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# Comparison Of The Effects Of Ticagrelor And Clopidogrel On Heart Rate Variability And Heart Rate Turbulence In Patients With Percutaneous Coronary Interventions

Pinar Yagcioglu
*Bursa Postgraduate Hospital, Departments of Cardiology, Bursa, Turkey*

Selma Ari
*Bursa Postgraduate HospitalDepartments of Cardiology, Bursa, Turkey*

Hasan Ari
*Bursa Postgraduate Hospital, Departments of Cardiology, Bursa, Turkey*

Mehmet Melek
*Bursa Postgraduate Hospital, Departments of Cardiology, Bursa, Turkey*



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# Comparison of the effects of ticagrelor and clopidogrel on heart rate variability and heart rate turbulence in patients with percutaneous coronary interventions

Pinar Yagcioglu, Selma Ari, Hasan Ari*, Mehmet Melek

Bursa Postgraduate Hospital, Departments of Cardiology, Bursa, Turkey

**Abstract**

*Introduction*: **Clopidogrel and ticagrelor are commonly used, antiplatelet agents. Ticagrelor has an effect of enhancing the plasma level of adenosine that may alter the autonomic function. The aim of this study is to compare the effects of ticagrelor and clopidogrel on heart rate variability (HRV) and heart rate turbulence (HRT).**

*Methods*: **Thirty subjects who performed percutaneous coronary intervention (PCI) were included in the randomized, crossover study. These patients were divided into two groups. Clopidogrel or ticagrelor was administered in two different testing sessions (1-month treatment for each session). In group 1, clopidogrel and ticagrelor treatment were used while in group 2, ticagrelor and clopidogrel treatment were used respectively. Three times rhythm Holter recording (baseline, 1st and 2nd month) was performed. The HRV (time domain and frequency domain) and HRT (turbulence onset (TO) and turbulence slope (TS)) parameters were analyzed from the Holter recordings.**

*Results*: **According to baseline Holter recording, pNN50 ($5.82 \pm 5.83$ vs $10.56 \pm 8.28$; $p = 0.03$) and HF(nu) ($6.85 \pm 9.33$ vs $9.53 \pm 7.41$; $p = 0.04$) parameters were higher in group 2 than in group 1, while TO($0.004 \pm 0.02$ vs $-0.01 \pm 0.02$; $p = 0.01$) parameter was positive and higher in group 1 than in group 2. In the second month, the LF/HF ratio ($4.47 \pm 2.43$ vs $3.18 \pm 2.45$; $p = 0.04$) was higher in group 1 than in group 2. However, when the evaluation was done within the groups themselves, there were no statistically significant differences in HRV and HRT parameters obtained before and after clopidogrel and ticagrelor administration in group 1 and group 2.**

*Conclusion*: **Ticagrelor and clopidogrel treatments did not have a significant effect on HRV and HRT parameters.**

*Keywords:* Ticagrelor, Clopidogrel, Heart rate variability, Heart rate turbulence

## 1. Introduction

In patients undergoing percutaneous coronary intervention (PCI), the use of antiagregan is a standard treatment. The most commonly used antiplatelet agents today are aspirin, clopidogrel, ticagrelor and prasugrel [1–4]. Unlike other agents, ticagrelor has an effect of enhancing the plasma level of adenosine by inhibiting adenosine reuptake [5,6]. This effect is considered to be the mechanism responsible for the side effects of ticagrelor such as dyspnea and ventricular pause [7]. On the other hand Ortega-Paz et al. found that the dispnea is related with the ticagrelor plasma concentration [8]. In vivo study, Gourine et al. showed that adenosine triphosphate dependent mechanism activated chemoreceptor neurons and increases in breathing [9]. Furthermore, increase the circulating levels of adenosine

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* Corresponding author. Kardiyoloji Kliniği, Bursa Yüksek İhtisas Eğitim ve Araştõrma Hastanesi, Yõldõrõm, Bursa, Turkey. Fax: +90 224 3605055.
E-mail addresses: pnrggh@yahoo.com (P. Yagcioglu), selmakulekci@yahoo.com.tr (S. Ari), hasanari03@yahoo.com (H. Ari), mehmetmelek73@gmail.com (M. Melek).

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or ticagrelor may effect the cardiac othonomic function [6,8,9].

