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Pharmacological Therapy in Stroke Prophylaxis : The New versus the Old Agents

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice. AF is a potent risk factor for stroke and systemic thromboembolism. Patients with AF have been observed to have a worse outcome following stroke, therefore prevention of stroke in patients with AF is of paramount importance. Antithrombotic therapy is crucial for prevention of stroke in patients with AF. Vitamin K antagonists (VKAs) have been the traditional anticoagulants for prevention of stroke in patients with AF. Drug treatment with VKAs is associated with significant management issues, such as an unpredictable dose response necessitating dose adjustments, frequent laboratory monitoring and multiple interactions with other drugs. Despite following best practices, VKAs are associated with limited efficacy and increased risk of hemorrhage. Due to these limitations a significant effort has been devoted towards development of newer anticoagulants. Dabigatran, Rivaroxaban, and more recently Apixaban have been approved by the F.D.A. for the prevention of stroke in patients with AF. These newer agents possess highly predictable pharmacokinetic and pharmacodynamics properties which allow a fixed dosing regimen and also eliminate the need of routine laboratory monitoring. This review discusses various anticoagulants for prevention of stroke in patients with AF.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice, affecting over 2.2 million people in the United States.[1,2] It is estimated that the number of people diagnosed with AF will approach nearly 16 million in the U.S. by 2050.[3] The risk of stroke is increased approximately fivefold in patients with AF.[4] Strokes in patients with AF have worse outcomes as compared to patients without AF and also have a significant impact on quality of life.[5] Aspirin and warfarin have been the mainstay of prevention of stroke in patients with AF. Aspirin alone and in combination with clopidogrel has been demonstrated to be inferior than warfarin for prevention of stroke in patients with AF.[6] Currently warfarin remains the most commonly prescribed anticoagulant for the purpose of stroke prevention. Despite its effectiveness, warfarin has numerous limitations such as slow onset and offset of action, drug- interactions and a narrow therapeutic window. Various randomized clinical trials have estimated that for warfarin-treated patients, the international normalized ratio (INR) was in target range for approximately 36-68% of the study days.[7-10]

Management of warfarin is also complicated by various drug and food interactions. These limitations of warfarin have prompted the research and development of alternative newer anticoagulants for AF-related stroke prevention. Dabigatran was the first newer oral anticoagulant to be approved by the FDA for prevention of stroke in patients with atrial fibrillation (AF) in 2010. Rivaroxaban was also recently approved for similar indication in November 2011. Recent

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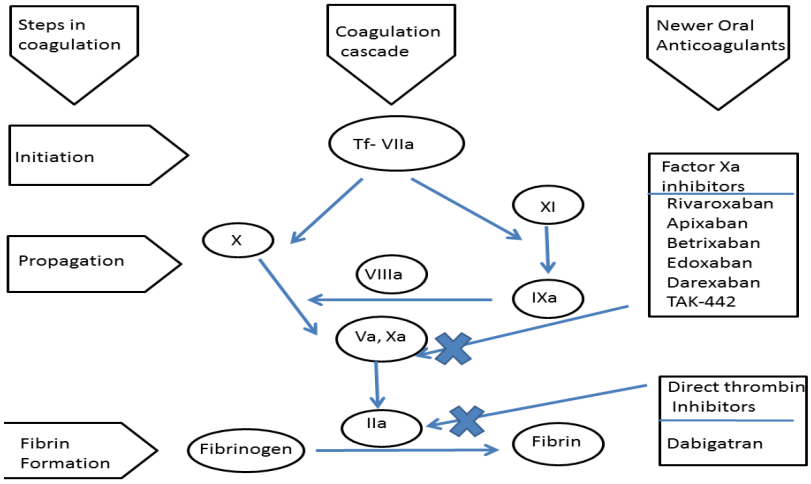

Figure 1: **Coagulation cascade and site of action of various newer anticoagulants**

approval of apixaban in December 2012 has further expanded the armamentarium of anticoagulants in clinical practice

Methods

We performed a comprehensive literature search in the PubMed database using the keywords; "newer oral anticoagulants", "dabigatran, rivaroxaban and apixaban", "atrial fibrillation", "monitoring of newer oral anticoagulants". Original studies and clinical trials describing various oral anticoagulants were included in the study. The language of clinical studies was limited to English.

