ORIGINAL ARTICLE

Incidence of aspirin resistance is higher in patients with acute coronary syndrome and atrial fibrillation than without atrial fibrillation

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SUMMARY

In patients with atrial fibrillation, standard anticoagulation with a vitamin K antagonist plus dual antiplatelet therapy with a P2Y12 inhibitor and aspirin is the standard of care after percutaneous coronary intervention (PCI). While this therapy reduces the risk of thrombosis and stroke, it increases the risk of bleeding. It is unclear whether the antiplatelet effect of aspirin and clopidogrel may worsen atrial fibrillation (AF).

OBJECTIVE: *Thus we aimed to analyze platelet aspirin resistance (AR) and clopidogrel resistance (CR) in acute coronary (ACS) patients based on sinus rhythm (SR) and AF.*

METHODS: *In this prospective trial, we included 543 patients (mean age: 62± 12 years; range: 26 - 89 years) who were on aspirin and clopidogrel therapy after the diagnosis of acute coronary syndrome. AR and CR were analyzed by a Multiplate® MP-0120 device by using the method of whole blood aggregometry.*

RESULTS: *AF patients had significantly higher age, mean platelet volume, and High-Sensitivity C-Reactive Protein (p< 0.01 for each parameter). Similarly, Arachidonic-acid induced (ASPI) aggregation was higher in AF patients compared to SR patients (666±218 vs. 187±179, p<0.001). Among the ACS patients, significantly more female patients had AF (p<0.001). The incidence of hypertension in the AF group was higher compared to the SR group (p<0.001). However, adenosine diphosphate levels were not at a significant level in the two groups.*

CONCLUSION: *Our findings indicate that the platelet inhibitory effect of Aspirin was worse for patients with AF, suggesting that the effectiveness of aspirin may be less in the prophylaxis of thromboembolism and more a bleeding risk.*

KEYWORDS: *Aspirin. Clopidogrel. Drug resistance. Acute coronary syndrome. Atrial fibrillation.*

INTRODUCTION

The incidence of atrial fibrillation in patients who undergo percutaneous coronary intervention is approximately 5% to 8%[1,2]. Oral anticoagulation (OAC) is indicated in these patients for the prevention of stroke and systemic embolism[3]. In addition, these patients must be administrated dual antiplatelet therapy with a P2Y12 inhibitor plus aspirin for the prevention of cardiovascular events, including stent

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thrombosis[4]. Until recently, most guidelines recommended both anticoagulation and dual antiplatelet therapy (triple therapy)[3,5]. However, it can be difficult to balance the prevention of thrombosis with the risk of bleeding[6]. In a recent study, ınvestigators omitted the use of aspirin from the standard regimen and used a single P2Y12 inhibitor in combination with an oral anticoagulant. They found that the risk of bleeding was lower with a regimen of reduced-dose rivaroxaban plus a P2Y12 inhibitor than with the standard triple therapy[7]. Another study supported the use of triple therapy for a short duration[8]. RE-DUAL PCI has shown that dual therapy was not inferior to triple therapy concerning the risk of thromboembolic events[9]. In the PIONEER trial, investigators reported that the administration of either low-dose rivaroxaban plus a P2Y12 inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT for 1, 6, or 12 months was associated with a lower rate of clinically significant bleeding than standard therapy with a vitamin K antagonist plus DAPT for 1, 6, or 12 months[10]. In the AUGUSTUS trial, similar results were found too. P2Y12 inhibitor plus apixaban without aspirin resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events than regimens that included a vitamin K antagonist, aspirin, or both[11]. OAC plus aspirin or a single P2Y12 inhibitor regimen has seemed to be adequate for the prevention of ischemic events. However, the optimal antithrombotic therapy for these patients remains controversial. There is no clear recommendation on the use of ASA or clopidogrel with anticoagulant therapy after ACS. We aimed to investigate whether there is an association between AF and ASA resistance in patients with ACS.

METHODS

This was a prospective observational sub-study parallel to an investigation of resistance to aspirin and clopidogrel in patients in the Isparta area of Turkey. The protocol was obtained from the patients or their substitutes. All patients were followed-up prospectively and retrospectively analyzed for this study. The overall study population included 628 patients with ACS. The inclusion criteria were the following: age greater than 18 years and the presence of ACS. The exclusion criteria included the following: clinical indications of prolonged use of heparin and fondaparinux, clinical indications for the use of ASA doses of >100 mg/day or clopidogrel at doses of >75 mg/day prior to enrolment in the study, rheumatic mitral disease, use of prasugrel, ticagrelor, clinical indications of use of oral anticoagulants, cardiogenic shock at admittance to the hospital, heart failure categorized as Class III or IV in the NYHA scale at admittance to the hospital, thrombocytopenia (<100 x 10 9 g/L), purpura, anemia with hemoglobin concentration <100 g/L, clinically present active inflammation or thrombosis in-stent revealed in the interview or during hospitalization, and co-existence of diseases with poor prognosis (less than a year of life). According to these criteria, 85 patients were excluded due to thrombocytopenia (n=5), high-dose clopidogrel usage (n=40), oral anticoagulant usage (n= 30), and cardiogenic shock (n= 10). Finally, 543 patients were included in this sub-study. The institutional ethics committee approved the study and all participants provided written informed consent.

