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Dabigatran Persistence and Outcomes Following Discontinuation in Atrial Fibrillation Patients from the GLORIA-AF Registry

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Prospective studies evaluating persistence to nonvitamin K antagonist oral anticoagulants in patients with atrial fibrillation are needed to improve our understanding of drug discontinuation. The study objective was to evaluate if and when patients with newly diagnosed atrial fibrillation stop dabigatran treatment and to report outcomes following discontinuation. Patients prescribed dabigatran in diverse clinical practice settings were consecutively enrolled and followed for 2 years. Dabigatran persistence over time, reasons for discontinuation, and outcomes post discontinuation were assessed. Of 4,859 patients, aged 70.2 ± 10.4 years, 55.7% were male. Overall 2-year dabigatran persistence was 70.9% (95% confidence interval [CI] 69.6 to 72.2). Persistence probability was lower in the first 6-month period (83.7% [82.7 to 84.8]) than in subsequent periods for patients on dabigatran at the start of each period (6 to 12 months, 92.5% [91.6 to 93.3]; 12 to 18 months, 95.1% [94.3 to 95.8]; 18 to 24 months, 96.3% [95.6 to 96.9]). Of 1,305 patients (26.9%) who discontinued dabigatran, adverse events were reported as the reason for discontinuation in 457 (35.0%). Standardized stroke incidence rate post discontinuation (per 100 patient-years) in patients discontinuing without switching to another oral anticoagulant was 1.76 (95% CI 0.89 to 2.76) and 1.02 (95% CI 0.43 to 1.76) in those who switched, consistent with the expected benefit of remaining on treatment. Patients persistent with treatment at 1 year had >90% probability of remaining persistent at 2 years suggesting clinical interventions to improve persistence should be focused on the early period following treatment initiation. **(Am J Cardiol 2020;125:383−391)**

Atrial fibrillation (AF) is well recognized as an important independent risk factor for stroke.[1] Although current guidelines recommend long-term oral anticoagulation (OAC) for stroke prevention in AF patients with at least 1 additional stroke risk factor,[2] high rates of OAC discontinuation have posed a barrier to achieving optimal outcomes. Discontinuation has been especially noteworthy in the era before the availability of nonvitamin K antagonist OACs (NOAC) with 1-year discontinuation rates exceeding 50%[3−5]; and investigations examining persistence or adherence have

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Drs Huisman and Lip are co-chairs of the GLORIA-AF registry, and Dr Nieuwlaat is principal supervisor of this analysis; all 3 are joint senior authors.

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See page 390 for disclosure information.

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primarily been based on claims databases,[6,7] national health registers,[8–11] or commercial databases.[12] Although some evidence indicates discontinuation rates may be lower with NOACs versus vitamin K antagonists,[5,7,13] periods of risk and reasons for NOAC discontinuation remain poorly understood. Reasons for early discontinuation may differ from reasons patients discontinue after more enduring periods of stable treatment and this information may be informative for clinicians implementing management strategies to address the important clinical barrier of treatment persistence. The objectives of this analysis from a large prospective global registry of clinical practice settings were to investigate in newly diagnosed AF patients initiating dabigatran: treatment persistence over 2 years; predictors of discontinuation; reported reasons for discontinuation as a function of time; and stroke, bleeding, and mortality outcomes following discontinuation.

Methods

Analyses were conducted using data from phase 2 of the GLORIA-AF registry program (registered at https://clinicaltrials.gov/ct2/home NCT01468701; NCT01671007; NCT01937377) whereby newly diagnosed AF patients from various outpatient settings (including hospitals and specialist and general practice offices) from 44 countries and 5 regions were prospectively and consecutively enrolled at 982 sites between 2011 and 2014 (Figure 1). Patients with at least 1 additional stroke risk factor (CHA_2DS_2-VASc[14] criteria, including female gender) were eligible for inclusion; patients with >60 days of previous vitamin K antagonist use were excluded. Patients prescribed dabigatran per routine clinical practice who took at least 1 dose were followed for 2 years, with the last patient follow-up visits conducted in December 2016. Baseline data only were collected for those prescribed other anticoagulation therapies in phase 2. Further details on the GLORIA-AF registry design have been previously published,[15] and clinical characteristics of all patients enrolled to phase 2 have been reported.[16] Patients provided informed consent and the study was approved by research ethics boards where required.

Baseline characteristics, including stroke and bleeding risk factors used to calculate CHA_2DS_2-VASc[14] and HAS-BLED[17] scores, as well as AF type (paroxysmal, persistent, and permanent), AF-related symptom burden based on the European Heart Rhythm Association classification,[18] antithrombotic treatment, medical history, concomitant medications, and reimbursement status of prescribed OAC, were collected, and follow-up occurred approximately 3, 6, 12, and 24 months after baseline. Changes to medical conditions, serious adverse events (SAEs), AEs related to any OAC treatment, and start/stop dates of medications (including antithrombotic treatments) were documented. Physicians could choose 1 main reason from a prespecified list for stopping oral anticoagulation treatment including AEs or "other reasons." As physicians could only select 1 reason, they were requested to select the main (and most specific) reason for discontinuation. If there was >1 reason (eg, major bleeding, also classified as an SAE), physicians were requested to select the more specific option—in this case, the bleeding event.

