Atrial fibrillation is a type of cardiac arrhythmia and it is associated with increased risk for ischemic stroke. Vitamin K antagonists were used to reduce thromboembolic risk; however, these medications require therapeutic monitoring and increase risk of bleeding. Novel oral anticoagulants (NOACs) were used as an alternative to vitamin K antagonists and several studies have showed the benefit of NOAC to decrease clotting as well as the risk of bleeding in over to vitamin K antagonists, such as warfarin. This study has found that NOACs are as effective as warfarin in reducing the risk of stroke through anticoagulation. Also, NOACs have a decreased risk of significant bleeding and other secondary risk effect.

**KEYWORD:** NOACs, warfarin, Atrial Fibrillation, anticoagulant, novel oral anticoagulant, vitamin K antagonist.

**INTRODUCTION**

Atrial Fibrillation (AF) is a common type of cardiac arrhythmia (P. Patel, Pandya, & Goldberg, 2017). AF affects 2.3 million Americans and its associated with increased risk of stroke (Kirley, GouthamRao, Bauer, & Masi, 2016). It is also associated with significant morbidity and mortality because of its potential to cause other thromboembolic events (Haas et al., 2019). In Asians found that the prevalence and incidence of AF in patients at advanced age (>80 years) has shown a significant increase of numbers (H. M. Kim et al., 2019). Warfarin was the type of oral anticoagulant approved for stroke prevention (P. Patel et al., 2017). Warfarin could reduce the thromboembolic risk; however, the use of warfarin could
increase the risk of bleeding, with intracranial hemorrhage being the most serious bleeding complication (Briasoulis et al., 2018).

Within past eight years, FDA approved novel oral anticoagulants (NOACs) for AF treatment include dabigatran, rivaroxaban and apixaban (Chua, 2018). NOACs had several advantages over warfarin, including straightforward dosing regimens, no requirement for monitoring, and lower risk of intracranial hemorrhage (H. Kim et al., 2019). Ximelagatran was a direct thrombin inhibitor and was never approved by FDA due to risk of hepatotoxic (Silva, 2014). Idraparinux is a factor Xa inhibitor subcutaneously longacting but its was also not approved due to the significant increase in bleeding (Silva, 2014). Dabigatran is a direct thrombin inhibitor, and rivaroxaban and apixaban, are factor Xa inhibitors, were type of NOACs used for prevention of embolism in patients with AF. Awareness of the action of these drugs, their dosage, adverse effects and interactions with other drugs are important (Silva, 2014).

Table 1: NOAC vs Warfarin.

<table>
<thead>
<tr>
<th>Warfarin (Chua, 2018)</th>
<th>NOAC (Chua, 2018)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow onset</td>
<td>Rapid onset</td>
</tr>
<tr>
<td>Long half life</td>
<td>Short half life</td>
</tr>
<tr>
<td>Many drug interaction</td>
<td>Less drug interaction</td>
</tr>
<tr>
<td>Need routine lab monitoring</td>
<td>No need routine lab monitoring</td>
</tr>
<tr>
<td>Food effect</td>
<td>No food effect</td>
</tr>
</tbody>
</table>

