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The New Anticoagulants: Which one is for You?

by *Hans R. Larsen*

Although there is no evidence that otherwise healthy lone afibbers have an increased risk of ischemic stroke, it is clear that atrial fibrillation (AF) patients with heart failure, diabetes or hypertension have a significantly increased risk and this risk is further magnified if the patient has already suffered a heart attack or stroke. To date, oral anticoagulation with vitamin K antagonists such as warfarin (Coumadin) is still considered to be the best preventive therapy for patients at risk for stroke. Unfortunately, warfarin interacts with many foods and drugs and treatment requires constant, costly monitoring. Its use also substantially increases the risk of hemorrhagic stroke and major internal bleeding, particularly in older people, a group that, ironically, is also most at risk for an ischemic stroke. Effective warfarin therapy is based on maintaining an INR (international normalized ratio) between 2.0 and 3.0. In real life this ratio is only achieved on a continuous basis in about 50 to 60% of patients. Too low a ratio increases the risk of ischemic stroke, while too high a ratio increases the risk of hemorrhagic stroke and major bleeding.

A study carried out by a team of researchers from Massachusetts General Hospital, University of California, and Kaiser Permanente of Northern California casts serious doubt on the benefits of prescribing warfarin to AF patients at low risk for ischemic stroke. The study involved 13,559 patients with nonvalvular atrial fibrillation who were followed for 6 years, accumulating a total of over 66,000 person-years of actual experience on warfarin usage in AF. At entry to the study about 53% of the patients were on warfarin.

In past studies aimed at proving the benefits of warfarin therapy among afibbers the focus has been entirely on the prevention of ischemic stroke with no, or very scant, attention paid to the harm done by the drug. The California study takes a bold step forward in this respect in that it introduces a new concept "net clinical benefit". In other words, it considers both the benefit (reduction in ischemic stroke) and harm (increase in hemorrhagic stroke) in administering the drug. Net clinical benefit (NCB) is defined as:

$$\text{NCB} = (\text{TE rate off warfarin} - \text{TE rate on warfarin}) - W \times (\text{ICH rate on warfarin} - \text{ICH rate off warfarin})$$

- **TE rate** is the annualized rate of thromboembolic events (ischemic stroke and systemic emboli)
- **W** is a weighting factor designed to reflect the fact that the consequences of a hemorrhagic stroke (intracranial bleeding) is far more serious than that of an ischemic stroke. The authors used a W equal to 1.5.
- **ICH rate** is the annualized rate of intracranial bleeding (incl. hemorrhagic stroke).

During the 6-year follow-up there were 407 thromboembolic events, 93% of which were ischemic strokes, in the total group treated with warfarin vs. 685 in patients not receiving warfarin, resulting in annualized TE rates of 1.25% and 2.29% respectively. ICH rates were 0.33% and 0.57%

respectively. Not surprisingly, the net clinical benefit of warfarin therapy was highest for patients with a serious risk of stroke and negligible to negative in other cases. Thus, afibbers with a CHADS₂ score (this score assigns 1 point each for congestive heart failure, hypertension, age 75 years or older and diabetes, and 2 points for previous stroke or TIA) of zero (no risk factors for stroke) had a NCB of -0.11% indicating that for this group, which includes most lone afibbers, warfarin therapy is actually more likely to be harmful than beneficial. The likelihood of harm was particularly strong among those aged 65 years or less where the NCB was -0.25%. On the other hand, for patients over the age of 85 years, NCB was a positive 2.34% and for those who had already suffered a stroke it was 2.48%.

