ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Dabigatran for stroke prevention in real life in a sample of population from Turkey: D-SPIRIT registry

Gerçek yaşamda dabigatran ile inmeden korunma; Türkiye'den bir popülasyon örneği: D-SPIRIT kayıt çalışması

Cihan Altın, M.D.[1], Caner Topaloğlu, M.D.[2], Nurullah Çetin, M.D.[2], Onur Dalgıç, M.D.[2], Veysel Yavuz, M.D.[3], Emin Alioğlu, M.D.[4], Nazile Bilgin, M.D.[5], Cenk Ekmekçi, M.D.[6], Nihat Pekel, M.D.[7], Mehmet Emre Özpelit, M.D.[7], Eşref Tunçer, M.D.[4], Ebru İpek Türkoğlu, M.D.[8], Kamil Tülüce, M.D.[2], Umut Kocabaş, M.D.[1], Kıvanç Yüksel, Ph.D[9], Uğur Önsel Türk, M.D.[10]

[1]Department of Cardiology, Başkent University School of Medicine, İzmir, Turkey
[2]Department of Cardiology, Karşıyaka State Hospital, İzmir, Turkey
[3]Department of Cardiology, Akhisar Mustafa Kirazoğlu State Hospital, Manisa, Turkey
[4]Department of Cardiology, Central Hospital, İzmir, Turkey
[5]Department of Cardiology, Menemen State Hospital, İzmir, Turkey
[6]Department of Cardiology, Tepecik Training and Research Hospital, İzmir, Turkey
[7]Department of Cardiology, İzmir Medical Park Hospital, İzmir, Turkey
[8]Department of Cardiology, Kemalpaşa State Hospital, İzmir, Turkey
[9]Department of Biostatistics, Ege University, İzmir, Turkey
[10]Center for Drug Research and Development and Pharmacokinetic Applications, Ege University, İzmir, Turkey

ABSTRACT

Objective: The D-SPIRIT registry is designed to investigate the safety and effectiveness of dabigatran etexilate in patients with atrial fibrillation in routine clinical practice.

Methods: D-SPIRIT is the first national, multicenter, prospective, observational, postmarketing registry that investigates the usage of dabigatran in real life. A total of 326 noveloral anticoagulant–eligible patients with atrial fibrillation who have been taking dabigatran etexilate therapy for stroke prevention at least 6 months from 9 different centers were enrolled into the registry. Patients were followed up for 2 years to evaluate the effectiveness and safety of the treatment. All adverse clinical events including bleeding, thromboembolic events, stroke, systemic embolism, transient ischemic attack, myocardial infarction, and all-cause death were recorded.

Results: The mean age was 71.1±9.6 years, and 57.4% of the study participants were female. The mean CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack [TIA], vascular disease, age 65-74 years, sex category) score was 3.4±1.6. The cumulative adverse clinical events rate was 6.30% per year. The rate for embolic events including TIA, ischemic stroke, and peripheral embolism was 1.26% per year. The rate for major bleeding was 2.20% per year, and the mortality rate was 0.94% per year.

Conclusion: This registry obtained an important overview of the current safety and effectiveness of the dabigatran etexilate in Turkey. Our results indicate similar rates of thromboembolic and bleeding events with pivotal phase 3 trial and other real-life registries. However, rate of undertreatment usage of dabigatran etexilate in real life was found to be considerable.

ÖZET

Amaç: D-SPIRIT kayıt çalışması atriyal fibrilasyon hastalarında dabigatran etexilate'ın günlük pratikteki güvenilirlik ve etkinliğinin değerlendirilmesi için tasarlanmıştır.

Yöntemler: D-SPIRIT kayıt çalışması, gerçek yaşamdaki dabigatran kullanımının araştırıldığı ilk ulusal, çok merkezli, ileriye dönük, gözlemsel, pazar erişimi sonrası veri tabanı kayıt çalışmasıdır. Yeni kuşak oral antikoagülan tedavisinin kullanımına uygun olan, atriyal fibrilasyon nedenli inmeden korunmak için en az 6 aydır düzenli dabigatran tedavisi alan, toplamda dokuz farklı merkezden 326 hasta çalışmaya dahil edildi. Olgular tedavinin etkinlik ve güvenilirliğinin değerlendirmesi amaçlı 2 yıl süre ile izlendi. Kanama, tromboembolik olaylar, inme, geçici iskemik atak, miyokart enfarktüsü, tüm nedenlerden ölümü içeren bütün advers klinik olay ve sonlanımlar kaydedildi.

Bulgular: Çalışma hastalarının ortalama yaşı 71.1±9.6 yıl olup %57.4'si kadındı. Ortalama CHA_2DS_2-VASc skoru: 3.4±1.6 idi. Kümülatif olumsuz klinik olay insidansı %6.30/yıl iken geçici iskemik atak, inme, periferik embolizmi içeren embolik olay insidansı %1.26/yıl idi. Major kanama insidansı %2.20/yıl ve mortalite insidansı %0.94/yıl idi.

