Dabigatran in real-world atrial fibrillation

Meta-analysis of observational comparison studies with vitamin K antagonists

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Summary

In the RE-LY clinical trial, dabigatran presented a better effectiveness/safety profile when compared to warfarin. However, clinical trials are not very representative of the real-world setting. We aimed to assess the performance of dabigatran in real-world patients with atrial fibrillation (AF) by means of a systematic review and meta-analysis of observational comparison studies with vitamin K antagonists (VKA). We searched PubMed, Embase and Scopus databases until November 2015 and selected studies according to the following criteria: observational study performed with nonvalvular AF patients; reporting adjusted hazard ratios (HR) of clinical events in a follow-up period; for dabigatran 75 mg, 110 mg or 150 mg versus VKA. Twenty studies were selected which included 711,298 patients, 210,279 of which were treated with dabigatran and the remaining 501,019 with VKA. Ischaemic stroke incidence was of 1.65 /100 patient-years for dabigatran and 2.85/100 patient-years for VKA (HR 0.86, 95 % confidence interval of 0.74–0.99). Major bleeding rate was 3.93/100 patient-years for dabigatran and 5.61/100 patient-years for VKA (0.79, 0.69–0.89). Risk of mortality (0.73, 0.61–0.87) and intracranial bleeding (0.45, 0.38–0.52) were significantly lower in patients treated with dabigatran when compared to patients on VKA. Risk of gastrointestinal (GI) bleeding was significantly higher in patients treated with dabigatran (1.13, 1.00–1.28). No significant difference was observed in risk of myocardial infarction (0.99, 0.89–1.11). In this combined analysis of real-world observational comparison studies with VKA, dabigatran was associated with a lower risk of ischaemic stroke, major bleeding, intracranial bleeding and mortality, higher risk of GI bleeding and a similar risk of myocardial infarction.

Keywords

Atrial fibrillation, dabigatran, vitamin K antagonist, real-world, meta-analysis

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Introduction

Atrial fibrillation (AF) is associated with a five-fold increase in thromboembolic risk, which determines significant morbidity and mortality (1). Oral anticoagulation significantly decreases the incidence of stroke and it is the only class I indication thromboprophylaxis in contemporary guidelines (2, 3). Dabigatran is a non-vitamin K antagonist oral anticoagulant (NOAC) that has demonstrated, when compared to warfarin, to reduce stroke and systemic embolism (150 mg dose twice daily [BID]), vascular mortality (150 mg dose BID), major bleeding (110 mg dose BID) and intracranial bleeding (IC) (both doses) in patients with nonvalvular AF (NVAF) (4, 5).

However, clinical trial populations are much selected, have a limited dimension and generally do not reflect all demographic features, such as advanced age and female gender, nor all clinical features, such as comorbidities, which are all representative of the real world. Additionally, patient follow-up in daily practice is also different from the more controlled clinical trial environment (6, 7). In this context, it is imperative to assess the safety and efficacy profiles of NOACs in observational studies of real-world representative populations.

Two systematic reviews and meta-analyses assessing the performance of dabigatran vs warfarin in real-world AF patients have shown a comparable effect in ischaemic stroke (8, 9) and major bleeding (8) but with wide confidence intervals (CIs). In this context, we performed an updated systematic review and meta-analysis of observational comparison studies of dabigatran with vitamin K antagonists (VKA) in patients with NVAF.

Methods

The current analysis was performed according to the Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) (10).

Database and search

We performed a systematic search of electronic databases PubMed, Embase and Scopus until November 2015 with the following search

terms – dabigatran, warfarin or vitamin K antagonist and atrial fibrillation. We also considered the studies identified in bibliographic references of articles selected by our research sentence and we did not exclude any study due to linguistic restrictions.

Eligibility criteria

We considered to be eligible all studies comprehending the following three criteria: observational study 1) performed with NVAF patients; 2) reporting adjusted hazard ratios (HRs) for clinical events in the follow-up period; 3) for dabigatran 75 mg, 110 mg or 150 mg and VKA. We excluded articles matching clinical trials, exclusive percutaneous ablation or cardioversion studies and abstracts.

Clinical events

For analysis purposes, we considered the following clinical events: 1) thromboembolic – ischaemic stroke, systemic embolism and myocardial infarction (MI); 2) bleeding – major, IC and gastrointestinal (GI); 3) mortality. Definitions of ischaemic stroke and major bleeding used across the studies are described in Suppl. Table 1 (available online at www.thrombosis-online.com).

Data extraction and study quality assessment

The eligibility of the articles found during database systematic search was assessed by two authors (JC and JF) independently and through abstract reading and, when necessary, of complete articles. The final selection of studies, which included the identification of duplicates, was performed by consensus. Data extraction was performed by both authors into a previously defined form, which included study identification data, design, population size and characteristics, time period, dabigatran doses, VKA, annual rates of clinical events, adjusted HR and 95% CI and confounding variables correction analyses. Study quality was assessed according to the Newcastle-Ottawa Scale (NOS) (11), which includes three components: selection (0–4 points), comparability (0–2 points) and exposure (0–3 points).

Statistical analysis

We performed a DerSimonian and Laird (12) random-effects meta-analysis to pool effect sizes (log-transformed HRs) estimates across studies. The collected data and pooled results where presented in forest plots. A two-sided p-value<0.05 was considered significant. We used the Review Manager (RevMan), V.5.3.

