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Comparison of clopidogrel *vs.* ticagrelor medication adherence in patients with acute coronary syndrome

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Abstract. – OBJECTIVE: Medication nonadherence to dual antiplatelet therapy increases major cardiovascular events. In this study, we investigated patients' post-acute coronary syndrome (ACS) medication adherence to clopidogrel and ticagrelor over a 12-month period. Furthermore, we also examined the factors that may affect medication adherence in this patient population.

PATIENTS AND METHODS: This study included 509 patients who were scheduled for dual antiplatelet therapy for one year following ACS (October 2018-December 2019). A proportion of days covered (PDC) method, based on a pharmacy database system, was used to determine their medication adherence. Medication adherence was defined as > 80% PDC.

RESULTS: No difference was found between clopidogrel and ticagrelor in terms of medication adherence (68.3% *vs.* 64.6%, *p* = 0.39). Moreover, higher education levels (B = 3.24, CI: 1.17-8.9, *p* = 0.023) and percutaneous coronary intervention (PCI) as a revascularization option (B = 0.35, CI: 0.17-0.71, *p* = 0.004) predicted medication adherence independently.

CONCLUSIONS: In this research, medication adherence was found to be similar between the clopidogrel and ticagrelor groups. It was also predicted by higher education levels and revascularization with PCI.

Key Words:
Clopidogrel, Ticagrelor, Medication adherence, Acute coronary syndromes.

Introduction

Among patients discharged from the hospital after experiencing acute coronary syndrome (ACS), poor adherence to dual antiplatelet therapy (DAPT – acetylsalicylic acid and P2Y12 inhibitor) has been associated with a higher risk of recurrent coronary events and death, placing an additional burden on the healthcare system[1-3].

Medication adherence is a complex problem influenced by many factors, including the perception of disease severity and understanding of disease burden[4]. The World Health Organization (WHO)[5] identified five main causes of medication nonadherence: patient, condition, therapy, socioeconomic, and healthcare system-related factors.

Studies[1] on DAPT have often determined the duration of the treatment regimen and showed that medication nonadherence increases major cardiovascular events. Twice-a-day posology and side effects such as dyspnea raised concerns about ticagrelor adherence[6]. Moreover, there has been limited research[7] comparing medication adherence among different P2Y12 inhibitors. Therefore, in this study, we investigated the post-ACS medication adherence of patients to clopidogrel and ticagrelor over a 12-month period. Furthermore, we investigated the factors that may affect medication adherence in this patient population.

Patients and Methods

Study Population and Data Source

This study involved 509 patients who were scheduled for a yearlong DAPT following ACS (October 2018-December 2019). Patients under the age of 18, those who had died in the hospital, those who were considered for short-term DAPT,

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and those who were using prasugrel were not included. Also, 43 patients who were switched between antiplatelet drugs (due to the development of dyspnea or the need for oral anticoagulant use or potent P2Y12 inhibitor) and whose medications were discontinued for essential reasons (such as bleeding or noncardiac surgery) (Figure 1) were excluded from the analysis. Informed consent was obtained from all the study participants. Additionally, this study complies with the Declaration of Helsinki. The protocol was approved by the Local Ethics Committee and the Ministry of Health.

All the patients' clinical variables and laboratory test panels during hospitalization were obtained from medical records. Data on demographics (age, sex, ethnicity), medical history (ischemic heart disease, diabetes mellitus, hypertension, atrial fibrillation), and current medical treatment were also gathered from the same source. Furthermore, we obtained information on all medications, including clopidogrel and ticagrelor, taken by the patients for a year from the pharmacy database. In addition, we visited the patients in the hospital at the end of the 12 months to assess their medication adherence with the greatest degree of accuracy.

Definitions

Based on the pharmacy database, this study defines drug exposure as the prescription use of clopidogrel and ticagrelor. Medication adherence was estimated using the proportion of days covered (PDC); PDC (%) = (number of months using the drug/number of months of use) × 100[8,9]. Patients with a PDC of 80% or higher were considered adherent to medications, while those below 80% were non-adherent[10,11].

