

ORIGINAL ARTICLE

Design and rationale of dabigatran's stroke prevention in real life in Turkey (D-SPIRIT)

Türkiye'de gerçek yaşamda dabigatran ile inmeden korunmanın temel ve tasarımı (D-SPIRIT)

Uğur Önsel Türk, M.D., Emin Alioğlu, M.D.,[#] Eşref Tunçer, M.D.,[#] Mehmet Emre Özpelit, M.D.,^{*} Nihat Pekel, M.D.,^{*} İstemihan Tengiz, M.D.,^{*} Nurullah Çetin, M.D.,[†] Onur Dalgıç, M.D.,[†] Caner Topaloğlu, M.D.,[†] Nazile Bilgin, M.D.,[‡] Cihan Altın, M.D.,[§] Tolga Özdemirkıran, M.D.,^{||} Kamil Tülüce, M.D.,[¶] Ebru İpek Türkoğlu, M.D.,^{**} Ebru Özpelit, M.D.^{††}

Ege University Center for Drug Research & Development and Pharmacokinetic Applications, İzmir, Turkey

[#]Department of Cardiology, Central Hospital, İzmir, Turkey

^{*}Department of Cardiology, İzmir University Faculty of Medicine, İzmir, Turkey

[†]Department of Cardiology, Karşıyaka State Hospital, İzmir, Turkey

[‡]Department of Cardiology, Menemen State Hospital, İzmir, Turkey

[§]Department of Cardiology, Başkent University Faculty of Medicine, Ankara, Turkey

^{||}Department of Neurology, İzmir University Faculty of Medicine, İzmir, Turkey

[¶]Department of Cardiology, Tepecik Training and Research Hospital, İzmir, Turkey

^{**}Department of Cardiology, Kemalpaşa State Hospital, İzmir, Turkey

^{††}Department of Cardiology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

ABSTRACT

Objective: The D-SPIRIT registry is designed to investigate the safety and efficacy of dabigatran etexilate in patients with nonvalvular atrial fibrillation (NVAF) and to collect data on outcomes in clinical practice.

Methods: The D-SPIRIT is a national, prospective, observational, post-marketing registry involving patients with NVAF who have been taking dabigatran etexilate therapy for stroke prevention for a minimum of 6 months prior to enrollment. The registry will collect and analyze data from routine care, enrolling up to 600 patients in 9 centers. Patients will be followed up for 2 years to evaluate effectiveness and safety. A sample size of 600 subjects is proposed based on the following assumptions; Two-sided significance level of 0.05 (1-sided significance level of 0.025), ischemic stroke incidence rate of 0.768%–1.111%, hemorrhagic stroke incidence rate of 0.109%–0.130%, transient ischemic attack incidence rate of 0.722%–0.623%, therapy discontinuation incidence rate of 40% at day 730, and duration of enrollment period of 12 months with non-uniformed enrollment rate. Ethics approval was given by Dokuz Eylül University Ethics Committee of Clinical Research (2014/54) and approved by the Turkish Ministry of Health.

Conclusion: Potential results of D-SPIRIT registry will add data from clinical practice to those from the RE-LY trial to expand knowledge of dabigatran etexilate treatment in patients with NVAF.

ÖZET

Amaç: D-SPIRIT kayıt çalışması, günlük pratikte, dabigatran tedavisi altındaki nonvalvüler atriyum fibrilasyonu (NVAF) bulunan olgularda ilacın etkinlik ve güvenilirliğinin değerlendirilmesi amacı ile tasarlandı.

Yöntemler: D-SPIRIT, dabigatran tedavisi altında olan NVAF'li hastaların değerlendirildiği ulusal, çok merkezli, ileriye dönük, gözlemsel bir veri tabanı kayıt çalışmasıdır. NVAF nedeniyle inmeden korunma amacı ile en az 6 aydır düzenli dabigatran tedavisi altındaki olgular hedef popülasyonu oluşturmaktadır. Dokuz farklı merkezden 600 NVAF'li olgunun araştırmaya alınması planlanmaktadır. Olgular etkinlik ve güvenilirliğinin değerlendirmesi amacı ile 2 yıl süre ile izlenecektir. Örnek büyüklüğü olan 600 katılımcıda şu özellikler dikkate alınmıştır: İki taraflı anlamlılık düzeyi 0.005 (tek taraflı anlamlılık 0.025); iskemik inme (%0.768–%1.111), hemorajik inme (%0.109–%0.130) ve geçici iskemik atak olaylarının (%0.722–%0.623) bir yıllık sürede meydana gelme oranları; tedaviden ayrılma oranı 730. günde %40 olması; tarama periyodunun 12 ay süre ile devam etmesi. Yerel etik kurul onayı Dokuz Eylül Üniversitesi Klinik Araştırmalar Etik Kurulu'ndan alınmış, (2014/54) proje Türkiye İlaç ve Cihaz Kurum Başkanlığı tarafından onaylanmıştır.