Adenosine receptors are widely found through the body and bring about very different effects, both directly and indirectly, wherever they are. It is known that adenosine has effects on the autonomic nervous system [10]. The most important factor in regulating heart rate is autonomic nervous system activity [11,12]. Heart rate variability (HRV) and heart rate turbulence (HRT) are reliable parameters used to evaluate autonomic functions in various diseases. HRV shows periodic changes in unit time over sinus velocity. With this method, spectral analysis of electrocardiographic (ECG) signals is performed, cardiac autonomic tonus can be assessed based on some specific frequency bands associated with the parasympathetic and sympathetic nervous system [13,14]. HRT is defined as physiologic changes in sinus velocity after premature ventricular extrasystole (VES) and is accepted as a sign of baroreflex sensitivity [15]. Several studies have shown that impaired HRT in cardiac disease is associated with mortality [16].

There is no previous study evaluating the efficacy of clopidogrel and ticagrelor on cardiac autonomic function. In this study, it was aimed to evaluate the effects of clopidogrel and ticagrelor on cardiac autonomic functions with HRT and HRV parameters.

**Abbreviations**

| | |
|---|---|
| ASDNN | Standard deviation of the average R–R interval |
| HF | High frequency |
| HRT | Heart rate turbulence |
| HRV | Heart rate variability |
| LF | Low frequency |
| PCI | Percutaneous coronary intervention |
| pNN50 | Percentage of pairs of adjacent R–R intervals differing by more than 50 ms |
| rMSSD | Root mean square of successive R–R interval differences |
| SDNN | Standard deviation of the R–R interval |
| TO | Turbulence onset |
| TP | Total power |
| TS | Turbulence slope |
| VLF | Very-low-frequency |

## 2. Materials and method

### 2.1. Subjects and study design

Two times (at least 6 h apart) troponin negative low-risk acute coronary syndrome patients who applied to our cardiology clinic were consecutively included in the study. These patients had not ECG changes, left ventricular wall motion abnormality and ongoing chest pain. Signed informed consent form was obtained from each patient. The study group consisted of 30 patients who were diagnosed with coronary artery stenosis after coronary angiography. Patients with myocardial infarction, diabetes mellitus, atrial fibrillation, malignant tumors, active infection findings, thyroid dysfunction, cerebrovascular events, chronic obstructive pulmonary disease (COPD), left ventricular wall motion abnormality, heart valve disease, pulmonary hypertension and requiring urgent coronary intervention were excluded from the study. Prior to PCI, clopidogrel and appropriate antiatherosclerotic treatment were given according to the clinical characteristics of the patient for 1 week. At the end of 1 week 24-h rhythm Holter records were taken and the patient was treated with PCI 1 day later. Cardiac enzymes, renal function tests and hemogram parameters were observed 1 day before the procedure and patients were discharged 1 day after the procedure with medical treatments according to their clinical characteristics. The patients were randomized into two groups automatically by a computer program according to their application number of our clinic.

15 patients were discharged with clopidogrel treatment, while 15 patients were discharged with ticagrelor treatment. After 1 month, 24-h rhythm Holter records of patients were taken again, after this recording, a crossover was done between groups taking clopidogrel and ticagrelor. One month later, the third 24-h rhythm Holter recordings were performed (Fig. 1).

### 2.2. HRV and HRT analysis

The 24-h rhythm Holter recording was performed with the Spiderview™ recorder (Ela Medical, Paris 2007). The rhythm Holter records (baseline, 1st and 2nd month) from all patients were loaded on the computer and analyzed by the Holter program (ELA Medical SYNESCOPE MultiChannel- Multiday Version 3.10). Three periods of recording were analysed separately. First, artefacts, normal and ventricular pulses were detected in the "template" tab. Then the maximum, minimum, and mean heart rates were recorded. The time-dependent HRV values were evaluated with PNN50 (percentage of pairs of adjacent R–R intervals differing by more than 50 ms), RMSSD (root mean square of

