# What Do Anticoagulants Say about Microemboli?

Serkan Demir, MD, Mehmet F. Ozdag, MD, Mustafa T. Kendirli, MD, and Rifat E. Togrol, MD

*Background:* In this study, we evaluated the microembolic signals (MES) frequency with transcranial Doppler ultrasound (TCD) in patients with atrial fibrillation (AF) under anticoagulant therapy, and we compared the treatment groups. *Methods:* Ninety-nine patients with nonvalvular AF with a history of stroke using warfarin (46%), 67 patients using rivaroxaban (31%), and 49 patients using dabigatran (23%), that is, a total of 215 patients, who have been referred to the stroke outpatient section of our department from May 2013 to November 2014, were included in the study. CHA(2)DS(2)VASc scoring was made for all patients, and International Normalized Ratio (INR) value was evaluated in patients using warfarin. All patients were monitored with TCD on the middle cerebral arteries bilaterally for 30 minutes. Embolic signals were evaluated according to their density and the mean number of signals in 2 consecutive recordings. *Results:* The incidence of emboli in the treatment group was 32 (32%) for warfarin, 24 (36%) for rivaroxaban, and 17 (35%) for dabigatran. The analysis of variance revealed that there was no statistically significant differences between the treatment groups in terms of patients' age ($P = .145$), CHA(2)DS(2)VASc scores ($P = .968$), and the number of emboli ($P = .783$). As CHA(2)DS(2)VASc score increases, number of emboli increase. A statistically significant negative correlation between the number of emboli and INR scores was found in the warfarin group. The number of emboli decreases as INR decreases. *Conclusions:* As we aim to reduce the risk of emboli to a minimum with anticoagulant therapy, this screening for MES can give us an idea for the risk of stroke. **Key Words:** Transcranial Doppler ultrasonography—dabigatran etexilate—warfarin—rivaroxaban—embolus—middle cerebral artery.


## Introduction

Atrial fibrillation (AF) is the most common permanent cardiac arrhythmia.[1] Its prevalence is approximately 1% in the general population, whereas being 5.9% older than 65 years. The prevalence increases with age.[2] AF is accepted as one of the high cardiac emboli causes according to the Trial of Org 10172 in Acute Stroke Treatment classification.[3,4] The AF-related stroke risk is estimated with the $CHA_{(2)}DS_{(2)}VASc$ score, and the risk increases with high scores. AF is treated with vitamin K antagonists, such as warfarin, which has been used for many years, and new-generation oral anticoagulants including the direct thrombin inhibitor dabigatran and factor Xa inhibitor rivaroxaban.[5]

Atheroma, thrombus, or thrombus–fibrin aggregates can cause ultrasound signals. The microembolic signals (MES) can be detected by transcranial Doppler ultrasound (TCD) as they pass the cerebral circulation.[6-8] Low-frequency MES is seen in AF as well.[9]

In this study, we evaluated the MES frequency with TCD in patients with AF under anticoagulant therapy, and we compared the treatment groups.

From the Department of Neurology, GATA Haydarpaşa Training Hospital, Istanbul, Turkey.

Received March 16, 2015; revision received May 16, 2015; accepted June 6, 2015.

Address correspondence to Serkan Demir, MD, Department of Neurology, GATA Haydarpaşa Training Hospital, Tıbbıye Cad., Selimiye, Istanbul, Turkey. E-mail: srkndemir@hotmail.com.

