RE-LY: Dabigatran versus Warfarin in Patients with Atrial Fibrillation [1]

Randomized Evaluation of Long-term anticoagulation therapY in patients with atrial fibrillation & who were at increased risk of stroke

BOTTOM LINE

In **RE-LY**, patients with atrial fibrillation (AF) (mean $CHADS_2$ score 2.1):

- Dabigatran both doses had less hemorrhagic strokes & intracranial bleeds.
- Dabigatran 150mg po bid had:
  - less stroke/systemic embolism 1° endpoint, but more gastrointestinal (GI) bleeds compared to warfarin & dabigatran 110mg po bid
  - a better net clinical benefit compared to warfarin
  - more major bleeding than dabigatran 110mg po bid but similar to warfarin
- Dabigatran 110mg po bid was similar to warfarin for stroke & systemic embolism, but had less major bleeding than warfarin.
  - consider in individuals ≥80 years of age or >75 years old + 1 bleeding risk factor (e.g. CrCl 30-50mL/min, concomitant treatment with strong P-glycoprotein inhibitors or antiplatelets, prior GI bleed)
- Dabigatran both doses also had more dyspepsia & discontinuation rates compared to warfarin.
- At time of publication, dabigatran for AF is ~$110/month; (75mg✗⊗ dose not studied in Phase III AF trials), 110mg, 150mg capsules ☎A Fib,⊗.

BACKGROUND

- Vitamin K antagonists (VKA) are used to ↓ the risk of stroke in AF patients; however, these agents require frequent monitoring, interact with drugs/food, & require several days of therapy to become therapeutic/discontinuation before clearing the body.
- New oral anticoagulants (apixaban ELIQUIS,[2,3] dabigatran PRADAXA & rivaroxaban XARELTO[4,5]) have been introduced to the market as alternatives to VKA such as warfarin.
- **Dabigatran** etexilate PRADAXA, a prodrug, is a new oral competitive "direct-thrombin inhibitor".
- **RE-LY:** 1st Phase III study to assess dabigatran for stroke prevention in AF patients. **PETRO:** Phase II dose finding study in AF patients.[6]

TRIAL BACKGROUND

DESIGN: randomized, multi-centre 44 countries, non-inferiority followed with pre-designed superiority, blinded dabigatran/open-label warfarin, intention-to-treat controlled trial with concealed allocation. Funded by Boehringer Ingleheim. Same lead author as ACTIVE trials.

INTERVENTION: dabigatran 110mg po twice daily vs dabigatran po 150mg twice daily vs dose-adjusted warfarin (INR 2-3 measured ≤1 month)

INCLUSION: AF ECG confirmed at baseline or within 6 months prior & ≥1 of the following: previous stroke or TIA, LVEF<40%, NYHA class II-IV HF within 6 months prior, ≥75 years old or 65-74 years old + DM, HTN, or CAD.

EXCLUSION: severe heart-valve disorder, stroke within 14 days prior or severe stroke within 6 months prior, conditions that ↑ risk of hemorrhage, CrCl <30mL/min, active liver disease, pregnancy.

POPULATION at baseline: n=18,113 non-valvular AF pts at risk of stroke

- AF ~ ⅓ paroxysmal, ⅓ persistent, ⅓ permanent; $CHADS_2$ mean = 2.1, ⅓ had a $CHADS_2$ score of 0-1, ⅓ a score of 2, ⅓ a score of 3-6.
- Mean age 72yrs; ~64% ♂; history of stroke or TIA ~20%, HTN ~79% baseline BP ~131/77, HF ~32%, DM ~23%, MI 16%.
- Baseline meds: VKA ≥ 61 days 50%, ASA 40% 20% at end of trial, ACE-I/ARB 66%, β-blocker 63%, statin 44%, PPI 14%, H_2RA 4%, amiodarone 11%

UPDATE: in November 2010, the authors announced they re-evaluated the study database & identified additional outcome events (reflected as **bold** data in the table below).[7,8,9]

RESULTS

follow-up: median 2 years

TABLE 1: EFFICACY & SAFETY NON-INFERIORITY DATA SUPERIORITY DATA **BOLD** DATA FROM RE-ANALAYSIS[7,8,9]

