Clinical Drug Investigation
https://doi.org/10.1007/s40261-021-01091-w

SYSTEMATIC REVIEW

Effectiveness and Safety of Dabigatran Compared to Vitamin K Antagonists in Non-Asian Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis

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Accepted: 5 October 2021

Abstract

Background and Objective Real-life data about the use of dabigatran in patients with non-valvular atrial fibrillation are warranted. The objective of this systematic review and meta-analysis was to assess the effectiveness and safety of dabigatran, globally and stratified by dose (110/150 mg twice daily), vs vitamin K antagonists in non-Asian patients with non-valvular atrial fibrillation from "real-world" studies.

Methods A systematic review was performed according to Cochrane methodological standards. The results were reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement) statement. The ROBINS-I tool was used to assess bias risk. MEDLINE and EMBASE, from inception up to May 2021, using appropriate controlled vocabulary and free search terms, were searched.

Results A total of 34 studies, corresponding to 37 articles involving 1,600,722 participants (1,154,283 exposed to vitamin K antagonists and 446,439 to dabigatran) were eligible for this review. Dabigatran 150 mg reduced the risk of ischemic stroke compared with vitamin K antagonists, with a 14% risk reduction (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.74–0.98). Globally, dabigatran reduced the risk of all-cause mortality compared with vitamin K antagonists (HR 0.76, 95% CI 0.69–0.84), with a greater effect observed with dabigatran 150 mg (HR 0.65, 95% CI 0.58–0.73). There was a trend towards a lower risk of myocardial infarction with dabigatran 150 mg (HR 0.86, 95% CI 0.71–1.04). Regarding the primary safety outcomes, dabigatran (either at a dose of 150 mg or 110 mg) reduced the risk of major bleeding compared with vitamin K antagonists (HR 0.77, 95% CI 0.70–0.83), as well as the risk of intracranial bleeding (HR 0.44, 95% CI 0.39–0.50) and fatal bleeding (HR 0.76, 95% CI 0.60–0.95), but with a slight increase in gastrointestinal bleeding risk (HR 1.16, 95% CI 1.08–1.26).

Conclusions Dabigatran has a favorable impact on effectiveness and safety outcomes compared with vitamin K antagonists in real-world populations.

1 Introduction

Atrial fibrillation (AF) markedly increases the risk of stroke and death [1]. In addition, AF-related stroke is associated with high rates of mortality, disability, and recurrence [2, 3]. Anticoagulation represents the cornerstone in the prevention of stroke and systemic embolism among patients with AF [1]. For decades, vitamin K antagonists (VKA) have been used for thromboembolic prevention in patients with AF. However, VKA exhibit many disadvantages, including the narrow therapeutic window, multiple drug–drug interactions, dietary restrictions, periodic monitoring, and multiple dose adjustments in routine practice [4].

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Published online: 13 October 2021

Key Points

In non-Asian real-life patients, dabigatran may reduce the risk of ischemic stroke and all-cause mortality compared with vitamin K antagonists, particularly with dabigatran 150 mg.

There was a trend towards a lower risk of myocardial infarction with dabigatran 150 mg.

Both doses of dabigatran reduce the risk of major, intracranial, and fatal bleeding compared with vitamin K antagonists.

Direct oral anticoagulants (DOACs) overcome some of these limitations and the use of DOACs in clinical practice is continuously growing [5, 6]. Dabigatran was the first DOAC to be marketed worldwide and it is currently the only DOAC that directly inhibits thrombin [7]. In the RE-LY trial, compared to warfarin, dabigatran 150 mg twice daily (b.i.d.) significantly reduced the risk of stroke or systemic embolism, with similar major bleeding rates, whereas dabigatran 110 mg b.i.d. exhibited a similar risk of stroke or systemic embolism to warfarin, but with a lower risk of major bleeding [8]. However, it has been widely reported that the clinical profile of patients included in clinical trials is somewhat different to those of observational studies, suggesting that data from clinical trials could not always be directly translated into real-life patients [9]. In recent years, many database studies have analyzed the use of dabigatran among patients with AF in clinical practice. However, discrepancies in the results of these studies may emerge as there are differences in data sources, the statistical analysis approach, and the patient clinical profile [7]. The aim of this systematic review was to assess the comparative effectiveness and safety of dabigatran b.i.d. globally and stratified by dose (110 or 150 mg b.i.d.), compared to VKA in non-Asian patients with NVAF from "real-world" studies.

