

Impact of Diabetes Mellitus on the Pharmacodynamic Effects of Ticagrelor Versus Clopidogrel in Troponin-Negative Acute Coronary Syndrome Patients Undergoing Ad Hoc Percutaneous Coronary Intervention

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Background—Diabetes mellitus (DM) is associated with enhanced platelet reactivity and impaired response to oral antiplatelet therapy, including clopidogrel. This post hoc analysis investigated the pharmacodynamic effects of ticagrelor versus clopidogrel loading dose (LD) in troponin-negative acute coronary syndrome patients with or without DM undergoing percutaneous coronary intervention in the Ad Hoc PCI study.

Methods and Results—Patients randomized (1:1) to receive ticagrelor 180 mg LD or clopidogrel 600 mg LD were assessed by diabetic status. Platelet reactivity (P2Y₁₂ reaction units [PRU] on VerifyNow[®] assay) was measured pre-LD, at 0.5, 2, and 8 hours post-LD, and at the end of the percutaneous coronary intervention. The primary endpoint was PRU levels 2 hours post-LD; secondary endpoints included rates of high on-treatment platelet reactivity (PRU \geq 208). Of 100 randomized patients, 51 received ticagrelor (DM, n=20; non-DM, n=31) and 49 clopidogrel (DM, n=16; non-DM, n=33). At 2 hours post-LD, mean (SD) PRU levels in DM patients were 130.1 (111.7) with ticagrelor versus 287.6 (71.9) with clopidogrel (mean [95%CI] difference -157.5 [-225.3 , -89.8]; $P<0.001$); in non-DM patients, they were 75.3 (75.7) versus 243.0 (72.4) (mean difference -167.7 [-207.1 , -128.3]; $P<0.001$). High on-treatment platelet reactivity rates at 2 hours post-LD were also significantly ($P<0.001$) reduced with ticagrelor versus clopidogrel in DM and non-DM patients. Between-treatment differences for PRU and high on-treatment platelet reactivity were not significant at earlier time points but were at 8 hours post-LD ($P<0.001$).

Conclusions—Compared with clopidogrel, ticagrelor achieved faster, enhanced platelet inhibition and reduced high on-treatment platelet reactivity rates, in DM and non-DM patients.

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Key Words: ad hoc percutaneous coronary intervention • clopidogrel • diabetes mellitus • platelet reactivity • ticagrelor

Diabetes mellitus (DM) is associated with a high risk of recurrent cardiovascular events.¹ Compared with non-DM patients, those with DM (particularly type 2) have greater atheromatous plaque burden² and also an increased tendency to activate and aggregate platelets despite antiplatelet therapy.³⁻⁷ In particular, studies have consistently shown that

DM patients have impaired clopidogrel-induced antiplatelet effects, leading to high on-treatment platelet reactivity (HPR).³⁻⁷ Importantly, HPR is a well-established marker of recurrent ischemic events, including stent thrombosis, and may thus contribute to the high event rates observed in DM patients undergoing percutaneous coronary intervention

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(PCI).^{8,9} These observations underscore the need for more potent platelet-inhibiting therapies in DM patients, particularly among those undergoing PCI.

Ticagrelor is an oral, direct-acting cyclopentyltriazolopyrimidine antiplatelet agent that binds reversibly to the P2Y₁₂ receptor and has a more rapid onset and robust antiplatelet effect, with low HPR rates, compared with clopidogrel.^{10,11} This pharmacodynamic profile is indeed advantageous across the spectrum of patients with acute coronary syndromes, irrespective of management, leading to a reduction in ischemic recurrences, including cardiovascular mortality and stent thrombosis.¹² However, there are relatively few studies evaluating the pharmacodynamic effects of ticagrelor versus clopidogrel in DM patients. The Ad Hoc PCI study investigated the periprocedural pharmacodynamic effects of ticagrelor versus clopidogrel loading dose (LD) in troponin-negative acute coronary syndrome (ACS) patients who were not pretreated with a P2Y₁₂ receptor inhibitor, showing ticagrelor to be associated with prompt (by the end of the PCI procedure) and persistent (up to 8 hours post-LD) potent platelet inhibitory effects.¹³ The aim of this study was to investigate the pharmacodynamic effects of ticagrelor versus clopidogrel according to diabetic status in the Ad Hoc PCI study.