CLINICAL ENDPOINTS	WARFARIN n=6022	DABIGATRAN 110mg bid n=6015	DABIGATRAN 150mg bid n=6076	ARR/ARI 110mg	ARR/ARI 150mg	NNT/NNH /2YRS 110mg	NNT/NNH /2YRS 150mg	COMMENTS
PRIMARY ENDPOINT								
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)**	p<0.001 NS	**1.14% (0.6%/yr)**	-	**88 (167/yr)**	**DABIGATRAN VS WARF:** - ↓ hemorrhagic stroke & intracranial bleed - ↑ dyspepsia† & discontinuation rates
SECONARY ENDPOINTS								
Stroke	**3.09% {n=186} (1.58%/yr)**	2.84% {n=171} (1.44%/yr)	2.01% {n=122} (1.01%/yr)	NS	**1.08% (0.57%/yr)**	-	**93 (175/yr)**	
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)	**DABIGATRAN 150MG:** vs warf & dabi 110mg - ↓ 1° endpoint &stroke - ↑ GI bleed†
Ischemic or Unspecified Stroke	**2.37% {n=143} (1.21%/yr)**	2.64% {n=159} (1.34%/yr)	1.83% {n=111} (0.92%/yr)	NS	**0.54% (0.29%/yr)**	-	**185 (345/yr)**	
Myocardial Infarction 28 silent & 4 clinical 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	**NS**	See RxFiles Q&A: Does Dabigatran ↑ MI Risk?[10]		vs warfarin - better net clinical benefit
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	NS p=0.051	-	-	
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)**	NS	**77 (143/yr)**	-	vs dabigatran 110mg - ↑ major bleed
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)**	**DABIGATRAN 110MG:**
Gastrointestinal Bleed	**2.09% {n=126} (1.07%/yr)**	**2.28% {n=137} (1.15%/yr)**	**3.09% {n=188} (1.56%/yr)**	NS	↑1% (0.49%/yr)	-	100 (204/yr)	vs warfarin - = 1° endpoint - ↓ major bleed
Minor Bleed	32% {n=1931} (16.37%/yr)	26% {n=1566} (13.16%/yr)	29.4% {n=1787} (14.85%/yr)	6% (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	**OTHER COMMENTS:** - ↑ LFT = NS - Subgroup analyses: NS
Discontinuation Rates	10.2% @1yr	14.5% @1yr	15.5% @1yr	↑4.3%	↑5.3%	23/yr	19/yr	
	16.6% @2yrs	20.7% @2yrs	21.2% @2yrs	↑4.1%	↑4.6%	25/2yrs	22/2yrs	
Net Clinical Benefit stroke, systemic embolism, PE, MI, death & major bleed	15.5% {n=933} (7.91%/yr)	14.5% {n=873} (7.34%/yr)	14.1% {n=855} (7.11%/yr)	NS	1.4% (0.8%/yr)	-	71 (125/yr)	

†Query if increase dyspepsia & GI bleed with dabigatran due to tartartic acid core. **Non-inferiority data** **Superiority data** **Bold** data from re-analaysis[7]

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:
- Important clinical endpoints (e.g. stroke & bleed)
- Blinded adjudication of outcomes
- Mean time in therapeutic range with warfarin was 64% ACTIVE-W 63.8%, ARISTOTLE 62.2%, ROCKET 55%
- Only 20 patients lost to follow-up (0.11%)

LIMITATIONS:
- Open label design → possible reporting bias e.g. minor bleeds in warfarin group

UNCERTAINITIES:
- A real increase in MIs? possible platelet-activating effect?; ↑ urinary 11-dehydrothromboxane B_2 in PETRO[6] which may? ↑ thrombotic risk, or does warfarin have a cardioprotective effect that dabigatran does not have?
  - See RxFiles Q&A on Does Dabigatran ↑ MI risk http://www.rxfiles.ca/rxfiles/uploads/documents/Dabigatran_MI%20Risk_QandA.pdf
- 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?
- Drug not yet studied in patients with CKD or liver disease?
- No antidote for reversing bleeding with dabigatran.
- ? real-world experience with dabigatran.