2 Methods

This systematic review was conducted according to the methodological standards by the Cochrane Collaboration [10] and is based on a protocol registered in PROSPERO (CRD42019145690) [11]. The report follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) Statement guidance [12].

Eligible studies were observational comparative studies (prospective or retrospective) assessing the effects of the exposition to dabigatran at a dose of 110 or 150 mg b.i.d. for at least 3 months (safety outcomes) or 6 months (effectiveness outcomes) vs VKA (warfarin, acenocumarol, or phenprocoumon) in real-world patients diagnosed with NVAF (either new users or switchers). Studies had to report at least one of the following outcomes: ischemic stroke, composite outcome of ischemic stroke plus systemic embolism, major bleeding, intracranial bleeding, fatal bleeding (considered as primary endpoints) and/or gastrointestinal bleeding, systemic embolism, myocardial infarction, pulmonary embolism, and all-cause mortality (secondary outcomes).

2.1 Inclusion/Exclusion Criteria

Inclusion criteria were limited to those studies using as a data source national or regional-wide registers, both administrative or clinical, covering a large non-Asian population ($N > 1000$ patients, restricted to dabigatran-treated and VKA-treated patients). Reanalyses or subgroup analyses from randomized controlled trials or modeling studies were not included. Studies conducted exclusively in Asian populations were excluded because Asian patients differ in their risk of bleeding and thrombosis under anticoagulant therapy conditions and this could bias the results [13]. Studies that contained an unspecified or lower dose (75 mg) of dabigatran were also excluded. Studies did not have to overlap with other studies already included. In the case of an overlap, for each specific outcome, we used data from the most complete report or the biggest sample population.

2.2 Search Methods

We searched MEDLINE (access via PubMed) and EMBASE (access through OVID), from inception up to May 2021, using appropriate controlled vocabulary and free search terms (Table 1 of the Electronic Supplementary Material [ESM]). Additionally, the reference lists from eligible studies as well as other reviews on this topic were screened to identify relevant studies. No language limitations were imposed. We did not search for gray literature, research that is either unpublished or has been published by organizations outside of the traditional commercial or academic publishing and distribution channels.

2.3 Study Selection and Data Extraction

Two authors (AA and CR) independently screened the search results based on the title and abstract. We retrieved a full-text copy of the references that was deemed to be eligible in this step, and the same researchers independently confirmed eligibility based on the inclusion criteria. Disagreements were solved by reaching consensus or by a third researcher. We used the bibliographic management software Rayyan QCRI in order to manage the results obtained and

perform the screening [14]. One reviewer (AA) extracted the relevant data from all included studies using a specific data form and a second researcher (CR) cross-checked the data extracted for accuracy.

2.4 Risk-of-Bias Assessment

We used ROBINS-I to assess the risk of bias of the included studies [15]. For each study, two authors independently assessed the following: confounding, selection bias, bias in measurement interventions, bias due to deviations from intended interventions, bias due to missing data, bias in outcome assessment, and bias in the selection of the reported results (Table 2 of the ESM).

All of the analyzed outcomes were defined as time-to-event variables. Accordingly, the effect measure considered for time-to-event outcomes was hazard ratio (HR) [95% confidence interval (CI)]. When feasible, we obtained pooled estimates of effect by means of formal meta-analytic techniques, applying the inverse-variance method under a random-effects model, using the Review Manager software (version 5.3.5). The heterogeneity across study results was assessed through the I^2 statistic. For the interpretation of results, we used the following cut-off values for I^2: values lower than 20% were considered unimportant; values from 21 to 65% were considered moderate; and values of I^2 over 65% were considered highly heterogeneous. When data allowed, a subgroup analysis was performed according to sex. Sensitivity analyses were conducted and restricted to naive participants and to participants aged older than 65 years. In addition, a sensitivity analysis was performed restricted to studies using a propensity score as a statistical matching tool. Subgroups and sensitivity analyses were only conducted for primary outcomes.

3 Results

The search results as well as the decisions made during the eligibility process are displayed in a PRISMA flowchart (Fig. 1). Search strategies yielded 7527 unique references. After completing the screening, we identified a total of 34 studies, corresponding to 37 articles, involving 1,600,722 (1,154,283 exposed to VKA and 446,439 to dabigatran) that were eligible for the review (Table 3 of the ESM) [16–52].

A total of 249 studies were excluded because of several reasons. See Table 4 of the ESM for details. We excluded 13 studies that reported overlapped data with other included studies (Table 5 of the ESM).

