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The effect of P2Y12 receptor inhibitors on clinical outcomes in patients with acute coronary syndrome undergoing primary percutaneous intervention and receiving abciximab

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ABSTRACT

Background: *Our study compared the effect of P2Y12 receptor inhibitors in combination with abciximab on clinical outcomes in patients with acute coronary syndrome (ACS).*

Methods: *Our study is retrospective, consisting of 852 consecutive ACS patients who presented to our clinic between 2015 and 2021, underwent primary percutaneous coronary intervention (PCI), and received abciximab in addition to dual antiplatelet therapy. The P2Y12 receptor inhibitors were compared in terms of in-hospital and 1-year major adverse cardiac events (MACE), and clinically significant in-hospital and 1-year bleeding complications.*

Results: *The patients' mean age was 60.4 ± 11 years, and 702 (82.4%) were male. In-hospital MACE, in-hospital mortality, 1-year MACE, and 1-year mortality were significantly higher in the clopidogrel group compared to the ticagrelor group. There was no significant difference in the development of in-hospital and 1-year bleeding between clopidogrel and the more potent P2Y12 receptor inhibitors. According to the BARC score, there was no difference in major bleeding between ticagrelor and clopidogrel ($p = 0.641$), but minor bleeding was significantly lower in the ticagrelor group ($p < 0.001$). In logistic regression analysis, the 1-year MACE rate was lower in the potent P2Y12 receptor inhibitors group compared to clopidogrel. At the same time, no association was found with short- and long-term mortality, bleeding, or in-hospital MACE.*

Conclusions: *In our study, potent P2Y12 receptor inhibitors combined with abciximab decreased 1-year MACE without significantly increasing bleeding in ACS patients undergoing PCI compared to clopidogrel. This study suggests that potent P2Y12 receptor inhibitors can be safely used with abciximab, considering the bleeding risk.* (Cardiol J 2025; 32, 5: 468–474)

Keywords: acute coronary syndrome, P2Y12 receptor inhibitors, glycoprotein IIB/IIIA inhibitors, abciximab, bleeding, mortality

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Introduction

Despite significant advancements in percutaneous coronary intervention (PCI) and the development of potent antithrombotic therapies, coronary artery disease (CAD), and specifically acute coronary syndromes (ACS), remain the leading global cause of mortality. This persistently high mortality rate is primarily attributable to complications such as bleeding and recurrent ischemic events [1, 2]. Acute coronary syndromes encompass a spectrum of conditions, including unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) [3].

Recent advancements in risk stratification, early intervention, invasive strategies, intensive care conditions, antiplatelet agents, anticoagulants, and urgent revascularization techniques have collectively contributed to reduced mortality associated with ACS [4]. Current clinical guidelines advocate for dual antiplatelet therapy (DAPT) comprising acetylsalicylic acid (ASA) and a P2Y12 receptor inhibitor for ACS patients undergoing primary PCI. Additionally, glycoprotein IIb/IIIa inhibitors (GPIs) are recommended as a significant therapeutic option for ACS patients undergoing PCI, particularly in scenarios involving high thrombus burden or compromised coronary flow [5, 6]. Abciximab, a widely utilized GPI, has effectively mitigated short-term and long-term ischemic complications in this patient population [7, 8]. Despite substantial evidence supporting the clinical benefits of combining GPIs with clopidogrel in ACS management, the safety and efficacy of such combinations with more potent P2Y12 receptor inhibitors, such as ticagrelor or prasugrel, remain inadequately explored. The potential for increased bleeding risk when combining GPIs with these potent inhibitors warrants further investigation and remains a subject of ongoing debate.

Our study aimed to compare the short- and long-term clinical outcomes of P2Y12 receptor inhibitors in patients undergoing PCI and receiving abciximab due to ACS.

