

RE-LY: Dabigatran versus Warfarin in Patients with Atrial Fibrillation (AF)¹

Randomized evaluation of long-term anticoagulation therapy in patients with AF and who were at increased risk of stroke.

RE-LY Bottomline for patients with AF & a mean CHADS2 score of ~2:

- Dabigatran non-inferior (possibly superior) to warfarin without need for INR monitoring, but with higher drug cost. *Cost Comparison (/month): Warfarin \$15 + monitoring (\$20) vs Dabigatran 110-150mg po bid \$110.*
- In AF: Dabigatran 150mg BID appears more effective than warfarin with marginally less bleeding; however there were more MI & GI bleeds. (The reanalysis of MI data suggests previous findings of more MI's now not significant).
- In AF: Dabigatran 110mg BID may be option in older, lower weight, CrCl 30-60ml/min and/or higher rate of bleeding, or possibly those in whom regular INR monitoring is entirely impractical and those who are unable to achieve therapeutic INR values.
- In AF: Dabigatran 150mg BID more effective than 110mg BID, but 110mg BID (non-inferior to warfarin) may have less bleeding, therefore can consider individual patient risks when selecting a dose.

• **CADTH recommendations:** Dabigatran be listed for prevention of stroke & systemic embolism in patients with AF meeting 1 of the following criteria: (1) Patients in whom warfarin is indicated but who fail to achieve adequate INR testing, dosage adjustment according to a validated nomogram, & pt education. Pts who fail to achieve adequate INR control should be referred to an anticoagulation management service, if available. OR (2) Pts who have a history of a serious hypersensitivity reaction to warfarin²

Background

- New oral anti-coagulants are being introduced to the market – potential to compete with, or replace, vitamin K antagonists (VKA) such as warfarin
- **Dabigatran etexilate (PRADAX®)**, a prodrug, is a new oral competitive “direct-thrombin inhibitor” – available as **75mg, 110mg & 150mg capsules**
 - In Canada, indicated for **atrial fibrillation**^{Oct10} & **post-op prevention of VTE** in patients who have undergone elective THR/TKR surgery; Dose: 110mg once on day of surgery (started 1-4hrs post-op), then 220mg once daily x 10 days for TKR, 28-35days for THR; [Major orthopedic trials compared dabigatran to enoxaparin. RE-MODEL_{TKA} & RE-NOVATE_{THR}: dabi 150 & 220mg daily vs enoxaparin 40mg daily found to be equivalent & no bleeding differences; RE-MOBILIZE_{TKA} dabi 150 & 220mg daily inferior to enox 30mg SubQ BID^{North American dosing}, bleeding rates similar]
 - Half-life ~11hrs (up to 17hrs after multiple doses); Cleared by kidney (80%), therefore contraindicated in those with severe renal failure CrCl<30ml/min
 - **Cost: THR/TKR surgery: 110mg on day of surgery then 220mg po od \$110/month; A. fibrillation 110-150mg po bid \$110/month; Not on Sask formulary**
 - **RE-COVER trial⁴:** dabigatran in **acute VTE treatment** (6 months): 150mg BID vs warfarin INR 2-3; efficacy, major bleed, & death similar after 6 months (minor bleeds less with dabigatran)
- Another new oral anticoagulant: rivaroxaban (**Xarelto®**,^{NOC2008}) **ROCKET AF** trial: preliminary non-inferior but not superior to warfarin, CHADS2=3, a factor Xa inhibitor others: apixaban,otimixaban,betrixaban & more, currently EDS on Sask formulary for post-orthopedic surgery VTE prophylaxis as was shown to be superior to enox 40mg daily in **RECORD-** trials I_{TKA}, II_{THA}, & III_{TKA} (but not superior to enox 30mg BID in **RECORD-IV**_{TKA}); Manufacturer economic evaluation favoured rivaroxaban over enox (significant throughout robust sensitivity analyses)
- Highlights of these new meds: more predictable anticoagulation (no required INR monitoring), oral administration, OD-BID dosing, possibly fewer drug/food interactions ^{than warfarin} (dabigatran - no CYP P450 interactions, but DI's with amiodarone, ketoconazole, quinidine, rifampin & verapamil), quick onset of action.
- Limitations of these meds: lack reversibility (no antidote), awaiting long-term efficacy & safety data (*watch for RELY-ABLE 4yr follow-up from RELY*), & ↑cost.

