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The effect of ticagrelor and clopidogrel on angiographic parameters according to diabetic status in patients with ST elevation myocardial infarction

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Aim. We aimed to compare post-interventional angiographic outcomes of ticagrelor versus clopidogrel according to glycosylated hemoglobin (HbA_{1c}) levels in patients with ST-elevation myocardial infarction.

Material and methods. The study included a total of 532 patients, with 334 receiving ticagrelor (62,8%) and 198 clopidogrel (37,2%). Diabetic status of the patients was assessed with HbA_{1c}. TIMI flow grade and TIMI frame count were calculated and compared between two groups.

Results. TIMI flow grade 3 was higher and TFC was lower after percutaneous coronary intervention of the infarct-related artery in patients treated with ticagrelor compared to clopidogrel (89,2% vs. 73,7%; p<0,001, 20 vs. 24; p<0,001). There was a positive correlation between the increases in HbA_{1c} and TFC levels in the whole group (r=0,225; p=0,004). In subgroup analysis, higher HbA_{1c} levels did not affect TFC in patients using ticagrelor (r=-0,060; p=0,326 for patients with no-reflow, r=-0,133; p=0,321 for patients with TIMI-3 flow). While level of HbA_{1c} did not affect TFC in patients with TIMI-3 flow, the presence of post-procedural no-reflow caused worsening of TFC in patients using clopidogrel as HbA_{1c} levels increased (r=0,374; p=0,005).

Conclusion. Ticagrelor was found to be better in terms of angiographic parameters regardless of diabetes.

Keywords: ticagrelor, TIMI flow grade, TIMI frame count.

Relationships and Activities: none.

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BMI — body mass-index, CI — confidence interval, DM — diabetes mellitus, HbA_{1c} — glycosylated hemoglobin, HT — hypertension, IPA — platelet inhibition, LAD — left anterior descending artery, MI — myocardial infarction, NR — no-reflow, OR — odds ratio, RCA — right coronary artery, PCI — percutaneous coronary intervention, PPCI — primary PCI, STEMI — ST elevated MI, TFC — TIMI frame count.

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Влияние тикагрелора и клопидогреля на ангиографические показатели в зависимости от статуса сахарного диабета у пациентов с инфарктом миокарда с подъемом сегмента ST

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Цель. Сравнить результаты ангиографии при применении тикагрелора и клопидогрела в зависимости от уровня HbA_{1c} у пациентов с инфарктом миокарда с подъемом сегмента ST.

Материал и методы. Всего в исследование было включено 532 пациента, из них 334 получали тикагрелор (62,8%) и 198 – клопидогрел (37,2%). Статус сахарного диабета оценивался по уровню HbA_{1c}. Степень кровотока (TIMI flow grade) и степень антеградного кровотока по количеству кадров (TIMI frame count, TFC) рассчитывали и сравнивали между двумя группами.

Результаты. У пациентов, получавших тикагрелор, кровоток 3 степени по TIMI регистрировался чаще, а показатель TFC был меньше после чрескожного коронарного вмешательства на инфаркт-связанной артерии, по сравнению с клопидогрелом (89,2% vs 73,7%; p<0,001, 20 vs 24; p<0,001). Отмечена положительная корреляционная связь между повышением уровня HbA_{1c} и TFC во всей группе (r=0,225; p=0,004). При анализе подгрупп более высокие уровни HbA_{1c} не влияли на TFC у пациентов, принимавших тикагрелор (r=-0,060; p=0,326 для пациентов с феноменом отсутствия дистального коронарного кровотока (no-reflow), r=-0,133; p=0,321 для пациентов с кровотоком 3 степени по TIMI). В то время как уровень HbA_{1c} не влиял на TFC у пациентов с кровотоком 3 степени по TIMI, наличие феномена no-reflow было связано с ухудшением TFC у пациентов, принимавших клопидогрел, по мере увеличения уровня HbA_{1c} (r=0,374; p=0,005).

Заключение. Было установлено, что прием тикагрелора связан с более благоприятными ангиографическими показателями независимо от сахарного диабета.

Ключевые слова: тикагрелор, степень кровотока по TIMI, степень антеградного кровотока по количеству кадров.

Отношения и деятельность: нет.

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The major cause of morbidity and mortality in patients with diabetes mellitus (DM) is primarily cardiovascular disease [1]. The presence of diabetes is an independent predictor of early and late mortality after acute myocardial infarction (MI) [2]. Diabetes is also considered a highly vascular disease with both microvascular and macrovascular complications [3]. The glycosylated hemoglobin (HbA_{1c}) is an important blood parameter in the diagnosis of DM and determination of blood glucose control. HbA_{1c} level is an important predictor of mortality and morbidity in patients with acute coronary syndrome and it can also provide an insight into the effectiveness of antiplatelet therapy [4, 5]. Therefore, intensified platelet inhibition is needed in patients with elevated HbA_{1c} levels undergoing percutaneous coronary intervention (PCI) [6].

