Risk versus Benefit of Non-Vitamin K Dependent Anticoagulants Compared to Warfarin for the Management of Atrial Fibrillation in the Elderly

Kelechi C. Ogbonna · Sean M. Jeffery

Abstract  The objective of this review was to compare the safety and efficacy of dabigatran, rivaroxaban and apixaban to warfarin for the management of atrial fibrillation (AF) in older adults. The prevalence and incidence of AF increase with age. Approximately 5 % of the United States population over the age of sixty-five years and 10 % over the age of seventy-nine years have AF. AF is associated with increased risk for thromboembolic events. Despite the increasing incidence and prevalence of AF in older adults and the risks of thromboembolic events, clinicians often avoid anticoagulants. Specifically with warfarin, the risk of hemorrhage may outweigh the benefit in stroke risk reduction in certain populations. Aspirin, while safer to use, is not as effective as warfarin in stroke risk reduction. Newer non-vitamin K dependent antithrombotic therapies (e.g. dabigatran, rivaroxaban, and apixaban) are redefining thromboprophylaxis of AF. Dabigatran, rivaroxaban, and apixaban are at least as effective as warfarin in stroke risk reduction. With new mechanisms of action and no need for therapeutic drug monitoring, countless new patients are potential candidates for anticoagulation. However patient adherence, lack of a reversal agent, cost, and other safety concerns remain reasons for caution and careful consideration. Furthermore, older adults exhibited greater adverse effects from these agents across the clinical trials. This review will examine the newer anticoagulants safety and efficacy with particular attention to their role in treating older adults with AF. Alternatives to warfarin therapy now exist for thromboprophylaxis of AF. Whether these agents represent advances in overall safety in older adults remains uncertain. More experience and research are needed before endorsing their widespread use as a replacement for warfarin in the geriatric population.

1 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia seen in clinical practice [1]. AF causes increased morbidity and mortality secondary to thromboembolic events among those affected. The prevalence and incidence of AF increases with age [2]. Approximately 5 % of the population over the age of sixty-five years and 10 % over the age of seventy-nine years are affected by AF [3]. As the proportion of patients 65 years and older expands, the number of geriatric patients with AF will also increase. The decision to initiate anticoagulant therapy is complicated in older adults. Factors that influence adherence, tolerability, access, drug–drug interactions, and complications are all more prevalent in older adults. Clinicians therefore must appropriately balance the benefits and risks of anticoagulation therapy in older adults. This review will examine the newer anticoagulants safety and efficacy with particular attention to their role in treating older adults with AF.
2 Determining Stroke Risk

AF can result in the thromboembolic events such as ischemic stroke, transient ischemic attacks and pulmonary embolism. Approximately 15 % of all strokes in the United States are due to AF [3]. The CHADS2 scoring system is one tool used for stroke risk stratification and determining antithrombotic therapy (Table 1) [4]. The terminology “CHADS2” is a mnemonic used to identify major stroke risk factors for patients with AF. One point is assigned for patients with congestive heart failure (C), hypertension (H), age ≥ 75 years (A), and diabetes (D). Two points are assigned for a previous stroke or transient ischemic attack (S2) [5, 6]. The CHADS2 scoring system guides clinicians in determining the need for anticoagulant therapy (Table 2). For example, a CHADS2 score of 1 would guide a practitioner to select between warfarin or aspirin therapy.

Current recommendations suggest the use of anticoagulation therapy over aspirin in the absence of contraindications for patients with CHADS2 = 1 [7]. Other tools are now available to further clarify appropriate therapy based on patient specific risk factors.

The Birmingham Schema was developed to better stratify intermediate risk patients who would benefit from warfarin therapy. Lip et al. [6] refined the CHADS2 scoring system into low (CHADS2 Score = 0), intermediate (CHADS2 Score = 1), or high risk (CHADS2 Score ≥ 2) patients. Known as the CHA2DS2-VASc, this mnemonic identifies vascular disease (V), age between 65 to 74 years, and female sex (S) as additional risk factors to the original risk stratification system (CHADS2) (Table 3). Each additional risk factor is assigned one point and age >75 years identified in the original CHADS2 was increased from 1 to 2 points.

To understand the differences in scoring systems consider the “Euro Heart Survey on Atrial Fibrillation”. Here the CHADS2 identified 60 % of patients as intermediate risk. By comparison, the Birmingham Schema identified only 15 % of patients as intermediate risk, while approximately 75 % were classified as high risk and needing warfarin therapy [6]. This CHA2DS2-VASc scoring system refined the open interpretation of intermediate risk and made identification of patients needing warfarin more concise.

3 Warfarin (Vitamin K Antagonist)

3.1 Description and Mechanism

Warfarin’s mechanism of action is best understood through its relationship with vitamin K. Vitamin K is a cofactor for carboxylation of vitamin K-dependent proteins, such as coagulation factors II, VII, IX, and X. These vitamin K-dependent factors require carboxylation for biologic activity. When warfarin interrupts conversion of vitamin K, Current recommendations suggest the use of anticoagulation therapy over aspirin in the absence of contraindications for patients with CHADS2 = 1 [7]. Other tools are now available to further clarify appropriate therapy based on patient specific risk factors.

The Birmingham Schema was developed to better stratify intermediate risk patients who would benefit from warfarin therapy. Lip et al. [6] refined the CHADS2 scoring system into low (CHADS2 Score = 0), intermediate (CHADS2 Score = 1), or high risk (CHADS2 Score ≥ 2) patients. Known as the CHA2DS2-VASc, this mnemonic identifies vascular disease (V), age between 65 to 74 years, and female sex (S) as additional risk factors to the original risk stratification system (CHADS2) (Table 3). Each additional risk factor is assigned one point and age >75 years identified in the original CHADS2 was increased from 1 to 2 points.

