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STROKE PREVENTION IN ATRIAL FIBRILLATION

Assessment of stroke risk and stroke prevention remain the first priority in the management of patients with atrial fibrillation. Given the introduction of new anticoagulants into the marketplace, the topic of stroke prevention plays a major part of the 2010 Canadian Cardiovascular Society's AF Guidelines. The guidelines advocate the use of the $CHADS_2$ risk score for assessment of stroke risk in all patients with AF (*Figure 1*), and have expanded the role of anticoagulation for stroke prevention (*Figure 2*). Recently, the Canadian Cardiovascular Research Network (CCRN) convened an Expert Forum to discuss the latest clinical trials and recommendations amongst some of the country's leading AF experts.

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study was presented in late 2009 and demonstrated the efficacy and safety of the oral direct thrombin inhibitor dabigatran versus warfarin for stroke prevention in atrial fibrillation.

Time in Therapeutic Range — Clinical Trials vs. Clinical Practice

Practitioners who treat patients with conditions like AF must embrace a systematic approach in order to maximize therapeutic effect, and prevent harmful medication errors and serious adverse events associated with warfarin anticoagulation therapy, according to a leading Canadian researcher-clinician.

"Warfarin is a drug that's here to stay, at least for the foreseeable future," explained Dr. Paul Dorian of St. Michael's Hospital in Toronto. "So, even though we have other anticoagulants to choose from, practitioners have a responsibility to understand how warfarin is used optimally, and we need to do our best to fulfill our responsibilities to our patients."

Optimizing time in a narrow therapeutic range (INR 2-3) can be difficult given warfarin's complex pharmacokinetic and pharmacodynamic profile and highly variable individual dosing. Treatment outcomes hinge on determining the appropriate loading dose, closely monitoring patients' INR levels and carefully adjusting doses to keep patients within targets. Scant consensus on how best to manage warfarin anticoagulation clouds these issues, Dr. Dorian noted.