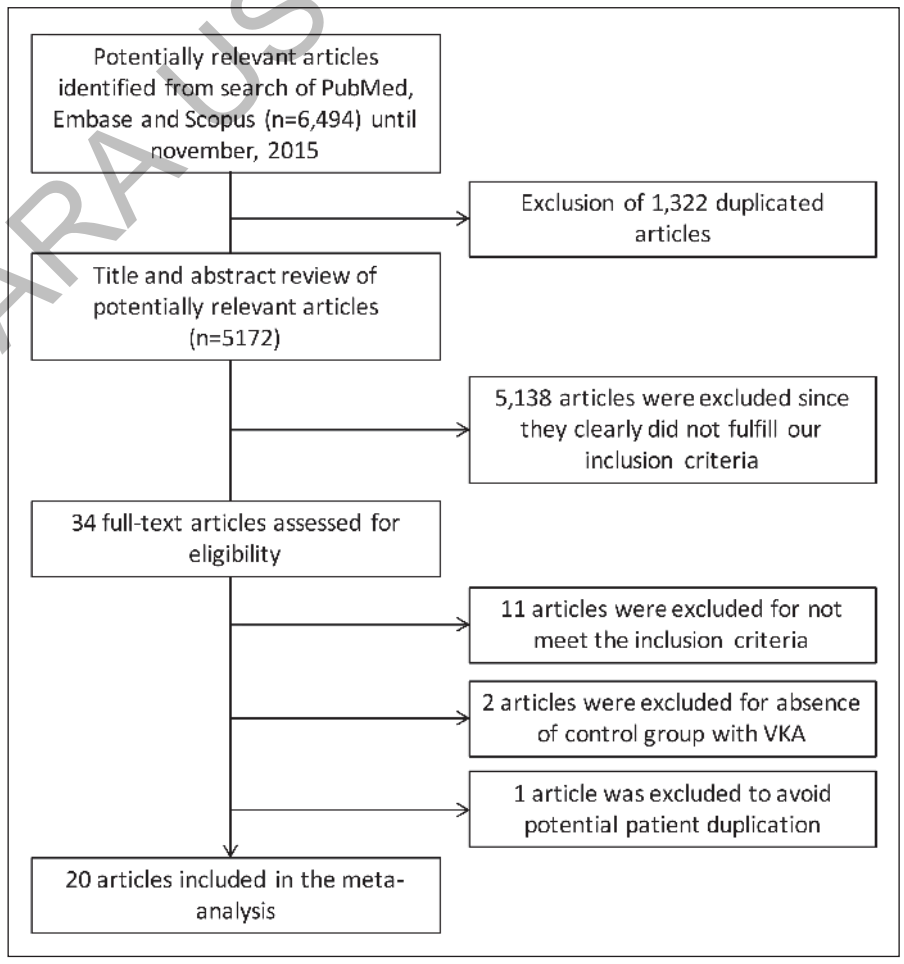

Figure 1: Flowchart diagram illustrating study selection methodology.

(Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) software to aggregate the meta-analysis results.

Heterogeneity across studies was assessed by I^2 (13) using Cochran's Q test, which estimates the proportion of variation in effect size attributable to inter-study heterogeneity, given that an I^2 test equal or higher than 50% determines significant heterogeneity (14). For sensitivity analyses, we examined the effects of studies performed in United States (US) and using new-user design; interactions were calculated using Cochran's Q test. Meta-regressions analyses were performed to investigate the impact of mean age and the proportion of females in the study population on the log-transformed HRs of ischaemic stroke and major bleeding. Publication bias was assessed by graphical inspection of funnel plots and by Egger test (15), using Comprehensive Meta-Analysis software (version 2).

Results

Database and bibliographic references systematic search generated 6,494 articles. After excluding studies that did not comply with eligibility criteria and duplicates, we identified 20 studies (16–35) that were considered for analysis (►Figure 1). Characteristics of selected studies are described in ►Table 1.

All studies were retrospective and included a total of 711,298 patients, 210,279 of which were treated with dabigatran and the remaining 501,019 with VKA. The studies of Graham et al. (21) and Villines et al. (33) reported all clinical events. Some studies did not report thromboembolic events, such as Vaughan Sarrazin et al. (20) and Ho et al. (16) which reported bleeding events and death, Hernandez et al. (23) and Nishtala et al. (35) that reported major and GI bleeding, and Chang et al. (27), where GI bleeding

Table 1: Main characteristics of the included studies.

Study	Period	Dabigatran	New-users (%)	Population	Age (years)	Female (%)	$CHADS_2$ $CHA2DS_2$-VASc*	Follow-up (years)
Ho et al. 2012 [16]	Jan/2010 to Nov/ 2011	110/150	100	244	70.1	46	2.4	0.85
Larsen et al. 2013 [17]	Aug/2011 to Jun/2012	110 and 150	100	13914	70.8	42	1.2	1.13
Larsen et al. 2014 [18]	Aug/2011 to Nov/2012	110 and 150	20	66198	74,6	42	1,5	1.33
Larsen et al. 2014 [19]	Aug/2011 to May/2013	110 and 150	62	33945	73.6	42	1,3	1.08
Vaughan Sarrazin et al. 2014 [20]	Jun/2011 to Sep/2012	75/150	0	85344	D: 69.7 W: 74.4	1,4	2.2	D: 0.73 W: 1.3
Graham et al. 2015 [21]	Oct/2010 to Dec/2012	75/150	100	134414	-	52	-	0.28
Ho et al. 2015 [22]	Jul/1997 to Dec/2011	110/150	NR	2178	79.5	57	4.1*	3
Hernandez et al. 2015 [23]	Oct/2010 to Oct/2011	75/150	100	9404	75	59	-	D: 0.48 W: 0.62
Bouillon et al. 2015 [24]	Jan/2011 to Nov/2012	75/110 and 150	0	15075	75	48	D: 3* VKA: 4*	0,83
Lauffenburger et al. 2015 [25]	2009–2012	75/150	100	64935	69.9	40	D: 2.3* W: 2.9*	0.98
Abraham et al. 2015 [26]	Nov/2010 to Sep 2013	75/150	100	15498	67	36	-	-
Chang et al. 2015 [27]	Oct/2010 to Mar/2012	75/150	100	44514	57.6	45	-	D:0.28 W: 0.23
Yap et al. 2015 [28]	Jan/2009 to Dec/2013	110/150	NR	1000	66	39	D: 2.7* W: 3.4*	D: 0.97 W: 0.86
Maura et al. 2015 [29]	Jul/2011 to Nov/2012	75/110 and 150	100	25110	74	46	3.2*	0.24
Avgil-Tsadok et al. 2015 [30]	1999–2013	110 and 150	34	63110	78.3	50	3,3*	1,3
Chan et al. 2015 [31]	2010–2013	110	NR	571	85	58	4.8*	2.6
Seeger et al. 2015 [32]	Jun/2011 to Sep/2012	75/150	100	38378	68	38	1.9	D: 0.42 W: 0.34
Villines et al. 2015 [33]	Oct/2009 to Jul/2013	75/150	100	25586	74	41	3.9*	D: 0.81 W: 0.59
Avgil-Tsadok et al. 2015 [34]	1999–2013	110 and 150	34	63110	78.3	50	3.3*	1.3
Nishtala et al. 2015 [35]	Jul/2011 to Dec/2012	110/150	100	8770	77	47	-	1.5

D: Dabigatran; NR: Not reported; VKA: Vitamin K antagonist; W: Warfarin.