To understand the differences in scoring systems consider the “Euro Heart Survey on Atrial Fibrillation”. Here the CHADS2 identified 60 % of patients as intermediate risk. By comparison, the Birmingham Schema identified only 15 % of patients as intermediate risk, while approximately 75 % were classified as high risk and needing warfarin therapy [6]. This CHA2DS2-VASc scoring system refined the open interpretation of intermediate risk and made identification of patients needing warfarin more concise.

3 Warfarin (Vitamin K Antagonist)

3.1 Description and Mechanism

Warfarin’s mechanism of action is best understood through its relationship with vitamin K. Vitamin K is a cofactor for carboxylation of vitamin K-dependent proteins, such as coagulation factors II, VII, IX, and X. These vitamin K-dependent factors require carboxylation for biologic activity. When warfarin interrupts conversion of vitamin K,
it inhibits the formation of vitamin K-dependent clotting factors (Figure 1) [7].

Warfarin’s efficacy is established for numerous indications including prophylaxis of venous thrombosis, treatment of venous thromboembolism, and atrial fibrillation [7]. For most indications, an INR range of 2.0 to 3.0 is recommended [7]. There have been five pivotal randomized control trials evaluating the safety and efficacy of warfarin in primary stroke prevention in patients with AF [4, 8–11]. In all five trials, warfarin utilization decreased the risk of stroke by approximately 68 % and had relatively low rates of hemorrhagic complications with low-intensity therapy [12].

3.2 Factors that Improve Warfarin Therapy Outcomes

To understand the potential value of new anticoagulants in older adults it is necessary to understand the known risks and benefits of warfarin therapy. All newer agents must demonstrate non-inferiority to warfarin therapy. Therefore, selecting suitable warfarin patients, achieving goal INRs, and maintaining a time in therapeutic range (TTR) > 65 % will significantly influence stroke risk reduction [13].

While warfarin utilization is highly effective in preventing stroke, the complexities of management create challenges for older adults [4, 8–10, 12]. In addition to the potential bleeding complications with warfarin use, patient monitoring requires significant care-coordination. Initiation of warfarin therapy requires frequent blood tests, patient-provider communication, dose adjustments, and potential dietary changes; all of which may be more difficult for elderly patients. In fact, age is an important variable in determining warfarin therapy success. There is an interaction between the complexity of warfarin management and a patient’s age that influences provider’s decisions to initiate therapy. McCrory and colleagues [14] conducted a nationwide survey to assess provider beliefs and attitudes regarding risks versus benefit of anticoagulation at certain ages (55, 65, and 75 years). The researchers found that elderly patients were less likely to receive anticoagulants when compared to their younger counterparts based solely on age.

Time in therapeutic range (TTR) is another major determining factor for warfarin efficacy and can be measured by a variety of methods. The advantages and disadvantages of each have been described elsewhere [15]. One of the more common methods, percent in range, divides the number of INR values for all patients within the target range by the number of INRs during the selected time period. The ability to maintain TTR directly correlates to warfarin’s derived benefit. Any advantage of warfarin over antiplatelet therapy is lost when the TTR falls below the threshold of 58 % to 65 % [16]. Therefore, positive outcomes are highly dependent on monitoring, adherence, and time in therapeutic range. The TTR with warfarin varies significantly depending on the setting, provider, and patient. McCormick et al. [17] reviewed the medical records of patients residing in 21 long-term care facilities in the state of Connecticut. Their objective was to determine the percentage of patients with AF and the number of “ideal warfarin patients” (i.e. AF patients with no risk factors for hemorrhage) receiving anticoagulation. In addition, data was collected to determine the amount of time patient’s INR was within a therapeutic range (INR between 2 and 3).

Of the 2,587 patient records that were reviewed, a diagnosis of AF was present in 429 patients or 17 %. Only 42 % of the 429 patients with AF were receiving warfarin therapy and the goal INR of 2 to 3 was maintained only 51 % of the time. There were 83 patients found to have no risk factors for hemorrhage. Of these “ideal candidates” for warfarin therapy, only 44 (53 %) were actually receiving warfarin therapy. McCormick and colleagues [17] concluded “the low percentage of residents who received warfarin still suggests that physicians may weigh more heavily the risk for bleeding complications of warfarin therapy than the risk for stroke in patients with untreated AF”. Furthermore, the intensity (target international normalized ratio [INR] or prothrombin time ratio) at which therapy was initiated was also lower among older patients.

TTR is dependent on the setting in which a patient is managed. As discussed above, McCormick et al. described substantial variability in long-term care patients being managed with warfarin. Aspinall et al. [18] evaluated warfarin prescribing and monitoring in Veteran Affairs (VA) nursing homes and also found significant variability in TTR. The VA setting was chosen because of access to and availability of computerized provider order entry,
in-house providers (pharmacist, physicians, etc.), and on-site laboratory services. VA patients in this setting achieved an average TTR of 55%. Patients on chronic therapy were more likely to maintain a TTR > 50% than those who initiated therapy during the study, suggesting a learning curve with warfarin.

Young et al. [19] compared a pharmacist-managed anticoagulation program to usual physician care within a family practice setting. Approximately 200 patients’ charts were reviewed over a 17-month period. The TTR obtained in the pharmacist group was 73% versus 65% in the usual care group (p < 0.0001). While both groups achieved satisfactory results, significantly more patients were better controlled in the pharmacist group.

These studies highlight the importance of the setting and resources available to both the patient and clinician in managing warfarin therapy. The continuous follow-up required for warfarin may also improve outcomes by increasing awareness and patient observation. While the INR provides a marker for degree of anticoagulation, it also requires frequent blood testing which can be burdensome and inconvenient.