Warfarin

Warfarin has been extensively studied in numerous clinical trials for prevention of stroke in patients with AF. Warfarin was demonstrated to be superior than aspirin and placebo for prevention of thromboembolic events and overall mortality in patients with AF in the Copenhagen AFSAK study.[11] Similar results confirming the superior efficacy of warfarin were observed in other randomized clinical trials.[12-14] Despite its superior clinical efficacy, warfarin has numerous limitations. Warfarin has a slower onset of action and has an early procoagulant effect due to inhibition of protein C and protein S; both these properties necessitate the use of a parenteral anticoagulant at the time of initiation and interruption of warfarin therapy. The clinical efficacy of warfarin for stroke prevention is measured using the International Normalized Ratio (INR). Clinical guidelines recommend an INR between 2.0 and 3.0 for an appropriate therapeutic effect of warfarin. Randomized clinical trials have estimated that for warfarin-treated patients INR was in the target range for approximately 36-68 % of the study days.[7-10,15] The time in therapeutic range INR decreases even further in actual clinical practice, in a review of the medical records of AF patients prescribed warfarin for stroke prevention; monitoring was performed less frequently than clinical trials (mean of 36.3-40.9 days vs.[21-28] days in clinical trials) and the target INR was achieved less often (50 % of days vs. 68% of days in clinical trials.[16] In another clinical study based on Medicare beneficiaries, warfarin was found to be less effective in African- American and Hispanic population. This was attributed to suboptimal monitoring and was independent of biological factors in this population.[17] Minority populations also have lesser access to cardiologists and to anticoagulation clinical services which are key in facilitating warfarin therapy.[18]

The clinical efficacy of warfarin is also significantly affected by other drugs which are commonly prescribed to the patient population on warfarin for various other cardiovascular indications.[19] Dietary content of vitamin K has also been shown to have significant impact on metabolism of warfarin leading to its diminished clinical efficacy and increased incidence of adverse events related to bleeding.[20,21] Warfarin's clinical efficacy and pharmacodynamics are also significantly influenced by interindividual variability which could partly be explained by the genetic variability secondary to the mutations in genes encoding for cytochrome P450, subfamily C, polypeptide 9 (CYP2C9) and vitamin K epoxide reductase subunit 1.[22-24] All these factors contribute to the narrow therapeutic index of warfarin and necessitated the need of alternative agents for anticoagulation.

Direct Thrombin Inhibitors

Dabigatran

Thrombin plays a key role in the coagulation cascade by converting fibrinogen to fibrin making it an attractive target for anticoagulation.[25,26] It has a multifactorial role including amplification of its own generation via the intrinsic pathway by activation of factor XI and VIII, activating extrinsic pathway and activating platelets, thereby creating the phospholipid surface on which these reactions occur.[27] (Figure 1)

Dabigatran is a competitive direct thrombin inhibitor which inhibits thrombin- dependent conversion of fibrinogen to fibrin and thrombin-induced platelet aggregation.[28,29] Dabigatran has an oral bioavailability of approximately 6-7 % in its prodrug form

and achieves a peak clinical effect in about 1-2 hours. The half-life of dabigatran is estimated to be approximately 12-17 hours.[30] Dabigatran has minimal drug-drug interactions since the cytochrome P450 isoenzyme system is not involved in its metabolism.[29,30] Dabigatran etexilate, the prodrug, is a substrate of the efflux transporter P- glycoprotein (P-gp). Potent P-gp inhibitors such as ketoconazole, verapamil, and amiodarone; thereby increase the plasma concentrations of dabigatran.[31] Dabigatran is predominantly excreted via the renal pathway; thereby the half-life and plasma levels are increased in patients with renal insufficiency.[30,32]

The clinical efficacy and safety of dabigatran for prevention of stroke in patients with AF was first investigated in the RE-LY (Randomized Evaluation of Long term anticoagulant therapy) trial. This study was a double-blind randomized noninferiority trial which compared two different doses of dabigatran with INR adjusted warfarin in patients with AF. A total of 18,113 patients were randomly assigned to receive either dabigatran (110 or 150 mg) twice daily dose or warfarin, adjusted to maintain an INR of 2.0 to 3.0. Dabigatran 150 mg was found to be more effective than warfarin in reduction of stroke (RR 0.66, 95 % CI: 0.53- 0.82). The rates of hemorrhagic stroke were significantly lower for both the doses of dabigatran as compared to warfarin (0.1 % per year for both doses of dabigatran vs. 0.4 % per year for warfarin; p< 0.001). The time in therapeutic range in patients assigned to warfarin arm was estimated to be 64%, the benefit of dabigatran was even greater when the INR was poorly controlled.[33,34]