Methods

Study Design and Patient Population

This was a post hoc analysis of the Ad Hoc PCI study, a prospective, open-label, randomized, multicenter, parallel-group, phase 4 pharmacodynamic study performed at 15 centers in the United States (clinicaltrials.gov identifier: NCT01603082). The study methods and main results, including safety outcomes, have been published previously.¹³ Briefly, troponin-negative, P2Y₁₂ inhibitor-naive, non-ST-segment elevation ACS patients (women or men, aged ≥ 18 years) undergoing ad hoc PCI were randomly assigned (1:1) to treatment with ticagrelor 180 mg LD or clopidogrel 600 mg LD, administered in the catheterization laboratory before starting PCI, on a background of aspirin therapy. Patients assigned to the ticagrelor group received a ticagrelor 90-mg maintenance dose 12 hours (± 1 hour) after the LD. The clopidogrel maintenance dose was chosen by the investigator for ongoing clinical care.

The study was blinded throughout the PCI procedure until ~ 1 hour after sheath removal. The study then became open-label for clinical staff, but the pharmacodynamic operator remained blinded to the patient's treatment.

Platelet reactivity was assessed as P2Y₁₂ reaction units (PRU) by VerifyNow[®] assay (Accriva Diagnostics, San Diego, CA), measured pre-LD, at 0.5, 2, and 8 hours post-LD, and at

the end of PCI. The primary endpoint was PRU at 2 hours after ticagrelor versus clopidogrel LD, and secondary endpoints included PRU at all other time points, percentage reduction from baseline in PRU, percentage inhibition of platelet aggregation (IPA; measured with VerifyNow[®]), and rates of HPR (defined as PRU ≥ 208) at all time points.¹³

Diabetic status was defined according to medical history as reported by the patient at the time of enrollment. However, randomization was not stratified by diabetic status.

The study complied with the Declaration of Helsinki, International Conference on Harmonisation/Good Clinical Practice guidelines, and applicable regulatory requirements. Institutional review board approval was obtained, and all patients provided informed consent.

Statistical Analysis

A repeated-measures analysis of variance model was used to examine the interaction effect between treatment group and diabetic status and to evaluate the treatment effect within DM and non-DM groups across time points for PRU levels. Continuous variables were reported as mean (SD), and categorical variables were reported as frequencies and percentages. Continuous variables were analyzed by using 2-sample t test to compare the treatment effect between ticagrelor and clopidogrel groups by diabetic status (DM and non-DM) and between DM and non-DM within each treatment group at each time point. Categorical variables were analyzed by using the Fisher exact test to compare the treatment effect between ticagrelor and clopidogrel groups by diabetic status.

The pharmacodynamic population included all patients with pharmacodynamic data and without a major protocol deviation and excluded patients with pre-LD PRU < 150 but included patients with a missing predose PRU measurement, as previously reported.¹³

Baseline and disease characteristics were reported by treatment group for all randomized patients in DM and non-DM groups. Treatment differences between ticagrelor and clopidogrel groups in PRU, percentage reduction from baseline in PRU, percentage IPA, and HPR rates were analyzed based on the pharmacodynamic population.

Results

Patient Population

Between July 2012 and June 2014, 100 patients were randomized to ticagrelor or clopidogrel. Of these, 36 patients had DM ($n=20$ in the ticagrelor group and $n=16$ in the clopidogrel group), and 64 were non-DM ($n=31$ in the ticagrelor group and $n=33$ in the clopidogrel group) (Table).

Table. Baseline Characteristics (All Randomized Patients)

Variable	DM (n=36)			Non-DM (n=64)		
	Ticagrelor (n=20)	Clopidogrel (n=16)	P Value	Ticagrelor (n=31)	Clopidogrel (n=33)	P Value
Treatment for DM, n						
Insulin only	5	2		N/A	N/A	
Oral antidiabetic agents only	8	6		N/A	N/A	
Insulin and oral antidiabetic agents	6	6		N/A	N/A	
Diet-controlled	1	2		N/A	N/A	
Age, y, mean (SD)	59.1 (10.1)	64.9 (9.0)	0.079	60.8 (11.3)	62.1 (9.2)	0.601
≥65 years, n (%)	4 (20.0)	8 (50.0)	0.061	11 (35.5)	11 (33.3)	0.854
Women, n (%)	7 (35.0)	5 (31.3)	0.818	10 (32.3)	8 (24.2)	0.475
Race, n (%) [*]			0.881			0.732
White	8 (47.1)	9 (60.0)		25 (86.2)	24 (77.4)	
Black	7 (41.2)	5 (33.3)		4 (13.8)	6 (19.4)	
Other [†]	2 (11.8)	1 (6.7)		0 (0)	1 (3.2)	
BMI >30 kg/m ² , n (%) [‡]	11 (55.0)	11 (68.8)	0.405	13 (43.3)	13 (39.4)	0.753
Cardiovascular risk factors, n (%)						
Dyslipidemia	15 (75.0)	15 (93.8)	0.138	23 (74.2)	27 (81.8)	0.466
Hypertension	19 (95.0)	15 (93.8)	0.877	25 (80.6)	33 (100)	0.008
Chronic kidney disease (GFR <60 mL/min per 1.73 m ²)	3 (15.0)	4 (25.0)	0.458	4 (12.9)	3 (9.1)	0.629
Prior cardiovascular disease and cardiovascular procedures, n (%)						
Congestive heart failure (past or current)	1 (5.0)	2 (12.5)	0.425	5 (16.1)	1 (3.0)	0.091
Peripheral arterial occlusive disease	0 (0)	0 (0)		1 (3.2)	1 (3.0)	0.964
Stroke, any	0 (0)	0 (0)		1 (3.2)	1 (3.0)	0.964
Transient ischemic attack, any	0 (0)	1 (6.3)	0.264	0 (0)	1 (3.0)	0.335
Prior myocardial infarction	1 (5.0)	6 (37.5)	0.016	8 (25.8)	10 (30.3)	0.691
Prior PCI	8 (40.0)	5 (31.3)	0.560	11 (35.5)	17 (51.5)	0.201
Prior coronary artery bypass graft	1 (5.0)	6 (37.5)	0.016	4 (12.9)	8 (24.2)	0.251

