Original Article

Assessment of the Compatibility of the Real-World Nonvalvular Atrial Fibrillation Patients in Turkey with the Study Population of Phase 3 Novel Oral Anticoagulant Trials: An Auxiliary Study of NOAC-TR

Sadik Volkan Emren, Mehdi Zoghi[1], Ugur Karagöz, Sinan Inci[2], Gönül Açiksari[3], Lütfü Bekar[4], Zeynep Yapan Emren[5], Oktay Ergene[6]

Department of Cardiology, School of Medicine, Katip Çelebi University, [1]Department of Cardiology, Ege University School of Medicine, [5]Department of Cardiology, Çigli State Hospital, [6]Department of Cardiology, School of Medicine, Dokuz Eylül University, İzmir, [2]Department of Cardiology, Aksaray University School of Medicine, Aksaray, Central Anatolia, [3]Department of Cardiology, School of Medicine, Göztepe Training and Research Hospital, Istanbul Medeniyet University, Istanbul, [4]Department of Cardiology, Hitit University School of Medicine, Corum, Turkey

ORCID:

Sadik Volkan Emren: https://orcid.org/0000-0002-7652-1123
Mehdi Zoghi: https://orcid.org/0000-0002-8156-2675
Ugur Karagöz: https://orcid.org/0000-0001-9748-5136
Sinan Inci: https://orcid.org/0000-0002-4576-128X
Gönül Açiksari: https://orcid.org/0000-0002-8380-3065
Lütfü Bekar: https://orcid.org/0000-0002-3920-1382
Zeynep Yapan Emren: https://orcid.org/0000-0002-5508-9474
Oktay Ergene: https://orcid.org/0000-0003-1775-4063

Abstract

Introduction: Although the indication of novel oral anticoagulant (NOAC) treatment in atrial fibrillation (AF) is comparatively similar, Phase 3 NOAC trials have variable inclusion criteria that differentiate each other and also from the real-world population. **Aim:** We aim to investigate the similarity between real-world nonvalvular AF patients and the population of Phase 3 NOAC trials in terms of eligibility. **Methods:** A total of 2802 patients using rivaroxaban, dabigatran, and apixaban were retrospectively evaluated. All the patients met the exclusion criteria of NOAC Phase 3 trials. These patient population were compared with the population of Phase 3 rivaroxaban (ROCKET-AF), dabigatran (RELY), apixaban (ARISTOTLE), and edoxaban (ENGAGE) trials in terms of inclusion criteria. Furthermore, the patients were stratified on the basis of CHA_2-DS_2–VASCc is enaogh score. **Results:** The proportion of population who met the eligible criteria for ARISTOTLE trial (91%) was different from that of RELY (78%), ROCKET-AF (50%), and ENGAGE (61%) trials ($P < 0{,}001$). For the population at intermediate risk (CHA_2DS_2–VASc score ≥1), the proportion which met the inclusion criteria for RE-LY trial (99%) was different from that of ARISTOTLE (91.2%), ROCKET-AF (50%), and ENGAGE trials (61%) ($P < 0.001$). For the population at high risk (CHA_2DS_2–VASc score ≥2), the proportion which met the inclusion criteria was as follows: 94% for ARISTOTLE, 83% for RELY, 65% for ENGAGE, and 53% for ROCKET-AF trials ($P < 0.001$). In this population, 38% of patients using rivaroxaban, 46% of patients using dabigatran, and 12% patients of using apixaban did not meet the inclusion criteria for the ROCKET-AF, RE-LY, and ARISTOTLE trials, respectively. **Conclusion:** Eligibility of the real-world population for NOAC trials is variable. A considerable number of real-world patients using NOAC do not meet the inclusion criteria of the corresponding drug.

Keywords: Atrial fibrillation, CHA_2DS_2–VASc score, $CHADS_2$ score, novel oral anticoagulants

Address for correspondence: Dr. Sadik Volkan Emren, Department of Cardiology, School of Medicine, Katip Celebi University, 35160 Izmir, Turkey.
E-mail: vemren@hotmail.com

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Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia which is associated with morbidity and mortality by causing stroke and thromboembolism in particular.[1] Oral anticoagulants (OACs) have become the mainstay treatment for the prevention of thromboembolism in patients with AF. For many decades, Vitamin K antagonists (VKAs) have been the only available OAC drugs.[2] Development of new OAC NOACs including rivaroxaban, apixaban, edoxaban, and dabigatran has created a paradigm shift in AF treatment. In Phase 3 trials, NOACs have been demonstrated favorable outcomes over VKA regarding efficacy and safety in nonvalvular AF (NVAF) population.[3-6] Moreover, advancement of NOAC therapy has provided many facilities and avoided many flaws of VKA such as drug and food interaction, frequent monitoring, difficulty in dose adjustment, and variability of anticoagulant effect.[7,8] Therefore, the NOAC market sharing has been growing rapidly for the last years.[9]