Primary PCI (PPCI) promotes an earlier and sustained restoration of epicardial flow in the target vessel in the treatment of acute MI [7]. TIMI flow grade and TIMI frame count (TFC), which evaluates angiographic coronary blood flow as a result of primary PCI, is an important scoring system associated with the development of heart failure, impaired left ventricular ejection fraction and mortality after ST elevated MI (STEMI) [8, 9]. Ticagrelor is an oral non-thienopyridine $P2Y_{12}$ inhibiting agent with a reversible and direct action on the receptor that provides faster, greater, and more consistent platelet inhibition than clopidogrel [10]. In the subgroup of the Platelet Inhibition and patient Outcomes (PLATO) trial, ticagrelor reduced the primary endpoint — a composite of cardiovascular death, myocardial infarction, or stroke — compared to clopidogrel by 12% [11]. Although there are studies in the literature showing that ticagrelor is appropriate treatment option for acute myocardial infarction, limited data showing the effect of ticagrelor on angiographic markers of epicardial reperfusion in patients with DM [12]. In our study, we aimed to investigate the effect of ticagrelor on angiographic parameters according to HbA_{1c} levels in patients with STEMI.

Material and methods

Study Population. This retrospective study was conducted in patients with STEMI who underwent primary PCI. STEMI was defined as typical angina >20 minutes with ST segment elevation >0,1 mV in at least two consecutive electrocardiography leads. Clopidogrel (600 mg) or ticagrelor (180 mg) with aspirin (300 mg) were administered to each patient at the time of diagnosis in emergency department and rapidly transferred to catheterization laboratory approximately in 5 minutes. Patient groups were not randomized, antiplatelet loading was performed according to the clinician's preference. During primary PCI, unfractionated heparin was administered at the appropriate dose. Demographic, clinical, and laboratory parameters including age, gender, presence of hypertension (HT) and DM, smoking status, body mass index (BMI), the levels of HbA_{1c}, blood glucose and serum creatinine, lipid profile, and complete blood count parameters were obtained from the hospital records. Patients with history of coronary artery bypass surgery, malignancy, oral anticoagulant use, prior use of antiplatelets, history of cerebrovascular event, those diagnosed with hemoglobinopathy or chronic liver disease were excluded from the study. The study was conducted following principles of the Declaration of Helsinki for Human Research and approved by the institutional ethics committee.

Percutaneous Coronary Intervention Procedure and Evaluation. Coronary angiography was routinely performed through the femoral approach using Judkins catheters (Philips DCI-SX Integris Monoplane system). Primer PCI was applied to the culprit vessel in all patients. The lesions were prepared in accordance to German Consensus recommendations of a balloon/vessel diameter ratio of 0,8-1,0, with the aim of achieving a final diameter [13]. Patients who underwent PCI were treated with direct stenting if possible, otherwise stent implantation was done after balloon angioplasty. Angiograms were recorded at 15 frames/s. The calculated value was doubled to reach the standardized 30 frames/second. The TIMI flow grade was assessed as previously defined at the TIMI Angiographic Core Laboratory [14]. Frame counts were determined by the method described previously by Gibson CM, et al. [15]. Briefly, the first frame used for TIMI frame counting is the frame in which dye fully enters the artery (Figure 1b). The last frame is defined as the frame when dye first enters the distal landmark branch. These landmarks are as follows: the distal bifurcation known as the "moustache", "pitch fork" or "whale's tail" in the left anterior descending artery (LAD) (Figure 1c), the distal branch of the lateral left ventricular wall artery furthest from the coronary ostium in the circumflex artery (Figure 1d) and the first branch of the posterolateral artery in the right coronary artery (RCA) (Figure 1e). These frame counts are corrected for the longer length of the LAD by dividing by 1,7 to arrive at the corrected TIMI frame count. The term of no-reflow (NR) was defined by TIMI <3 on the last

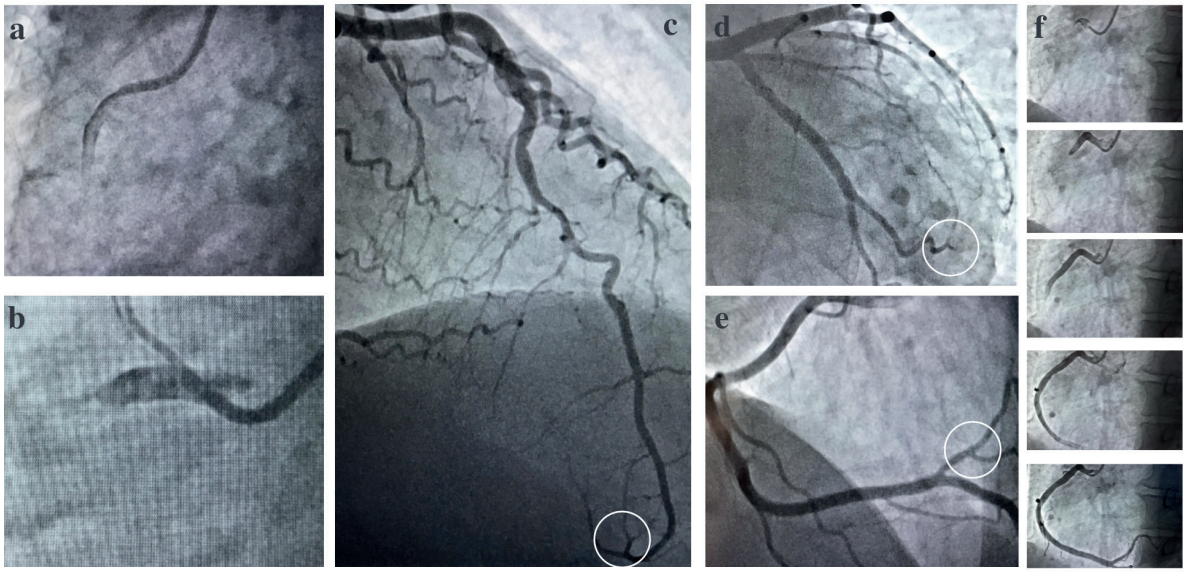

Figure 1. Calculating TIMI frame counts. When dye touches one or no borders, the frame count is 0 (**a**). The first counting frame (**b**) is the image where the contrast advances and fills at least 70% of the diameter of the arterial ostium. The last frame is the image where the contrast begins to fill the final landmark. Final landmark is Whales's tail or pitchfork or most distal branch at apex for LAD (**c**), last branch of most distal OM for CX (**d**) and first branch of posterolateral artery for RCA (**e**). In the absence of myocardial infarction normal frame count of RCA is 21±3,1 (**f**).