The researchers conclude that the net benefit of warfarin therapy is essentially zero in atrial fibrillation patients with a CHADS₂ score of 0 or 1, i.e. with, at the most, one risk factor for ischemic stroke.[1]

A group of Italian researchers followed 662 elderly AF patients (64% had hypertension, 45% coronary artery disease or heart failure, and 31% had suffered a previous stroke or TIA) on warfarin for an average of 3.6 years during which time a total of 32 thromboembolic events occurred corresponding to an annual incidence rate of 1.3%. The only factor that actually did confer an increased risk of stroke (5.6-fold) was a previous history of stroke, TIA or other systemic embolism. Age, hypertension, diabetes, heart failure, female gender, and low left ventricular ejection fraction did not increase the risk of stroke in this elderly, anticoagulated group of AF patients.[2,3]

Thus, although anticoagulation with warfarin has proven effective in tightly controlled clinical trials, "real world" evaluations of its benefits paint a somewhat less rosy picture.

Anticoagulation with warfarin is associated with an increased risk of hemorrhagic stroke (intracranial bleeding) and major gastrointestinal bleeding, particularly in elderly AF patients. Elaine Hylek and colleagues at the Boston University School of Medicine have questioned whether treating older patients with warfarin has a favorable benefit/risk ratio. Their clinical trial involved 472 AF patients with an average age of 77 years (32% were 80 years or older). Forty-seven percent of the patients were women and 91% had one or more risk factors for ischemic stroke (75% had hypertension and 35% had coronary artery disease). After being admitted with a first AF episode (59%), a recurrent episode (35%), or permanent AF (6%) all study participants were prescribed warfarin with an INR target of 2.0 – 3.0. Management of warfarin dosage was carried out by the hospital's own anti-coagulation clinic. More than 10,000 INR measurements were made during the 1-year follow-up period. The time spent within the prescribed INR range (2.0 – 3.0) was only 58% with 29% being spent below 2.0 and 13% above 3.0.

The overall incidence of major hemorrhage was 7.2% and that of intracranial hemorrhage (hemorrhagic stroke) was 2.5%. A third of the hemorrhagic strokes were fatal and 89% of them occurred in patients 75 years or older. The incidence of major hemorrhage was particularly high (13.1%) among patients 80 years or older. Age and an INR greater than 4 were strong risk factors and 58% of the major hemorrhages occurred within the first 90 days after initiation of warfarin therapy. Concomitant use of aspirin was also a significant risk factor for major bleeding and there was no indication that taking 81 mg/day was any safer than taking the standard 325 mg/day.

During the study 26% of participants aged 80 years or older were taken off warfarin – 81% because of safety concerns and 19% because they regained normal sinus rhythm. The Boston researchers conclude that the risk of major bleeding among older AF patients on warfarin has been significantly underestimated in previous trials. They also point out that the rate of bleeding observed in their closely controlled clinical trial would likely be significantly lower than that experienced in the "real world".[4]

In an accompanying editorial Dr. George Wyse of the Health Sciences Center in Calgary, Canada states, "there is reason to be skeptical about net benefit when warfarin is used in some elderly

patients with AF.” Dr. Wyse also points out that warfarin therapy would appear to be over-utilized in patients with low to moderate risk of ischemic stroke. A recent European study found that 50% of AF patients with no risk factors for stroke were being treated with warfarin or similar anticoagulants.[5]

The uncertain efficacy in preventing thromboembolism, the increased risk of major bleeding, the cost and inconvenience of regular INR monitoring, and the potential for interactions with many common foods and pharmaceutical drugs thus makes warfarin a less than perfect drug and it is not surprising that substantial effort has been expended on finding a replacement. Warfarin acts by inhibiting the activation of the vitamin K-dependent coagulation factors V, VII and X in the extrinsic and common pathways of the coagulation cascade. Research aimed at replacing warfarin has focused on developing new pharmaceutical drugs which will inhibit specific coagulation factors. Currently the three favorites are:

- Dabigatran (*Pradaxa*) developed by Boehringer Ingelheim
- Rivaroxaban (*Xarelto*) developed by Bayer and Johnson & Johnson
- Apixaban (*Eliquis*) developed by Pfizer and Bristol-Myers Squibb.

