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ORIGINAL ARTICLE

Combination of oral anticoagulant and antiplatelet therapy does not change the 1-year prognosis compared to oral anticoagulant alone in stroke patients with atherosclerosis and atrial fibrillation

Gökçe Zeytin Demiral[1] **Hayri Demirbaş**[1] **Abdullah Güzel**[1]
Selin Betaş Akın[2] **Sinem Yorgancı**[1] **Dilara Çulhaoğlu Gökçek**[1]
Hilal Hoşgeldi[1] **Furkan İncebacak**[1]

[1] Department of Neurology, Faculty of Medicine, Afyonkarahisar Health Sciences University. Afyonkarahisar / Türkiye
[2] Department of Neurology, Afyonkarahisar State Hospital. Afyonkarahisar / Türkiye

Abstract

This study aims to evaluate the effectiveness of combined antiplatelet and oral anticoagulant (OAC) therapy versus OAC therapy alone on one-year post-stroke outcomes in patients with non-valvular atrial fibrillation (NVAF) and systemic atherosclerosis. A retrospective study was conducted using the recorded data of patients diagnosed with ischemic cerebrovascular disease between January 1, 2022, and January 1, 2023, at the Neurology Clinic, Afyonkarahisar Health Sciences University. Patients with non-valvular atrial fibrillation (NVAF) and systemic atherosclerosis were included in the study. Collected data included demographic information, medical history. Patients were divided into two groups based on the treatment regimen used at discharge: those receiving OAC alone and those receiving a combination of OAC and antiplatelet therapy. Clinical outcomes were evaluated within one year following the stroke. A total of 671 stroke patients were screened, and 565 (84.2%) had ischemic stroke. Among these, 113 (20%) had NVAF, and 53 had both NVAF and systemic atherosclerosis. Data from these 53 patients were analyzed. The mean age was 71.81±11.90 years, with a female gender ratio of 52.8%. Logistic regression analysis showed no statistically significant differences between the two treatment groups in terms of all-cause mortality, bleeding, recurrent stroke, and hemorrhagic stroke (p>0.05 for all comparisons). The combination of antiplatelet and OAC therapy did not demonstrate superiority over OAC therapy alone in reducing the risks of recurrent ischemic stroke, hemorrhagic stroke, myocardial infarction, and mortality in patients with NVAF and systemic atherosclerosis. These findings suggest that OAC therapy alone may provide sufficient protection in this patient population. Prospective studies with larger samples are needed to confirm these results.

Keywords: Non-valvular atrial fibrillation, systemic atherosclerosis, ischemic stroke, oral anticoagulants, antiplatelet therapy

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Corresponding Author:
Gökçe Zeytin Demiral
Email: gokce_zeytin@hotmail.com

Introduction

Non-valvular atrial fibrillation (NVAF) is the most common cardioembolic cause of ischemic stroke [1]. To prevent systemic embolism, including ischemic stroke, NVAF patients are recommended to use oral anticoagulants (OAC), such as vitamin K antagonists (VKA) or direct oral anticoagulants (DOAC) [2]. Patients with NVAF may have coexisting atherosclerosis in several arteries [3-6]. The presence of systemic atherosclerosis in NVAF stroke patients increases the risk of vascular events in the same or different vascular beds, emphasizing the need for optimal antithrombotic strategies [4]. Adding an antiplatelet to OAC therapy is an option, but it can increase the risk of bleeding [2,7]. Specifically, dual antiplatelet plus anticoagulant therapy and triple therapy are major concerns as they increase the absolute risk of major bleeding [8]. Recent randomized studies indicate that OACs without antiplatelets do not increase systemic embolic events but reduce major bleeding compared to OACs with antiplatelets in patients with NVAF and stable coronary artery disease (CAD) [9,10]. Moreover, low-dose rivaroxaban combined with aspirin has been shown to improve cardiovascular outcomes in patients with coronary artery occlusive disease (CAOD) or peripheral artery occlusive disease (PAOD), suggesting potential benefits for NVAF patients with atherosclerosis [8,11].