Statistical Analysis

All statistical tests were conducted using the SPSS for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA). Moreover, the normal distribution of data was assessed using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as percentages (%). As needed, categorical variable differences were compared between groups using a Chi-square test, while unpaired samples were compared using the Student's *t*-test or the Mann-Whitney U test. Furthermore, independent variables of age, gender, medication group, marital status, education level, income level, and treatment options were determined using univariate and multivariate logistic regression analyses. Following univariate analyses, statistically significant variables were selected for a multivariate logistic regression analysis using the stepwise method. The univariate and multivariate regression analyses' findings were each presented as an odds ratio (OR) with a 95% confidence interval (CI). Significance was assumed at a two-sided p-value < 0.05.

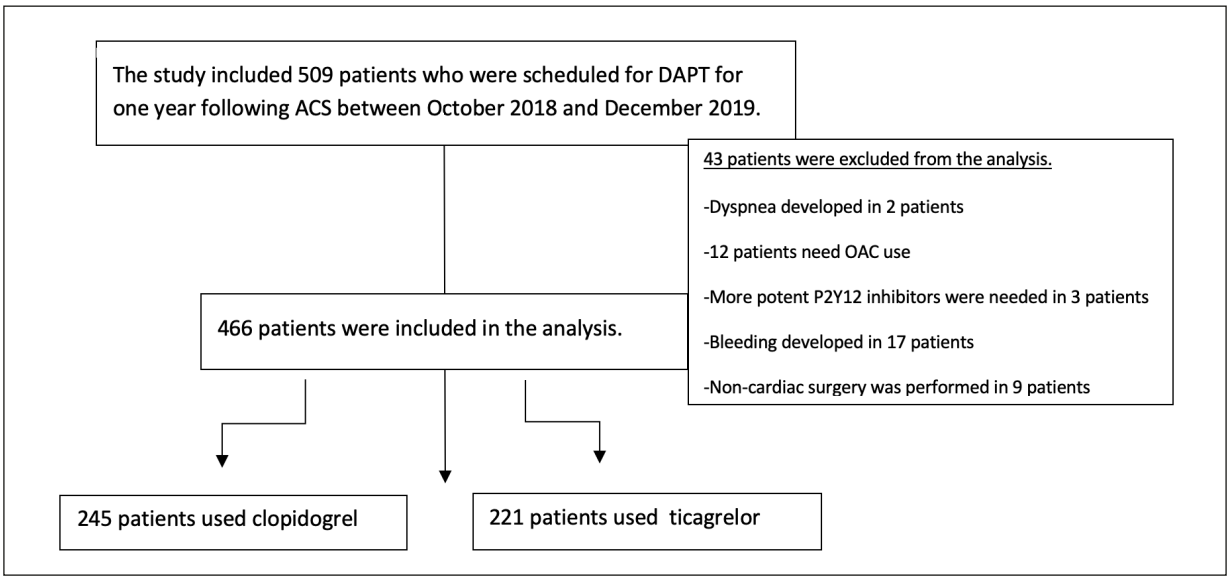

Figure 1. Flowchart of the study.

Results

Among the 509 study participants, 245 were in the clopidogrel group and 221 in the ticagrelor group. Regarding age, clopidogrel patients were older than ticagrelor patients (64.6 ± 11.2 *vs.* 58.9 ± 10.4, $p < 0.001$). There was no statistical difference between the two groups in terms of gender distribution. Moreover, both groups had similar medication adherence rates ($p = 0.900$). The proportion of medication-adherent patients was also similar between the two groups, with no statistically significant difference (68.3% *vs.* 64.6%, $p = 0.390$). Other clinical, demographic, and laboratory parameters are given in Table I.

