Original Article

Clopidogrel versus ticagrelor in elective percutaneous coronary intervention

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ABSTRACT

Recent guidelines revealed that patients with stable coronary artery disease (SCAD) benefit from percutaneous coronary intervention (PCI) with the placement of the stent, and this procedure is the best if medical treatment fails to improve the patient's condition. Oral antiplatelet drugs, particularly aspirin coupled with adenosine diphosphate (ADP) receptor blocking agents represent a crucial component of therapy for these patients to reduce the risk of ischemic events. This work aims to compare the clinical safety and efficacy of clopidogrel versus ticagrelor in patients undergoing elective PCI with the determination of actual plasma concentrations and the platelet inhibitory effect of both drugs with the help of ultra-high-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) and light transmission aggregometry (LTA) respectively. A total of 60 patients diagnosed with SCAD were enrolled in this study and scheduled for PCI. In addition to aspirin, half of the Patients received clopidogrel, 600 mg loading dose, and 75mg daily after PCI. The other thirty patients received ticagrelor at a loading dose of 180mg and 90 mg twice daily thereafter. Ticagrelor reduced the occurrence of major adverse cardiac events (MACE) but this reduction was not significant compared to clopidogrel. Meanwhile, it was associated with an increased risk of major bleeding and dyspnea. There was inter-individual variability in clopidogrel plasma concentration. Ticagrelor showed a significant reduction in the maximal ADP-induced platelet aggregation in comparison with clopidogrel. In patients undergoing elective PCI, ticagrelor was involved in lowering the MACE at the expense of increased major bleeding and dyspnea compared to clopidogrel.

Keywords: Antiplatelets, Elective percutaneous coronary intervention, Light transmission aggregometry, Ultra-high-performance liquid chromatography-tandem mass spectrometry

Introduction

Coronary artery disease (CAD) is one of the most detrimental cardiac disorders associated with significant morbidity and mortality worldwide [1, 2]. It implies cardiac ischemia, myocardial infarction, and sudden cardiac death and is usually caused by coronary atherosclerosis [3].

Recent guidelines consider percutaneous coronary intervention (PCI, formerly known as angioplasty with stent) one of the most common medical procedures performed for the treatment of CAD. It is a safe procedure in patients with stable coronary artery disease (SCAD) and it is indicated whenever medical treatment fails to improve the prognosis [4].

Anti-platelet therapy as adjunctive therapy for PCI is recommended before, during, and after elective PCI to reduce the risk of ischemic events. Aspirin has been the cornerstone anti-platelet drug in patients undergoing PCI. In addition to aspirin, recent guidelines have shown improved outcomes with newer antiplatelet drugs to reduce the incidence of ischemia [5].

There are two types of adenosine diphosphate (ADP) purinergic receptors P2Y1 and P2Y12. The P2Y12 is the predominant receptor involved in the process of platelet aggregation [6].

Different oral P2Y12-inhibitors are used frequently in clinical practice. Differences in the pharmacokinetic and pharmacodynamic properties of these agents such as the mechanism of their binding to the receptor site, their half-lives,

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the onset and offset of action and adverse effects are important factors in the determination of the most suitable regimen for loading and maintenance therapy [7].

Clopidogrel is a thienopyridine ADP receptor antagonist that produces an effective inhibition of platelet aggregation. Being a prodrug, hepatic biotransformation of clopidogrel via CYP450 pathway is essential for its anti-platelet activity. It causes irreversible receptor inhibition. Clopidogrel has a slow offset which may be problematic in some patients. In addition, several genetic and non-genetic factors influence the drug pharmacokinetics, producing inter-individual variability in response to clopidogrel [8].

Differently from thienopyridines, which block the receptor site directly, ticagrelor acts non-competitively, moreover, it has a faster onset of action with no need for previous metabolic activation contrary to clopidogrel [9].

This work was designed to compare the clinical safety and efficacy of clopidogrel versus ticagrelor, in patients undergoing elective PCI with the determination of actual plasma concentrations and the platelet inhibitory effect of both drugs with the help of ultra-high performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) and light transmission aggregometry (LTA) respectively.