OBSERVATIONAL LONG-TERM FOLLOW-UP STUDY

1) *Long-Term Multi-Centre Observational Study of Dabigatran Treatment in AF Patients – RELY-ABLE*[11]

- Patients who were randomized to receive dabigatran 150mg or 110mg BID in the RELY study & who did not permanently discontinue their therapy were eligible for the RELY-ABLE trial.
  - Permanent discontinuation of therapy was defined as an interruption in dabigatran therapy >8 weeks.
- RELY-ABLE patients continued to receive their originally assigned double-blind dabigatran dose from the RELY study.
- Median follow-up in RELY-ABLE: 2.3 years. Median follow-up in RELY: 2 years. The RELY-ABLE data analysis only included events which occurred during RELY-ABLE.
- At baseline, the patients enrolled in RELY-ABLE were more likely to have paroxysmal (versus permanent) AF, be on a beta-blocker or a statin; & less likely to have HF or to have experienced a stroke, MI or major bleed during RELY, (p<0.0001 for all).

TABLE 2: INDIRECT COMPARISON OF THE RELY VS RELY-ABLE OUTCOME DATA

EVENT	RELY† (median 2 years) Randomized, Intention-to-Treat, Adjudicated Outcomes			RELY-ABLE (median 2.3 years) Observational, Per-Protocol, Outcomes not Adjudicated		
	DABIGATRAN 150MG BID (n=6076)	DABIGATRAN 110MG BID (n=6015)	RELATIVE RISK (95% CI) DABI 150MG VS 110MG p-value	DABIGATRAN 150MG BID (n=2937)	DABIGATRAN 110MG BID (n=2914)	HAZARD RATIO (95% CI) (p-values not reported)
Stroke or systemic embolism	2.21% (n=134) 1.11%/yr	3.04% (n=183) 1.54%/yr	0.72 (0.58-0.9) 0.004	3.17% (n=93) 1.46%/yr	3.5% (n=102) 1.6%/yr	0.91 (0.69-1.2)
All Stroke	2.01% (n=122) 1.01%/yr	2.84% (n=171) 1.44%/yr	0.7 (0.56-0.89) 0.003	2.69% (n=79) 1.24%/yr	3.02% (n=88) 1.38%/yr	0.89 (0.66-1.21)
Ischemic or Unspecified Stroke	1.83% (n=111) 0.92%/yr	2.64% (n=159) 1.34%/yr	0.69 (0.54-0.88) 0.002	2.49% (n=73) 1.15%/yr	2.71% (n=79) 1.24%/yr	0.92 (0.67-1.27)
Hemorrhagic Stroke	0.20% (n=12) 0.10%/yr	0.23% (n=14) 0.12%/yr	0.85 (0.39-1.83) NS	0.27% (n=8) 0.13%/yr	0.31% (n=9) 0.14%/yr	0.89 (0.34-2.3)
All Cause Mortality	7.21% (n=438) 3.64%/yr	7.41% (n=446) 3.75%/yr	0.97 (0.85-1.11) NS	6.54% (n=192) 3.02%/yr	6.76% (n=197) 3.1%/yr	0.97 (0.8-1.19)
Myocardial Infarction	1.6% (n=97) 0.81%/yr	1.63% (n=98) 0.82%/yr	0.98 (0.74-1.3) NS	1.5% (n=44) 0.69%/yr	1.58% (n=46) 0.72%/yr	0.96 (0.63-1.45)
Major Bleed‡	6.57% (n=399) 3.32%/yr	5.69% (n=342) 2.87%/yr	1.16 (1-1.34) 0.04	8.1% (n=238) 3.74%/yr	6.52% (n=190) 2.99%/yr	1.26 (1.04-1.53)
Life-Threatening Bleed	2.95% (n=179) 1.49%/yr	2.44% (n=147) 1.24%/yr	1.21 (0.97-1.5) NS	3.88% (n=114) 1.79%/yr	3.43% (n=100) 1.57%/yr	1.14 (0.87-1.49)
Intracranial Bleed	0.63% (n=38) 0.32%/yr	0.45% (n=27) 0.23%/yr	1.39 (0.85-2.28) NS	0.72% (n=21) 0.33%/yr	0.55% (n=16) 0.25%/yr	1.31 (0.68-2.51)
Gastrointestinal Bleed	3.09% (n=188) 1.56%/yr	2.28% (n=137) 1.15%/yr	1.36 (1.09-1.7) 0.006	3.34% (n=98) 1.54%/yr	3.4% (n=99) 1.56%/yr	0.99 (0.75-1.31)
Net Clinical Benefit §	14.1% (n=855) 7.11%/yr	14.5% (n=873) 7.34%/yr	0.97 (0.88-1.07) NS	15.9% (n=468) 7.36%/yr	15% (n=438) 6.89%/yr	1.07 (0.94-1.22)
Dyspepsia	11.3% (n=688)	11.8% (n=707)	Not reported	5.3% (n=156)	4.8% (n=141)	Not reported
Discontinuation Rates	21.2% (n=1211)	20.7% (n=1161)		14.6% (n=429)	13.8% (n=403)	