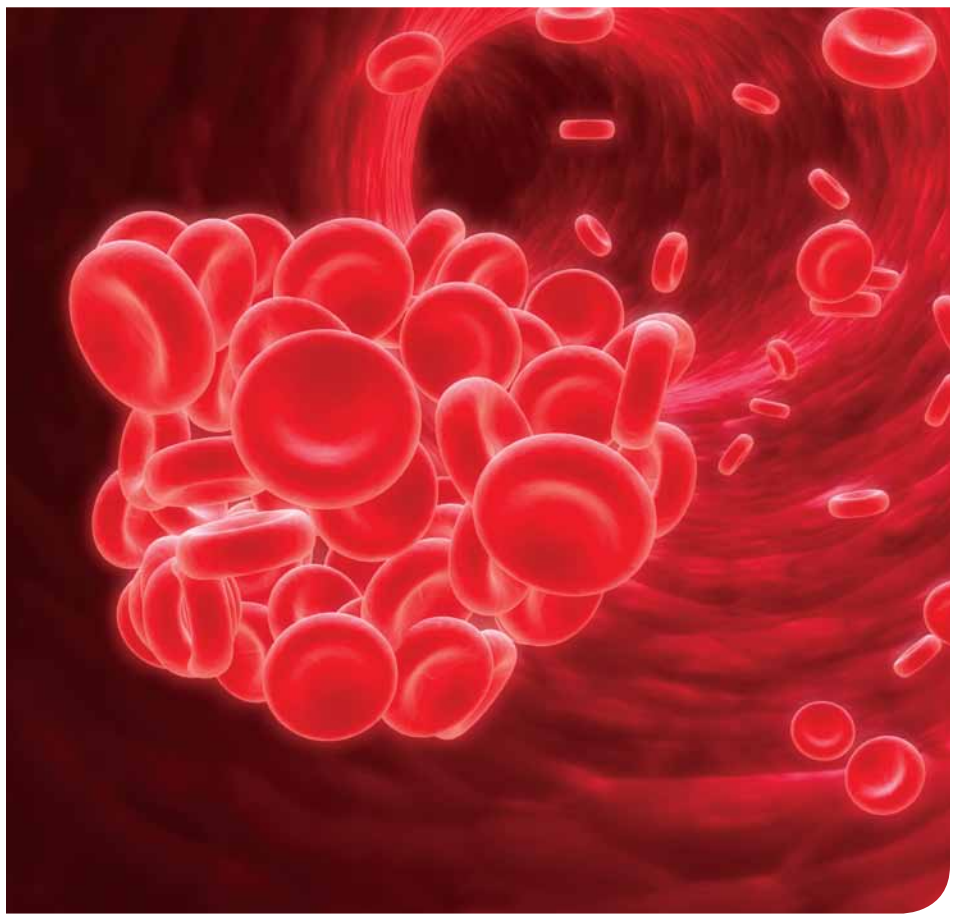


Figure 1: **Predictive Index for Stroke**

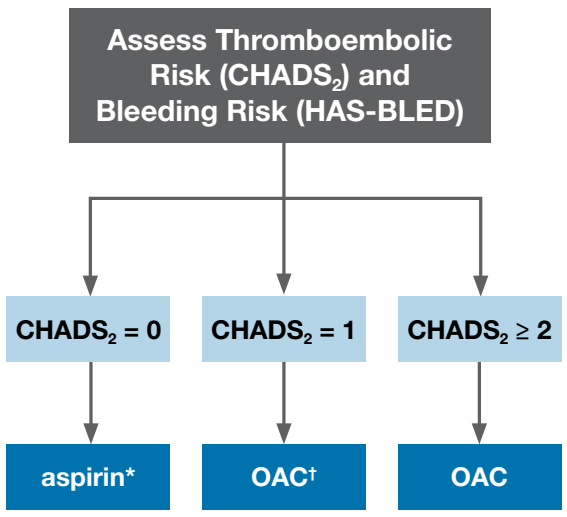
$CHADS_2$

Risk Factor	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75	1
Diabetes Mellitus	1
Stroke/TIA/Thromboembolism	2
Maximum Score	**6**

Patients (n=1733)	Adjusted Stroke Rate (%/yr) 95% CI	$CHADS_2$ Score
120	1.9 (1.2 to 3.0)	0
463	2.8 (2.0 to 3.8)	1
523	4.0 (3.1 to 5.1)	2
337	5.9 (4.6 to 7.3)	3
220	8.5 (6.3 to 11.1)	4
65	12.5 (8.3 to17.5)	5
5	18.2 (10.5 to 27.4)	6

Gage BG et al. *JAMA* 2001;285:2864–2870

Figure 2: **CCS AF Guidelines Recommendations for Stroke Prevention**



* No antithrombotic may be appropriate in selected young patients with no stroke risk factors.

† Aspirin is a reasonable alternative in some as indicated by risk/benefit

Dabigatran is preferred OAC over warfarin in most patients.

Cairns JA et al. *Can J Cardiol* 2011;27(1):74-90

THE BOTTOMLINE

Atrial fibrillation (AF) affects up to 250,000 Canadians and is associated with a 3 to 5-fold risk of stroke. All patients with atrial fibrillation (paroxysmal, persistent, or permanent) should be evaluated for stroke risk using the $CHADS_2$ risk score.

Key concepts:

1. Therapeutic anticoagulation with warfarin reduces stroke risk by approximately 65% (see *Figure 3* on page 2).
2. Optimal use of warfarin is difficult in clinical practice, with less than half of eligible patients receiving the drug, and even fewer achieving therapeutic INR levels.
3. Dabigatran 150 mg bid is superior to warfarin for stroke prevention, with less intracranial hemorrhage and similar rates of major bleeding.
4. Dabigatran 110 mg bid is noninferior to warfarin for stroke prevention, with less intracranial and less major bleeding.
5. New Canadian atrial fibrillation guidelines have expanded the role of anticoagulation in stroke prevention, and strongly recommend dabigatran 150 mg bid as the preferred choice in a large proportion of AF patients.

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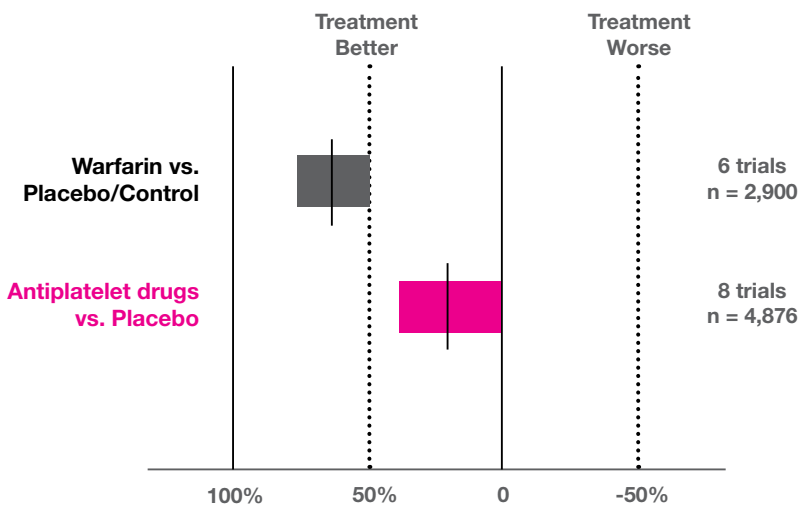
The Canadian Cardiovascular Research Network (CCRN) is a not-for-profi t academic research organization that aims to foster basic, translational, clinical and population level research efforts and generate new knowledge to improve cardiovascular care in Canada. An additional mandate is to develop state-of-the-art knowledge integration platforms that feature multidisciplinary and inter-specialty collaboration focusing on the future of health care delivery, research and academia-industry interface.

Figure 3: **Antithrombotic Therapy for Atrial Fibrillation**



Hart R, et al. *Ann Intern Med* 2007;146:857.

Establishing appropriate warfarin loading doses

Dr. Dorian presented data from a systematic review by Heneghan et al.[1] that showed no difference with either 5 mg or 10 mg loading doses of warfarin, doses that are commonly recommended worldwide. Eleven studies encompassing more than 1,300 patients newly started on warfarin were included in the analysis.

Two studies using single INR measures found more patients were in range on day five with a 10 mg loading dose versus 5 mg, yet two others found no difference between the two doses on day five as measured by two consecutive INRs. The benefits of age-adjusted and genotype-guided dosing were not established in the included studies, the authors noted, adding that overall the size and quality of most trials analyzing optimal loading doses was low.

"Most of the studies in this review were not placebo-controlled," Dr. Dorian stressed. "The bottom line is that there is no clear evidence that any one dose is better than any other dose at reaching a compromise between getting into the therapeutic range quickly while avoiding the first INR being too high and putting the patient at risk for bleeding."

Genotyping for warfarin responsiveness

Much attention has been devoted to the strategy of determining how quickly patients metabolize warfarin as a way to establish maintenance dosages, Dr. Dorian remarked. Variations in two single-nucleotide polymorphisms (SNPs) — CYP2C9 and VKORC1 — determine the how quickly the drug is cleared from the circulation. Roughly 20% to 25% of the population possess at least one of these SNPs, making them slow metabolizers of warfarin who therefore require lower maintenance doses.

The question of whether testing patients for genetic variation results in better control of INR was recently studied by McMillin et al.[2] Here, 229 adult patients requiring warfarin for prevention of venous thromboembolism after joint replacement surgery were assigned to either standard practice or genotype-based warfarin dosing. Loading doses were established using validated algorithms. While INR was used as the basis for the management of all patients, warfarin doses were adjusted less frequently in those with at least one CYP2C9 variant.

While patients in the genotype arm appeared to achieve therapeutic INRs more quickly and experienced fewer adverse events, the study's endpoints did not attain statistical significance.

"The idea that gene profiling translates into better control of INR is a concept that requires more proof, especially given the high costs of genetic testing and the fact that it is not widely available in all areas," Dr. Dorian said. "The alternative is to carefully monitor patients, particularly when you are starting the drug, and titrate to the appropriate dose."

Predictors of stable INR while on warfarin

Few data are available to identify characteristics that will predict which patients are most likely to do well on warfarin, Dr. Dorian said.

In a retrospective, longitudinal cohort study, Witt et al.[3] analyzed data from electronic databases to compare rates of thromboembolism, bleeding and death between patients with stable INRs (n = 533) and those with at least one INR outside the therapeutic range (n = 2,555). The authors suggested that older age (> 70 years), being male, the absence of heart failure, a target INR < 3.0 and a reduced burden of chronic illness were independently predictive of stable INR control.

"Within the vagaries of this analysis, however, no other factors panned out as being predictive of the likelihood, in retrospect, of having stable INRs," Dr. Dorian stressed.

DISCUSSION

"Available algorithms are all quite similar and seem to iterate to the same general approach — make small weekly dose changes of about 10% at a time, particularly if the INR is fairly close to the desired range, another 10% change if the INR is low, a change of 10% to 20% if INR is high, and if it is very high, consult an expert for advice," Dr. Dorian advised.

In discussing how frequently INR should be monitored in the average patient, there seems to be no advantage to weekly monitoring. General consensus remains that INR should be checked every 3-4 weeks.

Systematic care superior to usual care

Patients on warfarin who are monitored and managed using a standardized system of care are more likely to see better outcomes than those who receive usual care from a single physician, Dr. Dorian outlined. What's more, the use of widely available public and private dosing algorithms, nomograms and websites appears to produce similar results despite any differences in their approach.