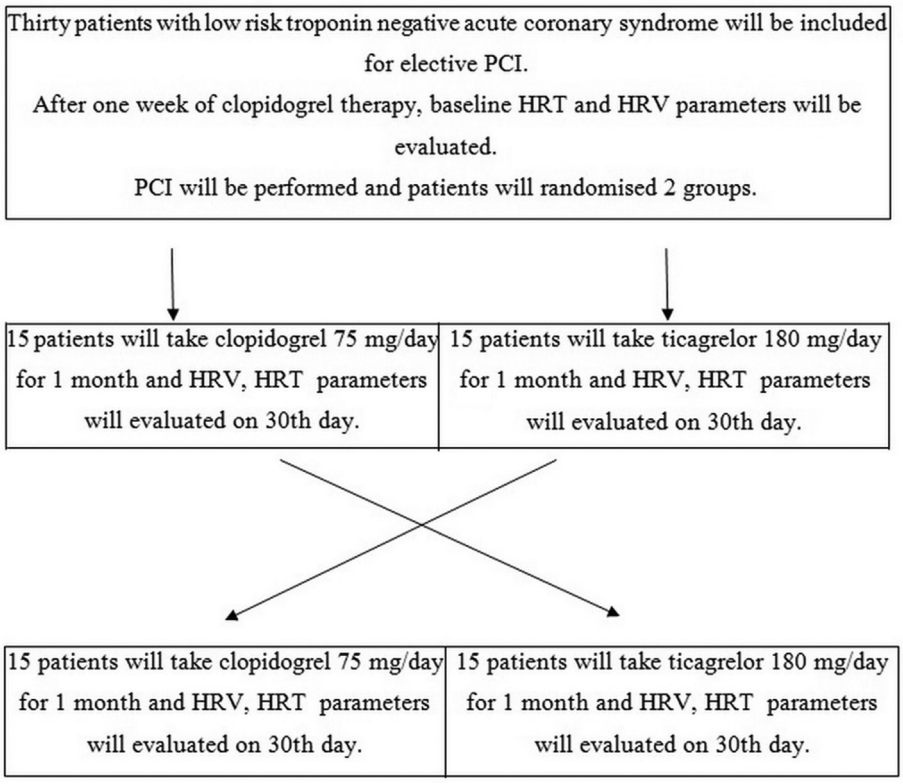


*Fig.1. Study design.*

successive R−R interval differences), ASDNN (standard deviation of the average R−R interval) and SDNN (standard deviation of the R−R interval) parameters. Frequency domain analysis was performed with Fast Fourier Transform. Frequency-dependent HRV parameters were detected at four different band intervals; high-frequency (HF) (0.15−0.4 Hz), Very-low-frequency (VLF) (0.0−0.04 Hz), low-frequency (LF) (0.04−0.15 Hz), total power (0.0−2.0 Hz) and LF/HF ratio. The normalized high frequency power (HF nu = 100 × high frequency power/total power), normalized low frequency power (LF nu = 100 × low frequency power/total power), very-low-frequency power (VLF nu = 100 x very-low-frequency power/total power) and low frequency power/high frequency power ratio (LF/HF ratio) were calculated to give the relative changes in HRV in the frequency domain.

The HRT parameters, turbulence onset (TO) and turbulence slope (TS) were automatically calculated by the HRT program (HRT View Version 0.60−0.1 Munich, Germany) using the appropriate VES for HRT measurement from the Holter recordings. Values less than 0% for TO and values greater than 2.5 msn/RR for TS were considered normal [12]. Loss of turbulence was recognized as an increase in TO and a decrease in TS.

### *2.3. Statistical analysis*

Statistical analysis was performed with the SSPS 22.0 software package (SPSS Inc., Chicago, IL). All numeric variables are expressed as the mean ± SD, and categorical variables are expressed as percentages. Inter-group comparisons were made by the Mann−Whitney U test for continuous variables and categorical variables were compared by the chi-squared test or Fisher's exact test. The repeated measurements (baseline, clopidogrel, and ticagrelor treatment periods) were analyzed with the Wilcoxon signed rank test. A p-value $< 0.05$ was considered statistically significant.

## 3. Results

The study patients were divided into 2 groups according to their treatment order. Group 1 was treated with clopidogrel-clopidogrel-ticagrelor order and group 2 was treated with clopidogrel-ticagrelor-clopidogrel order. The demographic characteristics, laboratory parameters and therapies