Diagnoses were recorded by the participating physicians based on clinical, electrocardiographic, and biochemical (elevated troponin levels) criteria. The type of myocardial infarction (ST-elevation vs non-ST-elevation) and unstable angina were homogeneously defined based on current guidelines[4].

Each patient was questioned about major cardiovascular risk factors including their family history of coronary artery disease, current smoking status, hyperlipidemia, hypertension, diabetes mellitus, and obesity. A family history of coronary artery disease was defined as the manifestation of the disease in first-grade male relatives younger than 55 years or in first-grade female relatives younger than 65 years of age. Hyperlipidemia was defined as fasting total cholesterol level >200 mg/dL or pharmacotherapy with lipid-lowering agents. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg measured before hospitalization or pharmacotherapy with antihypertensive drugs. Diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dL or pharmacotherapy with insulin or oral antidiabetic agents. Obesity was defined as body mass index >30 kg/m^2. Patients who were smoking prior to hospitalization were characterized as smokers.

The patients' clinical data, their previous medication history, and medications started after hospitalization were recorded. The patients were divided into two groups: with AF and without AF. A 12-lead electrocardiogram was recorded upon admission to the hospital. AF was defined as an irregular

rhythm with the absence of discrete P waves in the 12-lead electrocardiogram[12].

Patients were given 300 mg loading of ASA, 600 mg of clopidogrel, and, subsequently, maintenance doses of 75 mg clopidogrel and 100 mg ASA daily.

Blood sampling and analyses

Platelet function analysis was performed in the patients after they received a 600-mg clopidogrel loading dose in addition to pre-treatment with ASA. Blood samples were obtained 24h after percutaneous coronary intervention. Whole blood (5 ml) was collected using heparin as the anticoagulant in a Lithium Heparin bottle (non-gel). The blood was analyzed in a Multiplate Platelet Function Analyzer, which analyzes platelet function in whole blood samples based on impedance aggregometry, (Dynabyte Medical, Munich, Germany) 2006, using 20 µl of the activator. The following tests were performed: (i) ADP test with adenosine diphosphate (ADP) to assess P2Y12-dependent platelet aggregation; (ii) ASPI test with arachidonic acid (AA) to assess cyclooxygenase-dependent platelet aggregation

Arachidonic acid (ASPI) test reagent (20 µl of 15 mM stock solution) contains arachidonic acid. This triggers platelet aggregation via platelet cyclooxygenase, which is blocked by aspirin. Adenosine diphosphate (ADP, 20 µl of 0.2 mM stock solution) which triggers platelet activation via platelet ADP receptors (i.e. P2Y12 receptor that is inhibited by clopidogrel). All tests were performed within 2 h of blood sampling. The results were defined as the area under the curve (AUC) at the end of the 6 min measurement period. An AUC value of 500 min for ASA and 470 min for clopidogrel was considered as the minimum resistance value for patients under dual antiplatelet therapy[13-15].

Statistical analysis

SPSS version 16.0 software package program was used in the statistical analyses of the study. Categorical variables were expressed as frequency (%) and compared with the $\chi 2$ test. A Kolmogorov-Smirnov test was used to test the distribution of numeric variables, and those with normal distribution were expressed as mean ± standard deviation and were compared with the Student's t-test. Data without normal distribution were expressed as median (Inter-quartile range (IQR) of 25%-75% percentiles) and were compared with the Mann-Whitney U test. In all statistical analyses, p values <0.05 were considered as statistically significant.