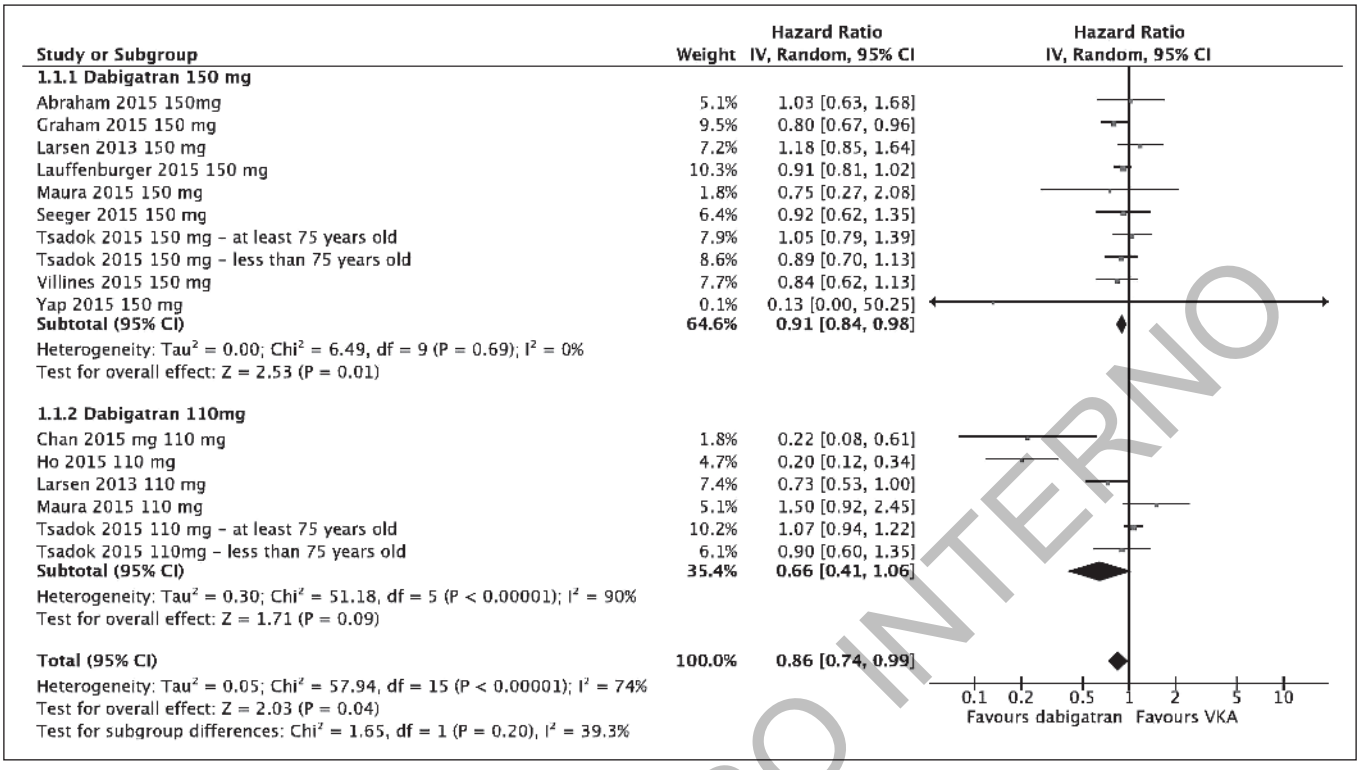

Figure 2: Forest plot comparing dabigatran vs VKA regarding ischaemic stroke. Hazard ratios (HR) and 95 % confidence intervals (CI) are shown for dabigatran 150 mg and 110 mg relative to VKA. Pooled estimates were calculated by random-effects meta-analysis. Level of significance was p<0.05.