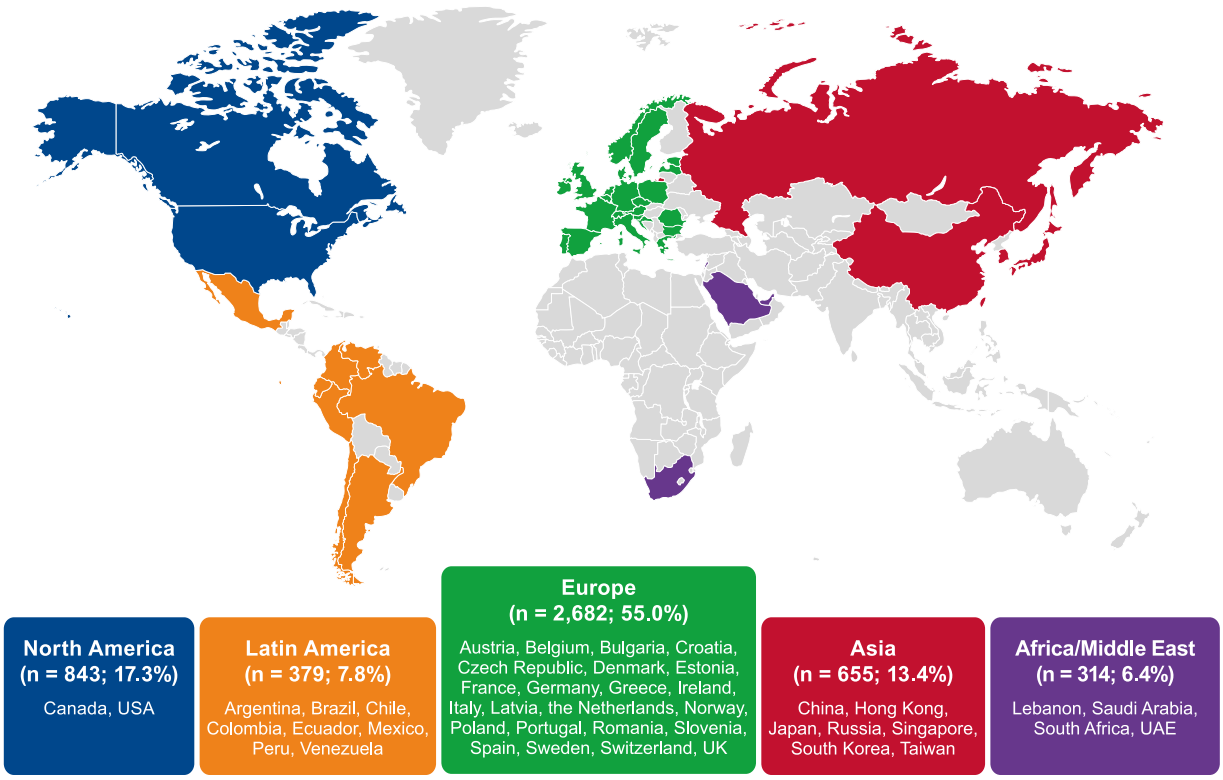

Figure 1. Distribution of GLORIA-AF patients prescribed dabigatran by region. UAE = United Arab Emirates; USA = United States of America; UK = United Kingdom.

Baseline data were summarized descriptively, with continuous variables reported as means (± standard deviation [SD]) and categorical variables reported as absolute frequencies and percentages.

To assess persistence, patients were followed from dabigatran initiation until study withdrawal, death, end of study, or dabigatran discontinuation, whichever came first. Discontinuation was defined as either a switch to another OAC from dabigatran or stopping dabigatran for ≥30 days (to exclude temporary treatment interruptions due to medical procedures [eg, percutaneous coronary intervention]). Dose adjustments were not considered in determination of discontinuation for this analysis. Kaplan-Meier time-to-event analyses were used to calculate probabilities and 95% confidence intervals (CIs) for dabigatran persistence over 2 years and for 6-month increments from the time of treatment initiation (for subsets of patients remaining on treatment at the start of each interval).

Reported reasons for dabigatran discontinuation were summarized descriptively and grouped into events representing AEs or SAEs, and other events (Table 1). Reported reasons for dabigatran discontinuation were described for 4 periods: following treatment initiation (0 to 3 and 3 to 6 months), stabilizing (6 to 12 months), and more enduring treatment (≥12 months). A sensitivity analysis to evaluate the potential effect of misclassifying discontinuation due to AEs/SAEs as "other" reasons was carried out by exploring whether any AEs/SAEs were reported 14 days before discontinuation in this group.

