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# Platelet reactivity patterns in patients treated with dual antiplatelet therapy

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## Abstract

**Aim:** The aim of the present study was to investigate the patterns of platelet reactivity and discriminators of therapeutic response to dual antiplatelet therapy (DAPT) with aspirin and ticagrelor or prasugrel in patients with acute coronary syndrome (ACS).

**Design:** In this multicentre prospective observational study, 492 patients with ACS were enrolled. Platelet aggregation was determined by multiple electrode aggregometry after stimulation with adenosine diphosphate (ADP) or arachidonic acid (AA) as agonists in the maintenance phase of treatment with prasugrel or ticagrelor.

**Results:** Age emerged as the strongest variable influencing aspirin response status: The mean AA-induced platelet aggregation in patients <49 years of age was 49% higher than in those >49 years (13.1 U vs 8.8 U; $P = 0.011$). The second strongest discriminator of aspirin response was sex: Male patients had a 40% higher AA-induced platelet aggregation values than female patients (9.5 U vs 6.8 U; $P = 0.026$). Platelet count emerged as the only variable influencing ADP antagonists response status showing that patients with platelet count >320 g/L displayed higher ADP-induced platelet aggregation. About 12% of patients had high on-treatment platelet reactivity (HTPR) to aspirin, 3% and 4% a HTPR to prasugrel and ticagrelor, respectively, and only 2% displayed HTPR to dual antiplatelet therapy.

**Conclusion:** When potent platelet inhibitors as prasugrel and ticagrelor are administered with aspirin, HTPR to DAPT plays only a marginal role.

**KEYWORDS**
ACS, HTPR, LTPR, MEA, platelets, prasugrel, ticagrelor

## 1 | INTRODUCTION

Dual antiplatelet therapy (DAPT) combining aspirin and a P2Y12 inhibitor is a widespread therapy with proven benefit to reduce recurrent adverse ischaemic events in patients after acute coronary syndrome (ACS).[1,2] Current guidelines of ACS primarily recommend ticagrelor and prasugrel combined with aspirin, leaving clopidogrel solely recommended in patients with contraindications for the novel P2Y12 inhibitors.[3] Both ticagrelor and prasugrel have been shown to

provide a significant mortality reduction, including prevention of major adverse cardiac events (MACE).[4,5] These benefits go in hand with increased procedural and nonprocedural bleeding risk.[6] Novel P2Y12 inhibitors harbour superior pharmacodynamic characteristics with a faster and more potent pharmacological response as compared to clopidogrel.[7] Although both substances were designed to overcome individual treatment responses, a significant proportion of ACS patients still exhibit high or low on-treatment reactivity with subsequent ischaemic or bleeding events.[8,9] To date, clinical benefits of platelet reactivity testing remain controversial, but it is a valuable tool to identify those patients at risk for adverse outcomes even in patients treated with novel P2Y12 inhibitors whose treatment responses are more predictable. In contrast, clinical role of high on-treatment reactivity (HTPR) to aspirin remains an issue of debate.[10]

For this purpose, we aimed to characterize platelet reactivity in a large prospectively enrolled registry of ACS patients treated with novel antiplatelet agents and aspirin to better depict those factors associated with individual response to mono and dual antiplatelet therapy.

## 2 | METHODS

### 2.1 | Study design

The study was a prospective observational cohort study performed at two Austrian University Hospitals: the Medical University of Vienna and the Medical University of Graz. The Ethics Committee of the Medical University of Vienna and the Medical University of Graz approved the study protocol in accordance with the Declaration of Helsinki. Participants were included in the study starting in July 2012 until December 2016. Inclusion criteria were a written informed consent obtained before the study entry, treatment with prasugrel or ticagrelor for ACS and age >18 years. The only exclusion criterion was participation in interventional trials. Patients were followed up by a telephone interview at 1, 6 and 12 months. Four hundred and ninety-two consecutive patients fulfilling the inclusion and exclusion criteria were enrolled. All patients received a loading dose of prasugrel (60 mg) or ticagrelor (180 mg) followed by a once daily dose of 10 mg prasugrel or two daily dose of ticagrelor (90 mg), respectively. The type of the P2Y12 blocker used was at the discretion of the treating interventional cardiologist according to the current guidelines and the intern standard operating procedures (SOP) for the antiplatelet treatment of ACS patients in the both study centres. According to the intern standard operating procedure (SOP) of the Department, which are based on the current guidelines[11,12] the following treatment algorithm was used: Prasugrel was the P2Y12 receptor inhibitor of the first choice in patients presenting with STEMI or patients with NSTE-ACS and diabetes, if the coronary angiography was already available (unless not contraindicated). Ticagrelor was the P2Y12 receptor inhibitor of the first choice in patients with NSTE-ACS (unless not contraindicated). Blood samples from patients were obtained in the in-hospital maintenance phase of treatment, at least 24 hour after loading dose of prasugrel/ticagrelor and after PCI, at 8 AM after the morning maintenance dose administration of prasugrel/ticagrelor. The study is reported according to the STROBE (strengthening the reporting of observational studies in epidemiology) standards.

