Atrial Fibrillation and Stroke
Making Sense of Recent Observations on Anticoagulation

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KEYWORDS

• Oral anticoagulant therapy • Thromboembolic risk • Vitamin K antagonist
• Non-vitamin K antagonist oral anticoagulants • Clinical characteristics

KEY POINTS

- Atrial fibrillation (AF) is associated with an increased stoke and thromboembolic risk, as well as mortality.
- Use of oral anticoagulant (OAC) therapy significantly reduces stroke and all-cause mortality.
- OAC use for stroke prevention in AF means well-managed vitamin K antagonists (VKA) with a time in therapeutic range greater than 70% or a non-VKA OAC (NOACs).
- Different characteristics of the various NOACs allow us to fit the right NOAC drug to particular patient characteristics.

INTRODUCTION

Atrial fibrillation (AF) is the most prevalent heart rhythm disorder, with recent epidemiologic data showing that the worldwide prevalence of AF increased to 33.5 million patients in 2010.[1] In European countries, the estimated prevalence of AF is about 9 million patients, projected to increase to 17.9 million.[1] Among patients age older than 65 years there was an increase in AF diagnosis from 41 to 85 per 1000 patients from 1993 to 2007.[1] AF also accounts for a great proportion of deaths in the general population, because AF independently increases all-cause mortality and cardiovascular mortality risks both in men and women.[1]

Ischemic stroke is the most common cardiovascular adverse event in AF patients, with an overall 5-fold increase in stroke risk[2] and reported incidence of 19.5 per 1000 patient-years in 2002.[3] Additionally, stroke severity and recurrence risks are higher with AF.[1]

Oral anticoagulation (OAC) therapy with the vitamin K antagonists (VKA; eg, warfarin), has been central for stroke prevention in the management AF.[4] More recently, several drugs with a direct inhibitory effects on thrombin and factor Xa have been developed.[5] These non-VKA oral anticoagulants (NOACs),[5] namely, dabigatran etexilate, rivaroxaban, apixaban, and edoxaban, are proved to be as effective as warfarin for the prevention of stroke and systemic thromboembolism events in patients with AF[6–10] (**Table 1**). Details of the clinical trials and study outcomes have been discussed in detail.[11,12]

The aim of this review is to provide an overview of current guidelines and summarize current evidence for the prevention of stroke in AF patients.

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Cardiol Clin 34 (2016) 317–328
http://dx.doi.org/10.1016/j.ccl.2015.12.006
0733-8651/16/$ – see front matter

Table 1
NOAC clinical trials in NVAF patients

Trial	Year	NOAC	Events Rate	Comparator	Events Rate	*p* for Noninferiority
RE-LY[6]	2009	Dabigatran 110 mg BD Dabigatran 150 mg BD	1.53%/y 1.11%/y	Adjusted dose warfarin (INR = 2–3)	1.69%/y	<.001 <.001
ROCKET AF[7]	2011	Rivaroxaban 20 mg OD	1.7% pts-yrs	Adjusted dose warfarin (INR = 2–3)	2.2% pts-yrs	<.001
ARISTOTLE[8]	2011	Apixaban 5 mg BD	1.27%/y	Adjusted dose warfarin (INR = 2–3)	1.60%/y	<.001
ENGAGE AF-TIMI 38[9]	2013	Edoxaban 30 mg OD Edoxaban 60 mg OD	1.61% pts-yrs 1.18% pts-yrs	Adjusted dose warfarin (INR = 2–3)	1.50% pts-yrs	.005 <.001

Abbreviations: ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BD, twice daily; ENGAGE AF-TIMI, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction; INR, International Normalized Ratio; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, nonvalvular atrial fibrillation; OD, once daily; pts-yrs, patient-years; RE-LY, Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

A BRIEF OVERVIEW OF CURRENT CLINICAL GUIDELINES

For many years, the VKAs were the only available option to treat nonvalvular AF patients with a high risk of developing an ischemic stroke.[13,14] After the introduction of NOACs, the guidelines have evolved accordingly.

In 2006, the American College of Cardiology, American Heart Association, and European Society of Cardiology (ESC) guidelines recommended thromboembolic risk stratification for patients with AF according to $CHADS_2$ (congestive heart failure, hypertension, age, diabetes, prior stroke) risk score[15] (class IIa, level A). Consideration of less validated risk factors such as coronary artery disease, age 65 to 75, female sex, and thyroid disease was mentioned. Accordingly, patients with at least $CHADS_2$ equal to 1 should be treated with VKAs (class I, level A) Antithrombotic therapy with aspirin was still considered acceptable as an alternative to VKA (class I, level A) or to treat patients at lower risk (class I, level A).

In 2010, the ESC published new guidelines[16] on AF management that recommended a risk factor–based approach using the CHA_2DS_2-VASc (congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category) score,[17] considering both 'major' and 'clinically relevant nonmajor' risk factors (class I, level A). Treatment with VKAs was recommended for patients with 1 major or 2 or more clinically relevant nonmajor risk factors (class I, level A). Patients with only 1 'clinically relevant nonmajor' risk factor were recommended to be treated either with VKAs (class I, level A) or aspirin (class I, level B), with a preference for OAC. Patients with low risk could still be recommended treatment with aspirin or no antithrombotic therapy, with a preference for the latter (class I, level B).

In 2012, the American College of Chest Physicians released the ninth version of their Antithrombotic Therapy and Prevention of Thrombosis Evidence-Based Clinical Practice Guidelines.[18] The $CHADS_2$ score was still recommended to stratify thromboembolic risk, but consideration of non-$CHADS_2$ stroke risk factors, such as age 65 to 74, vascular disease, and female sex, may favor OAC therapy. OAC therapy was recommended for with a $CHADS_2$ score of 1 rather than antiplatelet therapy (grade 2B). In patients with nonvalvular AF, the use of dabigatran 150 mg twice daily rather than adjusted-dose VKAs was recommended.[18]

In 2012, the ESC published a focused update of their previous guidelines. The CHA_2DS_2-VASc score was the risk score recommended for the stratification of thromboembolic risk in all patients with nonvalvular AF. Rather than the approach to identify high-risk patients, the guideline