BMI indicates body mass index; DM, diabetes mellitus; GFR, glomerular filtration rate; N/A, not applicable; PCI, percutaneous coronary intervention.

*Five patients in the ticagrelor group (3 DM and 2 non-DM) and 3 in the clopidogrel group (1 DM and 2 non-DM) were missing race values.

[†]Asian, American Indian, or Alaskan Native.

[‡]Data missing for 1 patient in the ticagrelor group (non-DM).

The pharmacodynamic population consisted of 92 patients: 45 in the ticagrelor group (19 DM and 26 non-DM) and 47 in the clopidogrel group (16 DM and 31 non-DM). Eight patients were excluded from the pharmacodynamic population: 6 in the ticagrelor group (1 with predose PRU <150, 1 missing analyzable data, and 4 with a protocol deviation), and 2 in the clopidogrel group (both with a protocol deviation).

Baseline characteristics are reported in the Table. DM patients treated with clopidogrel were significantly more likely than ticagrelor-treated patients to have had a prior myocardial infarction or to have undergone coronary artery bypass graft (both $P=0.016$), and they were also somewhat older (mean age 64.9 years versus 59.1 years [$P=0.079$], with 50% versus 20% aged ≥ 65 years [$P=0.061$]).

Pharmacodynamic Results

No statistically significant interaction effect between treatment group and diabetic status was observed for PRU levels across all time points. At 2 hours post-LD (primary endpoint), mean (SD) PRU levels in DM patients were 130.1 (111.7) with ticagrelor and 287.6 (71.9) with clopidogrel, with a mean (95% CI) between-treatment difference of -157.5 (-225.3 , -89.8 ; $P<0.001$) (Figure 1). In non-DM patients, PRU levels at 2 hours post-LD were 75.3 (75.7) and 243.0 (72.4) with ticagrelor and clopidogrel, respectively, with a between-treatment difference of -167.7 (-207.1 , -128.3 ; $P<0.001$).

At 0.5 hour post-LD and end-of-PCI (mean 0.6 hour post-LD) time points, there was no significant difference in mean PRU levels between ticagrelor and clopidogrel in the DM or

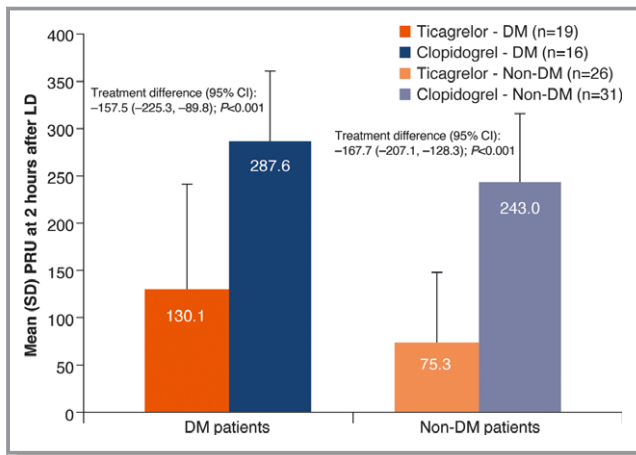


Figure 1. P2Y₁₂ reaction units (PRU) at 2 hours after loading dose (LD) (pharmacodynamic population). At 2 hours post-LD, mean (SD) PRU levels were significantly reduced with ticagrelor vs clopidogrel in DM and non-DM patients. The mean (95%CI) between-treatment differences in each case were -157.5 (-225.3 , -89.8 ; $P < 0.001$) and -167.7 (-207.1 , -128.3 ; $P < 0.001$), respectively. DM indicates diabetes mellitus.