### 2.2 | Impedance aggregometry

Whole blood aggregation was determined using multiple electrode aggregometry (MEA) on a new generation impedance aggregometer (Multiplate Analyzer, Verum Diagnostica GmbH, Munich, Germany).[13,14] The system detects the electrical impedance change due to the adhesion and aggregation of platelets on two independent electrode-set surfaces in the test cuvette. We used hirudin as anticoagulant, which is recommended by the manufacturer. We used adenosine diphosphate (ADP) and or arachidonic acid (AA) as agonists.[15] A 1:2 dilution of whole blood anticoagulated with hirudin and 0.9% NaCl was stirred at 37°C for 3 minute in the test cuvettes, ADP: 6.4 μmol/L or AA: 0.5 mmol/L were added, and the increase in electrical impedance was recorded continuously for 6 minute.[16] The mean values of the 2 independent determinations are expressed as the area under the curve (AUC) of the aggregation tracing. We reported AUC in units (U).[17] Platelet aggregometry was performed directly after blood sampling at the Department of Cardiology at the Medical University of Vienna. The tests were performed in each participant. According to the position document, ADP values up to 19 U were classified as low on-treatment platelet reactivity (LTPR), 20-45 U as moderate on-treatment platelet reactivity (MTPR) and values >46 as HTPR to prasugrel or ticagrelor.[18] AA values > 20 U were classified as HTPR to aspirin, according to the previous study.[10] For platelet aggregation analyses comparing ticagrelor and prasugrel, patients receiving abciximab were excluded.

### 2.3 | Study endpoints

The primary endpoint was ADP- and AA-induced platelet aggregation.

### 2.4 | Statistical analysis

We estimated an exploratory sample size of 492 patients to characterize patients treated with prasugrel or ticagrelor

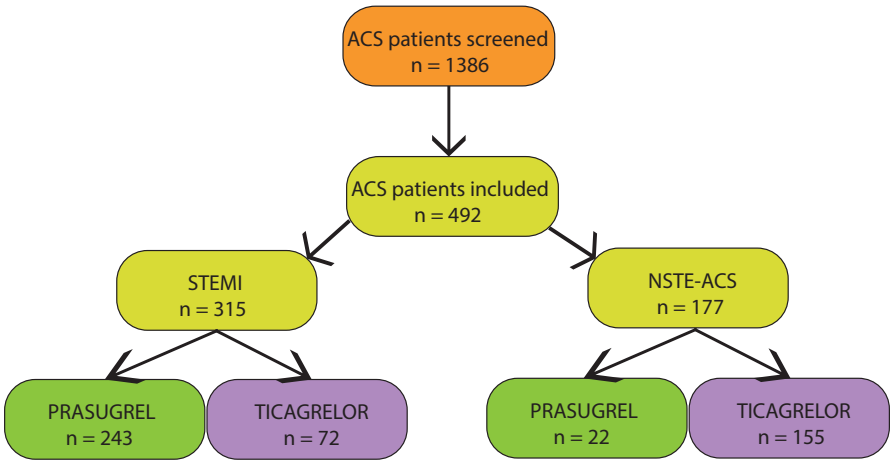


**FIGURE 1** Patient flow

and aspirin with regard to platelet aggregation under real-life clinical conditions. Normal distribution was tested with the Kolmogorov-Smirnov test. Data are expressed as mean, standard deviation (SD), 95% confidence intervals (CI) median or interquartile range (IQR), as appropriate. Statistical comparisons were performed with the Mann-Whitney *U* test and the chi-squared test when applicable. Classification tree analysis (chi-squared automatic interaction detection: CHAID) was used to detect discriminators of platelet reactivity to ADP and AA, as described previously.[19,20] The analysis included common risk factors for coronary artery disease (cigarette smoking, diabetes mellitus, hypertension, family history of coronary artery disease and hyperlipidemia), past medical history (stroke, previous PCI and previous myocardial infarction), co-morbidities (renal failure, periphery or cerebral vascular disease), age, status at hospitalization (STEMI or NSTE-ACS), laboratory values at the day of hospitalization and sex. All statistical calculations were performed using commercially available statistical software (IBM SPSS Version 22.0; Chicago, USA).

