

## Stroke Prevention in Atrial Fibrillation: Pharmacologic Update

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### ABSTRACT

For nearly half a century, the therapeutic options for the risk reduction of stroke in atrial fibrillation have been stagnant with vitamin K antagonists, such as warfarin, being the primary therapy. Although antiplatelet agents have been investigated over this time, they were never shown to reduce the risk of stroke at the level warfarin has. Considering the limited therapeutic options, the main decision facing clinicians was not determining which agent to use, but whether a patient was at high enough risk of stroke to benefit from anticoagulation. The CHADS2 and, more recently, the CHADSVASC risk assessment schemes have been shown to be a simple and predicable tool in determining an individual's risk for stroke. Now, after nearly 50 years with limited alternatives, there has been a surge in therapies in the form of dabigatran, rivaroxaban and apixaban, which have been shown to be non-inferior and in some cases, superior to warfarin in their respective randomized controlled trials. This increase in available options is exciting but at the same time adds another layer of confusion to the process of selecting the appropriate agent for individual patients.

**Keywords:** Atrial Fibrillation, Stroke, Anticoagulation

### 1. INTRODUCTION

Atrial fibrillation is well known to be the most common arrhythmia. Inherent in this disease is the risk of stroke, which is estimated to be increased five times compared to patients without atrial fibrillation. It has also been shown that as age increases, the prevalence of atrial fibrillation invariably increases. It is estimated that for ages 50-59, 60-69, 70-79 and 80-89 the prevalence of atrial fibrillation is 0.5, 1.8, 4.8 and 8.8%, respectively (Wolf *et al.*, 1991). Considering the advancing age of the population and thus the increasing prevalence of atrial

fibrillation, it is prudent to understand various treatment strategies by which its complications can be reduced, the most devastating being stroke.

Vitamin K antagonists, such as warfarin, have long been the sole option for anticoagulation in atrial fibrillation and there is strong evidence documenting the benefit of its use (Hart *et al.*, 1999; 2007; Connolly *et al.*, 2006). The use of warfarin, however, is quite cumbersome as it has a narrow therapeutic window, which necessitates frequent monitoring and dose adjustments. There are also many interactions with food and other drugs. This even further complicates its use.

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Alternative therapies have long been desired, however it was not until recently that any have been available. Now, with the data gathered from the mega multicenter trials investigating the direct thrombin inhibitor dabigatran (RE-LY) and two factor-Xa inhibitors rivaroxaban (ROCKET-AF) and apixaban (ARISTOTLE), we are left with the challenge of selecting the appropriate therapy (Connolly *et al.*, 2009a; Patel *et al.*, 2011; Granger *et al.*, 2011).

### 1.1. Risk Assessment

One of the major challenges for clinicians to initiate therapy has been risk stratification to determine which patients would truly benefit from anticoagulation. There have been several schemes applied to stratify risk, the most popular of these being the CHADS<sub>2</sub> scoring system, due to its simplicity. This approach readily identified patients who were at high risk by having a CHADS<sub>2</sub> score  $\geq 2$ , however it was limited in that the predictability of patients who are truly low risk was quite variable. A recent Danish cohort by Olesen *et al.* (2012) evaluated the utility of the CHADS<sub>2</sub> scheme in compared with CHA<sub>2</sub>DS<sub>2</sub>VASc in an attempt to improve the predictability of truly low risk patients. In this study 47,576 patients with a CHADS<sub>2</sub> score of 0-1 were followed for 12 years. The results demonstrated that patients with a CHADS<sub>2</sub> score of 0, whom were previously thought to be low risk, had a wide variability in risk when the CHA<sub>2</sub>DS<sub>2</sub>VASc scheme was applied. The event rate for 100 person years in patients with a CHADS<sub>2</sub> score of 0 was found to be 1.59 after one year of follow-up, however when the CHA<sub>2</sub>DS<sub>2</sub>VASc system was applied, the event rates at one year were 0.84, 1.75, 2.69 and 3.2 per 100 person years for a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 0, 1, 2 and 3, respectively (Olesen *et al.*, 2012). This clearly demonstrates the limitation of the CHADS<sub>2</sub> scoring system to predict patients who are at a low risk of stroke.