3.1 Description of the Studies

A summary description of included studies is provided in Table 3 of the ESM. All the studies reported findings from a cohort study design. Thirty-two studies were retrospective [16–36, 38–40, 42–52] and two studies were prospective [37, 41]. The source of the data was from an administrative database in 18 studies [16, 17, 20, 22–24, 26, 31, 35–41, 45, 48, 49, 51, 52] and four used a commercial database [21, 30, 42, 46]. Instead, in 12 studies [18, 19, 25, 27–29, 32–34, 44, 47, 50], data were extracted from a national healthcare database.

The studies used different approaches to control for confounding, the propensity score method was used more frequently in 23 studies [16–18, 20, 23, 24, 26–28, 30–32, 34–40, 42–49]. Ten studies performed adjusted analyses according to a Cox analysis [19, 21, 22, 25, 27, 29, 33, 41, 51, 52] and one study performed a multivariate competing risk regression [50]. Thirty-four articles provided data about our primary outcome/s, 23 of which also reported on secondary outcome/s. Three articles [29, 35, 45] provided data only on secondary outcome/s.

Three of the studies (with 15,157 participants) [33, 37, 44] had as an intervention dabigatran only at a dose of 110 mg; 15 studies (with 180,823 participants) [19–21, 23, 24, 28–32, 35, 36, 40–42, 46] had only dabigatran 150 mg, and eight studies [16–18, 22, 26, 27, 34, 48, 50] had both doses (with 44,666 participants at a dose of 110 mg and 31,785 at a dose of 150 mg). Moreover, there were eight studies (with 174,008 participants) [25, 38, 39, 45, 47, 49, 51, 52] that provided only unspecified doses (but not 75 mg).

With regard to the comparison group, 22 of the studies (with 439,174 participants) used warfarin [16, 17, 20–25, 27, 28, 30, 31, 33–38, 40–43, 46, 48, 50], two studies (with 47,477 participants) [26, 39] used phenprocoumon, one study (with 32,476 participants) [49] used acenocoumarol, and in nine of the studies (with 635,156 participants) [18, 19, 29, 32, 44, 45, 47, 51, 52] it was not specified which VKA was used. As for the follow-up, because the vast majority were retrospective analyses, the duration was different for each patient, with a range from 6 months to 3 years on average.

3.2 Risk of Bias of Included Studies

All of the included studies in the review had an overall moderate risk of bias mainly due to potential confounding (baseline). The risk of bias is summarized in Table 6 of the ESM.

3.3 Effects of the Intervention

Two effectiveness outcomes were pre-specified as primary outcomes: ischemic stroke and the composite of ischemic stroke/systemic embolism. Dabigatran did not modify the