Sonuç: Bu kayıt çalışması dabigatran etexilate'ın Türkiye'deki güncel güvenlik ve etkinlik verilerine genel bir bakış sağlamıştır. Çalışmamızdaki tromboemboli ve kanama oranları diğer faz 3 ve gerçek yaşam kayıt çalışmaları ile benzerdir. Ancak gerçek yaşam şartlarında dikkat çekici oranlarda gereksiz düşük doz dabigatran etexilate kullanımı görülmüştür.

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Correspondence: Cihan Altın, M.D., Department of Cardiology, Başkent University School of Medicine, İzmir, Turkey
Tel: +90 532 465 43 09 e-mail: drcihanaltin@hotmail.com

Atrial fibrillation (AF) is one of the leading causes of major cardiovascular events, including stroke, heart failure, and mortality, globally.[1] The prevalence of AF has been reported as 1% to 2% in the Turkish population, which is similar to the prevalence reported in epidemiologic studies conducted in the rest of the world.[2]

The main step of AF management is to reduce cardiovascular mortality and morbidity, which are commonly related to thromboembolic events, particularly ischemic stroke.[3-6] Oral anticoagulant use is the mainstay therapy in the prevention of thromboembolic events. Vitamin K antagonists (VKAs), which have several drawbacks such as a narrow therapeutic window, food and drug interactions, and labile pharmacodynamics effects, have been the treatment of choice for this indication until the development of novel oral anticoagulants (NOACs).[6] NOACs have predictable pharmacodynamic effects and have improved the safety to effectiveness ratio and convenience compared with VKAs.[7] Recent guidelines recommend NOACs including direct thrombin inhibitor dabigatran etexilate and factor Xa inhibitors over VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis) for stroke prevention.[8,9]

The pivotal phase 3 NOAC trials[10-13] showed that NOACs were at least noninferior or superior to warfarin in preventing stroke and systemic embolism with lower risks of serious bleeding. Therefore, recently, their clinical use has been dramatically increased in daily practice. The first NOAC, dabigatran etexilate, was approved by the US Food and Drug Administration in 2010 and is now available in most countries, including Turkey. Although its effectiveness and safety have been demonstrated in a large randomized controlled clinical trial,[10] the trial may not reflect real-world clinical settings because of the inclusion of highly selected patients as well as standardized trial protocols with closer monitoring. Thus, the trial may have low external validity, and the results should be validated in real-life settings. Postmarketing safety studies and pragmatic clinical trials as well as observational studies are needed to overcome these limitations.

To date, no prospective, observational, postmarketing registry have been conducted in Turkey to assess the effectiveness and safety of dabigatran etexilate in patients with AF. Therefore, this study aimed to obtain the safety and effectiveness of dabigatran etexilate in real-life conditions with a prospective, multicenter, postmarketing observational study.

METHODS

Study design

The rationale and design of the D-SPIRIT registry have been published previously.[6] The D-SPIRIT registry is the first national, multicenter, postmarketing, observational study with a prospective design to evaluate patients with AF who have already been receiving dabigatran etexilate therapy.

The study was approved by the Dokuz Eylül University Ethics Committee of Clinical Research (2014/54) and was conducted between August 1, 2015, and January 1, 2016. Written informed consent was obtained from all study participants.

Study population

The study was conducted in outpatient cardiology clinics of university, private, and training and research hospitals. Consecutive patients with AF (aged ≥18 years) who had been receiving dabigatran etexilate therapy for at least 6 months were included in the study. Patients could either be in sinus rhythm or AF at the time of enrollment. The diagnosis of AF; initiation and posology of dabigatran etexilate therapy; modification, maintenance, or discontinuation of the therapy; and the management and treatment of the related adverse events and complications were entirely the responsibility of the clinician. The D-SPIRIT project was an observational project and, as in any observa-

Abbreviations:

AF	*Atrial fibrillation*
CEC	*Clinical events committee*
CI	*Confidence interval*
DE	*Dabigatran etexilate*
GARFIELD-AF	*Global Anticoagulant Registry in the Field-Atrial Fibrillation*
GLORIA-AF	*Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation*
mEHRA	*Modified European Heart Rhythm Association*
NOAC	*Novel oral anticoagulant*
NOAC-TURK	*New Oral Anticoagulants-Turkey*
OR	*Odds ratio*
RAMSES	*Real-life Multicenter Survey Evaluating Stroke Prevention Strategies*
RE-LY	*Randomized Evolution of Long-Term Anticoagulation Therapy*
STROBE	*Strengthening the Reporting and Observational studies in Epidemiology*
TIA	*Transient ischemic attack*
VKA	*Vitamin K antagonist*
XANTUS	*Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation*

tional study, patients were managed according to local medical practice. The goals of the study were mirroring the real-life data and improving the external validity as much as possible. To avoid potential bias, improve external validity, and allow for projection of real-life data in a clear manner, the exclusion criteria were limited to the absence of informed consent and the persistent failure of a patient to comply with the protocol and study procedures.[6]