The ability of the CHA<sub>2</sub>DS<sub>2</sub>VASc system to reliably predict truly low risk patients has led to it being incorporated into guidelines set by the European Cardiology Society, 2010. Their recommendation was to combine the two systems and apply the CHA<sub>2</sub>DS<sub>2</sub>VASc system for patients who have a CHADS<sub>2</sub> score of 0 or 1. Their recommendation was those patients with one major (congestive heart failure, hypertension, age  $\geq 75$  years, diabetes and history of stroke, TIA, or thromboembolism) or two non-major (age 65-74, female sex, vascular disease) risk factors should receive oral anticoagulation. Patients with one non-major risk factor can receive either oral anticoagulation or aspirin dosed 75-325 mg, however oral anticoagulation is preferred. Finally, patients with no

major or minor risk factors could receive no therapy or aspirin, but no therapy is preferred (Camm *et al.*, 2010).

When considering the initiation of oral anticoagulation, clinicians must not only account for the risk of stroke, but also the risk of major bleeding. One scheme that has been established to help clinicians stratify patient's risk of bleeding is the HAS-BLED system. The risk factors of hypertension, abnormal renal or liver function (1 point for each), history of stroke, personal history of bleeding or predisposition to bleeding, labile INR, elderly (age  $\geq 65$ ) and use of drugs (antiplatelet or non-steroidal anti-inflammatory) or alcohol are evenly weighted at one point each. In an interesting cohort by Gallego *et al.* (2012), patients on anticoagulation for atrial fibrillation were monitored for bleeding. In the recruitment process, only patients with INR values of 2-3 were eligible for inclusion. As a result, the estimated time in therapeutic range was nearly 100%. The average CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc scores were 2 and 4 respectively. It was found that at HAS-BLED values  $>3$ , major bleeding episodes were more frequent than observed embolic events. When considering major hemorrhagic events, HAS-BLED  $>3$  was associated with a Hazard Ratio (HR) of 3.68; 95% CI, 2.37-5.78;  $p < 0.001$ . The author highlights that the HAS-BLED scoring system was not established to keep clinicians from treating patients with high bleeding risk. The goal, rather, is to make clinicians aware of patients at higher risk in order to establish close follow up and attempt to adjust any modifiable risk factors (Gallego *et al.*, 2012). The HAS-BLED score was also investigated in a cohort of patients from the SPORTIF III and V trials who were anticoagulated with either ximelagatran or adjusted-dose warfarin (Olsson, 2003; Albers *et al.*, 2005). The major bleeding rate for patients with HAS-BLED scores of 0, 1, 2, 3, 4, 5 and 6 were 1.2, 2.8, 3.6, 6.0, 9.5, 7.4 and 0%, respectively. The decreasing rates with scores of 5 and 6 are a manifestation of the decreasing number of patients with these scores. There was only a single patient with a score of 6 and no event was experienced. There was no significant difference in bleeding risk between ximelagatran and warfarin. This raises the question as to whether this system can be applied to the novel anticoagulants (Lip *et al.*, 2011).

### 1.2. Warfarin

Vitamin K antagonists, such as warfarin, have been the sole option for oral anticoagulation for greater than 50 years. Warfarin offers a clear benefit in preventing ischemic stroke and systemic embolism in patients with atrial fibrillation. In a meta-analysis by Hart *et al.* (1999)

adjusted-dose warfarin demonstrated a relative risk reduction of 62%; (95% CI, 48-72) when compared to placebo. Despite the long known benefit of warfarin in atrial fibrillation, clinicians have been hesitant to readily prescribe it due to the elevated bleeding risk, need for frequent INR monitoring and interactions with concomitant drugs and food. Warfarin use by clinicians vary tremendously among patients eligible for therapy with a range of 9.1-79.8% and a median of 49% in a meta-analysis by Baczek *et al.* (2012) Some of the more strongly associated characteristics with a negative association toward warfarin use were alcohol or drug use, predicted barriers to compliance, falls, gastrointestinal hemorrhage, intracranial hemorrhage, hepatic impairment and renal dysfunction. Based on these results, it can be estimated that nearly half of patients at risk of stroke due to non-valvular atrial fibrillation are not being anticoagulated.

