy (DAPT) in patients with diabetes mellitus (DM) who have undergone drug-eluting stent (DES) implantation is not clearly established. This study sought to impact of DAPT duration on real-world clinical outcome in patients with or without DM.

**Methods:** Using a nationwide cohort database, we investigate the association between DAPT duration and clinical outcome between 1 and 3 years after percutaneous coronary intervention (PCI). Primary outcome was all-cause death. Secondary outcomes were cardiovascular death, myocardial infarction, and composite bleeding events. After weighting, 90,100 DES-treated patients were included; 29,544 patients with DM and 60,556 without DM; 31,233 patients with standard DAPT (6–12 months) and 58,867 with prolonged DAPT (12–24 months).

**Results:** The incidence of all-cause death was significantly lower in patients with prolonged DAPT [8.3% vs. 10.5% in those with standard DAPT, hazard ratio (HR) 0.78, 95% confidence interval (CI) 0.72–0.84] in diabetic patients and non-diabetic patients (4.5% vs. 5.0% in those with standard DAPT, HR 0.89, 95% CI 0.83–0.96). The incidence of composite bleeding events was 5.7% vs. 5.4%, respectively, (HR 1.07, 95% CI 0.96–1.18) in diabetic patients and 5.6% vs. 5.0%, respectively, in non-diabetic patients (HR 1.13, 95% CI 1.05–1.21). There was a significant interaction between the presence of DM and DAPT duration for all-cause death (p for interaction, $p_{int}$ = 0.01) that further favored prolonged DAPT in diabetic patients. However, there was no significant interaction between the presence of DM and DAPT duration for composite bleeding events ($p_{int}$ = 0.38).

**Conclusions:** This study showed that prolonged rather than standard DAPT might be clinically beneficial in diabetic patients with DES implantation.

**Trial registration:** ClinicalTrial.gov (NCT04715594).

KEYWORDS

**drug-eluting stents, diabetes mellitus, dual antiplatelet therapy, coronary artery disease, treatment outcome**

# Introduction

Diabetes mellitus (DM) is a major risk factor for atherosclerotic cardiovascular disease including coronary artery disease (CAD). Therefore, diabetic patients have a greater prevalence of CAD and account for a substantial proportion of percutaneous coronary intervention (PCI) with drug-eluting stent (DES) in daily clinical practice (1). Even though PCI was performed successfully, the prognosis of diabetic patients showed worse clinical outcomes with higher rates of mortality, cardiovascular events and stent thrombosis during long-term follow-up (2). High platelet reactivity and activation, hypercoagulability (prothrombotic state) and suboptimal response to standard antiplatelet agents might be related to a high rate of adverse cardiovascular events in patients with DM (3). Prolonged dual antiplatelet therapy (DAPT) for more than 1 year was proposed to reduce the occurrence of adverse cardiovascular events in diabetic patients in the past (4, 5). However, use of next-generation DESs has markedly improved clinical outcome after PCI in high-risk patients including those with DM (6). A minimum duration of DAPT is currently advocated in professional guideline documents and adopted worldwide for management of patients receiving DES (7–9). The current guideline suggests that DM should not be the only appraised patient-specific feature when deciding upon the type or duration of DAPT (7). Despite the increased risk of adverse clinical events after PCI in patients with DM compared to those without, the data to support the need for prolonged DAPT (>12 months) are not sufficient in the era of next-generation DES. Therefore, we sought to investigate real-world clinical outcomes according to duration of DAPT in diabetic patients who underwent next-generation DES implantation in a large-volume nationwide cohort that covers the entire population who received first- and next-generation DES implantation for CAD in Korea (CONNECT DES cohort registry).

# Methods

This study was a nationwide retrospective analysis of the national health claims database established by the National Health Insurance Service (NHIS) of Korea, which contains claimed medical costs, drug prescription and adherence, use of medical devices including types of DES, and medical history presented as International Classification of Diseases, Tenth Revision (ICD-10) codes of nearly all inhabitants. Most of the Korean population (97.1%) must subscribe to the NHIS, which is a sole insurer managed by the Korean government. Given that NHIS also covers information for the remaining population (2.9%) categorized as medical aid subjects, this cohort is considered to represent the entire Korean population (10). We were also provided the death certificates and ICD-10 codes from the National Institute of Statistics of Korea. This study was approved by the Institutional Review Board of our institute. Informed consent was waived because personal information was masked after cohort generation according to the strict confidentiality guidelines of the Korean Health Insurance Review and Assessment Service. This study is registered at ClinicalTrial.gov (NCT04715594).

## Study population

The flow of this study is depicted in Figure 1. From the 52 million inhabitants included in the Korean NHIS database, this study included 273,670 patients (≥20 years old) who were treated with DES between January 2005 and December 2016 in Korea (CONNECT DES cohort registry). The list of included or excluded next-generation DES is presented in Supplementary Table 1. The both types of DESs with biodegradable polymer and durable polymers were included, however, polymer-free DESs were not included in this study. First-generation DES implantation was more frequently performed between 2005 and 2009. Next-generation DESs were more frequently implanted between 2010 and 2016. Following government policy, all information including patients' medical history, drug prescription, and use of medical devices including DES were provided after encryption to protect personal information.

Of the 273,690 patients who underwent DES implantation between 2005 and 2016, 94,362 were excluded for implanted with first-generation DES ($n = 69,316$); previous history of PCI or coronary artery bypass surgery ($n = 5,517$) because clinical events during follow-up cannot be discriminated whether those

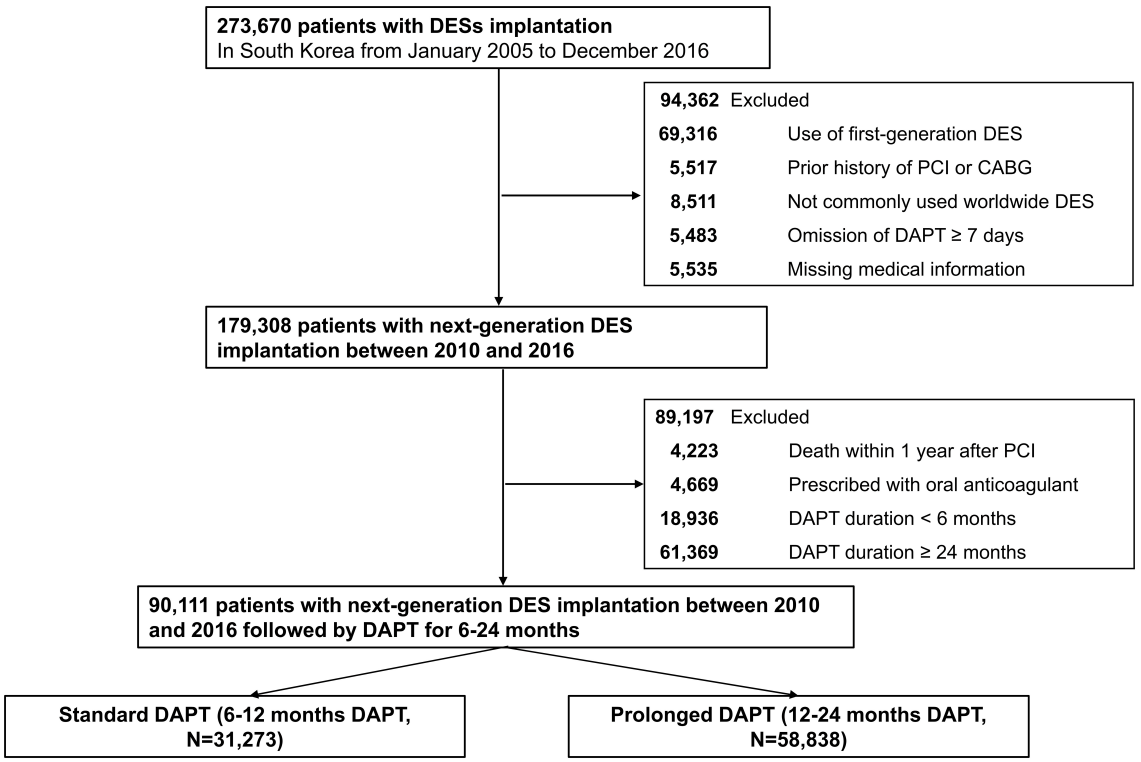


FIGURE 1
A flowchart of the study population. DES, drug-eluting stent; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; DAPT, dual antiplatelet therapy; Standard DAPT, DAPT between 6 and 12 months; Prolonged DAPT, DAPT between 12 and 24 months.

were caused by a prior PCI (coronary artery bypass surgery) or index PCI; implanted with DES that are not commonly used worldwide ($n$ = 8,511); omitted DAPT ≥ 7 days ($n$ = 5,483); and missing medical information ($n$ = 5,535). Then, 179,308 patients who were treated with next-generation DES remained. To minimize immortal time bias, we excluded those who died within 1 year after PCI from the analyses ($n$ = 4,223). Patients who were prescribed with oral anticoagulant ($n$ = 4,669), DAPT for <6 months ($n$ = 18,936) or DAPT for ≥24 months ($n$ = 61,369) were further excluded to minimize selection bias. Consequently, the remaining 90,111 patients who received next-generation DES implantation with DAPT for 6–24 months (standard DAPT, DAPT between 6–12 months, $n$ = 31,273; prolonged DAPT, DAPT between 12–24 months, $n$ = 58,838, Figure 1) were included in the analyses.

## Study procedures and outcomes

Patients with DM were defined as those who received oral hypoglycemic agents and/or injection of insulin. The duration of DAPT was identified using prescription data with Korean Drug and Anatomical Therapeutic Chemical codes (11). If prescription of aspirin along with any $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, or prasugrel) has been continued for ≥1 year after index PCI without discontinuation for more than 7 days, we considered the patient to be treated with prolonged DAPT. To minimize immortal time bias, we set the primary follow-up period as 12 to 36 months after index PCI. Patients who experienced ischemic or bleeding events and were alive within 1 year after index PCI were included in the analyses considering the recurrent nature of these clinical events. The history of those clinical events within 1 year after index PCI was adjusted for analyses of primary or secondary outcomes. Primary outcome was all-cause death. Secondary outcomes were composite ischemic events (cardiovascular death, myocardial infarction, or ischemic stroke), composite bleeding events (hemorrhagic stroke, gastrointestinal bleeding, or genitourinary bleeding requiring admission or medical intervention), and each component of an ischemic or bleeding event. Cardiovascular death was ascertained from the National Statistical Office of Korea, which provided death certificates with an accuracy of 92% for the specific cause of death (10, 12). Cardiovascular death was identified by a death certificate with at least one cardiovascular-related diagnosis (acute myocardial infarction, stroke, heart failure, or sudden cardiac death) (13). Myocardial infarction was defined as the simultaneous development of ICD-10 codes corresponding to acute myocardial infarction

(11), claims for coronary angiography, admission *via* the emergency department, and more than four rounds of cardiac biomarker testing. A detailed description for each clinical outcome is presented in Supplementary Table 2. We further included baseline comorbidities and drug prescription status before PCI for propensity score calculation, and inverse probability treatment of weighting (IPTW) was used to account for differences in baseline characteristics, medical history, and confounding bias (11, 13). Details regarding covariates included in the propensity score calculation are described in Supplementary Table 3.

## Statistical analysis

Continuous variables are reported as mean and standard deviation, while dichotomous variables are presented as frequency and percentage. Conformity to the normal distribution was assessed for continuous variables using the Kolmogorov-Smirnov test. To minimize the effect of confounding bias, we calculated the IPTW by the propensity score, which was calculated by logistic regression with covariates including age, sex, history of comorbidities and medications, and year of PCI (Supplementary Table 3). We also stabilized the weights by multiplying IPTW by the marginal probability of receiving treatment. The effect size difference between the two groups for all comorbidities and medications was calculated using the standardized mean difference (SMD) and Kernel density plots. SMD values above 0.2 were regarded as a potential imbalance between the two groups. Cumulative incidence curves and the rate of all-cause death, cardiovascular death, myocardial infarction, and composite bleeding events during follow-up were plotted using the Kaplan–Meier method. The adjusted hazard ratio (HR) for each clinical outcome of interest was calculated using a multivariable Cox proportional hazard regression model. The cause-specific hazard model was used to consider death as a competing risk when comparing the incidences of cardiovascular death and other components of secondary outcomes. A two-sided *p*-value of $< 0.05$ was considered significant. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.6 (The R Foundation, www.R-project.org).

# Results

After weighting, 90,100 DES-treated patients included 29,544 patients with DM and 60,556 patients without; 31,233 patients with standard DAPT and 58,867 patients with prolonged DAPT. Baseline demographics and medical history of the whole cohort population before and after stabilized IPTW are presented in Supplementary Table 4. After stabilized IPTW, there was no evidence of inequality in the baseline demographic characteristics and medical history between the two groups including the year of PCI and characteristics of DES (all SMD $< 0.1$, Supplementary Figures 1, 2). Furthermore, baseline characteristics were well balanced among the patients receiving standard and prolonged DAPT with or without DM (all SMD $< 0.1$, Table 1). The incidence and relative hazards of all-cause death, cardiovascular death, myocardial infarction, and composite bleeding events at 2 and 3 years after PCI between the two groups in patients with or without DM are presented in Table 2 and Figure 2.

At 3 years after PCI in patients without DM, the incidence of all-cause death, cardiovascular death and myocardial infarction was significantly lower in patients treated with prolonged DAPT [4.5% vs. 5.0% with standard DAPT, HR 0.89, 95% confidence interval (CI) 0.83–0.96; 3.8% vs. 4.1%, HR 0.91, 95% CI 0.84–0.99; 4.4% vs. 5.0%, HR 0.88, 95% CI 0.81–0.95, respectively].

However, the incidence of composite bleeding events was significantly greater in patients treated with prolonged DAPT (5.6% vs. 5.0% with standard DAPT, HR 1.13, 95% CI 1.05–1.21).

At 3 years after PCI in patients with DM, the incidence of all-cause death, cardiovascular death and myocardial infarction was significantly lower in patients treated with prolonged DAPT (8.3% vs. 10.5% with standard DAPT, HR 0.78, 95% CI 0.72–0.84; 7.3% vs. 9.0% HR 0.79, 95% CI 0.73–0.86; 6.9% vs. 8.6%, HR 0.78, 95% CI 0.71–0.85, respectively). There was no statistically significant difference in incidence of composite bleeding events between patients treated with prolonged DAPT and those treated with standard DAPT (5.7% vs. 5.4%, respectively, HR 1.07, 95% CI 0.96–1.18).

The number need to treat for preventing one case of all-cause death was 46 and 200 for patients with and without DM, respectively. The number need to treat or harm for other clinical outcomes among patients with or without DM are presented in Figure 1.

There was a significant interaction between the presence of DM and DAPT duration for all-cause death (p for interaction, $p_{int} = 0.01$), cardiovascular death ($p_{int} = 0.02$) and myocardial infarction ($p_{int} = 0.04$) that favored prolonged DAPT in patients with DM. However, there was no significant interaction between the presence of DM and DAPT duration for composite bleeding events ($p_{int} = 0.38$). In a subgroup analysis of diabetic patients, there was no significant interaction between the baseline comorbidities and DAPT duration for all-cause death (Figure 3) or cardiovascular death (Supplementary Figure 3).

# Discussion

This nationwide cohort analysis assessed mortality and clinical outcomes of standard vs. prolonged DAPT in diabetic patients with next-generation DES implantation. To the best of our knowledge, the results of our analyses were derived from a cohort that included a largest number of diabetic patients

TABLE 1 Baseline characteristics and medications in patients with and without DM.

| Characteristics | Non-DM patients ($N = 60,556$) | | | DM patients ($N = 29,544$) | | |
|---|---|---|---|---|---|---|
| | Standard DAPT ($N = 20,966$) | Prolonged DAPT ($N = 39,590$) | SMD | Standard DAPT ($N = 10,267$) | Prolonged DAPT ($N = 19,277$) | SMD |
| Age, years | 63.7 ± 11.9 | 63.7 ± 11.8 | 0.004 | 66.1 ± 10.9 | 66.0 ± 10.6 | 0.013 |
| Women | 5,865 (28.0) | 10,922 (27.6) | 0.009 | 3,574 (34.8) | 6,769 (35.1) | 0.006 |
| **Comorbidity** | | | | | | |
| Hypertension | 12,666 (60.4) | 24,007 (60.6) | 0.005 | 7,252 (70.6) | 13,517 (70.1) | 0.011 |
| Dyslipidemia | 8,888 (42.4) | 16,906 (42.7) | 0.006 | 4,006 (39.0) | 7,492 (38.9) | 0.003 |
| Chronic kidney disease with severe renal impairment[a] | 675 (3.2) | 1,349 (3.4) | 0.011 | 943 (9.2) | 1,631 (8.5) | 0.026 |
| DM duration ≥ 5 years | - | - | - | 6,669 (65.0) | 12,736 (66.1) | 0.023 |
| Insulin-dependent DM | - | - | - | 1,384 (13.5) | 2,622 (13,6) | 0.004 |
| Heart failure | 2,535 (12.1) | 4,756 (12.0) | 0.002 | 1,556 (15.2) | 2,870 (14.9) | 0.007 |
| Chronic liver disease | 1,972 (9.4) | 3,730 (9.4) | <0.001 | 1,072 (10.4) | 2,058 (10.7) | 0.008 |
| Chronic pulmonary disease | 1,462 (7.0) | 2,715 (6.9) | 0.005 | 732 (7.1) | 1,380 (7.2) | 0.001 |
| Peripheral arterial occlusive disease | 637 (3.0) | 1,208 (3.0) | 0.001 | 467 (4.5) | 869 (4.5) | 0.002 |
| Atrial fibrillation or flutter | 541 (2.6) | 1,021 (2.6) | <0.001 | 250 (2.4) | 442 (2.3) | 0.009 |
| Prior malignancy | 871 (4.2) | 1,657 (4.2) | 0.002 | 557 (5.4) | 1,036 (5.4) | 0.002 |
| Prior stroke or TIA | 1,516 (7.2) | 2,862 (7.2) | <0.001 | 1,129 (11.0) | 2,051 (10.6) | 0.012 |
| Prior ICH | 115 (0.5) | 206 (0.5) | 0.004 | 42 (0.4) | 80 (0.4) | 0.001 |
| Presentation as AMI | 3,869 (18.5) | 7,443 (18.8) | 0.009 | 1,697 (16.5) | 3,005 (15.6) | 0.026 |
| Thyroid disorder | 590 (2.8) | 1,102 (2.8) | 0.002 | 289 (2.8) | 536 (2.8) | 0.002 |
| Osteoporosis | 1,606 (7.7) | 3,007 (7.6) | 0.002 | 803 (7.8) | 1,466 (7.6) | 0.008 |
| Charlson comorbidity index | 1.5 ± 1.3 | 1.5 ± 1.3 | 0.002 | 3.1 ± 1.9 | 3.1 ± 1.8 | 0.017 |
| **Medication before PCI** | | | | | | |
| Anti-platelet agent | 7,680 (36.6) | 14,309 (36.1) | 0.010 | 5,367 (52.3) | 10,178 (52.8) | 0.010 |
| β-Blockers | 7,821 (37.3) | 14,806 (37.4) | 0.002 | 4,869 (47.4) | 9,004 (46.7) | 0.014 |
| BP-lowering agents [b] | 4,879 (23.3) | 9,098 (23.0) | 0.007 | 2,830 (27.6) | 5,393 (28.0) | 0.009 |
| RAAS blockade | 3,964 (18.9) | 7,380 (18.6) | 0.007 | 3,100 (30.2) | 5,781 (30.0) | 0.004 |
| **Procedural information** | | | | | | |
| Number of stents | 1.2 ± 0.4 | 1.2 ± 0.4 | 0.010 | 1.2 ± 0.5 | 1.2 ± 0.5 | 0.040 |
| **Drug** | | | | | | |
| Paclitaxel | 3,166 (15.1) | 6,116 (15.4) | 0.011 | 1,709 (16.6) | 3,118 (16.2) | 0.028 |
| Sirolimus | 1,807 (8.6) | 3,464 (8.7) | | 943 (9.2) | 1,646 (8.5) | |
| Everolimus | 11,861 (56.6) | 22,280 (56.3) | | 5,758 (56.1) | 10,924 (56.7) | |
| Biolimus A9 | 4,132 (19.7) | 7,730 (19.5) | | 1,857 (18.1) | 3,589 (18.6) | |
| Use of BP-DES | 7,298 (34.8) | 13,847 (35.0) | 0.004 | 3,570 (34.8) | 6,707 (34.8) | <0.001 |
| **Year of PCI** | | | | | | |
| 2010 | 1,790 (8.5) | 3,399 (8.6) | 0.008 | 834 (8.2) | 1,494 (7.8) | 0.026 |
| 2011 | 1,517 (7.2) | 2,882 (7.3) | | 746 (7.3) | 1,357 (7.0) | |
| 2012 | 1,366 (6.5) | 2,540 (6.4) | | 668 (6.5) | 1,244 (6.5) | |
| 2013 | 1,749 (8.3) | 3,233 (8.2) | | 794 (7.7) | 1,530 (7.9) | |
| 2014 | 3,271 (15.6) | 6,183 (15.6) | | 1,563 (15.2) | 2,882 (14.9) | |
| 2015 | 4,052 (19.3) | 7,637 (19.3) | | 1,990 (19.4) | 3,695 (19.2) | |
| 2016 | 7,221 (34.4) | 13,717 (34.6) | | 3,668 (35.7) | 7,076 (36.7) | |

Values are the mean ± standard deviation or n (%). AMI, acute myocardial infarction; BP-DES, biodegradable polymer drug-eluting stent; BP, blood pressure; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; ICH, intracranial hemorrhage; IPTW, inverse probability of treatment weighting; PCI, percutaneous coronary intervention; RAAS, renin-angiotensin-aldosterone-system; SMD, standardized mean difference; TIA, transient ischemic attack.

[a]Chronic kidney disease with advanced stage requiring intensive medical therapy and financial assistance from health insurance.

[b]Alpha receptor antagonists, calcium-channel blockers or diuretics.

TABLE 2 Risks of primary and secondary outcomes before and after stabilized IPTW.

| | | Non-DM patients | | | DM patients | | | *P* for interaction |
|---|---|---|---|---|---|---|---|---|
| | | **Standard DAPT** | **Prolonged DAPT** | **HR (95% CI)** | **Standard DAPT** | **Prolonged DAPT** | **HR (95% CI)** | |
| **Before stabilized IPTW** | | ***N* = 21,453** | ***N* = 39,179** | **Total *N* = 60,632** | ***N* = 9,820** | ***N* = 19,659** | textbfTotal *N* = 29,479 | |
| All-cause death | 2 y | 605 (2.8) | 976 (2.5) | 0.88 (0.79–0.97) | 602 (6.1) | 906 (4.6) | 0.74 (0.67–0.82) | 0.02 |
| | 3 y | 1,020 (4.8) | 1,747 (4.5) | 0.93 (0.86–1.01) | 1,012 (10.3) | 1,619 (8.2) | 0.79 (0.72–0.85) | 0.002 |
| Cardiovascular death | 2 y | 501 (2.3) | 838 (2.1) | 0.91 (0.81–1.02) | 509 (5.2) | 809 (4.1) | 0.78 (0.70–0.88) | 0.06 |
| | 3 y | 837 (3.9) | 1,480 (3.8) | 0.96 (0.88–1.05) | 862 (8.8) | 1,418 (7.2) | 0.81 (0.74–0.88) | 0.004 |
| Myocardial infarction | 2 y | 770 (3.6) | 1,323 (3.4) | 0.94 (0.86–1.02) | 669 (6.8) | 1,039 (5.3) | 0.76 (0.69–0.83) | 0.02 |
| | 3 y | 984 (4.6) | 1,734 (4.4) | 0.96 (0.89–1.04) | 816 (8.3) | 1,360 (6.9) | 0.81 (0.74–0.88) | 0.001 |
| Ischemic stroke | 2 y | 229 (1.4) | 585 (1.5) | 1.09 (0.95–1.25) | 253 (2.6) | 477 (2.4) | 0.93 (0.80–1.09) | 0.14 |
| | 3 y | 411 (1.9) | 784 (2.0) | 1.04 (0.93–1.18) | 301 (3.1) | 607 (3.1) | 0.99 (0.86–1.14) | 0.67 |
| Composite ischemic events [a] | 2 y | 1,267 (5.9) | 2,187 (5.6) | 0.94 (0.88–1.01) | 1,114 (11.3) | 1,833 (9.3) | 0.80 (0.74–0.86) | 0.001 |
| | 3 y | 1,728 (8.1) | 3,042 (7.8) | 0.96 (0.91–1.02) | 1,452 (14.8) | 2,527 (12.9) | 0.84 (0.79–0.90) | 0.003 |
| Composite bleeding events [b] | 2 y | 667 (3.1) | 1,381 (3.5) | 1.12 (1.03–1.23) | 322 (3.3) | 770 (3.9) | 1.18 (1.04–1.35) | 0.53 |
| | 3 y | 1,066 (5.0) | 2,202 (5.6) | 1.12 (1.05–1.22) | 527 (5.4) | 1,118 (5.7) | 1.04 (0.94–1.16) | 0.30 |
| Hemorrhagic stroke | 2 y | 10 (0.05) | 24 (0.06) | 1.30 (0.63–2.70) | 10 (0.1) | 19 (0.1) | 0.93 (0.43–2.00) | 0.54 |
| | 3 y | 17 (0.08) | 42 (0.11) | 1.35 (0.77–2.38) | 18 (0.18) | 29 (0.15) | 0.79 (0.44–1.43) | 0.21 |
| Gastrointestinal bleeding | 2 y | 460 (2.1) | 953 (2.4) | 1.12 (1.01–1.27) | 215 (2.2) | 553 (2.8) | 1.27 (1.09–1.49) | 0.21 |
| | 3 y | 721(3.4) | 1,490 (3.8) | 1.12 (1.03–1.23) | 349 (3.6) | 762 (3.9) | 1.08 (0.95–1.22) | 0.62 |
| Genitourinary bleeding | 2 y | 208 (1.0) | 433 (1.1) | 1.14 (0.96–1.35) | 103 (1.1) | 221 (1.1) | 1.07 (0.84–1.37) | 0.67 |
| | 3 y | 360 (1.7) | 745 (1.9) | 1.13 (1.00–1.29) | 181 (1.8) | 387 (2.0) | 1.07 (0.90–1.28) | 0.59 |
| **After stabilized IPTW** | | ***N* = 20,966** | ***N* = 39,590** | **Total *N* = 60,556** | ***N* = 10,267** | ***N* = 19,277** | **Total *N* = 29,544** | |
| All-cause death | 2 y | 627 (3.0) | 985 (2.5) | 0.83 (0.75–0.91) | 642 (6.3) | 896 (4.6) | 0.73 (0.66–0.81) | 0.08 |
| | 3 y | 1,047 (5.0) | 1,774 (4.5) | 0.89 (0.83–0.96) | 1,074 (10.5) | 1,598 (8.3) | 0.78 (0.72–0.84) | 0.01 |
| Cardiovascular death | 2 y | 523 (2.5) | 840 (2.1) | 0.85 (0.76–0.94) | 544 (5.3) | 802 (4.2) | 0.77 (0.69–0.86) | 0.24 |
| | 3 y | 866 (4.1) | 1,497 (3.8) | 0.91 (0.84–0.99) | 919 (9.0) | 1,401 (7.3) | 0.79 (0.73–0.86) | 0.02 |
| Myocardial infarction | 2 y | 823 (3.9) | 1,323 (3.3) | 0.85 (0.77–0.92) | 730 (7.1) | 1,012 (5.3) | 0.72 (0.66–0.80) | 0.02 |
| | 3 y | 1,041 (5.0) | 1,735 (4.4) | 0.88 (0.81–0.95) | 888 (8.6) | 1,325 (6.9) | 0.78 (0.71–0.85) | 0.04 |

*(Continued)*





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TABLE 2 Continued

| | | Non-DM patients | | | DM patients | | | *P* for interaction |
|---|---|---|---|---|---|---|---|---|
| | | Standard DAPT | Prolonged DAPT | HR (95% CI) | Standard DAPT | Prolonged DAPT | HR (95% CI) | |
| Ischemic stroke | 2 y | 300 (1.4) | 592 (1.5) | 1.05 (0.91–1.20) | 267 (2.6) | 482 (2.5) | 0.96 (0.83–1.11) | 0.60 |
| | 3 y | 418 (2.0) | 796 (2.0) | 1.01 (0.90–1.14) | 316 (3.1) | 611 (3.2) | 1.03 (0.90–1.18) | 0.39 |
| Composite ischemic events | 2 y | 1,316 (6.3) | 2,206 (5.6) | 0.88 (0.82–0.94) | 1,189 (11.6) | 1,816 (9.4) | 0.79 (0.74–0.85) | 0.04 |
| | 3 y | 1,776 (8.5) | 3,074 (7.8) | 0.91 (0.86–0.97) | 1,545 (15.1) | 2,479 (13.0) | 0.84 (0.79–0.90) | 0.07 |
| Composite bleeding events | 2 y | 656 (3.1) | 1,390 (3.5) | 1.12 (1.02–1.23) | 348 (3.4) | 762 (4.0) | 1.17 (1.03–1.32) | 0.60 |
| | 3 y | 1,044 (5.0) | 2,218 (5.6) | 1.13 (1.05–1.21) | 549 (5.4) | 1,098 (5.7) | 1.07 (0.96–1.18) | 0.38 |
| Hemorrhagic stroke | 2 y | 10 (0.1) | 23 (0.1) | 1.25 (0.59–2.64) | 13 (0.1) | 18 (0.1) | 0.77 (0.37–1.59) | 0.85 |
| | 3 y | 16 (0.1) | 42 (0.1) | 1.37 (0.77–2.42) | 21 (0.2) | 29 (0.1) | 0.71 (0.41–1.24) | 0.11 |
| Gastrointestinal bleeding | 2 y | 455 (2.2) | 962 (2.4) | 1.12 (1.00–1.25) | 227 (2.2) | 552 (2.9) | 1.29 (1.11–1.51) | 0.13 |
| | 3 y | 707 (3.4) | 1,501 (3.8) | 1.13 (1.03–1.23) | 367 (3.6) | 751 (3.9) | 1.09 (0.96–1.24) | 0.71 |
| Genitourinary bleeding | 2 y | 208 (1.0) | 436 (1.1) | 1.11 (0.94–1.31) | 114 (1.1) | 213 (1.1) | 0.99 (0.79–1.25) | 0.43 |
| | 3 y | 358 (1.7) | 754 (1.9) | 1.12 (0.98–1.27) | 189 (1.8) | 377 (2.0) | 1.07 (0.89–1.27) | 0.67 |

Numbers in parentheses represent the percentage. y indicates year. The hazard ratio (HR) and p value for interaction were calculated by Cox proportional hazard model. CI, confidence interval; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; IPTW, inverse probability of treatment weighting.

[a]Composite of cardiovascular death, myocardial infarction, and ischemic stroke.

[b]Composite of hemorrhagic stroke, gastrointestinal bleeding, and genitourinary bleeding.





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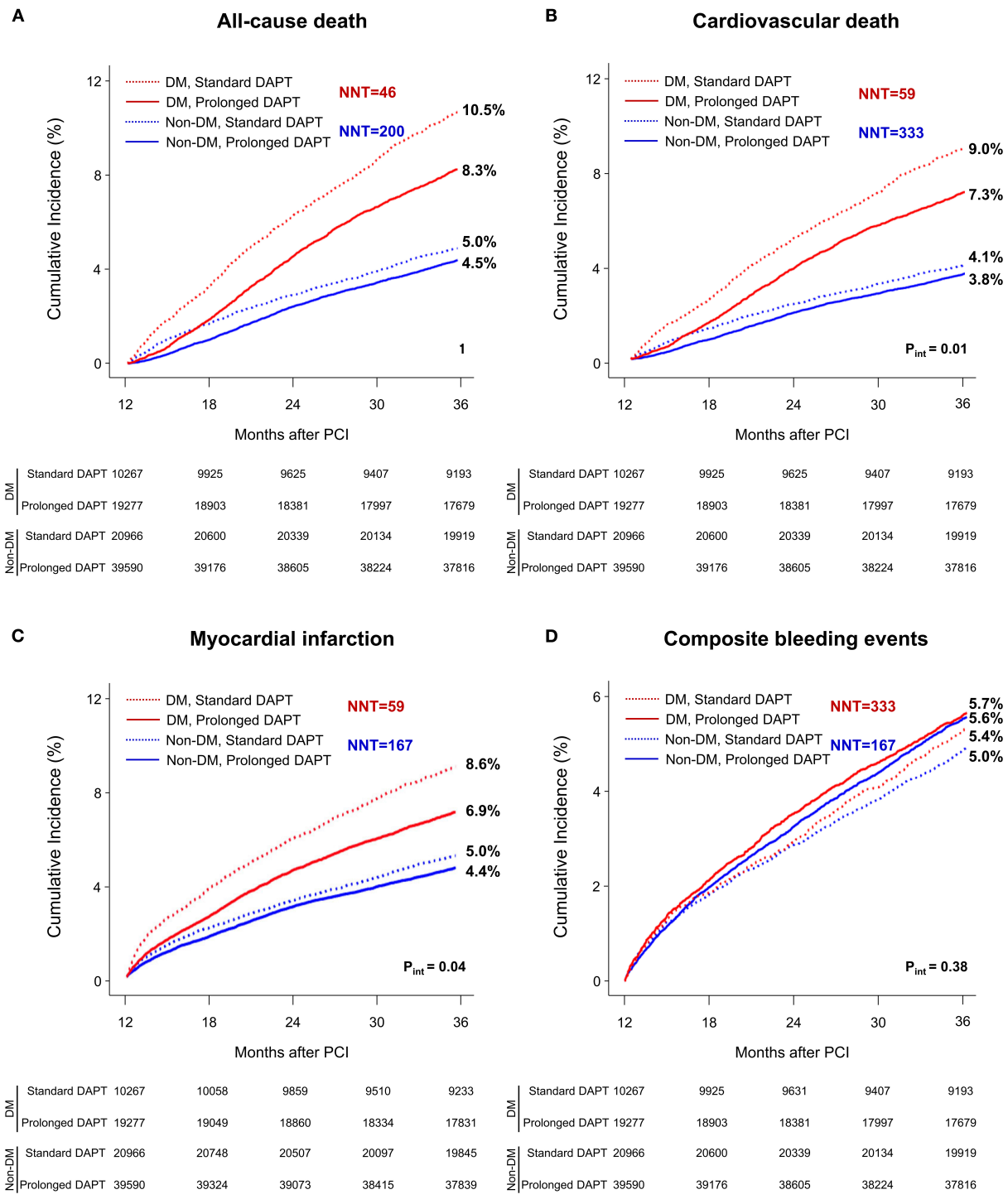


FIGURE 2
Time-to-event curves for all-cause death, cardiovascular death, myocardial infarction, or composite bleeding events between 1 and 3 years after PCI. The cumulative incidence of **(A)** all-cause, **(B)** cardiovascular mortality, **(C)** myocardial infarction and **(D)** composite bleeding events between 1 and 3 years after PCI. DAPT, dual antiplatelet therapy; DM, diabetes mellitus; PCI, percutaneous coronary intervention. NNT, number need to treat; NNH, number need to harm.

| Covariates | Standard DAPT | | Prolonged DAPT | | Hazard ratio (95% CI) | P for interaction |
|---|---|---|---|---|---|---|
| | Patient N | 3-year mortality | Patient N | 3-year mortality | | |
| **Age** | | | | | | |
| < 75 years | 7,755 | 560 (7.2) | 14,728 | 805 (5.5) | 0.74 (0.67-0.83) | 0.16 |
| ≥ 75 years | 2,512 | 514 (20.4) | 4,549 | 793 (17.3) | 0.83 (0.74-0.93) | |
| **Sex** | | | | | | |
| Male | 6,693 | 670 (10) | 12,508 | 977 (7.8) | 0.77 (0.69-0.85) | 0.69 |
| Female | 3,574 | 404 (11.3) | 6,769 | 621 (9.2) | 0.79 (0.70-0.90) | |
| **Hypertension** | | | | | | |
| No | 3,015 | 278 (9.2) | 5,760 | 410 (7.1) | 0.75 (0.65-0.88) | 0.66 |
| Yes | 7,252 | 796 (11) | 13,517 | 1,189 (8.8) | 0.79 (0.72-0.86) | |
| **Presentation as Acute MI** | | | | | | |
| No | 8,570 | 866 (10.1) | 16,272 | 1,340 (8.2) | 0.80 (0.73-0.87) | 0.17 |
| Yes | 1,697 | 208 (12.2) | 3,005 | 258 (8.6) | 0.69 (0.58-0.81) | |
| **Insulin-dependent DM** | | | | | | |
| No | 8,883 | 812 (9.4) | 16,655 | 1,224 (7.3) | 0.78 (0.72-0.86) | 0.78 |
| Yes | 1,384 | 262 (18.9) | 2,622 | 374 (14.3) | 0.75 (0.63-0.88) | |
| **Chronic kidney disease with severe renal impairment** | | | | | | |
| No | 9,324 | 708 (7.6) | 17,646 | 1,073 (6.1) | 0.80 (0.73-0.88) | 0.82 |
| Yes | 943 | 366 (38.8) | 1,631 | 525 (32.1) | 0.83 (0.72-0.95) | |

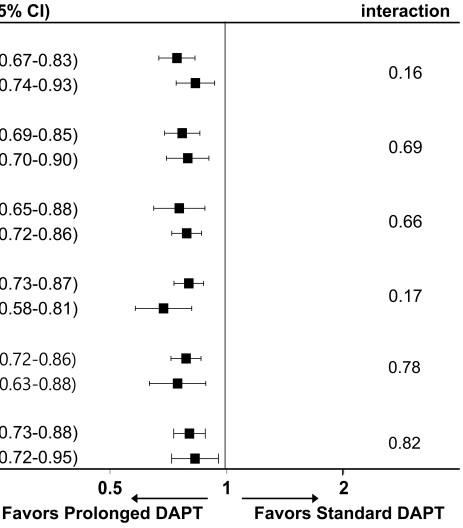


FIGURE 3
Subgroup analysis for all-cause death in diabetic patients. Numbers and percentages show the number of patients at risk and the all-cause mortality rate between 1 and 3 years after drug-eluting stent implantation. CI, confidence interval; MI, myocardial infarction; DM, diabetes mellitus.

who underwent next-generation DES implantation. This study included whole patients who were concurrently encountered in a catheterization laboratory and were very-high-risk (high bleeding risk, end-stage renal disease, and very elderly patients, etc.) who were usually excluded from other randomized studies. The major findings of our study are as follows: (1) in patients with DM, prolonged DAPT (vs. standard DAPT) was associated with lower all-cause mortality, cardiovascular mortality, and myocardial infarction without an increase in composite bleeding events. (2) In patients without DM, prolonged DAPT (vs. standard DAPT) was associated with a decrease in all-cause mortality and cardiovascular mortality and an increase in composite bleeding events.

Compared to bare-metal stents or first-generation DES, the favorable mechanochemical characteristics of next-generation DES have significantly reduced concern for stent thrombosis (6, 14). In this regard, a growing concern for the risk of bleeding according to prolonged DAPT has emerged as an important issue for long-term management of patients who underwent PCI, and attempts to balance ischemic and bleeding events have led to further shortening of the duration of DAPT (15, 16). A recent meta-analysis with 24 randomized trials reported that extended-term (>12 months) DAPT was associated with a reduced risk of myocardial infarction and a higher risk of major bleeding in comparison with short-term (<6 months) or standard (6–12 months) DAPT (17). There was no significant difference in mortality between the patients with extended-term DAPT and those with short-term or standard DAPT (17). In this regard, the bleeding risk of individual patients, as well as ischemic risk, are taken into consideration for deciding the appropriate length of DAPT (18, 19).

DM is a well-recognized key risk factor for CAD and worse prognosis after PCI (8), which is responsible for systemic atherosclerotic change of the entire vascular structure (20). Therefore, management for DM includes multifactorial life style modification together with intensive medical intervention through glucose lowering agents, lipid-lowering agents, and blood pressure-lowering agents. Indeed, adequate control of DM through sodium-glucose cotransporter-2 inhibitor (21) or glucagon-like peptide-1 receptor agonists (22) are known to reduce the risk of ischemic stroke or cardiovascular death as well as recurrent myocardial infarction, implying that systemic treatment (drugs) rather than local treatment (PCI) is essential for management of diabetic patients with cardiovascular complications. Altered systemic metabolism in patients with DM is associated with hypercoagulability, endothelial dysfunction, and platelet activation, together resulting in a prothrombotic state (23) that possibly requires long-term anti-thrombotic therapy or a more potent $P2Y_{12}$ inhibitor. Furthermore, patients with DM have been reported to have a suboptimal response to aspirin or clopidogrel, probably due to the altered metabolic and pharmacokinetic profile (3, 24).

Despite the theoretical benefit of long-term DAPT in diabetic patients with DES implantation, to date, the clinical benefit of long-term DAPT in the era of next-generation DES has not been clearly demonstrated. At an individual patient-level

meta-analysis that compared the clinical outcome between short-term (<6 months) and standard (6–12 months) DAPT in patients with and without DM after DES implantation, standard DAPT resulted in an augmented risk of bleeding without significantly reducing the ischemic events (8). All-cause or cardiovascular mortality within 1 year after PCI were not different among patients treated with short-term or standard DAPT regardless of presence of DM (7). However, in a *post-hoc* analysis of a randomized DAPT trial that investigated the clinical outcome between 12 and 30 months DAPT after PCI, extended DAPT (30 months) was associated with reduced risk of recurrent myocardial infarction in diabetic patients (25). Another *post-hoc* analysis for a randomized DAPT trial identified DM as a significant predictor for future coronary thrombotic events, and DM was incorporated as one of the positive predictors that would benefit from extended DAPT (26). Compared to the present study, part of the study population included in previous randomized studies were patients treated with first-generation DES. The previous randomized studies did not include clinically very-high-risk patients who might be expected to show worse prognosis despite successful DES implantation during long-term follow-up (8, 25, 26). Therefore, the findings of previous studies might have difficulty representing the current situation in an era of next-generation DES. Additionally, in contrast to a previous meta-analysis report from randomized trials that have mostly investigated 1-year clinical outcomes after index PCI in diabetic patients (8), our nationwide cohort analysis investigated the clinical outcome between 1 and 3 years after next-generation DES implantation in diabetic patients. Given that DM is a long-lasting risk factor that continuously hampers prognosis after PCI (27), investigating the clinical impact of DAPT in this period could be of noteworthy importance. Furthermore, the DAPT trial investigated the clinical outcomes between 12 and 30 months DAPT after index PCI excluding the patients who experienced ischemic or bleeding events before 12 months after index PCI (28). Whereas, the present study included patients who were alive and had experienced ischemic or bleeding events within 1 year after PCI and were considered to harbor clinical or procedural risk factors for future hard events (all-cause or cardiovascular death) (29).

In general, prolonged DAPT after PCI is related to significantly increased risk of bleeding compared to short or standard DAPT (30). However, the results of this study demonstrated that the significant reduction of ischemic events by prolonged DAPT in diabetic patients led to favorable outcome including reduced mortality, overwhelming the numerically, but statistically not significant, increased bleeding events. Indeed, there is no obvious correlation between the diabetes and augmented bleeding risk by DAPT after PCI (31). Taken together, the findings indicate that, after DES implantation, prolonged DAPT could be further favored in diabetic patients, as compared with non-diabetic patients to alleviate the risk of recurrent ischemic events and consequent cardiovascular or all-cause mortality.

## Limitations

This study has several limitations. First, observational studies that evaluated the clinical impact of DAPT after PCI are possibly prone to immortal time bias, although we excluded those who died within 1 year after PCI. Second, clinical events that occurred early after PCI or the patient's own characteristics might have influenced the physician's decision for the duration of DAPT. In this regard, there could be persistent residual confounding factors, although we tried to minimize the bias using stabilized IPTW. Third, because the NHIS database does not routinely collect laboratory profiles, the level of glycosylated hemoglobin A1c that represents the severity of DM, was not included as a covariate for the stabilized IPTW model or Cox regression analysis. However, since the Korean health insurance system strictly regulates the use of oral hypoglycemic agent according to the level of glycosylated hemoglobin A1c, it is presumable that the imbalance of DM severity between the two groups would be limited as we defined DM according to the performance of treatment rather than the presence of diagnostic codes. Furthermore, laboratory information regarding platelet reactivity that could give explanation for the suboptimal outcome of diabetic patients after cessation of DAPT was not available. Fourth, contemporary bleeding classification system with prognostic impact [e.g. BARC (Bleeding Academic Research Consortium), TIMI (Thrombolysis in Myocardial Infarction), GUSTO (Global Use of Strategies to Open Occluded Arteries), etc] could not be applied due to limited information. Finally, the occurrence of stent thrombosis was also could not be investigated due to lack of angiographic information. Taken together, the results from this observational study should not be used to establish a causal relationship, until our findings are recapitulated by well-conducted randomized studies.

# Conclusions

In this nationwide cohort of patients treated with new-generation DES in Korea, prolonged DAPT rather than standard DAPT might be clinically beneficial in diabetic patients with DES implantation.

# Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The datasets generated for the analyses are not publicly available because of strict government restrictions.

Requests to access these datasets should be directed to mkhong61@yuhs.ac.

## Ethics statement

The studies involving human participants were reviewed and approved by Yonsei University Health System. The Ethics Committee waived the requirement of written informed consent for participation.

## Author contributions

S-JL, D-WC, C-MN, and M-KH contributed to the conception and design, verified the data, and conducted all analyses. S-JL and M-KH wrote the study protocol. D-WC and C-MN performed the programming to extract the data from the NHIS database. M-KH and C-MN had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have provided a critical review of the manuscript, read, and approved the final publication.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.954704/full#supplementary-material

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# CYP2C19 loss-of-function alleles predicts clinical outcomes in East Asian patients with acute myocardial infarction undergoing percutaneous coronary intervention and stenting receiving clopidogrel

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**Background:** CYP2C19 loss-of-function (LOF) alleles reduce the effectiveness of clopidogrel and are associated with high rates of clinical events in patients undergoing percutaneous coronary intervention (PCI) and stenting in Northeast Asians. However, the prevalence and influence of CYP2C19 LOF alleles in Southeast Asians remain unclear.

**Objectives:** This study aims to retrospectively investigate the prevalence of CYP2C19 LOF alleles and clinical outcomes in East Asian patients taking clopidogrel and undergoing PCI.

**Methods:** Between June 2019 and June 2020, volunteer participants in a single medical center were consecutively selected. The genetic data of CYP2C19 were derived from the Taiwan Precision Medicine Initiative (TPMI). Patients receiving clopidogrel while undergoing PCI with stenting were retrospectively analyzed.

**Results:** A total of 999 patients (62.4 ± 11.1 years old, 83.7% men) were enrolled; 39.3% without the CYP2C19 LOF allele (normal metabolizers + rapid metabolizers, NM + RM); 44.9% with one LOF allele (intermediate metabolizers, IM); 15.7% with two LOF alleles (poor metabolizers, PM). The incidence of stroke was higher in the PM subgroup compared to the NM + RM subgroup or IM subgroup in patients presenting with acute myocardial infarction (AMI). The 1-year major adverse cardiac and cerebrovascular events (MACCE)-free survival rates in all participants were similar among the three groups. However, in the AMI group, the 1-year MACCE-free survival rates were significantly lower in the PM subgroup compared to the NM + RM subgroup or IM subgroup.

**Conclusion:** In East Asians presenting with AMI, CYP2C19 PM was associated with deleterious cardiovascular outcomes and stroke. Our results reinforce the crucial role of preemptive CYP2C19 genotyping in East Asian AMI patients receiving clopidogrel treatment.

KEYWORDS

**clopidogrel, coronary artery disease, CYP2C19, dual antiplatelet therapy, P2Y12 inhibitors**

# Introduction

For patients with coronary artery disease who underwent percutaneous coronary intervention (PCI) and stenting, dual antiplatelet therapy (DAPT) is mandatory to prevent stent thrombosis and in-stent restenosis. Clopidogrel as an adjunct to aspirin therapy has been shown to reduce clinical cardiovascular ischemic events in patients with coronary stenting (1, 2). DAPT with aspirin and clopidogrel is used exclusively in patients with chronic coronary syndrome and in selected patients with acute coronary syndrome (3). However, the response to clopidogrel is variable among patients, and individuals with resistance to clopidogrel are at an increased risk of recurrent atherothrombotic events (4).

Clopidogrel is a prodrug of the thienopyridine class, which is sequentially converted to its active metabolite in the liver by two cytochrome P450 (CYP) isoenzymes that are encoded by polymorphic genes (5). Among these genes, carriers with at least one reduced function of the CYP2C19 alleles are associated with a consistent attenuation of pharmacokinetic and pharmacodynamic responses to clopidogrel (6). Furthermore, these patients have a higher rate of major adverse cardiovascular events, including stent thrombosis (6, 7).

In East Asian patients who are treated with clopidogrel after PCI, the response to clopidogrel is variable and controversial. The prevalence of CYP2C19 loss-of-function (LOF) alleles is substantially higher in East Asians, compared to patients from other geographic regions (8); thus, more East Asian patients have high on-treatment platelet reactivity. In contrast, East Asian patients have lower stent thrombosis and ischemic events than patients in other geographical regions. Some experts argue that the "therapeutic window" in East Asian patients could differ from that in patients of other ethnic groups (5).

This study was conducted with the aim to evaluate the CYP2C19 genotypes and the ischemic outcomes of post-PCI clopidogrel treatment in East Asian patients.

# Materials and methods

## Study population

Patients who visited outpatient clinics at Taichung Veterans General Hospital (TCVGH), a tertiary teaching hospital in central Taiwan, were invited to participate in the Taiwan Precision Medicine Initiative (TPMI), a nationwide genetic project led by Academia Sinica and partner hospitals. Blood samples from each participant in the TPMI were collected, and DNA was extracted and genotyped. The genetic profiles were linked to their electronic health records in TCVGH, including medical history, biochemical reports, and coronary artery angiography reports. The detailed process of data collection has been reported previously (9).

Between June 2019 and June 2020, TPMI participants from TCVGH who used clopidogrel for at least 4 weeks from the outpatient clinic and underwent PCI for coronary artery lesions in the setting of stable coronary artery disease or acute coronary syndrome were enrolled in this study. This study was conducted

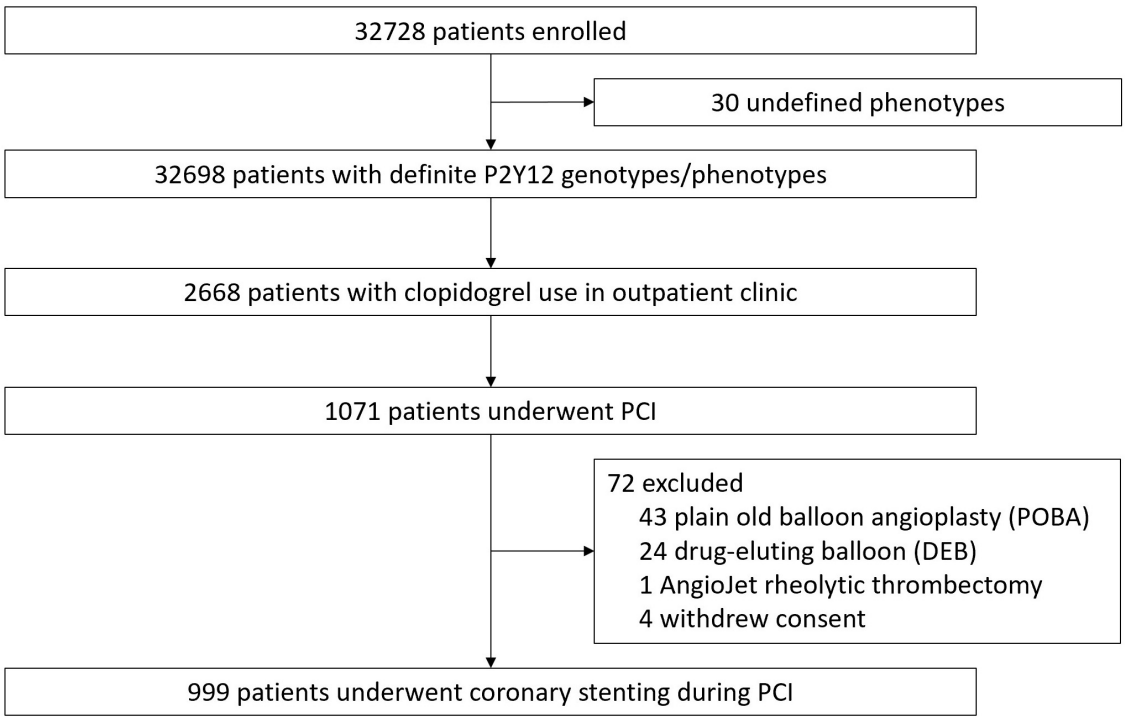


FIGURE 1
Flowchart of the enrollment process in the study.

in an all-comer design and patients with an undefined CYP2C19 phenotype were excluded. The study protocol was approved by the Institutional Review Board of TCVGH (CE20316A). Informed consents were obtained in accordance with the principles defined in the Declaration of Helsinki.

