Received: 6 October 2024 | Revised: 8 February 2025 | Accepted: 13 February 2025

https://doi.org/10.1016/j.rpth.2025.102704

ORIGINAL ARTICLE

Elderly patients are hyperresponsive to potent P2Y12 inhibitors

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Handling Editor: Dr Carsten Depperman

Abstract

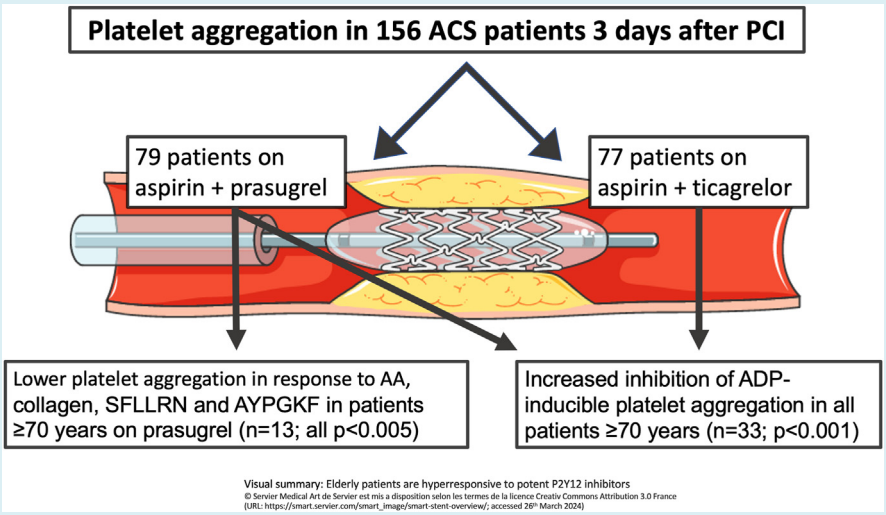
Background: Aging has recently been associated with increased basal platelet activation and platelet hyperreactivity in response to adenosine diphosphate (ADP) but with decreased platelet response to thrombin receptor stimulation in individuals without antiplatelet therapy.

Objectives: To investigate platelet response to agonist stimulation in elderly patients (≥70 years) on dual antiplatelet therapy with potent P2Y12 inhibitors.

Methods: Platelet aggregation in response to arachidonic acid (AA), ADP, collagen, the protease-activated receptor-1 agonist SFLLRN, and the protease-activated receptor-4 agonist AYPGKF was assessed by multiple electrode aggregometry in 79 prasugrel- and 77 ticagrelor-treated patients 3 days after acute percutaneous coronary intervention.

Results: In the overall study population (N = 156), patients aged ≥70 years (n = 33) had lower platelet aggregation in response to AA, ADP, and SFLLRN than younger patients (all $P < .05$). In prasugrel-treated patients (n = 79), those aged ≥70 years (n = 13) showed lower platelet aggregation in response to all agonists than younger patients (all $P < .05$). In contrast, in ticagrelor-treated patients (n = 77), those aged ≥70 years (n = 20) only had lower ADP-inducible platelet aggregation than younger patients (P = .03), whereas platelet aggregation in response to AA, collagen, SFLLRN, and AYPGKF was similar between elderly and younger patients (all $P > .05$). Among patients aged ≥70 years, prasugrel-treated patients showed lower platelet aggregation in response to AA, collagen, and AYPGKF than those receiving ticagrelor (all $P < .05$).

Conclusion: Patients aged ≥70 years on potent P2Y12 inhibitors exhibit increased inhibition of ADP-inducible platelet aggregation. In addition, elderly patients on prasugrel show a lower response to AA, collagen, SFLLRN and AYPGKF than younger patients.



KEYWORDS
age, elderly, platelet aggregation, prasugrel, ticagrelor

Essentials

- Aging may affect basal platelet activation and the response to platelet agonists.
- We assessed platelet aggregation in 156 prasugrel- and ticagrelor-treated patients.
- Patients aged ≥70 years exhibited increased inhibition of adenosine diphosphate-inducible platelet aggregation.
- Elderly patients on prasugrel also showed a low response to all other platelet agonists.

1 | INTRODUCTION

Despite advanced treatment options, acute coronary syndrome (ACS) remains the most common cause of death in the western world [1]. Antithrombotic therapy is a cornerstone of the therapeutic regimen, both in the acute treatment of ACS and in secondary prevention [2,3]. The P2Y12 receptor antagonists ticagrelor and prasugrel have shown greater efficacy than clopidogrel in reducing future ischemic events in ACS patients [4–6]. Accordingly, antithrombotic treatment with prasugrel or ticagrelor is recommended by current ACS guidelines following acute percutaneous coronary intervention (PCI) with stent implantation [5–9]. However, in contrast to their beneficial effects on ischemic endpoints, ticagrelor and prasugrel are associated with a higher risk of bleeding than clopidogrel [4,5].

Both ticagrelor and prasugrel exert their antiplatelet effect by inhibiting the purinergic P2Y12 receptor on the platelet surface [2]. Physiologically, the receptor is activated by adenosine diphosphate (ADP), which is released from platelet dense granules upon platelet activation and enhances further platelet activation and thrombus formation [2,10].