%/yr = per 100 patient years of follow-up. NS=non-significant.

† Includes re-analyzed RELY data, except for dyspepsia & discontinuation rates in which the original RELY data was used as these outcomes were not part of the re-analysis.

‡ Major Bleed = hemoglobin ↓≥20g/L, transfused ≥2units, or symptomatic bleeding in critical area or organ.

§ Net Clinical Benefit = stroke, systemic embolism, pulmonary embolism, myocardial infarction, death & major bleed

- The direction of the RELY-ABLE hazard ratios were similar to what was shown in RELY – i.e. dabigatran 150mg BID had less stroke/systemic embolism but more major bleeds compared to dabigatran 110mg BID. The investigators appropriately did not include p-values for the comparison of the two dabigatran doses in RELY-ABLE as there was no primary endpoint since the study was descriptive & the study was not powered to detect a difference between the groups.

- The RELY-ABLE authors concluded that there was no difference between the two dabigatran doses for the rates of stroke or death, but dabigatran 150mg BID had ↑ risk of bleeding. Whereas, RELY showed that dabigatran 150mg BID resulted in less strokes & systemic embolism (p-value=0.005), but there was no difference in the two doses for major bleeds (p-value=0.052). Some editorials have considered RELY-ABLE as a long-term extension of RELY. However, there are several differences in the trial designs & patient populations which need to be considered when interpreting these results, and a direct comparison of study outcomes should be avoided:
  - RELY was a randomized, intention-to-treat trial. RELY-ABLE was an observational, per-protocol trial.
  - RELY study outcomes were adjudication, whereas RELY-ABLE events were not.
    - In RELY, 84% of suspected strokes & 89% of suspected systemic embolisms were rejected upon adjudication. 93% of reported major bleeds were confirmed upon adjudication.
  - Warfarin was not included as a comparator in RELY-ABLE.
  - Only ~⅔ (63%) of the original RELY study sites were included in RELY-ABLE.
    - RELY: 951 clinical centres from 44 countries; 36% of participants were from North America
    - RELY-ABLE: 598 clinical centres from 35 countries; 38% of participants were from North America.
  - Only ~½ (48%, n=5851) of the RELY patients randomized to dabigatran were enrolled in RELY-ABLE.
    - RELY-ABLE patients had a lower risk profile as they were more likely to be on cardioprotective medications (i.e. beta-blockers or statins), less likely to have HF, & less likely to have experienced an event (i.e. death, stroke, MI, major bleed) during RELY.
  - There was no primary outcome for RELY-ABLE as the study was descriptive & not powered to detect a difference between the groups, as opposed to RELY.
  - Due to the differences in trial design & patient populations, the RELY & RELY-ABLE event rates have not been combined. Caution should be exercised when reading/interpreting some of the commentary on RELY-ABLE where it can be misconstrued that RELY-ABLE provides long-term efficacy & safety trial data. The median follow-up was 2 years for RELY and 2.3 years for RELY-ABLE (not a total of 4.3 years).
- The publication of RELY-ABLE should not change the previous recommendations for dabigatran; continue to recommend:
  - Dabigatran 150mg po BID in patients <80 years of age
  - Dabigatran 110mg po BID in patients ≥80 years of age, >75 years + 1 bleeding risk factor (e.g. CrCl 30-50mL/min) or at any age if at ↑ risk of bleeding