*Table 1. Baseline characteristics of two groups.*

| | Group 1 (n = 15) | Group 2 (n = 15) | p Value |
|---|---|---|---|
| Age (years) | 60.47 ± 7.41 | 58.07 ± 8.24 | 0.40 |
| Gender; n (%) | | | |
| Male | 14 (%93.3) | 12 (%80) | 0.59 |
| Female | 1 (%6.7) | 3 (%20) | |
| Smoking, n (%) | | | |
| (active and former) | 6 (%40) | 6 (%40) | 1 |
| Hypertension, n (%) | 11 (%73.3) | 6 (%40) | 0.06 |
| Heart rate (bpm) | 70.36 ± 5.67 | 72.09 ± 5.42 | 0.58 |
| SBP (mmHg) | 125.60 ± 7.60 | 120.66 ± 11.27 | 0.17 |
| DBP (mmHg) | 84.37 ± 4.17 | 80.33 ± 8.66 | 0.21 |
| Left ventricular EF (%) | 64.76 ± 2.14 | 65.23 ± 2.63 | 0.39 |
| Hemoglobin (gr/dl) | 14.23 ± 1.24 | 13.79 ± 1.56 | 0.40 |
| WBC ($10^3$/ul) | 8.88 ± 1.78 | 8.20 ± 1.86 | 0.31 |
| Platelet ($10^3$/ul) | 227.66 ± 45.60 | 222.06 ± 48.27 | 0.74 |
| BUN (mg/dl) | 16.33 ± 3.19 | 17.73 ± 7.86 | 0.52 |
| Creatinin (mg/dl) | 0.87 ± 0.18 | 0.87 ± 0.22 | 0.93 |
| Na (mmol/l) | 139.33 ± 2.49 | 140.60 ± 2.61 | 0.18 |
| K (mmol/l) | 4.32 ± 0.41 | 4.15 ± 0.99 | 0.54 |
| LDL (mg/dl) | 95.77 ± 60.17 | 104.82 ± 61.46 | 0.68 |
| HDL (mg/dl) | 45.08 ± 14.06 | 44.38 ± 10.27 | 0.87 |
| Medication, n (%) | | | |
| ASA | 15 (%100) | 15 (%100) | 1 |
| Beta blocker | 15 (%100) | 14 (%93.3) | 0.99 |
| ACEI | 11 (%73.3) | 9 (%60) | 0.43 |
| Statin | 11 (%73.3) | 14 (%93.3) | 0.33 |
| Nitrate | 1 (%6.7) | 1 (%6.7) | 1 |
| Diüretic | 7 (%46.7) | 4 (%26./) | 0.25 |

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, EF: Ejection fraction, ACEI:Angiotensin converting enzyme inhibitor.

were similar in both groups (Table 1). We prescript metoprolol for all patients and the two groups beta blocker dose was similar during the Holter recording periods (group 1: 81.6 ± 33.3 vs group 2: 89.2 ± 32.0; p = 0.53). According to the initial Holter analyzes of the study groups, there was a significant difference between the groups in HF (nu), pNN50 and TO parameters (Table 2). Parameters of HF (nu) and pNN50 in group 2 were significantly higher than in group 1 (Table 2). TO parameter of group 1 was positive and significantly higher than group 2 (Table 2). There was no significant difference between the two groups in terms of HRV and HRT parameters after one month of clopidogrel and ticagrelor treatment (Table 2). The HRT parameters were similar in both groups, however, there was a difference in the LF/HF ratio in the rhythm Holter recordings after 1 month of cross-over treatment of clopidogrel and ticagrelor (Table 2). No statistically significant differences were found in HRV and HRT parameters when examining the baseline, 1st and 2nd month Holter records of group 1 patients (Table 3). According to the three rhythm Holter record periods, in group 1 only the R–R period of the 1st month was shorter than R–R period of the baseline (Table 3). According to the three rhythm Holter record periods, in group 2 HRT and HRV parameters were similar in the three record periods (Table 4). We performed an HRV and HRT analysis for our 30 study patients in different treatment phase. All HRV and HRT parameters were similar for three treatment phase (Table 5).

Holter recordings showed no > 2 s pause, bradycardia, sustained or nonsustained tachycardia in both groups. Despite the shortness of breath during the early period of ticagrelor treatment in two patients, these complaints disappeared in following the treatment. There was no serious side effect that causes the cessation of treatment associated with respiratory functions in the study patients.

## 4. Discussion

In our study, the effects of clopidogrel and ticagrelor treatment on HRV and HRT were evaluated in patients with coronary artery disease treated with PCI. Both ticagrelor and clopidogrel treatments were tested in the same patient group with the cross over method. Ticagrelor and clopidogrel treatments did not have a significant effect on HRV and HRT parameters. This is the first study in the literature to evaluate the effects of ticagrelor and clopidogrel on HRT and HRV.

Ticagrelor may cause an increase in plasma concentration of adenosine by blocking intracellular reuptake of adenosine in erythrocytes, particularly through the non-sodium-dependent ENT-1 receptor [17]. In addition, the metabolites of ticagrelor (AR-C 124910, AR-C 133913 XX) inhibit ENT-1 weakly. No such effect was found in other P2Y12 inhibitor antiplatelet agents [17,18]. Adenosine shows biological effects via 4 piece G proteins. A1 and A3 act on the Gi protein receptor, A2A and A2B act on the Gs protein receptor [19,20].

However Ortega-Paz et al. showed that the dispnea is related with the ticagrelor plasma concentration and dispne is independent of plasma adenosine level [8]. On the other hand they did not evaluate the tissue adenosine levels and tissue sensitivity to adenosine. Higher ticagrelor concentration act these mechanism. Elevated ticagrelor may had direct pürinerjik effect to central nervous system [9]. Central nervous system could activated with chemoreceptor neurons via adenosine triphosphate [9]. This mechanism may be associated with respiratory changes.