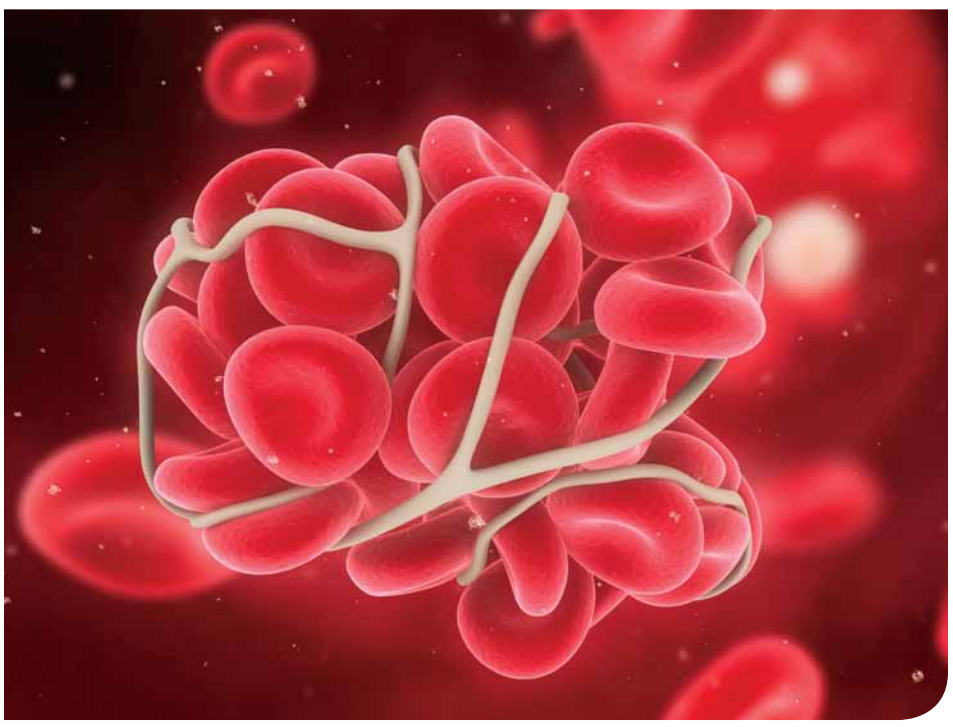
"At the patient level, success comes from attention to detail and using an algorithm," he explained. "At the system level, the bottom line is that you have to have a system. Whether patients are pharmacist managed, or managed by an anticoagulation clinic, or a localized system of care, these all seem to work really well, compared with usual care, which is often a family physician working alone who updates patients with blood lab results over the phone."

Notably, Bungard et al.[4] compared outcomes in patients (n = 125) who received warfarin therapy for four months prior to being managed by an anticoagulation management service (AMS) with results after four months within the AMS. They reported that patients were in the target INR range 66.5% of the time under AMS management versus 48.8% before referral. Reductions in thromboembolic and hemorrhagic events saved almost 600 hours in the emergency department (ED) and more than $120,000 in health care costs, as well.

As for the value of home self testing — another contested topic in the literature — Matchar et al.[5] failed to demonstrate that a weekly self test delayed time to a first stroke, major bleed, or death versus high-quality monthly clinic testing.

That leaves the systematic approach to warfarin management as the key to better outcomes, Dr. Dorian concluded.

"Warfarin is not going away," Dr. Dorian acknowledged. "We need to work with Canada's family physicians to adopt these better systems for our patients who require anticoagulation."



Stroke prevention in AF: the unmet medical need and clinical advances with dabigatran

The new oral direct thrombin inhibitor dabigatran is safer, more efficacious and shows an overall net benefit in stroke prevention in AF versus warfarin, says Dr. Stuart Connolly of McMaster University in Hamilton.

Health Canada's approval of dabigatran for this indication was based largely on results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) trial 6 lead by Dr. Connelly.

RE-LY was a multi-centre, randomized, prospective open-label noninferiority trial of more than 18,000 patients with AF and at least one risk factor for stroke. Participants were randomized to receive either dabigatran 110 mg or 150 mg twice daily in a blinded fashion, or adjusted-dose warfarin in an unblinded protocol. The primary outcome was a composite of stroke and non-CNS systemic embolism (*Figure 4*).

Patients enrolled in RE-LY were aged 71 years on average with mean CHADS2 scores of 2.1. The majority (63.6%) were male and half were warfarin-naive. The median duration of follow-up was two years, with complete follow-up achieved in 99.9% of patients.

