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Persistence With Dabigatran Therapy at 2 Years in Patients With Atrial Fibrillation

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ABSTRACT

BACKGROUND Guidelines recommend long-term oral anticoagulation therapy for stroke prevention in patients with atrial fibrillation (AF). Treatment discontinuation rates in vitamin K antagonist (VKA)-treated patients are high but may be lower with non-VKA oral anticoagulant agents.

OBJECTIVES The goal of this study was to describe and explore predictors of dabigatran etexilate persistence in patients with newly diagnosed AF over 2 years of follow-up.

METHODS Consecutive patients newly diagnosed with AF and ≥1 stroke risk factor were followed up for 2 years. Dabigatran nonpersistence was defined as discontinuation of dabigatran for >30 days. A multivariable Cox regression model included region as well as patient clinical and sociodemographic characteristics to explore predictors of nonpersistence.

RESULTS Eligible patients (N = 2,932) took ≥1 dabigatran dose; their mean age was 70.3 ± 10.2 years, and 55.3% were male. The 2-year probability of dabigatran persistence was 69.2%. Approximately 7% switched to a factor Xa inhibitor and 6% to a VKA. Approximately one-third of dabigatran discontinuations were primarily due to serious or nonserious adverse events. Patients from North America had the highest discontinuation risk, and Latin America had the lowest. Minimally symptomatic or asymptomatic AF and permanent AF were associated with a lower risk for dabigatran nonpersistence. Previous proton pump inhibitor use was associated with a higher risk for dabigatran nonpersistence.

CONCLUSIONS Probability of treatment persistence with dabigatran after 2 years was approximately 70%. Nearly one-half of the patients who stopped dabigatran switched to another oral anticoagulant agent. Patients from North America, and those with paroxysmal, persistent, or symptomatic AF, may be at a higher risk for discontinuing dabigatran. (J Am Coll Cardiol 2017;70:1573–83) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AE = adverse event
AF = atrial fibrillation
CI = confidence interval
HR = hazard ratio
NOAC = non-vitamin K oral anticoagulant
OAC = oral anticoagulant
SAE = serious adverse event
TIA = transient ischemic attack
VKA = vitamin K antagonist

Atrial fibrillation (AF) is the most common cardiac arrhythmia. It is a well-documented independent factor for ischemic stroke (1) that is associated with considerable mortality and morbidity (2–4). Current guidelines recommend long-term oral anticoagulant (OAC) therapy for stroke prevention in patients with AF who are at risk for stroke (5). Until 2010, when dabigatran etexilate, the first non-vitamin K oral anticoagulant (NOAC) became available, vitamin K antagonists (VKAs) were the standard anticoagulation therapy for patients with AF. Although VKAs are effective in preventing strokes, treatment discontinuation rates are pronounced, with only 39% to 60% remaining on VKA treatment after 1 year (6–8).

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Several factors contribute to suboptimal treatment adherence with VKAs. These factors include narrow therapeutic windows that require frequent laboratory monitoring, a variable dose-response relationship, and interactions with food and medications for comorbid conditions. These problems are diminished with NOACs, which have been endorsed as a Class Ia recommendation in the most recent guidelines for managing patients with AF from the European Society of Cardiology (5), as well as the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society (9).

Medication adherence is defined as the accurate intake of medications based on the dose, frequency, and schedule prescribed (10). A closely related concept, and the main target of the present investigation, is medication persistence, defined as "the duration of time from the initiation to discontinuation of therapy" (11). The evidence evaluating the persistence of VKA and NOAC therapies shows highly variable reports of both persistence and medication adherence, with generally better rates of adherence and persistence with NOACs versus VKAs (12).

Adherence and, particularly, persistence are expected to be affected by various factors, including the incidence of adverse events (AEs). Nonetheless, the reasons for treatment nonpersistence (used interchangeably with treatment discontinuation) in patients taking OACs for stroke prevention have not been extensively described, especially in large prospective patient cohorts.

We therefore sought to describe and assess reasons for nonpersistence with treatment, including those related to AEs. The present global, prospective cohort study aimed to describe dabigatran nonpersistence, with or without subsequent treatment with another OAC, in patients receiving dabigatran and enrolled in the GLORIA-AF (Global Registry on Long-term Oral Anti-thrombotic Treatment in Patients with Atrial Fibrillation) registry program between 2011 and 2014.

METHODS

The GLORIA-AF registry program enrolled consecutive adult patients with AF seen in routine clinical practice in 44 countries in 5 regions. Sources used to identify a broad range of potential sites and physicians included professional directories, referrals from selected investigators and national coordinators, and sites that had previously worked with the study sponsor that funded the registry. Sites were selected only on the basis of confirmation that they diagnosed and followed up patients with AF; previous research

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experience was not a prerequisite. Patients were managed according to routine standard practice and were not required to be prescribed any specific OAC or any OAC at all.

Once dabigatran was approved for the indication of stroke prevention in a respective country, countries were immediately approached to start phase II. The time to initiate the study in the countries varied and depended on site identification, regulatory review timelines, and ethical committee reviews at participating sites. Additional details on the design of the GLORIA-AF program have been published previously (13), and baseline characteristics of all eligible patients enrolled in the phase II program have been described elsewhere (14). In phase II of this study, follow-up included only dabigatran-treated patients who were recruited from various outpatient settings, including university and community hospitals as well as specialist and general practice offices. Patients with newly diagnosed documented AF within 3 months of the baseline visit and at least 1 risk factor for stroke according to CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack [TIA], vascular disease, age 65 to 74 years, sex category) criteria (15) were eligible for inclusion into the registry program. Patients with previous VKA therapy for >60 days, AF due to generally reversible causes, and patients with mechanical heart valves were excluded.

