



Senior Medicine Rotation: Evidence-Based Medicine Project

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Block: June

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Case SIGNOUT:

74 yr old thin Hispanic, Spanish-speaking only, female with HTN, HLD, CAD, a-fib on warfarin, who follows regularly at Coumadin clinic, admitted for a-fib with RVR. During hospital course, heart rate was controlled adequately with metoprolol and digoxin. Upon discharge, instructions included following up with Coumadin clinic in the next few days. Patient has a history of not coming in to Coumadin clinic for a few years while on warfarin. Patient does not have consistent outpatient PMD follow-up, but has been recently adherent to the majority of her Coumadin clinic appointments for the past year.

Clinical Question: Would this particular patient benefit from being transitioned to dabigatran instead of remaining on warfarin?

Background:

- Atrial fibrillation
 - o Embolization of atrial thrombi can occur with any form of a-fib (ie: paroxysmal, persistent, permanent)
- Risk stratification to guide therapy in nonvalvular a-fib:
 - o CHADS2 risk score: most popular, has been best validated in different patient populations
 - CHADS2 score of 0 = low risk of stroke
 - no antithrombotic therapy, as the risks likely outweigh the benefits.
 - CHADS2 score of 1 are at intermediate risk of stroke (2.0 percent per year, or perhaps somewhat less)
 - oral anticoagulant therapy or aspirin (75 to 325 mg daily).
 - CHADS2 score of 2 or higher are at relatively high risk of stroke (at least 4 percent per year).
 - oral anticoagulant therapy is strongly recommended
- Warfarin
 - o SPAF-I, SPAF-II, and SPAF-III trials, and AFASAK, BAATAF, SPINAF, and CAFA trials:
 - Anticoagulation with adjusted-dose warfarin [equivalent to INR 2-3] significantly reduced clinical stroke risk in patients with AF when compared with aspirin or placebo. The relative risk reduction compared to aspirin is about 50 percent.
 - o Many adverse properties:
 - Multiple interactions with food (Vitamin K content varies widely in foods)
 - Multiple interactions with drugs (binding of warfarin to plasma proteins and its metabolism by cytochrome P-450 enzymes facilitate drug interactions)
 - Inhibits the synthesis of sequential enzymes in the coagulation cascade, which imparts a drastically steep dose-response relationship
 - Need for frequent monitoring of INR
 - Increases risk of hemorrhage
- Newer anticoagulant agents:
 - RE-LY trial (2009): dabigatran vs warfarin
 - Dabigatran – direct, competitive inhibitor of thrombin
 - o 80% of given dose is excreted by the kidneys

- serum half life is 12-17 hours
- does not require regular monitoring
- ROCKET AF trial (2011): rivaroxaban vs warfarin
- ARISTOTLE trial (2011): apixaban vs warfarin
- All demonstrated equal or better efficacy and safety of these newer anticoagulants compared to warfarin

Search Strategy

Database: PUBMED

Search terms: “dabigatran” [MeSH Major Topic] AND “atrial fibrillation” AND “randomized controlled trial” [Publication Type]

Results: 18

Article chosen:

15.

Dabigatran versus warfarin in patients with atrial fibrillation.

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators.

N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30. Erratum in: N Engl J Med. 2010 Nov 4;363(19):1877.

PMID: 19717844 [PubMed - indexed for MEDLINE]



Senior Medicine Rotation: Based Medicine Project (Cont)

RE-LY trial: randomized trial designed to compare two fixed doses of dabigatran, each administered in a blind manner, with open-label use of warfarin in patients who had a-fib and were at increased risk for stroke.

Group	Criteria or definition	n
Population screened.	951 clinical centers in 44 countries.	Unknown
Inclusion criteria	Patients with atrial fibrillation documented on EKG performed at screening or within 6 months beforehand AND at least one of the following: previous CVA/TIA, LVEF<40%, NYHA Class II or higher heart-failure symptoms within 6 months before screening, age>75yo or age 65-75 with DM/HTN/CAD	18,113
Exclusion criteria	Presence of severe heart-valve disorder, CVA within 14 days, severe CVA within 6 months before screening, a condition that increased the risk of hemorrhage, Cr clearance <30 mL/min, active liver disease, pregnancy	Unknown
Treatment group (Dabigatran)	Dabigatran administered, in a blinded fashion, in capsules containing either 110mg or 150mg of dabigatran, to be taken twice daily. Concomitant use of ASA (<100mg qd) or other antiplatelet agents permitted.	600 + 600
Alternate treatment group (Warfarin)	Warfarin administered, in an unblinded fashion, in tablets of 1, 3, or 5 mg and was adjusted locally to an INR 2-3, with INR measured at least monthly. Concomitant use of ASA (<100mg qd) or other antiplatelet agents permitted.	600

