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ORIGINAL ARTICLE
Thrombosis and antithrombotic therapy

Ticagrelor 60 vs. 90 mg in elderly ACS patients undergoing PCI: a randomized, crossover trial

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Aims Although dual antiplatelet therapy with aspirin and a potent $P2Y_{12}$ receptor inhibitor is currently recommended in patients with acute coronary syndrome (ACS), its use in elderly patients remains challenging. The aim of this trial is to evaluate the pharmacodynamic and pharmacokinetic profile of ticagrelor 60 vs. 90 mg twice daily among elderly patients (≥75 years) with ACS undergoing percutaneous coronary intervention (PCI).

Methods and results PLINY The ELDER (NCT04739384) was a randomized, crossover trial testing the non-inferiority of a lower vs. standard dose of ticagrelor with respect to the primary endpoint of $P2Y_{12}$ inhibition as determined by pre-dose $P2Y_{12}$ reaction units (PRU) using the VerifyNow-$P2Y_{12}$ (Accumetrics, San Diego, CA, USA). Other pharmacodynamic tests included light transmittance aggregometry, multiple electrode aggregometry, and response to aspirin. Plasma levels of ticagrelor and its active metabolite AR-C124910XX were also evaluated. A total of 50 patients (mean age 79.6 ± 4.0 years, females 44%) were included in the trial. Ticagrelor 60 mg was non-inferior to ticagrelor 90 mg according to VerifyNow-$P2Y_{12}$ results (PRU 26.4 ± 32.1 vs. 30.4 ± 39.0; least squares mean difference: −4; 95% confidence interval: −16.27 to 8.06; P for non-inferiority = 0.002). Other pharmacodynamic parameters were similar between the two ticagrelor doses and there were no differences in response to aspirin. Plasma levels of ticagrelor (398.29 ± 312.36 ng/mL vs. 579.57 ± 351.73 ng/mL, $P = 0.006$) and its active metabolite were significantly lower during treatment with ticagrelor 60 mg.

Conclusion Although plasma concentrations were lower, ticagrelor 60 mg twice daily provided a similar magnitude of platelet inhibition compared with ticagrelor 90 mg twice daily among elderly patients undergoing PCI.

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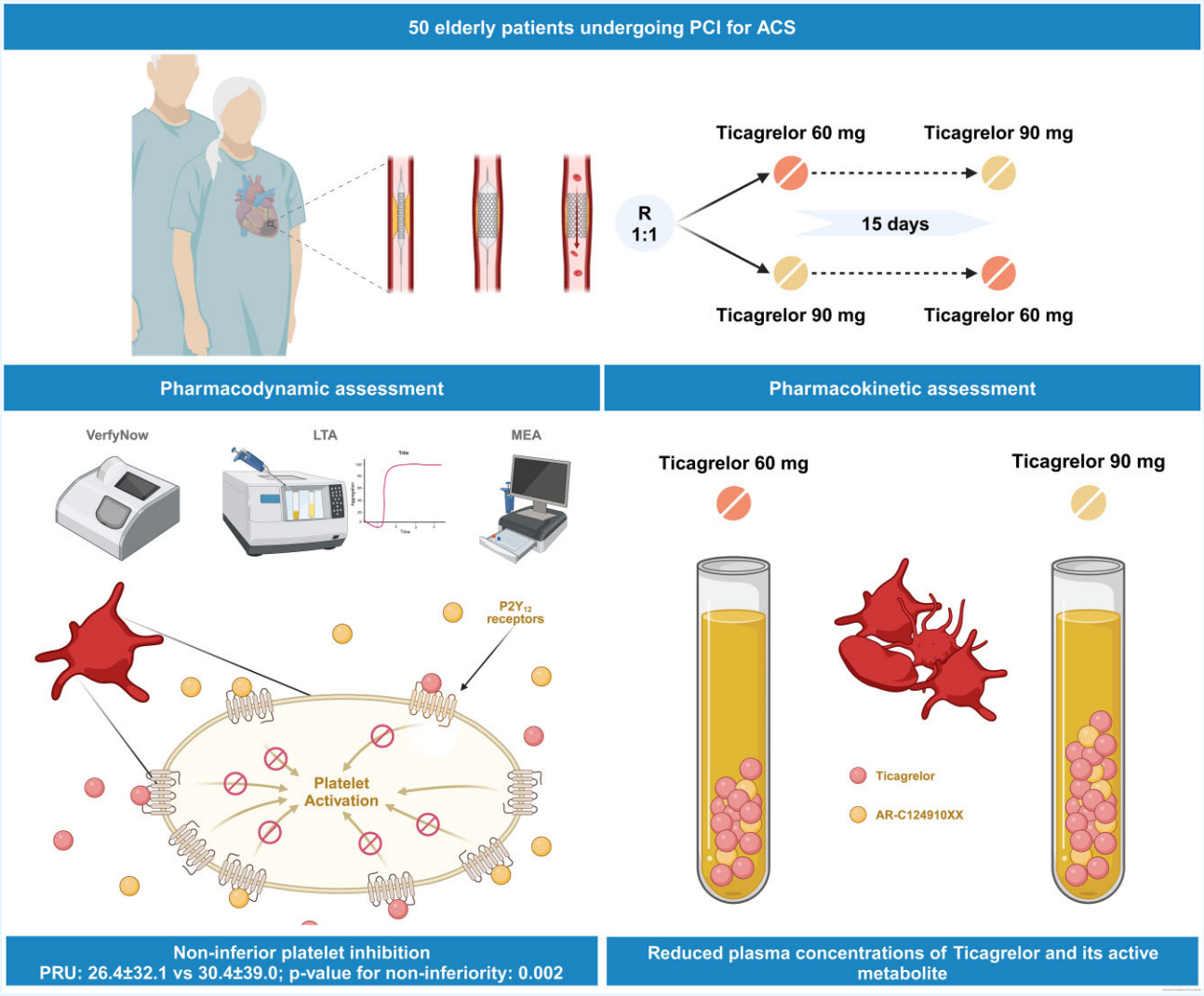
Graphical Abstract



Inhibition of platelet reactivity following ticagrelor 60 mg vs. 90 mg in elderly patients (≥75 years) undergoing PCI for ACS.