TABLE 1 Genotypes and phenotypes of the participants.

| Phenotype | Genotype | Number (%) |
|---|---|---|
| **Rapid metabolizer** | | **6 (0.6%)** |
| | *1/*17 | 6 (100%) |
| **Normal metabolizer** | | **387 (38.7%)** |
| | *1/*1 | 387 (100%) |
| **Intermediate metabolizer** | | **449 (44.9%)** |
| | *1/*2 | 397 (88.4%) |
| | *1/*3 | 48 (10.7%) |
| | *2/*17 | 4 (0.9%) |
| **Poor metabolizer** | | **157 (15.7%)** |
| | *2/*2 | 114 (72.6%) |
| | *2/*3 | 38 (24.2%) |
| | *2/*6 | 2 (1.3%) |
| | *3/*3 | 1 (0.6%) |
| | Novel* | 2 (1.3%) |

*Novel genotype: rs4244285 (*2) homozygous and rs72552267 (*6) heterozygous. The bold values means the number (%) of each phenotypes.

## Study endpoints

The endpoints of this study were a composite of major adverse cardiac and cerebrovascular events (MACCE) at 1 year, including non-fatal myocardial infarction, target vessel revascularization, stent thrombosis, or stroke.

## Genotyping and phenotyping of CYP2C19

The single-nucleotide polymorphism (SNP) array TWBv2 (Thermo Fisher Scientific, Inc., Santa Clara, CA, United States), which contains ∼415,000 markers for whole genome sequencing (WGS) and imputation, was designed for both genome-wide association studies (GWAS) and the test of known risk alleles. The high coverage, WGS data and genome-wide SNP data from large-scale Han Chinese ancestry using these custom arrays has been prescribed (10). We genotyped 32,728 participants in TPMI using the TWBv2 array; thirty of them who had an undefined CYP2C19 phenotype were excluded. The remaining 32,698 participants were classified according to CYP2C19 genotypes, including three variants known to have decreased CYP2C19 function [rs4244285 (*2), rs4986893 (*3) and rs72552267 (*6)], along with one variant with increased function [rs12248560 (*17)]. Subsequently,

TABLE 2 Baseline demographics of the participants.

| Variables | Total ($n$ = 999) | NM + RM ($n$ = 393) | IM ($n$ = 449) | PM ($n$ = 157) | *P-value* |
|---|---|---|---|---|---|
| Age, years, mean ± *SD* | 62.4 ± 11.1 | 62.8 ± 11.1 | 61.8 ± 11.1 | 63.0 ± 11.4 | 0.184 |
| Male, *n* (%) | 836 (83.7%) | 330 (84.0%) | 380 (84.6%) | 126 (80.3%) | 0.434 |
| BMI, kg/m$^2$, mean ± *SD* | 26.1 ± 3.6 | 26.2 ± 3.4 | 26.0 ± 3.7 | 26.5 ± 3.9 | 0.625 |
| Smoker, *n* (%) | 507 (50.8%) | 193 (49.1%) | 228 (50.8%) | 86 (54.8%) | 0.486 |
| Hypertension, *n* (%) | 844 (84.5%) | 335 (85.2%) | 371 (82.6%) | 138 (87.9%) | 0.253 |
| Diabetes mellitus, *n* (%) | 590 (59.1%) | 241 (61.3%) | 257 (57.2%) | 92 (58.6%) | 0.481 |
| Hyperlipidemia, *n* (%) | 844 (84.5%) | 335 (85.2%) | 377 (84.0%) | 132 (84.1%) | 0.867 |
| Heart failure, *n* (%) | 218 (21.8%) | 79 (20.1%) | 93 (20.7%) | 46 (29.3%) | 0.046* |
| PAD, *n* (%) | 44 (4.4%) | 19 (4.8%) | 17 (3.8%) | 8 (5.1%) | 0.684 |
| CKD, *n* (%) | 115 (11.5%) | 45 (11.5%) | 52 (11.6%) | 18 (10.5%) | 0.998 |
| **Presentation** | | | | | 0.310 |
| STEMI, *n* (%) | 126 (12.6%) | 49 (12.5%) | 57 (12.7%) | 20 (12.7%) | |
| Non-STEMI, *n* (%) | 101 (10.1%) | 25 (6.4%) | 56 (12.5%) | 20 (12.7%) | |
| Unstable angina, *n* (%) | 122 (12.2%) | 47 (12.0%) | 57 (12.7%) | 18 (11.5%) | |
| Stable angina, *n* (%) | 565 (56.6%) | 239 (60.8%) | 239 (53.2%) | 87 (55.4%) | |
| Ischemic CM, *n* (%) | 77 (7.7%) | 30 (7.6%) | 36 (8.0%) | 11 (7.0%) | |
| Other, *n* (%) | 8 (0.8%) | 3 (0.8%) | 4 (0.9%) | 1 (0.6%) | |
| Concomitant OAC, *n* (%) | 74 (7.4%) | 28 (7.1%) | 29 (6.5%) | 17 (10.8%) | 0.191 |

*$P$-values of the overall comparisons among the three groups. An unplanned post hoc pairwise multiple comparison showed no intergroup difference. BMI, body mass index; CKD, chronic kidney disease; CM, cardiomyopathy; IM, intermediate metabolizer; NM, normal metabolizer; non-STEMI, non-ST-elevation myocardial infarction; OAC, oral anticoagulant; PAD, peripheral arterial disease; PM, poor metabolizer; RM, rapid metabolizer; STEMI, ST-elevation myocardial infarction.

the phenotypes were defined according to the guidelines of the Clinical Pharmacogenetics Implementation Consortium (CPIC) (11, 12). Participants with one increased function and one normal function allele (*1/*17) were classified as rapid metabolizers (RM). Those who carried two wild-type alleles (*1/*1) were classified as normal metabolizers (NM). Those with one LOF allele and one normal function allele (*1/*2, *1/*3, *1/*6) were classified as intermediate metabolizers (IM), while those with two LOF alleles (*2/*2, *2/*3, *3/*3, *2/*6 *3/*6, *6/*6) were classified as poor metabolizers (PM).

## Baseline comorbidities and laboratory data collection

We extracted comorbidity data according to the international statistical classification of diseases and related health problems (ICD) 10th revision (ICD-10) and ICD-9 diagnostic codes from the electronic health records of TCVGH. Comorbidities of coronary artery disease (I20-I25/410-414), heart failure (I50.9/428), hypertension (I10-I13.2/401-404.93), diabetes mellitus (E08-E13/250), hyperlipidemia (E78.0-E78.5/414.00-414.05), stroke (I63/433.X1,434.X1), peripheral artery disease (I73/443.9), and chronic kidney disease (N18/585) were judged if the diagnostic codes (ICD-10 or ICD-9) presented at least twice in the medical records in the outpatient departments before index PCI. If the patient was hospitalized, the comorbidities were judged if the diagnostic codes presented once in the medical records during hospitalization before index PCI. The patients' hemoglobin level, lipid profile, HbA1C level, and serum creatinine level as well as peak values of cardiac enzymes were collected from the electronic health records.

## Statistical analysis

Continuous variables were expressed as mean ± standard deviation if they were normally distributed in the Kolmogorov–Smirnov test. Categorical variables were expressed as numbers and percentages. The intergroup differences in continuous variables were analyzed using the non-parametric Mann–Whitney $U$-test or the Kruskal–Wallis test. Differences in categorical variables were analyzed using the chi-square test or Fisher's exact test. Multivariate Cox regression analysis was performed to identify independent predictors of MACCE at 1 year with the adjustment for variables with $p$-values $< 0.05$ in the univariate analysis. Two-tailed $p$-values $< 0.05$ were considered statistically significant. Kaplan-Meier survival analysis was used to compare MACCE-free survival among participants with different CYP2C19 phenotypes. All statistical analyzes were performed using IBM

TABLE 3 Baseline laboratory and angiographic characteristics.

| Variables | Total ($n$ = 999) | NM + RM ($n$ = 393) | IM ($n$ = 449) | PM ($n$ = 157) | *P-value* |
|---|---|---|---|---|---|
| Hb (g/dL), mean ± *SD* | 13.5 ± 2.0 | 13.5 ± 2.0 | 13.5 ± 2.0 | 13.3 ± 1.9 | 0.464 |
| HbA1C (%), mean ± *SD* | 6.6 ± 1.4 | 6.5 ± 1.4 | 6.5 ± 1.4 | 6.7 ± 1.4 | 0.226 |
| Cholesterol (mg/dL), mean ± *SD* | 166.0 ± 41.2 | 167.5 ± 44.8 | 163.3 ± 37.6 | 170.2 ± 41.7 | 0.215 |
| LDL (mg/dL), mean ± *SD* | 99.4 ± 35.5 | 100.3 ± 37.8 | 98.0 ± 34.4 | 100.9 ± 33.0 | 0.555 |
| HDL (mg/dL), mean ± *SD* | 42.5 ± 11.0 | 42.6 ± 11.1 | 42.1 ± 10.5 | 43.7 ± 12.0 | 0.570 |
| TG (mg/dL), mean ± *SD* | 149.2 ± 107.4 | 145.9 ± 100.1 | 150.2 ± 110.0 | 154.5 ± 117.6 | 0.969 |
| eGFR (mL/min/1.73m$^2$), mean ± *SD* | 74.7 ± 31.0 | 74.1 ± 28.2 | 76.2 ± 32.4 | 72.2 ± 33.4 | 0.276 |
| CK (U/L), mean ± *SD* | 493.1 ± 1037.8 | 483.3 ± 936.9 | 467.7 ± 966.6 | 584.0 ± 1385.7 | 0.878 |
| CK-MB (U/L), mean ± *SD* | 21.3 ± 46.7 | 22.8 ± 44.4 | 19.5 ± 41.4 | 23.1 ± 63.0 | 0.720 |
| Troponin T (ng/mL), mean ± *SD* | 217.0 ± 960.9 | 362.5 ± 1390.9 | 155.6 ± 665.3 | 79.9 ± 215.4 | 0.801 |
| Troponin I (ng/mL), mean ± *SD* | 9.0 ± 23.9 | 9.2 ± 22.1 | 8.2 ± 23.4 | 11.3 ± 29.6 | 0.707 |
| **CAD numbers, *n* (%)** | | | | | 0.180 |
| One | 478 (47.9%) | 186 (47.3%) | 208 (46.3%) | 84 (53.5%) | |
| Two | 331 (33.1%) | 130 (33.1%) | 147 (32.7%) | 54 (34.4%) | |
| Three | 190 (19.0%) | 77 (19.6%) | 94 (20.9%) | 19 (12.1%) | |
| **Artery involved, *n* (%)** | | | | | |
| LM | 63 (6.3%) | 24 (6.1%) | 29 (6.5%) | 10 (6.4%) | 0.978 |
| LAD | 744 (74.5%) | 292 (74.4%) | 346 (77.1%) | 106 (67.5%) | 0.061 |
| RCA | 501 (50.2%) | 206 (52.4%) | 219 (48.8%) | 76 (48.4%) | 0.512 |
| LCX | 452 (45.3%) | 171 (43.5%) | 217 (48.3%) | 64 (40.8%) | 0.176 |
| DEB | 34 (3.4%) | 9 (2.3%) | 21 (4.7%) | 4 (2.6%) | 0.132 |
| BMS | 255 (25.5%) | 88 (22.4%) | 122 (27.2%) | 45 (28.7%) | 0.175 |
| BVS | 16 (1.6%) | 4 (1.0%) | 10 (2.2%) | 2 (1.3%) | 0.355 |
| DES-1st generation | 66 (6.6%) | 31 (7.9%) | 23 (5.1%) | 12 (7.6%) | 0.232 |
| DES-2nd generation | 703 (70.4%) | 287 (73.0%) | 311 (69.3%) | 105 (66.9%) | 0.285 |

BMS, bare metal stent; BVS, bioresorbable vascular scaffold; CAD, coronary artery disease; CK, creatine kinase; CK-MB, creatine kinase-MB isoenzyme; DEB, drug-eluting balloon; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; IM, intermediate metabolizer; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; LAD, left anterior descending artery; LCX, left circumflex artery; LDL, low-density lipoprotein; LM, left main coronary artery; NM, normal metabolizer; PM, poor metabolizer; RCA, right coronary artery; RM, rapid metabolizer; TG, triglyceride.

SPSS statistical software for Windows, version 22.0 (IBM corp., Armonk, NY, United States).

# Results

## Genotypes and phenotypes of CYP2C19

The summarized study flow is illustrated in **Figure 1**. During the study period, a total of 32,698 participants were successfully genotyped for the CYP2C19 gene. Among them, 1,071 clopidogrel users underwent PCI at our institute. Those patients who were treated without stenting were excluded, including 43 patients undergoing plain old balloon angioplasty (POBA), 24 patients undergoing drug-eluting balloon, as well as one patient undergoing AngioJet Rheolytic Thrombectomy (Boston Scientific, Marlborough, MA, United States) as a bailout procedure for a large thrombus burden. During follow-up, four patients requested to withdraw from the study. A total of 999 patients (62.4 ± 11.1 years old, 83.7% men) were enrolled. The details of the genotypes and phenotypes are presented in **Table 1**. Patients without the CYP2C19 LOF allele (normal metabolizers + rapid metabolizers, NM + RM) accounted for 39.3%, those with one LOF allele (intermediate metabolizers, IM) accounted for 44.9% and those with two LOF alleles (poor metabolizers, PM) accounted for 15.7% of the study population.

## Baseline demographic characteristics

The baseline demographic characteristics of the participants are shown in **Table 2**. In this study, 84.5% of the patients had hypertension, 59.1% had diabetes mellitus, and 21.8% had heart failure. Nearly one third of the participants underwent PCI in the setting of acute coronary syndrome (12.6% STEMI, 10.1% non-STEMI and 12.2% unstable angina). The baseline comorbidities and presentations were similar among the three groups

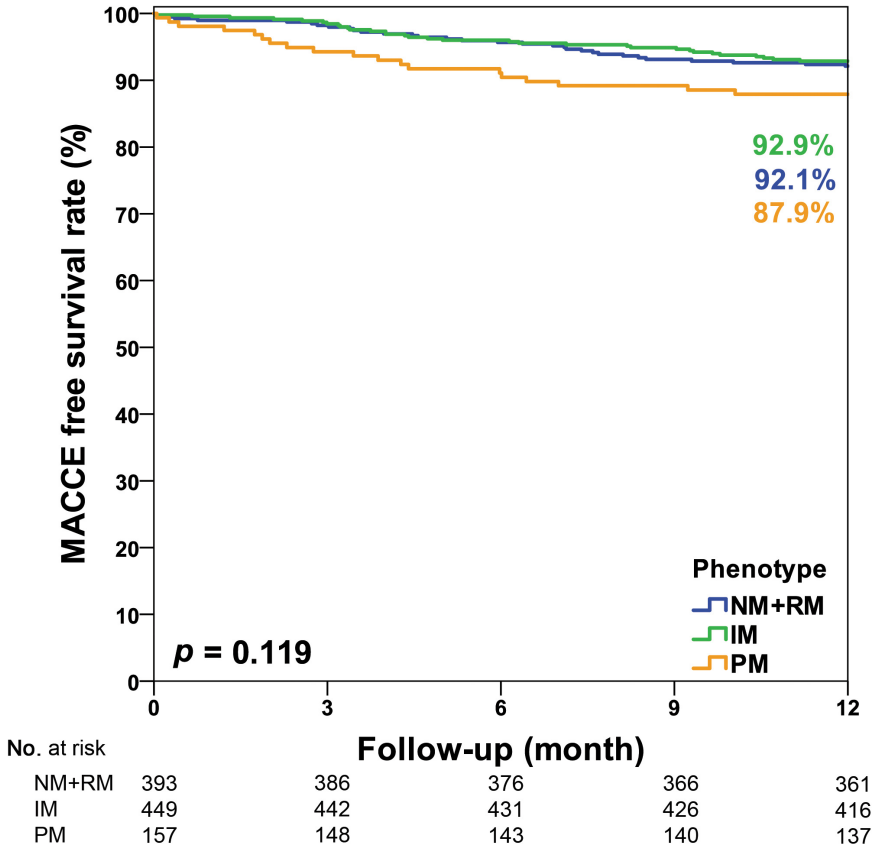


FIGURE 2
Kaplan–Meier curve of the cumulative incidence of major adverse cardiovascular and cerebrovascular events (MACCE) at the 1-year follow-up stratified based on the CYP2C19 phenotype of all study participants. IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer.

## Baseline laboratory and angiographic characteristics

The baseline laboratory and angiographic characteristics of the participants are shown in Table 3. In this study, half of the participants had multivessel disease (52.1%), 74.5% of the patients had LAD involvement, and 70.4% of the patients were treated with second-generation DES. In general, all three groups had similar baseline hemoglobin, lipid profile, HbA1C, renal function, peak values of cardiac enzymes, as well as angiographic characteristics.

## Clinical outcomes of the whole cohort and of the acute myocardial infarction group

In this study, CYP2C19 phenotypes were not associated with 1-year MACCE-free survival among all participants (NM + RM: 92.9% vs. IM: 92.1% vs. PM: 87.9%, $p = 0.119$, Figure 2). In the acute myocardial infarction (AMI) subgroup, we observed a significant association of CYP2C19 phenotypes and 1-year MACCE-free survival (NM + RM: 94.6% vs. IM: 91.2% vs. PM: 77.5%, $p = 0.007$, Figure 3). The incidence of stroke was higher in the PM subgroup compared to the NM + RM subgroup or the IM subgroup (PM group 5.0% vs. NM + RM group 0% vs. IM group 0%, $p = 0.009$). No intergroup differences were found with regard to non-fatal myocardial infarction, target vessel revascularization, stent thrombosis, and coronary artery bypass graft (Table 4).

## Multivariate logistic regression analyses for the 1-year major adverse cardiac and cerebrovascular events

Multivariate analysis identified independent predictors for MACCE at the 1-year follow-up as follows: left main lesion (HR: 2.69; 95% CI: 1.42–5.10; $p = 0.002$), drug-eluting balloon (HR: 2.61; 95% CI: 1.13–6.00; $p = 0.024$), and bare metal stent (HR: 2.85; 95% CI: 1.84–4.42; $p < 0.001$) (Table 5). In the

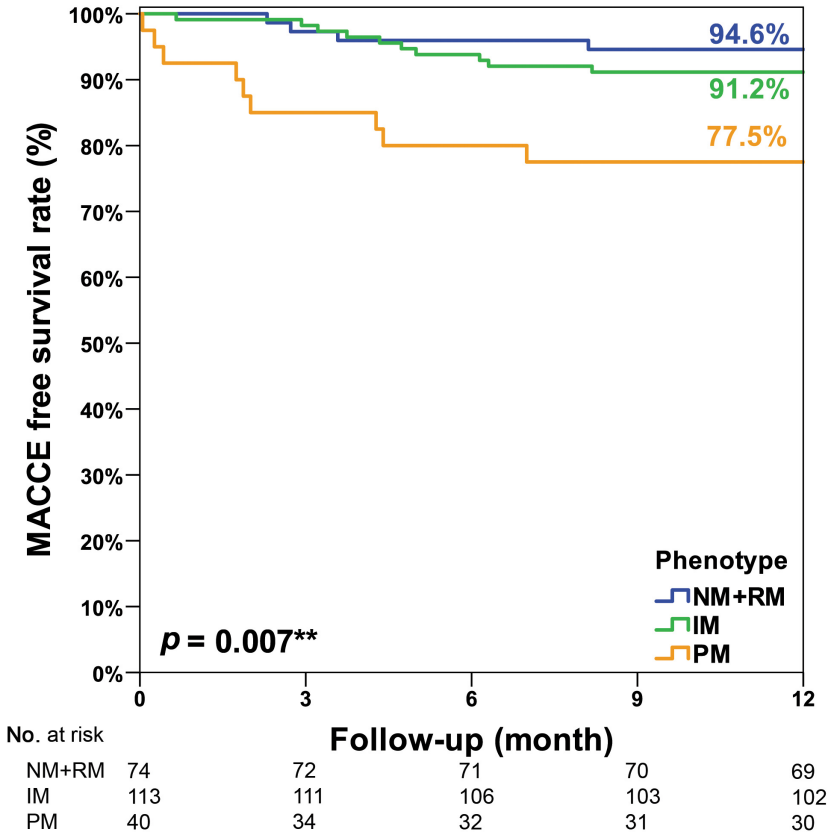


FIGURE 3
Kaplan–Meier curve of the cumulative incidence of major adverse cardiovascular and cerebrovascular events (MACCE) at the 1-year follow-up stratified based on the CYP2C19 phenotype of the AMI subgroup. An unplanned *post hoc* pairwise multiple comparison showed that there were significantly less MACCE in the NM + RM group than in the PM group ($p$ = 0.005). There were significantly less MACCE in the IM group than in the PM group ($p$ = 0.016). However, there was no intergroup difference between the NM + RM group and the IM group ($p$ = 0.393). IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer. **Means statistically significant.

AMI subgroup, CYP2C19 PM (compared to NM + RM; HR: 4.01; 95% CI: 1.18–13.64; $p$ = 0.026) were associated with a markedly increased risk of MACCE at 1 year. Triple-vessel disease (compared to single-vessel disease; HR: 3.10; 95% CI: 1.04–9.28; $p$ = 0.042) and bare-metal stent (HR: 2.55; 95% CI: 1.08–6.04; $p$ = 0.033) were other predictors of the 1-year MACCE (**Table 5**).

## Discussion

Our retrospective study demonstrated several important findings regarding the prevalence and ischemic outcomes among patients receiving clopidogrel after PCI in East Asians: (1) The prevalence of CYP2C19 LOF was high. Approximately 45% of the participants had one LOF allele (IM) and 16% of the participants had two LOF alleles (PM); (2) The 1-year MACCE-free survival rates were similar in the PM group compared to the NM + RM group or IM group; (3) In patients with AMI, the 1-year MACCE rates as well as the incidence of stroke, were significantly higher in the PM subgroup compared to the NM + RM subgroup or IM subgroup; (4) CYP2C19 poor metabolizer was a strong predictor for MACCE in patients presenting with AMI. In summary, our results supported the hypothesis that carrying the CYP2C19 LOF alleles exhibits a significant association with adverse cardiovascular outcomes in East Asians using clopidogrel after PCI in AMI.

The prevalence of CYP2C19 LOF alleles (IM and PM) accounted for one third of the cohorts in Italy (13) and nearly 30% of those in the United States (8). Patients with two LOF alleles (PM) only represented less than 5% of the Western population (8, 13). However, Asian populations had a substantially higher prevalence of carriers of CYP2C19 LOF, representing 60–65% of all patients with 10–15% harboring two LOF alleles (8). Nearly 60% of the patients in our cohort had LOF alleles (IM and PM), and 16% harboring two LOF alleles (PM), in line with Asian and Taiwanese populations (9, 10, 14, 15). Therefore, the clinical outcomes in Asians might be different from those of the western population due to the high prevalence of CYP2C19 LOF.

TABLE 4 Clinical outcomes of all participants and of the AMI subgroup.

**All participants (*n* = 999)**

| Variables | Total (*n* = 999) | NM + RM (*n* = 393) | IM (*n* = 449) | PM (*n* = 157) | *P-value* |
|---|---|---|---|---|---|
| MACCE | 82 (8.2%) | 31 (7.9%) | 32 (7.1%) | 19 (12.1%) | 0.142 |
| Non-fatal MI* | 3 (0.3%) | 1 (0.3%) | 0 | 2 (1.3%) | 0.042 |
| TVR | 68 (6.8%) | 25 (6.4%) | 30 (6.7%) | 13 (8.3%) | 0.715 |
| Sent thrombosis | 2 (0.2%) | 1 (0.3%) | 0 | 1 (0.6%) | 0.293 |
| CABG | 4 (0.4%) | 1 (0.3%) | 1 (0.2%) | 2 (1.3%) | 0.168 |
| Stroke | 10 (1.0%) | 6 (1.5%) | 1 (0.2%) | 3 (1.9%) | 0.076 |
| **AMI subgroup (*n* = 227)** | | | | | |
| **Variables** | **Total (*n* = 227)** | **NM + RM (*n* = 74)** | **IM (*n* = 113)** | **PM (*n* = 40)** | ***P-value*** |
| MACCE† | 23 (10.1%) | 4 (5.4%) | 10 (8.9%) | 9 (22.5%) | 0.013 |
| Non-fatal MI | 1 (0.4%) | 1 (1.4%) | 0 | 0 | 0.354 |
| TVR | 20 (8.8%) | 4 (5.4%) | 9 (8.0%) | 7 (17.5%) | 0.085 |
| Sent thrombosis | 1 (0.4%) | 0 | 0 | 1 (2.5%) | 0.096 |
| CABG | 3 (1.3%) | 1 (1.4%) | 1 (0.9%) | 1 (2.5%) | 0.744 |
| Stroke‡ | 2 (0.9%) | 0 | 0 | 2 (5.0%) | 0.009 |

Data are presented as number with percentage. *P-values of the overall comparisons among the three groups. An unplanned post hoc, pairwise multiple comparison showed no intergroup difference. †P-values of the overall comparisons among the three groups. An unplanned post hoc pairwise multiple comparison showed that there were significantly less major adverse cardiovascular and cerebrovascular events in the NM + RM group than in the PM group (p = 0.033). ‡P-values of the overall comparisons among the three groups. An unplanned post hoc, pairwise multiple comparison showed no intergroup difference. CABG, coronary artery bypass graft; IM, intermediate metabolizer; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; TVR, target vessel revascularization.

TABLE 5 Predictors of major adverse cardiovascular and cerebrovascular events (MACCE) during 1-year follow-up in all participants (*n* = 999) and in the AMI subgroup.

**All participants (*n* = 999)**

| Predictors | Unadjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *P-value* |
|---|---|---|---|---|
| **Phenotype** | | | | |
| NM + RM | Reference | | | |
| IM | 0.90 (0.55–1.47) | 0.674 | | |
| PM | 1.60 (0.90–2.83) | 0.108 | | |
| **CAD number** | | | | |
| One | Reference | | | |
| Two | 1.59 (0.94–2.68) | 0.083 | | |
| Three | 2.54 (1.48–4.34) | 0.001 | | |
| **LM** | 2.38 (1.26–4.49) | 0.007 | 2.69 (1.42–5.10) | 0.002 |
| **DEB** | 2.37 (1.03–5.45) | 0.041 | 2.61 (1.13–6.00) | 0.024 |
| **BMS** | 2.66 (1.72–4.10) | <0.001 | 2.85 (1.84–4.42) | <0.001 |
| **AMI subgroup (*n* = 227)** | | | | |
| **Predictors** | **Unadjusted HR (95% CI)** | ***p*-value** | **Adjusted HR (95% CI)** | ***P-value*** |
| **Phenotype** | | | | |
| NM + RM | Reference | | Reference | |
| IM | 1.65 (0.52–5.26) | 0.398 | 1.44 (0.44–4.67) | 0.543 |
| PM | 4.75 (1.46–15.44) | 0.010 | 4.01 (1.18–13.64) | 0.026 |
| **CAD number** | | | | |
| One | Reference | | Reference | |
| Two | 3.41 (1.24–9.39) | 0.017 | 2.60 (0.93–7.32) | 0.069 |
| Three | 3.10 (1.04–9.23) | 0.042 | 3.10 (1.04–9.28) | 0.042 |
| **BMS** | 2.88 (1.22–6.80) | 0.016 | 2.55 (1.08–6.04) | 0.033 |

BMS, bare metal stent; CAD, coronary artery disease; DEB, drug-eluting balloon; IM, intermediate metabolizer; LM, left main artery; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer.

A meta-analysis showed that CYP2C19 LOF carriers had a higher association with adverse cardiovascular outcomes in Asian populations using clopidogrel after PCI (16). Analysis of stent thrombosis outcomes supported differences in the effect size of CYP2C19 LOF allele carriers between Asian (RR 4.88) and white populations (RR of 1.73) (16). In our study, the 1-year MACCE-free survival rates in patients with AMI were also significantly lower in the PM subgroup compared to the IM subgroup or the NM + RM subgroup. However, the 1-year MACCE-free survival rates were only numerically, but not statistically significantly, lower in the PM group in the overall cohort. Other studies from East Asia also indicated increased MACE events in CYP2C19 PM in the setting of AMI but not in the setting of stable angina. Kim et al. reported that the poor metabolizer was significantly associated with a higher risk of MACCE in patients with AMI in Korea (hazard ratio, 2.88; 95% confidence interval, 1.27–6.53; $p = 0.011$). However, this finding was not observed in patients with stable angina (17). From a single center in Japan, in the ACS group, cardiovascular events were higher in carriers of the LOF allele (24.6%) vs. non-carriers (11.1%, $p < 0.05$), but such difference was not observed in the stable angina group (carriers: 14.8%; non-carriers: 7.9%, $p = 0.078$) (18). Another study in China that included only ACS patients showed that the carriage of two CYP2C19 LOF alleles was significantly associated with an increased risk of adverse ischemic events at 1-year follow-up (19). Our results are consistent with these studies in Northeast Asia and demonstrate the impact of CYP2C19 LOF alleles in patients with AMI.

The relationship between CYP2C19 LOF alleles in patients with AMI using clopidogrel and clinical events has been studied in Northeast Asia, whereas studies in Southeast Asia are limited (20, 21). In Taiwan, although the location was near northeast Asian, the island of Southeast Asia (ISEA) ancestry was one of the major genetic ancestries in Taiwan. Lo et al. identified considerable proportions of ISEA ancestry (also carried by many Austronesian speaking populations) in most Taiwanese Han individuals (average 15%, range 0.1–62%) (22). Our result addresses the knowledge gap for patients in Southeast Asia with CYP2C19 LOF alleles using clopidogrel after PCI. The results are consistent with the Singapore cohort (21), which revealed that LOF patients were significantly more likely to experience MACE compared to non-LOF subjects in acute coronary syndrome (8.0 vs. 5.4%, $p = 0.041$). In patients without ACS, another smaller cohort in Malaysia recruited patients who underwent elective PCI (20). The results showed that the presence of the CYP2C19*2 polymorphism was not significantly associated with 1-year MACE after the implantation of DES. Similar results were obtained in our group in the setting without AMI. Our study, the largest cohort in Southeast Asians with nearly 1,000 patients, had approximately four times the number of previous Singapore and Malaysian cohorts. All these studies highlighted the crucial rule of CYP2C19 LOF alleles in Southeast Asians with AMI, but not in patients with stable angina undergoing elective PCI.

In patients with ACS undergoing PCI, current guidelines recommend potent P2Y12 inhibitors, namely ticagrelor or prasugrel, in preference to clopidogrel to reduce ischemic events, including stent thrombosis (3, 23, 24). However, these potent P2Y12 inhibitors lead to more bleeding events. In selected patients with high bleeding risks, some experts suggest de-escalation of potent P2Y12 receptor inhibitors to clopidogrel, either based on clinical judgment, platelet function testing or CYP2C19 genotyping (24). Recently, the TALOS-AMI study found that in Korean patients with AMI after index PCI, a uniform unguided de-escalation strategy switching from ticagrelor to clopidogrel after 1 month significantly reduced the risk of net clinical events up to 12 months, mainly by reducing bleeding events. However, given the high prevalence of the CYP2C19 LOF allele in East Asians, as the well as the high rates of 1-year MACCE in patients carrying the CYP2C19 LOF allele after PCI in AMI, we believe that the unguided de-escalation approach in the TALOS-AMI study should be applied cautiously in East Asians. The results of this study are in agreement with the findings of recent meta-analyses which demonstrated that guided de-escalation of P2Y12 inhibitors reduces bleeding without any trade-off in ischemic events (25–27).

## Study limitations

Our study had several limitations. First, the retrospective study design was inevitably associated with selection bias and other confounding factors. Some critical parameters, such as coronary artery complexity, detailed analysis of antiplatelet duration, and concomitant use of anticoagulant, might not be collected completely in every patient and utilized for outcome analysis. Second, the enrollment of consecutive all-comers after different types of stents, including bare-metal stents, drug-eluting stents and bioresorbable vascular scaffolds, might influence the clinical results. However, this allowed us to investigate the associations of CYP2C19 LOF in patients after PCI taking clopidogrel in a real-world setting. Not surprisingly, the multivariate analysis in our study identified bare-metal stent as independent factors for MACCE both in overall cohort and in the AMI subgroup. However, poor metabolizer was the strongest independent predictor of 1-year MACCE in patients with AMI, which implies the importance of CYP2C19 genotyping in AMI patients. Third, our study focused on the influence of the CYP2C19 genotype. Platelet function tests were not included in the analysis of this study. Fourth, although our study demonstrated that CYP2C19 PM were associated with high 1-year MACCE in AMI, large-scale studies are still warranted to find the pragmatic approach in clinical practice of genotype-guided de-escalation of P2Y12 inhibitors in East Asians.

## Conclusion

In East Asians with AMI, the 1-year MACCE rates, as well as the incidence of stroke, were significantly higher in the CYP2C19 PM subgroup. Poor metabolizer of CYP2C19 was the strongest independent predictor of 1-year MACCE in patients with AMI. These results reinforce the crucial role of CYP2C19 genotyping in East Asian AMI patients receiving clopidogrel therapy.

## Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of TCVGH (CE20316A). The patients/participants provided their written informed consent to participate in this study.

## Author contributions

Y-WC, Y-JL, W-CC, and Y-MC contributed to the conception and design of the study. Y-WC, Y-JL, W-CC, T-HH, C-HL, and Y-MC contributed to the data collection. C-YH analyzed and interpreted the data. Y-WC drafted the report, which was critically revised for important intellectual content by T-JL, W-LL, and Y-MC. All authors have participated in the work, reviewed and agreed with the content of the article, and approved the final version of the report.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Evaluation of race and ethnicity disparities in outcome studies of *CYP2C19* genotype-guided antiplatelet therapy

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Dual antiplatelet therapy with a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor) and aspirin remains the standard of care for all patients undergoing percutaneous coronary intervention (PCI). It is well-established that patients carrying *CYP2C19* no function alleles have impaired capacity to convert clopidogrel into its active metabolite and thus, are at higher risk of major adverse cardiovascular events (MACE). The metabolism and clinical effectiveness of prasugrel and ticagrelor are not affected by *CYP2C19* genotype, and accumulating evidence from multiple randomized and observational studies demonstrates that *CYP2C19* genotype-guided antiplatelet therapy following PCI improves clinical outcomes. However, most antiplatelet pharmacogenomic outcome studies to date have lacked racial and ethnic diversity. In this review, we will (1) summarize current guideline recommendations and clinical outcome evidence related to *CYP2C19* genotype-guided antiplatelet therapy, (2) evaluate the presence of potential racial and ethnic disparities in the major outcome studies supporting current genotype-guided antiplatelet therapy recommendations, and (3) identify remaining knowledge gaps and future research directions necessary to advance implementation of this precision medicine strategy for dual antiplatelet therapy in diverse, real-world clinical settings.

KEYWORDS

**cytochrome P450 (CYP), precision medicine, clopidogrel, pharmacogenomics, race and ethnicity**

Abbreviations: PCI, percutaneous coronary intervention; MACE, major adverse cardiovascular events; ACS, acute coronary syndrome; CPIC, Clinical Pharmacogenetics Implementation Consortium; IM, Intermediate metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer; CDER, Center for Drug Evaluation and Research; ADP, adenosine diphosphate; STEMI, ST segment elevation myocardial infarction.

## Introduction

Cardiovascular disease, including coronary artery disease and stroke, remains among the leading cause of death in the United States (U.S.) and worldwide (1). In the U.S., the percentage of all deaths caused by cardiovascular disease in 2019 was approximately 32% in Black, 28% in Hispanic, and 30% in White individuals (1). Although significant advances in the diagnosis and treatment of cardiovascular disease have occurred over the past several decades, racial and ethnic disparities in cardiovascular disease prevalence and mortality continue to persist between White populations and both Black and Hispanic populations (2–4).

Racial and ethnic minority groups remain underrepresented in cardiovascular clinical trials, which has contributed to an incomplete understanding of these health disparities (5). According to the U.S. Food and Drug Administration's Center for Drug Evaluation and Research (CDER), of the 58,998 participants who participated in FDA registered cardiovascular trials from 2015 to 2016, only about 3% identified as Black or African American and about 8.5% identified as Hispanic (6). Lack of diversity in clinical trials results in lack of adequate data to rigorously evaluate the safety and efficacy of therapeutic interventions within underrepresented racial and ethnic minority groups (5). Diverse racial and ethnic representation is crucial for demonstrating generalizability of clinical trial results to more diverse real-world clinical settings, and to ensure equity when developing therapeutic recommendations.

A notable example of this lack of diversity is in the evaluation of therapeutics following percutaneous coronary intervention (PCI). A recent meta-analysis of 10 randomized coronary stent clinical trials reported that Black and Hispanic patients constituted only 4 and 2%, respectively, of the enrolled participants (7). However, Black patients (23.9%) and Hispanic patients (21.5%) had a higher 5-year risk for MACE when compared to White patients (18.8%) (7). The significant under representation of Black, Hispanic, and other minority participants has also been evident in clinical studies of antiplatelet therapy in patients undergoing PCI.

The standard of care in patients undergoing PCI is dual antiplatelet therapy with a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor) and aspirin to prevent major adverse cardiovascular events (MACE) such as death, stent thrombosis, myocardial infarction (MI), and stroke (8). Prasugrel and ticagrelor have shown superior efficacy compared to clopidogrel in clinical trials of acute coronary syndrome (ACS) patients in which the majority of patients underwent PCI; however, these alternative agents are more expensive and associated with higher bleeding risk and discontinuation rates compared to clopidogrel (9–11). Although clinical guidelines recommend use of prasugrel or ticagrelor over clopidogrel in ACS patients undergoing PCI, based on clinical trial results, clopidogrel remains the most widely prescribed $P2Y_{12}$ inhibitor in clinical practice (8, 11).

Clopidogrel is a prodrug that requires bioactivation by the CYP2C19 enzyme into its active metabolite. It is well established that *CYP2C19* no function alleles result in an impaired capacity to convert clopidogrel into its active metabolite and diminished inhibition of platelet reactivity (12). Thus, clopidogrel-treated patients who carry one or two *CYP2C19* no function alleles are at higher risk of MACE after PCI (13). In contrast, prasugrel and ticagrelor clinical response is not affected by *CYP2C19* genotype (14, 15). Accumulating evidence from multiple randomized and observational studies has demonstrated that *CYP2C19* genotype guided antiplatelet therapy following PCI improves clinical outcomes (12, 16). Although use of *CYP2C19* genotype to guide antiplatelet therapy selection has not been widely adopted, an increasing number of institutions have implemented this precision medicine strategy into clinical practice (17, 18). However, most pharmacogenomic studies evaluating *CYP2C19* genotype associations with clopidogrel response and clinical outcomes of genotype-guided antiplatelet therapy to date have lacked racial and ethnic diversity.

In this review, we will (1) summarize current guideline recommendations and clinical outcome evidence related to *CYP2C19* genotype-guided antiplatelet therapy, with a particular focus on ACS/PCI patients, (2) evaluate the presence of potential racial and ethnic disparities in the major outcome studies supporting current genotype-guided antiplatelet therapy recommendations, and (3) identify remaining knowledge gaps and future research directions necessary to advance implementation of precision medicine for dual antiplatelet therapy in diverse, real-world clinical settings.

## $P2Y_{12}$ inhibitor overview

Clopidogrel is a thienopyridine prodrug that requires hepatic biotransformation by CYP enzymes to generate an active metabolite, which irreversibly inhibits the adenosine diphosphate (ADP) $P2Y_{12}$ receptor. Approximately 85% of clopidogrel is hydrolyzed by carboxylesterase-1, leaving 15% available for active metabolite formation by CYP2C19 and other CYP isoforms. Prasugrel is also a thienopyridine prodrug. However, in contrast to clopidogrel, prasugrel undergoes bioactivation by CYP3A4 and CYP2B6, and to a lesser extent by CYP2C19 (16). Ticagrelor, a cyclopentyl-triazolopyrimidine, is a reversible and non-competitive $P2Y_{12}$ inhibitor that is bioactive and also metabolized by CYP3A4 into an active metabolite (16).

Overall, prasugrel and ticagrelor exhibit more predictable and consistent antiplatelet effect compared with clopidogrel (9, 10). In the Trial to Assess Improvement in Therapeutic

Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38 and Study of Platelet Inhibition and Patient Outcomes (PLATO) randomized clinical trials, prasugrel and ticagrelor displayed superior efficacy compared to clopidogrel in acute coronary syndrome (ACS) patients in the absence of *CYP2C19* genotyping; however, these agents were associated with increased bleeding risk (9, 10). Of note, approximately 92% of participants in the PLATO and TRITON-TIMI 38 trials were White; therefore, it remains unknown whether the clinical benefit of these agents also extend to underrepresented minority populations.

According to current clinical guidelines, prasugrel or ticagrelor is recommended over clopidogrel in ACS patients undergoing PCI based on data from these comparative trials with clopidogrel (8). Although use of prasugrel and ticagrelor has increased substantially over the past decade, clopidogrel remains the most widely prescribed $P2Y_{12}$ inhibitor in clinical practice (8, 11). A retrospective national cohort study evaluated the prescribing patterns of $P2Y_{12}$ inhibitors in patients who underwent PCI between 2008 and 2016 and found that approximately 74% patients filled a prescription for clopidogrel and approximately 25% of patients filled a prescription for prasugrel or ticagrelor (11). Evaluation of the demographic data from the study found that use of clopidogrel was similarly high in White patients (74%), Black patients (77%), and Hispanic patients (76%), and slightly lower in Asian patients (69%) (11). Therefore, clopidogrel remains the most common $P2Y_{12}$ inhibitor prescribed, irrespective of race and ethnicity (11). Several more recent studies among ACS patients have reported higher use of alternative therapies in White patients compared to non-White patients (19, 20). For instance, Hispanic ethnicity was found to be independently associated with the initiation of clopidogrel compared to prasugrel or ticagrelor among ACS patients (20).

Patient demographics and socioeconomic characteristics can influence medication adherence. Overall, prasugrel and ticagrelor are associated with lower medication adherence rates when compared to patients who are prescribed clopidogrel after PCI (11), which may be related to higher rates of minor bleeding and other factors such as cost and ticagrelor-associated dyspnea and twice daily dosing. Although prasugrel is available generically, clopidogrel prescription costs remain lower. Ticagrelor remains patent restricted and has the highest costs. A study also found that non-White race and residence in lower income communities were associated with lower $P2Y_{12}$ inhibitor adherence rates (11). Additionally, Black race, Asian race, and Hispanic ethnicity were associated with significantly lower $P2Y_{12}$ inhibitor adherence over 6 months following PCI for ACS patients (20). Taken together, these studies illustrate that race and ethnicity are associated with $P2Y_{12}$ inhibitor prescribing and adherence in clinical practice.

## Overview of *CYP2C19* genotype and response to $P2Y_{12}$ inhibitors

It is well established that substantial interpatient variability in CYP2C19 metabolism can be attributed to genetic polymorphisms in *CYP2C19* (12). Three alleles account for the majority of *CYP2C19* genetic variation across populations. *CYP2C19*2* (rs4244285, c861G > A) and *CYP2C19*3* (rs4986893, c.636G > A) are no function alleles that result in a metabolically inactive CYP2C19 protein, and *CYP2C19*17* (rs12248560, -806C > T) is an increased function allele that increases enzyme expression (12). As defined by the Clinical Pharmacogenetics Implementation Consortium (CPIC), the combination of no function and increased function alleles results in five predicted CYP2C19 activity phenotypes: ultrarapid metabolizers (UM) (**17/*17*), rapid metabolizers (RM) (**1/*17*), normal metabolizers (NM) (**1/*1*), intermediate metabolizers (IM) (e.g., **1/*2* or **2/*17*), and poor metabolizers (PM) (e.g., **2/*2*) (**Figure 1**) (12). The frequency of *CYP2C19* polymorphisms and metabolizer phenotypes vary across different biogeographical groups used by Pharmacogenomics Knowledge Base (PharmGKB) to annotate racial and ethnicity information about participants in pharmacogenomic studies (21). Approximately 30% of European, 40% of Sub-Saharan African, 40% of African American/Afro-Caribbean, 20% of Latino, 23% of American, 60% of East Asian, 50% of Central/South Asian, 25% of Near Eastern, and 94% of Oceanian populations carry a *CYP2C19* no function allele (**Figure 1**). Therefore, when compared to individuals of European ancestry, CYP2C19 IMs and PMs are slightly more prevalent in individuals of African ancestry, approximately two times more common in patients of East Asian ancestry, and almost exclusively prevalent in patients of Oceanian ancestry.

It is well-established that substantial interpatient variability in platelet inhibition exists in those treated with clopidogrel, and genetic polymorphisms significantly contribute to observed variability in clopidogrel response and platelet reactivity (22, 23). CYP2C19 IMs and PMs have a significantly reduced capacity to convert clopidogrel into its active metabolite and diminished inhibition of platelet activation compared to patients who do not carry a *CYP2C19* no function allele (24). Additionally, *CYP2C19* no function allele carriers treated with clopidogrel have significantly higher rate of high on-treatment platelet reactivity (HTPR), which is associated with a higher risk of MACE (25). Multiple retrospective studies and meta-analyses have consistently shown that CYP2C19 IM and PMs treated with clopidogrel have an increased risk of MACE and stent thrombosis after PCI compared to those without a no function allele (13, 15, 24, 26). In contrast to clopidogrel, the pharmacokinetics, antiplatelet effects, and clinical effectiveness of prasugrel and ticagrelor are not affected by *CYP2C19*

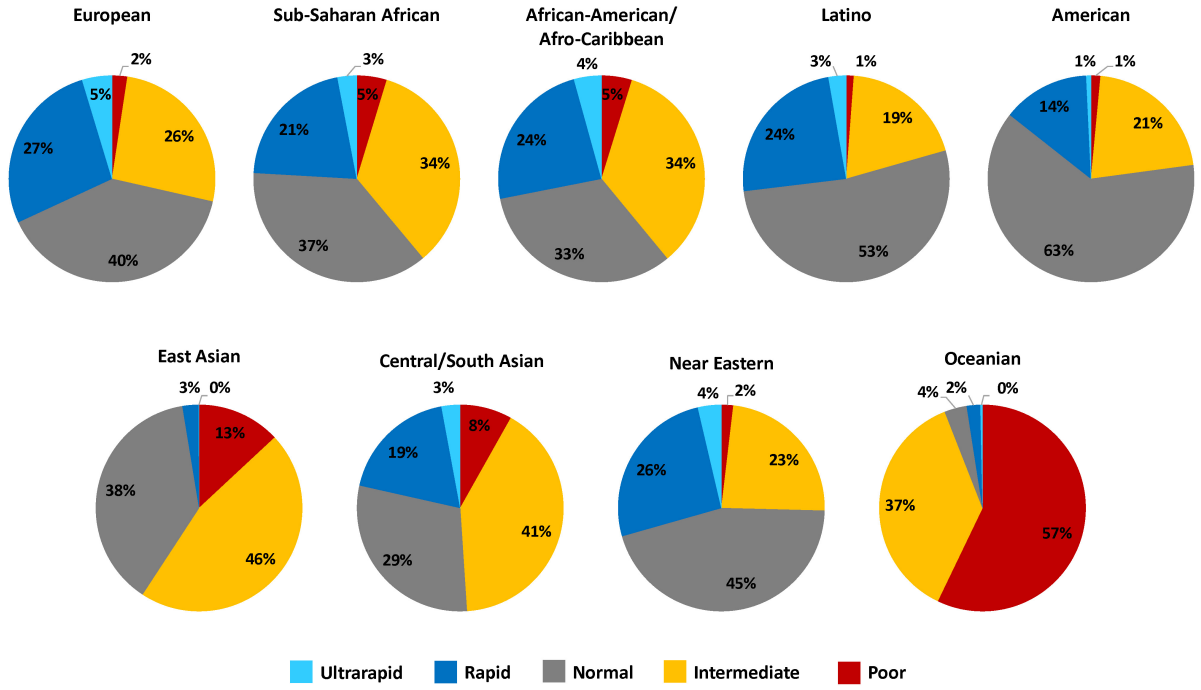


FIGURE 1
CYP2C19 metabolizer phenotype frequency estimates across diverse biogeographical groups. This figure summarizes the relative frequency estimates (in percentages) of CYP2C19 metabolizer phenotypes in the 9 distinct biogeographical groups defined by PharmGKB to annotate racial and ethnicity information about participants in pharmacogenomic studies (21). The CYP2C19 metabolizer phenotype and respective *CYP2C19* genotypes are as categorized: ultrarapid metabolizers (**17/*17*), rapid metabolizers (**1/*17*), normal metabolizers (**1/*1*), intermediate metabolizers (e.g., **1/*2* or **2/*17*), and poor metabolizers (e.g., **2/*2*). Frequency data was obtained from CPIC (12).

genotype (12). *Post hoc* genetic analyses of the TRITON-TIMI 38 and PLATO clinical trials demonstrated that *CYP2C19* genotype has no effect on outcomes after PCI among patients randomized to ticagrelor or prasugrel (14, 15, 27).

Increased risk for MACE and stent thrombosis in clopidogrel-treated IMs and PMs has been shown in prior meta-analyses of predominantly European ancestry populations (MACE: HR 1.55, 95% CI: 1.11–2.17 for IMs and HR 1.76, 95% CI: 1.24–2.50 for PMs; stent thrombosis: HR 2.81, 95% CI: 1.81–4.37 for IMs and PMs combined) (13) and East Asian ancestry populations (MACE: odds ratio [OR] 1.92, 95% CI: 1.34–2.76 for IMs and OR 3.08, 95% CI: 1.85–5.13 for PMs; stent thrombosis: OR 4.77, 95% CI: 2.84–8.01 for IMs and PMs combined) (26). Some studies have reported that carriers of the increased function *CYP2C19*17* allele exhibit higher clopidogrel active metabolite formation, inhibition of platelet activation, and bleeding risk compared to non-carriers (28, 29). However, the **17* allele does not occur on the same haplotype as the **2* allele; therefore, these associations may be related to the absence of the *CYP2C19*2* allele because other studies that account for the **2* allele observed no associations between CYP2C19 RMs or UM status and clopidogrel pharmacodynamics (30, 31). In addition, recent clinical outcome studies that account for the *CYP2C19* no function alleles have demonstrated no significant association between the *CYP2C19*17* allele and bleeding and ischemic outcomes in clopidogrel-treated PCI patients (31–33).

