Research Square

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Net Adverse Clinical Events of Clopidogrel vs Ticagrelor in Anemic Acute Coronary Syndrome Patients with CYP2C19 Loss-of-Function Alleles Undergoing Percutaneous Coronary Intervention

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Research Article

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Abstract

Objective

This study investigated the net clinical outcomes of clopidogrel versus ticagrelor in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) with anemia and CYP2C19 loss-of-function (LOF) alleles.

Methods

This real-world study included 6083 anemic ACS patients with CYP2C19 LOF variants who underwent PCI at the General Hospital of Northern Theater Command between January 2017 and December 2022. All participants received standard dual antiplatelet therapy (DAPT), a combination of clopidogrel or ticagrelor with aspirin for a minimum of 12 months. The primary endpoint was the 12-month net adverse clinical events (NACE), which included all-cause mortality, myocardial infarction, ischemic stroke, and Bleeding Academic Research Consortium (BARC) types 3–5 bleeding. Propensity score matching (PSM) was used to balance baseline characteristics between the two groups.

Results

Post-matching analysis revealed no significant difference in NACE incidence between the groups (5.4% vs. 5.0%; hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.67–1.24; P = 0.556). The ticagrelor group had a significantly increased risk of BARC types 2–5 bleeding compared with the clopidogrel group (7.8% vs. 4.7%; HR 1.68, 95% CI 1.25–2.25; P < 0.001), mainly attributed to an excess of BARC type 2 bleeding events.

Conclusion

In anemic ACS patients with CYP2C19 LOF alleles undergoing PCI, ticagrelor and clopidogrel offer comparable clinical benefits. However, ticagrelor significantly elevates bleeding risk.

Highlights

1.Ticagrelor vs clopidogrel compared in anemic ACS patients with CYP2C19 LOF

2.Net adverse clinical events were comparable between the two antiplatelet agents

3.Ticagrelor significantly increased BARC 2-5 bleeding risk after PCI

1. Background and Aims

Percutaneous coronary intervention (PCI) remains the cornerstone of revascularization therapy in patients with acute coronary syndrome (ACS) [1–3]. Despite advances in interventional technology and drug-eluting stents, patients undergoing PCI continue to face substantial risks of both ischemic events and bleeding complications [4–6]. Present in 12–25% of ACS patients at admission, anemia is a common comorbidity that independently predicts ischemic events and all-cause mortality in this population [7, 8]. Even with standard dual antiplatelet therapy (DAPT) [9], anemic patients continue to experience a high rate of net adverse clinical events (NACE), such as all-cause death, myocardial infarction (MI), ischemic stroke, and major bleeding, underscoring the need for optimized antiplatelet strategies for this high-risk group.

$P2Y_{12}$ receptor inhibitors, particularly clopidogrel and ticagrelor, are central to DAPT [10–12]. Clopidogrel requires biotransformation to generate active metabolites via hepatic cytochrome P450 enzymes, with CYP2C19 playing a key role[13, 14]. Ticagrelor is a direct-acting reversible antagonist with faster onset and stronger antiplatelet effects [15]. In ACS patients with CYP2C19 loss-of-function (LOF) alleles, efficacy of clopidogrel may be compromised due to impaired bioconversion. It remains unclear if switching to ticagrelor in these patients leads to increased bleeding risks in those with anemia, a comorbidity linked to high bleeding risk. Current studies primarily concentrate on general or non-anemic populations, lacking specific evidence for clopidogrel versus ticagrelor in ACS patients with anemia and CYP2C19 LOF alleles undergoing PCI.

This study evaluated the effects of ticagrelor versus clopidogrel on 12-month NACE and bleeding outcomes in anemic ACS patients with CYP2C19 LOF alleles. Using propensity score matching (PSM) to balance confounders in a real-world context, the study offers evidence-based guidance for personalized antiplatelet therapy in this group.

2. Methods

2.1 Research Framework and Participants

This retrospective, observational cohort study was conducted at the Department of Cardiology, General Hospital of Northern Theater Command in Shenyang, China. Patients who underwent PCI for ACS from January 2017 to December 2022 were screened. ACS was diagnosed according to the Chinese Society of Cardiology's criteria, which include clinical symptoms, ECG changes, elevated cardiac biomarkers and coronary angiography, and categorized into unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Anemia was defined by initial hemoglobin levels below 130 g/L for males and below 120 g/L for non-pregnant females [16]. Genotyping identified CYP2C19 loss-of-function alleles *2 and *3 [14], classifying participants as intermediate metabolizers (IM) with one LOF allele and poor metabolizers (PM) with two LOF alleles.