A total of 50 older patients with ACS undergoing PCI were randomized to ticagrelor 60 mg vs. 90 mg twice daily. Platelet reactivity was similar and non-inferior between the two ticagrelor maintenance doses, although plasma drug concentrations were significantly lower during treatment with ticagrelor 60 mg. ACS, acute coronary syndrome; LTA, light transmittance aggregometry; MEA, multiple electrode aggregometry; PCI, percutaneous coronary intervention; PRU, $P2Y_{12}$ reaction units.

Keywords P2Y12 • Antiplatelet therapy • Ticagrelor • Elderly

Introduction

Elderly individuals account for about one third of patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).[1] Their representation is rapidly increasing in view of the demographic shift in the population age and the growing preference for PCI over medical therapy in older patients. Dual antiplatelet therapy (DAPT), including aspirin and an oral $P2Y_{12}$ receptor inhibitor, remains the default strategy for antithrombotic therapy during the early phase of ACS.[2] However, there is consistent evidence showing that elderly patients undergoing PCI are exposed to a substantial risk of bleeding and ischaemic events due to additional comorbidities and frailty.[3,4] Given that bleeding events, especially major complications, are associated with a risk of death comparable to ischaemic events, minimizing haemorrhagic complications while retaining ischaemic efficacy could improve the net clinical benefit of antithrombotic therapy.[5] Strategies to reduce DAPT-related bleeding include abbreviation of DAPT duration and de-escalation of DAPT intensity, consisting of a guided or unguided downgrading from a potent to a less potent $P2Y_{12}$ receptor inhibitor (e.g. from prasugrel or ticagrelor to clopidogrel)

or to a reduced dose of the same potent $P2Y_{12}$ receptor inhibitor (e.g. from prasugrel 10 mg to prasugrel 5 mg daily or from ticagrelor 90 mg to ticagrelor 60 mg twice a day).[6] Recently, many studies and consensus documents focused on the potential advantages of DAPT de-escalation.[7] However, de-escalation of potent $P2Y_{12}$ inhibitors has been tested only for prasugrel,[8] whereas a reduced dose of ticagrelor (60 mg twice daily) has been evaluated solely during the longstanding phase after acute myocardial infarction.[9] Therefore, it remains unknown whether the 60-mg dose of ticagrelor provides adequate platelet inhibition compared with the 90-mg dose in the acute period after ACS. In this proof-of-concept trial, we compared the pharmacodynamic and pharmacokinetic profile of ticagrelor 60 mg twice daily vs. ticagrelor 90 mg twice daily in elderly patients with ACS undergoing PCI.

Methods

Study design and patients

PLINY THE ELDER (PLatelet INhibition with two different doses of potent P2y12 inhibitors in THE ELDERly population) was an investigator-initiated, single-centre, non-inferiority, open-label, two-by-two crossover, randomized clinical trial, testing the level of platelet inhibition with ticagrelor 60 mg twice daily compared with ticagrelor 90 mg twice daily in elderly patients with ACS undergoing PCI (ClinicalTrials.gov NCT04739384). The design of this study has been described previously.[10] Patients were eligible if they were aged 75 years or more, underwent successful PCI for non-ST-segment elevation ACS or ST-elevation myocardial infarction, and received a loading dose of ticagrelor of 180 mg. The principal exclusion criteria were indication to oral anticoagulant therapy, concomitant use of glycoprotein IIb/IIIa inhibitors or fibrinolytic agents, active bleeding, severe anaemia, and chronic kidney disease at stage 4 or 5 (estimated glomerular filtration rate less than 30 mL/min/1.73 m^2). The complete list of inclusion and exclusion criteria is reported in the Supplementary material online, Appendix. The crossover trial had 2-sequence and 2-period with patients randomized to either ticagrelor 60 mg twice daily (day 1–14) followed by ticagrelor 90 mg twice daily (day 15–28) or ticagrelor 90 mg twice daily (day 1–14) followed by ticagrelor 60 mg twice daily (day 15–28). A low dose aspirin (100 mg daily) was used in all patients. After the trial period, patients resumed their initial antiplatelet regimen if still indicated (ticagrelor 90 mg twice daily).

The study adhered to the ethical principles outlined in the Declaration of Helsinki, the specifications of the International Conference of Harmonization, and the guidelines of Good Clinical Practice. The study protocol was approved by the Italian Medicines Agency (EudraCT 2019-002391-13) and the Medical Ethics Committee of the University of Naples 'Federico II'. All patients provided written informed consent.

Blood sampling

Blood sampling to evaluate adenosine diphosphate (ADP) and non-ADP platelet aggregation was performed at three time points: (i) time 1 (baseline): before randomization; (ii) time 2 (crossover): 14 days after randomization, including 2 samples, before and 2 h after the last dose of the initial assigned treatment; (iii) time 3 (end of study): 28 days after randomization, including 2 samples, before and 2 h after the last dose of the second assigned treatment.

Pharmacodynamic assessment

Platelet function was assessed by using the VerifyNow, light transmittance aggregometry (LTA), and multiple electrode aggregometry (MEA).

The VerifyNow-$P2Y_{12}$ (Accumetrics, San Diego, CA, USA) measures ADP-induced platelet agglutination as an increase in light transmittance and utilizes a proprietary algorithm to report values as $P2Y_{12}$ reaction units (PRU), % inhibition, and baseline value (BASE) for platelet function. In general, a higher PRU result reflects an increased $P2Y_{12}$-mediated platelet reactivity, and, based on experts consensus, high platelet reactivity (HPR) is defined as PRU >208. The VerifyNow Aspirin (CPT 85576) is a qualitative test for the detection of aspirin-induced platelet dysfunction. The test is reported in Aspirin Reaction Units (ARU). The therapeutic range for platelet function is 350–549 ARU while the non-therapeutic range for platelet function is 550–700 ARU.

LTA uses a dual channel lumi-aggregometer (model 700; Chrono-Log, Havertown, PA). Platelet-rich plasma was obtained by whole blood sample centrifugation at 150 g for 15 min, and, after its extraction, platelet-poor plasma was obtained by re-centrifugation of blood tubes at 1500 g for 10 min. After ADP (5 and 20 μmol/L), acid arachidonic (1 μmol/L) and thrombin receptor activating peptide (TRAP) (15 μmol/L) in addition as a pro-aggregatory stimulus, platelet aggregation was monitored at 37°C with constant stirring (1200 rpm) and measured as the increase in light transmission for 6 min. LTA results are reported as a percentage of maximum platelet aggregation (MPA) and HPR is defined as MPA >59% (LTA 20 μmol/L ADP) and MPA >46% (LTA 5 μmol/L ADP).