Materials and Methods

Study Population

This study was self-funded and was conducted at the critical care department, Faculty of Medicine. The study protocol was approved by the Research Ethics Committee (REC), approval number (N-11-2019), and all patients gave written informed consent for participation. A total of 60 patients diagnosed with SCAD, aged between 18-80 years were enrolled in the study and scheduled for elective PCI with a single drug-eluting stent. Half of the patients received clopidogrel, 600 mg oral loading dose, and 75mg daily after the PCI. Oppositely, the oral loading dose of ticagrelor recommended for the other thirty patients was 180 mg and the maintenance dose was 90 mg twice daily thereafter. Aspirin 325 mg was the preferred loading dose.

The detailed history of the patients was recorded at the time of admission, before the PCI.

Patients were followed clinically during and after elective PCI for the occurrence of death, major adverse cardiac events (MACE), and major bleeding. During the follow-up period, dyspnea or any adverse side effect was also reported. Follow-up visits were for about 6 months. Patients with a history of acute myocardial infarction, bleeding disorder, anemia, thrombocytopenia, administration of thrombolytic drugs or anticoagulants within the 7 days before PCI, known intracranial vascular malformation, allergy to clopidogrel or ticagrelor, and those with creatinine clearance < 45 mL/min, elevated liver enzymes or other indication of clinically significant hepatic dysfunction were excluded from the study.

Sample collection

2-3 hours after a high loading dose with clopidogrel 600 mg or ticagrelor 180 mg, about 5 ml aliquot of blood was drawn from all patients in the two studied groups and collected in test tubes containing ethylene diamine tetra acetic potassium salt (EDTA-K) to evaluate the maximum plasma concentration of both drugs (Cmax). Blood centrifugation at 4000 round per minute (rpm) for about 10 minutes was performed to obtain plasma samples which were separated and stored at −70 °C until analysis by UPLC-MS/MS. Another 5 ml aliquot of blood was drawn in citrated tubes and centrifugated at 800 rpm for 15 minutes to obtain platelet rich plasma for assessment of alterations in light transmission of the stirred platelets exposed to ADP using LTA, samples were kept at room temperature and not refrigerated and the test was performed immediately.

Chemicals

Clopidogrel bisulphate, ticagrelor, rasagiline, methanol, formic acid, and acetonitrile were purchased from Sigma -Aldrich, Egypt. ADP was obtained from Biodata -USA. Drug-free human plasma was obtained from Vacsera, Egypt.

UPLC MS /MS study

- *Chromatographic conditions*

The analytes were separated in Poroshell 120EC- C18 (4.6x50) mm, 2.7 µm column (Agilent Technologies, USA) in case of ticagrelor and Luna® Omega 1.6 µm polar- C18 (150x2.1mm) column (Agilent Technologies, USA) in case of clopidogrel. The mobile phase was a mixture of acetonitrile and 0.2% formic acid. The flow rate was 0.8 mL/min.in case of ticagrelor and 0.3 ml/min in case of clopidogrel. Nitrogen was used as collision gas. The released eluent entered the mass spectrometry (MS) interface, using electrospray ionization in the positive ion mode. The multiple reaction monitoring (MRM) mode was used for the detection of specific transitions of the analytes.

- *Stock solutions*

Each clopidogrel and ticagrelor and rasagiline (used as internal standard) were weighed at 0.01 gm and dissolved in methanol to a concentration of 100 µg/ml. Dilution was performed to achieve different drug concentrations.

These concentrations were (20, 50, 100, 500, 1000, 1500, 2000, 4000) ng / ml in case of ticagrelor and (0.5, 1, 5, 10, 15, 20, 50, 100) ng/ml in case of clopidogrel and a rasagiline sample at a concentration of 1500 ng/ml was also prepared. Blank samples (plasma without drug or internal standard) and zero samples (plasma with internal standard) were prepared.

The plasma calibration standards were produced by the addition of a volume of 450 µL plasma with 50 µl of the different measured drug concentrations then vortexed for 20 seconds after that about 50 µl of rasagiline (1500 ng/ml) was added then vortexed for 20 seconds, extraction was done by protein precipitation by spiking 1ml of acetonitrile to each sample and vortex for 1 min followed by centrifugation at 6000 rpm for 30

minutes. Lastly, 10 µL of the supernatant was then introduced to UPLC- MS/MS. The most sensitive mass transition, mass to charge ratio (m/z) for the precursor /product ions was from 322 to 212, from 523.2 to 153, and from 172 to 117 for clopidogrel, ticagrelor, and rasagiline respectively.

- *Calibration curve*

The peak area obtained was recorded and then the calibration curve was constructed by plotting the measured peak area ratios versus different concentrations of standard samples. Linearity was determined by a linear regression equation with the calculation of the correlation coefficient.