Inclusion criteria included: (1) diagnosis of anemia and ACS who underwent PCI; (2) completion of CYP2C19 LOF alleles (*2 and *3) genotyping; (3) discharge prescription of DAPT (aspirin with clopidogrel or ticagrelor) for at least 12 months. Exclusion criteria included life expectancy less than 12 months, changes in $P2Y_{12}$ receptor inhibitors during hospitalization, inability to complete a 12-month follow-up, and missing essential exposure or outcome data.

A total of 6083 patients were initially screened, with 4334 receiving clopidogrel and 1749 receiving ticagrelor at discharge. After 1:1 PSM, 1535 patients were included in each group for the final analysis (Fig. 1). Follow-up data were collected through scheduled telephone interviews at 3, 6, 9, and 12 months post-discharge and verified against electronic inpatient and outpatient records to maintain data integrity.

2.2 Outcome Definitions

The main endpoint, NACE, was a composite of all-cause mortality, MI, ischemic stroke, and BARC types 3–5 bleeding within 12 months after discharge. Secondary endpoints included major ischemic events, comprising cardiac death, MI, and ischemic stroke. All-cause mortality referred to deaths from any cause [17]. MI was diagnosed according to the Third Universal Definition of MI [18]. Ischemic stroke was characterized as an acute cerebrovascular incident resulting in a lasting neurological deficit [19]. Bleeding events were categorized based on BARC criteria [20] into clinically relevant (types 2–5) and severe (types 3–5) bleeding. An independent, blinded Clinical Endpoint Committee adjudicated all outcomes.

2.3 Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range) and were compared using Student's t-test or the Mann-Whitney U test. Categorical variables are described as frequencies and percentages, with group comparisons performed using the χ^2 test or Fisher's exact test.

To mitigate selection bias inherent in observational studies, 1:1 nearest-neighbor propensity score matching without replacement was implemented. A logistic regression model incorporating all potential confounders–including age, sex, hypertension, diabetes mellitus, prior stroke, prior MI, prior PCI, smoking history, ACS subtype, estimated glomerular filtration rate (eGFR), admission hemoglobin level, left ventricular ejection fraction, serum creatinine, platelet count, CYP2C19 metabolizer phenotype, radial artery access, lesion characteristics, stent number and total length, and discharge medications (aspirin, statins, proton pump inhibitors, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and beta-blockers)-was developed to calculate propensity scores. Matching was performed using the nearest-neighbor method with a caliper width of 0.02. Standardized mean differences assessed covariate balance before and after matching, with values below 0.10 indicating adequate balance.

Kaplan-Meier cumulative incidence curves and log-rank tests were used to compare primary and secondary endpoints between groups before and after PSM. Cox proportional hazards models calculated hazard ratios (HRs) with 95% confidence intervals (CIs), and log-log plots verified the proportional hazards assumption. All statistical tests were two-sided, with $P < 0.05$ considered statistically significant. Analyses were performed using R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

2.4 Ethical Statement

This study complied with the Declaration of Helsinki and was approved by the Ethics Review Committee of the General Hospital of Northern Theater Command. Given its retrospective observational nature and the use of de-identified patient data, the requirement for written informed consent was waived.

3. Results

3.1 Baseline Characteristics

Between January 2017 and December 2022, 6083 anemic ACS patients with CYP2C19 LOF alleles were enrolled. Before PSM, the clopidogrel group (n = 4334) was older (66.0 ± 9.7 years vs. 60.5 ± 8.6 years; $P < 0.001$), had a lower proportion of males (59.5% vs. 72.7%; $P < 0.001$), and exhibited lower hemoglobin levels (115.2 ± 11.2 g/L vs. 118.3 ± 9.4 g/L; $P < 0.001$) and eGFR (84.4 ± 28.6 mL/min/1.73 m² vs. 92.0 ± 25.7 mL/min/1.73 m²; $P < 0.001$) compared with the ticagrelor group (n = 1749). The prevalence of CYP2C19 PM phenotype was lower in the clopidogrel group than in the ticagrelor group (19.2% vs. 28.5%; $P < 0.001$), and prior ischemic stroke was more frequent among clopidogrel-treated patients (17.2% vs. 11.8%; $P < 0.001$).