The incidence of major bleeding was significantly less with dabigatran 110 mg than warfarin (RR 0.80; 95 % CI: 0.69 -0.93). No statistical difference in bleeding was observed between dabigatran 150 mg and warfarin (RR 0.93; 95 % CI: 0.81- 1.07). The incidence of gastrointestinal bleeding was observed to be higher in the dabigatran arm (RR 1.50; 95 % CI: 1.19- 1.89). The rate of discontinuation of dabigatran in this study was 21 % which was significantly higher than patients taking warfarin (17%), this was attributed to dyspepsia associated with dabigatran. Based on the clinical results of this trial, dabigatran was approved for stroke prophylaxis by the FDA in 2010 at doses of 150 mg twice daily for patients with creatinine clearance (CrCl > 30) and 75 mg twice daily for patients with moderate renal insufficiency (CrCl of 15- 30). Dabigatran was also approved by Health Canada for stroke prophylaxis in patients with AF, an overall dose of 150 mg twice daily was recommended for most patients and a reduced dose of 110 mg twice daily was recommended for elderly patients aged 80 years and above, as well as for patients at an increased risk of bleeding. It was also approved by the European Medicines Agency (EMA) at doses of 150 mg twice daily for majority of the patients and at doses of 110 mg twice daily for patients older than 80 years and at increased risk of bleeding.

Table 1: Comparison of major clinical trials of newer anticoagulants

Clinical Trial	Mean $CHADS_2$ score	Mean time in therapeutic range in Warfarin arm	Study Drug and doses	Primary outcome (Stroke and Systemic Embolism)
RE-LY	2.1	64 %	Dabigatran etexilate 150 mg bid and 110 mg bid	0.66 (0.53- 0.82); p <0.001 for 150 mg dose 0.91 (0.74- 1.11); p=0.34 for 110 mg dose
ROCKET-AF	3.5	55 %	Rivaroxaban 20 mg once daily †	0.88 (0.74 -1.03); p=0.12
ARISTOTLE	2.1	62 %	Apixaban 5 mg bid §	0.79 (0.66- 0.95); p < 0.01

† Dose of rivaroxaban was reduced to 15 mg once daily in patients with renal insufficiency

§ Dose of apixaban was reduced to 2.5 mg bid in patients with Serum Creatinine > 1.5mg/dl, age >80 years and body weight < 60 kg

Cardiac Risk of Dabigatran

In a follow up study based on the RE-LY trial there was a modest increase in the risk of MI in patients taking dabigatran. The reported annual rate of MI in patients taking dabigatran was 0.82 % and 0.81 % at 150 mg and 110 mg doses respectively as compared to 0.64 % rate reported with warfarin (HR 1.29, 95 % CI; 0.96 -1.75, p= 0.09 for dabigatran 110 mg; HR 1.27; 95 % CI 0.94- 1.71, p= 0.12 for dabigatran 150 mg), this increased risk of MI in patients taking dabigatran was not associated with increased mortality in the RE-LY trial. The rate of overall mortality due to any cause was 4.13 % per year in the warfarin arm as compared to 3.75 % in the dabigatran 110 mg arm (relative risk with dabigatran, 0.91; 95 % CI: 0.80 to 1.03; p =0.13) and 3.64 % per year in the dabigatran 150 mg arm (relative risk with dabigatran, 0.88; 95 % CI: 0.77-1.00; p = 0.051).[33,35] Currently the data on the mechanism of the increased risk of cardiovascular events with the use of DTIs is limited due to the sparse clinical data and lack of randomized clinical trials comparing DTIs with antiplatelet therapy in patients at high risk of coronary events. One speculation for the observed increased incidence of MI is that rather than promoting myocardial infarction, dabigatran provides less protective effect against MI as compared to warfarin. Dabigatran has been shown to increase the excretion of 11-dehydrothromboxane B2 in patients who were not taking aspirin which suggests a potential platelet- activating effect of dabigatran.[36] Another explanation offered to explain the observed increased risk of MI in patients taking dabigatran is that there is less effective attenuation of thrombin generation as compared with warfarin.[37] Further investigations are needed to clarify the association between increased incidence of MI in patients taking dabigatran.