Trial Background

- Randomized, multi-centre^{44 countries}, non-inferiority & superiority, blinded dabigatran/open-label warfarin, controlled trial with allocation concealed – **dabigatran 110mg or 150mg twice daily vs dose-adjusted warfarin (INR 2-3^{measured ≤1 month}) to reduce stroke or systemic embolism** (Funded by Boehringer Ingelheim; Same lead author as ACTIVE trials)
- INCLUSION:** AF documented on EKG_{baseline} or w/in 6mos prior **& at least one of:** previous stroke/TIA, LVEF<40%, NYHA class II-IV HF w/in 6mos prior, 75yo or 65-74yo plus DM, HTN, or CAD
- EXCLUSION:** severe heart-valve disorder, **stroke within 14 days prior or severe stroke within 6mos prior**, conditions that ↑d risk of hemorrhage, CrCl<30ml/min, active liver disease, pregnancy
- POPULATION at Baseline** (n=18,113): Age_{mean} = 71; 63.6%♂; balance of pts who had VKAs for <61days lifetime & those who had ≥61days lifetime; AF ~1/3 persistent, 1/3 paroxysmal, 1/3 permanent; **CHADS₂ mean = 2.1**, CHADS₂ score ~1/3=0-1, 1/3=2, 1/3=3-6; 20% hx of stroke or TIA; 16% hx of MI; 23% diabetes mellitus; 79% hx of HTN (baseline BP ~131/77); **Baseline meds:** ASA^{40%}, ACE or ARB^{66%}, b-blocker^{63%}, statin^{44%}, PPI^{14%}, H2RA^{4%}, amiodarone^{11%}
- UPDATE:** Nov. 2010 the authors announced they re-evaluated the study database & identified additional outcome events (reflected in the table below).

Results: Efficacy & Safety –median follow-up of 2 yrs

Clinical Endpoints	Warfarin n=6022	Dabigatran		ARR		NNT/NNH		Comments
		110mg bid n=6015	150mg bid n=6076	110mg	150mg	110mg	150mg	
1st Stroke or systemic embolism	3.35% {n=202} (1.71%/yr)	3.04% {n=183} (1.54%/yr)	2.21% {n=134} (1.11%/yr)	NS (p=0.30) non-inferior (p<0.001)	1.14% (0.6%/yr) RRR=34%	-	88 (167/yr)	Efficacy of dabigatran: ⇒110mg BID was non-inferior to warfarin for 1° ⇒150mg BID was non-inferior & superior for 1°
Stroke (less ischemic or unspecified stroke with Dabi 150mg vs warfarin 1.8 vs 2.4% p=0.03)	3.09% {n=186} (1.58%/yr)	2.84% {n=171} (1.44%/yr)	2.01% {n=122} (1.01%/yr)	NS (p=0.38)	1.08% (0.57%/yr)	-	93 (175/yr)	⇒110mg vs 150mg in net clinical benefit. NS (p=0.56)
Hemorrhagic stroke	0.75% {n=45} (0.38%/yr)	0.23% {n=14} (0.12%/yr)	0.20% {n=12} (0.10%/yr)	0.52% (0.26%/yr)	0.55% (0.28%/yr)	192 (385/yr)	182 (357/yr)	Safety: ⇒Warf rates of life-threatening, intracranial, or minor bleeding were higher than either dose dabi ⇒Warf rates of major bleeding were higher than dabi 110mg BID (not statistically significantly different at the 150mg BID dose)
MI (28 cases of silent MI added on re-analysis)	1.25% {n=75} (0.64%/yr)	1.63% {n=98} (0.82%/yr)	1.6% {n=97} (0.81%/yr)	NS (p=0.09)	NS (p=0.12)	Concerning trend of ↑ of 0.35% p>0.05		⇒More dyspepsia with dabi (?due to tartaric acid added to capsules to ↓pH, thus improving absorption)
All Cause Mortality	8.09% {n=487} (4.13%/yr)	7.41% {n=446} (3.75%/yr)	7.21% {n=438} (3.64%/yr)	NS (p=0.13)	NS (p=0.051)	-	-	⇒Dabi 150mg BID, sig. higher rate of major GI bleed than warf (?due to tartaric acid); ARI=1% NNH=100
Major bleed Hgb ↓≥20g/L, transfused ≥2units, or symptomatic bleeding in critical area or organ	6.99% {n=421} (3.57%/yr)	5.69% {n=342} (2.87%/yr)	6.57% {n=399} (3.32%/yr)	1.3% (0.7%/yr) RRR=19.6%	NS (p=0.32)	77 (143/yr)	-	⇒no difference in LFT increases
Intracranial bleed	1.49% {n=90} (0.76%/yr)	0.45% {n=27} (0.23%/yr)	0.63% {n=38} (0.32%/yr)	1.04% (0.53%/yr)	0.86% (0.44%/yr)	96 (189/yr)	116 (227/yr)	Other: ⇒150mg was superior to 110mg for 1° (ARR=0.83%, NNT=120, RRR=38%), with ↑d risk of major bleed (p=0.04)
Minor bleed	32.0% {n=1931} (16.37%/yr)	26.0% {n=1566} (13.16%/yr)	29.4% {n=1787} (14.85%/yr)	6.0% (3.21%/yr)	2.6% (1.52%/yr)	17 (31/yr)	39 (66/yr)	
Dyspepsia	5.8% {n=348}	11.8% {n=707}	11.3% {n=688}	↑6%	↑5.5%	17	18	
Discontinuation rate	10.2% @ 1yr, 16.6% @2yrs	14.5% @ 1yr, 20.7% @2yrs	15.5% @ 1yr, 21.2% @2yrs	-	-	-	-	
Net clinical benefit outcome: Composite ¹ : PE, MI, death, or major hemorrhage	15.5% {n=933} (7.91%/yr)	14.5% {n=873} (7.34%/yr)	14.1% {n=855} (7.11%/yr)	NS (p=0.09)	1.4% (0.8%/yr) RRR=9%	-	71 (125/yr)	Sub-group analyses: ⇒No significant interactions identified/reported at either dose