Ticagrelor-treated patients underwent more complex PCI procedures, as evidenced by a greater number of stents implanted (1.8 ± 1.0 vs. 1.6 ± 1.0; P < 0.001), longer total stent length (47.5 ± 29.7 mm vs. 42.4 ± 28.7 mm; P < 0.001), and larger average stent diameter (2.8 ± 0.8 mm vs. 2.7 ± 0.9 mm; P < 0.001). The ticagrelor group also had a higher incidence of left main lesions (8.2% vs. 5.6%; P < 0.001). Discharge medication usage was significantly higher in the ticagrelor group for aspirin (99.4% vs. 93.8%; P < 0.001), statins (94.1% vs. 87.7%; P < 0.001), ACEI/ARB (57.6% vs. 48.3%; P < 0.001), and beta-blockers (65.0% vs. 53.3%; P < 0.001).

Following 1:1 PSM, 1535 patients were included in each group, with well-balanced baseline characteristics encompassing demographics, medical history, laboratory parameters, CYP2C19 genotype distribution, target vessel distribution, and procedural details (all P > 0.05; Table 1).

3.2 Clinical outcomes

In the analysis of the primary endpoint, NACE events occurred in 6.3% of patients in the clopidogrel group and 5.3% in the ticagrelor group before PSM, showing no significant difference (HR = 0.85, 95% CI = 0.67-1.07; P = 0.164). After 1:1 PSM, the incidence was similar between the clopidogrel (5.4%) and ticagrelor (5.0%) groups (HR = 0.91, 95% CI = 0.67-1.24; P = 0.556) (Table 2).

Prior to PSM, the ticagrelor group demonstrated a significantly lower risk of major ischemic events (cardiac death, MI, or ischemic stroke) compared with the clopidogrel group (2.7% vs. 3.8%; HR 0.71, 95% CI 0.51-0.98; P = 0.036). However, this difference was no longer significant after PSM (2.4% vs. 3.5%; HR 0.68, 95% CI 0.45-1.03; P = 0.068) (Fig. 2A and B). The individual components of ischemic events, including cardiac death, MI, and stroke, are detailed in Table 2. Similarly, all-cause mortality was lower in the ticagrelor group before PSM (1.9% vs. 3.3%; HR 0.59, 95% CI 0.41-0.86; P = 0.006), but showed only a non-significant trend toward reduction after PSM (1.4% vs. 2.4%; HR 0.59, 95% CI 0.35-1.00; P = 0.050) (Fig. 2C and D).

Clinically relevant bleeding (BARC types 2-5) was significantly more frequent in the ticagrelor group than in the clopidogrel group both before and after PSM. Before matching, BARC types 2-5 bleeding occurred in 8.9% of ticagrelor-treated patients versus 5.5% of clopidogrel-treated patients (HR 1.63, 95% CI 1.33-1.99; P < 0.001). After PSM, the cumulative incidence remained significantly higher in the ticagrelor group (7.8% vs. 4.7%; HR 1.68, 95% CI 1.25-2.25; P < 0.001) (Fig. 2E and F). This excess bleeding risk was predominantly attributable to BARC type 2 bleeding events (5.5% vs. 3.0% after PSM), whereas severe bleeding (BARC types 3-5) was numerically higher with ticagrelor without reaching statistical significance (HR 1.34, 95% CI 0.81-2.23; P = 0.257). Kaplan-Meier analysis demonstrated sustained divergence of bleeding risk curves throughout the 12-month follow-up, with log-rank tests confirming significant differences both before (χ^2 = 22.860, P < 0.001) and after PSM (χ^2 = 12.302, P < 0.001).

4. Discussion

In this real-world observational study, the net clinical outcomes of clopidogrel versus ticagrelor were compared in anemic ACS patients carrying CYP2C19 LOF alleles after PCI. The principal finding was that ticagrelor did not significantly reduce NACE compared with clopidogrel over 12 months of follow-up. Despite the more potent antiplatelet profile of ticagrelor, both groups exhibited equivalent net clinical benefits; however, ticagrelor was associated with a significantly increased risk of clinically relevant bleeding, predominantly minor (BARC type 2) bleeding events. These findings suggest that, in this specific high-bleeding-risk population, clopidogrel may offer a more favorable safety profile without compromising ischemic protection.