Two Cox regression model approaches were used. To identify overall predictors of dabigatran discontinuation during follow-up, a multivariable Cox regression model, including region and patient clinical and sociodemographic characteristics was used to explore predictors of nonpersistence. Variables included in the model were variables denoting region and patient characteristics such as CHA_2DS_2-VASc score, age, hypertension, categorization of AF, previous transient ischemic attack/stroke, and AF type. Hazard ratios (HR) and 95% CIs were calculated for these predictors. In addition, as patient clinical characteristics may not have constant effect on persistence over time, time-dependent effects of patient clinical characteristics on nonpersistence were evaluated with a separate multivariable Cox regression model that included interactions between covariates and indicator functions of time for the 4 following time intervals: 0 to 3, 3 to 6, 6 to 12, and ≥12 months.

Stroke, major bleeding, vascular, and all-cause death were assessed from discontinuation until end of study in those who discontinued without switching and in those who switched to another OAC within 30 days of discontinuation. Stroke was defined as an acute onset of a focal neurologic deficit of presumed vascular origin, lasting for 24 hours or more, or resulting in death. Major bleeding was defined as overt bleeding associated with a hemoglobin reduction of at least 20 g/L or leading to a transfusion of at least 2 units of blood or packed cells, symptomatic bleeding in a critical area or organ, or life-threatening or fatal bleeding. Incidence rates following discontinuation were standardized using averages of the stratum-specific incidence rates (4 strata using cutoffs for low and moderate HAS-BLED scores and CHA_2DS_2-VASc scores ≤3 or >3), weighted by total patient-years in each. Missing data were handled using multiple imputation to provide unbiased estimates of missing values, with added random error to compensate for the imputed information.[19] The imputation model was constructed upon 54 baseline patient characteristic variables including those used in the multivariable analyses (refer to footnote in Table 2 for information on missing data). Imputed datasets were analyzed separately, and results combined to provide estimates under the missing at random assumption. CIs of standardized incidence rates were constructed using the bootstrap method.[20] SAS version 9.4 (SAS Institute, Cary, NC) was used for all data analyses.

Table 1
Reported reasons for dabigatran discontinuation over 2 years according to time period

Variable	Time (months) after initiation of dabigatran				
	0 to 3 (n = 474)	3 to 6 (n = 282)	6 to 12 (n = 290)	12 to 24 (n = 259)	Total (n = 1305)
All adverse events*	189 (39.9%)	93 (33.0%)	95 (32.8%)	80 (30.9%)	457 (35.0%)
Serious adverse events	49 (10.3%)	17 (6.0%)	26 (9.0%)	25 (9.7%)	117 (9.0%)
Bleeding	39 (8.2%)	20 (7.1%)	14 (4.8%)	15 (5.8%)	88 (6.7%)
Dyspepsia	32 (6.8%)	20 (7.1%)	24 (8.3%)	10 (3.9%)	86 (6.6%)
Hypersensitivity to agents	17 (3.6%)	7 (2.5%)	6 (2.1%)	3 (1.2%)	33 (2.5%)
Severe concomitant medication interaction	4 (0.8%)	1 (0.4%)	2 (0.7%)	1 (0.4%)	8 (0.6%)
Bruising	1 (0.2%)	1 (0.4%)	2 (0.7%)	2 (0.8%)	6 (0.5%)
Other adverse events	47 (9.9%)	27 (9.6%)	21 (7.2%)	24 (9.3%)	119 (9.1%)
Other reasons	285 (60.1%)	189 (67.0%)	195 (67.2%)	179 (69.1%)	848 (65.0%)
Cost of treatment	4 (0.8%)	3 (1.1%)	1 (0.3%)	24 (9.3%)	32 (2.5%)
Bridging therapy start	5 (1.1%)	5 (1.8%)	5 (1.7%)	6 (2.3%)	21 (1.6%)
Social reason (eg, drug/alcohol abuse)	2 (0.4%)	9 (3.2%)	4 (1.4%)	1 (0.4%)	16 (1.2%)
Dementia	1 (0.2%)	2 (0.7%)	1 (0.3%)	0 (0.0%)	4 (0.3%)
Other reasons not specified	266 (56.1%)	167 (59.2%)	178 (61.4%)	145 (56.0%)	756 (57.9%)
Missing reason for switching	7 (1.5%)	3 (1.1%)	6 (2.1%)	3 (1.2%)	19 (1.5%)

Time periods are based on planned visit time (eg, 3 and 6 months). One category (reason for discontinuation) could be selected per patient. Does not include 173 patients who died while on dabigatran.

* As physicians could only select 1 reason, they were requested to select the main (and most specific) reason for discontinuation.