non-DM groups (Figure 2). At 8 hours post-LD, mean (SD) PRU levels remained significantly lower with ticagrelor versus clopidogrel in both DM patients (57.2 [57.5] versus 255.3 [85.7]; between-treatment difference [95%CI] -198.1 [-249.7 , -146.6]; $P < 0.001$) and non-DM patients (34.3 [33.3] versus 173.1 [77.8]; -138.8 [-173.0 , -104.5];

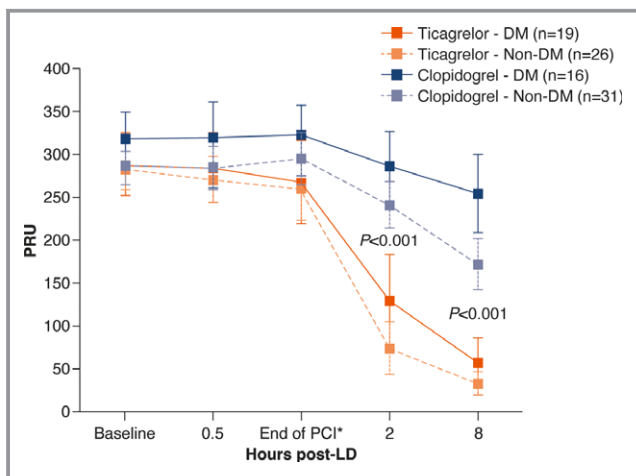


Figure 2. Time course of P2Y₁₂ reaction units (PRU) at 0.5, 2, and 8 hours after loading dose (LD) and at the end of percutaneous coronary intervention (PCI) (pharmacodynamic population). Mean (SD) PRU levels remained significantly lower with ticagrelor vs clopidogrel at 8 hours post-LD in DM patients (57.2 [57.5] vs 255.3 [85.7]; between-treatment difference [95% CI] -198.1 [-249.7 , -146.6]; $P < 0.001$) and non-DM patients (34.3 [33.3] vs 173.1 [77.8]; -138.8 [-173.0 , -104.5]; $P < 0.001$). *Mean time to end of PCI was 0.6 hour. DM indicates diabetes mellitus.

$P < 0.001$) (Figure 2). In DM patients, the changes in PRU at 2 hours post-LD represented mean reductions from baseline of 56.2% and 10.9% with ticagrelor and clopidogrel, respectively, with corresponding values in non-DM patients of 73.2% and 14.1% ($P < 0.001$ in each case) (Figure 3A and 3B). The between-treatment difference remained significant at 8 hours post-LD ($P < 0.001$). Mean percentage IPA was also significantly greater with ticagrelor versus clopidogrel at 2 and 8 hours post-LD in DM and non-DM patients ($P < 0.001$ in each case) (Figure 3C and 3D).

Mean PRU levels in DM versus non-DM patients were not significantly different at any time point in the ticagrelor group, but were significantly different at 8 hours post-LD in the clopidogrel group (255.3 versus 173.1; $P = 0.002$) (Figure 4).

Ticagrelor significantly reduced the rates of HPR, compared with clopidogrel, at 2 and 8 hours post-LD, irrespective of diabetic status. At 2 hours post-LD, HPR was present in 21.1% of DM patients in the ticagrelor arm and in 93.3% in the clopidogrel arm ($P < 0.001$), and in 7.7% and 71.0% of non-DM patients ($P < 0.001$), respectively (Figure 5). Corresponding values at 8 hours post-LD were 5.9% and 81.3% of DM patients ($P < 0.001$), and 0.0% and 37.9% of non-DM patients ($P < 0.001$) (Figure 5).

Exploratory analyses using the repeated-measures model showed that, within both the DM and non-DM groups, the treatment effects across time points on PRU between ticagrelor and clopidogrel were all statistically significant ($P < 0.001$).

Discussion

The results of this analysis indicate that ticagrelor has consistently more potent antiplatelet effects compared with clopidogrel in both DM and non-DM patients presenting with a low-risk ACS and undergoing ad hoc PCI. Importantly, the study also confirms how clopidogrel-induced antiplatelet effects are markedly impaired among DM patients, with HPR rates $> 80\%$ even at 8 hours after LD administration. Given the prognostic implications associated with HPR, the more favorable pharmacodynamic effects of ticagrelor as shown in this study make this a more desirable agent, particularly among DM patients, including those with low-risk ACS who have not been pretreated with a P2Y₁₂ receptor inhibitor undergoing ad hoc PCI. These findings are of clinical relevance, given that a considerable number of ACS patients undergoing ad hoc PCI are not pretreated with a P2Y₁₂ receptor inhibitor, particularly in the United States, underscoring the need for effective platelet inhibition in the peri-PCI period among these patients.¹⁴⁻¹⁶

Enhanced platelet reactivity in DM patients results from a complex process of interaction between biochemical factors

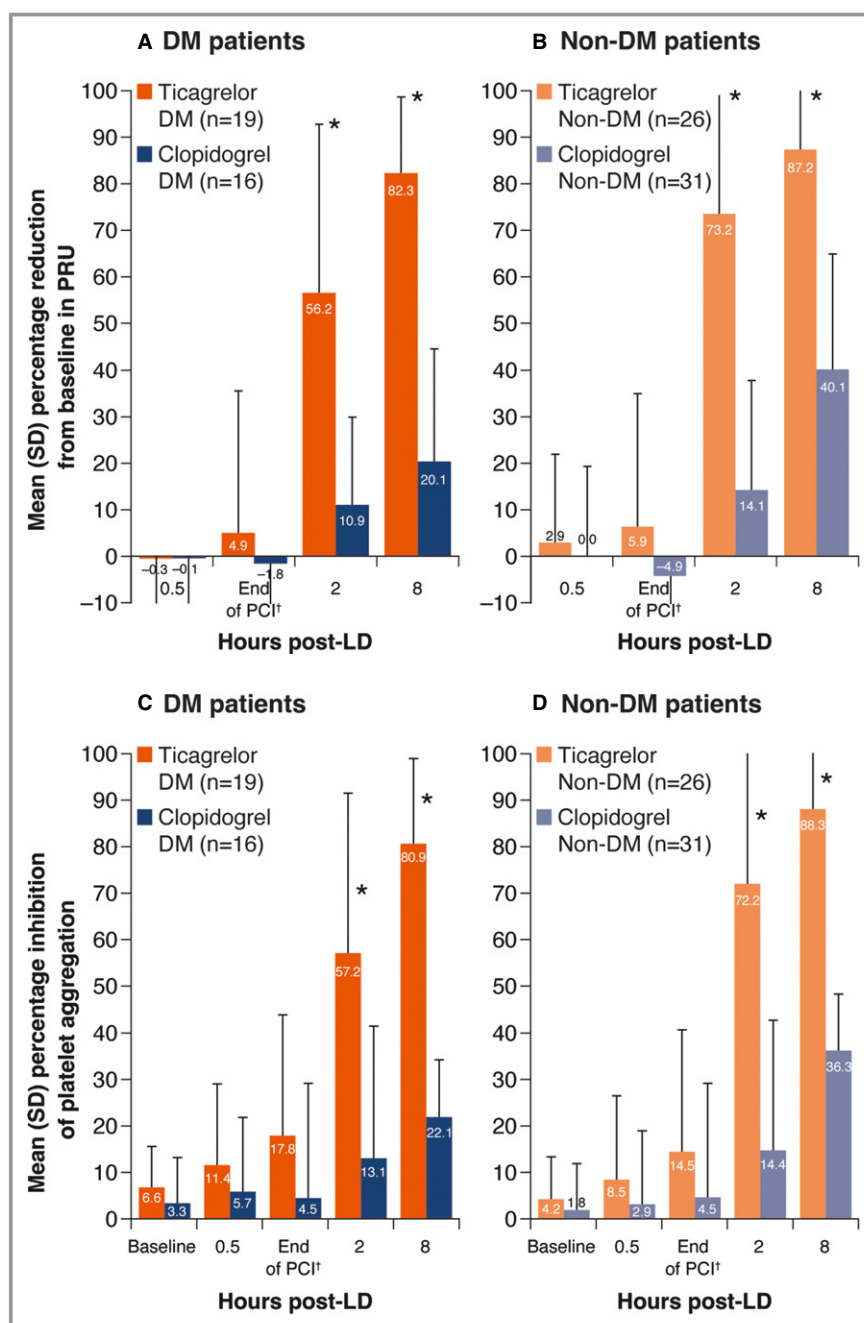


Figure 3. Percentage change from baseline in platelet reactivity. Mean percentage reduction from baseline in P2Y₁₂ reaction units (PRU) in (A) diabetes mellitus (DM) patients and (B) non-DM patients; and mean percentage inhibition of platelet aggregation in (C) DM patients and (D) non-DM patients (pharmacodynamic population). Mean percentage change in PRU and IPA was significantly greater with ticagrelor vs clopidogrel at 2 and 8 hours post-LD in both DM and non-DM patients ($P < 0.001$ in each case). * $P < 0.001$ for ticagrelor vs clopidogrel. †Mean time to end of PCI was 0.6 hour. IPA indicates inhibition of platelet aggregation; LD, loading dose; PCI, percutaneous coronary intervention.

