

Protease-Activated Receptor-Mediated Platelet Aggregation In Patients With Type 2 Diabetes On Potent P2Y12 Inhibitors

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Research Article

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Abstract

Background: Dual antiplatelet therapy is a cornerstone in the secondary prevention of ischemic events following percutaneous coronary intervention (PCI) with stent implantation. The new, more potent adenosine diphosphate (ADP) P2Y₁₂ receptor inhibitors prasugrel and ticagrelor have been shown to improve patients' outcomes. Whether or not these drugs have equal efficacy in diabetic as in non-diabetic individuals is disputed. Furthermore, platelets can be activated by thrombin, which is, at least in part, independent of ADP-inducible activation. Protease-activated receptor (PAR)-1 and -4 are thrombin receptors on human platelets activated by the agonists SFLLRN and AYPGKF, respectively. In the current study, we sought to compare the *in vitro* efficacy of prasugrel (n=121) and ticagrelor (n=99) to inhibit PAR-mediated platelet activation in patients with type 2 diabetes (n=55).

Materials and Methods: We compared P2Y₁₂-, PAR-1- and PAR-4-mediated platelet aggregation as assessed by multiple electrode platelet aggregometry between prasugrel- and ticagrelor-treated patients without and with type 2 diabetes who underwent acute PCI.

Results: There were no significant differences of on-treatment platelet aggregation in response to ADP, SFLLRN and AYPGKF between patients on prasugrel or on ticagrelor. Diabetic and non-diabetic patients responded equally. There was no significant correlation between either; ADP-, SFLLRN-, or AYPGKF-inducible platelet aggregation and levels of HbA1c or the body mass index. However, we observed patients with high residual platelet reactivity to SFLLRN and AYPGKF in all cohorts.

Conclusion: Prasugrel and ticagrelor inhibit platelet aggregation in diabetic and non-diabetic patients to a similar extent.

Introduction

The world health organization lists cardiovascular disease as the main cause of death in industrialized countries. Patients with diabetes are at particular risk. They frequently suffer from coronary artery disease often resulting in myocardial infarction (MI). Accordingly, many diabetics need to undergo percutaneous coronary intervention (PCI) with stent implantation. Secondary prevention following acute PCI comprises dual antiplatelet therapy (DAPT) with aspirin and one of the newer potent ADP P2Y₁₂ receptor blockers prasugrel or ticagrelor.

Clinical studies indicate, however, that despite state-of-the art DAPT approximately 10% have additional ischemic events [1,2,3]. Whether prasugrel or ticagrelor are more advantageous following acute PCI is a matter of ongoing debate [2,4,5,6], and in particular for patients with type 2 diabetes, this question cannot be definitively answered by clinical outcome data, so far. The ISAR-React 5 trial revealed no significant differences between the two drugs with respect to the 1-year outcome comprising MI, death, or ischemic stroke in diabetic patients, but prasugrel to be the better choice over ticagrelor in the overall study population [2]. Further analyses of this population confirmed the efficacy of ticagrelor to be comparable

with that of prasugrel in diabetics [7]. In line with these data, ticagrelor and prasugrel have been found to be similarly effective in another cohort. [8].

A variety of conditions may, particularly in diabetics, lead to an impaired response to antiplatelet therapy. First, platelet turnover may be accelerated in diabetes, and therefore young platelets that are naïve to inhibitory drugs may be more present in the circulation [9], particularly if administered once (prasugrel) versus twice daily (ticagrelor). Second, the enteric resorption of any drug can be affected in diabetes [10]. Therefore, the required *in vivo* concentration of the drug to achieve platelet inhibition may not be reached. Thereby, resorption may differ from one drug to the next. Third, prasugrel but not ticagrelor needs to be metabolized to become a potent platelet inhibitor but metabolism can be affected in diabetes [11]. Fourth, alterations of the platelet membrane due to hyperglycemia and failure of insulin to inhibit platelet signaling may be responsible for an increased reactivity to ADP [12,13]. Fifth, other clinical conditions known to be associated with high on-treatment residual platelet reactivity to ADP (HRPR ADP), which are frequent in diabetic patients might play a role, like kidney failure [14], high BMI [15], inflammation [16], drug–drug interactions [11]. These conditions may affect the potency of one drug more than of the other one.