Table 2
Patient characteristics

Variable	Total (n = 4,859)
Age, mean ± standard deviation (y)	70.2 ± 10.4
Age ≥75 years	1,784 (36.7%)
Body mass index, mean ± standard deviation (kg/m^2)*	28.9 ± 5.9
Women	2,154 (44.3%)
Prior stroke†	765 (15.7%)
Prior myocardial infarction‡	426 (8.8%)
Coronary artery disease§	928 (19.1%)
Heart failure‖	1,168 (24.0%)
Hypertension (history)¶	3,768 (77.5%)
Diabetes mellitus	1,104 (22.7%)
CHA_2DS_2-VASC risk score, mean ± standard deviation	3.2 ± 1.5
Prior bleeding#	248 (5.1%)
HAS-BLED score, mean ± standard deviation**	1.2 ± 0.9
Renal impairment††	18 (0.4%)
Permanent atrial fibrillation	626 (12.9%)
Persistent/paroxysmal atrial fibrillation	4,233 (87.1%)
Asymptomatic/minimally symptomatic	1,410 (29.0%)
Symptomatic	3,449 (71.0%)
Physician specialty‡‡	
Cardiology	4,251 (87.5%)
General practitioner/geriatrician	164 (3.4%)
Internist	152 (3.1%)
Neurologist	194 (4.0%)
Other	96 (2.0%)

* Missing: 48 patients.
† Missing: 1 patient.
‡ Unknown: 1 patient.
§ Unknown: 135 patients.
‖ Unknown: 46 patients.
¶ Unknown: 9 patients.
# Unknown: 95 patients.
** Unknown: 506 patients.
†† Unknown: 37 patients.
‡‡ Missing: 2 patients.

Results

A total of 15,308 patients were enrolled from 5 regions, of whom 4,873 were prescribed dabigatran (Figure 1) and the majority (n = 4,859; 99.7%) took ≥1 dose (14 patients who did not take any dose were excluded). The mean number of patients per site was 15.9 (SD ± 18.6) and median was 10 (interquartile range: 17). Baseline characteristics and medical history of patients are shown in Table 2.

The overall probability of dabigatran treatment persistence was 77.5% (CI 76.2% to 78.6%) at 1 year and 70.9% (CI 69.6% to 72.2%) at the end of follow-up (2 years). At end of follow-up, 1,305 patients (26.9%) stopped dabigatran, with 621 (12.8%) switching to another OAC and 684 (14.1%) not starting another OAC within 30 days. Of those switching, 260 (41.9%) switched to a vitamin K antagonist, 358 (57.6%) to a factor Xa inhibitor, and 3 (0.5%) to an antiplatelet drug with bridging therapy.

The evaluation of treatment persistence over time revealed that over half of the total discontinuations occurred in the first 6 months (n = 756; 57.9%). The estimated probability of persistence was lowest in the first 6-month interval following treatment initiation and was successively higher for each subsequent 6-month interval for those on treatment at the start of each respective period (Figure 2). For patients persistent at 1 year, the estimated probability of continuing treatment for an additional year was >90% (2-year persistence conditional on 1-year persistence [95.1 × 96.3]).

In the overall multivariable Cox regression analyses to evaluate predictors of dabigatran persistence, relative to patients in Europe, patients in North America and Asia had higher discontinuation, and patients in Latin America and Africa/Middle East had lower discontinuation (Figure 3). Patients with symptomatic AF, previous bleeding, and proton pump inhibitor (PPI) use had higher discontinuation and those with a higher body mass index (BMI) and previous stroke or transient ischemic attack had lower discontinuation (Figure 3). An increase in BMI of 10 units was associated with a 15% lower rate of discontinuation (HR 0.85 [95% CI 0.77 to 0.94]).

When evaluating predictors of discontinuation by time (0 to 3, 3 to 6, 6 to 12, and ≥12 months; Supplementary Table S1), the effect of symptomatic AF on discontinuation was observed in earlier periods (0 to 3 or 3 to 6 months), but less visible in the later period (≥12 months; HR [95% CI] 1.36 [1.13 to 1.65]; 1.48 [1.15 to 1.89]; 1.07 [0.83 to 1.40], respectively). PPI use was associated with higher risk for discontinuation in the later period (≥12 months) with HR (95% CI) 1.54 (1.17 to 2.06); in the earlier period (0 to 3 months), HR was 1.03 (0.82 to 1.29). The effect of private insurance compared with federal/statutory insurance was associated with greater discontinuation in the later period (≥12 months: HR [95% CI] 1.35 [1.00 to 1.82]), but not in the earlier period (0 to 3 months: 0.98 [0.76 to 1.26]).

Reasons reported for stopping dabigatran over 2 years of follow-up are presented in Table 1 and were further categorized into primary reasons related to AEs (including SAEs) or not related to AEs. These reasons for discontinuation reported to be due to AEs/SAEs were not directly linked to AEs reported in the system. AEs such as bleeding, bruising, dyspepsia, hypersensitivity to agents, or severe interactions with concomitant medication were reported as the reason for discontinuation in approximately a third of cases with the remaining two-thirds being reported as "other reasons" (Table 1).