### 1.3. Anti-Platelets

To overcome the challenges that are inherent for any clinician instituting therapy with warfarin, anti-platelet agents have long been sought as an alternative. In a meta-analysis by Hart *et al.* (2007), five trials were identified that compared aspirin therapy to placebo and another two studies comparing aspirin to no therapy. The studies comparing aspirin to placebo were AFASAK 1, SPAF 1, EAFT, ESPS II and UK-TIA, which dosed aspirin at 75, 325, 300, 50 and 300-1200 mg daily, respectively. These studies were associated with relative risk reductions of stroke ranging from 11-44% and meta-analysis estimated overall risk reduction was 22; 95 CI, 2-39% (Hart *et al.*, 2007; Petersen *et al.*, 1989; AHA, 1991; Benavente and Hart, 1997; EAFT, 1993; Benavente *et al.*, 2000). Two other studies (LASAF and JAST) compared no treatment to aspirin at doses of either 125mg daily or every other day for LASAF and 150g daily for JAST (Posada and Barriales, 1999; Sato *et al.*, 2006). Relative risks of 10 and 17% were observed in JAST and the arm of LASAF that dosed aspirin daily, respectively. When these two studies are taken into consideration among the other five studies evaluating aspirin versus placebo, results continue to demonstrate a benefit in favor of aspirin with a reduced risk of stroke of 19% (95, CI,-1-35%). When further analyzed, an interesting trend is identified that suggests there is an increased risk reduction for non-disabling strokes compared to disabling strokes with aspirin use at a rate of 29% (95, CI,-6-53%) and 13% (95, CI,-18-36%), respectively. This is consistent with a previous meta-analysis from Hart *et al.* (1999; 2000; 2007).

Considering that cardio-embolic strokes are typically more disabling than non-cardio-embolic strokes, this trend suggests that the greatest benefit from aspirin in preventing strokes is inhibiting intravascular thrombosis, rather than preventing the formation of left atrial thrombi (Hart *et al.*, 2000).

The use of clopidogrel combined with aspirin for stroke prevention was evaluated in the ACTIVE trials. The ACTIVE A trial studied the combination of clopidogrel and aspirin versus aspirin and placebo, whereas the ACTIVE W trial studied the combination versus adjusted-dose warfarin. Patients were included in ACTIVE A if they were either unwilling to take warfarin or considered unsuitable for anticoagulation and placed into ACTIVE W if they were suitable. In ACTIVE A, all strokes were decreased in the clopidogrel group with a relative risk of 0.72; 95% CI, 0.62-0.83;  $p < 0.001$ . This benefit, however was at the cost of an increased risk of major bleeding with relative risk of 1.57; 95% CI, 1.29-1.92;  $p < 0.001$  (Connolly *et al.*, 2009b). In ACTIVE W, the combination of aspirin and clopidogrel was compared to adjusted-dose warfarin. The results demonstrated an increased risk of stroke with the combination of aspirin and clopidogrel versus adjusted-dose warfarin at a rate of 2.39 and 1.4% per year, respectively (RR 1.72; 95% CI, 1.24-2.37;  $p = 0.001$ ). Despite having minimal differences in major bleeding profiles at rates of 2.42 and 2.21% per year for clopidogrel and aspirin versus warfarin, respectively ( $p = 0.53$ ), the combination of the antiplatelet agents had a significant increase in the rate of minor bleeding episodes at a rate of 15.40 and 13.21%, respectively (RR 1.23; 95% CI, 1.08-1.35;  $p = 0.001$ ). Despite these major differences, mortality was similar between the two groups (RR 1.01; 95% CI, 0.81-1.26;  $p = 0.91$ ) (Connolly *et al.*, 2006).

Many other studies have compared antiplatelet agents to adjusted-dose warfarin, however, antiplatelet therapy has clearly been shown to be inferior in the prevention of stroke. In the same meta-analysis by Hart *et al.* (2007), 12 trials were identified that compared warfarin to antiplatelet therapy in which warfarin was associated with a risk reduction of 37; 95, CI, 23-48%.

When considering only aspirin trials versus adjusted-dose warfarin, the relative risk reduction of ischemic and hemorrhagic stroke together was found to be 38; 95, CI, 18-52% in favor of adjusted-dose warfarin (Hart *et al.*, 2007).

