

Original Article



Why INR is outside the therapeutic range in patients with acute ischemic stroke and atrial fibrillation

Elyar Sadeghi Hokmabadi¹, Sheida Shaafi¹, Yalda Sadeghpour¹, Reza Deljavan¹, Javad Jalili^{2*}, Morteza Ghojzadeh³, Elyar Alizade Najmi⁴, Saeid Charsouei¹, Mehdi Farhoudi¹

¹Tabriz Neuroscience Research Center (NRSC), Neurology Department, Tabriz University of Medical Sciences, Tabriz, Iran

²Department of Radiology, Imam Reza Hospital, Faculty of Medicine, Tabriz, University of Medical Sciences, Tabriz, Iran

³Research Center for Evidence Based Medicine, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

⁴Tabriz University of Medical Sciences, Tabriz, Iran

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Abstract

Introduction: Warfarin is still the primary drug used to prevent vascular events in patients with atrial fibrillation (AF), especially in low-income countries. Therapeutic failure and non-adherence are common causes of recurrent embolic events. The aim of this study was to investigate possible reasons why INR was outside the therapeutic range in patients presenting with acute ischemic stroke and AF.

Methods: This prospective study was performed over a ten-month period and all patients admitted with acute ischemic stroke were enrolled. Patients with AF who did not have INR within the therapeutic range (INR=2-3) at the time of admission were identified. During a face-to-face interview, the reasons for INR being outside the therapeutic range were assessed based on a prepared checklist.

Results: During the study period, 810 patients had an acute ischemic stroke, of which 177 had AF heart rhythm (22%). The median age was 76 (IQR: 71-83), and 87 (52%) were male. Of these 177 patients, 44 (25%) had a previous history of AF ("previous AF" group) and 133 (75%) were diagnosed with AF during the current hospital admission ("new AF" group). Among patients on warfarin but with INR outside the therapeutic range (29 in all), 20 (69%) did not see a physician regularly and/or did not take medication according to the physician's instructions.

Conclusion: The most common reason for INR being outside the therapeutic range was patients lack of awareness of their heart disease (unrecognized AF). Other reasons included irregular visits to the physician and drug non-adherence.

Introduction

Cardioembolism is a cause of ischemic stroke in about 20% of cases. Among the leading causes of cardiac embolism, atrial fibrillation (AF) is a major cause of stroke. Despite the introduction of direct oral anticoagulants (DOACs), warfarin is the primary drug used to prevent vascular events in AF patients, especially in low-income countries. In addition, in patients with mechanical heart valve replacements, DOACs are not yet approved and warfarin is the only choice.¹

Despite warfarin usage, ischemic stroke occurs in a significant percentage of patients (25%) with AF. There are generally two different scenarios: in the first, stroke occurs despite regular and controlled warfarin use and INR within the therapeutic range (warfarin failure); in the second scenario, stroke occurs in patients whose INR is outside the therapeutic range despite taking warfarin, due to dose inadequacy, irregular visits to the physician, drug interactions, non-adherence to diet or non-adherence of the patient to the correct use of the drug (drug non-

adherence). Occurrences of recurrent strokes in patients with AF impose a great costs on the community health care system.^{2,3} Accordingly, we aimed to find out why INR is outside the therapeutic range in patients with acute ischemic stroke and AF in this study.

Methods

Type of research

This prospective study was performed over a ten-month period among all patients who presented to the emergency department of Imam Reza hospital with acute ischemic stroke. Imam Reza hospital is a tertiary referral educational center in Tabriz, Iran. Patients whose INR was within the therapeutic range were excluded. Other exclusion criteria were patients or their family's discomfort with the study or if it was not possible, for whatever reason, to obtain a detailed medical history.

Sampling method

All patients hospitalized in Tabriz Imam Reza hospital

*Corresponding Author: Javad Jalili, Email: javadjalili1979@gmail.com

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with acute ischemic stroke with AF rhythm whose INR was not in the therapeutic range during the period of study.

Methods and tools of data collection

Baseline and demographic information based on the objectives of the study, including questions about age, sex, anticoagulant use, type of anticoagulant, INR level, and reasons for lack of appropriate treatment were compiled with the research team. After obtaining informed consent, patients' records were reviewed to identify AF heart rhythm as well as INR levels at the time of stroke. A checklist, in the form of a face-to-face interview with the patient, was conducted by the researcher with patients whose INR was not within the therapeutic range at the time of the stroke (INR range = 2-3).

Statistical method

Statistical analysis was performed using SPSS software version 16. Data were expressed and analyzed using number (percentage) and mean frequency (SD standard deviation).