Sonuç: D-SPIRIT kayıt çalışmasının sonuçları RE-LY çalışmasının sonuçlarına ek NVAF olan hastalarda dabigatran eteksilat tedavisi ile ilgili klinik pratiği etkileyecek bilgiler katacaktır.

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Correspondence: Dr. Uğur Önsel Türk. 4016 Sokak, No: 10, K: 9, D: 42, Yeşilova, Bornova, İzmir, Turkey.
Tel: +90 232 - 341 67 67 e-mail: droturk@yahoo.com

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and is increasing in incidence and prevalence.^[1,2] It occurs in 1–2% of the general population.^[3] The prevalence in the Europe is 6 million, and this is expected to double in the next 50 years.^[3] Few studies have been conducted with similar prevalence and incidence ratios of AF in the Turkish population.^[4] Ischemic stroke and systemic embolism are major causes of morbidity and mortality in patients with AF, who have a 5-fold higher risk of stroke than those without AF.^[3] Up to 15% of all strokes are attributable to AF, and strokes in patients with AF have worse outcomes and higher mortality rates than those in patients without AF.^[5] The main aim of treatment is to reduce cardiovascular mortality and morbidity. This can be achieved by preventing thromboembolic events, particularly stroke, reducing symptoms and improving quality of life, and decreasing number of hospitalization and total mortality. The main treatment for stroke prevention in patients with AF is anticoagulants. Recent guidelines recommend vitamin K antagonist (VKA) for prevention stroke in valvular AF, and VKA or non-vitamin K antagonists (NOAC) in patients with nonvalvular atrial fibrillation (NVAf) after risk stratification.^[1]

Numerous risk stratification schemes have been developed to help predict levels of stroke risk in patients with AF (low, moderate, or high) and to manage them accordingly.^[6] The simplest and most widely used risk assessment scheme is the CHADS₂ scoring system. This scoring system is derived from criteria used in SPAF (Stroke Prevention in Atrial Fibrillation) researches: 2 points for a history of stroke or transient ischemic attack (TIA) and 1 point for age >75 years, history of hypertension, diabetes, or heart failure.^[7]

However, the CHADS₂ system did not include many stroke risk factors, and other “modifiers of risk of stroke” need to be considered in a comprehensive stroke risk assessment.^[3] Therefore, the CHADS₂ scoring system expanded to include other stroke risk factors and developed into the CHA₂DS₂-VASc scoring system.^[8] In this scheme, congestive heart failure, hypertension, diabetes mellitus, history of vascular disease, female sex and age 65-74 years are each assigned 1 point. History of previous stroke or transient ischemic attack and age ≥75 years are assigned 2 points.

VKAs, especially warfarin, have been in use for nearly 50 years and have proven effective agents in the

process of SPAF. In a meta-analysis, the relative risk reduction with warfarin therapy in all stroke has been reported as 64% (2-3). In the BAFTA study, when compared to warfarin,

Abbreviations:

AF	Atrial fibrillation
D-SPIRIT	Dabigatran's stroke prevention in real life in Turkey
NOAC	Non-vitamin K antagonists
NVAf	Nonvalvular atrial fibrillation
RCTs	Randomized controlled clinical trials
TTR	Time-in-therapeutic range
VKA	Vitamin K antagonist

aspirin showed no difference in the risk of major bleeding, and warfarin (target INR 2-3) was shown to provide 52% relative risk reduction in primary endpoint involving a disability causing a fatal stroke, intracranial bleeding or clinically significant arterial embolism.^[9] This finding is compatible with the results of the WASPO study, which showed significantly more adverse events, including severe bleeding, with aspirin when compared with warfarin.^[10] However, VKAs have important limitations, including a narrow therapeutic window, an unpredictable dose-response effect, numerous drug-drug and drug-food interactions, and a slow onset and offset of action.^[3] Warfarin is the most commonly used agent in Turkey for SPAF. Efficacy and safety of warfarin is markedly influenced by its time-in-therapeutic range (TTR), referring to the time patients treated with warfarin spend having an international normalized prothrombin time ratio (INR) within the therapeutic range, which requires regular blood test monitoring. A recent study showed very low TTR values in Turkey.^[4] With the approval of NOACs for SPAF, antithrombotic treatment patterns are changing around the world and in Turkey.