Dabigatran

Research aimed at replacing warfarin has essentially focused on developing new pharmaceutical drugs which will inhibit specific coagulation factors. A new direct thrombin inhibitor dabigatran etexilate (*Pradaxa*) has successfully undergone 3 large-scale phase III trials for the treatment of deep vein thrombosis (DVT). A recent trial involving 502 AF patients with at least one additional risk factor for stroke found that 150 mg of dabigatran twice a day is as effective and safe as standard warfarin therapy.

In September 2009 a large group of researchers from 41 countries reported on the RE-LY trial involving over 18,000 atrial fibrillation patients who had one or more risk factors for stroke (average CHADS₂ score was 2.1). NOTE: 79% of the participants had hypertension, 32% had heart failure, 20% had experienced a prior heart attack or stroke, and 23% had diabetes. The study participants were randomly allocated to receive 110 or 150 mg of dabigatran twice daily or standard warfarin therapy (INR range aim of 2.0 to 3.0). The patients were re-examined 2 weeks and 1 and 2 months after randomization, every 3 months thereafter in the first year, and then every 4 months until the end of the 2-year follow-up period. The INR of warfarin users was checked monthly, but no monitoring of blood levels of dabigatran was required. Warfarin users were within INR range 64% of the time.

A comparison of the incidence of ischemic stroke and systemic embolism, hemorrhagic stroke, major bleeding, heart attack, and overall mortality is shown below:

Annual Incidence of Events, %

	Warfarin <u>INR 2.0-3.0</u>	Dabigatran <u>110 mg twice daily</u>	Dabigatran <u>150 mg twice daily</u>
Ischemic stroke & embolism	1.69	1.53	1.11
Hemorrhagic stroke	0.38	0.12	0.10
Heart attack	0.53	0.72	0.74
Major bleeding	3.36	2.71	3.11
Overall mortality	4.13	3.75	3.64

It is clear that dabigatran, either at 110 mg or 150 mg twice daily, gives better protection against strokes (ischemic and hemorrhagic) and bleeding than does warfarin, although a slightly increased risk of heart attack (myocardial infarction) was noted at both levels of dabigatran. There was a significantly higher rate of major gastrointestinal bleeding with dabigatran at the 150 mg dose than with warfarin (1.51%/year versus 1.02%/year).

Adverse events were similar in the 3 groups except in the case of indigestion (dyspepsia) which was experienced by about 11.5% of dabigatran users versus only 5.8% among warfarin users. Several other direct thrombin inhibitors, most prominent among them, ximelagatran, proved to cause liver toxicity and, for this reason, has not been approved by the FDA for treatment of atrial fibrillation. In this 2-year long trial there was no indication that dabigatran caused a greater elevation of liver enzymes (alanine aminotransferase and aspartate aminotransferase) than did warfarin.

The RE-LY investigators concluded that low-dose dabigatran (110 mg twice daily) is associated with an ischemic stroke rate similar to that experienced with warfarin, but results in a lower incidence of hemorrhagic stroke and major bleeding. High-dose dabigatran (150 mg twice daily) is superior to warfarin when it comes to preventing ischemic and hemorrhagic stroke, but has a similar rate of major hemorrhage. NOTE: The description of the financial ties between the authors of this report and the pharmaceutical industry takes up half a page of fine print![6]

In September 2010 a FDA advisory panel recommended that dabigatran be approved for stroke prevention in atrial fibrillation patients. This was followed by full approval by the FDA on October 20, 2010. The approval covered two doses – a twice daily 150-mg dose for patients with normal kidney function, and a twice daily 75-mg dose for elderly patients and those with impaired kidney function. Impaired kidney function (creatinine clearance level less than 30 mL/min) has been found to double the half-life of dabigatran and increase systemic exposure (area under the curve) by a factor of 6.[7] Thus it is assumed that 75 mg twice a day will be effective in preventing ischemic stroke without increasing bleeding risk in this patient group. However, there is no long-term clinical data to prove that this assumption is correct.