Alternatively, adverse ischemic outcomes after PCI may be attributable to intact platelet aggregation via the human thrombin receptors protease-activated receptor (PAR)-1 and PAR-4 [17,18,19,20], overcoming P2Y₁₂ inhibition. Thrombin is a very strong endogenous platelet agonist [18] and its ongoing generation has been particularly recognized in diabetes and/or obese patients [21,22].

Thrombin-mediated platelet activation is not specifically targeted by current state-of-the-art DAPT with aspirin and a potent P2Y₁₂ antagonist following MCI, and may therefore reflect P2Y₁₂-independent platelet activation.

We therefore evaluated platelets' *in vitro* response to PAR-1 and -4, the two important thrombin receptors on human platelets, in diabetic patients receiving either prasugrel or ticagrelor after PCI. Differences between the two drugs may affect the treatment of diabetic patients following acute PCI.

Patients

The study population included 220 consecutive patients with MI, receiving DAPT with aspirin (loading dose of 250 mg, thereafter 100 mg once daily), and either prasugrel (loading dose of 60 mg, thereafter 10 mg once daily, n = 121), or ticagrelor (loading dose of 180 mg, thereafter 90 mg twice daily, n = 99) after acute PCI and stenting. There were 165 non-diabetic patients and 55 patients with diabetes type 2. Diabetes was based on the patients' history, a HbA1c value >6.5% and regular anti-diabetic therapy. The selection of the respective P2Y₁₂ inhibitor was at the discretion of the attending physician. All individuals were Caucasians from the Viennese urban area. All patients gave their written informed consent for participation. We excluded patients who had any major surgery during the last week before enrollment, or treatment with either vitamin K antagonists (phenprocoumon, acenocoumarol, warfarin), or rivaroxaban, apixaban, dabigatran, or edoxaban, respectively. Moreover, patients were excluded if they were taking

nonsteroidal anti-inflammatory drugs, ticlopidine, or dipyridamole. We also excluded patients with known bleeding disorders, severe hepatic failure, known qualitative defects in platelet function, a history of heparin-induced thrombocytopenia, or malignant myeloproliferative disorders. Patients were not eligible if they had a platelet count <100000 or $>450000/\mu\text{L}$, or a hematocrit $<30\%$.

The study was approved by the Ethics Committee of the Medical University of Vienna, in accordance with the declaration of Helsinki and its later amendments.

Materials And Methods

Blood samples were obtained median 72 hours (range 66 hours to 74 hours) after PCI, when both Prasugrel and Ticagrelor were at, or approached the steady state [23,24]. A butterfly needle (21-gauge, 0.8 × 19 mm; Greiner Bio-One, Kremsmünster, Austria) was inserted by aseptic venipuncture into an antecubital vein. All blood samples were collected by the same physician. Periprocedural platelet activation was avoided by discharging the first 3mL of blood. Blood samples were collected in hirudine-coated tubes (Roche Diagnostics, Mannheim, Germany), which then were immediately gently inverted. All samples were investigated by whole blood impedance aggregometry (multiple electrode aggregometry, MEA), as previously described [25,26]. One Multiplate test cell contains 2 independent sensor units and 1 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, the agonists ADP (P2Y₁₂ agonist, 6.5 μmol/L), SFLLRN (PAR-1 agonist, 32 μmol/L) or AYPGKF (PAR-4 agonist, 645 μmol/L), all from Roche Diagnostics), were added and aggregation was continuously recorded for six minutes. The respective concentrations of agonists have been established in our laboratory [27]. The adhesion of activated platelets to the electrodes led to an increase of 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. The thresholds for HRPR ADP, HRPR SFLLRN and HRPR AYPGKF were >47 AU [28], >71 AU, and >54 AU, respectively [27].

Statistical analysis

We used the Statistical Package for Social Sciences (SPSS version 24.0; SPSS, Chicago, IL) to conduct all statistical analyses. Continuous data are shown as median and interquartile ranges whereas categorical data are depicted as numbers and percentages. The non-parametric Mann-Whitney U-test was used to assess differences between continuous variables. The chi-square test was used to calculate differences between categorical values. Spearman's correlation was used to evaluate correlations. Two-sided P values <0.05 were considered statistically significant.

