Contents

0.1 Synthesis of the meta-analysis results

We found 6 trials concerning oral direct thrombin inhibitor.
Results obtained by the meta-analysis are reported in the following tables, with the endpoints categorized according their results. Three classes are considered: endpoints for wich a benefit effect was detected, endpoints revealing a harmful effect and the other for wich no statistically significant difference was obtained (no evidence).
Reports of 5 trials (including 31,954 patients) were identified .
Among these comparisons, one trial are about dabigatran 110mg,two about dabigatran 150mg and 3 about ximelagatran.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Dabigatran 110mg

Results obtained with dabigatran 110mg for all the endpoints with data in at least one trial are summarized table **??**.

Table 1: *Results summary - Dabigatran 110mg*

Benefit	**Harmful**	**No evidence**
Dabigatran 110mg versus warfarin standard dose		
↓ lifethreatening major bleeding RR=0.68¶ [0.56;0.84] k=1 ↓ major bleeding RR=0.81† [0.70;0.94] k=1 ↓ haemmorhagic stroke RR=0.31¶ [0.17;0.57] k=1		→ systemic thrombo-embolic complication RR=0.79NS [0.36;1.73] k=1 → thrombo-embolic event (cerebral or systemic) RR=0.92NS [0.75;1.12] k=1 → cardiovascular death RR=0.91NS [0.78;1.07] k=1 → TE event or ischemic stroke or systemic embolism RR=0.92NS [0.75;1.12] k=1 → stroke (fatal and non fatal) RR=0.93NS [0.75;1.14] k=1 → ischemic stroke RR=1.12NS [0.90;1.40] k=1 → non-lifethreatening major bleeding RR=0.95NS [0.79;1.15] k=1 → gastrointestinal major bleeding RR=1.11NS [0.87;1.42] k=1 → all cause death RR=0.92NS [0.81;1.04] k=1 → fatal stroke RR=0.95NS [0.74;1.23] k=1 → non fatal stroke RR=0.87NS [0.62;1.23] k=1

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

Dabigatran 150mg

Results obtained with dabigatran 150mg for all the endpoints with data in at least one trial are summarized table **??**.

Table 2: *Results summary - Dabigatran 150mg*

Benefit	**Harmful**	**No evidence**
Dabigatran 150mg versus warfarin standard dose		

continued...

Benefit	Harmful	No evidence
↓ thrombo-embolic event (cerebral or systemic) RR=0.67¶ [0.54;0.83] k=1 ↓ stroke (fatal and non fatal) RR=0.65¶ [0.52;0.82] k=1 ↓ ischemic stroke RR=0.77* [0.61;0.99] k=1 ↓ lifethreatening major bleeding RR=0.82* [0.67;1.00] k=1 ↓ fatal stroke RR=0.67† [0.51;0.89] k=1 ↓ non fatal stroke RR=0.63* [0.43;0.92] k=1 ↓ haemmorhagic stroke RR=0.26¶ [0.14;0.50] k=1 ↓ fatal bleeding RR=0.82* [0.67;1.00] k=1	↑ gastrointestinal major bleeding RR=1.50¶ [1.20;1.89] k=1	→ systemic thrombo-embolic complication RR=0.85NS [0.39;1.84] k=1 → cardiovascular death RR=0.86NS [0.73;1.00] k=1 → non-lifethreatening major bleeding RR=1.08NS [0.90;1.30] k=1 → all cause death RR=0.89NS [0.79;1.01] k=1 → major bleeding RR=0.94NS [0.82;1.07] k=1

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

Ximelagatran

Results obtained with ximelagatran for all the endpoints with data in at least one trial are summarized table **??**.

Table 3: *Results summary - Ximelagatran*

Benefit	Harmful	No evidence
Ximelagatran versus warfarin standard dose		
↓ major bleeding RR=0.73* [0.56;0.95] k=3	↑ hypertransaminasemia RR=7.81¶ [4.58;13.32] k=1	→ systemic thrombo-embolic complication RR=2.46NS [0.70;8.63] k=3 → thrombo-embolic event (cerebral or systemic) RR=0.99NS [0.52;1.89] H k=2 → cardiovascular death RR=1.21NS [0.77;1.91] k=1 → TE event or ischemic stroke or systemic embolism RR=0.93NS [0.53;1.66] k=2 → stroke (fatal and non fatal) RR=0.90NS [0.54;1.52] k=3 → ischemic stroke RR=0.93NS [0.58;1.50] k=3 → all cause death RR=0.96NS [0.79;1.16] k=3 → fatal stroke RR=1.56NS [0.65;3.72] k=3 → haemmorhagic stroke RR=0.54NS [0.20;1.42] k=3

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

1 Introduction

1.1 Aim of the report

This report review all the randomized clinical trials of direct antithrombins - oral direct thrombin inhibitor for the treatment of atrial fibrillation in all type of patients.

1.2 Search strategy

The search aimed to identify all randomized clinical trials relating to the clinical effectiveness of direct antithrombins - oral direct thrombin inhibitor for the treatment of atrial fibrillation in all type of patients.

1.2.1 Sources searched

The following electronic databases were searched for relevant published literature for the period up to 2012 - 8 - 8:

- MEDLINE,
- EMBASE,
- Cochrane Database of Systematic Reviews (CDSR),
- Cochrane Central Register of Controlled Trials (CCTR),
- Health Technology Assessment (HTA) database,
- ISI Web of Science âĂŞ Proceedings (Index to Scientific and Technical Proceedings),
- ISI Web of Science âĂŞ Science Citation Index Expanded,

Each database was searched as far back as possible, with no language restrictions.
Search strategies of relevant clinical keywords were developed through reference to published strategies, and by iterative searching, whereby keywords identified in references retrieved by initial scoping searches were used to extend the search strategy and so increase the sensitivity of retrieval.
In addition, the reference lists of relevant articles were handsearched.
Attempts to identify further studies were made by consulting health technology assessment and guideline producing agencies, and research and trials registers via the Internet.
Titles and, when available, abstracts of all studies identified in the searches were assessed by a single researcher for relevance to the review. In cases of doubt, the full article was obtained.

1.2.2 Search restrictions

No language, study/publication or date restrictions were applied to the main searches.

1.3 Inclusion criteria

Participants only those studies were included in which the participants had been diagnosed as having established atrial fibrillation.

Interventions studies in which direct antithrombins - oral direct thrombin inhibitor was used. Studies using other interventions in addition to direct antithrombins - oral direct thrombin inhibitor therapy were included only if the treatment received by the intervention and control groups was identical in all respects other than the use of direct antithrombins - oral direct thrombin inhibitor.

Methodology randomised controlled trials (RCTs). Trials were accepted as RCTs if the allocation of subjects to treatment groups was described by the authors as either randomised or double-blind.

1.4 Exclusion criteria

Studies considered methodologically unsound. The list of excluded studies with reason of their exclusion are given in a separate section for each treatment categories considered.

1.5 Meta-analysis strategy

Studies that met the reviewâĂŹs entry criteria were eligible for inclusion in the meta-analyses provided that they reported outcomes in terms of the number of subjects suffering clinical outcomes, as only this would allow calculation of the relative risk of subjects in the intervention group developing each outcome, compared with subjects in the control group.

Studies that only presented results in the form of relative risks, relative hazards or odds ratios, without the underlying numbers were also include in the meta-analyses.

Binary outcomes were analysed using the fixed-effect model. For continuous outcomes, weighted mean differences (WMDs) were analysed, using a fixed-effect model.

Heterogeneity was tested by the chi-2 test and the I2 statistic was obtained to describe the proportion of the variability.

Where quantitative heterogeneity was indicated, analysis using a random-effects model was conducted for comparison with results of fixed effect-based analysis. Results of the meta-analysis should be considered as being based on fixed-effect model unless stated otherwise.

Meta-analyses were conducted for data on ischemic stroke, systemic thrombo-embolic complication, thrombo-embolic event (cerebral or systemic), TE event or ischemic stroke or systemic embolism, Haemmorhagic stroke, Major bleeding, Minor bleeding, Bleeding, myocardial infarction (fatal and non fatal), Lifethreatening major bleeding, Non-lifethreatening major bleeding, Adverse events, intracranial hemorrhage, Gastrointestinal major bleeding, Fatal bleeding, hypertransaminasemia, Fatal stroke, All cause death, stroke (fatal and non fatal), Cardiovascular death, Non fatal stroke, .

1.6 Structure of the report

Each of the eligible studies is summarised in part **??**. A summary of the studies together with an evaluation of their quality is given in part **??** to **??**, listed by therapeutic class. The therapeutic classes included oral direct thrombin inhibitor,

In these sections, studies in which an active intervention was compared with placebo or no treatment are discussed first, by intervention, followed by a discussion of those studies in which two or more active interventions were compared.

2 Overview of oral direct thrombin inhibitor

2.1 Included trials

A total of 6 randomized comparisons which enrolled 31954 patients were identified. In all, 1 randomized comparison concerned dabigatran 110mg , two dabigatran 150mg and 3 ximelagatran. The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for dabigatran 110mg, in section **??** (page **??**) for dabigatran 150mg and in section **??** (page **??**) for ximelagatran.

The average study size was 5325 patients (range 236 to 12098). The first study was published in 2002, and the last study was published in 2009.
A total of 2 trials were double blind and 4 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

2.2 Summary of meta-analysis results

The meta-analysis of the available trials about oral direct thrombin inhibitor provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

2.2.1 Dabigatran 110mg

No significant difference was found between **dabigatran 110mg** and **warfarin standard dose** in terms of systemic thrombo-embolic complication (RR=0.79, 95% CI 0.36 to 1.73, p=0.5510, 1 trial), thrombo-embolic event (cerebral or systemic) (RR=0.92, 95% CI 0.75 to 1.12, p=0.3825, 1 trial), TE event or ischemic stroke or systemic embolism (RR=0.92, 95% CI 0.75 to 1.12, p=0.3825, 1 trial)and ischemic stroke (RR=1.12, 95% CI 0.90 to 1.40, p=0.3164, 1 trial). There is a statistically significant difference in favour of dabigatran 110mg for lifethreatening major bleeding (RR=0.68, 95% CI 0.56 to 0.84, p=0.0000, 1 trial), major bleeding (RR=0.81, 95% CI 0.70 to 0.94, p=0.0042, 1 trial)and haemmorhagic stroke (RR=0.31, 95% CI 0.17 to 0.57, p=0.0000, 1 trial).

2.2.2 Dabigatran 150mg

Dabigatran 150mg was superior to **warfarin standard dose** in terms of thrombo-embolic event (cerebral or systemic) (RR=0.67, 95% CI 0.54 to 0.83, p=0.0000, 1 trial)and ischemic stroke (RR=0.77, 95% CI 0.61 to 0.99, p=0.0418, 1 trial). However, no significant difference was found on systemic thrombo-embolic complication (RR=0.85, 95% CI 0.39 to 1.84, p=0.6782, 1 trial). Dabigatran 150mg appear to be associated with significantly greater risk of gastrointestinal major bleeding (RR=1.50, 95% CI 1.20 to 1.89, p=0.0000, 1 trial).
There is a statistically significant difference in favour of dabigatran 150mg for lifethreatening major bleeding (RR=0.82, 95% CI 0.67 to 1.00, p=0.0458, 1 trial), haemmorhagic stroke (RR=0.26, 95% CI 0.14 to 0.50, p=0.0000, 1 trial)and fatal bleeding (RR=0.82, 95% CI 0.67 to 1.00, p=0.0458, 1 trial).

2.2.3 Ximelagatran

No significant difference was found between **ximelagatran** and **warfarin standard dose** in terms of systemic thrombo-embolic complication (RR=2.46, 95% CI 0.70 to 8.63, p=0.1585, 3 trials), thrombo-embolic event (cerebral or systemic) (RR=0.99, 95% CI 0.52 to 1.89, p=0.9745, 2 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0257)(RR=0.93, 95% CI 0.53 to 1.66, p=0.8190, 2 trials)and ischemic stroke (RR=0.93, 95% CI 0.58 to 1.50, p=0.7698, 3 trials). Ximelagatran appear to be associated with significantly greater risk of hypertransaminasemia (RR=7.81, 95% CI 4.58 to 13.32, p=0.0000, 1 trial).
There is a statistically significant difference in favour of ximelagatran for major bleeding (RR=0.73, 95% CI 0.56 to 0.95, p=0.0197, 3 trials).

Table 2.1: *Main study characteristics - oral direct thrombin inhibitor*

Trial	Patients	Treatments	Trial design and method
Dabigatran 110mg			
Dabigatran 110mg versus warfarin standard dose			
RE-LY (110mg), 2009 [?, ?] n = 6015 vs. 6022	patients With Non-Valvular Atrial Fibrillation	dabigatran 110 mg twice a day **versus** warfarin adjusted dose to a 2-3 INR	open (blind assessment) parallel groups Primary endpoint: stroke or systemic embolism 951 centres, 44 countries
Dabigatran 150mg			
Dabigatran 150mg versus warfarin standard dose			
RE-LY (150mg), 2009 [?, ?] n = 6076 vs. 6022	patients With Non-Valvular Atrial Fibrillation	dabigatran 150 mg twice a day **versus** warfarin adjusted-dose to a 2.0 to 3.0 INR	open (blind assessment) parallel groups Primary endpoint: stroke or systemic embolism 951 centres, 44 countries
PETRO (150mg), 2007 [?] n = 166 vs. 70	patientswith AF at high risk for thromboembolic events	dabigatran 150 mg twice daily (alone or combined with 81- or 325-mg aspirin) **versus** warfarin administered to achieve an international normalized ratio of 2 to 3 for	double blind factorial plan Primary endpoint: bleedings 53 centres, Denmark, The netehrlands, Sweden, US
Ximelagatran			
Ximelagatran versus warfarin standard dose			
SPORTIF III, 2003 [?] n = 1704 vs. 1703	one or more stroke risk factor in addition to AF.High risk patients with non valvular atrial fibrillation.	ximelagatran 36 mg twice daily **versus** warfarin standard dose (target INR 2-3)	open parallel groups Primary endpoint: all stroke or systemic embolism 259 centres, europe,asia,australasia
SPORTIF V, 2005 [?, ?] n = 1960 vs. 1962	one or more stroke risk factor in addition to atrial fibrillation.High risk patients with non valvular atrial fibrillation.	ximelegatran 36 mg twice daily **versus** warfarin standard dose(target INR 2-3)	double blind parallel groups Primary endpoint: all stroke and systemic embolism 409 centres, north america

continued...

Trial	Patients	Treatments	Trial design and method
SPORTIF II (ximelagatran vs warfarin standard dose), 2002 [?] n = 187 vs. 67	medium to high risk patients with chronic non valvular atrial fibrillation.	ximelegatran 20,40,60 mg twice daily **versus** warfarin standard dose(target INR 2-3)	open parallel groups Primary endpoint: thrombo-embolic events and bleedings 37 centres, Europe ,USA

Table 2.2: *Summary of all results for dabigatran 110mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
dabigatran 110mg versus warfarin standard dose						
systemic thrombo-embolic complication	RR=0.79	0.36;1.73	0.5510	1.0000 (0.00)	1	12037
thrombo-embolic event (cerebral or systemic)	RR=0.92	0.75;1.12	0.3825	1.0000 (0.00)	1	12037
cardiovascular death	RR=0.91	0.78;1.07	0.2493	1.0000 (0.00)	1	12037
TE event or ischemic stroke or systemic embolism	RR=0.92	0.75;1.12	0.3825	1.0000 (0.00)	1	12037
stroke (fatal and non fatal)	RR=0.93	0.75;1.14	0.4582	1.0000 (0.00)	1	12037
ischemic stroke	RR=1.12	0.90;1.40	0.3164	1.0000 (0.00)	1	12037
lifethreatening major bleeding	RR=0.68	0.56;0.84	0.0000	1.0000 (0.00)	1	12037
non-lifethreatening major bleeding	RR=0.95	0.79;1.15	0.6221	1.0000 (0.00)	1	12037
gastrointestinal major bleeding	RR=1.11	0.87;1.42	0.4037	1.0000 (0.00)	1	12037
all cause death	RR=0.92	0.81;1.04	0.1681	1.0000 (1.00)	1	12037
fatal stroke	RR=0.95	0.74;1.23	0.6962	1.0000 (0.00)	1	12037
non fatal stroke	RR=0.87	0.62;1.23	0.4299	1.0000 (0.00)	1	12037
major bleeding	RR=0.81	0.70;0.94	0.0042	1.0000 (0.00)	1	12037
haemmorhagic stroke	RR=0.31	0.17;0.57	0.0000	1.0000 (0.00)	1	12037

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 2.3: *Summary of all results for dabigatran 150mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
dabigatran 150mg versus warfarin standard dose						
systemic thrombo-embolic complication	RR=0.85	0.39;1.84	0.6782	1.0000 (0.00)	1	12098
thrombo-embolic event (cerebral or systemic)	RR=0.67	0.54;0.83	0.0000	1.0000 (0.00)	1	12098
cardiovascular death	RR=0.86	0.73;1.00	0.0545	1.0000 (0.00)	1	12098
stroke (fatal and non fatal)	RR=0.65	0.52;0.82	0.0000	1.0000 (0.00)	1	12098
ischemic stroke	RR=0.77	0.61;0.99	0.0418	1.0000 (0.00)	1	12098
lifethreatening major bleeding	RR=0.82	0.67;1.00	0.0458	1.0000 (1.00)	1	12098
non-lifethreatening major bleeding	RR=1.08	0.90;1.30	0.4324	1.0000 (0.00)	1	12098
gastrointestinal major bleeding	RR=1.50	1.20;1.89	0.0000	1.0000 (0.00)	1	12098
all cause death	RR=0.89	0.79;1.01	0.0693	1.0000 (0.00)	1	12098
fatal stroke	RR=0.67	0.51;0.89	0.0057	1.0000 (0.00)	1	12098
non fatal stroke	RR=0.63	0.43;0.92	0.0169	1.0000 (0.00)	1	12098
major bleeding	RR=0.94	0.82;1.07	0.3440	1.0000 (1.00)	1	12098
haemmorhagic stroke	RR=0.26	0.14;0.50	0.0000	1.0000 (0.00)	1	12098
fatal bleeding	RR=0.82	0.67;1.00	0.0458	1.0000 (1.00)	1	12098