Patients who had important protocol violations (e.g., lack of appropriate informed consent, participation in a clinical trial or international registry) or data insufficiently cleaned (i.e., >2 open manual queries) were excluded from analysis. Only patients taking at least 1 dose of dabigatran and who had follow-up data available were included.

Standard electronic case report forms were used to record baseline characteristics, including stroke and bleeding risk factors that constitute the CHA_2DS_2-VASc (15) and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [age ≥65 years], drugs/alcohol concomitantly) scores (16), respectively. Other characteristics included were AF type (paroxysmal, persistent, or permanent), AF-related symptoms based on the European Heart Rhythm Association classification of symptomatic, minimally symptomatic, or asymptomatic (17), antithrombotic treatment, medical history, concomitant medications, and reimbursement status of prescribed OAC. Start and stop dates of antithrombotic therapies and concomitant medications were recorded by the treating physician based on information included in the patient source data records.

THERAPY PERSISTENCE. Index therapy was the treatment prescribed for long-term anticoagulation therapy after the diagnosis of AF and recorded at the baseline visit. At follow-up intervals (approximately 3, 6, 12, and 24 months after baseline), changes to medical conditions, antithrombotic treatment changes, and all serious adverse events (SAEs), interventions, and adverse drug reactions, including major and life-threatening bleeding events, were recorded. The primary and mutually exclusive reasons for discontinuing index dabigatran treatment were also captured. Physicians could choose 1 reason from a pre-specified list that included bleeding events, alcohol intake, dementia, AEs, dyspepsia, hypersensitivity, drug interactions, cost, or "other" if the former options did not apply.

Therapy nonpersistence was defined in 2 ways to characterize the probability of discontinuing the index dabigatran therapy: 1) dabigatran nonpersistence—patients who stop index dabigatran treatment (for >30 days) during the follow-up period or switch to another OAC within 30 days; or 2) dabigatran nonpersistence without switching—subgroup of patients from the first group who stop index dabigatran treatment (for >30 days) and do not start another OAC within 30 days of dabigatran discontinuation.

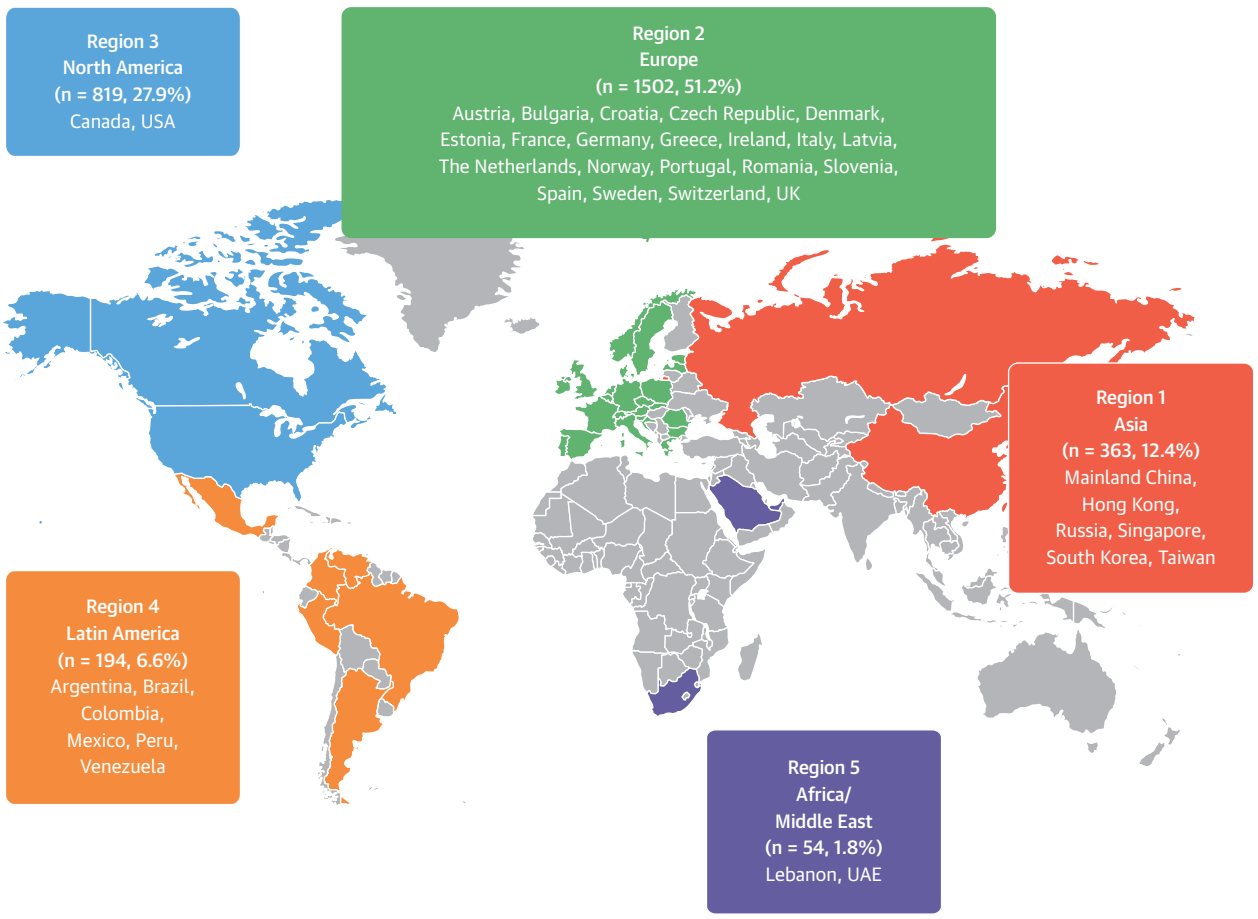
STATISTICAL ANALYSIS. All data were analyzed using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina). Baseline data were summarized descriptively overall, according to region, and for factors related to treatment nonpersistence. Continuous variables were reported as mean ± SD, and categorical variables were reported as absolute frequencies and percentages. In addition, reasons for discontinuation of dabigatran treatment at 2 years were summarized descriptively.