The present results are consistent with the TICA-KOREA and POPular AGE trials [21, 22], which found ticagrelor providing similar cardiovascular protection as clopidogrel but with higher bleeding risks in East Asian or elderly ACS patients, and comparable net adverse clinical event rates. The TICA-KOREA trial [21] specifically reported that the incidence of clinically significant bleeding at 12 months was significantly higher in the ticagrelor group than in the clopidogrel group (11.7% vs. 5.3%; HR 2.26, 95% CI 1.34-3.79; P = 0.002), with major bleeding and fatal bleeding also higher in the ticagrelor group. This stands in contrast to the PLATO trial [23], which reported ticagrelor reduced ischemic endpoints without increasing major bleeding risks in a more diverse ACS population. This difference may be attributed to the PLATO trial's broader demographic with a predominance of western participants, whereas our study emphasizes the 'East Asian Paradox', where East Asian patients show heightened sensitivity to ticagrelor's bleeding effects. Additionally, the TAILOR-PCI trial [24],found no significant advantage of ticagrelor for CYP2C19 LOF allele carriers using a genotype-guided approach. This suggests that genotype-guided escalation therapy requires further investigation for specific subgroups.

The CCC-ACS project [25] previously assessed the in-hospital effectiveness and safety of ticagrelor and clopidogrel in anemic ACS patients undergoing PCI across 240 hospitals in China, finding that anemic patients who received ticagrelor had increased susceptibility to bleeding events and comparable ischemic risks after PCI compared with those who received clopidogrel. This study evaluated the net clinical benefit of two $P2Y_{12}$ receptor inhibitors in anemic ACS patients with CYP2C19 LOF alleles undergoing PCI, addressing a gap in current guidelines for this dual high-risk phenotype. The findings suggest that for high-bleeding-risk East Asian patients, treatment decisions should consider both clinical characteristics, such as anemia and genotype, rather than defaulting to potent $P2Y_{12}$ inhibitors. For patients with functional impairments and high bleeding risk, combining clopidogrel with aspirin or using a de-escalation strategy based on platelet function testing may enhance efficacy and safety. Future research should include prospective randomized trials to validate precision antithrombotic strategies that integrate genotype and bleeding risk

factors, and explore the role of other genetic polymorphisms, such as ABCB1, in therapeutic response to develop a comprehensive individualized antiplatelet therapy system [26-27].

The increased risk of BARC type 2 bleeding warrants particular attention. Although BARC type 2 bleeding is categorized as minor, it has been associated with premature discontinuation of antiplatelet therapy, which in turn increases the risk of stent thrombosis and recurrent ischemic events. In this anemic population, even modest blood loss may be poorly tolerated and may necessitate blood transfusion or dose adjustment, further complicating the clinical management. Notably, the excess bleeding risk in the ticagrelor group was observed both before and after PSM, with Kaplan-Meier curves demonstrating sustained divergence throughout the 12-month follow-up period, suggesting that the bleeding hazard associated with ticagrelor is not confined to the early post-PCI period but persists during long-term maintenance therapy.

This study utilized a substantial cohort of over 6000 ACS patients, accurately representing the efficacy and safety profiles observed in routine clinical practice. We employed a 1:1 PSM method to systematically balance baseline clinical characteristics and procedural factors, significantly reducing the selection bias inherent in observational studies. Of particular importance, this study focused precisely on the high-risk population of patients with anemia carrying CYP2C19 LOF alleles, filling a key gap in evidence from previous large randomized controlled trials for this subgroup. Additionally, standardized endpoint definitions and an independent telephone follow-up system ensured the objectivity and reliability of outcome assessment.