Results

Clinical, laboratory and procedural characteristics of patients with diabetes type 2 and non-diabetic patients receiving prasugrel or ticagrelor are shown in Table 1.

The study cohort comprised 121 patients on prasugrel and 99 patients on ticagrelor. In the prasugrel and the ticagrelor group 26 and 29 patients had type 2 diabetes, respectively. Diabetic patients treated with either prasugrel or ticagrelor were younger than non-diabetic individuals ($P= 0.03$, and $P=0.05$ respectively), indicating their earlier onset of atherosclerosis. Patients on ticagrelor had significantly higher serum creatinine levels ($P<0.001$). As expected, diabetic patients in both, prasugrel and ticagrelor groups, had significantly higher HbA1c levels ($P<0.001$).

Residual platelet aggregation in response to ADP/ SFLLRN / AYPGKF

We first evaluated residual platelet response to ADP in prasugrel- and ticagrelor-treated patients. Patients on prasugrel responded similarly to platelet activation by ADP as patients on ticagrelor ($p=0.349$, Figure 1a). Among the patients on prasugrel, diabetic patients responded similarly as non-diabetic patients ($p=0.148$). Of note, 2 non-diabetic patients had HRPR ADP as their levels of AU was >47 , the cut-off for adequate platelet inhibition by ADP P2Y₁₂ receptor antagonists. Their responses to SFLLRN was 92 AU and 106 AU and to AYPGKF 62 AU and 100 AU, respectively.

Interestingly, among patients on ticagrelor, patients with type 2 diabetes had significantly lower MEA ADP AU values than non-diabetic patients ($p=0.019$, Figure 1a).

Patients on prasugrel responded similarly to platelet activation by SFLLRN as patients on ticagrelor ($P=0.227$, Figure 1b). Furthermore, there were no significant differences regarding the response to SFLLRN between diabetic and non-diabetic patients in both treatment groups (prasugrel: $p= 0.7129$, ticagrelor: $p=0.144$, Figure 1b).

Patients on prasugrel responded similarly to platelet activation by AYPGKF as patients on ticagrelor ($p=0.861$, Figure 1c). Moreover, there were no significant differences between diabetic and non-diabetic patients in both treatment groups (prasugrel: $p=0.399$, ticagrelor: $p=0.175$ Figure 1c).

In the prasugrel group 119 patients had on-treatment residual platelet reactivity below the cut-off for HRPR ADP. Of these, 51 patients (43%) had HRPR SFLLRN and 71 (60%) had HRPR AYPGKF. In the diabetic population we identified 12 patients (46%) with HRPR SFLLRN and 16 patients (62%) with HRPR AYPGKF.

All ticagrelor-treated patients had on-treatment residual platelet reactivity below the cut-off for HRPR ADP. Of these patients 30 (30%) had HRPR SFLLRN and 55 (56%) had HRPR AYPGKF. In the diabetic population, 7 patients (24%) had HRPR SFLLRN and 11 patients (38%) had HRPR AYPGKF.

As P2Y₁₂ inhibition also affects the response to PAR stimulation we subsequently assessed the correlations between on-treatment residual platelet reactivity in response to ADP and in response to both PAR agonists, SFLLRN and AYPGKF. Again, diabetic patients were evaluated separately from non-diabetic patients. We observed a similar correlation between the responses to ADP and SFLLRN in diabetic patients and in non-diabetic patients on prasugrel and ticagrelor (all $r= 0.556$, $p<0.001$). There was also a

significant correlation between the response to ADP and AYPGKF in diabetic patients on prasugrel and ticagrelor ($r= 0.273$, $p=0.048$), as well as in non-diabetic patients ($r= 0.527$, $p=0.001$).

The two platelet thrombin receptors PAR-1 and PAR-4 play a significant mutual role in platelet activation. Therefore, it was of interest to determine if the residual responsiveness to the specific PAR agonists SFLLRN and AYPGKF correlates similarly in diabetic patients compared to non-diabetic patients treated with prasugrel or ticagrelor. We observed significant correlations between the responses to SFLLRN and AYPGKF in diabetic patients ($r=0.711$, $p<0.001$) and in non-diabetic patients ($r= 0.556$, $p<0.001$).