Aging has recently been associated with increased basal platelet activation and hyperreactivity in response to adenosine diphosphate (ADP) on the one hand but with decreased platelet response to thrombin receptor stimulation on the other hand in individuals without antiplatelet therapy [11]. In detail, elderly individuals (aged 70 years or older) show a higher basal expression of platelet P-selectin, CD63, and activated glycoprotein (GP) IIb/IIIa, as well as higher platelet activation in response to ADP than younger individuals. Moreover, elderly individuals have a higher ADP P2Y12 receptor density. In contrast, thrombin-inducible expression of P-selectin, CD63, and activated GPIIb/IIIa is lower in individuals aged ≥70 years than in younger individuals. Likewise, elderly individuals showed lower platelet aggregation in response to SFLLRN (a protease-activated receptor [PAR]-1 agonist) and AYPGKF (a PAR-4 agonist), as well as lower thrombin-inducible cleavage of PAR-1 and PAR-4 than did younger individuals [11].

Data comparing agonist-inducible platelet aggregation between ACS patients aged ≥70 years and younger patients on potent P2Y12 inhibitors are lacking. However, the extent of platelet inhibition is of particular importance in the elderly because these patients are at high risk of both bleeding and thrombosis. In the current study, we therefore sought to investigate platelet response to agonist stimulation in elderly ACS patients on dual antiplatelet therapy (DAPT) with potent P2Y12 inhibitors.

2 | METHODS

2.1 | Study population

The study cohort has been described previously [12]. In total, 156 ACS patients on daily aspirin (100 mg/d) and either prasugrel (10 mg/d or 5 mg/d in patients aged ≥75 years and those weighing <60 kg; n = 79) or ticagrelor therapy (180 mg/d; n = 77) were included. Three days after successful PCI, blood was drawn after an overnight fast. Before collecting the blood samples, the attending physician ensured that the patient had correctly taken the last dose of DAPT the previous day and that the samples were drawn before the morning medication. The time interval between the last administration of prasugrel or ticagrelor and blood sampling was similar in all patients. As previously mentioned, exclusion criteria comprised oral anticoagulation with either vitamin K antagonists (warfarin, phenprocoumon, acenocoumarol) or direct oral anticoagulants (edoxaban, dabigatran, apixaban, rivaroxaban); a known aspirin, prasugrel, or ticagrelor intolerance (allergic reactions, gastrointestinal bleeding complications); a history of bleeding disorders; treatment with ticlopidine, dipyridamole, or nonsteroidal anti-inflammatory drugs; malignant myeloproliferative disorders or heparin-induced thrombocytopenia; major surgery within one week before enrollment; severe hepatic failure; known qualitative defects in platelet function; a platelet count <100,000/μL or >450,000/μL; and hematocrit <30% [12].

The study protocol was in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Vienna. All participants gave their written informed consent.

2.2 | Blood sampling

Blood was drawn by aseptic venipuncture from an antecubital vein using a 21-gauge butterfly needle (0.8 × 19 mm; Greiner Bio-One) as previously described [12,13]. To avoid procedural deviations, all blood samples were taken by the same physician applying a light tourniquet that was immediately released, and the samples were mixed by gently inverting the tubes. Whole blood was drawn into 3.2% sodium citrate tubes (Greiner Bio-One). All specimens were brought to the laboratory by the collecting physician immediately after blood sampling, and platelet function testing was performed within 30 minutes for all patients.

2.3 | Multiple electrode aggregometry (MEA)

As described previously, whole blood impedance aggregometry was performed with the Multiplate analyzer (Roche Diagnostics) [14–16]. One Multiplate test cell contains 2 independent sensor units. One unit consists of 2 silver-coated highly conductive copper wires with a length of 3.2 mm. After dilution (1:2 with 0.9% NaCl solution) of hirudin-anticoagulated whole blood and stirring in the test cuvettes for 3 minutes at 37 °C, arachidonic acid (AA; 0.5 mM), ADP (6.4 μM), collagen (2.7 μg/mL), SFLLRN (PAR-1 agonist; 32 μM), or AYPGKF (PAR-4 agonist; 645 μM; all from Roche Diagnostics) was added. Aggregation was then continuously recorded for 6 minutes. The concentrations of all agonists were chosen according to the manufacturer's recommendations. The adhesion of activated platelets to the electrodes led to an increase in impedance, which was detected for each sensor unit separately and transformed to aggregation units (AU) that were plotted against time. The AU at 6 minutes were used for calculations. One AU corresponds to 10 AU*min (area under the curve of AU) [14–16].

2.4 | Statistics

All continuous variables are expressed as median (IQR). Categorical variables are given as number (percentage). Continuous variables were compared by Mann–Whitney U-test or Kruskal–Wallis test. Chi-squared tests were performed for comparison of categorical variables. A 2-tailed $P \leq .05$ was considered statistically significant. All statistical analyses were performed with SPSS 29.0.2.

3 | RESULTS

In total, 156 patients were analyzed. Patient characteristics of the study cohort are shown in Tables 1 and 2. Median age was 58 years (IQR, 51-67 years) and 124 patients (79.5%) were male. Thirty-three patients (21.2%) were ≥70 years old, with no significant difference between patients on prasugrel and those on ticagrelor (16.5% vs 26%, P = .19; Table 1). Patients aged ≥70 years were more often female (33.3% vs 17.1%, P = .04; Table 2), had a lower body mass index (26.51 kg/m^2 [IQR, 23.99-29.05 kg/m^2] vs 27.95 kg/m^2 [IQR, 25.71-31.0 kg/m^2], P = .03; Table 2) and were more often nonsmokers (81.9% vs 36.6%, P < .001; Table 2). Moreover, patients aged <70 years were more often on angiotensin-converting enzyme inhibitor therapy (82.1% vs 60.6%, P = .02; Table 2), whereas elderly patients received angiotensin receptor blockers more often (36.4% vs 14.6%, P = .005; Table 2). Fifteen elderly patients (45.5%) were on DAPT with low-dose prasugrel (5 mg/d; Table 2). All patients ≥70 years had a HAS-BLED score ≥3. Compared with patients aged <70 years, we found significantly more elderly patients with a HAS-BLED score ≥3 (100% vs 51.2%, P < .001). Baseline serum creatinine was significantly higher in patients aged ≥70 years (1.16 mg/dL [IQR, 0.98-1.31 mg/dL] vs 0.94 mg/dL [IQR, 0.82-1.08 mg/dL], P < .001; Table 2), while baseline hemoglobin was significantly lower than in younger patients (13.3 g/dL [IQR, 12.6-14.1 g/dL] vs 13.9 g/dL [IQR, 13.0-14.8 g/dL], P = .01; Table 2).

