

Emergency Medicine Journal Club: Eastern Virginia Medical School

Discussant: Sarah Baddorf, MD

Date: April 25, 2011

CITATION: Dabigatran versus warfarin in patients with atrial fibrillation.

Connolly SJ, Ezekowitz MD, Yusuf S, et al. N Engl J Med 2009; 361 : 1139-1151

I. WHAT IS BEING STUDIED?	
1. Study Objective	Dabigatran, (Pradaxa) a new direct thrombin inhibitor -In patients with Atrial Fibrillation and at risk for Stroke, is Dabigatran (110mg BID or 150mg BID), compared to adjusted-dose Warfarin, noninferior for prevention of stroke or systemic thromboembolism
2. Study Design The authors complied with an FDA recommended calculation for acceptable margin of non-inferiority based upon 50% of the 95% CI of the lower limits of the treatment effect of warfarin in 6 prior RCT's	Prospective, Randomized, non-inferiority active control (Open label warfarin) Multinational trial (951 sites,44 countries, avg 10 subjects per site) patients into 3 treatment groups: Warfarin, Dabigatran 110mg bid, or Dabigatran 150mg bid; followed for 2 years for efficacy and safety. (Design described in: Ezekowitz MD, Connolly SJ, Parekh A, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 2009;157:805-10.)
3. Inclusion Criteria Most of these place patients in CHADS2 score of at least 2 which warrants intervention in most cases (see CHADS2 below) Mean CHADS2 was 2.1 however in 1/3 CHADS 2 was 0-1. This type of patient may not be treated based upon current recs. May bias the data.	-AFib documented on EKG at screening or within past 6 months at least 1 of the following: -previous stroke or TIA -LVEF < 40% -NYHA class II or higher heart failure symptoms within past 6 months -age > 75 or -age 65-74 AND DM, HTN, or CAD

4. Exclusion Criteria	-severe heart-valve disorder -stroke within 14 days, valvular dx., -severe stroke within 6 months -condition that increases hemorrhage -creatinine clearance <30mL/min -active liver disease -pregnancy, others recent surgery, uncontrolled HTN, peptic ulcer dx. etc
5. Interventions Compared Prior studies in DVT prevention after total joint replacement surgery has demonstrated efficacy at dosages ranging from 110 to 300 mg daily (RE-MOBILIZE, RE NOVATE)	Warfarin, adjusted-dose, goal INR 2.0-3.0 Dabigatran 110 mg BID Dabigatran 150 mg BID
6. Outcomes Evaluated	1° Primary outcome Stroke or Systemic Embolism stroke: sudden onset of focal neuro deficit, location consistent with major vessel systemic embolism: acute vascular occlusion of extremity or organ, by imaging, surgical confirmation, or autopsy 2° Major Bleeding (1° safety outcome) Defined as: Hg drop of 20 g/L, or transfusion of 2u, or symptomatic bleed in critical area or organ Hemorrhagic Stroke All cause Mortality also MI, PE, hospitalization, and adverse events, minor bleeding, dyspepsia, discontinuation rate.
II. Are the results of the study valid?	
1. Was the assignment of patients randomized?	Yes. treatment group randomly assigned by a Central, Interactive, Automated Telephone System
2. Were all patients who entered the trial properly accounted for and attributed at its conclusions?	99.9% achieved complete follow-up (mean of 2 years)