Nevertheless, the optimal management strategies for stroke and systemic atherosclerosis in NVAF patients are not well-defined. This study aims to evaluate the effectiveness of combining antiplatelet therapy with OACs versus OAC therapy alone on one-year post-stroke outcomes in patients with NVAF and systemic atherosclerosis.

Materials and Methods

We conducted a retrospective review of patients diagnosed with ischemic cerebrovascular disease between January 1, 2022, and January 1, 2023, using records from the Neurology Clinic at Afyonkarahisar Health Sciences University. Patients with non-valvular atrial fibrillation and systemic atherosclerosis were included. Comprehensive evaluations during hospitalization were conducted to gather demographic data, medical history, clinical symptoms, vascular risk factors, and comorbidities. Clinical demographic characteristics were obtained from existing files. Information from routine computerized tomography (CT) angiography, brain CT, and/or magnetic resonance imaging for all ischemic patients was recorded. The results of standard blood tests, 12-lead electrocardiography, Holter monitoring and echocardiography to determine the etiology of ischemic cerebrovascular disease are also documented.

Demographic information, vascular risk factors, and comorbidities such as hypertension, diabetes, dyslipidemia, coronary artery occlusive disease (CAOD), peripheral artery occlusive disease (PAOD), and previous stroke history were recorded. Smoking status was noted for individuals who had smoked at least one cigarette in the past month, and alcohol consumption was also recorded. Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS). Stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment classification [8]. Blood test results were categorized by glomerular filtration rate (GFR) into three groups: GFR<30, 30-50, and >50. Information on statin therapy prescribed at discharge was collected, with high-intensity statin therapy defined as atorvastatin doses greater than 40 mg or rosuvastatin doses greater than 20 mg.

Clinical Variables

The study population was categorized based on the antithrombotic regimen prescribed at discharge: OAC alone or a combination of OAC and antiplatelet therapy. OACs included VKAs and DOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban. Antiplatelet agents included aspirin, clopidogrel, cilostazol, prasugrel, ticlopidine, and ticagrelor.

Systemic Atherosclerotic Lesions

The presence of atherosclerotic lesions in the aortic arteries, brain, heart, and peripheral arteries was assessed using recorded data. Systemic atherosclerotic lesions were defined by one or more of the following conditions: (1)

cerebral atherosclerosis with >50% stenosis; (2) aortic atheroma > 4 mm in the ascending aorta or aortic arch as seen on echocardiography; (3) history of previous CAOD or PAOD; and (4) coronary or carotid stent placement. CAOD was defined by (1) a history of myocardial infarction or unstable angina, and (2) documented symptomatic or asymptomatic coronary artery stenosis on catheter coronary angiography or multidetector coronary CT. PAOD presence was documented based on a history of peripheral artery disease in the patient's medical records.

Outcome Measures

Data for patients who had a one-year follow-up examination after discharge were recorded. Causes of death were documented for deceased patients, with cardiovascular death recorded as death due to myocardial infarction, sudden cardiac death, heart failure, cardiovascular procedures, or stroke. Recurrent ischemic stroke (including TIA), hemorrhagic stroke, myocardial infarction, or bleeding events within oneyear post-stroke were recorded. Hemorrhagic stroke subtypes (intracerebral, intraventricular, subarachnoid, and subdural hemorrhages) were documented. All bleeding events, including hemorrhagic stroke, gastrointestinal bleeding, respiratory bleeding, and muscle bleeding requiring transfusion or hospitalization, were recorded. Fatal ischemic stroke, fatal hemorrhagic stroke, fatal myocardial infarction, and fatal bleeding events were defined as deaths occurring after the respective severe condition without any other obvious cause of death, as determined by the physician. The primary outcome of this study was the evaluation of all composite outcomes within one year after the index stroke. These predefined outcomes were compared based on medication within one year after the index stroke.