## 3 | RESULTS

### 3.1 | Patient demographics

Patient flow through the study is shown in Figure 1. Of 1386 ACS patients screened, 492 fulfilled the inclusion criteria and were included in the study. Due to the standard operating procedures (SOP) for the antiplatelet treatment of ACS patients in the both study centres, prasugrel was mainly administered to patients with STEMI (92%), whereas patients with NSTE-ACS were more frequently treated with ticagrelor (68%; $P < 001$; Table 1). The majority of further demographic differences between the both agents is most probably a consequence of this skew distribution of P2Y12 receptor blocker use between STEMI and NSTE-ACS patients. Prasugrel-treated patients were younger (57 vs 63 years of age; $P < 0.001$), more frequently male (86% vs 72%; $P < 0.001$), smoker (78% vs 58%; $P < 0.001$), with a family history of CAD (44% vs 35%; $P = 0.035$) and a higher procedural GpIIb/IIIa blocker use compared with ticagrelor-treated individuals, respectively (Table 1). Patients treated with ticagrelor had more frequently a history of hypertension (75% vs 64%; $P = 0.011$) and a longer median total stent length (33.8 mm vs 30.1 mm; $P = 0.004$) compared with prasugrel-treated individuals, respectively (Table 1).

### 3.2 | ADP- and AA-induced platelet aggregation

ADP-induced platelet aggregation was almost normally distributed in both ticagrelor- and prasugrel-treated patients (Figure 2A). In contrast, AA-induced platelet aggregation was skewed distributed in patients treated with ticagrelor and prasugrel (Figure 2B).

### 3.3 | ADP- and AA-induced platelet aggregation according to clinical presentation

In patients presenting with NSTE-ACS, the median level of ADP-induced platelet aggregation did not differ between prasugrel and ticagrelor (12 U, interquartile range IQR 8-22 U vs 12 U, IQR 7-21 U; respectively, $P = 0.605$; Figure 3A). In line, in STEMI patients, there was no difference in ADP-induced platelet aggregation between prasugrel and ticagrelor (11 U, interquartile range IQR 5-22 U vs 15 U, IQR 9-22 U; respectively, $P = 0.115$; Figure 3A).

In patients presenting with NSTE-ACS, the median level of AA-induced platelet aggregation did not differ between prasugrel and ticagrelor (6.4 U, interquartile range IQR 2-13 U vs 6 U, IQR 1-14 U; respectively, $P = 0.593$; Figure 3B). In line, in STEMI patients, there was no difference of AA-induced platelet aggregation between prasugrel and

