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# Dabigatran Etexilate and Risk of Myocardial Infarction, Major Bleedings and All-Cause Mortality: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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## Background

In RE-LY, signal of an increased risk of myocardial infarction (MI) with the use of dabigatran etexilate 110mg *bid* and 150mg *bid* when compared to warfarin was pointed out.[1,2]

This risk of MI was assessed in a previous meta-analysis of 7 non-inferiority randomized controlled trials (RCTs) showing a significant 33% increase in MI.[3] Unfortunately, this analysis included the initial RE-LY publication and did not take into account the additional events subsequently reported in the latest RCTs. The question whether dabigatran etexilate causes MI, or it is less efficacious than warfarin for the prevention of such events remains unanswered. There is a need to have robust evidence on the potential increased risk of MI when dabigatran etexilate is compared to other anticoagulants or placebo.

## Objectives

- Our primary aim was to perform an up-to-date meta-analysis of RCTs comparing dabigatran etexilate with active comparators or placebo to assess the effect of this agent on MI risk as a primary objective.
- The outcome of major bleeding and all-cause mortality was also assessed to provide global safety and efficacy measure.
- Stratifications by comparators (enoxaparin, warfarin or placebo) were performed. Additional analyses with studies using the two licensed doses in European Union for AF (150mg bid and 110mg bid) were also provided.

## Methods

We conducted searches of the published literature and a clinical-trials registry maintained by the drug manufacturer till **18th of October, 2013**. Criteria for inclusion in our meta-analysis included all RCTs and the availability of outcome data for **MI**, **major bleedings** (MB) or **all-cause mortality**. We referred to the definitions provided by the different RCTs for the outcome adjudication. All methodologies were performed according to the **PRISMA** Statement. The odds ratio and **95% CI** were calculated with the use of the **Peto** method. The reported P values were two-sided. Statistical heterogeneity across the various trials was tested using Cochran's Q statistic and quantified using the I2 value. Funnel plots were constructed to assess publication bias. Data were analysed with the use of Comprehensive Meta-Analysis software, version 2.2.046.

## Results

**Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram of study selection.**

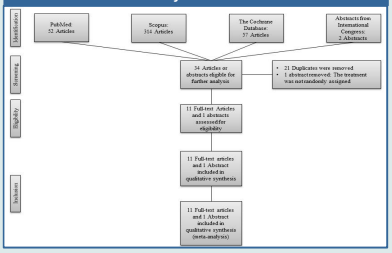
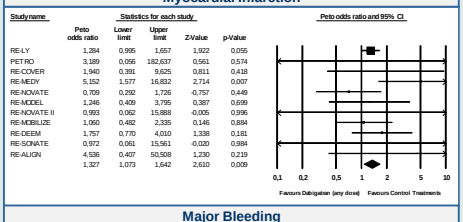
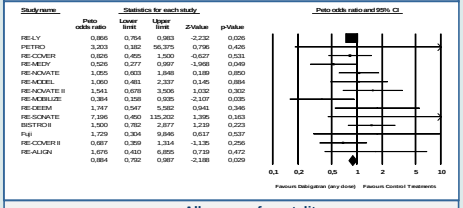



**Figure 2: Forest plot of the included studies for the risk of myocardial infarction, major bleedings and all-cause mortality (Fixed Effect Model analyses)**

**Myocardial Infarction**




**Major Bleeding**




**All-cause of mortality**

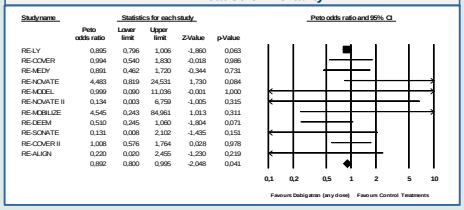



**Table 3: Risk of myocardial infarction, major bleeding and all-cause of death for the main analyses and stratification by dose and comparators**