Adenosine receptors are common and may have opposite effects relative to their localization. This is particularly striking in the effects on the autonomic nervous system [21]. For this reason, it is important to understand how adenosine acts on efferent,

*Table 2. Comparison of two groups baseline, first and second month HRV and HRT parameters.*

| | Group 1 (n = 15) | Group 2 (n = 15) | p Value | Group 1 (n = 15) | Group 2 (n = 15) | P Value | Group 1 (n = 15) | Group 2 (n = 15) | p Value |
|---|---|---|---|---|---|---|---|---|---|
| Treatment | Clopidogrel | Clopidogrel | | Clopidogrel | Ticagrelor | | Ticagrelor | Clopidogrel | |
| Study Period | Baseline Recording | | | First Month Recording | | | Second Month Recording | | |
| Mean R–R time (ms) | 890.46± 80.86 | 899.00± 119.71 | 0.82 | 838.26± 69.11 | 880.66± 119.04 | 0.24 | 872.80± 55.23 | 896.46± 150.29 | 0.57 |
| HRV (frequency domain) | | | | | | | | | |
| TP ($ms^2$) | 3674.73± 4831.70 | 2738.80± 1883.54 | 0.82 | 3342.06± 3063.51 | 3070.40± 2480.86 | 0.46 | 3155.66± 1694.67 | 2991.33± 2504.59 | 0.29 |
| VLF ($ms^2$) | 2838.73 ± 3278.46 | 2173.46 ± 1470.49 | 0.63 | 2597.93 ± 2023.48 | 2439 ± 1831.05 | 0.57 | 2473.73 ± 1242.95 | 2274.66 ± 1820.46 | 0.23 |
| VLF (nu) | 81.68 ± 5.27 | 79.76 ± 5.49 | 0.29 | 81.45 ± 6.00 | 80.97 ± 5.87 | 0.69 | 79.50 ± 5.26 | 78.03 ± 6.23 | 0.49 |
| LF ($ms^2$) | 836.00± 1561.29 | 565.33± 436.17 | 0.72 | 744.13± 1066.91 | 630.66± 674.49 | 0.72 | 681.93± 492.79 | 716.66± 719.92 | 0.41 |
| LF (nu) | 18.31± 5.27 | 20.23± 5.49 | 0.29 | 18.54± 6.00 | 19.02± 5.86 | 0.69 | 20.49± 5.26 | 21.96± 6.23 | 0.49 |
| HF($ms^2$) | 631.66± 2044.96 | 242.73± 203.92 | 0.14 | 542.86± 1455.76 | 202.53± 146.16 | 0.56 | 339.93± 571.48 | 323.06± 371.92 | 0.61 |
| HF (nu) | 6.85± 9.33 | 9.53± 7.41 | **0.04** | 8.13± 10.09 | 7.26± 4.14 | 0.49 | 7.81± 8.31 | 10.02± 7.17 | 0.14 |
| LF/HF ratio | 4.53± 2.51 | 3.33± 2.26 | 0.11 | 3.79± 2.11 | 3.50± 2.69 | 0.48 | 4.47± 2.43 | 3.18± 2.45 | **0.04** |
| HRV (time domain) | | | | | | | | | |
| SDNN (ms) | 99.91± 27.20 | 108.45± 42.10 | 0.78 | 113.53± 26.18 | 116.60± 37.29 | 0.85 | 110.55± 26.38 | 110.88± 34.46 | 0.78 |
| ASDNN (ms) | 55.73± 29.78 | 53.47± 16.89 | 0.91 | 52.06± 17.03 | 52.83± 18.99 | 0.98 | 54.43± 12.85 | 53.85± 22.50 | 0.31 |
| rMSSD(ms) | 39.04± 56.34 | 38.70± 17.58 | 0.08 | 38.33± 34.74 | 34.46± 13.43 | 0.63 | 36.40± 25.19 | 40.29± 24.57 | 0.57 |
| pNN50 (%) | 5.82± 5.83 | 10.56± 8.28 | **0.03** | 7.18± 6.27 | 7.61± 7.17 | 0.93 | 5.74± 4.94 | 9.07± 9.68 | 0.49 |
| HRTparameters | | | | | | | | | |
| TO (%) | 0.004± 0.02 | −0.01± 0.02 | **0.01** | −0.001± 0.02 | −0.012± 0.02 | 0.09 | 0.001± 0.03 | −0.010± 0.02 | 0.52 |
| TS (ms) | 5.55± 5.34 | 7.39± 6.05 | 0.19 | 5.94± 5.21 | 5.33± 6.57 | 0.24 | 9.06± 7.22 | 7.77± 5.21 | 0.78 |

