JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 17, NO. 17, 2024

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

CORONARY

Real-World Implementation of a Genotype-Guided $P2Y_{12}$ Inhibitor De-Escalation Strategy in Acute Coronary Syndrome Patients

Jaouad Azzahhafi, MD,[a,*] Wout W.A. van den Broek, MD,[a] Dean R.P.P. Chan Pin Yin, MD,[a] Niels M.R. van der Sangen, MD,[b] Shabiga Sivanesan, MD,[b] Salahodin Bofarid, MD,[a] Joyce Peper, MSc, PhD,[a] Daniel M.F. Claassens, MD, PhD,[c] Paul W.A. Janssen, MD, PhD,[d] Ankie M. Harmsze, PharmD, PhD,[e] Ronald J. Walhout, MD, PhD,[f] Melvyn Tjon Joe Gin, MD,[g] Deborah M. Nicastia, MD,[h] Jorina Langerveld, MD, PhD,[i] Georgios J. Vlachojannis, MD, PhD,[j] Rutger J. van Bommel, MD, PhD,[k] Yolande Appelman, MD, PhD,[l] Ron H.N. van Schaik, MSc, PhD,[m] José P.S. Henriques, MD, PhD,[b] Wouter J. Kikkert, MD, PhD,[b,k] Jurriën M. ten Berg, MD, PhD[a,n]

ABSTRACT

BACKGROUND *CYP2C19* genotype-guided de-escalation from ticagrelor or prasugrel to clopidogrel may optimize the balance between ischemic and bleeding risk in patients with acute coronary syndrome (ACS).

OBJECTIVES This study sought to compare bleeding and ischemic event rates in genotyped patients vs standard care.

METHODS Since 2015, ACS patients in the multicenter FORCE-ACS (Future Optimal Research and Care Evaluation in Patients with Acute Coronary Syndrome) registry received standard dual antiplatelet therapy (DAPT). Since 2021, genotype-guided $P2Y_{12}$ inhibitor de-escalation was recommended at a single center, switching noncarriers of the loss-of-function allele *CYP2C19*3* or *CYP2C19*2* from ticagrelor or prasugrel to clopidogrel, whereas loss-of-function carriers remained on ticagrelor or prasugrel. The primary ischemic endpoint, a composite of cardiovascular mortality, myocardial infarction, or stroke, and the primary bleeding endpoint, Bleeding Academic Research Consortium 2, 3, or 5 bleeding, were compared between a genotyped cohort and a cohort treated with standard DAPT after 1 year.

RESULTS Among 5,321 enrolled ACS patients, 406 underwent genotyping compared with 4,915 nongenotyped ACS patients on standard DAPT. In the genotyped cohort, 65.3% (n = 265) were noncarriers, 88.7% (n = 235) of whom were switched to clopidogrel. The primary ischemic endpoint occurred in 5.2% (n = 21) of patients in the genotyped cohort compared to 6.9% (n = 337) in the standard care cohort (adjusted HR: 0.82; 95% CI: 0.53-1.28). The primary bleeding rate was significantly lower in the genotyped cohort compared to the standard care cohort (4.7% vs 9.8%; adjusted HR: 0.47; 95% CI: 0.30-0.76).

CONCLUSIONS The implementation of a *CYP2C19* genotype-guided $P2Y_{12}$ inhibitor de-escalation strategy in a real-world ACS population resulted in lower bleeding rates without an increase in ischemic events compared to a standard DAPT regimen. (JACC Cardiovasc Interv. 2024;17:1996-2007) © 2024 by the American College of Cardiology Foundation.

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2024.06.020

Dual antiplatelet therapy (DAPT), including aspirin and a $P2Y_{12}$ inhibitor, is the default strategy to prevent ischemic events after percutaneous coronary intervention (PCI) and acute coronary syndrome (ACS).[1,2] Over time, improvements in stent technologies and management strategies (eg, more potent $P2Y_{12}$ inhibitors) have led to a decrease in ischemic events.[3-6] Although DAPT with more potent $P2Y_{12}$ inhibitors has reduced the risk for ischemic events, the associated increased bleeding risk remains challenging.[3,4,7,8] The adverse implications of bleeding, including an increased mortality risk, have paved the way for strategies that address this safety concern without compromising efficacy.[8-11] These strategies include shortening DAPT duration or de-escalation of DAPT intensity (ie, switching from more potent $P2Y_{12}$ inhibitors such as ticagrelor and prasugrel to a less potent inhibitor such as clopidogrel).[9,12-15] Although traditional risk stratification has encompassed clinical, demographic, angiographic, and laboratory factors, the advent of rapid genotyping assays enables a more personalized selection of $P2Y_{12}$ inhibitor therapy. This method is based on genotyping *CYP2C19*, the enzyme pivotal in clopidogrel activation.[16-19] The POPular Genetics (Cost-effectiveness of Genotype Guided Treatment With Antiplatelet Drugs in STEMI Patients: Optimization of Treatment) trial showed that in patients with ST-segment elevation myocardial infarction (STEMI), a genotype-guided de-escalation strategy led to fewer bleeding events without increasing thrombotic events compared to the standard of care including ticagrelor.[20] These results are backed by a meta-analysis of 15,949 coronary artery disease patients indicating that individuals carrying a *CYP2C219* loss-of-function allele had less thrombotic events when treated with ticagrelor or prasugrel compared to those treated with clopidogrel; yet, when compared solely in wild-type patients (normal metabolizers), clopidogrel demonstrated comparable efficacy in preventing thrombotic events.[21]

Despite the evidence of previous studies, on which the rationale for our implementation was based, results are limited by the controlled settings in which these studies were performed and may not reflect real-world outcomes. Thus, the question remains whether a genotype-guided de-escalation of $P2Y_{12}$ inhibitors is safe and effective in a real-world all-comers ACS population. Our study aimed to compare the bleeding and ischemic event rates of ACS patients undergoing routine *CYP2C19* genotype-guided de-escalation from ticagrelor to clopidogrel vs patient undergoing standard care.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

BARC = Bleeding Academic Research Consortium

DAPT = dual antiplatelet therapy

MI = myocardial infarction

NACE = net adverse clinical event(s)

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

MATERIALS AND METHODS

STUDY DESIGN. The FORCE-ACS registry (NCT03823547), as previously described, is a prospective, ongoing initiative involving 9 Dutch hospitals.[22] Participating medical centers possess the capacity to conduct coronary angiography, with 6 of them equipped for on-site PCI. Commencing in 2015, the registry has enrolled consecutive adult patients (18 years and older) presenting with (suspected) ACS. Follow-up has been instituted through questionnaires administered at the following predefined intervals: 1, 12, 24, and 36 months after admission. The primary objective of the FORCE-ACS registry is to facilitate a comprehensive understanding of diverse facets concerning the diagnosis, management, and longitudinal clinical and patient-reported outcomes of patients with ACS.

