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

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 1st 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 •AFR®.

**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 ELIQUIX, 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 Ingelheim. 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 ε month)

**INCLUSION:** AF ICG confirmed at baseline or within 6 months prior & 21 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 ~ % paroxysmal, % persistent, % permanent; CHADS$_2$ mean = 2.1, ½ had a CHADS$_2$, score of 0-1, ½ a score of 2, ½ a score of 3-6.
- Mean age 72yrs; ~64%; history of stroke or TIA ~20%, HTN ~79% baseline 88–132/77, HF ~32%, DM ~23%, MI 16%.
- Baseline meds: VKA ± 1.5% (0.64%/yr) 5%, ASA 40% 20% at end of trial, ACE-I/ARB 66%, β-blocker 63%, statin 44%, PPI 14%, H₂RA 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-ANALYSIS7, 8, 9 |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| CLINICAL ENDPOINTS | WARFARIN n=6022 | DABIGATRAN | ARR/ARI | NNT/NNH/2yrs | COMMENTS |
| PRIMARY ENDPOINTS | | | | | |
| Stroke or Systemic Embolism | 3.35% (n=202) | 3.04% (n=183) | 2.21% (n=134) | p<0.001 | NS | 88 (167/y) | DABIGATRAN VS WARF: ↓ hemorrhagic stroke & intracranial bleed ↓ dyspepsia & discontinuation rates |
| Stroke | 3.00% (n=186) (1.58%/yr) | 2.84% (n=171) (1.44%/yr) | 2.01% (n=122) (1.01%/yr) | 0.8% (0.57%/yr) | NS | 93 (175/y) | DABIGATRAN 150MG: ↓ 1st & stroke & stroke to warfarin ↓ GI bleed↑ warfarin |
| 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) |
| 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 72h silent & 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?6 |
| 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 | - | better net clinical benefit vs dabigatran 110mg minus major bleed |
| Major Bleed nbg ≥200/L transfused ≥2units, or symptomatic bleeding in critical area or organ | 6.99% (n=421) (3.57%/yr) | 5.69% (n=342) (3.37%/yr) | 6.57% (n=399) (3.32%/yr) | 1.3% (0.7%/yr) | NS | 77 (143/y) | - | vs warfarin |
| Intraocular 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% (0.48%/yr) | 96 (189/y) | 116 (227/y) | - | better net clinical benefit vs warfarin |
| 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) | - | (204/yr) | - | vs warfarin |
| Minor Bleed | 32% (n=1931) (16.37%/yr) | 26% (n=1566) (13.16%/yr) | 29.4% (n=1787) (14.85%/yr) | 6% (3.12%/yr) | 2.6% (1.52%/yr) | 6% (31/yr) | 39 (66/yr) | - | ≤ 1% endpoint & major bleed |
| Dyspepsia | 5.8% (n=348) | 11.8% (n=707) | 11.3% (n=688) | 7% | 5.5% | 17 (18/yr) | 19 (21/yr) | - | OTHER COMMENTS: ≥ LFT = NS Group subanalyses: NS |
| Discontinuation Rates | 10.2% @1yr | 14.5% @1yr | 15.5% @1yr | 7.4% | 7.5% | 17 (23/yr) | 19 (21/yr) | - | ≤ 1% endpoint & major bleed |
| Net Clinical Benefit stroke, systemic embolism, PE, MI, death & major bleed | 15.5% (n=933) | 14.5% (n=873) | 14.1% (n=853) | 7.1% (0.8%/yr) | 1.4% (0.7%/yr) | 7.1% (125/yr) | - | ≤ 1% endpoint & major bleed |

*Query if increase dyspepsia & GI bleed with dabigatran due to tartaric acid core. Non-inferiority data Superiority data Bold data from re-analysis

1Randomized Evaluation of Long-term anticoagulation therapy in patients with atrial fibrillation & who were at increased risk of stroke
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

UNCERTAINTIES:
- A real increase in MIs? possible platelet-activating effect?; † urinary 11-dehydrothromboxane B2 in PETROWhich may? † thrombotic risk, or does warfarin have a cardioprotective effect that dabigatran does not have?
- 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 – RELEY-ABLE‡

- Patients who were randomized to receive dabigatran 150mg or 110mg BID in the RELEY study & who did not permanently discontinue their therapy were eligible for the RELEY-ABLE trial.
  - Permanent discontinuation of therapy was defined as an interruption in dabigatran therapy >8 weeks.
  - RELEY-ABLE patients continued to receive their originally assigned double-blind dabigatran dose from the RELEY study.
  - Median follow-up in RELEY-ABLE: 2.3 years. Median follow-up in RELEY: 2 years. The RELEY-ABLE data analysis only included events which occurred during RELEY-ABLE.
  - At baseline, the patients enrolled in RELEY-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 RELEY, (p<0.0001 for all).

<table>
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% / yr = per 100 patient years of follow-up. NS = non-significant.
† Includes re-analyzed RELEY data, except for dyspepsia & discontinuation rates in which the original RELEY 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 RELEY-ABLE hazard ratios were similar to what was shown in RELEY – 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 RELEY-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 editorialists 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 ~6% 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 ~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

- 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

- 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.
RxFiles TRIAL SUMMARY  ORIGINALLY PREPARED BY: Z.DUMONT, B.BUNKA, REVISED BY: L.KOSAR – UPDATED AUG 2013 – WWW.RXFILES.ca

- 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 in 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 15% (19%) & 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

- 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
- Canadian Family Physician RxFiles: Article Oral anticoagulation in atrial fibrillation http://www.cfp.ca/content/58/8/850.full

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ADDITIONAL REFERENCES:


RELY TRIAL SUMMARY

REFERENCES:


