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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

Jonathan Douxfils[1], Fanny Buckinx[2], François Mullier[1,3], Valentine Minet[1], Véronique Rabenda[2], Jean-Yves Reginster[2], Philippe Hainaut[4], Olivier Bruyère[2], Jean-Michel Dogné[1]

[1] Department of Pharmacy, Namur Thrombosis and Hemostasis Center (NTHC), Namur Research Institute for LIfe Sciences (NARILIS), University of Namur, B-5000, Belgium. [2] Department of Public Health, Epidemiology and Health Economics, University of Liege, B-4000, Belgium. [3] Hematology Laboratory, Namur Thrombosis and Hemostasis Center (NTHC), Namur Research Institute for Life Sciences (NARILIS), CHU UCL Mont-Godinne - Dinant, Belgium. [4] Department of General Internal Medicine, Cliniques Universitaires Saint Luc, UCL, Bruxelles, Belgium.

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.

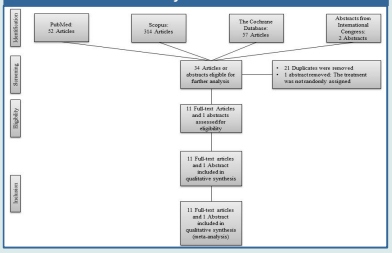
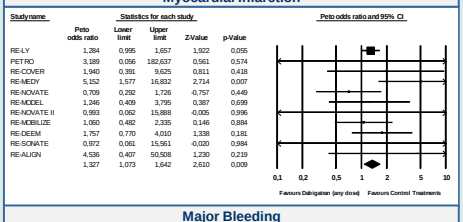
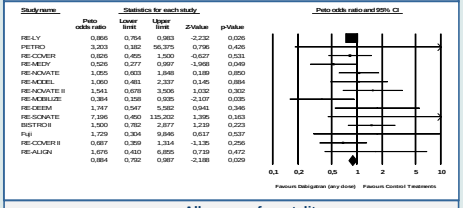


Figure 2: Forest plot of the included studies for the risk of myocardial infarction, major bleedings and all-cause mortality (Fixed Effect Model analyses)

Myocardial Infarction



Major Bleeding



All-cause of mortality

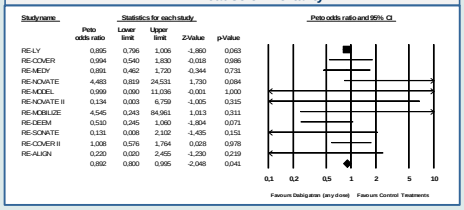


Table 3: Risk of myocardial infarction, major bleeding and all-cause of death for the main analyses and stratification by dose and comparators

	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

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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

J. Douxfils: jonathan.douxfils@unamur.be
J-M. Dogné: jean-Michel.dogne@unamur.be