AF=atrial fibrillation ARR=absolute risk reduction CAD=coronary heart disease CI=confidence interval CKD=chronic kidney disease DM=diabetes Hgb=hemoglobin MI=myocardial infarction NNT=number needed to treat NNH=number needed to harm NS=not significant PE=pulmonary embolism RRR=relative risk THR=total hip replacement TKR=total knee replacement VTE=venous thromboembolism

Strengths, Limitations, & Uncertainties

Strengths: ♦ Important clinical endpoints (e.g. stroke & bleed) ♦ Blinded adjudication of outcomes

♦ Warfarin was within therapeutic range 64% of the study period ^{ACTIVE-W 63.8%}

Limitations: ♦ Only 1/3 of patients with CHADS₂ score >2, therefore, difficult to assess benefit/risk in those at higher risk.

♦ Open label design – possible reporting bias E.g. minor bleeds in warfarin group. ♦ ~ 20% of pts in each arm of the trial was on concomitant aspirin tx

♦ Used Intention-to-treat vs per protocol (Per-protocol is generally recommended in non-inferiority trials⁵).

Uncertainties: ♦ A real increase in MIs? (a toxicity of dabigatran possible platelet-activating effect?; ↑ urinary 11-dehydrothromboxane B₂ in the Petro study⁶ which may? ↑ thrombotic risk, or loss of a protective factor intrinsic to warfarin?)

2008 CHEST guidelines = low-dose warfarin INR 1.5 can be used for 1^o & 2^o prevention of CAD in those at high risk and INR can be measured w/out difficulty⁷ – Grade 2A)

♦ Do PPIs (and other acid reducers) ↓ efficacy by ↑ pH (↓absorption), see sub-group analyses

♦ Drug interactions with P-glycoproteins? E.g. Trial protocol amended after 2yrs to prohibit use of quinidine

♦ Discontinuation rate increased for dabigatran trending towards significance?

♦ Did GI symptoms/events drive the discontinuation rate?

♦ Drug not yet studied in patients with CKD or liver disease?