While the indication for AF treatment is same among NOACs, eligibility criteria in Phase 3 NOAC trials, such as ARISTOTLE, RE-LY, ROCKET-AF, ENGAGE-TIMI-AF, are comparatively different.[10] Thus, Phase 3 NOAC trials represent different groups of AF patients. It is not clearly known whether real-world AF population using NOAC were eligible for the NOAC trials.

On the basis of these data, we aimed to assess the compatibility of the real-world AF patients with the study population in Phase 3 NOAC trials in terms of eligibility criteria.

Methods

We retrospectively analyzed the database of NOAC-TR study which was conducted between September 1, 2015, and February 28, 2016.[8] In NOAC-TR study, the patients were included if they had the following criteria: >18 years old; nonvalvular atrial fibrillation (NVAF) without end-stage renal failure; and use of any NOAC such as rivaroxaban, apixaban, edoxaban, and dabigatran. All these patients had used warfarin before they were given NOAC an account of the reimbursement conditions of the National Health Insurance. A total of 2802 patients were evaluated for the eligibility criteria of ARISTOTLE,[3] RE-LY,[4] ROCKET-AF,[5] and ENGAGE-TIMI-AF[6] trials. We got the information of patients including age, gender, hypertension, coronary artery disease, heart failure, diabetes mellitus, peripheral arterial disease, cerebrovascular disease (stroke and transient ischemic attack), chronic renal failure, nonsteroidal anti-inflammatory and acetylsalicylic acid use, previous bleeding especially gastrointestinal and intracranial bleeding, and types of NOAC they use.

Eligibility of patients for NOAC trials was also evaluated by stratifying to the Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus (CHADS) (1 point for the presence of each, and Stroke/transient ischemic attack [2 points]) $CHADS_2$ and CHA_2DS_2–VASc score respectively (Congestive heart failure [1 point], Hypertension [1 point], Age ≥ 75 years [2 point], Diabetes mellitus [1 point], Stroke/transient ischemic attack [2 points]; Vascular disease (history of myocardial infarction, presence of complex aortic plaque, or peripheral artery disease [1 point], age 65–74 years [1 point], and female sex [1 point]). Finally, we also determined the proportion of patients using inappropriate NOAC because of being ineligible for the corresponding NOAC trial. This study was approved by the ethical committee.

Statistical analysis

Statistical analysis was performed using the SPSS (version 15.0, SPSS Inc., Chicago, Illinois, USA) software package. Continuous variables were expressed as mean ± standard deviation (mean ± SD), and categorical variables were expressed as percentage (%). Chi-square test was used to compare the percentage of patients eligible for ARISTOTLE, RE-LY, ROCKET-AF, and ENGAGE-AF trials. A two-tailed $P < 0.05$ was considered statistically significant.

Results

The demographic and clinical characteristics of the patients are shown in Table 1. The mean age of the NVAF population was 70 ± 10.5 years, and a female predominance (1661 [59%]) was observed. Hypertension was the most common additional cardiovascular risk factor (79%). Only 12% of the patients had a history of cerebrovascular event. The most commonly used NOAC was dabigatran (44%) followed by rivaroxaban (38%) and apixaban (17%). The mean CHA_2DS_2–VASCc score was 3.45 ± 1.4, and the mean $CHADS_2$ score was 1.9 ± 1.14. The proportion of population who met the eligible criteria for ARISTOTLE trial (91%) was different from that of RELY (78%), ROCKET-AF (50%), and ENGAGE (61%) trials ($P < 0{,}001$). For the population at intermediate and high risk (CHA_2DS_2–VASc score ≥1), the proportion which met the inclusion criteria for RE-LY trial (99%) was different from that of ARISTOTLE (91.2%), ROCKET-AF (50%), and ENGAGE trials (61%) ($P < 0.001$). For the population at high risk (CHA_2DS_2–VASc score ≥2), the proportion which met the inclusion criteria was as follows: 94% for ARISTOTLE, 83% for RELY, 65% for ENGAGE, and 53% for ROCKET-AF trials ($P < 0.001$) [Table 2].