3.3 Challenges Associated with Warfarin Management

Response to warfarin therapy is highly variable and influenced by differences in absorption, clearance, genetic variations, dietary concerns, and drug interactions. As adults age, the body undergoes a variety of changes that affect the pharmacokinetics and pharmacodynamics of drug therapy. Older adults often have decreased serum protein, impaired renal function, and liver changes all of which are involved in warfarin distribution and metabolism [20]. Warfarin is metabolized through cytochrome P450 enzymes (2C9, 2C19, 2C8, 2C18, 1A2, and 3A4) and renally eliminated. The elimination half-life of warfarin can vary from 20 to 60 hours. Time to steady state ranges from 5 to 8 days [21]. These confounders partially explain the variable response to warfarin management, adverse effects, and diminished TTR often seen in the elderly.

Drug–drug interactions and drug–food interactions frequently complicate warfarin management. Warfarin’s metabolism is inhibited by drugs such as metronidazole and amiodarone or induced by agents such as rifampin and carbamazepine. Medication reconciliation and identification of interacting drugs is necessary prior to initiation of warfarin therapy. Consideration should be given to patients consuming foods high in vitamin K. By consuming vitamin K rich foods, vitamin K is recycled allowing the formation of vitamin K dependent clotting factors. If patients are consistent with vitamin K containing food intake, clinicians can adjust the warfarin dosing to account for this interaction.

3.4 Hemorrhagic Risks

Bleeding is the most common complication of warfarin therapy. Of the bleeding events that can occur, intracranial hemorrhaging (ICH) is associated with a high risk of death and lasting neurologic deficits [22]. An intracranial hemorrhage can be devastating and fatal in the elderly given frailty and other co-morbidities [14]. Patient co-morbidities and intensity of anticoagulant therapy affect a patient’s bleeding risk. There is approximately a 5% to 10% chance of bleeding associated with each year of anticoagulant [23]. Furthermore, several studies have proven that age alone does not increase the risk of anticoagulant-induced bleeding [24, 25].

Fang and colleagues [22] conducted a case-control study to evaluate the relationship of increasing age and INR to the risk for ICH among patients with non-valvular atrial fibrillation. The researchers evaluated 170 case-patients who developed intracranial hemorrhage during warfarin therapy and 1020 matched controls. The risk for ICH increased at age 85 years and older (adjusted odds ratio, 2.5 [95% CI, 1.3 to 4.7] referent age, 70 to 74 years) and at an INR range of 3.5 to 3.9 (adjusted odds ratio, 4.6 [CI, 2.3 to 9.4]; referent INR, 2.0 to 3.0). In addition, the risk of ICH did not differ between INR goals of < 2 versus 2.0 to 3.0 (adjusted odds ratio, 1.3 [CI, 0.8 to 2.2]). Patients evaluated in this study were older than controls and had higher median INRs (2.7 versus 2.3; p < 0.001). Based on their results, the risk for ICH is not diminished in elderly patients with AF when anticoagulation is maintained below an INR of 2.0.

To compensate for the potential of hemorrhage some providers target lower INR ranges. However this strategy may increase the risk of stroke particularly when an INR less than 2.0 is targeted [16, 26, 27]. The most recent American College of Chest Physicians’ (ACCP) CHEST Guidelines now recommend a goal INR range of 2.0 to 3.0 for the majority AF patients being treated with vitamin K antagonists (VKA) regardless of age [7].

In 2007 the American Heart Association evaluated the tolerability of warfarin in elderly patients with AF ≥ 65 years of age [28]. The outcomes of this study were major hemorrhage, time to termination of warfarin, and reason for discontinuation. Of the 472 patients enrolled, 32% were ≥ 80 years of age, and 91% had at least 1 stroke risk factor. Results revealed the rate of major hemorrhage was 7.2% (95% CI 4.9 to 10.6), and the rate of ICH was 2.5% (95% CI 1.1 to 4.7). Patients ≥ 80 years of age experienced higher rates of bleeding when compared to their younger counterparts (13.08 per 100 person-years versus 4.75 per 100 person-years, p < 0.010) [28].

Safety concerns accounted for 81% of those patients ≥ 80 years of age who stopped treatment during the first
year compared with just 37 % in patients < 80 years of age. Reasons for stopping in older patients were secondary to bleeding complications (n = 17), falls (n = 9), non-adherence (n = 5), coagulopathies (n = 3), and 1 dermatologic reaction. The researchers concluded major hemorrhage is underestimated in the geriatric population compared to younger, previously published non-inception cohort studies. Furthermore, the higher rates of bleeding seen in clinical practice and poor patient tolerability likely contribute to underutilization of warfarin.

Although older adults are at increased risk of bleeding when INR is above 3.0, both the BAATAF and SPAF III trials showed that targeting a median INR range less than 3.0 but greater than 1.4, is safe and effective in reducing the risk of stroke in elderly patients and results in relatively low bleeding events [8, 29, 30]. Further evaluating the importance of targeted therapy, the SPORTIF III and SPORTIF V studies revealed that rates of bleeding were higher in patients with poor INR control when compared to their counterparts with good INR control (goal 2.0-3.0) [31]. When managed appropriately and in the absence of contraindications, warfarin therapy can be used safely and effectively in older adults [32, 33].

3.5 Non-Vitamin K Dependent Anticoagulants

Warfarin is perhaps one of the most studied drugs in medicine. Providers however have longed for a replacement that allows for greater ease of use, reduced complications and greater efficacy. With the introduction of non-vitamin K dependent antithrombotic therapies (i.e. dabigatran, rivaroxaban, and apixaban) clinicians have new options that alter the risk to benefit ratio when treating elderly patients at high risk of thromboembolism. When compared to warfarin, these newer agents appear as effective, with potentially fewer side effects. Recent clinical trials all have demonstrated non-inferiority with warfarin [34–36]. However, the long term safety implications for the elderly are still evolving.