The retrospective studies establishing the effects of *CYP2C19* genetic variation on clopidogrel responsiveness and outcomes after PCI have been conducted predominantly in populations of European (13) or Asian ancestry (26), and studies investigating associations with clinical outcomes in populations of African ancestry, Hispanic ethnicity, and other under-represented populations are lacking. Therefore, the association between *CYP2C19* no function alleles, clopidogrel response, and major cardiovascular outcomes remains unclear in other racial and ethnic populations because of limited data and the lack of diversity in these clinical pharmacogenomic discovery studies. The best available evidence is derived from a race stratified analysis of the Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status (TRIUMPH) cohort, a multicenter U.S. registry of acute MI patients. An *ad hoc* genetic analysis of 2,732 patients (2,062 White patients, 670 Black patients) treated with clopidogrel revealed racial differences in the association between *CYP2C19* genotype and 1-year mortality (34). The investigators observed significantly higher mortality among White patients (adjusted HR 1.70, 95% CI: 1.01–2.86, $p = 0.046$) who carried the no function *CYP2C19*2* allele, when compared

to non-carriers; in contrast, a *2 allele association with mortality was not observed among Black patients (adjusted HR 0.63, 95% CI: 0.28–1.41, $p = 0.262$) (34). Among Black patients, however, clopidogrel-treated carriers of the increased function *CYP2C19*17* allele had a significantly higher risk of mortality and bleeding compared to *CYP2C19*1* homozygous individuals; no association between the *17 allele and outcomes was observed in White patients. Given the sample size limitations, these findings should be interpreted with caution until validated in an independent cohort.

## Current guideline recommendations for genotype guided antiplatelet therapy

Clopidogrel's prescribing information considers the association between *CYP2C19* no function alleles, clopidogrel pharmacokinetics, and diminished clinical effectiveness. In 2010, the US Food and Drug Administration (FDA) added a Boxed Warning to the clopidogrel label regarding the diminished effectiveness of clopidogrel in PMs (35). In 2016, this warning was extended to include all clopidogrel indications, and is among the strongest pharmacogenomic warnings provided by the FDA in a drug label (36). Notably, the FDA boxed warning does not require genetic testing to initiate clopidogrel therapy. Therefore, if a patient's genotype is not known, the decision to perform *CYP2C19* testing remains at the discretion of the clinician.

Clinical practice guidelines vary regarding recommendations for *CYP2C19* genetic testing. CPIC provides guidelines on the use of *CYP2C19* genotyping test results when considering clopidogrel as an antiplatelet therapy agent; notably, these recommendations are based under the assumption that genetic tests results are available (12). The recently published 2022 CPIC guideline update for *CYP2C19*-clopidogrel recommended to avoid clopidogrel and use prasugrel or ticagrelor in CYP2C19 IM or PMs in the absence of contraindications to alternative therapy, increased the strength of the recommendation for IMs in the setting of ACS or PCI to strong, and expanded recommendations to also consider patients receiving antiplatelet therapy for neurovascular indications (12). The American College of Cardiology Foundation, American Heart Association, and the Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) guidelines recommended that *CYP2C19* genetic testing may be considered in patients undergoing PCI who are at high risk for poor clinical outcomes due to inadequate platelet inhibition (Class IIB, Level of Evidence C) but recommended against routine *CYP2C19* genetic testing in all ACS patients undergoing PCI (8, 37). These recommendations have remained unchanged since 2011.

In 2019, the European Society of Cardiology (ESC) provided an updated expert consensus statement, which noted that *CYP2C19* genotyping in patients undergoing PCI with stable CAD or ACS on clopidogrel treatment may provide useful data for cardiovascular risk prediction for bleeding and ischemic events (23). However, routine genotyping to guide $P2Y_{12}$ inhibitor treatment was not recommended because clinical trial evidence supporting the utility of these strategies was lacking. In 2020, the ECS guidelines stated that *CYP2C19* genotyping to guide dual antiplatelet therapy de-escalation (switch from prasugrel or ticagrelor to clopidogrel) in selected Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients may be considered as an alternative to 12 months of potent platelet inhibition, especially for patients deemed unsuitable for maintained potent platelet inhibition (38).

Altogether, current clinical guidelines provide clinicians the opportunity to utilize *CYP2C19* genotyping to guide antiplatelet therapy selection after PCI in selected, high-risk patients. However, these guideline recommendations were based on evidence from clinical studies that were primarily conducted in patients of European or Asian ancestry and lacked racial and ethnic diversity, and do not directly comment on whether the evidence and recommendations should be extrapolated to underrepresented populations.

## Summary of major acute coronary syndrome/percutaneous coronary intervention clinical outcome studies that utilized *CYP2C19* genotyping

Recent studies support the use of a genotype-guided antiplatelet selection strategy in clinical practice (39). Collectively, multiple prospective randomized clinical trials (RCTs) (40–43) and observational studies (44–50) have demonstrated that *CYP2C19* genotype-guided selection of $P2Y_{12}$ inhibitor therapy improves clinical outcomes in the setting of ACS/PCI. The major randomized and observational outcome studies that evaluated prospective *CYP2C19* genotyping in ACS/PCI patients are summarized in **Table 1**, and the 4 major recent studies that reported race and ethnicity data are described in greater detail below.

These outcome studies have informed three recent major meta-analyses. A meta-analysis of 15,949 patients (98% ACS, 77% undergoing PCI) from 7 randomized trials reported that treatment with prasugrel or ticagrelor reduced major ischemic events compared to clopidogrel in CYP2C19 IMs and PMs (RR 0.70, 95% CI: 0.59–0.83), whereas no difference was observed in patients who were non-carriers of no function alleles (RR 1.0, 95% CI: 0.80–1.25) (51). A significant genotype-treatment interaction ($p = 0.013$) was reported, which suggests that

TABLE 1 Major prospective studies reporting clinical outcomes of *CYP2C19* genotype-guided antiplatelet therapy after PCI.

| | Study (Sample size) | Sites and location | Race and ethnicity reported | Treatment strategy | Major findings |
|---|---|---|---|---|---|
| **Prospective genotyping (Randomized trials)** | TAILOR-PCI ($N$ = 5,276) (51) | 40 centers in the U.S., Canada, South Korea, and Mexico | Yes | Universal clopidogrel vs. genotyped-guided escalation strategy: clopidogrel (NMs) or ticagrelor (IM/PMs) | Among CYP2C19 IM/PMs, genotype-guided therapy (ticagrelor) exhibited a numerically lower risk of MACE compared to conventional therapy (clopidogrel) at 1 year (4.0% vs. 5.9%, HR: 0.66; 95% CI: 0.43–1.02; $p$ = 0.06); however, this difference was not statistically significant. |
| | POPular-Genetics ($N$ = 2,488) (42) | 10 centers in Europe | Yes | Universal prasugrel or ticagrelor vs. genotype-guided de-escalation strategy: clopidogrel (NMs) or prasugrel/ticagrelor (IM/PMs) | *CYP2C19* genotype guided therapy was non-inferior to universal prasugrel or ticagrelor for the risk of MACE or major bleeding (5.1% vs. 5.9%, absolute difference: -0.7%; 95% CI: -2.0 to 0.7; $p < 0.001$ for non-inferiority). |
| | PHARMCLO ($N$ = 888)* (41) | 12 centers in Italy | No | Standard-of-care vs. genotype-guided escalation strategy with treatment at physician discretion | *CYP2C19* genotype guided therapy reduced the risk of MACE or major bleeding compared to standard of care at 1 year (15.9% vs. 25.9%; HR: 0.58; 95% CI: 0.43–0.78; $p < 0.001$). |
| | IAC-PCI ($N$ = 600) (40) | Single center in China | No | Universal clopidogrel vs. genotype-guided escalation strategy: clopidogrel (NMs), high dose clopidogrel (IMs), or high dose clopidogrel + cilostazol (PMs) | *CYP2C19* genotype guided therapy decreased risk of MACE compared to universal clopidogrel at 180 days (2.7% vs. 9.0%; $p$ = 0.001). |
| **Prospective genotyping (Observational trials)** | IGNITE ($N$ = 3,342) (50) | 9 centers in the U.S. | Yes | Genotype-guided therapy (prasugrel/ticagrelor recommended in IM/PMs) with treatment decision at physician discretion | Among CYP2C19 IM/PMs, patients prescribed alternative therapy had significantly lower risk of MACE over 1 year after PCI compared to those prescribed clopidogrel (adjusted HR: 0.56; 95% CI: 0.39–0.82; $p$ = 0.002). In non-IM/PMs, no difference observed (18.1 vs. 19.9 per 100-pt years; adjusted HR: 1.08; 95% CI: 0.72–1.62; $p$ = 0.715). |
| | GIANT ($N$ = 1,445) (48) | 57 centers in France | No | Genotype-guided therapy (prasugrel recommended in PMs and either prasugrel or high dose clopidogrel recommended in IMs) with treatment decision at physician discretion | Compared to CYP2C19 non-IM/PMs prescribed clopidogrel, MACE rates were significantly higher in IM/PMs prescribed clopidogrel (3.04% vs. 15.6%; $p < 0.05$) but not significantly different in IM/PMs prescribed alternative therapy (3.04% vs. 3.31%; $p$ = 0.82). |
| | PHARM-ACS (N = 1,361) (49) | Single center in China | Yes | Genotype-guided therapy (ticagrelor recommended in IM/PMs) with treatment decision at physician discretion | CYP2C19 IM/PMs prescribed clopidogrel experienced a significant higher risk of MACE compared to those prescribed ticagrelor (7.8% vs. 4.0%; adjusted HR: 2.14; 95% CI: 1.30–3.52). In non-IM/PMs, no significant difference was observed across the clopidogrel vs. ticagrelor groups (5.8% vs. 4.3%; adjusted HR:1.06; 95% CI: 0.59–1.90). |

*(Continued)*

TABLE 1 (Continued)

| Study (Sample size) | Sites and location | Race and ethnicity reported | Treatment strategy | Major findings |
|---|---|---|---|---|
| Sánchez-Ramos et al. (*N* = 719) (45) | Single center in Spain | No | Conventional therapy^ vs. genotype-guided clopidogrel (NMs) or prasugrel/ticagrelor (IM/PMs) | *CYP2C19* genotype guided therapy was associated with a lower risk of MACE compared to historical controls on conventional therapy at 1 year (10.1% vs. 14.1%; HR: 0.63; 95% CI: 0.41–0.97; $p = 0.037$). |
| Shen et al. (*N* = 628) (46) | Single center in China | No | Universal clopidogrel vs. genotype-guided clopidogrel (NMs), high dose clopidogrel (IMs), or ticagrelor (PMs) | *CYP2C19* genotype guided therapy was associated with a lower risk of MACE compared to universal clopidogrel at 1 year (4.2% vs. 9.4%; $p = 0.010$). |

MACE, major adverse cardiovascular events (the definition in each study was slightly different, and is described in the text); MI, myocardial infarction; BARC, Bleeding Academic Research Consortium; TIMI, Thrombolysis in Myocardial Infarction; GUSTO, Global Use of Strategies to Open Occluded Arteries; NMs, normal metabolizers; IMs, intermediate metabolizers; PMs, poor metabolizers.

*The study was discontinued prematurely due to lack of genotyping instrument certification, and only enrolled approximately 25% of the pre-specified sample size.

^Historical unguided control group (N = 402) in which a majority patients received clopidogrel and 7% received prasugrel.

the reduction of ischemic events by prasugrel or ticagrelor, in comparison with clopidogrel, was driven in large part by *CYP2C19* genotype and the magnitude of the benefit was greatest in CYP2C19 IMs and PMs (51). An additional meta-analysis that included 20,743 patients from 14 studies reported that genotyped-guided antiplatelet therapy selection significantly reduced the risk of MACE compared with standard non-guided antiplatelet therapy (RR 0.78, 95% CI: 0.63–0.95, $p = 0.015$) (52). A network meta-analysis of 61,898 ACS patients from 15 randomized trials also reported that a guided approach of $P2Y_{12}$ antiplatelet therapy selection was associated with reduced MACE [incidence rate ratios (IRR) 0.80, 95% CI: 0.65–0.98] without a significant increase in all bleeding (IRR 1.22, 95% CI: 0.96–1.55) compared to routine selection of prasugrel or ticagrelor without genotyping (53). Collectively, these meta-analyses support the use of genetic testing to optimize the choice of agent in patients undergoing PCI. However, the race and ethnicity composition of the meta-analysis populations were not reported.

# Prospective genotyping (Randomized trials)

## TAILOR-PCI

The Tailored Antiplatelet Initiation to Lessen Outcomes due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention (TAILOR PCI) was a randomized, open-label, superiority, multicenter trial of *CYP2C19* genotype-guided antiplatelet therapy conducted in 5,276 patients (43). The study population consisted of 66.4% White, 2.4% Black of African-American, 22.5% East Asian, 4.5% South Asian, and 2.8% Hispanic or Latino patients; 4.3% reported another race or were of unknown race (54). Patients undergoing PCI for an ACS or non-ACS indication were randomized within 72 h after PCI to conventional therapy (universal clopidogrel without initial genetic testing) or to genotype-guided therapy [ticagrelor in *CYP2C19* no function allele carriers (IMs or PMs), and standard-dose clopidogrel in non-carriers]. At the end of the trial, patients in the conventional therapy group underwent *CYP2C19* genotyping, and the primary analysis compared outcomes in *CYP2C19* no function allele carriers across the genotype-guided group ($n = 903$) and the universal clopidogrel group ($n = 946$). The primary outcome was a composite of cardiovascular death, MI, stroke, stent thrombosis, and severe recurrent ischemia at 12 months. Overall, CYP2C19 IM/PMs treated with ticagrelor in the genotyped-guided group had a numerically lower rate of the primary outcome compared to CYP2C19 IM/PMs receiving clopidogrel in the conventional therapy group (4.0% vs. 5.9%; HR: 0.66; 95% CI: 0.43–1.02; $p = 0.06$). However, the event rate was lower than anticipated and the difference was not statistically significant. In a *post hoc* analysis, IM/PMs receiving ticagrelor had a lower risk of ischemic events at 90 days compared to clopidogrel (HR 0.21; 95% CI: 0.08–0.54; $p = 0.001$). There was no significant difference in the primary safety end point of major or minor bleeding rates across groups (HR 1.22; 95% CI: 0.60–2.51; $p = 0.58$).

## POPular-genetics

The *CYP2C19* Genotype-Guided Antiplatelet Therapy in ST-Segment Elevation Myocardial Infarction Patients—Patient Outcome after Primary PCI (POPular Genetics) trial was a randomized, multicenter, open-label, non-inferiority

trial conducted in 2,488 ST segment elevation MI (STEMI) patients undergoing PCI (42). The study population consisted of 94.3% European or White, 0.2% Black, 2.8% Asian, and 1.0% Hispanic or Latino patients; < 2% of participants did not report race or ethnicity. POPular Genetics evaluated whether a *CYP2C19* genotype-guided antiplatelet therapy de-escalation strategy reduced bleeding risk without increasing thrombotic risk compared to conventional therapy with ticagrelor or prasugrel. The study randomized patients during or within 48 h after PCI to conventional treatment (universal ticagrelor or prasugrel without genetic testing) or genotype-guided therapy (prasugrel or ticagrelor in *CYP2C19* no function allele carriers [IMs and PMs], and standard-dose clopidogrel in non-carriers). Overall, the genotype-guided strategy was non-inferior to universal ticagrelor or prasugrel in occurrence of the primary composite outcome of death, MI, stent thrombosis, stroke, or major bleeding events at 12 months (5.1% vs. 5.9%; absolute difference: -0.7%; 95% CI: -2.0 to 0.7; $p < 0.001$ for non-inferiority). Additionally, the genotype guided de-escalation strategy significantly reduced the co-primary outcome of major or minor bleeding rates (9.8% vs. 12.5%; HR: 0.78; 95% CI, 0.61–0.98; $p = 0.04$), which was driven by a lower incidence of minor bleeding because no significant difference in major bleeding events were observed.

# Prospective genotyping (observational studies)

## Implementing genomics in practice

A multicenter pragmatic study conducted by U.S. early adopter institutions in the Implementing Genomics in Practice (IGNITE) Network, examined clinical outcomes following clinical implementation of *CYP2C19* genotype-guided antiplatelet therapy after PCI in a real-world clinical setting (47, 50). As part of the clinical implementation at each site, prasugrel or ticagrelor was recommended in CYP2C19 IMs and PMs in the absence of contraindications; however, the ultimate prescribing decision was left to the clinician. The initial analysis conducted in 1,815 patients across 7 centers demonstrated that CYP2C19 IM/PMs prescribed clopidogrel experienced significantly higher MACE rates over 12 months compared to IM/PMs prescribed alternative therapy (adjusted HR: 2.26; 95% CI: 1.18–4.32; $p = 0.013$) (47). A more recent analysis was conducted in an expanded cohort of 3,342 patients across 9 centers, and is described in greater detail below (50). The study population demographics of the initial and expanded cohort were comparable, and consisted of approximately 70% European or White, 20% African American or Black, 1% Asian, and 4% Hispanic or Latino patients; 1% of patients reported another race or multiple races, and 3% did not have race or ethnicity information available in the electronic health record.

The primary outcome assessed in the recent expanded cohort analysis was major atherothrombotic events, defined as a composite of death, MI, ischemic stroke, stent thrombosis, or hospitalization for unstable angina, over 12 months after PCI (50). Major atherothrombotic event rates were significantly lower in CYP2C19 IM/PMs prescribed alternative therapy vs. those who were prescribed clopidogrel (17.1 vs. 34.4 per 100 patient-years, respectively; adjusted HR: 0.56; 95% CI: 0.39–0.82; $p = 0.002$); however, no significant difference was observed across alternative therapy and clopidogrel groups in patients without a no function allele (18.1 vs. 19.9 per 100 patient-years, respectively; adjusted HR: 1.08; 95% CI: 0.72–1.62; $p = 0.715$). The observed differences in IM/PMs were most pronounced in ACS patients undergoing PCI (adjusted HR: 0.49; 95% CI: 0.32–0.76; $p = 0.001$), whereas use of clopidogrel or alternative therapy were similarly effective in ACS patients without a no function allele (adjusted HR: 1.05; 95% CI: 0.67–1.66; $p = 0.834$). There was no difference in major bleeding rates between the alternative therapy group vs. clopidogrel group in either IM/PMs (adjusted HR; 1.15; 95% CI: 0.60–2.20; $p = 0.685$), or non-IM/PMs (adjusted HR: 1.30; 95% CI: 0.71–2.38; $p = 0.397$). A separate analysis from this population focused on the increased function *CYP2C19*17* allele demonstrated that clopidogrel-treated RMs or UMs exhibited no difference in atherothrombotic (adjusted HR: 0.97; 95% CI: 0.73–1.29; $p = 0.808$) or bleeding events (adjusted HR: 1.34; 95% CI: 0.83–2.17; $p = 0.224$) compared to clopidogrel-treated NMs (33).

## PHARM-ACS

The PHARMacotherapy and long-term clinical outcomes in patients with ACS after PCI (PHARM-ACS) study was a single-center observational cohort study conducted in China that evaluated the effect of *CYP2C19* genotype-guided antiplatelet therapy on clinical outcomes in 1,361 patients with ACS after PCI (49). Approximately 98% of the participants identified as Han nationality, and 60.7% carried at least one no function allele. Ticagrelor was recommend in CYP2C19 IMs and PMs, but the ultimate prescribing decision was left to clinician's discretion. The primary endpoint was a composite of death, stent thrombosis, stroke, MI, and any urgent coronary revascularization within 1 year after PCI. Consistent with the IGNITE study results, use of clopidogrel in IM/PMs was associated with a significantly higher risk of MACE compared to IM/PMs prescribed ticagrelor (adjusted HR: 2.14; 95% CI: 1.30–3.52), and no differences in MACE risk were observed across groups in non-IM/PMs (adjusted HR: 1.06; 95% CI: 0.59–1.90). There was also no significant difference in bleeding events across groups.

## Racial and ethnic disparities in major *CYP2C19* genotyping outcome studies in acute coronary syndrome/percutaneous coronary intervention patients that support current genotype-guided antiplatelet therapy recommendations

In order to assess the presence of disparities in the major clinical outcome studies supporting current *CYP2C19* genotype-guided antiplatelet therapy recommendations, reported demographic data from 11 major clinical outcome studies of *CYP2C19* genotype guided antiplatelet therapy in ACS/PCI patients were summarized and compared (**Figure 2** and **Supplementary Table 1**). For reference, the demographic characteristics were compared to a national database derived from 667,424 patient records across 1,612 U.S. centers obtained from the National Cardiovascular Data Registry (NCDR). In 2014, the race and ethnicity distribution of patients who underwent PCI in the U.S. was 86.5% White or European, 8.8% Black or African American, 2.8% Asian, 0.7% Native American, 0.3% Pacific Islander, and 5.8% Hispanic or Latino ethnicity (55).

The retrospective genetic analyses of the TRITON-TIMI 38 and PLATO RCTs, which established that *CYP2C19* no function alleles significantly diminish clopidogrel but not ticagrelor or prasugrel clinical effectiveness, were conducted almost exclusively in patients of European ancestry (∼98%) (14, 15, 24, 27). Of the 9 major randomized and observational outcome studies that conducted prospective *CYP2C19* genotyping in ACS/PCI patients summarized in **Table 1**, **4** studies (TAILOR-PCI, POPular-Genetics, IGNITE, PHARM-ACS) reported participant-level data on the race and ethnicity of the study participants (42, 43, 49, 50). Of these 4 studies, 3 reported White or European representation, 3 reported Black or African American representation, 3 reported Hispanic or Latino representation, 4 reported Asian representation, and 3 reported representation of other races. Aggregation of race and ethnicity data across the 12,467 patients included in these 4 studies (**Figure 3**) demonstrated that the majority of the study participants identified as European or White (66%). There was also strong representation of Asian patients in these studies (23%), which predominantly included patients of East Asian ancestry. Moreover, of the 5 studies with unreported race and ethnicity data (**Figure 2**), PHARMCLO (multiple centers in Italy), GIANT (multiple centers in France), and Sánchez-Ramos et al. (single center in Spain) were conducted exclusively in Europe, and IAC-PCI and Shen et al. were conducted at single centers in China (40, 41, 45, 46, 48). Although the self-identified race and ethnicity of the study participants were not reported, the study locations suggest that the study participants predominantly represented European and East Asian ancestry, respectively. In contrast, only about 6% of participants in these 4 studies identified as Black or African American and 2% identified as Hispanic or Latino (**Figure 3**), which is lower than the U.S. PCI population reported by NCDR. Among the patients that identified as another race in these studies (1%), the proportion of Native American, Pacific Islander, and multiracial patients were unclear and thus these populations were also mostly likely underrepresented.

Although there is accumulating evidence supporting the clinical utility of *CYP2C19* genotype-guided antiplatelet therapy selection in the setting of ACS/PCI, our review of the evidence demonstrates a collective lack of racial and ethnic diversity in the major clinical outcome studies supporting recent guideline recommendations and has identified important evidence gaps regarding the effectiveness of this precision medicine strategy in underrepresented populations. There remain limited clinical outcome data in patient populations beyond those of European and East Asian ancestry. Therefore, the benefits and risks of this precision medicine strategy in Black, Hispanic, and other underrepresented populations remain unclear. Future outcome studies in diverse real-world clinical settings are critical to address racial and ethnic disparities in the evidence base and equitably evaluate clinical utility of *CYP2C19* genotype-guided antiplatelet therapy in ACS/PCI patients.

## Racial and ethnic disparities in discovery studies that identify and validate genetic predictors of clopidogrel response

It is well established that genomic and pharmacogenomic discovery studies have lacked racial and ethnic diversity and been predominantly conducted in populations of European ancestry (56–58). Evaluation of the distribution of ancestry categories within genome-wide association studies (GWAS) from 2005 to 2016 in the NHGRI-EBI GWAS Catalog revealed that European ancestry individuals have represented the overwhelming majority of participants in genetic discovery studies (78%) (59). The GWAS studies compromised Asian individuals (11%), with East Asian ancestry (9%) accounting for most and South/Central Asian ancestry (2%) less well represented, followed by African ancestry (2%), Hispanic or Latin American individuals (1%), all other populations (< 1%), and reported samples where the ancestry category could not be specified (6%) (59, 60). It is well-established that African populations have the greatest genetic diversity and largest number of population-specific alleles (61, 62). African ancestry populations have contributed to a disproportionately higher number of genome-wide significant associations (7%) when

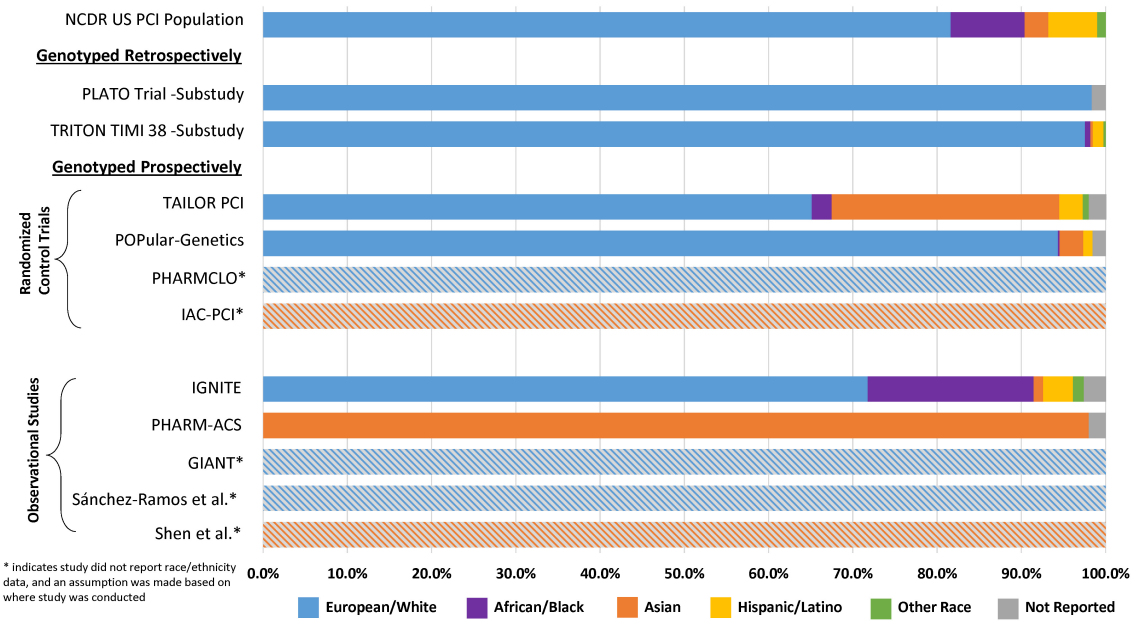


FIGURE 2
Reported race and ethnicity data from selected major clinical outcome trials utilizing clopidogrel and in which *CYP2C19* status was reported. This figure compares the relative percent distribution of reported race and ethnicity from study participants included major retrospective and prospective clinical outcome studies of *CYP2C19* genotype-guided antiplatelet therapy. *Studies with the gray hatched bars did not report race and ethnicity data, and an assumption about the population demographics was made based on the study site locations described in **Table 1** (Europe or China). For reference, the demographic characteristics of each study were compared to data obtained from the National Cardiovascular Data Registry (NCDR): the race and ethnicity distribution of patients who underwent PCI in the U.S. was 86.5% White or European, 8.8% Black or African American, 2.8% Asian, 0.7% Native American, 0.3% Pacific Islander, and 5.8% Hispanic or Latino ethnicity (55).

compared to the representation in GWAS studies (~2%); the opposite trend exists in individuals of European ancestry (54% of associations with 78% of participants) (59, 60). Therefore, failure to enhance ancestral diversity in genomic research studies will augment health disparities in underrepresented populations (58). Enhancing ancestral diversity in genomic discovery studies offers enormous potential to advance the discovery of genetic predictors of disease risk and drug response and optimize the development of precision medicine interventions that can more equitably improve outcomes in individual patients.

This problem is evident when specifically evaluating the evidence underlying the discovery of genetic factors associated with inter-patient variability in clopidogrel response. A GWAS in 429 healthy Amish volunteers of European ancestry determined that the *CYP2C19*2* no function allele accounted for approximately 12% of the variation in clopidogrel on-treatment platelet reactivity and was the only significant genome-wide association (63). A subsequent GWAS in 513 Amish volunteers from the same study population demonstrated that *CYP2C19*2* exhibited the strongest association with clopidogrel active metabolite levels (64). The largest GWAS of clopidogrel response was conducted in 2,750 ACS/PCI patients of European ancestry by the International Clopidogrel Pharmacogenomics Consortium and demonstrated that *CYP2C19*2* was the strongest determinant of clopidogrel on-treatment platelet reactivity (65). A GWAS conducted in 115 Chinese patients with CAD did not identify significant genome-wide associations with clopidogrel inhibition of platelet reactivity or active metabolite levels but was limited by sample size. In this study, *CYP2C19*2* accounted for approximately 11 and 16% of the variability in clopidogrel on-treatment platelet reactivity and active metabolite plasma concentrations, respectively (66). While these studies in European and East Asian ancestry populations identified other potential genetic variants that may contribute to variation in clopidogrel response (31, 63–66), they collectively demonstrate that *CYP2C19* no function alleles are the strongest genetic determinant of clopidogrel response and associated with clopidogrel clinical effectiveness in European and East Asian ACS/PCI patients (13, 26). Interestingly, East Asian populations are less likely to experience thromboembolic and ischemic complications but more likely to experience bleeding complications compared to European populations, which is known as the "East Asian Paradox" (67). It remains unclear whether genetic determinants of platelet function or antiplatelet drug effects underlie this effect, and thus additional genetic discovery research beyond *CYP2C19* is needed.

Rigorous studies seeking to identify genetic predictors of clopidogrel response in patients of African ancestry, Hispanic ethnicity, and other underrepresented populations have been

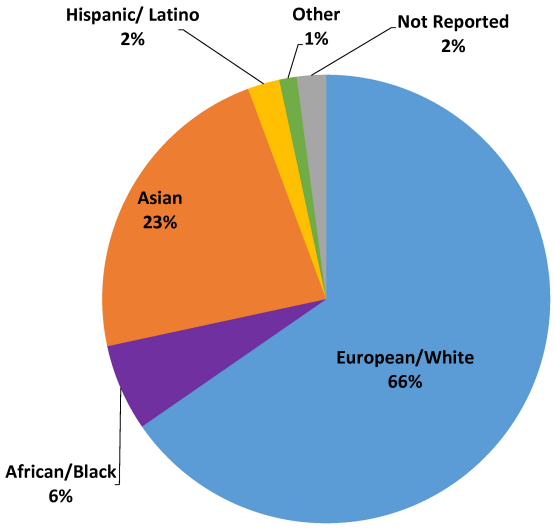


FIGURE 3
Representation of race and ethnicity data from selected *CYP2C19* outcome studies. This figure summarizes race and ethnicity distribution of individuals included in major prospective clinical outcome studies of *CYP2C19* genotype guided antiplatelet therapy (as summarized in **Supplementary Table 1**). Pie graph displays aggregated percent race and ethnicity composition from the *N* = 12,467 patients enrolled in the 4 studies with reported race and ethnicity data (TAILOR PCI, POPular Genetics, IGNITE, PHARM-ACS).

lacking. A notable exception is a recent study conducted in an admixed population of 474 Caribbean Hispanic ACS/PCI patients treated with clopidogrel across multiple sites in Puerto Rico (68). The average European, Native American, and African ancestry genomic proportions in the study population were 70, 11, and 19%, respectively. The study observed that the *CYP2C19**2 allele exhibited the strongest genetic association with high on-clopidogrel platelet reactivity. Moreover, genetic variants in *PON1*, *ABCB1*, and *PEAR1*, which have demonstrated inconsistent associations within European populations, were also associated with clopidogrel response. Notably, African ancestry was a significant independent predictor of clopidogrel response and an interaction between African ancestry and the *PEAR1* variant was observed. Overall, approximately 19% of the variability in clopidogrel response was attributed to independent genetic and clinical factors, with *CYP2C19***2* accounting for approximately 7% of the variability in this population (68). Together, these important and novel results demonstrated that *CYP2C19* no function alleles are associated with reduced clopidogrel response in a diverse population of Caribbean Hispanic patients and suggest that the effect size of the *CYP2C19***2* allele may be smaller compared to White populations, other genetic variants and ancestry may contribute to variation in clopidogrel response independent of *CYP2C19*, and these effects may be augmented in patients of African ancestry.

The relative contribution of *CYP2C19* no function alleles and other genetic variants to inter-patient variation in clopidogrel response in African ancestry populations has not been rigorously investigated to date. The clinical relevance of such studies is underscored by prior studies demonstrating that Black patients treated with clopidogrel undergoing PCI have a higher prevalence of HTPR compared to White patients (56% vs. 35%, respectively, $P = 0.003$) (69). As described above, an analysis of *CYP2C19* variants and outcomes in 670 Black clopidogrel-treated acute MI patients revealed that the *CYP2C19***2* no function allele was not associated with higher risk of adverse cardiovascular outcomes and mortality, whereas the *CYP2C19***17* increased function allele was associated with higher risk of bleeding and mortality (34). Together, this limited evidence demonstrates that Black patients are at a higher risk of clopidogrel non-response, and suggests that unique genes and alleles beyond *CYP2C19***2* are likely associated with clopidogrel response and effectiveness in Black populations. Therefore, a GWAS of clopidogrel response in patients of African ancestry is essential. To address this gap in precision medicine, the African American Cardiovascular Pharmacogenetic Consortium (ACCOuNT) was formed to discover novel genetic variants in African Americans related to clinically actionable cardiovascular phenotypes, which will include evaluation of clopidogrel clinical responsiveness (70).

Discovery pharmacogenomic studies in African ancestry and other underrepresented populations are needed to fully elucidate the presence and magnitude of *CYP2C19* and other genetic effects on clopidogrel clinical effectiveness, which may differ from prior studies conducted in predominantly European and East Asian populations. Discovery genetics studies across diverse populations are essential to ensure that genotype-guided approaches evaluated in clinical trials and implemented into clinical practice include the most informative and relevant alleles.

## Emerging studies evaluating *CYP2C19* genotype guided antiplatelet therapy in stroke patients

Clinical guidelines also recommend antiplatelet therapy for the treatment of acute ischemic stroke and the secondary prevention of ischemic stroke (71). Multiple RCTs have shown that short term (21–90 days) use of dual antiplatelet therapy with aspirin and clopidogrel reduces stroke recurrence in patients with acute ischemic stroke or transient ischemic attack (TIA) (72–74). Therefore, clopidogrel is commonly prescribed when a $P2Y_{12}$ inhibitor is clinically indicated for the treatment or prevention of ischemic stroke (75).

A meta-analysis of 15 studies demonstrated a significant association between *CYP2C19* no function alleles and clinical outcomes in 4,762 clopidogrel-treated patients with stroke or TIA (76). The study population consisted of East Asian (85%), European (8%), African (2%), and other (5%) ancestry patients. *CYP2C19* no function allele carriers receiving clopidogrel had a significantly higher risk of stroke (RR: 1.92, 95% CI: 1.57–2.35) and major vascular events (RR: 1.51, 95% CI: 1.10–2.06) compared to non-carriers (76). A race-stratified subgroup analysis observed a significant increased risk of stroke in *CYP2C19* no function allele carriers of Asian ancestry (RR 1.93; 95% CI: 1.55–2.39; $P < 0.001$) and European ancestry (RR 2.46; 95% CI: 1.06–5.72; $p = 0.04$); however, the association was not statistically significant among the limited sample of African ancestry ($n = 97$) patients (RR 1.74; 95% CI: 0.63–4.79; $p = 0.28$). Additional studies in more diverse populations are needed to elucidate the presence and magnitude of *CYP2C19* genotype associations with clopidogrel clinical effectiveness beyond populations East Asian ancestry.

Emerging prospective evidence supports the use of a *CYP2C19* genotype-guided antiplatelet strategy in stroke patients. The Ticagrelor vs. Clopidogrel in CYP2C19 Loss-of-Function Carriers with Stroke or TIA (CHANCE-2) trial was a multicenter, double-blinded, placebo-controlled, randomized control, superiority trial conducted across 202 centers in China (77). The study examined whether ticagrelor plus aspirin was superior to clopidogrel plus aspirin in 6,412 patients with minor ischemic stroke or TIA who were *CYP2C19* no function allele carriers. The primary efficacy outcome was new ischemic or hemorrhagic stroke at 90 days, which occurred in 6.0% of CYP2C19 IM/PMs in the ticagrelor group and 7.6% of IM/PMs in the clopidogrel group (HR 0.77; 95% CI: 0.64–0.94; $p = 0.008$). The incidence of a major vascular event, defined as the composite of ischemic stroke, hemorrhagic stroke, TIA, MI, or cardiovascular death, was also significantly reduced in the ticagrelor group (7.2% vs. 9.2%, respectively; HR 0.77; 95% CI: 0.65–0.92). Moderate or severe bleeding occurred at 0.3% of patients in both groups (HR 0.82; 95% CI, 0.34–1.98; $p = 0.66$); however, the incidence of any bleeding was higher in the ticagrelor compared to clopidogrel group (5.3% vs. 2.5%, respectively; HR 2.18; 95% CI: 1.66–2.85). These results illustrate the clinical utility of a *CYP2C19* genotype guided strategy in the setting of acute stroke.

Black and Hispanic patients have a higher prevalence of risk factors for stroke and a higher prevalence of stroke events compared to non-Hispanic White patients (1, 78), but have been underrepresented in prior neurovascular disease studies of clopidogrel pharmacogenomics. Therefore, outcome studies evaluating the clinical impact of a genotype guided strategy in acute stroke or TIA patients need to include more diverse populations to appropriate determine the factors that influence the stroke differences among these populations underrepresented in the studies to date. In addition, outcome studies in diverse populations of patients with other neurovascular indications for clopidogrel, including neuro-interventional procedures such as carotid artery stenting and intracranial aneurysm repair, are lacking and needed.

## Increased diversity in clinical trial participation and reporting

Federal efforts and policies from the National Institute of Health (NIH) and the U.S. Food and Drug Administration (FDA) have promoted diverse clinical trial representation over time. The NIH Inclusion Policy required the inclusion of women and individuals from underrepresented minority populations in clinical research studies to enhance generalizability of findings to the patient populations being treated and enable valid subgroup analyses that evaluate outcome differences stratified by sex and race/ethnicity (79). In 2017, an amendment to the NIH Inclusion Policy required that NIH-defined Phase 3 clinical trials submit sex, race, and ethnicity data to the ClinicalTrials.gov registry (79). Recently in April 2022, the U.S. FDA issued a new draft guidance to enhance inclusion of underrepresented racial and ethnic populations in clinical trials (80). However, FDA guidance documents are recommendations that are not legally enforceable mandates. Therefore, there are major challenges to ensure that these initiatives are translated into clinical practice. As highlighted in our analysis, comprehensive reporting of race and ethnicity data in clinical trials and observational precision medicine studies (including studies not registered with FDA or funded by NIH) is necessary first step to evaluate the presence of potential disparities in in the evidence base.

Despite having a greater burden of cardiovascular disease (3, 81, 82), racial and ethnic minorities, specifically Black and Hispanic individuals, are frequently underrepresented in cardiovascular clinical research (83, 84). As described herein, this disparity also is evident in pharmacogenomics discovery and outcomes research. Underrepresented groups may often face significant barriers to clinical trial participation, including systemic racism, mistrust of the clinical research system, transportation conflicts, logistical and financial constraints, and lack of awareness and access to research information (85, 86). Strategies proposed by the Heart Failure Collaboratory to improve clinical trial enrollment of underrepresented populations include methodical research study design and site selection, diversification of research leadership and staff, review of eligibility criteria, and increased patient, institution, and community engagement (86). These strategies to improve diversity in heart failure clinical trials could be applied to clinical trials and observational studies that evaluate precision medicine strategies such as genotype-guided antiplatelet therapy. In addition, real-world studies have become increasingly important to evaluate treatment effectiveness in clinical practice. Compared to randomized clinical trials, real-world effectiveness studies are often compromised of diverse

patient populations (87). Therefore, research in real-world clinical settings, such as the IGNITE Network (88), offer the potential to investigate and advance genomics discovery and implementation research into underrepresented populations.

## Summary and conclusion

Accumulating evidence from multiple randomized and observational clinical studies have demonstrated that using *CYP2C19* genotype to guide selection of antiplatelet therapy improves or is associated with improved clinical outcomes in patients with cardiovascular and neurovascular disease. This evidence has led to increased utilization of *CYP2C19* genotype-guided antiplatelet therapy in clinical practice. However, our review and analysis of major antiplatelet pharmacogenomic discovery and outcome studies revealed that these studies have lacked racial and ethnic diversity. There remain limited outcome data and major gaps in evidence regarding the effectiveness and utility of this precision medicine strategy in underrepresented minority patient populations. Additional discovery and outcomes studies that include more diverse patient populations are needed.

Although RCTs have increased rigor and decreased bias compared to observational outcome studies, RCTs of genotype guided antiplatelet therapy have not adequately represented the diversity of patient demographics within the ACS/PCI population. This is concerning particularly given the higher prevalence of cardiovascular disease and increased risk of MACE following ACS and PCI among Black and Hispanic compared to White populations. Although there are certain limitations, observational studies and pragmatic clinical trials conducted in real-world settings are more representative of the diversity of the patient population and can be used as a solution to bridge these gaps. This is evident in the diversity of the patient population included in the outcome studies conducted by the IGNITE Pharmacogenetics Working group (47, 50). In order to rigorously and equitably evaluate clinical utility, additional outcome studies of genotype-guided antiplatelet therapy conducted in diverse real-world ACS/PCI and neurovascular disease patient populations that target enrollment of key underrepresented groups should be pursued. Additional studies evaluating the clinical utility of risk stratification tools that integrate clinical and genetic factors, such as the ABCD-GENE score, in diverse patient population are warranted (89, 90).

*CYP2C19* no function alleles are common among individuals across various ancestries and certain non-European populations have higher prevalence of CYP2C19 IMs and PMs (**Figure 1**). Therefore, the adverse consequences of prescribing clopidogrel without genotype information is likely magnified in these populations. Most notably, Bristol-Myers Squibb Co., and Sanofi were ordered to pay the state of Hawaii more than $834 million in civil penalties for misleading marketing and failure to disclose the possibility of decreased effectiveness and diminished clopidogrel response of individuals of Asian or Pacific-Island descent (91, 92). Furthermore, because minority populations have been underrepresented in clopidogrel pharmacogenomics discovery studies, the presence and magnitude of effect of *CYP2C19* no function alleles on antiplatelet effects and MACE risk in Black, Hispanic, and other underrepresented minority populations (e.g., Native American, Pacific Islander) remains unclear. It is possible that the effect size of these associations varies across populations and genotypes beyond *CYP2C19* could be important in non-European and non-East Asian populations (68, 93). Therefore, in the absence of outcome evidence, it may not be appropriate to assume effectiveness and generalize clinical recommendations for *CYP2C19* genotype-guided antiplatelet therapy in populations that are underrepresented or excluded from these studies.

Although *CYP2C19*-clopidogrel is among the most rigorously evaluated pharmacogenomic interventions studied to date, significant racial and ethnic disparities in the evidence base remain. The conduct of discovery genetics and outcomes studies across diverse populations are essential to ensure that genotype-guided approaches used in clinical practice include the most informative and relevant alleles and improve health outcomes. In order to realize the full health benefits of genomic medicine, equitable access and inclusion of underrepresented groups is essential in research studies that seek to discover genomic predictors of disease risks, drug response, and to evaluate the clinical benefits of genomic and pharmacogenomic interventions on health outcomes.

## Author contributions

AN and CL conducted data analysis and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer LO-P declared a shared affiliation with one of the author, LC to the handling editor at the time of review.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.991646/full#supplementary-material

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# Gender-differences in antithrombotic therapy across the spectrum of ischemic heart disease: Time to tackle the Yentl syndrome?

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The incidence and clinical presentation of ischemic heart disease (IHD), as well as thrombotic and bleeding risks, appear to differ between genders. Compared with men, women feature an increased thrombotic risk, probably related to an increased platelet reactivity, higher level of coagulation factors, and sex-associated unique cardiovascular risk factors, such as pregnancy-related (i.e., pre-eclampsia and gestational diabetes), gynecological disorders (i.e., polycystic ovary syndrome, early menopause) and autoimmune or systemic inflammatory diseases. At the same time, women are also at increased risk of bleeding, due to inappropriate dosing of antithrombotic agents, smaller blood vessels, lower body weight and comorbidities, such as diabetes and chronic kidney disease. Pharmacological strategies focused on the personalization of antithrombotic treatment may, therefore, be particularly appealing in women in light of their higher bleeding and ischemic risks. Paradoxically, although women represent a large proportion of cardiovascular patients in our practice, adequate high-quality clinical trial data on women remain scarce and inadequate to guide decision-making processes. As a result, IHD in women tends to be understudied, underdiagnosed and

undertreated, a phenomenon known as a *"Yentl syndrome."* It is, therefore, compelling for the scientific community to embark on dedicated clinical trials to address underrepresentation of women and to acquire evidence-based knowledge in the personalization of antithrombotic therapy in women.

KEYWORDS

**antithrombotic therapy, antiplatelet therapy, anticoagulant therapy, ischemic heart disease, gender differences**

## Introduction

In a 1983 movie, a young woman, named Yentl, attempted to live as a man to pursue the education she desired, blurring lines between traditional gender roles and deeply rooted social boundaries. In 1991, on the basis of this plot, Dr. Bernadine Healy coined the expression "Yentl syndrome" to epitomize the phenomenon in which women affected by ischemic heart disease (IHD) are less likely than men to receive recommended diagnostic tests, pharmacotherapy and invasive procedures, thereby showing a higher incidence of adverse outcomes (1). In the same year, as director of the National Institutes of Health, she launched the Women's Health Initiative (WHI), consisting of an observational study and three clinical trials to address risk factors for cardiovascular disease, cancer and osteoporosis in postmenopausal women. The program is still ongoing and is expected to end in 2026, with over 160,000 women enrolled at present. Nevertheless, cardiovascular disease continues to be the leading cause of death among women, despite a considerable decline in cardiovascular deaths over several decades. In the last 30 years, cardiovascular research progressed significantly in order to achieve a personalized approach to care, including risk prediction models, preventive measures, and targeted therapeutic pathways. Antithrombotic therapy in patients undergoing percutaneous coronary intervention (PCI) has been deeply involved in this process. The propensity to ischemic recurrences after PCI and the understanding of prognostic implications associated with bleeding have prompted a substantial evolution in antithrombotic treatment regimens on the basis of a more accurate stratification of patients according to their ischemic and bleeding risks (2).

In this narrative review, the authors aim to explore the advancements and the limits of antithrombotic treatment in women, in the light of differences in epidemiology, clinical presentation, pathophysiology, bleeding, and ischemic risks among genders.

## Epidemiology of ischemic heart disease in women

Ischemic heart disease represents the principal cause of death in women globally, accounting for 35% of total deaths (3, 4). Women suffer from IHD approximately 5–10 years after men and have a 20% higher adjusted mortality risk in short term after successful PCI compared with men (5–7). Women with acute coronary syndromes (ACS) are more likely to present with non-ST-elevation acute myocardial infarction (NSTEMI), higher comorbidity burden at baseline and have less severe coronary atherosclerosis (8–12). Furthermore, women with ACS seek medical attention significantly later than men, thus also having prolonged door-to-balloon times (13, 14). The INTERHEART study revealed the importance of psychosocial risk factors, including depression, perceived stress at home or work, lower socioeconomic status, post-traumatic stress disorder and anxiety disorders, in the onset and clinical course of IHD (5, 15). They play a more significant role in women, due to a higher prevalence in this subset of patients. Notably, the impact of these risk factors on IHD are both direct, related to their pathophysiological consequences of the neuroendocrine and cardiovascular systems, and indirect, representing relevant predictors of non-adherence to medical treatment and unhealthy behaviors such as smoking and sedentary lifestyle (16–19). Furthermore, selective serotonin reuptake inhibitors (SSRIs), used as first-line drugs for many of the above conditions, have been demonstrated to impair hemostatic function through various mechanisms (i.e., blockade of intra-platelet calcium mobilization, depletion of intracellular serotonin and reduced secretion of platelet factors in response to chemical stimuli) and to increase the risk of bleeding (20). Conversely, certain SSRIs (i.e., fluoxetine and fluvoxamine) are potent inhibitors of CYP2C19, responsible for converting clopidogrel in its active form. In a large population-based cohort study of CYP2C19-inhibiting SSRI users ($n$ = 9284) vs. non-CYP2C19-inhibiting SSRI users ($n$ = 45,073), an increased risk of ischemic events was found in patients taking CYP2C19-inhibiting SSRIs (21).

Although classic type 1 acute myocardial infarction (AMI) occurs three times more commonly in men than in women, myocardial infarction in the absence of obstructive coronary arteries (MINOCA) is more common in women, being present in 10.5% of ACS presentations *vs.* 3.4% in men (22, 23). In women with MINOCA, mortality risk is significantly associated with the number of accompanying risk factors, ranging between

10% with ≤ 1 cardiovascular risk factor and 25% with > 3 risk factors (24).

Spontaneous coronary artery dissection (SCAD) is a rare cause of ACS, but 90% of the cases are reported in women and it accounts for 10–20% of AMI in women younger than 50 years of age (25, 26). Among the causes of MINOCA, vasospastic angina and microvascular angina play an important role. Whilst rest angina due to epicardial coronary arteries vasospasm is more common in men, the prevalence of coronary microvascular dysfunction among patients with chest pain and non-obstructive coronary artery disease is higher in women compared to men (27).

The prevalence of stress-induced cardiomyopathy, also known as Takotsubo syndrome (TS) has been reported to be approximately 2% of all patients presenting with clinical manifestation of ACS (28). Importantly, out of all TS cases, 90% of patients are post-menopausal women and it is estimated that this entity is present in 5–6% of all female patients presenting with suspected ST-elevation myocardial infarction (STEMI) (28).

In conclusion, although IHD has long been considered a disease affecting predominantly male patients, it constitutes also a considerable part among diseases affecting women. However, there are important differences in terms of clinical subtypes among men and women with ACS. Considering the high prevalence of MINOCA in women with ACS, a strategy of multimodality imaging assessment should be always pursued, using both invasive (i.e., provocative spasm test and intracoronary imaging -IVUS and OCT-) and non-invasive tests (i.e., echocardiogram and cardiac magnetic resonance) in order to identify the specific etiology and provide the right treatment option.

## Clinical presentation of ischemic heart disease in women

The presence of chest pain/discomfort is the hallmark symptom of IHD. A comprehensive analysis from the National Registry of Myocardial Infarction (NRMI), reporting hospital data on 1,143,513 registry patients admitted with confirmed AMI (481,581 women and 661,932 men), have demonstrated that women were more likely than men to present without chest pain (42.0% *vs.* 30.7% in men, respectively), with a larger sex difference in younger patients (29). Women, especially under the age of 65, show more frequently a wide spectrum of atypical symptoms, including weakness, fatigue, nausea, dyspnea, as well as unconventional event triggers (i.e., mental or emotional stress instead of physical exertion) and locations of chest-related symptoms, such as in the neck, jaw, and in the back (30). The reasons for sex-based differences in IHD symptom presentation are largely unknown. A possible explanation could be that younger women who experience AMI may have significantly less narrowing of the coronary arteries than older women or men due to a hypercoagulable state, inflammation, coronary spasm or plaque erosion instead of rupture (31). Furthermore, women exhibit differences in the neural receptors and pathways involved in nociception (32).