**TABLE 1** Patient demographics

| Patient demographics | Overall N = 492 | Prasugrel N = 265 | Ticagrelor N = 227 | *P* |
|---|---|---|---|---|
| Age (y) | 59 ± 12 | 57 ± 11 | 63 ± 13 | <0.001 |
| Gender (male) n (%) | 390 (79) | 227 (86) | 163 (72) | <0.001 |
| Risk factors/past medical history n (%) | | | | |
| Body mass index (BMI; mean ± SD) | 27.7 ± 4.8 | 27.9 ± 4.7 | 27.5 ± 4.9 | Ns |
| Hypertension | 337 (69) | 168 (64) | 169 (75) | 0.011 |
| Hyperlipidemia | 273 (56) | 139 (53) | 134 (59) | Ns |
| Smoking | 336 (67) | 205 (78) | 131 (58) | <0.001 |
| Family history of CAD | 196 (40) | 117 (44) | 79 (35) | 0.035 |
| Diabetes mellitus | 97 (20) | 47 (18) | 50 (22) | Ns |
| Prior PCI | 60 (12) | 31 (12) | 29 (13) | Ns |
| Prior myocardial infarction | 89 (18) | 47 (18) | 42 (19) | Ns |
| Peripheral arterial occlusive disease | 25 (5) | 16 (6) | 9 (4) | Ns |
| Cerebrovascular disease | 196 (40) | 117 (44) | 79 (35) | Ns |
| Laboratory data (mean ± SD) | | | | |
| Platelets ($x10^9$/L) | 233 ± 69 | 265 ± 66 | 235 ± 72 | Ns |
| C reactive protein (mg/dL) | 4.6 ± 7.2 | 3.4 ± 7.6 | 6.6 ± 6.4 | Ns |
| White blood cell count (WBC; $x10^9$/L) | 10.1 ± 3.8 | 11.5 ± 3.6 | 10.3 ± 3.9 | <0.001 |
| Creatinine (mg/dL) | 0.9 ± 0.3 | 0.9 ± 0.3 | 1.0 ± 0.4 | Ns |
| Haemoglobin (g/dL) | 14.2 ± 1.8 | 14.6 ± 1.7 | 13.8 ± 1.9 | <0.001 |
| Fibrinogen (mg/dL) | 387 ± 94 | 377 ± 88 | 399 ± 100 | 0.039 |
| Concomitant medications n (%) | | | | |
| GpIIb/IIIa blocker during the PCI | 146 (30) | 105 (40) | 41 (18) | <0.001 |
| Aspirin | 492 (100) | 265 (100) | 227 (100) | Ns |
| Proton pump Inhibitors (PPI) | 397 (83) | 212 (82) | 185 (83) | Ns |
| ß blockers | 429 (89) | 231 (89) | 197 (89) | Ns |
| Statins | 456 (95) | 249 (96) | 207 (93) | Ns |
| Angiotensin converting enzyme (ACE) inhibitors | 426 (88) | 233 (90) | 193 (87) | Ns |
| Calcium channel blockers | 34 (7) | 14 (5) | 20 (9) | Ns |
| ACS data | | | | |
| NSTE-ACS | 177 (36) | 22(8) | 155(68) | <0.001 |
| STEMI | 315 (64) | 243 (92) | 72 (32) | <0.001 |
| PCI | 452 (93) | 250 (94) | 202 (92) | Ns |
| Number of stents per patient | 1.5 ± 1.0 | 1.5 ± 0.9 | 1.6 ± 1.2 | Ns |
| Total stent length | 32.1 ± 22.0 | 30.1 ± 19.3 | 33.8 ± 24.8 | 0.004 |

CAD, coronary artery disease; MEA, multiple electrode aggregometry; NSTE-ACS, none ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.
Data are reported as Mean ± standard deviation (SD), n (number of patients) or percentages.

ticagrelor (7 U, interquartile range IQR 2-12 U vs 7 U, IQR 2-14 U; respectively, $P = 0.628$; Figure 3B).

## 3.4 | Distribution of ADP- and AA-induced platelet aggregation

According to a predefined cut-offs, only 3% of patients in the prasugrel group and 4% of study participants in the ticagrelor group had high on-treatment platelet reactivity (HTPR; Figure 4). Moderate on-treatment platelet reactivity (MTPR) was found in 27% prasugrel-treated patients and in 31% of ticagrelor-treated patients. The majority of patients displayed low on-treatment platelet reactivity (LTPR; prasugrel: 70%; ticagrelor: 65%; Figure 4).

According to a predefined cut-off, 12% of patients had HTPR to aspirin treatment.

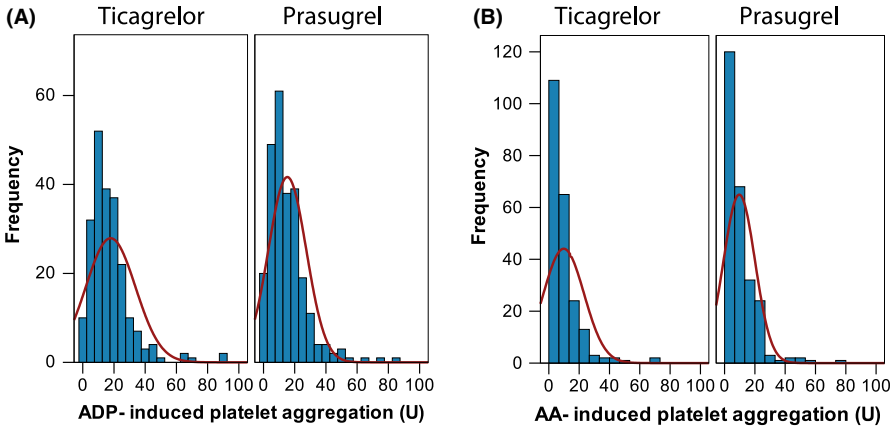


**FIGURE 2** Adenosine diphosphate (ADP)- and arachidonic acid (AA)-induced platelet aggregation assessed by multiple electrode aggregometry (MEA) in patients treated with ticagrelor or prasugrel and aspirin