Demographic, clinical, and laboratory characteristics of study participants were obtained through the survey database. The survey included questions about stroke and other embolic adverse events-related risk factors such as coronary heart disease, hypertension, diabetes mellitus, previous stroke, congestive heart failure, and vascular diseases. Patients were followed up for 2 years to evaluate the effectiveness and safety of dabigatran etexilate in patients with AF. A detailed visit calendar, which was previously given in a design article of the D-SPIRIT registry,[6] is summarized in a Supplementary Table 1. Adverse clinical events that are listed below were recorded as clinical outcomes during the study period.

- Stroke (hemorrhagic, ischemic, and uncertain classification)
- Transient ischemic attack (TIA)
- Systemic embolism
- Pulmonary embolism
- Myocardial infarction
- Major bleeding (life-threatening bleeding events)
- Death of unknown cause (nonvascular and vascular death)

Stroke and thromboembolism risks were assessed using the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or TIA, vascular disease, age 65-74 years, sex category) score. Stage IV-V chronic kidney disease were defined as glomerular flow rate of 15-30 mL/min and >30 mL/min, respectively. According to the International Society on Thrombosis and Hemostasis criteria, major bleeding is defined as a fall of at least 2 g/dL in hemoglobin levels; conditions requiring 2 or more units of whole blood or erythrocyte transfusion; or symptomatic bleeding in a critical organ or area, such as intracranial, intraocular, intraspinal, retroperitoneal, intra-articular, pericardial, and intramuscular bleeding, leading to compartment syndrome or fatality. Minor bleeding is defined as any bleeding other than major bleeding that is considered to be related to the use of NOACs.

The proper posology of dabigatran etexilate was defined as follows:

- For patients who are older than 80 years or with moderate chronic renal disease (creatinine clearance of 30-49 mL/min), high risk of bleeding, or concomitant use of verapamil therapy, 110 mg twice a day.
- For all the other patients, 150 mg twice a day.

Under or overtreatment usage of dabigatran etexilate is described as given below:

- Overtreatment: Usage without an indication (male patients with CHA_2DS_2-VASc score of 0 and/or females with CHA_2DS_2-VASc score of 1) or inappropriate overdosing according to the summary of product characteristics (overdosing).
- Undertreatment: Inappropriate underdosing according to the summary of product characteristics (underdosing).

Statistical analysis

Statistical analyses were performed using SAS (Version 9.4) (Cary, NC 27513-2414, USA) software. The demographic information of the patients was summarized according to the type of data using descriptive statistics (n, mean, standard deviation, median, the difference between percentiles) or frequency distribution (n and percentage). Baseline demographic, clinical characteristics, and adverse events were summarized according to the type of data using descriptive statistics (n mean, standard deviation) or frequency distribution (n and percentage). Annual event rates were obtained by dividing the number of events in question by the average annual number of patients who were followed up during the study. To determine the factors affecting undertreatment, multiple logistic regression analysis was used. Significance level was accepted as 0.05.

RESULTS

Although the enrollment of 600 patients with AF was planned, only 326 patients from 9 different centers

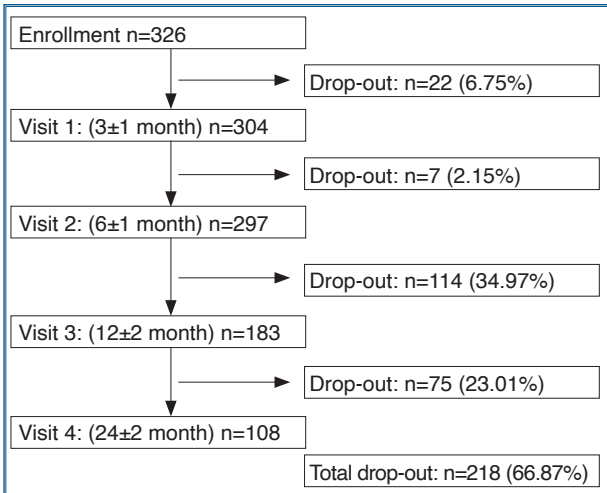

Figure 1. Dropouts and flowchart of the study.

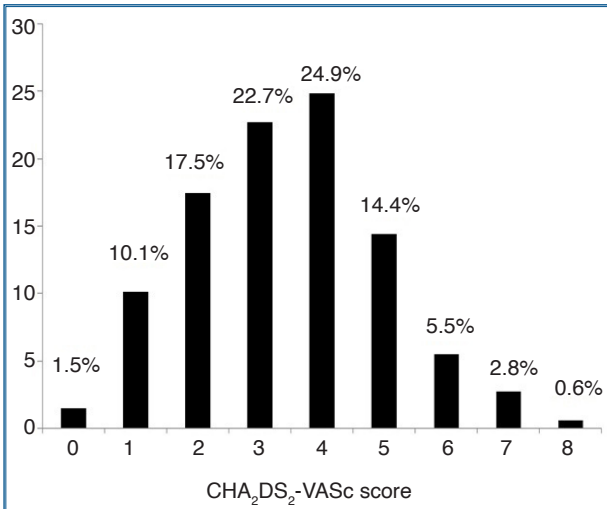

Figure 2. The distribution of the CHA_2DS_2-VASc score.
CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65-74 years, sex category.

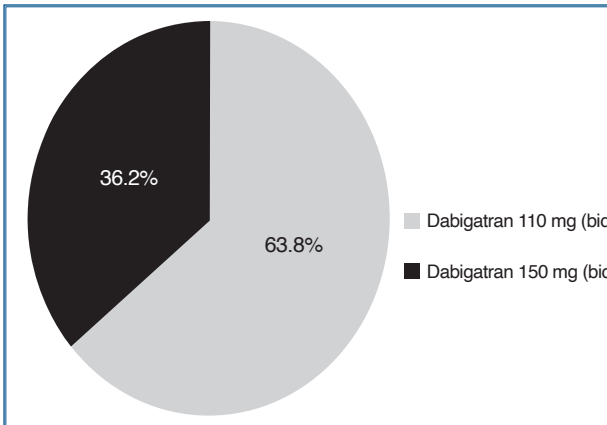

Figure 3. Dabigatran doses.

were recruited because of the slow recruitment process. The Strengthening the Reporting and Observational studies in Epidemiology (STROBE) flow diagram of the study is given in Figure 1.

The baseline demographic and clinical characteristics of patients are summarized in Table 1. The mean age was 71.1±9.6 years, and 57.4% of the study participants were female. Common comorbidities were hypertension (75.8%, n=247), diabetes mellitus (27.6%, n=90), dyslipidemia (21.2%, n=69), and heart failure (16.9%, n=55). In addition, 18% (n=58) of the population had a previous history of stroke and 2.5% of them had a previous history of malignancy.

The mean CHA_2DS_2-VASc score was 3.4±1.6 and the distribution of the score in the study population is detailed in Figure 2. The most common AF patterns were permanent AF (70.6%, n=230) and paroxysmal AF (18.7%, n=61). The current rhythm was sinus rhythm in 95% of patients with paroxysmal AF. AF patterns and the current symptom situation of the population are shown in Table 2. The rate of the previous cardioversion history was 2.1% (n=7). Furthermore, 7 patients (2.2%) had undergone pacemaker implantation and only 2 (0.6%) had a history of AF ablation. Most patients were previously receiving VKAs before the initiation of dabigatran etexilate therapy (81.6%, n=266). About 18.4% of patients were OAC naïve, and dabigatran etexilate was the first oral anticoagulant they had taken. Twelve patients (3.7%) had history of previous antiplatelet therapy for stroke prevention. The rate of previous hemorrhage history was 17.5% (n=57).

Clinical outcomes

The cumulative incidence of adverse clinical events was 6.30% (20 events) per year (Table 3). These adverse clinical events were observed in 16 patients (4.9%), which indicates that some patients experienced more than 1 clinical event. Mortality rate was 0.94% per year (n=3). One death was recorded in the second visit, and 2 deaths were recorded in the fourth visit.

The rate of cumulative thromboembolic events, including TIA, stroke, and peripheral embolism, was 1.26% (4 events) per year. Major bleeding rate was 2.2% (7 events) per year. The most common type of bleeding was gastrointestinal bleeding (57.1%, n=4). About 2 or more units of erythrocyte suspension re-

Table 1. Baseline demographic and clinical characteristics of our study population

