Confidence in the Use of Direct Oral Anticoagulants in the Acute Phase of Nonvalvular Atrial Fibrillation–Related Ischemic Stroke Over the Years: A Real-World Single-Center Study

Federico Moroni, MD,* Luca Masotti, MD,*† Vieri Vannucchi, MD,* Raffaella Chiarelli, RN,* Cristiana Seravalle, MD,* Alessandra Pesci, MD,* Francesca Pallini, MD,* Silvia Puliti, MD,* Barbara Cimolato, MD,* Lamberto Fattorini, MD,* Cornelia Scerra, MD,* Francesca Ristori, MD,* Maria Letizia Imbalzano, MD,* Stefano Spolveri, MD,‡ Giancarlo Landini, MD,* Elisa Grifoni, MD,† and Maurizio Paciaroni, MD§

Backgroud and Aim: The use of direct oral anticoagulants (DOACs) in patients with nonvalvular atrial fibrillation (NVAF)-related acute ischemic stroke (AIS) is controversial. The aims of our study were to analyze physicians' confidence in prescribing DOACs in NVAF-related AIS, the characteristics of patients receiving DOACs, and their 90-day prognosis. *Material and Methods:* Clinical records of consecutive patients admitted to our wards for NVAF-related AIS over the years 2014-2016 were reviewed. *Results:* One hundred forty-seven patients, 72.7% females, mean age ± standard deviation 83.4 ± 8.8 years, were admitted to our ward for atrial fibrillation (AF)-related AIS (38 in 2014, 47 in 2015, 62 in 2016). Of these patients, 141 had NVAF-related AIS. Median length of hospital stay was 8 days (interquartile range [IQR], 6-11). In-hospital mortality was 10.8%. Ninety-eight patients (69.5%) received DOACs for secondary prevention, with increasing percentages from 2014 (62.5%) to 2016 (88%). In 88% of them, DOACs were started during hospital stay, whereas in 12% DOACs were started during ambulatory follow-up. The median time for starting DOACs was 5 days (IQR, 3-8). In patients receiving DOACs, the median National Institutes of Health Stroke Scale score was 6 (IQR, 3-12), and large ischemic lesions were present in 48%; the median modified Rankin Scale score at hospital discharge was 3 (IQR, 1-4), whereas the score at 90 days was 2 (IQR, 1-3). At the 90-day follow-up, in patients receiving DOACs, overall mortality was 3.0%, stroke recurrence was 1%, and no patients had major intracranial or extracranial bleedings. *Conclusion:* Our study suggests that physicians are becoming increasingly confident in the use of DOACs in NVAF-related AIS. The use of DOACs seems effective and safe even when started in the acute phase of stroke. **Key Words:** Stroke—dabigatran—rivaroxaban—apixaban—edoxaban—oral anticoagulants.

From the *Internal Medicine and Center of Thromboembolic Diseases, Santa Maria Nuova Hospital, Florence, Italy; †Internal Medicine, San Giuseppe Hospital, Empoli, Italy; ‡Internal Medicine, Borgo San Lorenzo Hospital, Florence, Italy; and §Stroke Unit and Division of Cardiovascular Medicine, University of Perugia, Italy.

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Address correspondence to Luca Masotti, MD, Internal Medicine, Santa Maria Nuova Hospital, Piazza Santa Maria Nuova 1, 50122 Florence, Italy. E-mail: luca.masotti@tin.it.

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Background

Patients with acute ischemic stroke (AIS) associated with nonvalvular atrial fibrillation (NVAF) have a significant risk of adverse outcomes.[1,2] In order to reduce the risk of stroke recurrence, anticoagulant therapy is recommended as the treatment of choice for secondary prevention.[3] Although vitamin K antagonists (VKAs) have been available for clinical use for 50 years, these drugs have many limitations, such as the slow onset of action requiring overlapping with parenteral anticoagulants, the unpredictable response due to a wide genetic variability and multiple food and drug interactions, a narrow therapeutic window, and the need for routine laboratory monitoring of the International Normalized Ratio (INR).[4] These limitations led to their underuse in clinical practice, also in patients with known NVAF, especially when affected by multiple comorbidities.[5] An Italian multicenter study performed in 2010-2011 showed that VKAs were prescribed at hospital discharge after AIS in only 25.9 % of NVAF-related stroke patients.[6]

