Does Dabigatran PRADAX Increase the Risk of Myocardial Infarction?

BOTTOM LINE [1,2,3,5,6,7]

- It all depends. The data available has been analyzed in various ways resulting in conflicting conclusions.
- Factors that impact analysis include 1) combining or separating the two dabigatran doses studied, 2) combining silent myocardial infarction (MI) & clinical MI, and 3) excluding trials of ≤ 1 month duration.
- All analyses resulted in an MI risk that hovers just above or below the accepted threshold for statistical significance (e.g. $p < 0.05$). As a result, individuals may have more or less concern regarding the uncertainty & any potential MI risk.
- If there is an ↑ risk, data suggests the risk, in absolute terms, is small (NNH=250/2yrs) & not accompanied by an ↑ in mortality.
- Clinically, until additional data & post-marketing surveillance is available, antithrombotic therapy should balance the risk of stroke, MI & bleeding.

BACKGROUND

The original data from the RELY study suggested that dabigatran 150mg po bid ↑ the risk of MI in atrial fibrillation (AF) patients, p=0.048.[1] Subsequently, additional RELY data was found & the authors stated the risk of MI was no longer statistically significant.[2] In 2012, a meta-analysis assessed the risk of MI with dabigatran across different patient populations & concluded that dabigatran was associated with an ↑ MI risk.[3] As well, dabigatran has most often been compared to warfarin, & warfarin has established efficacy for secondary prevention of MI. This conflicting data has left health care providers wondering if the risk of MI truly does exist, or if dabigatran simply lacks the protective effect that warfarin provides.

SUMMARY OF THE LITERATURE & GUIDELINES

1) Original RELY (Randomized Evaluation of Long-term anticoagulation therapY) Data[1]

- ~2 year randomized open-label Phase III study comparing dabigatran 110mg po bid & 150mg po bid to warfarin INR 2-3 in AF patients.
- ~ 16% of the patient population had a history of MI & ~ 20% were on ASA at the end of the study.
- Risk of clinical MI (secondary endpoint):
  - Dabigatran 150mg po bid (n=89, 1.46%/2yrs) versus warfarin (n=63, 1.05%/2yrs) RR 1.38 (95% CI 1-1.91), p=0.048. ARI = ↑ 0.41%, NNH = 244/2 years. Note: the study also reported the data as %/year.
  - This endpoint was to include both clinical & silent MI, however all reported MIs were clinical see RELY Reanalysis below.
- Net Clinical Benefit (composite of stroke, systemic embolism, pulmonary embolism, MI, death or major bleeding): dabigatran 150mg po bid (n=832, 6.91%/yr) versus warfarin (n=901, 7.64%/yr) RR 0.91 (95% CI 0.82-1), p=0.04.
- Discontinuation rate due to serious adverse events: dabigatran either dose 2.7% versus warfarin 1.7%, p<0.001.
- **CONCLUSION pertaining to MI risk**: dabigatran 150mg po bid ↑ the risk of clinical MI compared to warfarin; however, the p-value was statistically significant but just below p=0.05 (i.e. p=0.048) & the study was underpowered to show a conclusive difference for this secondary endpoint.

2) RELY Reanalysis[2]

- RELY authors re-examined the original data → 4 additional clinical & 28 silent MI were identified see below Table.
- ~ ⅓ of clinical MI patients in each group had their MI after the study medication was discontinued (>6 days).
- Fatal MI within 30 days of drug discontinuation was not statistically significant.
- **CONCLUSION pertaining to MI risk:** when the newly identified clinical & silent MI was combined with the original data, dabigatran no longer had a statistically significant ↑ risk of MI compared to warfarin; however, the p-value was just above p=0.05 (i.e. p=0.06) & the study was underpowered to show a conclusive difference for this secondary endpoint.

TABLE 1: COMPARISON OF THE ORIGINAL RELY DATA & REANALYZED RELY DATA FOR MI SECONDARY ENDPOINT [1,2]

	Dabigatran 150mg po BID* n (%/yr)	Warfarin INR 2-3 n (%/yr)	Relative Risk or Hazard Ratio (95% CI)	p-value
Original RELY Data				
Clinical MI	89 (0.74)	63 (0.53)	RR 1.38 (1-1.91)	0.048
RELY Reanalysis Data				
Total MI	97 (0.81)	75 (0.64)	HR 1.27 (0.94-1.71)	0.12
Clinical MI	89 (0.74)	66 (0.56)	HR 1.32 (0.96-1.81)	0.09/0.06†
Silent MI	8 (0.07)	9 (0.08)	HR 0.87 (0.34-2.27)	0.72

*Dabigatran 110mg po BID versus warfarin: NS for all of the above secondary endpoints.
† p=0.06: when both doses of dabigatran were combined for clinical MI, the p-value was 0.06.