Variables	All patients (n=326)
Age (years)	71.1±9.6
Body mass index	29.0±4.9
Systolic blood pressure (mmHg)	125.1±17.8
Diastolic blood pressure (mmHg)	75.9±12.8
Serum creatinine (mg/dL)	0.9±0.3
CHA_2DS_2-VASc score (mean±standard deviation)	3.4±1.6
Female sex, n (%)	187 (57.4)
Smoking, n (%)	
Current smoker	33 (10.1)
Ex-smoker	77 (23.6)
Nonsmoker	212 (65.0)
Unknown	4 (1.2)
Alcohol intake, n (%)	
>Once in a week	6 (1.8)
<Once in a week	31 (9.5)
Never	284 (87.1)
Unknown	5 (1.5)
Medical history, n (%)	
Hypertension	247 (75.8)
-Uncontrolled	30 (9.2)
Coronary artery disease	86 (26.4)
Chronic heart failure	55 (16.9)
Ejection fraction <%40	21 (6.4)
Ejection fraction >%40	34 (10.4)
Cerebrovascular event	58 (17.8)
Ischemic stroke	45 (13.8)
Transient ischemic attack	39 (12.0)
Diabetes mellitus	90 (27.6)
Hyperlipidemia	69 (21.2)
Stage IV-V chronic kidney disease (eGFR <30 mL/min)	0 (0)
Chronic lung disease	43 (13.2)
Liver diseases	1 (0.3)
Other arterial embolism	3 (0.9)
Pulmonary embolism	3 (0.9)
Deep vein thrombosis	4 (1.2)
Peripheral artery disease	9 (2.8)
Hyperthyroidism	28 (8.6)
Malignancy	8 (2.5)
Chronic gastrointestinal diseases	90 (27.6)
Posology of dabigatran, 110 mg bid	208 (63.8)
Posology of dabigatran, 150 mg bid	118 (36.2)
Underuse of dabigatran for treatment	98 (30.4)
Overuse of dabigatran for treatment	22 (6.8)
Previous hemorrhage history	
Before the diagnosis of AF	16 (4.9)
After the diagnosis of AF	41 (12.6)
Hemorrhage under the treatment of:	
VKA	29 (8.9)
Antiplatelet	3 (0.9)
Dabigatran etexilate	8 (2.5)
Requirement of intervention for bleeding	1 (0.3)
Bleeding in critical organs*	1(0.3)
Bleedings lead to reduce hemoglobin <2 g/dL (1.24 mmol/L)	8 (2.5)
Bleedings requires 2 or more units of erythrocyte suspensions	5 (1.5)

*Intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular leads to compartment syndrome.
AF: atrial fibrillation; CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65-74 years, sex category; eGFR: estimated glomerular filtration rate; VKA: vitamin K antagonist.

placements were needed in 28.6% (n=2) of the patients, and none of them needed 4 or more erythrocyte suspension replacement or inotrope agent therapy. No bleeding in critical organs, including intracranial bleeding, was recorded.

From a posology perspective, 208 (63.8%) patients received dabigatran 110 mg twice a day, and 118 (36.2%) of patients received 150 mg twice a day (Figure 3). The rate of usage of additional antiplatelet therapy was 2.2% (7 patients). The rates of undertreatment and overtreatment were 30.4% and 6.8%, respectively. In a multiple logistic regression analysis among variables including age, sex, risk groups of the CHA_2DS_2-VASc score, coronary artery disease, chronic heart failure, diabetes mellitus, previous

Table 2. Patterns and clinical symptoms of atrial fibrillation in our study population

Patterns of atrial fibrillation	n	%
Paroxysmal	61	18.71
Persistent	18	5.52
Long-standing persistent	15	4.63
Permanent	230	70.55
Clinical symptoms		
Asymptomatic (mEHRA)	228	69.94
Symptomatic	98	30.06
Minimal (mEHRA 2a/b)	61	62.24
Effects daily activities (mEHRA 3)	31	31.63
Disabling (mEHRA 4)	4	4.08
NA	2	2.04

mEHRA: modified European Heart Rhythm Association; NA: not applicable.

Table 3. The incidence of clinical outcomes during the study period

Clinical outcomes	n	Event per year (%)
Transient ischemic attack	1	0.31
Stroke	2	0.63
Bleeding	7	2.20
Myocardial infarct	4	1.26
Other arterial embolism	2	0.63
Pulmonary embolism	1	0.31
Death	3	0.94
Total	20	6.30

hemorrhage history, chronic gastrointestinal diseases, cerebrovascular event history, and serum creatinine, only age (odds ratio [OR]=0.92, confidence interval [CI]=0.88-0.95) and cerebrovascular event history (OR=2.55, CI=1.07-6.11) were found to be independent predictors of undertreatment (Table 4).