such as hyperglycemia, insulin resistance/deficiency, oxidative stress, endothelial dysfunction, and lipid abnormalities, all leading to increased expression of platelet glycoprotein IIb/IIIa receptors, loss of insulin-related inhibition of the P2Y₁₂ pathway, upregulation of genes involved in thrombus

generation, increased generation of adhesion molecules, and several other features of increased platelet reactivity.³⁻⁷ These findings contribute to the higher rates of HPR observed in DM patients compared with non-DM patients and therefore can explain why DM patients carry a higher risk of thrombotic

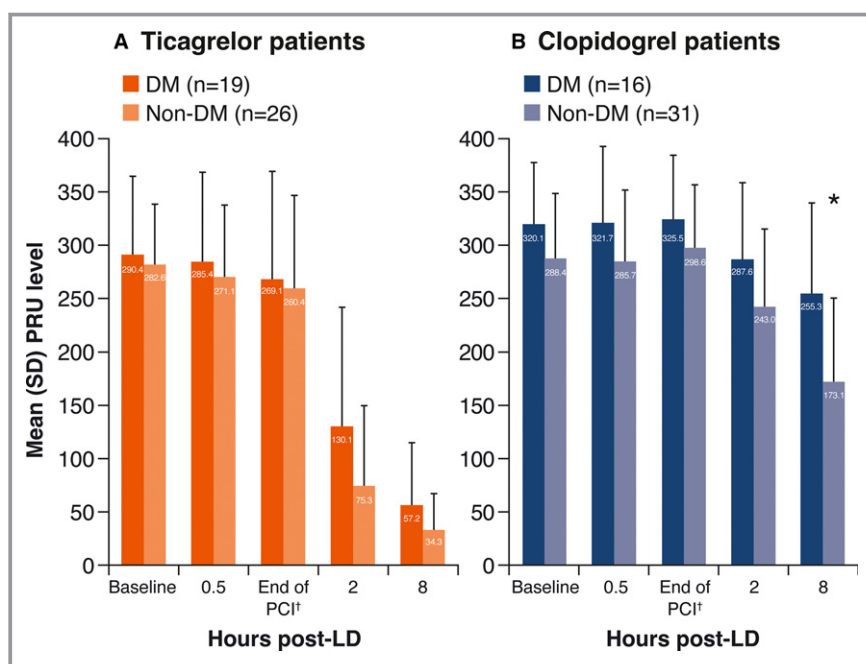


Figure 4. P2Y₁₂ reaction units (PRU) levels in (A) ticagrelor patients and (B) clopidogrel patients by diabetic status at 0.5, 2, and 8 hours after loading dose (LD) and at end of percutaneous coronary intervention (PCI) (pharmacodynamic population). Mean PRU levels in DM vs non-DM patients were similar at each time point in the ticagrelor group but were significantly different at 8 hours post-LD in the clopidogrel group ($P=0.002$). * $P=0.002$ for DM vs non-DM. †Mean time to end of PCI was 0.6 hour.

complications.³⁻⁹ Overall, these observations underscore the need for optimizing platelet inhibitory effects in DM patients.

In the acute phase of treatment, glycoprotein IIb/IIIa receptor inhibitors have been shown to achieve potent platelet inhibitory effects and to be particularly efficacious, including reducing mortality, among DM patients presenting with an ACS.¹⁷ However, these agents have been largely abandoned in routine practice given the increased risk of bleeding complications.¹⁸ Until the availability of the newer-generation P2Y₁₂ receptor inhibitors prasugrel and ticagrelor, strategies to optimize platelet inhibition in DM patients have included high clopidogrel dosing regimens and adjunctive therapy with cilostazol.^{19,20}

The association between HPR and variable response to clopidogrel has preceded the development of more potent antiplatelet agents that provide more rapid and predictable pharmacodynamic effects in both DM and non-DM populations.^{21,22} In the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS)-3 study, for example, prasugrel 60 mg LD followed by 10 mg once daily was shown to result in higher inhibitory antiplatelet activity than high-dose clopidogrel (600 mg LD followed by 150 mg once daily) in DM patients with coronary artery disease (CAD).²³ Similarly, a subgroup analysis from a study of Hispanic patients with stable CAD showed that ticagrelor 180 mg LD followed by 90 mg twice daily resulted in faster and greater inhibition of platelet

activity compared with clopidogrel 600 mg LD then 75 mg once daily in DM and non-DM patients, including significantly lower rates of HPR.²⁴ These findings are in line with the post hoc analysis presented here, which also demonstrated a rapid and more intensive antiplatelet effect with ticagrelor, compared with clopidogrel, in both DM and non-DM patients, in this case with troponin-negative ACS. Furthermore, the OPTIMUS-4 trial conducted in type 2 DM patients with CAD found that platelet reactivity was significantly reduced compared with baseline values with both prasugrel and ticagrelor LD and maintenance doses.²⁵ The degree of platelet inhibition was similar with both drugs at all time points according to all assays except for VerifyNow[®], which showed a greater reduction in PRU levels with ticagrelor at 1 week.