The authors concluded that overall rates of stroke and systemic embolism were similar with dabigatran 110 mg and warfarin, but that dabigatran was associated with lower rates of major hemorrhage. Dabigatran 150 mg achieved lower rates of stroke and systemic embolism versus warfarin, but rates of major hemorrhage were similar.

"The real science here is to be found not in the Kaplan-Meier curves (*Figure 5*), but in the point estimates and their confidence intervals," Dr. Connolly stressed (see *Figure 6*). "Both doses of dabigatran show a reduction in the primary outcome versus warfarin and at 95% the confidence interval falls well below the line of non-inferiority. With the 150 mg dose, we see a true reduction in stroke and systemic embolism over 110 mg — so, there is a statistically significant difference between the two dabigatran doses in terms of primary outcomes."

The rate of ischemic stroke was significantly lower with the 150 mg dose of dabigatran, while the 110 mg dose was non-inferior to warfarin.

The results for hemorrhagic stroke, however, were particularly noteworthy and illustrative of the degree to which newer anticoagulants may render warfarin obsolete in the near future, Dr. Connolly stressed (*Figure 7*). In patients receiving warfarin, rates of hemorrhagic stroke were 0.38% per year, versus 0.12% and 0.10% per year for dabigatran 110 mg and 150 mg, respectively.

"This may be the real pivot point around which dabigatran and all the new anticoagulants, some of which appear to have similar results, will replace warfarin," Dr. Connolly explained. "This is because warfarin can cause intracranial hemorrhage, and a lot of it — and there is absolutely nothing you can do about it."

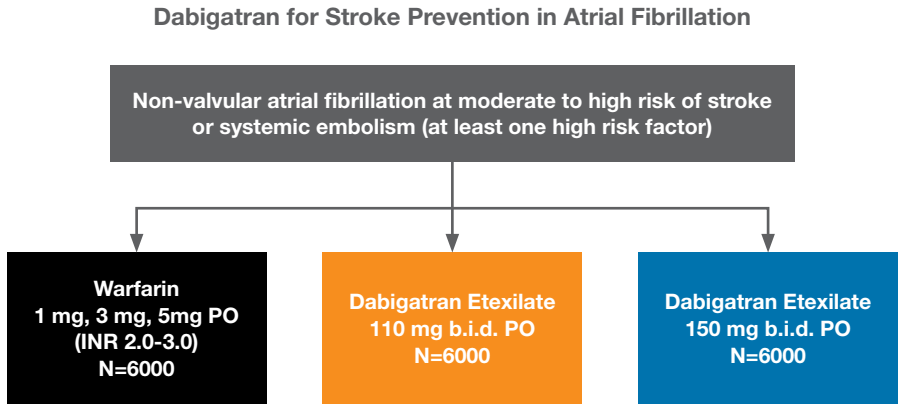
In terms of major bleeding rates among treatment arms — one of RE-LY's primary safety outcomes, loosely defined as a drop in hemoglobin of more than 2 g — dabigatran 110 mg achieved a 20% reduction versus dabigatran 150 mg or warfarin. When looking only at significant major bleeds (including those requiring surgery, bleeds into major organs and/or hemoglobin drops of 5 g or more), both doses of dabigatran showed superior outcomes that were statistically significant over warfarin. Bleeding rates for the 110 mg dose of dabigatran were 2.71% per year, versus 3.11% for dabigatran 150 mg, and 3.36% per year for warfarin. The differences between the two dabigatran doses were also statistically significant (see *Figure 8* on page 4).

The rates of adverse events were similar across all three arms of the RE-LY study, however, significantly more participants experienced dyspepsia with dabigatran than with warfarin. In RE-LY, about 2% of subjects in the dabigatran treatment groups stopped taking the drug because of dyspepsia. Dr. Connolly suggested that, based on experience, patients troubled by dyspepsia may try antacids (which do not block absorption of dabigatran) before being given a proton pump inhibitor. Taking dabigatran with meals may also minimize the risk of dyspepsia.