Factor Xa Inhibitors

Rivaroxaban

Factor Xa is another promising target of anticoagulation; it

Table 2: Various investigational coagulation assays for the newer anticoagulants

Investigational coagulation Assays	Effect of Newer Oral Anticoagulants	References
Ecarin Clotting time	Found to have a simple linear relationship with anticoagulation activity of dabigatran	29,46,47
Thrombin Time (TT)	Especially helpful in preoperative setting	48,49
Hemoclot direct thrombin inhibitor assay (HTI)	Investigated for dabigatran, has a higher sensitivity and good reproducibility	50
Prothrombin Time (INR)	Current data doesn't seem promising for its use in the setting of newer anticoagulants	51
Activated Partial Thromboplastin time (aPTT)	Prolonged in a dose-dependent exponential manner by Rivaroxaban	51
Anti Factor Xa chromogenic assays	Based on the release of color proportional to the amount of factor Xa present, currently investigational	56,57,58

occupies a critical juncture in the coagulation cascade and controls thrombin generation. Rivaroxaban is a factor Xa inhibitor which indirectly decreases the generation of thrombin, thus diminishing thrombin- mediating activation of both coagulation and platelets, without affecting the activity of thrombin itself.

Rivaroxaban has a high oral bioavailability; it achieves peak plasma concentrations in approximately 2-4 hours and has an estimated half-life of 5-9 hours. The extent of renal excretion of rivaroxaban has been estimated to be about 66 % and approximately 33 % of the drug is metabolized by the liver.[38,39] The metabolism of rivaroxaban is affected by concomitant intake of strong inhibitors of cytochrome P450 such as ketoconazole and ritonavir .[40]

Rivaroxaban was first investigated in the ROCKET- AF (The Rivaroxaban Once Daily Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) which included 14,264 patients who had a median age and CHADS2 score of 73 years and 3.0 respectively. Patients were assigned to receive either rivaroxaban 20 mg once daily or an INR adjusted dose of warfarin (to maintain a target INR of 2.0 to 3.0). In this non- inferiority clinical trial, rivaroxaban was demonstrated to be at least as effective as warfarin for prevention of stroke and systemic embolism (1.7% in rivaroxaban arm vs. 2.2 % in the warfarin arm; p < 0.001). Rivaroxaban was also demonstrated to have a lower incidence of hemorrhagic stroke (HR 0.59, 95 % CI: 0.37-0.93, p= 0.024). The rate of overall bleeding (major and clinically relevant nonmajor bleeding) was 14.9 % per year in the warfarin arm as compared to 14.5 % per year in the rivaroxaban arm (HR in rivaroxaban group, 1.03, 95 % CI: 0.96- 1.11; p = 0.44). The rate of major bleeding were similar in the rivaroxaban and warfarin groups (3.6 % and 3.4 % respectively; p = 0.58). There were fewer intracranial bleeds in the rivaroxaban arm as compared to warfarin (0.5 % vs.0.7 %; HR 0.67; 95 % CI 0.47-0.94; p= 0.019). The rate of major bleeding from a gastrointestinal site however was found to be increased in the rivaroxaban arm as compared to the warfarin arm (3.2 % vs. 2.2 % respectively; p < 0.001) .[41] Based on the favorable results of the ROCKET- AF trial, rivaroxaban was approved for prevention of stroke in patients with AF by the FDA in November 2011.