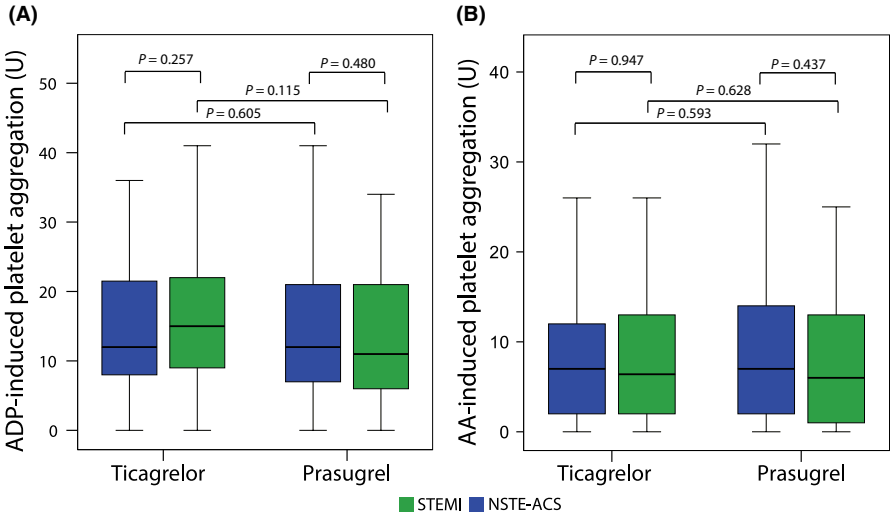


**FIGURE 3** A, Adenosine diphosphate (ADP)- and (B): arachidonic acid (AA) - induced platelet aggregation assessed by multiple electrode aggregometry (MEA) in patients treated with ticagrelor and prasugrel according to the clinical presentation: ST-elevation myocardial infarction (STEMI) vs. none ST-elevation acute coronary syndrome (ACS) during the hospital stay after the maintenance dose administration

Whereas AA- and ADP-induced platelet aggregation weakly correlated in ticagrelor-treated patients ($r^2 = 0.49$; $P < 0.001$), this correlation was moderate for prasugrel ($r^2 = 0.62$; $P < 0.001$). About 1% of ticagrelor- and 2% of prasugrel-treated patients were classified as displaying a HTPR phenotype to both agonists (right upper quadrant of Figure 5).

### 3.5 | Contribution of clinical characteristics to the phenotype of response to aspirin and ADP receptor blockers

Classification tree analysis (CHAID) was used to detect discriminators of the phenotype of response to antiplatelet agents. The analysis included common risk factors for coronary artery disease, past medical history, co-morbidities, co-medication, age, status at hospitalization (stable angina or acute coronary syndrome), laboratory parameters and sex. Age emerged as the strongest variable influencing aspirin response status (Figure 6): The mean AA-induced platelet aggregation in those younger than 49 years of age was 49% higher as in older patients (13.1 U vs 8.8 U; $P = 0.011$). The second strongest discriminator was sex: Male patients had 40% higher AA-induced platelet aggregation values than female patients (Figure 6: 9.5 U vs 6.8 U; $P = 0.026$).

Platelet count emerged as the only variable influencing ADP antagonists response status showing that those with higher platelet count (>320 g/L) had higher ADP-induced platelet aggregation (Figure 6).

## 4 | DISCUSSION

In the present study, we aimed to characterize platelet reactivity and discriminators of therapeutic response in ACS patients treated with dual antiplatelet therapy consisting of potent platelet inhibitors prasugrel or ticagrelor and aspirin. We found that both ADP-blockers show a similar potency to inhibit platelet reactivity during the maintenance phase of treatment: We observed in both ACS entities NSTE-ACS and STEMI that only 3% of all patients treated with prasugrel and 4% treated with ticagrelor exhibited HTPR. This frequency is somehow remarkable as previous