In the sensitivity analysis examining the extent to which discontinuation with the primary reason documented as "other" (n = 756) followed an SAE or AE/adverse drug reaction within 14 days, 44 (5.8%) had an SAE and 14 (1.9%) an AE/adverse drug reaction in the 14 days before discontinuation.

Patient death was a censoring point for discontinuation, and therefore these patients did not have a reason for discontinuation (n = 173). Of these patients who died, 135 (78.0%) had an SAE within 14 days and 5 (2.9%) had an AE. As these were not reported by treating physicians as due to AEs/SAEs, they were not combined with AE/SAE-attributed discontinuations.

Standardized incidence rates per 100 patient-years for stroke, major bleeding, vascular, and all-cause death following discontinuation are presented for patients who permanently discontinued with and without switching; higher stroke and mortality rates were observed in the latter group (Figure 4). The average follow-up duration was ~1.3 years for different patient groups and different outcomes. For the full cohort of patients evaluated as part of a separate

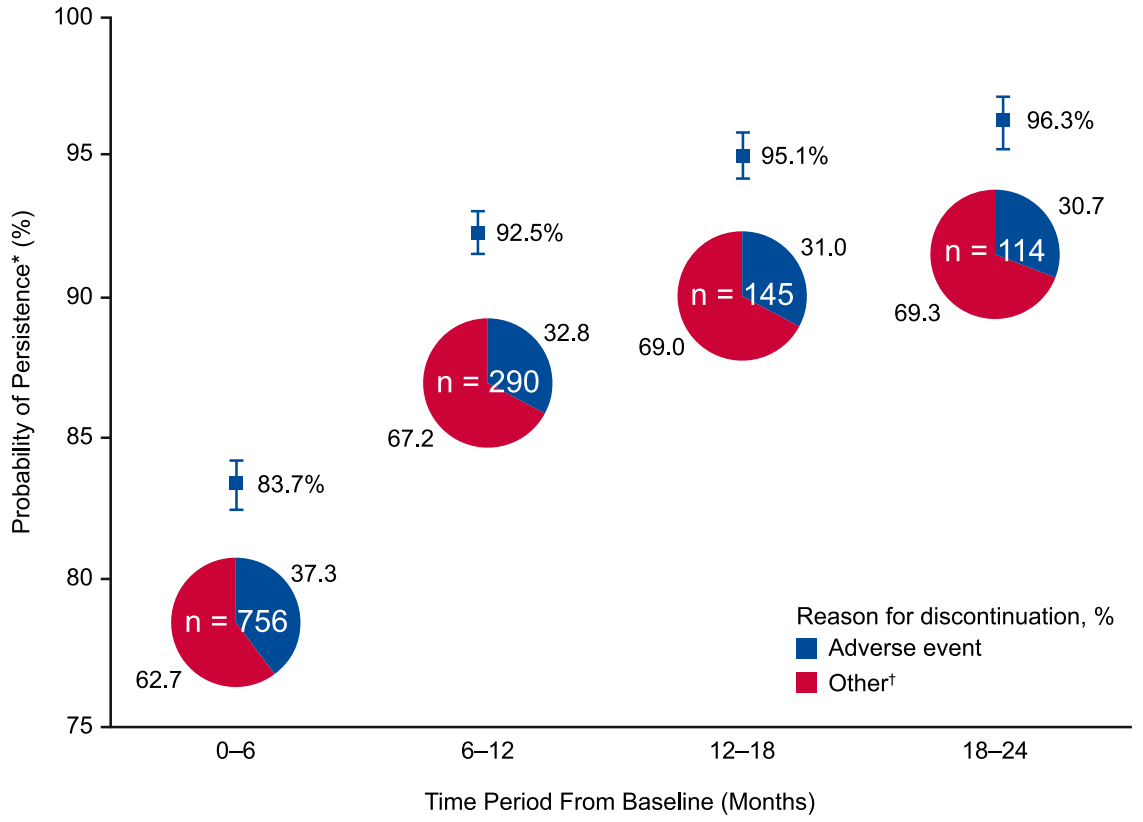

Figure 2. Risk of discontinuation is highest in the early period following dabigatran treatment initiation and most reasons for discontinuation are not due to adverse events. The figure shows probabilities and reasons for dabigatran discontinuation (with or without switching to another oral anticoagulant) over 2 years. *Cumulative incidence of persistence at the end of the time period for patients on treatment at the start of the period are shown as Kaplan-Meier estimates and 95% confidence intervals. †"Other" reasons for discontinuation included cost of treatment, bridging therapy start, social reason (eg, drug/alcohol abuse), dementia, "other" reasons not specified or reason was missing.