Such characteristics demonstrate that women who suffer from IHD may represent a heterogeneous patient group compared to men, requiring both an adaptation of diagnostic criteria and tailored medical anti-ischemic therapy due to a different underlying pathophysiology of coronary disease.

## Sex differences in platelet function

Platelets are blood cells with several important biological functions as they regulate the integrity of the vascular wall, play a key role in primary hemostasis, and modulate thrombotic and inflammatory responses at the blood-vascular interface (28). Sexual dimorphism and age differences in human platelet aggregation dynamics have been known for several decades (33). Such findings may be of clinical relevance since antiplatelet therapy is the fundamental constituent in the treatment of IHD and might require sex-specific tailoring (33).

In a work by Becker et al., women presented a higher platelet reactivity to arachidonic acid and adenosine diphosphate (ADP) at baseline and after treatment with low-dose aspirin, although they experienced the same or greater decreases in platelet reactivity after treatment (34). Similarly, Gremmel et al. found that women were associated with a more pronounced formation of leukocyte-platelet aggregates and increased protease-activated receptor mediated platelet reactivity after PCI (35). The higher platelet reactivity in women was proposed also in patients undergoing double anti-platelet therapy (DAPT) with aspirin and clopidogrel, using thrombin receptor-activating peptide as a stimulator (36). Furthermore, in a cohort of 760 patients undergoing cardiac surgery, clopidogrel-treated women had higher platelet reactivity (HRP) to ADP (37). Similarly, recent data from Myocardial Ischemia Detection By Circulating Biomarkers (MYOMARKER) study showed attenuated flow-citometry-based platelet reactivity to $P_2Y_{12}$ inhibitor (mainly clopidogrel) among female outpatients with suspected myocardial ischemia when compared to men (38). Moreover, a recent analysis of 177 participants on clopidogrel after ACS, showed that the risk of an atherothrombotic event was greater in female carriers loss-of-function allele, compared to men carriers of the same allele, suggesting a possible interaction between sex and genes for clopidogrel (39). The potential increased platelet reactivity in women may be due to multiple causes, such as a higher platelet count and higher number of surface receptors in females in general which points to a greater agonist-induced platelet activation and aggregation

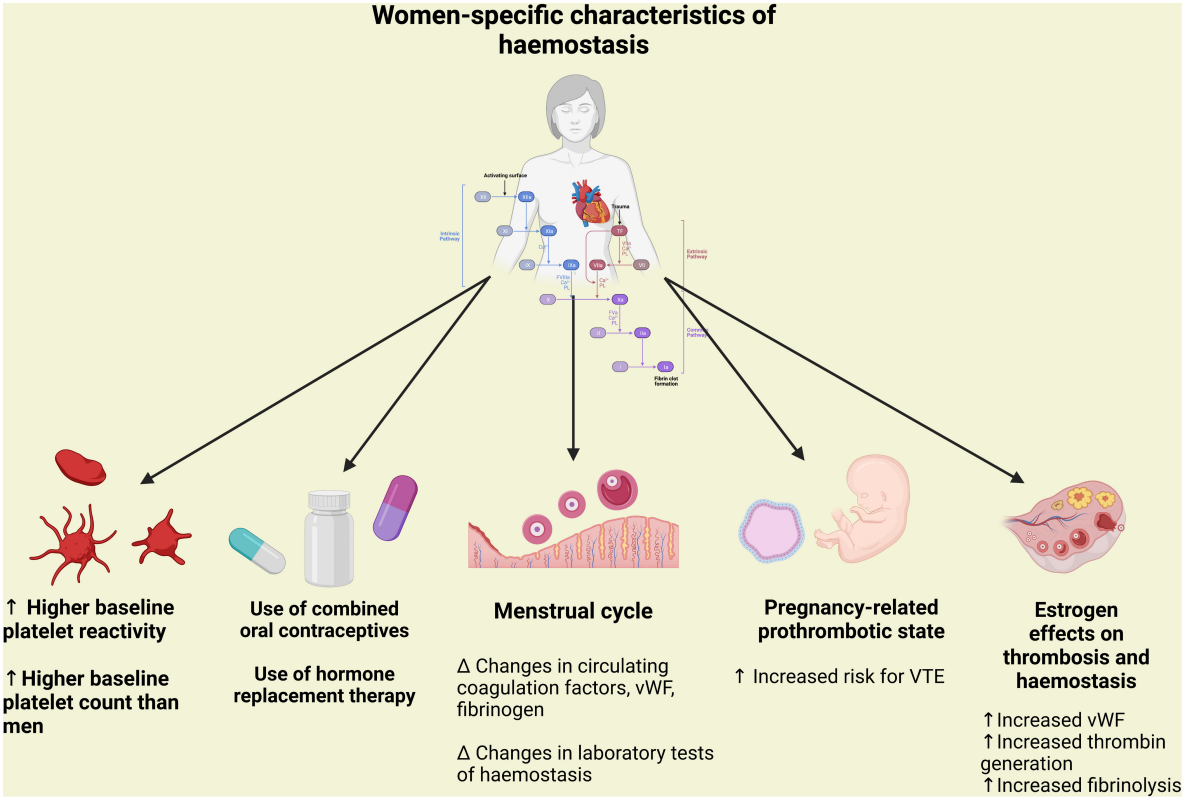


FIGURE 1
Peculiarity of hemostasis in women in terms of platelet aggregation and coagulation associated with pregnancy and hormonal status. vWF, Von Willebrand factor; VTE, venous thromboembolism.

(30). However, other studies opposed the previous ones, suggesting an equal platelet response to aspirin and P2Y12 inhibitors (40, 41–43).

However, the clinical implications of these findings remain unclear. Although the occurrence of major adverse cardiovascular and cerebrovascular events (MACCE) was significantly correlated to HPR, a recent meta-analysis, evaluating cardiovascular efficacy of clopidogrel, opposes the above-mentioned results and suggests no significant difference in treatment efficacy between men and women (44, 45). Similarly, two meta-analyses found no evident differences in clinical outcomes between sexes in patient treated with cardioaspirin (46, 47).

Taken together, women seem to have higher platelet reactivity than men at baseline, whereas conflicting data have been reported regarding platelet response to aspirin and P2Y12 inhibitors (**Figure 1**). Future studies are needed to determine if the possible sex difference in platelet reactivity could be addressed by the use of newer or different dosages of antiplatelet agents and if this will portend any impact on relevant clinical endpoints.

## Sex differences in coagulation

The coagulation cascade of secondary hemostasis is constituted by a series of reactions catalyzed by different enzymes, known as coagulation factors, ultimately resulting in cross-linked fibrin (48). This process is considerably influenced by fluctuations in hormone status associated with the menstrual cycle, pregnancy, menopause, hormone-based contraceptives and hormone replacement therapy (HRT) preparations (49). A cyclic variations of von Willebrand factor (VWF), fibrinogen, and activated factor VII have been reported during the normal menstrual cycle. Moreover, pregnancy and the oral administration of synthetic estrogens are associated with a progressive increase in the levels of procoagulant factors, VWF and fibrinogen and to a reduction in the activity of some coagulation regulatory proteins (tissue factor pathway inhibitor, protein S, protein C and antithrombin), leading to a hypercoagulable state (**Figure 1**) (49). These hormonal influences increase significantly the risk of venous thromboembolism, whereas their association with a higher risk of arterial thrombosis is still a matter of debate (31). Caution should be warranted when interpreting data on sex

differences in platelet function and coagulation, given the heterogeneity of *in vitro*, *ex vivo* and *in vivo* studies, the multiple clinical scenarios (i.e., pre-/post-menopausal states or pregnancy) and the different dosages, routes of administration and combinations of hormone-based therapies.

## Thrombotic risk in women within the spectrum of ischemic heart disease

Recently, the applicability of traditional risk factors in women (i.e., diabetes, smoking) has been questioned, as the majority of studies are predominantly conducted in the male population. Sex differences in the relative excess of cardiovascular risk associated with diabetes mellitus (DM) have been reported in several studies and have been confirmed by a recent meta-analysis of individual data from 980,793 adults; this analysis showed that women with DM exhibited a three-fold increased risk of cardiovascular mortality, whereas DM only doubles cardiovascular mortality risk in men (50). To date, the reason of this relative excess risk in women associated with the presence of DM is not elucidated.

Similarly, the impact of smoking on the development of IHD seems to be greater in women than in men (51). A recent meta-analysis including 2.4 million individuals reported that female smokers have a 25% greater risk of IHD compared with male smokers (52). Furthermore, obesity has a greater prognostic impact on women compared to men. In fact, the Framingham Heart Study showed that obesity increased the relative risk of IHD by 64% in women, as opposed to 46% in men (53). Data from 15,624 Norvegian individuals revealed that a similar increase in male or female body-mass index (BMI) was associated with a greater increase in systolic blood pressure in women than in men (54). However, BMI cannot be used as a comparable measure of fat tissue distribution between sexes, because it cannot discriminate between fat and fat-free mass. In fact, women result to have significantly greater amounts of total body fat than men with an equivalent BMI (55). Indeed, the pattern of lipid accumulation differs in women and men: women more often develop peripheral adiposity, with gluteal fat accumulation, whereas men are more prone to central or android obesity. However, after menopause, body fat distribution shifts to a more male pattern. Central fat, unlike peripheral adiposity, releases inflammatory mediators, which affect glucose and fat metabolisms and contribute to the development of metabolic syndrome (56). Nevertheless, BMI does not reflect fat distribution, as it is an exclusively quantitative parameter. In summary, BMI alone is not sufficient to properly assess the cardiometabolic risk associated with increased adiposity in women and other strategies, such as waist circumference measurement and bioimpedance analysis, should be implemented (57). Apart from traditional cardiovascular risk factors, there are a number of clinical conditions unique to women that have been identified to be associated with increased thrombotic risk. These include pregnancy disorders, such as pre-eclampsia, eclampsia, and gestational diabetes, gynecological disorders (i.e., polycystic ovary syndrome, early menopause), autoimmune and/or systemic inflammatory disease, known to disproportionally affect women compared to men (49) (**Figure 2**). As confirmation of the prognostic impact of non-traditional risk factors, nearly 20% of all coronary events occur in the absence of any traditional risk factors in women (51). Unfortunately, acquired awareness in thrombotic risk has not yet translated into changes in standard clinical care.

Double anti-platelet therapy score is the only tool endorsed by European and North-American guidelines to assess specifically thrombotic risk after PCI, identifying patients expected to derive benefit from continuing $P_2Y_{12}$ inhibitors beyond 1 year after PCI (58, 59). It was developed from the DAPT trial and validated in the PROTECT trial, but the proportion of women participating in each trial was subpar – 27 and 24%, respectively (60, 61). Even more, recent studies have shown women are less often prescribed antiplatelet therapy for secondary prevention, compared to men (51). Further outreach and awareness raising are necessary to ensure that gender with associated unique cardiovascular risk factors are included as important modifiers in thrombosis risk stratification scores, in order to guide clinicians in tailoring antithrombotic therapy after PCI, in terms of duration and intensity.

## Strategies aimed at reducing ischemic events

Multiple strategies focused on reducing the residual burden of ischemic events among patients at high ischemic risk, undergoing PCI, have been developed over the years (2). These include the use of newer $P_2Y_{12}$ inhibitors (i.e., prasugrel, ticagrelor, and cangrelor) instead of clopidogrel or the addition of GP IIb/IIIa inhibitors (GPI), prolonging DAPT duration and the addition of a novel oral anticoagulants (NOACs) to standard antiplatelet treatment regimens, a strategy also known as dual pathway inhibition (DPI) (2, 62–70). As mentioned above, women represent a category with a higher ischemic burden compared to men with similar cardiovascular risk factors. Therefore, women could potentially benefit from these strategies even more than men, although robust evidence is currently lacking due to low percentage of women enrolled in trials (**Table 1**). The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) trial, evaluating the addition of clopidogrel to aspirin in 12,562 patients with NSTEMI, showed women presented a smaller relative risk reduction (12% *vs.* 25%) in the composite endpoint of cardiovascular death, non-fatal AMI, or stroke compared with men at 1-year follow-up (71). Similar results were found in the subgroup of patients undergoing PCI (71).

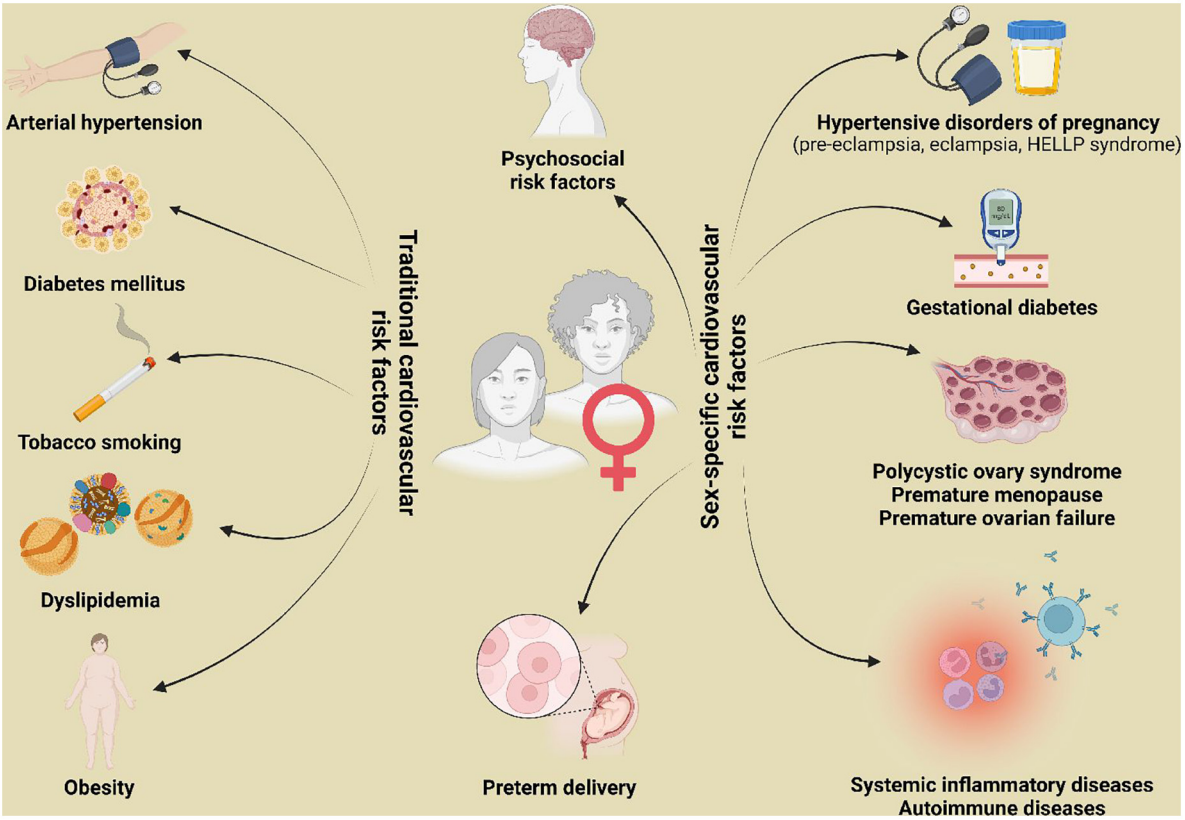


FIGURE 2
Traditional and sex-specific cardiovascular risk factors. HELLP, hemolysis, elevated liver enzymes and low platelets.

A subsequent meta-analysis of all blinded randomized clinical trials (RCTs) comparing clopidogrel and placebo and involving a total of 79,613 patients, confirmed the reduced efficacy in women compared to men: clopidogrel reduced only the risk of AMI and not that for stroke or all-cause mortality in women, whereas it reduced significantly all three endpoints in men (72, 73). Concerning ticagrelor and prasugrel, the PLATO trial and the TRITON-TIMI 38 trial, respectively, showed a similar reductions in the primary endpoint both in women and men, although these studies were not powered to examine treatment interactions among subgroups (74, 75). Similarly, two meta-analysis of randomized trials about PCI with adjunctive use of irreversible GPI (i.e., abciximab) or reversible GPIs (i.e., tirofiban or eptifibatide), demonstrated a similar efficacy both in men and women with no sex difference in terms of major adverse outcomes (76, 77). Accordingly, in a prespecified subgroup analysis of the CHAMPION PHOENIX trial, cangrelor demonstrated a similar reduction in the odds of major adverse cardiovascular events (MACE) in both sex (78).

Another strategy to reduce ischemic recurrences in patients at high ischemic risk, particularly those with prior AMI, is represented by prolongation of DAPT duration beyond 1 year. Dual Antiplatelet Therapy (DAPT) study, enrolling 9,961 patients, demonstrated, for the first time, that 30-month DAPT (with either clopidogrel 75 mg or prasugrel 10 mg) significantly reduced the primary endpoint of MACE, compared to 12-month DAPT (60). In a sub-group analysis, women randomly assigned to prolonged DAPT had a similar treatment effect for reduction in ischemic risk compared with males (79). Finally, the last strategy focused on reducing ischemic events is represented by DPI. To date, the low-dose rivaroxaban is so far the only NOAC to have been successfully tested as part of a DPI strategy in a phase III trial in patients with ACS (80). In particular, for patients with a recent ACS, low-dose rivaroxaban on top of standard of care antiplatelet therapy, most commonly aspirin and clopidogrel, reduced the risk of MACE and this benefit was significantly consistent only in the female subgroup of patients (81). In aggregate, a clear trend to a higher incidence of ischemic complications has been consistently reported in women. Strategies focused on reducing ischemic events appear to be equally effective in men and women, although the majority of trials are underpowered to assess differences in sex-specific subgroup analysis. Indeed, the main drawback of such intensive antithrombotic therapies is an enhanced risk of bleeding. It is, therefore, compelling for the scientific community to embark on dedicated clinical trials that will be equally inclusive to women as they are to men.

TABLE 1 List of major randomized controlled trials evaluating antiplatelet strategies focused on reducing ischemic events with sub-group analysis by sex.

| Name of study, year of publication | Drugs compared | Total patients | Number of women% | Primary outcome (reached?) | Gender difference in primary outcome |
|---|---|---|---|---|---|
| **Clopidogrel** | | | | | |
| CURE, 2001 | Clopidogrel + aspirin vs. aspirin | 12,562 | 38 | Death, non-fatal MI, stroke (yes) | Yes: lower primary outcomes among men taking clopidogrel |
| CREDO, 2002 | Clopidogrel + aspirin vs. aspirin | 2,116 | 28.6 | Death, non-fatal MI, stroke (yes) | Yes: lower primary outcome among men taking clopidogrel |
| **Potent P2Y12 inhibitors** | | | | | |
| TRITON-TIMI 38, 2007 | Prasugrel + aspirin vs. clopidogrel + aspirin | 13,608 | 5.8 | Death, MI, stroke (yes) | Yes: lower primary outcomes among men taking prasugrel |
| PLATO, 2009 | Ticagrelor + aspirin vs. clopidogrel + aspirin | 18,624 | 28.3 | Death, MI, stroke (yes) | No |
| ALPHEUS, 2020 | Ticagrelor + aspirin vs. clopidogrel + aspirin | 1,910 | 21 | PCI-related type 4 (a or b) MI or major myocardial injury (no) | No |
| **Prolonging DAPT duration** | | | | | |
| DAPT, 2014 | 12 months versus 30 months DAPT | 9,960 | 25.4 | ST, death, MI or stroke (yes) | Yes: lower primary outcome among men treated with 30 months DAPT |
| PEGASUS, 2015 | Ticagrelor + aspirin vs. clopidogrel + aspirin | 21,162 | 23.6 | Death, MI, stroke (yes) | No |
| THEMIS, 2020 | Ticagrelor + aspirin vs. placebo + aspirin among stable patients with DM | 19,220 | 31.4 | Cardiovascular death, MI or stroke (yes) | Yes: lower primary outcome among men treated with ticagrelor |
| **Guided escalation of P2Y12 inhibitors** | | | | | |
| GRAVITAS, 2011 | High-dose clopidogrel (150 mg) versus standard dose clopidogrel (75 mg) among clopidogrel non- responders | 2,214 | 35 | Cardiac death, non-fatal MI, or ST (no) | No |
| ARCTIC, 2012 | High-dose prasugrel versus standard dose clopidogrel (75 mg) among clopidogrel non- responders | 2,440 | 19 | All death, MI, ST, stroke and urgent revascularization (no) | No |
| PATH-PCI, 2019 | Ticagrelor among clopidogrel non-responders versus standard therapy | 2,285 | 17 | Cardiac death, MI, stroke, ST, urgent revascularization and bleeding (BARC 2,3 or 5) | Yes: lower primary outcome among men treated with ticagrelor |
| TAILOR PCI, 2020 | Ticagrelor among clopidogrel non-responders versus standard therapy | 5,302 | 25 | No | No |

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; PCI, percutaneous coronary intervention; ST, stent thrombosis.



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## Bleeding risk in women within the spectrum of ischemic heart disease

Bleeding events have a significant downstream impact on mortality and morbidity outcomes among patients undergoing PCI (82). Sex-related differences have been observed also in terms of bleeding risk. Data from 24,045 patients with ACS from the GRACE registry showed that female sex was significantly associated with a higher risk of bleeding (adjusted odds ratio of 1.43), even after controlling for the influence of other variables, including age, antithrombotic therapies, performance of invasive procedure and clinical presentation (83). These findings have been recently confirmed by a recent analysis of 4 post-approval ACS registries showing that the prevalence of high bleeding risk (HBR) according to the Bleeding Academic Research Consortium (BARC) definition was higher in women compared to men, with a consequent higher rate of major bleeding at 4 years (84).

This phenomenon can have multiple explanations. First, women tend to be older and more likely to have comorbidities such as diabetes, cronic kidney disease and hypertension at the time of IHD – these are well-known risk factors for future hemorrhagic events (32). Second, women have a higher risk for the development of vascular complications following PCI, probably due to smaller blood vessels in women, as well as difference in vascular reactivity (85). Finally, women may have a tendency to receive inappropriate dosing of antithrombotic agents, because no difference in dose recommendation currently exist, although women have, at least in part, a lower body weight, an older age, and a higher rate of renal insufficiency, despite similar serum creatinine levels, compared to men (30).

In order to estimate bleeding risk in patients with IHD, European Society of Cardiology (ESC) and North-American guidelines recommend the use of several scores, such as the CRUSADE score, the ACUITY score, the PARIS score and the ARC-HBR criteria. Furthermore, PRECISE-DAPT score have been designed to guide and inform decision making for patients on DAPT following PCI, integrating both ischemic and bleeding risks (86). Surprisingly, female sex appears only in the CRUSADE and in the ACUITY scores among predictor variables, although it clearly represents a risk factor for bleeding after PCI.

In conclusion, in the last two decades, a remarkable amount of data has consistently demonstrated sex-related differences in bleeding risk after PCI. Nevertheless, it has not translated into the adoption of standardized different recommendations, according to patient's sex. This uncertainty is reflected by international recommendations on duration of DAPT, with female sex being included among the bleeding risk factors in the North-American but not the European guidelines (58, 87).

## Strategies aimed at reducing bleeding events

Bleeding has been recognized as a prognostically unfavorable event to the same extent as having a new or recurrent ischemic or thrombotic complication (88). The risk of bleeding tends to be stable over time while ischemic risk decreases after 1–3 months post-PCI, with a variability according to the clinical presentation of the patients and the complexity of the procedure (89). Therefore, after 1–3 months post-PCI, a series of pharmacological strategies can be implemented in order to reduce bleeding, possibly yielding a more favorable balance between bleeding and ischemic risk.

These strategies might include shortening of DAPT duration, the use of $P_2Y_{12}$ monotherapy and de-escalation of $P_2Y_{12}$ inhibitors (2, 90). Although they may be particularly appealing in women in light of their higher bleeding risk, these strategies are not extensively investigated in this subset of patients (**Table 2**). In addition, there are other non-pharmacological bleeding avoidance strategies, such as vascular closure device application, the use of radial access or the combination of these (88). Of note, the use of radial access resulted in a decrease in the rate of bleeding events to a greater extent in women, compared to men (91).

Shortening of the DAPT duration has been the most largely investigated strategy and traditionally consists of the withdrawal of the $P_2Y_{12}$ inhibitor at the time earlier than conventional (12 months post-ACS) (2, 92–96). Sawaya et al. (97) pooled individual patient data from six RCTs comparing short- ($\leq$6 months) versus long-term ($\geq$1 year) DAPT after PCI. They showed short-term DAPT is associated with similar rates of MACE but lower risk of bleeding when compared with prolonged DAPT, with no significant difference between sexes. Although the hazard ratio of any bleeding and major bleeding suggest benefit in the subgroup of women, the *p*-value did not reach statistical significance. This is likely due to the fact that women were largely underrepresented in the above RCTs (about 30% of the overall population) thus not allowing a formal statistical power to be reached (97). Another important finding of this patient-level meta-analysis is that patient factors (ACS and diabetes) and lesion complexity (number of lesions stented and number of stents used) predicts the occurrence of MACE in women, underlying the importance of an accurate baseline risk stratification (97).

In the past 5 years, early aspirin discontinuation in patients undergoing PCI has emerged as a potential strategy to reduce bleeding without any increase in thrombotic events. To date, six RCTs with 36,350 patients (23.3% patients were female) have compared DAPT versus $P_2Y_{12}$ inhibitor monotherapy after a short duration of DAPT in patients after PCI (2, 98–102). An individual patient data meta-analysis of these six RCTs has been performed and showed that the use of $P_2Y_{12}$ monotherapy was associated with a significant reduction in the

TABLE 2 List of major randomized controlled trials evaluating antiplatelet strategies focused on reducing bleeding events with sub-group analysis by sex.

| Name of study, year of publication | Drugs compared | Total patients | Number of women% | Primary outcome (reached?) | Gender difference in primary outcome |
|---|---|---|---|---|---|
| **Shortening DAPT** | | | | | |
| ISAR-SAFE | 6 versus 12 months DAPT | 2,015 | 19.4 | All-cause death, MI, ST, stroke, and TIMI major bleeding (yes) | No |
| NIPPON, 2017 | 6 versus 18 months DAPT | 3,773 | 21 | All-cause death, MI, stroke and major bleeding (yes) | No |
| SMART DATE, 2018 | 6 versus 12 months DAPT | 2,712 | 25 | All-cause death, MI or stroke (yes) | No |
| One-month DAPT, 2021 | 1 versus 6–12 months DAPT in non-complex PCI | 3,020 | 31 | Cardiac death, non-fatal MI, target vessel revascularization, stroke or major bleeding (yes) | No |
| MASTER DAPT, 2021 | 1 versus 5 months DAPT in HBR patients | 4,434 | 30.7 | All-cause death, MI, stroke or major bleeding (yes) | No |
| **P2Y12 monotherapy** | | | | | |
| GLOBAL LEADERS, 2018 | Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy versus aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy | 15,968 | 23 | All-cause death and MI (yes) | No |
| TWILIGHT, 2019 | Ticagrelor monotherapy after 3 months DAPT versus DAPT in high-risk PCI | 7,119 | 23.8 | BARC (2, 3, or 5) bleeding and all-cause death, non-fatal MI or non-fatal stroke (yes) | No |
| SMART-CHOICE, 2019 | P2Y12 monotherapy after 3 months DAPT versus standard DAPT | 2,993 | 26 | All-cause death, MI or stroke (yes) | No |
| STOPDAPT-2, 2019 | Clopidogrel monotherapy after 1 month of DAPT versus standard DAPT | 3,045 | 22 | Cardiac death, MI, stroke, ST, bleeding (yes) | No |
| TICO, 2020 | Ticagrelor monotherapy after 3 months of DAPT versus standard DAPT | 3,056 | 20.5 | Major bleeding, death, MI, ST, stroke, or target-vessel revascularization (yes) | Yes: lower primary outcomes among women taking ticagrelor monotherapy |
| STODAPT-2-ACS, 2021 | Clopidogrel monotherapy after 1 month of DAPT versus standard DAPT among ACS | 4,169 | 22 | Cardiac death, MI, any stroke, definite ST or bleeding (no) | No |
| **Guided de-escalation** | | | | | |
| ANTARTIC, 2016 | Guided de-escalation versus standard DAPT | 877 | 39 | Cardiac death, MI, stroke, ST, urgent revascularization and BARC (types 2, 3, or 5) bleeding (no) | No |
| TROPICAL-ACS, 2017 | Guided de-escalation versus standard DAPT | 2,610 | 21.5 | Cardiac death, MI, stroke and BARC (types 2, 3, or 5) bleeding (yes) | No |
| POPular genetics, 2019 | Guided de-escalation versus standard DAPT | 2,488 | 25 | All-cause death, MI, ST, stroke or major bleeding (yes) | No |

*(Continued)*



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TABLE 2 (Continued)

| Name of study, year of publication | Drugs compared | Total patients | Number of women% | Primary outcome (reached?) | Gender difference in primary outcome |
|---|---|---|---|---|---|
| **Unguided de-escalation** | | | | | |
| TOPIC, 2017 | Clopidogrel-based DAPT versus standard DAPT | 646 | 18 | Cardiac death, urgent revascularization, stroke and BARC (2, 3, or 5) bleeding (no) | No |
| HOST-REDUCE-POLYTECH-ACS, 2020 | Prasugrel 5 mg-based DAPT versus prasugrel 10 mg-based DAPT | 3,429 | 10.7 | All-cause death, non-fatal MI, ST, repeat revascularization, stroke and BARC (2, 3 or 5 bleeding) (yes) | No |
| TALOS-MI, 2021 | Ticagrelor among clopidogrel non-responders versus standard therapy | 2,697 | 16.5 | Cardiac death, MI, stroke, ST, urgent revascularization and bleeding (BARC 2, 3, or 5) | Yes: lower primary outcome among men treated with ticagrelor |

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; PCI, percutaneous coronary intervention; ST, stent thrombosis; TIMI, thrombolysis in myocardial infarction.

rate of bleeding without any increase in the rate of ischemic events (103). Interestingly, they investigated the consistency of these findings according to sex. Concerning the bleeding events, the treatment effect was consistent both in male and female patients, with a statistically significant reduction in both groups (103). Surprisingly, they observed a treatment-by-subgroup interaction with sex suggesting that $P_2Y_{12}$ inhibitor monotherapy lowers the risk of the primary ischemic endpoint in women but not in men (103). Whether this depends on a different response to aspirin and/or $P_2Y_{12}$ inhibitor remains the matter of debate. Female patients represent a subgroup, therefore, this finding should be considered hypothesis-generating only, due to intrinsic methodological and statistical limitations of subgroup analyses.

De-escalation of $P_2Y_{12}$ inhibiting therapy consists in switching from more potent (i.e., prasugrel or ticagrelor) to less potent (i.e., clopidogrel) agents, in order to reduce bleeding without any trade-off in ischemic events (104). De-escalation can be un-guided or guided through the aid of platelet function or genetic tests (105–108). A guided de-escalation strategy has been investigated in three RCTs, using either platelet function testing ($n$ = 2) or genetic testing ($n$ = 1) (109–112). TROPICAL ACS trial showed that guided de-escalation was non-inferior for the primary composite endpoint of net adverse cardiovascular events (NACE) as compared to standard of care, with a trend, although not statistically significant, toward reduced bleeding at 12 months compared to the standard group. Furthermore, a prespecified analysis of the TROPICAL-ACS trial investigated the impact of sex on clinical outcomes and found no significant interaction of sex with combined endpoint, ischemic events and bleeding.

POPular GENETICS trial showed that genotype-guided strategy was non-inferior for NACEs and superior in terms of PLATO major or minor bleeding, as compared to standard of care at 12-month follow-up. However, the reduction of bleeding became statistically insignificant in the subgroup of female patients, due to a relatively small sample size, which resulted in a broad 95% confidence interval.

Finally, it is worth considering the possible impact of herbal therapies on hemostasis and, consequently, on bleeding events. Multiple surveys have shown that women (especially white, middle-aged women, with good sociocultural status) are likely to be users of unconventional therapies, among which herbs play a prominent role (113). One of the most used is Ginkgo biloba, a species of tree native to China, from which an extract is obtained. It is commonly used as an antioxidant, to treat claudication intermittens and vascular dementia, although there is no evidence for its beneficial effects. Since it antagonizes platelet-activating factor, it predisposes to bleeding, especially in patients on aspirin or warfarin (114).

In short, it has been well-established for decades that women are at greater risk of bleeding. However, although various pharmacological strategies have been developed to minimize

TABLE 3 Safety of anti-thrombotic drugs during pregnancy and breastfeeding.

| Drugs | Risk category | Placenta permeable | Transfer to breast milk | Safety data |
|---|---|---|---|---|
| **Antiplatelet drugs** | | | | |
| Abciximab | C | Unknown | Unknown | Inadequate human studies |
| Acetylsalicylic acid (low dose) | B | Yes | Yes (no adverse effects reported) | No teratogenic effects (inadequate human studies regarding the use of doses between 100–500 mg/day) |
| Cangrelor | C | Unknown | Unknown | No human data |
| Clopidogrel | B | Unknown | Yes | No adequate human data |
| Prasugrel | – | Unknown | Yes | Inadequate human data |
| Ticagrelor | – | Unknown | Yes | Inadequate human data; not recommended |
| Ticlopidine | C | Unknown | Yes | Inadequate human data |
| Vorapaxar | – | Unknown | Yes | Inadequate human data |
| Anticoagulants | | | | |
| Acenocoumarol | D | Yes | Yes (no adverse effects reported) | Embryopathy (mainly first trimester), |
| Apixaban | – | Yes | Yes | No human data: not recommended |
| Dabigatran | – | Yes | Unknown | No human data; not recommended |
| Edoxaban | – | Unknown | Yes (contraindicated in breastfeeding) | Contraindicated; Hokusai-VTE study: 10 cases with exposure in first trimester, for up to 6 weeks. Results: six live births (four full term and two pre-term), one first trimester spontaneous abortion, and three elective terminations |
| Fondaparinux | – | Yes | Yes | Inadequate human data |
| Heparin (low molecular weight) | B | No | No | Retrospective cohort study with 693 live births: no increased risk of major developmental abnormalities |
| Heparin (unfractionated) | B | No | No | Human data: no fetus abnormalities |
| Phenprocoumon | D | Yes | Yes | Coumarin embryopathy |
| Rivaroxaban | – | Yes | Yes | Inadequate human data (contraindicated) |
| Warfarin | D | Yes | Yes | Coumarin embryopathy |

this risk, none of these have been extensively tested in female population. Therefore, evidence on their safety and efficacy in this subset of patients is lacking.

# Specific clinical conditions

## Atrial fibrillation

The prevalence and incidence of atrial fibrillation (AF) has been increasing in both sex over time (115). The number of women and men with AF are similar, despite the higher risk of AF in men, due to women's increased longevity (115). AF increases the risk of stroke fivefold, but this risk is not homogeneous, depending on the presence of specific stroke risk factors. Common stroke risk factors are summarized in the $CHA_2DS_2$-VASc score, among which female sex is included (115). Of note, female sex has to be considered a stroke risk modifier rather than a risk factor *per se* (115). In the absence of other risk factors, women have a stroke risk similar to men, whereas women with other risk factors have significantly higher stroke risk than men (116). Women affected by AF and concomitant IHD are on average older and with more comorbidities than their male counterparts (117). Nevertheless, although they are at greater risk for stroke than men, they are significantly less likely to receive oral anticoagulants at all levels of the $CHA_2DS_2$-VASc score, paradoxically (118). The efficacy and

safety of NOACs have been broadly demonstrated in overall population, even within 5 days after cardioembolic stroke (119, 120).

Sex differences in the efficacy and safety of warfarin compared to NOACs have long been investigated. According to a meta-analysis of 26,260 patients, women with AF have a significantly greater residual risk of systemic thromboembolism (STE) when treated using warfarin, whereas women treated with NOACs are at equivalent residual risk of STE and less major bleeding risk compared with men (121). Therefore, NOACs should be the anticoagulants of choice even more than in men.

Since NOACs have a different pharmacological profile compared to vitamin K antagonists, they may differ from one another in their effects on women with AF. An indirect comparison of them was performed, using data from foundational anticoagulant trials such as ROCKET-AF, RE-LY, ENGAGE-AF-TIMI and ARISTOTLE in which warfarin was used as an indirect comparator. No significant difference was found for any NOAC in terms of safety and efficacy in women with AF (122). Thus, a recent consensus document of the European Heart Rhythm Association (EHRA) indicates that the choice of the type of NOAC in females should follow general principles set for the overall population (123).

Nevertheless, data from adequately powered RCTs are needed to reach high quality evidence in the use of NOACs in women with concomitant AF for the prevention of STE. In general, 10–15% of AF patients undergo PCI for IHD and guidelines recommended TAT (triple antithrombotic therapy) for a certain time period after PCI in AF patients (115). However, there is still uncertainty whether TAT or double antithrombotic therapy (DAT) should be the first line choice for the majority of patients after hospital discharge. Holm et al. conducted an analysis on 272 patients discharged with TAT registered in the SWEDEHEART registry and showed that women discontinued TAT prematurely due to bleeds to a very high extent compared to men (124). Despite this, the rate of coronary events did not differ between sexes, although the study was underpowered to assess a possible sex difference in association between TAT discontinuation and ischemic events (124). To date, there are no sex analyses derived from RCTs regarding DAT and TAT to guide in treatment strategies, since data from RCTs were not powered to assess MACE, nor even differences among sex-specific subgroups (125–127).

## Spontaneous coronary artery dissection

Spontaneous coronary artery dissection is the most common cause of pregnancy-associated AMI and represents 35% of ACS cases among women under the age of 50 (49). The gold standard for diagnosis of SCAD is coronary angiography (128). However, the use of intravascular imaging, such as optical coherence tomography (OCT) or intravascular ultrasound (IVUS), could be useful to differentiate SCAD from atherosclerotic plaque, when diagnostic uncertainty exists, or to guide coronary intervention, when clinically required (128).

There seems to be a general consensus indicating that the initial conservative medical management is appropriate in most SCAD cases, whereas interventional treatment (i.e., PCI or coronary artery bypass grafting, CABG) should be considered in selected cases such as SCAD complicated by refractory ongoing ischemia, hemodynamic instability or sustained ventricular tachyarrhythmias (128).

The antiplatelet regimen to be used in patients treated conservatively is still a matter of debate, since there are no RCTs comparing different pharmacological treatment strategies for SCAD. Whilst DAPT is the most commonly prescribed strategy in SCAD (usually with aspirin and clopidogrel rather than newer $P_2Y_{12}$ inhibitors), recent data from DISCO registry showed that DAPT was associated with a higher rate of MACE at 12 months of follow-up, driven by an early excess of non-fatal AMI or unplanned PCI (129). DAPT may cause enhancement of intramural bleeding, with subsequent propagation of the dissection and higher rate of adverse events. To support this hypothesis, Garcia-Guimaraes et al. reported that the presence of long intramural hematoma (>20 mm) is an independent predictor of in-hospital MACE in patients treated with DAPT (130). Therefore, DAPT may be actually harmful in conservatively managed SCAD patients, especially in those with contained IMH (i.e., type 2 SCAD). In case of SCAD occurring during pregnancy, particular attention should be paid to the choice of antithrombotic drugs, due to potential adverse effects to fetus (**Table 3**).

In conclusion, intravascular imaging plays a key role in the diagnosis and management of ACS in women, allowing to differentiate SCAD from other causes of ACS and, in case of SCAD, to characterize its specific endotype and to guide medical therapy.

# Gender differences in participation in clinical trials: The who, what, why, when, how, and where

Women are still underrepresented in both early and later phase studies. The reasons for this phenomenon may be several. Traditionally, females were considered to have a more biological variability than males due to hormonal

variations associated with estrous and menstrual cycles (131). Preclinical and clinical studies, recently, have refuted this theory, showing that females data are not more variable than those of males (132). Another reason could be that women affected by IHD are on average older than male counterparts and the enrollment of elderly patients in clinical trials has been historically low due to their frailty and comorbidities (133). Furthermore, women are less frequently referred to interventional treatment for ACS due to underestimation or misinterpretation of symptoms and are less likely to be treated with guideline-directed medical therapy (134). Interestingly, an RCT, enrolling 783 participants across 13 clinical centers, demonstrated that women present lower distrust of medical researchers and perceived greater risk of harm from trial participation than men (135). However, after disclosure of investigator patent ownership or monetary incentives, willingness to participate increased more in women than in men. This suggests that female aversion for participating in a scientific experiment could be, at least partially, overcomed by active and informed involvement in trial's participation. Lastly, the research for sex differences may not necessarily involve a doubling of the pre-determined sample size (and costs) in order to reach an adequate statistical power. A recent statistical model, using factorial designs and tested for now only in animal studies, revealed necessary increases of only 14–33% to include both sexes, even after statistical correction for the use of multiple factors (136). Nevertheless, further studies are needed to validate this model in clinical trials.

## Conclusion

Thirty one year after defining the "Yentl syndrome," women are still understudied, underdiagnosed and undertreated. Their representation in RCTs is still too low (at most 30% of the overall trial population), although their pharmacodynamic and pharmacokinetic responses to antithrombotic drugs and their baseline bleeding and ischemic risks may differ significantly from males. Furthermore, investigations about antiplatelet drug safety and efficacy should not end with regulatory approval. Phase 4 studies, real-world data and systematic adverse-event reporting are critical to detect bleeding, ischemic events and off-target toxicities. A recent report from Hilleary et al. compared the proportion of females with an established diagnosis of IHD that received patient education, in terms of diet, exercise, tobacco use and weight reduction, with the corresponding proportion of males (137). Surprisingly, it revealed that a lower proportion of women received patient education related to managing cardiovascular risk, after adjusting for covariates. Accordingly, a lower proportion of women reaches cardiovascular risk factor target levels, as EUROASPIRE V registry has recently showed (138). Overall, a gender gap still exists for risk factor target management in secondary prevention, mostly in disfavor of women. Therefore, more deliberate and intentional effort needs to be performed in closing this gender gap, especially since risk factors like smoking and diabetes may have an even more detrimental effect in female patients, as mentioned above. In the era of precision medicine, it is unacceptable that women are treated "just like men" and viewed as a negligible minority. Historically, women's health research has focused on reproductive health, a phenomenon known as "bikini medicine" (139). Now, it's time that cardiovascular research efforts move away from mere awareness about gender differences to palpable and concrete action. "Go Red for Women" campaign, launched in 2004 by the American Heart Association, is pushing in this direction, in order to increase awareness and foster specific guidelines for prevention and treatment of IHD in women. Recently, POPular AGE trial and ELDERLY-ACS trial have evaluated safety and efficacy of different anti-platelet regimens in elderly, a clinical minority under-represented in RCTs, as women (140–142). Similarly, RCTs recruiting a significant proportion of women could be the solution to overcome the "Yentl syndrome."

## Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

## Conflict of interest

Author MG was declares that he has received consulting fees or honoraria from Terumo, outside the present work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Short dual antiplatelet therapy and dual antiplatelet therapy de-escalation after primary percutaneous intervention: For whom and how

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Dual antiplatelet therapy (DAPT) for 6–12 months, followed by lifelong aspirin monotherapy is considered an effective standard therapy for the prevention of thrombo-ischemic events in patients with acute and chronic coronary syndrome (ACS, CCS) undergoing percutaneous coronary intervention (PCI) or after a primarily conservative treatment decision. In ACS patients, the stronger $P2Y_{12}$-inhibitors ticagrelor or prasugrel are recommended in combination with aspirin unless the individual bleeding risk is high and shortening of DAPT is warranted or clopidogrel is preferred. However, also in patients at low individual bleeding risk, DAPT is associated with a higher risk of bleeding. In recent years, new antithrombotic treatment strategies, such as shortening DAPT followed by early $P2Y_{12}$-inhibitor monotherapy and de-escalating DAPT from potent $P2Y_{12}$-inhibitors to clopidogrel by maintaining DAPT duration time, have been investigated in clinical trials and shown to reduce bleeding complications in cardiovascular high-risk patients without negative effects on ischemic events. In this review, we summarize the current knowledge and discuss its implication on future antithrombotic strategies in terms of a personalized medicine.

KEYWORDS

**percutaneous coronary intervention (PCI), short dual antiplatelet therapy (short DAPT), de-escalation, $P2Y_{12}$-inhibitor, bleeding**

## Introduction

Dual antiplatelet therapy (DAPT) is the cornerstone in the prevention of thrombo-ischemic events in patients with acute and chronic coronary syndrome (ACS, CCS) after primary percutaneous intervention (PCI). European Society of Cardiology (ESC) guidelines recommend a combination of aspirin with ticagrelor or with prasugrel for

a period of 6 (CCS) to 12 (ACS) months, followed by a lifelong aspirin monotherapy in patients with low bleeding risk (Class Ia indication) (1, 2). DAPT duration should be adjusted to the individual patient's bleeding risk using appropriate risk scores, such as the DAPT and the PRECISE-DAPT score. In patients at high bleeding risk (HBR), DAPT can be shortened (< 6 or < 12 months) by early withdrawal of the $P2Y_{12}$-inhibitor (1, 2). In patients with high ischemic risk and without increased risk of major bleeding, DAPT can be extended (> 12 months) after ACS (1). However, standard DAPT has been shown to effectively reduce major adverse cardiovascular events (MACE) in patients after PCI but is associated with increased risk of bleeding (3). Accordingly, safe antiplatelet strategies reducing bleeding rates but without adverse effects on ischemic outcomes are mandatory. To address this issue, new antithrombotic treatment strategies for cardiovascular high-risk patients have been evolved and investigated in clinical trials in recent years. In this review, we focus on the current knowledge of short DAPT followed by early $P2Y_{12}$-inhibitor monotherapy and on DAPT de-escalation from potent $P2Y_{12}$-inhibitors to clopidogrel in terms of a personalized medicine (**Figure 1**).

## P2Y12-inhibitor monotherapy after short dual antiplatelet therapy

According to ESC guidelines, short DAPT originally consists of early $P2Y_{12}$-inhibitor withdrawal and subsequent lifelong aspirin monotherapy, as it should be considered for non-ST-elevation (NSTE)-ACS patients with stent implantation who are at high risk of bleeding (1). More recently, however, short DAPT refers to discontinuation of aspirin in favor of monotherapy with a strong oral $P2Y_{12}$-inhibitor after an initial 1–3-month period of DAPT. This intriguing treatment approach presents a promising option to reduce bleeding risk in CCS and ACS patients after PCI and has recently been investigated in several trials (4–10).

Moreover, three meta-analyses demonstrated that withdrawal of aspirin in favor of $P2Y_{12}$-inhibitor monotherapy after 1–3 months of DAPT significantly reduced the risk of major bleeding without increasing ischemic endpoints (11–13). In ACS patients, $P2Y_{12}$-inhibitor monotherapy reduced bleeding risk by 50% (HR 0.50, 95% CI 0.41–0.61, $p < 0.001$) with no significant change in MACE rates when compared with standard DAPT (HR 0.85, 95% CI 0. 70–1.0, $p = 0.09$) (12). Current data highlight the large contribution of aspirin to the bleeding risk of DAPT (13). However, it is important to note that between trials, patient populations differed in terms of their bleeding risk and selection of $P2Y_{12}$-inhibitor.

## Trials on $P2Y_{12}$-inhibitor monotherapy after short dual antiplatelet therapy

### With clopidogrel

Three large scaled randomized controlled trials (RCTs) provide 1-year data on clopidogrel monotherapy after short DAPT in patients undergoing PCI (**Table 1**) (4–6). In a population of CCS (58%) and ACS (42%) patients at low-to-moderate bleeding risk, the results of the Effect of $P2Y_{12}$ Inhibitor Monotherapy vs. Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention (SMART-CHOICE) trial showed, that clopidogrel monotherapy after 3 months of DAPT was non-inferior to standard DAPT with respect to the primary ischemic endpoint (all-cause death, MI, or stroke) (95% CI $-\infty$-1.3%, $p_{\text{non-inferiority}} = 0.007$) (4). In addition, the short DAPT strategy resulted in significantly lower bleeding rates [Bleeding Academic Research Consortium (BARC) 2–5] when compared with standard therapy (2.0% vs. 3.4%, HR 0.58, 95% CI 0.36–0.92, $p = 0.002$) (4).

Moreover, the Japanese Results of the Effect of 1-month Dual Antiplatelet Therapy followed by Clopidogrel vs. 12-month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients receiving PCI (STOPDAPT-2) trial indicated that in ACS (38%) and CCS (62%) patients at low-to-moderate bleeding risk, clopidogrel monotherapy following an even shorter DAPT period of 1 month reduced bleeding rates [Thrombolysis in Myocardial Infarction (TIMI) major or minor bleedings] without causing a significant increase in primary combined endpoint event rates [cardiovascular (CV) death, myocardial infarction (MI), stent thrombosis (ST), stroke or TIMI major or minor bleeding] (HR 0.26, 95% CI 0.11–0.64, $p = 0.004$ and HR 0.64, 95% CI 0.42–0.98, $p = 0.04$, respectively) (5). While these data have shown safety for very early clopidogrel monotherapy in predominantly stable patients, the results of the STOPDAPT-2-ACS trial suggest, that this does not apply to unstable patients (6). This study, enrolling only ACS patients ($n = 4{,}169$), failed to meet their primary non-inferiority endpoint (of CV death, MI, ST, stroke or TIMI major or minor bleeding) at 12 months (HR 1.14, 95% CI 0.80–1.6, $p_{\text{non-inferiority}} = 0.06$) (6). Patients in the short DAPT group further presented a numerically but not significantly higher incidence of the major secondary cardiovascular endpoints than patients treated with standard DAPT (2.76% vs. 1.86%, HR 1.50 95% CI 0.99–2.26) (6).

The aforementioned trials show that clopidogrel monotherapy after short DAPT presents a safe therapeutic option to reduce bleeding rates in stable patients at low-to-moderate bleeding risk and mixed ischemic risk (includes low, moderate, and high ischemic risk). However, these data do not extend to patients in high-risk settings. In this regard, the High

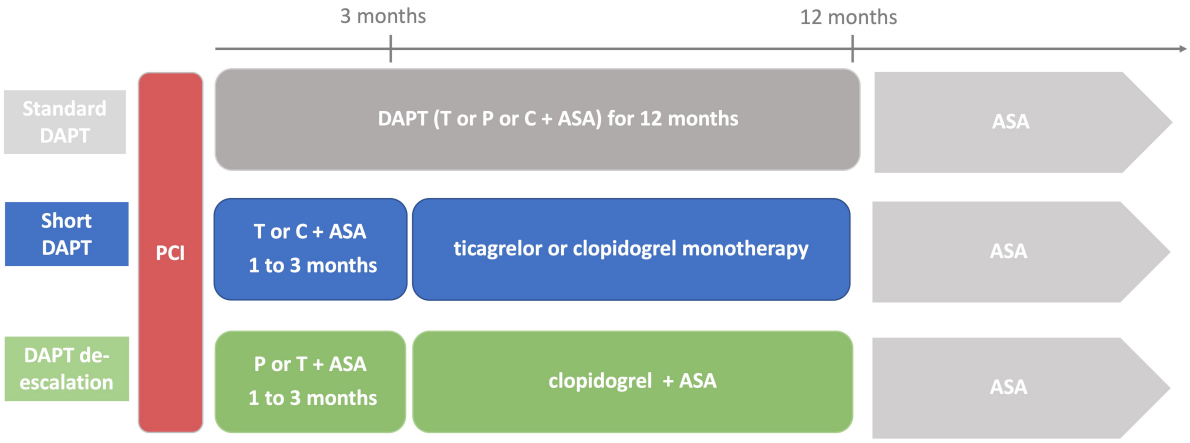


FIGURE 1
Antithrombotic strategies of Standard DAPT, Short DAPT and DAPT De-escalation. DAPT: dual antiplatelet therapy, T: Ticagrelor, P: Prasugrel, C: Clopidogrel, ASA: Acetylsalicylic Acid.

Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated vs. Standard DAPT Regimen (MASTER-DAPT) trial was the first to selectively include patients at high bleeding risk, demonstrating that even in these patients, short DAPT followed by single antiplatelet therapy is a safe strategy to prevent bleeding after PCI (**Table 1**) (7). Specifically, 1-month DAPT proved non-inferior to standard DAPT in terms of the primary combined endpoint (all-cause death, MI, stroke, BARC type 3, or 5) and was associated (95% CI:-1.80 to 33, $p_{\text{non-inferiority}} < 0.001$) with a lower incidence of major or clinically relevant non-major bleedings (BARC type 2, 3, or 5) (6.5% vs. 9.11%, 95% CI:-4.40 to 1.24, $p_{\text{non-inferiority}} < 0.001$) at 11 months (7).

## With ticagrelor

The GLOBAL LEADERS (Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs. aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent) trial compared 1-month DAPT followed by ticagrelor monotherapy with 12 months of DAPT after PCI. In this trial, patients at low bleeding risk and mixed ischemic risk were included (**Table 2**) (8). The trial failed to show that 23-month ticagrelor monotherapy after short DAPT was associated with lower primary endpoint events (all-cause death, MI) (RR 0.87, 95% CI 0.75–1.01, $p = 0.073$). However, non-inferiority was met and bleeding rates (BARC type 3, or 5) were similar between groups (2.04% vs. 2.12%, RR 0.97, 95% CI 0.78–1.20, $p = 0.77$) (8). Consistent findings with respect to the primary efficacy and safety endpoints were demonstrated in the prespecified GLOBAL LEADERS Adjudication Sub-Study (GLASSY) (9). Moreover, a 31% relative risk reduction in urgent target vessel revascularization (TVR) (1.87% vs. 2.72%, RR 0.69, 95% CI 0.51–0.93) was found in the experimental arm and shown to increase consistently over time (9). Short DAPT was further associated with lower rates of MI (RR 0.54, 95% CI 0.33–0.88, $p_{\text{interaction}} = 0.062$) and ST (RR 0.14, 95% CI 0.03–0.63; $p_{\text{interaction}} = 0.007$) at 12-month follow-up, indicating that ticagrelor monotherapy may have beneficial effects on the occurrence of MI and ST when compared with aspirin alone (9).

In The Ticagrelor with or without Aspirin in High-Risk Patients after PCI (TWILIGHT) trial, 7,119 patients (64% ACS, 36% CCS) at low bleeding and mixed ischemic risk were enrolled (10). Ticagrelor monotherapy after DAPT of 3 months was associated with a 44% lower risk of bleeding (BARC type 2,3, or 5) than standard DAPT (HR 0.56, 95% CI 0.45–0.68, $p < 0.001$) with no significant increase in MACE (death, MI, stroke) (HR 0.99, 95% CI 0.78–1.25, $p_{\text{non-inferiority}} < 0.001$) over 15 months after PCI (10). Several prespecified subgroup-analyses (patients at HBR, ACS, complex PCI, diabetes, gender) demonstrated comparable outcomes (11–15).

Further, the Ticagrelor Monotherapy vs. Dual-Antiplatelet Therapy After PCI (SIDNEY) meta-analysis, including data from GLASSY and TWILIGHT, provides strong evidence for the reduction of bleeding rates with ticagrelor monotherapy (16).

Focusing on unstable patients after PCI, Franzone et al. demonstrated that safety effects of ticagrelor monotherapy after 1-month DAPT on ischemic endpoints were consistent in patients with or without ACS, but only ACS patients had a net clinical benefit in regards of a composite endpoint of both co-primary study endpoints from GLASSY (17). The South Korean Effect of Ticagrelor Monotherapy vs. Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome (TICO) trial was the only trial to prospectively investigate ticagrelor monotherapy exclusively in ACS patients (18, 19). Switching to ticagrelor monotherapy after 3 months of DAPT significantly reduced primary adverse clinical events (TIMI major bleeding, all-cause

TABLE 1 Baseline characteristics of randomized-controlled trials on short dual antiplatelet therapy following clopidogrel monotherapy.

| Study | *n* | Ischemic and bleeding risk | Ethnicity | Clinical setting (%) | | DAPT duration | Follow-up (months) | Primary endpoint | Primary endpoint met |
|---|---|---|---|---|---|---|---|---|---|
| | | | | ACS | CCS | | | | |
| SMART-CHOICE | 2,993 | Low-to-moderate bleeding risk, low-to-moderate ischemic risk | East Asian | 58 | 42 | 3 vs. 12 months | 12 | All-cause death, MI, or stroke | Yes |
| STOPDAPT-2 | 3,045 | Low-to-moderate bleeding risk, low-to-moderate ischemic risk | East Asian | 38 | 62 | 1 vs. 12 months | 12 | CV death, MI, ST, stroke, or TIMI major or minor bleeding | Yes |
| STOPDAPT-2-ACS | 4,169 | Low-to-moderate bleeding risk, mixed ischemic risk* | East Asian | 100 | 0 | 1 vs. 12 months | 12 | CV death, MI, ST, stroke, or TIMI major or minor bleeding | NO |
| MASTER-DAPT | 4,434 | HBR, mixed ischemic risk* | Caucasian | 49 | 51 | 1 vs. ≥3 months | 11 | All-cause death, MI, stroke, or BARC type 3, or 5 | Yes |

n, number of patients; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; MI, myocardial infarction; CV, cardiovascular; ST, stent thrombosis; TIMI, Thrombolysis in Myocardial Infarction; BARC, Bleeding Academic Research Consortium. *Mixed ischemic risk includes low, moderate and high ischemic risk.

death, MI, ST, stroke, TVR) (HR 0.66, 95% CI 0.48–0.92, $p = 0.01$) and was associated with lower risk of major bleeding (HR 0.56, 95% CI 0.34–0.91, $p = 0.02$) (18). Importantly, only patients at low bleeding risk were included in this trial. The results from the STOPDAPT-2-ACS and TICO trials suggest that ticagrelor but not clopidogrel monotherapy presents a safe antiplatelet treatment regimen for ACS patients after short DAPT. Therefore, it has been discussed whether clopidogrel monotherapy initiated 1 month after DAPT is less effective in ACS patients due to the increased ischemic risk up to 3 months post ACS and the lower $P2Y_{12}$-inhibiting capacity of the agent.

### With prasugrel

The clinical benefit of prasugrel monotherapy in patients after PCI has not been sufficiently investigated to date. The Aspirin-free Prasugrel Monotherapy Following Coronary Artery Stenting in Patients with Stable CAD (ASET) study assessed prasugrel monotherapy (60 mg loading dose followed by 10 mg/day) after PCI in 202 CCS patients at low ischemic risk. Until PCI, patients received clopidogrel-based DAPT. At 3 months of follow-up, there was no primary endpoint event and only one fatal intracranial hemorrhage 6 h after PCI (20).

## Ongoing trials on $P2Y_{12}$-inhibitor monotherapy and short dual antiplatelet therapy

Several ongoing trials are addressing the above-mentioned issues through different approaches.

The Ticagrelor Monotherapy in Patients Treated With New-generation Drug-eluting Stents for Acute Coronary Syndrome (T-PASS) (NCT03797651) trial evaluates ticagrelor monotherapy following very-short DAPT less than 1 month after PCI in ACS patients.

Results from the A Randomized Comparison of Clopidogrel Monotherapy vs. Extended Dual-antiplatelet Therapy Beyond 12 Months After Implantation of Drug-eluting Stents in High-risk Lesions or Patients trial (A-CLOSE) (NCT03947229) are expected at the end of 2023, investigating clopidogrel monotherapy vs. extended clopidogrel-based DAPT from 12 to 36 months after PCI in patients at high risk for either ischemic or bleeding complications.

The $P2Y_{12}$-Inhibitor Monotherapy vs. Extended DAPT in Patients Treated With Bioresorbable Scaffold trial (SMART-CHOICE II) (NCT03119012) currently compares clopidogrel or ticagrelor monotherapy from 12 to 36 months after PCI with extended ticagrelor-based DAPT for 36 months after PCI. Long-term clopidogrel monotherapy vs. aspirin monotherapy after 12 months of DAPT is currently being investigated in patients at high risk for recurrent ischemic events in The Choice of Optimal Anti-Thrombotic Strategy in Patients Undergoing

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TABLE 2 Baseline characteristics of randomized-controlled trials on short DAPT following ticagrelor monotherapy.

| Study | *n* | Bleeding and ischemic risk | Ethnicity | Clinical setting (%) | | DAPT duration | Follow-up (months) | Primary endpoint | Primary endpoint met |
|---|---|---|---|---|---|---|---|---|---|
| | | | | ACS | CCS | | | | |
| GLOBAL-LEADERS | 15,968 | Low bleeding risk, mixed ischemic risk* | Caucasian | 47 | 53 | 1 vs. 12 months | 24 | All-cause death, MI | NO |
| TWILIGHT | 7,119 | Low bleeding risk, mixed ischemic risk | Caucasian<br>East Asian | 64 | 36 | 3 vs. 12 months | 15 | BARC type 2,3, or 5 | Yes |
| TICO | 3,056 | Low bleeding risk, mixed ischemic risk | East Asian | 100 | 0 | 3 vs. 12 months | 12 | TIMI major bleeding, all-cause death, MI, ST, stroke, or TVR | Yes |

n, number of patients; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; MI, Myocardial infarction; BARC, Bleeding Academic Research Consortium; TIMI, Thrombolysis in Myocardial Infarction; ST, stent thrombosis; TVR, target vessel revascularization. *Mixed ischemic risk includes low, moderate and high ischemic risk.

Implantation of Coronary Drug-Eluting Stents 3 trial (SMART-CHOICE III) (NCT04418479).

Further data on prasugrel monotherapy in CCS and non-STE elevation ACS (NSTE-ACS) patients are expected from the still ongoing Acetyl Salicylic Elimination Trial JAPAN (ASET-JAPAN pilot study) (NCT 05117866) in 2024.

## Dual antiplatelet therapy de-escalation strategies

The benefit of potent $P2Y_{12}$-inhibitors regarding ischemic risk reduction is greatest during the acute and sub-acute phase after the index event whilst bleeding risk persists during maintenance therapy (21, 22). Hence, in a significant amount (up to 28%) of ACS patients, physicians tend to switch from standard DAPT by using ticagrelor or prasugrel in association with aspirin to clopidogrel and aspirin within 1 year after PCI (23). Besides economic factors, bleeding complications are the most common reason for a so-called DAPT de-escalation (24). Clinical data justifying this strategy have long been limited. However, in recent years, different studies have provided data on the safety and efficacy of switching to clopidogrel after a short period of DAPT with potent $P2Y_{12}$-inhibitors in ACS patients (**Table 3**) (25–28).

The monocentric, randomized, open-label Timing of Platelet Inhibition After Acute Coronary Syndrome (TOPIC) trial investigated DAPT de-escalation in 646 ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) patients at low-to-moderate bleeding risk (26). At 1 month after PCI, patients in the experimental group were switched to clopidogrel-based DAPT while standard DAPT was maintained in the control group. At 12 months after the index event, the de-escalation strategy was superior to standard DAPT in terms of the primary combined endpoint (CV death, urgent revascularization, stroke, BARC type $\geq$ 2) (HR 0.48 95% CI 0.34–0.68, $p < 0.01$) and was further associated with a lower risk of bleeding (BARC type $\geq$ 2) (HR 0.30, 95% CI 0.18–0.50, $p < 0.01$) (26).

Similarly, results of the multicentric, randomized Ticagrelor vs. Clopidogrel in Stabilized Patients with Acute Myocardial Infarction (TALOS-AMI) study have shown that unguided DAPT de-escalation was associated with a 45% lower risk of net clinical events (CV death, MI, stroke, BARC type 2,3,5) (HR 0.55, 95% CI 0.40–0.76, $p_{\text{non-inferiority}} < 0.001$) and with reduced risk of bleeding complications (BARC type 2,3, or 5) (HR 0.52, 95% CI 0.35–0.77, $p = 0.0012$) when compared with ticagrelor-based DAPT at 12 months after PCI (27). However, only South Korean STEMI and NSTEMI patients at low-to-moderate bleeding risk were included. The validity of these data must therefore be qualified for Caucasian populations due to the higher

TABLE 3 Baseline characteristics of randomized-controlled trials on DAPT de-escalation.

| Study | *n* | Bleeding and ischemic risk | Ethnicity | Clinical setting (%) | | De-escalation strategy | Timing of de-escalation | Follow-up (months) | Primary endpoint | Primary endpoint met |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | ACS | CCS | | | | | |
| **Unguided de-escalation** | | | | | | | | | | |
| TOPIC | 646 | Low-to-moderate bleeding risk, mixed ischemic risk* | Caucasian | 100 | 0 | Clopidogrel-based DAPT vs. ticagrelor-/prasugrel-based DAPT | 30 days after PCI | 12 | CV death, TVR, stroke, BARC type ≥ 2 | Yes |
| TALOS-AMI | 2,697 | Low-to-moderate bleeding risk, mixed ischemic risk | East Asian | 100 | 0 | Clopidogrel-based DAPT vs. ticagrelor-based DAPT | 30 days after PCI | 12 | CV death, MI, stroke, BARC type 2,3, or 5 | Yes |
| **Guided de-escalation** | | | | | | | | | | |
| TROPICAL-ACS | 2,610 | Low-to-moderate bleeding risk, mixed ischemic risk | Caucasian | 100 | 0 | Clopidogrel-based DAPT vs. prasugrel-based DAPT | Days 7–14 after discharge | 12 | CV death, MI, stroke, BARC type ≥ 2 | Yes |
| POPULAR GENETICS | 2,488 | Low-to-moderate bleeding risk, mixed ischemic risk | Caucasian | 100 | 0 | Clopidogrel-based DAPT vs. ticagrelor-based DAPT | Day 1–3 after PCI | 12 | All-cause death, MI, ST, stroke, or PLATO major bleeding; | Yes |

n, number of patients; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; CV, cardiovascular; TVR, target vessel revascularization; BARC, Bleeding Academic Research Consortium; MI, Myocardial infarction; PFT, Platelet Function Testing; ST, stent thrombosis; PLATO, Platelet Inhibition and Patient Outcomes.
*Mixed ischemic risk includes low, moderate and high ischemic risk.





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prevalence of *CYP2C19* loss-of-function alleles in the East Asian population (29).

Recently, two large-scaled RCTs provided data on clopidogrel-based DAPT in Caucasian ACS patients (25, 28). Both trials performed platelet function- and genetic-directed de-escalation, respectively. In the Testing Responsiveness to Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndromes (TROPICAL-ACS) trial, 2,610 STEMI and NSTEMI patients after PCI were treated with standard therapy consisting of prasugrel and aspirin (25). Seven days after discharge, patients randomized to the de-escalation group were switched to clopidogrel for another 7 days whereas standard DAPT was maintained in the control group. Platelet Function Testing (PFT) was performed on day 14 to identify clopidogrel non- or low-responder patients and readjust them to prasugrel. At 12 months follow-up, clopidogrel-based DAPT was not inferior to standard DAPT in terms of the primary combined endpoint (CV death, MI, stroke, BARC type $\geq$ 2) (HR 0.81, 95% CI 0.62–1.06, $p_{\text{non-inferiority}} = 0.0004$) (25). Despite a trend toward lower bleeding risk in the de-escalation group, bleeding rates (BARC type $\geq$ 2) did not significantly differ between groups (5% vs. 6%, HR 0.82, 95% CI 0.59–1.13, $p = 0.23$) (25).

In the Genotype-Guided Strategy for Oral $P2Y_{12}$ Inhibitors in Primary PCI (POPULAR GENETICS) trial *CYP2C19*-directed genetic testing was used as safety tool in 2488 STEMI patients (28). Within 3 days after PCI, non-carriers received clopidogrel-based DAPT whereas carriers of *CYP2C19*2* or *CYP2C19*3* LOF-alleles received standard DAPT with prasugrel or ticagrelor (28). The results demonstrated non-inferiority of guided de-escalation in terms of net clinical events (all-cause death, MI, ST, stroke, Platelet Inhibition and Patient Outcomes (PLATO) major bleeding) (95% CI 2.0–0.7, $p_{\text{non-inferiority}} < 0.001$) as well as significantly lower bleeding rates (PLATO major or minor bleeding) compared to standard DAPT at 12-month follow-up (HR 0.78, 95% CI 0.61–0.98, $p = 0.04$) (28). However, it should be noted that patients enrolled in the TROPICAL-ACS and POPULAR GENETICS trials only had low-to-moderate bleeding and mixed ischemic risk.

Finally, two recent meta-analyses demonstrated overall efficacy and safety of DAPT de-escalation (30, 31). In one study, guided selection of antiplatelet therapy after PCI was shown to reduce the risk of MACE (RR 0.78, 95% CI 0.63–0.95, $p = 0.015$) without any trade-off in bleeding rates when compared with standard DAPT (RR 0.88, 95% CI 0.77–1.01, $p = 0.069$) (30). Importantly, this analysis included studies that investigated both de-escalation and escalation strategies in ACS and CCS patients. The other meta-analysis by Tavenier et al. exclusively focused on RCTs that studied DAPT de-escalation in ACS patients (31). The results demonstrated that a strategy of de-escalation vs. standard DAPT reduces both clinically relevant bleedings (BARC type $\geq$ 2) (HR 0.57, 95% CI 0.42–0.78) and MACE rates (HR 0.77, 95% CI 0.62–0.96) (31).

TABLE 4 Advantages and disadvantages of platelet function vs. CYP2C19-directed genetic testing, modified after Sibbing et al. (34).

| | PFT | Genetic testing |
|---|---|---|
| Availability of different assays | Yes | Yes |
| Absence of interassay variability | No | Yes |
| No need to perform on-treatment | No | Yes |
| Assessment of non-genetic factors | Yes | No |
| Direct measurement of treatment response | Yes | No |
| Absence of temporal variability | No | Yes |

PFT, platelet function testing.

## Antiplatelet responsiveness of clopidogrel

When using clopidogrel, interpatient variability in antithrombotic efficacy must be considered (32, 33). Genetic and metabolic factors influence pharmacologic response to clopidogrel resulting in increased ischemic risk in certain patients (32). In the TROPICAL-ACS and POPULAR GENETICS trials, PFT and genetic testing were used as safety tools, whereas unguided de-escalation was performed in the TOPIC and TALOS-AMI trials. According to ESC guidelines, routine use of PFT or genetic testing in the selection of antiplatelet therapy is not recommended. When de-escalation to clopidogrel is performed, the strategy (guided vs. unguided) should be determined based on the patient's risk profile and the availability of respective assays (1). However, guidelines do not specify in which patients a guided approach should be considered, leaving this decision to the treating physician. In this regard, an expert consensus from 2019 provides more detailed recommendations (34). Unfortunately results from the POPULAR GENETICS trial and from more recent meta-analyses were not included at this time but are considered in the present work.

Tavenier et al. demonstrated that significant bleeding risk reduction was consistent in both guided (HR 0.79, 95% CI 0.66–0.94) and unguided (HR 0.44, 95% CI 0.32–0.59) de-escalation (31). Interestingly, unguided de-escalation was associated with a greater reduction of bleeding risk ($p_{\text{interaction}} = 0.037$) when compared with guided de-escalation (31). However, the authors noted that the bleeding benefit may be explained by the fact that the proportion of patients who received clopidogrel was higher in the unguided than in the guided de-escalation group (31).

If PFT or genetic testing is considered, limitations of the respective test methods must be taken into account (**Table 4**). PFT results vary significantly depending on the different assays available (VerifyNow, Multiplate, VASP, TEG platelet mapping), which not only makes it difficult to compare data from different studies but may also influence clinical decisions (35). Conversely, there are no relevant discrepancies between validated genetic assays (32). Since PFT can only be performed on-treatment, initial

clopidogrel therapy and, if needed, subsequent medication adjustment is required (28). This could affect patient compliance.

In the TROPICAL-ACS trial, patients received clopidogrel treatment from days 7 to 14 after hospital discharge (25). Given the increased ischemic risk in the acute and subacute phase after the index event, early clopidogrel therapy may not guarantee adequate platelet inhibition in patients on high on-treatment platelet reactivity (HPR) (24, 36).

*CYP2C19* genetic testing, as performed in the POPULAR GENETICS trial, does not require clopidogrel treatment. However, it does not directly reflect treatment response as various intrinsic and extrinsic factors that influence clopidogrel efficacy (BMI $\geq$ 30 kg/m$^2$, diabetes mellitus, gastrointestinal absorption, drug interactions, patient adherence) are not taken into account (37, 38). It should also be noted that a single platelet function test only reflects the current status of response to treatment, and the optimal timing of measurement is unknown (34).

In this regard, a pre-specified TROPICAL-ACS sub-study showed that platelet reactivity during clopidogrel therapy is subject to diurnal variability, with a peak in platelet reactivity at the end of the dosing interval (39). However, clinical outcomes of these findings have not been investigated. Since these epigenetic factors vary over time, it could be questioned whether a single measurement is sufficient or whether PFT should be repeated during maintenance therapy.

To summarize, one meta-analysis provides data suggesting a greater reduction in bleeding risk with unguided vs. guided de-escalation and similar ischemic risk reduction with both strategies (31). Current knowledge does not show superiority of specific assays (PFT vs. *CYP2C19* genetic testing) and therefore respective limitations should be considered when de-escalation to clopidogrel is performed.

# Implications of short dual antiplatelet therapy and P2Y$_{12}$-inhibitor de-escalation strategies for future antiplatelet therapy

Both withdrawal of aspirin 1–3 months after PCI with continued use of P2Y$_{12}$-inhibitor monotherapy and de-escalation of P2Y$_{12}$-inhibitor therapy by switching from more potent inhibitors to clopidogrel reduce bleeding risk without any trade-off in MACE when compared with standard DAPT. These findings now raise the question of which patient populations may benefit from a personalized antiplatelet strategy and how early aspirin should be discontinued or ticagrelor or prasugrel replaced with clopidogrel.

## Dual antiplatelet therapy de-escalation

Based on the positive results of the TROPICAL-ACS trial, ESC Guidelines recommend guided or unguided de-escalation as an alternative treatment regimen in ACS patients who are not suitable for 12 months potent platelet inhibition (Class IIb indication) (25). However, guidelines do not comment on the timing of DAPT de-escalation. Trials investigating guided de-escalation (TROPICAL-ACS, POPULAR GENETICS) switched to clopidogrel maintenance therapy within 14 days after PCI (25, 28). Unguided de-escalation was performed at 1 month after PCI in the TOPIC and TALOS-AMI trials (26, 27). Given the highest ischemic risk in the first month after the index event, the timing of unguided de-escalation seems to be appropriate to prevent recurrence of ischemic events (24, 36). A guided approach, in turn, allows the identification of non- or low-responder patients at high ischemic risk at an early stage and seems to justify the timing of de-escalation. The above-mentioned trials have shown short-term safety of DAPT de-escalation for ACS patients at low-to-moderate bleeding risk but clinical outcomes beyond 1 year have not been investigated yet. Further, the studies were not adequately powered with respect to primary ischemic endpoints. Finally, it must be noted that patients at high thrombotic risk (HTR) may not have been adequately enrolled and the results may apply only to populations with balanced ischemic risk. To the best of our knowledge, no ongoing trials are currently addressing these issues.

## P2Y$_{12}$-inhibitor monotherapy after short dual antiplatelet therapy

Results on short DAPT had already an impact on recent guidelines recommending early P2Y$_{12}$-inhibitor monotherapy in certain patient populations (40).

The MASTER-DAPT trial has shown that also patients at high bleeding risk are suitable for clopidogrel monotherapy after short DAPT. However, certain patient populations, like elderly patients, were underrepresented in the above-mentioned trials. This population, which bears an increased bleeding risk in itself, might be suitable for short DAPT or de-escalation as recently discussed in an editorial of the European Heart Journal (41).

While trials have provided evidence on patients with low-to-moderate and high bleeding risk, no clear conclusion can be drawn from existing data for the treatment of patients at high thrombotic risk. This could be due to inclusion bias in the existing studies, as HTR patients are not represented in sufficient numbers.

Ticagrelor but not clopidogrel monotherapy after very short DAPT has been shown to be a safe strategy to treat ACS patients. Therefore, it has been discussed whether clopidogrel monotherapy initiated 1 month after DAPT is less effective due to the increased ischemic risk in the early phase after ACS and

the lower $P2Y_{12}$-inhibitory capacity of the agent. Here, DAPT of up to 3 months, measurement of response to clopidogrel, or switching to a more potent $P2Y_{12}$-inhibitor as monotherapy (theoretically, as not yet tested) might be useful to keep the rate of ischemic events low. Nevertheless, existing data only apply for ACS patients at low-to-moderate bleeding risk since ACS patients at HBR were not included in previous trials.

It is currently unclear whether $P2Y_{12}$–inhibitor monotherapy should be prolonged (which was done for 24 months in the GLOBAL LEADERS trial), switched back to aspirin lifelong after 12 months (as done in TWILIGHT and TICO), or switched to clopidogrel lifelong, as shown in a recent study (42). In the Aspirin vs. Clopidogrel for Chronic Maintenance Monotherapy after Percutaneous Coronary Intervention (HOST-EXAM) trial, more than 5,000 patients after PCI, who received 6–18 months of DAPT, were investigated (42). Subsequent clopidogrel monotherapy resulted in a significant reduction in the net clinical endpoint (death, MI, insult, ACS, BARC type 3, or 5) when compared with aspirin monotherapy at 24 months (HR = 0.73, 95% CI: 0.59–0.90, $p = 0.0035$) (42).

## Summary

The use of short DAPT and DAPT de-escalation is currently limited to HBR patients, while patients at normal-to-low bleeding risk usually continue to be treated with standard DAPT. To determine a tailored antiplatelet regimen that strikes the balance between bleeding risk reduction and prevention of recurrent ischemic events, several trials have shown efficacy and safety of DAPT de-escalation and $P2Y_{12}$-inhibitor monotherapy after short DAPT. However, based on inclusion bias, patients at very high thrombotic risk only represent a low percentage in the aforementioned trials and elderly patients have not been included in sufficient numbers. Especially, for elderly with no additional risk factors other than their age, the new antiplatelet strategies of short DAPT and DAPT de-escalation might be of interest for future clinical practice. Prospective RCTs in specific patient groups and long-term safety data regarding hard ischemic endpoints are pending which still limits broad use of short DAPT and DAPT de-escalation in patients after PCI. Finally, personalized antiplatelet treatment should equally consider the patient's ischemic and bleeding risk and in case clopidogrel is used, potential interindividual differences in platelet responsiveness must always be taken into account.

## Author contributions

MM and KH worte the manuscript. All authors contributed to the article and approved the submitted version.

## Conflict of interest

Author KH received lecture fees from AstraZeneca, Bayer, Daiichi Sankyo, and Sanofi Aventis. Author FV received honoraria for consulting and presentations from AstraZeneca, Bayer Healthcare, and Daiichi-Sankyo.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Clinical benefit of long-term use of dual antiplatelet therapy for acute myocardial infarction patients with the PEGASUS-TIMI 54 criteria

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**Background:** We evaluated the effectiveness of extended dual antiplatelet therapy (DAPT) usage after 2nd-generation drug elution stent implantation in acute myocardial infarction (AMI) survivors with high ischemic risk characteristics who had no major bleeding for 24 months under at least 1 year of DAPT maintenance.

**Materials and methods:** The primary ischemic and bleeding endpoints were the risk of mortality and the risk of BARC 3 or 5 (major) bleeding. We investigated the event rates for 2–5 years after the index procedure.

**Results:** Of 3382 post-AMI survivors who met the PEGASUS-TIMI 54 (PEGASUS) criteria and without major bleeding until 2 years, 2281 (67.4%) maintained DAPT over 24 months, and 1101 (32.5%) switched DAPT to a single antiplatelet agent. The >24 M DAPT group showed a lower risk of mortality than the 12–24 M DAPT group (7.2 vs. 9.2%; adjusted hazard ratio: 0.648; 95% confidence interval: 0.595–0.976; $p < 0.001$). The mortality risk was significantly greater as the number of PEGASUS criteria increased ($p < 0.001$). DAPT > 24 months was not significantly associated with a decreased risk for major bleeding in the population meeting the PEGASUS criteria (2.0 vs. 1.1%; $p = 0.093$). The results were consistent after propensity-score matching and inverse probability weighting to adjust for baseline differences.

**Conclusion:** Extended DAPT over 24 months was associated with a lower risk of mortality without increasing the risk of major bleeding among 2 years survivors after AMI who met the PEGASUS criteria and had no major bleeding events before 24 months.

KEYWORDS

PEGASUS-TIMI 54, percutaneous coronary intervention (PCI), acute myocardial infarction, dual antiplatelet therapy (DAPT), drug-eluting stents (DES)

# Introduction

Despite modern advanced intervention devices and optimal medical therapy, patients with acute myocardial infarction (AMI) have a high risk of death and myocardial infarction (MI) recurrence. In particular, the probability of recurrent ischemic events is higher in the first year after AMI and persists in parallel with the number of cardiovascular risk factors over the next few years (1, 2). Therefore, the current guidelines strongly recommend an early evaluation of the risk of ischemia and bleeding after AMI to identify patients who may benefit from long-term dual antiplatelet therapy (DAPT) (3, 4). To this end, several risk scores have been proposed (1, 5, 6). However, most risk scores have been developed primarily for all-comer patients undergoing percutaneous coronary intervention (PCI), including elective procedures. Moreover, they have not been implemented in routine clinical practice, probably because there has been recognized complexity due to a large number of integrated variables. The PEGASUS-TIMI 54 trial was the major study to focus prospectively on patients with AMI history and one or more additional ischemic risk factors (7). Additional risk factors include old age, diabetes mellitus, multivessel coronary artery disease (CAD), chronic kidney disease (CKD), and secondary MI. This study demonstrated that adding a potent P2Y12 inhibitor (ticagrelor) to aspirin reduces the risk of long-term ischemia in these patients. (8). Since reducing the ischemic risk is associated with increased major bleeding, identifying AMI patients who can benefit the most from long-term DAPT remains an open issue. In addition, there are few data on how long it will be good to use after one year of PCI. In previous studies, we noted that the benefits of reducing the ischemic risk might exceed the risk of bleeding in patients with AMI who meet the PEGASUS-TIMI 54 criteria (9, 10). We investigated whether long-term DAPT use in this high ischemic risk group could reduce the risk of ischemia without increasing major bleeding. Among AMI survivors with PEGASUS-TIMI 54 criteria who had no major bleeding events before 24 months, we compared the occurrence of ischemic and bleeding events for 24–60 months between the group that maintained DAPT for more than 24 months and the group that changed to single antiplatelet therapy (SAPT) within 12–24 months.

# Materials and methods

## Study protocols and population selection

The COREA-AMI registry, designed to evaluate the long-term clinical outcomes of AMI patients, examined subjects from a total of nine major cardiac centers located in urban areas throughout Korea. Each center regularly performs a high volume of PCI procedures. Split into two parts, the COREA-AMI I registry included AMI patients who underwent PCI between January 2004 and December 2009, while the COREA-AMI II registry included an extended follow-up of COREA-AMI I patients as well as newly enrolled AMI patients between January 2010 and August 2014. All clinical, angiographic, and follow-up data of these AMI patients were sequentially registered in a web-based case reporting system. The COREA-AMI study was approved by the Institutional Review Board (IRB), conducted in adherence to the Declaration of Helsinki, and executed according to the guidelines of STROBE (11). The registry is registered on ClinicalTrials.gov (study ID: NCT02806102).

A total of 10,719 AMI patients who received drug-eluting stent implantations were enrolled in the registry, while a total of 390 patients who did not undergo PCI were excluded. A total of 1,423 patients who died or were lost to follow-up within 12 months were also excluded. We excluded patients with cardiac arrest, anticoagulant use, diagnosed atrial fibrillation, no use of second-generation drug elution stent, or changes to a single antiplatelet within 12 months (65, 276, 182, 2,833, 971). After exclusion of 214 patients who died, were lost to follow-up, or had major bleeding (BARC 3, 5) within 24 months, 4,365 remained. Overall, 4,365 post-AMI 2 years survivors who underwent second-generation DES and continued DAPT beyond 1 year were included. Among them, 3,382 (77.5%) patients met the PEGASUS-TIMI 54 criteria and were finally used for analysis. A study flowchart is depicted in **Figure 1**. The enrolled patients who met the PEGASUS-TIMI 54 criteria had to have at least one criterion associated with a high risk of ischemic events based on a previous report (7). The atherothrombosis risk factors used in our study were old age (65 years and above), diabetes mellitus requiring medication, multivessel CAD (≥50%

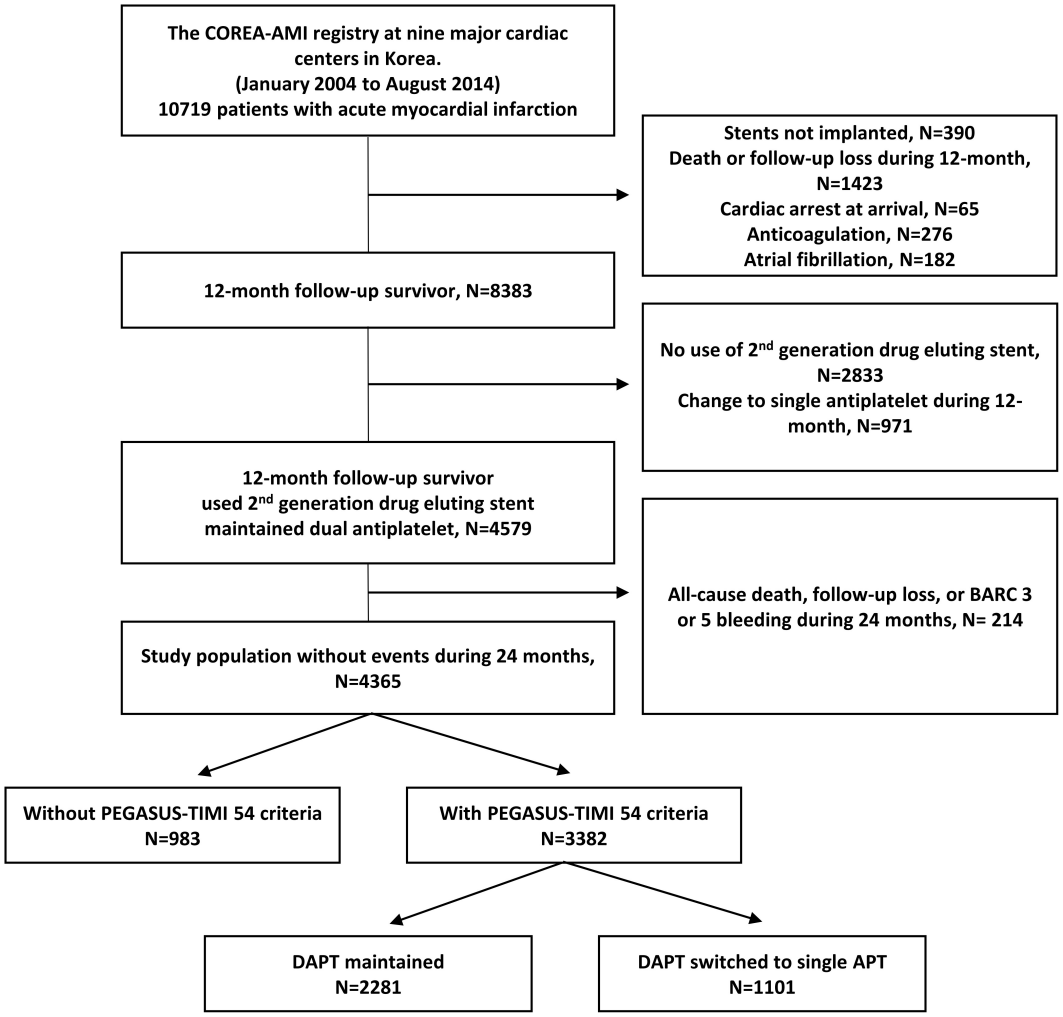


FIGURE 1
Study flowchart. DAPT, dual antiplatelet therapy; BARC, bleeding academic research consortium.

stenosis in ≥2 coronary territories), CKD, and a second prior spontaneous myocardial infarction. The patients were separated into two groups based on the duration of their dual antiplatelet maintenance (greater than or less than 24 months) and their respective characteristics and outcomes were compared.

## Treatment and data collection

All patients received PCI treatment within 48 h of admission, with coronary artery angiography (CAG) and primary PCI both performed in adherence to standard guidelines. Coronary disease was considered significant if the epicardial coronary arteries had angiographic stenosis ≥70% and if the left main coronary artery had stenosis ≥50%. Loading doses of the antiplatelet agents (aspirin, 300 mg; clopidogrel, 300 mg or 600 mg; cilostazol, 200 mg; ticagrelor, 180 mg; or prasugrel, 60 mg) were prescribed for all patients before or during PCI. Patients with DES were prescribed 100 mg of aspirin daily and/or a P2Y12 inhibitor (75 mg of clopidogrel once daily, 90 mg of ticagrelor twice daily, or 10 mg of prasugrel once daily). The duration of dual antiplatelet agent administration was determined by a physician in accordance with the final diagnosis at baseline and the complexity of the revascularization procedure. The postintervention medications included aspirin, clopidogrel, statins, ACE inhibitors or angiotensin II receptor blockers (ARBs), and β-blockers. These medications were administered within 24 h of PCI and, unless contraindicated, were continued after discharge. Each physician used his own judgment when choosing to perform predilation, direct stenting, postadjunct balloon inflation, or administering glycoprotein IIb/IIIa receptor.

Blinded to results, trained reviewers then gathered relevant patient data using hospital chart reviews and phone interviews

TABLE 1 Baseline characteristics.

| | Original cohort | | | | | Propensity-score matched cohort | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | >24 M DAPT | >12 M, ≤24 M DAPT | *P*-value | SMD | >24 M DAPT | >12 M, ≤24 M DAPT | *P*-value | SMD |
| **Clinical characteristics** | – | 2281 | 1101 | – | – | 952 | 952 | – | – |
| Age, years | 61.8 ± 12.2 | 64.8 ± 11.6 | 64.3 ± 11.6 | 0.213 | 0.093 | 63.6 ± 12.2 | 64.4 ± 11.7 | 0.114 | 0.072 |
| ≥75 | 713 (16.3) | 483 (21.2) | 230 (20.9) | 0.884 | <0.001 | 181 (19.0) | 203 (21.3) | 0.23 | 0.058 |
| Female | 1122 (25.7) | 685 (30.0) | 327 (29.7) | 0.876 | 0.057 | 252 (26.5) | 274 (28.8) | 0.282 | 0.052 |
| BMI | 24.3 ± 3.1 | 24.1 ± 3.2 | 24.1 ± 3.1 | 0.631 | 0.009 | 24.1 ± 3.2 | 24.1 ± 3.1 | 0.853 | 0.008 |
| DM | 1293 (29.6) | 884 (38.8) | 409 (37.1) | 0.388 | <0.001 | 335 (35.2) | 346 (36.3) | 0.633 | 0.024 |
| With insulin treatment | 81 (1.9) | 58 (2.5) | 23 (2.1) | 0.491 | <0.001 | 14(1.5) | 18 (1.9) | 0.593 | 0.033 |
| Hypertension | 2215 (50.7) | 1341 (58.8) | 577 (52.4) | 0.001 | 0.004 | 488 (51.3) | 497 (52.2) | 0.714 | 0.019 |
| Dyslipidemia | 843 (19.3) | 436 (19.1) | 209 (19.0) | 0.964 | 0.026 | 167 (17.5) | 178 (18.7) | 0.552 | 0.03 |
| History of stroke | 278 (6.4) | 171 (7.5) | 77 (7.0) | 0.649 | 0.18 | 54 (5.7) | 68 (7.1) | 0.224 | 0.06 |
| Smoker | 1909 (43.7) | 857 (37.6) | 450 (40.9) | 0.07 | 0.022 | 403 (42.3) | 387 (40.7) | 0.485 | 0.034 |
| Previous MI | 127 (2.9) | 96 (4.2) | 31 (2.8) | 0.057 | <0.001 | 27(2.8) | 29 (3.0) | 0.892 | 0.012 |
| Previous PCI | 225 (5.2) | 171 (7.5) | 41 (3.7) | <0.001 | 0.093 | 32 (3.4) | 35 (3.7) | 0.804 | 0.017 |
| Previous CABG | 16 (0.4) | 11 (0.5) | 5 (0.5) | 1 | <0.001 | 4 (0.4) | 5 (0.5) | 1 | 0.015 |
| eGFR < 60, ml/min/1.73m$^2$ | 833 (19.1) | 598 (26.2) | 235 (21.4) | 0.003 | <0.001 | 204 (21.4) | 197 (20.7) | 0.736 | 0.018 |
| LVEF | 54.3 ± 10.4 | 53.5 ± 11.0 | 54.1 ± 10.3 | 0.157 | 0.178 | 54.3 ± 9.7 | 54.2 ± 10.4 | 0.822 | 0.01 |
| LVEF ≤ 35% | 222 (5.1) | 159 (7.0) | 50 (4.5) | 0.008 | 0.061 | 38 (4.0) | 46 (4.8) | 0.435 | 0.041 |
| Cardiogenic shock | 329 (7.5) | 179 (7.8) | 94 (8.5) | 0.533 | 0.066 | 59 (6.2) | 77 (8.1) | 0.13 | 0.073 |
| ST-segment elevation MI | 2251 (51.6) | 1112 (48.8) | 557 (50.6) | 0.334 | 0.098 | 489 (51.4) | 472 (49.6) | 0.463 | 0.036 |
| CK-MB, peak, ng/ml | 122.3 ± 248.1 | 120.5 ± 309.4 | 114.8 ± 146.9 | 0.464 | 0.177 | 120.0 ± 135.2 | 109.2 ± 129.0 | 0.075 | 0.082 |
| GRACE score | 127.7 ± 40.5 | 134.0 ± 39.7 | 134.0 ± 42.6 | 0.955 | 0.014 | 130.6 ± 38.8 | 134.2 ± 43.0 | 0.057 | 0.087 |
| DAPT score ≥ 2 | 1767 (52.2) | 1178 (51.6) | 589 (53.5) | 0.33 | 0.037 | 554 (50.9) | 583 (53.5) | 0.230 | 0.053 |
| **Medication at discharge** | – | – | – | – | – | – | – | – | – |
| Aspirin | 4330 (99.2) | 2260 (99.1) | 1093 (99.3) | 0.708 | 0.101 | 942 (98.9) | 948 (99.6) | 0.18 | 0.074 |
| Clopidogrel | 3505 (80.3) | 1922 (84.3) | 859 (78.0) | <0.001 | 0.129 | 793 (83.3) | 736 (77.3) | 0.001 | 0.151 |
| Ticagrelor | 342 (7.8) | 158 (6.9) | 109 (9.9) | 0.003 | 0.036 | 77 (8.1) | 98 (10.3) | 0.113 | 0.076 |
| Prasugrel | 522 (12.0) | 204 (8.9) | 132 (12.0) | 0.007 | 0.146 | 83 (8.7) | 118 (12.4) | 0.011 | 0.12 |
| Potent P2Y12 inhibitor | 864 (19.8) | 362 (15.9) | 241 (21.9) | <0.001 | 0.151 | 160 (16.8) | 216 (22.7) | 0.002 | 0.148 |
| Beta-blocker | 3969 (90.9) | 2060 (90.3) | 999 (90.7) | 0.741 | 0.081 | 870 (91.4) | 862 (90.5) | 0.576 | 0.029 |
| ACEi or ARB | 3367 (77.1) | 1758 (77.1) | 852 (77.4) | 0.873 | 0.011 | 697 (73.2) | 734 (77.1) | 0.056 | 0.09 |
| Statin at discharge | 4309 (98.7) | 2239 (98.2) | 1093 (99.3) | 0.018 | 0.066 | 945 (99.3) | 944 (99.2) | 1 | 0.012 |

*(Continued)*





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TABLE 1 (Continued)

| | Original cohort | | | | | Propensity-score matched cohort | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | >24 M DAPT | >12 M, ≤24 M DAPT | *P*-value | SMD | >24 M DAPT | >12 M, ≤24 M DAPT | *P*-value | SMD |
| High-dose statin | 1119 (25.6) | 530 (23.2) | 310 (28.2) | – | – | 245 (25.7) | 264 (27.7) | – | – |
| Moderate-dose statin | 3047 (69.8) | 1613 (70.7) | 763 (69.3) | – | – | 639 (67.1) | 663 (69.6) | – | – |
| Low-dose statin | 199 (4.6) | 138 (6.0) | 28 (2.5) | – | – | 68 (7.1) | 25 (2.6) | – | – |
| **Angiographic characteristics** | – | 2281 | 1101 | – | – | – | – | – | – |
| MVD | 2265 (51.9) | 1522 (66.7) | 743 (67.5) | 0.689 | <0.001 | 618 (64.9) | 644 (67.6) | 0.226 | 0.058 |
| 3VD with multivessel PCI | 500 (11.5) | 357 (15.7) | 143 (13.0) | 0.046 | <0.001 | 127 (13.3) | 129 (13.6) | 0.946 | 0.006 |
| Target vessels | – | – | – | – | – | – | – | – | – |
| Left main | 174 (4.0) | 123 (5.4) | 22 (2.0) | <0.001 | 0.055 | 23 (2.4) | 18 (1.9) | 0.528 | 0.036 |
| Left anterior descending | 2610 (59.8) | 1381 (60.5) | 640 (58.1) | 0.192 | 0.111 | 562 (59.0) | 556 (58.4) | 0.816 | 0.013 |
| Left circumflex | 1207 (27.7) | 706 (31.0) | 347 (31.5) | 0.769 | 0.036 | 303 (31.8) | 306 (32.1) | 0.922 | 0.007 |
| Right coronary artery | 1696 (38.9) | 991 (43.4) | 462 (42.0) | 0.435 | 0.085 | 398 (41.8) | 399 (41.9) | 1 | 0.002 |
| Graft | 2 (0.0) | 1 (0.0) | 0 (0.0) | 1 | 0.077 | 0 (0.0) | 0 (0.0) | 1 | <0.001 |
| Ostial lesion | 169 (3.9) | 108 (4.7) | 36 (3.3) | 0.059 | 0.093 | 31 (3.3) | 33 (3.5) | 0.899 | 0.012 |
| Bifurcation | 173 (4.0) | 95 (4.2) | 36 (3.3) | 0.242 | 0.08 | 22 (2.3) | 30 (3.2) | 0.325 | 0.052 |
| Chronic total occlusion | 225 (5.2) | 145 (6.4) | 53 (4.8) | 0.087 | 0.046 | 52 (5.5) | 41 (4.3) | 0.288 | 0.054 |
| **Procedural characteristics** | – | – | – | – | – | – | – | – | – |
| Bifurcation with two stents | 60 (1.4) | 43 (1.9) | 15 (1.4) | 0.339 | 0.029 | 10 (1.1) | 13 (1.4) | 0.675 | 0.029 |
| Long stenting (>60 mm) | 163 (3.7) | 106 (4.6) | 40 (3.6) | 0.204 | 0.067 | 29 (3.0) | 32 (3.4) | 0.795 | 0.018 |
| Restenosis lesion | 71 (1.6) | 54 (2.4) | 12 (1.1) | 0.017 | 0.017 | 6 (0.6) | 9 (0.9) | 0.604 | 0.036 |
| Thrombus aspiration device usage | 544 (12.5) | 231 (10.1) | 157 (14.3) | 0.001 | 0.064 | 124 (13.0) | 125 (13.1) | 1 | 0.003 |
| Total stent length, mm | 33.5 ± 20.2 | 36.9 ± 22.4 | 35.3 ± 19.6 | 0.036 | 0.056 | 35.8 ± 20.3 | 35.5 ± 19.4 | 0.773 | 0.013 |
| Total stent number | 1.6 ± 0.9 | 1.8 ± 0.9 | 1.6 ± 0.8 | <0.001 | 0.125 | 1.7 ± 0.9 | 1.7 ± 0.8 | 0.73 | 0.016 |
| Mean stent diameter, mm | 3.2 ± 0.4 | 3.1 ± 0.4 | 3.1 ± 0.4 | 0.263 | 0.099 | 3.2 ± 0.4 | 3.1 ± 0.4 | 0.031 | 0.099 |
| Second-generation DES | 4365 (100.0) | 2281 (100.0) | 1101 (100.0) | NA | <0.001 | 952 (100.0) | 952 (100.0) | NA | NA |
| ECMO/IABP | 83 (1.9) | 54 (2.4) | 19 (1.7) | 0.281 | 0.02 | 15 (1.6) | 14 (1.5) | 1 | 0.009 |

Data are presented as the *n* (%) for categorical variables unless otherwise indicated. The *p*-values for differences were determined using the chi-square test, Fisher's exact test or the independent sample *t*-test. DAPT, dual antiplatelet therapy; BMI, body mass index; DM, diabetes mellitus; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; MVD, multivessel disease; 3VD, three vessel disease; PCI, percutaneous coronary intervention; MI, myocardial infarction; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; LVEF, left ventricle ejection fraction; CK-MB, creatinine kinase MB isoenzyme; DES, drug-eluting stents; ECMO, extracorporeal membrane oxygenation; IABP, intraaortic balloon pump.





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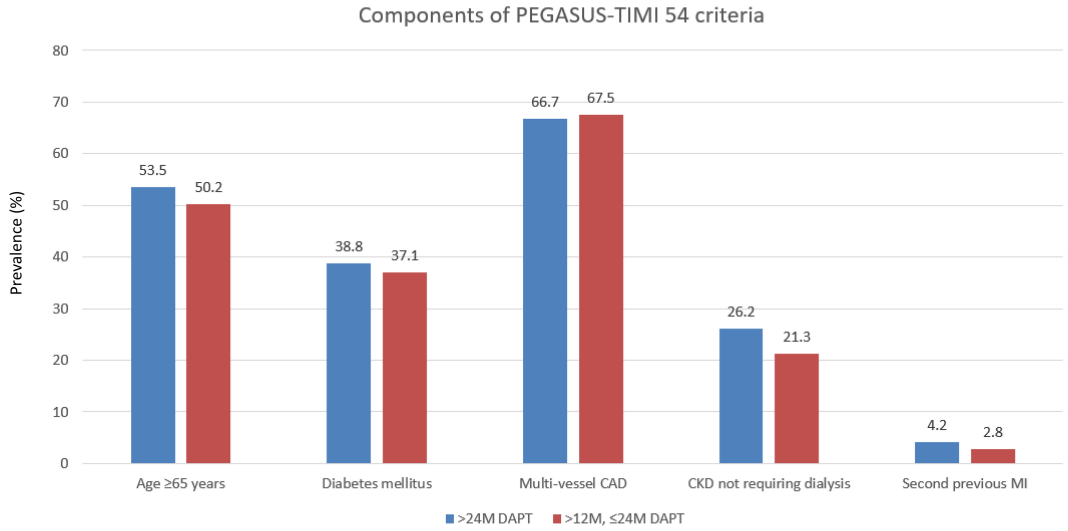


FIGURE 2
Prevalence of the individual qualifying variables within the "with PEGASUS-TIMI 54 criteria" group. CAD, coronary artery disease; MI, myocardial infarction.