HRV: Heart rate variability, HRT: Heart rate turbulence, TO: Turbulence onset, TS: Turbulence slope.
Statistically significant ($p < 0.05$) parameters were stated as bold.

central and afferent autonomic pathways in order to understand the total effect on the cardiovascular system. The total effect of adenosine on cardiovascular autonomic regulation, via afferent pathways (via chemoreceptors) have a sympathetic activity enhancing effect and vasoconstriction and blood pressure enhancing effect, thus increasing the tissue perfusion pressure. On the other hand, it has local vasodilator effects [22]. This creates a protective effect on ischemia.

While the LF in HRV analysis represents a complex combination of sympathetic and parasympathetic effects on cardiac autonomic function, the HF generally represent innervation of the vagal of the heart [13,23]. The LF/HF ratio is accepted as the sympathovagal balance index [13]. The fact that baseline HF (nu) and pNN50 values in group 2 were higher than in group 1 suggests that sympathovagal balance favors the parasympathetic system in group 2. Similarly, 2 months after the treatment, the LF/HF ratio was lower in group 2 than in group 1, like that in the baseline of study, suggesting the autonomic function of group 2 in favor of the parasympathetic system. Although there was a difference between the two groups HRV parameters, according to a comparison of repeated measurements (baseline, 1st, and 2 nd month), HRV parameters for each group were not different. This result indicates that the drugs used

*Table 3. Comparison of the baseline, first and second month HRV and HRT parameters of group 1.*

| Group 1 (n:15) | | | | P Value Baseline vs first month | P Value Baseline vs Second month | P Value First month vs Second month |
|---|---|---|---|---|---|---|
| Treatment | Clopidogrel | Clopidogrel | Ticagrelor | | | |
| Study Period | Baseline Recording | First Month Recording | Second Month Recording | | | |
| Mean R–R time (ms) | 890.46 ± 80.86 | 838.26 ± 69.11 | 872.80 ± 55.23 | **0.03** | 0.33 | 0.06 |
| HRV (frequency domain) | | | | | | |
| TP ($ms^2$) | 3674.73 ± 4831.70 | 3342.06 ± 3063.51 | 3155.66 ± 1694.67 | 0.95 | 0.88 | 0.65 |
| VLF ($ms^2$) | 2838.73 ± 3278.46 | 2597.93 ± 2023.48 | 2473.73 ± 1242.95 | 0.91 | 0.92 | 0.99 |
| VLF (nu) | 81.68 ± 5.27 | 81.45 ± 6.00 | 79.50 ± 5.26 | 0.92 | 0.10 | 0.24 |
| LF ($ms^2$) | 836.00 ± 1561.29 | 744.13 ± 1066.91 | 681.93 ± 492.79 | 0.82 | 0.57 | 0.25 |
| LF (nu) | 18.31 ± 5.27 | 18.54 ± 6.00 | 20.49 ± 5.26 | 0.91 | 0.11 | 0.23 |
| HF ($ms^2$) | 631.66 ± 2044.96 | 542.86 ± 1455.76 | 339.93 ± 571.48 | 0.36 | 0.73 | 0.97 |
| HF (nu) | 6.85 ± 9.33 | 8.13 ± 10.09 | 7.81 ± 8.31 | 0.23 | 0.86 | 0.91 |
| LF/HF ratio | 4.53 ± 2.51 | 3.79 ± 2.11 | 4.47 ± 2.43 | 0.08 | 0.57 | 0.12 |
| HRV (time domain) | | | | | | |
| SDNN (ms) | 99.91 ± 27.20 | 113.53 ± 26.18 | 110.55 ± 26.38 | 0.08 | 0.11 | 0.65 |
| ASDNN (ms) | 55.73 ± 29.78 | 52.06 ± 17.03 | 54.43 ± 12.85 | 0.82 | 0.73 | 0.28 |
| rMSSD(ms) | 39.04 ± 56.34 | 38.33 ± 34.74 | 36.40 ± 25.19 | 0.28 | 0.33 | 0.95 |
| pNN50 (%) | 4.82 ± 5.83 | 7.18 ± 6.27 | 5.74 ± 4.94 | 0.17 | 0.28 | 0.82 |
| HRT parameters | | | | | | |
| TO (%) | 0.004 ± 0.02 | −0.001 ± 0.02 | 0.001 ± 0.03 | 0.58 | 0.42 | 0.77 |
| TS (ms) | 5.55 ± 5.34 | 5.94 ± 5.21 | 9.06 ± 7.22 | 0.86 | 0.17 | 0.19 |

HRV: Heart rate variability, HRT: Heart rate turbulence, TO: Turbulence onset, TS: Turbulence slope.
Statistically significant ($p < 0.05$) parameters were stated as bold.