From 2021 onward, 1 of the hospitals implemented a *CYP2C19* genotype-guided $P2Y_{12}$ inhibitor de-escalation strategy from ticagrelor or prasugrel to clopidogrel. Information regarding the genotyping process has been described previously.[23] In brief,

From the [a]Department of Cardiology, St. Antonius Hospital, Nieuwegein, the Netherlands; [b]Department of Cardiology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam Cardiovascular Sciences, Amsterdam, the Netherlands; [c]Department of Cardiology, Isala Hospital, Zwolle, the Netherlands; [d]Department of Cardiology, Haga Hospital, The Hague, the Netherlands; [e]Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, the Netherlands; [f]Department of Cardiology, Hospital Gelderse Vallei, Ede, the Netherlands; [g]Department of Cardiology, Rijnstate Hospital, Arnhem, the Netherlands; [h]Department of Cardiology, Gelre Hospitals, Apeldoorn, the Netherlands; [i]Department of Cardiology, Rivierenland Hospital, Tiel, the Netherlands; [j]Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands; [k]Department of Cardiology, Tergooi Hospital, Blaricum, the Netherlands; [l]Department of Cardiology, Amsterdam University Medical Center, Vrije Universiteit University, Amsterdam Cardiovascular Sciences, Amsterdam, the Netherlands; [m]Department of Clinical Chemistry, Erasmus MC University Medical Center, Rotterdam, the Netherlands; and the [n]Department of Cardiology, University Medical Center Maastricht, Maastricht, the Netherlands. *Drs Azzahhafi and van den Broek contributed equally to this work.

Manuscript received January 28, 2024; revised manuscript received June 4, 2024, accepted June 18, 2024.

patients with ACS and an indication for DAPT were genotyped on the day of admittance if performed by the buccal swab or within 2 working days if performed by a laboratory blood test. Loss-of-function carriers (intermediate or poor metabolizers, carrying at least 1 loss-of-function *CYP2C19*2* or *CYP2C19*3* allele) remained on ticagrelor. In noncarriers ([ultra]rapid or normal metabolizers), a switch to clopidogrel was recommended. In alignment with the 2017 European Society of Cardiology guidelines on DAPT, patients transitioning from ticagrelor to clopidogrel received a 600-mg loading dose of clopidogrel 24 hours after the last ticagrelor intake followed by a maintenance dose of 75 mg daily. For those switching from prasugrel to clopidogrel, a 75-mg daily maintenance dose of clopidogrel was initiated 24 hours after the last dose of prasugrel without an additional loading dose.[1] Written informed consent was obtained from each patient.

The research protocol of the FORCE-ACS registry was approved by the Institutional Review Boards of all participating medical centers. This study adheres to the principles of the Declaration of Helsinki. Results were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[24]

STUDY POPULATION. The total population was divided into 2 cohorts: a standard care cohort in which patients were treated with a $P2Y_{12}$ inhibitor (ticagrelor, prasugrel, or clopidogrel) at the discretion of the treating physician and a genotyped cohort in which all patients received a *CYP2C19* genotype test with a treatment recommendation based on the *CYP2C19* test result.

Sensitivity analyses were conducted in a more selected subgroup of patients to provide a more targeted assessment of the treatment effect of the genotype-guided strategy. In the first sensitivity analysis, patients who were not treated according to their *CYP2C19* genotype were excluded from the genotyped cohort, meaning that noncarriers treated with ticagrelor or prasugrel and loss-of-function carriers treated with clopidogrel were excluded. This genotype-guided group was compared to the standard care cohort. In a second sensitivity analysis, all patients treated with clopidogrel and prasugrel were excluded from the standard care group. This ticagrelor-only standard care group was compared to the genotype-guided group.

The implementation was part of a pilot program in which health insurers reimbursed a part of the costs for genetic testing. This analysis was part of an initial review to assess the effectiveness and safety of the implementation, evaluating whether further expansion of the implementation of genetic testing was appropriate and advisable. Therefore, this analysis was not based on a predetermined sample size.

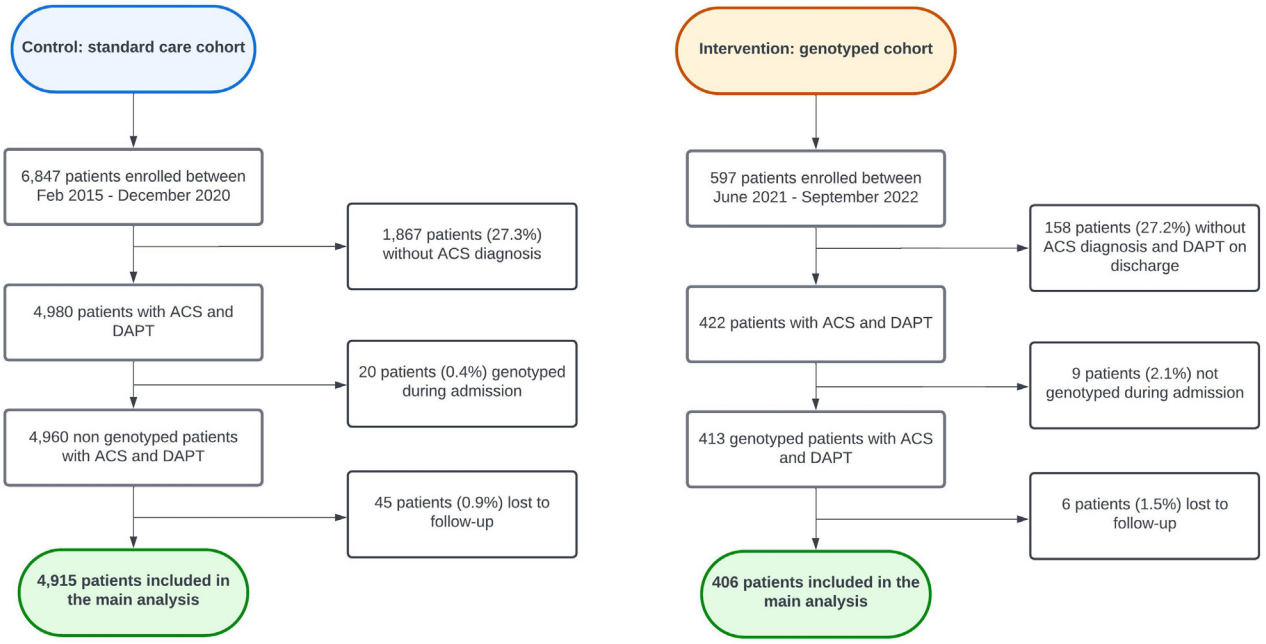
CLINICAL ENDPOINTS. The primary ischemic endpoint was a composite of cardiovascular mortality, myocardial infarction (MI), and stroke. The primary bleeding endpoint was a composite of Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding. The secondary endpoints consisted of all individual endpoints of the primary endpoints and of net adverse clinical events (NACEs) defined as a composite of all-cause mortality, MI, stent thrombosis, stroke, and BARC 3 or 5 bleeding. All patients were monitored for a 1-year follow-up period.