Results

During the study period, 810 patients were admitted with acute ischemic stroke, of whom 177 had AF heart rhythm (22%). The median age was 76 (IQR: 71-83), and 87 (52%) were male.

Patients with AF heart rhythm were divided into two groups according to the existence of AF rhythm before and during hospitalization: previous AF and new AF which the first group included patients with a known history of AF before the stroke and the second group included patients with a diagnosis of AF made during the index hospitalization. Of the 177 patients with AF heart rhythm, 44 (25%) patients were enrolled in the first group and 133 (75%) in the second group respectively. As we were evaluating the INR range in patients taking Warfarin, 14 patients were excluded in the "previous AF" group as following: 7 patients were on rivaroxaban, 3 patients were on enoxaparin, 2 patients were not taking warfarin due to arbitrary discontinuation of the drug (non-adherence) and 2 other patients were not taking any type of anticoagulation due to lack of a prescription. Among the remaining 30 patients on warfarin, only one had INR in the therapeutic range and was thus excluded. Finally, of the remaining 29 patients in "previous AF" patients on warfarin whose INR was not in the therapeutic range, 28 patients had an INR below 2, and 1 patient had an INR above 3. The frequency of patients with or without "Regular physician visit" and "Regular drug use" are shown in Table 1. According to Table 1, 20 (69%) patients whose INR was not in the therapeutic range did not see a physician regularly and/or did not take medication according to the physician's instructions.

Table 1. Frequent visits to the physician and proper use of the drug in patients treated with warfarin

Variable		Regular physicians visit		
		Yes	No	Total
		No. (%)	No. (%)	No. (%)
Regular drug use	Yes	9 (31)	5 (17)	14 (48)
	No	2 (7)	13 (45)	15 (52)
	Total	11 (38)	18 (62)	29 (100)

Discussion

In this prospective study, on patients presenting with acute ischemic stroke and AF, the main reason that most patients were not receiving anticoagulation medication was due to a lack of diagnosis of AF (new AF), and stroke was the first presenting sign of AF. AF is often asymptomatic, but asymptomatic AF rhythm increases the risk of ischemic stroke by 2.5 times and is a difficult diagnostic challenge for physicians. In addition, patients with asymptomatic AF often refuse treatment and as a result they are at increased risk of thromboembolic events, including embolic ischemic stroke.^{4,5}

The results of a study conducted by the GARFIELD World Anti-Coagulant Registry show that half of the patients with AF heart rhythm did not receive medication from a physician's prescription.⁶ According to Bungard et al, its reason could be physician's hesitation in prescribing the drug. Also, many physicians were not aware of new treatment guidelines, and those physicians who were aware of these guidelines were not sure of the obtained results. This made them to be so hesitant to prescribe the drug. Because the disease is more common in the elderly and these people are at higher risk of falls and bleeding due to medication, physicians are more cautious in prescribing anticoagulants.⁷ However, whether due to patient-related factors or physician-related factors, improper use of anti-coagulant drugs increases the risk of ischemic and hemorrhagic stroke. To improve patients' adherence to anticoagulant therapy, several strategies with different efficacy have been recommended, including identification of diagnostic and prevention tools, screening of high-risk individuals, and providing complete and detailed explanations.⁸⁻¹⁴ However, this finding was contrary to our findings; of the 33 patients aware of their disease, warfarin was prescribed to 31 patients. Thus it seems that the burden of unrecognized AF is much higher than under-treatment of these patients: this is the novel finding of this study.

This study had some limitations: 1. it was a single center study with a limited number of cases and therefore cannot be generalized to the whole community. 2. One of the important reasons for INR being outside the therapeutic range is diet non-adherence. Since investigating this requires the use of detailed questionnaires and weekly diet control of patients, it was not feasible in this study.

Study Highlights

What is current knowledge?

- Cardioembolism is a main cause of ischemic stroke and among the leading cause of cardioembolism,
- AF is a major source of stroke
- Despite warfarin usage, ischemic stroke occurs in a significant percentage of patients with AF

What is new here?

- The burden of unrecognized AF was more than what we expected and was one of the main causes of stroke in patients with AF
- Drug non-adherence is another important cause of stroke in the AF patients

Conclusion

This study found the most common reason for INR being outside the therapeutic range was patient's lack of awareness about their heart disease. Other reasons were irregular visits by the physician and drug non-adherence.

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Authors' Contribution

All of the authors contributed equally.

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Ethical Approval

This study was approved with ethics no: IR.TBZMED.REC.1397.083 by Tabriz University of Medical Sciences Ethics Committee.

Conflict of Interest

There is no conflict of interests associated with this study.

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