- *Sample preparation*

Briefly, 500 µL Plasma containing the analyte was spiked with 50 µl of rasagiline (1500ng/ml) then Vortexed for 20 seconds. Precipitation of proteins was done by incorporating 1ml of acetonitrile into each sample. The mixture was vortexed for 1 minute followed by centrifugation for about 30 minutes at 6000 rpm. The resultant supernatant (10 µL) was then injected onto the UPLC- MS/MS.

Pharmacodynamic study

Determination of maximal ADP induced platelet aggregation was done using

Light transmission aggregometer Chrono log: (Havertown, USA).

As the platelets aggregate, changes in the light transmission were registered and calculated as the percentage of maximal ADP-induced aggregation**.** The aggregometer was calibrated by placing a cuvette containing platelet-poor plasma in the test well (100% light transmission)

Statistical methods

The statistical package for the Social Sciences (SPSS) version 26 (IBM Corp, Armonk, NY, USA) was used for coding data. Data were organized using mean and standard deviation (SD). An unpaired t-test was used to compare between groups. A Chi-square test was performed for comparing categorical data.
P-values less than 0.05 indicate statistically significant findings.

Results and Discussion

Baseline data

The detailed history of the patients which includes age, sex, body mass index, cardiovascular risk factors, and medications on admission was taken with no statistically significant difference between both groups as presented in **Table 1**.

Table 1. Baseline data of the patients treated with clopidogrel and ticagrelor

	No. of patients in Clopidogrel group (n=30)	No. of patients in Ticagrelor group (n=30)	P value
Age, years	57.37 ± 8.58	60.43 ± 7.67	0.15
Male, n.(%)	27 (90.0%)	23 (76.7%)	0.166
Female, n (%)	3 (10.0%)	7 (23.3%)	
Body mass index , kg/m2	30.56 ± 0.96	30.81± 1.00	0.327
Statin	28 (93.3%)	30 (100.0%)	0.492
Beta blocker	21 (70 %)	20 (66.7%)	0.781
Angiotensin converting enzyme inhibitor	15 (50.0%)	13 (43.3%)	0.605
Proton pump inhibitor	6 (20.0%)	10 (33.3%)	0.243
Hypertension	24 (80.0%)	26 (86.7%)	0.488
Diabetes mellitus	18 (60.0%)	20 (66.7%)	0.592
Smoking	5 (16.7%)	7 (23.3%)	0.592
Hyperlipidemia	25 (83.3%)	27 (90.0%)	0.592
Family history	9 (30.0%)	12 (40.0%)	0.417

Values were expressed as mean ±SD or number of patients and percentage (n.and (%))

Clinical data

As shown in **Table 2,** the results revealed that ticagrelor was effective in reducing MACE but this reduction was not significant compared to clopidogrel (P-value = 0.472). No mortality was detected in the study. In the ticagrelor group, the occurrence of major bleeding was significantly higher contrary to the clopidogrel group (P-value =0.038). In addition, there was a significant increase in dyspnea in ticagrelor-treated patients compared to clopidogrel (P-value =0.007).

Table 2. Clinical data of the patients treated with clopidogrel and ticagrelor

	No. of patients in Clopidogrel group n =30	No. of patients in Ticagrelor group n = 30	P value
Major adverse cardiac events	6 (20%)	3 (10%)	0.472
Major bleeding	2 (6.7%)	8 (26.7)	0.038
Dyspnea	3 (10%)	12 (40%)	0.007

Values were expressed using several patients and percentage (n and (%))

Pharmacokinetic study for clopidogrel

The calibration curve for clopidogrel was linear based on the previously mentioned concentrations plus blank and zero samples. as shown in **Figure 1**.

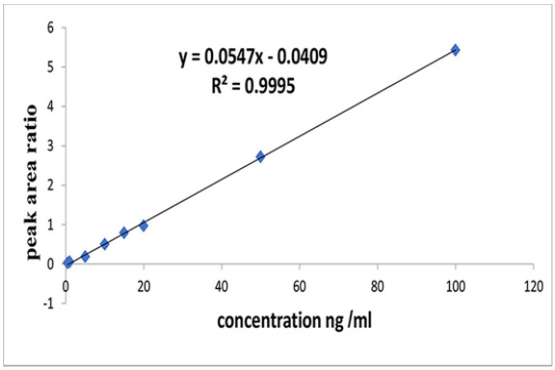


Figure 1. Calibration curve for clopidogrel, (600mg).