With application of the established cutoff value for high on-treatment residual platelet reactivity (HRPR) of >46 AU by MEA in response to ADP [17], we found 2 HRPR patients (1.3%) in our study cohort (Tables 1 and 2). Both of these patients received prasugrel, and they were 32 and 60 years old. Furthermore, according to the established cutoff value for low on-treatment residual platelet

TABLE 1 Baseline characteristics in patients treated with prasugrel vs ticagrelor.

Characteristics	Prasugrel (*n* = 79)	Ticagrelor (*n* = 77)	*P*
Demographics			
Age, y, median (IQR)	58 (51-66)	59 (51-70)	.19
Caucasian, White, *n* (%)	79 (100)	77 (100)	1.00
Patients ≥70 y, *n* (%)	13 (16.5)	20 (26.0)	.19
Male patients, *n* (%)	64 (81.0)	60 (77.9)	.58
Body mass index, kg/m^2, median (IQR)	27.89 (25.31-31.05)	27.57 (25.29-30.29)	.74
HRPR by MEA ADP, *n* (%)	2 (2.5)	0	.19
LRPR by MEA ADP, *n* (%)	42 (53.2)	35 (45.5)	.30
Medical history, *n* (%)			
Prior myocardial infarction	14 (17.7)	13 (16.9)	.60
Prior stroke or TIA	3 (3.8)	2 (2.6)	.66
Arterial hypertension	53 (67.1)	54 (70.2)	.60
Hyperlipoproteinemia	60 (75.9)	56 (72.7)	.87
Peripheral artery disease	6 (7.6)	5 (6.5)	.83
Diabetes mellitus, type 2	13 (16.5)	14 (18.2)	.18
Smoking	47 (59.5)	37 (48.1)	.23
HAS-BLED score ≥3	43 (54.4)	53 (68.8)	.07
Laboratory data, median (IQR)			
Serum creatinine, mg/dL	0.94 (0.84-1.08)	1.00 (0.82-1.19)	.09
Platelet count, /L	229 (194-251)	226 (186-265)	.84
High sensitivity CRP, mg/dL	1.44 (0.70-3.74)	1.12 (0.47-3.43)	.23
Hemoglobin, g/dL	13.9 (13.1-14.6)	13.6 (12.7-14.6)	.59
Medication, *n* (%)			
Aspirin	79 (100)	77 (100)	1.00
Statin	78 (98.7)	75 (97.4)	1.00
β-blocker	76 (96.2)	74 (96.1)	.65
ACE inhibitor	64 (81.0)	57 (74.0)	.40
ARB	12 (15.2)	18 (23.4)	.16
SGLT2 inhibitor	2 (2.5)	3 (3.9)	.70
Calcium channel blocker	7 (8.9)	8 (10.4)	.69

Continuous data are shown as median (IQR). Dichotomous data are shown as *n* (%).

ACE-I = angiotensin-converting enzyme inhibitor, ADP, adenosine diphosphate; ARB, angiotensin receptor blocker; CRP, C-reactive protein; HRPR, high on-treatment residual platelet reactivity; LRPR, low on-treatment residual reactivity; MEA, multiple electrode aggregometry; SGLT2, sodium/glucose cotransporter 2; TIA, transient ischemic attack.

reactivity (LRPR) of <18 AU by MEA in response to ADP [18,19], we detected 77 LRPR patients (49.4%) in our study population (Tables 1 and 2). There were no significant differences in HRPR and LRPR patients between prasugrel- or ticagrelor-treated patients (both $P > .05$; Table 1). However, patients aged ≥70 years had LRPR more often than younger individuals (72.7% vs 43.0%, $P = .002$; Table 2).

In the overall patient population ($N = 156$), elderly patients ($n = 33$) showed significantly lower platelet aggregation in response to AA (12 AU [IQR, 5-17 AU] vs 17 AU [IQR, 12-21 AU], $P = .003$), ADP (15 AU [IQR, 10-20 AU] vs 20 AU [IQR, 16-24 AU], $P < .001$), and SFLLRN (53 AU [IQR, 42-74 AU] vs 67 AU [IQR, 50-84 AU], $P = .049$) as compared with patients aged <70 years. In contrast, there were no significant differences in collagen-inducible platelet aggregation (58 AU [IQR, 30-69 AU] vs 60 AU [IQR, 30-78 AU], $P = .20$) and AYPGKF-inducible platelet aggregation (58 AU [IQR, 29-76 AU] vs 63 AU [IQR, 46-82 AU], $P > .05$) between patients aged ≥70 years and younger patients.

TABLE 2 Baseline characteristics in patients aged <70 years vs ≥70 years.