MEA is assessed in whole blood by the Multiplate analyzer (Roche-Dynabyte Medical, Munich, Germany). Platelet aggregation was measured after addition of agonists in the whole blood. After dilution of 300 μL of hirudin-anticoagulated whole blood with 0.9% NaCl solution for 3 min at 37°C, 20 μL of ADP test was added. For non-ADP-induced pathways, different tests were performed: aspirin and thrombin receptor-activating peptide. Platelet aggregation was recorded for 6 min and the mean values of 2 independent determinations were reported as AUC (area under curve) in arbitrary units. HPR is defined as AUC >46 U.

Pharmacokinetic assessment

Plasma levels of ticagrelor and its active metabolite AR-C124910XX were evaluated to determine the pharmacokinetic profile of ticagrelor 60 and 90 mg. Approximately 30% of ticagrelor-induced platelet inhibition derives from its active metabolite AR-C124910XX, generated through cytochrome P450 3A4, which is at least as potent at the $P2Y_{12}$ receptor as ticagrelor. Hence, the pharmacokinetic profile was determined by measuring plasma concentrations of both ticagrelor and its metabolite using high performance liquid chromatography-tandem mass spectrometry.

Study endpoints

The primary endpoint of the trial was the pre-dose PRU using the VerifyNow-$P2Y_{12}$ at 14 days after treatment with ticagrelor 60 or 90 mg twice daily. Secondary endpoints included HPR status by VerifyNow-$P2Y_{12}$, ADP-induced platelet reactivity (and HPR status) measured by LTA and MEA, non-ADP-induced platelet reactivity by MEA, and plasma level of ticagrelor and its active metabolite AR-C124910XX. Clinical outcomes of interest were all-cause and cardiovascular death, myocardial infarction, unstable angina, any revascularization, urgent target-lesion revascularization, stroke, and bleeding events according to the BARC scale. All clinical events were adjudicated by an independent clinical event committee blinded to the randomization arm.

Randomization and masking

Randomization was allowed between 1 and 3 days after PCI and was conducted via a website (RedCap) using a computer-generated sequence with variable block sizes of 2 or 4. The sequence of block sizes was also randomly generated to further enforce concealment. Patients and treating physicians were aware of group allocations, whereas personnel performing pharmacodynamic and pharmacokinetic testing were masked to the assigned treatment.

Statistical analysis

The study was designed to show the non-inferiority of ticagrelor 60 mg twice daily vs. ticagrelor 90 mg twice daily with respect to the primary endpoint of pre-dose PRU. Based on prior data from the PEGASUS-TIMI