Ximelagatran, a first-generation direct thrombin inhibitor, was found to increase liver enzymes in about 5% of patients taking it. For this reason it was never approved for long-term use. The RE-LY trial specifically excluded participants with compromised liver function but there was no indication that liver function was affected by dabigatran. Nevertheless, dabigatran is not recommended for patients with impaired liver function.

One of the major disadvantages of warfarin is that it is metabolized by CYP 450 enzymes. These enzymes are also involved in the metabolism of numerous pharmaceutical drugs, common foods, and supplements thus setting the stage for many interactions that may increase or decrease the blood level of warfarin. CYP 450 enzymes are not involved in the metabolism of dabigatran so the potential for interactions is substantially less. As a matter of fact, the detailed monograph on dabigatran only cautions that its use may be contraindicated in conjunction with verapamil, amiodarone, quinidine, clopidogrel, aspirin, clarithromycin, and St. John's wort.[7] Another major advantage of dabigatran is that its use does not involve the constant monitoring of INR levels required when using warfarin. However, while warfarin-induced bleeding can be controlled with injection of vitamin K, there is no known antidote for dabigatran-induced hemorrhage. Thus patients involved in contact sports or prone to falls may not be good candidates for dabigatran. Dabigatran was approved in Canada and Europe more than a year ago and has been used extensively on a short-term basis following knee- and hip-replacement surgery.

A follow-up study specifically aimed at quantifying bleeding risk associated with dabigatran was reported in May 2011. The researchers looked at the effect of age and kidney impairment on intracranial (intracerebral, hemorrhagic stroke) and extracranial (mainly gastrointestinal) bleeding. They conclude that low-dose dabigatran therapy (110 mg twice daily) compared with warfarin is associated with a 20% lower relative risk of major bleeding and a 70% reduced risk of intracranial bleeding (0.23%/year vs. 0.76%/year) with no significant difference in extracranial bleeding. There was no significant difference in the incidence of ischemic stroke between low-dose dabigatran and warfarin. The incidence of major bleeding in patients under the age of 75 years was significantly lower in the dabigatran group, but no difference was observed in the 75 years or older group. The incidence of intracranial bleeding was substantially lower in the dabigatran group irrespective of

age, whereas the incidence of gastrointestinal bleeding was substantially higher among patients aged 75 years or older (2.19%/year for dabigatran vs. 1.59%/year for warfarin).

High-dose dabigatran therapy (150 mg twice daily) was associated with a major bleeding risk similar to that of warfarin and a 58% reduced risk of intracranial bleeding (0.32%/year vs. 0.76%/year) with no difference in extracranial bleeding. The incidence of ischemic stroke in the high-dose dabigatran group was significantly lower than in the warfarin group (1.69%/year vs. 1.10%/year) irrespective of age.

However, the incidence of gastrointestinal bleeding was substantially higher among patients aged 75 years or older (2.80%/year for dabigatran vs. 1.59%/year for warfarin). The researchers observed that the risk of major bleeding increased with the concomitant use of aspirin. They also found that renal impairment (kidney dysfunction) was a strong risk factor for bleeding with a creatinine clearance of less than 50 mL/min associated with a 2-fold higher risk of major bleeding than if creatinine clearance was more than 80 mL/min. The researchers speculate that renal impairment may be a major cause of the increased tendency for gastrointestinal bleeding observed with dabigatran therapy in elderly patients (dabigatran is renally excreted so a kidney dysfunction may result in higher blood concentrations of the drug).[8]

During the RE-LY trial 1270 participants underwent cardioversion (84% electrical). The number of cardioversions performed in the three study groups – dabigatran, 110 mg twice daily (D110), dabigatran, 150 mg twice daily (D150), and warfarin to achieve an INR of 2.0 to 3.0 were similar at 647, 672, and 664.