Characteristics	<70 y (*n* = 123)	≥70 y (*n* = 33)	*P*
Demographics			
Age, y, median (IQR)	55 (50-61)	74 (72-77)	<.001
Caucasian, White, *n* (%)	123 (100)	33 (100)	1.00
Male patients, *n* (%)	102 (82.9)	22 (66.7)	.04
Body mass index, kg/m^2, median (IQR)	27.95 (25.71-31.0)	26.51 (23.99-29.05)	.03
HRPR by MEA ADP, *n* (%)	2 (1.6)	0	.50
LRPR by MEA ADP, *n* (%)	53 (43.0)	24 (72.7)	.002
Medical history, *n* (%)			
Prior myocardial infarction	22 (17.9)	5 (15.2)	.79
Prior stroke or TIA	5 (4.1)	0	.23
Arterial hypertension	85 (69.1)	22 (66.7)	.60
Hyperlipoproteinemia	92 (74.8)	24 (72.7)	.48
Peripheral artery disease	9 (7.3)	2 (6.0)	1.00
Diabetes mellitus, type 2	19 (15.4)	8 (24.2)	.28
Smoking	78 (63.4)	6 (18.1)	<.001
HAS-BLED score ≥3	63 (51.2)	33 (100.0)	<.001
Laboratory data, median (IQR)			
Serum creatinine, mg/dL	0.94 (0.82-1.08)	1.16 (0.98-1.31)	<.001
Platelet count, /L	228 (197-258)	204 (183-262)	.16
High sensitivity CRP, mg/dL	1.57 (0.73-3.23)	1.42 (0.64-3.80)	.94
Hemoglobin, g/dL	13.9 (13.0-14.8)	13.3 (12.6-14.1)	.01
Medication, *n* (%)			
Aspirin	123 (100)	33 (100)	1.00
Prasugrel low dose	1 (0.8)	15 (45.5)	<.001
Statin	121 (98.4)	32 (97.0)	.31
β-blocker	118 (96.0)	32 (97.0)	.94
ACE inhibitor	101 (82.1)	20 (60.6)	.02
ARB	18 (14.6)	12 (36.4)	.005
SGLT2 inhibitor	3 (2.4)	2 (6.0)	.29
Calcium channel blocker	9 (7.3)	6 (18.2)	.06

Continuous data are shown as median (IQR). Dichotomous data are shown as *n* (%).

ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRP, C-reactive protein; HRPR, high on-treatment residual platelet reactivity; LRPR, low on-treatment residual reactivity; MEA, multiple electrode aggregometry; SGLT2, sodium/glucose cotransporter 2; TIA, transient ischemic attack.

In the subgroup of prasugrel-treated patients (*n* = 79), elderly patients (*n* = 13) showed significantly lower platelet aggregation in response to AA (8 AU [IQR, 3-14 AU] vs17 AU [IQR, 12-22 AU], *P* < .001), ADP (14 AU [IQR, 10-18 AU] vs 20 AU [IQR, 16-23 AU], *P* = .003), collagen (26 AU [IQR, 14-58 AU] vs 64 AU [IQR, 33-78 AU], *P* = .01), SFLLRN (46 AU [IQR, 34-74 AU] vs 69 AU [IQR, 56-84 AU], *P* = .03), and AYPGKF (29 AU [IQR, 20-59 AU] vs 63 AU [IQR, 45-86 AU], *P* = .005) as compared with younger patients (Figure 1).

In contrast, in ticagrelor-treated patients (*n* = 77), those aged ≥70 years (*n* = 20) only showed significantly lower ADP-inducible platelet aggregation compared with younger patients (16 AU [IQR, 12-21 AU] vs 21 AU [IQR, 16-25 AU], *P* = .03), whereas platelet aggregation in response to AA, collagen, SFLLRN, and AYPGKF was comparable between elderly and younger patients (all *P* > .05; Figure 2).

Among patients aged ≥70 years, prasugrel-treated patients showed significantly lower platelet aggregation in response to AA (8