1052-3057/$ - see front matter



http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.06.001

## Methods

Patients with nonvalvular AF with a history of stroke using anticoagulant and who have been referred to the stroke outpatient section of our department from May 2013 to November 2014 were included in the study. Among the patients using warfarin, those with an International Normalized Ratio (INR) value lower than 2 were not included. The $CHA_{(2)}DS_{(2)}VASc$ scoring was made for all patients, and INR value was evaluated in patients using warfarin. All patients were monitored with TCD (Multi-Dop X-4; DWL, TCD-8 for multirange embolus detection software MDX, version 8.00 K) with the 2 MHz probes of the device on the middle cerebral arteries (MCA) bilaterally for 30 minutes. Both MCA were visualized synchronously from the temporal window at a depth of 50- to 55-mm wave depth. In multigated Doppler ultrasound evaluations, each artery was viewed from 2 different depths, and the distance between passageways was 5 mm. Sweeping speed was approximately 6 seconds, and the speed range 100-150 cm/s was used. We used 128-point Fast Fourier variable transformer. High-pass filter was arranged at 100 Hz. Power was 160 $mW/cm^2$, and the pulse frequency was 6500 Hz. To detect microembolic conditions, the lower limit was designated as ≥9 dB. MCA imaging results were evaluated locally. The criteria for identification and detection of microemboli were those of the International Consensus Group on Microembolus Detection: (1) characteristic acoustic qualities, (2) short duration (<.3 milliseconds), (3) random appearance in the cardiac cycle, (4) unidirectional signal, and (5) an intensity increase at least 9 dB above background noise. Differentiation of MES from artifacts was also performed in accordance with the Consensus conference criteria. Signals were assumed to be artifacts if they were recorded simultaneously from both sides or above and below the baseline. All data were reported in the digital environment for subsequent re-analysis. Observations were re-evaluated after recording for control. Only signals detected in both observations were considered in favor of emboli. Embolic signals were evaluated according to their density and the mean number of signals in 2 consecutive recordings.

### *Statistical Analyses*

The relation of treatment groups and MES was evaluated in this study. The mean and median values of age, $CHA_{(2)}DS_{(2)}VASc$ score, number of MES (in patients with shown MES), and INR score (in the warfarin group) were summarized. To determine if there is a significant difference among the means of 3 or more data groups, analysis of variance is an appropriate inferential technique and was therefore applied. The relation of the number of emboli and $CHA_{(2)}DS_{(2)}VASc$ score was evaluated with Pearson correlation coefficient.

## Results

In this study, 99 patients (46%) using warfarin, 67 patients (31%) using rivaroxaban, and 49 patients (23%) using dabigatran, that is, a total of 215 patients, were evaluated. The incidence of emboli in the treatment group was 32 (32%) for warfarin, 24 (36%) for rivaroxaban, and 17 (35%) for dabigatran.

The mean and median values of age, characteristic score, number of emboli (among the group with emboli), and INR score (for warfarin group) are summarized in Table 1. The analysis of variance revealed that there was no statistically significant differences between the treatment groups in terms of patients' age ($P$ = .145), $CHA_{(2)}DS_{(2)}VASc$ scores ($P$ = .968), and number of emboli ($P$ = .783).

A statistically significant moderate positive correlation between number of emboli and $CHA_{(2)}DS_{(2)}VASc$ scores in all treatment groups was shown with Pearson correlation coefficient ($P$ = .000 for all patients, $P$ = .000 for warfarin, $P$ = .000 for rivaroxaban, $P$ = .000 for

**Table 1.** *Age, $CHA_{(2)}DS_{(2)}VASc$ score, number of emboli, and INR score summary statistics for treatment groups*

| | Warfarin (n = 99) | | Rivaroxaban (n = 67) | | Dabigatran (n = 49) | | Total (n = 215) | |
|---|---|---|---|---|---|---|---|---|
| Patients' characteristics | Mean ± SD | Median (min, max) | Mean ± SD | Median (min, max) | Mean ± SD | Median (min, max) | Mean ± SD | Median (min, max) |
| Age | 72.1 ± 10.6 | 72 (44, 92) | 74.5 ± 8.1 | 75 (55, 92) | 74.8 ± 9.4 | 76 (45, 88) | 73.5 ± 9.6 | 74 (44, 92) |
| $CHA_{(2)}DS_{(2)}VASc$ score | 5.4 ± 1.2 | 5 (3, 8) | 5.4 ± 1.0 | 6 (3, 7) | 5.4 ± 1.1 | 5 (3, 8) | 5.4 ± 1.3 | 5 (3, 8) |
| Number of emboli* | 2.5 ± .9 | 2 (1, 4) | 1.9 ± .7 | 2 (1, 3) | 2.2 ± 0.8 | 2 (1, 4) | 2.2 ± 0.8 | 2 (1, 4) |
| INR score† | 2.4 ± 0.3 | 2.3 (2, 3, 4) | | | | | | |

Abbreviations: INR, International Normalized Ratio; max, maximum; min, minimum.
*Emboli summary statistics have been calculated according to data from patients with emboli.
†INR score is calculated only for warfarin group.