4 Dabigatran (Direct Thrombin Inhibitor)

4.1 Description and Mechanism

Dabigatran is the first new oral anticoagulant in over 50 years. More importantly, dabigatran does not require routine blood level monitoring and dietary adherence. Dabigatran represents a new approach to anticoagulation as it is a specific, competitive, and reversible direct thrombin inhibitor. Thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade. Inhibiting thrombin prevents the development of a thrombus. Both free and clot-bound thrombin and thrombin-induced platelet aggregation are inhibited by dabigatran’s active moieties. Unlike warfarin, dabigatran only acts on one factor of the coagulation cascade, possibly allowing for a more predictable pharmacokinetic profile (Figure 1).

4.2 Indication and Clinical Evidence

Dabigatran was approved by the Food and Drug Administration (FDA) in 2010 to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The Randomized Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY) compared two fixed doses of dabigatran to warfarin in patients with AF who were at increased risk of stroke [34]. A total of 18,113 patients were randomized to receive either 110 mg or 150 mg of dabigatran in a blinded fashion or INR targeted warfarin in an un-blinded fashion. Dabigatran 150 mg was superior to warfarin with significantly lower rates of stroke and systemic embolism (1.11 % versus 1.69 %; p < 0.001), with similar rates of bleeding (3.31 % versus 3.57 %; p = 0.32). The dabigatran 110 mg dose had similar rates of stroke and systemic embolism compared to warfarin (1.53 % versus 1.69 %; p < 0.001) with lower rates of major bleeding (2.87 % versus 3.57 %; p < 0.002). The estimated relative risk for ischemic stroke, hemorrhagic stroke, and pulmonary embolism with dabigatran 150 mg BID was 0.76 [95 % CI 0.60–0.98], 0.26 [95 % CI 0.14–0.49], 0.65 [95 % CI 0.52–0.81] respectively.

Overall results indicated dabigatran was as effective (110 mg dose) or superior to warfarin (150 mg dose). However several important caveats need further consideration. Important to geriatrics, all patients in RE-LY were > 65 years of age, with an average age of 71. Most were male (63.6 %) with an average CHADS2 score of 2.1, suggesting they were a lower risk population. Discontinuation rates at years 1 and 2 were higher with dabigatran than warfarin irrespective of dose (p < 0.001). Serious adverse events were reported as the most common reason for discontinuation. The median TTR was 67 % in the control arm. This suggests warfarin was adequately managed [34]. In the centers that achieved an INR range above the median TTR of 67 %, dabigatran failed to show a statistically significant decrease in risk of stroke or systemic embolism (RR 0.76, 95 % CI 0.55–1.05).

The 110 mg dose studied in the RE-LY trial was not approved in the United States as it failed to demonstrate an advantage over warfarin [37]. The FDA did however approve a 75 mg dose intended for patients with renal impairment [CrCl 15–30 mL/min]. This 75 mg dose was never studied in clinical trials and was approved solely on analysis of preclinical data [38].

△ Adis
4.3 Pharmacokinetic and Pharmacodynamic Properties

Dabigatran is formulated as a pro-drug and is absorbed as the dabigatran etexilate ester. The etexilate ester is then hydrolyzed forming dabigatran, the active moiety. Dabigatran etexilate is more consistently absorbed in an acidic environment. Therefore, dabigatran etexilate is applied to a tartaric acid core which is then encapsulated. The tartaric acid core creates a stable acidic environment allowing for less dependence on gastrointestinal acidity (Figure 2).

The absolute bioavailability of dabigatran etexilate is approximately 7%. Hydrolysis is mediated by esterases creating four active acyl glucuronides that have pharmacological activity similar to the parent compound, dabigatran (Table 4). Dabigatran absorption is affected by P-glycoprotein (P-gp) transporters. This efflux pump prevents the absorption of dabigatran etexilate and forces the drug back into the lumen. Any concomitant drug capable of inducing or inhibiting the P-gp transporter will effects dabigatran plasma concentrations.

Dabigatran is eliminated via renal excretion. During the RE-LY study, patients with reduced renal function experienced increased dabigatran trough levels prior to each dose. This resulted in dabigatran half-life increasing from the expected 13 hours to 15, 18, and 27 hours in mild, moderate, and severe renal dysfunction respectively. Patients receiving dabigatran should have renal function assessed at baseline and at regular intervals.

4.4 Contraindications and Precautions

Active bleeding and predisposition to hemorrhage are contraindications to dabigatran. The manufacturer recommends precaution in advanced age. A follow-up analysis by Eikelboom and colleagues [39] concluded that dabigatran 110 mg twice a day, when compared to warfarin, was associated with a lower risk of major bleeding in patients aged <75 years of age (1.89 % versus 3.04 %; p < 0.001). However, those ≥ 75 years of age had similar risk of major bleeding (4.43 % versus 4.37 %; p = 0.89).

The analysis also evaluated dabigatran 150 mg twice a day compared with warfarin. The 150 mg dose of dabigatran was associated with a lower risk of major bleeding in those aged <75 years of age (2.12 % versus 3.04 %; p < 0.001), but a trend toward higher risk of major bleeding in those aged ≥75 years of age (5.10 % versus 4.37 %; p = 0.07). This overall trend with dabigatran therapy was only observed with extra-cranial bleeding. Intracranial bleeding was lower with both doses of dabigatran compared with warfarin regardless of age [39]. The potential for an “age-interaction” with dabigatran therapy requires further observation to confirm and therefore caution is suggested before prescribing dabigatran to patients greater than age 75 years.