Probabilities of dabigatran persistence were evaluated by using a Kaplan-Meier time-to-event analysis. Dose changes (e.g., lowering dose from 150 mg twice daily to 110 mg twice daily) were not considered as switched treatment because dose adjustments represented part of the antithrombotic therapy management process.

Variables included in the Cox regression models to evaluate risk factors associated with dabigatran discontinuation included region, reimbursement status of medication, and patient clinical and sociodemographic characteristics. Patients were followed up until study withdrawal, death, end of study, or occurrence of dabigatran nonpersistence, whichever came first.

To evaluate whether reclassification of patients who switched treatments after a longer period after dabigatran discontinuation (i.e., >30 days) would

FIGURE 1 Distribution of Patients Initiated on Dabigatran



The heaviest concentration of patients was in Europe, followed by North America. UAE = United Arab Emirates; UK = United Kingdom; USA = United States of America.

change the results, an additional sensitivity analysis was conducted, reclassifying the 28 patients who switched to another OAC following the 30-day period after dabigatran discontinuation.

RESULTS

A total of 3,002 patients were enrolled; 65 were ineligible (2.2%), including 45 who did not meet inclusion criteria or who met exclusion criteria, and 20 who did not meet data cleaning requirements. The main reason for not meeting inclusion criteria was absence of a new AF diagnosis (n = 35). The remainder (n = 10) had AF with a reversible cause, >60 days of warfarin treatment, or exclusionary valve disease. Five patients (0.5%) were prescribed dabigatran but were not treated, producing a total of 2,932 patients eligible for analysis who were prescribed dabigatran and took at least 1 dose. Most patients were enrolled in Europe (51.2%), followed by North America (27.9%); these were the regions in which NOACs were first approved. In regions with later NOAC approvals, fewer dabigatran-treated patients were enrolled: Asia (12.4%), Latin America (6.6%), and Africa and the Middle East (1.8%) (Figure 1).

PATIENT CHARACTERISTICS. Patients' mean age was 70.3 ± 10.2 years, and slightly more than one-half of patients were male. Approximately one-half had paroxysmal AF (n = 1,481; 50.5%), 1,063 (36.3%) had persistent AF, and a minority had permanent AF at the time of enrollment (n = 388; 13.2%). Approximately one-quarter of the patient group had symptomatic AF (26.5%), 46.5% reported minimally symptomatic AF, and 27.0% reported asymptomatic AF.

TABLE 1 Patient Characteristics and Predictors of Nonpersistence

	Previous Stroke/TIA*		PPI Use		AF Type		AF Symptoms		
	Yes (n = 414)	No (n = 2,517)	Yes (n = 572)	No (n = 2,360)	Paroxysmal or Persistent (n = 2,544)	Permanent (n = 388)	Minimally or Asymptomatic (n = 2,155)	Symptomatic (n = 777)	Total (N = 2,932)
Age, yrs	72.6 ± 9.6	69.9 ± 10.2	71.8 ± 9.4	69.9 ± 10.3	69.9 ± 10.2	73.1 ± 9.9	70.5 ± 9.9	69.8 ± 10.9	70.3 ± 10.2
Age ≥75 yrs	184 (44.4)	891 (35.4)	235 (41.1)	841 (35.6)	890 (35.0)	186 (47.9)	780 (36.2)	296 (38.1)	1,076 (36.7)
BMI, kg/m^2†	28.1 ± 5.6	29.4 ± 6.2	29.4 ± 6.2	29.2 ± 6.1	29.3 ± 6.2	28.9 ± 5.6	29.2 ± 6.0	29.4 ± 6.5	29.2 ± 6.1
Male	224 (54.1)	1,395 (55.4)	286 (50.0)	1,334 (56.5)	1,410 (55.4)	210 (54.1)	1,237 (57.4)	383 (49.3)	1,620 (55.3)
MI*	45 (10.9)	203 (8.1)	62 (10.8)	186 (7.9)	215 (8.5)	33 (8.5)	191 (8.9)	57 (7.3)	248 (8.5)
Coronary artery disease‡	102 (24.6)	489 (19.4)	138 (24.1)	454 (19.2)	517 (20.3)	75 (19.3)	441 (20.5)	151 (19.4)	592 (20.2)
Congestive heart failure§	68 (16.4)	664 (26.4)	139 (24.3)	593 (25.1)	591 (23.2)	141 (36.3)	473 (21.9)	259 (33.3)	732 (25.0)
History of hypertension‖	325 (78.5)	1,896 (78.9)	466 (81.5)	1,846 (78.2)	2,003 (78.7)	309 (79.6)	1,699 (78.8)	613 (78.9)	2,312 (78.9)
Diabetes mellitus	93 (22.5)	572 (22.7)	157 (27.4)	508 (21.5)	580 (22.8)	85 (21.9)	503 (23.3)	162 (20.8)	665 (22.7)
CHA_2DS_2-VASc risk score	5.0 ± 1.3	2.9 ± 1.2	3.6 ± 1.5	3.1 ± 1.4	3.2 ± 1.4	3.6 ± 1.4	3.2 ± 1.4	3.3 ± 1.4	3.2 ± 1.4
Previous bleeding event¶	41 (9.9)	106 (4.2)	48 (8.4)	99 (4.2)	133 (5.2)	14 (3.6)	111 (5.2)	36 (4.6)	147 (5.0)
HAS-BLED score#	2.0 ± 0.9	1.1 ± 0.7	1.4 ± 0.9	1.2 ± 0.8	1.2 ± 0.8	1.3 ± 0.8	1.3 ± 0.9	1.2 ± 0.8	1.2 ± 0.8
Renal impairment**	1 (0.2)	11 (0.4)	1 (0.2)	11 (0.5)	10 (0.4)	2 (0.5)	9 (0.4)	3 (0.4)	12 (0.4)
Physician specialty††									
Cardiology	341 (82.4)	2,328 (92.5)	506 (88.5)	2,164 (91.7)	2,325 (91.4)	345 (88.9)	1,934 (89.7)	736 (94.7)	2,670 (91.1)
General practitioner or geriatrician	12 (2.9)	92 (3.7)	24 (4.2)	80 (3.4)	93 (3.7)	11 (2.8)	83 (3.9)	21 (2.7)	104 (3.5)
Internist	6 (1.4)	57 (2.3)	12 (2.1)	51 (2.2)	43 (1.7)	20 (5.2)	54 (2.5)	9 (1.2)	63 (2.1)
Neurologist	46 (11.1)	2 (0.1)	33 (1.4)	2 (0.1)	45 (1.8)	3 (0.8)	47 (2.2)	1 (0.1)	48 (1.6)
Other	9 (2.2)	36 (1.4)	13 (2.3)	32 (1.4)	37 (1.5)	8 (2.1)	35 (1.6)	10 (1.3)	47 (1.6)