**Dabigatran**

Dabigatran was the first NOAC approved in many countries worldwide for the prevention of stroke from AF based on the results of the RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy, Warfarin, compared with Dabigatran) trial. Patients were randomized to dose-adjusted warfarin or blinded doses of dabigatran with dose of dabigatarn is 150 mg twice daily or 110 mg twice daily. Dabigatran 150 mg twice-daily dabigatran dose was superior to warfarin in reducing stroke or system embolism with the result RR 0.66; 95% CI 0.53–0.82; p < 0.001); it happen because of both had significant reduction in ischaemic stroke with RR 0.76; 95% CI 0.60–0.98; p = 0.03 and in haemorrhagic stroke with RR 0.26; 95% CI 0.14–0.49; p < 0.001. There were fewer intracranial haemorrhages with RR 0.40; 95% CI 0.27–0.60; p < 0.001, a higher rate of gastrointestinal bleeds with RR 1.50; 95% CI 1.19–1.89; p < 0.001 but overall, no difference in major bleeding events with RR 0.93; 95% CI 0.81–1.07; p = 0.31 in this 150mg dabigatran group (Connolly et al., 2009).
Dabigatran with 110 mg twice-daily dose was noninferior to warfarin for prevention of stroke or systemic embolism with RR 0.91; 95% CI 0.74–1.11; \( p < 0.001 \). There was a significantly lower rate of haemorrhagic strokes, RR 0.31; 95% CI 0.17–0.56; \( p < 0.001 \) with no significant reduction in ischaemic strokes with RR 1.10; 95% CI 0.89–1.40; \( p = 0.35 \) compared to warfarin. This group demonstrated favourable bleeding outcomes with fewer intracranial haemorrhages with RR 0.31; 95% CI 0.20–0.47; \( p < 0.001 \). Overall of this study showed result a lower risk of major bleeding with RR 0.80; 95% CI 0.69–0.93; \( p = 0.003 \) compared with warfarin (Connolly et al., 2009).

**Rivaroxaban**

Rivaroxaban is a direct factor Xa inhibitor, which connects reversibly to the active site of factor Xa, and acts independently of endogenous antithrombin. Rivaroxaban suppresses the production of new molecules and plasma thrombin has no significant effect on the activity of the existing thrombin (Harder & Graf, 2013).

Based on the results of the ROCKET AF trial with 14,264 patients, 60.3% male, median age 73 years, and mean CHADS 3.47. The study is a double-blind trial with the primary end point systemic embolism or stroke. The result of primary end point outcome occurred at the rate of 1.7% per year in the rivaroxaban group that given dose of 20 mg per day and at the rate of 2.2% per year in the warfarin group (p value <0.001 for non-inferiority). Overall, the result of this trial showed a decrease in stroke and critical bleeding in rivaroxaban compared to warfarin, with several advantages to using Xa inhibitors, such as rapid onset/offset, no requirement for regular INR monitoring and fewer drug interactions (M. R. Patel et al., 2011).

**Apixaban**

Apixaban was compared to warfarin in a randomized, double-blind trial with 18,201 patients with AF and at least one risk factor for stroke. Patient in apixaban group got apixaban 5 mg twice daily, with the primary outcome being ischemic or hemorrhagic stroke or SE. Secondary outcomes were death from any cause and myocardial infarction, and the primary safety outcome was major bleeding (Granger et al., 2011).

Patients in apixaban group had a lower stroke or SE outcome rate at 1.27% compared to patient in warfarin group at 1.60% (HR, 0.79; 95% CI, 0.66 to 0.95), and were statistically significant for noninferiority and superiority. The primary safety outcome of major bleeding...
was 2.13% per year in the apixaban group compared with 3.09% in the warfarin group (HR 0.69, 95% CI, 0.60 to 0.80). From this trial, apixaban showed to be statistically significantly superior compared warfarin in preventing stroke or SE and also causing less major bleeding and death from any cause (Granger et al., 2011).

**Edoxaban**

Edoxaban is another factor Xa inhibitors, are in evaluation but not yet recommended by the FDA. Edoxaban has showed no significant result compared to warfarin regarding prevention of stroke or systemic embolism and had a significant reduction of bleeding and death from cardiovascular causes in the study with 21,105 patients with moderate to high risk AF (follow-up, 2.8 years) (Giugliano et al., 2013).