DISCUSSION

Although dabigatran etexilate has been routinely used as an anticoagulant for 9 years, D-SPIRIT is the first national, prospective, observational, post-marketing registry conducted in Turkey. The most comprehensive data regarding the effectiveness and safety of dabigatran were obtained from the Randomized Evolution of Long-Term Anticoagulation Therapy (RE-LY) trial,[10] a study in which Turkey was a participant. The RE-LY trial[10] includes 18,113 patients with mean $CHADS_2$ score of 2.1 who were followed up for 2 years. Regarding primary composite outcomes of stroke and systemic embolism, dabigatran etexilate at 110 mg twice a day was noninferior (1.54% per year) to warfarin (1.71% per year), whereas dabigatran etexilate at 150 mg twice a day (1.11% per year) was found to be superior to warfarin. In the group receiving 110 mg of dabigatran, the rate of major bleeding was observed to be 2.71% per year, and in the group receiving 150 mg of dabigatran, it was observed to be 3.11% per year. The mortality rate was 3.75% per year in patients taking 110

Table 4. Multiple logistic regression analysis to determine independent predictors of underuse of dabigatran etexilate for treatment

	Odds ratio	Confidence interval (95%)	
Age	0.918	0.883	0.954
Sex (male)	1.081	0.586	1.994
CHA_2DS_2-VASc score (moderate vs low risk)*	0.768	0.174	3.396
CHA_2DS_2-VASc score (high vs low risk)*	1.262	0.271	5.866
Coronary artery disease	1.316	0.668	2.593
Chronic heart failure	0.738	0.305	1.786
Chronic gastrointestinal diseases	1.708	0.869	3.356
Previous hemorrhage history	1.086	0.304	3.871
Diabetes mellitus	0.656	0.329	1.308
Cerebrovascular event	2.552	1.066	6.108
Serum creatinine	0.603	0.253	1.437

*CHA_2DS_2-VASc score was classified as follows: 0=low risk, 1=moderate risk, ≥2=high risk.
CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 years, sex category.

Table 5. Comparison of baseline characteristics, medical history, and clinical outcomes of D-SPIRIT patients with randomized controlled trials and other observational studies

Variables	D-SPIRIT	RE-LY[10]	RE-LY[10] 110 mg	RE-LY[10] 150 mg	NOAC-TURK[17]	RAMSES[18]	GLORIA-AF[15]	Aslan et al.[20] 110 mg	Aslan et al.[20] 150 mg
Number	326	18,1113	6015	6076	2862	6273	4859	96	124
Age (years)	71.1±9.6	71.5±8.7	71.4±8.6	71.5±8.8	70.3±10.2	69.6±10.7	70.2±10.4	76 (47-90)	61 (26-79)
CHA_2DS_2-VASc	3.4±1.6				3.4±1.4	3.3±1.6	3.2±1.5	4 (1-9)	3 (0-7)
$CHADS_2$		2.1±1.1	2.1±1.1	2.2±1.2					
Female, n (%)	187 (57.4)	6599 (36.4)	2150 (35.7)	2236 (36.8)	1731 (60.5)	3504 (56)	2154 (44.3)	59 (61.5)	60 (48.4)
Medical history, n (%)									
Hypertension	247 (75.8)	14,283 (78.8)	4738 (78.8)	4795 (78.9)	2320 (81.1)	4305 (69)	3,768 (77.5)	65 (67.7)	76 (61.3)
Coronary artery disease	86 (26.4)	3005 (16.6)	1008 (16.8)	1029 (16.9)		1828 (29)	928 (19.1)	13 (13.5)	15 (12.1)
Chronic heart failure	55 (16.9)	5793 (32.0)	1937 (32.2)	1934 (31.8)	765 (26.7)	1386 (22)	1,168 (24.0)	27 (28.1)	25 (20.2)
Previous cerebrovascular event	58 (17.8)	3623 (20.0)	1195 (19.9)	1233 (20.3)	326 (11.4)	845 (13.5)	765 (15.7)	37 (38.5)	43 (34.7)
Diabetes mellitus	90 (27.6)	4221 (23.3)	1409 (23.4)	1402 (23.1)	568 (19.8)	1389 (22)	1,104 (22.7)	29 (30.2)	37 (29.8)
Hyperlipidemia	69 (21.2)				1070 (37.4)				
Pulmonary embolism and deep vein thrombosis	7 (2.1)				66 (2.3)				
Peripheral artery disease	9 (2.8)				177 (6.2)				
Malignancy	8 (2.5)				58 (2.0)				
DE regimen and rate (%)	DE110: 63.8% DE150: 36.2%	DE110: 33% DE 150: 33%	DE110: 100%	DE150: 100%	DE: 38.1%	DE: 18%	DE: 32%	DE110: 100%	DE150: 100%
Clinical Outcomes, event/year (%)									
Transient ischemic attack	0.31				0.6				
Stroke	0.63		1.44	1.02	0.6		0.65	5.2	0.8
Major bleeding	2.20		2.71	3.11	7.6		0.97	2.1	3.2
Myocardial Infarct	1.26		0.72	0.74			0.50	0	0
Other arterial embolism	0.63		0.09	0.1	1.3		0.04		
Pulmonary embolism	0.31		0.12	0.15	0.1			2.1	0
Death	0.94		3.75	3.64			2.48	1	0

CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65-74 years, sex category; DE: dabigatran etexilate.

mg of dabigatran and 3.64% per year in patients taking 150 mg of dabigatran. The RE-LY trial showed that administration of a low dose was associated with similar rates of stroke and systemic embolism to warfarin with lower rates of major hemorrhage, whereas administration of a high dose was associated with lower rates of stroke and systemic embolism but with similar rates of major hemorrhage.