Values are mean ± SD or n (%), with percentages expressed as the number of patients with the condition present divided by the total number of patients with data available. *Unknown in 1 patient. †Unknown or missing in 20 patients. ‡Unknown in 74 patients. §Unknown in 32 patients. ‖Unknown in 7 patients. ¶Unknown in 52 patients. #Unknown or missing in 300 patients. **Unknown in 26 patients. ††Unknown in 2 patients.

AF = atrial fibrillation; BMI = body mass index; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (age ≥65 years), drugs/alcohol concomitantly; MI = myocardial infarction; PPI = proton pump inhibitor; TIA = transient ischemic attack.

About one-third of patients were ≥75 years of age, and most were considered at high risk for stroke (CHA_2DS_2-VASc score ≥2 in 88.2% of patients). The majority of patients were considered at low risk for bleeding (HAS-BLED score <3 in 83.5% of patients), and only 5.0% had a previous bleeding event. The majority of patients had a history of hypertension, and 1 in 5 had coronary artery disease. The baseline characteristics of patients according to region and other risk factors for discontinuation are shown in **Tables 1 and 2**.

OVERALL TREATMENT PERSISTENCE. The probability of dabigatran treatment persistence was 76.6% at 1 year and 69.2% at 2 years. This finding was even higher when considering those who remained on dabigatran or discontinued dabigatran to start another OAC within 30 days (i.e., 87.7% at 1 year and 84.1% at 2 years) (**Central Illustration**).

At the end of follow-up, 828 patients had discontinued dabigatran. Of the total 2,932 dabigatran-treated patients, 1,859 remained on dabigatran (63.4%) until study termination, 438 (14.9%) discontinued treatment without switching to another OAC, and 390 (13.3%) switched to another OAC. Baseline characteristics of the patients who remained on dabigatran, discontinued with switching to another OAC, or discontinued without switching are shown in Online Table 1. There were 214 patients (7.3%) who switched to a factor Xa inhibitor, and 176 patients (6.0%) who switched to a VKA; 128 patients (4.4%) were lost to follow-up, and 117 (4.0%) died before the end of follow-up.

REASONS FOR NONPERSISTENCE AT 2 YEARS. Primary reasons given for discontinuing dabigatran treatment are presented in **Table 3**. Among patients discontinuing dabigatran (n = 828), 66 (8.0%) stopped primarily due to dyspepsia and approximately 25% stopped primarily due to other AEs (64 [7.7%] SAEs; 62 [7.5%] nonserious AEs; 58 [7.0%] bleeding events; 22 [2.7%] hypersensitivity to agent; 2 [0.2%] bruising; and 2 [0.2%] due to concomitant medication interactions). The majority of respondents (59.8%) cited "other" (reason not otherwise specified) as the primary reason for discontinuation of dabigatran. Upon further investigation of the proportion of patients who discontinued treatment citing AEs as the primary reason (including bleeding, bruising, dyspepsia, hypersensitivity or interactions with the agent, or other AEs or

TABLE 2 Patient Characteristics According to Geographic Region

	Region					
	Europe (n = 1,502)	North America (n = 819)	Asia (n = 363)	Latin America (n = 194)	Middle East or Africa (n = 54)	Total (N = 2,932)
Age, yrs	70.7 ± 10.0	70.8 ± 10.2	67.1 ± 10.6	71.3 ± 10.1	70.4 ± 9.5	70.3 ± 10.2
Age ≥75 yrs	574 (38.2)	315 (38.5)	88 (24.2)	81 (41.8)	18 (33.3)	1,076 (36.7)
BMI, kg/m^2*	28.6 ± 5.4	30.9 ± 7.3	28.3 ± 5.7	28.3 ± 5.1	29.6 ± 6.1	29.2 ± 6.1
Male	811 (54.0)	484 (59.1)	195 (53.7)	109 (56.2)	21 (38.9)	1,620 (55.3)
MI†	113 (7.5)	86 (10.5)	31 (8.5)	14 (7.2)	4 (7.4)	248 (8.5)
Coronary artery disease‡	237 (15.8)	220 (26.9)	101 (27.8)	21 (10.8)	13 (24.1)	592 (20.2)
Congestive heart failure§	396 (26.4)	132 (16.1)	139 (38.3)	57 (29.4)	8 (14.8)	732 (25.0)
History of hypertension‖	1,145 (76.2)	665 (81.2)	303 (83.5)	151 (77.8)	48 (88.9)	2,312 (78.9)
Diabetes mellitus	318 (21.2)	211 (25.8)	81 (22.3)	36 (18.6)	19 (35.2)	665 (22.7)
CHA_2DS_2-VASc risk score	3.2 ± 1.4	3.2 ± 1.5	3.2 ± 1.4	3.3 ± 1.4	3.6 ± 1.4	3.2 ± 1.4
Previous bleeding event¶	57 (3.8)	64 (7.8)	16 (4.4)	9 (4.6)	1 (1.9)	147 (5.0)
HAS-BLED score#	1.2 ± 0.8	1.4 ± 0.9	1.1 ± 0.8	1.2 ± 0.8	1.2 ± 0.7	1.2 ± 0.8
Renal impairment**	4 (0.3)	6 (0.7)	0 (0.0)	2 (1.0)	0 (0.0)	12 (0.4)
Physician specialty††						
Cardiology	1,447 (96.3)	661 (80.7)	334 (92.0)	175 (90.2)	54 (100.0)	2,670 (91.1)
General practitioner or geriatrician	11 (0.7)	65 (7.9)	15 (4.1)	13 (6.7)	0 (0.0)	104 (3.5)
Internist	10 (0.7)	47 (5.7)	0 (0.0)	6 (3.1)	0 (0.0)	63 (2.1)
Neurologist	8 (0.5)	40 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	48 (1.6)
Other	25 (1.7)	6 (0.7)	14 (3.9)	0 (0.0)	0 (0.0)	47 (1.6)