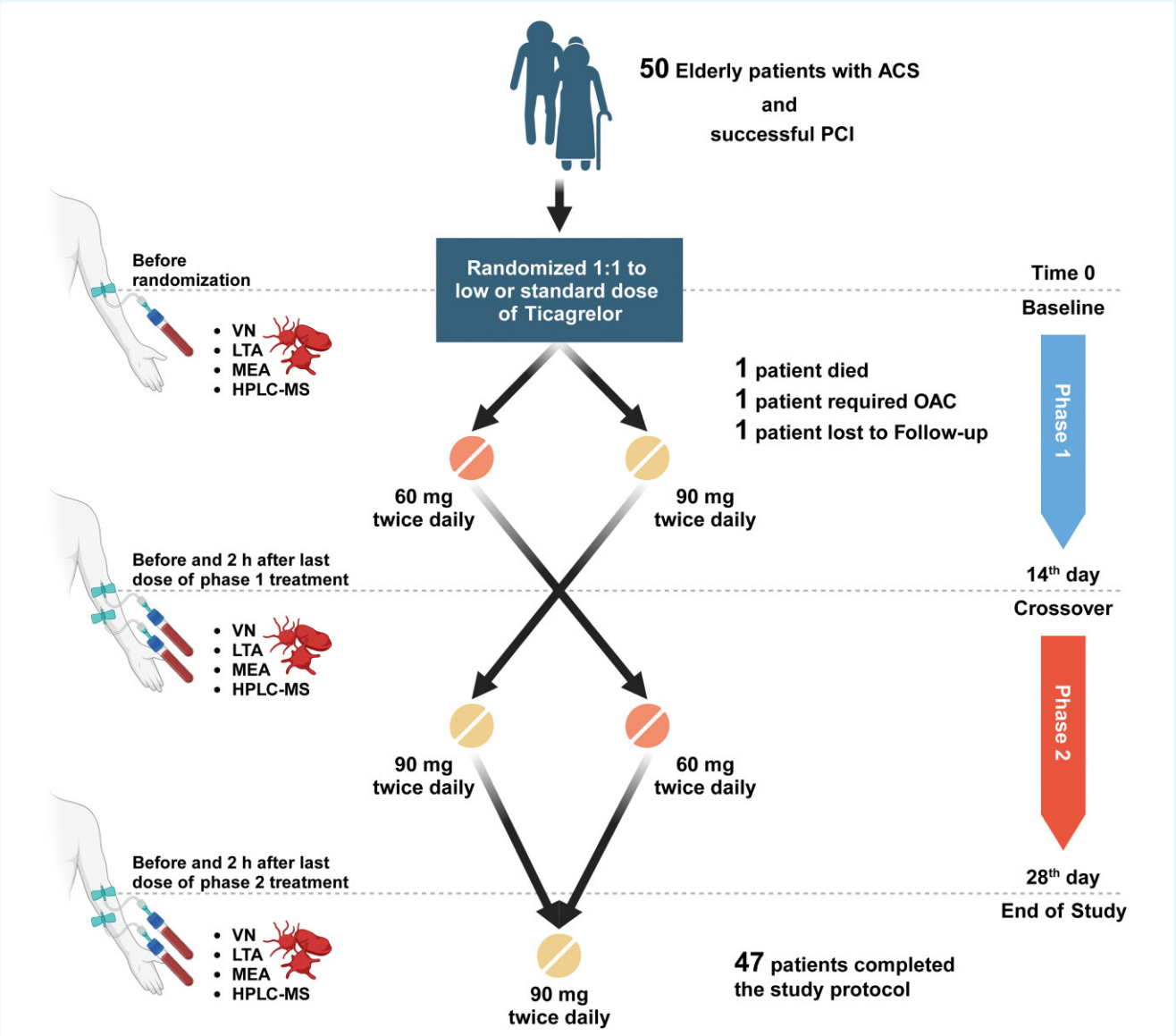


Figure 1 Study flow chart of the Pliny the Elder trial. Crossover characteristics of the study with the number of participants and dropouts. Times and characteristics of blood samples performed are also illustrated on the left. ACS, acute coronary syndrome; HPLC-MS, high performance liquid chromatography-tandem mass spectrometry; LTA, light transmittance aggregometry; MEA, multiple electrode aggregometry; OAC, oral anti-coagulant; PCI, percutaneous coronary intervention; VN, VerifyNow.

54 trial,[11] we assumed standard deviation of the pre-dose of PRU of 50 in the control arm and estimated that a total sample size of 50 patients would provide more than 90% power to show the non-inferiority of ticagrelor 60 mg twice daily compared with ticagrelor 90 mg twice daily with a margin of 15 PRU and an alpha error of 0.05. The final sample size assumed a 10% rate of dropouts or invalid test results. All statistical analyses were conducted by accounting for the crossover design (i.e. repeated measurements, intra- and inter-patient variability). Treatment effects were evaluated by comparing the functional parameters observed in the overall patient population after treatment with ticagrelor 60 mg twice daily with those achieved after ticagrelor 90 mg twice daily, regardless of the sequence. For the primary and secondary endpoints with continuous variables, we used a linear mixed-effect model with treatment group, sequence, and period as fixed effects, patient as a random effect, and baseline value of the corresponding platelet function test as a covariate.[12]

A 2-tailed P value of <0.05 was considered statistically significant. All analyses were performed using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

As shown in *Figure 1*, between 1 April 2021 and 24 May 2022, we randomized 50 elderly patients with a mean age of 79.6 ± 4.0 years, of which 22 (44%) were females. Baseline characteristics are reported in *Table 1*. Diabetes was present in 24 (48%) patients and ST-segment elevation myocardial infarction was the indication to PCI in 29 cases (58%). The mean time from PCI to randomization was 2 ± 0.8 days. Overall, 1 patient died during the study, 1 patient required concomitant use of oral anticoagulant therapy, and 1 patient was lost to follow-up. Hence, a total of 47 patients were included in the

Table 1 Baseline and procedural characteristics

Variable		
Age, mean ± SD	$n = 50$	79.6 ± 4.0
Male, *n* (%)	$n = 50$	28 (56.0)
BMI, mean ± SD	$n = 50$	27.6 ± 4.6
Medical history and cardiovascular risk factors		
Family history of CAD, *n* (%)	$n = 50$	7 (14.0)
Diabetes mellitus, *n* (%)	$n = 50$	24 (48.0)
Diabetes mellitus treatment, *n* (%)	$n = 24$	
Diet		2 (8.3)
Oral treatment		13 (54.2)
Insulin therapy		9 (37.5)
Smoking, *n* (%)	$n = 50$	23 (46.0)
Hypertension, *n* (%)	$n = 50$	42 (84.0)
Hypercholesterolaemia, *n* (%)	$n = 50$	34 (68.0)
Previous myocardial infarction, *n* (%)	$n = 50$	12 (24.0)
Congestive heart failure, *n* (%)	$n = 50$	6 (12.0)
Previous PCI, *n* (%)	$n = 50$	7 (14.0)
Previous coronary bypass grafting, *n* (%)	$n = 50$	3 (6.0)
Peripheral artery disease, *n* (%)	$n = 50$	1 (2.0)
Chronic kidney disease, *n* (%)	$n = 50$	23 (46.0)
Chronic obstructive lung disease, *n* (%)	$n = 50$	8 (16.0)
Anemia, *n* (%)	$n = 50$	25 (50.0)
History of bleeding, *n* (%)	$n = 50$	2 (4.0)
Indication to PCI		
ST-segment elevation myocardial infarction	$n = 50$	29 (58.0)
Non-ST-elevation myocardial infarction	$n = 50$	19 (38.0)
Unstable angina	$n = 50$	2 (4.0)
PCI characteristics		
Number of treated lesions, mean ± SD	$n = 70$	1.4 ± 0.7
Target-vessel	$n = 70$	
Left main artery		2 (2.9)
Left anterior descending artery		38 (54.3)
Left circumflex artery		16 (22.9)
Right coronary artery		14 (20.0)
Direct stenting, *n* (%)	$n = 68$	23 (33.8)
TIMI flow pre-PCI, *n* (%)	$n = 70$	
0		10 (14.3)
1		6 (8.6)
2		11 (15.7)
3		43 (61.4)
Total stent length (mm), mean ± SD	$n = 48$	40.9 ± 22.8
Stent diameter (mm), mean ± SD	$n = 48$	3 ± 0.4
Implantation pressure (atm), mean ± SD	$n = 48$	13.9 ± 2.2
Overlapping stents, *n* (%)	$n = 48$	9 (18.7)
Post-dilation, *n* (%)	$n = 68$	34 (50.0)
Treatment of bifurcation lesion, *n* (%)	$n = 70$	9 (12.9)
Side branch stenting, *n* (%)	$n = 9$	4 (44.4)
Residual stenosis (%), mean ± SD	$n = 70$	5 ± 7.1

BMI, body mass index; CAD, coronary artery disease; PCI, percutaneous coronary intervention.

pharmacodynamic and pharmacokinetic assessments. Additional clinical and procedural data are reported in Supplementary material online, *Tables S1* and *S2*. In view of the study's specific design, baseline, in-hospital, and procedural characteristics were the same in both cohorts.