DAPT adherence was analyzed during the follow-up period. This involved categorizing changes in medication adherence into alterations (any change in $P2Y_{12}$ inhibitor) and disruptions (discontinuation of a $P2Y_{12}$ inhibitor therapy longer than 14 days). Data collection focused on the genotyped cohort and a subset of the standard care group for whom complete DAPT adherence data were available.

STATISTICAL METHODS. Continuous variables were reported as median values with IQRs or mean ± SD, whereas categoric variables were described in frequencies and percentages. Comparisons between cohorts (standard care vs genotyped) were made using Mann-Whitney or *t*-tests for continuous variables and chi-square or Fisher exact tests for categoric variables. The primary analyses were performed using the Cox proportional hazards model to calculate the HR and its 95% CI. Possible confounders were included in the multivariable model and were selected based on clinical relevance. Violation of the proportional hazards assumption was evaluated by calculating Schoenfeld residuals. Both primary outcomes were also assessed in 6 subgroups based on sex, age, kidney function, discharge diagnosis, bleeding risk, and diabetes. Kaplan-Meier curves were used for a time-to-event analysis. For sensitivity analysis, we conducted propensity score matching using covariates selected for their clinical relevance and differences at baseline. Matching followed a 1-to-3 protocol without replacement (nearest neighbor method) with a caliper of 0.2 SDs of the logit of the propensity score.

We refrained from testing for statistical significance to mitigate the risk of alpha spending, particularly considering our intention to perform additional analyses based on a predetermined sample in subsequent phases of the study. Consequently, we focused solely on assessing outcome rates and constructing

FIGURE 1 Flowchart of the Study



The standard care cohort consisted of patients enrolled between 2015 and 2020. The genotyped cohort consisted of patients enrolled between 2021 and 2022. For both cohorts, only patients diagnosed with acute coronary syndrome (ACS), treated with dual antiplatelet therapy (DAPT), and not lost to follow-up were selected for the main analysis.

CIs, aimed at determining any potential patterns in outcomes.

All statistical analyses were conducted using SPSS version 26 (IBM Corp) and R studio version 3.6.1 (The R Foundation).

RESULTS

PATIENT CHARACTERISTICS. Among the 6,847 patients enrolled in the registry study between February 2015 and December 2020, 4,915 patients had ACS, were treated with DAPT, did not undergo *CYP2C19* genotyping, and had a complete follow-up. These patients were selected for the standard care cohort. Of the 579 patients enrolled in the study between June 2021 and September 2022, 406 were genotyped, had ACS, were treated with DAPT, and had a complete follow-up. These patients were selected for the genotyped cohort (Figure 1).

The baseline characteristics of the study population are presented in Table 1. The median age in the genotyped cohort was 64 years (Q1-Q3: 55-73 years), whereas in the standard care cohort, it was 66 years (Q1-Q3: 56-74 years). Overall, 27.8% of the patients were women. Patients in the genotyped cohort more often had previous spontaneous bleeding at baseline (10.8% [n = 44/406] vs 4.3% [n = 208/4,915]) and an initial presentation with STEMI (57.6% [n = 234/406] vs 42.4% [n = 2,086/4,915]) compared to patients in the standard care cohort. On the other hand, patients receiving standard care more often had a previous MI (19.9% [n = 57/406] vs 14.0% [n = 975/4,915]), previous PCI (20.5% [n = 1,006/4,915] vs 14.0% [n = 57/406]), atrial fibrillation (3.2% [n = 158/4,915] vs 0.5% [n = 2/406]), peripheral artery disease (6.8% [n = 336/4,915] vs 3.2% [n = 13/406]), and a presentation with either unstable angina pectoris (7.5% [n = 368/4,915] vs 3.0% [n = 12/406]) or non-ST-segment elevation myocardial infarction (47.0% [n = 2,309/4,915] vs 36.2% [n = 147/406]). All other baseline characteristics were similar across the 2 cohorts.

TREATMENT AND MANAGEMENT. The median duration of hospital admission was 3 days (Q1-Q3: 2-5 days) for the standard care cohort vs 3 days (Q1-Q3: 2-4 days) for the genotyped cohort. During the index hospital admission, coronary angiography was performed in 96.6% (n = 392/406) of all genotyped patients and in 96.1% (n = 4,725/4,915) of all standard care patients. Radial access was used in 82.3% (n = 320/389) of the genotyped and 83.8% (n = 2,849/3,401) of the standard care patients. In addition, the

TABLE 1 Baseline Table for the Genotyped Cohort Compared to the Standard Care Cohort

	Genotyped Cohort (n = 406)	Standard Care Cohort (n = 4,915)	*P* Value
Age, y	64.00 (55.25-73.00)	66.00 (56.00-74.00)	0.077
Female	115 (28.3)	1,369 (27.9)	0.884
BMI[a]	27.83 ± 5.00	27.50 ± 4.41	0.153
Current smoking	144 (30.3)	1,488 (35.5)	0.034
Hypertension	202 (49.8)	2,649 (53.9)	0.047
Hypercholesterolemia	341 (84.0)	2,698 (57.5)	<0.001
Diabetes mellitus	80 (19.7)	959 (19.5)	1.000
Medical history			
Previous MI	57 (14.0)	975 (19.9)	0.005
Previous PCI	57 (14.0)	1,006 (20.5)	0.002
Previous CABG	21 (5.2)	347 (7.1)	0.181
Previous stroke	21 (5.2)	377 (7.7)	0.082
Atrial fibrillation	2 (0.5)	158 (3.2)	0.003
Heart failure	4 (1.0)	73 (1.5)	0.552
Renal failure[b]	13 (3.2)	131 (2.7)	0.630
Peripheral artery disease	13 (3.2)	336 (6.8)	0.006
Active malignancy	12 (3.0)	111 (2.3)	0.467
Relevant spontaneous bleeding[c]	44 (10.8)	208 (4.3)	<0.001
Index event diagnosis			
UA	12 (3.0)	368 (7.5)	<0.001
NSTEMI	147 (36.2)	2,309 (47.0)	<0.001
STEMI	234 (57.6)	2,086 (42.4)	<0.001
Semirecent MI[d]	13 (3.2)	152 (3.1)	0.88
OHCA	13 (3.2)	174 (3.5)	0.847
GRACE risk score >140	54 (13.3)	635 (12.9)	0.886
High-bleeding risk (PRECISE-DAPT ≥25)[a]	75 (20.8)	1,030 (22.4)	0.525

Values are median (Q1-Q3), n (%), or mean ± SD. [a]BMI was missing in 5.2% of patients (n = 275), and the PRECISE-DAPT score was missing in 6.9% of all patients. [b]Renal failure was estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 for a duration of 3 months or longer. [c]Relevant spontaneous bleeding was non–intervention-related or nontraumatic bleeding events significant enough to require medical assessment (≥ Bleeding Academic Research Consortium 2). [d]Semirecent MI was MI occurring more than 12 hours before presentation but still influencing the current clinical management of the patient.

