ABSTRACT

Atrial fibrillation is the most common Cardiac arrhythmia and the third major cause of death in elderly. Atrial fibrillation is considered as a major cause for stroke in UK and England. Atrial fibrillation (AF) is associated with stroke due to thromboembolism. Atrial fibrillation is affecting more than 600,000 people all over world.

Warfarin is the first anticoagulant which was used for atrial fibrillation patient. There is need for proper patient care and safety regulation while using warfarin, since there is risk of blood clotting in more for patients using warfarin. Novel Oral Anticoagulants (NOACs) which are new class of anticoagulant drugs and used instead of warfarin due to less risk of blood clotting in patients. Apixaban, Dabigatran and Rivaroxaban are most commonly used NOACs drugs.

This review article gives complete description about efficacy and comparative use of Anti-coagulants and Novel Oral Anticoagulants in Atrial fibrillation patients having risk of stroke. It mainly focuses on use of NOACs in place of warfarin which is safe to use.

INTRODUCTION

Anticoagulants are used for the patients suffering from atrial fibrillation related stroke. Warfarin is the most commonly used anticoagulant, which prevents thrombosis and thromboembolism. In other words we can say it is useful in reducing the risk of stroke in patients with AF by inhibiting formation of future blood clots especially in veins and artery [1-9]. Warfarin is also used in antiphospholipid syndrome. Warfarin should not be used for patients having bleeding disorders or high blood pressure because warfarin increases the risk of bleeding in patients which can be fatal. Warfarin can cause bleeding easily in patients suffering from cancer, people more than 65 years old, kidney or liver disease patients etc. [10-19].

Warfarin is prescribed for patients who had a condition of stroke, heart attack, deep vein thrombosis or pulmonary embolism [20-27].

There are many limitation associated with the use of warfarin. Adjustment of dose and routine monitoring is very important in use of warfarin for a patient’s international normalized ratio (INR) and careful adjustment of the dose of particular patient. Warfarin levels can be affected by diet of patients, alcohol use or any other drug use [28-36]. For example:

• There is higher risk of blood clotting or increases risk of stomach bleeding associated with the patients if they are using any other medicine for pain, fever, swelling etc.
• Patient should avoid food which contains higher amount of Vitamin K such as leafy vegetables, vegetables oils.
• Patient should not drink some particular juices like grapefruit, pomegranate, cranberry which leads to some major side effects while using warfarin.

Some major points to remember while using warfarin:
• Patient should use warfarin as prescribed by doctor.
• It should be taken in time everyday.
• Patients should stop taking warfarin before 5-7 days of any surgery.
• It should be stored at room temperature.
Novel Oral Anticoagulants (NOACs)

NOACs (Novel Oral Anticoagulants) are also known as Directly Acting Oral anticoagulants (DOACs). It is a new class of anticoagulant drugs which are used in prevention of blood clotting to reduce the risk of stroke in patient with atrial fibrillation [37-41].

NOACs are direct inhibitors of thrombin and Xa (Xa-INHS) due to which these are used in place of warfarin. NOACs, interrupts the formation of blood clots due to which it takes more time for blood clotting and hence it reduces the risk of stroke. NOACs half-life is in the range of 8-14 hours. Blood concentration in NOACs is constant and peak. Thrombin generated in constant period of NOACs is small and plays a significant role [42-49].

Some commonly used NOACs are: Apixaban, Dabigatran and Rivaroxaban.

Comparison between Warfarin and NOACs

NOACs function will be more effective and rapid in comparison with warfarin due to fast onset action and short half-life. Anticoagulation effect of NOACs is reducing quickly by drugs. Adjustment of dose and routine monitoring of NOACs is not that much important as it is important in warfarin due to its superior expected anticoagulation activity. NOACs have less influence of diet and medication in comparison with warfarin. NOACs are more costly than warfarin (Table 1).

Table 1: Comparison between mechanism of warfarin and NOACs.

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Warfarin</th>
<th>NOACs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Half-life period</td>
<td>More</td>
<td>Less</td>
</tr>
<tr>
<td>Food Interaction</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable</td>
<td>Fixed</td>
</tr>
<tr>
<td>Routine Laboratory Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Duration of blood-thinning effect</td>
<td>Long</td>
<td>Short</td>
</tr>
</tbody>
</table>

NOAC in non-valvular atrial fibrillation

NOACs are available in Ireland first in 2008 for thromboprophylaxis post orthopedic surgery. Dabigatran exexilate is a direct thrombin inhibitor and it was licensed in 2011 for stroke prevention in NVAF [50]. In NVAF the factor Xa inhibitor and apixaban was licensed in 2013 for stroke prevention. NOACs are all licensed for thromboprophylaxis post elective hip and knee replacement surgery. Some patient factors (age, renal function, weight), varying dose options, specific administration considerations are required by NOACs therapy [51-57].

List of non-inferiority randomized controlled Clinical trials in non valvular atrial fibrillation for stroke prevention:

- Apixaban: ARISTOTLE (vs. warfarin), AVERROES (vs. aspirin).
- Dabigatran: RE-LY (vs. warfarin).
- Rivaroxaban: ROCKET-AF (vs. warfarin).

In these trials ARISTOTLE and RE-LY were based on intention to treat population and ROCKET-AF used the per protocol population. In these NOACs Dabigatran is direct thrombin inhibitor and apixaban and rivaroxaban are Xa inhibitors.