Transesophageal echocardiography (TEE) was performed in 21% of patients and left atrial appendage thrombi were found in 1.8% of patients in the D110 group, 1.2% in the D150 group, and 1.1% in the warfarin group. The incidence of stroke and systemic embolism within 30 days of cardioversion was not significantly different in the three groups and neither was the incidence of major bleeding.

	<u>D110</u>	<u>D150</u>	<u>Warfarin</u>
Stroke and systemic embolism	0.77	0.30	0.60
Major bleeding	1.70	0.60	0.60

NOTE: The reason that the differences in the incidence of stroke and bleeding events are not statistically significant relates to the fact that the total number of patients affected was very small (only 11 cardioversions were followed by a stroke or thromboembolism, and only 19 were followed by major bleeding).

There was no difference in the incidence of stroke and systemic embolism between patients who had a TEE prior to cardioversion and those who had not, likely indicating that TEE may not be necessary in patients who have been adequately anticoagulated for at least 3 weeks prior to cardioversion. NOTE: This study was funded by Boehringer Ingelheim, the manufacturer of dabigatran, and all the authors had received grants or consulting fees from the company.[9]

In August 2011 the Japanese Ministry of Health, Labor, and Welfare issued a safety advisory noting that there had been 81 cases of serious side effects from dabigatran use including gastrointestinal bleeding.[10]

In October 2011 the Therapeutic Goods Administration in Australia issued a safety advisory prompted by an increase in the number of bleeding-related adverse events reported since more people began taking dabigatran. Some of the bleeding events occurred during the transition from warfarin to dabigatran and the most common site of serious bleeding was the gastrointestinal tract. [11]

Apart from the bleeding concerns, especially among patients with kidney impairment, emergency room physicians have also expressed concern about the fact that there is no known antidote to stop dabigatran-induced bleeding.[12]

In early January 2012 the association between dabigatran use and an increased risk of heart attack (myocardial infarction) and acute coronary syndrome (unstable angina, heart attack and cardiac death) was confirmed. A meta-analysis of 7 studies comparing dabigatran (150 mg twice daily) to warfarin, enoxaparin or placebo found that dabigatran use was associated with a relative 33% (absolute 0.27%) increased risk of heart attack or acute coronary syndrome.[13]

As of January 2012 the recommended dosage in the USA for dabigatran is 150 mg twice daily for patients under the age of 75 years with normal kidney function and 75 mg twice daily for older patients and those with impaired kidney function. The drug is not recommended for patients with impaired liver function. It should be noted that there is no clinical data supporting the use of the 75-mg dose and that only the 110- and 150-mg doses have been approved in Europe.

Rivaroxaban

Rivaroxaban is a direct inhibitor of factor Xa, the first member of the common pathway in the coagulation cascade. Like dabigatran it was initially approved for temporary use following knee and hip operations. After lengthy deliberations and some controversy, the drug was approved by the FDA in November 2011 for stroke prevention in AF patients. The FDA approval was based on the results of a large clinical trial (ROCKET AF) involving 14,000 patients with non-valvular AF treated at 1178 participating sites in 45 countries. The average (median) age of the patients was 73 years and 40% were female. Most of the study participants had persistent (probably including permanent) AF and had a CHADS₂ score of at least 2 (mean score of 3.5). All in all, the trial involved a group of very sick people – in no way comparable to a group of otherwise healthy afibbers. Over 90% of the group had hypertension, 63% had heart failure, and 55% had experienced a prior stroke or transient ischemic attack (TIA).

The study participants were randomized to receive standard therapy with oral warfarin (INR range of 2.0 – 3.0) or 20 mg/day of rivaroxaban (15 mg/day for patients with kidney disorder). All patients also received a placebo pill and regular INR checks to blind them to the treatment received. The warfarin-treated patients were within INR target range 55% of the time. During an average follow-up of about 2 years, 188 patients (1.7%/year) in the rivaroxaban group experienced a stroke, TIA or systemic embolism as compared to 241 patients (2.2%/year) in the warfarin group. Major and non-major clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9%/year) and in 1449 patients (14.5%/year) in the warfarin group. The incidence of hemorrhagic stroke (intracranial hemorrhage) and fatal bleeding was significantly less in the rivaroxaban group (0.5% and 0.2%/year) than in the warfarin group (0.7% and 0.5%/year). However, the incidence of major gastrointestinal (GI) bleeding was higher in the rivaroxaban group (3.2%/year) than in the warfarin group (2.2%/year).