When stratifying patients according to the CHADS score, for intermediate and high risk ($CHADS_2 \geq 1$), the proportion which met the inclusion criteria for ARISTOTLE trial (100%) was different from that of RE-LY (86%), ROCKET-AF (55%), and ENGAGE trials (67%) ($P < 0.001$). For high-risk population ($CHADS_2 \geq 2$), the proportion which met the inclusion criteria for ARISTOTLE and ENGAGE trials (100%) was different from that of RE-LY (94%) and ROCKET-AF (81%) trials ($P < 0{,}001$).

In this population, 38% of patients using rivaroxaban, 46% of patients using dabigatran, and 12% patients using apixaban did not meet the inclusion criteria for ROCKET-AF, RE-LY, and ARISTOTLE trials, respectively [Figure 1].

Discussion

The results of this study show that eligibility of the real-world population to Phase 3 trials is significantly different. According to our findings, ARISTOTLE trial most commonly represents real-world population in Turkey on the basis of eligibility criteria. Yet, with the increasing risk of thromboembolism, higher number of patients become eligible for all over NOAC trials. Although indications are same for all NOACs, a considerable number of patients who use NOAC do not meet the eligibility criteria of the corresponding trial.

There are several factors that make the NOAC studies variable in terms of inclusion and exclusion criteria. Yet, the main determinant factor is supposed to be the inclusion criteria. ROCKET and ENGAGE trials included high thromboembolic risk patients which required at least two points in the $CHADS_2$ score. However, the ARISTOTLE trial included patients with only one thromboembolic risk factor. Besides, in the ROCKET trial, the patients were given 1 point if they had more severe heart failure (ejection fraction [EF] ≤35%) compared to those in RE-LY and ARSITOTLE trials who were given 1 point if they had EF ≤40. Our real-world population consisted of relatively younger population as only 39% were aged ≥75 years. Hence, most of them got no points for $CHADS_2$ score regarding age. The history of stroke rate was considerably low. Moreover, our population had lower thromboembolic risk (mean $CHADS_2$ score of 1.9) compared to ROCKET-AF (mean $CHADS_2$ risk score of 3.48), RE-LY (mean $CHADS_2$ risk score of 2.1), ARISTOTLE (mean $CHADS_2$ risk score of 2.2), and ENGAGE (mean $CHADS_2$ risk score of 2.2) trials. Another main factor was the selection of thromboembolic risk score. Although Phase 3 NOAC trials used CHADS score for risk stratification, the current guidelines recommend to use CHA_2DS_2–VASc score to determine the commensal of oral anticoagulation.[2] Some risk factors such as vascular disease,

Table 1: Demographic characteristics of patients

Age (years), mean±SD	70±10.5
Age ≥65 years, *n* (%)	2018 (75)
Age ≥75 years, *n* (%)	1090 (39)
Gender, Female, *n* (%)	1661 (59)
Hypertension, *n* (%)	2200 (79)
Diabetes mellitus, *n* (%)	686 (25)
Heart failure, *n* (%)	712 (25)
Coronary heart disease, *n* (%)	768 (27)
Cerebrovascular event, *n* (%)	343 (12)
Peripheral arterial disease, *n* (%)	85 (3)
Chronic renal failure, *n* (%)	200 (7)
NSAID use, *n* (%)	495 (18)
ASA use, *n* (%)	352 (13)
NOAC, *n* (%)	
Dabigatran	1234 (44)
Apixaban	486 (17)
Rivaroxaban	1075 (38)
Gastrointestinal hemorrhage, *n* (%)	67 (2.4)
Intracranial hemorrhage, *n* (%)	15 (1)
CHA_2DS_2-VASCc score, mean±SD	3.45±1.4
CHA_2DS_2-VASCc score ≥1, *n* (%)	2802 (100)
CHA_2DS_2-VASCc score ≥2, *n* (%)	2632 (94)
$CHADS_2$ score, mean±SD	1.9±1.14
$CHADS_2$ ≥1, *n* (%)	2554 (91)
$CHADS_2$ ≥2, *n* (%)	1712 (61)

ASA: Acetylsalicylic acid, NOAC: Novel oral anticoagulants, NSAID: Nonsteroidal anti-inflammatory drug, $CHADS_2$ score: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus (1 point for the presence of each), and Stroke/transient ischemic attack (2 points), CHA_2DS_2–VASc score : Congestive heart failure (1 point), Hypertension (1 point), Age ≥75 years (2 points), Diabetes mellitus (1 point), Stroke/transient ischemic attack (2 points), Vascular disease history of myocardial infarction, presence of complex aortic plaque, or peripheral artery disease (1 point), age 65-74 years (1 point), female sex (1 point), SD: Standard deviation