Values are mean ± SD or n (%), with percentages expressed as the number of patients with the condition present divided by the total number of patients with data available. *Unknown or missing in 20 patients. †Unknown in 1 patient. ‡Unknown in 74 patients. §Unknown in 32 patients. ‖Unknown in 7 patients. ¶Unknown in 52 patients. #Unknown or missing in 300 patients. **Unknown in 26 patients. ††Unknown in 2 patients.

Abbreviations as in Table 1.

SAEs), more than one-half of these discontinuations (58.3%) occurred in the first 6 months. Most individual AEs were reported in the first 6 months, including the following: bleeding events or bruising, 65.0%; dyspepsia, 57.8%; hypersensitivity to agents, 72.7%; and general adverse drug reactions, 62.9%. For SAEs that were not necessarily related to dabigatran, 43.8% were reported in the first 6 months.

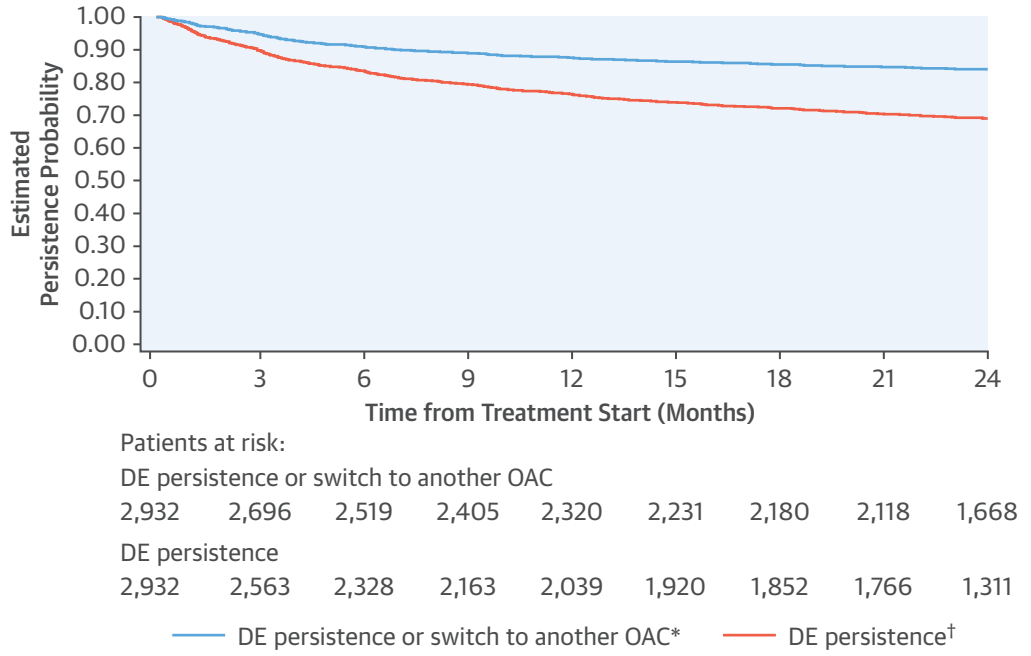
Overall, primary discontinuation due to cost of treatment was reported relatively infrequently, with <3% of all primary reasons for discontinuation cited due to cost (Table 3). When evaluating the main reasons for discontinuation in North America compared with Europe, for example, where we might expect higher rates of reimbursement, the proportion of primary reasons for discontinuation due to cost were not markedly different (North America, 1.0%; Asia, 4.0%; Europe, 3.1%; and Latin America, 0.0%).

Upon further investigation of patients who discontinued treatment with a primary reason documented as "other," only a small proportion of the patients overall (8.1%) had adverse drug reactions or serious AEs that were reported within 30 days before discontinuation (not necessarily related to treatment discontinuation). Furthermore, there were no thromboembolic events observed within 30 days before discontinuation in this group of patients.

PREDICTORS OF TREATMENT PERSISTENCE. Factors associated with dabigatran nonpersistence were region, type of AF, type of site, categorization of AF, physician specialty, and previous proton pump inhibitor use (Table 4). In particular, patients in North America were at higher risk of dabigatran discontinuation (hazard ratio [HR]: 1.66; 95% confidence interval [CI]: 1.35 to 2.04) compared with those in Europe, and patients in Latin America were at lower risk (HR: 0.61; 95% CI: 0.40 to 0.90). Patients with asymptomatic or minimally symptomatic AF were more likely to be persistent compared with symptomatic patients. Those with permanent AF were similarly less at risk for nonpersistence versus those with paroxysmal or persistent AF, as were patients followed up by a primary care physician compared with those followed up at a community hospital. Previous proton pump inhibitor use was predictive of dabigatran nonpersistence (HR: 1.26; 95% CI: 1.04 to 1.51).