investigation, incidence rates for the period on treatment, censored at the point of discontinuation (per 100 patient-years, 95% CI) for stroke, major bleeding, vascular death, and all-cause death were lower than both groups of patients who discontinued (0.65 [0.48 to 0.87], 0.97 [0.76 to 1.23], 0.85 [0.65 to 1.09], and 2.48 [2.13 to 2.87] respectively].[21]

Discussion

This prospective study of patients on dabigatran showed the probability of persistence over 2 years exceeded 70%, which is higher than previously reported persistence rates to warfarin[3,4] and claims-based estimates of persistence to NOACs.[8,10] Furthermore, it was also shown that the greatest risk for discontinuation is in the early period following treatment initiation. There are limited prospective studies of NOAC persistence, and to our knowledge, this is the first investigation in clinical practice settings examining discontinuation over long-term follow-up.

Patients in Asia and North America had greater discontinuation than patients in Europe, and patients in Latin America had less discontinuation. Patients with symptomatic AF, previous bleeding, and PPI use had more discontinuation and those with higher BMI and previous stroke/transient ischemic attack had lower discontinuation. These factors may be related to perceived differences in stroke or bleeding risk factors, or due to AEs.

Patients with certain characteristics may simply be more prone to discontinue earlier, due to factors such as lifestyle, low treatment satisfaction, or poor tolerance among others (ie, patients remaining persistent over time become less susceptible to discontinue; the concept of "depletion of susceptibles"[22]). Closer clinical management in the early period could be warranted to improve commitment to treatment or to help manage side effects and identification of characteristics associated with discontinuation could support targeted interventions in these patients.

Discontinuations attributed to AEs occurred with lower frequency than discontinuations reported due to other reasons. For patients who remained persistent at 1 year, the probability of remaining on treatment for an additional year exceeded 90%, suggesting that this is a period of stable management where less intensive follow-up may be justified, at least in terms of mitigating poor persistence. It may be that once tolerance is established (ie, absence of early AEs), patients are more likely to continue anticoagulation, although AEs alone did not account for the majority of reasons for discontinuation.

The reasons for discontinuation are complex. Fewer than half of all reported reasons for discontinuation were directly related to AEs. Although specific details are not available for these "other" reasons for discontinuation reported by clinicians, they are still informative as they represent discontinuations not attributed to bleeding or other AEs that