The Cmax (Mean ± SD, ng/ml) calculated 2-3 h after administration of clopidogrel 600mg was 54.33 ± 28.3, with a range: 15-98**, Figure 2**.

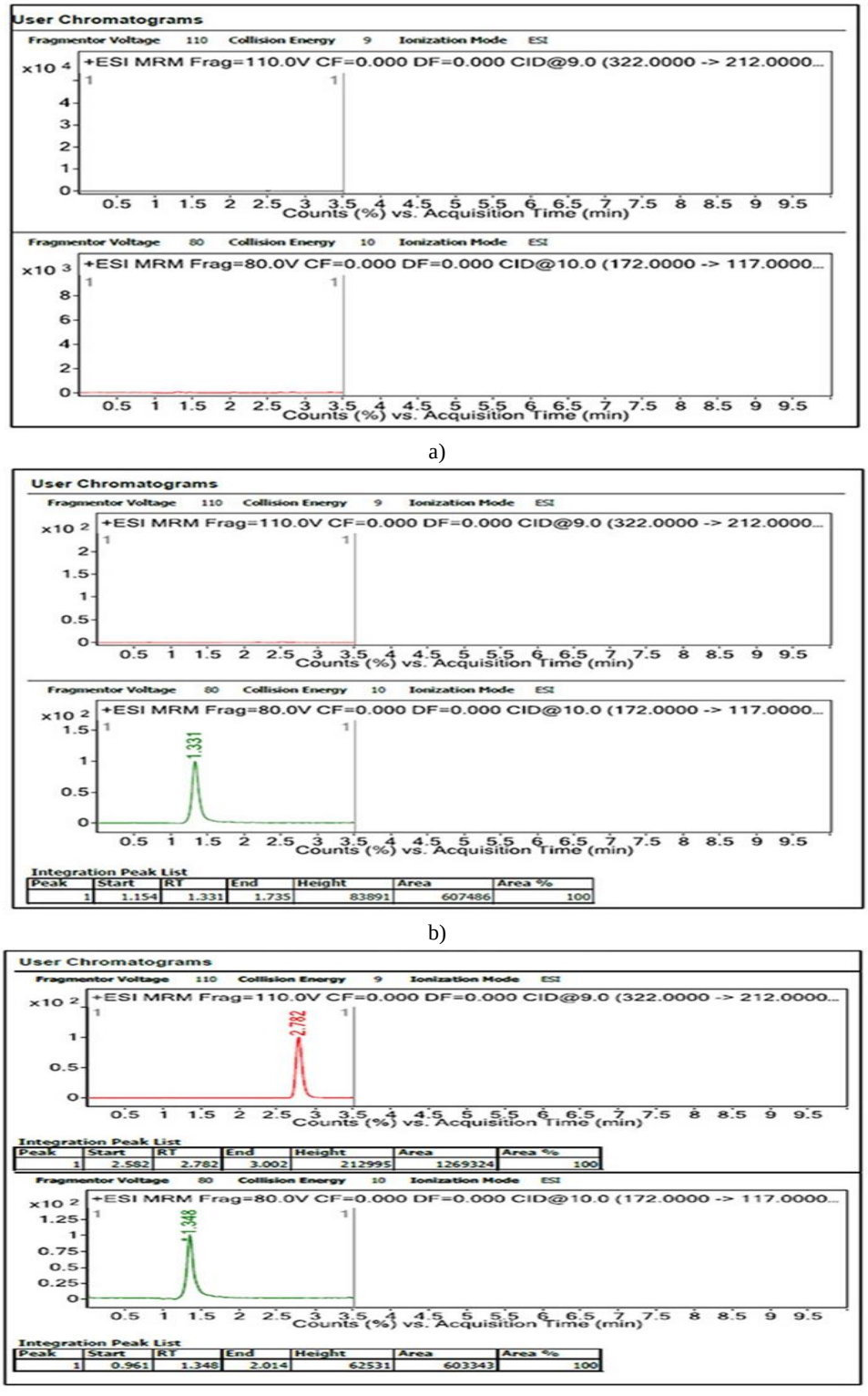


Figure 2. UPLC MS/MS chromatogram of clopidogrel and internal standard. (a) Blank samples (plasma without drug or internal standard (b) zero samples (plasma with internal standard) (c) plasma sample spiked with IS, 2-3 h after oral administration of 600 mg clopidogrel.