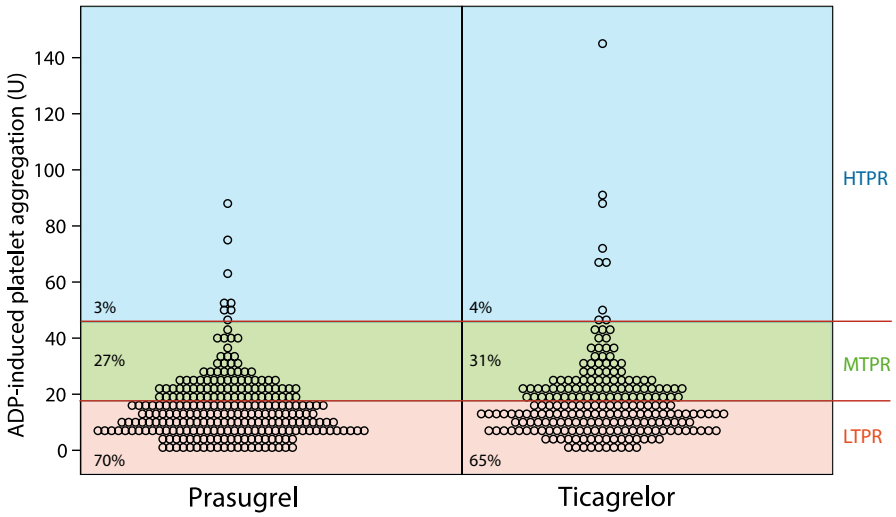


**FIGURE 4** Scatter plot showing distribution of adenosine diphosphate (ADP)- induced platelet aggregation values in relation to high on-treatment platelet reactivity (HTPR), moderate on treatment platelet reactivity (MTPR) and low on treatment platelet reactivity (LTPR) in patients treated with ticagrelor and prasugrel

reports stated up to 4-fold higher incidence of HTPR in patients under prasugrel or ticagrelor treatment, with some reports even reporting 35%-46% of those patients inadequately responding to the novel P2Y12 inhibitors.[8,21,22] We assume that this difference might be due to the characteristics of our study cohort of ACS patients that have not been pre-treated with clopidogrel. Previous studies that reported higher HTPR incidences in prasugrel- and ticagrelor-treated patients have enrolled significant numbers of patients that displayed HTPR under clopidogrel.[23,24] Data from haemodialysis patients [25] or from randomized controlled trials have remarkably shown that despite the switch to a novel more potent P2Y12 inhibitor up to 20% of the patients continue to exhibit a HTPR phenotype if they have already been it on clopidogrel treatment.[25-27] For this purpose, HTPR in clopidogrel can be assumed as an independent risk factor for HTPR in patients treated with novel platelet inhibitors. In our treatment naive study cohort, we found satisfying levels of platelet inhibition as consequence of treatment with novel P2Y12 inhibitors. In a next step, we aimed to characterize the response to aspirin treatment as previous observational studies have shown that HTPR to arachidonic acid (AA) which reflects low responsiveness to acetylsalicylic acid might occur in up to 45% of all patients.[19,28] In contrast HTPR to P2Y12 inhibitors, the pathomechanism of low responsiveness to aspirin is less well characterized. Current literature indicates that it is a consequence of pharmacodynamic characteristics (under dosing, poor absorption and noncompliance) and altered metabolism (stress-induced generation of COX-2 and polymorphisms in the COX-1).[19,29] HTPR to aspirin translates into markedly increased risk of all course mortality and risk for stent thrombosis.[10] In our study cohort, we found 12% of our patients to exhibit HTPR while on treatment with aspirin. Nevertheless, ACS patients are treated with DAPT within the highly vulnerable phase of 12 months post-ACS, in which low response to one antiplatelet agent might be compensated by the second agent. Not surprisingly, dual nonresponsiveness to antiplatelet treatment has been shown to increase the risk for cardiovascular events.[19,30] Current literature shows that up to 9% of all patients treated with clopidogrel and aspirin exhibit this high-risk phenotype. However, the prevalence of dual nonresponsiveness to novel P2Y12 inhibitors and aspirin in ACS patients was unknown. To the best of our knowledge, we are the first to investigate the incidence of dual nonresponsiveness when using ticagrelor or prasugrel in combination with aspirin. We observed that only 1% of ticagrelor- and 2% of prasugrel-treated patients were classified as displaying a HTPR phenotype to both aspirin an ADP-blockers, further reassuring the benefit of DAPT in those patients.