Analysis of secondary end points identified a higher risk of myocardial infarction (MI) and acute coronary syndrome (ACS) with dabigatran [40]. This increased risk of MI/ACS did not differ among patients with or without pre-existing cardiac disease. This finding was inconclusive and will require further post-market surveillance to determine if the risk of MI or ACS is clinically significant [40].

4.5 Drug Interactions and Adverse Effects

Dabigatran has less drug–drug interactions than warfarin. Any drug–drug interactions are limited to agents that effect

\[ \Delta \text{Adis} \]

Table 4 Anticoagulant Comparison

<table>
<thead>
<tr>
<th>Property</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endogenous Target</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>6</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>Dosing Frequency</td>
<td>BID</td>
<td>Daily</td>
<td>BID</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>½ Life (h)</td>
<td>12–17</td>
<td>7–11</td>
<td>9–14</td>
</tr>
<tr>
<td>Protein Binding (%)</td>
<td>35</td>
<td>95</td>
<td>87</td>
</tr>
<tr>
<td>CYP Metabolism</td>
<td>None</td>
<td>32</td>
<td>15</td>
</tr>
<tr>
<td>P-Glycoprotein Substrate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Renal Excretion (%)</td>
<td>80</td>
<td>66</td>
<td>25</td>
</tr>
<tr>
<td>Comparison to warfarin</td>
<td>150 mg</td>
<td>Non-inferior</td>
<td>Superior</td>
</tr>
<tr>
<td></td>
<td>110 mg</td>
<td>Inferior</td>
<td>Superior</td>
</tr>
</tbody>
</table>

* Adapted from CHEST 2012; 141(2)(Suppl):e120S–e151S
efflux pump activity or acidity of the gastrointestinal tract. Drugs that inhibit P-glycoprotein (i.e. dronedarone, ketoconazole, etc.) will potentiate the anticoagulant effect, while those that induce P-glycoprotein activity such as rifampin will decrease the amount of drug available to exert an effect. Because of the significance of P-glycoprotein activity on dabigatran exposure, the manufacturer has revised the product labeling regarding renal dosing. For patients with a CrCl between 30–50 mL/min a dose reduction can be considered if being administered with dronedarone or ketoconazole. Concomitant use with any P-gp inhibitor should be avoided in patients with CrCl < 30 mL/min. Caution should also be taken with drugs capable of promoting achlorhydria. The tartaric acid core was formulated to ensure an acidic environment for absorption, but drugs that promote achlorhydria (i.e. proton pump inhibitors, H2 antagonists, etc.) may lead to decrease absorption.

Overall, dabigatran appears to be well tolerated. However, gastrointestinal adverse reactions were reported in 35% of patients during clinical trials. GI symptoms ranged from dyspepsia, abdominal pain and discomfort to significant GI bleeds. Dyspepsia associated with dabigatran is likely related to the tartaric acid core needed for absorption. The risk of major gastrointestinal bleeding was significantly higher with dabigatran 150 mg compared to 110 mg (RR 1.36 p = 0.007) and warfarin (RR 1.50 p < 0.001) [34]. Major gastrointestinal bleeding continues to be observed in multiple post-market case reports [41].

In the first quarter of 2011 the Institute for Safe Medication Practices (ISMP) identified 932 serious adverse drug events (ADEs) attributed to dabigatran [41]. Out of the 932 ADEs identified 293 were further classified as gastrointestinal hemorrhage. The ISMP elaborated further by highlighting elderly patient’s predisposition to hemorrhagic complications with dabigatran therapy. The median age for dabigatran case reports during this quarter was 80 years compared to a median age of 56 for all other drugs.

4.6 Special Consideration

Unlike warfarin, monitoring is not required with dabigatran therapy. The INR may rise while on therapy indicating dabigatran activity, however this level does not correlate with the degree of anticoagulation. It is important to note that a specific reversal agent for dabigatan does not exist. Dialysis may remove dabigatran due to its low affinity for protein binding. Approximately 60% of the drug can be dialyzed over 2–3 hours, however data is limited regarding this approach. Activated prothrombin complex concentrates, recombinant Factor VIIa, or concentrates of coagulation factors II, IX or X may be considered, but the use of these agents has not been evaluated in clinical trials.

Protamine sulfate and vitamin K will not have an appreciable effect on the anticoagulant activity of dabigatran.

Adherence to dabigatran remains an additional area of concern. Dabigatran’s relatively short half-life requires twice daily dosing. Therefore, like warfarin careful attention to patient adherence is required. However, unlike warfarin, without routine monitoring identifying non-adherent patients will require scrutiny of refill histories and direct questioning of overall patient adherence. It remains unknown how periods of non-adherence can affect overall stroke prophylaxis. Any significant decrease in adherence in the general population may attenuate some of the superiority of the 150 mg dose when compared to warfarin.

Dabigatran offers an exciting alternative to warfarin therapy, but it is important that utilization is avoided in populations where potential risks have been identified. Dabigatran does not require monitoring or dietary considerations, but it is dosed twice a day and a reversal agent has yet to be identified. Its current place in therapy for elderly patients suggests it is a promising alternative to warfarin.

5 Rivaroxaban (Anti-Factor Xa Inhibitor)

5.1 Description and Mechanism

Rivaroxaban represents the second non-vitamin K dependent anticoagulant to the US market. Differing from dabigatran, rivaroxaban has the ability to inhibit both free factor Xa and factor Xa bound in the prothrombinase complex. Inhibition of both forms prevents thrombin formation and thrombus development (Figure 1). Rivaroxaban is structurally similar to the antibiotic linezolid, but does not possess antimicrobial activity. In addition, rivaroxaban is highly protein bound and readily bioavailable. Due to its high bioavailability, rivaroxaban does not require any special formulation.