Statistical Analysis

Statistical analyses were conducted using SPSS 26.0 software (IBM Corp. 2019, IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY: IBM Corp). To compare demographic and clinical variables between groups, the Chi-square test and *Fisher's* exact test were utilized. Categorical data were presented as frequencies and percentages. The *Shapiro-Wilk* test evaluated the normality of the quantitative data distribution. Continuous variables were compared using either the Independent Samples t-test or the *Mann-Whitney U* test. Logistic regression analysis was employed to examine the relationship between treatment groups and clinical outcomes such as all-cause mortality, bleeding, hemorrhagic stroke, and recurrent stroke. The analysis results were expressed as β (beta) coefficients, standard error (SE), *p*-values, Odds Ratios (OR), and confidence intervals (CI). Statistical significance was set at $p<0.05$.

Ethical Considerations and Consent

The study received approval from the Ethics Committee of Afyonkarahisar Health Sciences University (Date: 19.04.2024, Decision No: 2024/38). Due to the retrospective nature of the study, informed consent from individuals was not required.

Results

A total of 671 stroke patients were screened in the study. Of these patients, 106 (15.8%) had hemorrhagic stroke and 565 (84.2%) had ischemic stroke. Atrial fibrillation was detected in 113 (20%) of the ischemic stroke patients. Twenty-nine of the patients with atrial fibrillation were excluded due to insufficient data. Eighty-four patients had diagnoses of ischemic stroke and atrial fibrillation. Systemic atherosclerosis was found in 53 of these patients. Data from a total of 53 patients were evaluated in the study. The mean age of these patients was 71.81±11.9, with a female gender ratio of 28 (52.8%) and 23 (43.4%) patients over the age of 75. Thirty-eight (71.7%) patients had hypertension, 18 (34%) had diabetes mellitus, 33 (62.3%) had hyperlipidemia, and 21 (39.6%) had chronic heart failure. Cerebral atherosclerosis was found in 28 (52.8%) patients, coronary atherosclerosis in 25 (47.2%), peripheral atherosclerosis in 9 (17%), aortic atheroma plaque in 11 (20.8%), and coronary artery stent in 17 (32.1%). Twenty-two (41.5%) patients were smokers and 3 (5.7%) consumed alcohol. Thirty (56.6%) patients were on statin therapy, with 10 (18.9%) of them on high-dose statin therapy. As antiplatelet therapy, 10 (18.9%) patients were using clopidogrel and 8

(15.1%) were using aspirin. Recurrent stroke was observed in 18 (34%) patients, of which 2 (3.8%) were hemorrhagic strokes. One of the patients with intracranial hemorrhage was taking edoxaban 30 mg 1x1 and the other was taking apixaban 2.5 mg 2x1. Table 1 presents the clinical and demographic characteristics of patients receiving oral anticoagulant+antiplatelet and oral anticoagulant therapy.

Table 1. Comparison of demographic and clinical characteristics of patients receiving oral anticoagulant + antiplatelet and oral anticoagulant therapy.

Variables	**Groups**		***p-value***
	Oral Anticoagulant + Antiplatelet (n:18)	Oral Anticoagulant (n:35)	
Age	9(50%)	21(60%)	0.565
75 >	9(50%)	14(40%)	
75≤			
Gender	10(55.6%)	15(42.9%)	0.402
Male	8(44.4%)	20(0.6%)	
Female			
Cerebral Atherosclerosis	11(61.1%)	17(48.6%)	0.562
Coronary Artery Atherosclerosis	9(50%)	16(45.7%)	0.497
Peripheral Artery Atherosclerosis	4(22.2%)	5(14.3%)	0.469
Aortic Atheroma Plaque	6(33.3%)	5(14.3%)	0.105
Coronary Artery Stent	6(33.3%)	11(31.4%)	1.000
Cerebral Artery Stent	1(5.6%)	3(8.6%)	0.581
DOAC Type			0.719
Dabigatran	1(5.6%)	2(5.7%)	
Rivaroxaban	10(55.6%)	14(40%)	
Apiksaban	6(33.3%)	15(42.9%)	
Edoxaban	1(5.6%)	4(11.4%)	
DOAC Dose			0.357
Low	4(22.2%)	11(31.4%)	
Effective	14(77.8%)	24(68.6%)	
Statin	12(66.7%)	18(51.4%)	0.384
High Dose Statin	2(11.1%)	8(22.9%)	0.150
TOAST			0.880
Large Artery	5(27.8%)	8(22.9%)	
Cardioembolic	9(50%)	20(57.1%)	
Unknown Cause	4(22.2%)	7(20%)	
Etiological Cause			0.689
Single	1(5.6%)	4(5.7%)	
Multiple	17(94.4%)	33(94.3%)	
Hypertension	12(66.7%)	26(74.3%)	0.560
Diabetes	8(44.4%)	10(28.6%)	0.248

Table 1. (continued) Comparison of demographic and clinical characteristics of patients receiving oral anticoagulant + antiplatelet and oral anticoagulant therapy.