Residual platelet aggregation in response to ADP/ SFLLRN / AYPGKF and the correlation to HbA1c

Metabolic control may influence the responsiveness to ADP. We therefore correlated levels of HbA1c, as a measure of a long-term blood glucose control, with on-treatment residual platelet aggregation in response to ADP. There was no significant correlation between levels of HbA1c and the response to ADP in the study population. ($r=0.07$, $p>0.05$, Figure 2a).

Based on the assumption that impaired diabetic control influences particularly thrombin-inducible platelet activation, we also assessed the correlation of HbA1c levels with the platelet response to the PAR-1 and -4 agonists SFLLRN and AYPGKF, respectively. There were no significant correlations between levels of HbA1c and the response to SFLLRN ($r= 0.09$, $p>0.05$, Figure 2b) or the response to AYPGKF ($r= 0.07$, $p>0.05$, Figure 2c) in the study population.

Residual platelet aggregation in response to ADP/ SFLLRN / AYPGKF and the correlation to the BMI

As high BMI levels may impair the response to treatment with prasugrel or ticagrelor we assessed the correlation between BMI and the residual response to. There was no significant correlation between levels of the BMI and the response to ADP ($r= -0.02$, $p>0.05$, Figure 3a) in the study population.

High levels of BMI have been associated with increased thrombin generation and PAR-1-mediated platelet aggregation [16]. We therefore anticipated a correlation between BMI and the responsiveness to the PAR-1 and PAR-4 agonists. However, there was no significant correlation between BMI and the response to SFLLRN ($r=0.06$, $p>0.05$ Figure 3b), or the response to AYPGKF ($r= 0.07$, $p>0.05$ Figure 3c) in the study population.

Discussion

This study investigated if prasugrel and ticagrelor are equally potent in the inhibition of PAR-1- and PAR-4-mediated platelet aggregation in diabetic patients. Our data show no significant differences between platelet PAR-1 and PAR-4 response in patients on prasugrel when compared to patients on ticagrelor. Diabetic and non-diabetic patients responded similarly. Moreover, the response to the agonists did not correlate with levels of HbA1c or BMI.

Prasugrel and ticagrelor inhibited the platelet response to ADP at a similar level, i.e. all patients on ticagrelor and all but 2 patients on prasugrel exhibited a residual platelet response below the internationally-agreed threshold of 47 AU for HRPR ADP. This threshold has been established based on clinical data from patients on clopidogrel therapy [28], and may therefore need to be adjusted for the newer drugs.

Our findings are in contrast to a previous report, showing stronger platelet suppression in the prasugrel than the ticagrelor group [29]. These findings were similar if samples were analyzed median 11.8 hours or 38.5 hours after loading with the respective P2Y₁₂ inhibitor [29]. Whether or not the different results in our cohort can be explained by the later time point of blood sampling, namely 72 hours after PCI and stent implantation in our study, remains unclear. Of note, at this later time point patients had already received either prasugrel or ticagrelor for three consecutive days, possibly representing a better steady-state after the intervention [23,24]. In accordance with our data ticagrelor has been found to allow a higher platelet reactivity inhibition compared to prasugrel in patients with type 2 diabetes [30].

Unexpectedly, our data show that platelets from diabetic patients are more susceptible to P2Y₁₂ inhibition by ticagrelor than non-diabetics. No statistical significant differences were seen between diabetics and non-diabetics in the prasugrel group (even after exclusion of the two patients with HRPR). Prasugrel needs conversion in the liver and intestines into its active metabolite, which then binds covalently to the P2Y₁₂ receptor [31]. This biotransformation to the active substance is more likely to be impaired if metabolism is affected by diabetes. Thus, patients with diabetes who are on prasugrel may have a reduced generation of the active metabolite and consequently less platelet inhibition compared to non-diabetic patients [32,33].

In contrast to prasugrel, the cyclopentyl-triazolopyrimidine ticagrelor acts directly without prior biotransformation. While the active metabolites of prasugrel irreversibly block the P2Y₁₂ receptor, ticagrelor inhibits ADP-induced signalling reversibly in a non-competitive manner at a different binding site [34,35,36,37]. Further pointing at *in vitro* differences between prasugrel and ticagrelor- inhibited platelets are previous findings that ticagrelor exerts a stronger inhibitory effect on toll-like receptor-1/2 and PAR mediated platelet activation in acute coronary syndrome than prasugrel [38]. As diabetic patients may have a higher inflammatory status and thus cytokine storms with up-regulated TLR receptors, it may be speculated that ticagrelor, but not prasugrel, “calms” the innate immune system in diabetics thereby being particularly effective in inhibiting their platelets. In line with these findings, Jeong et al. found a significant reduction of inflammatory markers in the ticagrelor group when comparing prasugrel with ticagrelor in a randomized manner, suggesting more clinical benefit by ticagrelor in this population [39].