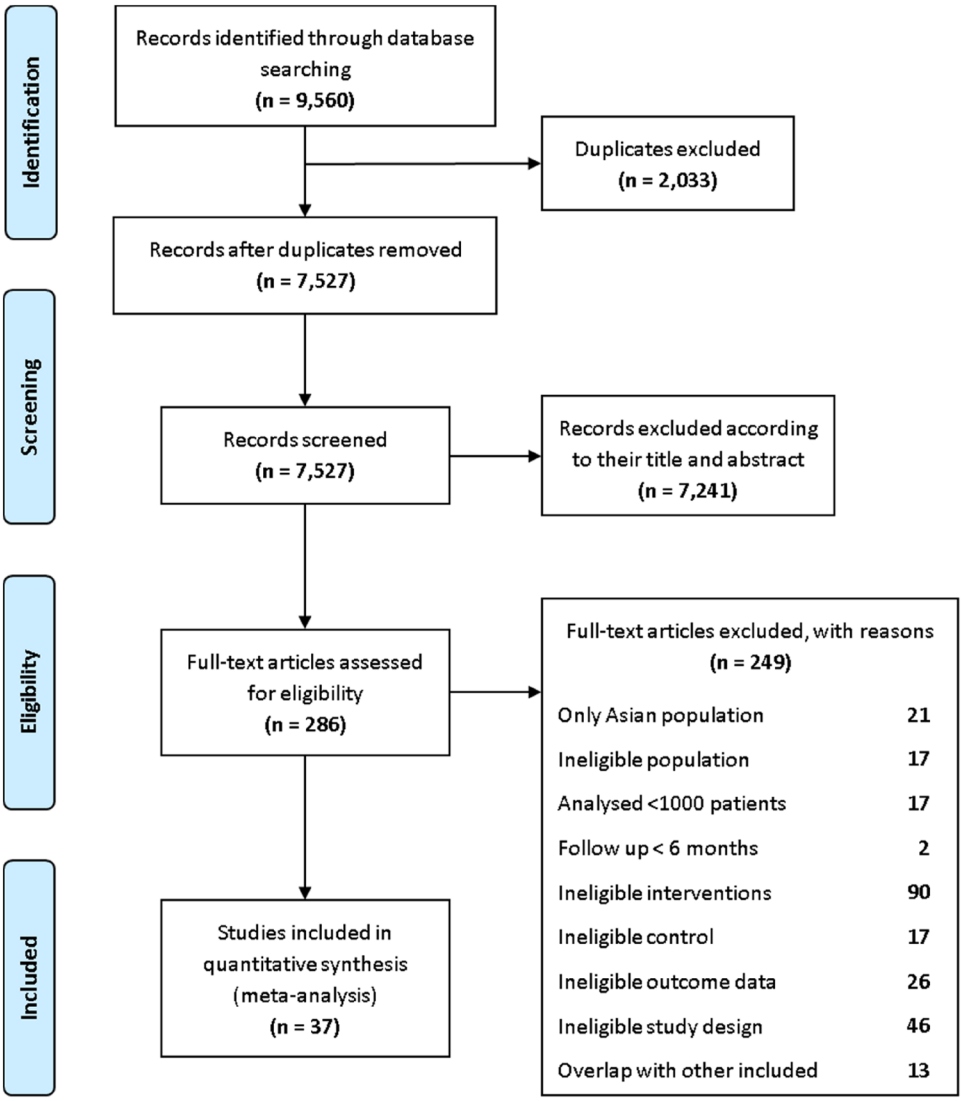
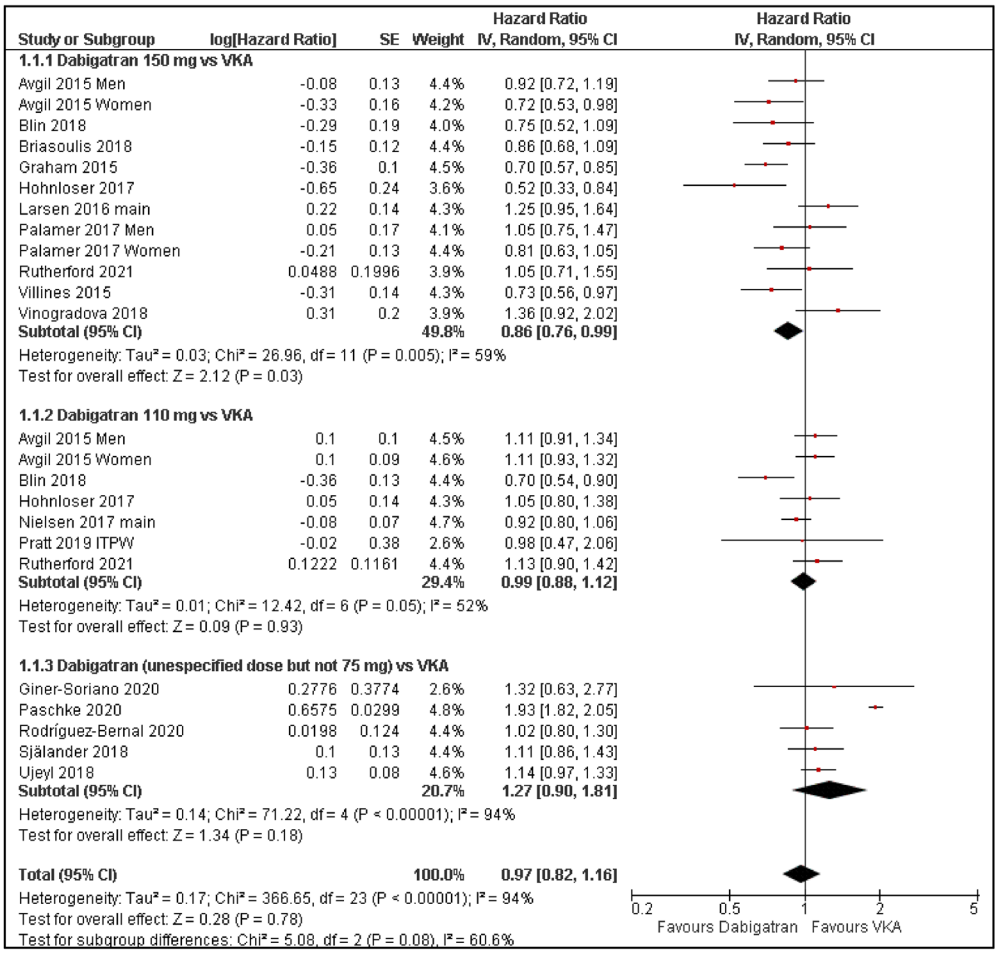


