



## Dabigatran: Implications for Clinical Practice



Innovation

**Dabigatran** (Pradaxa), was approved by the FDA in October of 2010, and as expected was just placed in the US atrial fibrillation (AF) management guidelines as an alternative to warfarin for preventing strokes and thromboembolism. The drug received the *highest class I recommendation*, based primarily on its showing in the randomized **RE-LY** trial. This *Heartbeat* will review results of the RE-LY trial, AF guidelines and discuss ‘real world’ implications for clinical practice.

### RE-LY:

Treatment with vitamin K antagonists (warfarin) significantly reduces the risk of stroke in AF. However, this effective treatment increases bleeding risk with a subsequent need for intensive monitoring. Against this background, dabigatran (Pradaxa) is welcomed as a new compound (a direct thrombin inhibitor-10a) in the prevention of thrombo-embolic diseases. In the recently published RE-LY study 18,113 patients, who suffer from AF, were randomized between dabigatran (110 mg or 150 mg twice daily) or, unblinded, adjusted-dose warfarin.<sup>1</sup> Median follow-up period was 2.0 years. Rates for the primary outcome of all stroke (ischemic or hemorrhagic) or systemic embolism were

1.71% per year in the warfarin group. *Dabigatran etexilate, 150 mg twice daily—the available dosage, reduced the rate by 34%* (to 1.11% per year; P value 0.001 for superiority; RR: 0.65; 95% CI: 0.52 to 0.81), and at this dose there was *no increase in major bleeding*. Major bleeding was 3.36% per year in the warfarin group, as compared with 3.11% per year in the 150 mg dabigatran group (reduced intra-cerebral bleeding with a slight increase in GI bleeds). The authors conclude that, “In patients with AF, dabigatran, given at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.” These results of RE-LY are fantastic as *overall this is the only trial where warfarin has been beaten*

This is the first randomized intervention study in which a therapeutic dose of a new anti-coagulant (Dabigatran—Pradaxa) showed non-inferiority and in some aspects even superior effects compared to warfarin. Given the limitations in maintaining appropriately INR-levels in vitamin K antagonist treatment (patients in the study attained goal INR only 64% of the time), these results could be regarded as a promising step forward. However other aspects now need attention, like an antidote, long-term side-effects, and compliance of a treatment which needs far less monitoring compared to warfarin.

## Update on Dabigatran:

*No routine anti-coagulation monitoring is necessary and in fact is unreliable. If an INR was 4 or 5 in a stable patient, it would mean nothing.* The new focused update on the management of AF regarding dabigatran states there is **no specific antidote for dabigatran** related bleeding, which has a half-life of 12 to 17 hours.<sup>2</sup> General supportive care and “tincture of time” usually work. Therapy for severe hemorrhage may include transfusions of fresh-frozen plasma, packed red blood cells, recombinant factor VIIa or consideration of emergency hemodialysis or surgical intervention if appropriate.

A dose of 150 mg twice daily was approved for patients with a glomerular filtration rate (GFR) > 30 mL/min, whereas in patients with severe renal insufficiency—Stage IV CKD—GFR 15 to 30 mL/min) the approved dose is 75 mg twice daily. **Monitoring of renal function is extremely important** as 80 % of dabigatran is excreted through the kidneys. *Dabigatran is not an option for patients with a GFR less than 15 mL/min—even on dialysis—or severe hepatic dysfunction.*

The decision to put a patient with AF on warfarin or dabigatran should be based upon whether the patient can adhere to twice-daily dosing, patient preference, cost, and whether an anticoagulation management program is available for routine INR monitoring. Dabigatran will be used primarily in patients who have problems with warfarin such as low rates of INR control<sup>3</sup>, or who are at high-risk for bleeding or for poor compliance to treatment. Based on expert consensus, the authors say that patients taking warfarin who have sufficient INR control might not benefit by switching to dabigatran.

## Lower threshold for Anti-coagulation

Dabigatran, with its lower stroke rate lower intracranial bleeding rate compared with warfarin, will lower the threshold for anticoagulation to prevent stroke in AF patients. There are many borderline cases that can go “either way” with respect to anticoagulation (*CHADS<sub>2</sub> score of 1 plus*). The efficacy and safety of dabigatran will ultimately increase the proportion of AF patients who receive indefinite duration anticoagulation.

*AF confers a 5-fold risk of stroke*, and one in five of all strokes are attributed to this arrhythmia. Ischemic strokes in association with AF are often fatal and frequently disabling. There has been a lot of research into stroke prevention, which has influenced determining stroke risk in all of the guidelines.

A recent study showed that the CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system from the European Society of Cardiology 2010 AF guidelines<sup>4</sup> is better than CHADS<sub>2</sub> from the American College of Cardiology Foundation/American Heart Association/ 2011 AF guidelines<sup>5</sup> at predicting which patients with atrial fibrillation are at high risk for thromboembolism.<sup>6</sup>

Risk Factor	CHADS <sub>2</sub>	CHA <sub>2</sub> DS <sub>2</sub> -VASc
	(Maximum score, 6)	(Maximum score, 9)
Congestive heart failure	1	1
Hypertension	1	1
Diabetes	1	1
Vascular disease	N/A	1
Age 65-74	N/A	1
Age ≥75	1	2
Female sex	N/A	1
Previous stroke/TIA	2	2

CHA<sub>2</sub>DS<sub>2</sub>-VASc also appears to be better at predicting which patients are truly at low risk thereby avoiding unnecessary

anticoagulation. Using this system with the extra ones, for age > 65, vascular disease and female sex (all of which increase stroke risk in AF), would bump a lot of *CHADS<sub>2</sub> scores of 1 plus* to  $\geq 2$  (considered an indication for anticoagulation treatment) resulting in the expansion of anticoagulation with warfarin or the better and safer dabigatran to decrease the number of strokes in this high-risk population.