Methods

Study type and patient selection

This single-center, retrospective study evaluated 852 patients aged 18 to 85 years, who underwent PPCI for ACS at Atatürk University Faculty of Medicine Research Hospital in Türkiye between 2015 and 2021. Inclusion criteria encompassed patients who received abciximab, ASA, and a P2Y12 receptor inhibitor as part of their ACS management. The study cohort comprised individuals who, after PCI for ACS, were treated with DAPT (consisting of 300 mg aspirin followed by 100 mg/day maintenance, 600 mg clopidogrel followed by 75 mg/day maintenance, 180 mg ticagrelor followed by 90 mg twice daily maintenance, or 60 mg prasugrel followed by 10 mg/day maintenance) and unfractionated heparin (50–70 IU/kg intravenous bolus to maintain activated clotting time between 200 and 250 seconds), along with abciximab (0.25 mg/kg intracoronary bolus followed by a continuous intravenous infusion of 0.125 μg/kg/min, up to a maximum of 10 μg/min for 12 hours). Exclusion criteria included patients who received thrombolytic therapy, those on oral anticoagulants, individuals with thrombocytopenia (< 100,000 cells/mcL), those who had undergone major surgery or experienced trauma within the past 6 weeks, individuals with significant gastrointestinal or genitourinary bleeding within the past 6 weeks, those with a history of cerebrovascular bleeding or accidents in the previous 2 years, individuals with advanced liver or renal disease, and those under 18 years of age. The flowchart of our study is shown in Figure 1.

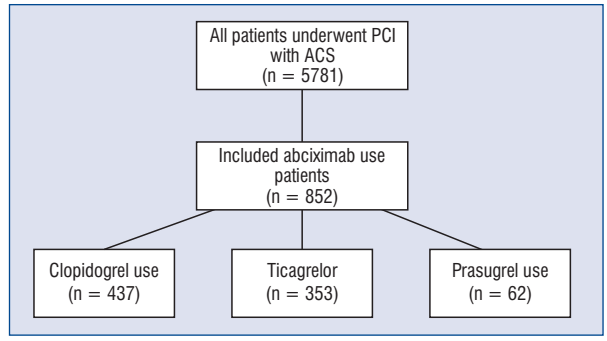

Figure 1. Flowchart of patients who underwent percutaneous coronary intervention (PCI) with acute coronary syndromes (ACS), according to use of P2Y12 receptor inhibitors and abciximab

Definitions and data preparation

The diagnosis of ACS was established according to the fourth universal myocardial infarction (MI) criteria [9]. Diabetes mellitus was identified based on a fasting blood glucose level ≥ 126 mg/dL or the use of antidiabetic medications. Hypertension was defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg or the use of antihypertensive drugs. A history of CAD was characterized by a previous PCI or coronary artery bypass grafting with documented evidence of CAD. Chronic kidney disease was

defined as a creatinine clearance rate < 60 mL/ /min. Anemia was classified as a hemoglobin (Hgb) level < 12 g/dL in women or < 13 g/dL in men. Major adverse cardiovascular events (MACE) were defined to include myocardial infarction, stroke, acute stent thrombosis, and cardiovascular death. Bleeding events encompassed clinical occurrences such as hematoma at the access site, intracranial bleeding, gastrointestinal bleeding, genitourinary bleeding, and cardiac tamponade. A hemoglobin drop was defined as a reduction in hemoglobin level ≥ 3 g/dL. We used the Bleeding Academic Research Consortium (BARC) classification for bleeding events [10]. According to BARC classification, major bleeding was categorized as BARC 3b and above, while minor bleeding was classified as BARC 3a and below. Platelet reduction was defined as a decrease in platelet count below 100,000/mL. The estimated glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula [11].

Study data were retrospectively gathered by examining the hospital's information management system. Patient records were reviewed to extract information on anamnesis, physical examination findings, electrocardiography results, echocardiography data (using the Vivid 7 device, GE Vingmed Ultrasound, Horten, Norway), laboratory findings at the time of admission, administered medications, and in-hospital clinical outcomes. This information was sourced from patient files, the hospital's electronic information system, the E-Nabız system, and the Ministry of Health's death notification system. Coronary angiograms were evaluated and documented by two independent cardiologists. All stents employed during the procedures were drug-eluting stents (Everolimus-coated).

Endpoints

The study's primary endpoints comprised 1-year MACE, such as MI, stroke, acute stent thrombosis, and cardiovascular death. Secondary endpoints encompassed in-hospital MACE, mortality (both in-hospital and at 1 year), bleeding events (both in-hospital and at 1 year), hemoglobin drop, and platelet drop in patients receiving dual antiplatelet therapy (clopidogrel, ticagrelor, or prasugrel) in combination with abciximab.