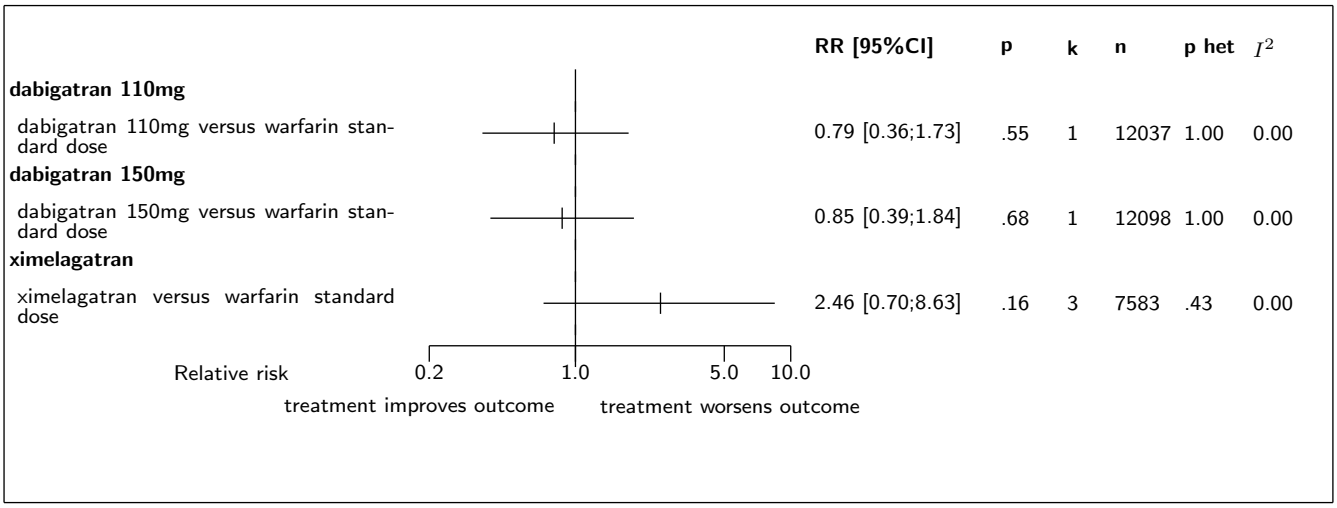
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 2.4: *Summary of all results for ximelagatran*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
ximelagatran versus warfarin standard dose						
systemic thrombo-embolic complication	RR=2.46	0.70;8.63	0.1585	0.4331 (0.00)	3	7583
thrombo-embolic event (cerebral or systemic)	RR=0.99 [1]	0.52;1.89	0.9745	0.0257 (0.80) †	2	7329
cardiovascular death	RR=1.21	0.77;1.91	0.4098	1.0000 (0.00)	1	3407
TE event or ischemic stroke or systemic embolism	RR=0.93	0.53;1.66	0.8190	0.0642 (0.71)	2	7329
stroke (fatal and non fatal)	RR=0.90	0.54;1.52	0.6979	0.1221 (0.52)	3	7583
ischemic stroke	RR=0.93	0.58;1.50	0.7698	0.1781 (0.42)	3	7583
all cause death	RR=0.96	0.79;1.16	0.6734	0.9619 (0.00)	3	7583
fatal stroke	RR=1.56	0.65;3.72	0.3193	0.2976 (0.17)	3	7583
hypertransaminasemia	RR=7.81	4.58;13.32	0.0000	1.0000 (0.00)	1	3922
major bleeding	RR=0.73	0.56;0.95	0.0197	0.7013 (0.00)	3	7583
haemmorhagic stroke	RR=0.54	0.20;1.42	0.2109	0.7674 (0.00)	3	7583

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

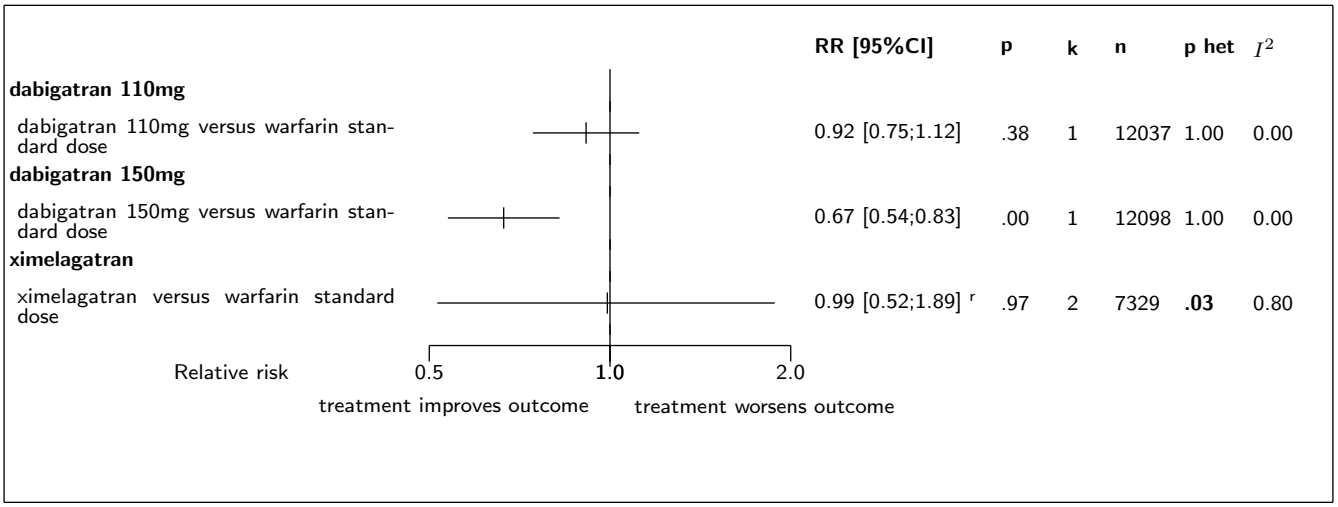
Figure 2.1: *Forest's plot for systemic thrombo-embolic complication*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

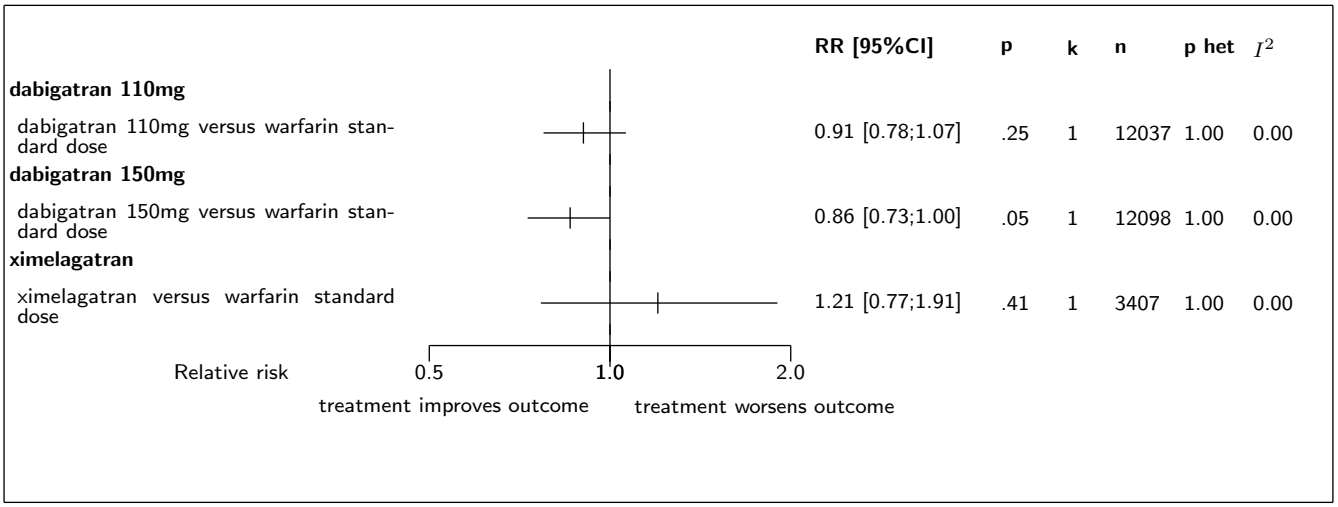
[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.98 95% CI 0.73;1.31

Figure 2.2: *Forest's plot for thrombo-embolic event (cerebral or systemic)*



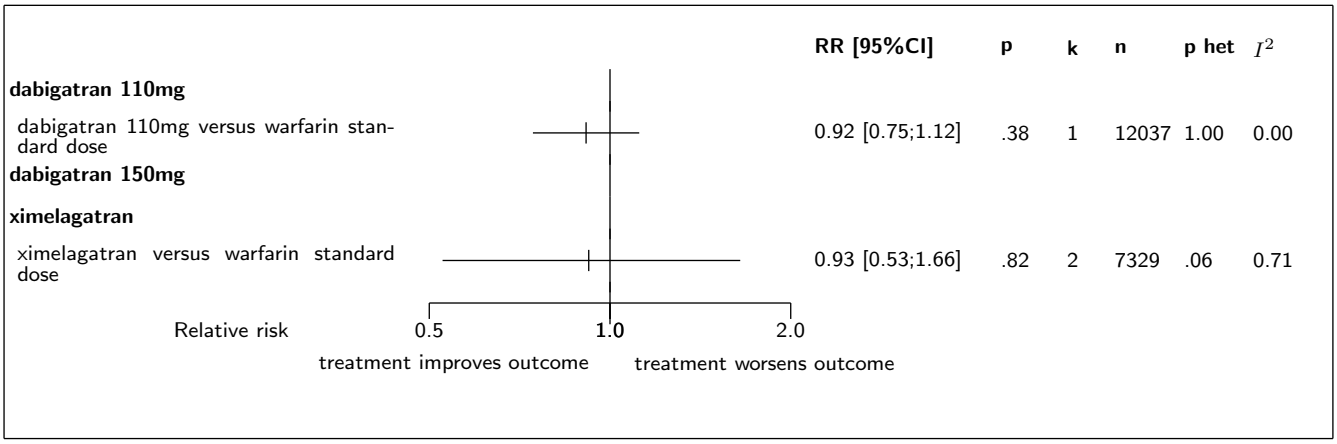
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 2.3: *Forest's plot for cardiovascular death*



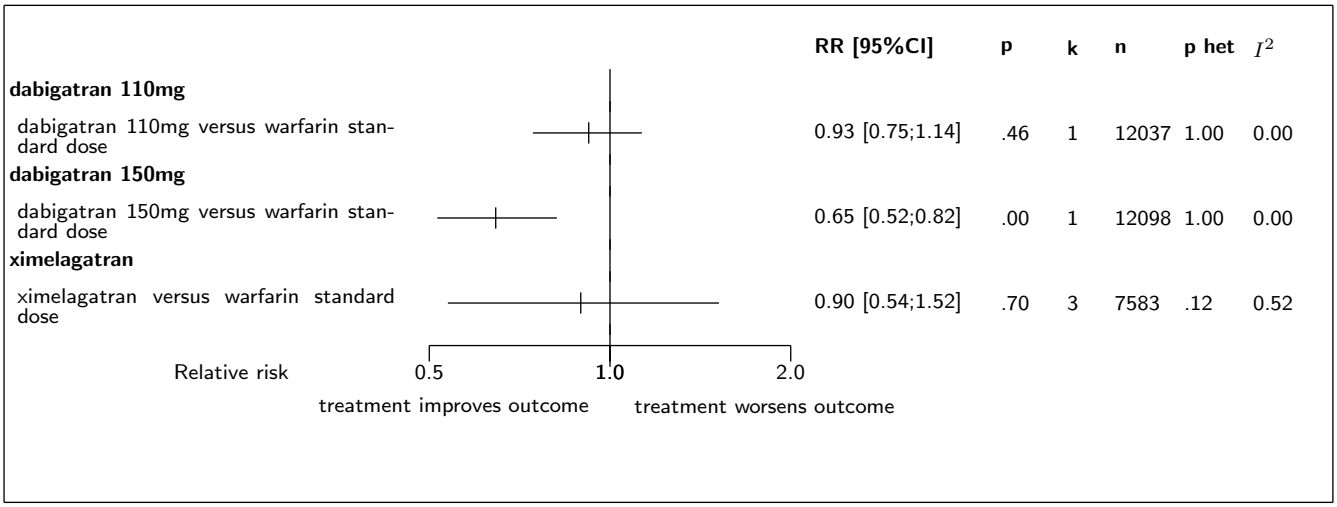
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 2.4: *Forest's plot for TE event or ischemic stroke or systemic embolism*



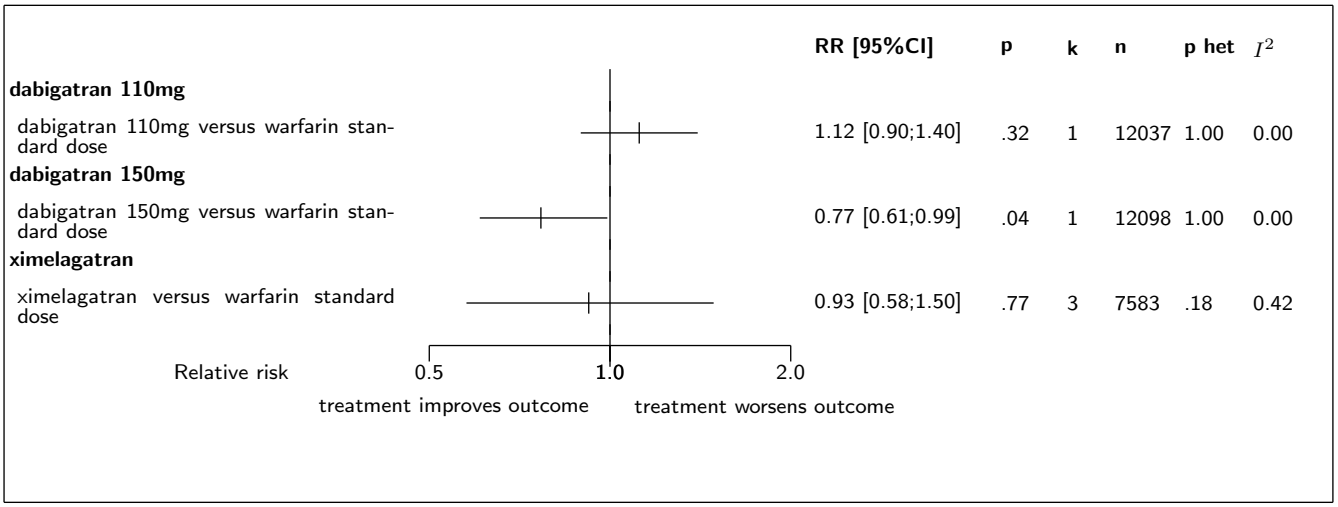
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 2.5: *Forest's plot for stroke (fatal and non fatal)*



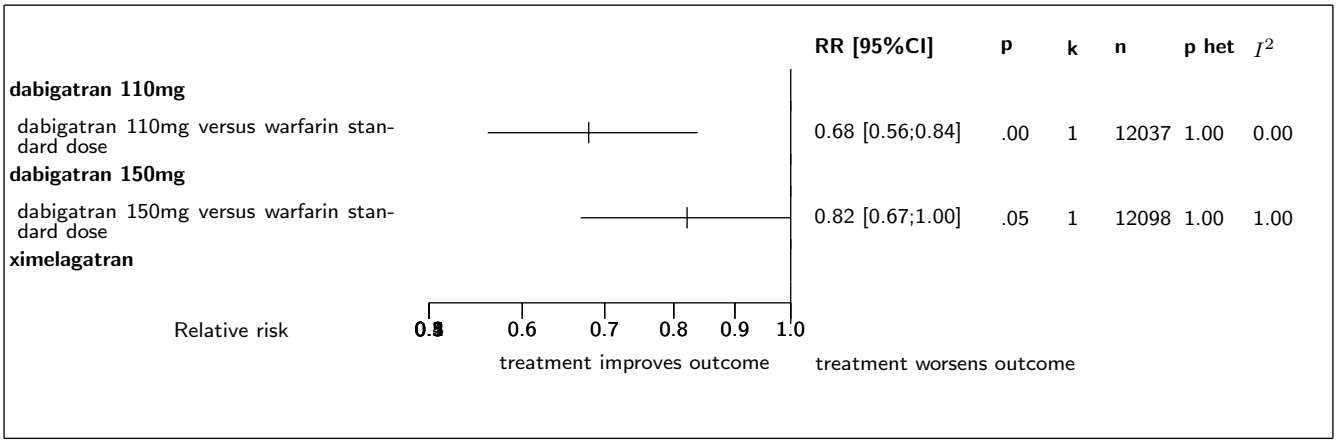
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 2.6: *Forest's plot for ischemic stroke*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.7: *Forest's plot for lifethreatening major bleeding*

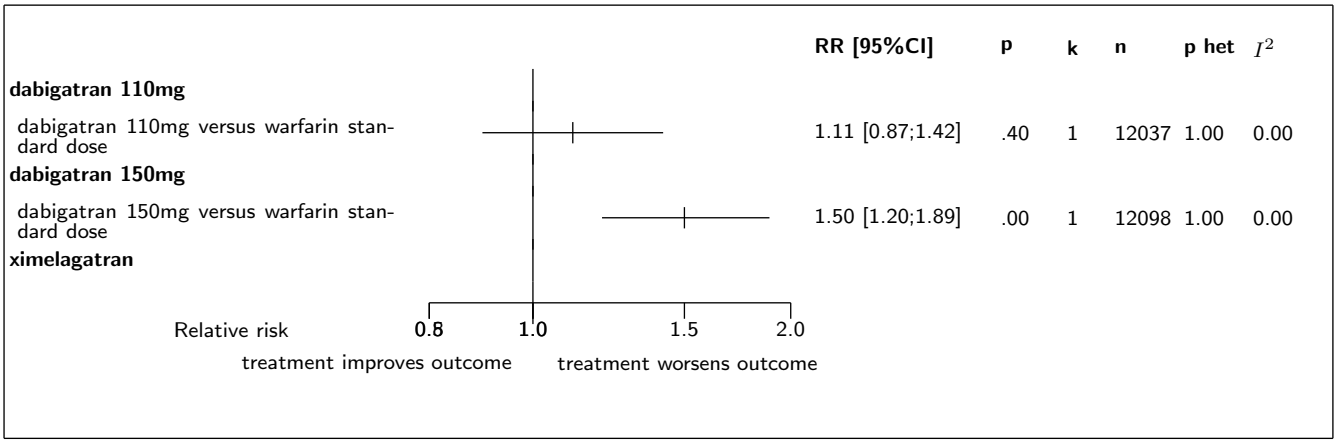


Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.8: *Forest's plot for non-lifethreatening major bleeding*

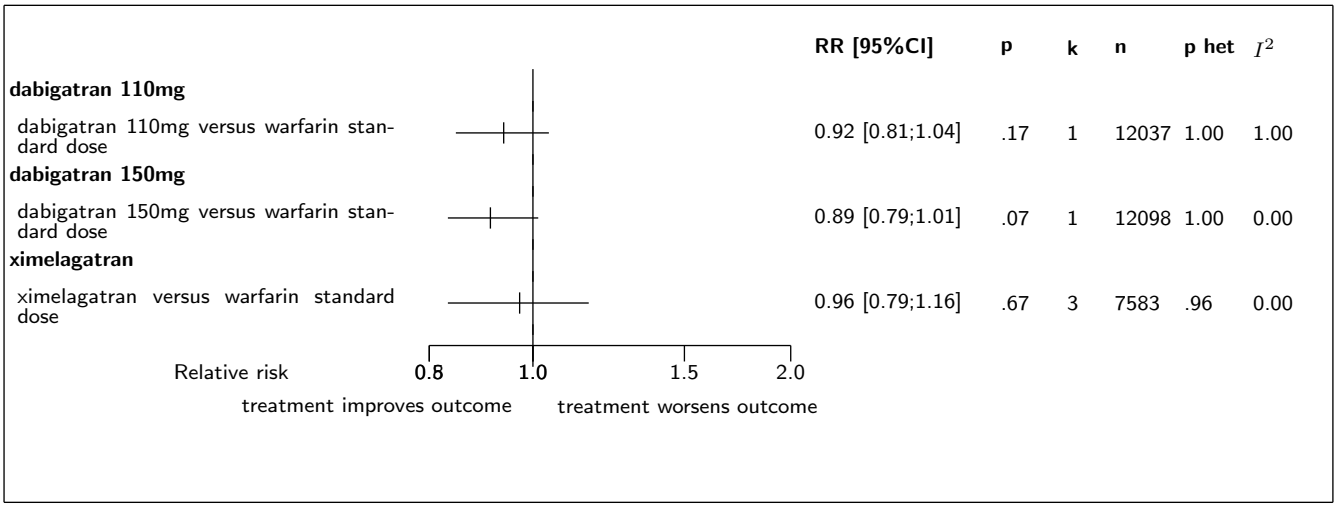
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.9: *Forest's plot for gastrointestinal major bleeding*