Measures of platelet $P2Y_{12}$ inhibition

Ticagrelor 60 mg twice daily was non-inferior to ticagrelor 90 mg twice daily according to pre-dose VerifyNow-$P2Y_{12}$ results [PRU 26.4 ± 32.1 vs. 30.4 ± 39.0; least squares (LS) mean difference: −4; 95% CI: −16.27 to 8.06; P for non-inferiority = 0.002; P for superiority 0.52]. There was no difference in post-dose measurements (PRU 28.6 ± 36.5 vs. 27.0 ± 36.3, ticagrelor 60 mg vs. 90 mg twice daily, respectively; LS mean difference: 1.6; 95% CI: −8.29 to 11.38; $P = 0.759$). Similarly, no significant differences were observed in ADP-induced aggregation using LTA and MEA tests for both pre and post-dose samples, with the exception of pre-dose LTA following stimulation with 20 μmol/L ADP, where ticagrelor 60 mg yielded a significantly higher MPA than ticagrelor 90 mg (MPA: 30.9 ± 11.3 vs. 26.3 ± 10.0; LS mean difference: 4.6; 95% CI: 0.88–8.46; $P = 0.02$) (*Table 2*). Individual values of the results of these platelet reactivity tests are shown in *Figure 2*. Platelet inhibition with ticagrelor 60 mg vs. 90 mg was similar in patients with ST-elevation myocardial infarction (post-dose PRU 31.8 ± 34.9 vs. 29.8 ± 33.5) and in those with non-ST-elevation ACS (post-dose PRU 19.0 ± 27.0 vs. 31.1 ± 46.3).

High $P2Y_{12}$-mediated platelet reactivity

HPR was infrequent in the $P2Y_{12}$ functional platelet assays conducted. Using the VerifyNow-$P2Y_{12}$, none of the patients exhibited a PRU greater than 208, either pre- or post-dose. In the ticagrelor 60 mg cohort, HPR was observed in one patient (2%) during the pre-dose LTA test with 5 μmol/L ADP stimulation and in three patients (6%) during the pre-dose MEA testing. Additionally, two patients (4%) exhibited HPR at MEA post-dose. Conversely, in the ticagrelor 90 mg cohort, only one patient (2%) was identified with HPR during the post-dose LTA with 20 μmol/L ADP stimulation. *Figure 3* displays the proportions of patients not exhibiting HPR status.

Other measures of platelet response

In both arms and phases of the study, the VerifyNow ASPI test, LTA with arachidonic acid, and MEA ASPI test were conducted. No significant differences were detected in aspirin pharmacodynamics between the groups. However, the ticagrelor 60 group showed significantly higher MPA values in the post-dose LTA test when stimulated with TRAP (MPA: 56.2 ± 18.1 vs. 50.6 ± 17.4; LS mean difference: 5.6; 95% CI: 0.80–10.58; $P = 0.028$) (*Table 2*).

Pharmacokinetics results

Mean plasma levels of ticagrelor were significantly lower in the 60 mg group compared to the 90 mg group both pre-dose (398.29 ± 312.36 ng/mL vs. 579.57 ± 351.73 ng/mL; 95% CI: −299.72 to −57.32; $P = 0.006$) and post-dose (729.88 ± 354.28 ng/mL vs. 1220.36 ± 648.94 ng/mL; 95% CI: −630.89 to −331.03; $P < 0.0001$). Similarly, plasma values of the active metabolite AR-C124910XX were also significantly lower in the ticagrelor 60 mg group compared to the 90 mg group (251.96 ± 158.57 ng/mL vs. 378.96 ± 250.50 ng/mL, $P < 0.001$, *Figure 2* and *Table 3*).

Clinical outcomes

Within the study cohort, one patient died 3 days post-randomization, and another developed a pulmonary embolism 5 days post-randomization; both were subsequently excluded from the platelet

Table 2 Pharmacodynamic profile of ticagrelor 60 vs. 90 mg twice daily

	Ticagrelor 60 mg ($n = 47$)	Ticagrelor 90 mg ($n = 47$)	LSM difference	95% CI	*P*-value for non-inferiority	*P*-value
Pre-dose assessment (before the last dose of ticagrelor)						
Platelet aggregation at VerifyNow-P2Y$_{12}$ assay						
P2Y$_{12}$ test—PRU, mean ± SD	26.4 ± 32.1	30.4 ± 39.0	−4	[−16.27, 8.06]	0.002	0.518
P2Y$_{12}$ test—BASE, mean ± SD	230.0 ± 53.0	224.5 ± 59.4	5.5	[−9.84, 20.34]		0.499
P2Y$_{12}$ test—% inhibition, mean ± SD	87.4 ± 17.5	88.4 ± 14.3	−1	[−7.00, 5.06]		0.758
VerifyNow-Aspirin						
ASPI test—ARU, mean ± SD	424.0 ± 120.1	430.5 ± 80.9	−6.5	[−45.98, 33.24]		0.754
Light transmittance aggregometry (LTA)						
ADP 5 μmol/L (%), mean ± SD	22.1 ± 9.8	18.9 ± 9.2	3.2	[−0.15, 6.67]		0.072
ADP 20 μmol/L (%), mean ± SD	30.9 ± 11.3	26.3 ± 10.0	4.6	[0.88, 8.46]		0.02
Arachidonic acid 1 μmol/L (%), mean ± SD	5.0 ± 10.5	3.5 ± 2.9	1.5	[−1.21, 4.32]		0.277
Thrombin receptor-activating peptide 15 μmol/L (%), mean ± SD	56.0 ± 19.0	53.7 ± 21.3	2.3	[−4.21, 8.66]		0.502
Multiplate electrode aggregometry (MEA)						
ADP test (AUC), mean ± SD	17.7 ± 11.4	17.8 ± 8.9	−0.1	[−3.22, 3.33]		0.975
ASPI test (AUC), mean ± SD	12.0 ± 10.4	11.8 ± 7.0	0.2	[−2.81, 3.41]		0.848
Thrombin receptor-activating peptide test (AUC), mean ± SD	92.3 ± 34.8	84.8 ± 34.4	7.5	[−3.04, 18.62]		0.166
Post-dose assessment (2 h after the last dose of ticagrelor)						
Platelet aggregation at VerifyNow-P2Y$_{12}$ assay						
P2Y$_{12}$ test—PRU, mean ± SD	28.6 ± 36.5	27.0 ± 36.3	1.6	[−8.29, 11.38]		0.759
P2Y$_{12}$ test—BASE, mean ± SD	243.3 ± 44.2	230.5 ± 44.6	12.8	[3.58, 21.99]		0.009
P2Y$_{12}$ test—% inhibition, mean ± SD	88.4 ± 13.9	88.7 ± 14.6	−0.3	[−4.46, 3.79]		0.874
VerifyNow-Aspirin						
ASPI test—ARU, mean ± SD	443.1 ± 92.5	435.9 ± 77.9	7.2	[−21.68, 35.71]		0.635
Light transmittance aggregometry (LTA)						
ADP 5 μmol/L (%), mean ± SD	18.9 ± 8.7	16.4 ± 8.2	2.5	[−0.15, 5.10]		0.071
ADP 20 μmol/L (%), mean ± SD	26.8 ± 11.1	26.9 ± 28.1	−0.1	[−8.48, 8.25]		0.979
Arachidonic acid 1 μmol/L (%), mean ± SD	5.4 ± 12.9	3.6 ± 3.0	1.8	[−1.61, 5.46]		0.292
Thrombin receptor-activating peptide 15 μmol/L (%), mean ± SD	56.2 ± 18.1	50.6 ± 17.4	5.6	[0.80, 10.58]		0.028
Multiplate electrode aggregometry (MEA)						
ADP test (AUC), mean ± SD	17.8 ± 11.0	17.4 ± 9.6	0.4	[−2.83, 3.74]		0.788
ASPI test (AUC), mean ± SD	12.3 ± 11.1	12.1 ± 8.0	0.2	[−3.52, 3.96]		0.908
Thrombin receptor-activating peptide test (AUC), mean ± SD	90.2 ± 32.9	84.4 ± 33.0	5.8	[−3.80, 15.79]		0.237