In 2010, the first NOAC for stroke prevention in patients with AF, dabigatran etexilate (herein after dabigatran), was approved by the US Food & Drug Administration and is now available in >80 countries. Dabigatran is a direct thrombin inhibitor with rapid onset and offset of action, limited drug-drug interactions, and no significant drug-food interactions. It can be administered without routine anticoagulation monitoring.^[11] Other NOACs are the factor Xa inhibitors, rivaroxaban (first approved in 2011), apixaban (first approved in 2012), and edoxaban (first approved in 2015).^[12-15]

The most comprehensive clinical data about dabigatran was obtained from a phase III RE-LY trial.^[11] The RE-LY trial included 18,113 patients with average

CHADS₂ score of 2.1 and was followed for 2 years.^[11] In terms of primary outcomes such as stroke and systemic embolism, dabigatran 110 mg was non-inferior (1.54%/year) compared with warfarin (1.71%/year), while a dose of dabigatran 150 mg (1.11%/year) was found to be superior to warfarin.^[11] In terms of major and fatal bleeding, low-dose dabigatran was found less risky than warfarin, while high-dose dabigatran was found to have similar risk to warfarin.^[11]

In this context, dabigatran is prescribed with increasing frequency for SPAF in Turkey. Dabigatran has been available in Turkey in 2 doses (either 150mg b.i.d. or 110 mg b.i.d.) and reimbursed since May 2013 for SPAF with 1 or more risk factors. Although efficacy and safety of NOACs have been shown in large randomized controlled clinical trials (RCTs) in patients with NVAf,^[12–15] these trials may not reflect real-world clinical settings due to inclusion of selected patients. RCTs generally have standardized protocols with closer monitoring of patients constituting an obstacle to their implementation in routine clinical practice. Observational studies and multinational registries have been performed to overcome these limitations.^[16–20] However, Turkey has not been included or represented with only small numbers of patients in these registries. Also a post-marketing observational study with a prospective design to assess drug safety and effectiveness has not yet been conducted in our country.

In short, the D-SPIRIT registry is designed to investigate safety and efficacy of dabigatran etexilate in patients with nonvalvular atrial fibrillation and to collect data on outcomes in clinical practice.

Rationale, aim, risk-benefit assessment

No study has been conducted in Turkey to assess safety and effectiveness in real life of dabigatran, which has been routinely used as an anticoagulant for 3.5 years. The most comprehensive data on its effectiveness and safety were obtained from the RE-LY study, in which Turkey was a participant.^[11] However, RE-LY was a phase 3 trial and included important limitations in adapting its results to real life.

The most important of these limitations was the fact that the therapeutic window (TTR) in the treatment group using warfarin as active comparator was 64%.^[11] This TTR rate is much higher than the real life rate in Turkey, and in warfarin treatment it indicates relatively successful anticoagulant therapy.^[4] Another

point in the RE-LY study is that the average age is 71, with the 80+ age groups constituting a low proportion. However, in real life a significant portion of patients with AF are aged 80 and over. This situation illustrates the need for assessment of drug efficacy and safety in octogenarians. Pharmacogenetic factors are valid for each drug, and these play a decisive role for dabigatran, which is a pro drug. Enzymes that play a role in the process of transformation of a drug to active metabolite show ethnic differences, which may lead to pharmacodynamic variability that should not be ignored. This assumption reveals the necessity for testing of dabigatran in different ethnic groups. A recent pharmacokinetic study in patients who use Dabigatran revealed that there is up to 5 times variation in the level of active metabolite.^[21] Moreover, the study demonstrated that these differences make sense in terms of evaluating efficacy and safety in clinical events. The aim of the present study is observation of the effectiveness and safety of Dabigatran in NVAf in the Turkish population. The primary purpose is observation and registration of clinical events in real-life conditions in NVAf patients under treatment with Dabigatran. Other purposes are; determination of demographic, clinical profile and risk factors which affect the effectiveness and safety of dabigatran therapy; evaluation of patient compliance with anticoagulant treatment, and recording of the potential side effects of the drug. As in all other observational studies, risk-benefit assessment of patients, administration of medical treatment, and the management of disease and treatment-related clinical events are the responsibility of the clinician observing the patient. In this context, with the scope of work involving only questionnaire-based data collection and participation, there will be no additional risk brought to those patients participating. Additional medical diagnoses, treatment or intervention initiatives will not be undertaken. Valuable information about disease and the effectiveness and safety of treatment with dabigatran in terms of real-world data are expected from the study.