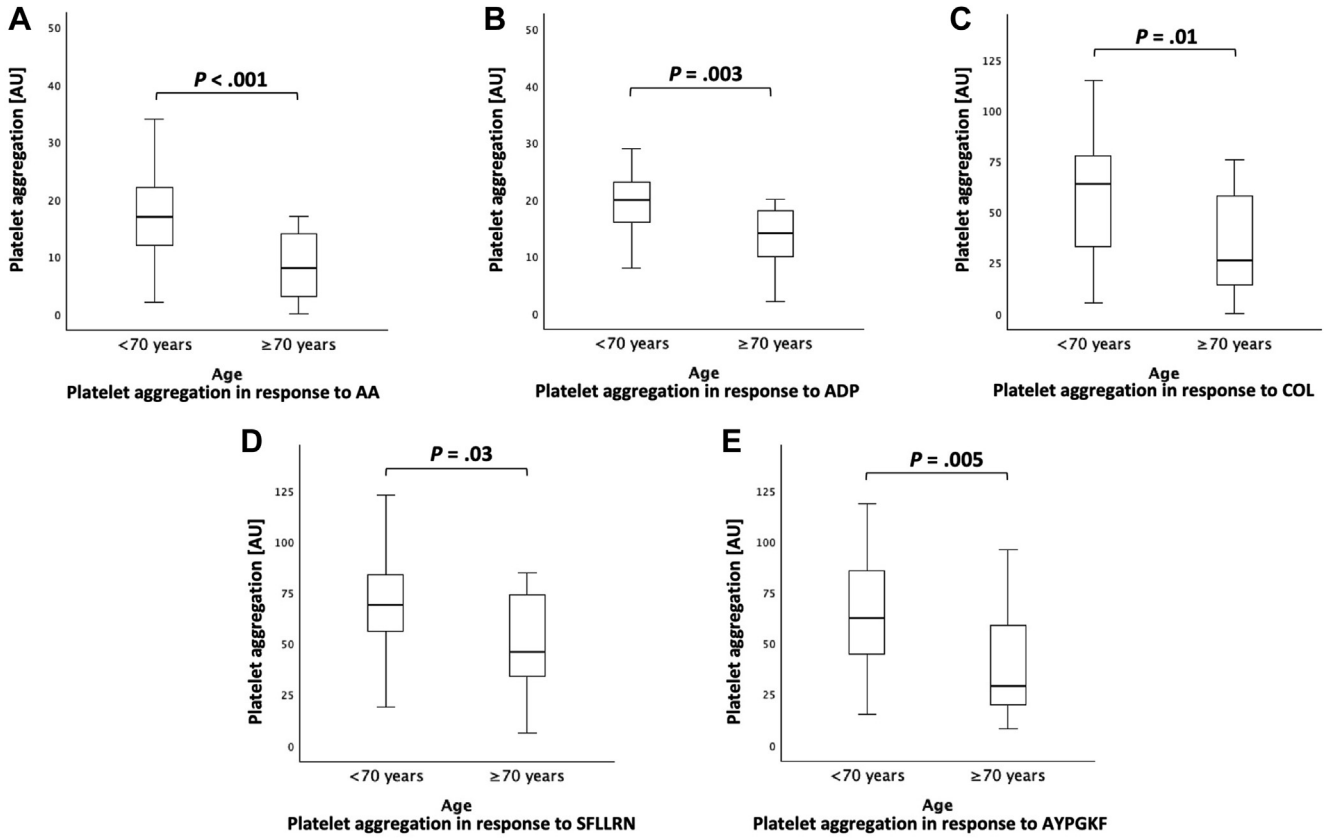


FIGURE 1 Platelet aggregation in aggregation units (AU) by multiple electrode aggregometry in response to (A) arachidonic acid (AA), (B) adenosine diphosphate (ADP), (C) collagen (COL), (D) SFLLRN, and (E) AYPGKF in prasugrel-treated patients <70 years and ≥70 years. The boundaries of the box show the lower and upper quartiles, the line inside the box represents the median. Whiskers are drawn from the edge of the box to the highest and lowest values that are outside the box but within 1.5 times the box length.

AU [IQR, 3-14 AU] vs 15 AU [IQR, 10-20 AU], *P* = .02), collagen (26 AU [IQR, 14-58 AU] vs 61 AU [IQR, 43-73 AU], *P* = .01), and AYPGKF (29 AU [IQR, 20-59 AU] vs 62 AU [IQR, 43-82 AU], *P* = .02) than those receiving ticagrelor. In contrast, ADP- and SFLLRN-inducible platelet aggregation was comparable between prasugrel- and ticagrelor-treated patients aged ≥70 years (ADP: 14 AU [IQR, 10-18 AU] vs 16 AU [IQR, 12-21 AU], *P* = .29; SFLLRN: 46 AU [IQR, 34-74 AU] vs 58 AU [IQR, 48-73 AU], *P* = .30).

In an additional subgroup analysis, patients aged ≥70 years exhibited the lowest ADP-inducible platelet response (15 AU [IQR, 10-20 AU]), as compared with patients aged 65 to 69 years (20 AU [IQR, 16-24 AU]), 60 to 64 years (22 AU [IQR, 18-23 AU]), and <60 years (20 AU [IQR, 15-24 AU], Kruskal–Wallis test *P* = .004; Figure 3).

4 | DISCUSSION

In the present study, we compared residual platelet aggregation in response to various agonists between ACS patients aged ≥70 years and younger ACS patients on DAPT with aspirin plus prasugrel or ticagrelor. In the overall study population, patients aged ≥70 years showed lower platelet aggregation in response to AA, ADP, and SFLLRN than younger patients. In the subgroup of prasugrel-treated patients, those aged ≥70 years had significantly lower platelet aggregation in response to all agonists than younger patients. In contrast, ticagrelor-treated patients aged ≥70 years only had significantly lower ADP-inducible platelet aggregation than younger patients, whereas platelet aggregation in response to AA, collagen, SFLLRN, and AYPGKF was comparable between elderly and younger patients. Among patients aged ≥70 years, prasugrel-treated patients showed significantly lower platelet aggregation in response to AA, collagen, and AYPGKF than those receiving ticagrelor.

In an additional subgroup analysis, patients aged ≥70 years showed significantly lower platelet aggregation in response to ADP when compared to patients aged 65 to 69 years, 60 to 64 years, and <60 years.

Overall, we detected a strong inhibition of platelet aggregation in patients on prasugrel and ticagrelor, respectively. Seventy-seven patients had LRPR according to the established cutoff value of <18 AU by MEA in response to ADP [18,19], and LRPR was more frequent in elderly patients. Using the established cutoff value for HRPR of >46 AU by MEA in response to ADP, we detected 2 patients with HRPR [20]. Both patients with HRPR received prasugrel, and they were 32 and 60 years old. No poor responders to P2Y12 inhibitors were seen in patients aged ≥70 years.