This study has several limitations. As a single-center retrospective observational study, it identified statistical associations without establishing causality. Despite using PSM to adjust for known confounders, unmeasured variables like anemia duration and iron reserve status may still exist. Secondly, the study excluded patients who changed $P2Y_{12}$ inhibitors during their hospital stay, had a life expectancy under 12 months, or were unable to adhere to telephone follow-up. The study did not assess the effect of ticagrelor-related dyspnea on medication adherence, nor did it comprehensively document the actual duration of DAPT or group crossover. These exclusions restricted the generalizability of the results to populations with terminal illness, low treatment adherence, or cognitive impairments. Thirdly, the study did not classify anemia etiology (iron-deficiency anemia vs. anemia of chronic disease), which may have differential effects on bleeding and ischemic risk. Additionally, the study focused exclusively on Chinese high-risk patients with anemic CYP2C19 LOF carriers. Given the differences in genetic polymorphisms and anemia prevalence across populations, these findings should be applied cautiously to non-East Asian populations.

5. Conclusion

In anemic ACS patients with CYP2C19 LOF alleles undergoing PCI, ticagrelor and clopidogrel demonstrated comparable 12-month net adverse clinical event rates. Ticagrelor significantly increased the risk of BARC types 2-5 bleeding, predominantly through an excess of minor (type 2) bleeding events. Consequently, clopidogrel may represent a safer antiplatelet option in this high-bleeding-risk population, and genotype-guided escalation to potent P2Y12 inhibitors should be weighed carefully against bleeding risk in individualized clinical decision-making.

Declarations

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Authorship Contribution Statement

Xuefei Mu: Writing – original draft. Dali Zhang: Conceptualization, Writing – review & editing. Miaohan Qiu: Data curation, Formal analysis. Kai Xu and Quanmin Jing: Writing – review & editing. Yi Li: Supervision, Writing – review & editing. Yaling Han: Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval and consent to participate

This study complied with the Declaration of Helsinki and was approved by the Ethics Review Committee of the General Hospital of Northern Theater Command. Given its retrospective observational nature and the use of de-identified patient data, the requirement for written informed consent was waived by the Ethics Review Committee.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Xuefei Mu: Writing – original draft. Dali Zhang: Conceptualization, Writing – review & editing. Miaohan Qiu: Data curation, Formal analysis. Kai Xu and Quanmin Jing: Writing – review & editing. Yi Li: Supervision, Writing – review & editing. Yaling Han: Supervision, Writing – review & editing.

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Clinical trial number

Not applicable.

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Tables

Table 1. Baseline characteristics of the study population.

	Before Matching			After Matching		
	Clopidogrel (N=4334)	Ticagrelor (N=1749)	P value	Clopidogrel (N=1535)	Ticagrelor (N=1535)	P value
Age, year	66.0±9.7	60.5±8.6	<0.001	61.4±9.6	61.3±8.1	0.942
Male	2579 (59.5%)	1272 (72.7%)	<0.001	1118 (72.8%)	1102 (71.8%)	0.519
Medical histoy						
Hypertension	2823 (65.2%)	1080 (61.8%)	0.013	961 (62.6%)	951 (62.0%)	0.710
Diabetes	1572 (36.4%)	590 (33.9%)	0.072	550 (35.8%)	521 (33.9%)	0.272
Previous MI	583 (13.5%)	263 (15.1%)	0.099	218 (14.2%)	224 (14.6%)	0.758
Previous stroke	746 (17.2%)	206 (11.8%)	<0.001	182 (11.9%)	185 (12.1%)	0.868
Previous PCI	795 (18.4%)	369 (21.1%)	0.014	304 (19.8%)	320 (20.8%)	0.473
Smoking			<0.001			0.802
Never	2280 (52.8%)	744 (42.6%)		638 (41.6%)	656 (42.7%)	
Active	1514 (35.0%)	759 (43.4%)		678 (44.2%)	666 (43.4%)	
Former	528 (12.2%)	244 (14.0%)		219 (14.3%)	213 (13.9%)	
Presentation			0.001			0.304
UA	2597 (59.9%)	956 (54.7%)		849 (55.3%)	852 (55.5%)	
NSTEMI	776 (17.9%)	370 (21.2%)		300 (19.5%)	327 (21.3%)	
STEMI	961 (22.2%)	423 (24.2%)		386 (25.1%)	356 (23.2%)	
eGFR	84.4±28.6	92.0±25.7	<0.001	90.2±27.5	91.2±25.3	0.285
Hemoglobin	115.2±11.2	118.3±9.4	<0.001	118.2±9.7	118.1±9.4	0.694
LVEF	57.1±8.9	56.4±9.1	0.009	56.5±8.9	56.7±8.9	0.617
CYP2C19 genotype			<0.001			0.871
IM	3502 (80.8%)	1250 (71.5%)		1121 (73.0%)	1117 (72.8%)	
PM	832 (19.2%)	499 (28.5%)		414 (27.0%)	418 (27.2%)	
Procedure information						
Transradial access	3984 (92.0%)	1617 (92.6%)	0.471	1429 (93.1%)	1421 (92.6%)	0.576
Coronary arteries treated						
LM	241 (5.6%)	144 (8.2%)	0.000	110 (7.2%)	118 (7.7%)	0.582
LAD	2087 (48.2%)	855 (48.9%)	0.606	745 (48.5%)	751 (48.9%)	0.829
LCX	1116 (25.7%)	478 (27.3%)	0.205	419 (27.3%)	423 (27.6%)	0.872
RCA	1907 (44.0%)	707 (40.4%)	0.011	639 (41.6%)	625 (40.7%)	0.608
Number of stents	1.6±1.0	1.8±1.0	<0.001	1.7±1.0	1.7±1.0	0.281
Total length of stents, mm	42.4±28.7	47.5±29.7	<0.001	45.9±30.0	46.9±29.1	0.387
Average stent diameters, mm	2.7±0.9	2.8±0.8	<0.001	2.8±0.8	2.8±0.8	0.831
Medical treatment at discharge						
Aspirin	4066 (93.8%)	1739 (99.4%)	<0.001	1530 (99.7%)	1526 (99.4%)	0.284
Statins	3803 (87.7%)	1645 (94.1%)	<0.001	1432 (93.3%)	1445 (94.1%)	0.334
ACEI/ARB	2094 (48.3%)	1008 (57.6%)	<0.001	882 (57.5%)	868 (56.5%)	0.610
βblockers	2312 (53.3%)	1136 (65.0%)	<0.001	990 (64.5%)	978 (63.7%)	0.652
PPI	1366 (31.5%)	562 (32.1%)	0.641	496 (32.3%)	501 (32.6%)	0.847