*Table 4. Comparison of the baseline, first and second month HRV and HRT parameters of group 2.*

| Group 2 (n:15) | | | | P Value Baseline vs First Month | P Value Baseline vs Second Month | P Value First Month vs Second Month |
|---|---|---|---|---|---|---|
| Treatment | Clopidogrel | Ticagrelor | Clopidogrel | | | |
| Study Period | Baseline Recording | First MonthRecording | Second MonthRecording | | | |
| Mean R–R time (ms) | 899.00 ± 119.71 | 880.66 ± 119.04 | 896.46 ± 150.29 | 0.64 | 0.95 | 0.33 |
| HRV (Frequency domain) | | | | | | |
| TP ($ms^2$) | 2738.80 ± 1883.54 | 3070.40 ± 2480.86 | 2991.33 ± 2504.59 | 0.11 | 1.00 | 0.51 |
| VLF($ms^2$) | 2173.46 ± 1470.49 | 2439 ± 1831.05 | 2274.66 ± 1820.46 | 0.21 | 0.86 | 0.57 |
| VLF (nu) | 79.76 ± 5.49 | 80.97 ± 5.87 | 78.03 ± 6.23 | 0.87 | 0.27 | 0.15 |
| LF ($ms^2$) | 565.33 ± 436.17 | 630.66 ± 674.49 | 716.66 ± 719.92 | 0.19 | 0.57 | 0.65 |
| LF (nu) | 20.23 ± 5.49 | 19.02 ± 5.86 | 21.96 ± 6.23 | 0.86 | 0.28 | 0.14 |
| HF($ms^2$) | 242.73 ± 203.92 | 202.53 ± 146.16 | 323.06 ± 371.92 | 0.59 | 0.95 | 0.29 |
| HF (nu) | 9.53 ± 7.41 | 7.26 ± 4.14 | 10.02 ± 7.17 | 0.36 | 0.86 | 0.07 |
| LF/HF ratio | 3.33 ± 2.26 | 3.50 ± 2.69 | 3.18 ± 2.45 | 0.60 | 0.95 | 0.49 |
| HRV (Time domain) | | | | | | |
| SDNN (ms) | 108.45 ± 42.10 | 116.60 ± 37.29 | 110.55 ± 26.38 | 0.07 | 0.69 | 0.33 |
| ASDNN (ms) | 53.47 ± 16.89 | 52.83 ± 18.99 | 54.43 ± 12.85 | 0.73 | 0.69 | 0.95 |
| rMSSD (ms) | 38.70 ± 17.58 | 34.46 ± 13.43 | 36.40 ± 25.19 | 0.69 | 0.82 | 0.46 |
| pNN50 (%) | 10.56 ± 8.28 | 7.61 ± 7.17 | 5.74 ± 4.94 | 0.17 | 0.28 | 0.62 |
| HRT parameters | | | | | | |
| TO (%) | −0.01 ± 0.02 | −0.012 ± 0.02 | −0.010 ± 0.02 | 0.46 | 0.39 | 0.80 |
| TS (ms) | 7.39 ± 6.05 | 5.33 ± 6.57 | 7.77 ± 5.21 | 0.91 | 0.53 | 0.10 |

HRV: Heart rate variability, HRT: Heart rate turbulence, TO: Turbulence onset, TS: Turbulence slope.

(clopidogrel, ticagrelor) had no effect on the parameters of HRV. Previous studies showed that, the VLF values was changing with respiratory oscillation and oxygen-sensitive mechanism [24,25]. Giannoni et al., found that ticagrelor may lead to periodic breathing, with alternating apnea and hyperventilation [26]. In the light of these data, respiratory and VLF variation in ticagrelor is expected. However there was no change in the VLF values of our patients. The absence of a significant change in the VLF values of our patients can be explained by the absence of a significant respiratory distress in our patients.