METHODS

Design

D-SPIRIT is national, multi-center, prospective, observational registry database, and will evaluate NVAf patients under dabigatran treatment. Investigation of 600 NVAf patients from 9 different centers in the

province of Izmir is planned. There is a single arm, so there are not placebo and/or active drug arms. Diagnosis of disease, initiation of dabigatran therapy and maintenance, management of disease or treatment-related adverse events and complications are beyond the scope of research, and are the responsibility of the clinician. However, if they find it necessary, the participating physicians accept the responsibility of sharing, illness, and/or relating elements of medical treatment to the responsible clinician. The goal of the research is mirroring real-life data as much as possible, and for this reason attempts are made to avoid factors that could lead to bias. A detailed flow chart and visit calendar are shown in Table 1.

Definition of research population

Planned for inclusion in the research project are patients over 18 years old with NVAF and under dabigatran treatment for at least 6 months. Diagnosis, and determination of indications is outside the scope of the project and is the responsibility of the clinician monitoring the patient. As in any observational study, patients will be managed according to local medical practice. Choice of treatment is solely at the discre-

tion of the participating physicians. This means there are no additional risks to patients by participating in this registry. No additional medical procedures are required, over and above those that the patient would receive if not enrolled.

To avoid potential bias and allow for projection of real-life data in a clear manner, exclusion criteria are limited to absence of informed consent, and persistent failure by a patient to comply with the protocol and study procedures.

Anticoagulation therapy

D-SPIRIT project is an observational project and initiation of anticoagulant treatment, modification of treatment, posology management and discontinuation of therapy are not within the scope of work. Management of treatment is entirely the responsibility of the clinician. However, in terms of medical ethics, clinicians monitoring patients accept responsibility for providing feedback to the center, if medically necessary.

Clinical outcomes

Demographic and clinical characteristics of the patients and posology of Dabigatran treatment will be

Table 1. Detailed flow chart of the D-SPIRIT project and visit calendar

Data	Baseline/Screening Visit	Visit 1 (3±1 month)	Visit 2 (6±1 month)	Visit 3 (12±2 month)	Visit 4 (24±2 month)
Informed consent	X				
Inclusion/exclusion	X				
Demographic data	X				
Lifestyle data	X				
Characteristic of NVAF	X		X		
Medical history	X				
Comorbidities	X	X			
Antithrombotic treatment	X ¹	X ²	X ²	X ²	X ²
Additional drugs	X	X	X	X	X
Clinical outcomes ³	X ⁴	X	X	X	X
Serious adverse event (SAE)	X ⁴	X	X	X	X
Adverse drug reaction (ADR)	X ⁴	X	X	X	X
Vital signs	X ⁴				

¹Dabigatran posology usage with the goal of stroke prevention.

²Compliance of patient to dabigatran treatment, possible dose change, planned or unplanned interruption of anticoagulation therapy, temporary or permanent discontinuation of anticoagulation therapy leading to presence of a clinical condition.

³Clinical outcomes are defined in the relevant section.

⁴Data between beginning of dabigatran therapy and screening visit will be considered as retrospective data.

NVAF: Nonvalvular atrial fibrillation; D-SPIRIT: Dabigatran's stroke prevention in real life in Turkey.

saved at the screening visit. Compliance with dabigatran therapy during the research period, possible changes in dose of treatment and reasons, release of treatment and reasons, discontinuation of dabigatran treatment and reasons, changing anticoagulant treatment and reasons shall be recorded. Clinical events listed below will be evaluated as “clinical outcomes/events”.

- Stroke (Hemorrhagic, ischemic, uncertain classification)
- Transient ischemic attack (TIA)
- Systemic embolism
- Pulmonary embolism
- Myocardial infarction
- Life-threatening bleeding events
- Major bleedings
- All cause death
- Non-vascular death
- Vascular death
- Death of unknown cause.