5.2 Indication and Clinical Evidence

Rivaroxaban was originally approved to reduce the risk of blood clots, deep vein thrombosis and pulmonary embolism, following knee or hip replacement surgery. Subsequently, the FDA approved rivaroxaban to reduce the risk of stroke in patients with non-valvular atrial fibrillation.

The Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD) studies provided evidence for prophylactic use of rivaroxaban following knee or hip replacement [42–44]. Four trials were conducted comparing rivaroxaban to enoxaparin for DVT prophylaxis in patients who underwent hip or knee replacement. Three of those trials, involving more than 9,000 patients, showed that fewer patients...
receiving rivaroxaban 10 mg daily had a venous thromboembolism compared to those receiving enoxaparin 40 mg daily. Rivaroxaban was deemed superior to enoxaparin in preventing DVT following knee or hip replacement.

The Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) was designed to assess efficacy in non-valvular atrial fibrillation [35]. Rivaroxaban was compared to dose-adjusted warfarin in over 14,000 patients with non-valvular AF at increased risk for stroke. Patients enrolled in this study had an average CHADS2 score of approximately 3.4, suggesting a higher risk population than that seen in the RE-LY study [35]. Rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism (2.1 % versus 2.4 %; HR 0.88; 95 % CI 0.74–1.03) [35]. The intention-to-treat analysis identified no significant differences in the risk of major bleeding between treatment groups. However intracranial and fatal bleeding occurred less frequently in the rivaroxaban group [35]. Both thrombotic and bleeding event rates were higher in older adults receiving rivaroxaban when compared to younger counterparts. Yet thrombotic and bleeding events observed with rivaroxaban were less than those seen in patients receiving warfarin.

One key difference between the ROCKET-AF and RE-LY trial was the TTR.ROCKET-AF warfarin patients achieved a mean TTR of 55 % compared to 67 % in the RE-LY study [34]. Whether the lower TTR amplified the difference between rivaroxaban and warfarin aiding to the superiority of rivaroxaban is unknown.

5.3 Pharmacokinetic and Pharmacodynamic Properties

Unlike dabigatran, rivaroxaban is highly protein bound (92–95 %) to albumin (Table 4). Poor nutritional status, hepatic impairment, and competitive protein binding can result in increased drug levels. Rivaroxaban’s pharmacokinetic and pharmacodynamic characteristics vary in different patient types (i.e. body weight, age, and gender) [45]. Elimination of rivaroxaban from the plasma differs slightly depending on age. Terminal half-lives of 5 to 9 hours in young patients increase to 12 to 13 hours in subjects 75 years of age or greater [35, 46]. While the Cmax of rivaroxaban was not affected by age, rivaroxaban exposure was 41 % higher in elderly patients compared to the younger cohort [35, 46]. These differences being deemed not clinically relevant, however the manufacturer recommends caution in patient with moderate renal impairment (CrCl 30 to 50 mL/min) and to avoid use all together in patients with severe renal dysfunction (CrCl < 30 mL/min for DVT prophylaxis, CrCl < 15 mL/min for AF).

Rivaroxaban appears to display genetic polymorphism resulting in increased exposure to rivaroxaban in patients of Japanese descent. In the ROCKET-AF study, Japanese patients were found to have 50 % higher rivaroxaban exposure when compared to other ethnicities. The increased exposure is thought to be due to variability in enzyme expression responsible for drug metabolism. Noting this trend, the manufacturer developed another Phase III trial (J-ROCKET-AF) comparing rivaroxaban to warfarin therapy [47].

The J-ROCKET AF was a prospective, randomized, double-blind Phase III study in which Japanese patients were enrolled from over 160 centers across Japan. Patients were randomized to rivaroxaban 15 mg once daily (10 mg in patients with moderate renal impairment at screening) or to warfarin with a target INR of 2.0–3.0 for patients aged < 70, or 1.6–2.6 for those >70, reflecting Japanese practice guidelines. Available published abstracts of J-ROCKET AF showed a 51 % reduction of stroke and non-CNS systemic embolism in the rivaroxaban group compared with patients receiving warfarin, which was not statistically significant [47]. The manufacturer claims these results correlate with the efficacy and safety endpoints seen from the original ROCKET-AF study [47].

5.4 Contraindications and Precautions

In addition to active bleeding and predisposition to hemorrhage, abrupt discontinuation is also contraindicated. In the ROCKET-AF trial, there was a significantly increased risk for stroke in the rivaroxaban group during the 28-day period after rivaroxaban was stopped. Investigators attributed this finding to the short half-life of rivaroxaban. The FDA now requires a boxed warning.

5.5 Drug Interactions and Adverse Effects

When compared to dabigatran, rivaroxaban has significantly more drug interactions due to its metabolic pathway. Hydrolysis and oxidative degradation by CYP3A4 and CYP2J2 are the primary pathways for drug biotransformation. Agents that inhibit (i.e. ketoconazole, cimetidine) or promote induction (i.e. rifampin, St John’s wort) of these enzymes when given concurrently with rivaroxaban could adversely affect drug levels. Rivaroxaban is also a substrate of P-gp and ABCG2 transporters. Inhibitors and inducers of these transporters may result in changes in rivaroxaban exposure.

5.6 Special Consideration

Routine monitoring is not required with rivaroxaban therapy. As with dabigatran, a specific reversal agent for rivaroxaban does not exist. Dialysis is not an option for patients over-anticoagulated with rivaroxaban due to its high protein binding. Activated charcoal may be utilized to
6 Apixaban (Anti-Factor Xa Inhibitor)

6.1 Description and Mechanism

Akin to rivaroxaban, apixaban directly and selectively inhibits Factor Xa. Apixaban inhibits both free factor Xa and factor Xa bound in the prothrombinase complex. The ability to inhibit both forms results in inhibition of thrombin formation and development of a thrombus (Figure 1).