HRT is primarily a reflection of the vagal tone that antagonizes the sympathetic increase [16]. It is also

*Table 5. Comparison of the HRV and HRT parameters in different treatment phase.*

| (n:30) | | | | P 1 Value | P 2 Value | P 3 Value |
|---|---|---|---|---|---|---|
| Study Period | Clopidogrel (Baseline) | Clopidogrel (After PCI) | Ticagrelor (After PCI) | | | |
| Mean R–R time (ms) | 894.60 ± 100.46 | 867.37 ± 118.74 | 876.71 ± 91.29 | 0.09 | 0.23 | 0.50 |
| HRV (Frequency domain) | | | | | | |
| TP ($ms^2$) | 2738.80 ± 1883.54 | 3070.40 ± 2480.86 | 2991.33 ± 2504.59 | 0.94 | 0.24 | 0.42 |
| VLF($ms^2$) | 2506.10 ± 2519.36 | 2436.30 ± 1898.31 | 2456.73 ± 1537.75 | 0.97 | 0.30 | 0.60 |
| VLF (nu) | 80.72 ± 5.38 | 79.74 ± 6.26 | 80.23 ± 5.53 | 0.44 | 0.32 | 0.86 |
| LF ($ms^2$) | 700.66 ± 734.71 | 730.40 ± 894.39 | 656.30 ± 580.98 | 0.78 | 0.19 | 0.83 |
| LF (nu) | 19.27 ± 5.38 | 20.25 ± 6.26 | 19.76 ± 5.52 | 0.44 | 0.32 | 0.84 |
| HF($ms^2$) | 437.20 ± 441.54 | 432.96 ± 149.93 | 271.23 ± 41.76 | 0.62 | 0.96 | 0.18 |
| HF (nu) | 8.19 ± 8.39 | 9.08 ± 8.66 | 7.53 ± 6.46 | 0.47 | 0.64 | 0.17 |
| LF/HF ratio | 3.93 ± 2.43 | 3.48 ± 2.72 | 3.98 ± 2.57 | 0.21 | 0.49 | 0.12 |
| HRV (Time domain) | | | | | | |
| SDNN (ms) | 104.18 ± 35.09 | 112.20 ± 30.10 | 113.57 ± 31.88 | 0.09 | 0.06 | 0.84 |
| ASDNN (ms) | 54.60 ± 23.81 | 52.95 ± 19.63 | 53.63 ± 15.95 | 0.64 | 0.62 | 0.50 |
| rMSSD (ms) | 38.87 ± 41.01 | 39.31 ± 29.58 | 35.43 ± 19.86 | 0.54 | 0.62 | 0.55 |
| pNN50 (%) | 7.69 ± 7.62 | 8.12 ± 8.07 | 6.68 ± 6.12 | 0.97 | 0.68 | 0.59 |
| HRT parameters | | | | | | |
| TO (%) | −0.0056 ± 0.02 | −0.0058 ± 0.02 | −0.0054 ± 0.02 | 0.78 | 0.23 | 0.18 |
| TS (ms) | 6.47 ± 5.68 | 6.85 ± 5.20 | 7.33 ± 7.06 | 0.59 | 0.28 | 0.90 |

HRV: Heart rate variability, HRT: Heart rate turbulence, TO: Turbulence onset, TS: Turbulence slope. P 1 value:Clopidogrel (baseline) ve Clopidogrel (after PCI), P 2 Value: Clopidogrel (baseline) vs Ticagrelor (after PCI), P 3 Value: Clopidogrel (after PCI) vs Ticagrelor (after PCI).

considered as a noninvasive indicator of spontaneous baroreceptor sensitivity [27]. The European Heart Association has stated that HRT is a good indicator of vagal activity and an independent predictor of total mortality [28]. In our study, the TO parameter of group 1 was positive at baseline and higher than group 2. This is consistent with the fact that parasympathetic autonomic functions of group 1 are weaker than group 2. Sympathetic activity in group 1 seems to be more dominant. However, the applied treatments (clopidogrel, ticagrelor) did not make any difference in terms of HRT parameters in the comparison between the two groups and in each group. That is, clopidogrel and ticagrelor did not have a significant effect on HRT parameters.

### *4.1. Limitations of the study*

The present study only included a small number of patients, and only short-term records were obtained. Our study population left ventricular function was in normal value. HRV and HRT parameters can alter in low ventricular function population. Furthermore, there were no complications such as respiratory distress and arrhythmia in our study population. Also, respiratory distress may affect the HRV and HRT parameters. Another limitation is that the levels of adenosine, ticagrelor and platelet reactivity unit were not measured. However, our randomized crossover design study could overcome these limitations and may serve as a guide for larger-scale studies.

## 5. Conclusion

Clopidogrel and ticagrelor therapy in PCI patients have been shown to have no effect on cardiac autonomic functions assessed by the HRV and HRT parameters. This study will be a guide to studies in larger and different patient populations.

## Statement of ethics

The study was performed after approval was obtained from the local Ethics Committee.

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## Declaration of Competing Interest

The authors have no relevant conflicts of interest to disclose.

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