### Recommendations about Application

**Cardioversion:** The guidelines remain the same with dabigatran for anticoagulation with planned elective cardioversion: 3 weeks of therapeutic anticoagulation before the procedure and *at least* 4 weeks of therapeutic anticoagulation after (Chest 2008;133:546S). *Please remember if the patient has a CHADS<sub>2</sub> Score of > 2 they should be anti-coagulated indefinitely even if in NSR. Dabigatran becomes therapeutic within 2 hours of administration.*

When an asymptomatic patient presents with new-onset atrial fibrillation in the office setting, oral anticoagulation with dabigatran can be started without intravenous heparin.

If the patient with new-onset atrial fibrillation is symptomatic, cardioversion may need to be performed imminently (if no thrombus is visualized on transesophageal echocardiography). In the symptomatic patient, there are two options:

- Begin therapy with intravenous heparin. (Cardioversion has not been extensively studied using dabigatran alone in patients with new-onset atrial fibrillation.)
- Begin therapy with dabigatran but not intravenous heparin. (In the largest cardioversion experience to date, the stroke rate was low in dabigatran recipients, especially if

they had been "cleared" first by transesophageal echocardiography; Circulation 2011; 123:131.)

### How should a patient be transitioned on and off dabigatran from other antithrombotic agents (e.g., warfarin, enoxaparin, dalteparin, heparin)?

For patients switching from warfarin to dabigatran, give the first dose of dabigatran after the international normalized ratio (INR) has declined to less than 2.0. In practice, this usually means withholding one or two doses of warfarin. For patients receiving parenteral subcutaneous anticoagulation, give the first dose of dabigatran just before the next scheduled injection of parenteral anticoagulation. For patients receiving intravenous heparin, give the first dose of dabigatran about 2 hours after discontinuing intravenous heparin. If going from dabigatran to warfarin, start warfarin 3 days before discontinuing dabigatran.

**Monitoring:** No anti-coagulation monitoring is necessary but monitoring of compliance and patient education is extremely important because of the GI side effects with patients deciding to stop the medication. *Lapses in therapy should be avoided to minimize stroke risk.* Patients should be seen at 1 month and then every 3 to 4 months thereafter. Renal function should be checked every 6 months.

**Peri-op Plan:** For most non-cardiac procedures omitting the afternoon dose the day before the procedure and obviously the AM of the procedure should suffice. If possible, discontinue dabigatran 1 to 2 days (GFR  $\geq 50$  mL/min) or 3 to 5 days with GFR < 50 mL/min) before more invasive surgical procedures because of the increased risk of bleeding. Treatment should be initiated as soon as possible post operatively.

## **FDA: Dabigatran Should Only Be Stored in Original Containers**

The FDA is reminding patients and pharmacists that the anticoagulant dabigatran (Pradaxa) should only be dispensed and stored in its original manufacturer bottle or blister pack, *not in pill organizers or pill boxes*. Nor should it be cut. Otherwise, due to humidity, the drug can break down and lose potency. The manufacturer's bottle comes with a drying agent in the cap to protect the pills from moisture. Once a bottle has been opened, the pills must be used within 60 days.

## **Conclusions:**

Patients with atrial fibrillation (AF) at risk of stroke are not always anti-coagulated with warfarin despite lack of contraindication. Dabigatran, an oral direct thrombin inhibitor, is a new option with proven safety and improved effectiveness in these patients and should expand treatment. The advantages of dabigatran are its more predictable response, obviating coagulation monitoring and possible lower frequency of bleedings. Its drawbacks are cost (~\$227/mo), lack of antidote and long-term data, frequency of dyspepsia and the twice daily dosage.

The major question about dabigatran has now shifted from efficacy to cost. Hopefully with the approval of other efficacious similar agents, cost will go down and usage will expand. In the future, hopefully, we can transfer all of our patients to thrombin inhibitors and relegate warfarin to a fitting pharmaceutical graveyard.

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***Heartbeat is a South Jersey Heart Group publication.***

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<sup>1</sup> Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation (RE-LY). *N Engl J Med*. September 17 2009; 361:1139–1151.

<sup>2</sup> 2011 ACCF/AHA/HRS Focused Update on the Management of patients With atrial fibrillation (Update on Dabigatran). A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* March 15 2011;123:1144-1150.

<sup>3</sup> Wallentin L et al. Efficacy and safety of dabigatran compared to warfarin at different levels of international normalized ratio control for stroke prevention in atrial fibrillation : An analysis of the RE-LY trial. *Lancet* Sept 18 2010; 376: 975.

<sup>4</sup> Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) *Eur Heart J* 2010; 31(19): 2369-2429.

<sup>5</sup> Wann LS et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* Jan 4/11 2011; 123:104.

<sup>6</sup> Olesen JB et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: Nationwide cohort study. *BMJ* Jan 31 2011; 342: d124.