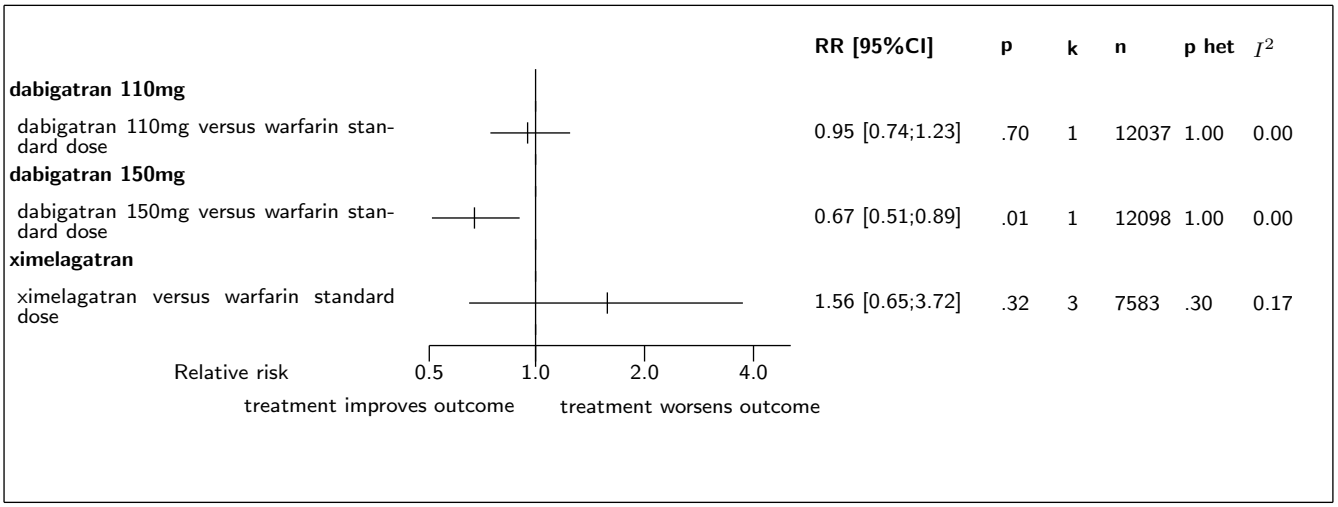
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.10: *Forest's plot for all cause death*



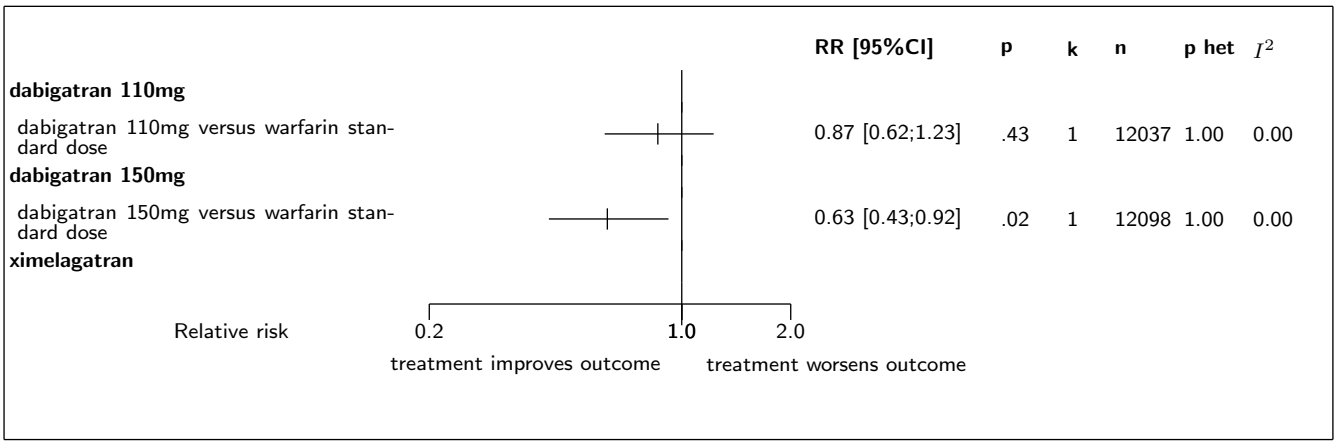
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.11: *Forest's plot for fatal stroke*



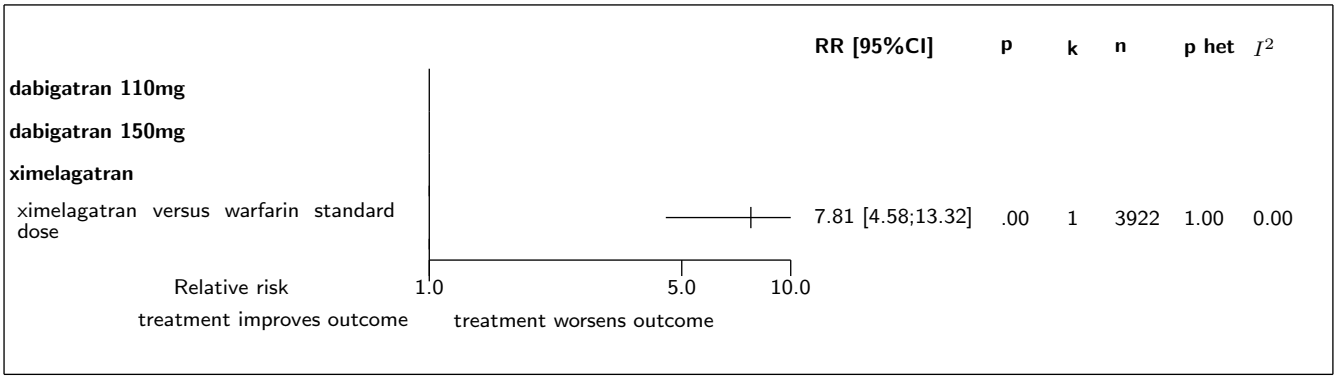
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.12: *Forest's plot for non fatal stroke*



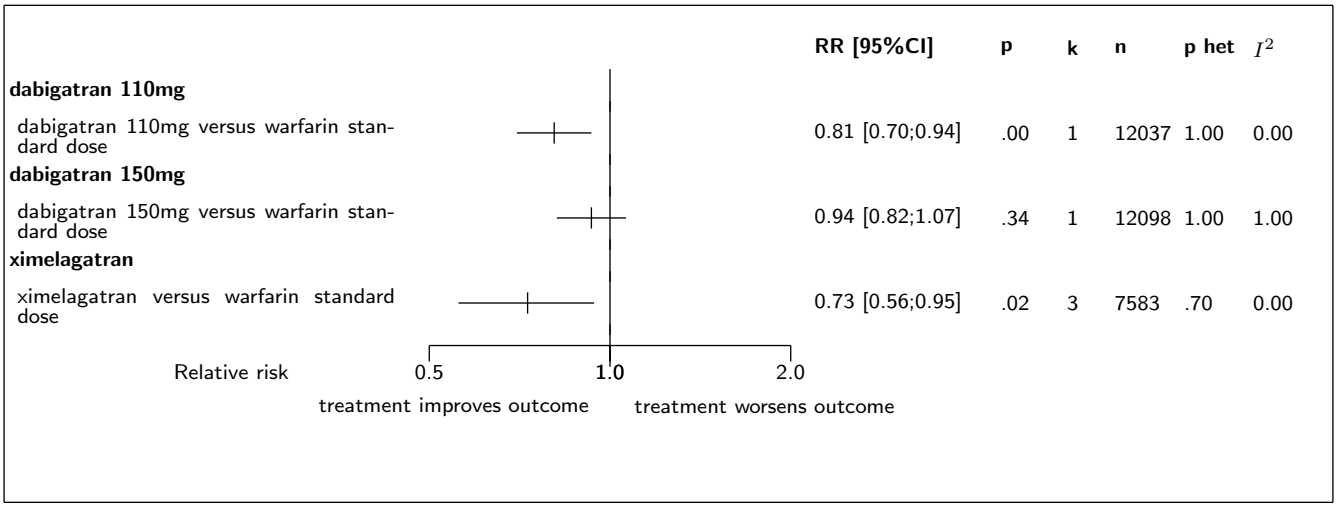
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.13: *Forest's plot for hypertransaminasemia*



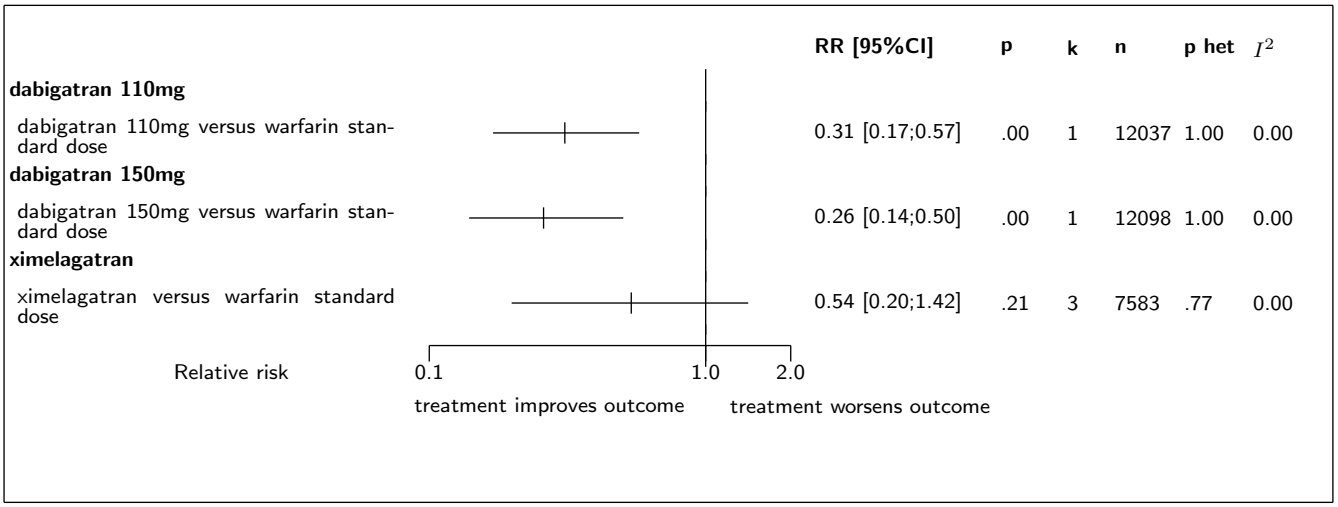
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.14: *Forest's plot for major bleeding*



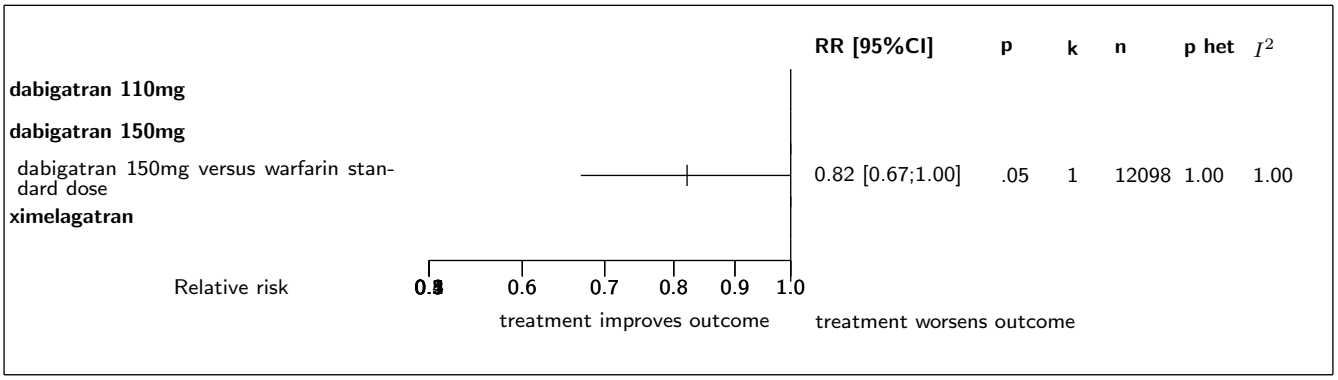
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.15: *Forest's plot for haemmorhagic stroke*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.16: *Forest's plot for fatal bleeding*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

3 Detailed results for dabigatran 110mg

3.1 Available trials

Only one trial which randomized 12037 patients was identified: it compared dabigatran 110mg with warfarin standard dose.
This trial included 12037 patients and was published in 2009.
This trial was open-label in design.
It was reported in English language.
TE event or ischemic stroke or systemic embolism data was reported in 1 trials; 1 trials reported data on thrombo-embolic event (cerebral or systemic); 1 trials reported data on ischemic stroke; 1 trials reported data on systemic thrombo-embolic complication; 1 trials reported data on non-lifethreatening major bleeding; 1 trials reported data on major bleeding; 1 trials reported data on myocardial infarction (fatal and non fatal); 1 trials reported data on gastrointestinal major bleeding; 1 trials reported data on lifethreatening major bleeding; 1 trials reported data on minor bleeding; 1 trials reported data on bleeding; 1 trials reported data on haemmorhagic stroke; 1 trials reported data on intracranial hemorrhage; 1 trials reported data on cardiovascular death; 1 trials reported data on non fatal stroke; 1 trials reported data on all cause death; 1 trials reported data on stroke (fatal and non fatal); and 1 trials reported data on fatal stroke.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trial including in this systematic review of randomized trials of dabigatran 110mg.

Table 3.1: *Treatment description - oral direct thrombin inhibitor - dabigatran 110mg*

Trial	Studied treatment	Control treatment
Dabigatran 110mg versus warfarin standard dose		
RE-LY (110mg) (2009) [**?**, **?**] [a]	dabigatran 110 mg twice a day	warfarin adjusted dose to a 2-3 INR

a) 3 arms: dabigatran 110 mg, 150mg and warfarin

Table 3.2: *Descriptions of participants - oral direct thrombin inhibitor - dabigatran 110mg*

Trial	Patients	
Dabigatran 110mg versus warfarin standard dose		
RE-LY (110mg) (2009) [**?**, **?**]	Patients With Non-Valvular Atrial Fibrillation **Inclusion criteria:** patients with non-valvular atrial fibrillation (AF), at moderate to high risk of stroke, or systemic embolism with at least one additional risk factor (i.e. pre vious ischemic stroke, TIA, or systemic embolism, left ventricular dysfunction, age >=75 years, age >=65 with either diabetes mellitus, history of coronary artery disease or hy pertension)	**Exclusion criteria:**
Dabigatran 150mg versus warfarin standard dose		

continued...

Trial	Patients	
RE-LY (150mg) (2009) [?, ?]	Patients With Non-Valvular Atrial Fibrillation	
	Inclusion criteria: patients with non-valvular atrial fibrillation (AF), at moderate to high risk of stroke, or systemic embolism with at least one additional risk factor (i.e. pre vious ischemic stroke, TIA, or systemic embolism, left ventricular dysfunction, age >=75 years, age >=65 with either diabetes mellitus, history of coronary artery disease or hy pertension)	**Exclusion criteria:**
PETRO (150mg) (2007) [?]	Patientswith AF at high risk for thromboembolic events	
Ximelagatran versus warfarin standard dose		
SPORTIF III (2003) [?]	One or more stroke risk factor in addition to AF.High risk patients with non valvular atrial fibrillation.	
	Inclusion criteria: age >18,Persistent or paroxysmal AF verified by at least 2 ECG,One or more stroke risk factors in addition to AF(hypertension,age >75,previous stroke TIA or systemic embolism,left ventricular dysfunction,age >65+coronary artery disease,age >65+diabete mellitus)	**Exclusion criteria:** mitral stenosis,Transient AF caused by reversible disorder,Stroke within the previous 30 days or TIA within 3 days,Condition associated with increased risk of bleeding,Active infective endocarditis,Current atrial myxoma or left ventricular thrombus,Admission for acute coronary syndrome or percutaeous coronary intervention within 30 days,Requirement for chronic anticoagulation treatment for disorders other than AF,planned cardioversion,Planned major surgery,treatment with platelet inhibitor drugs other than aspirin 100mg/day or less within 10 days or fibrinolytic agents within 30 days before randomisation,Regular use of NSAI drugs,Renal insuffiency,Active liver disease or persistent elevationof liver enzymes,Childbearing potential,pregnancy or lactation,Drug addiction alcohol abuse or both,Anaemia or thrombopenia

continued...

Trial	Patients	
SPORTIF V (2005) [?, ?]	One or more stroke risk factor in addition to atrial fibrillation.High risk patients with non valvular atrial fibrillation.	
	Inclusion criteria: age >18,Persistent or paroxysmal AF verified by at least 2 ECG,One or more stroke risk factors in addition to AF(hypertension,age >75,previous stroke TIA or systemic embolism,left ventricular dysfunction,age >65+coronary artery disease,age >65+diabete mellitus)	**Exclusion criteria:** mitral stenosis,Transient AF caused by reversible disorder,Stroke within the previous 30 days or TIA within 3 days,Condition associated with increased risk of bleeding,Active infective endocarditis,Current atrial myxoma or left ventricular thrombus,Admission for acute coronary syndrome or percutaeous coronary intervention within 30 days,Requirement for chronic anticoagulation treatment for disorders other than AF,planned cardioversion,Planned major surgery,treatment with platelet inhibitor drugs other than aspirin 100mg/day or less within 10 days or fibrinolytic agents within 30 days before randomisation,Regular use of NSAI drugs,Renal insuffiency,Active liver disease or persistent elevationof liver enzymes,Childbearing potential,pregnancy or lactation,Drug addiction alcohol abuse or both,Anaemia or thrombopenia
SPORTIF II (ximelagatran vs warfarin standard dose) (2002) [?] [c]	Medium to high risk patients with chronic non valvular atrial fibrillation.	
	Inclusion criteria: -one or more stroke risk factor in addition to AF:history of hypertension,age >65,previous stroke or TIA,previous systemic embolism,left ventricular dysfunction,diabete mellitus,coronary heart disease-age >18-paroxysmal or persistent NVAF verified by at least 2 ECG	**Exclusion criteria:** stroke and /or systemic embolism within the previous 2 years,Condition associated with increased risk of bleeding,NVAF secondary to other reversible disorders,presence of mecanical heart valves,Myocardial infarction,coronary artery bypass grafting or Percutaneous transluminal coronary angioplasty within previous 3 month,Diagnosis of left ventricular aneurysm or atrial myxoma,Treatment with NSAIDs or fibrinolytics within previous week,Renal impairment,Blood pressure >180/100,History of rheumatic fever,Liver insufficiency,Hb <100g/l,Plat <100000,Contra-indication to warfarin treatment

Table 3.3: *Design and methodological quality of trials - oral direct thrombin inhibitor - dabigatran 110mg*

Trial	Design	Duration	Centre	Primary endpoint
Dabigatran 110mg versus warfarin standard dose				
RE-LY (110mg), 2009 [?, ?] n=12037	Parallel groups open (blind assessment) confirmatory trial at risk of bias	2 y (median) inclusion period: dec 2005 - dec 2007	44 countries 951 centres	stroke or systemic embolism
Dabigatran 150mg versus warfarin standard dose				

continued...