Patient that give 60 mg once daily showed result no significant compared to warfarin in reducing stroke and systemic embolism with HR 0.87; 95% CI 0.73– 1.04; \( p < 0.001 \), and the comparable rates of ischaemic strokes with the warfarin group with HR 1.00; CI 0.83–1.19; \( p = 0.97 \) and a reduction in haemorrhagic stroke with HR 0.54; 95% CI 0.38– 0.77; \( p < 0.001 \). There was a reduction in intracranial haemorrhage (HR 0.47; 95% CI 0.34–0.63; \( p < 0.001 \)) and a reduction in major bleeds (HR 0.80; 95% CI 0.71–0.91; \( p < 0.001 \)) but has a higher rate in gastrointestinal bleeds (HR 1.23; 95% CI 1.02–1.50; \( p = 0.03 \)) in the high dose edoxaban group compared with the warfarin group (Giugliano et al., 2013).

**Table 2: Pharmacology and Pharmacokinetic of NOAC.**

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Dabigatan (Silva, 2014)</th>
<th>Rivaroxaban (Silva, 2014)</th>
<th>Apixaban (Silva, 2014)</th>
<th>Edoxaban (Gallego, Roldan, &amp; Lip, 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>6%</td>
<td>66% without food</td>
<td>&gt;50%</td>
<td>62%</td>
</tr>
<tr>
<td>Half life, hour</td>
<td>12-17</td>
<td>5-13</td>
<td>8-15</td>
<td>9-11</td>
</tr>
<tr>
<td>Clearance</td>
<td>80% renal</td>
<td>66% liver</td>
<td>75% fecal</td>
<td>65% liver</td>
</tr>
<tr>
<td></td>
<td>20% liver</td>
<td>33% renal</td>
<td>25% renal</td>
<td>35% renal</td>
</tr>
<tr>
<td>Plasma protein</td>
<td>35</td>
<td>&gt; 90</td>
<td>87</td>
<td>55</td>
</tr>
<tr>
<td>blinding, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time do peak levels</td>
<td>3</td>
<td>5-12</td>
<td>9-15</td>
<td>1-2</td>
</tr>
</tbody>
</table>
SAFETY AND EFFICACY OF NOACS

There are no direct head-to-head trials to compared NOACs against one another to facilitate a direct evaluation between drugs in this group. In the trial there are differences in the populations of each study of NOAC trials. These factors make deciding between NOACs a challenge in patients with AF once a decision has been made to treat with a NOAC over a VKA. There is no significant evidence to preference one NOAC over another and there is no guidelines on how to choose which agent to use in individual patient (Hammersley & Signy, 2017).

In patients with a high risk of gastrointestinal bleeding, the choice of NOAC would be the agent with a lower rate of gastrointestinal bleeding reported in the trials. Apixaban and dabigatran 110 mg twice daily had lower rates of gastrointestinal bleeding compared with warfarin. These two agents should be considered in such a patient group. The other NOACs all demonstrated a higher rate of GI bleeding compared with warfarin (Freedman, Potpara, & Lip, 2016; Savelieva & Camm, 2014). In terms of safety, all 4 NOACs have been associated with a lower risk of intracranial hemorrhage compared with warfarin (Farmakis et al., 2018).

The NOACs have more predictable pharmacological profiles, less interactions with other drugs, and less risk of intracranial hemorrhage compared to warfarin. They have rapid onset of action so it is not necessary to give patient bridge with parenteral and anticoagulation for initiation. The bridge therapy may not necessary in patients with chronic therapy who undergo invasive procedures with short interruption of anticoagulation. However, temporary suspension of these agents may increase the risk of thromboembolism, therefore, its recommended to use another anticoagulant such as heparin as the bridge therapy. Dose adjustment is needed for patients with chronic kidney disease or according to body weight. These novel agents do not require regular monitoring for INR or partial thromboplastin time (January et al., 2014).

CONCLUSION

Based on the available study about NOACs, NOACs showed result similar or superior stroke reduction in patients with AF as compared to warfarin. Overall, NOACs are superior to warfarin based on their efficacy for ischemic stroke prevention in patients with AF, reduced number of major bleeding events, and convenience of usage. The most current study support this conclusion by recommending NOACs over warfarin in patients with AF.
REFERENCES


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