We also analyzed the study participants according to medication adherence (Table II). No difference was observed between the two groups in terms of age, gender, marital status, occupation, and clinical parameters such as diabetes mellitus (DM) or hypertension. Medication-non-adherent patients had lower education levels than medication-adherent patients (87.2% *vs.* 96.4%, $p = 0.005$). Moreover, as expected, medication-adherent patients had higher income levels (48.0% *vs.* 41.2%, $p = 0.022$). Among laboratory parameters, only low-density cholesterol (LDL-C) was significantly lower in adherent patients. When compared to other treatment options, percutaneous coronary intervention (PCI) as a revascularization option increased medication adherence (89.4% *vs.* 83.9%, $p = 0.012$). The effects of medication adherence on clinical endpoints were also as expected: death (1% *vs.* 10.3%, $p < 0.001$), myocardial infarction (MI) (7.1% *vs.* 13.5% $p = 0.025$), and combined clinical outcomes [death, MI, and stroke/transient ischemic attack (TIA)] (9.7% *vs.* 21.8%, $p < 0.001$) were all lower in medication-adherent patients.

Due to major differences between the study groups, we performed multivariate logistic regression analysis to identify independent predictors of medication adherence. Variables such

Table I. The demographic and clinical data of the study population.

Variables	Clopidogrel (n: 245)	Ticagrelor (n: 221)	p-value
Age (years)	64.6 ± 11.2	58.9 ± 10.4	< 0.001
Male, % (n)	73.5 (180)	79.4 (177)	0.100
Married, % (n)	90 (206)	84.7 (182)	0.120
Adherence rate (%)	81.3 ± 29.0	81.0 ± 27.1	0.900
Proportion of medication-adherent patients, % (n)	68.3 (166)	64.6 (144)	0.390
PCI as a revascularization option, % (n)	80.2 (195)	93.7 (209)	< 0.001
Smoker, % (n)	43.4 (106)	66.4 (148)	< 0.001
Medical history, % (n)			
Diabetes Mellitus	56.7 (139)	64.1 (143)	0.100
Hypertension	31.4% (77)	55.6% (124)	< 0.001
Hyperlipidemi	67.3% (165)	87.4% (195)	< 0.001
Stroke/TIA	6.1 (15)	1.8 (4)	0.018
PAD	4.5 (11)	4.5 (10)	0.900
COPD	14.3 (35)	5.4 (12)	0.001
Laboratory findings			
Creatinine (mg/dl)	1.04 ± 0.4	1.01 ± 1.0	0.640
Hemoglobin (g/dl)	13 ± 1.9	13.7 ± 1.6	0.280
Total Cholesterol (mg/dl)	171.9 ± 37.9	176.3 ± 54.2	0.300
HDL-C (mg/dl)	43.4 ± 9.5	39.1 ± 8.7	0.100
LDL-C (mg/dl)	118.9 ± 36.5	116 ± 44.8	0.400
Triglyceride (mg/dl)	137.1 ± 61.4	181 ± 160	< 0.001
Fasting glucose, (mg/dl)	129.8 ± 44.4	126.9 ± 51.8	0.500
HbA1c (%)	6.3 ± 0.9	6.3 ± 1.9	0.770
Clinical endpoints, % (n)			
Death	5.3 (13)	2.7 (6)	0.150
Myocardial İnfarction	8.6 (21)	9.9 (22)	0.620
Combined clinical outcome (death, MI, stroke/TIA), % (n)	14.7 (36)	12.6 (28)	0.500

PCI, percutaneous coronary intervention; TIA, transient ischemic attack; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1C, hemoglobin A1C; MI, myocardial infarction.

Table II. Baseline characteristics of medication adherent/non-adherent patients.