Fig. 1 Eligibility PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement) flowchart

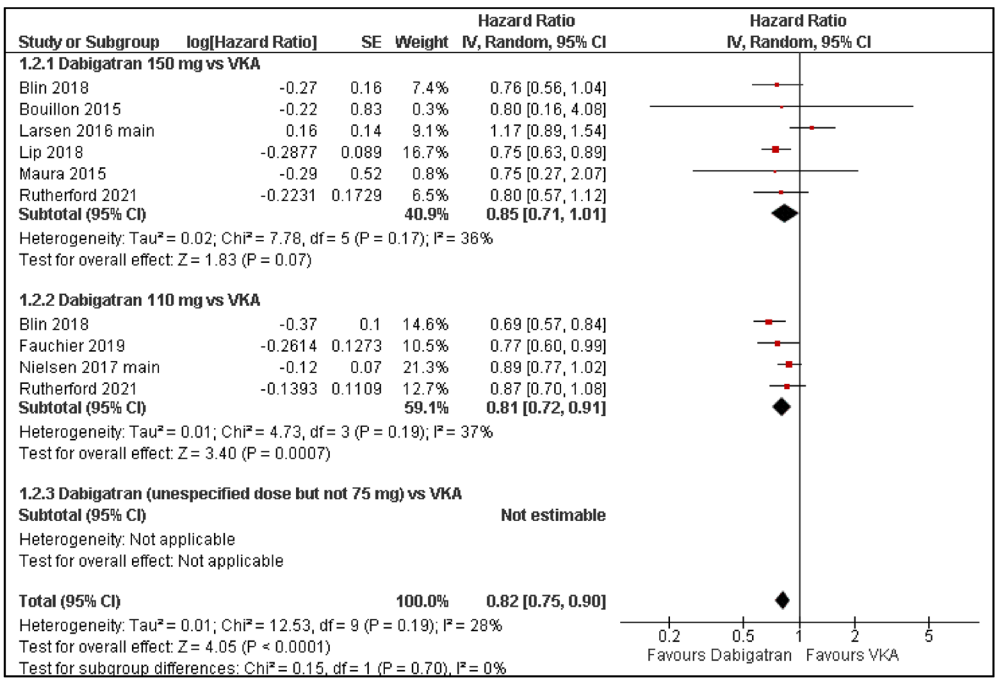
hazard (or instantaneous risk) to develop an ischemic stroke compared to VKA (HR 0.97, 95% CI 0.82–1.16; 24 comparison groups; $I^2 = 94\%$) (Fig. 2a). Of note, there was a subgroup effect suggesting the results are affected by the dose. Dabigatran at a dose of 150 mg significantly reduced the risk of ischemic stroke (14% lower risk, HR 0.86, 95% CI 0.76–0.99; 12 comparisons; $I^2 = 59\%$), whereas no difference was found with dabigatran at a dose of 110 mg compared to VKA (HR 0.99, 95% CI 0.88–1.12; seven comparisons; $I^2 = 52\%$). Regarding the composite of ischemic stroke/systemic embolism, dabigatran (either at a dose of 150 mg or 110 mg) reduced the risk of developing this outcome compared with VKA (an 18% lower risk as indicated by an HR of 0.82, 95% CI 0.75–0.90; ten comparisons; $I^2 = 28\%$) (Fig. 2b). No subgroup effect related to the dose was observed for this outcome. With regard to myocardial infarction, dabigatran 150 mg may reduce slightly, despite non-significantly, the risk of developing this outcome compared with VKA (HR 0.86, 95% CI 0.71–1.04; ten comparisons; $I^2 = 49\%$), whereas dabigatran 110 mg did not modify the risk of myocardial infarction compared to VKA (HR 1.02, 95% CI 0.83–1.25; five comparisons; $I^2 = 27\%$) (Fig. 2c). Globally, dabigatran also reduced the risk of all-cause mortality compared with VKA (a 24% lower risk as indicated by an HR of 0.76, 95% CI 0.69–0.84; 22 comparisons; $I^2 = 90\%$). Of note, there was a subgroup effect suggesting the comparisons were affected by the dose, with a greater effect observed with dabigatran at a dose of 150 mg (35% lower mortality, HR 0.65, 95% CI 0.58–0.73; $I^2 = 69\%$), while it was only a trend with dabigatran at a dose of 110 mg (14% lower mortality, HR 0.86, 95% CI 0.73–1.01; $I^2 = 91\%$) (Fig. 2d).