RESULTS

A total of 543 patients (mean age: 62± 12 years; range: 26 - 89 years) were included in this study. At admission, 32 patients (10 %) had AF. The demographic and clinical characteristics of the patients with and without AF are listed in Table 1. The patients with AF were predominantly female when compared to patients without AF (p<0.001). Diabetes mellitus and hypertension were more common (p=0.06, p<0.001, respectively), but smoking was less commonly seen in patients with AF as compared to those without AF (p = 0.069). The incidence of obesity was similar in both patient populations (p=0.541). Total cholesterol, triglycerides, low-density lipoprotein cholesterol, and HDL levels were similar between the two groups of patients (p= 0.283, p= 0.071, p= 0.282, p=0.343, respectively). ASPI levels were higher in the AF group (p<0.001). Mean platelet volume (MPV) and Hs-CRP levels were higher in AF patients (p<0.001, p=0.001, respectively). The presence of AF was positively correlated with MPV (r=0.16 p<0,001), Hs-CRP (r=0.45, p<0.001). Univariate analysis showed that the presence of AF was a predictor of AR (OR 5.18, 95% CI 1.88-14.2, p < 0.001).

DISCUSSION

The present study showed that AF patients with ACS had increased AR compared to SR patients with ACS. Moreover, ASA was observed to be inadequate for the treatment of AF.

Antiplatelet therapy is the cornerstone of the therapeutic approach in coronary artery disease for the prevention of stent thrombosis and the reduction of cardiovascular events in patients who undergo coronary stenting and suffer acute coronary syndromes. Anticoagulation is needed for stroke prevention in patients with atrial fibrillation. In general, guidelines advise the continuation of anticoagulation and using triple oral antithrombotic therapy (TOAT), for a short period after PCI, the duration of which depends on bleeding risk and stent type. In addition, they recommended using bare-metal stents, targeting an INR range of 2.0–2.5 for patients receiving TOAT, and using radial access during PCI. They recommend OAC and single oral antiplatelet therapy (SAPT) with ASA or a P2Y12 receptor antagonist, for a short period after PCI[3,16]. However, there is no clear opinion on whether SAPT is ASA or a P2Y12 receptor antagonist.

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS WITH AND WITHOUT ATRIAL FIBRILLATION (AF).

	Patients without AF (n=511)	Patients with AF (n= 32)	P value
Age, year	61± 11	71± 7	< 0.001
Female Gender n(%)	103 (20%)	16 (50%)	< 0.001
BMI (kg/m^2)	26± 3	27± 3	0.541
Smoking n(%)	269 (52%)	12 (37%)	0.069
Diabetes Mellitus n(%)	177 (34.6%)	16 (50%)	0.06
Hyperlipidemia n(%)	162 (31.7%)	8 (25%)	0.281
Hypertension n(%)	216 (42%)	26 (81%)	<0.001
Total Cholesterol (mg/dL)	183 ± 39	191± 48	0.283
HDL Cholesterol (mg/dL)	39 ± 11	40 ± 7	0.343
LDL Cholesterol (mg/dL)	110 ± 32	117 ± 43	0.282
Triglyceride Cholesterol (mg/dL)	160 ± 84	199 ± 115	0.071
BUN (mg/dL)	18 ± 8	21± 9	0.023
Creatinine (mg/dL)	1.6 ±7	1.0 ± 0.3	0.094
ASPI	187 ± 179	666 ± 218	<0.001
ADP	263	306	0.261
HGB(g/dL)	13.8 ± 1.7	13.8 ± 1.7	0.848
Platelet count (x10^3/mm^3)	230 ± 68	228± 58	0.848
Mean platelet volume (fL)	8.2 ±0.9	9.2±1.4	<0.001
Hs CRP (mg/dL) (mean)	131	250	<0.001

BMI: Body mass ındex, HDL: High density lıpoprotein, LDL: Low density lıpoprotein, ADP: adenosine diphosphate, ASPI: Arachidonic acid HGB: Hemoglobin, Hs-CRP: High sensitive C reactive protein

In the Re-DUAL PCI study, investigators showed that, among patients with atrial fibrillation who had undergone PCI, dual therapy with OAC and a P2Y12 inhibitor had a lower bleeding risk than with triple therapy with warfarin, a P2Y12 inhibitor, and aspirin. Additionally, dual therapy with dabigatran was non-inferior to triple therapy with warfarin concerning the rate of thromboembolic events[9]. In the WOEST trial, patients were assigned to receive clopidogrel alone (double therapy) or clopidogrel and aspirin (triple therapy). They established that treatment with clopidogrel and oral anticoagulants was associated with a significantly lower risk of bleeding complications than aspirin, clopidogrel, and oral anticoagulation in patients with atrial fibrillation who had undergone PCI. Furthermore, they did not determine an increased risk of thrombotic events by omitting aspirin[7]. In our study, AR was higher in patients with AF. Additionally, AF is an independent risk factor of AR, based on multivariate analysis. Our findings are supported by recent studies. Clopidogrel can be recommended in patients with atrial fibrillation who had undergone PCI with an OAC according to these findings.