Patients who were enrolled at a specialist's office had a similar risk for discontinuation compared with those at a community hospital (HR: 0.99; 95% CI: 0.80 to 1.23); however, patients enrolled at a university hospital did not seem to be markedly at higher risk of discontinuation (Table 4). Other factors included in the model are shown in Online Table 2.

CENTRAL ILLUSTRATION **Therapy Persistence With DE: Kaplan-Meier Curve of Time to Treatment Discontinuation Over 2 Years**



Paquette, M. et al. J Am Coll Cardiol. 2017;70(13):1573–83.

This study explored predictors of dabigatran etexilate (DE) persistence in patients with newly diagnosed atrial fibrillation over 2 years of follow-up. The probability of dabigatran treatment persistence was 76.6% at 1 year and 69.2% at 2 years. All eligible patients are represented, excluding those prescribed but not treated with DE. *Persistence was even higher in those patients who remained on DE or switched to another oral anticoagulant (OAC). †Patients remaining on DE are considered persistent, and patients who switch or discontinue are considered nonpersistent.

PATIENTS WITHOUT SWITCH TO ANOTHER OAC. Region was the strongest predictor of nonpersistence without switch, with North America having the greatest risk of dabigatran nonpersistence. In this subgroup analysis, patients in Asia had similar rates of discontinuation as Europe but were at higher risk of discontinuing without switching (HR: 1.64; 95% CI: 1.20 to 2.21) (Table 4). Latin America and the Middle East (including South Africa) had the lowest risk of dabigatran nonpersistence in this subgroup versus Europe. The main clinical variables associated with a lower risk of dabigatran nonpersistence without switch in the Cox model were previous stroke or TIA and permanent AF versus paroxysmal or persistent AF. Previous myocardial infarction was associated with a higher risk of nonpersistence, as was treatment at a university hospital compared with a community hospital. Other factors included in the model are shown in Online Table 2.

The sensitivity analysis considering patients as switchers if they had started another OAC after

TABLE 3 **Reasons for Discontinuation of DE Treatment at 2 Years**

	Patients Who Discontinued DE and Did Not Use Another OAC After Stopping (n = 438)	Patients Who Switched From DE to Another OAC Within 30 Days* (n = 390)	Total (N = 828)
Other†	285 (65.1)	210 (53.8)	495 (59.8)
Dyspepsia	10 (2.3)	56 (14.4)	66 (8.0)
Adverse events‡	27 (6.2)	35 (9.0)	62 (7.5)
Serious adverse events‡	43 (9.8)	21 (5.4)	64 (7.7)
Bleeding events	40 (9.1)	18 (4.6)	58 (7.0)
Hypersensitivity to agent	6 (1.4)	16 (4.1)	22 (2.7)
Cost of treatment	10 (2.3)	9 (2.3)	19 (2.3)
Social reason (drug, alcohol abuse)	7 (1.6)	6 (1.5)	13 (1.6)
Bruising	0 (0.0)	2 (0.5)	2 (0.2)
Bridging therapy start	7 (1.6)	2 (0.5)	9 (1.1)
Dementia	2 (0.5)	2 (0.5)	4 (0.5)
Severe interaction with concomitant medication	1 (0.2)	1 (0.3)	2 (0.2)

Values are n (%). *Data are missing for 12 patients who switched from DE to another OAC. †Reason was not specified. ‡Does not include adverse events listed in the table.

DE = dabigatran etexilate; OAC = oral anticoagulant.

TABLE 4 Main Predictors of DE Nonpersistence

	N	DE Nonpersistent Patients (n = 828)	Adjusted HR* (95% CI)	DE Nonpersistent Patients Without Subsequent OAC† (n = 438)	Adjusted HR* (95% CI)
Region					
Europe	1,502	383 (25.5)	Ref.	187 (12.5)	Ref.
North America	819	303 (37.0)	1.66 (1.35–2.04)	156 (19.0)	1.53 (1.15–2.03)
Asia	363	101 (27.8)	1.18 (0.92–1.50)	72 (19.8)	1.64 (1.20–2.21)
Latin America	194	30 (15.5)	0.61 (0.40–0.90)	17 (8.8)	0.62 (0.35–1.03)
Africa or Middle East	54	11 (20.4)	0.72 (0.36–1.27)	6 (11.1)	0.86 (0.33–1.84)
Categorization of AF					
Symptomatic	777	248 (31.9)	Ref.	132 (17.0)	Ref.
Minimally symptomatic or asymptomatic	2,155	580 (26.9)	0.78 (0.66–0.91)	306 (14.2)	0.84 (0.67–1.05)
Previous TIA or stroke					
No or missing	2,518	726 (28.8)	Ref.	398 (15.8)	Ref.
Yes	414	102 (24.6)	0.84 (0.66–1.06)	40 (9.7)	0.66 (0.46–0.93)
Type of AF					
Paroxysmal or persistent AF	2,544	749 (29.4)	Ref.	401 (15.8)	Ref.
Permanent AF	388	79 (20.4)	0.73 (0.56–0.93)	37 (9.5)	0.66 (0.46–0.93)
PPIs					
No	2,360	640 (27.1)	Ref.	350 (14.8)	Ref.
Yes	572	188 (32.9)	1.26 (1.04–1.51)	88 (15.4)	1.04 (0.80–1.36)
Type of site					
Community hospital	866	220 (25.4)	Ref.	105 (12.1)	Ref.
University hospital	635	187 (29.4)	1.16 (0.94–1.44)	100 (15.7)	1.35 (1.00–1.81)
Specialist office	1,065	332 (31.2)	0.99 (0.80–1.23)	182 (17.1)	1.31 (0.97–1.76)
GP or primary care	226	51 (22.6)	0.71 (0.50–0.98)	31 (13.7)	1.10 (0.70–1.69)
Outpatient health care or anticoagulation clinic	117	31 (26.5)	0.88 (0.57–1.31)	17 (14.5)	0.89 (0.49–1.51)
MI					
No or missing	2,684	748 (27.9)	Ref.	395 (14.7)	Ref.
Yes	248	80 (32.3)	1.10 (0.81–1.47)	43 (17.3)	1.43 (0.95–2.11)
CHA_2DS_2-VASc score class					
High (score ≥2)	2,587	715 (27.6)	Ref.	365 (14.1)	Ref.
Moderate (score = 1)	345	113 (32.8)	1.13 (0.88–1.45)	73 (21.2)	1.31 (0.94–1.80)
Age class					
<75 yrs	1,856	536 (28.9)	Ref.	303 (16.3)	Ref.
≥75 yrs	1,076	292 (27.1)	0.95 (0.80–1.12)	135 (12.5)	0.84 (0.66–1.06)
Congestive heart failure					
No or missing	2,200	639 (29.0)	Ref.	325 (14.8)	Ref.
Yes	732	189 (25.8)	0.96 (0.80–1.15)	113 (15.4)	1.16 (0.92–1.46)
History of hypertension					
No or missing	620	183 (29.5)	Ref.	93 (15.0)	Ref.
Yes	2,412	645 (26.7)	0.90 (0.75–1.08)	345 (14.3)	1.01 (0.79–1.31)
Coronary artery disease					
No or missing	2,340	646 (27.6)	Ref.	352 (15.0)	Ref.
Yes	592	182 (30.7)	1.05 (0.84–1.30)	86 (14.5)	0.79 (0.57–1.06)