angiogram [16]. Measurements were made with a Philips Inturis Suite R2.2 by an independent observer blinded to the medical treatment of the patients.

Statistical analysis. Statistical analyses were performed using SPSS statistical software for Windows 20 (IBM SPSS Inc., USA). Distributional properties of the variables were assessed using the Shapiro-Wilk test. Student t-test was used to analyze the normally distributed variables that were expressed as mean ± standard deviation. Mann-Whitney U test was used for non-normally distributed variables that were expressed as median (interquartile range). Correlation coefficients were evaluated using Spearman's rank to investigate the relationship between HbA_{1c} and TFC. The parameters that may be clinically related with TFC were first evaluated by univariable regression analysis. Then, a multivariable regression analysis including the variables with a p-value ⩽0,25 at univariate analysis was performed. In the power analysis made by considering the TIMI-frame count values in the clopidogrel and ticagrelor groups; assuming an alpha of 0,05 and a power of 90%, we calculated that the number sufficient to detect the postulated effect size difference was 189 patients per group (total 378). The power of our study was 0,96. P values <0,05 were considered statistically significant.

Results

A total of 573 patients were assessed with a diagnosis of STEMI. Seventeen patients were excluded due to a history of coronary artery bypass surgery, 10 patients due to need for surgery after angiography and 13 patients for other reasons (chronic total occlusion, vasospastic MI, subacute MI). After the evaluation regarding the exclusion criteria, the remaining 532 patients were divided into two groups according to receiving ticagrelor (334, 62,8%) or clopidogrel (198, 37,2%). The mean age (62,2±14 vs. 58±12; p<0,001), heart rate (80,4±17,6 vs. 75,7±15,6; p=0,001), rates of HT (54,5% vs. 42,5%; p=0,007), and DM (33,3% vs. 25,1%; p=0,043) were higher in patients using clopidogrel compared to ticagrelor. On the other hand, smoking (63,5% vs. 36,4%; p<0,001), and hemoglobin level (14,8±1,8 vs. 14,2±2,1; p=0,001) were higher in ticagrelor group than in clopidogrel group. Otherwise, the groups had no significant differences in terms of sex, BMI, blood pressure, glucose, creatinine, troponin, HbA_{1c}, lipid profile, and ejection fraction. Table 1 summarizes the patients' baseline characteristics.

Angiographic parameters are shown in Table 2. Accordingly; infarct related arteries were mostly LAD (43,8%) and RCA (37,4%). One stent was implanted in 69,7%, two stents in 20,5% and three or more stents in 3,8% of the patients. The infarct related artery did not differ significantly between the two groups (p=0,461). Post dilation was performed in 38,7% (n=206) of the patients and thrombus aspiration rate was 9,8% (n=52). Basal TIMI flow was grade 0 in 66,9% of the patients and after the procedure TIMI flow grade 3 was achieved in 83,5%. Pre-procedural TIMI flow grade was similar and there was no significant difference as expected.

There was no significant difference in terms of stent diameter, stent length, post-dilatation, and thrombus aspiration before the procedure between the two groups. Presence of TIMI flow grade 2 was higher (21,2% vs. 9,3%; p<0,001) and post-procedural TIMI flow grade 3 was

Table 1

Baseline characteristics of the patients

	All patients n=532	Clopidogrel n=198	Ticagrelor n=334	P value
Age (years), mean±SD	59,5±12,9	62,2±1,4	58±1,2	<0,001
Male, n (%)	391 (73,5)	138 (69,7)	253 (75,7)	0,126
BMI (kg/m^2), mean±SD	27,7±4,4	27,8±4,2	27,6±4,6	0,620
Smoking, n (%)	284 (53,4)	72 (36,4)	212 (63,5)	<0,001
Hypertension, n (%)	250 (47,0)	108 (54,5)	142 (42,5)	0,007
Diabetes mellitus, n (%)	150 (28,2)	66 (33,3)	84 (25,1)	0,043
Previous history of CAD, n (%)	111 (20,9)	38 (19,2)	73 (21,9)	0,465
Previous anti-platelet exposure, n (%)	74 (13,9)	25 (12,6)	49 (14,6)	0,510
Previous anticoagulant use, n (%)	5 (0,9)	2 (1,0)	3 (0,8)	0,897
Heart rate (bpm), mean±SD	77,4±16,5	80,4±17,6	75,7±15,6	0,001
SBP (mmHg), mean±SD	132,1±27,0	129,8±28,6	133,6±25,9	0,118
DBP (mmHg), mean±SD	79,9±16,0	78,2±15,6	81±16,1	0,057
Hemoglobin (g/dL), mean±SD	14,6±1,9	14,2±2,1	14,8±1,8	0,001
Platelet (10^3/μL), mean±SD	259,1±67,3	256,5±56,0	260,6±73,1	0,496
Glucose (mg/dL), median (IQR)	129 (105-171)	131 (103-180)	129 (106-167)	0,919
Creatinine (mg/dL), median (IQR)	1,04 (0,91-1,19)	1,05 (0,89-1,25)	1,03 (0,92-1,16)	0,226
Sodium (mmol/L), mean±SD	136,6±2,6	136,7±2,4	136,6±2,6	0,676
Potassium (mmol/L), mean±SD	4,1±0,5	4,1±0,5	4,1±0,4	0,436
ALT (U/L), median (IQR)	45,5 (25-86)	47 (25-86)	45 (24-86)	0,956
LDL (mg/dL), mean±SD	130,6±34,1	127,1±34,3	132,5±33,8	0,081
Troponin (ng/mL), median (IQR)	28,6 (8,0-91,2)	33,9 (8,6-98,7)	27,7 (7,3-80,1)	0,736
HbA_{1c}, mean±SD	6,9±2,0	6,9±2,0	6,8±1,9	0,522
LVEDD (cm), mean±SD	4,7±0,4	4,7±0,4	4,7±0,4	0,677
LVEF (%), mean±SD	45,3±9,1	44,6±9,9	45,7±8,5	0,208