ADP, adenosine diphosphonate; ARU, aspirin reaction units; AUC, area under the curve; PRU, P2Y$_{12}$ reaction units.

function analyses. Of the 47 patients analysed, one experienced a peri-procedural myocardial infarction (during ticagrelor 90 mg treatment), classified under Society for Cardiovascular Angiography and Interventions (SCAI) and Academic Research Consortium (ARC) definitions but not according to the 4th Universal Definition of Myocardial Infarction criteria. During treatment with ticagrelor 60 mg, five patients reported bleeding events (1 BARC 1, 2 BARC 3a, and 2 BARC 3b). In contrast, 13 patients treated with ticagrelor 90 mg experienced bleeding episodes (5 BARC 1, 5 BARC 2, 2 BARC 3a, and 1 BARC 3b). No cases of dyspnoea were reported by patients throughout the duration of the study.

Discussion

In this crossover, randomized trial, we compared the pharmacodynamic and pharmacokinetic profile of ticagrelor 60 mg twice daily vs. ticagrelor 90 mg twice daily during the acute phase of ACS among elderly patients undergoing PCI. The principal findings are as follows: (1) the pharmacodynamic profile of ticagrelor 60 mg twice daily was non-inferior to ticagrelor 90 mg twice daily with respect to the primary endpoint of PRU using the VerifyNow-P2Y$_{12}$; (2) this comparable platelet inhibitory effect was achieved despite plasma concentrations of ticagrelor and its active metabolite were approximately 30% lower with the reduced compared with the standard dose; (3) As expected,