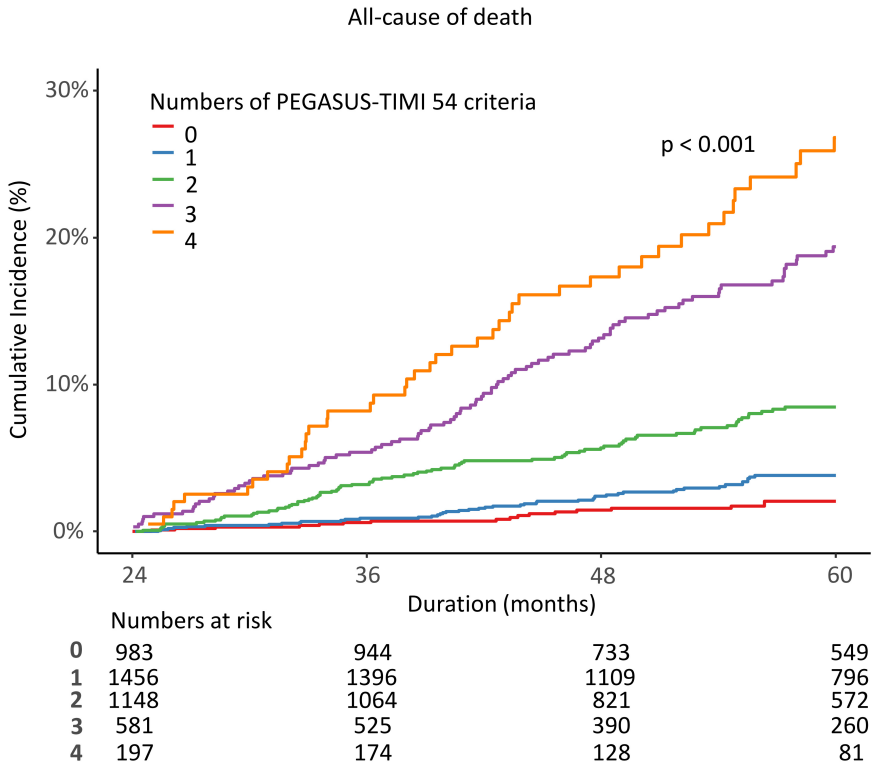


FIGURE 3
K-M curve comparison according to the number of PEGASUS-TIMI 54 criteria.

and, after removing personally identifiable information, organized the data into a web-based system. These data included follow-up, survival, and clinical event data and were collected through March 31st, 2019. Electronic medical records and phone interviews were similarly, used to evaluate clinical events and outcome data. Angiographic and procedural data were evaluated by independent reviewers and interventional cardiologists, while independent research personnel gathered

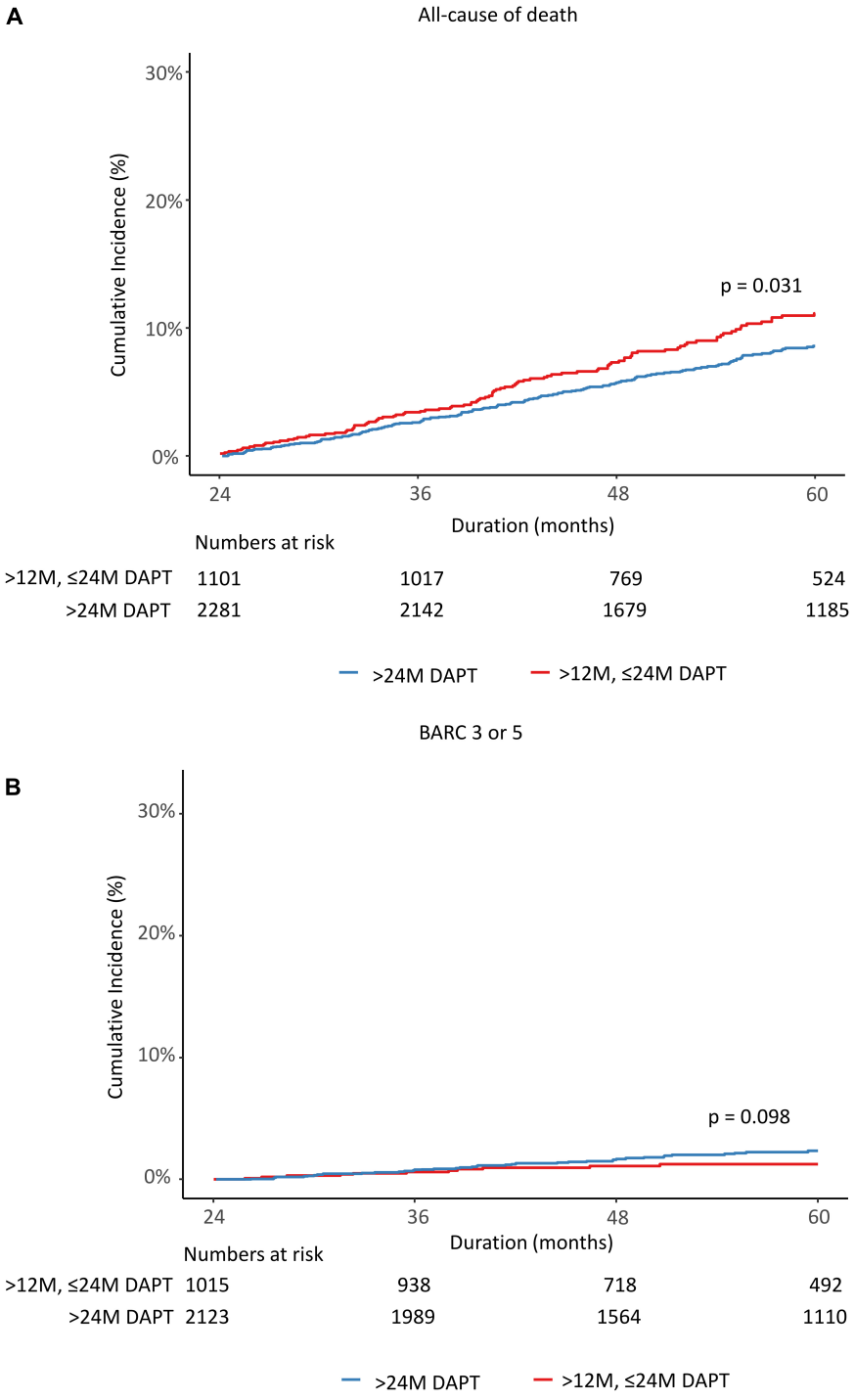


FIGURE 4
Rates of all causes of death **(A)** and major bleeding **(B)** from 24 to 60 months after the index percutaneous coronary intervention. DAPT, dual antiplatelet therapy; BARC, bleeding academic research consortium.

baseline, clinical, laboratory, and medication data. Any adverse clinical events of interest were confirmed by the committee of the Cardiovascular Center of Seoul St. Mary's Hospital, and mortality was confirmed based on disqualification from the National Health Insurance Service, Korea's single-payer, universal healthcare program. Independent statisticians at the clinical research coordinating center handled the final dataset, with the clinical research associate sealing it with a code.

## Study endpoints and definitions

The primary ischemic endpoint of this analysis was all causes of death. The secondary ischemic outcomes were cardiovascular death, recurrent MI, any revascularization, target vessel revascularization, target lesion revascularization (TLR), definite or probable stent thrombosis, and stroke. The primary bleeding endpoint was major bleeding (BARC type 3 or 5) (12). The secondary bleeding endpoints included BARC types 2, 3, and 5 or any bleeding. We investigated the event rates for 2–5 years after the index procedure. After 24 months, comparisons of clinical outcomes were made between the two groups separated based on the length of DAPT maintenance. All deaths were considered cardiovascular except when an unequivocally non-cardiovascular cause was present. Cardiovascular death was defined as death resulting from MI, sudden cardiac death, heart failure, stroke, or other vascular causes. Recurrent MI was defined as the presence of recurrent symptoms and new ECG changes that were compatible with MI or cardiac markers that were expressed at least 2-fold above the normal limit. Clinically driven revascularization that occurred after discharge from the index hospitalization was coded as a revascularization event, according to the Academic Research Consortium definitions. TLR was defined as any unscheduled repeat PCI between 5 mm proximal and 5 mm distal to a stent in a previously treated segment with significant restenosis, as well as recurrence of chest pain or evidence of ischemia. Stroke was defined as the presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting more than 24 h. Ischemic risk was assessed using the GRACE risk score (13).

## Statistical analysis

Categorical variables were presented as numbers and relative frequencies (percentages) and were compared using the Chi-squared test or Fisher's exact test. Continuous variables were expressed as the mean ± standard deviation, and were compared using the independent sample *t*-test. The cumulative ischemic and bleeding event rates of each group (>24 DAPT vs. 12–24 M DAPT) were calculated using a Kaplan-Meier estimator and compared using the log-rank statistic. Unadjusted hazard ratios from 24 to 60 months were determined from Cox proportional hazards models. Because differences in the baseline characteristics could significantly affect outcomes, sensitivity analyses were performed to adjust for confounders as much as possible. First, a multivariable Cox proportional hazard regression model was used. The adjusted variables for the multivariate model were selected if they were significantly different between the two groups (showing a *p*-value of <0.05 in the univariable analysis) for the baseline characteristics except antiplatelet agent usage (**Table 1**). The adjusted variables were hypertension, previous PCI, estimated glomerular filtration rate (eGFR) ≤ 60, left ventricular ejection fraction (LVEF) ≤ 35%, statin usage, three-vessel disease with multivessel PCI, left main lesion, restenosis lesion PCI, thrombus aspiration, total stent length, and total stent number. Second, Cox proportional hazard regression in a propensity-score matched cohort and inverse probability weighted (IPW) Cox proportional hazard regression were performed. Propensity-score matching yielded 1,093 patients in the >24 M DAPT group and 1,093 control subjects in the 12–24 M DAPT group. For the IPW adjustment, the inverse of the propensity-score was adjusted by the proportional hazard regression model. Balance between the two groups after propensity-score matching or IPW adjustment was assessed by calculating percent standardized mean differences. The percent standardized mean differences after propensity-score matching were within ±10% across all matched covariates demonstrating successful balance achievement between the comparative groups (**Table 1**). To identify independent predictors of all-cause death, we used a multivariable Cox proportional hazard model. In addition, comparisons of the primary outcome between the >24 M DAPT and 12–24 M DAPT groups according to the exploratory subgroups of interest were followed, and the interaction between the treatment effect and these covariates was assessed with a Cox regression model. All probability values were two-sided, and *p*-values <0.05 were considered statistically significant. Each measure was analyzed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

# Results

## Baseline patient characteristics

A total of 3,382 post-AMI 2 years survivors who met the PEGASUS-TIMI 54 inclusion criteria (≥1 high-risk criterion; age ≥65 years, diabetes mellitus requiring medication, multivessel CAD, CKD, and a second prior spontaneous MI) without major bleeding for 2 years were analyzed. The baseline clinical, medication at discharge, angiographic, and procedural characteristics are listed in **Table 1**. All patients used second-generation DES. The mean age of all the included patients was 61.8 ± 12.2 years. Overall, 29.6% of the patients had diabetes, 50.7% had hypertension, 2.9% had a previous MI, 19.1% had CKD (eGFR < 60), 51.9% had multivessel CAD, 7.5% had cardiogenic shock during admission, and 1.9% of the patients required hemodynamic support device use. A total of 51.6% presented with ST-segment elevation MI, and 48.4% presented with non-ST-segment elevation MI.

Of the 3,382 patients, 2,281 (67.4%) patients maintained DAPT over 24 months (>24 M), and 1,101 (32.6%) patients changed from DAPT to SAPT during 12–24 months (12–24 M) (**Figure 1**). The mean DAPT duration of the maintained DAPT > 24 M group was 33.76 ± 4.36 months, and that of the 12–24 M group was 14.13 ± 2.87 months. Among 1,101 patients

in the 12–24 M DAPT group, only three patients used a potent P2Y12 inhibitor (prasugrel), and 1,098 patients used aspirin or clopidogrel as a SAPT regimen. Among the components of the PEGASUS-TIMI 54 criteria, CKD was more prevalent among the >24 M DAPT group compared to the 12–24 M group (7.5 vs 3.7%; $p < 0.001$), while no significant between-group differences were found for older age, diabetes mellitus, multivessel CAD, and ($p = 0.213$, $p = 0.388$, $p = 0.689$, and $p = 0.057$) (**Figure 2**). In addition, hypertension, previous PCI, and left ventricle ejection fraction ≤35% were more prevalent in the >24 M DAPT group than in the 12–24 M group (58.8 vs. 52.4%; $p = 0.001$, 26.2 vs. 21.4%; $p = 0.003$) (**Table 1**). Clopidogrel and statins were more commonly used (84.3 vs. 78.0%, $p < 0.001$), while ticagrelor, prasugrel, and thrombus aspiration devices were less commonly used in the >24 M DAPT group than in the 12–24 M group (6.9 vs. 9.9%; $p = 0.003$, 8.9 vs. 12.0%; $p = 0.007$, 10.1 vs. 14.3%; $p = 0.001$, respectively). There were more three vessel diseases with multivessel PCI, left main PCI, and restenosis lesion PCI in the >24 M DAPT group than in the 12–24 M group (15.7 vs. 13.0%; $p = 0.046$, 5.4 vs. 2.0%; $p < 0.001$, 2.4 vs. 1.1%; 0.017, respectively). The mean total stent length was longer, and the mean total stent number used was greater in the >24 M DAPT group ($p = 0.036$ and $p < 0.001$, respectively). No significant differences were observed for the GRACE scores between the two groups ($p = 0.955$).

## Clinical outcomes according to the dual antiplatelet therapy duration

Among the post-AMI 2 years survivors who maintained DAPT beyond 1 year, 3,382 met the PEGASUS-TIMI 54 high-risk criteria. All participants underwent second-generation DES. The median follow-up duration was 3.02 (1.88, 4.44) years from 2 years after index AMI. The all-cause death rate was also dependent on the number of PEGASUS-TIMI 54 high-risk criteria that were present, with mortality increasing as the number of concomitant risk components increased (**Figure 3**). Multivariable Cox proportional hazard models identified independent predictors of the primary ischemic endpoint. CKD (eGFR < 60 ml/min/1.73 $m^2$) and severe LV dysfunction (LVEF < 35%) were independently associated with a decreased risk of all-cause death (adjusted HR: 3.07, 95% CI: 2.388–3.945, $p < 0.001$; HR 2.342, 95% CI 1.662–3.3, $p < 0.001$). On the other hand, thrombus aspiration at index PCI was a negative predictor of all-cause death (HR: 0.579, 95% CI: 0.359–0.936, $p = 0.026$).

A total of 3,382 patients were divided into two groups based on whether DAPT was changed to SAPT before 24 months or remained over 24 months. Therefore, we observed the cumulative incidence of mortality and major bleeding from 24 to 60 months. The K-M estimated all-cause death rate was significantly lower in the >24 M DAPT group than in the control group (7.2 vs. 9.2%; log-rank $p = 0.031$; **Figure 4A**). There was no significant difference in the incidence of major bleeding between the two groups (2.0 vs. 1.1%, $p = 0.098$) (**Figure 4B**). In a multivariate Cox regression analysis, the patients who maintained DAPT > 24 M showed a lower risk of all-cause death than those who stopped DAPT between 12 and 24 months (adjusted HR: 0.648, 95% CI: 0.504–0.835, $p < 0.001$) (**Table 2**). The difference was mainly driven by a lower risk of cardiovascular death in patients with complex PCI. However, there were no significant differences in the event rates of myocardial infarction, revascularization, stent thrombosis, ischemic stroke, BARC 2, 3, and 5 bleeding, or any bleeding ($p = 0.901$, 0.315, 0.829, 0.708, 0.241, and 0.192, respectively). On the other hand, the maintained DAPT > 24 M strategy was not associated with the risk of major bleeding events (HR: 1.77, 95% CI: 0.91–3.444, $p = 0.093$). The results were consistent after propensity-score matching and inverse probability weighting to adjust for baseline differences. The potent P2Y12 inhibitor ticagrelor or prasugrel was less prescribed for the > 24 M DAPT group than for the 12–24 M DAPT group at discharge and at the 1 year follow-up time (15.9 vs. 21.9%; $p < 0.001$, 12.8 vs. 18.8%; $p < 0.001$). At the time of follow-up in the second year, the ratio of potent P2Y12 inhibitor prescriptions between the two groups changed in reverse (2.9 vs. 0.3%, $p < 0.001$).

## Subgroup analysis

**Figure 5** presents the prognostic impact of the extended (>24 M) DAPT strategy among the various subgroups. The significantly lower risk of all-cause death in the >24 M DAPT group than in the 12–24 M DAPT group was consistent across all subgroups without significant interaction *p*-values.

# Discussion

In the present study, we compared 3 years clinical outcomes between >24 M DAPT versus 12–24 M DAPT in AMI patients who met PEGASUS TIMI 54 criteria using data from a large multicenter observational study. All participants were post-AMI 2 years survivors who did not experience major bleeding before 24 months. We investigated the event rates for 2–5 years after the index procedure. The main findings were as follows. First, 77.5% of the post-AMI 2 years survivors met the PEGASUS-TIMI 54 trial inclusion criteria. Among them, 67.4% maintained DAPT over 24 months. Second, the risk of mortality was significantly greater as the number of PEGASUS criteria increased. Third, extended DAPT over 24 months showed a significantly lower risk of mortality than those patients who changed DAPT to SAPT between 12 and 24 months. Impaired renal function, severe LV dysfunction, and thrombus aspiration at index PCI were independent predictors of the primary

TABLE 2 Ischemic and bleeding outcomes in acute myocardial infarction (AMI) patients with the PEGASUS-TIMI 54 criteria according to the dual antiplatelet therapy (DAPT) duration.

| | Original cohort | | | | | | Propensity-score matched | | IPW | |
|---|---|---|---|---|---|---|---|---|---|---|
| | >24 M DAPT | >12 M, ≤24 M DAPT | Univariate HR* (95% CI) | *P*-value† | Multivariate HR (95% CI) | *P*-value | HR* (95% CI) | *P*-value† | HR* (95% CI) | *P*-value† |
| **Ischemic endpoints** | 2281 | 1101.000 | – | – | – | – | – | – | – | – |
| All-cause of death | 165 (7.2%) | 101 (9.2%) | 0.762 (0.595–0.976) | 0.032 | 0.648 (0.504–0.835) | <0.001 | 0.59 (0.43–0.81) | 0.001 | 0.649 (0.502–0.84) | 0.001 |
| Cardiovascular death | 113 (5.0%) | 69 (6.3%) | 0.764 (0.566–1.031) | 0.078 | 0.652 (0.48–0.885) | 0.006 | 0.629 (0.432–0.917) | 0.016 | 0.665 (0.489–0.906) | 0.01 |
| Myocardial infarction | 40 (1.8%) | 18 (1.7%) | 1.05 (0.602–1.832) | 0.863 | 1.036 (0.589–1.822) | 0.901 | 1.17 (0.63–2.19) | 0.613 | 0.975 (0.542–1.753) | 0.931 |
| Revascularization | 102 (5.0%) | 41 (3.9%) | 1.244 (0.866–1.788) | 0.237 | 1.207 (0.836–1.744) | 0.315 | 1.07 (0.697–1.641) | 0.758 | 1.166 (0.795–1.712) | 0.431 |
| Target vessel revascularization | 51 (2.3%) | 21 (1.9%) | 1.167 (0.702–1.94) | 0.552 | 1.151 (0.688–1.927) | 0.592 | 1.158 (0.648–2.069) | 0.621 | 1.087 (0.638–1.853) | 0.759 |
| Target lesion revascularization | 33 (1.5%) | 13 (1.2%) | 1.209 (0.636–2.296) | 0.563 | 1.24 (0.646–2.379) | 0.519 | 1.115 (0.531–2.344) | 0.774 | 1.113 (0.562–2.204) | 0.758 |
| Definite or probable ST | 10 (0.4%) | 4 (0.4%) | 1.154 (0.362–3.681) | 0.808 | 1.139 (0.352–3.683) | 0.829 | 1.387 (0.391–4.917) | 0.612 | 1.167 (0.361–3.774) | 0.796 |
| Stroke | 29 (1.3%) | 11 (1.0%) | 1.228 (0.614–2.459) | 0.561 | 1.144 (0.567–2.309) | 0.708 | 1.206 (0.547–2.657) | 0.6423 | 1.183 (0.585–2.393) | 0.639 |
| **Bleeding endpoints** | – | – | – | – | – | – | – | – | – | – |
| BARC 3 or 5 | 44 (2.0%) | 11 (1.1%) | 1.866 (0.964–3.613) | 0.064 | 1.77 (0.91–3.444) | 0.093 | 1.736 (0.832–3.624) | 0.142 | 1.841 (0.948–3.576) | 0.072 |
| BARC 2, 3, or 5 | 71 (3.3%) | 24 (2.4%) | 1.381 (0.869–2.194) | 0.171 | 1.323 (0.829–2.111) | 0.241 | 1.182 (0.691–2.022) | 0.542 | 1.32 (0.824–2.114) | 0.249 |
| Any bleeding | 94 (4.5%) | 33 (3.4%) | 1.317 (0.886–1.958) | 0.173 | 1.306 (0.875–1.95) | 0.192 | 1.22 (0.775–1.921) | 0.39 | 1.324 (0.885–1.983) | 0.172 |

Values are number of events (%) unless otherwise indicated.
*Generated with univariate Cox regression.
† *P*-value from univariate Cox regression.
DAPT, dual antiplatelet therapy; CI, confidence interval; HR, hazard ratio; ST, stent thrombosis; IPW, inverse probability weighting; BARC, bleeding academic research consortium.





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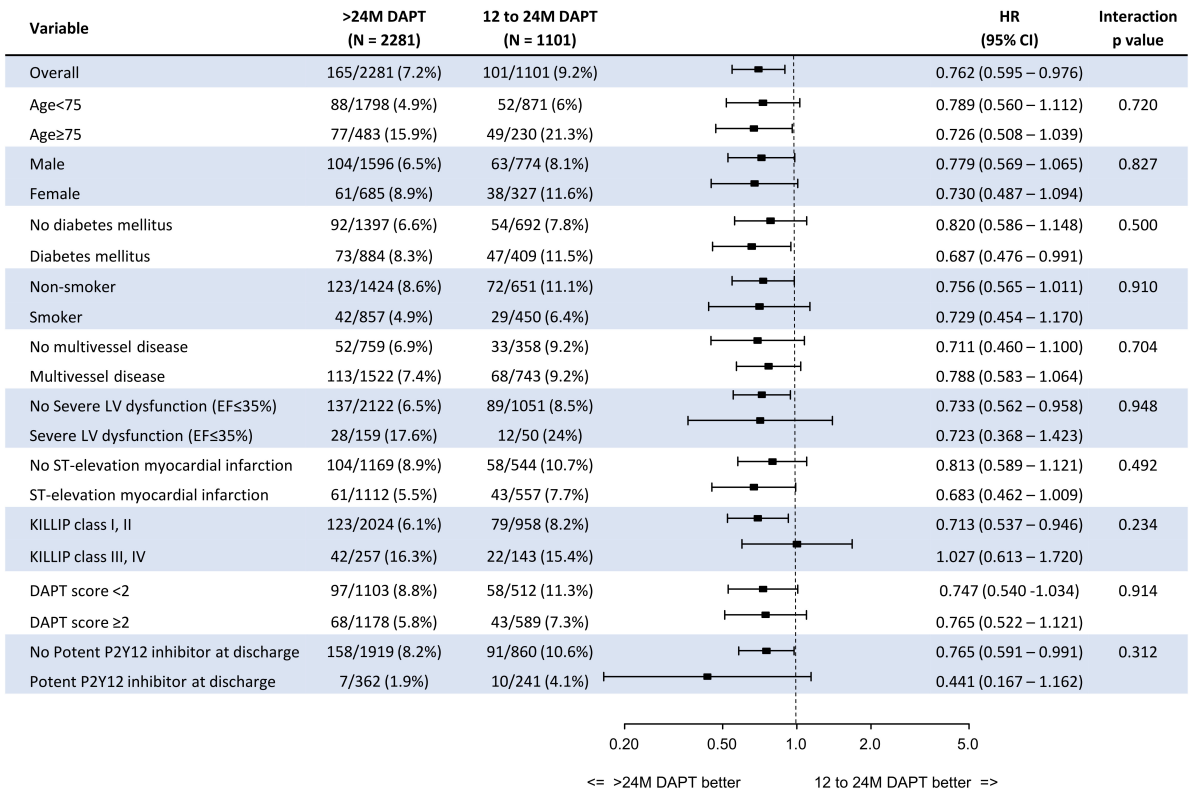


FIGURE 5
Subgroup analysis. DAPT, dual antiplatelet therapy; HR, hazard ratio; LV, left ventricle.

ischemic endpoint. Fourth, however, there was no significant difference in the risk of major bleeding (BARC 3, 5) between the two groups. Fifth, the significantly lower risk of all-cause death in the >24 M DAPT group compared with the 12–24 M DAPT group was consistently observed in various subgroups without significant interaction *p*-values.

## Trends of the dual antiplatelet therapy strategy and evidence of extended dual antiplatelet therapy duration

Dual antiplatelet therapy prevents the recurrence of ischemic events after PCI. The current guidelines based on several randomized controlled trials recommend more potent dual antiplatelet strategies for patients with acute coronary syndrome (3, 4, 14). The clinical benefits of strategies using potent P2Y12 inhibitors to reduce ischemic events or extended DAPT treatment after one year are mitigated due to a high risk of bleeding at the same time. Therefore, these strategies are applicable to patients at high risk of ischemia, and we should carefully consider the duration of treatment (15). According to the development of contemporary techniques and advanced devices (newer generation stents with thinner struts or advanced polymer profiles), there were temporal trends of decreasing ischemic adverse events and relatively more prominent bleeding events occurring (16, 17). Generally, the risk of ischemic events occurs intensively in the early stages and progressively decreases over time. Recently, newer generations of stents have tended to shorten the early stages when potent drugs are needed. Indeed, recent trials demonstrated that shorter (approximately 1–3 months) potent P2Y12 inhibitor usage (e.g., de-escalation strategies) is more beneficial to ACS patients who underwent PCI in terms of net clinical benefit, including MACE and overt bleeding (18–20). However, the prolonged DAPT strategy (not including potent P2Y12 inhibitors) for selective patients, such as AMI survivors with high ischemic risk subsets, could still have a role in improving future clinical outcomes (9). From the DAPT. DES LATE and PEGASUS TIMI-54 trials, we observed that high-ischemic clinical risk subsets are independently associated with a higher risk of ischemic events, and they have the advantage of using longer-term potent DAPT (2, 8). *Post-hoc* analyses from RCTs and other studies have also suggested a benefit of a longer duration of more intensive antiplatelet therapy for high-risk populations (21–23). The PEGASUS TIMI 54 trial evaluated the benefits of using DAPT over 12 months in patients with AMI history and high ischemia risk (7). The patients were administered aspirin and additional ticagrelor

twice daily or as a placebo and were followed up for 3 years. Compared to placebo, ticagrelor was associated with a reduced risk of CV death, MI, or stroke for 3 years without a significant difference in major bleeding and a neutral effect on overall mortality (8).

## Areas of uncertainty that need future clarification: How long does dual antiplatelet therapy need to be maintained?

Based on the PEGASUS TIMI 54, DAPT, and other trials, the current practice guidelines recommend treatment with DAPT for 1 year after a myocardial infarction (3, 4, 14). However, there is a debate about how long DAPT should be maintained (24). To date, only a few studies have addressed the significant association between extended DAPT beyond one year and hard clinical endpoints, such as cardiovascular mortality, and data from the AMI population are especially scarce (2, 25, 26). A network meta-analysis with ACS suggests that extended-term DAPT reduces myocardial infarction at the expense of more bleeding events (27). However, some previous clinical trials and meta-analyses showed that the benefits of reducing ischemic events associated with the extended use of DAPT over 12 months were counterbalanced by an increased risk of bleeding. (25, 26, 28, 29). Even the findings from some clinical trials have suggested no apparent benefit but instead suggested that there is harm when DAPT is extended beyond 1 year after stenting with DES and when no event has occurred within the first year after stenting, although that study included stable angina patients (30, 31). Therefore, it has been proposed that DAPT should only be used for a short period of approximately 6 months in patients at risk of high bleeding (4), and the potential benefits of extended DAPT for long-term secondary prevention after ACS are controversial.

## How can high-risk subsets that need extended dual antiplatelet therapy be distinguished?

In addition, there remains uncertainty about which high-risk subset of the scoring system is valid (24). Several scoring systems (e.g., DAPT, PRECISE-DAPT, PARIS) have been proposed to help distinguish the high-risk group and determine the DAPT period but have thus far failed to provide sufficiently robust prediction for use in real-world practice (1, 5, 6). Factors such as advanced age and diabetes increase both bleeding and ischemic risks, making the determination of optimal DAPT duration more difficult. Moreover, in the case of the DAPT and DES-LATE trials, which are representative studies that showed the effectiveness of the extended DAPT strategy, past 1st generation stents accounted for approximately 40 and 70% (2, 32). A recently published paper has shown that the results may differ if a reanalysis is performed by applying this trend (33). In real-world clinical practice, the risk of high ischemia and high bleeding is high, and the risks increase as the aging society progresses (34). In addition, changes in the procedural tools and skills, patient factors related to procedure risk, and event rate during the follow-up period gradually progressed over time. Therefore, it is questionable whether the data and risk scores from past clinical trials can be applied to current clinical practice (16). A recent study confirmed that the predictive power was excellent when scoring the components of the PEGASUS TIMI 54 criteria. (10). However, no studies have yet adopted these patient groups to validate the use of DAPT for a period that is extended to more than 1 year.

## Clinical implications of the extended dual antiplatelet therapy strategy for high-risk subsets with the PEGASUS TIMI 54 criteria

In our study, we adopted a high ischemic risk category from the PEGASUS TIMI 54 trial and evaluated the clinical implications of an extended DAPT strategy in our long-term follow-up AMI cohort. Our study enrolled only second-generation DES users among all AMI survivors and excluded anticoagulation users for analysis. The mortality of the patients who met the PEGASUS TIMI 54 criteria was significantly higher and positively related to the number of associated high ischemic risk components: the greater the number of components, the greater the risk of all-cause death. This is consistent with prior reports in similar analyses of ACS patients who underwent PCI (9, 35). Scoring or modification of these criteria could adequately identify subsets with more favorable outcomes from prolonged DAPT with regard to the net clinical benefit (36). In our data, using the PEGASUS TIMI 54 criteria to screen high-risk subsets and the maintenance of DAPT over 24 months beneficially affected long-term mortality (during 24–60 months) without increasing major bleeding (**Figure 3**). In addition, sensitivity analysis was performed in various ways (PS-matching, IPW) to improve the reliability of the results (**Table 2**). At baseline, clinical risk factors and procedural risk factors were even more common in the >20 M DAPT group (**Table 1**). Although the potent P2Y12 inhibitor was less prescribed at discharge and 1 year follow-up time, the mortality was lower in the >24 M DAPT group than in the 12–24 M DAPT group. Interestingly, the ratio of potent P2Y12 inhibitor prescriptions between the two groups changed in reverse at the second year of follow-up (2.9 vs. 0.3%, $p < 0.001$).

## Limitations

The first limitation of this study was that it was a non-randomized, retrospective study, which decreased the statistical power to detect differences. However, with the extensive sensitivity analyses and large population cohort data, the possible confounders were adjusted to minimize the bias from different baseline characteristics. Second, new P2Y12 inhibitors, such as ticagrelor or prasugrel, which achieved superior results compared to clopidogrel in ACS patients, were used instead of clopidogrel in only 19.8% of patients. This is because powerful P2Y12 inhibitors have been available in Korea since 2014. Although the proportion of potent P2Y12 inhibitor use at discharge differed significantly between the two groups, this difference may not be significantly related to the results considering the low prescription rate. Third, in our cohort, the overall incidence of bleeding events was low. Accordingly, the difference in the major bleeding event rate between the two groups may not have widened. This may be due to the exclusion of patients who underwent anticoagulation or were prescribed anticoagulation during the follow-up period. In addition, since this study was analyzed in stabilized patients for 2 years after AMI, it may have already been changed to SAPT by a physician if maintaining DAPT treatment is complex. For the same reason, other ischemic endpoints, except for mortality, did not significantly decrease even if DAPT was used for a long time. Fourth, the population of patients analyzed in our study is limited to AMI survivors at risk of high ischemic events (who meet PEGASUS-TIMI 54 criteria) and less likely to bleed (who have not experienced bleeding for 24 months). A large-scale RCT study is needed to clearly conclude that DAPT maintenance therapy is needed in this patient group. However, the results of our study based on real-world practice data may be helpful to specify a group of patients who need DAPT maintenance therapy when designing prospective studies in the future.

## Conclusion

The PEGASUS-TIMI 54 criteria, as defined by high-ischemic risk features, were associated with a significantly higher risk of ischemic events. The present study results suggest that extended DAPT over 24 months may be beneficial in decreasing mortality without a significant increase in major bleeding compared to switching DAPT to SAPT between 12 and 24 months in AMI patients who were successfully treated with second-generation DES and met the PEGASUS-TIMI 54 criteria. The population of our study was 2 years survivors after AMI who did not suffer significant bleeding before 24 months; therefore, we cannot extend the results of this analysis to other patients.

## Data availability statement

The datasets are not publicly available. Requests to access these datasets should be directed to KYL, cycle0210@gmail.com.

## Ethics statement

The studies involving human participants were reviewed and approved by the Catholic Medical Center Central Institutional Review Board (IRB). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## Author contributions

KYL contributed to the conceptualization, methodology, formal analysis, writing—original draft preparation, and visualization. B-HH contributed to the conceptualization, writing—review and editing, supervision, and project administration. CJK and E-HC helped with validation, investigation, and resources. JB helped with formal analysis. J-JK and SL helped with the investigation. IJC, GCO, KDY, YA, MHJ, WSC, and YSC helped with resources. KC helped with data curation and project administration. All authors critically revised the manuscript and approved the final version of the manuscript.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Atrial cardiomyopathy markers predict ischemic cerebrovascular events independent of atrial fibrillation in patients with acute myocardial infarction

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**Background:** Contemporary data on atrial cardiomyopathy (ACM) markers and ischemic cerebrovascular events (ICVE) in patients with acute myocardial infarction (AMI) is lacking. We aimed to examine whether ACM markers predict ICVE among AMI patients.

**Materials and methods:** A total of 4,206 AMI cases diagnosed in clinical examinations between January 2016 and June 2021 were assessed for markers of ACM including B-type natriuretic peptide (BNP), P-wave terminal force in ECG lead V1 (PTFV1), and left atrium diameter (LAD). Left atrial enlargement (LAE) and abnormal PTFV1 were defined by previously published cut-off points. The primary outcome was incident ICVE composed of ischemic stroke (IS) and transient ischemic attack (TIA). Receiver operating curve analyses were used to compare the predictive performance of the $CHA_2DS_2$-VASc score combined with ACM markers to the $CHA_2DS_2$-VASc score alone.

**Results:** During a median follow-up of 44.0 months, 229 (5.44%) ICVE occurred. Of these, 156 individuals developed IS and the remaining 73 cases were diagnosed with TIAs. The ICVE group showed larger PTFV1 and increased LAD as well as elevated BNP levels at baseline. In the multivariate analysis, we found significant associations with ICVE for PTFV1 (HR per 1,000 μV*ms, 1.143; 95% CI, 1.093–1.196), LAD (HR per millimeter, 1.148; 95% CI, 1.107–1.190), but not BNP after adjusting for known ICVE risk factors and interim atrial fibrillation (AF). The addition of abnormal PTFV1 and LAE improved the predictive accuracy of the $CHA_2DS_2$-VASc score with C-statistic increasing from 0.708 to 0.761 ($p < 0.001$).

**Conclusion:** Atrial cardiomyopathy markers including PTFV1 and LAD were associated with incident ICVE independent of well-established risk factors and AF occurrence. The addition of ACM markers with $CHA_2DS_2$-VASc score may well discriminate individuals at high risk of ICVE in AMI patients.

KEYWORDS

**atrial cardiomyopathy, ischemic cerebrovascular events, P wave terminal force, left atrium diameter, B-type natriuretic peptide**

# Introduction

Ischemic cerebrovascular event (ICVE) is one of the most dangerous complications after acute myocardial infarction (AMI), which is a well-established factor of poor prognosis (1). Previous studies have reported that new-onset atrial fibrillation (NOAF) is independently associated with ischemic stroke (IS) in acute coronary syndrome (ACS) patients (2). In contrast, some studies found that atrial cardiomyopathy (ACM) could cause cardioembolic stroke in the absence of AF (3). Whether NOAF is etiologically involved in the disease process or just a marker of ACM in patients with AMI remains unclear.

Over the recent years, increasing number of studies have significantly drawn attention to ACM, the complex disturbance in electrophysiology of the heart, or structural changes that negatively impact the normal function of the atria (4). According to a study conducted among the general population, ACM is considered to exist prior to AF and stroke (3). Although the diagnostic criteria for ACM are not clear at present, different biomarkers have been used to identify ACM (5, 6). In an ongoing cohort study, ACM is defined as NT-proBNP $>$ 250 pg/mL, or P-wave terminal force in ECG lead V1 (PTFV1) $>$ 5,000 $\mu V^*ms$, or severe LAE (5).

The $CHA_2DS_2$-VASc score has been routinely used to assess future ICVE risk and guide anticoagulant therapy for patients with atrial fibrillation (AF) clinically. In recent years, the use of the $CHA_2DS_2$-VASc score in predicting ICVE has extended beyond the originally proposed. For instance, a recent study by Mitchell L. B. et al. reported that the $CHA_2DS_2$-VASc scores obtained similar ICVE predicting accuracy in patients with ACS but free of AF to that observed in populations with non-valvular AF (7). To the extent of our knowledge, no study investigated the association of ACM markers with ICVE and whether ACM markers could improve $CHA_2DS_2$-VASc scores to detect ICVE occurrence in AMI patients independent of AF. Therefore, the present study aimed to examine (a) the association between baseline ACM markers and ICVE occurrence, and (b) whether the addition of these markers to the $CHA_2DS_2$-VASc score would improve the prediction of ICVE in patients with AMI.

# Materials and methods

## Study participants

This hospital-based retrospective analysis was conducted among 5,763 AMI patients with complete clinical examinations and data on coronary angiography (CAG) between January 2016 and June 2021. Patients who died during hospitalization, patients with AF and valvular disease history, and patients who refused or were lost to follow-up were excluded. Ultimately, 4,206 patients were finally enrolled in this study. The remaining patients were categorized into two groups according to the presence of ICVE. The flow chart that demonstrates the included and excluded population is indicated in **Figure 1**. The Institutional Review Board of the First Affiliated Hospital of Dalian Medical University (FAHDMU) approved the study. This research abided and conform to the Helsinki declaration. The requirement for informed consent was waived due to the nature of our study design and all procedures comply with the approved research guidelines.

## Electrocardiogram parameters

The electrocardiogram (ECG) records were based on the initial ECG which was performed during AMI diagnosis. GE Healthcare MAC 5500 was used to record and download ECG parameters, which were calibrated at a speed of 25 mm/s with a voltage of 10 mm/1 mV. The multiplication of the duration (ms) and the depth ($\mu V$) of the terminal negative part the P wave in lead V1 was considered as PTFV1. In this study, we defined PTFV1 $>$ 5,000 $\mu V^*ms$ as abnormal PTFV1 (5, 8). Of note, two independent cardiologists examined the PTFV1 values and their intra-observer correlation coefficient was found to be 0.92 ($P < 0.001$).

## Measurements and covariates

The electronic medical record of FAHDMU was searched for demographic, clinical, and laboratory data. An increase in

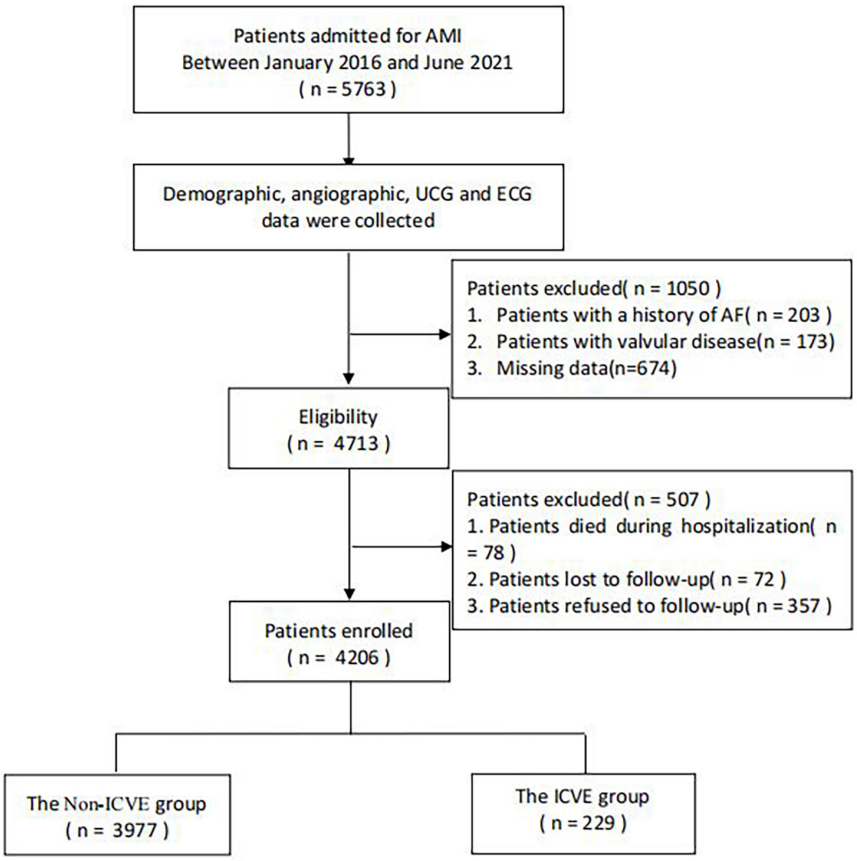


FIGURE 1
The overview of the selection of study participants. AF, atrial fibrillation; AMI, acute myocardial infarction; ECG, electrocardiogram; ICVE, ischemic cerebrovascular events; UCG, ultrasound cardiogram.

systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg or a history of antihypertensive drug use was defined as hypertension (HTN) (9). Diabetes mellitus (DM) was defined as previously [random blood sugar (RBS) level ≥ 200 mg/dL, fasting blood sugar (FBS) level ≥ 126 mg/dL or anti-diabetic drug use] (10). We defined dyslipidemia based on at least one of the below listed criteria: the presence of triglyceride (TG) ≥ 2.26 mmol/L (200 mg/dL), low density lipoprotein cholesterol (LDL-C) ≥ 4.14 mmol/L (160 mg/dL), high density lipoprotein cholesterol (HDL-C) ≤ 1.04 mmol/L (40 mg/dL), total cholesterol (TC) ≥ 6.22 mmol/L (240 mg/dL), or use of lipid-lowering medication (11). As previously defined in other studies, we compiled data from the clinical symptoms, echocardiography, chest X-ray, and electrocardiography to define congestive heart failure (CHF) (12). AF was defined based on 12-lead ECG or Holter ECG recordings. AMI was defined based on elevated cardiac troponin values (suggestive of myocardial injury) followed by one of the following criteria: (1) symptoms of myocardial ischemia, (2) ischaemic ECG changes, (3) evidence of pathological Q wave on ECG, or (4) availability of new regional wall motion abnormality in echocardiography. Further AMI was classified into ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) in accordance with the fourth universal definition of myocardial infarction (13).

## Follow-up

We obtained follow-up data either by reviewing medical records or by telephone interview. To obtain and censor ICVE outcomes, AMI patients were followed from their first admission until the occurrence of the primary outcome, death, or last follow-up (1 January 2022), whichever came first.

## Outcome assessment

The primary outcome was ICVE which was defined as fatal or non-fatal transient ischemic attack (TIA) or IS. In this study, IS was defined as new onset of a documented focal neurologic deficit lasting at least 24 h or until death or evidence of lesion on brain imaging. TIA was defined as a transient episode of

focal neurologic deficit lasting less than 24 h and without brain imaging suggesting cerebral infarction.

## Statistical analysis

Continuous data were compared using the student's *t*-test and the Mann–Whitney test depending on the nature of their distribution. The outcome was expressed as mean and standard deviation (SD) for normally distributed data and the median and interquartile range (IQR) for the non-normally distributed data. Categorical data were presented as count and percentage and differences were checked using the Chi-square test or Fisher exact test. Multivariate Cox proportional hazards models with incremental adjustments were used to examine the association of ACM markers with incident ICVE. Model 1 adjusted for age and gender. Model 2 included covariates from Model 1 plus variables with a *P*-value of $< 0.05$ in the univariate COX analyses and known variables associated with ICVE including prior history of hypertension, DM, stroke, peripheral arterial disease, CHF, SBP, heart rate at admission, KILLIP $> 1$, estimated glomerular filtration rate, log-transformed BNP, PTFV1 (per 1,000 μV*ms), left atrium diameter, left ventricular ejection fraction, use of diuretics, smoking status, and dyslipidemia. Model 3 included Model 2 covariates plus incident AF. We further dichotomized continuous ACM markers by the previously published cut-off points: abnormal PTFV1 (PTFV1 $>$ 5,000 μV*ms) (5) and left atrial enlargement (LAE) (LAD $>$ 38 mm for women and $>$ 40 mm for men) (14). Subgroup analysis was executed between normal PTFV1 and abnormal PTFV1 groups as well as for normal LAD and LAE groups. The interaction between ACM markers and covariates was assessed with a Cox regression model.

The Kaplan–Meier curves and log-rank test were used to compare the freedom distributions and study the differences in ICVE freedom as stratified by ACM markers, respectively. We further executed time-dependent receiver operating characteristics of four different models, including $CHA_2DS_2$-VASc score (Model 1), $CHA_2DS_2$-VASc score + abnormal PTFV1 (Model 2), $CHA_2DS_2$-VASc score + LAE (Model 3), and $CHA_2DS_2$-VASc score + LAE + abnormal PTFV1 (Model 4). Harrell's concordance statistics, a goodness of fit measure for models which produce risk scores, was calculated to measure the predictive power of ACM indicators and the combined models. The net reclassification index (NRI) was calculated to estimate the net change in the proportion of AMI patients assigned a more appropriate ICVE risk under the new model. Also, integrated discrimination improvement (IDI) was calculated to compare the discriminatory capacity among the models. *P*-value $< 0.05$ was considered statistically significant. All analyses were performed using R software.

# Results

## Baseline characteristics of the participants

A total of 4,206 patients (3,235 men and 971 women) were enrolled in the final analysis. After a median follow-up of 44.0 months, 229 individuals (5.44%) experienced incident ICVE (156 ISs and 73 TIAs). ICVE cases were older and likely to have more comorbidities such as hypertension, DM, stroke, peripheral arterial disease, and CHF. In addition, the ICVE group had higher values of log-transformed B-type natriuretic peptide (BNP), hypersensitive troponin I (hsTNI), PTFV1, left atrium diameter (LAD), and $CHA_2DS_2$-VASc score than those without ICVE. The Killip classification and the GRACE score were also higher in ICVE than in the non-ICVE group. Compared with non-ICVE cases, AMI patients with ICVE exhibited longer hospitalization lengths and more frequent in-hospital cardiac arrest (IHCA). At discharge, patients with ICVE were more likely to be prescribed diuretics than patients without ICVE. Participants in the ICVE group developed a higher proportion of AF (18.8 vs. 7.2%, respectively) during the follow-up than those in ICVE free group. The demographic and baseline clinical characteristics of the AMI patients included in the analysis are shown in **Table 1**.

## Relationship between atrial cardiomyopathy markers, incident atrial fibrillation and ischemic cerebrovascular events

**Figure 2** illustrates the comparison of ACM markers between ICVE and non-ICVE groups with or without incident AF. Individuals with ICVE had larger LAD and PTFV1 values than those without ICVE regardless of their AF status ($P < 0.001$). Similarly, ICVE patients had higher LogBNP values than those without ICVE in non-AF patients ($P < 0.001$). However, there were no significant differences in LogBNP values between ICVE and non-ICVE groups in patients with incident AF (**Figure 2**).

Univariable analysis between baseline and incident ICVE for the entire cohort were shown in **Supplementary Table 1**. In the multivariate model (Model 2), we found positive relationship between PTFV1 and incident ICVE (HR per 1,000 μV*ms, 1.148; 95% CI, 1.097–1.201, $P < 0.001$), LAD (HR per millimeter, 1.152; 95% CI, 1.111–1.194, $P < 0.001$) but not for LogBNP (HR per doubling of BNP, 1.058; 95% CI, 0.962–1.164, $P = 0.244$).