It has been shown that diabetics have a higher thrombin generation potential than non-diabetic patients [21]. Further, it is possible that ongoing thrombin generation is a main reason for recurrent events despite potent inhibition of ADP- inducible platelet activation. In detail, platelets, which have been successfully inhibited for ADP-inducible activation, may still be responsive to platelet activation via PAR.

We therefore assumed that particularly platelets from diabetic patients are poised for activation by thrombin and the exogenous addition of the respective platelet agonists for PAR-1 and PAR-4 will reveal higher activation values in diabetic compared to non-diabetic patients. However, in the overall cohort, we saw no difference in the response to the PAR-directed agonists SFLLRN or AYGPKF in prasugrel- versus ticagrelor-treated patients. Further analyses revealed also no difference between diabetic and non-diabetic patients with the two platelet inhibitors indicating their equal potency to suppress platelet activation via the two PAR receptors. In our in vitro investigations, we observed a significant correlation between platelet response to ADP and platelet response to both PAR agonists. This correlation was similar in diabetic and non-diabetic individuals. The observation indicates that a very potent inhibition of ADP-inducible platelet activation leads also to inhibition of thrombin-inducible platelet activation. It shall be emphasized, that almost all patients in the prasugrel cohort and all patients on ticagrelor had an adequately inhibited response to ADP. However, among these patients who adequately responded to P2Y₁₂ inhibition by prasugrel or ticagrelor we identified a number of individuals who still responded to activation by either SFLLRN or AYGPKF or both. The latter ones were seen equally frequent in the diabetic as in the non-diabetic cohort. We therefore conclude that both drugs were equally potent platelet inhibitors of ADP-inducible platelet activation, but less potent to inhibit PAR- mediated platelet activation, in diabetic and non-diabetic patients.

Metabolic control is beneficial in diabetic patients for their response to antiplatelet therapy. Clinically, ticagrelor was shown to reduce the primary endpoint, all-cause mortality, and stent thrombosis in patients with levels of HbA1c above the median [40]. High BMI levels have been associated with high thrombin generation potential [22]. We followed the hypothesis, that ongoing thrombin generation is responsible for increased platelet responsiveness to PAR-1- and PAR-4-mediated platelet activation. Thereby, we investigated, if the platelet responsiveness to PAR-1 and PAR-4 stimulation is correlated with levels of HbA1c, as an indicator of long-term metabolic control, and with BMI, a rough overall indicator of impaired metabolism, which can be associated with inflammation [22]. The data from our study indicate that neither HbA1c levels nor BMI were associated with the response to platelet activation by the two PAR agonists. Apparently, the potency of the newer inhibitors prasugrel and ticagrelor can overcome the unfavorable conditions, like poor diabetic control or high BMI, that have been associated with a reduced platelet inhibition in the past.

Study Limitations

Each patients' sample was analyzed only once. The laboratory staff was blinded to the origin of the samples. Samples were only obtained at a single time point, namely 72 hours after PCI. We cannot rule out that results would be slightly different, if samples are analyzed at other time points.

We cannot rule out that the non-diabetic cohort included a few patients with pre-diabetes. However, we were interested to investigate differences between overt diabetes and non-diabetes.

Our study was not designed to assess clinical outcomes. The aim of the study was the evaluation of the *in vitro* response to PAR agonists despite potent suppression of ADP-inducible platelet activation in diabetic patients. According to our data a considerable number of patients show platelet activation by PAR *in vitro*, irrespective if diabetic or not, without a significant difference between the patients receiving prasugrel and those receiving ticagrelor. Whether or not individuals, who still respond to PAR-mediated platelet aggregation, can benefit from inhibition of thrombin-mediated platelet activation, e.g. with the PAR-1 inhibitor vorapaxar [41] or the thrombin inhibitor dabigatran [42,43] needs to be evaluated in clinical trials. However, a therapeutic regimen aimed at PAR inhibition may be considered only for very high-risk patients with defined residual response to PAR-mediated platelet reactivity.