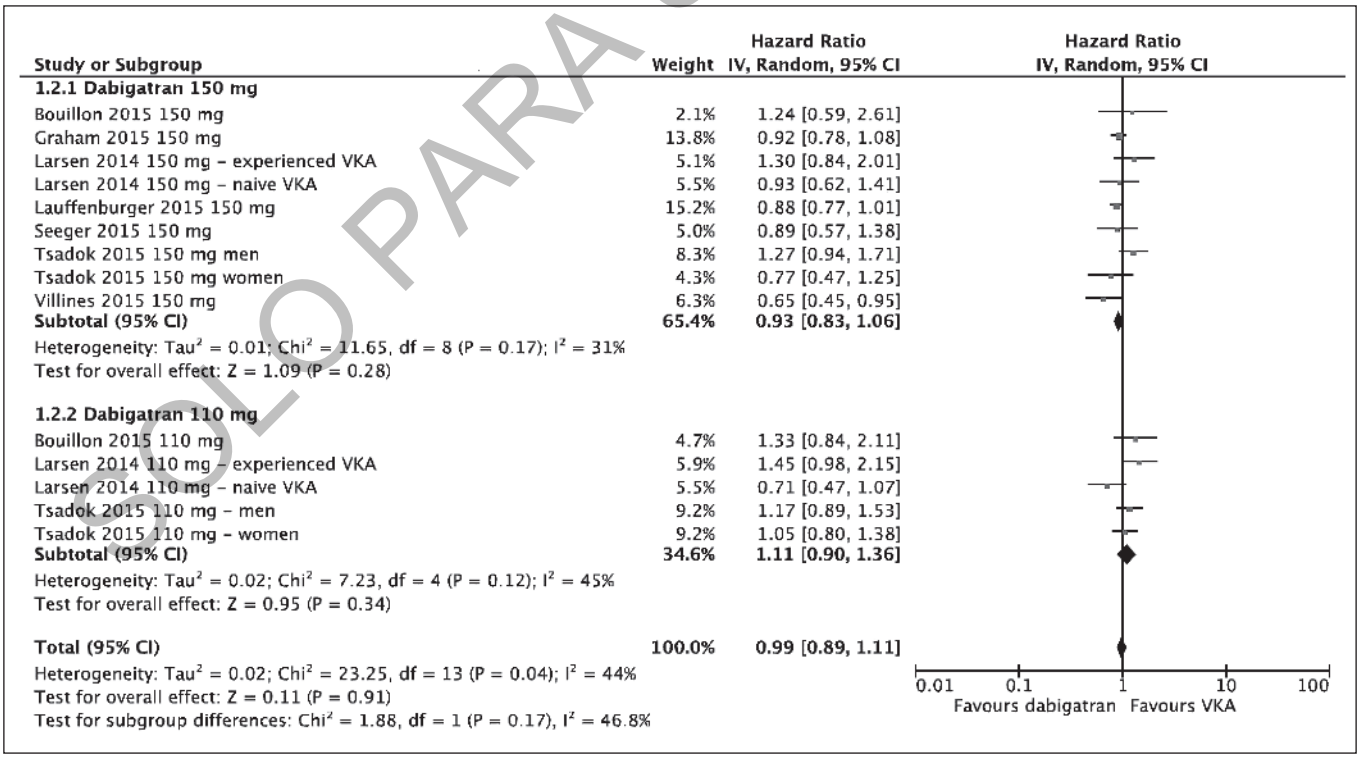

Figure 3: Forest plot comparing dabigatran vs VKA regarding myocardial infarction. Hazard ratios (HR) and 95 % confidence intervals (CI) are shown for dabigatran 150 mg and 110 mg relative to VKA. Pooled estimates were calculated by random-effects meta-analysis. Level of significance was p<0.05.

was the only reported event. Although some studies have selected patients from the same database, such as Larsen et al. (17–19) and Avgil-Tsadok et al. (30, 34), we only included the largest study whenever a clinical event was reported by two or more of these studies.

Studies were performed in different areas of the world, namely in the USA (20, 21, 23, 25–27, 32, 33), China (16, 22, 31), Denmark (17–19), France (24, 29), Canada (30, 34), Malaysia (28), and New Zealand (35). US studies were pooled in the dabigatran 150 mg group, which was the dominant dosage of the American label (21, 23). The same criterion was applied to the study of Yap et al., reporting 59 % of patients under 150 mg (28). Chinese studies were pooled in the dabigatran 110 mg group, since they reported utilisation rates of this dosage from to 90.2 16 to 100 % (31).

The number of patients enrolled varied from 244 to 134,414 and, in most studies that reported it, average age was higher than 70 years old and the $CHADS_2$ and CHA_2DS_2-VASc scores were higher than 2 and 3, respectively. Average follow-up varied between 0.23 and 3 years. Warfarin was the only VKA used in all studies, except in France (24, 29).

Average time of international normalised ratio (INR) within therapeutic range (TTR) was described in three studies, with 57 % for Vaughan Sarrazin et al. (20), 53.2 % for Yap et al. (28), and 38.8 % for Ho et al. (22).

The great majority of studies showed good quality within NOS, between 7 and 8 points (Suppl. Table 1, available online at www.thrombosis-online.com).

Thromboembolic events

In the 11 studies reporting ischaemic stroke (▶Figure 2) (17, 21, 22, 25, 26, 28–33), the incidence was 1.65 events per 100 patient-years for dabigatran and 2.85 events per 100 patient-years for VKA (HR 0.86 and 95 % CI 0.74–0.99; I^2 = 74 %). Systemic embolism was reported by Larsen et al. (17) (0.3 %/year vs 0.4 %/year for dabigatran 110 mg compared with VKA matched and 0.2 %/year for both dabigatran 150 mg and VKA matched), and Maura et al. (29), in aggregate with ischaemic stroke. In the pooled analysis, dabigatran 150 mg was associated with a significant lower risk of ischaemic stroke as compared to VKA (HR 0.91, 0.84–0.98; I^2 = 0 %).

Seven studies reported MI (▶Figure 3) (18, 21, 24, 25, 32, 33, 34), and the risk was similar in patients treated with dabigatran and VKA (HR 0.99, 0.89–1.11; I^2 = 44 %).

Bleeding events

Major bleeding was reported in 11 studies (▶Figure 4) (19, 21–23, 25, 28, 29, 32–35). In patients treated with dabigatran, the rate of