A FEW PUBLISHED SUBGROUP ANALYSES

- There have been several published subgroup analyses of the RELY trial, & the following summaries represent only a very small percentage of what is available. This document only includes subgroup analyses which were used to answer questions we received in regard to the RELY study.
- Subgroup analyses are not powered to detect a conclusive difference between treatments groups.

1) *Efficacy & Safety of Dabigatran Compared with Warfarin at Different Levels of INR Control for Stroke Prevention in RELY AF Patients*[12]

- Effectiveness & safety of warfarin is associated with the time in therapeutic range (TTR, calculated using the Rosendaal Method).
- Mean RELY TTR for all countries involved in the study was 64%. Canada had a mean TTR of 71%.
- TTR was divided into quartiles for the sub-analysis, by centre (cTTR): <57.1%, 57.1-65.5%, 65.5-72.6%, >72.6%.
- **Stroke & systemic embolism**: dabigatran 150mg po BID remained superior & dabigatran 110mg po BID remained non-inferior to warfarin, regardless of INR control. However, dabigatran 150mg po BID was not superior to warfarin for ↓ non-hemorrhagic stroke at higher cTTR quartiles.
- **Intracranial hemorrhage**: both doses of dabigatran had less intracranial bleeds compared to warfarin, regardless of cTTR.
- **Major bleeding & GI bleeding**:
  - For patients on warfarin, centres that achieved higher cTTR quartiles had less major/GI bleeding than lower cTTR quartiles sites.
  - Dabigatran 110mg po BID had lower major/GI bleeding than warfarin, regardless of cTTR control.
  - Dabigatran 150mg po BID had less major bleeds than warfarin with cTTR ≤65.5% & had a similar rate of major bleeds to warfarin with cTTR ≥65.5%. Dabigatran 150mg po BID had more GI bleeds than warfarin with higher cTTR.

2) *Variation in Warfarin Dose Adjustments Practice is Responsible for Differences in the Quality of Anticoagulation Control between Centres & Countries*[13]

- RELY investigators ***encouraged*** study sites to use the following warfarin dosing algorithm:
  - INR ≤1.5: ↑ weekly dose by 15%
  - INR 1.51-1.99: ↑ weekly dose by 10%
  - INR 2-3 (INR 2-2.5 for Japan): no dose adjustment
  - INR 3.01-4: ↓ weekly dose by 10%
  - INR 4-4.99: hold dose for 1 day, then ↓ weekly dose by 10%
  - INR 5-8.99: hold dose until INR therapeutic, then ↓ weekly dose by 15%
  - Maximum interval between INRs was 4 weeks. Weekly INRs were recommended for out-of-range values.

- Use of the suggested algorithm was not confirmed, but warfarin dosage changes were assessed for "algorithm consistency" (defined as within 5% of the recommended algorithm dose). INR values during warfarin discontinuation or within 7 days of (re) starting were excluded.
- 77% of patients were managed at primary care centres. 15% were managed at anticoagulation clinics.
- Mean (SD): TTR 64% (20%), monthly frequency of INR testing 1.6 (1.3), time below therapeutic range 22% (19%) & above therapeutic range 13% (13%).
  - North American data (n=2167, 36%): mean (SD) TTR 67% (17%), algorithm consistency 64% (17%), time below therapeutic range 19% (15%) & above therapeutic range 14% (11%).
- Warfarin dose adjustments based on the above recommendations were associated with an improved TTR & clinical outcomes.
  - Each 10% ↑ in algorithm consistency was associated with a 6.12% ↑ in TTR & a 8% ↓ in the rate of the composite outcome of stroke, systemic embolism or major bleeding

3) *Risk of Major Bleeding with 2 doses of Dabigatran Compared with Warfarin in Older & Younger RE-LY AF Patients*[14]