3) Dabigatran Association with Higher Risk of Acute Coronary Events: Meta-analysis of Non-Inferiority RCT [3]

- Included 7 studies, n=30,514.
  - 2 AF trials: PETRO, RELY (original & reanalyzed data), versus warfarin
  - Acute VTE treatment: RECOVER, versus warfarin
  - 3 VTE prophylaxis trials: RENOVATE, REMODEL, RENOVATE II, versus enoxaparin
  - Acute coronary syndrome (ACS): REDEEM, versus placebo
- Risk of MI, or ACS (confirmed unstable angina, MI & cardiac death) if MI was not reported as an adverse event:
  - Original RELY data: dabigatran n=237 of 20,000 (1.19%) versus control n=83 of 10,514 (0.79%) OR 1.33 (95% CI 1.03-1.71), p=0.03, NNH=250; I^2=0%, p≥0.3. Note: I^2 value assesses if effect is due to differences in the combined groups versus by chance; values <20% represents minimal variability in the groups (i.e. groups were more similar than different).[4]
  - RELY reanalysis data: dabigatran n=257 out of 19,743 (1.3%) versus control n=95 out of 10,419 (0.91%) OR 1.27 (95% CI 1-1.61), p=0.05, NNH=256.
- Mortality (secondary endpoint, 6 trials):
  - Dabigatran n=945 of 19,555 (4.83%) versus control n=524 of 10,444 (5.02%) OR 0.89 (95% CI 0.8-0.99), p=0.04
- Results were primarily driven by RELY (59% of the cohort, 74% of the events).
- Meta-analysis included two Phase II trials, & MI was not a primary endpoint in any of the included studies.
- **CONCLUSION:** Numerically, dabigatran had a greater number of MI across different patient populations & comparators; however, this agent also had a lower mortality rate.

4) RELY-ABLE Long-Term Multi-Centre Observational Study of Dabigatran Treatment in AF Patients [4]

- RELY-ABLE was a follow-up study of RELY patients randomized to dabigatran. The median follow-up was 2.3 years.
- The data analysis only included events which occurred during RELY-ABLE, i.e. did not combine event rates from RELY & RELY-ABLE & there was no published statistical analysis comparing RELY versus RELY-ABLE outcomes. The rates of MI from both studies were similar, see Table 2.
- See the RxFiles RELY Trial Summary for additional information http://www.rxfiles.ca/rxfiles/uploads/documents/RE-LY-Trial-Dabigatran.pdf

TABLE 2: COMPARISON OF THE RELY & RELY-ABLE MI DATA

Event	RELY Reanalysis (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) p-value	Dabigatran 150mg BID (n=2937)	Dabigatran 110mg BID (n=2914)	Hazard Ratio (95% CI) (p-values not reported)
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)

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

Canadian Cardiovascular Society Atrial Fibrillation Guidelines

- In the 2010 CCS Guidelines,[6] warfarin was preferred over dabigatran in patients with a high risk of coronary events based on the original RELY data.[1]
- The 2012 CCS Guideline Update[7] removed the above statement based on:
  - RELY reanalysis: ↑ risk of MI was no longer statistically significant, & net clinical benefit favoured dabigatran over warfarin.[2]
  - Meta-analysis: ↑ risk of MI, but ↓ risk of mortality.[3]
- **2012 Guideline Recommendation:** AF patients with a history of ACS, or who have undergone PCI, should receive antithrombotic therapy which balances their risk of stroke, ACS & bleeding with the use of combined antithrombotics. Patients at a higher risk of stroke may require ASA + clopidogrel + oral anticoagulant. (Conditional Recommendation, Low-Quality Evidence).[7]

IS AN ↑ RISK OF MYOCARDIAL INFARCTION WITH DABIGATRAN BIOLOGICALLY PLAUSIBLE?

- Potentially, however, the possible biological explanation is theoretical & has never been proven to cause MI.
- The **PETRO** (**P**revention of **E**mbolic & **T**hrombotic events in patients with pe**R**sistent atrial fibrillati**O**n) study was a 12 week open-label Phase II dose finding study comparing dabigatran ± ASA to warfarin in AF patients: [7]
  - All patients on dabigatran without ASA had a non-dose dependent ↑ in urinary thromboxane metabolite excretion. The authors acknowledged this may suggest a platelet-activating effect which could potentially ↑ thrombotic risk, but the risk would need to be confirmed in a clinical outcomes trials.
  - **CONCLUSION pertaining to MI risk**: dabigatran ↑ urinary thromboxane metabolite excretion; however, as a theoretical surrogate secondary endpoint, this is less important than the randomized controlled trial outcome data.
  - Note: A few of the authors from PETRO were part of the RELY study. In the RELY article, PETRO is referenced in the introduction but is not mentioned in the discussion section regarding the ↑ number of MI with dabigatran.

UNCERTANTIES

- Warfarin has been proven to protect against MI. Does dabigatran ↑ risk of MI relative to warfarin?
- Impact of dabigatran on the risk of MI in the real world population is unknown.

ACS=acute coronary syndrome **AF**=atrial fibrillation **ARI**=absolute risk increase **ASA**=acetylsalicylic acid **CI**=confidence interval **HR**=hazard ratio **MI**=myocardial infarction **NNH**=number needed to harm **NS**=non-statistically significant **OR**=odds ratio **PCI**=percutaneous coronary intervention **RCT**=randomized controlled trial(s) **RR**=relative risk **VTE**=venous thromboembolism **yr**=year

References available on-line www.Rxfiles.ca

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