Regarding bleeding risk, the majority of our patients exhibited LTPR with 70% of the prasugrel- and 65% of the ticagrelor-treated patients exhibiting this exaggerated treatment response. In line with our previous findings,[24] we observed an skewed distribution of HTPR vs. LTPR for prasugrel (3% vs. 70%, respectively) and ticagrelor (4% vs. 64%; respectively) as compared to published data for clopidogrel (41% vs. 20%; respectively).[24,31] Overall, the proportion of patients with moderate on-treatment reactivity (MTPR) was in line with previous observations (prasugrel: 27%, ticagrelor: 31%),[24] which is comparable to MTPR rates in clopidogrel-treated patients.[20,32] Bearing in mind that roughly only one third of all patients exhibit this phenotype with the most favourable net clinical benefit, we ought to identify discriminators of response phenotype to antiplatelet agents. The most potent discriminator of the response to aspirin was age, as those older than 49 years of age, especially female patients, displayed the lowest platelet aggregation values. This might explain why females, especially older ones, under treatment with aspirin might be at increased bleeding risk, as reported in several studies.[33,34] In opposite, younger males had less potent aspirin effect on average, which, however, was sufficient in the majority of them with only 12% HTPR.

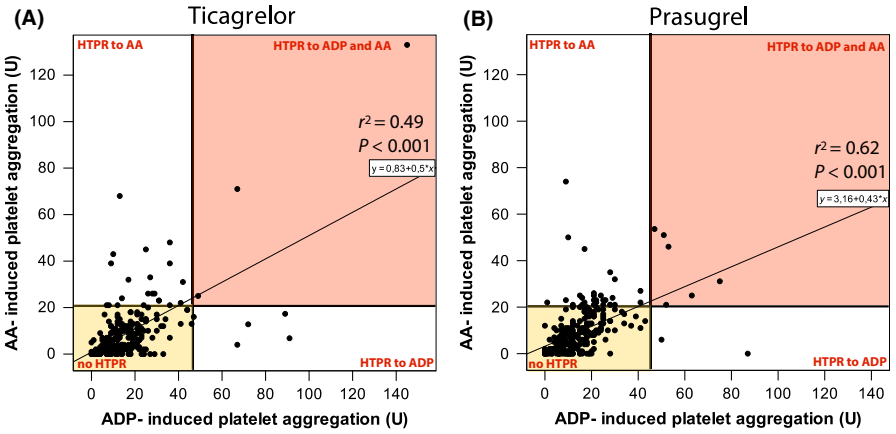


**FIGURE 5** Scatter plot showing the correlation between arachidonic acid (AA) and adenosine diphosphate (ADP) – induced aggregation assessed by multiple electrode aggregometry (MEA) in ticagrelor (A) and prasugrel treated patients (B). HTPR: high on treatment platelet reactivity