- Number of patients by age: <75 years: n=10,855 (60%), ≥75 years: n=7258 (40%)
- **For patients <75 years of age**:
  - Both dabigatran doses had less major bleeds than warfarin (dabi 110mg 1.89% vs warf 3.04%, p<0.001; dabi 150mg 2.12% vs warf 3.04%, p<0.001)
- **For patients ≥75 years of age:**
  - dabigatran 110mg po bid had a similar risk of major bleeding as warfarin (4.43% vs 4.37%, NS)
  - dabigatran 150mg po bid had a trend towards a higher risk of major bleeding compared to warfarin (5.1% vs 4.37%, p=0.07)
- Both doses of dabigatran had less risk of **intracranial hemorrhage** compared to warfarin, regardless of age.
- Compared to warfarin, **extracranial bleeding** with dabigatran both doses was less in patients <75 years of age, & higher in patients ≥75 years of age.

RxFILES RELATED LINKS

- Atrial Fibrillation Treatment Overview http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Atrial-Fibrillation.pdf
- Oral Antiplatelet & Antithrombotic Agents Comparison Chart http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-AntiThrombotics.pdf
- Canadian Family Physician RxFiles: Article Oral anticoagulation in atrial fibrillation http://www.cfp.ca/content/58/8/850.full
- ARISTOTLE (apixaban ELIQUIS vs warfarin in AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/ARISTOTLE-AF-Apixaban.pdf
- ROCKET-AF (rivaroxaban XARELTO vs warfarin in AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/ROCKET-AF-Rivaroxaban.pdf
- ACTIVE-A (ASA ± clopidogrel PLAVIX in AF) & ACTIVE-W (ASA + clopidogrel PLAVIX vs warfarin in AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/ACTIVE-A-Trial-Summary.pdf
- RACE-II (lenient vs strict rate control in AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/RACE-II-trial.pdf
- PALLAS (dronedarone MULTAQ in permanent AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/PALLAS-trial%20summary.pdf

✗ =non-formulary in SK ⊗=not covered by NIHB ☎=Exceptional Drug Status in SK **1°**=primary ♂=male **ACE-I**=angiotensin converting enzyme inhibitor **AF**=atrial fibrillation **ARB**=angiotensin receptor blocker **ARI**=absolute risk increase **ARR**=absolute risk reduction **ASA**=acetylsalicylic acid **β**=beta **CAD**=coronary heart disease **CHADS$_2$**=congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke or transient ischemic attack **CI**=confidence interval **CKD**=chronic kidney disease **CrCl**=creatinine clearance **DM**=diabetes **ECG**=electrocardiogram **GI**=gastrointestinal **HF**=heart failure **Hgb**=hemoglobin **H$_2$RA**=histamine-2 receptor antagonist **HTN**=hypertension **INR**=international normalized ratio **LFT**=liver function test **LVEF**=left ventricular ejection fraction **MI**=myocardial infarction **NNT**=number needed to treat **NNH**=number needed to harm **NS**=not statistically significant **NYHA**=New York Heart Association **PE**=pulmonary embolism **PPI**=proton pump inhibitor **TIA**=transient ischemic attack **VKA**=vitamin K antagonist **yr**=year

ACKNOWLEDGEMENTS: Contributors & Reviews: Dr. Rodney Zimmermann FRCPC, FACC (Cardiology, Regina) **Prepared By**: Z.Dumont, B.Bunka, L.Kosar, B.Jensen, L.Regier

ADDITIONAL REFERENCES:

ACCF- AHA-HRS Atrial Fibrillation 2011 Focused Update. Circulation 2011. http://circ.ahajournals.org/cgi/reprint/CIR.0b013e3181fa3cf4v1 Wann LS, Curtis AB, January CT, 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 2010; DOI: 10.1161/CIR.0b013e3181fa3cf4.)

Avorn Jerry. The Relative **Cost-Effectiveness of Anticoagulants**: Obvious, Except for the Cost and the Effectiveness. Circulation 2011, 123: 2519-2521.