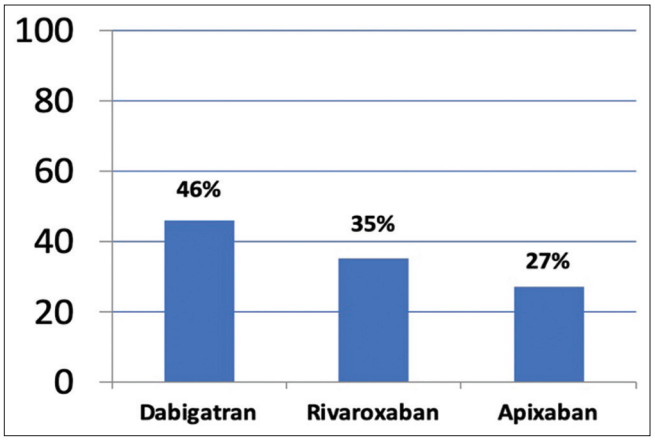

Figure 1: Percentage of patients misusing novel oral anticoagulants based on the eligibility criteria of the corresponding trial

Table 2: Representativeness of the novel oral anticoagulants trials to real-world population stratified by risk scores

	n	ARISTOTLE, *n* (%)	RE-LY, *n* (%)	ROCKET, *n* (%)	ENGAGE, *n* (%)
Total	2802	2554 (91)	2199 (78)	1392 (50)	1712 (61)
$CHADS_2$ ≥1	2554	2554 (100)	2188 (86)	1392 (55)	1712 (67)
CHA_2DS_2-VASc ≥1	2802	2554 (91)	2781 (99)	1392 (50)	1712 (61)
$CHADS_2$ ≥2	1712	1712 (100)	1604 (94)	1392 (81)	1712 (100)
CHA_2DS_2-VASc ≥2	2632	2468 (94)	2181 (83)	1384 (53)	1703 (65)

$CHADS_2$ score: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus (1 point for the presence of each), and Stroke/transient ischemic attack (2 points), CHA_2DS_2-VASCc score: Congestive heart failure (1 point), Hypertension (1 point), Age ≥75 years (2 points), Diabetes mellitus (1 point), Stroke/transient ischemic attack (2 points), Vascular disease history of myocardial infarction, presence of complex aortic plaque, or peripheral artery disease (1 point), age 65-74 years (1 point), female sex (1 point)

>65 years, and female gender do not play a role in $CHADS_2$ score, but play in CHA_2DS_2–VASc score. These variables were significantly prevalent in our population.

There are also other studies which investigate the representativeness of the NOAC trials to real-world population. Lee *et al*. found that the study population in RE-LY (64%) and ARISTOTLE (61%) trials were more compatible than that of ROCKET-AF (48%) trial to real-world AF patients in the United Kingdom health-care database.[11] Yoon *et al*. investigated the eligibility of patients with and without stroke to NOAC trials. Although they did not make statistical comparison, the ARISTOTLE trial (72.8%) was most eligible to real-world patients with stroke than RE-LY (65.6%), ROCKET (64.8%), and ENGAGE (57.4%) trials. Furthermore, the most representative trial to nonstroke AF patients was ARISTOTLE (67.3%) followed by RE-LY (45.1%), ROCKET-AF (41%), and ENGAGE (39%) trials.[12] Fanning *et al*. also demonstrated that ARISTOTLE and RE-LY trials were the most representative of hospitalized AF patients in Australia.[13] Our findings were comparable to the above-mentioned studies as the ARISTOTLE trial was the most representative real-world AF population in Turkey. Regarding the eligibility, we also found that only few patients using apixaban did not comply with the ARISTOTLE trial. However, substantial number of patients using dabigatran and rivaroxaban did not comply with RE-LY and ROCAKET-AF trials, respectively. On the other hand, it should be kept in mind that divergences of eligibility of NOAC trials do not link to the indications and effectiveness of NOACs. All these patients meet the indications of NOACs.

Study limitations

This was a retrospective study; therefore, some data of the patients might be missed especially necessary for the exclusion criteria of NOAC trials. Another issue is that edoxaban was not given to patients at the time when this study was conducted as there was no reimbursement for edoxaban. Thus, the proportion of prescribed NOACs among patients might be changed thereafter.

Conclusion

Eligibility of the real-world population for NOAC trials is variable. The most representative NOAC trial of real-world population is ARISTOTLE in Turkey. Besides, a considerable number of patients using NOAC are not eligible for the corresponding trial. Nevertheless, eligibility should not be confused with indication. It is obvious that variation of the eligibility criteria of the NOAC trials is not meant to change the indication of NOACs.

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Conflicts of interest

There are no conflicts of interest.

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