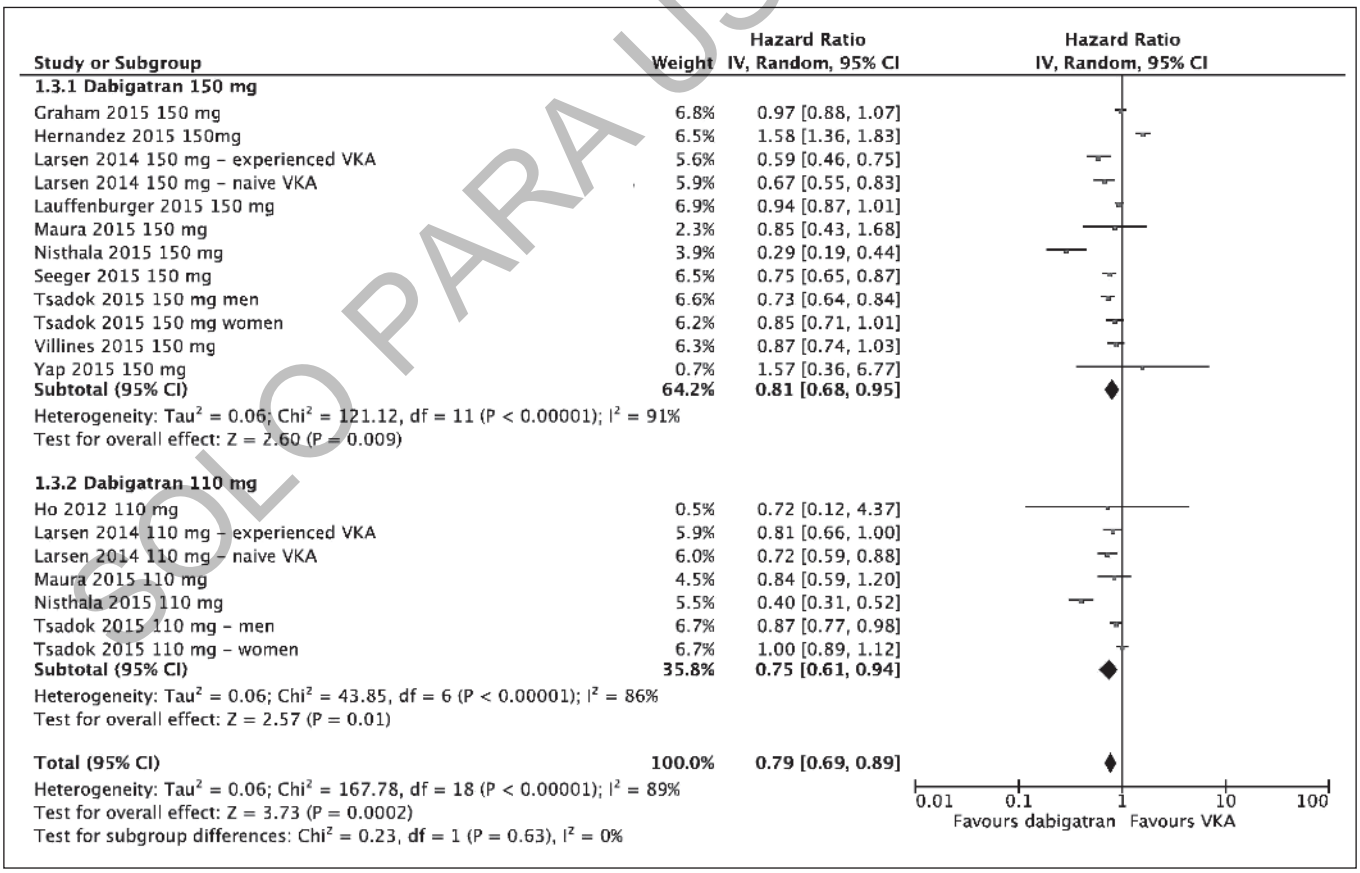

Figure 4: Forest plot comparing dabigatran vs VKA regarding major bleeding. Hazard ratios (HR) and 95 % confidence intervals (CI) are shown for dabigatran 150 mg and 110 mg relative to VKA. Pooled estimates were calculated by random-effects meta-analysis. Level of significance was p<0.05.

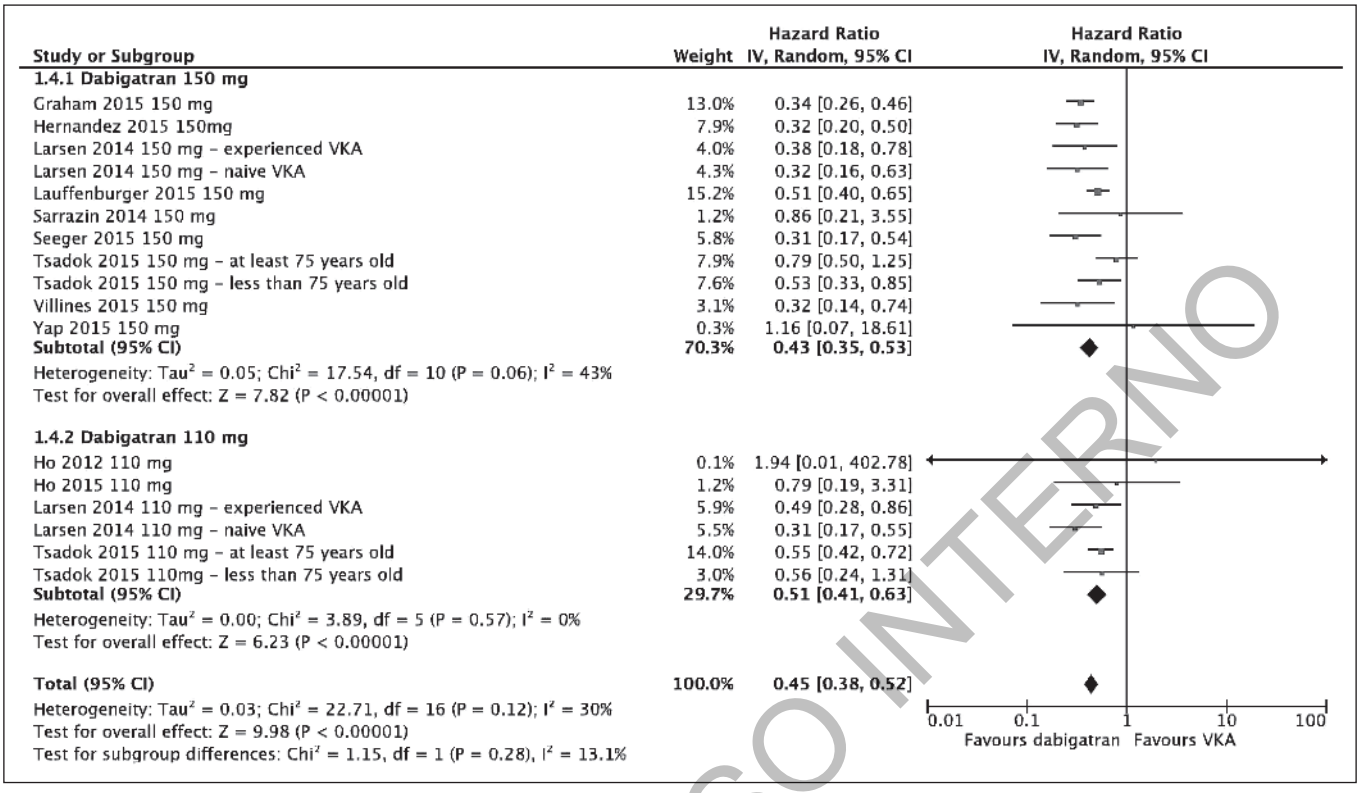

Figure 5: Forest plot comparing dabigatran vs VKA regarding intracranial bleeding. Hazard ratios (HR) and 95 % confidence intervals (CI) are shown for dabigatran 150 mg and 110 mg relative to VKA. Pooled estimates were calculated by random-effects meta-analysis. Level of significance was p<0.05.

major bleeding was 3.93 per 100 patient-years vs 5.61 per 100 patient-years for VKA (HR 0.79, 0.69–0.89; I^2 = 89 %). Both dosages of dabigatran were associated with significant lower hazard of major bleeding vs VKA.