Beasley BN, Unger EF, Temple R. Anticoagulant options- Why the FDA approved a **higher but not a lower dose of dabigatran**. New Engl J Med 2011; DOI: 10.1056/NEJM/1103050.

Bovio JA, Smith SM, Gums JG. **Dabigatran** etexilate: a novel oral thrombin inhibitor for thromboembolic disease. Ann Pharmacother. 2011 May;45(5):603-14.

Cairns JA, Connolly S, McMurtry S, et al. CCS Atrial Fibrillation Guidelines Committee. **Canadian cardiovascular society atrial fibrillation guidelines 2010**: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. Can J Cardiol. 2011 Jan-Feb;27(1):74-90.

Callahan T, Baranowski B. **Managing newly diagnosed atrial fibrillation**: Rate, rhythm, and risk. Cleve Clin J Med. 2011 Apr;78(4):258-64.

Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L; Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial. N Engl J Med. 2010 Nov 4;363(19):1875-6.

Connolly SJ, Wallentin L, Ezekowitz MD, et al. The Long Term Multi-Center Observational Study of **Dabigatran** Treatment in Patients with Atrial Fibrillation (**RELY-ABLE**) study. Circulation 2013.

Cotton, BA, McCarthy JJ, Holcomb JB. **Acutely injured patients** on dabigatran. N Engl J Med 2011; 365:2039-2040.

Dans AL, Connolly SJ, Wallentin L, et al.Concomitant use of **antiplatelet therapy with dabigatran or warfarin** in the Randomized Evaluation of Long-term Anticoagulation Therapy **RE-LY** trial. Circulation.2013;127:634–640.

Diener, Hans-Christoph, Connolly, Stuart J, Ezekowitz Michael D. Dabigatran compared with warfarin in patients with atrial fibrillation and **previous transient ischaemic attack** or stroke: a subgroup analysis of the RE-LY trial .The Lancet Neurology, Early Online Publication, 8 November 2010 doi:10.1016/S1474-4422(10)70274.

Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation. Circulation 2011; 123:2363-2372.

Eikelboom JW, Connolly SJ, Hart RG, et al. Balancing the benefits and risks of **two doses of dabigatran** compared with warfarin in atrial fibrillation. J Am Coll Cardiol 2013.

Ezekowitz MD, et al.. Dabigatran and Warfarin in Vitamin K Antagonist–Naive and –Experienced Cohorts With Atrial Fibrillation. Circulation. 2010 Nov 30; 122: 2246-2253.

Freeman James V., Zhu Ruo P., Owens Douglas K., et al. **Cost-Effectiveness of Dabigatran Compared With Warfarin** for Stroke Prevention in Atrial Fibrillation. Ann Intern Med January 4, 2011 154:1-11; published ahead of print Nov 1, 2010, doi:10.1059/0003-4819-154-1-201101040-00289.

Hankey GJ, Eikelboom JW. **Dabigatran** etexilate: a new oral thrombin inhibitor. Circulation. 2011 Apr 5;123(13):1436-50.

Harper P, Young L, and Merriman E. **Bleeding risk with dabigatran in the frail elderly**. N Engl J Med 2012; 366:864-866.