The observed pharmacodynamic effects of ticagrelor and clopidogrel illustrate some key differences between the 2 drugs. Whereas ticagrelor is a direct-acting agent, clopidogrel is a prodrug, requiring metabolic activation in the liver by cytochrome P450.²⁶ Moreover, a large proportion of the clopidogrel prodrug is inactivated by esterases in the blood before it even reaches the liver.^{11,22} In DM patients, the reduced responsiveness is amplified by impaired metabolism of clopidogrel, resulting in ~40% reduced exposure to the active metabolite compared with non-DM patients.⁷ Because ticagrelor does not follow the same metabolic pathway as clopidogrel, this explains, at least in part, the disparity between

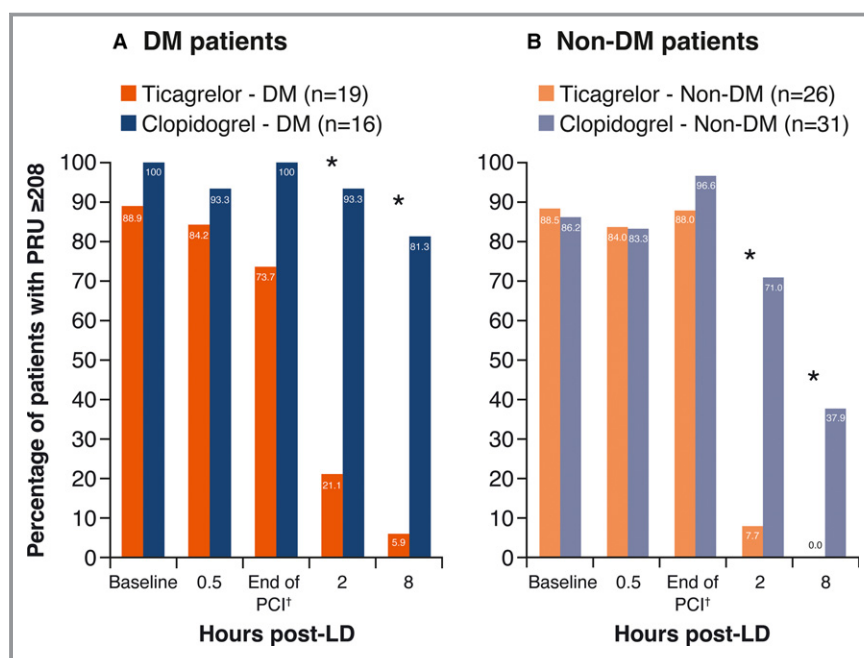


Figure 5. Percentage of (A) diabetes mellitus (DM) patients and (B) non-DM patients with high on-treatment platelet reactivity (HPR: P2Y₁₂ reaction units [PRU] ≥208) (pharmacodynamic population). Rates of HPR were significantly lower with ticagrelor vs clopidogrel at 2 and 8 hours post-LD in both DM and non-DM patients ($P < 0.001$ in each case). At 8 hours post-LD, 81.3% of clopidogrel-treated DM patients still had HPR compared with only 5.9% of those treated with ticagrelor. * $P < 0.001$ for ticagrelor vs clopidogrel. †Mean time to end of PCI was 0.6 hour. LD indicates loading dose; PCI, percutaneous coronary intervention.

the 2 drugs in terms of speed and degree of platelet reactivity and HPR rates in DM and non-DM patients. There is also a proportion of patients who are poor responders to clopidogrel, including—but far from limited to—those with genetic variations, such as CYP2C19 polymorphisms.^{27–30} Data from the Escalating Clopidogrel by Involving a Genetic Strategy—Thrombolysis in Myocardial Infarction 56 (ELEVATE-TIMI 56) trial in patients with CAD showed that those with both DM and the CYP2C19 polymorphism required 4-fold increases in the clopidogrel maintenance dose to achieve the platelet inhibitory effects seen in patients without these risk factors.³¹