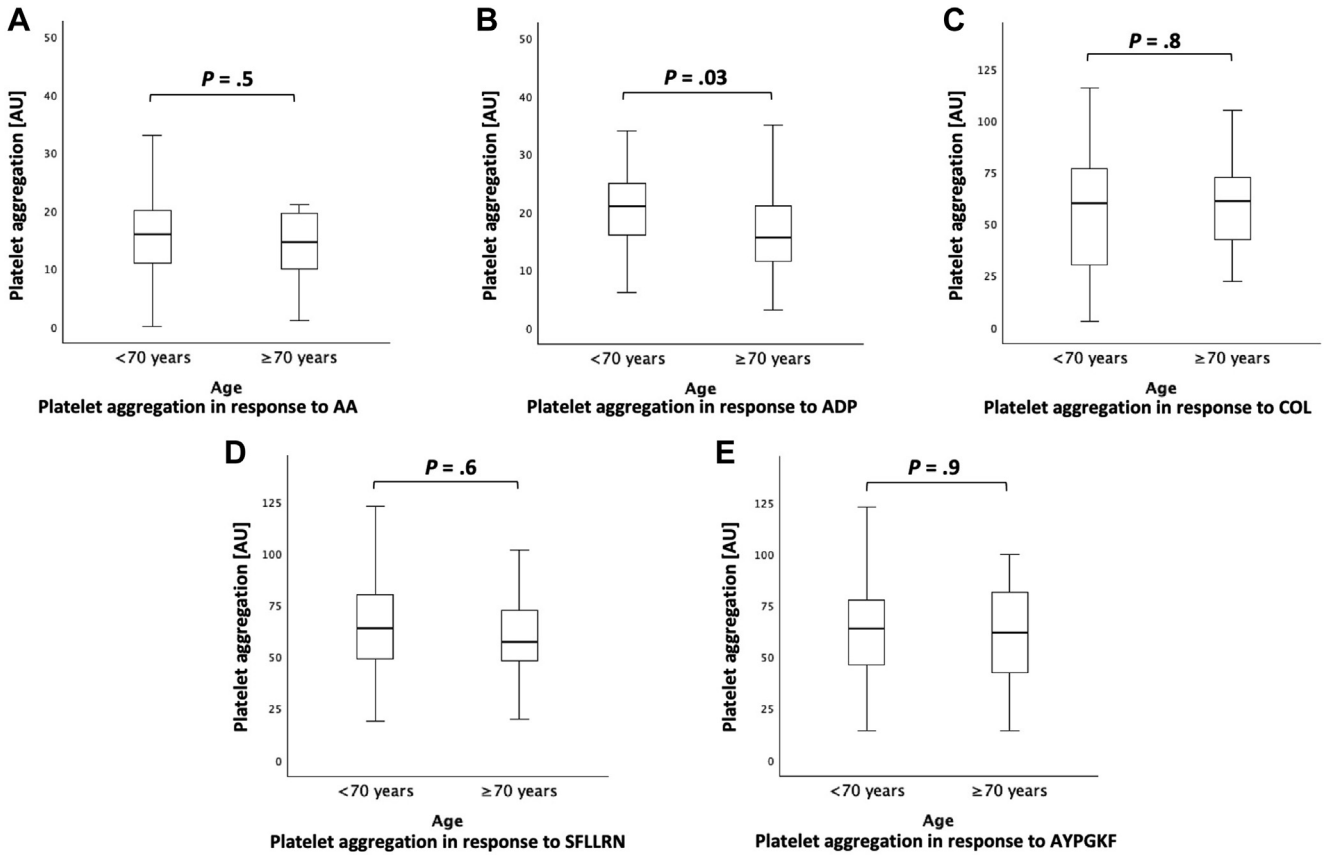


FIGURE 2 Platelet aggregation in aggregation units (AU) by multiple electrode aggregometry in response to (A) arachidonic acid (AA), (B) adenosine diphosphate (ADP), (C) collagen (COL), (D) SFLLRN, and (E) AYPGKF in ticagrelor-treated patients <70 years and ≥70 years. The boundaries of the box show the lower and upper quartiles, the line inside the box represents the median. Whiskers are drawn from the edge of the box to the highest and lowest values that are outside the box but within 1.5 times the box length.

Based on previous data [17], the observed differences in platelet aggregation by MEA in our study appear rather small. However, since patients ≥70 years are particularly vulnerable and prone to both thromboembolic and bleeding events, even small differences in platelet reactivity may be associated with clinical outcomes. In summary, our results should be considered hypothesis-generating only and will hopefully encourage larger clinical trials.

We chose MEA to analyze residual platelet aggregation in our study cohort because it is a fast, well-standardized and therefore reproducible platelet function test [14–16]. MEA uses the principle of impedance aggregometry to assess platelet function in diluted whole blood. As a whole blood method, MEA offers the advantage of preserving the natural cellular environment to approximate *in vivo* platelet aggregation. However, physiological factors such as blood flow dynamics or endothelial influences cannot be captured using MEA. Nonetheless, the major advantage over light transmission aggregometry, as the "historical" gold standard, is that no centrifugation steps are required [17,21]. Moreover, MEA allows the assessment of platelet response to different agonists at the same time, and its results have repeatedly been associated with adverse outcomes following PCI [20,22].

Gnanenthiran et al. [11] recently demonstrated ADP hyperreactivity, ie, increased platelet aggregation via the P2Y12 receptor pathway, and a higher ADP P2Y12 receptor density in elderly individuals without antiplatelet therapy. In our study, however, elderly patients aged ≥70 years on prasugrel or ticagrelor showed significantly lower residual platelet aggregation in response to ADP than younger patients. Taken together, these findings may at least in part explain the increased bleeding risk in elderly patients on potent P2Y12 antagonists as well as the increased risk of atherothrombotic events in elderly patients without antiplatelet therapy. Of note, we and others have previously shown that the antiplatelet effect of the third P2Y12 receptor inhibitor, clopidogrel, decreases with the patient age, which may explain the higher bleeding risk but lower incidence of ischemic events risk with prasugrel and ticagrelor compared to clopidogrel in the elderly [4,5,23,24].