Variables	Medication adherent patients (n: 310)	Medication non-adherent patients (n: 156)	*p*-value
Age (years)	61.4 ± 11.1	62.9 ± 11.7	0.160
Male, % (n)	77.4 (240)	74.4 (116)	0.460
Married, % (n)	89.4 (271)	82.7(115)	0.090
Lower education level, % (n)	87.2 (267)	96.4 (134)	0.005
Lower income level, % (n)	41.2 (128)	48.0 (75)	0.022
PCI as a revascularization option, % (n)	89.4 (277)	83.9 (156)	0.012
Smoker, % (n)	46.1 (143)	43.9 (68)	0.330
Medical History, % (n)			
Diabetes Mellitus	39.4 (122)	40.4 (63)	0.830
Hypertension	56.6 (176)	56.7 (106)	0.980
Hyperlipidemi	20.9 (65)	24.6 (46)	0.330
Stroke/TIA	4.2 (13)	3.2 (6)	0.580
PAD	3.5 (11)	5.9 (11)	0.210
COPD	9.7 (30)	10.7 (20)	0.710
Laboratory findings			
Creatinine (mg/dl)	1.03 ± 0.92	1.04 ± 0.98	0.860
Hemoglobin (g/dl)	13.4 ± 1.8	13.3 ± 1.7	0.690
Total Cholesterol (mg/dl)	171.3 ± 45.1	179.6 ± 48.6	0.060
HDL-C (mg/dl)	41.6 ± 9.3	40.7 ± 9.4	0.320
LDL-C (mg/dl)	115 ± 40.6	122.6 ± 40.7	0.057
Triglyceride (mg/dl)	156 ± 112.8	162.7 ± 136.5	0.570
Fasting glucose (mg/dl)	127.2 ± 46.9	131.2 ± 50.4	0.400
HbA1c (%)	6.25 ± 1.3	6.47 ± 1.6	0.140
Clinical endpoints, % (n)			
Death	10.3 (16)	1 (3)	< 0.001
Myocardial Infarction	7.1 (22)	13.5 (21)	0.025
Combined clinical outcome (death, MI, stroke/TIA), % (n)	9.7 (30)	21.8 (34)	< 0.001

PCI, percutaneous coronary intervention; TIA, transient ischemic attack; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1C, hemoglobin A1C; MI, myocardial infarction.

as medication group (clopidogrel/ticagrelor), age, gender, marital status, education level, income level, and treatment option were evaluated through logistic regression analysis (Table III). Accordingly, higher education levels (B = 3.24, CI: 1.17-8.9, $p = 0.023$) and PCI as a revascularization option (B = 0.35, CI: 0.17-0.71, $p = 0.004$) independently predicted medication adherence.

Discussion

In this study, we investigated patients' post-ACS medication adherence to clopidogrel and ticagrelor over a 12-month period. We also examined the factors that may influence medication adherence in this patient population. Our study's main results are as follows:

Table III. Logistic regression analysis of independent variables determining medication non-adherence.

Variable	OR	95% CI	*p*-value
Medication group (clopidogrel)	0.74	0.45-1.20	0.22
Age (> 70)	0.74	0.44-1.24	0.25
Male	1.09	0.65-1.83	0.73
Married	0.67	0.36-1.25	0.21
Lower education level	3.24	1.17-8.96	0.023
Lower income level	1.74	0.76-4.01	0.18
PCI as a revascularization option	0.35	0.17-0.71	0.004

PCI, percutaneous coronary intervention.

Clopidogrel and ticagrelor medication adherence rates were similar (81.3 ± 29% *vs.* 81 ± 27.1%, $p = 0.9$).

Higher education levels (B = 3.24, CI: 1.17-8.9, $p = 0.023$) and PCI as a revascularization method (B = 0.35, CI: 0.17-0.71, $p = 0.004$) independently predicted medication adherence.

DAPT reduces the risk of thrombotic events and is crucial in treating ACS patients[12,13]. Although numerous studies[7,13-15] have shown that antiplatelet medication nonadherence can increase major cardiovascular events, the level of adherence to these drugs has yet to be clarified. Therefore, research determining the level of medication adherence in patients using antiplatelet drugs, as well as the factors affecting adherence, are scarce.