Note: the data without normal distribution is presented as median (interquartile range-IQR).

Abbreviations: ALT — alanine aminotransferase, BMI — body mass index, CAD — coronary artery disease, DBP — diastolic blood pressure, HbA_{1c} — hemoglobin A1c, LDL — low density lipoprotein, LVEDD — left ventricular end-diastolic diameter, LVEF — left ventricular ejection fraction, SBP — systolic blood pressure, SD — standard deviation.

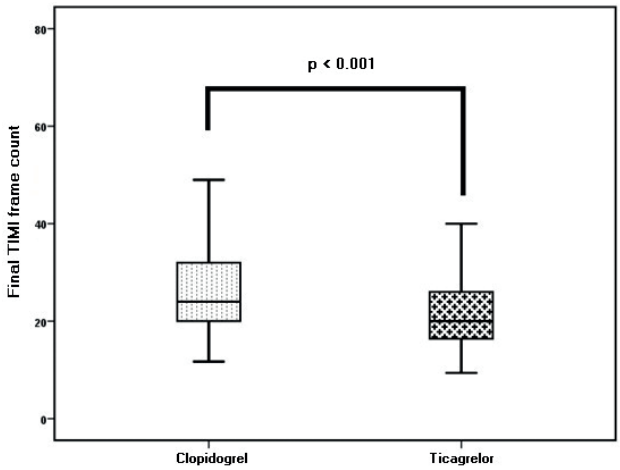

Figure 2. Comparison of the two antiplatelets according to their effects on TIMI frame count. Post procedural no-reflow rate and median of TIMI frame count were lower in ticagrelor group than in clopidogrel group (20 vs. 24; p=0,001).

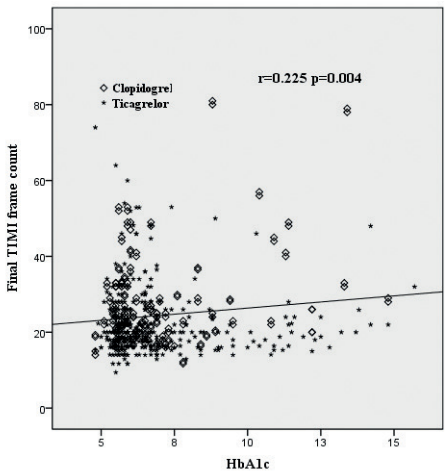

Figure 3. Statistically significant and positive correlation between the increases in HbA_{1c} and TIMI frame count in the whole group (r=0,225, p=0,004).

lower (73,7% vs. 89,2%; p<0,001) in clopidogrel-treated patients compared to those using ticagrelor. The median TFC was higher in clopidogrel-treated patients compared to those using ticagrelor (24 vs. 20; p<0,001) (Figure 2).

There was a positive correlation between the increases in HbA_{1c} levels and TFC in the whole study group (r=0,225; p=0,004) (Figure 3). A significant positive correlation was found between HbA_{1c} levels