To investigate the effect of AF, we considered incident AF as a single variable during the adjustment for the multivariate model. The association between ACM markers and ICVE

TABLE 1 Baseline characteristics.

| Variable | Overall | No ICVE | ICVE | *P*-value |
|---|---|---|---|---|
| | (*n* = 4206) | (*n* = 3977) | (*n* = 229) | |
| Age, years | 62.9 (11.9) | 62.6 (11.9) | 67.6 (10.6) | < 0.001 |
| Male, *n* (%) | 3235 (76.9) | 3060 (76.9) | 175 (76.4) | 0.855 |
| Smoking, *n* (%) | 1940 (46.1) | 1843 (46.3) | 97 (42.4) | 0.240 |
| Drinking, *n* (%) | 897 (21.3) | 853 (21.4) | 44 (19.2) | 0.472 |
| **Medical history** | | | | |
| HTN, *n* (%) | 2456 (58.4) | 2293 (57.7) | 16 (71.2) | < 0.001 |
| DM, *n* (%) | 1450 (34.5) | 1343 (33.8) | 107 (46.7) | < 0.001 |
| Dyslipidemia, *n* (%) | 2790 (66.3) | 2634 (66.2) | 156 (68.1) | 0.605 |
| Prior MI, *n* (%) | 54 (1.3) | 52 (1.3) | 2 (0.9) | 0.791 |
| Previous stroke, *n* (%) | 278 (6.6) | 226 (5.7) | 52 (22.7) | < 0.001 |
| PAD, *n* (%) | 413 (9.8) | 374 (9.4) | 39 (17.0) | < 0.001 |
| CHF, *n* (%) | 272 (6.5) | 241 (6.1) | 31 (13.5) | < 0.001 |
| **Initial presentation** | | | | |
| SBP, mmHg | 131.2 (24.3) | 130.9 (24.2) | 136.3 (24.8) | 0.001 |
| DBP, mmHg | 78.1 (13.4) | 78.1 (13.4) | 79.3 (12.9) | 0.169 |
| HR at admission, b.p.m. | 74.8 (15.6) | 74.7 (15.6) | 77.3 (15.7) | 0.014 |
| KILLIP > 1, *n* (%) | 683 (16.2) | 627 (15.8) | 56 (24.5) | 0.001 |
| STEMI, *n* (%) | 2004 (47.6) | 1903 (47.9) | 101 (44.1) | 0.300 |
| Anterior wall, *n* (%) | 969 (48.4) | 919 (48.3) | 50 (49.5) | 0.812 |
| Inferior wall, *n* (%) | 1026 (51.2) | 978 (51.4) | 48 (47.5) | 0.449 |
| Others, *n* (%) | 392 (19.6) | 370 (19.4) | 22 (21.8) | 0.564 |
| $CHA_2DS_2$-VASc Score | 2 (1–3) | 2 (1–3) | 3 (2–4) | < 0.001 |
| GRACE score | 143.0 (31.8) | 142.4 (31.8) | 152.8 (31.0) | < 0.001 |
| **Culprit lesion** | | | | |
| LM, *n* (%) | 93 (2.2) | 89 (2.2) | 4 (1.7) | 0.795 |
| LAD, *n* (%) | 1669 (39.7) | 1573 (39.6) | 96 (41.9) | 0.520 |
| LCX, *n* (%) | 717 (17.0) | 678 (17.0) | 39 (17.0) | 1.000 |
| RCA, *n* (%) | 1402 (33.3) | 1321 (33.2) | 81 (35.4) | 0.548 |
| **Laboratory data and ECG parameters** | | | | |
| eGFR, ml/(min·1.73 $m^2$) | 91.2 (28.3) | 91.8 (28.1) | 80.6 (30.8) | < 0.001 |
| Uric Acid, μmol/L | 353 (291–415) | 353 (292–414) | 361 (286–448) | 0.220 |
| BNP, pg/ml | 124 (52–311) | 122 (51–294) | 255 (84–578) | < 0.001 |
| LogBNP | 7.0 (5.7–8.3) | 6.9 (5.7–8.2) | 8.0 (6.4–9.2) | < 0.001 |
| hsTnI, pg/ml | 8.4 (1.2–54.4) | 8.8 (1.2–56.0) | 5.0 (0.7–25.7) | 0.003 |
| PTFV1, μV*ms | 2210 (0–3710) | 2112 (0–3552) | 3944 (2279–5655) | < 0.001 |
| **Echocardiographic parameters** | | | | |
| LAD, mm | 37.4 (3.7) | 37.2 (3.6) | 39.9 (4.7) | < 0.001 |
| LVEF, % | 51.8 (8.4) | 51.9 (8.4) | 50.4 (9.5) | 0.023 |
| **Initial treatment** | | | | |
| PCI, *n* (%) | 3692 (87.8) | 3490 (87.8) | 202 (88.2) | 0.920 |
| CABG, *n* (%) | 35 (0.8) | 33 (0.8) | 2 (0.9) | 1.000 |
| Thrombolysis, *n* (%) | 50 (1.2) | 49 (1.2) | 1 (0.4) | 0.443 |
| Length of hospitalization, day | 6 (5–7) | 6 (5–7) | 6 (5–8) | 0.001 |
| IHCA, *n* (%) | 88 (2.1) | 78 (2.0) | 10 (4.4) | 0.025 |
| Incident AF, *n* (%) | 331 (7.9) | 288 (7.2) | 43 (18.8) | < 0.001 |
| **Medication at discharge** | | | | |
| ACEI/ARB, *n* (%) | 2900 (68.9) | 2731 (68.7) | 169 (73.8) | 0.119 |
| βblocker, *n* (%) | 3373 (80.2) | 3180 (80.0) | 193 (84.3) | 0.131 |

*(Continued)*

TABLE 1 (Continued)

| Variable | Overall ($n = 4206$) | No ICVE ($n = 3977$) | ICVE ($n = 229$) | *P*-value |
|---|---|---|---|---|
| Statins, *n* (%) | 4190 (99.6) | 3962 (99.6) | 228 (99.6) | 1.000 |
| OAC, *n* (%) | 62 (1.5) | 56 (1.4) | 6 (2.6) | 0.231 |
| Aspirin, *n* (%) | 4156 (98.8) | 3931 (98.8) | 225 (98.3) | 0.626 |
| $P2Y_{12}$ receptor inhibitor, *n* (%) | 4200 (99.9) | 3971 (99.8) | 229 (100.0) | 1.000 |
| Diuretic, *n* (%) | 1097 (26.1) | 1015 (25.5) | 82 (35.8) | 0.001 |

ACEI, angiotensin-Converting Enzyme Inhibitors; ARB, angiotensin-converting enzyme receptor blockers; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CHF, congestive heart failure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GRACE, global registry of acute coronary events; HR, heart rate; hsTnI, hypersensitive troponin I; HTN, hypertension; IHCA, in-hospital cardiac arrest; LAD, left anterior descending coronary artery; LAD, left atrium diameter; LCX, left coronary circumflexus artery; LM, left main coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OAC, oral anticoagulants; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PTFV1, P-wave terminal force in ECG lead V1; RCA, right coronary artery; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction.

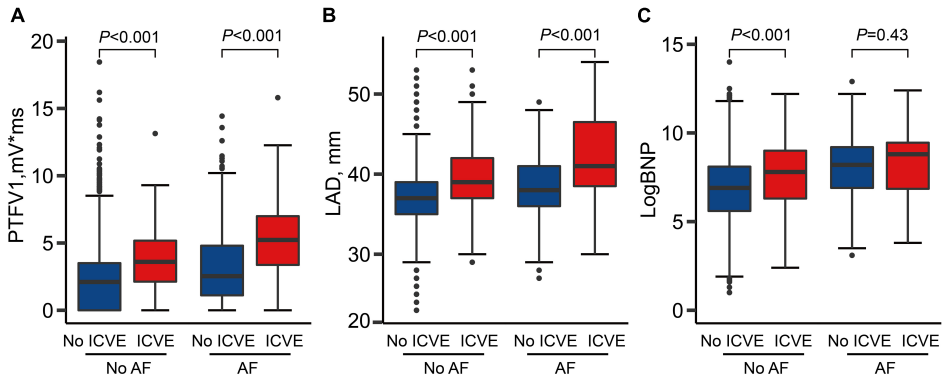


FIGURE 2
Atrial cardiomyopathy markers by strata of atrial fibrillation (AF) and ischemic cerebrovascular events (ICVE). **(A)** PTFV1 levels by strata of AF and ICVE; **(B)** LAD levels by strata of AF and ICVE; **(C)** LogBNP levels by strata of AF and ICVE.

occurrence was attenuated but still remained significant for PTFV1 (HR per 1,000 μV*ms, 1.140; 95% CI: 1.090–1.193, $P < 0.001$) and LAD (HR: 1.147 per millimeter; 95% CI: 1.106–1.189, $P < 0.001$), suggesting the association between ACM markers and ICVE independent of AF occurrence. The association between ACM markers and ICVE is shown in Table 2. To test whether the proportional hazard assumption was satisfied, we checked Schoenfeld residual tests. The result indicated that there was no collinearity violation between Schoenfeld residuals and time (Supplementary Figure 1).

## Subgroup analysis

We further dichotomized continuous PTFV1 and LAD covariates based on previously published cut-off points to run a sub-group analysis. Supplementary Figures 2, 3 present the prognostic effect of PTFV1 and LAD in different subgroups. We observed a low risk of ICVE in the normal PTFV1 and LAD groups. However, our data indicate that there were obvious differences in ICVE occurrence between patients with normal and abnormal PTFV1 (Figure 3A). Similarly, we observed a significant difference in ICVE occurrence between normal LAD and LAE groups (Figure 3B). Hence, the applied cut-off points can effectively draw the line for the ICVE risk between the lower-risk and higher-risk groups.

Further, we divided patients into four groups based on the previously defined cut-off points of PTFV1/LAD (Figure 3C). Each group represented combinations of two different markers: Group 1: patients with both normal PTFV1 and LAD; Group 2: patients with abnormal PTFV1 and normal LAD; Group 3: patients with LAE and normal PTFV1; Group 4: patients with abnormal PTFV1 and LAE. Patients in group 4 had the highest incidence of ICVE (log-rank test, $P < 0.001$).

## The combined effect of atrial cardiomyopathy markers on the $CHA_2DS_2$-VASc score

The results of the receiver operating characteristics (ROC) analysis that compared the performance of ACM markers

TABLE 2 The relationship between ACM markers and ICVE.

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | Hazard ratio | *P*-value | Hazard ratio | *P*-value | Hazard ratio | *P*-value |
| PTFV1 (per 1000 μV*ms) | 1.231 (1.182–1.281) | < 0.001 | 1.148 (1.097–1.201) | < 0.001 | 1.140 (1.090–1.193) | < 0.001 |
| LAD, mm | 1.199 (1.161–1.238) | < 0.001 | 1.152 (1.111–1.194) | < 0.001 | 1.147 (1.106–1.189) | < 0.001 |
| LogBNP | 1.279 (1.183–1.383) | < 0.001 | 1.058 (0.962–1.164) | 0.244 | 1.053 (0.957–1.159) | 0.288 |

Model 1 adjusted for age and gender. Model 2 included covariates from model 1 plus smoking status, prior history of hypertension, diabetes mellitus, dyslipidemia, stroke, peripheral arterial disease, congestive heart failure, systolic blood pressure, heart rate at admission, KILLIP > 1, estimated glomerular filtration rate, log-transformed BNP, PTFV1 (per1000 μV*ms), left atrium diameter, left ventricular ejection fraction and use of diuretics. Model 3 included Model 2 covariates plus incident AF.

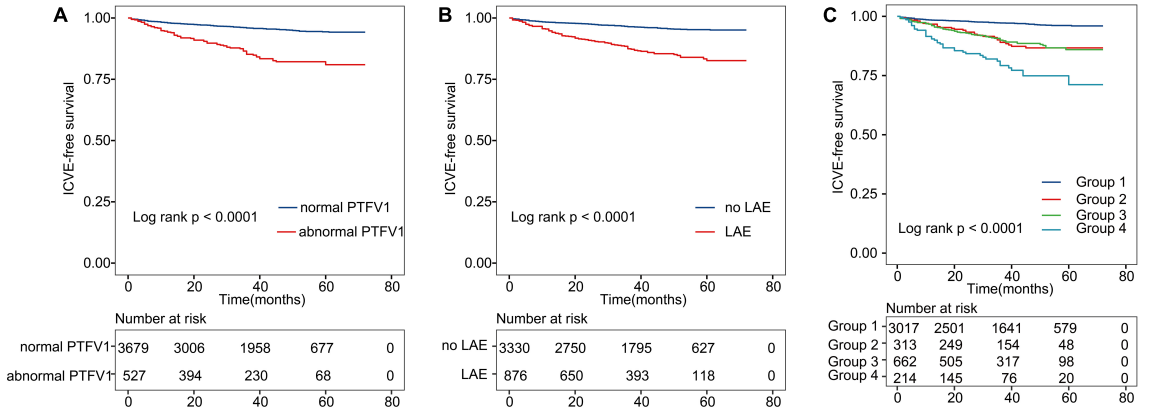


FIGURE 3
Kaplan–Meier curves show ICVE-free survival. **(A)** Kaplan–Meier survival curves for abnormal PTFV1. **(B)** Kaplan–Meier survival curves for LAE. **(C)** All patients were divided into four categories. The lines represent the following: Group 1: patients with both normal PTFV1 and no LAE; Group 2: patients with abnormal PTFV1 and no LAE; Group 3: patients with LAE and normal PTFV1; Group 4: patients with both abnormal PTFV1 and LAE. ICVE, ischemic cerebrovascular events.

(PTFV1 and LAD) against the $CHA_2DS_2$-VASc score to discriminate the ICVE patients are indicated in **Figure 4**. The $CHA_2DS_2$-VASc score alone had a moderate predictive ability, with a C-Statistic of 0.708 (95% CI: 0.667–0.749). The C-Statistic of the $CHA_2DS_2$-VASc score + abnormal PTFV1 and $CHA_2DS_2$-VASc score + LAE were 0.743 (95% CI: 0.707–0.779) and 0.742 (95% CI: 0.708–0.776), respectively. Notably, the greatest improvement in $CHA_2DS_2$-VASc predictive utility was observed when both abnormal PTFV1 and LAE were added, with C-Statistic increasing from 0.708 to 0.761 ($P < 0.001$) (**Table 3**). The IDI and NRI output demonstrates the superiority of the combined model compared to the $CHA_2DS_2$-VASc score alone, suggesting that the use of the combined final model could stratify the risk of ICVE better than the $CHA_2DS_2$-VASc score alone.

## Discussion

The findings of the present study demonstrated that two ACM markers including abnormal PTFV1 and LAD were positively linked with a substantial risk of incident ICVE in the Chinese population with AMI. The relationship persisted even after adjusting for conventional cerebrovascular disease risk factors and interim incident AF. The addition of abnormal PTFV1 and LAE to the $CHA_2DS_2$-VASc score significantly improved the prediction of ICVE risk.

The $CHA_2DS_2$-VASc score has been used to assess the individual stroke risk and determine anticoagulation therapy indications for AF patients in routine clinical practice. Current guidelines recommend short-term use of triple antithrombotic treatment including dual antiplatelet therapy (DAPT) and oral anticoagulants in high-risk individuals ($CHA_2DS_2$-VASc score $\geq$ 2) with AMI and AF for stroke prevention (15). However, ICVE could even occur in the absence of AF (16). This indicates intensive work is needed to efficiently identify high-risk patients and to improve the currently available risk stratification approaches. In the present study, we found that LAE and abnormally increased PTFV1 improved the predictive ability of the $CHA_2DS_2$-VASc score for ICVE. These findings suggest that the addition of LAE and abnormal PTFV1 with a $CHA_2DS_2$-VASc score may offer an improved predictive capacity performance for ICVE in individuals with AMI.

Recent evidence showed that ACM summarizes pathological functional, electrical, and structural remodeling in the atria

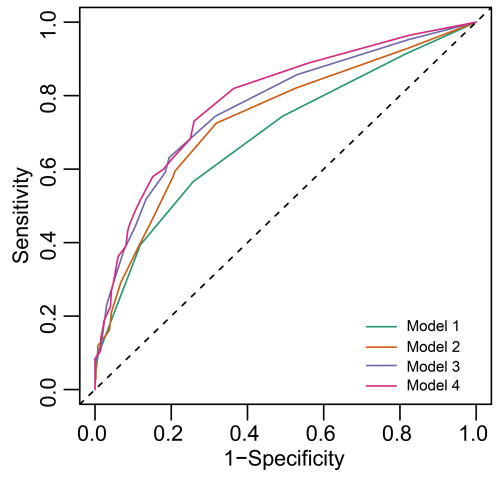


FIGURE 4
Receiver operating characteristics (ROC) curves of freedom from ICVE at 5 years for the different risk prediction models. Model 1, $CHA_2DS_2$-VASc score; Model 2, $CHA_2DS_2$-VASc score + abnormal PTFV1; Model 3, $CHA_2DS_2$-VASc score + LAE; Model 4, $CHA_2DS_2$-VASc score + abnormal PTFV1 + LAE.

(4) and could result in a pro-arrhythmogenic and pro-thrombotic atrial substrate. Several prospective studies with large sample sizes showed that ACM markers (including PTFV1, LAD, and NT-proBNP/BNP) could predict the occurrence of ICVE (3) in the general population. To our knowledge, no study has reported the predictive role of ACM markers for ICVE in AMI cases independent of AF. Hence, this study reflects the significant relationship between the ACM indicators (particularly, LAE and abnormal PTFV1) and ICVE after AMI, even after considering the confounding effect of several known risk factors and incident AF. This article built on previous literature which was conducted in general population, verifying and expanding the clinical applications of ACM markers to predict ICVE in patients with AMI. The main difference between the present study and previous studies is that BNP value was not associated with ICVE in AMI patients. Our results are in line with the previous studies (17). One possible reason for the lack of such association is that hemodynamics was not stable during AMI and BNP levels are vulnerable to hemodynamic changes. Therefore, the BNP level during the acute phase of myocardial infarction is not a good reflection of the long-term pressure overload after AMI. Atrial natriuretic peptide (ANP), a member of the natriuretic peptide hormone family, is released from the atria in response to stretch, as a result, elevated ANP level may reflect increased filling pressure and dysfunction of atria. ANP is reported to be associated with incidence of AF and stroke (18). Moreover, ANP significantly improved the prediction of AF and stroke when added to a predictive model consisting of conventional risk factors (19). Due to the retrospective nature of this study, serum ANP level was not available. Further studies should be performed to investigate the association between ANP level and ICVE in AMI patients and whether ANP could serve as ACM biomarkers in clinical practice.

The PTFV1 is a widely reported indicator for left atrial-related changes independent of structural deformity or pressure alterations in the left atrium of the heart (20, 21). Therefore, it has been considered a marker for electrical and functional remodeling of the atria (22). Besides, there exists substantial evidence regarding the link between PTFV1 and stroke (especially cryptogenic or cardioembolic stroke) regardless of AF in the general population (23). Abnormal PTFV1 may reflect atrial changes, such as fibrosis, delayed interatrial conduction, increased LA volume, and decrease LA function (24), all of which are reported to be associated with IS. The present study further corroborates the association between PTFV1 and ICVE among patients with AMI, even after adjustment for other indicators of ACM such as LAD and BNP, suggesting PTFV1 may reflect atrial changes that could not be fully represented by echocardiographic or serum biomarkers. Therefore, PTFV1, which is easily available in clinical practice and does not require complex calculations, can be beneficial as a cost-effective prognostic marker to recognize subjects at high risk for ICVE after AMI.

TABLE 3 Comparison of different risk prediction models.

| | Model 1 | Model 2 | Model 3 | Model 4 |
|---|---|---|---|---|
| AUC (95% CI) | 0.700 (0.657–0.743) | 0.742 (0.701–0.783) | 0.757 (0.719–0.796) | 0.782 (0.745–0.819) |
| *P*-value | – | 0.002 | < 0.001 | < 0.001 |
| C-Statistic (95% CI) | 0.708 (0.667–0.749) | 0.743 (0.707–0.779) | 0.742 (0.708–0.776) | 0.761 (0.729–0.793) |
| *P*-value | – | < 0.001 | 0.002 | < 0.001 |
| IDI (95% CI) | Ref | 0.022 (0.010–0.041) | 0.027 (0.013–0.045) | 0.041 (0.025–0.067) |
| *P*-value | – | < 0.001 | < 0.001 | < 0.001 |
| NRI (95% CI) | Ref | 0.211 (0.149–0.271) | 0.309 (0.230–0.383) | 0.384 (0.308–0.457) |
| *P*-value | – | < 0.001 | < 0.001 | < 0.001 |

Model 1, $CHA_2DS_2$-VASc score; Model 2, $CHA_2DS_2$-VASc score + abnormal PTFV1; Model 3, $CHA_2DS_2$-VASc score + LAE; Model 4, $CHA_2DS_2$-VASc score + abnormal PTFV1 + LAE. AUC, Area under ROC curve; IDI, integrated discrimination improvement; NRI, net reclassification index.

Tissue fibrosis and abnormally enlarged atrial size, which could spot by echocardiography, indicate the sign of left atrial remodeling (25). Previous studies showed that left atrial size was a significant risk factor for stroke or stroke recurrence, after adjustment for incident AF (26, 27). In addition, LAE was also shown to increase IS risk in patients with sinus rhythm across studies (28). We similarly found a positive relationship between LAE and ICVE after adjustment for incident AF and other risk factors of stroke. The underlying etiology behind the higher risk is likely to be multifactorial. It is also important to consider that LAE and ICVE share similar risk factors, namely, advanced age, hypertension, diastolic dysfunction, and left ventricular hypertrophy (29). In this study, the relationship between LAD and incident ICVE was diminished after adjusting for the aforementioned variables and other known stroke risk factors. This may imply that the mechanism of ICVE in patients with LAE could be partially explained by coexisting risk factors. In the past, AMI patients with LAE were found to develop new-onset AF (30). Apparently, reduced flow velocity in the left atrial appendage due to an increase in left atrial volume contributes to stasis and clot formation. This is consistent with transesophageal echocardiographic data which suggest that LAE was an independent risk factor for left atrial thrombus or spontaneous echocardiographic contrast and embolic events (31). Moreover, our study consolidated the relationship between the LAE and ICVE in AMI patients, and LAE may also represent a potential indication either for initiating or monitoring anticoagulant therapy for the prevention of stroke before the onset of AF in patients with AMI (17).

In the past, it was generally held that AF is a major cause of IS due to the blood flow stasis and thrombus formation in the LA during AF episodes. However, the lack of a clear temporal association between AF episodes and stroke development (16, 32) and the comparable risk of stroke between rate- and rhythm-control strategies among AF patients have challenged this theory. The above findings drive us to rethink the relationship between AF and stroke and a new model including both atrial substrate and the AF in thrombogenesis has been well established (33). In this model, AF is no longer necessary for stroke. An abnormal atrial substrate may cause thromboembolism independent of AF despite AF being associated with increased thromboembolic risk. This implies that AF was more likely a marker of later stages of ACM rather than an etiology of stroke. Our findings are similar to this model, as both abnormal PTFV1 and LAE, two markers of ACM, were associated with the development of ICVE independent of incident AF.

Additionally, the low usage rate of oral anticoagulation (OAC) in our population which was consistent with a Chinese national registry (34) might also have contributed to the increased risk of ICVE. According to previous studies, appropriate caution of OAC consideration is vital after AMI because the addition of OAC to DAPT does not significantly prevent thromboembolism (35, 36). Another study detected a decrease in stroke recurrence with rivaroxaban over aspirin therapy in individuals with LAE (37). Whether ACM markers could aid in identifying AMI patients who were most likely to benefit from anticoagulation in addition to antiplatelet therapies remain unclear. In the future, further multi-institutional prospective studies with a greater number of subjects are warranted to investigate the optimal antithrombotic therapy both assessing atrial rhythm and substrate to permit efficient anticoagulant therapy for high-risk patients while avoiding unnecessary bleeding events from anticoagulation for those at low risk.

## Study limitations

This was a retrospective study with inherent limitations. First, the number of patients who developed ICVE in this study is limited, further prospective, multicenter, large-sample studies are highly desirable. Second, data on stroke subtypes were unavailable. The likelihood between left atrial abnormality and ICVE may be partly due to atherosclerosis. In addition, due to the retrospective nature of the study, left atrial volume index and left atrial speckle tracking which are considered as more reliable parameters to represent left atrial structural and functional remodeling as well as other risk factors for ICVE were not available in the present study. More future studies adjusting more comprehensive confounding factors should be designed to investigate the relationship between these parameters and ICVE and whether ACM is an independent risk factor of ICVE in AMI patients in the future. Third, participants did not undergo continuous heart-rhythm monitoring to detect subclinical AF. As 80–90% of AF cases were asymptomatic (38), some patients with pre-existing asymptomatic AF may either remain undiagnosed or erroneously regarded to have NOAF. Finally, the prevalence of asymptomatic brain vascular lesions is substantially higher than the clinically overt disease (39). Participants did not undergo regular brain imaging examinations to rule out subclinical IS, and we therefore may underestimate the number of patients with ICVE.

# Conclusion

In this study, ACM markers including abnormal PTFV1 and LAE were independently associated with ICVE. The addition of abnormal PTFV1 and LAE could improve the ICVE risk prediction of the $CHA_2DS_2$-VASc risk score in patients with AMI. Further prospective studies are warranted to confirm these findings.

# Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of First Affiliated Hospital of Dalian Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## Author contributions

XY and YX designed the study. ZL, XW, and QL were in charge of the data analysis. ZL drafted the article. JG, YY, and BW conducted the data collection. CL was in charge of the data administration and the literature collection. CL, XW, QL, TH, and FL did the critical revision of the article. All authors have read and approved the final manuscript.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1025842/full#supplementary-material

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# Antiplatelet efficacy of ticagrelor versus clopidogrel in Mediterranean patients with diabetes mellitus and chronic coronary syndromes: A crossover pharmacodynamic investigation

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**Introduction:** Patients with diabetes mellitus (DM) have augmented platelet reactivity and diminished responsiveness to clopidogrel. Ticagrelor, a more potent $P2Y_{12}$ inhibitor, is clinically superior to clopidogrel in acute coronary syndromes, although its role in chronic coronary syndromes (CCS) is still the subject of debate. The aim of this investigation was to compare the pharmacodynamic effectiveness of ticagrelor and clopidogrel in Mediterranean DM patients with CCS.

**Materials and methods:** In this prospective, randomized, crossover study, patients ($n$ = 20) were randomized (1:1) to receive, on top of aspirin therapy, either ticagrelor 180 mg loading dose (LD)/90 mg maintenance dose (MD) b.i.d. or clopidogrel 600 mg LD/75 mg MD o.d. for 1 week in a crossover fashion with a 2–4 week washout period between regimens. Platelet function measurements were performed at 4 timepoints in each period (baseline, 2 h and 24 h after LD, and 1 week), including light transmission aggregometry (LTA, primary endpoint), VASP assay, Multiplate and VerifyNow $P2Y_{12}$.

**Results:** The ticagrelor LD achieved greater platelet inhibitory effect than clopidogrel LD, assessed with LTA (20 μM ADP as agonist), at 2 h (34.9 ± 3.9% vs. 63.6 ± 3.9%; $p < 0.001$) and 24 h (39.4 ± 3.5% vs. 52.3 ± 3.8%; $p = 0.014$).

After 1 week of therapy, platelet reactivity was again significantly inferior with ticagrelor compared to clopidogrel (30.7 ± 3.0% vs. 54.3 ± 3.0%; $p < 0.001$). The results were consistent with the other platelet function assays employed.

**Conclusion:** In Mediterranean patients with DM and CCS, ticagrelor provides a more potent antiplatelet effect than clopidogrel after the LD and during the maintenance phase of therapy.

**Clinical trial registration**: [ClinicalTrials.gov], identifier [NCT02457130].

KEYWORDS

**ticagrelor, chronic coronary syndrome, antiplatelet therapy, high platelet reactivity, diabetes mellitus**

# Introduction

Subjects with diabetes mellitus (DM) have a higher risk of developing cardiovascular disease and experiencing atherothrombotic events, which have poorer prognosis than those occurring in patients without DM (1). One of the factors involved in the augmented atherothrombotic risk of DM patients with coronary artery disease (CAD) is a hyper-reactive platelet phenotype, which contributes to an impaired responsiveness to antiplatelet drugs, mainly to clopidogrel (2, 3). Therefore, the augmented ischemic risk among DM patients with CAD clearly emphasizes the need to optimize platelet inhibition in this population with the goal of ameliorating clinical outcomes (4).

The use of more potent and less variable $P2Y_{12}$ receptor antagonists such as prasugrel or ticagrelor has demonstrated a reduction in adverse ischemic events when compared to clopidogrel in patients suffering an acute coronary syndrome (ACS) (5, 6). However, the observed clinical superiority of ticagrelor or prasugrel over clopidogrel in ACS patients has not been replicated in patients with stable CAD or undergoing elective percutaneous coronary intervention (PCI) (7, 8). In fact, clopidogrel is still widely used in real-life clinical practice as part of dual antiplatelet therapy (DAPT), e.g., in patients undergoing elective PCI or in those with stabilized symptoms after an ACS following a strategy of DAPT de-escalation. It is well established that clopidogrel has a large interindividual variability in response with genetic factors, such as polymorphisms of cytochrome P450 (CYP) isoforms (mainly CYP2C19), playing a key role in this phenomenon (9, 10). Evidently, the prevalence of genetic polymorphisms may vary greatly among races and, therefore, it is relevant that pharmacodynamic (PD) investigations take into consideration ethnicity when evaluating antiplatelet agents.

Since the evidence regarding the PD effectiveness of clopidogrel compared to ticagrelor in DM patients with a chronic coronary syndrome (CCS) is relatively scarce (11, 12), we designed the Comparison of Ticagrelor and clopidogrel in patients with Coronary artery disease and type 2 Diabetes Mellitus (TICS-DM) study, with the aim of assessing the platelet inhibitory effects of these two $P2Y_{12}$ inhibitors in a Mediterranean population with a comprehensive panel of platelet function assays.

# Materials and methods

## Subject population and study design

This was a prospective, open-label, two-sequence, two-period, randomized, crossover study conducted in Mediterranean (Spanish nationality) type 2 DM patients with 18–75 years of age and known stable CAD (angiographically documented) on a background of aspirin therapy (NCT 02457130). The World Health Organization criteria were used to define DM status. Exclusion criteria included: known allergies to clopidogrel or ticagrelor, blood dyscrasia or bleeding diathesis, any recent acute coronary event (<1 year), hemodynamic instability, recent treatment with any other antiplatelet agent (<14 days) with the exception of aspirin, oral anticoagulation with a coumarin derivative, any active bleeding or malignancy, history of stroke (<6 months prior to inclusion) or any intracranial bleeding, platelet count $<100 \times 10^6/\mu l$, severe chronic kidney disease (creatinine clearance <30 ml/min) and pregnant females.

Subjects were randomized in a 1:1 fashion to ticagrelor [180-mg loading dose (LD) followed by 90-mg maintenance dose] or clopidogrel (600-mg loading dose followed by 75-mg daily maintenance dose) for 1 week (**Figure 1**). All patients were on chronic aspirin therapy (100 mg o.d.), that was maintained at the same dose throughout the study. Patients crossed-over treatment regimen after a 2 to 4-week washout period. Blood sampling for platelet function measurements were performed at the two phases of the study at the following timepoints: (1) baseline, (2) 2 h after LD, (3) 24 h after LD, and (4) 7 days (in the morning, with last dose of study drug administered the

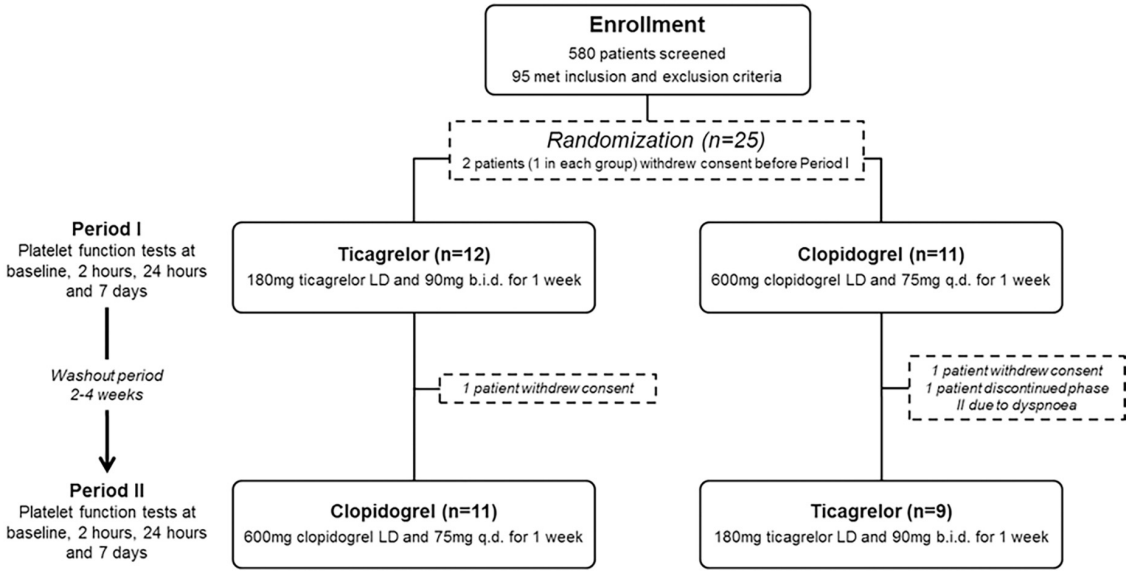


FIGURE 1
Flow diagram of the study design and enrollment process. LD, loading dose.

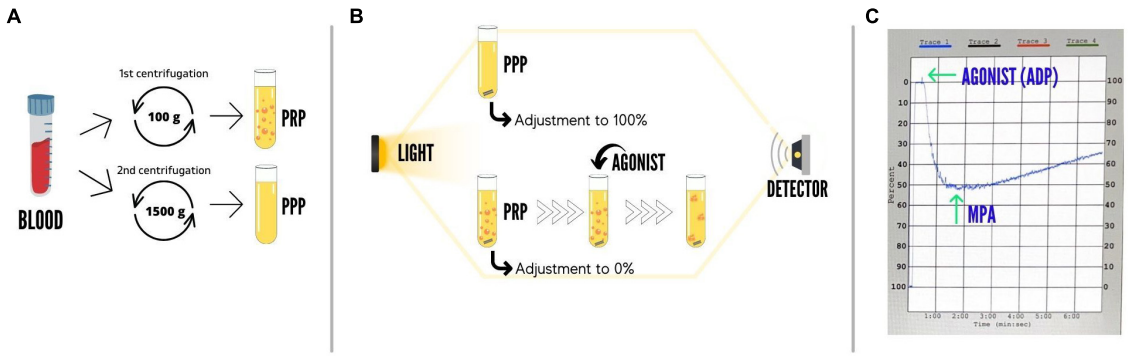


FIGURE 2
Schematic representation of the light transmission aggregometry assay. **(A)** Sample preparation. Platelet-rich plasma (PRP) is obtained as a supernatant after centrifugation of citrated blood at 100 *g* for 10 min; afterward, platelet-poor plasma (PPP) is obtained by a second centrifugation of the blood fraction at 1500 *g* for 15 min. **(B)** Methodology. In the aggregometer, light transmission is adjusted to 0% for PRP and to 100% for PPP for each measurement; during light transmission aggregometry, samples are constantly stirred at 1000 rpm; the addition of an agonist (ADP, arachidonic acid, collagen, etc.) to the PRP causes platelet aggregation, which is reflected by an increase in light transmission; platelet aggregation is monitored for at least 6 min. **(C)** Example of an aggregation curve. Baseline tracings are observed for stability and oscillations before the addition of an agonist (e.g., ADP); which can be seen in the curve as a spike; results are commonly reported as maximal platelet aggregation, which represents the maximal amplitude or% aggregation during the monitoring period. ADP, adenosine diphosphate; MPA, maximal platelet aggregation; PPP, platelet-poor plasma; PRP, platelet-rich plasma.

previous day). The washout periods were included in order to minimize carryover effects. A follow-up visit was performed at least 2 weeks after the last dose of the study drug to verify the absence of adverse events. Patient compliance was assessed by pill counting and interview.

The study was performed in compliance with the Declaration of Helsinki and was approved by the institutional Ethics Committee. All subjects included provided written informed consent.

## Sample collection and platelet function assays

Blood samples for platelet function assessment were collected at the scheduled time points from an antecubital vein; the first 2–4 ml of blood were discarded in order to avoid spontaneous platelet activation. Samples were processed by trained laboratory personnel (blinded to allocated treatment). Platelet function tests (PFT) included light

transmission aggregometry (LTA), flow cytometric analysis of the phosphorylation status of the vasodilator-stimulated phosphoprotein (VASP), multiple electrode aggregometry (MEA) and VerifyNow $P2Y_{12}$ ($VN\text{-}P2Y_{12}$) assay.

### Light transmission aggregometry

Light transmission aggregometry (a schematic example is shown in **Figure 2**) was performed according to standard protocols (13). Briefly, platelet aggregation was assessed using platelet-rich plasma (PRP) and platelet-poor plasma (PPP) by the turbidometric method in a two-channel aggregometer (Chrono-Log 490 Model, Chrono-Log Corp., Havertown, PA, USA). PRP was obtained as a supernatant after centrifugation of citrated blood at 100 *g* for 10 min and PPP was obtained by a second centrifugation of the blood fraction at 1500 *g* for 15 min. Light transmission was adjusted to 0% for PRP and to 100% for PPP for each measurement. Maximal platelet aggregation (MPA) was stimulated by 20 and 5 μmol/L adenosine diphosphate (ADP) as agonists. High on-treatment platelet reactivity (HPR) was defined as MPA > 64.5% and >42.9% with ADP 20 and 5 μmol/L, respectively (14).

### Vasodilator-stimulated phosphoprotein assay

Vasodilator-stimulated phosphoprotein-phosphorylation (VASP-P) is a marker of the $P2Y_{12}$ receptor reactivity and, therefore, $P2Y_{12}$ inhibitors-induced inhibition. VASP was assessed according to standard protocols (15). Adding ADP to $PGE_1$-stimulated platelets diminishes $PGE_1$-induced VASP-P levels. If $P2Y_{12}$ receptors are successfully inhibited, the addition of ADP will not decrease the $PGE_1$-stimulated VASP-P levels. VASP-P levels were quantified with labeled monoclonal antibodies by flow cytometry with the Platelet VASP-FCM kit (Biocytex Inc., Marseille, France). The platelet reactivity index (PRI) was calculated once measured the VASP-P levels after stimulation with $PGE_1$ (MFI $PGE_1$) and also $PGE_1$ + ADP (MFI $PGE_1$ + ADP) with the following formula: PRI = ([MFI $PGE_1$]–[MFI $PGE_1$ + ADP]/[MFI $PGE_1$]) × 100%. A reduced PRI indicates a greater inhibition of the $P2Y_{12}$ signaling pathway, and a cut-off point of ≥50% PRI was utilized to define low responsiveness (16).

### Multiple electrode aggregometry

Multiple electrode aggregometry (MEA) was assessed in whole blood with the Multiplate analyzer (Roche Diagnostics, Basel, Switzerland), which measures the change in impedance caused by platelets adhesion onto silver-covered electrodes working as sensor units (17). Curves were recorded for 6 min and platelet aggregation was determined as area under the curve of arbitrary aggregation units (AU*min) using 6.4 μmol/L ADP as agonist. The cut-off value used to define HPR was >468 AU*min (16).

### VerifyNow $P2Y_{12}$ assay

The VerifyNow System is a turbidimetric based optical detection system which measures platelet induced aggregation as an increase in light transmittance (Accumetrics, San Diego, CA, USA) and was utilized according to manufacturer's instructions (18). The VerifyNow $P2Y_{12}$ Assay measures changes in platelet function specific to $P2Y_{12}$ inhibition by combining ADP + $PGE_1$ stimuli. The reagents are incorporated into the assay channel to induce platelet activation and light transmittance increases as activated platelets bind and aggregate fibrinogen-coated beads. The device then measures this change in optical signal and reports results in $P2Y_{12}$ Reaction Units (PRU). A cut-off point of >208 PRUs was used to define HPR (16).

## Study endpoints and sample size calculation

The primary endpoint of the present study was the comparison of MPA measured with LTA (20 μM ADP as agonist) and achieved after 1 week of therapy with ticagrelor or clopidogrel using the treatment regimens described above. An initial sample size of 30 patients was planned, but a mid-course recalculation of the sample size due to an overestimation of the standard deviation was performed and specified in an amendment to the protocol. The revised calculation of the sample size was as follows: assuming a standard deviation of MPA of 13 (19, 20), a difference between treatment groups of 10 with 90% power and 2-sided alpha = 0.05 will be detected with 18 completed subjects per regimen group. Randomization of a total of 25 subjects was allowed, considering an approximate dropout of 25%, in order to ensure that complete data from 18 subjects would be available for analysis.

Other secondary end points included: (a) evaluation of platelet reactivity between clopidogrel and ticagrelor with all the PFT after 1 week of treatment; (b) comparison of the 2 treatment regimens at 2 and 24 h after LD with all the PFT; and (c) determination at the different time points assessed of the proportion of patients with HPR (measured with all tests).

## Statistical analysis

Baseline continuous variables are expressed as mean ± SD, while categorical variables are reported as frequencies and percentages. Only those subjects who successfully completed the two treatment periods were considered for analysis. All statistical comparisons of platelet reactivity for the primary and secondary endpoints were performed using linear mixed-effects models with treatment, sequence, period, and treatment*period (treatment by period interaction to test for carryover effects) as fixed effects, subject as a random effect, and the baseline

value of each corresponding platelet function test (MPA, PRI, AU*min, or PRU) as a covariate. Results are reported as least-squares mean (LSM) ± standard error of the mean (SEM). Comparisons between HPR rates were conducted using the McNemar test or the binomial exact test. All the analyses performed were evaluated with a 2-tailed probability value <0.05 to indicate a statistically significant difference. Statistical analysis was performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA).

# Results

Among 580 patients screened for eligibility, 95 met inclusion and exclusion criteria. Of these, 25 patients agreed to participate and were randomized to start with ticagrelor ($n$ = 13) or clopidogrel ($n$ = 12). Following randomization, four patients withdrew consent and one patient discontinued ticagrelor treatment due to side effects (dyspnea). Therefore, 20 patients successfully completed the two periods of the study and were included in the analysis. The flow chart of the study is illustrated in **Figure 1**, whereas baseline demographics and clinical variables are reported in **Table 1**. No significant dissimilarities were found between patients that initiated with either ticagrelor or clopidogrel. Among patients that completed the two phases of the study, 4 (20%) developed mild and transient dyspnea on ticagrelor therapy whereas no patient on clopidogrel therapy developed dyspnea. No patient experienced any ischemic or bleeding event during the study.

TABLE 1 Baseline characteristics.

| | $n$ = 20 |
|---|---|
| Age, mean ± SD | 65.45 ± 4.88 |
| Male gender, n (%) | 16 (80) |
| BMI, median [IQR] | 29.7 [27.4–32.5] |
| **Cardiovascular risk factors** | |
| Active smoking, n (%) | 1 (5) |
| Hypertension, n (%) | 16 (80) |
| Dyslipidemia, n (%) | 18 (90) |
| Peripheral artery disease, n (%) | 3 (15) |
| Chronic kidney disease, n (%) | 2 (10) |
| Prior stroke, n (%) | 0 |
| DM complications*, n (%) | 8 (40) |
| Insulin treatment, n (%) | 7 (35) |
| Oral antidiabetics, n (%) | 20 (100) |
| **Cardiovascular history** | |
| Prior myocardial infarction, n (%) | 14 (70) |
| Diseased vessels, mean ± SD | 2.15 ± 0.75 |
| Prior PCI, n (%) | 17 (85) |
| Prior CABG, n (%) | 4 (20) |
| LVEF, mean ± SD | 58.5 ± 9.0 |
| **Laboratory measurements** | |
| HbA1c, median [IQR] | 6.8 [6.4–7.9] |
| Hb, mean ± SD | 13.62 ± 1.66 |
| Platelet count ($\times 10^3$), mean ± SD | 228 ± 51 |
| MPV, mean ± SD | 11.45 ± 1.10 |

*Complications of DM: Neuropathy, nephropathy, retinopathy, or vasculopathy. BMI. body mass index; CABG, coronary artery bypass grafting; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; MPV, mean platelet volume; PCI, percutaneous coronary intervention.

## Pharmacodynamic effects of ticagrelor vs. clopidogrel

At baseline, there were no statistical differences between the two regimens studied. After 1 week of treatment, MPA (using 20 μM ADP as agonist, the primary endpoint of the present investigation) was significantly lower (**Figure 3**) with ticagrelor compared to clopidogrel (MPA: 30.7 ± 3.0% vs. 54.3 ± 3.0%; $p < 0.001$). When assessing the PD efficacy of the LD, ticagrelor also provided greater platelet inhibition than clopidogrel both at 2 h (MPA: 34.9 ± 3.9% vs. 63.6 ± 3.9; $p < 0.001$) and 24 h (MPA: 39.4 ± 3.5% vs. 52.3 ± 3.8%; $p = 0.014$), as shown in **Figure 3**. No statistically significant differences were found by sequence, period, or the treatment-by-period interaction, which suggest no carryover effect. Similar findings were observed with 5 μM ADP and the other platelet function tests employed, showing greater inhibition of platelet aggregation at 2 h, 24 h, and 1 week in the ticagrelor group compared with the clopidogrel group (**Figure 4**). Of note, no differences in clopidogrel- or ticagrelor- mediated platelet inhibition were found when comparing patients with or without insulin therapy (data not shown).

## High platelet reactivity rates according to treatment

Ticagrelor HPR rates ranged from 17.6 to 35.3% at 2 h, from 0 to 28.6% at 24 h, and from 0 to 12.5% at 1 week depending on the platelet function assay employed, whereas HPR rates with clopidogrel were higher, ranging from 29.4 to 93.8% at 2 h, from 23.1 to 81.8% at 24 h, and from 15.0 to 75.0% at 1 week, reaching statistical significance in most of the comparisons (**Figure 5**).

# Discussion

The present study was specifically designed to compare the antiplatelet effect of ticagrelor and clopidogrel in Mediterranean patients with DM and CCS, consisting on stable patients with prior ACS or coronary revascularization. The main finding of this investigation is that in such patients the PD benefit of ticagrelor over clopidogrel is maintained. Indeed, a LD of ticagrelor 180 mg has a faster and greater effect on platelet inhibition compared to the LD of clopidogrel 600 mg, an effect

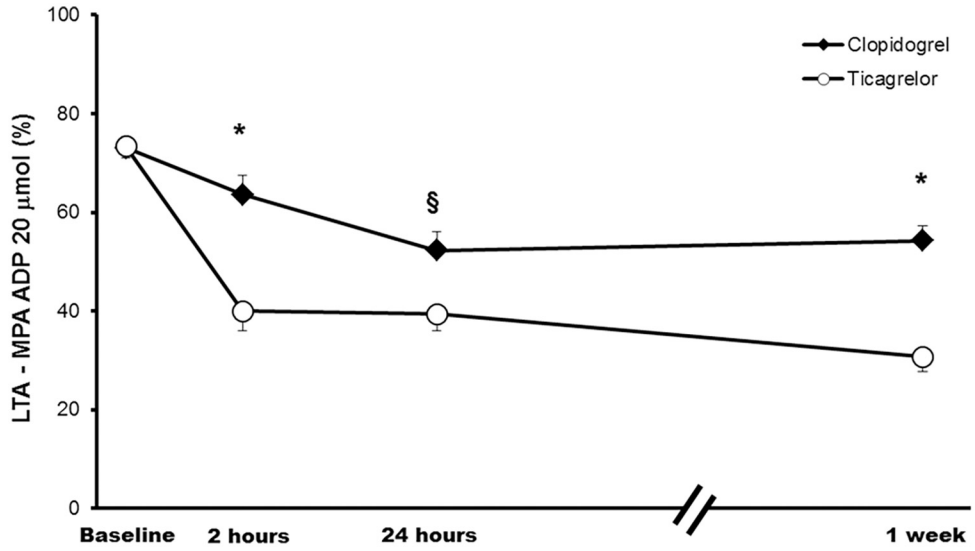


FIGURE 3
Platelet reactivity across study time points. Comparison of platelet reactivity over time measured with LTA and using 20 µmol ADP as agonists (primary endpoint). Values are expressed as least-squares means. Error bars indicate standard errors of the mean. *$p < 0.001$; $^{§}$ $p < 0.05$. ADP, adenosine diphosphate; LTA, Light transmission aggregometry, MPA, maximal platelet aggregation.

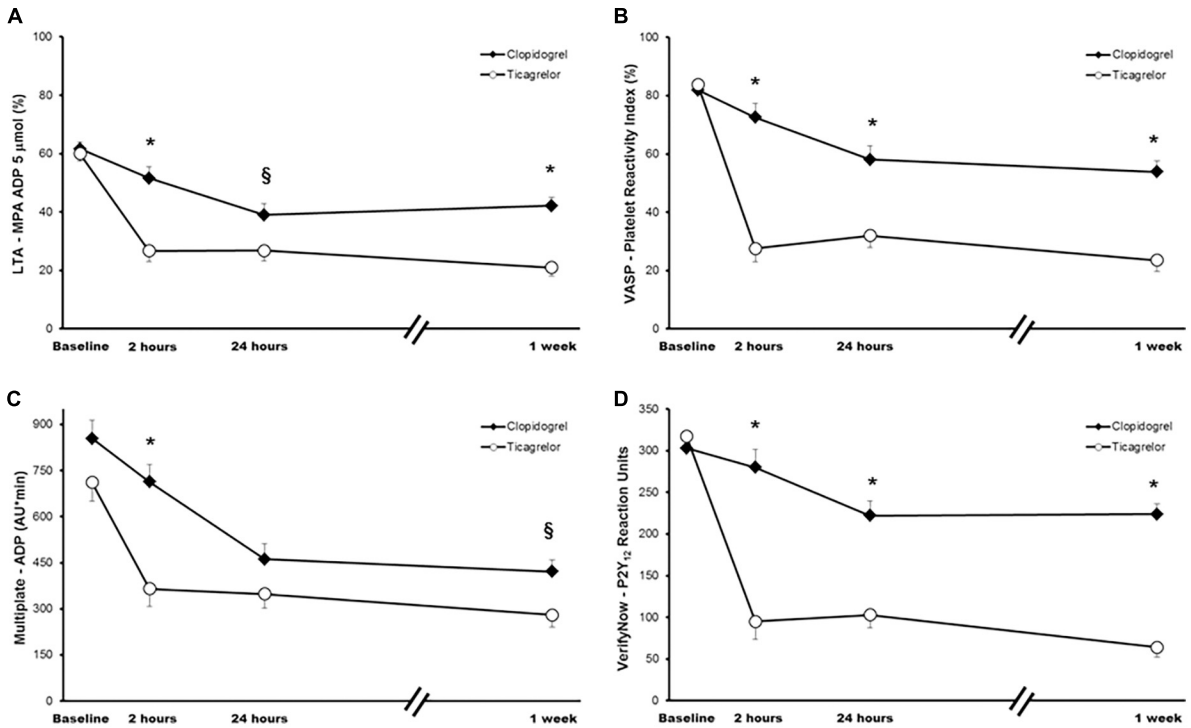


FIGURE 4
Platelet function measurements across study time points. **(A)** Light transmittance aggregometry using 5 µM adenosine diphosphate (ADP) as agonist. **(B)** Flow cytometric VASP analysis. **(C)** Multiple electrode aggregometry using ADP as agonist. **(D)** VerifyNow $P2Y_{12}$ assay. Values are expressed as least-squares means. Error bars indicate standard errors of the mean. *$p < 0.001$; $^{§}p < 0.05$. LTA, light transmission aggregometry; MPA, maximal platelet aggregation; VASP, vasodilator-stimulated phosphoprotein.

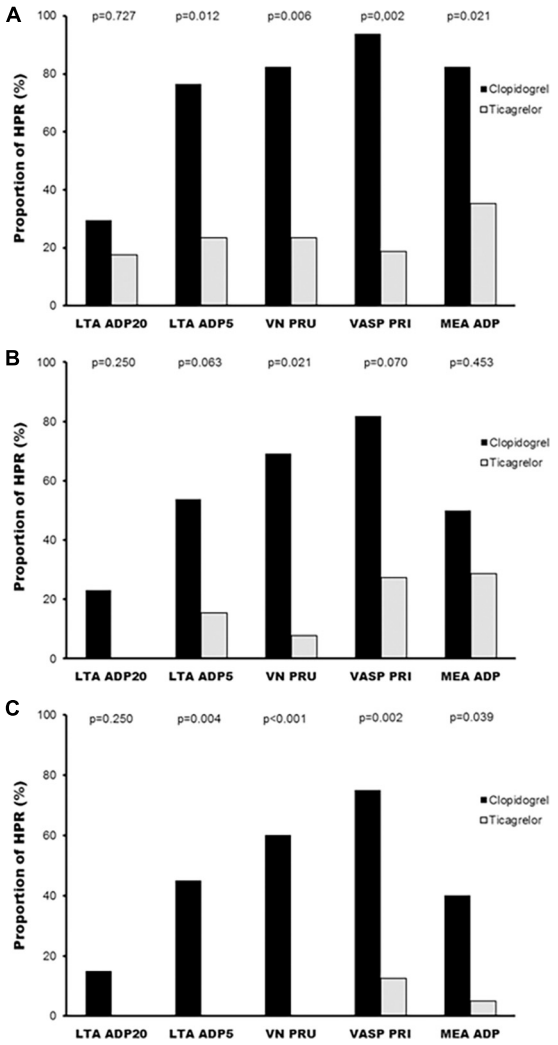


FIGURE 5
Percentage of patients with high platelet reactivity according to treatment with all platelet function tests and agonists. **(A)** HPR rates at 2 h; **(B)** HPR rates at 24 h; **(C)** HPR rates at 1 week. HPR, high on-treatment platelet reactivity; LTA, light transmission aggregometry; MEA, multiple electrode aggregometry; PRI, platelet reactivity index; PRU, $P2Y_{12}$ reaction units; VN, VerifyNow; VASP, vasodilator-stimulated phosphoprotein.

that is seen as soon as 2 h after intake of the LD of the drug. These outcomes were also consistently observed during the maintenance phase of therapy. This PD effect translated into ticagrelor achieving significantly lower rates of HPR at any time point of the study and with all platelet function tests employed.