	20 patients lost to follow-up.
3. Was follow-up complete?	
4. Were patients, health workers and study personnel “blind” to treatment?	<p>Warfarin administration was unblinded; Dabigatran dose-blinded in capsules</p> <p>1° and 2° outcome events adjudicated by 2 independent investigators unaware of treatment group</p> <p>International team of adjudicators reviewed documents in local languages after blinding, or documents were translated by independent groups and centrally blinded</p>
5. Were study groups similar at the start of the trial?	<p>Yes</p> <p>age, weight, BP S and D, gender, type of Afib, CHADS₂ score, previous stroke or TIA, previous MI, heart failure, DM, HTN, medication use at baseline (ASA, ARB or ACE-I, B blocker, Amiodarone, Statin, PPI, H₂R antagonist.</p> <p>added later was balance of VKI naïve (<61 days) and VKI-experienced; but no difference was found between these groups</p> <p>disproportionate number of males</p>
6. Aside from the experimental intervention, were the groups treated equally	<p>Yes. Interventions such as use of BP meds, PPI’s, statins and other meds was not different between groups. Follow-up was at 14 days, 1 month, 3 month, q3month x 1 year, then q4month</p> <p>Warfarin group had INR measured at least monthly</p>
III. What were the results?	
1. How large was the treatment effect? (difference between experimental t and active control group (warfarin)).	<p>1° outcome stroke or systemic embolus</p> <p>Warfarin 1.69% per year</p> <p>Dab 110 1.53% RR 0.91 [0.74-1.11] <0.001</p> <p>Dab 150 1.11% RR 0.66 [0.53-0.82] <0.001</p>

<p>2. What was the estimated treatment effect at a 95% confidence interval?</p>	<p>superior to Warfarin</p> <p>2° outcome major bleeding Warfarin 3.36% per year Dab 110 2.17% RR 0.80 [0.69-0.93] =0.003 superior to Warfarin Lower does demonstrated statistically significant decrease in major bleeding rate Dab 150 3.11% RR 0.93 [0.81-1.07] =0.31 Not significant</p> <p>2° outcome hemorrhagic stroke Warfarin 0.38% per year Dab 110 0.12% RR 0.31 [0.17-0.56] <0.001 Dab 150 0.10% RR 0.26 [0.14-0.49] <0.001</p> <p>2° outcome mortality Warfarin 4.13% per year Dab 110 3.75% RR 1.35 [0.80-1.03] =0.13 Dab 150 3.64% RR 1.38 [1.0-1.91] =0.051 No statistically significant difference</p> <p>2° outcome MI Warfarin 0.53% per year Dab 110 0.72% RR 0.91 [0.80-1.03] =0.07 Dab 150 0.74% RR 0.88 [0.77-1.00] =0.048 Higher rate of MI in higher dose</p>
<p>IV. Will the results help me in caring for my patients?</p>	<p>In the ED we won't be prescribing long-term anticoagulation, but I think we will be seeing more patients on Dabigatran, so it will be helpful to know about it, including risks and benefits compared to alternate.</p>
<p>1. Were all clinically important outcomes considered?</p>	<p>Net Composite Clinical Benefit Outcome (including major vascular events, major bleeds, or death)</p> <ul style="list-style-type: none"> -Warfarin 7.64% -Dab 110 7.09% -Dab 150 6.91%
<p>2. Are treatment outcomes worth the potential harms?</p>	<p>Anticoagulate or not? -ICH doubles with Warfarin vs. ASA</p> <p>Warfarin vs. Dabigatrain -only significantly different adverse event where Dab was worse than Warfarin is dyspepsia</p> <ul style="list-style-type: none"> -Warfarin 5.8% -Dab 110 11.8% -Dab 150 11.3%

	<p>Discontinuation rates were sig. higher for dabigatrin compared to warfarin which may reflect severity of dyspspsia or other unaccounted for side effects Dabigatran dose can be tailored to different risk factors.</p>

Clinical Bottom Line:

Less clinically relevant for EM physicians, since we don't do the long-term anti-coagulation, but very good to know about this new drug, which I think we will see often. Appears Dabigatrin may be non-inferior and at certain dosages may be superior.

Cost comparison including need for testing INR not included (weekly appointments, co-pays, lab fees, transportation). Warfarin cost is approx. 15.00/month. Dabigatrin approx. 125.00.

There were more MI's and GI bleeds in Dabigatrin. When deciding on which anticoagulation to use, need to consider individual patients' risks, such as use of PPI's or hx of GI bleeds. Longer f/u periods may demonstrate additional untoward effects particularly since this is a long term medication.