Aging has recently been linked to platelet PAR-1 and PAR-4 mediated thrombin resistance, ie, less platelet activation in response to thrombin and selective PAR-1 and PAR-4 agonists [11]. In detail, Gnanenthiran et al. [11] reported lower thrombin-inducible expression of platelet P-selectin, CD63, and activated GPIIb/IIIa in elderly than in younger individuals. Moreover, those aged ≥70 years

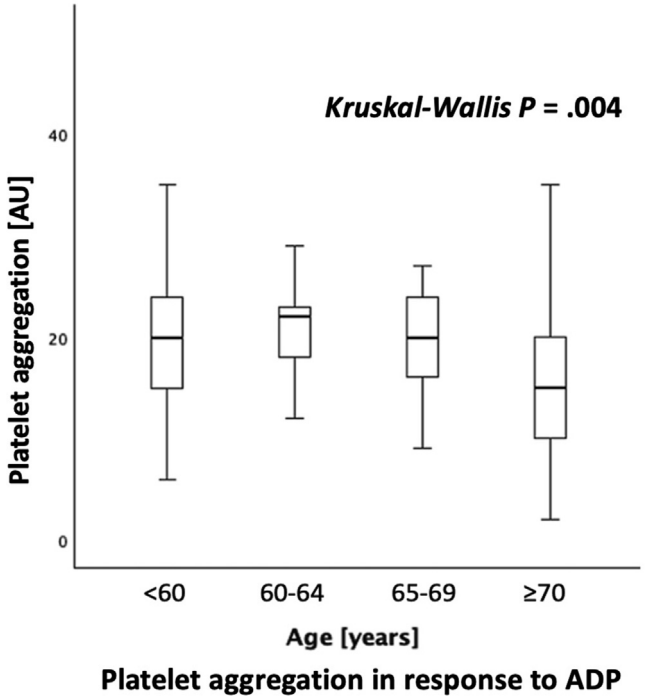


FIGURE 3 Platelet aggregation in aggregation units (AU) by multiple electrode aggregometry in response to adenosine diphosphate (ADP) in patients aged <60 years, 60 to 64 years, 65 to 69 years, and ≥70 years. The boundaries of the box show the lower and upper quartiles, the line inside the box represents the median. Whiskers are drawn from the edge of the box to the highest and lowest values that are outside the box but within 1.5 times the box length.

showed lower platelet aggregation in response to SFLLRN and AYPGKF as well as lower thrombin-inducible cleavage of PAR-1 and PAR-4 in their study. In agreement with these observations, we found lower SFLLRN-inducible platelet aggregation in elderly ACS patients in the overall study population as well as lower platelet aggregation in response to SFLLRN and AYPGKF in prasugrel-treated patients aged ≥70 years. The latter was not observed in the subgroup of ticagrelor-treated ACS patients, suggesting different effects of prasugrel and ticagrelor on platelet aggregation via PAR-1 and PAR-4 in the elderly. Previously, we found significantly lower PAR-1 and PAR-4 mediated platelet activation in ticagrelor-treated ACS patients as compared to ACS patients receiving prasugrel [12]. Together with the current findings, one may speculate that prasugrel specifically reduces residual platelet aggregation in response to SFLLRN and AYPGKF in patients aged ≥70 years, whereas ticagrelor reduces PAR-1 and PAR-4 mediated platelet aggregation irrespective of the patient's age. However, as shown in Figures 1 and 2, SFLLRN- and AYPGKF-inducible platelet aggregation is lower in elderly patients on prasugrel than in those on ticagrelor.

The reasons for thrombin resistance in the elderly and thus for the more pronounced effects of prasugrel on PAR-1 and PAR-4 mediated platelet aggregation in patients aged ≥70 years may be multifactorial. Previous data show a stable PAR-1 density and even an increase in PAR-4 density with increasing age [11]. It has been hypothesized that reduced calcium flux and secondary ADP contribution to thrombin-mediated platelet activation may be responsible for thrombin resistance in the elderly [11]. Furthermore, previous studies have shown platelet depletion with desensitization of the thrombin receptors in stroke patients and patients with malignant diseases [25,26]. It is therefore also being discussed that *in vivo* thrombin formation and the resulting increase in D-dimer could possibly lead to desensitization of PAR-1 and PAR-4 in elderly patients [11]. In summary, the processes leading to thrombin resistance in elderly patients are not fully understood yet and warrant further mechanistical investigations [11,27].

Interestingly, our study shows lower platelet aggregation in response to all agonists in prasugrel-treated patients aged ≥70 years compared to younger patients, and lower platelet aggregation in response to AA, collagen, and AYPGKF in elderly patients on prasugrel as compared to elderly patients on ticagrelor. In this regard, it needs to be mentioned that the TRITON-TIMI 38 study showed a significantly higher risk of major bleeding in prasugrel-treated patients ≥75 years compared to those receiving clopidogrel [4]. This observation led to the ESC guideline recommendation to reduce the daily dose of prasugrel from 10 mg to 5 mg in patients aged ≥75 years [28]. Since this dose reduction was also performed in our study population, our results indicate that even at the reduced daily dose, elderly patients exhibit a very strong response to prasugrel. One may therefore speculate that—even at the reduced daily dose—prasugrel leads to a higher risk of bleeding compared to clopidogrel in patients aged ≥70 years. However, the superiority of clopidogrel over low-dose prasugrel in terms of safety has never been proven [29]. In detail, the ANTARCTIC trial showed similar outcomes in terms of ischemic endpoints and bleeding events between low-dose prasugrel and clopidogrel in ACS patients ≥75 years undergoing PCI [30]. Similarly, the TRILOGY-ACS study and the GENERATIONS trial found no significant differences in clinical endpoints between DAPT with low-dose prasugrel vs clopidogrel in elderly patients [31,32]. In summary, our data together with previously published studies highlight that further randomized controlled trials assessing the risk of bleeding events on DAPT with low-dose prasugrel vs clopidogrel in elderly patients would be of clinical importance.