Conclusion

To the best of our knowledge, this is the first study addressing PAR-1 and PAR-4 mediated *in vitro* platelet aggregation in diabetic patients on DAPT with either prasugrel or ticagrelor. The results obtained with the two P2Y₁₂ blockers were similar, without any difference between diabetic and non-diabetic patients. Moreover, levels of metabolic control, as estimated by HbA1c and BMI shared no correlation with residual platelet response to ADP, or the PAR-1 and PAR-4 specific agonists.

Abbreviations

ADP	adenosine diphosphate
AU	aggregation units
AYPGKF	Ala-Tyr-Pro-Gly-Lys-Phe
BMI	body mass index
DAPT	dual anti-platelet therapy
HRPR	high residual platelet reactivity
MEA	multiple electrode aggregometry
MI	myocardial infarction
PAR-1	protease-activated receptor-1
PAR-4	protease-activated receptor-4
PCI	percutaneous coronary intervention
SFLLRN	Ser-Phe-Leu-Leu-Arg-Asn

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Medical University of Vienna, in accordance with the declaration of Helsinki and its later amendments.

Consent for publication

All patients gave their written informed consent for participation.

Data availability

Raw data generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Competing Interests

All authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Authors' relationships and contributions

BP assembled data, performed statistical analyses, designed graphs and wrote the manuscript, PPW recruited the patients, assembled their clinical data, advised statistical analyses, revised the manuscript, KH advised the study, revised the manuscript, SP assisted in data interpretation and writing the manuscript, TG initiated and designed the study, and wrote the manuscript. All authors consented to the submission of the Manuscript in its current form.

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Availability of data

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

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Table

Table 1: Characteristics of patients with diabetes type 2 and non-diabetic patients receiving prasugrel or ticagrelor

Prasugrel (n = 121)

	non diabetics (n = 95)	diabetics (n = 26)
Demographics		
Age, y	55 (46-62)	60 (55-66)
Male sex, n (%)	77 (81)	20 (77)
BMI, kg/m ²	28 (25-31)	28 (26-30)
Medical history		
Previous MCI, n (%)	14 (15)	4 (15)
Hypertension, n (%)	59 (61)	19 (73)
Active smoking, n (%)	56 (59)	16 (62)
Stent implantation, n (%)	95(100)	26 (100)
Number of stents/patient	1 (1-2)	1 (1-2)
Laboratory data		
HbA1c, mmol/mol	36.6 (33.9-38.8)	54.1 (42.6-69.4)
HbA1c (%)	5.5 (5.25-5.70)	7.1 (6.05-8.50)
Serum creatine, mg/dL	0.87 (0.76-1.00)	0.92 (0.80-1.09)
Platelet count, G/L	199 (166-228)	198 (156-237)
High sensitivity C-reactive protein, mg/dL	1.26 (0.73-2.60)	2.65 (0.90-5.59)
Hemoglobin, g/dL	13.95 (13.10-14.78)	13.90 (13.25-14.95)
White Blood Cell Count, G/L	8.57 (7.69-10.06)	10.31 (8.49-11.96)
Medication		
Statins, n (%)	92 (97)	26 (100)
Beta blockers, n (%)	89 (94)	26 (100)
ACE inhibitors, n (%)	77 (81)	23 (88)
Calcium channel blockers, n (%)	7 (7)	3 (12)
Angiotensin receptor blockers, n (%)	13 (14)	4 (15)
Diabetes therapy		
GLP-1-Receptor-Agonists, n (%)	0 (0)	0 (0)
Gliptins, n (%)	0 (0)	5 (19)
Sylfonylureas, n (%)	0 (0)	3 (12)
Metformin, n (%)	0 (0)	16 (62)
Glitazones, n (%)	0 (0)	1 (4)
SGLT-2 inhibitors, n (%)	0 (0)	4 (15)