BMI = body mass index; CABG = coronary artery bypass grafting; GRACE = Global Registry of Acute Coronary Events; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; OHCA = out-of-hospital cardiac arrest; PCI = percutaneous coronary intervention; PRECISE-DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

genotyped cohort more often underwent PCI (82.0% [n = 333/406]) compared to the standard care cohort (75.5% [n = 3,710/4,915]).

ANTITHROMBOTIC THERAPY. At discharge, clopidogrel was prescribed to 59.4% (n = 241/406) of genotyped patients compared to only 24.6% (n = 1,207/4,915) in the standard care cohort, whereas ticagrelor was prescribed in 40.4% (n = 164/406) of the genotyped cohort and 74.8% (n = 3,674/4,915) of the standard care cohort.

In the genotyped cohort, 265 (65.3%) patients were identified as noncarriers (ultrarapid, rapid, or normal metabolizer), with 88.7% (n = 235) of these patients being successfully treated with clopidogrel (Supplemental Figure 1). The remaining 141 (34.7%) patients of the genotyped patients were classified as loss-of-function allele carriers (intermediate or poor metabolizers), and 95.0% (n = 134/141) of them were discharged with ticagrelor and 0.7% with prasugrel (n = 1/141) (Supplemental Table 1).

In contrast, in the standard care cohort, a majority of patients (74.8% [n = 3,674/4,915]) were treated with ticagrelor, 24.6% (n = 1,207/4,915) were treated with clopidogrel, and only 0.7% with prasugrel (n = 34/4,915). Furthermore, optimal medical therapy consisting of DAPT, an angiotensin-converting enzyme inhibitor or an angiotensin II antagonist, beta blocker, and a lipid-lowering drug was prescribed to 54.2% (n = 220/406) of genotyped and 58.3% (n = 2,864/4,915) of standard care patients. Notably, the use of triple therapy was less common in the genotyped cohort (0.5% [n = 2/406]) compared to the standard care cohort (5.4% [n = 267/4,915]; **Table 2**).

In the genotyped cohort, a switch from one $P2Y_{12}$ inhibitor to another occurred in 7.1% of patients (n = 29/406), whereas this was 16.5% in the standard care cohort (n = 810/4,915; **Table 3**). Disruption of $P2Y_{12}$ inhibitor treatment because of side effects or nonadherence occurred in 2.0% (n = 8/406) of the patients in the genotyped cohort and 1.6% (n = 79/

4,915) in the standard care cohort. Dyspnea was a common reason for $P2Y_{12}$ alteration or disruption and occurred in 3.4% (n = 14/406) of the genotype patients and 6.6% (n = 323/4,915) in the standard care cohort.

OUTCOMES. Primary outcomes. At the 1-year follow-up, the primary ischemic endpoint occurred in 358 (6.7%) patients in the total population (Table 4). The primary bleeding endpoint, consisting of BARC 2, 3, or 5 bleeding at 1 year, occurred in 501 patients (9.4%). NACEs occurred in 9.1% of patients (n = 483/5,321). The primary ischemic endpoint rate was comparable between the genotyped cohort and standard care cohort, even after adjusting for the potential confounders of age, discharge diagnosis, and PCI during index admission (5.2% [n = 21/406] vs 6.9% [n = 337/4,915]; adjusted HR: 0.82; 95% CI: 0.53-1.28). The rate of the primary bleeding endpoint was significantly lower in the genotyped cohort (4.7% [n = 19/406] vs 9.8% [n = 482/4,915]; adjusted HR: 0.47; 95% CI: 0.30-0.76) compared to the standard care cohort. This reduction is mainly driven by BARC 2 bleeding (4.4% [n = 18/406] vs 8.1% [n = 400/4,915]). Kaplan-Meier curve analysis showed congruent results with comparable survival curves for the primary ischemic outcome, whereas the lines for the primary bleeding outcome consistently diverged over time (Figures 2A and 2B).

Secondary outcomes. At the 1-year follow-up, there were no clear differences with regard to the rate of all-cause mortality, cardiovascular mortality, MI, stroke, or stent thrombosis (Table 4). However, the rates for BARC 3 bleeding (0.2% [n = 1/406] vs 1.6% [n = 78/4,915]; adjusted HR: 0.16; 95% CI: 0.02-1.16) and BARC 2 bleeding (4.4% [n = 18/406] vs 8.1% [n = 400/4,915]; adjusted HR: 0.54; 95% CI: 0.34-0.88) were numerically lower in the genotyped cohort compared to the standard care cohort (Table 4). The rate of NACEs was 6.4% (n = 26/406) in the genotyped cohort and 9.3% (n = 457/4,915) in the standard care cohort (adjusted HR: 0.71; 95% CI: 0.48-1.06). BARC 3 or 5 bleeding occurred in 0.2% (n = 1/406) of the genotyped patients and in 1.7% (n = 82/4,915) of patients treated with standard DAPT (adjusted HR: 0.15; 95% CI: 0.02-1.11) as outlined in Table 4 and Supplemental Figure 2 (Central Illustration).

SENSITIVITY ANALYSIS. After propensity score matching, all 406 patients in the genotyped cohort were matched to 1,203 patients in the standard care cohort, which resulted in a more balanced population based on baseline characteristics (Supplemental Tables 2 and 3). Analysis of the primary outcome rates showed robust results with the primary analysis in the unmatched cohorts, showing similar rates for the primary ischemic endpoint (5.2% [n = 21/406] vs 5.7% [n = 69/1,203]; HR: 0.90; 95% CI: 0.54-1.46; Supplemental Table 4) and lower rates for the primary bleeding outcome (4.7% [n = 19/406] vs 13.8% [n = 166/1,203]; HR: 0.33; 95% CI: 0.20-0.52).

In the sensitivity analysis focusing on 370 patients adequately treated according to their *CYP2C19* genotype and compared with 4,915 patients in the

TABLE 2 Procedural and Treatment Characteristics

	Genotyped Cohort (n = 406)	Standard Care Cohort (n = 4,915)	*P* Value
Procedural characteristics			
CAG	392 (96.6)	4,725 (96.1)	0.77
Radial access site[a]	320 (82.3)	2,849 (83.8)	0.49
Femoral access site[a]	69 (17.7)	505 (14.8)	0.15
1-vessel disease	181 (44.6)	1,448 (29.5)	<0.001
2-vessel disease	115 (28.3)	867 (17.6)	<0.001
3-vessel disease	79 (19.5)	751 (15.3)	0.03
PCI	333 (82.0)	3,710 (75.5)	<0.001
DES	311 (93.4)	3,395 (91.5)	0.23
Other/unknown	22 (6.6)	315 (8.5)	
CABG	29 (7.1)	442 (9.0)	0.29
Antithrombotic or anticoagulant therapy			
Acetylsalicylic acid	406 (100)	4,915 (100)	–
$P2Y_{12}$ inhibitor			
Clopidogrel	241 (59.4)	1,207 (24.6)	<0.001
Ticagrelor	164 (40.4)	3,674 (74.8)	<0.001
Prasugrel	1 (0.2)	34 (0.7)	0.46
Oral anticoagulation			
Vitamin K antagonist	1 (0.2)	124 (2.5)	0.006
DOAC	1 (0.2)	144 (2.9)	0.002
DAPT	406 (100)	4,915 (100)	–
Dual therapy[b]	2 (0.5)	267 (5.4)	<0.001
Triple therapy[c]	2 (0.5)	267 (5.4)	<0.001
Other relevant drugs			
ACE inhibitors or AT-II antagonists	296 (72.9)	3,760 (76.5)	0.12
Beta blockers	298 (73.4)	3,696 (75.2)	0.46
Lipid-lowering drugs	385 (94.8)	4,652 (94.6)	0.97
Diuretics	73 (18.0)	1,076 (21.9)	0.08
PPI	390 (96.1)	4,167 (84.8)	<0.001
Optimal medical therapy	220 (54.2)	2,864 (58.3)	0.12