In our study, the rate of embolic complications was 1.26% per year, major bleeding was 2.20% per year, and mortality was 0.94% per year in patients with a mean CHA_2DS_2-VASc score of 3.4. We observed lower rates of stroke, major bleeding, and death in our study than in the RE-LY trial.[10] Although reporting bias, higher dropout rates, lack of event adjudication may play a role in the differences between the rates; these event rates may confirm the safety and effectiveness of dabigatran in clinical practice. Direct comparisons of incidence rates in D-SPIRIT and RE-LY can be misleading because of the differences in study design (randomization), conduction, outcome evaluation (PROBE vs survey records only), and patient characteristics. The RE-LY study[10] was a phase 3 trial and there were important limitations in adapting its results to a real-life setting. Unlike phase trials that require regular visits and close follow-ups, drug adherence may not be sufficiently high in real-life patients in routine clinical practice. D-SPIRIT registry did not have a clinical events committee (CEC) or an outcome adjudication committee. Clinical outcome adjudications and submissions were conducted by researchers.

Similar to our results, the rates of major bleeding and stroke were found to be low in a real-life trial such as the Xarelto for Prevention of Stroke in Patients with Atrial Fibrillation (XANTUS) trial[14] than in trials such as the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF).[10] XANTUS is the first large, international, prospective study describing the use of rivaroxaban for stroke prevention in a broad AF patient population. In this study, there were 6784 patients with a mean age of 71.5 years (41% were female). The mean $CHADS_2$ and CHA_2DS-VASc scores were 2.0 and 3.4, respectively. Major bleeding occurred in 2.1 events per 100 patient-years, death in 1.9 events per 100 patient-years, and stroke in 0.7 events per 100 patient-years. Discrepancies between the phase trials and postmarketing studies in terms of safety and efficacy outcomes were confirmed by some nationwide cohort studies and registries.[14-16]

The Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF)[15] is a large, prospective, global registry that supports our results in terms of long-term safety and effectiveness of dabigatran etexilate over 2 years of observation in patients with newly diagnosed AF. The overall incidence rates per 100 person-years were as follows: stroke, 0.65%; major bleeding, 0.97%; and death, 2.48%. The Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF)[16] is a global observational study of adults with newly diagnosed AF. The 2-year outcomes of 17,162 patients who prospectively enrolled had all-cause mortality, stroke, and major bleeding rates of 3.83, 1.25, and 0.70 per 100 person-years, respectively.

With the exception of a few small-scale retrospective studies, no prospective real-life study that focuses on the safety and effectiveness of dabigatran etexilate has been done in Turkey. The New Oral Anticoagulants-Turkey (NOAC-TURK),[17] Real-life Multicenter Survey Evaluating Stroke Prevention Strategies (RAMSES),[18] and Atrial Fibrillation in Turkey: Epidemiologic Registry (AFTER)[19] are large-scale, important cross-sectional observational studies on Turkish populations. The incidence of embolic events in the present study was observed to be similar or less than these studies.[17-19] The mean age and female dominance in our study were also similar to these previous studies. Hypertension was the most common comorbidity in our study group, similar to these previous observational studies and randomized controlled trials.[10-12,17-19] In contrast to other multinational registries, female dominance and low rates of heart failure were demonstrated in our study population, as seen in most of the Turkish registries. This might have an impact on the interpretation of the results. Dabigatran was the most frequently used NOAC in the NOAC-TURK[16] and RAMSES[17] studies. Similar to our study, a 110 mg dose of dabigatran was more frequently preferred than a dose of 150 mg in these studies. Aslan et al.[20] found that ischemic stroke and all-cause mortality were lower in

the dabigatran group than warfarin in their retrospective study, which included 439 patients. Aslan et al.[20] showed that ischemic stroke rates in the warfarin, dabigatran 110-mg, and dabigatran 150-mg groups were 6.8%, 5.2%, and 0.8%, respectively (p=0.015). Intracranial hemorrhage rate was 2.7% in the warfarin group compared with 2.4% in the 150-mg dabigatran group (p=0.104). In this study, death from any cause was 4.6% in the warfarin group compared with 1.0% in the 110-mg dabigatran group (p=0.005).

Comparison of the baseline characteristics and clinical outcomes of D-SPIRIT registry patients with randomized controlled trials and observational studies is given in Table 5.