About 23% of participants dropped out of the study before its completion. The rate of ischemic stroke, TIA and systemic embolism during a median 117 days of follow-up was 4.7% in the rivaroxaban drop-out group and 4.3% in the warfarin drop-out group. The ROCKET AF investigators conclude that rivaroxaban is non-inferior to warfarin in the treatment of AF patients at moderate to high risk of stroke. NOTE: This study was funded by Johnson & Johnson and Bayer, and all the investigators had substantial financial ties to the pharmaceutical industry.[14]

Rivaroxaban is partially excreted through the kidneys thus raising concerns that poor kidney function may result in an increase in drug concentration and commensurate increase in bleeding risk. The ROCKET AF trial included 2950 patients with moderately impaired kidney function (creatinine clearance between 30 and 49 ml/min) who were randomized to receive 15 mg/day of rivaroxaban or warfarin. The average age of these patients was 79 years and their average CHADS₂ score was 3.7, 82% had persistent AF (probably including permanent AF), 50% had suffered a prior stroke or TIA, 92% had hypertension, and 66% had congestive heart failure. The

annual rate of ischemic stroke and systemic embolism was 2.32% as compared to 2.77% in the warfarin control group. The major bleeding rate among rivaroxaban-treated patients was 4.49%/year as compared to 4.70% in the warfarin group. Intracranial bleeding (including hemorrhagic stroke) occurred in 0.71%/year among rivaroxaban-treated patients and in 0.88%/year among those treated with warfarin. Thus, it would appear that rivaroxaban is at least as safe as warfarin in patients with moderate renal impairment. NOTE: This study was funded by Johnson & Johnson and Bayer Healthcare.[15,16]

A recent notification from the FDA warns of an increased stroke risk if rivaroxaban is discontinued without replacing it with an adequate alternative anticoagulant and also point out that the drug should be taken with an evening meal in order to be fully effective.[17]

Apixaban

Apixaban is a direct inhibitor of factor Xa, the first member of the common pathway in the coagulation cascade. A study comparing apixaban (5 mg twice daily) with aspirin (81 – 324 mg/day) in a group of 5600 AF patients found that apixaban reduced the relative risk of stroke and systemic embolism by about 50% when compared to aspirin (yearly event rates 1.6% with apixaban and 3.7% with aspirin) without significantly increasing the risk of major bleeding.[18]

A very large-scale study (ARISTOTLE) comparing apixaban to warfarin was recently completed. It involved 18,200 patients with AF and at least one additional risk factor for ischemic stroke. The average (median) age of the patients was 70 years and 35% were female. Most of the participants (85%) had persistent or permanent AF and had a CHADS₂ score of at least 1 (mean score of 2.1). All in all, the trial involved a group of very sick people, in no way comparable to a group of otherwise healthy afibbers. Almost 90% were being treated for hypertension, 35% had heart failure or abnormally low left ventricular ejection fraction, over 30% had experienced a prior heart attack, stroke, TIA (transient ischemic attack) or systemic embolism, and 25% had diabetes. None of the study participants had a CHADS₂ score of zero.