Ethics Committee approval

Ethics Committee approval was obtained on November 25, 2021, during the 8th meeting of the local Clinical Research Ethics Committee, under decision number 40, in compliance with the Helsinki Declaration.

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows, Version 22.0. Categorical variables are reported as percentages, while continuous variables are presented as mean ± standard deviation or median (interquartile range), depending on their distribution. Parametric variables were analyzed using the t-test between two independent groups and ANOVA for comparisons among three independent groups. Categorical variables were assessed with the χ^2 test. For non-normally distributed variables, the Mann–Whitney U test was employed for comparisons between two groups, and the Kruskal–Wallis H test for comparisons among three groups. Because the number of patients using prasugrel was low, the number of patients using prasugrel and ticagrelor were added together and defined as potent P2Y12 receptor inhibitors, and the parameters with significant differences in the univariate analysis with the clopidogrel group were included in the multivariate logistic regression analysis. A p-value of < 0.05 was considered statistically significant.

Results

The average age of the patients included in the study was 60.4 ± 11 years, and 702 (82.4%) were male. Clopidogrel was preferred as P2Y12 receptor inhibitor therapy for 437 (51.3%) patients, ticagrelor for 353 (41.4%) patients, and prasugrel for 62 (7.3%) patients. Clopidogrel was more commonly chosen for older patients and women than for those who were prescribed ticagrelor or prasugrel. Prasugrel was more frequently preferred in the patient group with a known history of CAD and heart failure (HF). Baseline characteristics data are shown in Table 1.

The primary endpoint, 1-year MACE, was significantly higher in the clopidogrel group than in the ticagrelor group (p < 0.001). Secondary endpoints, in-hospital MACE, 1-year mortality, and in-hospital mortality, were significantly higher in the clopidogrel group than in the ticagrelor group. Other secondary endpoints, in-hospital and 1-year bleeding outcomes, showed no significant difference between clopidogrel and more potent P2Y12 receptor inhibitors. A more significant reduction in hemoglobin was observed in patients given clopidogrel than in patients given ticagrelor. According to the BARC score, there was no difference in major bleeding between ticagrelor and clopidogrel (p = 0.641); however, minor bleeding was significantly lower in the ticagrelor group (p < 0.001).

Table 1. Baseline demographic data of the study according to use of P2Y12 receptor inhibitors

Variables	Clopidogrel (n = 437)	Ticagrelor (n = 353)	Prasugrel (n = 62)	P-value
Age [years]	63.7 ± 10.5	57.2 ± 10.8	55.6 ± 8.8	< 0.001[1,2]
Sex male [n, %]	330 (75.5)	313 (88.7)	59 (95.2)	< 0.001[1, 2]
HT [n, %]	238 (54.5)	150 (42.5)	26 (41.9)	0.002[1]
DM [n, %]	179 (41)	113 (32)	22 (35.5)	0.034[1]
CAD [n, %]	124 (28.4)	99 (28)	42 (67.7)	< 0.001[2, 3]
HF [n, %]	65 (14.9)	37 (10.5)	20 (32.3)	< 0.001[2, 3]
STEMI [n, %]	251 (57.4)	215 (60.9)	25 (40.3)	0.01[2, 3]
Smoking [n, %]	241 (55.1)	231 (65.4)	39 (62.9)	0.012[1]
LVEF [%]	44.8 ± 7.9	46.5 ± 6.5	46.4 ± 6.6	0.002[1]
HGB [g/dL]	14.9 ± 1.8	15.5 ± 1.6	15.5 ± 1.5	< 0.001[1]
PLT [10^3/mL]	254 ± 62	260 ± 66	260 ± 68	0.335
WBC [10^3/mL]	12.6 ± 3.2	12.2 ± 2.9	11.8 ± 2.7	0.051
GFR [mL//min/1.73 m^2]	78.3 ± 28.3	86.1 ± 25.2	87.2 ± 22.8	< 0.001[1, 2]
Peak troponin [pg/mL, 25–75 percentile)	5748 (2293–15956)	5668 (1965–15089)	3044 (1289–12444)	0.08
HDL [mg/dL]	43.2 ± 9.6	41.5 ± 8.6	40.3 ± 8.9	0.005[1, 2]
LDL [mg/dL]	138.1 ± 34.6	142 ± 34.9	122.8 ± 44.7	< 0.001[2, 3]
TG [mg/dL, 25–75 percentile]	112 (82–161)	134 (91–208)	134 (101–222)	0.001[1, 2]
Total cholesterol [mg/dL]	203.4 ± 47.1	207.8 ± 49.4	190.9 ± 58.3	0.037[3]
HbA1c [%]	6.8 ± 1.9	6.5 ± 1.7	6.6 ± 1.8	0.026[1]
Radial intervention [n, %]	34 (7.8)	36 (10.2)	6 (9.7)	0.484