Other clinically relevant RE-LY findings:

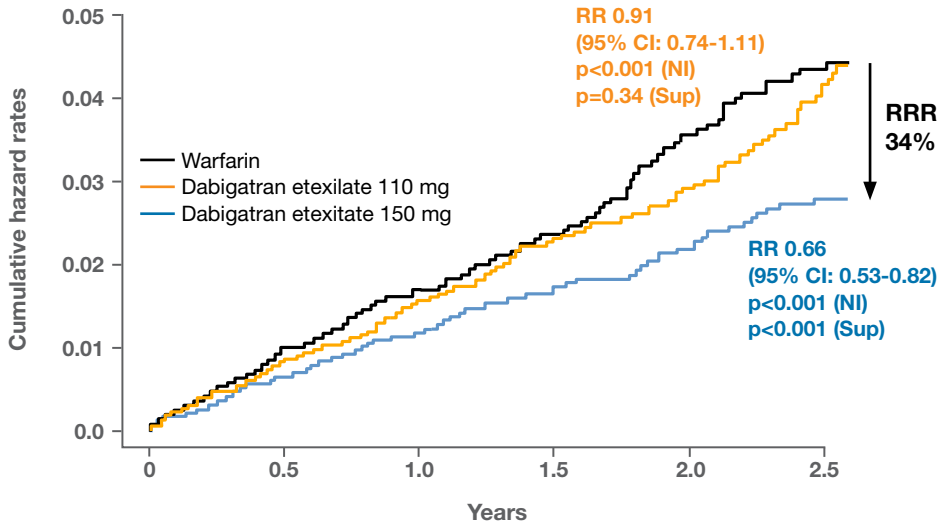
- While RE-LY data initially showed an increased risk for myocardial infarction (MI) with dabigatran use versus warfarin, Dr. Connolly said that later analyses suggested the risk appeared not to be statistically significant. The data that suggested warfarin use led to slightly fewer MIs might have been the result of that agent's ability to neutralize the coagulation cascade, he noted.

Figure 4: **RE-LY® Protocol Schema**



Ezekowitz MD et al. *Am Heart J.* 2009;157:805-810.

Figure 5: **RE-LY®: Primary Outcome – Time to First Stroke/SSE**



Connolly SJ, et al. *N Engl J Med* 2009;361:1139-1151.

Figure 6: **RE-LY®: Primary Outcome – Stroke or Systemic Embolism (SSE)**

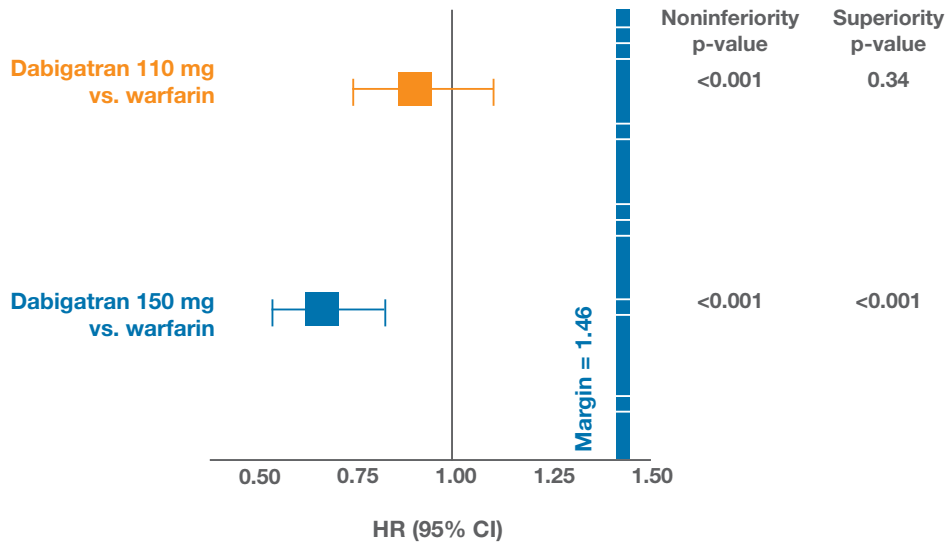
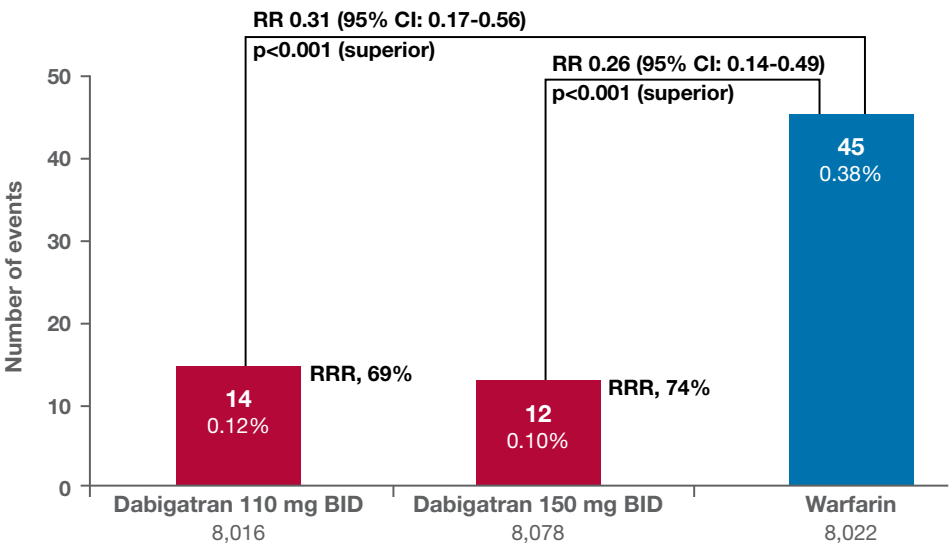