The participants were randomized to receive standard therapy with oral warfarin (INR range of 2.0 to 3.0) or 5 mg twice daily of apixaban (2.5 mg twice daily for elderly or frail persons and those with impaired kidney function). The warfarin-treated patients were within INR target range 66% of the time (median value). During an average (median) follow-up of 1.8 years, 212 patients (1.3%/year) in the apixaban group experienced a stroke, TIA or systemic embolism as compared to 265 patients (1.6%/year) in the warfarin group. The rate of major bleeding was 2.13%/year in the apixaban group compared to 3.09%/year in the warfarin group. The incidence of hemorrhagic stroke (intracranial bleeding) was 0.24%/year in the apixaban group compared to 0.47%/year in the warfarin group. The incidence of major gastrointestinal bleeding was 0.76%/year in the apixaban group and 0.86%/year in the warfarin group. Overall, 1009 patients (6.13%/year) in the apixaban group and 1168 patients (7.20%/year) in the warfarin group died (from any cause) or suffered a stroke, systemic embolism or major bleeding during follow-up.

The ARISTOTLE AF investigators conclude that apixaban is superior to warfarin in regard to preventing stroke and systemic embolism and non-inferior in all other aspects where a comparison was made. NOTE: This study was funded by Bristol-Myers Squibb and Pfizer and all the investigators have substantial financial ties to the pharmaceutical industry.[19,20,21]

The manufacturers of apixaban have applied for FDA approval and a decision regarding this application is expected by March 2012. As in the case of dabigatran and rivaroxaban, concerns have been raised about the non-availability of drugs for halting apixaban-induced bleeding.

Comparison of Anticoagulants

A direct comparison of the efficacy and safety of the three novel anticoagulants is not possible due to the heterogeneity of the patient populations involved in the clinical trials. Average (mean) CHADS₂ scores varied from 2.1 (dabigatran and apixaban trials) to 3.5 (rivaroxaban trial). However, it is possible to compare the extent to which the novel anticoagulants were superior (or

inferior) to warfarin in the reported outcomes. For example, considering the incidence of stroke and thromboembolism, it is clear that dabigatran (150 mg twice daily) is superior to warfarin inasmuch as the yearly incidence of stroke/embolism for dabigatran-treated patients is 1.11%/year as compared to 1.69%/year for warfarin, or a “superiority” of 0.58%/year. Corresponding numbers for dabigatran (110 mg twice daily), rivaroxaban (20 mg/day) and apixaban (5 mg twice daily) are given below.

Total stroke and thromboembolism, %/year

		<u>Warfarin</u>	<u>Drug*</u>	<u>Superiority</u>	<u>P-value</u>
Dabigatran	110 mg twice daily	1.69	1.53	0.16	0.34
Dabigatran	150 mg twice daily	1.69	1.11	0.58	< 0.001
Rivaroxaban	20 mg once daily	2.20	1.70	0.50	< 0.001
Apixaban	5 mg twice daily	1.60	1.27	0.33	0.01

* dabigatran, rivaroxaban, apixaban as indicated

It is clear that dabigatran (150 mg twice daily), rivaroxaban and apixaban are all superior to warfarin in protecting against total stroke/embolism and that dabigatran (110 mg twice daily) is not significantly better than warfarin.

Major bleeding, %/year

		<u>Warfarin</u>	<u>Drug*</u>	<u>Superiority</u>	<u>P-value</u>
Dabigatran	110 mg twice daily	3.36	2.71	0.65	0.003
Dabigatran	150 mg twice daily	3.36	3.11	0.25	0.31
Rivaroxaban	20 mg once daily	3.4	3.6	- 0.20	0.58
Apixaban	5 mg twice daily	3.09	2.13	0.96	< 0.001

* dabigatran, rivaroxaban, apixaban as indicated

It is clear that apixaban is the safest of the new anticoagulants when it comes to major bleeding.

Combined superiority

If total stroke/thromboembolism and major bleeding is considered to be of equal seriousness, then an indication of the overall benefit/risk profile of a drug can be obtained by adding superiority for total stroke/embolism to superiority in major bleeding. Using this approach, it is clear that apixaban has the best efficacy/risk profile with a total superiority score of 1.29%/year followed by dabigatran (150 mg twice daily) at 0.83%/year, dabigatran (110 mg twice daily) at 0.81%/year, and rivaroxaban at 0.30%/year.