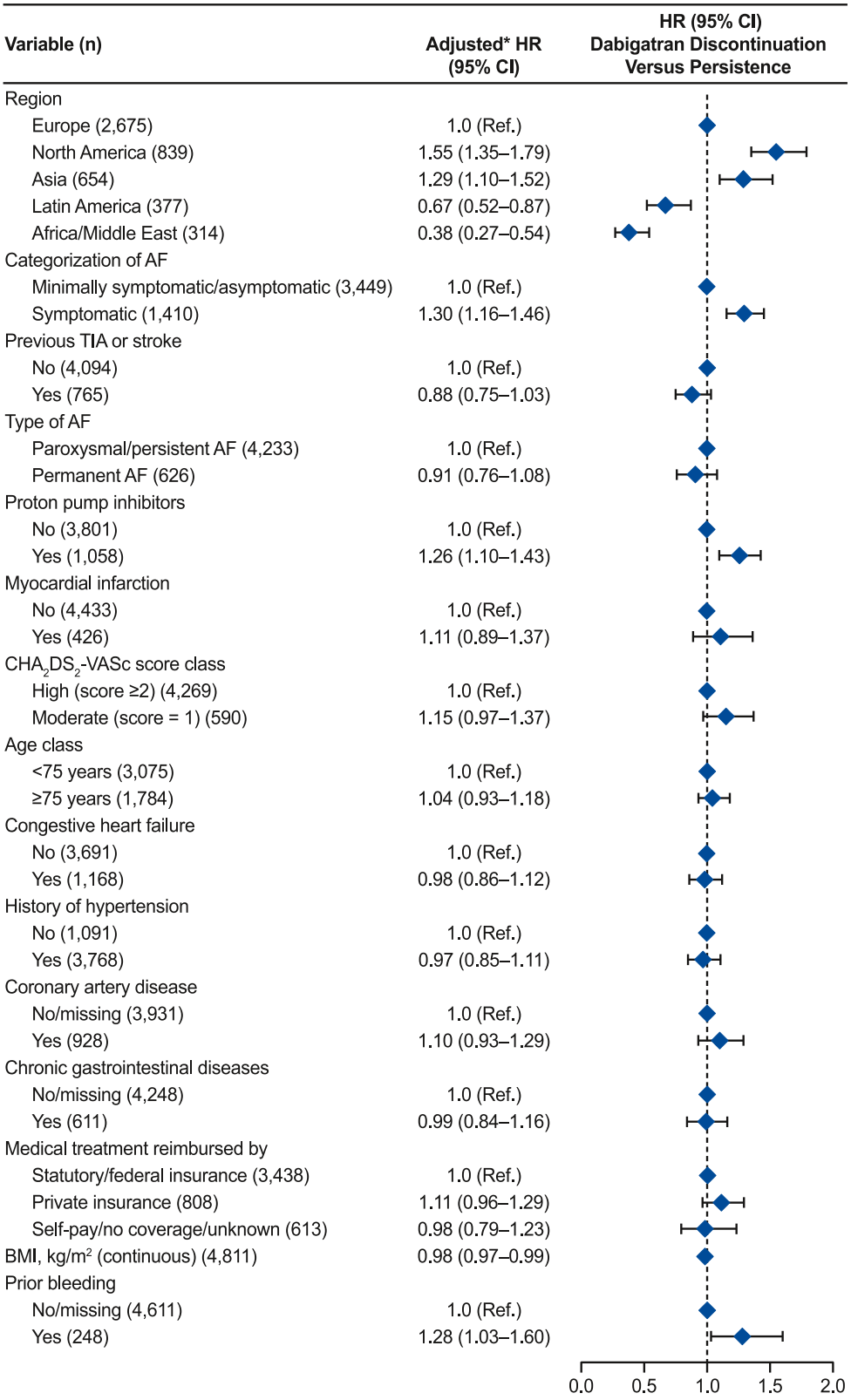

Figure 3. Forest plot of multivariable predictors of dabigatran treatment persistence. Missing data were imputed using a multiple imputation approach (based on the eligible population) before the analysis. *Adjusted HRs were estimated from a multivariable Cox model including all variables listed here. AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; HR = hazard ratio; Ref. = reference; TIA = transient ischemic attack.