Statistical method

In statistical analysis, 0.05 will be accepted as the level of significance. Patients' demographic information will be summarized according to the type of data by descriptive statistics (n, mean, standard deviation, minimum, maximum, median, the difference between percentiles) or frequency distribution (n and %). Binary logistic regression will be used to determine factors related to clinical outcomes at each study visit. Each outcome will be evaluated separately with a binary logistic regression model. In addition to binary logistic regression, generalized estimating equation (GEE) will be used repeated measure binary data obtained during the study for each clinic outcome separately, if appropriate. Disease-free (clinical without hardware) survival time will be calculated using the Kaplan-Meier method. In the determination of possible factors, the Cox regression model will be used.

Calculation of sample size

In determination of sample size, the yearly probability of occurrence of events (ischemic stroke, hemorrhagic stroke, and transient ischemic attack) have been taken into account. Depending on dabigatran dose, probability of ischemic stroke is 0.768%–1.111%, probability of hemorrhagic stroke is 0.109%–0.130, and probability of transient ischemic attack is

0.722%–0.623% per annum. In estimating this ratio with a confidence limit of 95% and 0.01% error rate, it was determined that the study should be completed with a minimum of 422 patients. With the drop-out rate assumed to be approximately 40%, the minimum number to be included in the sample was calculated as 591. Finally, with consideration of length of the study period and eligibility, it was decided to begin work with 600 patients.

DISCUSSION

The D-SPIRIT will be the first national, prospective, observational, post-marketing registry involving NVAF patients already taking dabigatran. The principal objective of this nationwide cohort study is to assess the efficacy and safety in an “everyday clinical practice” population of patients with NVAF treated with dabigatran in Turkey. The results will inform future decisions and enhance understanding of public health aspects of this highly prevalent condition.

Observational studies are an effective tool in observing the course of illness and evaluating treatment effectiveness and safety. Observational studies can also provide data that supplements data collected in randomized clinical trials, which generally have stricter inclusion criteria and structured monitoring schemes. With the exception of one small-scale retrospective study by Aslan et al., no studies have been done in Turkey on assessment of the safety and effectiveness of dabigatran in real life.^[22] Aslan et al. included 439 patients and found that ischemic stroke and all-cause mortality were lower in the dabigatran group.^[22]

The most comprehensive data on the effectiveness and safety of dabigatran were obtained from the RE-LY study, in which Turkey participated.^[11] RE-LY was a phase-3 trial and there were important limitations in adapting its results to real life. Discrepancy between the RE-LY trial and postmarketing studies in terms of safety and efficacy outcomes were confirmed by some nationwide cohort studies and registries.^[16,23] Quality of anticoagulation with warfarin, drug adherence, patient demographics (age, female gender), comorbidities such as chronic kidney disease, coronary artery disease, and heart failure are main reasons for discrepancies in outcomes.

One important reason for these discrepancies is the TTR value in the treatment group using warfarin as

active comparator being 64%.^[11] This TTR rate is significantly higher than in real life in Turkey, and these values in warfarin treatment arm indicate relatively successful anticoagulant therapy.^[4,11] Unlike phase trials which require regular visits and close follow-ups, drug adherence may not be sufficiently high in real life patients in routine clinical practice. As common characteristics of real life patients, polypharmacy and elderliness are the main reasons behind poor drug compliance. Another point in RE-LY study, that the average age is 71 and 80 and over age group represented in the study is a low proportion. However, in real life a significant portion of patients with AF aged 80 and over. This situation illustrates the need for assessment of drug efficacy and safety in octogenarians. Pharmacogenetic factors valid for each drug and it have a decisive role for dabigatran, which is a pro drug. Enzymes that play a role in the process of transformation drug to active metabolite show ethnic differences which can lead to pharmacodynamic variability that should not be ignored. This assumption reveals the necessity of dabigatran to be tested in different ethnic groups. A recent pharmacokinetic study in patients who use Dabigatran revealed that there is up to 5 times variation in the level of active metabolite.^[21] Moreover, it has demonstrated that these differences make sense in terms of evaluating efficacy and safety in clinical events.

Conclusion

The D-SPIRIT registry will provide valuable data for clinical practice in Turkey with respect to dabigatran management for patients with NVAf.

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Keywords: Atrial fibrillation; dabigatran etexilate; prevention; registry stroke; Turkey.

Anahtar sözcükler: Atriyum fibrilasyonu; dabigatran eteksilat; korunma; inme; kayıt çalışması; Türkiye.