Trial	Design	Duration	Centre	Primary endpoint
RE-LY (150mg), 2009 [?, ?] n=12098	Parallel groups open (blind assessment) confirmatory trial at risk of bias	2 y (median) inclusion period: dec 2005 - dec 2007	44 countries 951 centres	stroke or systemic embolism
PETRO (150mg), 2007 [?] n=236	Factorial plan double blind exploratory trial	12 weeks	Denmark, The netehrlands, Sweden, US 53 centres	bleedings
Ximelagatran versus warfarin standard dose				
SPORTIF III, 2003 [?] [(a)] n=3407	Parallel groups Open confirmatory trial at risk of bias	17.4 months inclusion period: aug 2000-sept 2001	europe,asia,australasia 259 centres	All stroke or systemic embolism
SPORTIF V, 2005 [?, ?] n=3922	Parallel groups Double blind confirmatory trial at low risk of bias	20 months inclusion period: july 2000-dec 2001	north america 409 centres	All stroke and systemic embolism
SPORTIF II (ximelagatran vs warfarin standard dose), 2002 [?] [(c)] n=254	Parallel groups Open confirmatory trial at risk of bias	16 weeks	Europe ,USA 37 centres	Thromboembolic events and bleedings

Table 3.4: *Trial characteristics - oral direct thrombin inhibitor - dabigatran 110mg*

Trial	subgroup test	CHADS2 Score (mean)	CHADS2 Score = 2 (%)	CHADS2 Score = 3 (%)
Dabigatran 110mg versus warfarin standard dose				
RE-LY (110mg), 2009 [?, ?]	a			

3.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Dabigatran 110mg versus warfarin standard dose

The single study eligible for this comparison provided data on **systemic thrombo-embolic complication**. There was no statistically significant difference in systemic thrombo-embolic complication between dabigatran 110mg and warfarin standard dose, with a RR of 0.79 (95%CI 0.36 to 1.73, p=0.5510) in favour of dabigatran 110mg. In other words, systemic thrombo-embolic complication was slightly lower in the dabigatran 110mg group , but this was not statistically significant.
The single study eligible for this comparison provided data on **thrombo-embolic event (cerebral or systemic)**. No statistically significant difference between the groups was found in thrombo-embolic event (cerebral or systemic), with a RR of 0.92 (95% CI 0.75 to 1.12, p=0.3825).
The single study eligible for this comparison provided data on **TE event or ischemic stroke or systemic embolism**. No statistically significant difference between the groups was found in TE event or ischemic stroke or systemic embolism, with a RR of 0.92 (95% CI 0.75 to 1.12, p=0.3825).
The single study eligible for this comparison provided data on **ischemic stroke**. No statistically significant difference between the groups was found in ischemic stroke, with a RR of 1.12 (95% CI 0.90 to 1.40, p=0.3164).

Table 3.5: *Results details - oral direct thrombin inhibitor - dabigatran 110mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
dabigatran 110mg versus warfarin standard dose						
systemic thrombo-embolic complication	RR=0.79	[0.36;1.73]	0.5510	1.0000 (I^2=0.00)	1	12037
thrombo-embolic event (cerebral or systemic)	RR=0.92	[0.75;1.12]	0.3825	1.0000 (I^2=0.00)	1	12037
cardiovascular death	RR=0.91	[0.78;1.07]	0.2493	1.0000 (I^2=0.00)	1	12037
TE event or ischemic stroke or systemic embolism	RR=0.92	[0.75;1.12]	0.3825	1.0000 (I^2=0.00)	1	12037
stroke (fatal and non fatal)	RR=0.93	[0.75;1.14]	0.4582	1.0000 (I^2=0.00)	1	12037
ischemic stroke	RR=1.12	[0.90;1.40]	0.3164	1.0000 (I^2=0.00)	1	12037
lifethreatening major bleeding	RR=0.68	[0.56;0.84]	0.0000	1.0000 (I^2=0.00)	1	12037
non-lifethreatening major bleeding	RR=0.95	[0.79;1.15]	0.6221	1.0000 (I^2=0.00)	1	12037
gastrointestinal major bleeding	RR=1.11	[0.87;1.42]	0.4037	1.0000 (I^2=0.00)	1	12037
all cause death	RR=0.92	[0.81;1.04]	0.1681	1.0000 (I^2=1.00)	1	12037
fatal stroke	RR=0.95	[0.74;1.23]	0.6962	1.0000 (I^2=0.00)	1	12037
non fatal stroke	RR=0.87	[0.62;1.23]	0.4299	1.0000 (I^2=0.00)	1	12037
major bleeding	RR=0.81	[0.70;0.94]	0.0042	1.0000 (I^2=0.00)	1	12037
haemmorhagic stroke	RR=0.31	[0.17;0.57]	0.0000	1.0000 (I^2=0.00)	1	12037

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 3.1: *Forest's plot for systemic thrombo-embolic complication*