Figures

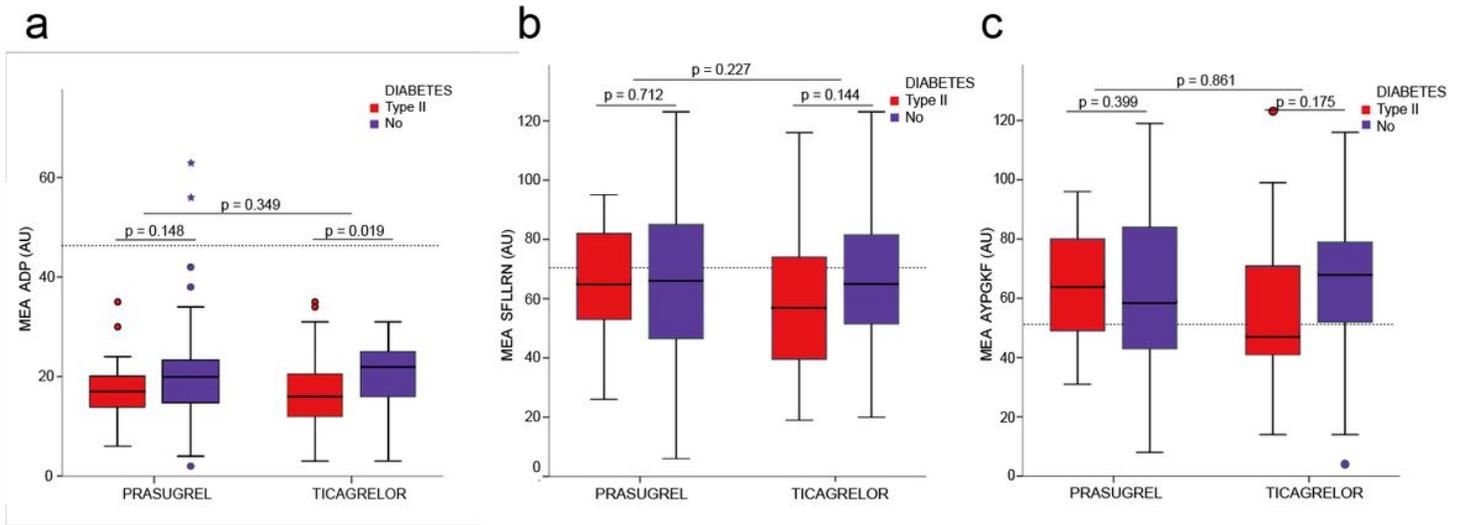


Figure 1

On-treatment residual platelet aggregation in response to (A) ADP, (B) SFLLRN and (C) AYGPKF in diabetic and non-diabetic patients receiving prasugrel or ticagrelor. The boundaries of the box show the lower and upper quartile of data. 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 boxes length. Outliers are shown by full circles and extremes by asterisk. The dotted line indicates the threshold for high on-treatment residual platelet reactivity (ADP: >47AU, SFLLRN: >71AU, AYGPKF: >54AU) AU, aggregation units; MEA, multiple electrode aggregometry