Apixaban

Apixaban is another direct, oral, selective inhibitor of factor Xa which has a bioavailability of 43- 46 % and it achieves its peak plasma concentration in about 1-3 hours. Apixaban has multiple pathways of elimination; renal and fecal excretion both account for approximately 25 % each .[42] Apixaban is metabolized by CYP3A4/3A5 dependent pathways, these multiple pathways of elimination makes apixaban a suitable anticoagulant for patients with renal insufficiency .[43]

Apixaban was investigated for prevention of stroke in patients with AF in the AVERROES (Apixaban Versus Acetylsalicylic Acid to prevent Stroke in Atrial Fibrillation patients who have failed or are unsuitable for VKA treatment). This study compared apixaban at a dose of 5 mg twice daily with aspirin at a dose of 81-324 mg for prevention of stroke. The dose of apixaban was reduced to 2.5 mg twice daily in patients who were availolder than 80 years, weighed < 60 kg and had a serum creatinine of > 1.5 mg/dl. In this study apixaban was found to reduce the risk of stroke and systemic embolism (1.6% in the apixaban arm vs. 3.7 % in the aspirin arm; p < 0.001). The use of apixaban was not found to be associated with increased incidence of bleeding (1.4 % in apixaban arm vs. 1.2 % in aspirin arm, p = 0.57).[44]

Apixaban was compared head-to-head with warfarin in the ARISTOTLE (Apixaban for Reduction In STroke and Other ThromboemboLic Events in atrial fibrillation) trial. This trial compared apixaban at a dose of 5 mg twice daily with a dose adjusted warfarin for a target INR of 2.0 to 3.0 in a total of 18,201 patients with AF. After a median follow up of 1.8 years, apixaban was found to be superior than warfarin for reduction of stroke (1.27 % per year in apixaban arm vs. 1.60 % per year in warfarin arm, p= 0.01 for superiority of apixaban). The use of apixaban was also found to have comparatively lesser risk of bleeding than warfarin (2.13 % per year in apixaban arm vs. 3.09% per year in the warfarin arm, p < 0.001). Apixaban was also found to be associated with a reduction in all-cause mortality as compared to warfarin (3.52 % per year vs. 3.94 %; HR, 0.89; 95 % CI: 0.80-0.99; p = 0.047).[45] Following these

Table 3: Advantages and disadvantages of Newer oral anticoagulants in comparison with warfarin

Drug	Advantages	Disadvantages
Warfarin	Long history of clinical experience [11-14] Once-a-dosing Availability of antidote	Narrow therapeutic window [7-10, 15,16] Slower onset and offset of action [7-10] Drug-drug and drug-food interactions [19-21]
Dabigatran	Predictable dose related clinical effect [29,30] Comparatively lesser drug interactions [29,30] No requirement of routine monitoring [29,33] Cost effective than warfarin for stroke prevention in AF [65,66,69]	Accumulation in renal insufficiency [30,32] Gastrointestinal side effects [33] Twice daily dosing [33] Increased cardiac risk reported [33,35] Lack of monitoring assays in the setting of bleeding complications [29,46-49] Lack of monitoring options to confirm compliance [29,46-49] Lack of antidote for reversal [59-64]
Rivaroxaban	Once-a-day dosing [38,39] Predictable dose related clinical effect [38,39] Lower incidence of hemorrhagic stroke as compared to warfarin [41] Cost effective than warfarin for stroke prevention in AF [67,69]	Metabolism is affected by CYP 450 inhibitors [40] Shown to have increased risk of gastrointestinal bleeding as compared to warfarin [41] Lack of clinically validated monitoring options for compliance and bleeding complications [52-56] Lack of antidote for reversal [59,60]
Apixaban	Predictable clinical effect [42] Minimal drug interactions [42,43] Relatively safer option in renal impairment [43] Shown to have mortality benefit [45] Cost effective than warfarin for stroke prevention in AF [69]	Twice daily dosing [42] Lack of clinically validated monitoring options for compliance and bleeding complications [52-56] Lack of antidote for bleeding complications [64]

results, apixaban was approved by the FDA for prevention of stroke in patients with AF in December 2012.

The risk of overall mortality was also found to be reduced in the dabigatran arm of the RE-LY trial but it did not reach statistical significance (4.13 % per year in the warfarin arm vs. 3.75 % per year in the dabigatran 110 mg arm; RR with dabigatran, 0.91; 95 % CI: 0.80-1.03; p = 0.13) and 3.64 % in the dabigatran 150 mg arm (RR with dabigatran, 0.88; 95 % CI: 0.77-1.00; p = 0.051).[33] Similar results of a decreased mortality although statistically insignificant were also observed in the rivaroxaban arm in the ROCKET AF arm (1.9 % per year in the rivaroxaban arm vs. 2.2 % per year in the warfarin arm, HR with rivaroxaban, 0.85; 95 % CI: 0.70-1.02; p = 0.07).[41]

Monitoring of Newer Anticoagulants

The recent development and increased use of newer anticoagulants has created the necessity for newer coagulation assays for monitoring of these agents. The use of these assays will be especially useful in the setting of outpatient clinical practice to monitor compliance and to treat patients in the event of overdose and bleeding complications.