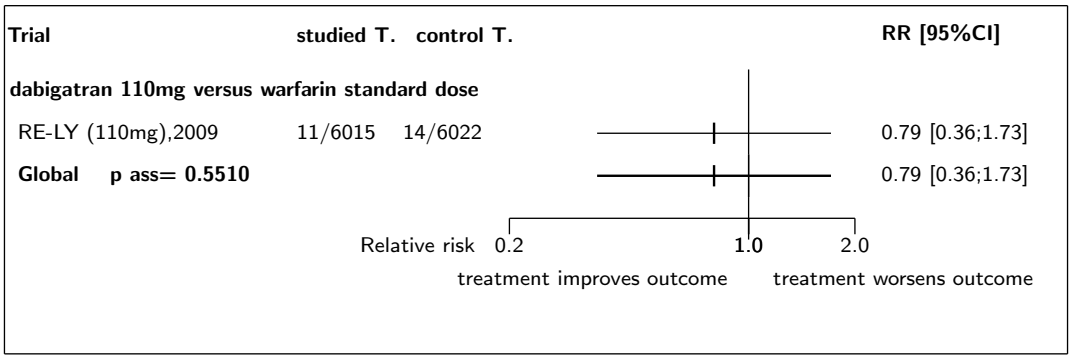


Figure 3.2: *Forest's plot for thrombo-embolic event (cerebral or systemic)*

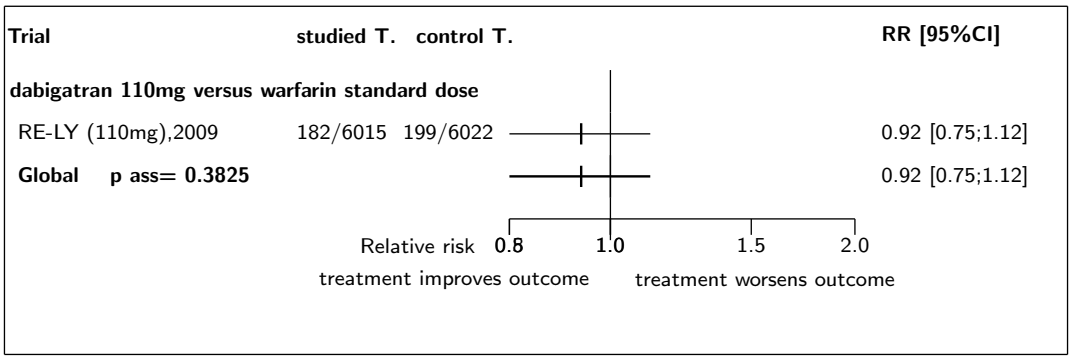


Figure 3.3: *Forest's plot for cardiovascular death*

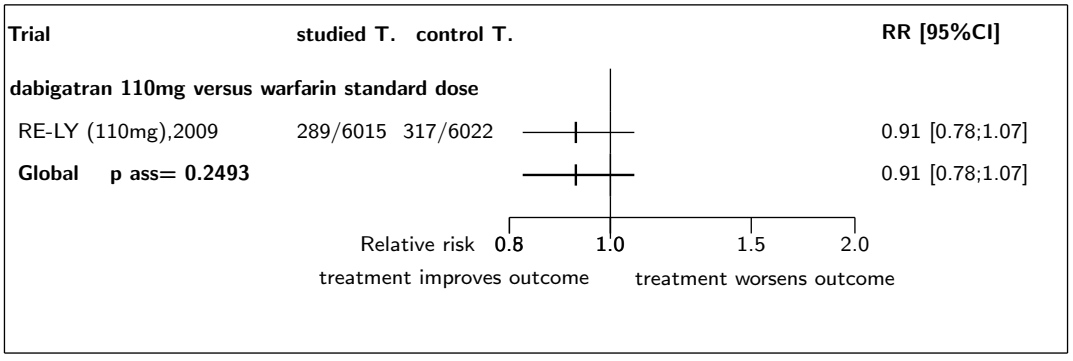


Figure 3.4: *Forest's plot for TE event or ischemic stroke or systemic embolism*

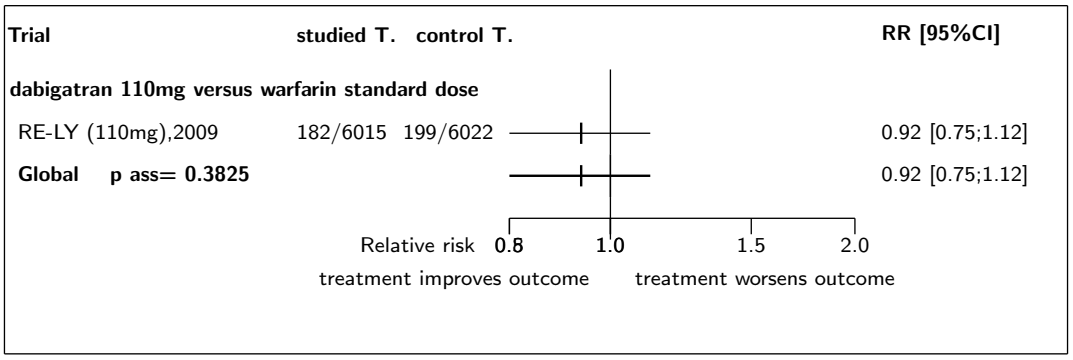


Figure 3.5: *Forest's plot for stroke (fatal and non fatal)*

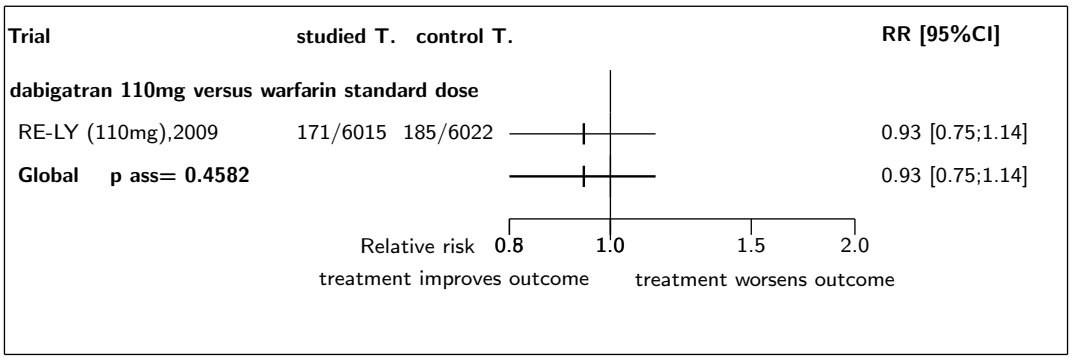


Figure 3.6: *Forest's plot for ischemic stroke*

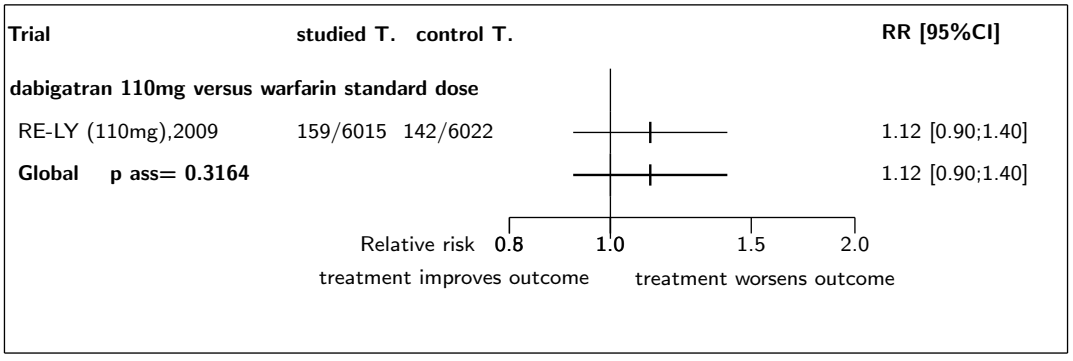


Figure 3.7: *Forest's plot for lifethreatening major bleeding*

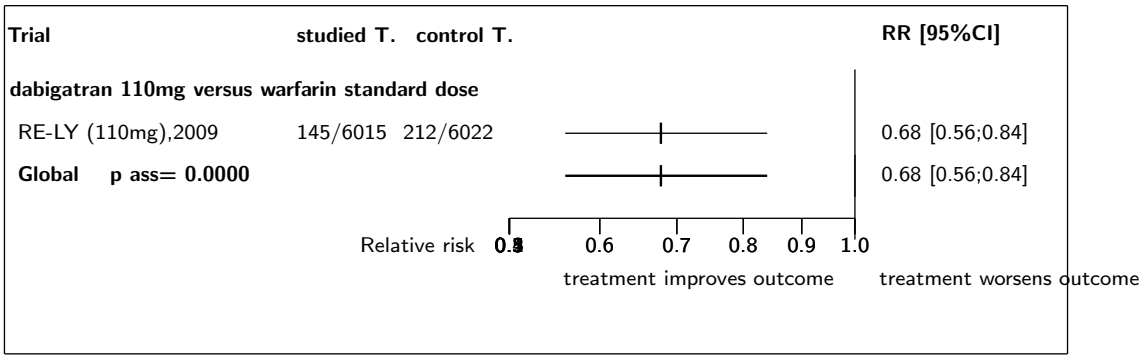


Figure 3.8: *Forest's plot for non-lifethreatening major bleeding*

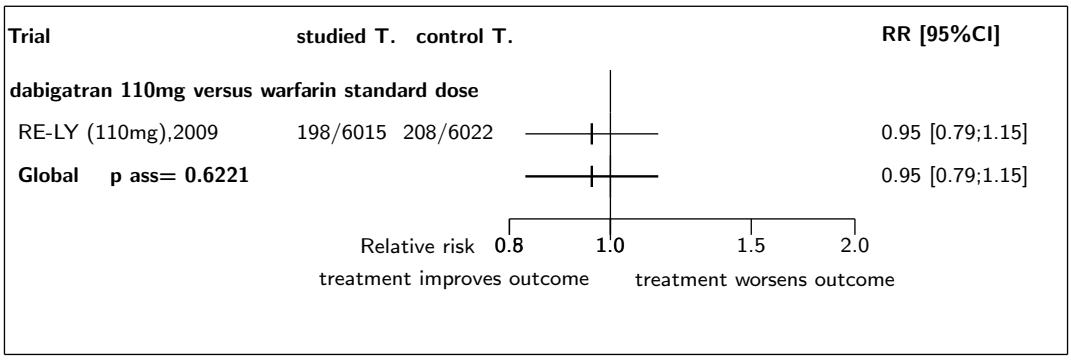


Figure 3.9: *Forest's plot for gastrointestinal major bleeding*

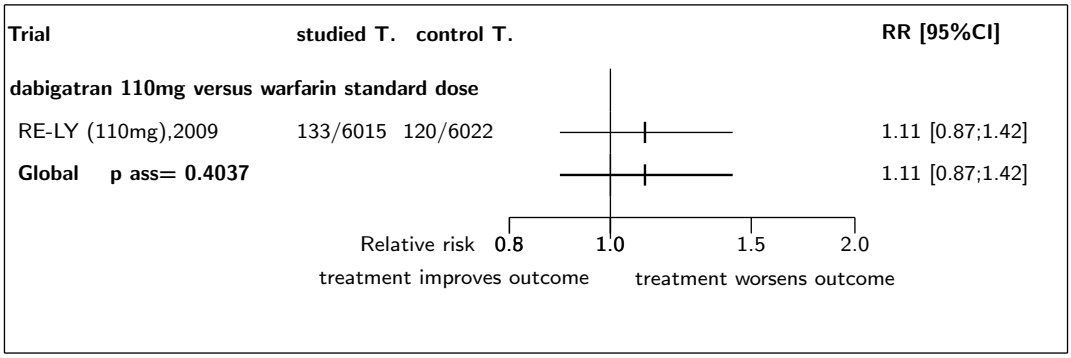


Figure 3.10: *Forest's plot for all cause death*

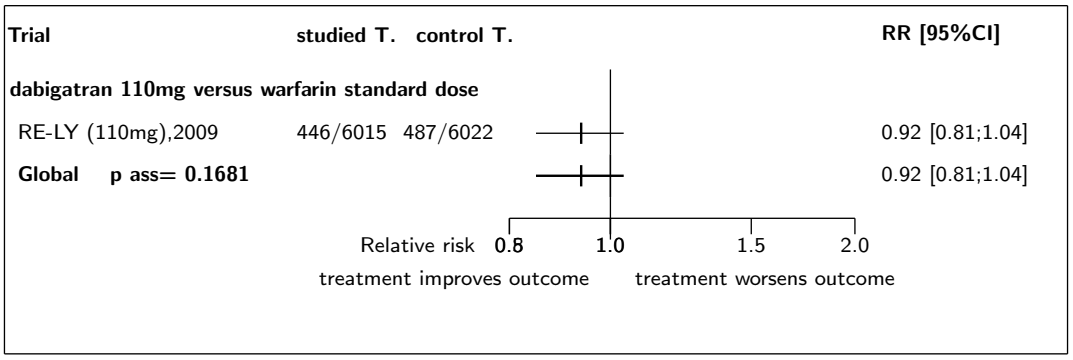


Figure 3.11: *Forest's plot for fatal stroke*

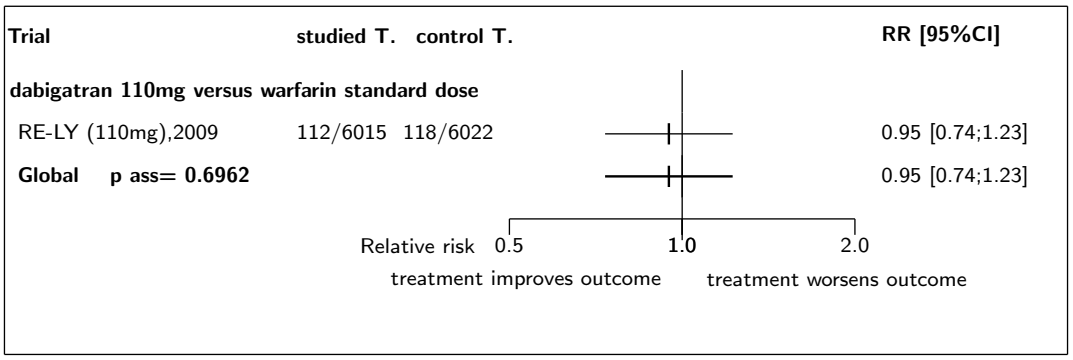


Figure 3.12: *Forest's plot for non fatal stroke*

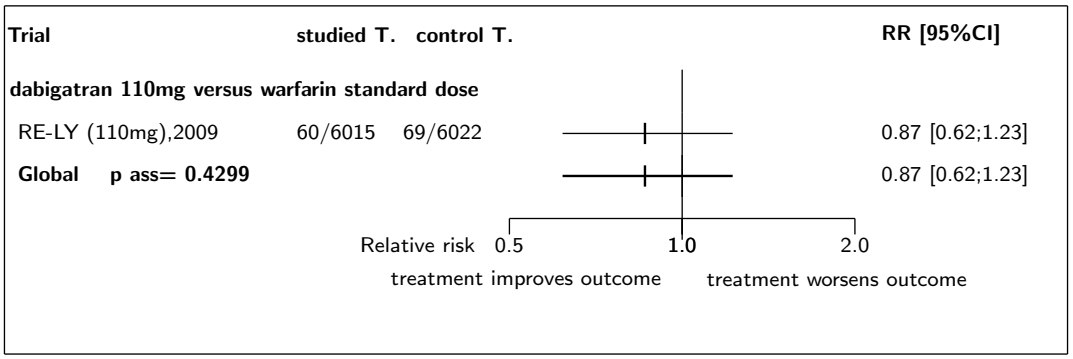


Figure 3.13: *Forest's plot for major bleeding*

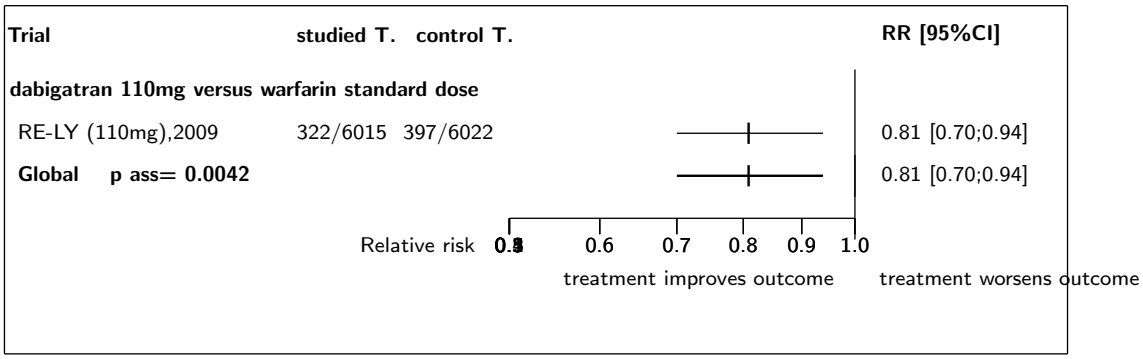
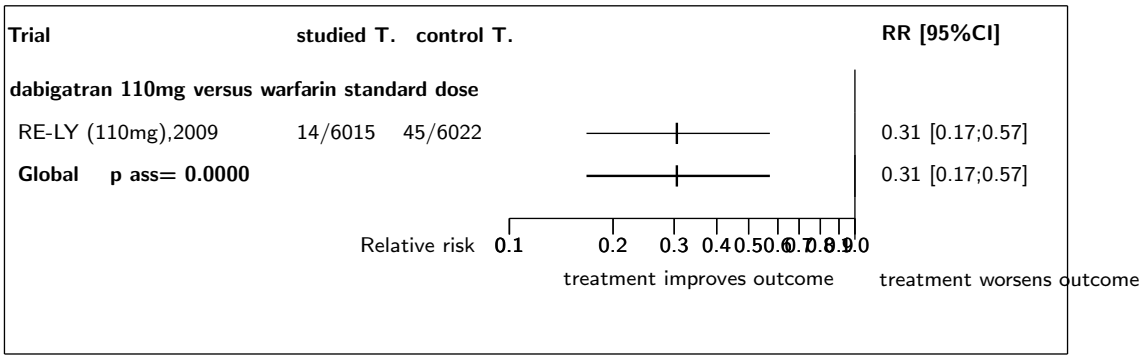


Figure 3.14: *Forest's plot for haemmorhagic stroke*



References

[1] Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, Oldgren J, Themeles E, Wallentin L, Yusuf S. . Am Heart J 2009;157:805-10, 810.e1-2. [PMID=19376304]

[2] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2009 Aug 30;:. [PMID=19717844]

3.3 Individual trial summaries

Table 3.6: *RE-LY (110mg), 2009 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=12037 (6015 vs. 6022) **Follow-up duration:** 2 y (median) **Study design:** Randomized controlled trial Parallel groups Open (blind assessment) Confirmatory trial at risk of bias 44 countries, 951 centres **Inclusion period:** dec 2005 - dec 2007	Patients With Non-Valvular Atrial Fibrillation **Inclusion criteria:** Patients with non-valvular atrial fibrillation (AF), at moderate to high risk of stroke, or systemic embolism with at least one additional risk factor (i.e. pre vious ischemic stroke, TIA, or systemic embolism, left ventricular dysfunction, age >=75 years, age >=65 with either diabetes mellitus, history of coronary artery disease or hy pertension)	**Studied treatment:** dabigatran 110 mg twice a day **Control treatment:** warfarin adjusted dose to a 2-3 INR **note:** 3 arms: dabigatran 110 mg, 150mg and warfarin	Systemic thrombo-embolic complication RR=0.79 [0.36;1.73] (imputed) Thrombo-embolic event (cerebral or systemic) RR=0.92 [0.75;1.12] (Stroke or systemic embolism) Cardiovascular death RR=0.91 [0.78;1.07] (Death from vascular causes) TE event or ischemic stroke or systemic embolism RR=0.92 [0.75;1.12] (Stroke or systemic embolism) Stroke (fatal and non fatal) RR=0.93 [0.75;1.14] (Stroke) Ischemic stroke RR=1.12 [0.90;1.40] (Ischemic or unspecified stroke) Lifethreatening major bleeding RR=0.68 [0.56;0.84] (Life threatening Major bleeding) Non-lifethreatening major bleeding RR=0.95 [0.79;1.15] (Nonlife threatening Major bleeding) Gastrointestinal major bleeding RR=1.11 [0.87;1.42] (Gastrointestinal Major bleeding) All cause death RR=0.92 [0.81;1.04] (Death from any cause)

continued...

trial details	Patients	Treatments	Outcomes

References

Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, Oldgren J, Themeles E, Wallentin L, Yusuf S. . Am Heart J 2009;157:805-10, 810.e1-2 [PMID=19376304]

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2009 Aug 30;: [PMID=19717844]

4 Detailed results for dabigatran 150mg

4.1 Available trials

A total of 2 RCTs which randomized 12334 patients were identified: all compared dabigatran 150mg with warfarin standard dose.
The average study size was 6167 patients (range 236 to 12098). The first study was published in 2007, and the last study was published in 2009.
A total of 1 trials were double blind and 1 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Thrombo-embolic event (cerebral or systemic) data was reported in 1 trials; 1 trials reported data on ischemic stroke; 1 trials reported data on systemic thrombo-embolic complication; 1 trials reported data on non-lifethreatening major bleeding; 1 trials reported data on major bleeding; 1 trials reported data on bleeding; 1 trials reported data on fatal bleeding; 1 trials reported data on myocardial infarction (fatal and non fatal); 1 trials reported data on gastrointestinal major bleeding; 1 trials reported data on lifethreatening major bleeding; 1 trials reported data on minor bleeding; 1 trials reported data on haemmorhagic stroke; 1 trials reported data on intracranial hemorrhage; 1 trials reported data on cardiovascular death; 1 trials reported data on all cause death; 1 trials reported data on non fatal stroke; 1 trials reported data on stroke (fatal and non fatal); and 1 trials reported data on fatal stroke.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of dabigatran 150mg.

Table 4.1: *Treatment description - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	Studied treatment	Control treatment
Dabigatran 150mg versus warfarin standard dose		
RE-LY (150mg) (2009) [**?**, **?**] [a]	dabigatran 150 mg twice a day	warfarin adjusted-dose to a 2.0 to 3.0 INR
PETRO (150mg) (2007) [**?**] [b]	dabigatran 150 mg twice daily (alone or combined with 81- or 325-mg aspirin)	warfarin administered to achieve an international normalized ratio of 2 to 3 for

a) 3 arms: dabigatran 110 mg, 150mg and warfarin b) factorial design: Three doses of dabigatran etexilate (50, 150, and 300 mg twice daily) were combined in a 3 3 factorial fashion with no aspirin or 81- or 325-mg aspirin once daily.

Table 4.2: *Descriptions of participants - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	Patients
Dabigatran 110mg versus warfarin standard dose	

continued...

Trial	Patients	
RE-LY (110mg) (2009) [?, ?]	Patients With Non-Valvular Atrial Fibrillation	
	Inclusion criteria: patients with non-valvular atrial fibrillation (AF), at moderate to high risk of stroke, or systemic embolism with at least one additional risk factor (i.e. pre vious ischemic stroke, TIA, or systemic embolism, left ventricular dysfunction, age >=75 years, age >=65 with either diabetes mellitus, history of coronary artery disease or hy pertension)	**Exclusion criteria:**
Dabigatran 150mg versus warfarin standard dose		
RE-LY (150mg) (2009) [?, ?]	Patients With Non-Valvular Atrial Fibrillation	
	Inclusion criteria: patients with non-valvular atrial fibrillation (AF), at moderate to high risk of stroke, or systemic embolism with at least one additional risk factor (i.e. pre vious ischemic stroke, TIA, or systemic embolism, left ventricular dysfunction, age >=75 years, age >=65 with either diabetes mellitus, history of coronary artery disease or hy pertension)	**Exclusion criteria:**
PETRO (150mg) (2007) [?]	Patientswith AF at high risk for thromboembolic events	
Ximelagatran versus warfarin standard dose		
SPORTIF III (2003) [?]	One or more stroke risk factor in addition to AF.High risk patients with non valvular atrial fibrillation.	
	Inclusion criteria: age >18,Persistent or paroxysmal AF verified by at least 2 ECG,One or more stroke risk factors in addition to AF(hypertension,age >75,previous stroke TIA or systemic embolism,left ventricular dysfunction,age >65+coronary artery disease,age >65+diabete mellitus)	**Exclusion criteria:** mitral stenosis,Transient AF caused by reversible disorder,Stroke within the previous 30 days or TIA within 3 days,Condition associated with increased risk of bleeding,Active infective endocarditis,Current atrial myxoma or left ventricular thrombus,Admission for acute coronary syndrome or percutaeous coronary intervention within 30 days,Requirement for chronic anticoagulation treatment for disorders other than AF,planned cardioversion,Planned major surgery,treatment with platelet inhibitor drugs other than aspirin 100mg/day or less within 10 days or fibrinolytic agents within 30 days before randomisation,Regular use of NSAI drugs,Renal insuffiency,Active liver disease or persistent elevationof liver enzymes,Childbearing potential,pregnancy or lactation,Drug addiction alcohol abuse or both,Anaemia or thrombopenia

continued...

Trial	Patients	
SPORTIF V (2005) [?, ?]	One or more stroke risk factor in addition to atrial fibrillation.High risk patients with non valvular atrial fibrillation.	
	Inclusion criteria: age >18,Persistent or paroxysmal AF verified by at least 2 ECG,One or more stroke risk factors in addition to AF(hypertension,age >75,previous stroke TIA or systemic embolism,left ventricular dysfunction,age >65+coronary artery disease,age >65+diabete mellitus)	**Exclusion criteria:** mitral stenosis,Transient AF caused by reversible disorder,Stroke within the previous 30 days or TIA within 3 days,Condition associated with increased risk of bleeding,Active infective endocarditis,Current atrial myxoma or left ventricular thrombus,Admission for acute coronary syndrome or percutaeous coronary intervention within 30 days,Requirement for chronic anticoagulation treatment for disorders other than AF,planned cardioversion,Planned major surgery,treatment with platelet inhibitor drugs other than aspirin 100mg/day or less within 10 days or fibrinolytic agents within 30 days before randomisation,Regular use of NSAI drugs,Renal insuffiency,Active liver disease or persistent elevationof liver enzymes,Childbearing potential,pregnancy or lactation,Drug addiction alcohol abuse or both,Anaemia or thrombopenia
SPORTIF II (ximelagatran vs warfarin standard dose) (2002) [?] [c]	Medium to high risk patients with chronic non valvular atrial fibrillation.	
	Inclusion criteria: -one or more stroke risk factor in addition to AF:history of hypertension,age >65,previous stroke or TIA,previous systemic embolism,left ventricular dysfunction,diabete mellitus,coronary heart disease-age >18-paroxysmal or persistent NVAF verified by at least 2 ECG	**Exclusion criteria:** stroke and /or systemic embolism within the previous 2 years,Condition associated with increased risk of bleeding,NVAF secondary to other reversible disorders,presence of mecanical heart valves,Myocardial infarction,coronary artery bypass grafting or Percutaneous transluminal coronary angioplasty within previous 3 month,Diagnosis of left ventricular aneurysm or atrial myxoma,Treatment with NSAIDs or fibrinolytics within previous week,Renal impairment,Blood pressure >180/100,History of rheumatic fever,Liver insufficiency,Hb <100g/l,Plat <100000,Contra-indication to warfarin treatment

Table 4.3: *Design and methodological quality of trials - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	Design	Duration	Centre	Primary endpoint
Dabigatran 110mg versus warfarin standard dose				
RE-LY (110mg), 2009 [?, ?] n=12037	Parallel groups open (blind assessment) confirmatory trial at risk of bias	2 y (median) inclusion period: dec 2005 - dec 2007	44 countries 951 centres	stroke or systemic embolism
Dabigatran 150mg versus warfarin standard dose				

continued...

Trial	Design	Duration	Centre	Primary endpoint
RE-LY (150mg), 2009 [?, ?] n=12098	Parallel groups open (blind assessment) confirmatory trial at risk of bias	2 y (median) inclusion period: dec 2005 - dec 2007	44 countries 951 centres	stroke or systemic embolism
PETRO (150mg), 2007 [?] n=236	Factorial plan double blind exploratory trial	12 weeks	Denmark, The netehrlands, Sweden, US 53 centres	bleedings
Ximelagatran versus warfarin standard dose				
SPORTIF III, 2003 [?] [(a)] n=3407	Parallel groups Open confirmatory trial at risk of bias	17.4 months inclusion period: aug 2000-sept 2001	europe,asia,australasia 259 centres	All stroke or systemic embolism
SPORTIF V, 2005 [?, ?] n=3922	Parallel groups Double blind confirmatory trial at low risk of bias	20 months inclusion period: july 2000-dec 2001	north america 409 centres	All stroke and systemic embolism
SPORTIF II (ximelagatran vs warfarin standard dose), 2002 [?] [(c)] n=254	Parallel groups Open confirmatory trial at risk of bias	16 weeks	Europe ,USA 37 centres	Thromboembolic events and bleedings

Table 4.4: *Trial characteristics - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	subgroup test	CHADS2 Score (mean)	CHADS2 Score = 2 (%)	CHADS2 Score = 3 (%)
Dabigatran 150mg versus warfarin standard dose				
RE-LY (150mg), 2009 [?, ?]	a			
PETRO (150mg), 2007 [?]	c			

4.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Dabigatran 150mg versus warfarin standard dose

Only one of the 2 studies eligible for this comparison provided data on **systemic thrombo-embolic complication**. There was no statistically significant difference in systemic thrombo-embolic complication between dabigatran 150mg and warfarin standard dose, with a RR of 0.85 (95%CI 0.39 to 1.84, p=0.6782) in favour of dabigatran 150mg. In other words, systemic thrombo-embolic complication was slightly lower in the dabigatran 150mg group , but this was not statistically significant.
Only one of the 2 studies eligible for this comparison provided data on **thrombo-embolic event (cerebral or systemic)**. The analysis detected a statistically significant difference in favor of dabigatran 150mg in thrombo-embolic event (cerebral or systemic), with a RR of 0.67 (95% CI 0.54 to 0.83, p=0.0000).
Only one of the 2 studies eligible for this comparison provided data on **ischemic stroke**. The analysis detected a statistically significant difference in favor of dabigatran 150mg in ischemic stroke, with a RR of 0.77 (95% CI 0.61 to 0.99, p=0.0418).

Table 4.5: *Results details - oral direct thrombin inhibitor - dabigatran 150mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
dabigatran 150mg versus warfarin standard dose						
systemic thrombo-embolic complication	RR=0.85	[0.39;1.84]	0.6782	1.0000 (I^2=0.00)	1	12098
thrombo-embolic event (cerebral or systemic)	RR=0.67	[0.54;0.83]	0.0000	1.0000 (I^2=0.00)	1	12098
cardiovascular death	RR=0.86	[0.73;1.00]	0.0545	1.0000 (I^2=0.00)	1	12098
stroke (fatal and non fatal)	RR=0.65	[0.52;0.82]	0.0000	1.0000 (I^2=0.00)	1	12098
ischemic stroke	RR=0.77	[0.61;0.99]	0.0418	1.0000 (I^2=0.00)	1	12098
lifethreatening major bleeding	RR=0.82	[0.67;1.00]	0.0458	1.0000 (I^2=1.00)	1	12098
non-lifethreatening major bleeding	RR=1.08	[0.90;1.30]	0.4324	1.0000 (I^2=0.00)	1	12098
gastrointestinal major bleeding	RR=1.50	[1.20;1.89]	0.0000	1.0000 (I^2=0.00)	1	12098
all cause death	RR=0.89	[0.79;1.01]	0.0693	1.0000 (I^2=0.00)	1	12098
fatal stroke	RR=0.67	[0.51;0.89]	0.0057	1.0000 (I^2=0.00)	1	12098
non fatal stroke	RR=0.63	[0.43;0.92]	0.0169	1.0000 (I^2=0.00)	1	12098
major bleeding	RR=0.94	[0.82;1.07]	0.3440	1.0000 (I^2=1.00)	1	12098
haemmorhagic stroke	RR=0.26	[0.14;0.50]	0.0000	1.0000 (I^2=0.00)	1	12098
fatal bleeding	RR=0.82	[0.67;1.00]	0.0458	1.0000 (I^2=1.00)	1	12098

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 4.1: *Forest's plot for systemic thrombo-embolic complication*