MI = myocardial infarction; PCI = percutaneous coronary intervention; UA = unstable angina; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; eGFR = estimated glomerular filtration rate；IM = intermediate metabolizer; PM = poor metabolizer; LM = left main; LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; PPI = proton pump inhibitor.

Table 2.Clinical outcomes.

		Before Matching					After Matching				
		Clopidogrel (N=4334)	**Ticagrelor (N=1749)**	**Hazard ratio (95%CI)**	**P value (Wald)**	**P value (Score - Log-rank)**	**Clopidogrel (N=1535)**	**Ticagrelor (N=1535)**	**Hazard ratio (95%CI)**	**P value (Wald)**	**P value (Score - Log-rank)**
Primary Endpoint	NACE	271 (6.3%)	93 (5.3%)	0.85 (0.67-1.07)	0.164	0.164	83 (5.4%)	76 (5.0%)	0.91 (0.67-1.24)	0.556	0.555
Secondary Efficacy Endpoints	Ischemic events	166 (3.8%)	48 (2.7%)	0.71 (0.51-0.98)	0.036	0.035	54 (3.5%)	37 (2.4%)	0.68 (0.45-1.03)	0.068	0.067
	Cardiac death	99 (2.3%)	27 (1.5%)	0.67 (0.44-1.03)	0.068	0.066	28 (1.8%)	18 (1.2%)	0.64 (0.35-1.16)	0.139	0.136
	MI	29 (0.7%)	10 (0.6%)	0.85 (0.41-1.74)	0.653	0.653	10 (0.7%)	10 (0.7%)	0.99 (0.41-2.38)	0.986	0.986
	Stroke	48 (1.1%)	12 (0.7%)	0.61 (0.33-1.15)	0.129	0.125	18 (1.2%)	10 (0.7%)	0.55 (0.25-1.19)	0.128	0.123
	Death from any cause	142 (3.3%)	34 (1.9%)	0.59 (0.41-0.86)	0.006	0.005	37 (2.4%)	22 (1.4%)	0.59 (0.35-1.00)	0.050	0.048
Secondary Safety Endpoints	BARC types 2-5 bleeding	240 (5.5%)	155 (8.9%)	1.63 (1.33-1.99)	<0.001	<0.001	72 (4.7%)	119 (7.8%)	1.68 (1.25-2.25)	0.001	0.001
	BARC types 3-5 bleeding	79 (1.8%)	42 (2.4%)	1.31 (0.90-1.91)	0.153	0.152	26 (1.7%)	35 (2.3%)	1.34 (0.81-2.23)	0.257	0.255

NACE = net adverse clinical event; BARC = bleeding endpoints criteria defined by Bleeding Academic Research Consortium.