Ecarin clotting test (ECT) is currently being investigated for monitoring the effects of DTIs. Studies in healthy volunteers have demonstrated a close linear relationship between ECT prolongation and plasma concentration of DTIs .[29,46] ECT ratios of 2-4 have been observed after administration of dabigatran at a dose of 150 mg bid.[46] Clinical experience so far supports the use of use of ECT as a sensitive test for measuring anticoagulant activity in orthopaedic patients and during cardiopulmonary by-pass surgery, with superiority over the aPTT. Further investigation is warranted to further support the use of ECT for monitoring the effects of dabigatran.[47]

Thrombin time (TT) is another coagulation assay which is currently being investigated to monitor the effect of newer anticoagulants. The TT assay directly assesses the activity of thrombin in a plasma sample and therefore provides a direct measure of the activity of DTIs. TT assay displays a linear dose-response over therapeutic concentrations. A normal TT assay can be used to rule out excessive anticoagulant effect of dabigatran especially in the surgical setting prior to procedures.[48,49]

Hemoclot direct thrombin inhibitor assay is also currently being investigated for detecting the anticoagulant effect of dabigatran. Current data suggest that this assay could be useful for determining the anticoagulant activity and calculating plasma concentrations of dabigatran using simple and widely available chronometric coagulation devices.[50] A study by Douxfils aimed at investigating the effect of dabigatran on various coagulation assays also supported the use of Hemoclot direct thrombin inhibitor assay as a tool to monitor the anticoagulation activity of dabigatran.[51] (Table 2)

Rivaroxaban has been widely shown to have well-defined effects on the coagulation assays; however the standardized tests are not yet avail older able for monitoring for its anticoagulant effect. The traditional coagulation assays such as Prothrombin time (PT) are not suitable for the monitoring of rivaroxaban.[52] Rivaroxaban also has a weak concentration-dependent effect on activated partial thromboplastin time (APTT) making it a less sensitive measure of rivaroxaban activity.[53]

Anti- Factor Xa chromogenic assays have been investigated for measurement of the anticoagulation effect of rivaroxaban and apixaban. In the anti-Factor Xa assay, a FXa chromogenic substrate is used and the color released is proportional to the amount of FXa present. When a known amount of FXa is added to the plasma containing the drug, the amount of inhibitory (anti-FXa) activity in the plasma can be determined from a standard curve. HepTest and Prothrombinase -induced clotting time (PiCT) with a shortened or no incubation time to increase sensitivity could be used as sensitive pharmacodynamic parameters to measure the anticoagulant effect of rivaroxaban. Based on the current data so far it seems reasonable to use PT as an initial screening test for rivaroxaban and if the value exceeds the cut-off then the chromogenic assays can be utilized.[54-56]

Apixaban also has a prolonging effect on the PT and APTT but this effect cannot be standardized and compared across the laboratories. Chromogenic assays are also being investigated for measuring the anticoagulant effect of apixaban; currently available data suggest that the chromogenic assays could be more sensitive as compared to the PT and INR. Currently the chromogenic assays can be used with either the automated coagulometers or with low-cost manual spectrometers, however these assays are not currently approved for patient care purposes and additional validation is required before they can be made widely available for clinical purposes.[57,58]

Comparison of Older versus Newer Anticoagulants

Warfarin has been used for various indications of anticoagulation over several decades. Despite its proven clinical efficacy, various drawbacks associated with its use make its use inconvenient for patients and health care providers. The safety and clinical efficacy of warfarin are directly influenced by the time spent by patients in the therapeutic range. Anticoagulation clinical services are a crucial element for the use and monitoring of warfarin. Newer anticoagulants offer a distinct advantage of having a fixed dose related effect and eliminating the need of constant monitoring of anticoagulant effect. The newer anticoagulants also have an advantage of fewer drug- drug and drug-food interactions which offers a superior safety profile as compared to warfarin. Warfarin has a slower onset and offset of action which necessitates the use of parenteral anticoagulants at the time of its initiation and interruption especially in the surgical settings, newer anticoagulants have the advantage of rapid onset and offset of action which allows them to be discontinued before the procedure and obviates the need of bridging therapy.