Inappropriate underdosing according to the summary of product characteristics is common in our study population, as seen in previous national studies.[17,18,21] In a study including results of the RAMSES study,[21] among 2086 patients, 1247 (59.8%) were treated with the recommended dose, whereas 634 (30.4%) patients were undertreated and 205 (9.8%) patients were overtreated. Previous registries showed detrimental results of inappropriate NOAC underdosing.[22,23] In a study conducted by Yao et al.,[24] among 13,392 patients with no indication for dose reduction, 13% received lower-than-standard doses. They showed underdosing of apixaban was associated with a 5-fold higher stroke risk, compared with standard dosing; however, there was a similar risk for major bleeding. Dose reductions of dabigatran and rivaroxaban were not associated with changes in the risks for stroke or bleeding. Similarly, in our study, despite the high rate of underdosing dabigatran, embolic complications were found to be low.

The use of low-dose dabigatran in patients who are at risk of hemorrhage is reasonable. However, a post hoc analysis of the RE-LY trial showed better outcomes with dabigatran etexilate usage that is in accordance with EU label.[25] In the PROPER study, Basaran et al.[26] investigated the potential misuse of NOACs and the effect of adherence to the current recommendations in a real-world setting, using the large data set from the RAMSES study in Turkey. Similar to the D-SPIRIT population, among 1015 patients receiving dabigatran, 626 (61.7%) were receiving 110 mg, and undertreatment ratio was found to be 27% in the subgroup analysis.[26] These results are very similar to our results. This indicates that underuse of dabigatran is still very common in real life. The prescribing patterns of physicians may be influenced by the fear of bleeding events. However, underuse and the lack of adherence to recent guidelines may lead to adverse clinical outcomes. Therefore, a greater emphasis should be given to prescribe the recommended dose.

Pharmacogenetic factors are valid for each drug and these factors 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 an active metabolite exhibit ethnicity-based 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 metabolites.[27] Moreover, the study demonstrated the need of evaluating the efficacy and safety in clinical events, given the differences. The present study reported on the effectiveness and safety of dabigatran in the Turkish population with AF.

In conclusion, the D-SPIRIT registry as a first national, prospective, multicenter, postmarketing, observational study provided an important overview of the current dabigatran regimens in Turkey. The results validated the conclusion of pivotal phase 3 trials in terms of safety and effectiveness.[10] The D-SPIRIT registry also indicated considerable rates of underuse of dabigatran etexilate for treatment in real-life settings. The fear of bleeding complications may be associated with the tendency of physicians to underdose. Although there were higher rates of underdosing, rates of embolic complications were not higher than those seen in the pivotal study. However, type II statistical error because of the small sample size could not be ignored.

Limitations

There are several limitations in the present study. First, although the enrollment of 600 patients was planned initially, only a total of 326 patients were included the study because of the slow recruitment process. Type II statistical error due to the small sample size could not be ignored. Second, our study population was limited to only outpatient cardiology clinics and may not reflect all health provider settings such

as in patient and intensive care patients. Third, as an open-label study, the D-SPIRIT is sensitive to numerous biases such as selection bias and recall bias. The study was a single-arm study and determining direct comparative conclusions of the results with VKA or other NOACs therapy was not possible. The study did not have any CEC or outcome adjudication committee. Clinical outcome adjudications and submissions were conducted by researchers. Thus, this was also sensitive to submission bias. Patients agreeing to participate in the study may, to some extent, have self-selected for risks of stroke or bleeding, and conscientious participation and a selection bias based on the intact cognitive function could have arisen with the investigator.

Conclusion

Finally, a high dropout rate was the other main limitation of our study as seen in many real-life studies. The D-SPIRIT registry is an observational study and not funded by industry. As seen in any observational study, the management of patients were entirely the responsibility of the clinician. Patients' visits were done during their routine controls and patients were not forced to visit.

Ethics Committee Approval: Ethics committee approval was received for this study from the Dokuz Eylül University Ethics Committee of Clinical Research (2014/54).

Informed Consent: Written informed consent was obtained from all participants of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - U.Ö.T.; Design - U.Ö.T.; Supervision - U.Ö.T., K.Y.; Resources - U.Ö.T., K.Y.; Materials - C.A., K.Y.; Data Collection and/or Processing - C.A., C.T., N.Ç., O.D., V.Y., E.A., N.B., C.E., N.P., M.E.Ö., E.T., E.İ.T., K.T., U.K.; Analysis and/or Interpretation - C.A., K.Y., U.Ö.T.; Literature Search - C.A., U.Ö.T.; Writing - C.A., K.Y., U.Ö.T.; Critical Revision - K.Y., U.Ö.T.

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Anahtar Kelimeler: Dabigatran eteksilate; atriyal fibrilasyon; gerçek yaşam; Türkiye

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

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