Fig. 2 Effectiveness endpoints: ischemic stroke (**a**), composite of ischemic stroke/systemic embolism (**b**), myocardial infarction (**c**), and all-cause mortality (**d**). *CI* confidence interval, *DOAC* direct oral anticoagulants, *SE* standard error, *VKA* vitamin K antagonists

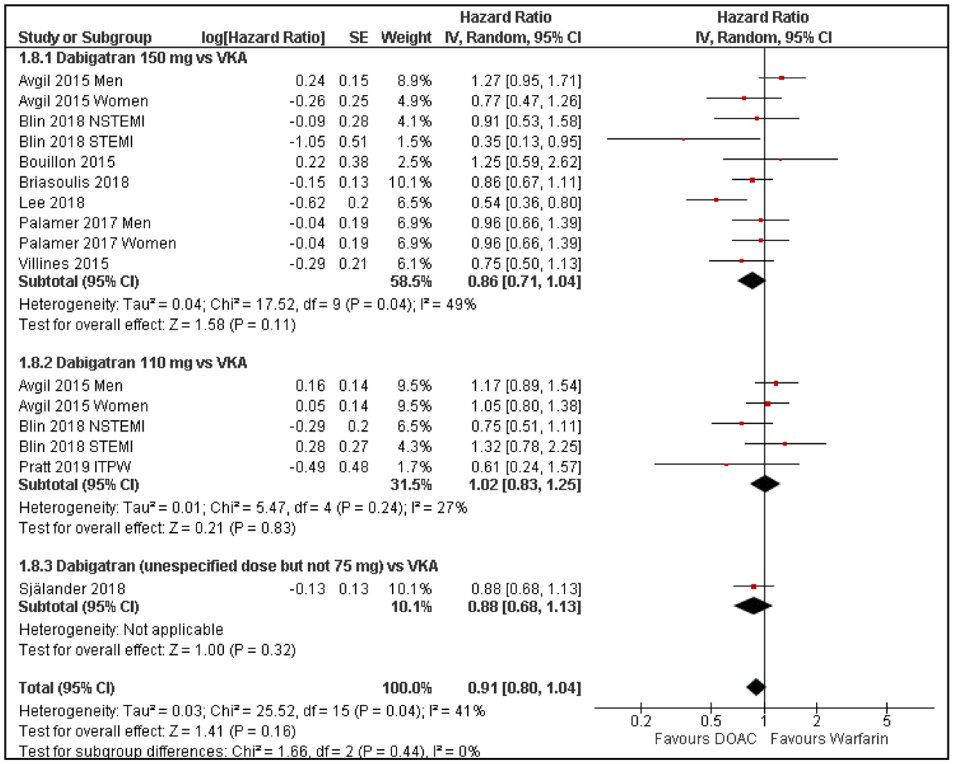
2a. Ischemic stroke.



2b. Ischemic stroke/systemic embolism.



2c. Myocardial infarction.



2d. All-cause mortality.