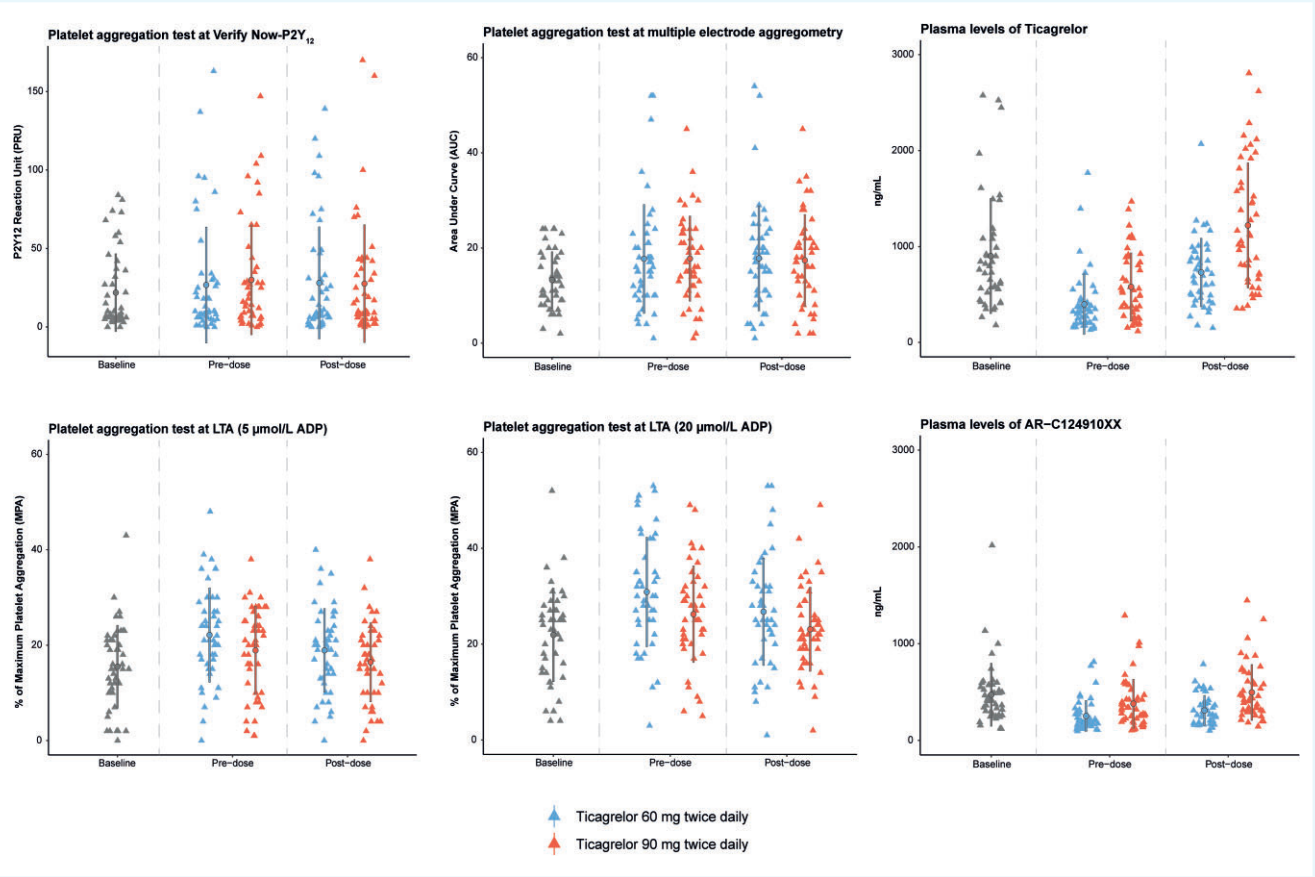


Figure 2 Individual values of the results of $P2Y_{12}$ tests. In this illustration, the results of the main $P2Y_{12}$ inhibition and pharmacokinetics platelet tests are shown. The triangles represent the single result for each test performed. Dots represent the mean values and lines represent the standard deviations. ADP, adenosine diphosphate; LTA, light transmittance aggregometry.

no differences in aspirin response were detected with the use of ticagrelor 60 mg twice daily, supporting the assumption that ticagrelor does not affect aspirin-related signalling.

Older age configured the most frequent inclusion criterion in dedicated randomized trials for high-bleeding risk patients and is presently recognized as a minor criterion for high-bleeding risk status according to Academic Research Consortium for High Bleeding Risk (ARC-HBR).[13] Although aging is associated with a parallel increase in both thrombotic and bleeding risks, advanced age may prevail in attenuating the net clinical benefit of DAPT.[14–16] Among potent $P2Y_{12}$ receptor inhibitors, a standard dose of prasugrel is not recommended in older patients in view of lack of net clinical benefit in comparison to clopidogrel.[17] A lower dose of prasugrel (5 mg daily) is indicated in patients aged ≥75 years; however, this dose regimen is less studied, and available randomized trials do not support superiority over clopidogrel in terms of efficacy outcomes.[18,19] Along this line, the improvement in efficacy with a standard dose of ticagrelor compared with clopidogrel in ACS was more related to younger than older patients, with the latter having more than a 2-fold higher absolute rate of bleeding.[20] Furthermore, in the POPular AGE trial, clopidogrel compared with ticagrelor was associated with a significant reduction of bleeding events without an increase in ischaemic events among patients with non-ST-elevation ACS aged 70 years or more.[21] However, clopidogrel irrespective of age is not effective in approximately 30% of patients, leading to poor outcomes after.[22,23] Taken together, available evidence suggests that the type and the optimal dose of $P2Y_{12}$ receptor inhibitors remains controversial in the context of DAPT for elderly patients with ACS.[24]

Our study corroborates previous findings of a similar pharmacodynamic efficacy between the 60 mg and 90 mg ticagrelor dose regimens. In the PEGASUS-TIMI 54 trial, there was a similar platelet $P2Y_{12}$ inhibition with ticagrelor 60 mg and 90 mg twice daily, with levels of ticagrelor in the 60-mg group at approximately two-thirds of the ticagrelor levels in the 90-mg group.[11] Consistent findings were reported by the ELECTRA study, in which, similarly to our study, elderly patients were enrolled.[25] However, at variance with these two trials that tested the use of a lower dose of ticagrelor in the chronic (>1-year) or late (>1-month) phases of ACS, respectively, our trial randomized patients during the acute phase of ACS, with a median time from PCI to randomization of 2 days. Of interest, while the PEGASUS-TIMI 54, ELECTRA, and PLINY the Elder trials had a comparable sample size, our study was designed with a crossover randomization scheme, thereby allowing for increased statistical power compared with a parallel-group trial with the same number of participants. Additionally, the use of a crossover design is expected to minimize inter-individual variability as each participant serves as their own control.

The confirmation that a lower ticagrelor dose regimen retained the pharmacodynamic properties of the standard dose in the acute setting of ACS, where the prothrombotic milieu is still active, and the thrombotic risk has not yet plateaued,[26] is a novel finding and, in part, unexpected. Indeed, this dose regimen was originally conceived to provide a slightly lower intensity of antiplatelet therapy in the chronic