### 1.4. Novel Oral Anticoagulants

Dabigatran is an oral direct thrombin inhibitor that was studied in the large RE-LY (Randomized Evaluation

of Long-Term Anticoagulation) trial (Connolly *et al.*, 2009a). This was a multicenter trial that randomized dabigatran at doses of 150 mg twice daily and 110 mg twice daily in a blinded fashion versus an open label use of warfarin with the primary endpoint being stroke or systemic embolism. The study involved 18,113 patients with non-valvular atrial fibrillation and at least one risk factor for stroke. The mean CHADS<sub>2</sub> score was determined to be 2.2 and the mean time in The Therapeutic Range (TTR) of INR 2-3 was 64% for patients treated with warfarin. Adjusted-dose warfarin was associated with a 1.69% per year risk of stroke or systemic embolism whereas dabigatran at a dose of 110 and 150 mg was associated with a 1.53 and 1.11% per year risk of stroke or systemic embolism, respectively. It was determined that both doses of dabigatran were non-inferior to adjusted-dose warfarin ( $p < 0.001$ ), whereas only dabigatran at a dose of 150 mg was superior to warfarin (relative risk, 0.66; 95% CI, 0.53 to 0.82;  $p < 0.001$ ). There were also fewer hemorrhagic strokes with dabigatran than warfarin with rates of 0.12, 0.10 and 0.38% per year for dabigatran 150 mg, dabigatran 110mg and warfarin, respectively, with both doses of dabigatran reaching statistical significance ( $p < 0.001$ ). One of the more striking findings was that dabigatran was associated with decreased risk of intracranial bleeding at both doses with rates of 0.23 and 0.30% per year for 110 mg and 150 mg, respectively when compared to warfarin with rate of 0.74% per year ( $p < 0.001$  for both doses). Rates of major bleeding, however, were found to be similar in dabigatran 150mg and warfarin at rates of 3.11 and 3.36% per year, respectively ( $p = 0.31$ ). In the group receiving 110 mg of dabigatran, however, the rate was significantly less at 2.71% per year (relative risk 0.80; 95% CI, 0.69-0.93;  $p = 0.003$ ). Despite having lower rates of bleeding in general, dabigatran was found to have increased risk of gastrointestinal hemorrhage at a dose of 150 mg with a rate of 1.51% per year versus warfarin with a rate of 1.02% per year ( $p < 0.001$ ). Dabigatran at a dose of 110 mg did not reach statistical significance despite having a slightly higher rate of 1.12% per year ( $p = 0.43$ ). The authors of the study comment that a possible explanation of the slightly increased rate of gastrointestinal bleeding could be the tartaric acid core of the dabigatran capsule which is necessary to promote absorption (Connolly *et al.*, 2009b).

Results from the RE-LY trial have already led to adjustments of guidelines for stroke prevention in non-valvular atrial fibrillation. In the 2010 publication of the European Society of Cardiology (ESC), dabigatran is

offered as an alternative to Vitamin K Antagonism (VKA), although they make no strong recommendation for preference of dabigatran over VKA. The guidelines also highlight the usefulness of the CHA<sub>2</sub>DS<sub>2</sub>VASc and HAS-BLED scoring system in selecting doses of dabigatran. Their recommendation was for patients with a low risk of bleeding (HAS-BLED 0-2), dabigatran 150 mg twice daily should be considered. Dabigatran at dose of 110 mg twice daily should be considered in patients with a greater risk of bleeding (HAS-BLED  $\geq 3$ ) or lower risk of stroke (one clinically relevant non-major risk factor) (Camm *et al.*, 2010). The dose of 110 mg, however, is not currently available in the United States.

The American College of Cardiology Foundation, American Heart Association and Heart Rhythm Society (ACCF/AHA/HRS) also updated their guidelines in 2011 to include dabigatran after FDA approved dabigatran at doses of 150 mg twice daily for creatinine clearance  $> 30$  mL min<sup>-1</sup> and 75 mg twice a day for creatinine clearance 15-30 mL min<sup>-1</sup>. In this update, dabigatran was suggested as a class IB recommendation as an alternative to warfarin for stroke and systemic embolism prevention in patients with atrial fibrillation who do not have prosthetic or hemodynamically significant valvular disease, renal failure (creatinine clearance  $< 15$  mL min<sup>-1</sup>), or advanced liver disease. They suggest each patient should be evaluated for individual characteristics including the likelihood of compliance with twice daily dosing, cost, personal preference of the patient and INR monitoring. They also add that patients already on warfarin with little problems maintaining a therapeutic INR may have little to gain by switching to dabigatran (Wann *et al.*, 2011).