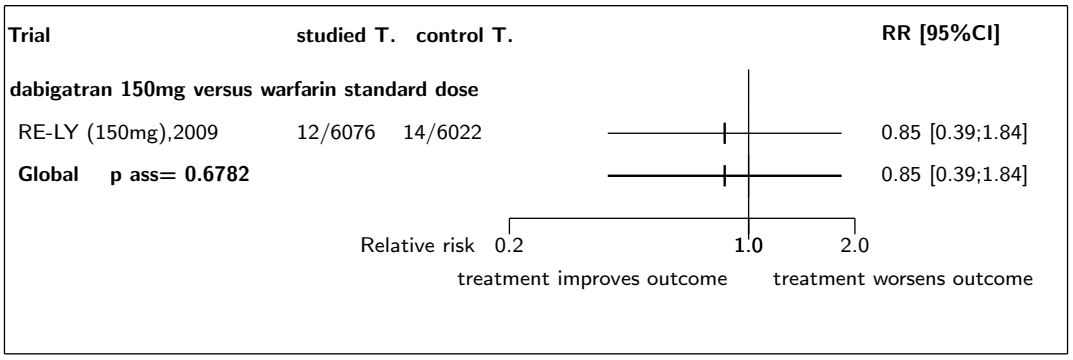


Figure 4.2: *Forest's plot for thrombo-embolic event (cerebral or systemic)*

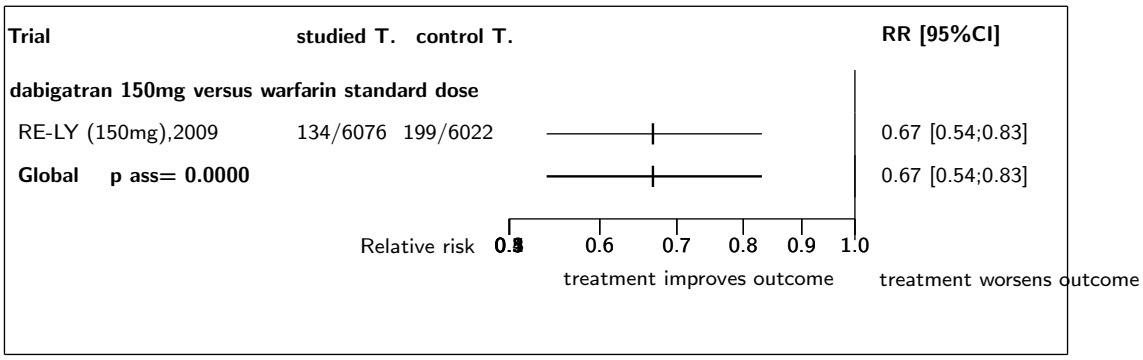


Figure 4.3: *Forest's plot for cardiovascular death*

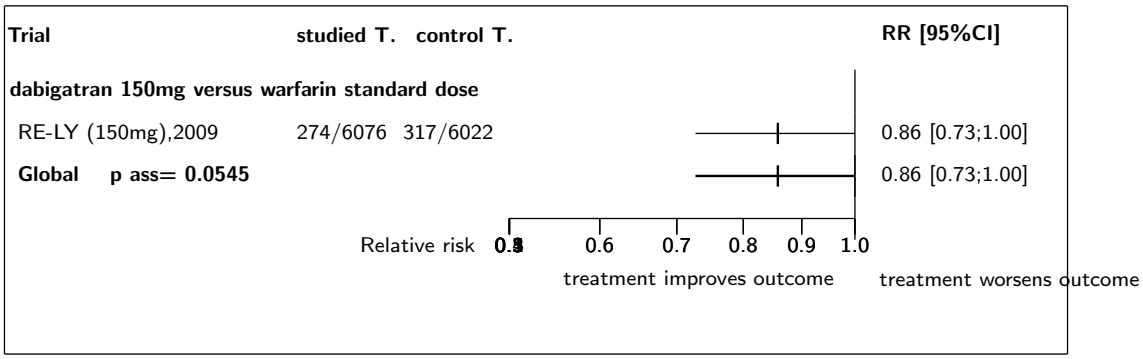


Figure 4.4: *Forest's plot for stroke (fatal and non fatal)*

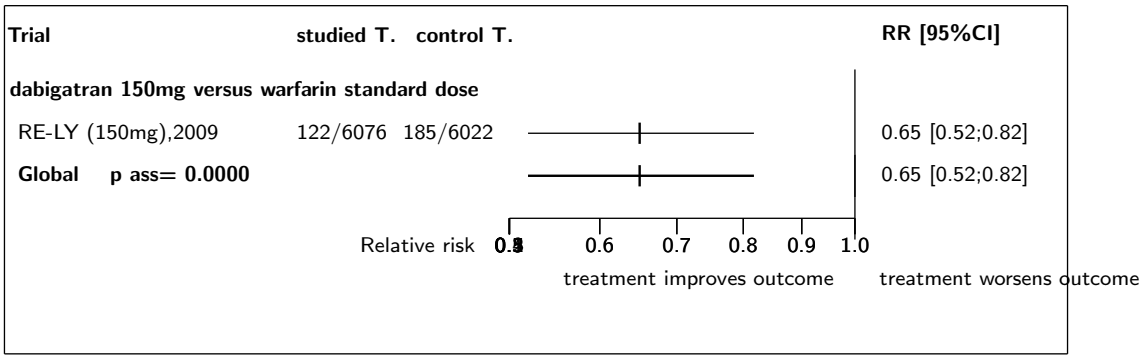


Figure 4.5: *Forest's plot for ischemic stroke*

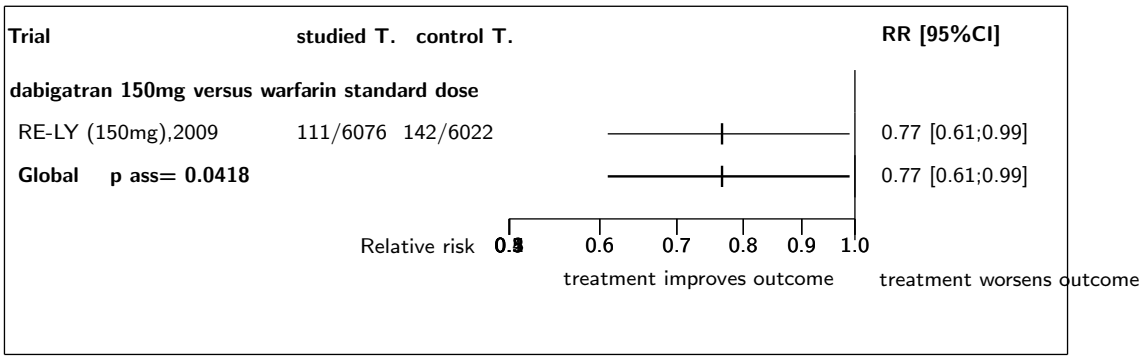


Figure 4.6: *Forest's plot for lifethreatening major bleeding*

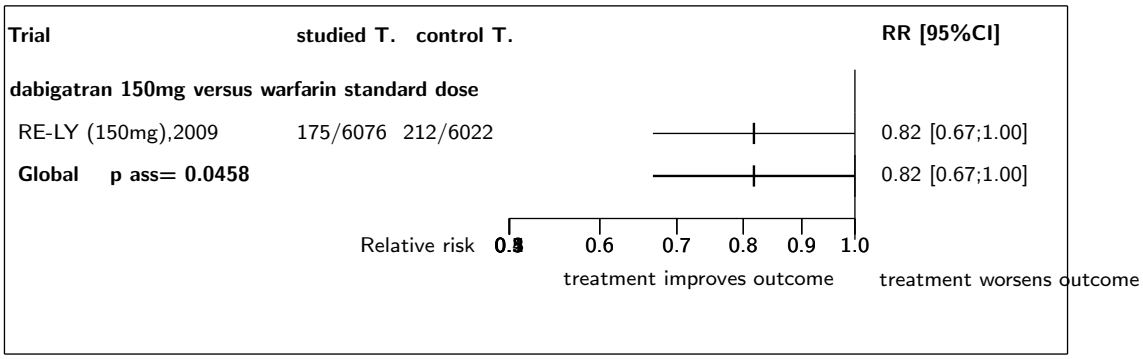


Figure 4.7: *Forest's plot for non-lifethreatening major bleeding*

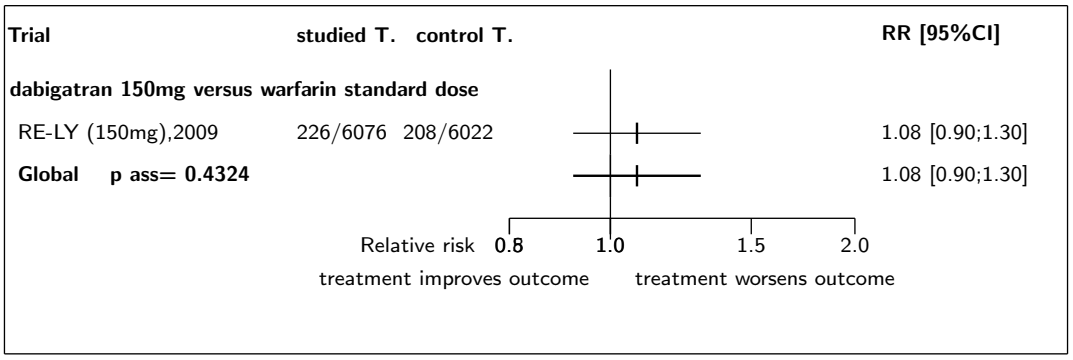


Figure 4.8: *Forest's plot for gastrointestinal major bleeding*

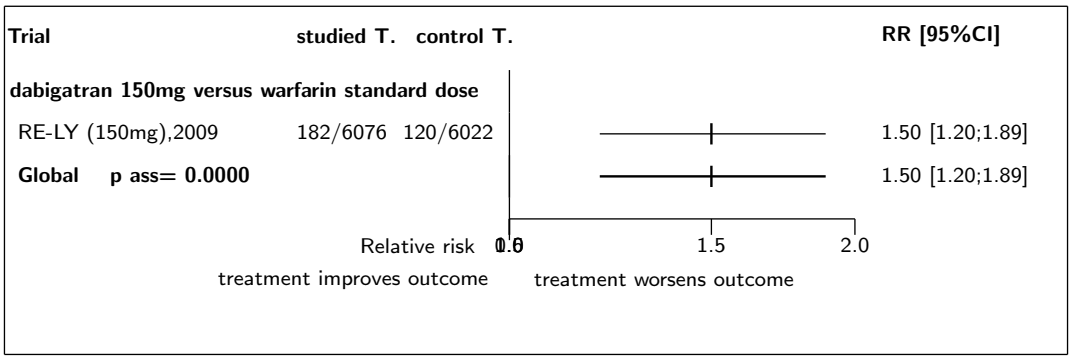


Figure 4.9: *Forest's plot for all cause death*

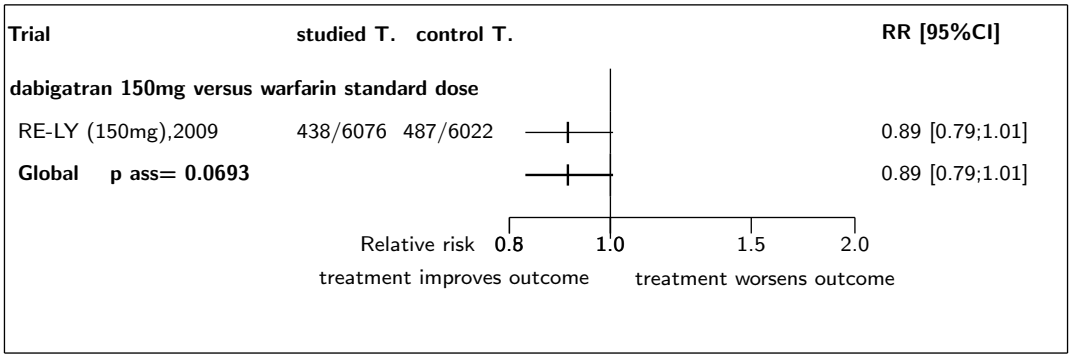


Figure 4.10: *Forest's plot for fatal stroke*

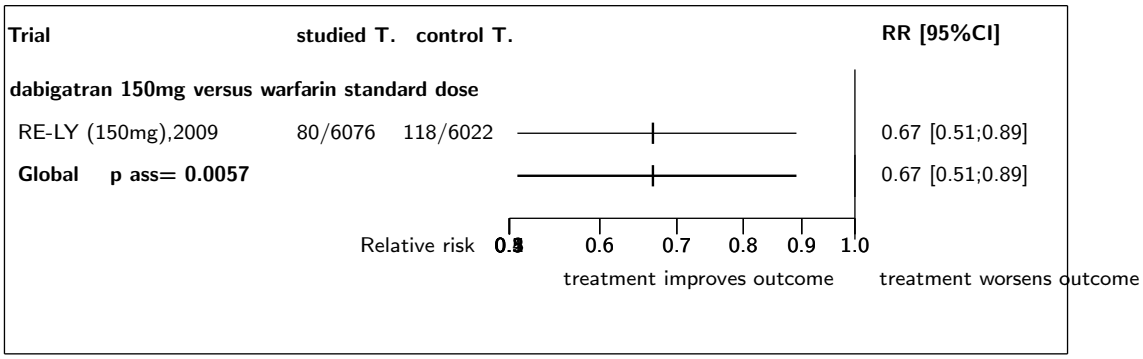


Figure 4.11: *Forest's plot for non fatal stroke*

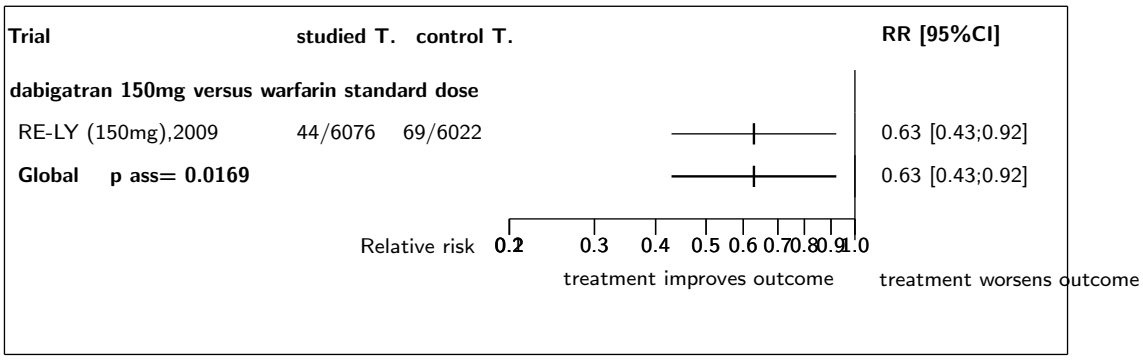


Figure 4.12: *Forest's plot for major bleeding*

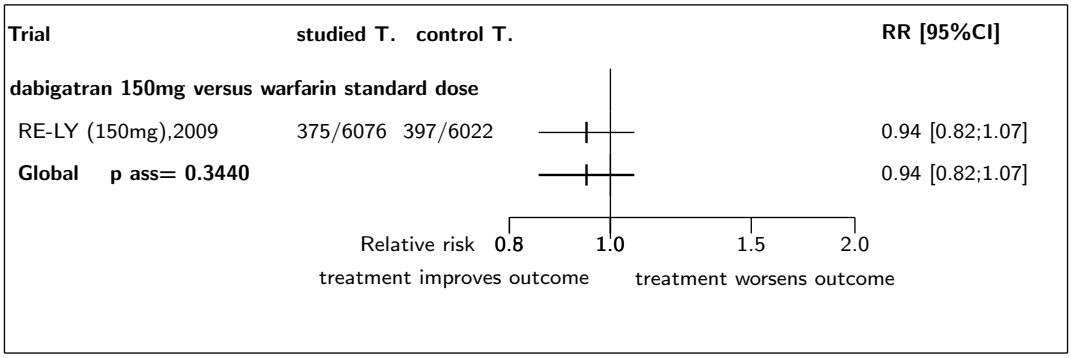


Figure 4.13: *Forest's plot for haemmorhagic stroke*

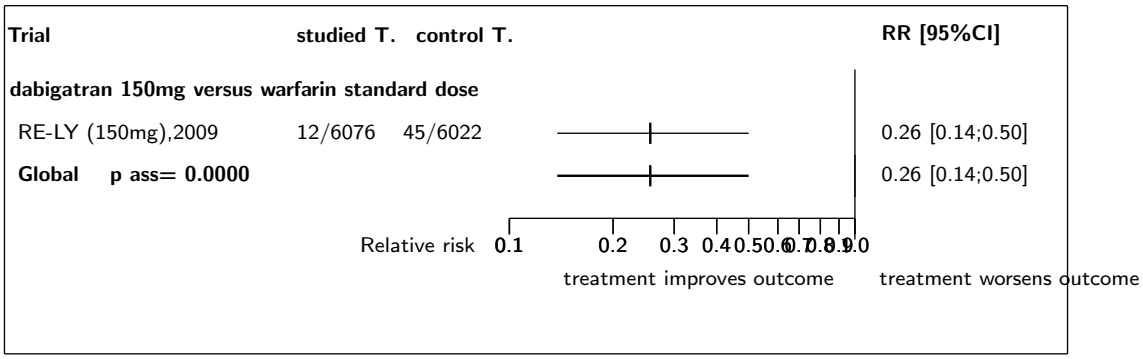
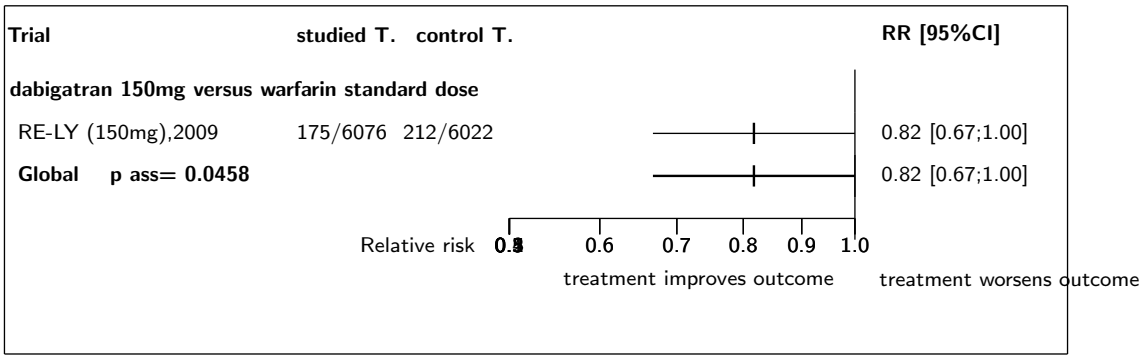


Figure 4.14: *Forest's plot for fatal bleeding*



References

[1] Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, Oldgren J, Themeles E, Wallentin L, Yusuf S. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 2009;157:805-10, 810.e1-2. [PMID=19376304]

[2] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009 Sep 17;361:1139-51. [PMID=19717844]

[3] Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, Pedersen KE, Lionetti DA, Stangier J, Wallentin L. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol 2007;100:1419-26. [PMID=17950801]

4.3 Individual trial summaries

Table 4.6: *RE-LY (150mg), 2009 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=12098 (6076 vs. 6022) **Follow-up duration:** 2 y (median) **Study design:** Randomized controlled trial Parallel groups Open (blind assessment) Confirmatory trial at risk of bias 44 countries, 951 centres **Inclusion period:** dec 2005 - dec 2007	Patients With Non-Valvular Atrial Fibrillation **Inclusion criteria:** Patients with non-valvular atrial fibrillation (AF), at moderate to high risk of stroke, or systemic embolism with at least one additional risk factor (i.e. pre vious ischemic stroke, TIA, or systemic embolism, left ventricular dysfunction, age >=75 years, age >=65 with either diabetes mellitus, history of coronary artery disease or hy pertension)	**Studied treatment:** dabigatran 150 mg twice a day **Control treatment:** warfarin adjusted-dose to a 2.0 to 3.0 INR **note:** 3 arms: dabigatran 110 mg, 150mg and warfarin	Systemic thrombo-embolic complication RR=0.85 [0.39;1.84] (imputed) Thrombo-embolic event (cerebral or systemic) RR=0.67 [0.54;0.83] (Stroke or systemic embolism) Cardiovascular death RR=0.86 [0.73;1.00] (Death from vascular causes) Stroke (fatal and non fatal) RR=0.65 [0.52;0.82] (Stroke) Ischemic stroke RR=0.77 [0.61;0.99] (Ischemic or unspecified) Lifethreatening major bleeding RR=0.82 [0.67;1.00] (Life threatening Major bleeding) Non-lifethreatening major bleeding RR=1.08 [0.90;1.30] (Nonlife threatening Major bleeding) Gastrointestinal major bleeding RR=1.50 [1.20;1.89] (Gastrointestinal Major bleeding) All cause death RR=0.89 [0.79;1.01] (Death from any cause)

continued...

trial details	Patients	Treatments	Outcomes
References			
Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, Oldgren J, Themeles E, Wallentin L, Yusuf S. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 2009;157:805-10, 810.e1-2 [PMID=19376304] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009 Sep 17;361:1139-51 [PMID=19717844]			

Table 4.7: *PETRO (150mg), 2007 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=236 (166 vs. 70) **Follow-up duration:** 12 weeks **Study design:** Randomized controlled trial Factorial plan Double blind Exploratory trial Denmark, The netehrlands, Sweden, US, 53 centres	Patientswith AF at high risk for thromboembolic events	**Studied treatment:** dabigatran 150 mg twice daily (alone or combined with 81- or 325-mg aspirin) **Control treatment:** warfarin administered to achieve an international normalized ratio of 2 to 3 for **note:** factorial design: Three doses of dabigatran etexilate (50, 150, and 300 mg twice daily) were combined in a 3 3 factorial fashion with no aspirin or 81- or 325-mg aspirin once daily.	