Table 2

Angiographic characteristics of patients

	All patients n=532	Clopidogrel n=198	Ticagrelor n=334	P value
Culprit lesion location, n (%)				0,461
Left anterior descending	233 (43,8)	88 (44,4)	145 (43,4)	
Left circumflex	83 (15,6)	36 (18,2)	47 (14,1)	
Right coronary artery	199 (37,4)	70 (35,4)	129 (38,6)	
Diagonal	11 (2,1)	2 (1,0)	9 (2,7)	
Other	6 (1,2)	2 (1,0)	4 (1,2)	
No stent, n (%)	32 (6,0)	10 (5,1)	22 (6,6)	0,914
1, n (%)	371 (69,7)	138 (69,7)	233 (69,8)	
2, n (%)	109 (20,5)	42 (21,2)	67 (20,1)	
3+, n (%)	20 (3,8)	8 (4,0)	12 (3,6)	
Stent diameter, median (min-max)	3 (2,0-4,5)	3 (2-4,5)	3 (2-4,5)	0,078
Stent length, median (min-max)	25 (4-104)	25 (12-89)	25 (4-104)	0,301
Post-dilatation, n (%)	206 (38,7)	82 (41,4)	124 (37,1)	0,326
Manual thrombus aspiration, n (%)	52 (9,8)	18 (9,1)	34 (10,2)	0,683
Glycoprotein IIb/IIIa inhibitor, n (%)	159 (29,8)	67 (33,8)	92 (27,5)	0,125
Iv narcotics, n (%)	16 (0,3)	5 (0,2)	11 (0,3)	0,616
Initial TIMI flow grade, n (%)				
0	356 (66,9)	134 (67,7)	222 (66,5)	0,172
1	46 (8,6)	16 (8,1)	30 (9,0)	
2	86 (16,2)	26 (13,1)	60 (18,0)	
3	44 (8,3)	22 (11,1)	22 (6,6)	
Final TIMI flow grade, n (%)				
0	2 (0,4)	-	2 (0,6)	<0,001
1	13 (2,4)	10 (5,1)	3 (0,9)	
2	73 (13,7)	42 (21,2)	31 (9,3)	
3	444 (83,5)	146 (73,7)	298 (89,2)	
In-hospital bleeding events*				
Major	7 (1,3)	2 (1,0)	5 (1,5)	0,934
Minor	16 (3,0)	5 (2,5)	11 (3,2)	0,811
Symptom to wire crossing time (minutes), median (IQR)	125 (103-165)	121 (103-160)	130 (104-168)	0,340
Door to wire crossing time (minutes), median (IQR)	57 (47-75)	52 (44-72)	60 (49-76)	0,019
Initial TIMI frame count, median (IQR)	42 (32-56)	42 (32-53)	42 (32-56)	0,863
Final TIMI frame count, median (IQR)	21 (18-28)	24 (20-32)	20 (16-26)	<0,001

Note: * — major bleeding was defined if one of the following holds: fatal bleeding, intracranial bleeding, intraocular bleeding, retroperitoneal bleeding, bleeding with hemodynamic compromise, >5 cm hematoma, hemoglobin drop (g/dL) ⩾4, bleeding not corresponding to these values was considered minor.

and post-procedure TFC in clopidogrel users (r=0,304; p<0,001). But no significant such relationship was found in ticagrelor users (r=-0,021; p=0,699) (Figure 4). Furthermore, it was observed that TFC did not change with higher HbA_{1c} level in both ticagrelor and clopidogrel groups in patients with normal coronary flow at the end of the primary PCI (r=-0,060; p=0,326, r=-0,003; p=0,973 respectively). In patients using ticagrelor, higher HbA_{1c} levels did not affect TFC whether or not TIMI-3 flow was achieved (r=-0,060, p=0,326; r=-0,133, p=0,321, respectively). However, there was significant correlation between HbA_{1c} level and TFC in the clopidogrel group with NR unlike in patients with TIMI-3 flow at the end of the procedure (r=0,374; p=0,005, r=-0,003; p=0,973) (Figure 5). When age, gender, HbA_{1c} level, heart rate, blood pressure, low density lipoprotein level, presence of HT and smoking were selected as potential covariates, in the multivariable regression analysis HbA_{1c} level was found to be the independent predictors of TFC in patients using clopidogrel with NR (odds ratio (OR): 2,30, 95% confidence interval (CI): 0,70-3,90, p=0,006). However, there was no predictive role of HbA_{1c} for TFC in patients using clopidogrel with TIMI-3 flow and in ticagrelor group irrespective of TIMI flow (OR: 0,35, 95% CI: -0,28-0,98, p=0,275 for clopidogrel group with TIMI-3 flow; OR: -0,18, 95% CI: -0,26-2,26, p=0,879 for ticagrelor group with NR; OR: -0,14, 95% CI: -0,32-0,95, p=0,930 for ticagrelor group with TIMI-3 flow) (Table 3). On the other hand, when predictors of TFC

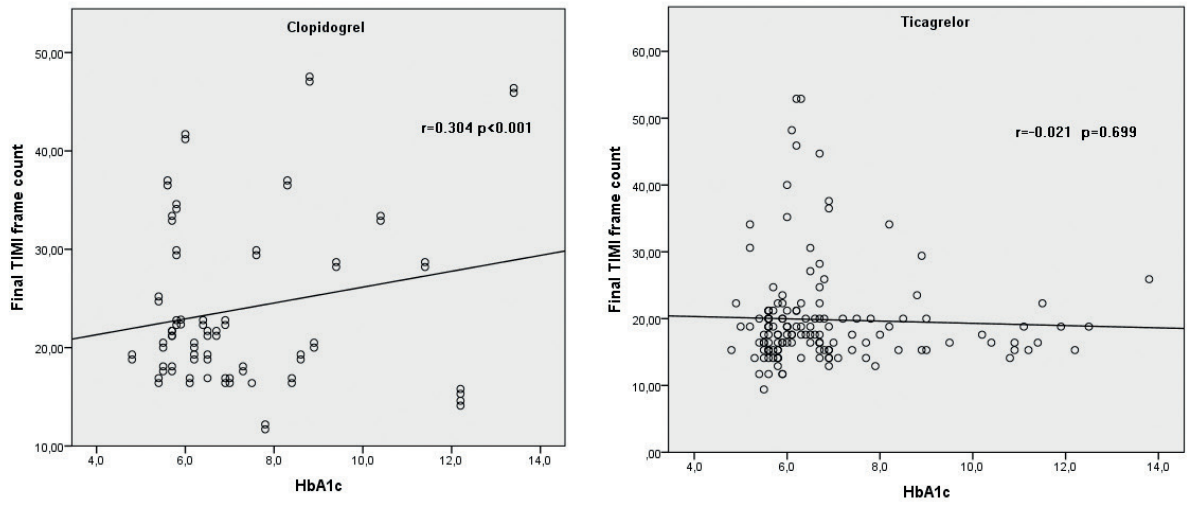

Figure 4. There was a statistically significant and positive correlation between HbA_{1c} and post-procedural TFC levels in clopidogrel group (r=0,304; p<0,001), this relation was not observed in ticagrelor group (r=0,021; p=0,699).