Hyperlipidemia	13(72.2%)	20(57.1%)	0.283
Smoking	10(55.6%)	12(34.3%)	0.137
Alcohol	2(11.1%)	1(2.9%)	0.263
Chronic Heart Failure	10(55.6%)	11(31.4%)	0.089
Initial NIHSS	6(33.3%)	16(45.7%)	0.386
≤4	12(66.7%)	19(54.3%)	
>4			
GFR	0(0)	1(2.9%)	0.534
<30	5(27.8%)	6(17.1%)	
≥30-50	13(72.2%)	28(80%)	
50<			
Recurrent Stroke	1(5.6%)	4(11.4%)	0.708
Fatal	1(5.6%)	3(8.6%)	
Non-fatal			
Recurrent MI			0.291
Fatal	1(5.6%)	0	
Non-fatal	0	1(2.9%)	
Hemorrhagic Stroke	0	2(5.7%)	0.432
Non-Fatal			
Hemorrhagic Stroke Classification			0.301
İntracerebral	0	2(5.7%)	
Bleeding	0	4(11.4%)	0.136
Bleeding Classification			0.329
Intracerebral Bleeding	0	2(5.7%)	
Gastrointestinal Bleeding	0	2(5.7%)	
Death from All Causes	7(38.9%)	12(34.3%)	0.741
Death from Cardiovascular Causes			0.320
Sudden Cardiac Death	3(16.7%)	6(17.1%)	
Heart Failure	1(5.6%)	0	
Ischemic Stroke	0	3(8.6%)	

DOAC: Direct Oral Anticoagulant; TOAST: Trial of Org 10172 in Acute Stroke Treatment; NIHSS: National Institutes of Health Stroke Scale; GFR: Glomerular Filtration Rate; MI: Myocardial Infarction

Table 2. Logistic regression analysis results on the effect of treatment groups on the frequency of death from all causes.

Variables	**Groups**	**β**	**SE**	***p***	**Odds Ratio**	**95% CI**	
						Lower	**Upper**
Group	Oral Anticoagulant + Antiplatelet	0.199	0.600	0.741	1.220	0.376	3.957
	Anticoagulant				Reference		

SE: *Standard Error;* ***CI:*** *Confidence Interval*

Logistic regression analysis comparing the two treatment groups revealed no statistically significant differences in all-cause mortality, bleeding, recurrent stroke, and hemorrhagic stroke (p=0.741, p=0.998, p=0.998, p=0.421, respectively). Tables 2, 3, 4, and 5 present logistic regression analyses of the effects of the two treatments on the frequency of all-cause mortality, bleeding, hemorrhagic stroke, and recurrent stroke.

Discussion

The results of this study reveal that in patients with NVAF and arterial atherosclerosis, combining antiplatelet and anticoagulant therapies did not prove superior to anticoagulant therapy alone regarding the risks of recurrent ischemic stroke (including transient ischemic attacks), hemorrhagic stroke, myocardial infarction, and mortality. Contrary to some studies, the combination therapy did not increase bleeding risk. There was no significant difference in the rates of bleeding, recurrent stroke, and mortality between the two treatment groups over the one-year follow-up period. Atrial fibrillation (AF) and carotid artery stenosis (CAS) frequently coexist in acute stroke patients [4]. Atherosclerotic diseases are often observed in the carotid artery (up to 64%), coronary artery (17-38%), or peripheral arteries (6.7%) [12,13]. In this study, the most common site of atherosclerosis was cerebral atherosclerosis (52.8%), followed by coronary atherosclerosis (47.2%). Carotid artery stenosis significantly elevates the risk of ischemic stroke and TIA in NVAF patients [14]. Therefore, determining the most effective treatment for post-stroke patients with AF and arterial stenosis who require both OAC and antiplatelet (AP) therapy is crucial. However, the optimal antithrombotic treatment strategy remains under debate [15]. Managing NVAF patients with systemic atherosclerosis thus presents substantial challenges. Studies have shown that OAC monotherapy is linked to lower composite outcomes and mortality risks within one year following an ischemic stroke due to AF