Figure 7: **RE-LY®: Hemorrhagic Stroke**



Connolly SJ et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51.

COMMENT

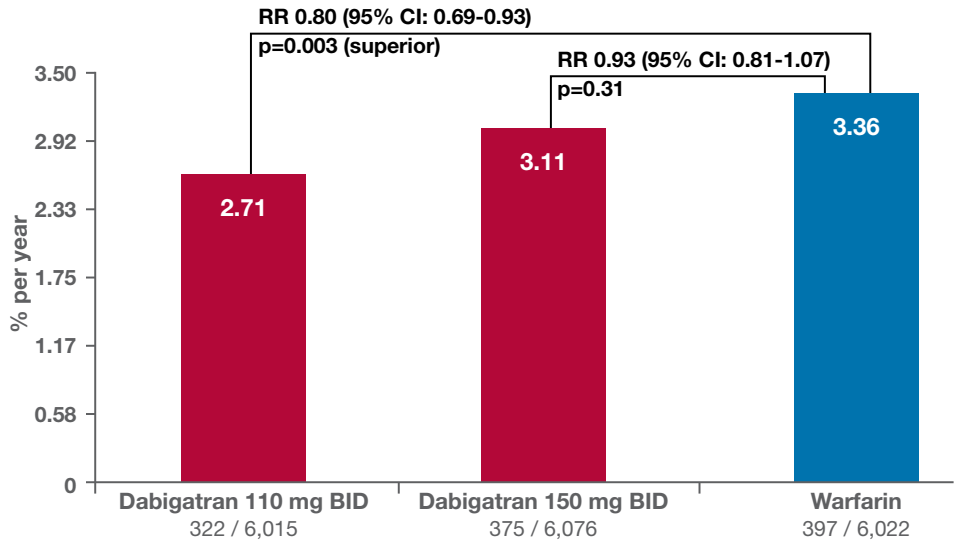
"In my research, the use of amiodarone, the presence of diabetes requiring insulin, and cognitive impairment all appear to be predictive of poor INR control. We are working on an analysis of the RE-LY trial data, and it appears amiodarone and male gender are predictive of bad control."

Dr. Stuart Connolly

"We looked at the data on serious myocardial ischemic events that might be associated with an increase in MI, and we found nothing on new angina hospitalizations, nothing on an increased risk for coronary artery bypass grafting (CABG) and nothing on percutaneous coronary intervention," he said. "Cardiovascular death is also going in the right direction — so, in spite of the fact that there may be something going on with respect to MI risk and dabigatran use, overall the drug's CV profile looks favourable."

- In terms of mortality, data trends suggested dabigatran 150 mg was superior to the other two treatments with borderline statistical significance, and that it was associated with a statistically significant 15% reduction in vascular death.
- A recent paper by Nagarakanti et al. [7] examined data from patients in RE-LY who underwent cardioversion during either warfarin or dabigatran therapy. The authors looked at 1,983 cardioversions performed in 1,270 patients and concluded that the 30-day risk of stroke or major bleeding was low with all three treatments, reassuring clinicians that cardioversion can indeed be performed safely in patients taking dabigatran.

Figure 8: **RE-LY®: Major Bleeding* Rates**



*Major bleeding was defined as a reduction in the hemoglobin level of at least 20 g per liter, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ.

Connolly SJ, et al. *N Engl J Med* 2009;361:1139-1151z.

DISCUSSION

Were there any clues as to which patients bled in RE-LY?

Dr. Eikelboom: "Poor INR control, increased age and hypertension were associated with bleeding."