6.2 Indication and Clinical Evidence

Apixaban is FDA approved for patients with nonvalvular AF to prevent stroke or systemic embolism. In Europe, apixaban is approved for venous thromboembolism prophylaxis after hip or knee surgery. Multiple trials have established apixaban’s efficacy and safety in VTE prophylaxis following orthopedic surgery [48–50].

There are two trials evaluating apixaban’s efficacy in AF patients. The Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) study was developed to determine if apixaban was superior to ASA in patients unsuitable for warfarin therapy [51]. This study randomized 5,559 patients with AF and ≥ 1 stroke risk factor, to receive ASA (81 mg to 324 mg) or apixaban 5 mg twice daily. The primary efficacy outcome was stroke or systemic embolism, while the safety outcome was major and non-major clinically relevant bleeding.

Apixaban patients experienced 1.6 stroke or systemic embolism events per year compared to 3.7 events per year among those receiving aspirin (HR, 0.45; CI: 0.32 to 0.62). No significant differences were observed in major (HR, 1.13; p = 0.57) and non-major bleeding (HR, 1.24; p = 0.05) between groups. Apixaban reduced the risk of stroke or systemic embolism when compared to aspirin without increasing the risk for major bleeding or intracranial hemorrhage. Among patients with AF with elevated risk for stroke and not suitable for warfarin therapy, apixaban was beneficial. Overall apixaban was superior to aspirin in stroke prevention with a similar side-effect profile, and risk for bleeding [51].

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial compared apixaban 5 mg twice daily to warfarin (INR 2.0 to 3.0) in patients with AF who had one additional risk factor for stroke [36]. The primary end-point for this study was stroke or systemic embolism. Results showed that apixaban was superior to warfarin in reducing the risk of stroke or systemic embolism [1.27 % per year for apixaban, 1.60 % per year for warfarin (HR, 0.79; 95 % CI, 0.66 to 0.95; p = 0.01)]. Patients receiving apixaban experienced lower rates of bleeding (HR, 0.69; p < 0.001) and lower mortality (HR, 0.89; p = 0.047).

6.3 Pharmacokinetic and Pharmacodynamic Properties

Apixaban pharmacokinetic profile is similar to what is seen with rivaroxaban therapy. Apixaban is rapidly absorbed, highly protein bound, and has multiple routes of elimination. When administered orally approximately 25 % will be recovered as metabolites, with the majority excreted in the feces (Table 4). Renal excretion of apixaban accounts for approximately 27 % of total clearance. Additional contributions from biliary and direct intestinal excretion can also be observed.

Patients with severe renal insufficiency (serum creatinine >2.5 mg/dL or CrCl <25 mL/min) should not receive apixaban as this patient population was excluded from clinical trials. In addition to renal elimination, apixaban is also partially metabolized by the CYP-3A4 isoenzyme and P-glycoprotein. Use with systemic azoles (i.e. ketoconazole, itraconazole), HIV-protease inhibitors (i.e. ritonavir) and other strong inhibitors of CYP3A4 and/or P-glycoprotein should be avoided. In both the AVERROES and ARISTOTLE studies, the reduced dose of apixaban 2.5 mg twice a day was given to patients who met two of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, Scr ≥ 1.5 mg/dL [36, 51]. Based on the criteria used during the clinical trials, many geriatric and renally impaired patients would require dose reductions.

6.4 Contraindications and Precautions

Current guidance regarding contraindications or warnings is limited. Caution should be used in patients with hepatic...
impairment, elderly patients with concomitant aspirin, and those with hemorrhagic risk.

6.5 Drug Interactions and Adverse Effects

The drug interactions associated with apixaban utilization are similar to those observed with rivaroxaban. Conjugation by CYP3A4 is the predominant pathway for drug biotransformation. Apixaban is also a substrate of P-gp transporter. Inhibitors and inducers of CYP3A4 or P-gp can result in changes in apixaban exposure.

6.6 Special Consideration

Apixaban lacks a specific reversal agent. Dialysis is not an option for patients over-anticoagulated with apixaban due to high protein binding. There is limited evidence utilizing activated charcoal in apixaban overdose. A preclinical study in dogs demonstrated that oral administration of activated charcoal up to 3 hours after apixaban administration reduced apixaban exposure [52]. While difficult to extrapolate this data to humans, in an emergent situation activated charcoal may be a consideration. Activated prothrombin complex concentrates, recombinant factor VIIa, or concentrates of coagulation factors II, IX or X may be options, but the use of these agents has not been evaluated in clinical trials.

Apixaban appears to be a viable alternative to warfarin therapy, but many unknowns still remain. The potential for drug interactions along with possible dose adjustments could make utilization more challenging. Apixaban appears to have similar benefits to those seen with rivaroxaban, yet requires twice daily dosing like dabigatran.

7 Discussion

Dabigatran, rivaroxaban, and apixaban appear to be effective alternatives to warfarin therapy. However, there are a number of other considerations with each agent that warrant caution and even concern. Patient characteristics of each trial provide valuable insight to better guide agent selection in clinical practice, especially for older adults. Of the three landmark trials (RE-LY, ROCKET-AF, and ARISTOTLE) that earned each agent its approval for non-valvular AF, only ARISTOTLE included patients with a creatinine clearance ≤ 30 ml/min. Furthermore, patients with CrCl ≤ 30 ml/min only account for 1.5% of study subjects (Table 5). Based on renal function alone, utilization of dabigatran, rivaroxaban, and apixaban for elderly patients should be carefully evaluated [34–36, 53].