Hart RG, Diener HC, Yang S, et al. **Intracranial hemorrhage** in atrial fibrillation patients during anticoagulation with warfarin or **dabigatran**: The **RE-LY** trial. Stroke 2012.
Healey J S, Eikelboom J, Douketis J, et al. **Peri-procedural bleeding** and thromboembolic events with dabigatran compared to warfarin: Results from the RE-LY randomized trial. Circulation 2012.
Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: An analysis of patients undergoing **cardioversion**. Circulation 2011; DOI:10.1161/CIRCULATIONAHA.110.977546.
Oldgren J, Alings M, Darius H, et al. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the **CHADS2 score**: a subgroup analysis of the **RE-LY** trial. Ann Intern Med. 2011;155:660-7.
Paré G, Eriksson N, Lehr T, et al. **Genetic determinants** of dabigatran plasma levels and their relation to bleeding. (Rely) Circulation. 2013 Apr 2;127(13):1404-12.
Patel MR, Mahaffey KW, Garg J, et al. **Rivaroxaban** versus warfarin in nonvalvular atrial fibrillation (**Rocket-AF**). N Engl J Med. August 10, 2011. http://www.nejm.org/doi/full/10.1056/NEJMoa1009638
Pisters R, Lane DA, Nieuwlaat R, et al. A novel userfriendly score (**HAS-BLED**) to assess one-year risk of major bleeding in atrial fibrillation patients: The Euro Heart Survey. Chest 2010; published online March 18. DOI:10.1378/chest.10-013 4.
Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous **thromboembolism. (RE-MEDY, RE-SONATE)** N Engl J Med 2013; 368:709-718.
Shah Shimoli V., Gage Brian F.. **Cost-Effectiveness of Dabigatran** for Stroke Prophylaxis in Atrial Fibrillation. Circulation 123: 2562-2570.
Van Spall HG, Wallentin L, Yusuf S, et al. Variation in warfarin dose adjustment practice is responsible for differences in the quality of anticoagulation control between centers and countries: an analysis of patients receiving warfarin in the **RE-LY** trial. Circulation2012.
Wallentin L et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: An analysis of the RE-LY trial. Lancet 2010 Aug 29; [e-pub ahead of print]. (http://dx.doi.org/10.1016/S0140-6736(10)61194-4)
Wann L. Samuel, Curtis Anne B., Ellenbogen Kenneth A., et al. **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 published February 14, 2011, doi:10.1161/CIR.0b013e31820f14c0 http://circ.ahajournals.org/cgi/reprint/CIR.0b013e31820f14c0v1

RELY TRIAL SUMMARY REFERENCES:

[1] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. NEJM 2009;361. (**RELY**)
[2] Granger CB, Alexander JH, McMurray JJV et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med August 28, 2011 http://www.nejm.org/doi/pdf/10.1056/NEJMoa1107039 (**ARISTOTLE)**
[3] Jin M. RxFiles Trial Summary – ARISTOTLE: Apixaban versus warfarin in patients with atrial fibrillation. Saskatoon, SK: RxFiles; 2011. Available from: www.rxfiles.ca. Accessed April 30th, 2012.
[4] Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883-91. (**ROCKET-AF**)
[5] Jin M. RxFiles Trial Summary – ROCKET-AF: rivaroxaban versus warfarin in patients with atrial fibrillation. Saskatoon, SK: RxFiles; 2011. Available from: www.rxfiles.ca. Accessed April 30th, 2012.
[6] Ezekowitz MD, Reilly PA, Nehmiz G, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation. Am J Cardiol. 2007Nov1;100(9):1419-26. (**PETRO**)
[7] Uchino K, Hernandez AV. Dabigatran association with **higher risk of acute coronary events**: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med.
[8] Connolly SJ, Ezekowitz, Yusuf S, Reilly PA, Wallentin L; Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the **RE-LY** trial. N Engl J Med. 2010 Nov 4;363(19):1875-6.
[9] Hohnloser SH, Oldgren J, Yang S, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the **RE-LY** trial. Circulation 2012.
[10] Kosar L. RxFiles Q&A: Does Dabigatran increase the risk of myocardial infarction? Saskatoon, SK: RxFiles; 2012. Available from: www.rxfiles.ca. Accessed November 2012.
[11] Connolly SJ, Wallentin L, Ezekowitz MD et al. The Long Term Multi-Center Observational Study of Dabigatran Treatment in Patients with Atrial Fibrillation: (**RELY-ABLE**) Study. Circulation. 2013 Jun 14. [Epub ahead of print] PubMed PMID: 23770747.
[12] Wallentin L, Yusuf S, Ezekowitz MD et al; RE-LY investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet. 2010 Sep 18;376(9745):975-83.
[13] Van Spall HG, Wallentin L, Yusuf S et al. Variation in warfarin dose adjustment practice is responsible for differences in the quality of anticoagulation control between centers and countries: an analysis of patients receiving warfarin in the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial.Circulation. 2012 Nov 6;126(19):2309-16.
[14] Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation. Circulation 2011; 123:2363-2372.