Increased platelet turnover resulting from infection, inflammation, diabetes mellitus, or hypertension can result in an increased proportion of non-aspirinated platelets[17]. Additionally, hypertension and diabetes mellitus were risk factors for the development of AF[18]. Moreover, the overall effect of aspirin-induced inhibition of platelet aggregation may be diminished. Our results showed that the incidence of diabetes mellitus and hypertension were higher in patients with AF. Thus, an increase in the proportion of non-aspirinated platelets may contribute to pathogenesis in these patients.

An association between inflammation and AF has been indicated in the literature[19,20]. Activated platelets release inflammatory mediators and induce the expression of these mediators in monocytes/macrophages and granulocytes[21]. Inflammation is an important factor in the initiation and maintenance of AF[22,23]. HsCRP and interleukin-6 levels were reported to be elevated in patients with paroxysmal, persistent, and permanent AF compared to those with sinus rhythm[24]. Moreover, thrombogenesis markers correlated with CRP levels. Erdogan et al.[25] reported that elevated MPV values positively correlated with higher CRP in different types of hypertensive patients. Similarly, in the present study, hsCRP and MPV levels were significantly higher in patients with AF. Increased inflammation in AF may be another factor that could contribute to AR.

CONCLUSION

The present study suggests that in a patient population with ACS, inflammation, prothrombotic state, and ASA resistance were significantly higher in patients with AF compared to those without it. The results of our study support the hypothesis that ASA may be less indicated for prophylaxis of thromboembolism and increases bleeding risk. A P2Y12 inhibitor may be used with OAC instead of ASA for long-term treatment in AF patients who undergo PCI. Nevertheless, this study was not powered to detect differences in the occurrence of thrombotic events, such as stent thrombosis, when aspirin was omitted, and this feature would need to be studied in a larger trial. We think that aspirin does not need to be used in patients receiving oral anticoagulants and undergoing PCI. Further studies are needed to establish the pathophysiological and clinical significance of increased oxidative stress and inflammation and investigate the effect of antioxidant and anti-inflammatory agents in patients with AMI.

Author Contributions

Hasan Aydın Baş: Methodology, Validation; Fatih AKSOY: Conceptualization, Formal analysis, Writing-original draft, Writing-review & editing, Project administration, performing coronary angiography; Ali Bağcı: Formal analysis; Ercan Varol: Final editing; Ahmet Altınbaş: Project administration, performing coronary angiography.

RESUMO

Em pacientes com fibrilação atrial, a anticoagulação padrão com antagonista da vitamina K mais terapia antiplaquetária dupla (DAPT) com inibidor de P2Y12 e aspirina é o padrão de tratamento após intervenção coronária percutânea (ICP). Enquanto essa terapia reduz o risco de trombose e derrame, aumenta o risco de sangramento. Não está claro se o efeito antiplaquetário da aspirina e do clopidogrel pode piorar a fibrilação atrial (FA).

OBJETIVO: *Analisar a resistência à aspirina plaquetária (AR) e ao clopidogrel (CR) em pacientes coronarianos agudos (SCA) com base no ritmo sinusal (SR) e na FA.*

MÉTODOS: *Neste estudo prospectivo, foram incluídos 543 pacientes (idade média: 62±12 anos; intervalo: 26-89 anos) em uso de aspirina e clopidogrel após o diagnóstico de síndrome coronariana aguda. AR e CR foram analisados por um dispositivo Multiplate® MP-0120, utilizando o método de agregometria de sangue total.*

RESULTADOS: *Os pacientes com FA apresentaram valores significativamente maiores para idade, volume médio de plaquetas e proteína C reativa de alta sensibilidade (p<0,01 para cada parâmetro). Da mesma forma, a agregação induzida por ácido araquidônico (Aspi) foi maior nos pacientes com FA em comparação com os pacientes com SR (666±218 vs. 187±179, p<0,001). Entre os pacientes com SCA, significativamente mais pacientes do sexo feminino apresentaram FA (p<0,001). A incidência de hipertensão no grupo FA foi maior em comparação com o grupo SR (p<0,001). No entanto, os níveis de difosfato de adenosina não foram expressivamente significativos nos dois grupos.*

CONCLUSÃO: *Nossos achados indicam que o efeito inibitório plaquetário da aspirina foi pior em pacientes com FA, sugerindo que a eficácia da aspirina pode ser menor na profilaxia do tromboembolismo, com maior risco de sangramento.*

PALAVRAS-CHAVE: *Aspirina. Clopidogrel. Resistência a medicamentos. Síndrome coronariana aguda. Fibrilação atrial.*

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