The favorable pharmacodynamic profile of ticagrelor irrespective of DM status, as shown in this study, may explain the consistent benefit of ticagrelor in DM and non-DM patients in the PLATElet Inhibition and Patient Outcomes (PLATO) trial, a large-scale clinical investigation of high-risk patients with ACS, demonstrating superior outcomes with ticagrelor.^{12,32} In the diabetes substudy from PLATO, ticagrelor achieved reductions in the primary composite endpoint, all-cause mortality, and stent thrombosis, compared with clopidogrel, with no increase in major bleeding. The results were also consistent for DM patients with or without ongoing insulin treatment.³² More recently, a secondary prevention study composed of patients with prior (1–3 years) myocardial

infarction showed a consistent ischemic benefit, albeit at the expense of more bleeding, of ticagrelor versus placebo in DM and non-DM patients.³³ The clinical benefit of ticagrelor versus placebo in type 2 DM patients with stable CAD not undergoing PCI is currently unknown and is being evaluated in the ongoing Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS) trial (NCT01991795). The benefit of ticagrelor in stable patients undergoing elective PCI is unknown and will be investigated in the Assessment of Loading with the P2Y₁₂ Inhibitor Ticagrelor or Clopidogrel to Halt Ischemic Events in Patients Undergoing Elective Coronary Stenting (ALPHEUS) trial, which will also include both DM and non-DM patients (NCT02617290).

The Ad Hoc PCI study enrolled low-risk patients undergoing PCI, and the results observed in this study, in combination with the clinical ischemic benefits seen in PLATO, may be specific to patients undergoing PCI, as there was no comparison with patients not treated with PCI. To this end, ticagrelor monotherapy did not show any significant benefit compared with clopidogrel monotherapy for ischemic event reduction in patients with peripheral artery disease in the Examining Use of ticagrelor In paD (EUCLID) trial³⁴ or compared with aspirin for the prevention of recurrent events in patients with prior stroke or transient ischemic attack in the Acute Stroke or Transient

Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial.³⁵ Although there was no treatment interaction by diabetic status in the latter study, the results from our current study in the context of these recent primary and secondary prevention trials suggest that the benefit of ticagrelor, in addition to aspirin, may be limited to DM patients undergoing PCI.

In this study, there were 3 subjects with diet-controlled DM. In order to assess a potential interaction between diet-controlled DM and those diabetic subjects treated with antidiabetic therapy, an additional sensitivity analysis excluding the 3 diet-controlled patients was performed on the primary endpoint of PRU at 2 hours post-LD for the DM group. The result is consistent with the primary result with these patients included.

The results of the current study demonstrate the pharmacodynamic benefits (greater inhibition of platelet reactivity and reduced rates of HPR) of intensified antiplatelet therapy in low-risk ACS diabetic patients with a ticagrelor LD versus a clopidogrel LD in the peri-intervention period. How this pharmacodynamic benefit translates into potential therapeutic strategies (such as intensified antiplatelet therapy with ticagrelor in the peri-intervention period followed by less intensive antiplatelet therapy) should be the focus of further clinical studies.

Study Limitations

The Ad Hoc PCI study is a pharmacodynamic study and therefore was not designed or powered to assess clinical events. The safety and efficacy of ticagrelor in elective or urgent PCI, including high-risk patients with DM, are currently being evaluated in a separate study (NCT02270242). Furthermore, this was a post hoc analysis, and patients were not randomized within DM and non-DM groups. Also, due to the small numbers of patients in each group (DM and non-DM), the results should be interpreted with caution.

The current study demonstrates that mean (SD) baseline PRU levels in the ticagrelor group were similar in DM and non-DM patients: 290.4 (74.6) and 282.6 (56.1), respectively. Many studies have shown that baseline platelet reactivity is actually higher in diabetic patients. The discrepant findings from our study may be the result of an artifact due to the relatively small number of subjects, in addition to the broad range of values within the DM and non-DM patient groups: median (min-max) 282 (163-451) versus 276 (197-418), respectively.

It should also be noted that there were differences in several baseline characteristics between the randomized treatment arms when stratified by DM status (ie, age, prior myocardial infarction, and prior coronary artery bypass grafting). The influence of these baseline characteristics, and that of the different numbers of patients excluded from

analysis in each treatment arm when stratified by DM status, on platelet reactivity cannot be excluded. The use of only 1 platelet function test may also be considered a limitation, as well as the lack of pharmacokinetic measurements in this analysis. Furthermore, HbA1c values were not collected prospectively, so we were unable to determine any association between HbA1c levels and platelet response as a marker of well versus poorly controlled DM. Finally, this study included only P2Y₁₂ inhibitor-naive patients, and the pharmacodynamic effects of ticagrelor in patients pretreated with clopidogrel were not explored.

Conclusions

In troponin-negative ACS patients undergoing ad hoc PCI, compared with clopidogrel, ticagrelor was associated with more rapid and enhanced platelet inhibition irrespective of diabetic status. Importantly, HPR rates remained markedly elevated in DM patients treated with clopidogrel, a phenomenon that was largely overcome by ticagrelor therapy. The results indicate that ticagrelor may be an important option for nonpretreated low-risk ACS patients with DM undergoing ad hoc PCI.

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