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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

Professor Diener has received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from Abbott, Allergan, AstraZeneca, Bayer Vital, Bristol-Myers Squibb, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daiichi-Sankyo, D-Pharm, Fresenius, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, Merck Sharp & Dohme, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo Nordisk, Paion, Parke-Davis, Pfizer, Sanofi, Schering-Plough, Servier, Solvay, St. Jude, Syngis, Talecris, Thrombogenics, WebMD Global, Wyeth, and Yamanouchi; has received financial support for research projects from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi, Syngis, and Talecris; and his institution, the Department of Neurology at the University Duisburg-Essen, has received research grants from the German Research Council, German Ministry of Education and Research, European Union, the National Institutes of Health, Bertelsmann Foundation, and Heinz-Nixdorf Foundation. Dr. Dubner has received consultancy fees for serving as a steering committee member for Boehringer Ingelheim; and holds research grants from St. Jude Medical. Professor Ma has received consultancy fees/honoraria from Bayer Healthcare Pharmaceuticals, Bristol-Myers Squibb, Boehringer Ingelheim, Johnson & Johnson, and Pfizer. Dr. Rothman is an employee of RTI Health Solutions, an independent, nonprofit research organization that does work for government agencies and pharmaceutical companies. Dr. Halperin has received consulting fees/honoraria or research support from Bayer HealthCare, Boehringer Ingelheim, Daiichi-Sankyo Pharma, Janssen Pharmaceuticals, Johnson & Johnson, Sanofi, Boston Scientific, Medtronic, and Pfizer. Dr. Nieuwlaat has reported that he has no relationships relevant to the contents of this paper to disclose. 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. Peter R. Kowey, MD, served as Guest Editor for this paper.

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