Continued on the next page

remaining untreated for >30 days (28 patients identified) yielded similar results.

DISCUSSION

In this prospective assessment of clinical practice data from a global registry program, overall dabigatran persistence in an incident AF population was high, with the probability of remaining on dabigatran treatment after 1 year at approximately 75% and approximately 70% after 2 years. Of clinical importance, about one-half of those patients who discontinued treatment during follow-up did not start another OAC within 30 days, leaving patients at risk for stroke at least in the early period after initial discontinuation. To our knowledge, this trial was the

TABLE 4 Continued

	N	DE Nonpersistent Patients (n = 828)	Adjusted HR* (95% CI)	DE Nonpersistent Patients Without Subsequent OAC† (n = 438)	Adjusted HR* (95% CI)
Chronic gastrointestinal diseases					
No or missing	2,526	690 (27.3)	Ref.	359 (14.2)	Ref.
Yes	406	138 (34.0)	1.08 (0.87–1.33)	79 (19.5)	1.25 (0.94–1.64)
Medical treatment reimbursed by					
Statutory or federal insurance	1,999	559 (28.0)	Ref.	283 (14.2)	Ref.
Private insurance	578	183 (31.7)	1.06 (0.88–1.29)	96 (16.6)	1.06 (0.81–1.38)
Self-pay, no coverage, or unknown	355	86 (24.2)	1.01 (0.78–1.28)	59 (16.6)	1.24 (0.90–1.66)
BMI, kg/m^2					
<30	1,832	518 (28.3)	Ref.	279 (15.2)	Ref.
≥30	1,080	307 (28.4)	0.95 (0.81–1.12)	158 (14.6)	0.84 (0.67–1.04)
DE monotherapy vs. combination					
DE monotherapy	2,539	704 (27.7)	Ref.	360 (14.2)	Ref.
DE combination	393	124 (31.6)	1.00 (0.80–1.25)	78 (19.8)	1.27 (0.95–1.70)

Values are n or n (%), unless otherwise indicated. A total of 333 patients from other types of site or having missing values for BMI or HAS-BLED score were excluded from the multivariable analyses. *Adjusted HRs were estimated from a multivariable Cox model including all variables listed in this table and in Online Table 2. †Represents patients who discontinue DE but do not start another OAC within 30 days.

CI = confidence interval; GP = general practice; HR = hazard ratio; Ref. = reference group; other abbreviations as in Tables 1 and 3.

first global, prospective study cohort describing regional differences in persistence patterns, specifically with an NOAC (dabigatran).

PUBLISHED STUDIES OF OAC PERSISTENCE. Previous evaluations of persistence have consistently shown relatively poor persistence with warfarin treatment, with 1-year discontinuation rates ranging from approximately 25% (18,19) to >60% (7). Some studies defined discontinuation as a treatment gap of 45 to 60 days, a definition less stringent than the one used here (30 days). Comparing persistence across studies is difficult, because even those focused on the same OAC may differ with respect to the patient populations, study designs, and definitions of nonpersistence.

In XANTUS (Xarelto for Prevention of Stroke in Patients with Atrial Fibrillation), another prospective registry of patients treated with the NOAC rivaroxaban, persistence over a 1-year period was high, with discontinuation rates of approximately 20% (20). A database study by Jackevicius et al. (21), which evaluated NOAC treatment persistence, defined nonpersistence as >14-day gaps between prescriptions. Persistence was described at 6-month follow-up, and approximately one-third of patients were nonpersistent to dabigatran and rivaroxaban. This population was considerably older, had a higher prevalence of comorbidity, and did not represent an incident AF population, with just over one-half of the population having a history of warfarin use. Importantly, in this study, the risk of stroke, TIA, or death was significantly higher in those nonpersistent to dabigatran or rivaroxaban compared with those who were persistent.