Values are n (%). [a]Data on access site was missing in 28.8% of patients (n = 1,531), 4.1% (n = 17) in the genotyped cohort, and 30.8% (n = 1,514) in the standard of care cohort. [b]Dual therapy was the combination of a single antiplatelet agent (a $P2Y_{12}$ inhibitor) and an anticoagulant. [c]Triple therapy was the concurrent use of aspirin (acetylsalicylic acid), a $P2Y_{12}$ inhibitor, and an anticoagulant.

ACE = angiotensin-converting enzyme; AT-II = angiotensin II; CABG = coronary artery bypass grafting; CAG = coronary angiography; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor.

TABLE 3 Distribution of $P2Y_{12}$ Switches During Follow-Up

	Genotyped Cohort (n = 406)	Standard Care Cohort (n = 4,915)
Alteration	29 (7.1)	810 (16.5)
Disruption	8 (2.0)	79 (1.6)
Dyspnea	14 (3.4)	323 (6.6)

Values are n (%).

TABLE 4 Event Rates of the Primary Endpoints and Individual Components of the Primary Outcomes

	Total (N = 5,321)	Genotyped Cohort (n = 406)	Standard Care Cohort (n = 4,915)	Adjusted HRs[a] HR (95% CI)
Primary ischemic endpoint	358 (6.7)	21 (5.2)	337 (6.9)	0.82 (0.53-1.28)
NACEs	483 (9.1)	26 (6.4)	457 (9.3)	0.71 (0.48-1.06)
Primary bleeding outcome	501 (9.4)	19 (4.7)	482 (9.8)	0.47 (0.30-0.76)
All-cause mortality	138 (2.6)	9 (2.2)	129 (2.6)	0.91 (0.46-1.81)
Cardiovascular mortality	82 (1.5)	5 (1.2)	77 (1.6)	0.88 (0.35-2.18)
Myocardial infarction	220 (4.1)	12 (3.0)	208 (4.2)	0.77 (0.43-1.38)
Stroke	82 (1.5)	6 (1.5)	76 (1.5)	1.03 (0.45-2.39)
Stent thrombosis	50 (0.9)	1 (0.2)	49 (1.0)	0.20 (0.03-1.46)
BARC 3 or 5 bleeding	83 (1.6)	1 (0.2)	82 (1.7)	0.15 (0.02-1.11)
BARC 5 bleeding	4 (0.1)	0 (0.0)	4 (0.1)	–
BARC 3 bleeding	79 (1.5)	1 (0.2)	78 (1.6)	0.16 (0.02-1.16)
BARC 2 bleeding	418 (7.9)	18 (4.4)	400 (8.1)	0.54 (0.34-0.88)

Values are n (%) unless otherwise indicated. [a]HRs are adjusted for age, discharge diagnosis, and percutaneous coronary intervention during index admission.
BARC = Bleeding Academic Research Consortium; NACE = net adverse clinical event(s).

standard care cohort, we observed consistent results with the primary analysis for the primary ischemic outcome (4.9% [n = 18/370] vs 6.9% [n = 337/4,915]; adjusted HR: 0.78; 95% CI: 0.49-1.26). A similar reduction was noted for the primary bleeding outcome with rates of 4.9% (n = 18/406) in the genotype-guided group compared to 9.8% (n = 482/4,915) in the standard care cohort (adjusted HR: 0.50; 95% CI: 0.31-0.81; Supplemental Table 5). Additionally, a sensitivity analysis was performed comparing 370 genotype-guided patients with 3,674 ticagrelor-only treated patients in the standard care cohort. Baseline characteristics were now more comparable between both groups (Supplemental Tables 6 and 7). Clinical outcomes still indicated a similar rate of the primary ischemic endpoint in the genotype-guided group compared to the ticagrelor-only treated group (4.9% [n = 18/370] vs 5.9% [n = 215/3,674]; adjusted HR: 0.84; 95% CI: 0.52-1.37; Supplemental Table 8), whereas the primary bleeding outcome rate was again lower (4.9% [n = 18/370] vs 8.8% [n = 323/3,674]; adjusted HR: 0.55; 95% CI: 0.34-0.89) with a similar observation for NACEs (5.9% [n = 22/370] vs 8.0% [n = 295/3,674]; adjusted HR: 0.72; 95% CI: 0.47-1.11).