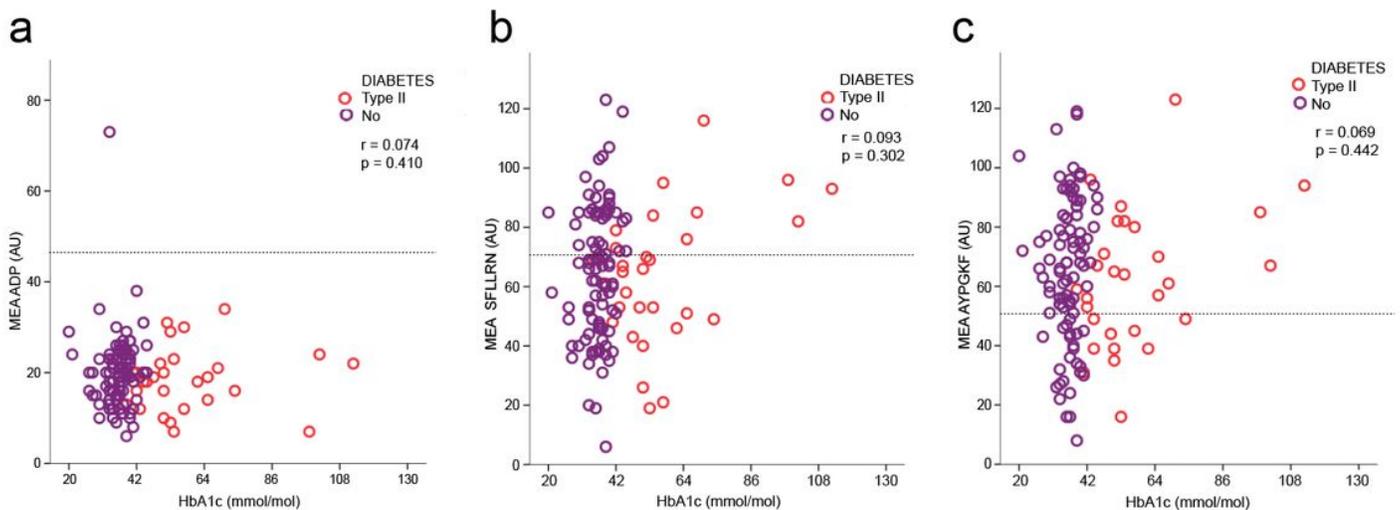


Figure 2

Correlations between HbA1c and on-treatment residual platelet aggregation in response to ADP (A), SFLLRN (B) and AYGPKF (C) in diabetic and non-diabetic patients receiving prasugrel or ticagrelor. The correlation between levels of HbA1c and the response to agonists in diabetic and non-diabetic patients on either prasugrel or ticagrelor. Each circle represents a single patient. The dotted line indicates the

threshold for high residual platelet reactivity (design as in Figure 1). AU, aggregation units; MEA, multiple electrode aggregometry.

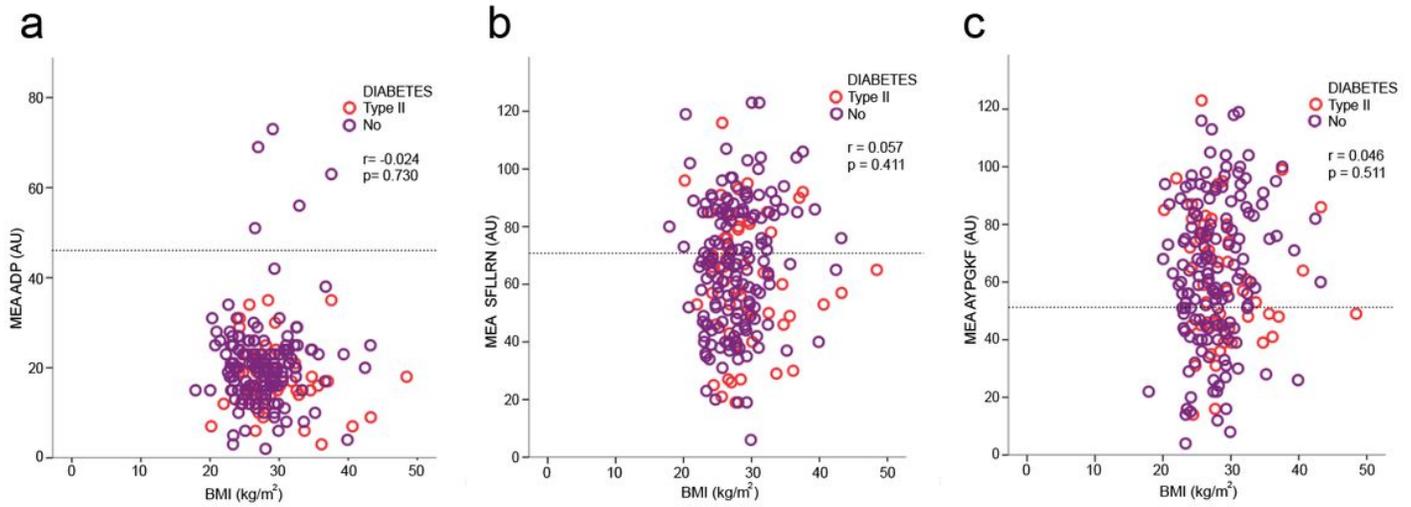


Figure 3

Correlations between BMI and on-treatment residual platelet aggregation in response to ADP (A), SFLLRN (B) and AYGPKF (C) in diabetic and non-diabetic patients receiving prasugrel or ticagrelor. Experimental design as in Figure 2.