Table 3. Logistic regression analysis results on the effect of treatment groups on the frequency of bleeding.

Variables	Groups	β	SE	*p*	Odds Ratio	95% CI	
						Lower	Upper
Group	Oral Anticoagulant + Antiplatelet	-19.155	9473.570	0.998	0.000	0.000	
	Oral Anticoagulant				Reference		

SE: *Standard Error;* ***CI:*** *Confidence Interval*

Table 4. Logistic regression analysis results on the effect of treatment groups on the frequency of hemorrhagic stroke.

Variables	Groups	β	SE	*p*	Odds Ratio	95% CI	
						Lower	Upper
Group	Oral Anticoagulant + Antiplatelet	-18.400	9473.574	0.998	0.000	0.000	
	Oral Anticoagulant				Reference		

SE: *Standard Error;* ***CI:*** *Confidence Interval*

Table 5. Logistic regression analysis results on the effect of treatment groups on the frequency of recurrent stroke.

Variables	Groups	β	SE	*p*	Odds Ratio	95% CI	
						Lower	Upper
Group	Oral Anticoagulant + Antiplatelet	-0.693	0.861	0.421	0.500	0.093	2.702
	Oral Anticoagulant				Reference		

SE: *Standard Error;* ***CI:*** *Confidence Interval*

and arterial atherosclerotic stenosis. Moreover, combining antiplatelet and OAC has been found to increase the risk of major bleeding [16,17]. Cardiac guidelines suggest OAC monotherapy without antiplatelet therapy (APT) for NVAF patients with stable coronary artery disease more than one-year post-myocardial infarction or percutaneous coronary intervention. OAC monotherapy presents similar risks for stroke, myocardial infarction, and mortality but carries a lower bleeding risk [18,19]. Certain clinical studies support combining antiplatelet therapy with anticoagulant therapy in patients with AF, carotid artery disease, or both in specific situations. One study suggests temporarily adding antiplatelet drugs to anticoagulation therapy to reduce risk in patients with atherosclerosis [20,21]. This approach is considered because not all strokes in AF patients are cardioembolic, and evidence suggests warfarin may not prevent non-cardioembolic strokes [22]. According to our data, anticoagulant therapy alone offers adequate protection for NVAF patients with atherosclerosis, with no increased bleeding risk. Therefore, it may be necessary to reconsider adding antiplatelet therapy to oral VKA anticoagulation in NVAF patients with stable coronary artery disease. Among the limitations of this study is that due to its retrospective nature, it is not known whether patients adhered to their medication or took it regularly as recorded in the system. Although the initial number of patients included in the study appears high, the number of patients analyzed after exclusion is limited. Silent myocardial infarctions, transient ischemic attacks or ischemic or hemorrhagic strokes that did not result in hospitalization may have been missed. If sudden deaths occurred at home, they may not have been reflected in hospital records and therefore not included in the analysis. There was no analysis to differentiate between different types of antiplatelet agents.

Conclusion

In this study, the combination of antiplatelet and anticoagulant therapy in patients with non-valvular atrial fibrillation (NVAF) and arterial atherosclerosis did not demonstrate superiority over anticoagulant therapy alone in reducing the risks of recurrent ischemic stroke, hemorrhagic stroke, myocardial infarction, and mortality. These findings suggest that anticoagulant therapy alone may provide adequate protection for patients with NVAF and atherosclerosis. Further prospective studies with larger sample sizes are needed to validate these results.

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Conflict of interest

The authors declared no conflict of interest regarding this study.

Data availability statement

All data used in this study are available from the corresponding authors upon request.

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