

# Stroke prevention with novel oral anticoagulants in patients with non-valvular atrial fibrillation.

Dylan Rajaratnam<sup>1</sup>, Rohan Rajaratnam<sup>2,3,4,5\*</sup>

<sup>1</sup>University of Newcastle, NSW, Australia

<sup>2</sup>Liverpool Hospital, NSW, Australia

<sup>3</sup>Campbelltown Hospital, NSW, Australia

<sup>4</sup>Western Sydney University, NSW, Australia

<sup>5</sup>University of New South Wales, NSW, Australia

## Abstract

**Due to the ease of treatment with Novel Oral Anticoagulants (NOACs) when compared to Vitamin K antagonist, Warfarin, this is increasingly becoming the first line anticoagulant in most circumstances. Here we review the major trials of the more readily available NOACs in stroke prevention in the setting of non-valvular atrial fibrillation.**

*Accepted on January 23, 2017*

## Introduction

Stroke is a syndrome caused by the reduction or cessation of blood flow to the brain causing neurological dysfunction. While some strokes may be the result of a haemorrhage, majority (85%) are due to ischaemia [1]. Many ischaemic events are cardio embolic, of these the majorities are due to atrial fibrillation (AF) [2].

There are currently four novel anticoagulants (NOACs) which can be prescribed for the prophylaxis of stroke in those with non-valvular AF. These NOACs include dabigatran, a direct thrombin inhibitor, and the others, rivaroxaban, apixaban and Edoxaban are Factor-Xa inhibitors.

Vitamin K antagonist, warfarin, has certain limitations that NOACs overcome with fixed dosing regimens corrected to renal function, no necessity to regularly monitor coagulation parameters and fewer interactions with food and medications [2,3].

## The NOACs

### *Dabigatran*

The RE-LY trial [4] was a randomized trial of a large cohort of patients with non-valvular AF, testing two doses of dabigatran (110 mg BD and 150 mg BD) against dose-adjusted warfarin, with the primary outcome of stroke or systemic embolism.

The outcome of the RE-LY trial revealed that both doses of dabigatran were non-inferior to warfarin. Interestingly it also demonstrated that the higher dose (150 mg BD) was superior with a 34% relative reduction in either strokes or systemic embolic events. This reduction in stroke is mainly due to reduction in ischaemic stroke.

However, there were increased rates of Gastrointestinal tract bleeding, which was 50% more frequent on the higher dose (150 mg BD) of dabigatran than those on warfarin, as well as, an increased rate of dyspepsia.

### *Rivaroxaban*

The ROCKET AF trial [5] was a large randomized trial of patients with non-valvular AF, testing 20 mg once daily of

rivaroxaban (15 mg once daily of rivaroxaban in those with moderate renal dysfunction) against dose-adjusted warfarin, with the primary outcome of stroke or systemic embolism.

The outcome of the ROCKET AF trial demonstrated that rivaroxaban was non-inferior to warfarin. This is supported by a statistically significant reduction (33%) of intracranial hemorrhages in the patients taking rivaroxaban compared to those on warfarin.

The group taking the rivaroxaban had no increased rates of significant bleeding, however, the gastrointestinal tract bleeding was higher than those taking warfarin (3.15% vs. 2.16%, respectively). Patients in the rivaroxaban group also had a larger proportion of patients experiencing epistaxis and haematuria.

Patients with moderate renal impairment (creatinine clearance 30 mL/min to 49 mL/min) had similar bleeding rates to warfarin and demonstrated similar benefits with stroke and systemic embolism prophylaxis.

### *Apixaban*

The ARISTOTLE trial [6] was a large randomized trial of patients with non-valvular AF, testing 5 mg BD (2.5 mg BD in those at high risk of bleeding) against dose adjusted warfarin, with the primary outcome of stroke or systemic embolism.