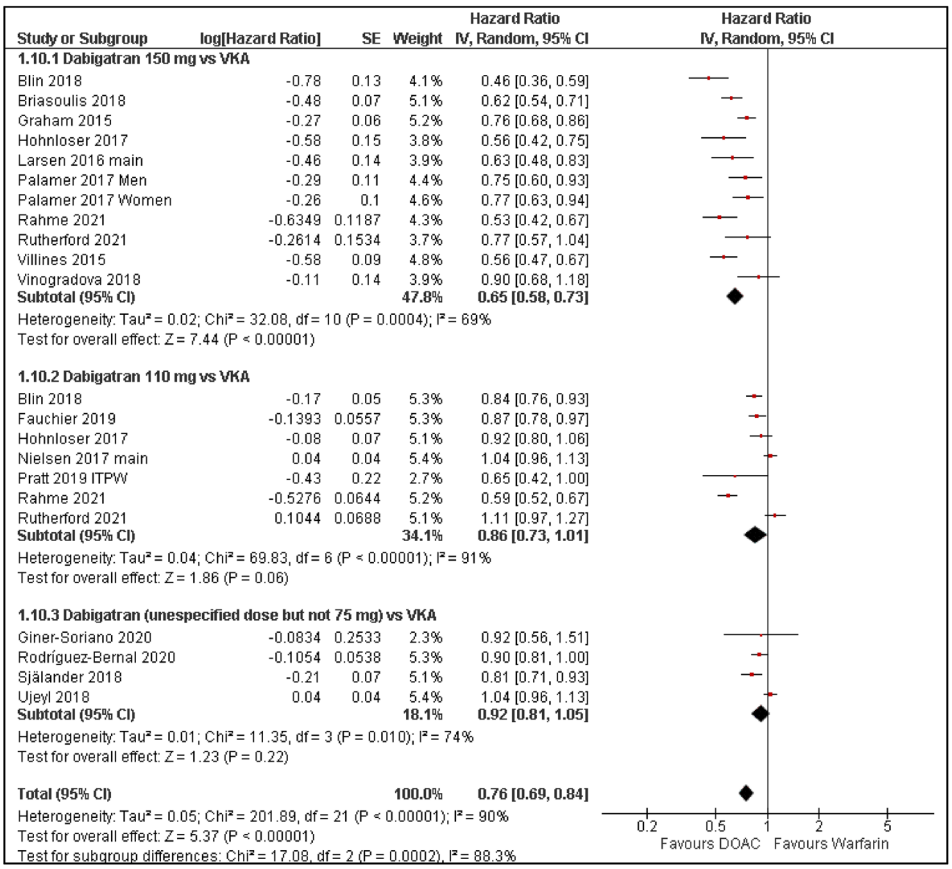


Fig. 2 (continued)

Regarding the safety outcomes, dabigatran (either at a dose of 150 mg or 110 mg) reduced the risk of developing a major bleeding compared with VKA (a 23% lower risk at any particular time during the study period as indicated by an HR of 0.77, 95% CI 0.70–0.83; 29 comparisons; I^2 = 83%) (Fig. 3a) as well as the risk of an intracranial bleeding (a 56% lower risk at any particular time during the study period as indicated by an HR of 0.44, 95% CI 0.39–0.50; 26 comparisons; I^2 = 18%) (Fig. 3b). The reduction in the risk of major bleeding was higher with dabigatran at a dose of 150 mg (HR 0.70, 95% CI 0.62–0.78; I^2 = 76%) than with dabigatran at a dose of 110 mg (HR 0.81, 95% CI 0.67–0.99; I^2 = 84%). In addition, among the secondary outcomes, dabigatran (either at a dose of 150 mg or 110 mg) may reduce the risk of developing a fatal bleeding compared with VKA (a 24% lower risk as indicated by an HR of 0.76, 95% CI 0.60–0.95; I^2 = 0%) (Fig. 3c), based on five comparison groups corresponding to only three studies. As for gastrointestinal bleeding, dabigatran (either at a dose of 150 mg or 110 mg) increased slightly the risk of developing gastrointestinal bleeding compared with VKA (HR 1.16, 95% CI 1.08–1.26; 32 comparisons; I^2 = 67%) (Fig 3d). No subgroup effect related to the dose was observed. A summary of the effectiveness and safety results is shown in Table 1. Other secondary outcomes such as systemic embolism and pulmonary embolism are shown in Fig. 1 of the ESM.

3.4 Sensitivity and Subgroup Analyses

The subgroup analysis related to participants aged older than 65 years, sex and naïve to DOAC/VKA for primary outcomes is reported in Fig. 2 of the ESM. The sensitivity analysis for the primary outcomes using propensity scores is shown in Fig. 3 of the ESM. Both the subgroup and sensitivity analyses demonstrated no major differences from the main analysis. Nevertheless, the limited number of studies available for some outcomes precludes reaching solid conclusions.

4 Discussion

This systematic review, based exclusively in real-world studies in non-Asian patients, showed that dabigatran (either at a dose of 150 mg or 110 mg) had a favorable impact on effectiveness and safety outcomes compared with VKA. The subgroup analysis suggests that the magnitude of the effects observed with dabigatran were related to the dose used, with dabigatran at a dose of 150 mg presenting a bigger risk reduction in ischemic stroke and all-cause mortality without increasing the risk of bleeding, similarly to the randomized controlled clinical trials.

For a majority of the analyzed outcomes, there were a large number of studies (and participants) available, which allowed the detection of small-magnitude differences, if they existed. For all outcomes, a moderate statistical heterogeneity was found, which is not surprising in the case of observational studies, whereas there may be some relevant differences in the study populations or methods that could affect the results. Consequently, the clinical recommendations that can be derived from this review should consider the specific risk profile of each patient. However, results were mostly consistent across studies, reinforcing the conclusion that the observed effects, on average, are widely applicable.

