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Global Prospective Safety Analysis of Rivaroxaban

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ABSTRACT

BACKGROUND The efficacy of direct oral anticoagulants (DOACs) for stroke prevention in patients with atrial fibrillation (AF) has been established in clinical trials. However, well-conducted, prospective, real-world observational studies of the safety and effectiveness of DOACs are needed.

OBJECTIVES This study sought to assess the real-world safety profile of rivaroxaban through a pooled analysis of patients with AF enrolled in the XANTUS (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation) program worldwide.

METHODS A pre-planned pooled analysis of the XANTUS, XANAP (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Asia), and XANTUS-EL (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Latin America and EMEA Region) registries was performed. Patients with AF newly starting rivaroxaban for stroke prevention were followed for 1 year. Primary outcomes were treatment-emergent major bleeding, adverse events (AEs)/serious AEs, and all-cause death. Secondary outcomes included treatment-emergent thromboembolic events and nonmajor bleeding. Major outcomes were centrally adjudicated.

RESULTS Overall, 11,121 patients were included (mean age 70.5 ± 10.5 years; female 42.9%). Comorbidities included heart failure (21.2%), hypertension (76.2%), and diabetes (22.3%). Event rates were: events/100 patient-years: major bleeding 1.7 (95% confidence interval [CI]: 1.5 to 2.0; lowest: Latin America 0.7; highest: Western Europe, Canada, and Israel 2.3); all-cause death 1.9 (95% CI: 1.6 to 2.2; lowest: Eastern Europe 1.5; highest: Latin America, Middle East, and Africa 2.7); and stroke or systemic embolism 1.0 (95% CI: 0.8 to 1.2; lowest: Latin America 0; highest: East Asia 1.8). One-year treatment persistence was 77.4% (lowest: East Asia 66.4%; highest: Eastern Europe 84.4%).

CONCLUSIONS This large, prospective, real-world analysis in 11,121 patients from 47 countries showed low bleeding and stroke rates in rivaroxaban-treated patients with AF, with low treatment discontinuation in different regions of the world. Results were broadly consistent across regions. (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation [XANTUS]; NCT01606995; Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Latin America and EMEA Region [XANTUS-EL]; NCT01800006; and Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Asia [XANAP]; NCT01750788) (J Am Coll Cardiol 2018;72:141–53) © 2018 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
CNS = central nervous system
CrCl = creatinine clearance
DOAC = direct oral anticoagulant
ICH = intracranial hemorrhage
ISTH = International Society on Thrombosis and Haemostasis
MI = myocardial infarction
o.d. = once daily
SAE = serious adverse event
SE = systemic embolism
TIA = transient ischemic attack
VKA = vitamin K antagonist

Atrial fibrillation (AF) is estimated to affect 33.5 million patients worldwide (1). Although often asymptomatic, AF is associated with a major disease burden, including stroke, cardiovascular death, and heart failure, as well as unplanned hospitalizations, which often have cardiovascular causes (2,3). Use of appropriate anticoagulation can greatly reduce the risk of ischemic stroke in patients with AF (4,5), with options including vitamin K antagonists (VKAs) and the direct oral anticoagulants (DOACs) (apixaban, dabigatran, edoxaban, and rivaroxaban). On the basis of the results of large phase III trials that demonstrated the favorable benefit-risk profile of DOACs over VKAs (5–9), various guidelines recommend DOACs as an alternative, or in preference to, VKAs (10,11). DOACs are increasingly used for stroke prevention in patients with AF (12). Real-world evidence complements the results from phase III trials and is important for assessing the safety and effectiveness of approved medications and in obtaining information on patterns of use in routine clinical practice (13).

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The XANTUS program provides a unique source of real-world data on the use of rivaroxaban for stroke prevention in patients with AF. The XANTUS program included 3 prospective studies conducted in 47 countries from different regions of the world, providing a broad spectrum of global data. Patients were enrolled from Western and Eastern Europe, Canada, and Israel in the XANTUS (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation) study, the Asia-Pacific region in the XANAP (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Asia) study, and Eastern Europe, the Middle East, Africa, and Latin America in the XANTUS-EL (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Latin America and EMEA Region) study (14,15). The purpose of this pooled analysis of the XANTUS, XANAP, and XANTUS-EL studies was to assess the global safety profile of rivaroxaban in routine clinical practice.

METHODS

We performed a pre-planned pooled analysis of the studies in the XANTUS program (the XANTUS, XANAP, and XANTUS-EL studies). Detailed methods have been described previously (14,15). The XANTUS, XANAP, and XANTUS-EL studies were international, prospective, observational, noninterventional cohort studies in consenting adult patients (≥18 years of age) with AF initiating rivaroxaban for the prevention of stroke or non-central nervous system (non-CNS) systemic embolism (SE). Patients were prescribed rivaroxaban in accordance with country-specific drug approvals. The label-recommended dose is rivaroxaban 20 mg once daily (o.d.) in patients with creatinine clearance (CrCl) ≥50 ml/min and 15 mg o.d. in patients with CrCl <50 ml/min in all included countries except Taiwan, where either rivaroxaban 15 mg o.d. or 20 mg o.d. can be prescribed for patients with CrCl >50 ml/min and either 10 mg o.d. or 15 mg o.d. can be prescribed for patients with CrCl 15 to 50 ml/min (16,17). In order to limit selection bias, participating investigators were asked to enroll consecutive patients by screening and documenting patients with a diagnosis of AF in an anonymous patient log file. The screening documentation was completed before eligible, consenting patients signed an informed consent form, and it was not permitted for patient-related data to be collected from the remaining ineligible or nonconsenting patients.

Patients were enrolled from 47 countries across 5 regions of the world (Western Europe/Canada/Israel: Austria, Belgium, Canada, Denmark, France, Germany, Ireland, Israel, the Netherlands, Norway,

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