Pharmacokinetic study for ticagrelor

The calibration curve for ticagrelor was linear based on the previously mentioned concentrations plus blank and zero samples **Figure 3**.

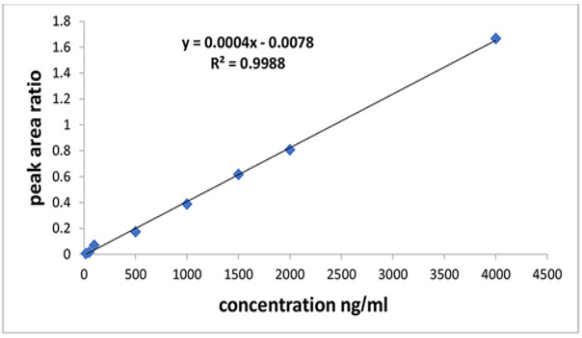
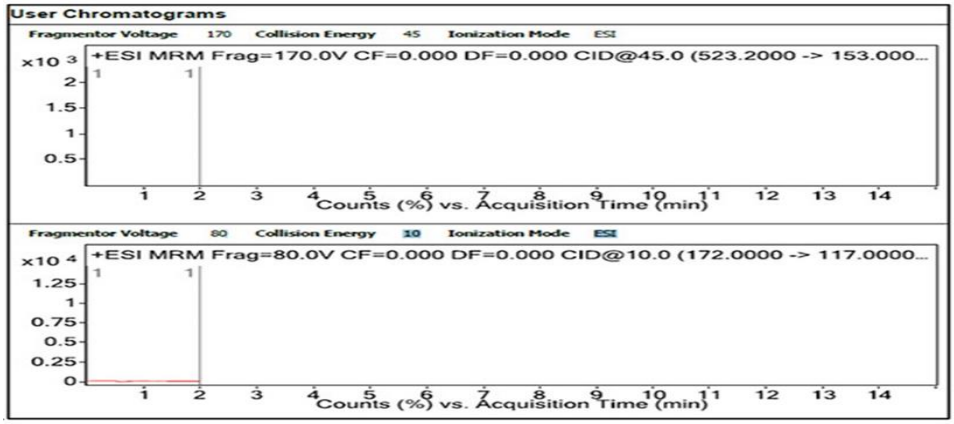
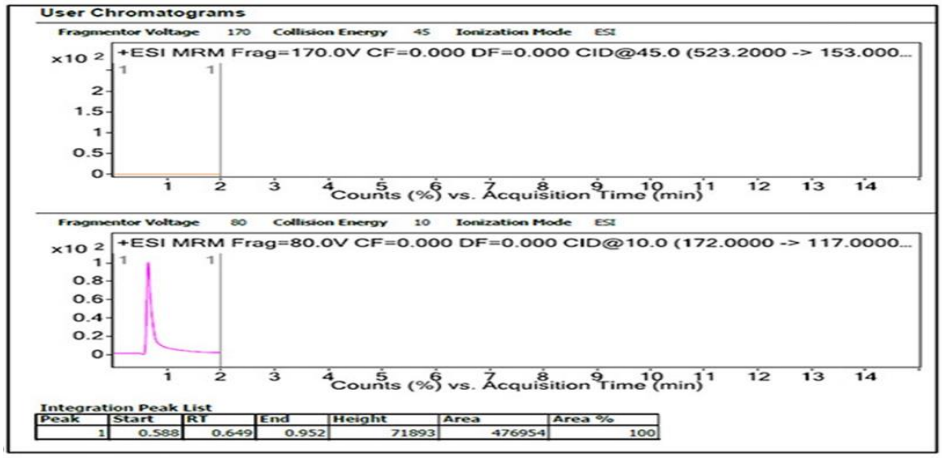


Figure 3. Calibration curve for ticagrelor (180mg).