CAD — coronary artery disease, DM — diabetes mellitus, GFR — glomerular filtration rate, HDL — high-density lipoprotein, HF — heart failure, Hgb — hemoglobin, HT — hypertension, LDL — low-density lipoprotein, LVEF — left ventricular ejection fraction, PLT — platelet, STEMI — ST-elevation myocardial infarction, TG — triglycerides, WBC — white blood cell count; [1]Clopidogrel vs. ticagrelor; [2]Clopidogrel vs. prasugrel; [3]Ticagrelor vs. prasugrel

The reduction in platelet count was similar among the P2Y12 receptor inhibitors. GFR was observed to be lower in the clopidogrel group. Clinical outcomes according to P2Y12 receptor inhibitors are presented in Table 2.

A logistic regression analysis conducted among significant parameters showed no significant difference between potent P2Y12 receptor inhibitors and clopidogrel regarding in-hospital mortality, in-hospital MACE, in-hospital bleeding, 1-year mortality, and 1-year bleeding. However, for 1-year MACE, potent P2Y12 receptor inhibitors were associated with a significantly lower incidence than clopidogrel (OR: 3.081, 95% CI: 1.494–6.354, p = 0.002).

Discussion

In our study, in-hospital MACE, in-hospital mortality, 1-year MACE, and 1-year mortality were significantly higher in the clopidogrel group compared to the ticagrelor group. Nevertheless, in the multivariate logistic regression analysis, only 1-year MACE remained substantially higher in the clopidogrel group, with no significant differences observed regarding in-hospital mortality, 1-year mortality, or in-hospital MACE. Furthermore, no significant differences were detected between clopidogrel and prasugrel or between ticagrelor and prasugrel concerning in-hospital and 1-year MACE and mortality. Additionally, there was no significant difference in the incidence of in-hospital and 1-year bleeding events between clopidogrel and the more potent P2Y12 receptor inhibitors. This lack of difference may be attributed to the preferential use of clopidogrel in patients with a higher bleeding risk, which could have resulted in fewer bleeding events in the potent P2Y12 receptor inhibitors group than anticipated. Moreover, while the reduction in Hgb was significantly more significant in the clopidogrel group compared to the ticagrelor group, no significant difference was observed in platelet (Plt) reduction. Patients receiving clopidogrel were older and more frequently female than those receiving ticagrelor or prasugrel,

Table 2: Comparison of clinical outcomes according to use of P2Y12 receptor inhibitors

Variables	Clopidogrel (n = 437)	Ticagrelor (n = 353)	Prasugrel (n = 62)	P-value
Hgb reduction [g/dL]	2.02 ± 1.09	1.75 ± 0.9	1.76 ± 0.73	0.001[1]
≥ 3 g/dL Hgb reduction	84 (19.2)	29 (8.2)	5 (8.1)	0.001[1, 2]
BARC 3A	78 (17.8)	25 (7.1)	5 (8.1)	< 0.001[1]
BARC 3B and above bleeding	6 (1.4)	4 (1.1)	0 (0)	0.641[1]
PLT reduction [10^3/mL, 25–75 percentile]	27 (7–59.5)	27 (7–49)	27 (8.7–57.5)	0.787
In-hospital bleeding [n, %]	35 (8)	22 (6.2)	2 (3.2)	0.306
1-year bleeding outcomes	38 (8.7)	26 (7.4)	4 (6.5)	0.728
In-hospital MACE	14 (3.2)	2 (0.6)	0 (0)	0.013[1]
1-year MACE [n, %]	38 (8.7)	11 (3.1)	0 (0)	< 0.001[1]
In-hospital mortality [n, %]	11 (2.5)	1 (0.3)	0 (0)	0.018[1]
1-year mortality [n, %]	20 (4.6)	2 (0.6)	0 (0)	0.001[1]

BARC — bleeding academic research consortium, Hgb — hemoglobin, MACE — major adverse cardiac events, PLT — platelet

suggesting that clopidogrel was preferentially chosen for patients with a higher risk of bleeding.