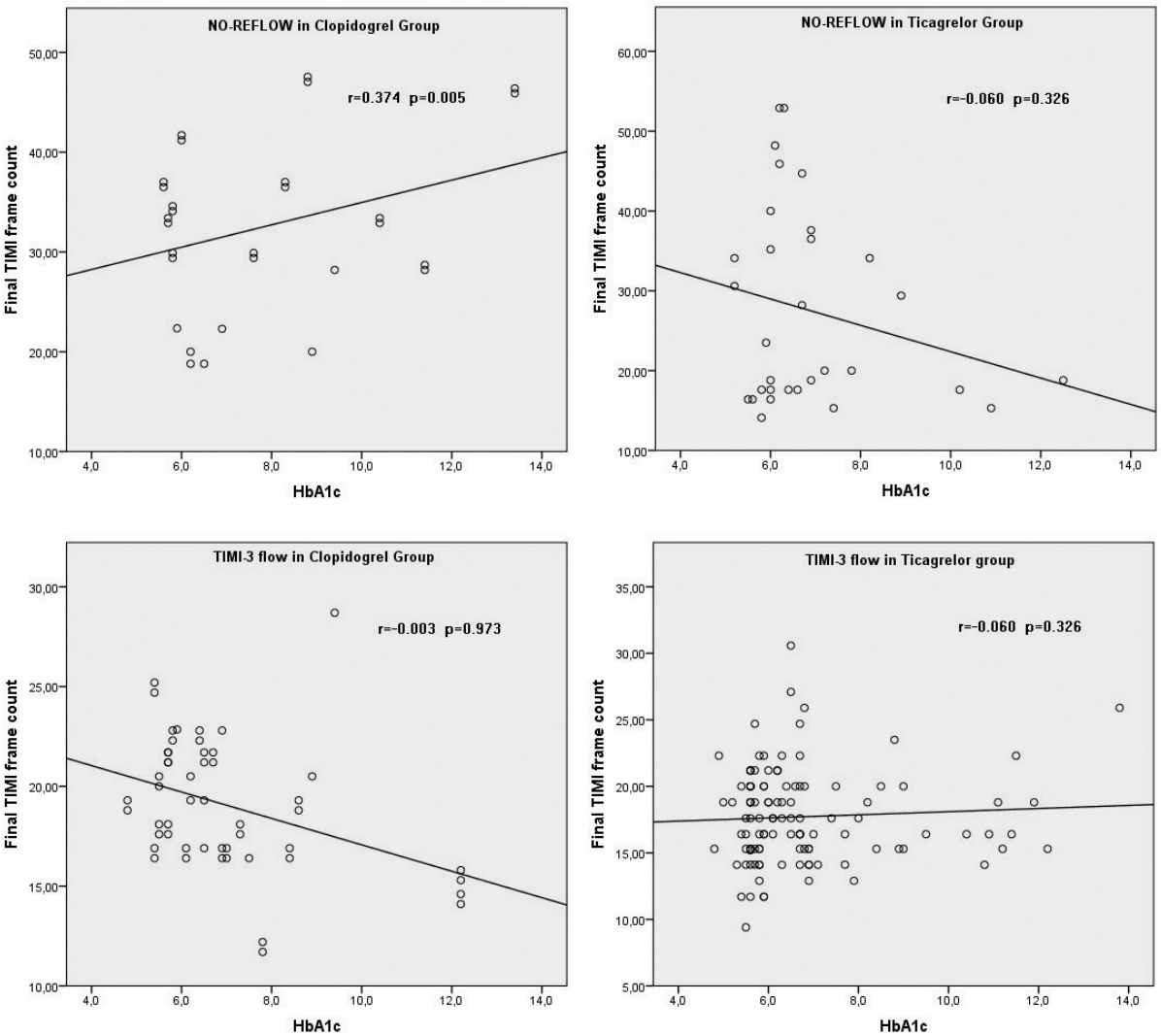

Figure 5. In ticagrelor and clopidogrel groups who had TIMI-3 flow at the end of the procedure, there was no correlation between HbA_{1c} levels and TFC. Furthermore, no relationship was found between HbA_{1c} and TFC in the ticagrelor group, whether or not "TIMI-3 flow" was provided. In contrast, in the clopidogrel group who had no-reflow, HbA_{1c} was significantly related with post-procedural TFC (r=0,374; p=0,005).