When assessing efficacy endpoints it is also important to determine condition severity. The 150 mg dose of dabigatran was proven superior to warfarin therapy, however this superiority was seen in a population with an average CHADS2 of 2.1 indicating intermediate risk. A similar CHADS2 score was seen in ARISTOTLE, while patients in ROCKET-AF were considered high-risk (average CHADS2 = 3). Providers should be cautious when prescribing dabigatran or apixaban for high-risk individuals [34–36, 53].

In order to appropriately compare and contrast newer anticoagulants to warfarin therapy Time in therapeutic range (TTR) must also be assessed. As stated previously, any advantage of warfarin therapy can be lost when the TTR falls below the threshold of 58% to 65% [16]. In RE-LY, dabigatran failed to show a decreased risk of stroke or systemic embolism in study centers where INR control was above the median Time in therapeutic range (TTR) of 67% [34]. In ROCKET-AF the median TTR was only 55% which may have attenuated the benefit of warfarin therapy [35]. The aforementioned results do not invalidate the findings, but instead should cause pause and careful consideration. Patients who are stable on warfarin and able to maintain therapeutic TTR should continue on therapy unless constant monitoring and dietary considerations significantly impact quality of life.

While all the agents were generally well-tolerated, some adverse-effects could also prove problematic. Dabigatran has been associated with dyspepsia, GI bleeds, and may be linked to cardiovascular events. Rivaroxaban while still relatively new, should not be abruptly discontinued secondary to potential increased risk of thrombus formation.

Bleeding risk, as discussed throughout this review, is the predominant factor that dictates anticoagulant therapy in older adults. The risk, particularly with intracranial hemorrhage, appears to be improved with the newer agents.

<table>
<thead>
<tr>
<th>Trial Data</th>
<th>RE-LY</th>
<th>ROCKET AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Subjects</td>
<td>18,133</td>
<td>14,264</td>
<td>18,201</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 (mean)</td>
<td>73 (median)</td>
<td>70 (median)</td>
</tr>
<tr>
<td>CHADS2 Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>5,775</td>
<td>0</td>
<td>6,183</td>
</tr>
<tr>
<td>2</td>
<td>6,455</td>
<td>1,859</td>
<td>6,516</td>
</tr>
<tr>
<td>&gt;2</td>
<td>5,882</td>
<td>12,402</td>
<td>5,502</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 ml/min (n)</td>
<td>0</td>
<td>0</td>
<td>270</td>
</tr>
<tr>
<td>&gt;30 to 50 ml/min (n)</td>
<td>3,505</td>
<td>2,949</td>
<td>2,747</td>
</tr>
<tr>
<td>&gt;50 ml/min (n)</td>
<td>14,592</td>
<td>11,205</td>
<td>15,105</td>
</tr>
<tr>
<td>Mean TTR (%)</td>
<td>64</td>
<td>55</td>
<td>62</td>
</tr>
</tbody>
</table>
Whether this risk reflects what is seen in general use warrants careful observation. As discussed previously, the Institute for Safe Medication Practices reported that there were over 500 incidences of fatal, disabling, and other severe hemorrhages in the first quarter of 2011 with dabigatran therapy [41]. Furthermore, the threshold between efficacy and safety with non-vitamin K dependent anticoagulants appears to change with increasing age. As observed in the RE-LY study, there was a trend toward higher risk of major bleeding in those patients 75 years or older on dabigatran therapy. Judicial use in older, frail medically complex patients is suggested.

The cost of these new agents will also impact widespread use. Deitelzweig et al. [54] evaluated the medical cost reductions associated with the use of dabigatran, rivaroxaban, and apixaban. The investigators estimated clinical event rates based on data from the RE-LY, ROCKET-AF, and ARISTOTLE studies [34–36]. One year medical costs were estimated to be lower for AF patients taking the newer agents vs. warfarin. In particular, the medical cost reductions per year associated with dabigatran, rivaroxaban, and apixaban were $−179, $−89, and $−485, respectively. These costs do not reflect drug cost likely to be the primary factor with these new agents or INR testing associated with warfarin. Instead, the investigators only accounted for efficacy and adverse event endpoints relating to incurred cost on a healthcare system.

Alia et al. [55] evaluated the cost-effectiveness of dabigatran versus warfarin. Unlike the previous study, this included an estimated drug cost for warfarin and dabigatran. Drug price constituted 94 % of total cost for dabigatran and only 13.6 % for warfarin. Total cost of anticoagulation to prevent one stroke per year was £6,219 ($6,219) and £25,181 ($40,742) for warfarin and dabigatran 150 mg, respectively. The authors concluded that the cost of anticoagulation was driven by drug price for dabigatran and quality of INR control for warfarin.

Finally, the most concerning aspect of anticoagulant therapy with dabigatran, rivaroxaban, or apixaban is the lack of a reversal agent. Warfarin has multiple flaws that make management very difficult, but in urgent situations its effects can be reversed. Dialysis can be considered with dabigatran, with approximately 60 % of the drug being removed over a few hours, but experience is quite limited. Other options for reversal of any of these agents are limited to small studies and case reports.

8 Summary

Dabigatran, rivaroxaban, and apixaban all demonstrate comparable or superior efficacy in large clinical trials when compared to warfarin. These agents not only provide benefit but also offer convenience. The non-vitamin K dependent anticoagulants represent an alternative to warfarin therapy for some patients unable to tolerate the requirements of warfarin management. Patient characteristics, cost, adherence, and lack of a reversal agent will need to be addressed on a case by case basis. What has yet to be determined is whether or not these agents are safer alternatives to warfarin and can provide long-term efficacy, particularly within the geriatric population. Studies evaluating these newer anticoagulants need to include a larger proportion of elderly patients with chronic conditions and organ dysfunction to better understand the risk to benefit ratio in this population.”

Conflict of interest statement The authors of this manuscript report no conflict of interest related to this subject matter.

References


Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.