Dabigatran in Atrial Fibrillation Pros & Cons: Not dabigatran if prosthetic heart valves, sig valve dx, renal dx ^{CrCl<15ml/min} or advanced liver dx ^{ACC¹¹}

Pros vs warfarin	Cons vs warfarin
Non-inferior ^{110mg bid} or superior ^{150mg bid} to warfarin for stroke/systemic embolism	Higher drug cost & twice daily administration with dabi
Less hemorrhagic stroke than warfarin	No antidote with dabi ^{? dialysis helpful}
Less major bleeding with lower dabi 110mg bid dose	Possibly more MI's with dabi, but not significantly
Less intracranial bleeding than warfarin	More dyspepsia & major GI bleeds with dabi
Less all cause mortality with dabi, but not significantly	Higher discontinuation rates with dabi
No INR monitoring required	No long term (greater than 2yr) follow up
Less clinically significant drug interactions	New drug; lacks “real life” data and postmarketing surveillance

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Extra:

The CHADS₂ Score^{8,9}: Stroke Risk in Atrial Fibrillation

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 (10), ACC ⁷ 06 (11), CCS'10, ACCF/AHA'11
C Congestive heart failure	1	0-1	Low (≤ 3%/year)	Aspirin (esp. if age ≥60yrs) ¹² (No antithrombotic if young & no stroke risk factors).
H Hypertension (or treated hypertension)	1	1-2	Moderate (~ 3-4%/year)	VKA (e.g. Warfarin) or Dabigatran. See Pros & Cons list above. {Warfarin/dabigatran most effective in decreasing stroke risk.} VKA=vitamin K antagonist
A Age >75 years	1	3-5	High (~ 6-12%/year)	
D Diabetes	1	6	Very High (~ 18%/year)	
S₂ Prior Stroke or TIA	2			<u>Not dabigatran</u> if prosthetic heart valves, sig valve dx, renal dx ^{CrCl<15ml/min} or advanced liver dx ^{ACC¹¹}

AF Patient Description	Treatment Option(s)
Moderate → high risk for stroke + no contraindication (CI) to VKA	VKA e.g Warfarin (target INR 2 - 3) unless CI* or Dabigatran (demonstrates max stroke prevention with an acceptable major bleed risk; esp. if CHADS ₂ ≥ 2, >85yr of age if no bleed hx, or an ischemic stroke hx ¹³)
Moderate → high risk for stroke + cannot/will not tolerate VKA OR high-quality anticoag not achieved with VKA OR low risk for stroke	ASA monotherapy ^{75-100mg daily} or Clopidogrel ^{75mg daily} + ASA ^{75-100mg daily} or Dabigatran Choice depends on overall bleed risk & cost considerations: ♦ ASA+clopidogrel will lower stroke/vascular risk marginally over ASA; however, ASA will have lowest bleed risk and is lower cost. Bleed risk with ASA+clopidogrel is similar to that with warfarin; ∴ those who are not suitable for warfarin due to bleed risk, may also not be suitable for ASA+clopidogrel. ♦ Thus ASA+clopidogrel option really only suitable for patients who are not candidates for warfarin due to factors <u>other than</u> high risk of bleeding e.g. purple toe syndrome, lack of access to lab for required INR tests, likely not to be adherent to therapy/INR testing requirements, etc.
High bleed risk ^{HAS-BLED Score} & low-mod stroke risk	ASA (75-100mg daily)

* **VKA** contraindications (e.g., history of falls especially frequent, clinically significant GI bleeding, inability to obtain regular INR testing)

⇒ **On the horizon:**

1) Dabigatran ^{PRADAX} 110-150mg cap BID will offer an alternative to warfarin (RE-LY trial² ^{trial})¹³. At the lower dose, it was as effective as warfarin with less bleeding; at the higher dose it was more effective than warfarin ^{NNT=173/yr} but with similar bleeding rates. There were more dropouts ^{tartaric acid in cap} in the dabigatran group ^{21% vs 17%}.

Abnormal liver function was not a problem in dabigatran patients compared to warfarin ^{0.2% vs 0.3%} }

2) Rivaroxaban ^{XARELTO}; currently being evaluated in ROCKET AF, a phase 3 trial in AF patients. See RxFiles Rocket-AF Summary Aug 2011 (published in NEJM Aug 2011)

3) Apixaban ^{Eliquis}; currently being evaluated in Aristotle for AF. See RxFiles Aristotle Summary Sep 2011 (published in NEJM Aug 2011)

For References – see full trial summary online at RxFiles.ca

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