The PLATO trial demonstrated that ticagrelor was associated with lower rates of stent thrombosis and higher rates of minor and major bleeding than clopidogrel. A subgroup analysis of the PLATO trial, which included 4020 patients, utilized GPIs to compare the efficacy and safety of clopidogrel versus ticagrelor in patients with ACS undergoing PCI. This analysis revealed no significant differences in efficacy and safety endpoints between ticagrelor and clopidogrel when GPIs were used [12]. Consistent with these findings, our study observed that the 1-year MACE rate was lower in the ticagrelor group compared to the clopidogrel group, with no significant differences regarding in-hospital and 1-year bleeding events.

In the TIRTON TIMI-38 study, a subgroup analysis assessed the efficacy and safety of GPIs in patients with ACS undergoing PCI, who were treated with clopidogrel or prasugrel. Among the 7414 patients, 54% received GPIs, and cardiovascular events and bleeding outcomes were evaluated over 30 days. The study found that prasugrel was more effective than clopidogrel in reducing 30-day cardiovascular death, MACE, and stent thrombosis. Furthermore, the use of GPIs further decreased MACE when prasugrel was used. Regardless of GPI use, prasugrel significantly reduced the risk of cardiovascular events and increased bleeding risk in ACS patients post PCI. The study concluded that using GPIs did not increase the relative bleeding risk of prasugrel compared to clopidogrel [13]. Our findings align with this conclusion, showing no significant differences regarding in-hospital and 1-year bleeding events between potent P2Y12 receptor inhibitors and clopidogrel.

A meta-analysis incorporating data from seven studies with 11,874 patients assessed the efficacy and safety of clopidogrel-based regimens compared to prasugrel or ticagrelor-based therapies, with the addition of GPIs. The analysis found that using GPIs in combination with prasugrel or ticagrelor-based treatment was associated with a significant reduction in MACE. Subgroup analyses indicated that the observed clinical benefits of GPIs were primarily attributable to a decrease in the incidence of 1-year MACE. These findings suggest that in patients undergoing PCI, therapy based on prasugrel or ticagrelor combined with GPIs significantly reduced MACE without increasing bleeding events compared to clopidogrel-based treatment [14]. Our study corroborates these results, demonstrating a lower 1-year MACE rate in the potent P2Y12 receptor inhibitors group than clopidogrel, with no significant differences regarding in-hospital or 1-year bleeding events.

Additional prospective studies support these observations. One study involving 824 patients with ACS evaluated the safety and potential advantages of adding GPIs to potent P2Y12 receptor inhibitors. It reported no increase of in-hospital or 3-month mortality related to the use of GPIs, with bleeding endpoints remaining similar [15]. Another study comparing clopidogrel with ticagrelor/prasugrel for 30-day major cardiovascular adverse events and bleeding complications found no significant differences [16]. Conversely, a prospective study noted a reduction in 1-year MACE with potent P2Y12 receptor inhibitors compared to clopidogrel

Tablo 3. Logistic regression analysis of 1-year MACE

Variables	Univariate OR, 95 CI%	P value	Multivariate OR, 95 CI%	P-value
Age	1.049 (1.020–1.079)	0.001	1.023 (0.989–1.058)	0.182
Gender	0.483 (0.253–0.924)	0.028	0.605 (0.287–1.274)	0.186
CAD history	2.686 (1.502–4.804)	0.001	3.003 (1.615–5.584)	0.001
EF	0.936 (0.899–0.974)	0.001	0.958 (0.915–1.002)	0.061
Hgb reduction	0.524 (0.314–0.936)	0.023	0.731 (0.310–1.726)	0.475
GFR	0.985 (0.974–0.997)	0.014	0.998 (0.984–1.013)	0.824
Clopidogrel using	3.597 (1.813–7.139)	< 0.001	3.081 (1.494–6.354)	0.002

CAD — coronary artery disease, EF — ejection fraction, GFR — glomerular filtration rate, Hgb — hemoglobin

but observed an increase in major bleeding events [17]. In contrast, our study identified a lower 1-year MACE rate in the ticagrelor group than in the clopidogrel group, with no significant difference in 1-year bleeding events. Our study uniquely demonstrates a reduction in 1-year MACE with potent P2Y12 receptor inhibitors without an associated increase in bleeding events.