Only 1/3 of patients had a CHADS2 score of >2 therefore hard to assess benefit/risk in those at highest CHADS risk categories

Does evidence support non-inferiority to warfarin? Yes. Non-inferiority is in comparison to warfarin studies where average therapeutic INR rate was 65%. This is not necessarily a problem as it reflects a pragmatic real world number as opposed to an untenable 100% therapeutic INR.

Limited follow-up therefore long-term effects not yet known.

Does the evidence suggest possible harms: Trend towards increased rate of MI in higher dosing may need dose adjusting in the higher risk patient.

Discontinuation rate remains a question. The drug is combined in formulation with tartonic acid which creates an acidic environment needed for drug absorption. The dyspepsia must have been particularly distressing.

They used a single meta-analysis to determine their Margin Score. Some may argue that this may be limited by the quality of the Meta-analysis and an individual assessment of each of the RCT's is preferable

Algorithm for predicting the risk of stroke in pts with AF. The score assigns points for various risk factors, as follows: 1 point for: CHF, HTN, age ≥ 75 yrs, DM. 2 points for history of stroke or TIA. The score = sum of points (range 0-6).
 {New CHA₂DS₂-VASc score ^{9 points} may predict stroke risk better: CHF, Hypertension, Age ^{65-74, or ≥ 75} , Diabetes, prev Stroke/TIA, Vascular dx, sex ^{female}}

	Condition	Points	Score	Stroke Risk	Therapy Chest'08 (9), ACC'06 (10), CCS'10, ACCF/AHA'11
C	Congestive heart failure	1	0-1	Low ($\leq 3\%$ /year)	Aspirin (esp. if age ≥ 60 yrs) ¹¹ (No antithrombotic if young & no stroke risk factors). VKA (e.g. Warfarin) or Dabigatran. See Pros & Cons list above. (Warfarin/dabigatran most effective in decreasing stroke risk.) VKA=vitamin K antagonist Not dabigatran if prosthetic heart valves, sig valve dx, renal dx ^{CrCl$<$15ml/min} or advanced liver dx ^{ACC'11}
H	Hypertension (or treated hypertension)	1		Moderate (~ 3-4%/year)	
A	Age >75 years	1		High (~ 6-12%/year)	
D	Diabetes	1		Very High (~ 18%/year)	
S₂	Prior Stroke or TIA	2			

Characteristic	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Warfarin	D 110 mg vs warfarin RR; 95% CI	D 150 mg vs warfarin RR; 95% CI
Randomized	6,015	6,076	6,022		
Mean age (yrs)	71.4	71.5	71.6		
Male (%)	64.3	63.2	63.3		
CHADS ₂ score (mean; %)					
0 - 1	32.6	32.2	30.9		
2	34.7	35.2	37.0		
3 +	32.7	32.6	32.1		
Prior stroke/TIA (%)	19.9	20.3	19.8		
Prior MI (%)	16.8	16.9	16.1		
CHF (%)	32.2	31.8	31.9		
Baseline ASA (%)	40.0	49.8	51.4		
Warfarin Naive (%)	49.9	49.8	51.4		
Discontinuation (%)	21	21	17	P<0.001	P<0.001
Stroke or Systemic embolism (%/yr)	1.53	1.11	1.69	0.91; 0.74-1.11 P = 0.34	0.66; 0.53-0.82 P < 0.001
Major Bleed (%/yr)	2.71	3.11	3.36	0.80; 0.69-0.93 P=0.003	0.93; 0.81-1.07 P=0.31
Intracranial hemorrhage (%/yr)	0.23	0.30	0.74	0.31; P < 0.001	0.40; P < 0.001
Gastrointestinal hemorrhage (%/yr)	1.12	1.51	1.02	1.10; 0.86-1.41 P=0.43	1.50; 1.19-1.89 P<0.001
Life threatening hemorrhage (%/yr)	1.22	1.45	1.80	0.68; 0.55-0.83 P<0.001	0.81; 0.66-0.99 P=0.04
Acute MI (%/yr)	0.72	0.74	0.53	P = 0.07	P = 0.048
Mortality (%/yr)	3.75	3.64	4.13	P=0.13	P=0.051