Dr. Connolly: "Gastrointestinal bleeding also goes up with dabigatran use – more so with the 150 mg dose, but it is not significantly increased with 110 mg. It was thought that the bleeding was related to dyspepsia, which was experienced by 5.8% of patients in the warfarin group and by 11.8% and 11.3% in the dabigatran 110 mg and 150 mg groups, respectively. There is some evidence to suggest it is lower GI bleeding and not upper GI bleeding."

What about bleeding and age?

Dr. Connolly: "One of the more curious things about the RE-LY study findings is that the reduction in bleeding is greatest in younger patients. The p-values are very significant for this. The benefit diminishes with age; indeed, it is almost gone by age 75 or greater, when the bleeding rates are similar with dabigatran 110 mg and warfarin, and possibly with dabigatran 150 mg and warfarin. But there is a clear advantage for younger ages – the diminishing advantage is all about extracranial bleeding, both GI and non-GI.

"In terms of intracranial bleeding, there was also demonstrable benefit in the elderly, for both dabigatran 110 mg and 150 mg versus warfarin."

If my patient is at high risk for MI, is there a risk in putting him on dabigatran?

Dr. Connolly: "I think it's clear that, even in the patient who is at high risk of MI, there is an overall net benefit of being on dabigatran, especially in terms of reduction of ischemic stroke and intracranial hemorrhage." (See *Tables 6 and 7*)

How do I decide which patient should be given dabigatran and at which dose?

Dr. Connolly: "Basically, patients who are elderly are reasonable candidates for dabigatran 110 mg, however 150 mg is predominantly used in Canada."

Dr. Dorian: "My algorithm is simple: any new patient gets dabigatran if they can pay for it, provided their creatinine clearance is normal. I ask patients on warfarin if they are happy, and if they are, they stay on it. The CCS Guidelines say patients at high risk of coronary events should preferentially get warfarin over dabigatran, but I think it's fair to say that there is some disagreement about that. As for the dabigatran dose, if my patient is close to 75 to 80 years of age with additional risk factors for bleeding they get 110 mg. However, I see older patients, so I'm not sure if that is reflected in the community."

Dr. Eikelboom: "For the average patient under a GP's care, it's reassuring to know that the evidence suggests it doesn't matter which dose you select. I divide the population into high risk of bleeding or not – if you choose 110 mg, the patient will still benefit."

New ORAL ANTICOAGULANTS ON THE HORIZON

Several ongoing trials are testing additional new oral anticoagulants in AF patients. These drugs, like dabigatran, provide predicable levels of anticoagulation without the need for INR monitoring, and with fewer drug-drug and drug-food interactions than warfarin.

Rivaroxaban (Xarelto), apixaban, edoxaban, betrixaban, YM150, and TAK442 are direct factor Xa inhibitors while dabigatran and AZD0837 are direct thrombin inhibitors. Rivaroxaban was recently shown to be non-inferior to warfarin in the ROCKET-AF study.

Most are being tested head-to-head against warfarin, explained McMaster University's Dr. John Eikelboom, Canada Research Chair in cardiovascular medicine, thereby leaving out an important segment of the population.

"Focusing trials of new agents versus warfarin is only half the problem," he said. "The biggest problem is on the other side of the equation, with patients who are not suitable for warfarin. The reality is that many registries in North America and Europe show that only about 50 - 60% of patients with AF who have additional risk factors actually receive warfarin. This is a consistent statistic that has not changed over time. The remaining patients are not treated at all, or are treated with ASA, which as we know is relatively ineffective."

Only two recent major trials have compared newer agents as alternatives to ASA, Dr. Eikelboom noted. The ACTIVE-A study demonstrated that the combination of ASA plus clopidogrel was superior to ASA alone for stroke prevention in patients not eligible for warfarin. However, this dual antiplatelet combination was proven to be inferior to warfarin in the ACTIVE W study. Recently, the factor Xa inhibitor apixaban was also shown to be superior to ASA in warfarin-intolerant patients, with surprisingly no increase in bleeding compared to ASA.

Thus, clinicians who want to weigh their options between promising drugs must therefore make indirect comparisons.

"Indirect comparisons are limited by their very nature," Dr. Eikelboom said. "They are potentially confounded, and we are not making comparisons in a randomized fashion.

Nonetheless, clinicians have to make hard decisions about which drug to use, and we do that best by comparing outcomes of clinical trials as opposed to relying on pharmacological profiles alone."

"Indirect comparisons across trials are very difficult to do. If you are going to do it, I think you have to compare relative risk across trials. By and large that is more transferable. So, when we are facing a patient we are comparing several trials – if, for example, we had dabigatran and rivaroxaban in front of us, how do we decide between one and the other? It has to be by indirect comparison."

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