Superiority by sub-group

Ischemic stroke, %/year

		<u>Warfarin</u>	<u>Drug*</u>	<u>Superiority</u>	<u>P-value</u>
Dabigatran	110 mg twice daily	1.20	1.34	- 0.14	0.35
Dabigatran	150 mg twice daily	1.20	0.92	0.28	0.03
Rivaroxaban	20 mg once daily	-	-	-	-
Apixaban	5 mg twice daily	1.05	0.97	0.08	0.42

* dabigatran, rivaroxaban, apixaban as indicated

Dabigatran (150 mg twice daily) is the only one of the three drug regimens for which data is available that is significantly superior to warfarin when it comes to protecting against ischemic stroke.

Hemorrhagic stroke, %/year

		<u>Warfarin</u>	<u>Drug*</u>	<u>Superiority</u>	<u>P-value</u>
Dabigatran	110 mg twice daily	0.38	0.12	0.26	< 0.001
Dabigatran	150 mg twice daily	0.38	0.10	0.28	< 0.001
Rivaroxaban	20 mg once daily	-	-	-	-
Apixaban	5 mg twice daily	0.47	0.24	0.23	< 0.001

* dabigatran, rivaroxaban, apixaban as indicated

It is clear that dabigatran and apixaban are both associated with a significantly reduced risk of hemorrhagic stroke when compared to warfarin.

Intracranial bleeding, %/year

		<u>Warfarin</u>	<u>Drug*</u>	<u>Superiority</u>	<u>P-value</u>
Dabigatran	110 mg twice daily	0.74	0.23	0.51	< 0.001
Dabigatran	150 mg twice daily	0.74	0.30	0.44	< 0.001
Rivaroxaban	20 mg once daily	0.70	0.50	0.20	0.02
Apixaban	5 mg twice daily	0.80	0.33	0.47	< 0.001

* dabigatran, rivaroxaban, apixaban as indicated

The novel anticoagulants are all significantly superior to warfarin when it comes to the prevention of intracranial bleeding.

Gastrointestinal bleeding, %/year

		<u>Warfarin</u>	<u>Drug*</u>	<u>Superiority</u>	<u>P-value</u>
Dabigatran	110 mg twice daily	1.02	1.12	- 0.10	0.43
Dabigatran	150 mg twice daily	1.02	1.51	- 0.49	< 0.001
Rivaroxaban	20 mg once daily	-	-	-	-
Apixaban	5 mg twice daily	0.86	0.76	0.10	0.37

* dabigatran, rivaroxaban, apixaban as indicated

When it comes to avoiding gastrointestinal bleeding apixaban would probably be the preferred anticoagulant.

Conclusion

Preventing the coagulation of blood on a permanent basis clearly increases the risk of prolonged and serious bleeding and there is no such thing as an entirely safe pharmaceutical-based anticoagulant. Thus, it is best to avoid anticoagulation unless one has definite specific risk factors for ischemic stroke. If, however, anticoagulation is required, then individual circumstances must be taken into account.

If one has a tendency to bleeding, especially gastrointestinal bleeding, then apixaban would likely be the best choice. If one is prone to falls or is involved in contact sports, downhill skiing, mountain biking or similar activities, then warfarin would probably be the preferred option as its anticoagulant effect can be reversed by a vitamin K infusion. A second choice would be apixaban. Dabigatran and apixaban both significantly reduce the risk of hemorrhagic stroke compared to warfarin, while dabigatran (150 twice daily) would appear to be the best choice if one wishes to focus solely on avoiding an ischemic stroke.

However, dabigatran (150 mg twice daily) is not recommended for patients with impaired kidney or liver function and should be used with caution in patients over the age of 75 years as it materially increases gastrointestinal bleeding in this patient group. It is now also clear that dabigatran is associated with a small but significant increased risk of heart attack and acute coronary syndrome.

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E-mail: editor@afibbers.org
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