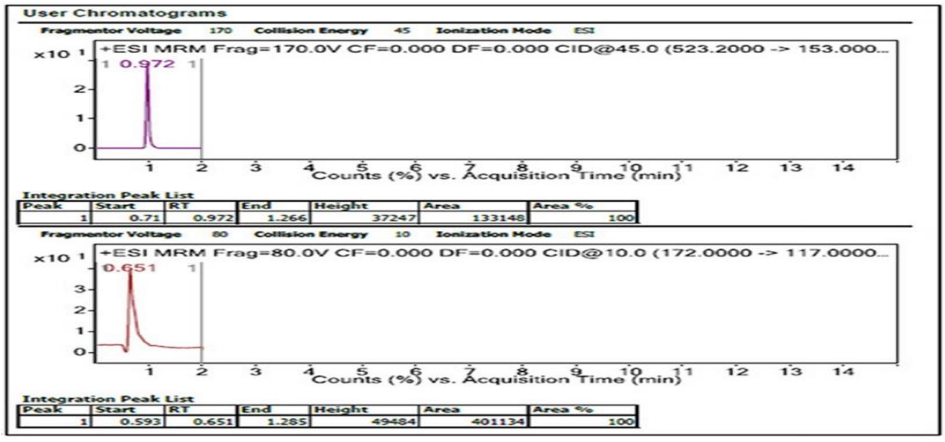
and The Cmax (Mean ± SD, ng/ml) calculated 2-3 h after administration of ticagrelor 180 mg was 972.80 ± 189.**7** as presented in **Figure 4**.



a)



b)



c)

Figure 4. UPLC MS/MS chromatogram of ticagrelor and internal standard. (a) Blank samples (plasma without drug or internal standard). (b) zero samples (plasma with internal standard) (c) plasma sample spiked with IS, 2-3 h after oral administration of 180 mg ticagrelor.

Results of pharmacodynamic study

The maximal ADP- (5μmol/L) induced platelet aggregation (Mean ± SD, %) in patients treated with clopidogrel 600 mg and ticagrelor 180mg was 47.00 ± 9.93 and 37.00 ± 7.95 respectively .

Patients treated with ticagrelor had significantly lower maximal ADP- induced Platelet aggregation compared with patients treated with clopidogrel (P-value =0.043) as shown in **Figure 5**.

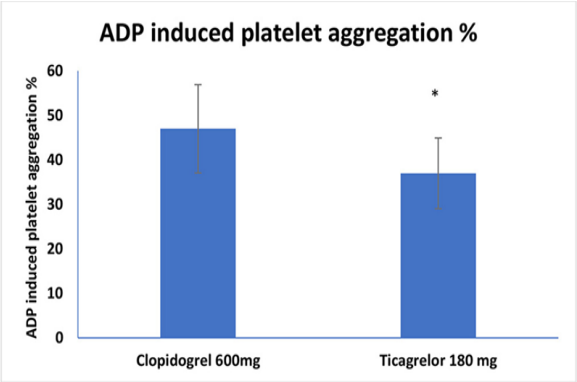


Figure 5. Maximal ADP-induced platelet aggregation 2-3 hours after loading dose with clopidogrel 600 mg and ticagrelor 180 mg.
* indicates statistically significant difference between the two studied groups, P-value =0.043

CAD is considered a global cause of cardiac mortality that occurs due to coronary atherosclerosis [10].

Effective platelet inhibition in patients undergoing elective PCI reduces the risk of MACE. Although aspirin has been the cornerstone anti-platelet drug, dual antiplatelet therapy, where, ADP receptor blocker is added to aspirin, has been proved to be beneficial in patients undergoing elective PCI to reduce the magnitude of peri-procedural and post-procedural cardiovascular complications [11].

There are contradictions in the preference of choice of either clopidogrel or ticagrelor in these patients.

This study aimed to compare the clinical safety and efficacy of clopidogrel versus ticagrelor, as a part of dual antiplatelet therapy with aspirin, in patients undergoing elective PCI with the determination of the actual plasma concentrations and the platelet inhibitory effect of both drugs by the help of chromatographic and aggregometry studies.

This study did not report any mortality and revealed that the occurrence of MACE was lower in ticagrelor-treated patients but this reduction was not significant compared to the clopidogrel-treated group. The occurrence of major bleeding and dyspnea was significantly higher in ticagrelor-treated patients compared to clopidogrel.

The effect of clopidogrel and ticagrelor in blunting the peri-procedural myocardial necrosis in patients with SCAD undergoing elective PCI was reported by a previous study which concluded that ticagrelor was not more effective than clopidogrel in lowering periprocedural myocardial necrosis after coronary intervention [12].

The role of ticagrelor in reducing MACE can be explained not only by acting as an ADP antagonist but also by modulating the endogenous adenosine concentration by preventing its intracellular degradation through inhibition of equilibrative nucleoside transporter-1, thereby enhancing its role in improving coronary blood flow [13].