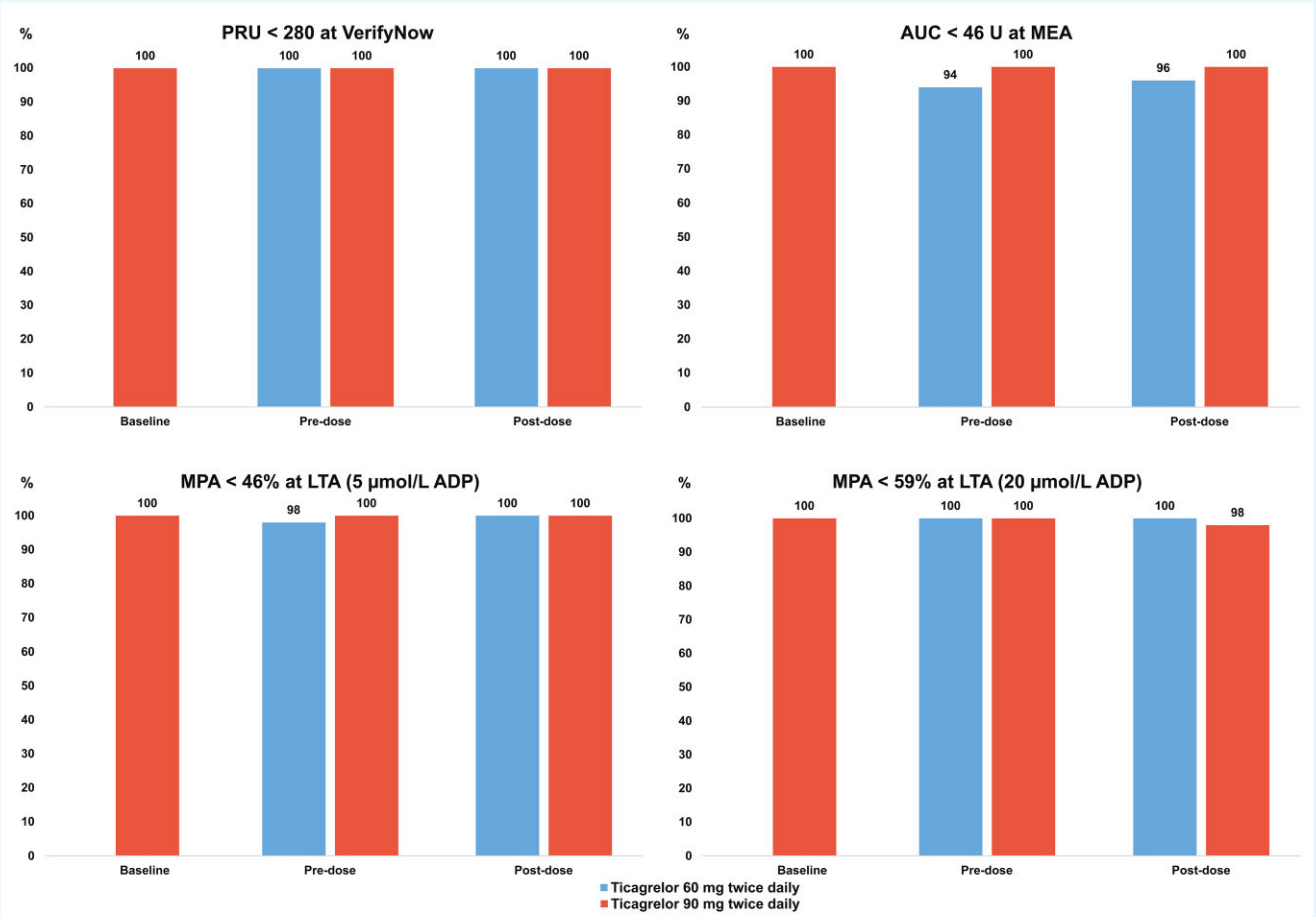


Figure 3 Proportions of patients without HPR status. Proportions of patients who did not meet HPR criteria divided for treatment, platelets aggregation test performed, and blood sampling (pre and 2 h after the last ticagrelor dose). ADP, adenosine diphosphate; AUC, area under curve; HPR, high platelet reactivity; LTA, light transmittance aggregometry; MEA, multiple electrode aggregometry; MPA, maximum platelet aggregation; PRU, $P2Y_{12}$ reaction units.

Table 3 Pharmacokinetic profile of ticagrelor 60 vs. 90 mg twice daily

	Ticagrelor60 mg	Ticagrelor90 mg	95% CI	*P*-value
Ticagrelor (ng/mL)				
Pre-dose, mean ± SD	398.29 ± 312.36	579.57 ± 351.73	[−299.72, −57.32]	0.006
Post-dose, mean ± SD	729.88 ± 354.28	1220.36 ± 648.94	[−630.89, −331.03]	<0.001
AR-C124910XX (ng/mL)				
Pre-dose, mean ± SD	251.96 ± 158.57	378.96 ± 250.50	[−191.45, −70.82]	<0.001
Post-dose, mean ± SD	308.84 ± 151.31	498.37 ± 282.17	[−259.85, −131.66]	<0.001

SD, standard deviation.
Assessment was done per protocol before (pre-dose) and 2 h after (post-dose) the last dose of the assigned treatment.

phase of long-term therapy after acute myocardial infarction.[27] Using multiple definitions, we found that HPR was rare and occurred at a similar rate with both maintenance dose regimens of ticagrelor. As a secondary finding of our trial, there was no difference in response to aspirin when patients were treated with different doses of ticagrelor using the VerifyNow ASPI, LTA with arachidonic acid, and MEA ASPI tests. This observation is in keeping with prior studies showing that $P2Y_{12}$ receptor inhibitors do not influence the effect of aspirin on the ability of platelets to generate thromboxane.[28,29] As proof-of-concept trial, our study provides the basis for testing in appropriately powered trials the use of ticagrelor 60 mg twice daily as standard antiplatelet regimen for ACS patients undergoing PCI. In the PEGASUS-TIMI 54 trial, although the two ticagrelor doses were associated with a similar magnitude of efficacy, the rates of bleeding and dyspnoea were

numerically decreased with the 60-mg as compared to the 90-mg dose of ticagrelor, leading to a lower risk of drug discontinuation.[9] Since premature ticagrelor cessation in routine clinical practice has been reported in 1 of 6 patients during the first year after PCI, with bleeding and dyspnoea representing the most frequent reasons for discontinuation, a lower dose of ticagrelor might improve adherence to DAPT.[30] Despite the absence of a dedicated subanalysis on elderly patients enrolled in the PEGASUS-TIMI 54 trial, participants aged ≥75 years attained the lowest rate of the primary efficacy endpoint with ticagrelor 60 mg twice daily, which was accompanied by numerically reduced major bleeding events.[9] Therefore, because the expected event rate of adverse events is substantially higher during the acute than during the chronic phase of ACS, implementing a low-dose ticagrelor after PCI may improve drug adherence, and, ultimately, clinical outcomes. Finally, a low-dose of ticagrelor might provide a similar efficacy and safety profile in comparison to a guided-descalation strategy, which improved ischaemic outcomes as opposed to a standard ticagrelor dose in a network meta-analysis of randomized trials.[31]

Limitations

This study presents several limitations. First, the study was single-centre and open-label. However, although clinicians were not blinded to the ticagrelor dose regimen, laboratory personnel performing pharmacodynamic and pharmacokinetic assessments were blinded to the allocated treatment. Second, the study was not powered for clinical outcomes. Therefore, whether a reduced dose of ticagrelor is non-inferior to the standard dose with respect to clinical outcomes in the acute setting of ACS remains currently unknown. Third, the study specifically enrolled elderly patients, who were considered high-bleeding risk patients when the trial was designed. Hence, our findings cannot be extrapolated to other high-bleeding risk categories as well as to ACS patients aged less than 75 years.

In conclusion, this trial, including ACS patients aged 75 years or more undergoing PCI, showed that ticagrelor 60 mg twice daily provides a similar magnitude of platelet inhibition compared with ticagrelor 90 mg twice daily. These results support the hypothesis that the lower ticagrelor dose can be equally effective than the standard dose in the acute phase of ACS.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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