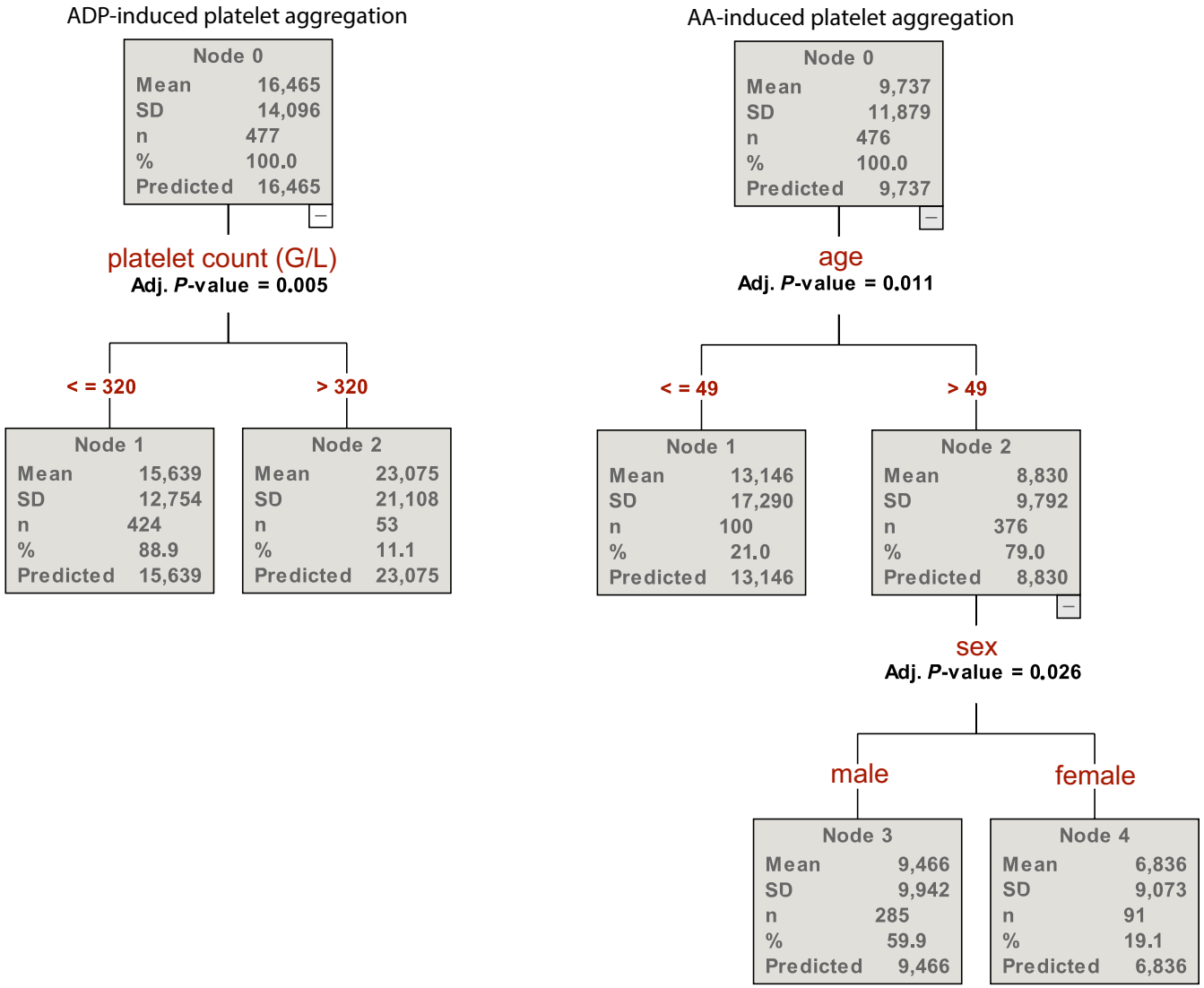


**FIGURE 6** Chi-squared automatic interaction detection (CHAID) analysis for the discriminators of arachidonic acid (AA) and adenosine diphosphate (ADP) – induced aggregation assessed by multiple electrode aggregometry (MEA)

For ADP antagonists, we identified platelet count (>320 g/L) as a risk factor for higher platelet reactivity, which might be only of minor clinical importance. Platelet count also emerged as a predictor of response to clopidogrel in several studies.[35] Interestingly, and in contrary to clopidogrel,[2,7] no co-morbidities or other clinical characteristic

influenced the response to prasugrel or ticagrelor. Especially in diabetes mellitus, an attenuated response to clopidogrel and aspirin therapy has been shown.[36-39] However, in our study cohort we could not identify diabetes as discriminator in the chi-squared automatic interaction detection analysis for inadequate treatment response, proving that the novel more potent antiplatelet agents ticagrelor and prasugrel seem to overcome this shortcoming.

### 4.1 | Limitations

The main limitation of the study is lack of outcome data. Additionally, the time point of platelet function testing might have influenced our observations. Platelet function testing was performed within the hospital stay after the maintenance dose administration of P2Y12 receptor inhibitors, and not direct during the acute phase of infarction. Mean platelet volume has been shown to be an indicator of platelet activation and plays a pivotal role in the pathophysiology of atherosclerotic disease and is an independent risk factor for acute myocardial infarction.[40-42] Subsequently, some observations proposed that MPV can predict nonresponsiveness to clopidogrel treatment.[43,44] Unfortunately, in the present study we did not record MPV or other platelet indices. However, previous studies have shown that MPV does not affect the response to novel antiplatelet therapies and does not influence the risk of HTPR with ticagrelor.[45] For this purpose, we assume that the influence might be negligible in our study cohort treated with potent novel antiplatelet agents.

## 5 | CONCLUSION

High on-treatment reactivity to dual antiplatelet therapy is infrequent in patients concomitantly treated with potent P2Y12 inhibitors and aspirin in acute coronary syndrome. Age and gender were predictors of platelet reactivity to aspirin, which was lowest in patients older than 49 years of age, especially in female patients, suggesting that they might be at increased risk for bleeding. Whether such association exists, it must be explored in outcome studies.

## CONFLICT OF INTEREST

DvL received honoraria for advisory boards from AstraZeneca and Daiichi Sankyo. JSM received lecture or consultant fees from Daaichi, Eli Lilly, Bayer, Roche and Astra Zeneca. All other authors report no conflict of interests.

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