In this study, ticagrelor was associated with a higher rate of major bleeding compared to clopidogrel. A study performed in patients diagnosed with acute coronary syndrome suggested that newer oral ADP blocking agents decreased the MACE and myocardial infarction however they were associated with a significant increase in the risk of bleeding [14].

Contrary to our findings, no statistically significant difference was observed in the rates of life-threatening bleeding between the ticagrelor and clopidogrel group in the study done by Kumar and his team [15].

Another study done on diabetic patients after elective PCI for SCAD showed that ticagrelor was not associated with major bleeding [16], probably due to its advantage of being a reversible P2Y12 receptor inhibitor [17].

In the follow-up period during maintenance therapy, dyspnea was significantly reported in ticagrelor-treated patients than clopidogrel. This finding may be consistent with results from meta-analysis comparing new P2Y12 inhibitors with clopidogrel. This study suggested that ticagrelor therapy was associated with dyspnea more than clopidogrel [18]. Similarly, our results were broadly in line with a previous study that reported discontinuation of ticagrelor therapy because of severe dyspnea [19].

Previous analysis suggested that cessation of ticagrelor therapy due to dyspnea was prone to occur during the first year of treatment [20]. Dyspnea may be due to increased endogenous adenosine concentration by ticagrelor [21]. The significant occurrence of major bleeding and dyspnea with ticagrelor together with its cost may affect patient adherence [22].

It was apparent from the aggregometry study that a greater degree of platelet inhibition was achieved with ticagrelor treatment contrary to clopidogrel.

These results were consistent with what has been found in a previous study that investigated the anti-platelet effect of clopidogrel and ticagrelor using two platelet function tests; LTA and Vasodilator-stimulated phosphoprotein assay. The study showed that ticagrelor had a superiority in inhibiting platelet aggregation more than clopidogrel [23].

These findings were also following findings reported by Jiang and his team who showed that ticagrelor provided a more potent platelet inhibition than clopidogrel. They also suggested the presence of an anti-inflammatory effect for ticagrelor [24]. Previous research showed that after elective PCI for SCAD in diabetic patients, ticagrelor achieved a greater antiplatelet effect than clopidogrel [16].

The present study also showed the presence of inter-individual variability in clopidogrel concentration and revealed that Cmax

levels obtained 2-3 hours after a loading dose of 600mg clopidogrel were variable between the patients.

Postulation for the inter-individual variability of clopidogrel plasma concentrations was suggested [25] and claimed that the diversity of the anti-platelet activity of clopidogrel was due to CYP2C19 loss of function alleles.

Another explanation may be deduced from a previous study which showed that diabetic patients had about half the concentrations of the active metabolite of clopidogrel compared to non-diabetics after clopidogrel loading [26]. This may be clarified by the reduction of activity of CYP450 enzymes as a consequence of the released pro-inflammatory cytokines [27].

Another clinical pharmacokinetic study of clopidogrel was done and announced that the Cmax value of clopidogrel was 2.0 ng/mL after administration of clopidogrel 75mg [28] and it was 0.9 ng/mL on Argentinean populations [29]. On the other hand, Egyptian healthy volunteers had a Cmax of 4.4 ng/mL [30].

In 2010, the FDA approved a black box warning on the relationship between CYP2C19 pharmacogenetics and the anti-platelet response of clopidogrel but this warning was not accompanied by compulsory genetic testing before initiating clopidogrel therapy [31]. However, several studies suggested that clopidogrel therapy has to be tailored for individuals based on their tested genetic results [32].

Conclusion

In this study, Inhibition of P2Y12 receptor by clopidogrel or ticagrelor combined with aspirin, as a part of dual anti-platelet treatment improved the outcome of patients with SCAD undergoing elective PCI. While Ticagrelor therapy increased the risk of major bleeding and dyspnea in the setting of elective PCI, it reduced the occurrence of MACE but this reduction was not significant compared to clopidogrel. Ticagrelor loading significantly inhibited the platelet aggregation compared to clopidogrel. Inter-individual variability in the Cmax values of clopidogrel was observed in the study. The cost of the drugs and their adverse effect profile are critical factors that should be taken into consideration during management.

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Conflict of interest: None

Financial support: None

Ethics statement: This study was conducted at the critical care department, Faculty of Medicine, Cairo University. The study protocol was approved by the Cairo University Research Ethics Committee (REC), approval number (N-11-2019), and all patients gave written informed consent for participation.

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