Since ticagrelor-treated patients aged ≥70 years only showed lower platelet aggregation in response to ADP compared to younger patients, it may be speculated that ticagrelor is safer than prasugrel in elderly patients. However, it has to be noted that the present data should be considered rather exploratory due to the cohort size and study design. Unfortunately, data on bleeding risk of DAPT with ticagrelor in elderly patients is limited [33]. The ISAR-REACT 5 trial found a numerically higher incidence of bleeding events in ACS patients on ticagrelor when compared to antithrombotic therapy with prasugrel without reaching statistical significance [34]. However, a subgroup analysis specifically addressing elderly patients was not performed in the ISAR-REACT 5 trial.

In agreement with our findings of a significantly lower residual platelet aggregation in response to ADP in ticagrelor-treated elderly

patients, Szummer et al. [35] reported a significantly higher bleeding risk in ACS patients ≥80 years on DAPT with ticagrelor as compared to clopidogrel. Likewise, Gimbel et al. [36] found a significantly higher risk of major bleeding in ACS patients aged ≥70 years on ticagrelor compared to clopidogrel. Further randomized controlled trials are needed to evaluate the safety profile of antithrombotic therapy with ticagrelor in the elderly.

Our results suggest that elderly ACS patients aged ≥70 years are hyperresponsive to potent P2Y12 inhibitors at the currently recommended dosages, resulting in significantly decreased residual platelet aggregation in response to ADP. Further randomized controlled trials are needed to assess the clinical impact of our findings, especially with regard to the risk of bleeding. Whether reduced agonist-inducible platelet aggregation in elderly ACS patients is associated with an increased risk of bleeding and whether these patients may benefit from less aggressive antithrombotic therapy remains to be clarified.

4.1 | Limitations

The present study has the following limitations. First, our data were derived from a single center. Second, our study was not powered for clinical outcomes. Third, the pharmacological differences between prasugrel and ticagrelor imply that physiological factors could influence their respective efficacies. As a prodrug, prasugrel requires metabolic transformation—primarily via hepatic enzymes—to be converted to its active form [4]. In contrast, ticagrelor acts directly without prior metabolization [5]. This could be particularly relevant in elderly patients, where changes in liver function, enzyme activity, or drug absorption may variably affect the active drug level of each agent. Consequently, the pharmacokinetic and -dynamic differences between prasugrel and ticagrelor may influence on-treatment platelet reactivity in elderly patients and have to be considered when interpreting our results. Fourth, we did not determine the immature platelet fraction (IPF) and therefore cannot provide any data on the IPF. With regard to the investigated P2Y12 inhibitors, it is important to emphasize that, unlike ticagrelor, prasugrel exerts an irreversible effect on platelets, while having a shorter half-life. Consequently, the extent of the IPF may affect residual platelet aggregation differently during antiplatelet therapy with prasugrel and ticagrelor. Fifth, as a reversibly binding agent with a long half-life, the effect of ticagrelor largely depends on its plasma concentration [37]. When interpreting our results, it must be taken into account that the elderly patients had a significantly lower body mass index than the younger patients. Sixth, due to missing variables (history of bleeding events) we cannot provide the exact HAS-BLED score for all patients in our study cohort. However, as shown in Table 2, all patients aged ≥70 years had a HAS-BLED score ≥3. Finally, the choice of the P2Y12 antagonist was made by the treating physician, which may have led to patient selection bias. However, the 2 treatment groups were well-matched, and there were no significant differences regarding the most relevant patient characteristics.

5 | CONCLUSION

Patients aged ≥70 years on potent P2Y12 inhibitors exhibit increased inhibition of ADP-inducible platelet aggregation. In addition, elderly patients on prasugrel show a significantly lower response to AA, collagen, SFLLRN, and AYPGKF than do younger patients.

FUNDING

This research was funded by the "Medical Scientific Fund of the Mayor of the City of Vienna," grant number 14016, by the "Anniversary Fund of the Austrian National Bank," grant number 16155, and by the "Austrian Heart Fund," grant number 202003, to T.G.

AUTHOR CONTRIBUTIONS

Conceptualization T.G.; methodology, S.P. and T.G.; software, D.M., P.P.W., J.P., C.W., and S.L.; validation, M.T. and T.G.; formal analysis, D.M. and T.G.; investigation, D.M., M.T., S.L., and T.G.; resources, S.P. and T.G.; data curation, M.T., P.P.W., S.L., J.P., and C.W.; writing — original draft preparation, D.M. and T.G.; writing — review and editing, all authors; visualization, D.M.; supervision, T.G.; project administration, T.G.; funding acquisition, M.T., S.P., and T.G. All authors have read and agreed to the published version of the manuscript.

RELATIONSHIP DISCLOSURE

T.G. received speaker fees from Amgen, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Novartis, and Pfizer, and grant support from Boehringer-Ingelheim, Bristol Myers Squibb, Medtronic, and Abbott. The other authors have no relevant conflicts of interest to declare.

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