Compelling data from previous PD investigations have demonstrated a greater, and also faster, inhibition of platelet reactivity achieved with ticagrelor compared with clopidogrel (19, 21). However, very few studies have addressed this issue in DM patients, a subpopulation at high risk of recurrent ischemic events. Of note, the available studies addressing this issue are actually *post-hoc* analyses and, thus, are not exclusively performed in DM patients (11, 22). In addition, it is quite relevant to consider ethnicity when evaluating responsiveness to antiplatelet agents (11, 23). In fact, the prevalence of loss-of-function alleles of the CYP2C19 isoform varies greatly among races (9), which has a huge impact on clopidogrel responsiveness. This investigation is, to the best of our knowledge, the first to specifically compare the antiplatelet efficacy of ticagrelor vs. clopidogrel in a Mediterranean Caucasian population with DM and provides a valid confirmation of the PD superiority of ticagrelor over clopidogrel irrespective of ethnicity.

DM patients have augmented platelet reactivity, leading to greater rates of HPR to clopidogrel than non-DM subjects, which is clearly associated with poorer clinical outcomes (2–4). This problem has incited the evaluation of more potent antiplatelet regimens in this high-risk population. The PD effectiveness in DM patients of other $P2Y_{12}$ inhibition strategies, more potent than clopidogrel, has been compared among them in a number of mechanistic studies. For instance, in the CLOTILDIA study, ticagrelor displayed a greater platelet inhibitory effect than high-dose clopidogrel (150 mg daily) in stable patients at least 1 month after PCI (12). More importantly, a number of PD investigations have compared the platelet inhibitory efficacy of ticagrelor vs. prasugrel specifically in DM patients (24–26), although results were not completely consistent. Briefly, two studies have suggested separately a slightly greater antiplatelet efficacy of ticagrelor, although no differences in the rates of HPR to both agents were observed in any of these studies (24, 25). However, in the comprehensive OPTIMUS-4 investigation, the platelet inhibitory effectiveness of both agents were similar with most of the platelet function assays employed to evaluate the LD and MD regimens (26). In line with these findings, Galli et al. (27) observed in a recent investigation a similar PD efficacy of ticagrelor and prasugrel, after switching from clopidogrel, both in patients with and without DM; of note, despite an important increase in platelet inhibition after escalation of antiplatelet agents, platelet reactivity persisted higher among DM patients compared to those without DM.

Whether there is a clinical advantage of one of the two more potent $P2Y_{12}$ antagonists, prasugrel, or ticagrelor, in DM patients is yet to be determined. In fact, in a prespecified analysis of patients with DM of the ISAR-REACT 5 trial, conducted in ACS patients with planned invasive therapy, no differences in ischemic or hemorrhagic events were seen between prasugrel and ticagrelor (28). The latter is in contrast with the somewhat surprising findings of the main trial, in which prasugrel significantly reduced the rates of the primary efficacy outcome, a composite of death, myocardial infarction and stroke (29, 30).

The favorable PD profile of ticagrelor in CAD patients with DM may contribute to explain the consistent benefit in terms

of reduction of atherothrombotic outcomes observed in large-scale clinical trials that have evaluated different antiplatelet regimens with ticagrelor in several scenarios across the CAD spectrum. In the DM subgroup of the pivotal PLATO trial, dual antiplatelet therapy (DAPT) with ticagrelor diminished ischemic events compared to DAPT with clopidogrel in ACS patients at moderate to high ischemic risk, without differences in major bleedings (31). Nevertheless, the relative benefit achieved with ticagrelor in DM patients, although consistent with the global trial results, was somewhat attenuated (17 vs. 12% relative risk reduction of ischemic events in non-DM and DM patients, respectively), since a numerical (although not statistically significant) reduction of the occurrence of the primary efficacy endpoint was observed. In a different clinical setting, the addition of ticagrelor on top of aspirin as secondary prevention in patients with a prior myocardial infarction, which was evaluated in the PEGASUS-TIMI 54 trial, led to a significant reduction of recurring ischemic events with ticagrelor (pooled doses of 60 and 90 mg b.i.d.) compared to the control arm (aspirin monotherapy), including both cardiovascular and coronary heart disease mortality in the DM subgroup, although with the counterpart of a heightened risk of major bleeding (32, 33). Interestingly, a platelet function substudy of this trial showed a similar platelet inhibition of ticagrelor 60 mg and 90 mg b.i.d. doses regardless of diabetes status (34). More recently, the THEMIS trial, conducted in stable DM patients with CAD and without a history of myocardial infarction or stroke, showed that adding ticagrelor to aspirin resulted in a reduction of ischemic cardiovascular events albeit at the cost of a higher rate of major bleedings, when compared to aspirin monotherapy (35). Overall, these findings underline the need for carefully addressing the ischemic and bleeding risk of each and every patient in order to decide the most suitable antiplatelet strategy.

Clopidogrel is the preferred $P2Y_{12}$ antagonist in patients with stable CAD undergoing PCI but it is also commonly prescribed in ACS patients deemed not suitable for potent DAPT due to increased bleeding risk. Moreover, the results of recent trials have suggested that a de-escalation of dual antiplatelet therapy (DAPT) strategy by reducing the intensity of DAPT through switching from more potent $P2Y_{12}$ inhibitors (i.e., prasugrel or ticagrelor) to clopidogrel, could be useful to reduce hemorrhagic events in ACS patients at high risk of bleeding without losing efficacy in terms of preventing ischemic events (36–38). For these reasons among others, clopidogrel is still widely utilized in real-life clinical practice as part of DAPT (39, 40). However, the superior platelet inhibitory effect of prasugrel or ticagrelor compared to clopidogrel, as shown in the present study and other abovementioned investigations, suggest that high-risk subgroups such as DM patients may obtain a greater benefit from maintaining more potent antiplatelet regimens. Noteworthy, recent evidence points toward a potential benefit of personalized antiplatelet therapy using platelet function of genetic assessment (e.g., guided escalation of $P2Y_{12}$ inhibitors) in the PCI setting, which may be of particular relevance in DM patients due to the heightened platelet reactivity and the high rates of clopidogrel suboptimal response that characterize this population (41, 42). Indeed, an individualized approach taking into consideration the balance between ischemic and bleeding risks is certainly recommendable before deciding the $P2Y_{12}$ inhibition strategy in CAD patients.

## Limitations

We acknowledge several limitations of the present investigation, such as the open-label design and the relatively small sample size. Further, no pharmacokinetic or genetic (e.g., loss-of-function CYP2C19 alleles) assessments were done, which could have provided important insights on the mechanisms contributing to the differences observed in platelet reactivity between clopidogrel and ticagrelor. However, prior investigations in DM patients used a single platelet function assay to compare the PD effectiveness of ticagrelor vs. clopidogrel (10, 20), whereas four different assays were employed in the present study to evaluate the LD and MD effect, which yields a great consistency to the results obtained. Ultimately, the ticagrelor 90 mg b.i.d regiment is not routinely employed in long-term secondary prevention and our results cannot be extrapolated to the 60 mg b.i.d. dose of ticagrelor, which is approved in this scenario due to the results obtained in the PEGASUS–TIMI 54 trial.

# Conclusion

In Mediterranean DM patients with CCS, ticagrelor yields a more potent platelet inhibition than clopidogrel, which is detected promptly after the loading dose and is maintained after 1 week of treatment. This PD benefit results in significantly lower HPR rates with ticagrelor compared to clopidogrel both with the load and maintenance doses. Of note, ticagrelor HPR rates are almost negligible after 1 week of therapy. The present investigation is a valid confirmation of the consistent and favorable PD profile of ticagrelor among different high-risk subgroups, such as patients with DM.

# Data availability statement

The data analyzed in this study are not publicly available due to internal policy. Any requests can be directed to the

corresponding author. Requests to access the datasets should be directed to JF, jlferreiro@bellvitgehospital.cat.

## Ethics statement

The studies involving human participants were reviewed and approved by CEIm Hospital Universitario de Bellvitge. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

AM and JF contributed to the conception and design of the study, analysis and interpretation of data. AM acquired data for the work and drafted the manuscript, which was critically revised for important intellectual content by the other authors. All authors approved the final version submitted.

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## Conflict of interest

JF reports: Speaker fees from Eli Lilly Co., Daiichi Sankyo, Inc., AstraZeneca, Roche Diagnostics, Pfizer, Abbott, Ferrer, Rovi, Boehringer Ingelheim, and Bristol-Myers Squibb; consulting fees from AstraZeneca, Eli Lilly Co., Ferrer, Boston Scientific, Pfizer, Boehringer Ingelheim, Daiichi Sankyo, and Bristol-Myers Squibb; and research grant from AstraZeneca.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Abatement of potent P2Y12 antagonist-based dual antiplatelet therapy after coronary intervention: A network meta-analysis of randomized controlled trials

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**Introduction:** Dual antiplatelet therapy (DAPT) including prasugrel or ticagrelor is recommended in patients with acute coronary syndromes (ACS) treated with coronary intervention (PCI). Acknowledging the importance of bleeding, multiple trials tested abatement schemes including uniform or guided de-escalation from the potent P2Y12 inhibitor (P2Y12-De) or P2Y12 inhibitor monotherapy (P2Y12-Mo) with heterogeneous results. We aimed to perform a systematic review and network meta-analysis of the impact of DAPT abatement strategies in patients with PCI.

**Methods:** Electronic databases were searched for relevant randomized clinical studies evaluating clinical outcomes of patients after PCI. The rate of adverse events was evaluated using a frequentist network metanalysis. The random-effects model was used to combine risk estimates across trials and risk ratio (RR) with 95% confidence intervals (95% CIs) served as summary statistics. The primary endpoints of interest were the rate of major cardiac adverse events (MACE, defined as the composite of cardiovascular mortality, myocardial infarction and stroke) and bleeding.

**Results:** Ten studies were identified randomizing 42511 patients. 6359 switched to the P2Y12-De and 13062 switched to the P2Y12-Mo. The risk of MACE, reflected a 24% reduction in the P2Y12-De and a 14% in the P2Y12-Mo in comparison with the DAPT strategy using potent P2Y12 inhibitors (RR: 0.76 [0.62, 0.94], and RR: 0.86 [0.75, 0.99], $p < 0.05$ both). A 35% risk reduction of major bleeding was seen with monotherapy (RR: 0.65 [0.46, 0.91],) contrasting the de-escalation trials where this effect was not significant (RR: 0.84 [0.57, 1.22]). All bleeding and minor bleeding events were reduced with both strategies. Indirect P2Y12-Mo versus P2Y12-De comparisons exhibited them as similar alternatives without significant differences.

**Conclusion:** Our analysis suggests that both P2Y12-De and P2Y12-Mo reduce ischemic events and bleeding among PCI-treated ACS patients. Ischemic benefit was more expressed with P2Y12-De, however, reduction of major bleeding was only significant with P2Y12-Mo strategy.

**Systematic review registration:** https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021258502, identifier CRD42021258502.

KEYWORDS

ticagrelor, prasugrel, network meta-analysis, coronary intervention, P2Y12 de-escalation therapy

# Introduction

P2Y12 inhibitors are routinely administrated, in addition to aspirin, to reduce thrombotic complications of patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). Recent guidelines support the preferential use of the potent inhibitors, prasugrel or ticagrelor, as they showed a better reduction of ischemic events in their respective pivotal trials, as compared to the less effective clopidogrel (1, 2). However, these benefits come with disadvantages such as a higher risk of bleeding or side effects that may undermine patient compliance. Therefore, as observational data reflect, P2Y12 inhibitors are frequently switched during treatment in patients with ACS (3). Early after an ACS event, the higher thrombotic risk may outweigh the bleeding risk, whereas, during the chronic phase, the decrease in thrombotic risk is more pronounced than that in the bleeding risk. Abatement strategies include uniform or guided de-escalation to a less potent P2Y12 inhibitor or early cessation of aspirin and the use of potent P2Y12 inhibitor monotherapy. In addition to the pharmacological contribution to bleeding avoidance strategies, these schemes may offer potential economic benefits and, thus, are commonly practiced (4).

Nevertheless, de-escalation of antiplatelet therapy from a potent P2Y12 inhibitor may account for the large response variability of clopidogrel and the consequential issue of high on-treatment platelet reactivity (HPR), which appears in a substantial proportion of patients with ACS. Part of this response variation is explainable by genetic variations, such as the CYP2C19*2 and CYP2C19*3 loss-of-function alleles. In patients without these alleles, clopidogrel has shown a similar efficacy to those of ticagrelor and prasugrel (5). Platelet function testing (PFT) or genetic testing may, thus, make de-escalation safer by identifying patients with characteristics exposing them to an increased risk of thrombotic events and selectively maintaining potent P2Y12 inhibition for these cases (6).

Recently, multiple randomized trials were performed to test different abatement schemes. However, these were typically underpowered in order to accurately assess the efficacy and safety. Moreover, both strategies represent a potentially mutually exclusive alternative. They were tested against conventional long-term potent P2Y12 inhibitor-based DAPT treatment; however, data is lacking regarding their comparison. We aimed to evaluate the clinical outcomes of P2Y12 inhibitor de-escalation and P2Y12 inhibitor monotherapy compared with continuation of DAPT in patients treated with PCI, as well as to perform a systematic review and network meta-analysis in order to achieve greater statistical power and more precise effect estimates of the impact of DAPT abatement strategies in patients undergoing coronary intervention.

Abbreviations: ACS, Acute coronary syndrome; BARC, Bleeding Academic Research Consortium; DAPT, Dual antiplatelet therapy; HPR, High on-treatment platelet reactivity; MACE, major adverse cardiac events; NMA, network meta-analysis; 95% Cis, 95% confidence intervals; PCI, Percutaneous coronary intervention; PFT, Platelet function testing; RR, Risk ratio.

# Methods

## Search strategy

This systematic review was performed as per the standards outlined in the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Healthcare Interventions (7) and was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021258502).

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

## Study selection

A keyword-based search for relevant articles was performed in PubMed (MEDLINE), EMBASE, and the Cochrane Library from January 2007 to October 2021. No language restriction was used. The query included the following medical subject heading (MeSH) terms which were linked with Boolean operators: "coronary artery disease" [MeSH] OR "acute coronary syndrome" [MeSH] OR "cardiovascular disease" [MeSH] AND "de-escalation" [MeSH] AND "ticagrelor" [MeSH] OR "prasugrel" [MeSH] OR "clopidogrel" [MeSH]. Furthermore,

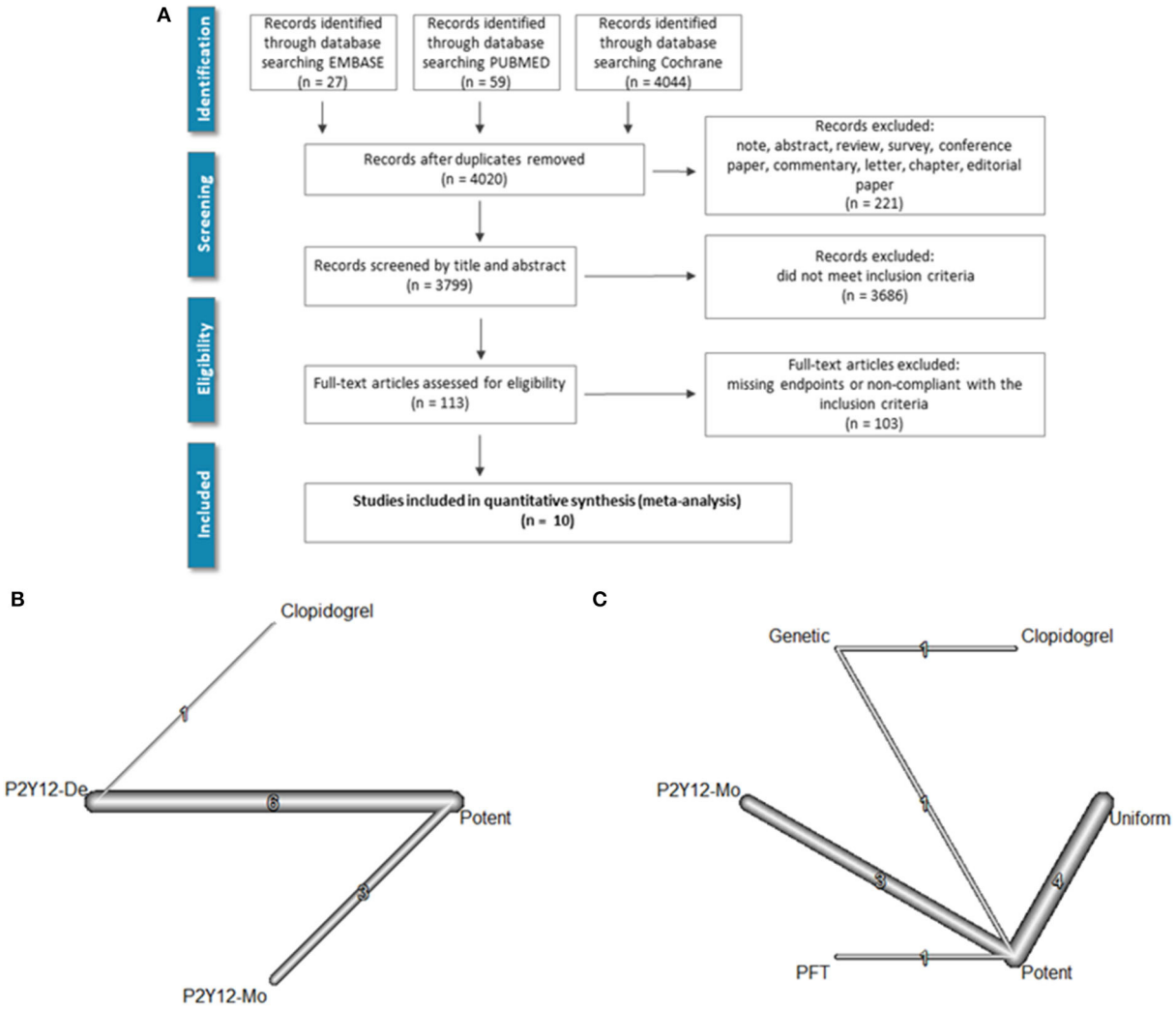


FIGURE 1
Literature search and evidence network. PRISMA flowchart of the literature search is shown in **(A)**. **(B)** Depicts the evidence network as a network of P2Y12 de-escalation (P2Y12-De), potent P2Y12 monotherapy (P2Y12-Mo), and dual antiplatelet therapy controls [i.e., DAPT with potent P2Y12 inhibitors (potent) or with clopidogrel]. In **(C)**, the network with subgrouping of de-escalation strategies is presented. De-escalation studies used three strategies either switching back to less potent P2Y12 inhibitor in every patient (uniform) or only selective de-escalation based on platelet function (PFT) or genetic characteristics (genetic).

we searched the reference list of relevant guidelines, reviews, editorials, and studies on this topic. The literature screening process is summarized in Figure 1A.

Studies were considered eligible if they fulfilled all the following criteria: (1) Clinical studies with a prospective design, including patients who received DAPT schemes for the treatment of percutaneous coronary intervention. (2) Randomized studies comparing the clinical outcomes of a group of patients with P2Y12 inhibitor-based dual antiplatelet therapy. (3) Studies that evaluate the benefit of P2Y12 inhibitor monotherapy or switching to clopidogrel at a predefined time point ($\leq$3 months), assisted by genetic testing, platelet function testing, or without.

## Quality assessment and endpoints

Two investigators (O.A.A and D.T) independently evaluated the titles and abstracts of all citations, in line with the PICOS criteria; any discrepancies were resolved by a third investigator (A.K.).

Articles, that met predefined eligibility criteria, were chosen for full-text screening and were reviewed by the two investigators against the eligibility criteria outlined in the PICOS framework: Patients who underwent coronary stent implantation (P), whether an intervention with dual antiplatelet abatement strategy with P2Y12 inhibitor monotherapy or P2Y12 inhibitor de-escalation to clopidogrel (I), compared with P2Y12

inhibitor plus aspirin dual antiplatelet therapy (C) has a favorable effect on bleeding, or major adverse cardiovascular events (MACE) or mortality (O).

The primary efficacy outcome of our analysis was the occurrence of MACE, defined as the composite of cardiovascular mortality, MI, and stroke. Major bleeding and all-cause mortality were assessed as main safety endpoints. Secondary outcomes included the individual components of MACE and stent thrombosis, defined according to the ARC criteria. Furthermore, safety outcomes, such as the frequency of major and minor bleeding complications, were also evaluated. In the case of the availability of multiple bleeding definitions, we extracted data according to the Bleeding Academic Research Consortium (BARC) criteria, defining type 3 or type 5 as major and type 2 as minor bleeding. The data were extracted, and the endpoints of interest were collected up to the 1st year after the coronary intervention.

The methodological qualities of the studies were also assessed using the Cochrane Collaboration tool for assessing the quality of RCTs.

## Data analysis

We pre-specified the use of multiple treatment network meta-analysis (NMA). The rates of events with each antiplatelet treatment combination were entered as an individual study arm, and data were pooled in a multiple treatment NMA that allows integration of direct and indirect comparisons. We calculated the risk ratio (RR) and its standard error using a frequentist approach to construct an NMA model accounting for the correlated treatment effects (8, 9). A random-effects model was applied by adding the estimated heterogeneity to the variance of each comparison, using an adaptation of the DerSimonian–Laird estimator. The random-effects model was chosen based on the consideration that the true preventive effect of antithrombotic treatment may vary from study to study and is influenced by the heterogeneity of the included trials. Values of $I^2$ representing the amount of inconsistency, and Cochran's $Q$ statistic and its corresponding $p$-value measuring the heterogeneity in the network were also calculated (8, 10).

Effect sizes are depicted as forest plots with potent dual antiplatelet therapy set as a reference. Furthermore, a comparative ranking of the treatments according to the $P$-scores method [a frequentist analog of SUCRA (Surface Under the Cumulative Ranking curve) was also performed (9)].

We appraised potential bias in the individual studies using the Cochrane Collaborations' bias assessment tool. To assess publication bias, a comparison-adjusted funnel plot supplemented with Eggers' test results was used (11).

The assumption of consistency; that the direct evidence for the effect size between two treatments in a network does not differ from the indirect evidence, was assessed by comparing and visualizing direct and indirect evidence.

Additional exploratory analyses included stratification and subgrouping based on the different de-escalation strategies and the included patient population, study size, and follow-up time.

Calculations were performed using R statistical software package version 4.0.3 (12), using the packages "meta 4.11-0," "netmeta 1.2-0," and "gemtc 0.8-4" (13). A $p$-value of $< 0.05$ was considered to represent statistical significance.

# Results

Ten studies that included 42,511 patients met the inclusion criteria. Among the included patients, 6,359 were randomized to a P2Y12 inhibitor de-escalation strategy, while 13,062 received potent P2Y12 inhibitor monotherapy. The included trials randomized patients treated with coronary intervention and stent implantation after an acute coronary syndrome event except for two studies where patients after a planned coronary intervention were also included. Potent P2Y12 inhibitor-based dual antiplatelet therapy control involved 18,540 cases while clopidogrel and aspirin combination involved 946. The characteristics and design of the included RCTs are shown in Table 1. The P2Y12 inhibitor de-escalation strategy was guided based on platelet function testing in two studies, based on genetic testing in two, and unguided, uniform in four. The size of the trials ranged from 131 to 15,968 participants, and the follow-up time was from 1 week to 12 months. The Global Leaders trial followed patients for 24 months after coronary intervention; however, as the patient received ticagrelor monotherapy or conventional DAPT during the 1st year, while during the 2nd-year, patients in the control received aspirin and in the experimental arm ticagrelor monotherapy, we extracted data from the first 12 months landmark analysis.

Three trials used selective P2Y12 inhibitor de-escalation strategies. Among these, the POPular Genetics trial (5) and the TAILOR-PCI trial (14) used genetic testing with TaqMan assays. In the POPular Genetics trial, carriers of the loss-of-function CYP2C19 allele were treated with ticagrelor or prasugrel (49%), whereas non-carriers (CYP2C19*1/*1) received clopidogrel (51%). In the TAILOR-PCI trial, patients identified as possessing CYP2C19*2 or *3 LOF alleles (CYP2C19 LOF carriers) were prescribed ticagrelor for maintenance therapy or prasugrel for patients who did not tolerate ticagrelor, and non-carriers or those with inconclusive results were prescribed clopidogrel.

In the TROPICAL-ACS trial (6), a platelet-function testing-based de-escalation treatment algorithm was applied. Patients in the P2Y12 inhibitor de-escalation group received a post-discharge treatment consisting of 1-week prasugrel treatment (10 or 5 mg per day) followed by 1 week of clopidogrel treatment (75 mg per day) and a platelet function measurement (on

TABLE 1 Main characteristics of the included studies.

| First author | Claassens | Cuisset | Kim | Sibbing | Pereira | Ueno | Park | Kim | Mehran | Vranckx |
|---|---|---|---|---|---|---|---|---|---|---|
| Publication year | 2019 | 2017 | 2020 | 2017 | 2020 | 2016 | 2021 | 2020 | 2019 | 2018 |
| Acronym | POPular Genetics | TOPIC | HOST-REDUCE-POLYTECH-ACS | TROPICAL-ACS | TAILOR-PCI | - | TALOS-AMI | TICO | TWILIGHT | GLOBAL LEADERS |
| Design | R open label | R, open label, single center | R, open label, multi-center | R, open label, multi-center | R, open label, multi-center | R, open label, multi-center | R, open label, multi-center | R, multi-center | R, open label | R, OPEN LABEL |
| Number of patients | 2,751 | 646 | 2,338 | 2,610 | 5,302 | 131 | 2,590 | 3,056 | 7,119 | 15,968 |
| Time between PCI and randomization | 48 h | 1 month | 1 month | 2 weeks | 72 h | At the PCI | 1 month | 3 months | 3 months | 1 month |
| STEMI (%) | 100 | 40 | 14 | 55 | 22 | 48 | 54 | 36 | 0 | 13 |
| NSTEACS (%) | 0 | 60 | 85.2 | 44 | 59 | 52 | 46 | 64 | 30 | 34 |
| UAP (%) | 0 | NA | 60 | 0 | 30 | 39 | 0 | 31. | 70 | 13 |
| CCS (%) | 0 | 0 | 0 | 0 | 18 | 47. | 0 | 0 | 35 | 47 |
| Clopidogrel (experimental/control; %) | 60.6/7.0 | 100/0 | - | 100/0 | 15/99 | 100/0 | 100/0 | 36/33 | - | 53/53.2 |
| Prasugrel (experimental/control; %) | 1 / 2.3 | 56/59 | 100/100 | 0/100 | - | 0/100 | - | - | - | - |
| Ticagrelor (experimental/control; %) | 38.1/90.5 | 44/42 | - | - | 85/1 | - | 0/100 | 73/70 | 0/100 | 47/46.8 |
| Study group type | P2Y12-De | P2Y12-De | P2Y12-De | P2Y12-De | P2Y12-De | P2Y12-De | P2Y12-De | P2Y12-Mo | P2Y12-Mo | P2Y12-Mo |
| Definition of bleeding (primary/secondary) | PLATO/BARC | TIMI/BARC | BARC | BARC | BARC/TIMI | BARC/TIMI | BARC | TIMI | BARC/TIMI, GUSTO, and ISTH | BARC |
| End point | Bleeding, MACE, ST, and TVR | Bleeding, UREV, and MACE | Bleeding, TVR, MACE, and ST | Bleeding, MACE, UREV, and ST | CVD, MI, ST, stroke, and SRI | PRU | CVD, MI, stroke, and bleeding | Major bleeding, death, MI, ST, TVR, and stroke | Bleeding, MI, stroke, and death | Q-wave MI, and death |
| Follow-up, months | 12 | 12 | 12 | 12 | 12 | 15 | 12 | 12 | 12 | 24 |
| Age (mean ± SD) | 61.7 ± 11.3 | 60.0 ± 10.2 | 58.8 (9.0) | 58.7 (10.2) | 62 (21–95) | 68.8 ± 10.3 | 60 ± 11 | 61 (11) | 65.01 ± 10.3 | 64.5 ± 10.3 |
| Female, *N* (%) | 317 (25.5) | 114 (18) | 251 (10.75) | 2,052 (78.5) | 1,738 (32.78) | 32 (24.4) | 454 (16.8) | 628 (20.5) | 1,698 (23.8) | 3,714 (23.2) |
| DM, *N* (%) | 288 (11.6) | 177 (27) | 990 (42.3) | 527 (20) | 1,938 (36.55) | 53 (40.5) | 731 (27.2) | 835 (27) | 2,620 (36.8) | 4,038 (25.3) |

*(Continued)*





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TABLE 1 (Continued)

| First author | Claassens | Cuisset | Kim | Sibbing | Pereira | Ueno | Park | Kim | Mehran | Vranckx |
|---|---|---|---|---|---|---|---|---|---|---|
| Smoking, *N* (%) | 1,127 (45.8) | 286 (44) | 838 (71.7) | 1,182 (45) | 1,752 (33.04) | NR | - | 1,142 (37) | 1,548 (21.7) | 4,169 (26.2) |
| HTN, *N* (%) | 1,032 (41.4) | 313 (48) | 1,476 (63.1) | 1,599 (61.5) | 4,409 (83.15) | 89 (67.9) | 1,318 (48.9) | 1,541 (50.5) | 5,154 (72.4) | 11,705 (73.6) |
| DES, *N* (%) | NR | 585 (91) | 2,338 (100) | 2,005 (77) | NR | NR | - | NR | NR | 19,415 (94.6) |
| PCI approach (%) | NR | Femoral (4)<br>Radial (96) | NR | NR | NR | NR | Femoral (49.4)<br>Radial (49.4) | NR | NR | Femoral (26)<br>Radial (74) |

R, randomized; ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium Criteria; DES, drug-eluting stent; DM, diabetes mellitus; HTN, hypertension; LD, loading dose; MD, maintenance dose; MACE, major adverse cardiac events; NR, not reported; O, observational study; R, retrospective; SD, standard deviation; ST, stent thrombosis; TIMI, Thrombolysis in Myocardial Infarction; TVR, target vessel revascularization; UREV, urgent revascularization; PLATO, Platelet Inhibition and Patient Outcomes; MI, Myocardial infarction; SRI, Severe Recurrent Ischemia; PRU P2Y12, Reaction Unit; STEMI ST, segment elevation MI; NSTEACS, non-ST-segment elevation acute coronary syndrome; UAP, unstable angina pectoris; CCS, chronic coronary syndrome; De, de-escalation; Mo, monotherapy.

clopidogrel) 2 weeks after hospital discharge (PFT-guided de-escalation group). The network of evidence, both regardless of, and with regard to the applied de-escalation strategies, is depicted in Figures 1B, C.

The risk of bias was assessed for all the trials, showing a minimal risk in all biases. The results derived from direct comparisons were identical to those computed with the help of indirect comparisons (Supplementary Figures 1–3).

When compared to a potent dual antiplatelet strategy, both P2Y12 inhibitor de-escalation and P2Y12 inhibitor monotherapy were associated with a significant ischemic risk reduction. The estimated cumulative effect reached a 24% risk reduction with P2Y12 inhibitor de-escalation and a 14% risk reduction with P2Y12 inhibitor monotherapy [RR: 0.76 (0.62, 0.94), $p < 0.05$, and RR: 0.86 (0.75, 0.99), $p < 0.05$, respectively]. The results were consistent without important heterogeneity ($p = 0.91$ within designs), and the $I^2$ test showed low levels of inconsistency (between designs): $I^2 = 0\%$ (0.0%; 17.6%) (Figure 2).

When different de-escalation strategies were considered, a similar tendency for risk reduction was observed; however, this association did not reach the level of statistical significance in any case (Figure 3).

Individual components of the composite endpoint showed beneficial trends, with a lower risk of ischemic events in the abatement strategies except for the risk of myocardial infarction, stent thrombosis, and stroke. These showed an increased risk after P2Y12 inhibitor monotherapy; however, none of these differences reached the level of statistical significance (Supplementary Figure 4).

Treatment ranking gave the highest rank to P2Y12 inhibitor de-escalation (0.92), followed by P2Y12 inhibitor monotherapy (0.62), and the lowest to the clopidogrel or potent P2Y12 inhibitor-based dual antiplatelet therapy (0.24 and 0.22, respectively) in terms of MACE. P2Y12 inhibitor monotherapy (0.78) ranked higher than clopidogrel (0.67) and P2Y12 inhibitor de-escalation (0.42) as well as potent P2Y12 inhibitor-based-dual antiplatelet therapy (0.12) in terms of major bleeding.

Major bleeding rates were similar between P2Y12 inhibitor de-escalation and the control, without major differences among trials [RR: 0.84 (0.57, 1.22)]; however, P2Y12 inhibitor monotherapy resulted in a 35% reduction [RR: 0.65 (0.46, 0.91), $p < 0.05$, $I^2 = 0\%$]. Differences were more expressed in the analyses of all bleeding events and were substantially influenced by minor bleeding. Both P2Y12 inhibitor de-escalation and P2Y12 inhibitor monotherapy resulted in a 36–42% reduction (Figure 2). The most expressed reduction was observed for uniform de-escalation, followed by the other strategies. In the case of PFT-guided de-escalation, no bleeding endpoint was significantly reduced (Figure 3).

Each comparison between de-escalation and monotherapy resulted in an effect estimate that did not reach the level

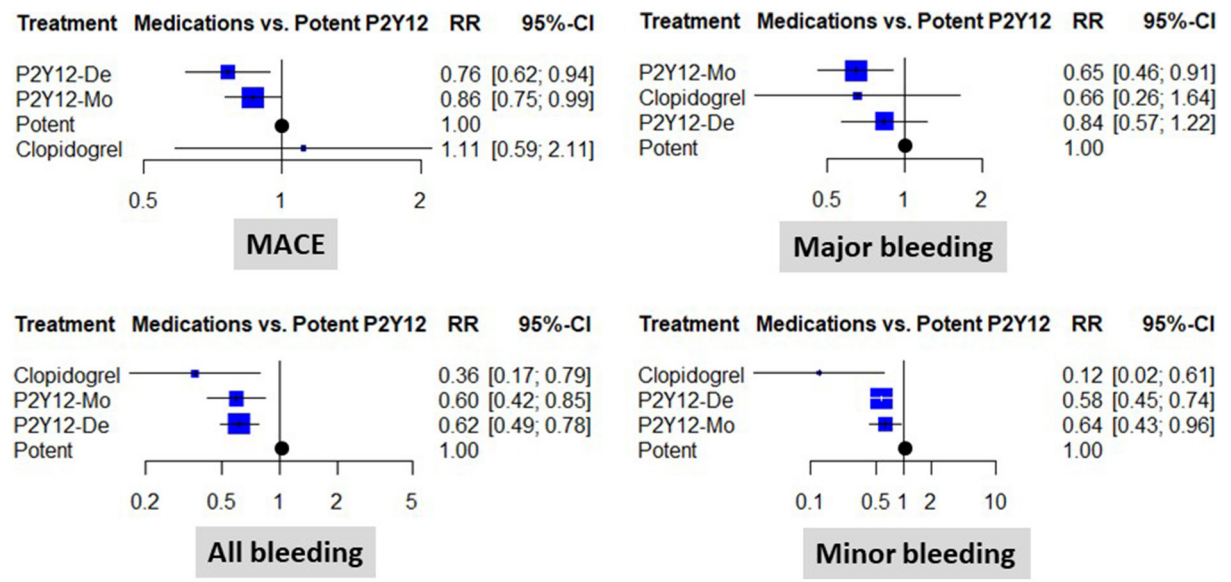


FIGURE 2
Clinical results of using different abatement strategies. The forest plots depict the results of the network meta-analysis computed based on direct and indirect comparisons as risk ratio (RR) and 95% confidence intervals (95% CI). Data are presented as compared to the potent P2Y12 inhibitor-based dual antiplatelet therapy (marked as "Potent). MACE, major adverse cardiovascular events; P2Y12-De, P2Y12 inhibitor de-escalation; P2Y12-Mo, potent P2Y12 inhibitor monotherapy; Clopidogrel, clopidogrel based DAPT.

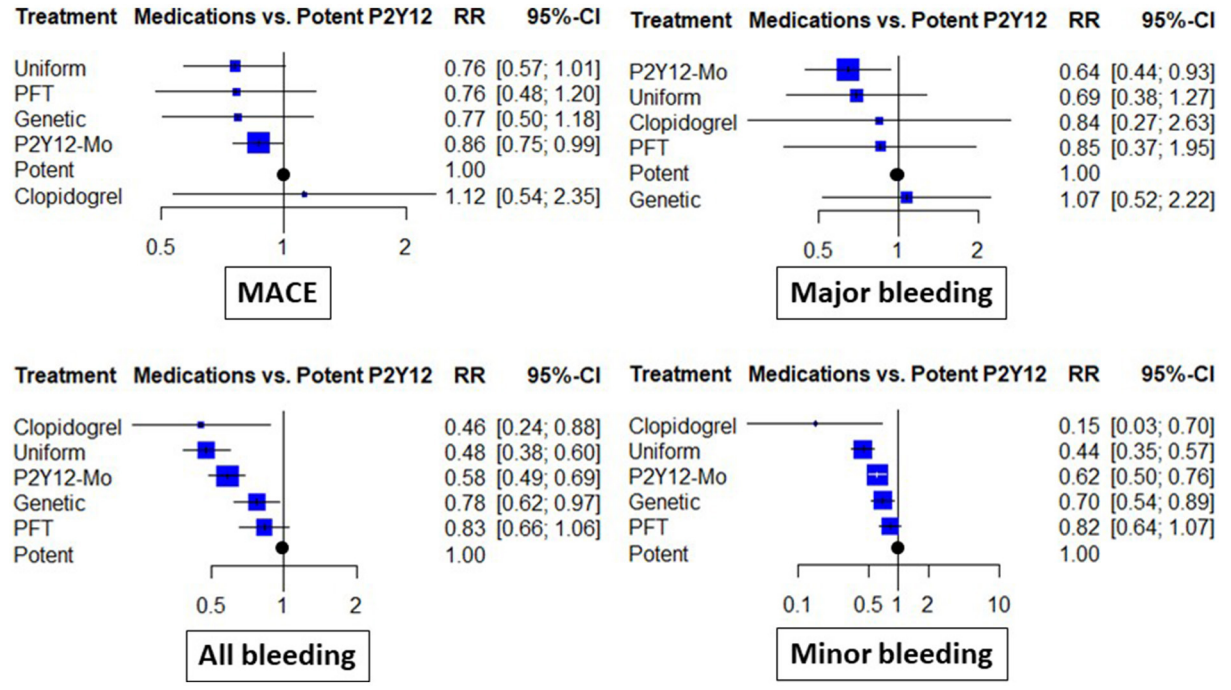


FIGURE 3
Clinical results of abatement strategies considering de-escalation strategies separately. The forest plots depict the risk ratio (RR) and 95% confidence interval (95% CI) achieved with the abatement strategies compared to the potent P2Y12 inhibitor-based dual antiplatelet therapy for major adverse cardiovascular events (MACE), all bleeding (including major and minor events), as well as major bleeding and minor bleeding. In these analyses, de-escalation strategies were considered separate subgroups based on the use of genetic or platelet-function (PFT) testing guidance or uniform de-escalation. P2Y12-Mo, potent P2Y12 inhibitor monotherapy; Clopidogrel, clopidogrel based DAPT.

of statistical significance. When considering, however, the different subgroups of de-escalation strategy results, with uniform de-escalation, the estimates were similar to that of monotherapy, while the rates of minor and major bleeding were significantly higher than that for monotherapy (Supplementary Table 1).

Leave-one-out sensitivity exercises did not show any signal of individual studies having excessive influence in the network (Supplementary Figure 5). Further subgroup analyses supported the consistency of the findings (Supplementary Figure 6).

## Discussion

In this network meta-analysis of DAPT abatement strategies, we found that both switching to a less potent P2Y12 inhibitor, with a P2Y12 inhibitor de-escalation strategy, or using potent P2Y12 monotherapy with aspirin cessation, were associated with better results with regard to the ischemic endpoints. Benefits in terms of bleeding risk reduction were also associated with both strategies; however, reduction of major bleeding was only significant with P2Y12 monotherapy.

Bleeding events represent an important Achilles' heel of adjunctive pharmacotherapy after coronary interventions. To improve prognosis, bleeding avoidance strategies are widely applied and include both pharmacological and non-pharmacological approaches. The benefits of intensified antiplatelet therapy were demonstrated in cases with the highest ischemic risks as well as in the timeframe closest to the intervention. However, as time passes, this advantage may be overweighted by the cumulative risk of bleeding. Multiple trials were conducted to test alternative protocols, with the potential to attenuate long-term bleeding risk. In a comprehensive analysis of these recent studies, we found that abatement from a potent P2Y12 inhibitor-based dual antiplatelet treatment was associated with an important reduction of bleeding events in patients treated with PCI. Both strategies, with de-escalation of P2Y12 inhibitor and P2Y12 inhibitor monotherapy, showed advantages; however, the analysis also explored important differences which have potential practical implications. While both strategies reduced the risk of all bleeding, P2Y12 inhibitor monotherapy, but not P2Y12 inhibitor de-escalation schemes, was associated with a significant reduction of major bleeding events. Our analysis also suggests that this benefit is not counterbalanced with a higher risk of ischemic events. Nonetheless, the individual trials showed only beneficial trends; this was associated with a significant reduction only in the cumulative analyses. These findings suggest routine use of abatement in patients with ACS undergoing PCI in the early phase. If applied according to the trials, i.e., between 48 h and 3 months, these strategies could be beneficial in terms of improvement of ischemic and bleeding risk.

The three oral P2Y12 inhibitors currently used in patients with ACS and PCI exhibit important pharmacodynamic and pharmacokinetic differences. Clopidogrel and prasugrel are prodrugs that are transformed into their active metabolites by hepatic cytochrome P450 enzymes (15). This activation step is faster and more effective in the case of prasugrel, and the active metabolite of both substances irreversibly inhibits the P2Y12 receptor on platelets. Ticagrelor reversibly inhibits the binding of ADP to the P2Y12 receptor in a non-competitive manner. Ticagrelor is an active drug that does not require *in vivo* biotransformation (16). Compared with clopidogrel, both alternatives have faster onsets, are more potent, and have less response variabilities (17).

One of the main limitations of clopidogrel is that the achieved platelet function inhibition reflects high-interindividual variability, which, among high-risk patients, also represents an important risk marker (18). High-platelet reactivity can be verified with the help of platelet function testing and is present in a higher frequency among mutation carriers of cytochrome enzymes involved in thienopyridine metabolism. These include CYP2C19 mutant alleles such as loss-of-function CYP2C19*2 and *3 alleles. Carriers of these two non-functional copies of the CYP2C19 gene are classified as CYP2C19 poor metabolizers and are characterized by a reduced efficacy of clopidogrel. Other variations include the CYP2C19*17 gain-of-function allele, which can be found in rapid clopidogrel metabolizers. Due to genetics and the high rate of potential drug interactions, there is large interindividual variability in response to clopidogrel, and 15–40% of individuals, depending on the criteria used, are considered "non-responders," or "clopidogrel-resistant," with high residual platelet aggregation. There is a vast amount of evidence indicating that high-platelet reactivity, despite clopidogrel treatment, is a risk factor for cardiovascular events and stent thrombosis, while lower levels of residual platelet aggregation are associated with a higher frequency of bleeding complications (19).

While P2Y12 inhibitor monotherapy was associated with a significant reduction of both major bleeding and adverse events, the effects of P2Y12 inhibitor de-escalation strategies were different. The cumulative ischemic risk reduction was more expressed with these strategies; however, despite favorable tendencies, only the risk of minor bleeding was significantly reduced. All three P2Y12 inhibitor de-escalation strategies resulted in a similarly lower rate of ischemic events; the reduction of bleeding events was most associated with uniform de-escalation. Guided de-escalation with platelet function genetic testing showed less expressed reduction of the bleeding endpoints.

Therefore, P2Y12 inhibitor de-escalation strategies seem to be more efficient in decreasing ischemic risk, while P2Y12 inhibitor monotherapy is a safer strategy for reducing bleeding

in patients with ACS. However, using ticagrelor in the P2Y12 inhibitor monotherapy strategy could lead to lower ischemic risks than clopidogrel (20).

While abatement strategies reduced the rate of MACE and bleeding compared to potent P2Y12-based DAPT, indirect comparisons of P2Y12 inhibitor monotherapy and de-escalation only explored signals that may guide decision-making. The reduction of bleeding was similar between the two alternatives; however, subgroup analyses showed that genetic testing and platelet function test-guided de-escalation strategies lagged behind P2Y12 inhibitor monotherapy. This suggests that if bleeding reduction is the main interest, P2Y12 inhibitor monotherapy or unguided de-escalation may offer better alternatives. In indirect comparisons of the rate of ischemic events, however, a tendency for an 11–12% reduction with P2Y12 inhibitor de-escalation strategies was observed; these differences did not reach the level of statistical significance. Thus, more data is required to inform ischemic risk reduction-based decision-making.

Both pivotal clinical trials verifying the benefits of prasugrel and ticagrelor over clopidogrel in ACS showed a reduction of recurrent ischemic events with more effective P2Y12 inhibition but counterbalanced with some degree increase of bleeding risk. The importance of bleeding reduction strategies in ACS was recently emphasized (20, 21). Moreover, because of the publication of alternative antiplatelet protocols, multiple meta-analyses were published. Our meta-analysis differs from these in several aspects (22). Guo et al. (23) included in their meta-analysis both randomized and observational studies. In addition to updating the literature search to include the latest trials, we restricted our inclusion criteria to randomized controlled studies. As observational trials suffer from multiple downsides due to inclusion bias, we considered excluding them to improve the robustness of our analysis. Angiolillo et al. (24) included in their meta-analysis only studies of de-escalation from ticagrelor to clopidogrel, while our meta-analysis also includes de-escalation from both potent P2Y12 inhibitors to clopidogrel. A number of studies focused on the outcomes and benefits of guided de-escalation. Galli et al. (25) found that guided de-escalation improved both composite and individual efficacy outcomes and that it is associated with the most favorable balance between safety and efficacy (26). Tavenier et al. (27) presented results that suggest that both guided and unguided de-escalation were associated with lower rates of bleeding and ischemic events, which aligns with our results. However, the latter meta-analysis excluded aspirin monotherapy trials, which were included in this meta-analysis. Furthermore, with the inclusion of trials testing P2Y12 inhibitor monotherapy and P2Y12 inhibitor de-escalation, our analysis enables the comparison of different abatement strategies.

Thus, far, many randomized controlled trials have investigated the optimal duration of DAPT and meta-analyses comparing different DAPT lengths (3, 6, 12, 24, or 30 months) following DES implantation. The association of prolonged DAPT with an increased bleeding risk, along with a potential reduction of recurrent myocardial infarction (MI) and ST, has been assessed. In an NMA of these trials, D'Ascenzo et al. found that the type of stent impacts the risk of adverse events in addition to DAPT duration. However, there is limited data that directly compare different DAPT durations in patients treated with different generation DES or bioresorbable scaffolds.

Earlier analyses in line with our results reported that P2Y12 inhibitor de-escalation reduces ischemic risk and bleeding in patients with ACS. We extended these observations, with a similar reduction observed in the P2Y12 inhibitor monotherapy trial. Our analysis also enabled comparison of the two strategies. Our results align with the outcomes of the recent meta-analyses by Laudani et al. (28) and Ullah et al. (29), where P2Y12 inhibitor de-escalation decreased ischemic risk, and P2Y12 inhibitor monotherapy decreased bleeding.

## Limitations

This meta-analysis has some limitations such as differences in the definition and adjudication of clinical outcomes, diverse follow-up duration, and inconsistency in the timing of switching. Also, few trials were identified, and the low number of events was a typical characteristic of the included studies. Not all studies restricted their inclusion to patients with ACS; however, when relative risk measures are used, differences in absolute risk are less influential to a network. Thus, neither exclusion nor subgroup analyses reflected an important influence attributable to the inclusion of a lower-risk population. We still support the need for adequately powered RCTs to evaluate de-escalation and to further elucidate the role of risk stratification, including potential genetic and PFT characteristics, before applying antiplatelet abatement. It is important to underline that several treatment combinations were not directly compared in specifically designed trials, and thus, an important part of the effect estimates are only based on indirect comparisons. Furthermore, the inclusion of multiple treatment options may also weaken the consistency of the analysis. Thus, the results should be interpreted as observational and only hypothesis-generating.

A new randomized study, the ELECTRA-SIRIO 2 study, which is still underway, aims to evaluate the safety and efficacy of two ticagrelor-based de-escalation antiplatelet strategies in patients with ACS. The results of this study could help inform and confirm the benefits of de-escalation.

Despite these limitations, this systematic review, with a meta-analysis, provides robust evidence evaluating the risks and benefits of abatement strategies.

## Conclusion

Our findings suggest that the abatement of antiplatelet treatment gives better results in terms of the bleeding risk, without compromising the major adverse cardiovascular events risk, which turns out to be significantly lower. P2Y12 inhibitor monotherapy and P2Y12 inhibitor de-escalation exhibit differences that may influence their clinical use. P2Y12 inhibitor monotherapy resulted in a reduction of both major and minor bleeding, while ischemic risk reduction was less expressed. The de-escalation strategy was quite the opposite, as there was no difference in major bleeding between this strategy and the control; however, ischemic risk was strongly reduced. Despite their plausible background data, trials with guided de-escalation showed less expressed benefits. It is of note that, in selected patients with high-ischemic risk, these strategies may still offer a safe alternative compared to the long-term potent P2Y12 inhibitor DAPT.

## Impact on daily practice

Dual antiplatelet therapy, using a potent P2Y12 inhibitor in patients with acute coronary syndrome receiving percutaneous coronary intervention, maintained for up to 12 months is a guideline-recommended therapy.

Alternative abatement schemes may improve safety outcomes such as major bleeding, without increasing the frequency of ischemic endpoints, creating an optimal balance between bleeding and ischemic complications.

P2Y12 inhibitor monotherapy significantly reduced both major and minor bleeding, while with P2Y12 inhibitor de-escalation, only minor bleeding risk was reduced. Both strategies also significantly reduced the rate of ischemic complications.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

## Author contributions

OE and DT performed the literature search and the data extraction. DT and AK performed the statistical analysis. All authors participated in the conception and drafting the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1008914/full#supplementary-material

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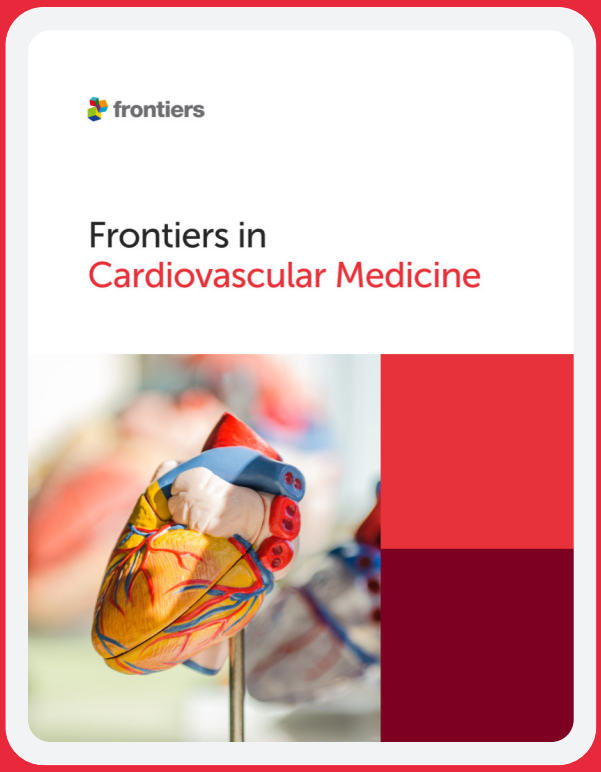


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