One such study was conducted by Turgeon et al[16], which centered on clopidogrel and ticagrelor adherence among ACS patients similar to ours; they also used a pharmacy database to extract patient adherence rates. They found no difference in major cardiac events between patients using clopidogrel or ticagrelor after a year; however, interestingly, patients were more likely to adhere to ticagrelor (81.6% *vs*. 73.9%, $p < 0.001$). Contrary to our methodology, however, they classified patients who switched from clopidogrel to ticagrelor or *vice versa* as non-adherent. Hence, it cannot be said that their study's main focus was on patients' medication adherence. Ma et al[17] compared the therapeutic effects of ticagrelor and clopidogrel on patients with acute myocardial infarction. They stated that the effect of ticagrelor on acute myocardial infarction (AMI) patients was significantly better and safer than clopidogrel. Moreover, in a REAL-TICA study conducted by Zeymer et al[18], 22% of patients taking ticagrelor after ACS discontinued their medication early, with less than 3% doing so due to side effects. A MINAP-GPRD study published by Boggon et al[19] revealed that statins were prescribed at a much higher rate than clopidogrel after ACS (82-85% *vs.* 53-54%, $p < 0.001$). Furthermore, to evaluate the DAPT adherence of patients undergoing coronary PCI, Czerny et al[20] ran a meta-analysis and reviewed 34 studies, a few of which sought to investigate the causes of medication nonadherence. In particular, Quadros et al[21] (2011) revealed that drug costs, lack of information, and marital status were all essential in the cessation of P2Y12 inhibitors after ACS. Jura-Szoltys and Chudek[22] added that a high education level was important for medication adherence. Comparably, education level was found to be one of the significant determinants of medication adherence in our study; however, since all study participants had social health insurance, medication cost was not considered a variable.

There has been limited research comparing adherence to clopidogrel and ticagrelor in the literature. As seen above, any studies that do exist produced distinct results. In addition, these studies were insufficient to evaluate the factors affecting medication adherence. In this study, while investigating the differences in adherence between the two drugs, we also examined the factors that may cause medication non-adherence. Our findings have similarities and differences with other studies in terms of methodology, patient population, and treatment methods. Unlike other research, however, patients undergoing medically required drug discontinuation/changes were excluded from our analysis since we aimed to identify truly medication-adherent and non-adherent patients.

As in other studies[13-16], side effects' role in drug cessation was found to be limited in our research; death, MI, and combined clinical outcomes (death, MI, and stroke/TIA) were likewise observed at lower rates in medication-adherent patients. These results corroborate previous findings[14,15] that early cessation of P2Y12 inhibitors is associated with an increased risk of death, hospitalization, and stent thrombosis.

We believe this study will add important findings to the literature about medication adherence to clopidogrel and ticagrelor. Although ticagrelor is a more potent antiplatelet drug, it has some concerns that it may cause medication non-adherence (twice-daily posology, dyspnea side effects, etc.). We think that these concerns will be eliminated as a result of our study.

Limitations

In addition to using the pharmacy database for maximum accuracy in medication adherence, we made hospital visits to all patients at the end of one year. Despite our best efforts, we were unable to evaluate medication adherence with 100% accuracy, which was the most significant limitation of our study. Another constraint was the study groups' non-homogeneous ACS type, age, and gender distributions; we, nevertheless, attempted to overcome this by performing a multivariate analysis.

Conclusions

In our study, clopidogrel and ticagrelor medication adherence rates were found to be similar. Regarding medication nonadherence, rather than drug side effects, patient education levels and treatment options were the decisive factors.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethics Approval

The Internal Review Board approved the study protocol at the Istanbul University-Cerrahpasa Ethics Committee (Protocol date and number: 06/11/2019-170576).

Availability of Data and Materials

The datasets of the current study are available upon reasonable request.

Authors' Contribution

All authors contributed to one or more of the following steps; the design of the study, data acquisition, or analysis and interpretation of data, drafting or revising the article and final approval of the manuscript to be published.

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