The outcome of the ARISTOTLE trial revealed a statistically significant 21% reduction in rates of the primary outcome (stroke or systemic embolism) compared to those on dose-adjusted warfarin. Apixaban was also shown to have a significant reduction (31%) in major bleeding when compared to patients who were on warfarin. Interestingly, patients did not have a higher rate of Gastrointestinal tract bleeding when on apixaban, which was a side-effect present in the other novel anticoagulants (NOACs). Patients with moderate renal impairment (CrCl  $\leq$  50 mL/min) surprisingly had a reduction in major bleeding compared to the patients on warfarin.

### *Edoxaban*

ENGAGE AF-TIMI 48 trial [7] was a large randomized trial of patients with non-valvular AF, testing two doses of Edoxaban

(60 mg daily and 30 mg daily, doses were further halved in those at high risk of bleeding), with the primary outcome of stroke or systemic embolism.

The outcome of the ENGAGE AF-TIMI 48 trial showed that both the higher and lower doses of Edoxaban were non-inferior to warfarin. Both doses of Edoxaban resulted in less rates of haemorrhagic stroke, which was statistically significant when compared to the patients on warfarin, however, the lower dose (30 mg daily) was associated with 41% more ischaemic strokes.

Both doses of Edoxaban demonstrated less major bleeding, however, the higher dose (60 mg daily) resulted in an increased rate of Gastrointestinal tract bleeding in patients compared to those on dose-adjusted warfarin, although interestingly the lower dose (30 mg daily) resulted in lower rates of Gastrointestinal tract bleeding than that of the warfarin group.

### **NOACs post-stroke**

The benefits of anticoagulation in preventing a further ischaemic stroke or embolic event needs to be balanced against haemorrhagic transformation of the stroke. Current guidelines from the American Heart Association and American Stroke Association recommended commencing NOAC anticoagulation within 2 weeks of a cardio embolic stroke unless it is particularly large or severe [2,8].

### **Summary**

The NOACs in these studies have generally shown that they are non-inferior to dose-adjusted warfarin in preventing strokes and systemic embolism in non-valvular atrial fibrillation. Apixaban and higher dose Dabigatran (150 mg BD) may be even superior to dose-adjusted warfarin in this patient population. However, NOAC use is contraindicated in those with significant renal dysfunction and the absence, until recently, of an antidote to the NOACs has also proven a stumbling block. More recently monoclonal antibody, Idarucizumab, has been approved as a reversal agent for Dabigatran. Agents such as Ciraparantag (for direct thrombin inhibitors and factor Xa inhibitors) and Andexanet alfa (for factor Xa inhibitors) may soon become available [9]. This would further establish the role of NOACs

in stroke prophylaxis for patients with non-valvular atrial fibrillation.

### **References**

1. Berry SM, Wilson BR, Fallon LF. Strokes. Magill's Medical Guide. 2016;6:1-2.
2. Lee A, Rajaratnam R. Tailoring the novel anticoagulants to the stroke patient-one size does not fit all Novel anticoagulants in stroke. J Neurol Neurophysiol. 2014;5:6,1-7.
3. Oqab Z, McIntyre WF, Hopman WM, et al. Which factors influence resident physicians to prescribe NOACs to patients with non-valvular atrial fibrillation. JAFIB;9:2:12-5.
4. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus Warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139-51.
5. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in non-valvular atrial fibrillation. N Engl J Med. 2011;365:883-91.
6. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92.
7. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093-104.
8. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischaemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160-236.
9. Hu TY, Vaidya VR, Asirvatham SJ. Reversing anticoagulant effects of novel oral anticoagulants: Role of Ciraparantag, Andexanet alfa, and Idarucizumab. Vasc Health Risk Manag. 2016;12:35-44.

### **\*Correspondence to:**

Rohan Rajaratnam  
Department of cardiology  
Liver pool hospital  
Liver pool  
NSW 2170  
Australia  
Tel: 0419949302  
E-mail: rohanrr@bigpond.com.au