| | Peto Odds Ratio (95% CI) | | | | Heterogeneity | |
|---|---|---|---|---|---|---|
| | Fixed-effect Model | p-value | Random Effect Model | p-value | $I^2$ statistics | Q test p-value |
| **Myocardial Infarction** | | | | | | |
| Any dose vs any control treatments | 1.327 (1.073 - 1.642) | 0.009 | 1.327 (1.073 - 1.642) | 0.009 | 0 | 0.507 |
| Any dose vs Enoxaparin | 0.958 (0.574 - 1.599) | 0.869 | 0.958 (0.574 - 1.599) | 0.869 | 0 | 0.869 |
| Any dose vs Warfarin | 1.399 (1.095 - 1.786) | 0.007 | 2.103 (1.026 - 4.314) | 0.042 | 36.741 | 0.176 |
| Any dose vs Placebo | 1.674 (0.759 - 3.693) | 0.202 | 1.674 (0.759 - 3.693) | 0.202 | 0 | 0.689 |
| 150mg bid vs any control treatments | 1.441 (1.092 - 1.901) | 0.010 | 1.794 (1.042 - 3.089) | 0.035 | 29.128 | 0.227 |
| 150mg bid vs Enoxaparin | NA | | NA | | NA | NA |
| 150mg bid vs Warfarin | 1.412 (1.060 - 1.882) | 0.018 | 2.070 (0.833 - 5.143) | 0.117 | 60.943 | 0.077 |
| 150mg bid vs Placebo | 1.885 (0.656 - 5.413) | 0.239 | 1.885 (0.656 - 5.413) | 0.239 | 0 | 0.613 |
| 110mg bid vs any control treatments | 1.326 (0.991 - 1.774) | 0.057 | 1.326 (0.991 - 1.774) | 0.057 | 0 | 0.760 |
| 110mg bid vs Enoxaparin | NA | | NA | | NA | NA |
| 110mg bid vs Warfarin | NA | | NA | | NA | NA |
| 110mg bid vs Placebo | NA | | NA | | NA | NA |
| **Major Bleeding** | | | | | | |
| Any dose vs any control treatments | 0.884 (0.792 - 0.987) | 0.029 | 0.927 (0.751 - 1.145) | 0.483 | 24.232 | 0.192 |
| Any dose vs Enoxaparin | 1.068 (0.777 - 1.468) | 0.685 | 1.044 (0.681 - 1.598) | 0.845 | 41.876 | 0.142 |
| Any dose vs Warfarin | 0.849 (0.754 - 0.956) | 0.007 | 0.849 (0.754 - 0.956) | 0.007 | 0 | 0.495 |
| Any dose vs Placebo | 2.031 (0.816 - 5.056) | 0.128 | 2.031 (0.816 - 5.056) | 0.128 | 0 | 0.639 |
| 150mg bid vs any control treatments | 0.923 (0.811 - 1.051) | 0.228 | 0.921 (0.668 - 1.269) | 0.615 | 42.907 | 0.105 |
| 150mg bid vs Enoxaparin | NA | | NA | | NA | NA |
| 150mg bid vs Warfarin | 0.895 (0.785 - 1.022) | 0.101 | 0.840 (0.674 - 1.047) | 0.122 | 19.506 | 0.292 |
| 150mg bid vs Placebo | 2.857 (0.711 - 11.473) | 0.139 | 2.857 (0.711 - 11.473) | 0.139 | 0 | 0.450 |
| 110mg bid vs any control treatments | 0.817 (0.707 - 0.946) | 0.007 | 1.355 (0.375 - 4.902) | 0.643 | 77.276 | 0.036 |
| 110mg bid vs Enoxaparin | NA | | NA | | NA | NA |
| 110mg bid vs Warfarin | NA | | NA | | NA | NA |
| 110mg bid vs Placebo | NA | | NA | | NA | NA |
| **All-Cause Death** | | | | | | |
| Any dose vs any control treatments | 0.892 (0.800 - 0.995) | 0.041 | 0.885 (0.719 - 1.090) | 0.252 | 11.026 | 0.339 |
| Any dose vs Enoxaparin | 2.238 (0.678 - 7.389) | 0.186 | 2.143 (0.598 - 7.672) | 0.242 | 8.532 | 0.350 |
| Any dose vs Warfarin | 0.900 (0.805 - 1.005) | 0.061 | 0.900 (0.805 - 1.005) | 0.061 | 0 | 0.813 |
| Any dose vs Placebo | 0.467 (0.230 - 0.947) | 0.035 | 0.467 (0.230 - 0.947) | 0.035 | 0 | 0.354 |
| 150mg bid vs any control treatments | 0.881 (0.779 - 0.997) | 0.045 | 0.881 (0.779 - 0.997) | 0.045 | 0 | 0.636 |
| 150mg bid vs Enoxaparin | NA | | NA | | NA | NA |
| 150mg bid vs Warfarin | 0.894 (0.789 - 1.013) | 0.078 | 0.894 (0.789 - 1.013) | 0.078 | 0 | 0.955 |
| 150mg bid vs Placebo | 0.475 (0.208 - 1.088) | 0.078 | 0.475 (0.208 - 1.088) | 0.078 | 0 | 0.341 |
| 110mg bid vs any control treatments | 0.896 (0.785 - 1.022) | 0.103 | 0.743 (0.403 - 1.371) | 0.343 | 57.176 | 0.126 |
| 110mg bid vs Enoxaparin | NA | | NA | | NA | NA |
| 110mg bid vs Warfarin | NA | | NA | | NA | NA |
| 110mg bid vs Placebo | NA | | NA | | NA | NA |