Two smaller-scale retrospective studies are relevant to our research. The first study retrospectively examined bleeding complications in patients with ACS, who were administered tirofiban and DAPT. The study found that decreases in Hgb and bleeding complications and differences between the ticagrelor/prasugrel and clopidogrel groups were comparable. Although creatinine levels were associated with a ≥ 3 g/dL drop in Hgb, no specific association was identified between the type of antiplatelet agent and a ≥ 3 g/dL decrease in Hgb. The clopidogrel group was noted to be older and had a higher proportion of female patients [18]. The second study investigated the impact on in-hospital bleeding and mortality. It reported that the clopidogrel group was older and included more women than the ticagrelor/prasugrel group. Additionally, the rate of in-hospital bleeding was significantly higher in the clopidogrel group. Overall, studies comparing potent P2Y12 receptor inhibitors with clopidogrel have generally indicated no significant differences regarding in-hospital bleeding and mortality [19]. In our study, similar demographic patterns were observed, with the clopidogrel group being older and having a higher proportion of female patients. However, our study found that the decrease in Hgb was significantly lower in the ticagrelor group. This difference may reflect a tendency among physicians to prefer clopidogrel for patients at higher risk. Consistent with the other studies, no significant difference regarding in-hospital and 1-year bleeding events was observed. Notably, our study also assessed in-hospital and 1-year MACE events, revealing no significant difference regarding in-hospital MACE but a significant reduction in 1-year MACE in the potent P2Y12 receptor inhibitors group.

Limitations

A significant limitation of our study is its retrospective and single-center design. Due to its non-randomized nature, there were differences in age and gender between the clopidogrel, ticagrelor, and prasugrel groups, and physicians chose different antiplatelet agents based on patients' overall clinical status and comorbidities, which could have introduced heterogeneity in the patient groups. Despite the preference for potent P2Y12 receptor inhibitors in ACS patients at our center, clopidogrel was observed to be preferred in patients with higher bleeding risk, which may explain the lower number of bleeding events in the potent P2Y12 receptor inhibitors group. Because only abciximab was available at our center, our results cannot be attributed to using other GPIs. In addition, after matching for age, gender, HT, DM, HF, and CAD parameters, propensity score matching analysis could not be performed due to insufficient sample size.

Conclusions

Our study suggests that abciximab can be safely used with modern PCI strategies and potent P2Y12 receptor inhibitors in ACS patients, considering bleeding risk. For ACS patients requiring PCI, potent antiplatelet therapy may be preferred over clopidogrel-based treatment. The use of abciximab in addition to potent P2Y12 receptor inhbitor-based treatment, significantly reduced MACE without increasing bleeding rates. These findings provide significant efficacy and safety information for clinicians considering potent P2Y12 receptor inhibitors in combination with abciximab for patients undergoing PCI.

Conflict of interest: None.

Funding: None.

Data availability statement: The dataset examined in this study is available upon reasonable request from the corresponding author.

Ethics statement: Ethics Committee approval was obtained on November 25, 2021, during the 8th meeting of the local Clinical Research Ethics Committee, under decision number 40, in compliance with the Helsinki Declaration.

Author contributions: Concept — O.A, S.A; Design — O.A, S.A, E.A, Supervision —O.A, Y.K, M.H.T; Materials — O.A, R.M, M.Ö; Data Collection or Processing — O.A, R.M, M.Ö; Analysis or Interpretation: S.A, E.A; Literature Search — S.Ş.A, M.Ö, I.S; Writing — O.A, S.A, S.Ş.A; Critical Review — M.H.T, Y.K, S.A.

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