Management of Bleeding with Newer AntiCoagulants

A major limitation associated with the use of newer anticoagulants is the lack of an effective antidote unlike warfarin, which is of key importance especially in the setting of excessive anticoagulant effect and an urgent intervention is warranted. There is a paucity of large randomized clinical studies investigating strategies to reverse the effects of newer oral anticoagulants, lack of standardized coagulation assays for monitoring also makes the management of bleeding complication difficult. Recombinant factor VIIa (rfVIIa) is increasingly being investigated for its use as a potential reversal agent for DTIs and FXa inhibitors. Preclinical studies have shown it to be more effective in reversing the effect of Fxa inhibitors as compared to DTIs.[59,60] (Table 3)

Prothrombin complex concentrate (PCC) is another antidote which is also being investigated for its ability to reverse the anticoagulant effect of rivaroxaban and dabigatran, in a small study on 12 healthy male volunteers, PCC at a dose of 50 IU/Kg was found

to reverse the effect of rivaroxaban but was ineffective in reversing the effect of dabigatran.[61]

Dabigatran exhibits low protein binding and therefore it may be feasible to remove it from the circulation by dialysis. The plasma concentration of dabigatran can be reduced by 50-60% after 4 hours of dialysis.[62,63] Hemodialysis if readily available can be a useful strategy particularly in emergency situations to treat the bleeding complications in patients taking dabigatran.

Tranexamic acid is another useful agent which can be utilized to manage the bleeding complications of dabigatran in emergency setting. It inhibits fibrinolysis by inhibiting the binding of plasmin to fibrin. In an event of a major bleeding secondary to dabigatran, 1 gram tranexamic acid can be given intravenously as one of the initial interventions.[62] It is also worth keeping in mind that although both dabigatran and rivaroxaban prolong the PT and APTT, they do so by inhibition rather than depletion of factors, thus fresh frozen plasma (FFP) might not be effective in management of bleeding due to these agents .[64]

Cost Efficacy of Newer Anticoagulants

Multiple studies have investigated the cost effectiveness of newer anticoagulants in comparison to warfarin. A study by Sorensen et al demonstrated that dabigatran was more cost-effective as compared to warfarin for prevention of stroke and systemic embolism in patients with AF.[65] Similar favorable results for cost-effectiveness of dabigatran were also observed in another study by Freeman et al.[66] Rivaroxaban was also found to be a cost- effective alternative to a dose-adjusted regiment of warfarin for stroke prevention in patients with AF based on the ROCKET-AF and other studies of anticoagulation.[67] In another recently published study by Kamel et al, apixaban was compared with warfarin based on the ARISTOTLE trial and other trials of warfarin therapy for stroke prevention in patients with AF, based on the cost-effective analysis model, apixaban was found to be cost-effective relative to warfarin for stroke prevention in patients with AF.[68] Another cost efficacy analysis for stroke prevention in patients with AF which compared dabigatran 150 mg , rivaroxaban 20 mg and apixaban 5 mg found all the newer oral anticoagulants to be cost-effective than warfarin. [69]

The superior cost efficacy of newer anticoagulants could be partly explained by the fact that newer anticoagulation agents do not routinely require anticoagulation services for monitoring and are associated with less severe bleeding complications as compared to warfarin.

Conclusions:

Research over the last decade has led to expansion of the therapeutic options for anticoagulation. Since the approval of dabigatran in 2010 by the FDA its use in day to day clinical practice continues to increase. Rivaroxaban and apixaban have also been recently approved for prevention of stroke in patients with AF. Along with warfarin these newer anticoagulants have provided physicians multiple options for anticoagulation in clinical practice. Patients with highly variable INRs, with concurrent interacting medications, or who are unable to comply with the frequent laboratory monitoring associated with warfarin may be suitable candidates for the use of newer anticoagulants. Further randomized clinical trials will also provide useful information about safety of these agents in a wide range of patient subgroups and pertinent clinical data based on direct comparison of these agents. Considerable effort is being devoted to develop newer coagulation assays which will help in further management of patients on newer anticoagulants. Further research will continue to expand the armamentarium of anticoagulant options in clinical practice.

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