Figures

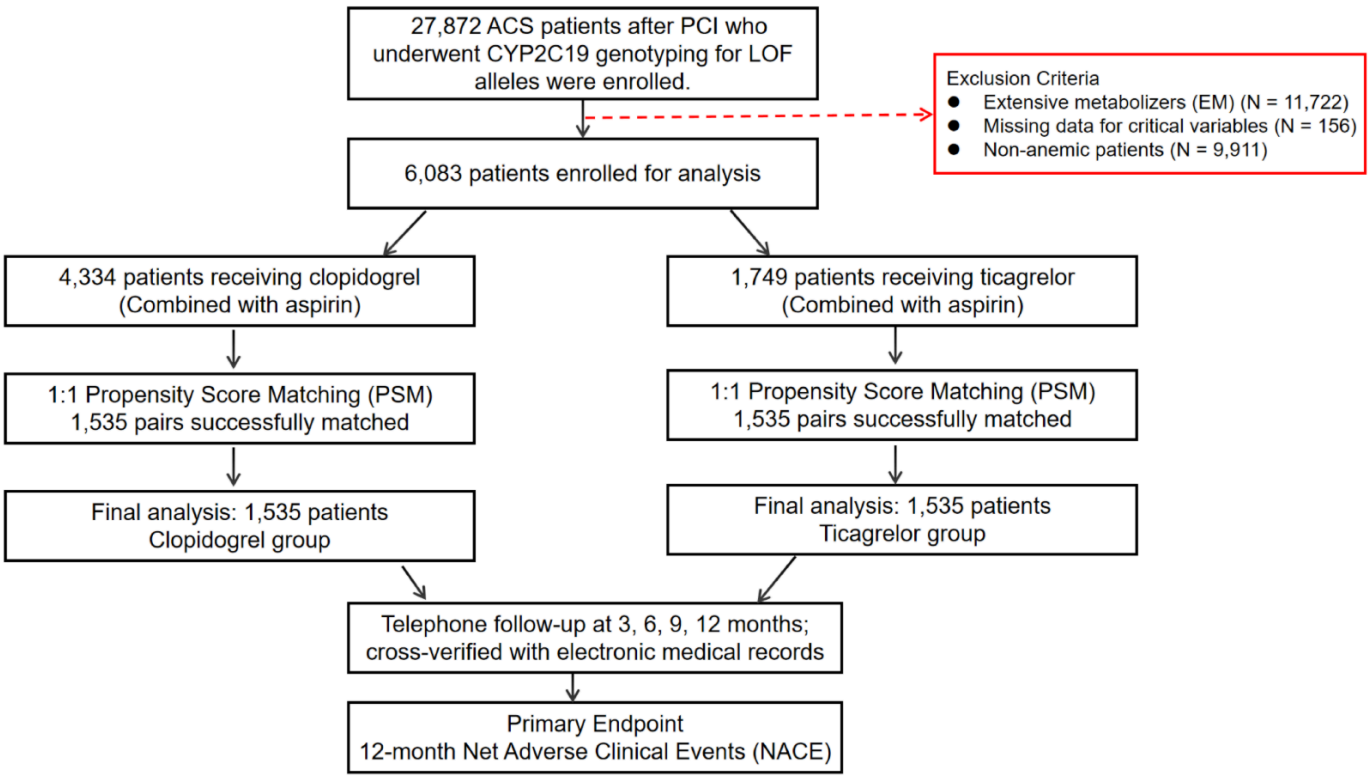

Fig. 1. Flow chart of enrollment and follow-up.

Figure 1

Flow chart of enrollment.