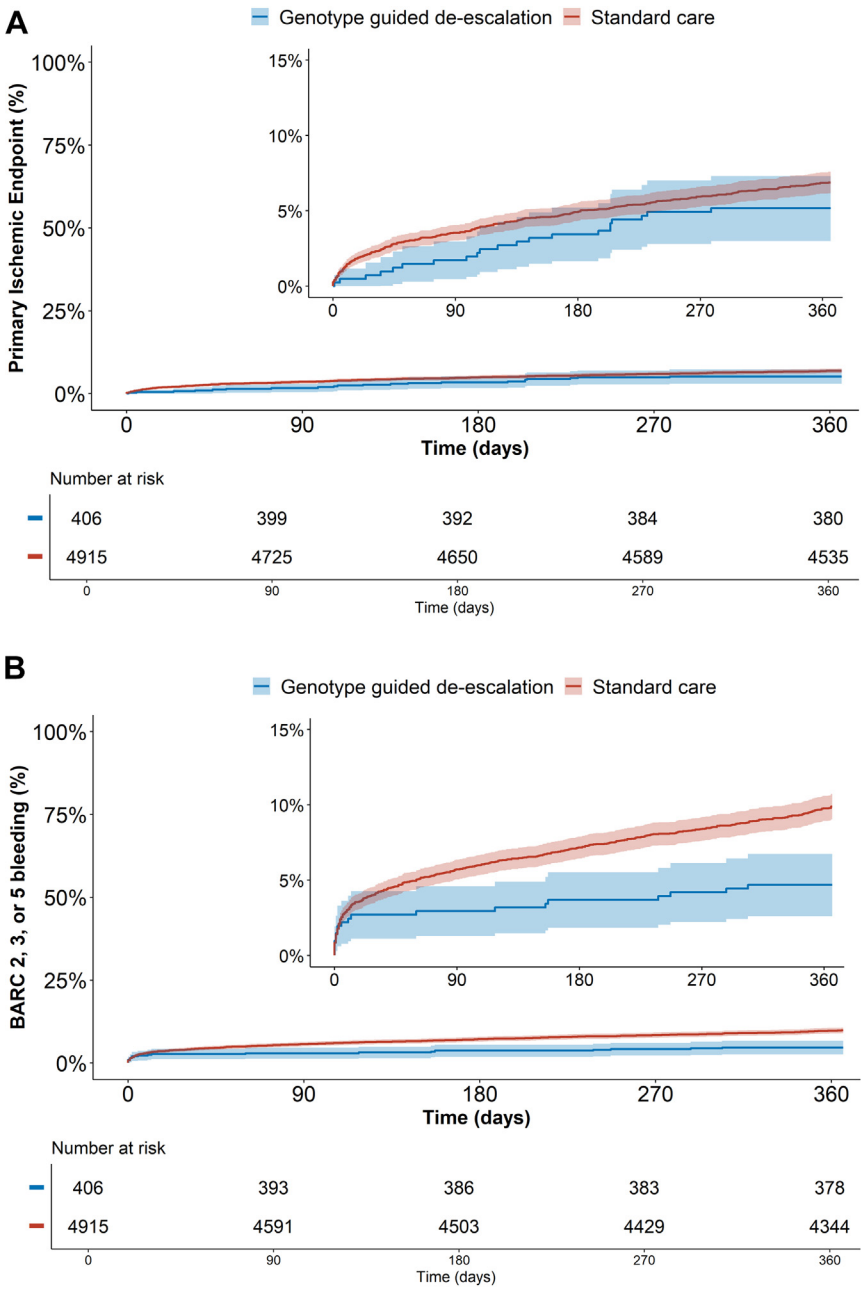
Analyses of the primary outcomes were performed in 6 subgroups (Supplemental Figures 3 and 4). Although the results were generally consistent with those in the whole cohort, the results for the primary ischemic endpoint in the sex and diabetes subgroups seemed to be discordant.

DISCUSSION

In this large prospective observational registry, we assessed the impact of a *CYP2C19* genotype-guided de-escalation strategy on the rate of bleeding and ischemic events in patients with ACS treated with DAPT. The main findings suggest that genotype-guided de-escalation is associated with a lower bleeding rate, whereas it did not seem to result in an opposing increased rate of ischemic events. These findings support the potential safety and efficacy of a genotype-guided approach to DAPT de-escalation in an all-comers ACS population.

Our study shows a near 50% lower rate of BARC 2, 3, or 5 bleeding in the genotyped cohort compared to the standard care cohort, with consistent results after propensity score matching and several other sensitivity analyses. Additionally, we did not observe an increase in ischemic event rates despite the more frequent use of the less potent clopidogrel, which aligns with a meta-analysis showing comparable efficacy with clopidogrel compared to ticagrelor/prasugrel in patients without a *CYP2C19* loss-of-function allele.[21] Our findings are consistent with the results of the POPular Genetics trial and provide additional real-world evidence for the beneficial impact on bleeding risk because of a *CYP2C19* genotype-guided antiplatelet therapy.[20] The POPular Genetics trial enrolled 2,488 STEMI patients and found a 22% decrease in major or minor bleeding events in the genotype-guided group (9.8% vs 12.5%; HR: 0.78; 95% CI: 0.61-0.98) and a lower numerical rate for the combined ischemic outcome of cardiovascular death, MI, definite stent thrombosis, or stroke (2.7% vs 3.3%; HR: 0.83; 95% CI: 0.53-1.31). Compared to the patients enrolled in the POPular Genetics trial, the patients in the current analysis were older, more often presented with non-ST-segment elevation myocardial infarction, and had more comorbidities and more complex medical backgrounds, which can explain the higher ischemic event rates in the current analysis. On the other hand, POPular Genetics exclusively enrolled patients treated with PCI, and the rates for the femoral access sites were higher, which may explain the higher bleeding rates in the POPular Genetics population compared to the event rates in this analysis. Of interest is that, similar to the POPular Genetics trial, the reduction in bleeding was mainly driven by minor bleeding (defined as BARC 2).