Recently, findings from 4 randomized clinical trials on direct oral anticoagulants (DOACs) have been published. Overall, DOACs demonstrated to be not inferior in efficacy and safety compared with warfarin for cardioembolism prevention in NVAF patients.[7] Moreover, DOACs showed a better safety profile compared with warfarin in reducing the incidence of hemorrhagic stroke.[7] All randomized trials comparing DOACs with warfarin had subgroups of patients with prior stroke or transient ischemic attack (TIA). Analyses of secondary stroke prevention subgroups, although of inadequate statistical power, showed no significant interaction between previous stroke or TIA and the effects on the primary efficacy outcome of stroke or systemic embolism, suggesting that the treatment effect in this specific subgroup did not differ from the overall population. In a subsequent meta-analysis of phase III trials of DOACs conducted on 14,527 patients with NVAF and prior stroke or TIA, DOACs seemed to be associated with a significant reduction in the rates of stroke or systemic embolism, hemorrhagic stroke, and major bleeding when compared with warfarin.[8]

Due to these findings, DOACs have been marketed worldwide, representing a real opportunity for stroke prevention in NVAF patients. In Italy, DOACs have become available for use in the facilities of the national health system since July 2013.

Although patients with AIS were excluded from the 4 randomized clinical trials comparing DOACs with warfarin, except for a few patients enrolled in the ARISTOTLE trial 1 week after stroke, it has become immediately clear that DOACs could be an opportunity also in patients with NVAF-related AIS.[9] A number of recent reports of limited sample size suggest that DOACs, administered within 2-5 days after an AIS, reduce recurrences without increasing the risk of intracranial bleedings in patients with NVAF.[10-13]

The aim of our study was to analyze the confidence of physicians in prescribing DOACs in atrial fibrillation (AF)-related AIS in real-world practice over the years since DOACs were marketed and to describe clinical characteristics and outcomes of patients receiving DOACs.

Materials and Methods

This is a retrospective analysis of the clinical data records of all consecutive patients with AIS and known or newly diagnosed NVAF admitted to our ward in the period January 1, 2014, to December 31, 2016.

Each patient with suspected stroke was clinically evaluated at hospital admission using the National Institutes of Health Stroke Scale (NIHSS). A first cerebral computed tomography (CT) scan without contrast was routinely performed at hospital admission in order to rule out intracranial bleeding. Appropriate treatment (including systemic thrombolysis and/or endovascular therapy) was then given according to a standard local protocol. All patients were monitored for blood pressure, heart rate, body temperature, glucose level, and electrolyte level. AF was classified according to international guidelines in paroxysmal (episodes terminating spontaneously within 7 days), persistent (episodes lasting more than 7 days, requiring pharmacological or electric treatment), or permanent (persisting for more than 1 year because cardioversion either failed or was not attempted). Physicians were free to decide the type of antithrombotic treatment (aspirin or other antiplatelet agents, VKAs, or DOACs).

A second brain CT or magnetic resonance imaging was performed 24-48 hours after hospital admission. The size of the ischemic lesion was classified as small when less than 1.5 cm in the anterior or posterior circulation; medium when a lesion was in a cortical superficial branch of the middle cerebral artery (MCA), in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of the posterior cerebral artery (PCA), or in a cortical superficial branch of the anterior cerebral artery (ACA); large anterior when a lesion involved the complete territory of the MCA, PCA, or ACA in 2 cortical superficial branches of the MCA, was in a cortical superficial branch of the MCA associated with the MCA deep branch, or was in more than 1 artery territory (e.g., MCA associated with ACA territories); and large posterior when a lesion was greater than or equal to 1.5 cm in the brain stem or cerebellum.[14,15] Hemorrhagic transformation (HT) was also evaluated. HT was defined on CT scan as any degree of hyperdensity within the area of low attenuation and was classified as either hemorrhagic infarction (HI) or parenchymal hematoma (PH). On magnetic resonance imaging, HT was defined as hypointensity on axial T1-weighted and T2-weighted images. HT was considered symptomatic if associated with