Reference

Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, Pedersen KE, Lionetti DA, Stangier J, Wallentin L. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol 2007;100:1419-26 [PMID=17950801]

5 Detailed results for ximelagatran

5.1 Available trials

A total of 3 RCTs which randomized 7583 patients were identified: all compared ximelagatran with warfarin standard dose.
The average study size was 2527 patients (range 254 to 3922). The first study was published in 2002, and the last study was published in 2005.
A total of 1 trials were double blind and 2 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Ischemic stroke data was reported in 3 trials; 3 trials reported data on systemic thrombo-embolic complication; 2 trials reported data on TE event or ischemic stroke or systemic embolism; 2 trials reported data on thrombo-embolic event (cerebral or systemic); 3 trials reported data on haemmorhagic stroke; 3 trials reported data on major bleeding; 2 trials reported data on minor bleeding; 2 trials reported data on bleeding; 2 trials reported data on adverse events; 2 trials reported data on myocardial infarction (fatal and non fatal); 1 trials reported data on hypertransaminasemia; 3 trials reported data on fatal stroke; 3 trials reported data on all cause death; 3 trials reported data on stroke (fatal and non fatal); and 1 trials reported data on cardiovascular death.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of ximelagatran.

Table 5.1: *Treatment description - oral direct thrombin inhibitor - ximelagatran*

Trial	Studied treatment	Control treatment
Ximelagatran versus warfarin standard dose		
SPORTIF III (2003) [**?**] [a]	ximelagatran 36 mg twice daily	warfarin standard dose (target INR 2-3)
	Concomittant treatment: Aspirin <100mg/day allowedOther antithrombotic drugs were prohibited.	
SPORTIF V (2005) [**?**, **?**]	ximelegatran 36 mg twice daily	warfarin standard dose(target INR 2-3)
	Concomittant treatment: -aspirin <100 mg-other antithrombotic agents are prohibited within 10 days of randomisation and during the treatment phase.-NSAIDs are authorized up to 7 days per month-COX-2 inhibitors are permitted ad lib.-concomitant therapies are at the discretion of the treating physician (anticoagulants and antiplatelet agents excepted).	
SPORTIF II (ximelagatran vs warfarin standard dose) (2002) [**?**] [c]	ximelegatran 20,40,60 mg twice daily	warfarin standard dose(target INR 2-3)
	Concomittant treatment: Beta-blockers,angiotensin-converting enzyme inhibitors,calcium antagonistsLow doses of aspirin are accepted(up to 160 mg/day)	

a) Aspirin was used concurrently for at least half the period on study drug by 13% patients assigned to ximelagatran and 10% on warfarin(p=0.01). c) -treatment with either NSAI agents or fibrinolytic agents within the week before the start was prohibited-patient previously receiving warfarin were given ximelegatran once INR value was 1.5 or under/after the end of the study patients who stopped ximelegatran began warfarin 12 to 24 h after last intake.

Table 5.2: *Descriptions of participants - oral direct thrombin inhibitor - ximelagatran*

Trial	Patients	
Dabigatran 110mg versus warfarin standard dose		
RE-LY (110mg) (2009) [?, ?]	Patients With Non-Valvular Atrial Fibrillation	
	Inclusion criteria: patients with non-valvular atrial fibrillation (AF), at moderate to high risk of stroke, or systemic embolism with at least one additional risk factor (i.e. pre vious ischemic stroke, TIA, or systemic embolism, left ventricular dysfunction, age >=75 years, age >=65 with either diabetes mellitus, history of coronary artery disease or hy pertension)	**Exclusion criteria:**
Dabigatran 150mg versus warfarin standard dose		
RE-LY (150mg) (2009) [?, ?]	Patients With Non-Valvular Atrial Fibrillation	
	Inclusion criteria: patients with non-valvular atrial fibrillation (AF), at moderate to high risk of stroke, or systemic embolism with at least one additional risk factor (i.e. pre vious ischemic stroke, TIA, or systemic embolism, left ventricular dysfunction, age >=75 years, age >=65 with either diabetes mellitus, history of coronary artery disease or hy pertension)	**Exclusion criteria:**
PETRO (150mg) (2007) [?]	Patientswith AF at high risk for thromboembolic events	
Ximelagatran versus warfarin standard dose		
SPORTIF III (2003) [?]	One or more stroke risk factor in addition to AF.High risk patients with non valvular atrial fibrillation.	
	Inclusion criteria: age >18,Persistent or paroxysmal AF verified by at least 2 ECG,One or more stroke risk factors in addition to AF(hypertension,age >75,previous stroke TIA or systemic embolism,left ventricular dysfunction,age >65+coronary artery disease,age >65+diabete mellitus)	**Exclusion criteria:** mitral stenosis,Transient AF caused by reversible disorder,Stroke within the previous 30 days or TIA within 3 days,Condition associated with increased risk of bleeding,Active infective endocarditis,Current atrial myxoma or left ventricular thrombus,Admission for acute coronary syndrome or percutaeous coronary intervention within 30 days,Requirement for chronic anticoagulation treatment for disorders other than AF,planned cardioversion,Planned major surgery,treatment with platelet inhibitor drugs other than aspirin 100mg/day or less within 10 days or fibrinolytic agents within 30 days before randomisation,Regular use of NSAI drugs,Renal insuffiency,Active liver disease or persistent elevationof liver enzymes,Childbearing potential,pregnancy or lactation,Drug addiction alcohol abuse or both,Anaemia or thrombopenia

continued...

Trial	Patients	
SPORTIF V (2005) [?, ?]	One or more stroke risk factor in addition to atrial fibrillation.High risk patients with non valvular atrial fibrillation.	
	Inclusion criteria: age >18,Persistent or paroxysmal AF verified by at least 2 ECG,One or more stroke risk factors in addition to AF(hypertension,age >75,previous stroke TIA or systemic embolism,left ventricular dysfunction,age >65+coronary artery disease,age >65+diabete mellitus)	**Exclusion criteria:** mitral stenosis,Transient AF caused by reversible disorder,Stroke within the previous 30 days or TIA within 3 days,Condition associated with increased risk of bleeding,Active infective endocarditis,Current atrial myxoma or left ventricular thrombus,Admission for acute coronary syndrome or percutaeous coronary intervention within 30 days,Requirement for chronic anticoagulation treatment for disorders other than AF,planned cardioversion,Planned major surgery,treatment with platelet inhibitor drugs other than aspirin 100mg/day or less within 10 days or fibrinolytic agents within 30 days before randomisation,Regular use of NSAI drugs,Renal insuffiency,Active liver disease or persistent elevationof liver enzymes,Childbearing potential,pregnancy or lactation,Drug addiction alcohol abuse or both,Anaemia or thrombopenia
SPORTIF II (ximelagatran vs warfarin standard dose) (2002) [?] [c]	Medium to high risk patients with chronic non valvular atrial fibrillation.	
	Inclusion criteria: -one or more stroke risk factor in addition to AF:history of hypertension,age >65,previous stroke or TIA,previous systemic embolism,left ventricular dysfunction,diabete mellitus,coronary heart disease-age >18-paroxysmal or persistent NVAF verified by at least 2 ECG	**Exclusion criteria:** stroke and /or systemic embolism within the previous 2 years,Condition associated with increased risk of bleeding,NVAF secondary to other reversible disorders,presence of mecanical heart valves,Myocardial infarction,coronary artery bypass grafting or Percutaneous transluminal coronary angioplasty within previous 3 month,Diagnosis of left ventricular aneurysm or atrial myxoma,Treatment with NSAIDs or fibrinolytics within previous week,Renal impairment,Blood pressure >180/100,History of rheumatic fever,Liver insufficiency,Hb <100g/l,Plat <100000,Contra-indication to warfarin treatment

c) -SPORTIF II is a dose guiding study-66 patient received 20mg,62 received 40mg,59 received 60 mg

Table 5.3: *Design and methodological quality of trials - oral direct thrombin inhibitor - ximelagatran*

Trial	Design	Duration	Centre	Primary endpoint
Dabigatran 110mg versus warfarin standard dose				
RE-LY (110mg), 2009 [?, ?] n=12037	Parallel groups open (blind assessment) confirmatory trial at risk of bias	2 y (median) inclusion period: dec 2005 - dec 2007	44 countries 951 centres	stroke or systemic embolism
Dabigatran 150mg versus warfarin standard dose				

continued...

Trial	Design	Duration	Centre	Primary endpoint
RE-LY (150mg), 2009 [?, ?] n=12098	Parallel groups open (blind assessment) confirmatory trial at risk of bias	2 y (median) inclusion period: dec 2005 - dec 2007	44 countries 951 centres	stroke or systemic embolism
PETRO (150mg), 2007 [?] n=236	Factorial plan double blind exploratory trial	12 weeks	Denmark, The netehrlands, Sweden, US 53 centres	bleedings
Ximelagatran versus warfarin standard dose				
SPORTIF III, 2003 [?] (a) n=3407	Parallel groups Open confirmatory trial at risk of bias	17.4 months inclusion period: aug 2000-sept 2001	europe,asia,australasia 259 centres	All stroke or systemic embolism
SPORTIF V, 2005 [?, ?] n=3922	Parallel groups Double blind confirmatory trial at low risk of bias	20 months inclusion period: july 2000-dec 2001	north america 409 centres	All stroke and systemic embolism
SPORTIF II (ximelagatran vs warfarin standard dose), 2002 [?] (c) n=254	Parallel groups Open confirmatory trial at risk of bias	16 weeks	Europe ,USA 37 centres	Thromboembolic events and bleedings

a) Premature termination of study treatment was the result of study endpoint (4% warfarin group,3% ximelegatran) and adverse effects(4% warfarin group,8% ximelegatran group:this difference is related to elevation of liver enzymes in some patients treated with ximelegatran).The trial was a non inferiority trial but the primary analysis was only by intention to treat. c) it is a dose guiding study

Table 5.4: *Trial characteristics - oral direct thrombin inhibitor - ximelagatran*

Trial	**subgroup test**	**CHADS2 Score (mean)**	**CHADS2 Score = 2 (%)**	**CHADS2 Score = 3 (%)**
Ximelagatran versus warfarin standard dose				
SPORTIF III, 2003 [?]	a			
SPORTIF V, 2005 [?, ?]	a			
SPORTIF II (ximelagatran vs warfarin standard dose), 2002 [?]	d			

5.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Ximelagatran versus warfarin standard dose

All the 3 studies had extractable data about the number of participants with **systemic thrombo-embolic complication**. There was no statistically significant difference in systemic thrombo-embolic complication between ximelagatran and warfarin standard dose, with a RR of 2.46 (95%CI 0.70 to 8.63, p=0.1585) in favour of warfarin standard dose. In other words, systemic thrombo-embolic complication was slightly lower in the warfarin standard dose group , but this was not statistically significant. No heterogeneity was detected (p = 0.4331, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **thrombo-embolic event (cerebral or systemic)**. When pooled together, there was no statistically significant difference between the groups in thrombo-embolic event (cerebral or systemic), with a RR of 0.99 (95% CI 0.52 to 1.89, p=0.9745). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0257, I^2 = 0.80%).
A total of 2 of the 3 studies eligible for this comparison provided data on **TE event or ischemic stroke or systemic embolism**. When pooled together, there was no statistically significant difference between the groups in TE event or ischemic stroke or systemic embolism, with a RR of 0.93 (95% CI 0.53 to 1.66, p=0.8190). No heterogeneity was detected (p = 0.0642, I^2 = 0.71%).
All the 3 studies had extractable data about the number of participants with **ischemic stroke**. When pooled together, there was no statistically significant difference between the groups in ischemic stroke, with a RR of 0.93 (95% CI 0.58 to 1.50, p=0.7698). No heterogeneity was detected (p = 0.1781, I^2 = 0.42%).

Table 5.5: *Results details - oral direct thrombin inhibitor - ximelagatran*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
ximelagatran versus warfarin standard dose						
systemic thrombo-embolic complication	RR=2.46	[0.70;8.63]	0.1585	0.4331 (I^2=0.00)	3	7583
thrombo-embolic event (cerebral or systemic)	RR=0.99	[0.52;1.89]	0.9745	0.0257 (I^2=0.80)	2	7329
cardiovascular death	RR=1.21	[0.77;1.91]	0.4098	1.0000 (I^2=0.00)	1	3407
TE event or ischemic stroke or systemic embolism	RR=0.93	[0.53;1.66]	0.8190	0.0642 (I^2=0.71)	2	7329
stroke (fatal and non fatal)	RR=0.90	[0.54;1.52]	0.6979	0.1221 (I^2=0.52)	3	7583
ischemic stroke	RR=0.93	[0.58;1.50]	0.7698	0.1781 (I^2=0.42)	3	7583
all cause death	RR=0.96	[0.79;1.16]	0.6734	0.9619 (I^2=0.00)	3	7583
fatal stroke	RR=1.56	[0.65;3.72]	0.3193	0.2976 (I^2=0.17)	3	7583
hypertransaminasemia	RR=7.81	[4.58;13.32]	0.0000	1.0000 (I^2=0.00)	1	3922
major bleeding	RR=0.73	[0.56;0.95]	0.0197	0.7013 (I^2=0.00)	3	7583
haemmorhagic stroke	RR=0.54	[0.20;1.42]	0.2109	0.7674 (I^2=0.00)	3	7583

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 5.1: *Forest's plot for systemic thrombo-embolic complication*