Rivaroxaban, an oral direct factor Xa inhibitor, is a second novel agent. It was investigated in the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) study in which rivaroxaban once daily was compared to adjusted-dose warfarin in a randomized double-blinded manner (Patel *et al.*, 2011). Rivaroxaban was given at a dose of 20mg daily or at a dose of 15mg daily for a creatinine clearance of 30-49 mL min<sup>-1</sup>. An interesting contrast to the RE-LY trial was that only patients with a CHADS<sub>2</sub> score of 2 or higher were recruited for this study which resulted in a higher mean score of 3.5 compared to the other two studies (Connolly *et al.*, 2009a; Patel *et al.*, 2011; Granger *et al.*, 2011). The mean TTR with an INR 2-3 was calculated to be 55%. The primary endpoint was again stroke (ischemic or hemorrhagic) and systemic embolism, which was encountered at a rate of 1.7% per year in the rivaroxaban group compared to

2.2% per year in the warfarin group. These rates equated to a hazard ratio in the rivaroxaban group of 0.79 (95% CI 0.66-0.96;  $p < 0.001$ ) for non-inferiority. Rates of major bleeding were relatively similar between rivaroxaban and warfarin at a rate of 3.6 and 3.4% per year, respectively ( $p = 0.58$ ), however the rate of intracranial hemorrhage was reduced in the rivaroxaban group at a rate of 0.5% per year compared to warfarin at a rate of 0.7% per year ( $p = 0.02$ ). It was also observed that fatal bleeding occurred less in the rivaroxaban group compared with warfarin at a rate of 0.2 and 0.5 % per year, respectively (HR 0.50; 95% CI 0.47-0.93;  $p = 0.003$ ). Considering this evidence the authors concluded that once daily rivaroxaban was non-inferior to warfarin for primary prevention of stroke and systemic embolism. It was also highlighted that despite having similar major and non-major bleeding risks, the rate of fatal and intracranial bleeding was improved in the rivaroxaban group (Patel *et al.*, 2011).

Apixaban, also an oral factor Xa inhibitor, is a third novel agent. It was investigated in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) study (Granger *et al.*, 2011). In this study apixaban 5mg twice daily (2.5 mg twice daily for patients with weight  $\leq 60$ kg, age  $\geq 80$  years and serum creatinine  $\geq 1.5$  mg  $dL^{-1}$ ) was compared to adjusted-dose warfarin in a randomized double-blinded manner. Again, as in the RE-LY study, the primary inclusion criteria were non-valvular atrial fibrillation with at least one risk factor for stroke. The mean CHADS<sub>2</sub> score was determined to be 2.1 and the mean TTR for INR 2-3 was 62.2%. Primary efficacy outcomes of stroke or systemic embolism for apixaban and warfarin were found to be 1.27 and 1.6% per year, respectively (HR, 0.79; 95% CI, 0.66-0.95;  $p < 0.001$  for non-inferiority and  $p = 0.01$  for superiority). Interestingly, there was no significant difference in ischemic strokes between the two agents with a risk of 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (HR, 0.92; 95% CI, 0.74-1.13;  $p = 0.42$ ). The benefit of apixaban, however, comes from the decreased risk of hemorrhagic stroke when compared to warfarin with a risk of 0.24% and 0.42% per year, respectively (HR, 0.51; 95% CI, 0.35-0.75;  $p < 0.001$ ). Major bleeding rates were significantly lower in patients treated with apixaban at a rate of 2.13% when compared to 3.09% per year in patients treated with warfarin (HR, 0.69; 95% CI, 0.60-0.80;  $p < 0.001$ ). Intracranial hemorrhage rates were improved for patients treated with apixaban at a rate of 0.33% per year compared to 0.8% per year for patients treated with warfarin (HR, 0.42;

95% CI, 0.3-0.58;  $p < 0.001$ ). Death from any cause was also found to have a significant difference in favor of apixaban at a rate of 3.52% per year when compared to warfarin at a rate of 3.94% (HR, 0.89; 95% CI, 0.80-0.99;  $p = 0.047$ ). Considering these findings, the authors of this study concluded that apixaban was superior to warfarin in prevention of stroke and systemic embolism, with a considerable amount of the benefit coming from a decrease in hemorrhagic stroke (AHA, 1991). Apixaban is not currently available for use in the United States.