IC (►Figure 5) (16, 19–23, 25, 28, 30, 32, 33) and GI bleeding (►Figure 6) (16, 19–21, 23, 25–27, 30, 32, 33, 35) were reported in 11 and 12 studies, respectively. The risk of IC bleeding was significantly lower (HR 0.45, 0.38–0.52; I2 = 30 %) and the risk of GI bleeding was significantly higher (HR 1.13, 1.00–1.28; I^2 = 81 %) in patients treated with dabigatran compared to VKA. The increased risk of GI bleeding was only significant in patients receiving dabigatran 150 mg relative to VKA (HR 1.18; 1.02–1.36; I^2 = 85 %)

Death

Death from any cause was reported in five studies (►Figure 7) (16, 17, 20, 21, 33), with an incidence of 3.60 per 100 patient-years for dabigatran and 6.07 per 100 patient-years for VKA (HR 0.73, 0.61–0.87; I^2 = 69 %).

Sensitivity analyses

Results were consistent among studies performed in the US or outside the US (►Table 2) except for MI, with a lower risk for dabigatran in studies performed in the US (p for interaction=0.023), and major bleeding, with a lower risk for dabigatran in studies performed outside the US (p for interaction=0.049). Results were consistent in studies with new-user design or including experienced VKA patients (►Table 3), except for MI, with a significant higher hazard for dabigatran vs VKA in studies with experienced VKA patients (HR 1.18, 1.03–1.34), and for IC bleeding (p for interaction=0.002).

Subgroup analyses

Meta-regression analyses investigating potential effects of demographic characteristics on the efficacy of dabigatran compared to VKA on ischaemic stroke (Suppl. Figure 1, available online at www.thrombosis-online.com) revealed significant effects of mean age (coefficient –0.072, 95 % CI –0.146 to –0.004; p=0.04) and the proportion of females (coefficient –0.048, 95 % CI –0.090 to –0.006; p=0.029). There were no significant relationships between the safety of dabigatran compared to VKA on major bleeding (Suppl. Figure 2, available online at www.thrombosis-online.com) and mean age (coefficient: –0.018, 95 % CI –0.100 to 0.063; p=0.62) or proportion of females (coefficient 0.026, 95 % CI –0.003 to 0.055; p=0.073).

Publication bias

No publication biases were found in any of the analyses performed (Suppl. Table 2, available online at www.thrombosis-online.com).

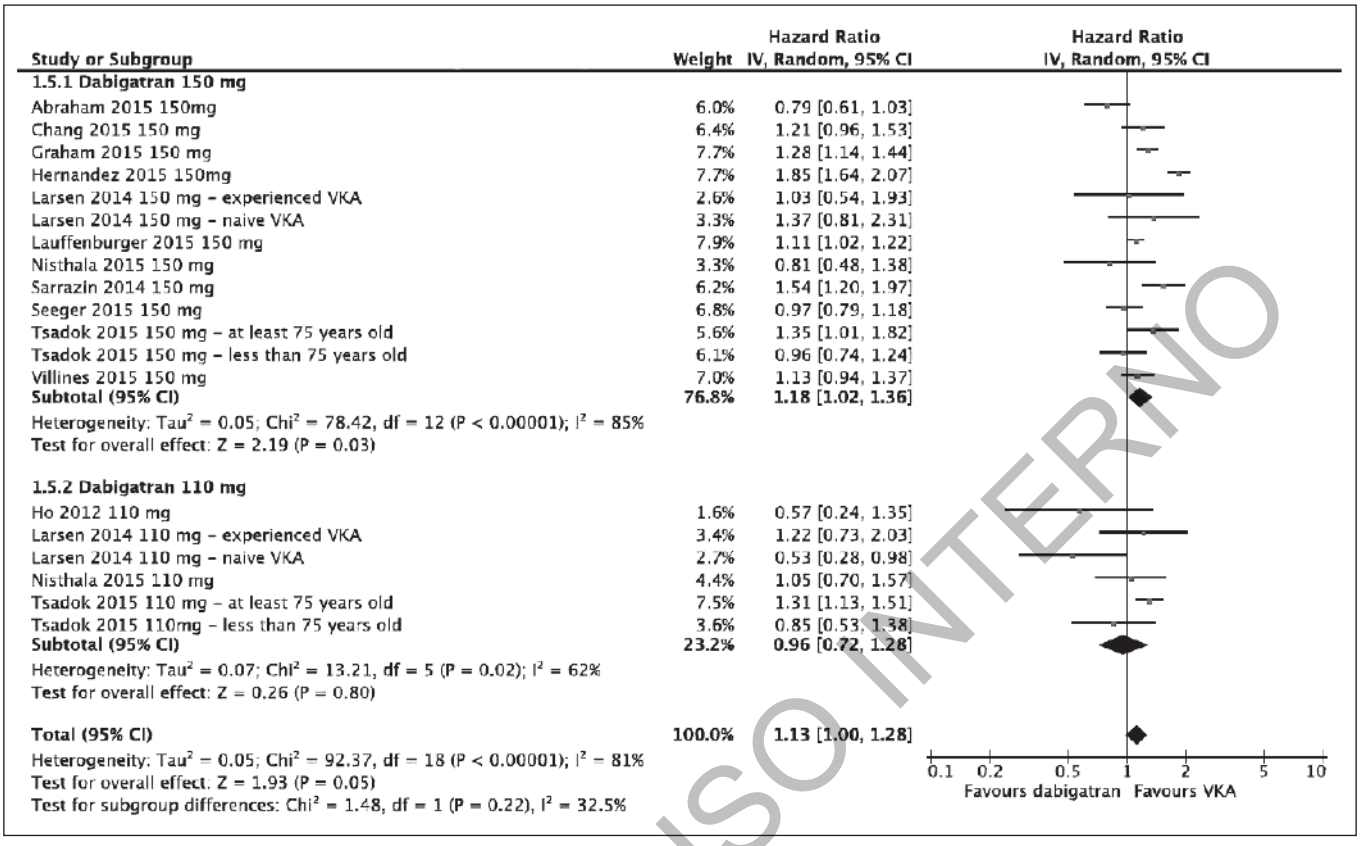

Figure 6: Forest plot comparing dabigatran vs VKA regarding gastrointestinal bleeding. Hazard ratios (HR) and 95 % confidence intervals (CI) are shown for dabigatran 150 mg and 110 mg relative to VKA. Pooled estimates were calculated by random-effects meta-analysis. Level of significance was p<0.05.