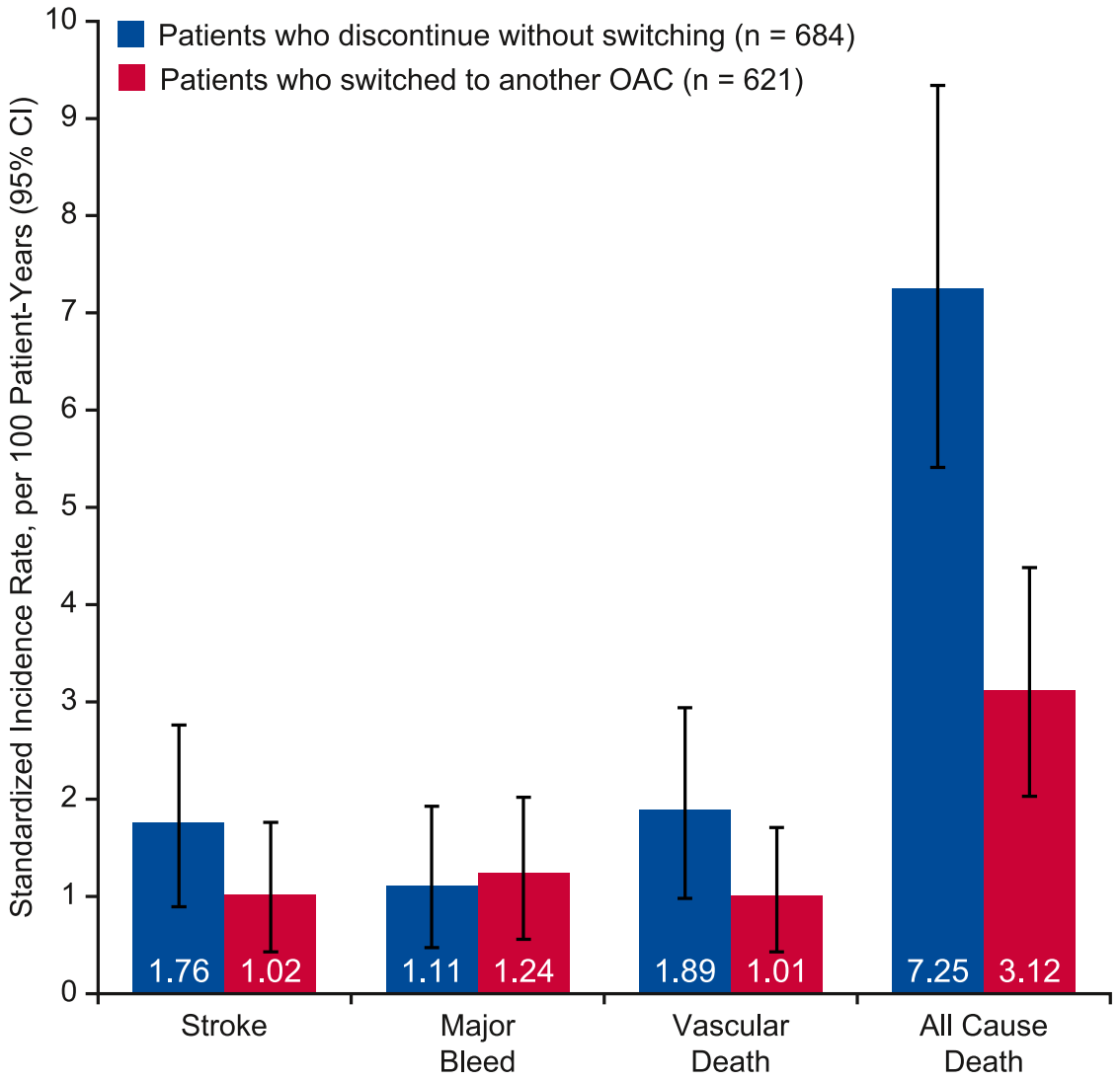

Figure 4. Standardized (by CHA_2DS_2-VASc and HAS-BLED) incidence rates of outcomes in patients who discontinued dabigatran treatment. In case of recurrent events after dabigatran discontinuation, the first event was considered. As death is a competing risk for discontinuation, patients who died without date of discontinuation reported were separately examined. CI = confidence interval; OAC = oral anticoagulant.

would be considered clinically appropriate. This finding has important implications for practice, as well as future research. It remains an open question whether these "other" reasons represent potential opportunities to reduce discontinuations through education or other interventions. These other reasons could relate to patient or physician preference, or perceived higher risk for outcome events that prompt changes in treatment. These are not likely discontinuations prompted through "curative" interventions such as ablation as earlier data in this cohort (presented at the European Heart Rhythm Association [2017]) reported that >90% of interventions were conducted with an uninterrupted anticoagulation regimen.

The importance of the patient's perspective for making decisions around anticoagulant choice has been reported in other studies,[23] and these preferences could also have implications for treatment persistence or switching to an alternative OAC. Furthermore, if patients' knowledge of their AF and risk for thromboembolic outcomes is limited, perceptions surrounding treatment necessity may affect their motivation to continue treatment. Indeed, studies have demonstrated that many patients have poor knowledge of AF and its treatment.[24] There may be an opportunity to improve treatment persistence through education or patient decision aids with shared decision-making.

The incidence of postdiscontinuation stroke, vascular, and all-cause death was higher (albeit with broad 95% CIs) in patients who discontinued without switching to another OAC compared with those who switched, and both groups had higher stroke and mortality outcomes following discontinuation than overall patient outcome rates before discontinuation. This finding is consistent with the expected benefit of remaining on oral anticoagulation and similar to retrospective studies of dabigatran and rivaroxaban prophylaxis.[10] However, it should be noted that the decision not to restart an anticoagulant after discontinuation of dabigatran could have been due to patients being moribund, resulting in higher mortality rates in patients not switching, independent from

the effect of discontinuing OAC use. Although outcome numbers were small, major bleeding rates postdiscontinuation were similar between those discontinuing with or without switching to another OAC.

The use of reported start/stop dates of dabigatran may provide greater accuracy, compared with claims database analyses that rely on prescription fill dates. Furthermore, estimated rates of persistence to NOACs can vary even between studies focused on the same treatment due to differences with respect to patient characteristics, timing of investigation relative to treatment initiation, retrospective compared with prospective evaluations, study design, and definitions of nonpersistence. For example, defining nonpersistence by a treatment gap of 14 days[10] could include temporary discontinuations due to procedures, which has been shown in 1 study to represent almost a quarter of their patient population.[25] As the risk of nonpersistence appears to stabilize within a year following treatment initiation, clinicians may consider this early period most critical for evaluation and intervention.

There are some limitations of this analysis including the fact that data were collected as part of an observational registry, which could modify behavior of both treating physicians and patients based on awareness that data would be reviewed and monitored ("Hawthorne effect"[26]). Despite this, there may be benefits of prospective data collection compared with retrospective database studies in which risk of missing or inaccurate information is common. Furthermore, patients who consent to participate in a study may be more likely to persist with treatment than a general AF population. Notwithstanding this, the diverse selection of clinical practice sites, practitioners, and extensive geographical representation in this study suggest broad clinical applicability of the results. A further notable limitation is that no specific information on the "other" reasons for discontinuation was collected and start/stop dates were used as a surrogate marker for drug intake. Finally, interpretation of incidence rates of outcomes after dabigatran discontinuation according to presence or absence of switch to another OAC is limited by relatively high levels of random error as evidenced by the wide CIs, and potential for unmeasured confounding.

In conclusion, this prospective analysis of newly diagnosed patients with AF showed overall probability of 2-year persistence in patients taking dabigatran was 70.9%. The period of greatest risk for discontinuation was in the first 6 months following treatment initiation, and for those persistent at 1 year, the probability of remaining on treatment for an additional year was >90%. Thus, closer clinical management in the early period following treatment initiation could potentially enhance commitment to treatment, improve management of side effects, and ultimately support better patient outcomes through improved persistence.

Disclosures

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