Primary endpoints: Stroke or systemic embolism

Secondary endpoints: Death, MI, PE, TIA, hospitalization

• **Are the Results of the Trial Valid?**

- **Randomized?** YES, randomized with a central, interactive, automated phone system.
- **All patients accounted for at end?** ALMOST. Complete follow-up achieved in 99.9% of patients, with 20 patients lost to follow-up.
- **Intention to treat?** YES, non-inferiority of both doses of dabigatran was established.
- **Blinding?** YES/NO/YES. Blinding was performed in regards to dosages of dabigatran. No blinding was done for warfarin. An international team of adjudicators reviewed documents in local languages after blinding, or documents were translated by an independent group and were centrally blinded. Each primary and secondary outcome event was adjudicated by two independent investigators who were unaware of the treatment assignments.
- **Groups similar at start of trial?** YES, treatment groups were well balanced in respect to baseline characteristics (Table 1 in paper). Mean age: 71yo. Mean CHADS2 score: 2.1.
- **Equal treatment of groups?** Almost. Warfarin group had INR measured monthly. Dabigatran groups had regular follow-up visits at month 1, month 3, then q 3 months in the first year, then q 4 months until the study ended.
- **Did randomization work?** YES

- **Are the Results of the Trial important?** Yes. 110-mg dose of dabigatran was associated with similar rates of stroke and systemic embolism but lower rates of major hemorrhage than warfarin. The 150-mg dose of dabigatran was associated with lower rates of stroke and systemic embolism but with a similar rate of major hemorrhage as warfarin. The findings suggest that the dose of dabigatran could potentially be tailored to take into consideration the risk characteristics of a specific patient, and also suggests the superiority of dabigatran compared to warfarin.
 - **Size of treatment effect?**
 - Due to low event rate, large sample size was needed to maintain statistical power
 - Significant in primary and secondary endpoints (for 150-mg dabigatran) and adverse effects
 - **Precision of the estimate of the effect?**
 - Yes, 95% CI that do not cross zero, see table below

Endpoint	Result	Significance
Stroke or systemic embolism	<u>150-mg dabigatran:</u> 134 patients (1.11%) <u>110-mg dabigatran:</u> 182 patients (1.53%) <u>Warfarin:</u> 199 patients (1.69%)	<u>150-mg dose of dabigatran superior to warfarin</u> (RR 0.66; 95% CI 0.51 – 0.82; P<0.001). <u>110-mg dose of dabigatran was not</u> (RR 0.91; 95% CI 0.74 – 1.11; P = 0.34)
Death from any cause	<u>150-mg dabigatran:</u> 3.64% <u>110-mg dabigatran:</u> 3.75% <u>Warfarin:</u> 4.13%	Rate higher with warfarin compared to 150-mg dabigatran. <u>150-mg dabigatran:</u> RR 0.88, 95% CI 0.77 – 1.00; P = 0.051 <u>110-mg dabigatran:</u> RR 0.91, 95% CI 0.80 – 1.03; P = 0.13
MI	<u>150-mg dabigatran:</u> 0.74% <u>110-mg dabigatran:</u> 0.72% <u>Warfarin:</u> 0.53%	Rate of MI was higher with dabigatran. <u>150-mg dabigatran:</u> RR 1.38, 95% CI 1.00 – 1.91; P = 0.048 <u>110-mg dabigatran:</u> RR 1.35, 95% CI 0.98 – 1.87; P = 0.07
Adverse effects	Result	Significance
Hemorrhagic stroke	<u>150-mg dabigatran:</u> 0.10% <u>110-mg dabigatran:</u> 0.12% <u>Warfarin:</u> 0.38%	<u>The rate of this complication with both doses of dabigatran was less than one third the rate with warfarin without a reduction in the efficacy against ischemic stroke. Suggests an important advantage of dabigatran.</u> <u>150-mg dabigatran:</u> RR 0.26, 95% CI 0.14 – 0.49; P <0.001 <u>110-mg dabigatran:</u> RR 0.31, 95% CI 0.17 – 0.56; P < 0.001
Life-threatening bleeding, intracranial bleeding, major or minor bleeding	<u>150-mg dabigatran:</u> 1.45%, 0.30%, 16.42% <u>110-mg dabigatran:</u> 1.22%, 0.23%, 14.62%, <u>Warfarin:</u> 1.80%, 0.74%, 18.15%	Rates higher with warfarin. P<0.05 for all comparisons of dabigatran with warfarin
Major gastrointestinal bleeding	<u>150-mg dabigatran:</u> 1.15% <u>110-mg dabigatran:</u>	Significantly higher rate with dabigatran 150-mg than with warfarin. <u>150-mg dabigatran:</u>

	1.12% Warfarin: 1.02%	RR 1.50, 95% CI 1.19 – 1.89; P <0.001 110-mg dabigatran: RR 1.10, 95% CI 0.86 – 1.41; P = 0.43
Dyspepsia	150-mg dabigatran: 11.3% 110-mg dabigatran: 11.8% Warfarin: 5.8%	Significantly more common with dabigatran than with warfarin. P<0.001

2010 correction:

Table 1. Published and Revised Data for Primary Efficacy and Safety Outcomes and Myocardial Infarction, According to Treatment Group.*

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin	
	no. of patients	%/yr	no. of patients	%/yr	no. of patients	%/yr	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Stroke or systemic embolism										
Published	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	0.34	0.66 (0.53–0.82)	<0.001
Revised	183	1.54	134	1.11	202	1.71	0.90 (0.74–1.10)	0.30	0.65 (0.52–0.81)	<0.001
Major bleeding										
Published	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31
Revised	342	2.87	399	3.32	421	3.57	0.80 (0.70–0.93)	0.003	0.93 (0.81–1.07)	0.32
Myocardial infarction										
Published	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048
Revised	98	0.82	97	0.81	75	0.64	1.29 (0.96–1.75)	0.09	1.27 (0.94–1.71)	0.12

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. P values are for superiority. CI denotes confidence interval.

- **Can I apply these results to my patient?**
 - **Comparison of my patient to trial patients.**
 - This trial was applicable to my patient in that my patient met the inclusion criteria, as she had atrial fibrillation documented on EKG upon presentation and was age 65-75 with HTN/CAD. She also did not meet any of the exclusion criteria: even though she was elderly, her creatinine clearance was calculated to be 35.92. In addition, she was on ASA for her CAD, which was permitted during this trial. Also, this patient (age 74, CHADS score 2) was the exact embodiment of the average trial participant (age 72 +/- 8, and a CHADS2 score of 2.1).
 - **All clinically important outcomes considered?** Yes
 - Yes, many important clinical outcomes were considered, including failure of anticoagulation (stroke, systemic embolism, MI, death) and adverse outcomes to dabigatran (hemorrhagic stroke, life-threatening bleeding, intracranial bleeding, major or minor bleeding, major gastrointestinal bleeding, dyspepsia being the most common adverse side effect, AST, ALT >3 x ULN)
 - **Likely benefits outweigh potential harms and cost?** Yes
 - Based on this clinical trial, the patient would benefit from being switched to dabigatran. Compared with warfarin, the 110-mg dose of dabigatran was associated with similar rates of stroke and systemic embolism, but lower rates of hemorrhage, which would be important for a frail, thin, elderly lady such as this patient, who may be prone to falls. The 150-mg dose of dabigatran was associated with similar rates of hemorrhage to warfarin, but lower rates of stroke and systemic embolism, which would also be beneficial. However, it seems that

the 110-mg dose would be more beneficial to the patient given her old age and risk factors for falling.

- Due to the rapid clearance of dabigatran from the body, dabigatran does not require laboratory monitoring. In addition, it may be less susceptible to dietary and drug interactions, and does not have warfarin's narrow therapeutic window. This makes it attractive to the elderly patient who has limited ability to attend anticoagulation clinics and who is taking multiple medications.
- Potential arguments against dabigatran:
 - Patient has been on warfarin for such a long time, and is comfortable with periodic INR measurement. Her visits to the Coumadin clinic serve almost as regular outpatient care. Patients already taking warfarin with excellent INR control have little to gain by switching to dabigatran.
 - Dabigatran is a BID medication while warfarin is a qd medication, and that makes it harder to comply to dabigatran.
 - This elderly patient may be at risk of developing creatinine clearance <30 mL/min, which is a contraindication for this medication. Dose in the meantime has to be adjusted for decreased renal function.
 - Dabigatran has a higher pharmaceutical cost compared to warfarin.
 - Dabigatran lacks an antidote or reversing agent for patient if she bleeds while taking this drug.
 - There is a lack of long-term safety data in older adults.
- **Weaknesses / Limitations of this trial:**
 - The adoption of "one size fits all" dosing has probably undermined the performance of dabigatran. Dabigatran appeared to be more efficacious in patients who weighed less and in patients with impaired renal function (in whom the drug accumulates), pointing to significant interpatient variability in response. Individualized dosing, based on weight and estimated creatinine clearance, might improve the drug's risk-benefit ratio.
 - An important concern that this clinical trial did not address is the absence of antidotes to rapidly reverse the anticoagulant effect of dabigatran in the case of life-threatening hemorrhage or surgery.
 - Does not represent the elderly well. The mean age and weight of patients in RE-LY trial study were 71 years and 83 kg, respectively, with a mean creatinine clearance of 68 ml per minute. Less than one third of the patients in that study were over 80 years of age or weighed less than 63 kg, and less than 20% had a creatinine clearance of less than 50 ml per minute.

References:

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2. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener HC, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation*. 2011;123(21):2363.
3. Jessica L. Mega. A New Era for Anticoagulation in Atrial Fibrillation. *N Engl J Med* 2011; 365:1052-1054
4. Gregory J. del Zoppo, M.D., and Misha Eliasziw, Ph.D. New Options in Anticoagulation for Atrial Fibrillation. *N Engl J Med* 2011; 365:952-953
5. Bleeding Risk with Dabigatran in the Frail Elderly. *N Engl J Med* 2012; 366:864-866