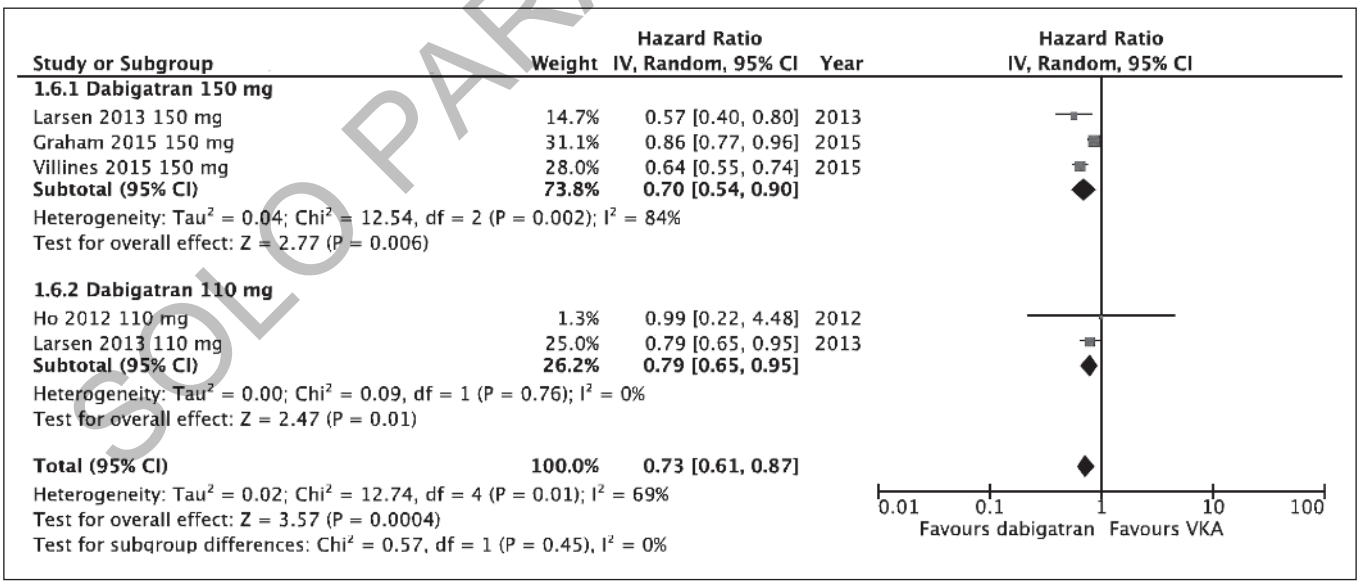

Figure 7: Forest plot comparing dabigatran vs VKA regarding mortality. Hazard ratios (HR) and 95 % confidence intervals (CI) are shown for dabigatran 150 mg and 110 mg relative to VKA. Pooled estimates were calculated by random-effects meta-analysis. Level of significance was p<0.05.

Discussion

In this systematic review and meta-analysis of real world observational studies, patients with NVAF treated with dabigatran showed a lower risk of ischaemic stroke, major bleeding and death than with VKA. These results are generally similar to those of the RE-LY clinical trial (4, 5), and they do not support the projection of lower benefits of dabigatran when exposed to older patients, with a lower level of renal function, higher bleeding risk, and lower adhesion potential of therapy (36).

These results are apparently discordant from previous meta-analysis, which showed no statistically significant reduction in ischaemic stroke (8, 9) and major bleeding (8) associated with dabigatran when compared with VKA. There are differences in size of the CIs, since our systematic review had not the same eligibility criteria (9) and had extended the research period to November 2015, compared to December 2014 (8) and March 10, 2015 (9) of previous meta-analyses, which more than doubled the number of patients included (711,298 vs 291,703 [8] and 348.750 [9]).

As expected in a comparison between a registry and a clinical trial, ischaemic stroke, major bleeding and death event rates were higher in this combined analysis of real world observational studies than in the RE-LY trial (4, 5). However, the differences were not substantial and can be justified by the fact that the population included in the RE-LY clinical trial represented almost 75% of AF patients included in a contemporary registry coming from the UK (37).

Ischaemic stroke risk reduction associated with dabigatran was consistent with the one observed in RE-LY (4, 5). In fact, we observed a significant 14% relative risk reduction in ischaemic stroke mainly due to the performance of studies conducted in Asia and reporting combined or isolated results of dabigatran 150 mg BID. Asian guidelines recommend a lower target INR, based on the assumption that Asian patients are at unacceptably higher risk of bleeding while receiving VKA (38), which can result in reduced protection against stroke. We performed a sensitivity analysis to evaluate the performance of the American label, e.g. with the 150 mg dose BID, except in patients with creatinine clearance levels between 15 and 30 ml/minute that received 75 mg BID (39), in the real world. The benefit of this label has been subject of debate (40), resulting from the higher risk of bleeding vs improved stroke protection of dabigatran 150 mg in the elderly. Indeed, in patients treated according to the American label in studies performed in the US (20, 21, 23, 25–27, 32, 33) risk reduction was 11%.

An interesting finding of the subgroup analyses is that the benefit of dabigatran compared to VKA on ischaemic stroke growths with increasing mean age and proportion of females in the study population, features that are established risk factors for stroke in AF.

MI risk associated with dabigatran was not higher in this meta-analysis of observational studies, unlike the non-significant increase observed in the RE-LY clinical trial (4, 5). These results do not support the thesis of dabigatran being associated with higher MI risk (41) and underlines the relevance of looking at the result in view of the statistical strength of the study (42).