Better persistence with NOACs may stem from better overall acceptance of NOAC therapies, resulting from a lower burden of monitoring and fewer food and drug interactions compared with VKAs. Conversely, it also could be posited that persistence with NOACs could be less favorable due to fewer overall visits with health care providers, resulting in fewer opportunities to have the importance of treatment persistence emphasized.

It has been shown that risk of discontinuation is highest in the early period after treatment initiation (6 months to 1 year), after which discontinuation rates level off or decline more gradually (18,19,22). Therefore, studies evaluating treatment persistence for only limited periods after treatment initiation might not accurately predict the discontinuation rates over the long term. Persistence should thus be measured directly for at least a period of 1 year or longer where possible.

REASONS FOR DISCONTINUATION. The data from this analysis suggest that the reasons for discontinuation of treatment are complex and might not be fully explained solely by examining adverse drug reactions such as bleeding or other AEs. Approximately one-third of all reasons for primary dabigatran discontinuation were cited as due to an AE or SAE.

The majority of primary reasons cited for treatment discontinuation or switch were "other"; that is, not related to AEs or SAEs or to AEs associated with OAC treatment, such as bleeding or dyspepsia. A separate analysis in this group of patients found only a small number of AEs reported within 30 days before discontinuation, confirming that the responses indicated under the other reasons for discontinuation did not seem to include adverse events.

There might be an influence of patient or physician preference, potentially a higher perceived risk for outcomes that prompted changes in treatment, or other factors that were not directly explored. Indeed, in a review of adherence to NOACs, the importance of the patient's perspective was emphasized for making decisions around anticoagulant choice (23), and these preferences could also have strong implications for treatment persistence or switching to an alternative OAC.

PREDICTORS OF TREATMENT DISCONTINUATION. In the present study, clinical factors predicted which patients were most likely to discontinue dabigatran treatment, with or without switching to an alternative OAC. The multivariable analyses showed that factors such as region (North America) and previous proton pump inhibitor use might be associated with dabigatran nonpersistence. Measures that might be markers of disease severity, such as permanent AF, were associated with persistence.

This pattern was also seen in predictors of the subgroup that discontinued dabigatran but did not switch to another OAC within 30 days. In this group, which better reflects those who are at risk of complications stemming from lack of prophylaxis, the factors associated with a lower risk of nonpersistence included permanent AF (vs. paroxysmal or persistent AF) and previous stroke or TIA. Previous myocardial infarction was also associated with a higher risk of nonpersistence. Patients from Asia and North America had a higher risk of nonpersistence with dabigatran compared with patients from Europe.

Treatment-related AEs, such as dyspepsia or hypersensitivity reactions, were a more prevalent reason for switching than for discontinuing treatment. In cases of discontinuation without switching, SAEs and bleeding events were more often cited compared with those who switched, suggesting that patients who have more serious OAC-related side effects would more often remain untreated.

Clinical factors such as permanent AF, previous stroke, and low symptom burden, all associated with treatment persistence, might be important clinical surrogates for disease severity. Physicians might provide more vigorous reminders or directives regarding the importance of OACs in stroke prevention for patients with these markers, or patients themselves could be more committed to remaining on treatment after experiencing a previous stroke or TIA or experiencing more longstanding episodes of AF. Longer episodes of AF duration could, indeed, relate to the perception that a higher AF burden increases stroke risk and, thus, influence patients to remain on OAC therapy.

STUDY LIMITATIONS. To our knowledge, this study was the first prospective study to describe regional differences in persistence patterns. These regional differences might be secondary to differences in clinical standards, patient preferences, or patient management. Of note, the predictors of increased risk for treatment nonpersistence seemed to relate to factors associated with lower disease severity and to geographic differences.

Our study had several limitations that should be noted. Patients consented to participate in the study, and physicians were aware that persistence to treatment would be recorded, potentially modifying behaviors (i.e., the Hawthorne effect) (24). There could be increased attention from the treating physician, influencing patients to remain on treatment. Also, patients more likely to have good adherence might agree to participate in a registry, resulting in higher overall rates of treatment persistence.

Patients were not followed up in the VKA group in this phase of the registry, which limited our ability to make comparisons. Another limitation was that only 1 primary reason was ascertained for treatment discontinuation. Furthermore, for a large proportion of patients, no specific information on the reason for discontinuation was available, as the "other" category of reason for discontinuation was chosen without an option for additional free field text. Finally, phase II started later in certain regions (Latin America, Africa and the Middle East), which are therefore less well represented in the data.

CONCLUSIONS

In this analysis of patients newly diagnosed with AF, we found evidence for long-term persistence with dabigatran, with an approximately 30% probability of discontinuing index dabigatran treatment after 2 years. About one-half of those who discontinued dabigatran received another OAC within 30 days. Most of the primary reasons noted for treatment discontinuation did not directly relate to AEs, which implies that other factors, such as perceived

thromboembolic and bleeding risks or patient preferences, might play an important role in decisions to persist with treatment. Surrogate markers of AF severity, such as permanent AF, were associated with a lower risk of treatment discontinuation, suggesting that patients without these characteristics might be an important group to target to increase treatment persistence.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

Persistence with OAC therapy in patients with AF is a barrier to achieving optimum clinical outcomes. Long-term persistence with dabigatran was high, with approximately 70% remaining on treatment after 2 years. Factors associated with discontinuation of dabigatran included region (North America and Asia with the highest risk compared with Europe), high AF symptom burden, paroxysmal or persistent rather than permanent AF, previous use of proton pump inhibitor inhibitors, and absence of previous stroke or TIA.

TRANSLATIONAL OUTLOOK: Future studies should evaluate reasons for discontinuing OAC therapy over time in patients with AF to develop interventions that improve treatment persistence.

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KEY WORDS discontinuation, non-VKA oral anticoagulant, oral anticoagulation, stroke prevention, vitamin K antagonist

APPENDIX For supplemental tables, please see the online version of this article.