### Tips

**When the heterogeneity, assessed by the I2 statistic is above 50%, it is preferable to refer to the random effect model analysis**

### References

[1] 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 (randomized evaluation of long-term anticoagulation therapy) trial. *Circulation*. 2012;125:669-676

[2] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139-1151

[3] Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: Meta-analysis of noninferiority randomized controlled trials. *Arch Intern Med*. 2012;172:397-402

## Discussion

***Overall analyses***

Dabigatran etexilate significantly increased the risk of MI by 33% versus any controls (► **Figure 2 & Table 1**). There was a reduction in the risk of major bleeding and all-cause mortality compared to controls using the fixed effect model. Compared to warfarin, the increase in the risk of MI still remained and even grown up (40% and 110% for the fixed and random effect model, respectively) the reduction of major bleedings is statistically significant while the reduction in all-cause mortality is not whatever the use of a fixed or random effect model (►**Table 1**).

***Stratification by doses of dabigatran etexilate***

The overall increased risk of MI with the 150mg *bid* dose is significant (44% and 79% with the fixed and random effect model, respectively) but there was a 12% reduction of all-cause mortality. The reduction in major bleeding is non-statistically significant (►**Table 1**). Versus warfarin, there was no statistically significant results for the 150mg *bid* dose regimen, except for the risk of MI which was increased with the fixed effect model. However, we cannot rely on this result since the heterogeneity excess 50% using the $I^2$ statistic. For the 110mg *bid* dose regimen, there was no statistically significant results but the increase risk of MI is of borderline significancy (p = 0.0057).

However, in terms of absolute risk, such an increased risk of MI should be tempered when compared to the outcomes of stroke or systemic embolism, major bleeding and all-cause mortality. The results from the RE-LY trial showed that the benefits of DE over warfarin outweigh the increase risk of MI. The risk difference was greatly in favor of DE regarding the composite of stroke/systemic embolism, MI, major bleeding and all-cause mortality.

## Conclusions

**This meta-analysis of RCTs provides robust evidence that DE is associated with an overall significant 33% increase in the risk of MI. The risk was principally identified when warfarin is used as comparator (40% increase). In RCTs using the 150mg *bid* DE dose, a significant 44% overall increased risk of MI was identified. No definitive conclusion about the absence of the risk of MI with the 110mg *bid* DE dose can be drawn at that time. However, this increase risk has to be tempered with the overall benefit of DE especially in patients with NVAF. In conclusion, we suggest that health care professionals and regulators should consider additional risk minimization strategy to identifiy vulnerable population and prevent the risk in such patients.**

### Disclosure

The authors have no relevant conflicts of interest to disclose.

### Contact

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