FIGURE 2 **Kaplan-Meier Curves for the Primary Ischemic and Bleeding Endpoint**

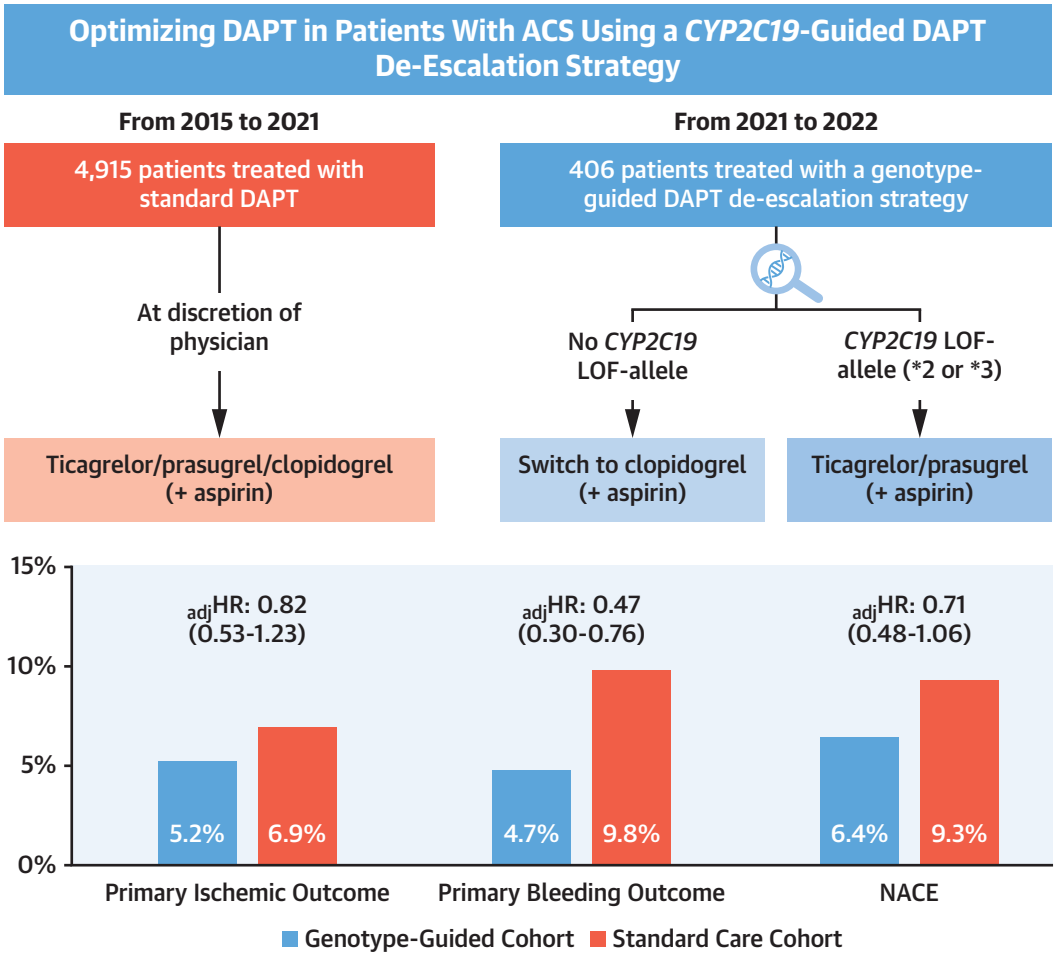


Kaplan-Meier curves for the cumulative incidence of (A) the primary ischemic endpoint (composite of cardiovascular mortality, myocardial infarction, or stroke) showing a comparable event rate between the genotyped cohort (blue) and the standard care cohort (red) and (B) the primary bleeding endpoint (Bleeding Academic Research Consortium [BARC] 2, 3, or 5 bleeding) demonstrating lower bleeding rates in the genotyped cohort (blue) with diverging curves over time compared to the standard care cohort (red).

Previous studies have underlined the clinical relevance for these bleeding events, showing that even minor bleeding events are linked to an increased risk of mortality.[8,25,26] In addition, bleeding continues to represent the most common noncardiac adverse event after PCI and is also associated with morbidity, prolonged hospitalization, and incremental costs.[26]

Furthermore, it is important to consider the temporal distribution of our patient cohorts. Although there is no immediate rationale to suggest significant

CENTRAL ILLUSTRATION Main Results Using a *CYP2C19*-Guided DAPT De-Escalation Strategy



Azzahhafi J, et al. JACC Cardiovasc Interv. 2024;17(17):1996-2007.

differences between patients treated before and after 2021, this time frame could be a contributing factor to the observed variances. The post-2021 cohort, potentially more aligned with updated guideline-based treatment and risk score-driven management, might have undergone a more individualized assessment of bleeding risks, thereby influencing the choice of $P2Y_{12}$ therapy. However, this aspect was not directly examined in our study.

The TAILOR-PCI (Tailored Antiplatelet Initiation to Lessen Outcomes due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention) also evaluated ticagrelor vs clopidogrel in patients with ACS or chronic coronary syndrome requiring PCI. This study compared the efficacy and safety of an escalation strategy in the subset of patients with at least 1 loss-of-function allele. The authors reported no significant difference in major or minor bleeding between the genotype-guided group and conventional therapy after 12 months (HR: 1.22; 95% CI: 0.60-2.51; $P = 0.58$).[27] In contrast to our de-escalation approach, Beitelshees et al[28] conducted a study across 9 medical centers investigating an escalation strategy in a real-world setting. This retrospective analysis found no significant difference in bleeding events between loss-of-function allele carriers who

were escalated from clopidogrel to prasugrel or ticagrelor. Furthermore, at the University of North Carolina at Chapel Hill, where a genotype-guided therapy was implemented, a subgroup of 316 patients initiated treatment with ticagrelor or prasugrel.[29] Among these, 69 patients (21.8%) were de-escalated to clopidogrel. Nonetheless, the analysis showed no significant difference in major adverse cardiovascular or cerebrovascular events or clinically significant bleeding between standard care and de-escalation groups, although the small number of events limited the study's power to detect such differences.

Building on these observed advantages regarding safety and efficacy, it is pertinent to also highlight the broader implications of our findings. First, the ability to de-escalate the $P2Y_{12}$ inhibitor in 60% to 70% of patients from a strong and more expensive $P2Y_{12}$ inhibitor to the cheap and safer clopidogrel (in loss-of-function allele noncarriers) is an important finding. Our findings, supplemented by previous feasibility analysis, demonstrate that the majority of noncarriers were effectively transitioned to clopidogrel within 24 hours, affirming the practical implementation of genotype-guided therapy in a real-world clinical setting.[23] Second, this switch has been shown to also decrease health care costs as shown in the POPular Genetics cost-effectiveness analysis.[30,31] Third, rapid (median turnaround time of 6.3 hours) and reliable (point-of-care) genetic tests facilitate the implementation of personalized antiplatelet therapy without delaying treatment commencement.[23]

STUDY LIMITATIONS. First, there is a potential for temporal bias because the genotyped cohort represents a more recent cohort (2021-2022) compared to the standard care cohort, which spans from 2015 to 2020. This difference in time frames could have influenced the outcomes because of evolving clinical practices and advancements in treatment. We sought to mitigate this through adjustments for confounders regarding treatment in the Cox proportional hazards model. Continuing using genotype de-escalation in our registry will make it possible to substantiate or refute our findings in the future. Second, the patients in the genotyped cohort who were not de-escalated were included in the primary analysis to represent the real-world situation. This inclusion might have introduced variability in our findings. However, we performed sensitivity analyses, confirming the robustness of our primary findings. Third, the primary endpoint consisting of BARC 2, 3, or 5 bleeding events and the ischemic endpoints of cardiovascular mortality, MI, or stroke may seem disproportionate because BARC 2 bleedings are not clinically equivalent to the other severe ischemic events. However, this comparison is standard in larger randomized controlled trials, offering a context for interpretation, and earlier studies showed that BARC 2 bleeding is associated with higher morbidity, mortality, and incremental costs.[8,26,32] Fourth, it is important to highlight that in the Netherlands the predominant use of ticagrelor or prasugrel as a $P2Y_{12}$ inhibitor necessitates a focus on de-escalation strategies. Consequently, our findings centered on this approach may not be directly applicable to settings in which clopidogrel is the mainstay of treatment and escalation strategies are more common. This regional practice pattern must be considered when extrapolating our results to different international contexts in which treatment protocols may vary significantly. Importantly, our study was not powered to definitively demonstrate noninferiority for ischemic events or superiority for bleeding events, necessitating further research with a larger sample size for conclusive results.

CONCLUSIONS

In an all-comers ACS population, a *CYP2C19* genotype-guided de-escalation strategy showed no increase in ischemic events and a lower rate of bleeding compared to a standard DAPT regimen. These findings underline the improved safety of implementing a genotype-guided de-escalation strategy in clinical practice without affecting efficacy and support a more extensive clinical adoption.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The FORCE-ACS registry is supported by grants from ZonMw, the St. Antonius Research Fund, and AstraZeneca. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents. Dr Vlachojannis has received institutional research grants from MicroPort and Ferrer; and has received personal fees from Terumo and AstraZeneca. Dr Appelman has received an institutional research grant from the Dutch Heart Foundation. Dr Henriques has received institutional research grants from Abbott Vascular, AstraZeneca, B. Braun, Getinge, Ferrer, Infraredx, and ZonMw. Dr Kikkert has received an institutional research grant from AstraZeneca. Dr ten Berg has received institutional research grants from AstraZeneca, Daiichi-Sankyo, and ZonMw; and has received personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, CeleCor Therapeutics, Daiichi-Sankyo, Eli Lilly, Ferrer, and Idorsia. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Jaouad Azzahhafi, Department of Cardiology, St. Antonius Ziekenhuis, Koekoekslaan 1, 3435 CM, Nieuwegein, the Netherlands. E-mail: j.azzahhafi@antoniusziekenhuis.nl.