Apixaban

Apixaban is a direct oral factor Xa inhibitor which has rapid absorption. It has 12 hour half-life, and 25% renal excretion. ARISTOTLE randomized clinical trial which was carried out to test apixaban for reducing stroke in atrial fibrillation. Age of ≥ 80 years is included in these criteria for lower dose selection in patients. Apixaban have greater effect on hemorrhagic stroke, major bleeding and clinically relevant non major bleeding than warfarin [58-66]. There are various differences were observed in studies of apixaban and warfarin use. While using apixaban there is less risk of gastrointestinal bleeding and other bleeding rates across age groups. ARISTOTLE was the first study in which it is found that Apixaban is more suitable than warfarin in preventing stroke causing less bleeding, and resulting in lower mortality [67-71].
Here are some outcomes of study in relation with warfarin and apixaban

a. Primary outcome for apixaban group was 1.27% per year and for warfarin group it is 1.6%.
b. Rate of major bleeding for apixaban group was 2.13% per year and for warfarin it is 3.09%.
c. Death from any cause for apixaban group is 3.52% per year and for warfarin group it is 3.94%.
d. Rate of haemorrhagic stroke for apixaban group is 0.24% per year and for warfarin group it is 0.47%.
e. Rate of ischemic stroke for apixaban group is 0.97% per year and for warfarin group it is 1.05%.
f. Intracranial haemorrhage for apixaban group is 0.33% per year and for warfarin group it is 0.80%.

Below provided is the apixaban trial data for different age groups (Table 2).

Table 2: Apixaban trial data for different age groups.

<table>
<thead>
<tr>
<th>Age category</th>
<th>&lt; 80 Years</th>
<th>80-89 Years</th>
<th>90+ Years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>15,765</td>
<td>2352</td>
<td>84</td>
<td>18201</td>
</tr>
<tr>
<td>%</td>
<td>86.62</td>
<td>12.92</td>
<td>0.46</td>
<td>100</td>
</tr>
</tbody>
</table>

Dabigatran

It is a direct thrombin inhibitor. RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) Trials is a randomized trial which is carried out to compare two different doses of dabigatran. Two doses are: 110 mg for < 75 years and 150 mg for higher risks of patients with ≥ 75 years. For this trial patient over 80 years are approximately 16.5% [72-81]. Reduction in hemoglobin is at least 2.0 g/dl for major bleeding is defined by RE-LY. Dabigatran 150 mg is the only NOAC in comparison with warfarin which has lower rates of ischaemic stroke and it is best for patient with atrial fibrillation. Some major criteria for reducing dose of dabigatran are age, renal impairment and bleeding issue. Myocardial infarction (MI) [82-90] rate is more for both doses of Dabigatran in comparison with warfarin. Along with this if there is high dose of dabigatran there is risk for gastrointestinal bleeding due to which a low gastric pH is required to increase the absorption of dabigatran [91-97].

Rivaroxaban

It is a factor Xa inhibitor. ROCKET AF trial was a randomized trial for Rivaroxaban in which 14,264 patients with moderate or high risk for stroke were randomized. For this trail patient over 80 years were approximately 18.3%. In which it is found that Rivaroxaban is also useful like warfarin in stroke prevention and it also reduces the risk of bleeding in and around the brain. Patient age is not considered as criteria for reduced dose with rivaroxaban. Fatal bleeding is less frequent in the rivaroxaban group due to lower rates of hemorrhagic stroke. Along with this gastrointestinal bleeding was more frequent in the rivaroxaban group [98-100].

DISADVANTAGES OF NOACS

- Dabigatran dose can result in stomach upset.
- There is no antidote for NOACs patients.
- There is lack of monitoring ability in NOACs.
- It is cost effective.
- There is risk of bleeding in taking NOACs.

GUIDELINES FOR USE OF NOAC

Some of guidelines which are to be used while using NOAC:

- Practical start up and follow up scheme for patients on new oral anticoagulants.
- In emergency situation there may be need of quantitative assessment of drug exposure and anticoagulant effect.
- Physicians should have to consider pharmacokinetic effect of pilot drugs and of co morbidities when prescribing NOACs.
- When physicians are using different anticoagulant therapy there is need to screen the continuation of anticoagulant therapy while minimizing the risk of bleeding.
- Physicians should develop different ways to optimize the actions with new oral anticoagulant intake.
- Physicians and patients should be aware from the dose errors and how to overcome the errors.
- NOAC should be used properly with chronic disease patients.
• Physicians should take care of bleeding complications.
• Patient’s characteristic and surgical factors should be observed properly while using NOAC.
• While using emergency intervention NOAC should be stopped.

DISCUSSION

Looking and analyzing through use of anticoagulants and novel oral anticoagulants in atrial fibrillation patients it is found that we can use both for patient’s but there is need for careful monitoring and more risk of blood clotting in patients using warfarin while patients using novel oral anticoagulants there is no need for regular patient monitoring and there is less risk of blood clotting which reduced risk of stroke in patients. Pros (i.e., Anticoagulation effect of NOACs is reducing quickly by drugs, it has short half-life period, no routine monitoring requirement, onset of faction is fast, there is no effect of food on patients using NOACs, etc.) and cons (i.e., There is no antidote for NOACs patients. it is cost effective, risk of bleeding in patients, etc.). Based on the trials carried out, NOACs have been proven more efficient.

REFERENCES

86. Roever L and Resende ES. Diabetes and metabolic syndrome can contribute to recurrent vascular events in patients with lacunar stroke? J Neurol Disord. 2015;S1:e101.