Table 3

Independent risk factors to predict no-reflow

Risk Factors	All Patients		Clopidogrel		Ticagrelor	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Univariable regression analysis						
Age	1,04 (1,03-1,06)	<0,001*	1,05 (1,03-1,08)	<0,001*	1,03 (1,01-1,05)	0,011*
Body mass index	1,05 (0,99-1,09)	0,058	1,10 (1,02-1,18)	0,017*	1,01 (0,95-1,08)	0,683
Smoking status	0,41 (0,27-0,62)	0,001*	0,56 (0,30-1,07)	0,079	0,41 (0,23-0,72)	0,002*
Alanine transaminase	1,03 (1,01-1,04)	0,001*	1,03 (1,01-1,05)	0,013*	1,02 (1,01-1,05)	0,026*
Troponin	1,10 (1,08-1,20)	<0,001*	1,20 (1,10-1,30)	<0,001*	1,12 (1,10-1,18)	0,012*
HbA_{1c}	1,14 (1,03-1,025)	0,009*	1,19 (1,02-1,38)	0,024*	1,10 (0,96-1,25)	0,166
Ejection Fraction	0,97 (0,95-0,99)	0,013*	0,97 (0,94-1,00)	0,08	0,98 (0,94-1,01)	0,139
Anti-platelet therapy						
Clopidogrel	ref		-	-	-	-
Ticagrelor	0,49 (0,33-0,74)	0,001*	-	-	-	-
Angiographic findings						
Culprit lesion						
Left anterior desending	ref		ref		ref	
Left circumflex	0,58 (0,31-1,07)	0,082	0,58 (0,25-1,36)	0,21	0,50 (0,19-1,27)	0,145
Right coronary artery	0,52 (0,33-0,82)	0,005*	0,41 (0,20-0,84)	0,015*	0,62 (0,34-1,15)	0,131
Stent length	1,20 (1,10-1,30)	0,004*	1,20 (1,05-1,40)	0,044*	1,20 (1,01-1,40)	0,037*
Post-dilatation	1,72 (1,14-2,58)	0,009*	2,02 (1,10-3,72)	0,024*	1,44 (0,82-2,53)	0,203
Door-to-wire crossing time	1,10 (1,02-1,17)	0,017*	1,10 (0,99-1,17)	0,0118	1,13 (1,02-1,24)	0,022*
Multivariate regression analysis						
Age	1,05 (1,03-1,07)	<0,001*	1,05 (1,02-1,08)	0,001*	1,03 (1,01-1,06)	0,014*
Troponin	1,10 (1,08-1,20)	<0,001*	1,20 (1,10-1,30)	<0,001*	1,10 (1,02-1,20)	0,017*
HbA_{1c}	1,12 (1,01-1,25)	0,038*	1,22 (1,03-1,48)	0,046*	-	-
	Nagelkerke R^2=0,270; p<0,001		Nagelkerke R^2=269; p<0,001		Nagelkerke R^2=0,267; p<0,001	

Abbreviations: CI — confidence interval, HbA_{1c} — glycosylated hemoglobin, OR — odds ratio.

Table 4

Linear regression analyses of potential variables related to TFC in patients with no-reflow

Variables	Univariable analysis β (95% CI) p		Multivariable analysis β (95% CI) p	
Patients with HbA_{1c} <6,5%				
Anti-platelet agent	-4,63 (-6,94 — -2,31)	<0,001	0,64 (-6,11-7,39)	0,849
Age	0,16 (0,08-0,24)	<0,001	-0,11 (-0,44-0,21)	0,479
BMI	-0,17 (-0,44-0,10)	0,218	-0,86 (-1,76 — -0,04)	0,063
ALT	0,01 (-0,01-0,02)	0,082	-0,01 (-0,06-0,03)	0,595
Smoking	4,17 (1,88-6,45)	<0,001	7,24 (-1,18-15,67)	0,090
Troponin	0,04 (0,00-0,07)	0,010	0,13 (0,04-0,22)	0,003
Door to wiring time	0,01 (0,00-0,01)	0,097	0,00 (-0,01-0,01)	0,757
Patients with HbA_{1c} ⩾6,5%				
Anti-platelet agent (clopidogrel as a reference)	-6,30 (-9,34 — -3,26)	<0,001	-9,69 (-18,90 — -0,47)	0,040
Age	0,12 (-0,01-0,26)	0,064	0,21 (-0,32-0,75)	0,434
ALT	0,01 (0,00-0,02)	0,055	0,02 (-0,01-0,06)	0,144
Smoking	3,82 (0,71-6,93)	0,016	3,07 (-7,51-13,65)	0,562
Gender (female as a reference)	7,95 (-1,89-17,81)	0,111	6,24 (-3,35-15,84)	0,197

Abbreviations: ALT — alanine aminotransferase, BMI — body mass-index, CI — confidence interval, HbA_{1c} — glycosylated hemoglobin, TFC — TIMI frame count.

in patients with NR were evaluated by linear regression analysis, no effect of anti-platelet agents was found in patients with HbA_{1c} below 6,5% (β: 0,64, CI: -6,11 to 7,39, p=0,849). However, ticagrelor was found to be an independent predictor of low TFC in patients with HbA_{1c} greater than 6,5 (β: -9,69, CI: -18,90 to -0,47, p=0,040) (Table 4).

Discussion

The present study evaluated the effects of ticagrelor and clopidogrel on relation between HbA_{1c} and post-interventional coronary flows. We found that ticagrelor was more successful than clopidogrel in post-PCI coronary flow measurements independent of HbA_{1c} levels. In addition, clopidogrel appears to be as successful as ticagrelor when the HbA_{1c} level is low, while its effectiveness decreased as HbA_{1c} levels increased especially in patients with NR.