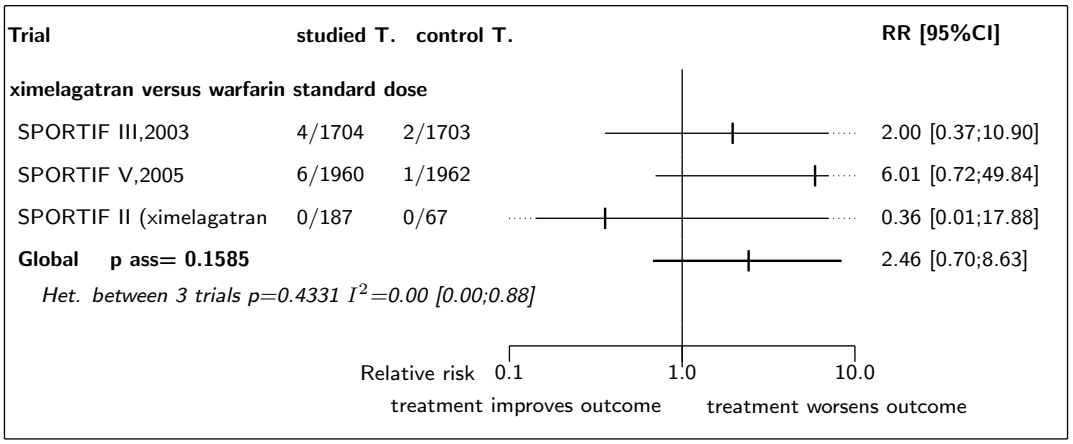


Figure 5.2: *Forest's plot for thrombo-embolic event (cerebral or systemic)*

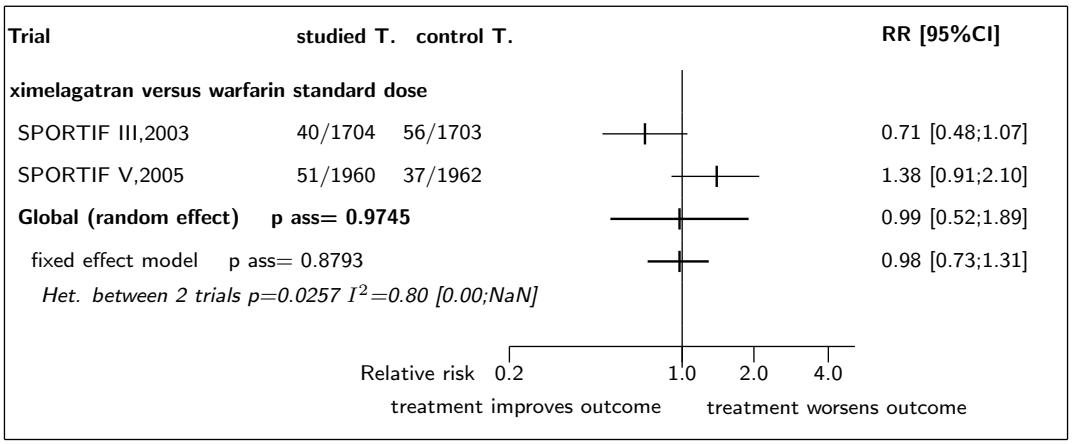


Figure 5.3: *Forest's plot for cardiovascular death*

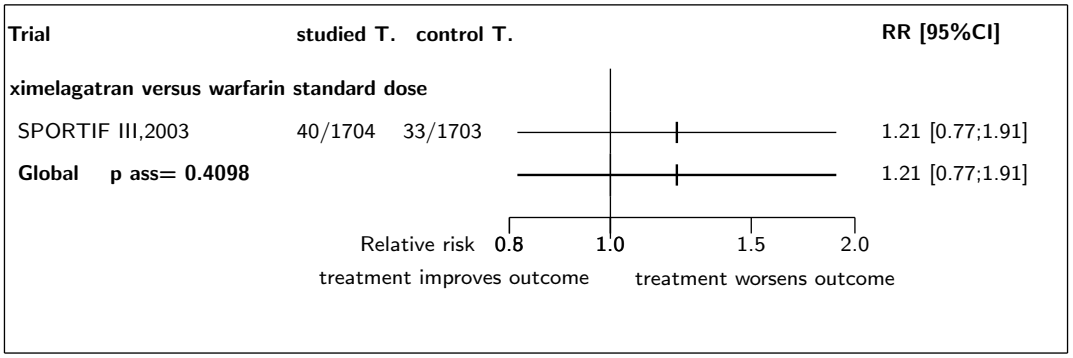


Figure 5.4: *Forest's plot for TE event or ischemic stroke or systemic embolism*

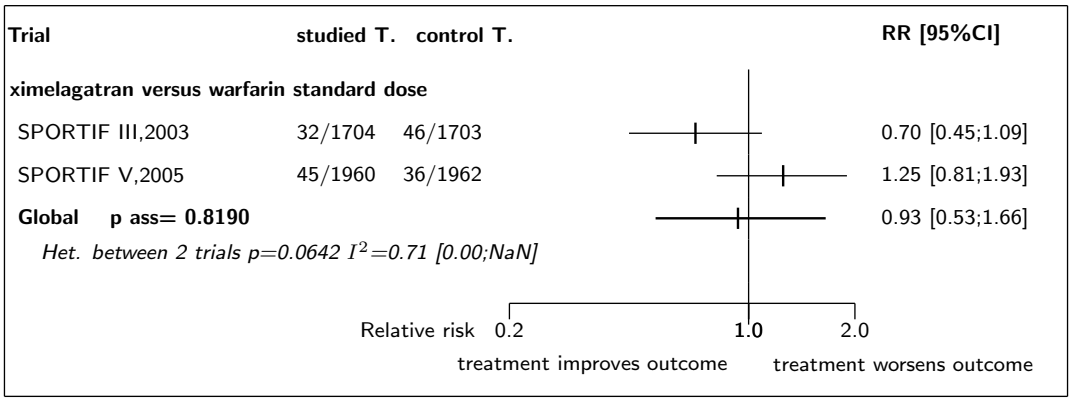


Figure 5.5: *Forest's plot for stroke (fatal and non fatal)*

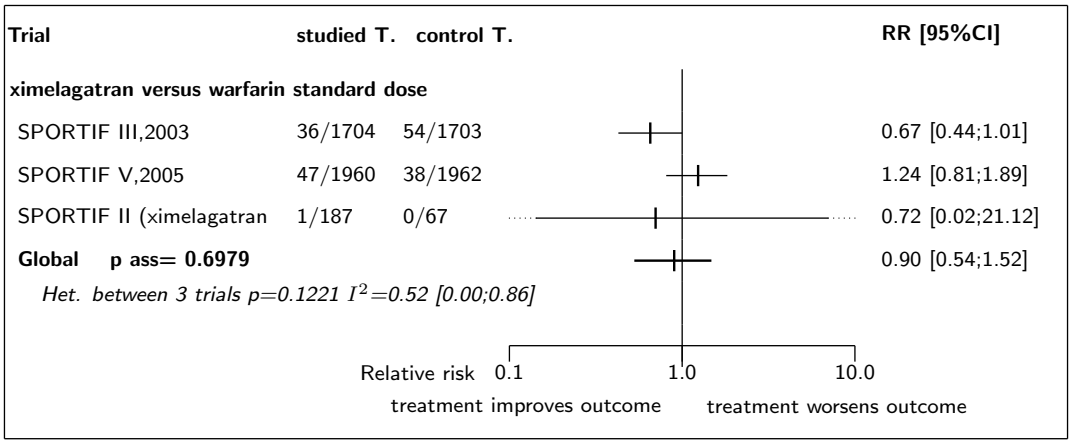


Figure 5.6: *Forest's plot for ischemic stroke*

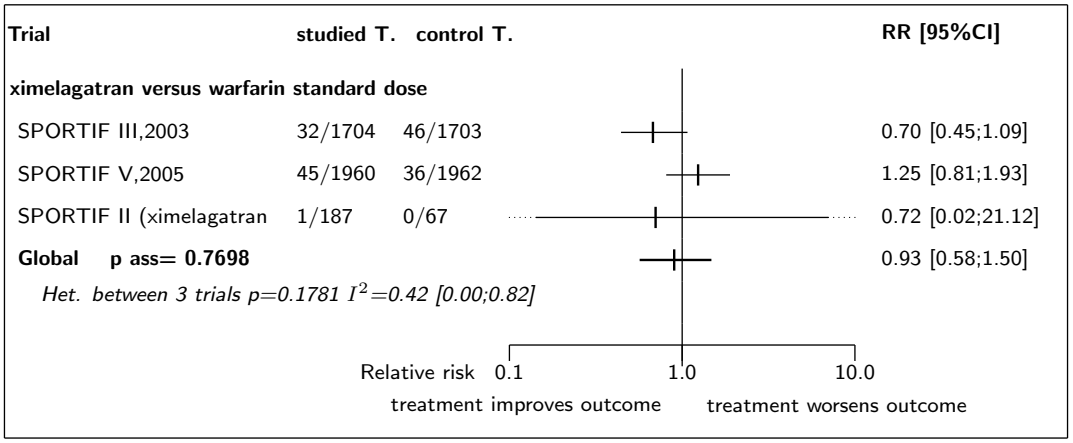


Figure 5.7: *Forest's plot for all cause death*

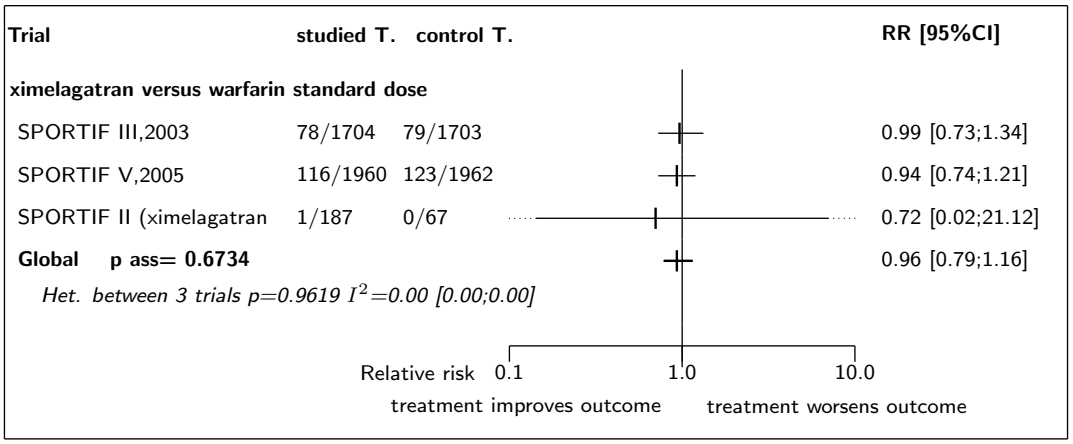


Figure 5.8: *Forest's plot for fatal stroke*

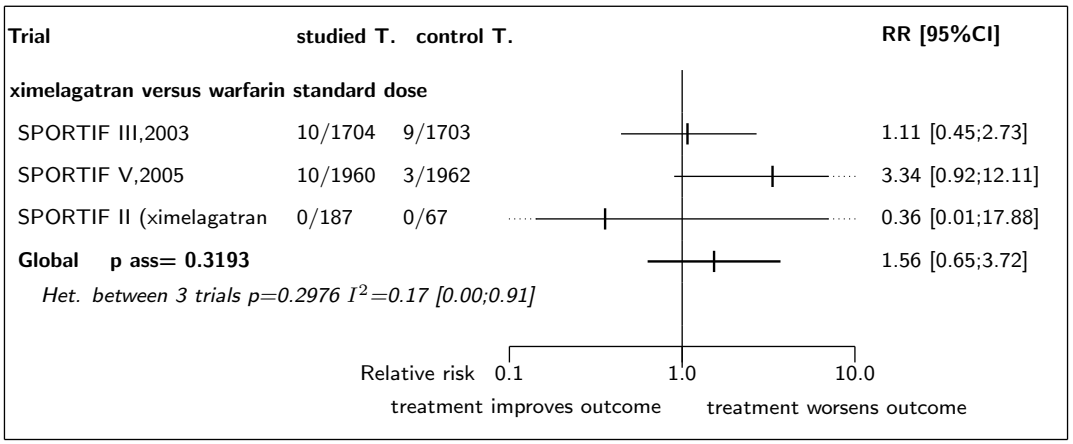


Figure 5.9: *Forest's plot for hypertransaminasemia*

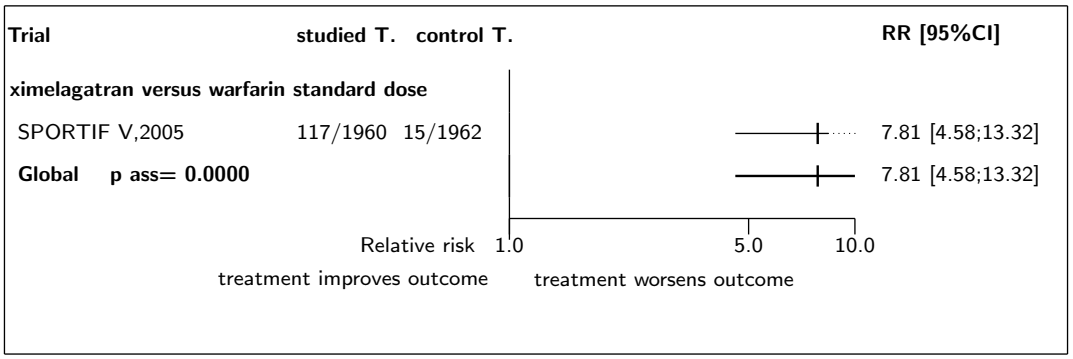


Figure 5.10: *Forest's plot for major bleeding*

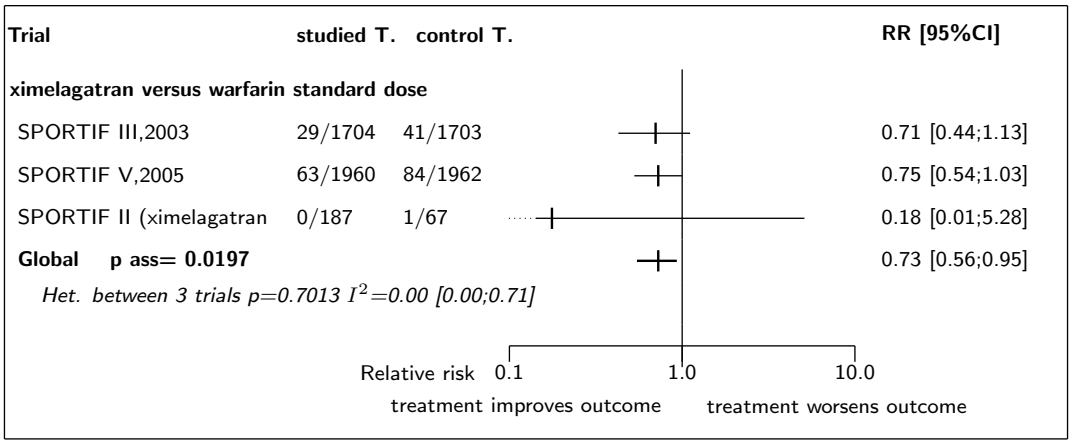
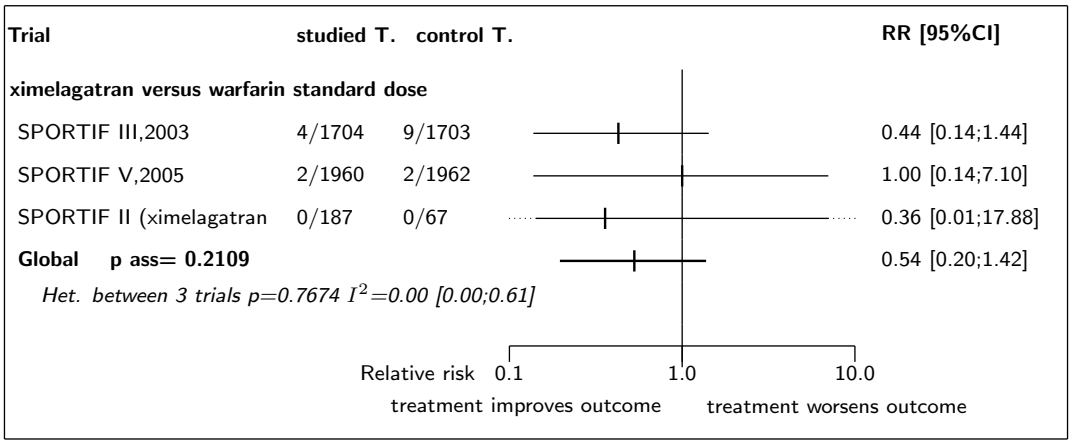


Figure 5.11: *Forest's plot for haemmorhagic stroke*



References

[1] Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. Lancet 2003 Nov 22;362:1691-8. [PMID=14643116]

[2] Halperin JL. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: Rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). Am Heart J 2003 Sep;146:431-8. [PMID=12947359]

[3] Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, Halperin JL, Horrow J, Olsson SB, Petersen P, Vahanian A. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005 Feb 9;293:690-8. [PMID=15701910]

[4] Petersen P, Grind M, Adler J. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. J Am Coll Cardiol 2003 May 7;41:1445-51. [PMID=12742279]

5.3 Individual trial summaries

Table 5.6: *SPORTIF III, 2003 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3407 (1704 vs. 1703) **Follow-up duration:** 17.4 months **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias europe,asia,australasia, 259 centres **Inclusion period:** aug 2000-sept 2001	One or more stroke risk factor in addition to AF.High risk patients with non valvular atrial fibrillation. **Inclusion criteria:** Age >18,Persistent or paroxysmal AF verified by at least 2 ECG,One or more stroke risk factors in addition to AF(hypertension,age >75,previous stroke TIA or systemic embolism,left ventricular dysfunction,age >65+coronary artery disease,age >65+diabete mellitus) **Exclusion criteria:** Mitral stenosis,Transient AF caused by reversible disorder,Stroke within the previous 30 days or TIA within 3 days,Condition associated with increased risk of bleeding,Active infective endocarditis,Current atrial myxoma or left ventricular thrombus,Admission for acute coronary syndrome or percutaeous coronary intervention within 30 days,Requirement for chronic anticoagulation treatment for disorders other than AF,planned cardioversion,Planned major surgery,treatment with platelet inhibitor drugs other than aspirin 100mg/day or less within 10 days or fibrinolytic agents within 30 days before ra	**Studied treatment:** ximelagatran 36 mg twice daily **Control treatment:** warfarin standard dose (target INR 2-3) **Concomittant treat.:**Aspirin <100mg/day allowedOther antithrombotic drugs were prohibited. **note:** Aspirin was used concurrently for at least half the period on study drug by 13% patients assigned to ximelagatran and 10% on warfarin(p=0.01).	Systemic thrombo-embolic complication RR=2.00 [0.37;10.90] (abrupt vascular insufficiency asociated with clinical and radiological evidence of arterial occlusion in the absence of another likely mechanism) Thrombo-embolic event (cerebral or systemic) RR=0.71 [0.48;1.07] Cardiovascular death RR=1.21 [0.77;1.91] TE event or ischemic stroke or systemic embolism RR=0.70 [0.45;1.09] (thrombo-embolic event, ischemic stroke or systemic embolism) Stroke (fatal and non fatal) RR=0.67 [0.44;1.01] (abrupt onset of a focal neurological deficit in the distribution of a brain artery persisting more than 24 hours or due to intracerebral hemorrhage) Ischemic stroke RR=0.70 [0.45;1.09] All cause death RR=0.99 [0.73;1.34]

Reference

Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. Lancet 2003 Nov 22;362:1691-8 [PMID=14643116]

Table 5.7: *SPORTIF V, 2005 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3922 (1960 vs. 1962) **Follow-up duration:** 20 months **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias north america, 409 centres **Inclusion period:** july 2000-dec 2001	One or more stroke risk factor in addition to atrial fibrillation.High risk patients with non valvular atrial fibrillation. **Inclusion criteria:** Age >18,Persistent or paroxysmal AF verified by at least 2 ECG,One or more stroke risk factors in addition to AF(hypertension,age >75,previous stroke TIA or systemic embolism,left ventricular dysfunction,age >65+coronary artery disease,age >65+diabete mellitus) **Exclusion criteria:** Mitral stenosis,Transient AF caused by reversible disorder,Stroke within the previous 30 days or TIA within 3 days,Condition associated with increased risk of bleeding,Active infective endocarditis,Current atrial myxoma or left ventricular thrombus,Admission for acute coronary syndrome or percutaeous coronary intervention within 30 days,Requirement for chronic anticoagulation treatment for disorders other than AF,planned cardioversion,Planned major surgery,treatment with platelet inhibitor drugs other than aspirin 100mg/day or less within 10 days or fibrinolytic agents within 30 days before ra	**Studied treatment:** ximelegatran 36 mg twice daily **Control treatment:** warfarin standard dose(target INR 2-3) **Concomittant treat.:**-aspirin <100 mg-other antithrombotic agents are prohibited within 10 days of randomisation and during the treatment phase.-NSAIDs are authorized up to 7 days per month-COX-2 inhibitors are permitted ad lib.-concomitant therapies are at the discretion of the treating physician (anticoagulants and antiplatelet agents excepted).	Systemic thrombo-embolic complication RR=6.01 [0.72;49.84] (abrupt vascular insufficiency asociated with clinical and radiological evidence of arterial occlusion in the absence of another likely mechanism) Thrombo-embolic event (cerebral or systemic) RR=1.38 [0.91;2.10] TE event or ischemic stroke or systemic embolism RR=1.25 [0.81;1.93] (thrombo-embolic event, ischemic stroke or systemic embolism) Stroke (fatal and non fatal) RR=1.24 [0.81;1.89] (abrupt onset of a focal neurological deficit in the distribution of a brain artery persisting more than 24 hours or due to intracerebral hemorrhage) Ischemic stroke RR=1.25 [0.81;1.93] All cause death RR=0.94 [0.74;1.21]

References

Halperin JL. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: Rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). Am Heart J 2003 Sep;146:431-8 [PMID=12947359]
Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, Halperin JL, Horrow J, Olsson SB, Petersen P, Vahanian A. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005 Feb 9;293:690-8 [PMID=15701910]

Table 5.8: *SPORTIF II (ximelagatran vs warfarin standard dose), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=254 (187 vs. 67) **Follow-up duration:** 16 weeks **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias Europe ,USA, 37 centres	Medium to high risk patients with chronic non valvular atrial fibrillation. **note:** -SPORTIF II is a dose guiding study-66 patient received 20mg,62 received 40mg,59 received 60 mg **Inclusion criteria:** -one or more stroke risk factor in addition to AF:history of hypertension,age >65,previous stroke or TIA,previous systemic embolism,left ventricular dysfunction,diabete mellitus,coronary heart disease-age >18-paroxysmal or persistent NVAF verified by at least 2 ECG **Exclusion criteria:** Stroke and /or systemic embolism within the previous 2 years,Condition associated with increased risk of bleeding,NVAF secondary to other reversible disorders,presence of mecanical heart valves,Myocardial infarction,coronary artery bypass grafting or Percutaneous transluminal coronary angioplasty within previous 3 month,Diagnosis of left ventricular aneurysm or atrial myxoma,Treatment with NSAIDs or fibrinolytics within previous week,Renal impairment,Blood pressure >180/100,History of rheumatic fever,Liver insufficiency,Hb <100g/l,Plat <100000,Contra-indication t	**Studied treatment:** ximelegatran 20,40,60 mg twice daily **Control treatment:** warfarin standard dose(target INR 2-3) **Concomittant treat.:**Beta-blockers,angiotensin-converting enzyme inhibitors,calcium antagonistsLow doses of aspirin are accepted(up to 160 mg/day) **note:** -treatment with either NSAI agents or fibrinolytic agents within the week before the start was prohibited-patient previously receiving warfarin were given ximelegatran once INR value was 1.5 or under/after the end of the study patients who stopped ximelegatran began warfarin 12 to 24 h after last intake.	

Reference

Petersen P, Grind M, Adler J. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. J Am Coll Cardiol 2003 May 7;41:1445-51 [PMID=12742279]

6 Global meta-analysis: all oral direct thrombin inhibitor

6.1 Global meta-analysis: all oral direct thrombin inhibitor versus warfarin standard dose

Table 6.1: *All oral direct thrombin inhibitorversus warfarin standard dose*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
systemic thrombo-embolic complication	RR=0.99	0.58;1.69	0.9769	0.3818 (0.04)	5	31718
thrombo-embolic event (cerebral or systemic)	RR=0.86 [1]	0.65;1.13	0.2772	0.0114 (0.73) †	4	31464
TE event or ischemic stroke or systemic embolism	RR=0.93	0.71;1.20	0.5624	0.1785 (0.42)	3	19366
ischemic stroke	RR=0.94	0.73;1.19	0.5929	0.0843 (0.51)	5	31718

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

7 Ongoing studies

No ongoing trial was identified.

8 Excluded studies

No trial was excluded.

References

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.83 95% CI 0.73;0.94