PERSPECTIVES

WHAT IS KNOWN? The POPular Genetics trial demonstrated that a genotype-guided de-escalation strategy in a selected ST-segment elevation myocardial infarction population was noninferior to standard antiplatelet therapy with ticagrelor or prasugrel with respect to thrombotic events and resulted in a lower incidence of bleeding. Additionally, previous work indicated that *CYP2C19* genotype-guided de-escalation is feasible in an all-comers ACS population with short turnaround times and high physician adherence.

WHAT IS NEW? This study confirms that the implementation of a genotype-guided de-escalation strategy in patients with ACS did not result in a numerical increase in ischemic events, whereas it was associated with lower rates of the primary bleeding outcome.

WHAT IS NEXT? The current study, although not powered to demonstrate a significant advantage in reducing bleeding or proving noninferiority regarding ischemia, sets the stage for further large-scale research. Future studies with larger sample sizes are essential to confirm these findings, potentially establishing genotype-guided therapy as a standard for safely reducing bleeding risk in ACS patients.

REFERENCES

1. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur J Cardiothorac Surg*. 2017;53:34–78.

2. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44(38):3720–3826. https://doi.org/10.1093/eurheartj/ehad191

3. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.

4. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.

5. Wijns W, Steg PG, Mauri L, et al. Endeavour zotarolimus-eluting stent reduces stent thrombosis and improves clinical outcomes compared with cypher sirolimus-eluting stent: 4-year results of the PROTECT randomized trial. *Eur Heart J*. 2014;35:2812–2820.

6. Yoshikawa Y, Shiomi H, Morimoto T, et al. Stent-related adverse events as related to dual antiplatelet therapy in first- vs second-generation drug-eluting stents. *JACC Asia*. 2021;1:345–356.

7. Urban P, Gregson J, Owen R, et al. Assessing the risks of bleeding vs thrombotic events in patients at high bleeding risk after coronary stent implantation: the ARC-high bleeding risk trade-off model. *JAMA Cardiol*. 2021;6:410–419.

8. Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *Eur Heart J*. 2016;38:804–810.

9. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381:2032–2042.

10. Costa F, Van Klaveren D, Feres F, et al. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. *J Am Coll Cardiol*. 2019;73:741–754.

11. Vranckx P, White HD, Huang Z, et al. Validation of BARC bleeding criteria in patients with acute coronary syndromes the TRACER trial. *J Am Coll Cardiol*. 2016;67:2135–2144.

12. Valgimigli M, Frigoli E, Heg D, et al. Dual antiplatelet therapy after PCI in patients at high bleeding risk. *N Engl J Med*. 2021;385:1643–1655.

13. Hahn JY, Song Y Bin, Oh JH, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA*. 2019;321:2428–2437.

14. Watanabe H, Domei T, Morimoto T, et al. 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: the STOPDAPT-2 randomized clinical trial. *JAMA*. 2019;321:2414–2427.

15. Kim CJ, Park MW, Kim MC, et al. Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): an investigator-initiated, open-label, multicentre, non-inferiority, randomised trial. *Lancet*. 2021;398:1305–1316.

16. Kheiri B, Abdalla A, Osman M, et al. Personalized antiplatelet therapy in patients with coronary artery disease undergoing percutaneous coronary intervention: a network meta-analysis of randomized clinical trials. *Catheter Cardiovasc Interv*. 2019;94:181–186.

17. Cavallari LH. Genetic determinants of P2Y(12) inhibitors and clinical implications. *Interv Cardiol Clin*. 2020;6:141–149.

18. Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet*. 2010;376:1320–1328.

19. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA*. 2010;304:1821–1830.

20. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral P2Y 12 inhibitors in primary PCI. *N Engl J Med*. 2019;381:1621–1631.

21. Pereira NL, Rihal C, Lennon R, et al. Effect of CYP2C19 genotype on ischemic outcomes during oral P2Y12 inhibitor therapy: a meta-analysis. *JACC Cardiovasc Interv*. 2021;14:739–750.

22. Chan Pin Yin DRPPPP, Vos G-JAJA, van der Sangen NMRR, et al. Rationale and design of the Future Optimal Research and Care Evaluation in Patients with Acute Coronary Syndrome (FORCE-ACS) registry: towards "personalized medicine" in daily clinical practice. *J Clin Med*. 2020;9:E3173.

23. Azzahhafi J, van den Broek WWA, Chan Pin Yin DRPP, Harmsze AM, van Schaik RHN, Ten Berg JM. The clinical implementation of CYP2C19 genotyping in patients with an acute coronary syndrome: insights from the FORCE-ACS registry. *J Cardiovasc Pharmacol Ther*. 2023;28:10742484231210704.

24. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12:1495–1499.

25. Mehran R, Pocock S, Nikolsky E, et al. Impact of bleeding on mortality after percutaneous coronary intervention: results from a patient-level pooled analysis of the REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to Reduced

Clinical Events), ACUITY (Acute Catheterization and Urgent In. *JACC Cardiovasc Interv*. 2011;4:654–664.

26. Piccolo R, Oliva A, Avvedimento M, et al. Mortality after bleeding versus myocardial infarction in coronary artery disease: a systematic review and meta-analysis. *EuroIntervention*. 2021;17:550–560.

27. Pereira NL, Farkouh ME, So D, et al. Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. *JAMA*. 2020;324:761–771.

28. Beitelshees AL, Thomas CD, Empey PE, et al. CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention in diverse clinical settings. *J Am Heart Assoc*. 2022;11:e024159.

29. Martin J, Williams AK, Klein MD, et al. Frequency and clinical outcomes of CYP2C19 genotype-guided escalation and de-escalation of antiplatelet therapy in a real-world clinical setting. *Genet Med*. 2020;22:160–169.

30. Limdi NA, Cavallari LH, Lee CR, et al. Cost-effectiveness of CYP2C19-guided antiplatelet therapy in patients with acute coronary syndrome and percutaneous coronary intervention informed by real-world data. *Pharmacogenomics J*. 2020;20:724–735.

31. Claassens DMF, van Dorst PWM, Vos GJA, et al. Cost effectiveness of a cyp2c19 genotype-guided strategy in patients with acute myocardial infarction: results from the POPular genetics trial. *Am J Cardiovasc Drugs*. 2022;22(2):195–206. https://doi.org/10.1007/s40256-021-00496-4

32. Giustino G, Mehran R, Dangas GD, et al. Characterization of the average daily ischemic and bleeding risk after primary PCI for STEMI. *J Am Coll Cardiol*. 2017;70:1846–1857.

KEY WORDS acute coronary syndrome(s), *CYP2C19*, dual antiplatelet therapy, genotype-guided therapy

APPENDIX For supplemental tables and figures, please see the online version of this paper.