Enhanced platelet reactivity in DM patients results from a complex process of interaction between biochemical factors such as hyperglycemia, insulin resistance/deficiency, oxidative stress, endothelial dysfunction, and lipid abnormalities, all of which lead to increased expression of platelet glycoprotein IIb/IIIa receptors, loss of insulin-related inhibition of the $P2Y_{12}$ pathway, upregulation of genes involved in thrombus generation, increased generation of adhesion molecules, and several other features of increased platelet reactivity [17-19]. Overall, these observations underscore the need for optimizing platelet inhibitory effects in DM patients. Moreover, not all patients with DM have the same risks. HbA_{1c} reflects the previous 2 to 3 mounts of glycemic control that represents well established pro-thrombotic conditions, as inadequate glycemic control can lead to impaired responsiveness to antiplatelet therapies [20]. HbA_{1c} estimation clearly and quickly differentiates stress hyperglycemia from hyperglycemia of diabetes mellitus in acute coronary syndrome [21]. Each 1% rise in HbA_{1c} results in more coronary events and more hospitalizations due to worsening of heart failure [22].

TIMI flow grade basically has been an important and consistent predictor of outcomes in STEMI patients. However, it became clear that there was variability in TIMI flow grade assessment, in particular for TIMI 2 flow. In addition, early data indicated that only one third of patients with TIMI 3 flow had a normal corrected TIMI frame count. Therefore, the concept was enhanced by the development of the TFC, a continuous and more quantitative variable for measurement of coronary artery perfusion [15]. According to our study, the positive relationship between HbA_{1c} levels and TFC was observed only in the clopidogrel group. However, in the ticagrelor group, despite the increase in HbA_{1c}, there was no significant change in TFC. There are several reasons for why ticagrelor is better than clopidogrel and shows the same efficacy even in high-risk diabetic patients with poor glycemic control.

As it is now widely used and known, ticagrelor is not prodrug and does not require a metabolic activation to reach its effectiveness [23]. After administration, it is swiftly adsorbed with a median time to peak concentration (Tmax) of 2-3 hours and it reaches 40-50% inhibition of platelet aggregation in approximately 30 minutes while it takes 2-4 hours for clopidogrel to reach a similar efficacy rate [24-26]. The difference in effect seen in this short period of time may be one of the main factors in explaining the difference in the patient groups in which the time between taking antiplatelet therapy and PTCA is short. Ticagrelor improves post-PCI flow, because it inhibits platelet function to a greater degree and has a faster onset of action compared to clopidogrel [23]. The ONSET/OFFSET study demonstrated that platelet inhibition (IPA) was higher at 0,5 hours after loading with ticagrelor (41% vs. 8%, P<0,0001) and at all times in the first 24 hours after loading and in the maintenance phase (P<0,0001); within 1 hour of ticagrelor loading, IPA was greater than the maximum IPA achieved after clopidogrel loading [27]. In a meta-analysis, nine articles including 3,125 patients, reported the change of coronary TIMI flow of infarct-related artery after PPCI. The fixed effect model meta-analysis result showed that compared with the clopidogrel group, the preoperative loading dose ticagrelor significantly improved the number of patients whose coronary blood flow of infarct-related artery restored TIMI3 after PPCI [28]. It is believed that the main mechanism of NR/slow-flow is thrombus and plaque debris caused by stenting or balloon dilatation moving downstream, leading to distal vascular mechanical microembolization [29]. Thus, strengthening dual antiplatelet therapy, may inhibit platelet function and reduce the occurrence of microembolization by decreasing platelet adhesion to debris and improving reperfusion more effectively. Therefore, the preoperative loading dose of ticagrelor may provide potential benefits in patients with STEMI.

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 [19]. There is also a proportion of patients who are poor responders to clopidogrel, including those with genetic variations, such as CYP2C19 polymorphisms [30, 31]. Because ticagrelor does not follow the same metabolic pathway as clopidogrel, this explains, at least in part, the disparity between the two drugs in terms of speed and degree of platelet reactivity in diabetic and non-diabetic patients. In addition, predicted steady-state plasma exposure of ticagrelor and its active metabolite are not affected by diabetic condition [32]. In an *in vitro* experiment, ticagrelor was increased the concentration of extracellular adenosine by inhibiting its uptake by red blood cells [33]. It has been shown that ticagrelor has adenosine-mediated pleiotropic effect which is associated with upregulation of nitric oxide release and cyclooxygenase-2 activation from endothelium via adenosine. In subjects using ticagrelor, properties of adenosine diphosphate receptor antagonism increase adenosine-related epicardial flow velocity that reduces TFC even in patients with normal coronary arteries [34, 35]. In this regard, ticagrelor significantly reduced the primary composite endpoint like all-cause

mortality, and stent thrombosis compared to clopidogrel and importantly, this clinical benefits of ticagrelor did not differ according to diabetic status.

The present study has some limitations. First, it included a relatively small number of patients. The long-term effects of research findings on cardiovascular events such as cardiovascular death and non-fatal myocardial infarction are unknown, as follow-up data of all patients were not available. Myocardial perfusion grade could not be performed as myocardial blush data were not available in all patients. Finally, it was not established whether the patients were using oral antidiabetics/insulin prior to the procedure. Nevertheless, the diabetic status of the patients was determined with a reliable biomarker, HbA_{1c}.

Conclusion

The present study shows that ticagrelor is an efficient antiplatelet agent in the light of angiographic data regardless of diabetic condition. However, clopidogrel efficiency was found to be lower than ticagrelor, especially in patients with NR and higher HbA_{1c} levels.

Relationships and Activities: none.

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