Table 2: Sensitivity analysis for studies performed in the US vs outside the US.

Clinical event	HR and 95% CI	Interaction p-value
Ischemic stroke		0.790
US	0.89 [0.68, 1.15]	
Outside US	0.83 [0.67, 1.02]	
Myocardial infarction		0.023
US	0.88 [0.79, 0.97]	
Outside US	1.10 [0.96, 1.26]	
Major bleeding		0.049
US	0.99 [0.81, 1.20]	
Outside US	0.75 [0.65, 0.86]	
Intracranial bleeding		0.100
US	0.39 [0.32, 0.48]	
Outside US	0.50 [0.42, 0.61]	
Gastrointestinal bleeding		0.366
US	1.21 [1.02, 1.43]	
Outside US	1.07 [0.88, 1.30]	
Mortality		0.770
US	0.75 [0.60–0.94]	
Outside US	0.71 [0.53–0.94]	

US: United States.

Table 3: Sensitivity analysis for studies with new-user design and studies including experienced VKA patients (Others).

Clinical event	HR and 95% CI	Interaction p-value
Ischemic stroke		0.150
New-users	0.90 [0.81, 1.01]	
Others	0.67 [0.46, 0.98]	
Myocardial infarction		<0.001
New-users	0.87 [0.79, 0.95]	
Others	1.18 [1.03, 1.34]	
Major bleeding		0.920
New-users	0.78 [0.63, 0.97]	
Others	0.79 [0.70, 0.88]	
Intracranial bleeding		0.002
New-users	0.38 [0.31, 0.45]	
Others	0.57 [0.47, 0.68]	
Gastrointestinal bleeding		0.310
New-users	1.08 [0.91, 1.28]	
Others	1.22 [1.05, 1.42]	

All studies reporting mortality used new-user design.

We found a significant lower risk of MI in studies performed in the US that can be related to the lower representativeness of switchers from VKA to dabigatran, which was associated to higher risk of myocardial events (18).

This combined analysis of the observational studies reveals a significant lower risk of major bleeding for dabigatran, as compared to VKA and validates the high safety profile of dabigatran regarding IC bleeding risk. These results are in line with the RE-LY, and the significant 21% relative risk reduction in major bleeding is mainly due to the performance of dabigatran adjusted to age, as demonstrated in the European label sub-analysis of the RE-LY (43), which uses its lowest dose of 110 mg BID in elderly patients, with a higher bleeding risk or treated with verapamil. Indeed, risk of major bleeding was lower in patients included outside the US. The lower rate of INR monitoring within therapeutic range, verified in the observational studies that reported it (20, 22, 28), may have contributed to significant lower risk of major bleeding with dabigatran vs VKA. There were no significant relationships between the safety of dabigatran compared to VKA on major bleeding and demographic features associated with increased haemorrhagic risk.

The significant increase of GI bleeding risk in this meta-analysis is also in line with the RE-LY trial, since the majority of patients were treated with dabigatran 150 mg BID. The increased risk of GI bleeding associated with NOACs may be related to the presence of active drug in the intestinal lumen generated by limited oral bioavailability.

Risk of death from any causes associated with dabigatran was significantly lower than with VKA and this result was also reproduced in sensitivity analyses. The reduction in mortality is in agreement with RE-LY data, particularly with the European label analysis, which demonstrated a 14% reduction in relative risk of death from any causes and a 20% reduction in vascular death (43). Impact in mortality is essentially due to a strong reduction in IC bleeding, which is associated with a premature lethality of approximately 40% (44).

We included studies with VKA experienced patients to represent real-world practice. Although the new-user design may reduce biases, such as confounding, it may also induce loss of precision in estimates of comparative effectiveness (45). Indeed, there was no significant interaction between the risk of ischaemic stroke or major bleeding for dabigatran compared to VKA and studies following or not the new-user design. We found a significant 18% relative hazard increase of MI for dabigatran vs VKA in studies with experienced VKA patients, largely due to the study of Larsen et al., possibly related to the selection of poor adherence older patients with more comorbidity to switch from VKA to dabigatran (18).

This systematic review and meta-analysis presents several limitations. Selected studies do not report all clinical events included in the analysis and follow-up duration is lower than one year in most studies, which reduces its statistical power. However, its representativeness is high as the dimension of population is more than 30 times larger than RE-LY, all selected studies reported adjusted HRs for clinical outcomes and, as mentioned earlier, annual rates of clinical events are compatible with the real world. Quality assessed by NOS score scale 9 show good quality and no publication biases were found. Only three studies reported average TTR values, which does not allow for an assessment of anticoagulation quality obtained with VKA. This shortcoming is in line with the difficulty of monitoring the anticoagulation effect of VKA in day-to-day clinical practice (46). Finally, heterogeneities across studies for ischaemic stroke, major and GI bleeding and mortality were significant, which limits the validity of the results. However, it must be highlighted that the consistency of the results demonstrated in the sensitivity analyses make them more robust.

In conclusion, in this systematic review and meta-analysis of 20 observational studies with more than 700,000 AF patients, the risks of ischaemic stroke, major and IC bleeding, and death associated with dabigatran were lower and the risk of MI was similar to VKA. GI bleeding was significantly higher in patients treated with dabigatran. These results support that the benefits of dabigatran demonstrated in RE-LY can be generally used in real world. Studies with long-term follow-up are needed.

What is known about this topic?

- In the RE-LY trial, dabigatran was non-inferior to warfarin for stroke prevention in patients with nonvalvular atrial fibrillation.
- Data on the safety and effectiveness in real-world atrial fibrillation is expanding.

What does this paper add?

- This paper provides evidence for improved health outcomes with dabigatran relative to VKA in a real-world setting.
- In our meta-analysis of 711,298 patients, dabigatran was associated with lower risk of ischaemic stroke, major bleeding, intracranial bleeding and mortality, similar risk of myocardial infarction and a higher risk of gastrointestinal bleeding, when compared to VKA.

Conflicts of interest

Dr Ferreira reports having received consultancy fees and payment for lectures for Boehringer-Ingelheim. None of the other authors declares any conflicts of interest.

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