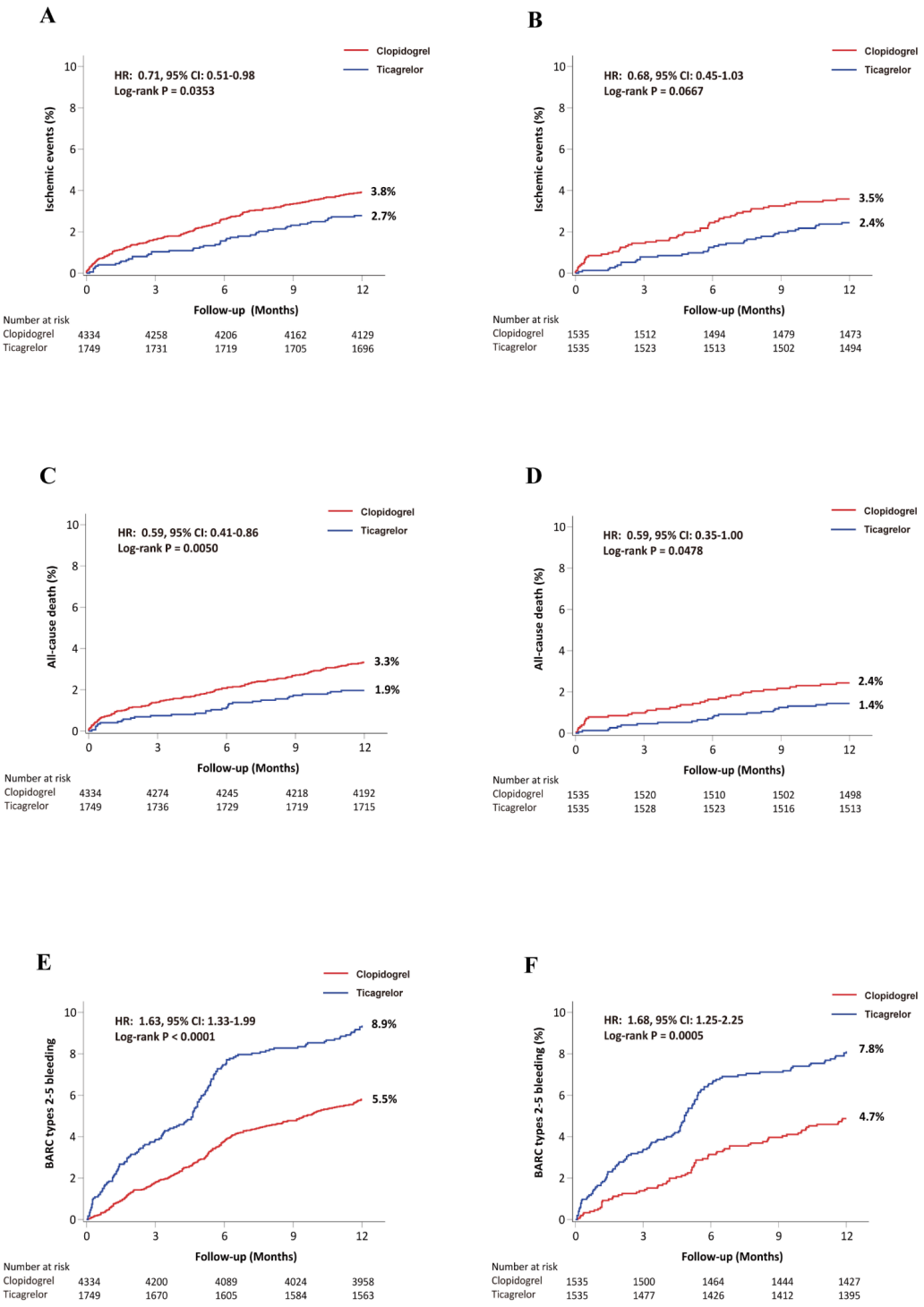

Figure 2

Kaplan-Meier cumulative incidence curves of ischemic events (A, B), all-cause death (C, D) and BARC types 2-5 bleeding (E, F) in the clopidogrel and ticagrelor groups before (A, C, E) and after PSM (B, D, F). The incidence of ischemic events was significantly lower in the ticagrelor group than in the clopidogrel group before PSM, whereas this difference was not significant after PSM. All-cause mortality was lower in the ticagrelor group before PSM, with a reduction trend observed after PSM. The incidence of BARC types 2-5 bleeding was significantly increased in the ticagrelor group compared with the clopidogrel group both before and after PSM. HR = hazard ratio; CI = confidence interval; PSM = propensity score matching; BARC = Bleeding Academic Research Consortium.