Confirming the benefits of the novel anticoagulants as a whole is difficult due to the limited number of studies available, however this was attempted by Miller *et al.* (2012) in a meta-analysis comparing novel anticoagulants as a class to warfarin (Miller *et al.*, 2012). In this study, the relative risk reduction of the novel anticoagulants was found to be 22% for the primary endpoint of stroke and systemic embolism when compared to warfarin (RR 0.78; 95% CI, 0.67-0.92). There was also data to support a significant improvement in rates of both ischemic and hemorrhagic stroke with the novel anticoagulants with relative risk of 0.87 and 0.45, respectively. The safety endpoint of intracranial hemorrhage was found to have a significant improvement for patients receiving novel anticoagulants with a RR of 0.49; 95% CI, 0.36-0.66. There was no significant difference observed in the rates of major bleeding (RR 0.88, 95% CI 0.71-1.09) or gastrointestinal hemorrhage (RR 1.25, 95% CI 0.91-1.72) (Miller *et al.*, 2012).

A major concern with any new therapy is cost effectiveness of the new intervention. There are many parameters affecting cost of both warfarin and the novel anticoagulants, some of which are the cost of the drug, laboratory monitoring and healthcare cost for clinical events experienced. In a cost analysis, it was calculated that all three of the novel agents would have a reduced cost compared to adjusted-dose warfarin. When the three trials highlighted above were applied to financial analysis, it was observed that dabigatran, rivaroxaban and apixaban had a reduced cost of \$179, \$89 and \$485, respectively, per year (Deitzelzweig *et al.*, 2012). This estimate suggests that the improved outcomes of the novel agents offset the higher cost of the drugs.

Despite the evidence in favor of these novel agents highlighted in the studies above, there have been some proposed drawbacks when these drugs are distributed amongst a general population rather than a tightly controlled study. For example, there is no assay to determine the level of coagulation and therefore clinicians are unable to monitor for compliance, assess for drug failure, or titrate doses. They also have quite

short half-lives raising the concern if non-compliance is an issue, as a patient would drift in and out of a therapeutic level of anticoagulation quite rapidly (Ansell, 2012). Antidote for newer anticoagulation agents is yet to be made. Therefore an acute bleeding situation is a challenging scenario.

## 2. CONCLUSION

The development of these novel agents is quite exciting considering the limited options of oral anticoagulation prior to these agents. All three agents demonstrated either superiority (dabigatran 150 mg twice daily and apixaban) or non-inferiority (dabigatran 110 mg twice daily and rivaroxaban) in the prevention of stroke and systemic embolism when compared to warfarin (Connolly *et al.*, 2009b; Patel *et al.*, 2011; Granger *et al.*, 2011).

The results of these trials identify individual characteristics that distinguish these agents from each other. For instance, with dabigatran, while maintaining improved rates of stroke, intracranial bleeding was significantly improved with both doses. A drawback, however, was increased rates of gastrointestinal bleeding (Connolly *et al.*, 2009b). Although rivaroxaban did not reach statistical significance for superiority in prevention of stroke or systemic embolism, it was non-inferior. The ability for it to be dosed once daily may be appealing to clinicians for patients who have compliance issues (Patel *et al.*, 2011). In regards to apixaban, there was not a significant improvement in ischemic strokes, but there was a large benefit identified with apixaban for hemorrhagic strokes (Granger *et al.*, 2011).

Some subtle differences in study design such as variable TTR and CHADS<sub>2</sub> scores raises the question if these agents can be directly compared to each other. Only after head to head comparisons have been performed can the benefit of one agent versus another be derived.

Guidelines have already been updated to include dabigatran by the ESC and ACCF/AHA/HRS. The ESC recommended considering stroke risk and bleeding risk when selecting doses of dabigatran (Camm *et al.*, 2010). It will be interesting to see, as more evidence becomes available for stroke risk, bleeding risk and characteristics of individual agents, if there will be a shift toward individualized therapy to aid in agent selection as the repertoire of oral anticoagulants continues to increase in numbers.

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