In the RE-LY trial, dabigatran 150 mg significantly reduced the risk of stroke or systemic embolism by 34%, and the risk of ischemic stroke by 24%, whereas dabigatran 110 mg had a neutral effect compared to warfarin [8]. This was also observed in a meta-analysis of six randomized clinical trials involving 20,086 patients with NVAF [53]. Our meta-analysis showed that these results can be translated into real-life patients, with a 15% risk reduction in both outcomes with dabigatran 150 mg and a 19% risk reduction in the combined ischemic stroke/systemic embolism outcome with dabigatran 110 mg compared with VKA. Of note, a recent study has shown that early dabigatran treatment after a transient ischemic attack and a minor ischemic stroke is safe [54].

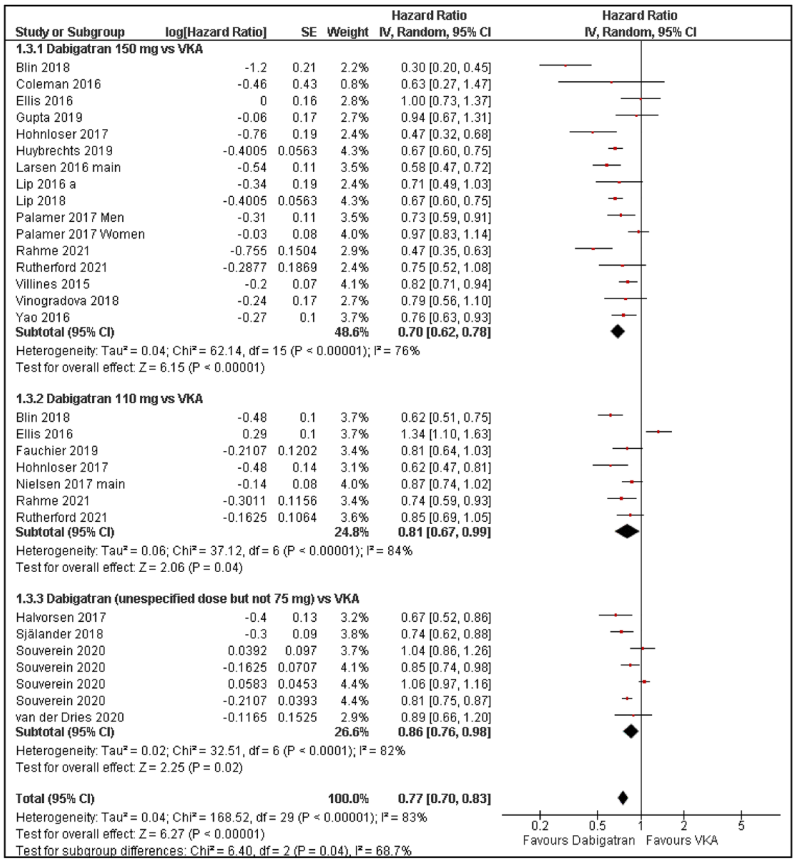
After the first reported RE-LY trial results, there was some concern about the risk of myocardial infarction with dabigatran, although this was not confirmed after a detailed examination [8, 55]. Our data showed that in clinical practice, there was inversely a trend towards a lower risk of myocardial infarction with dabigatran compared with warfarin, particularly with dabigatran 150 mg. As a result, it is well demonstrated that dabigatran can be safely used among patients at high risk of atherosclerotic cardiovascular outcomes.

The risk of death is doubled among patients with AF [1]. In the RE-LY trial, there was a trend towards a reduction in death from any cause with dabigatran compared with warfarin [8]. In our study, dabigatran significantly reduced the hazard of all-cause mortality compared with VKA by 24%, with a greater effect of dabigatran 150 mg, with a 35% risk reduction.

With regard to safety outcomes, our study showed that in routine practice, dabigatran reduced the risk of major, intracranial, and fatal bleeding compared with VKA, without a subgroup effect related to the dose. These data are in line with those reported in clinical trials [8, 43]. Overall, a higher risk of gastrointestinal bleeding with dabigatran was observed, but a non-significant trend was shown when the doses were considered separately. In the RE-LY trial, this was also observed with dabigatran 150 mg, but not with dabigatran 110 mg [8]. It has been reported that this risk

Fig. 3 Safety endpoints: major bleeding (**a**), intracranial bleeding (**b**), fatal bleeding (**c**), and gastrointestinal bleeding (**d**). *CI* confidence interval, *DOAC* direct oral anticoagulants, *SE* standard error, *VKA* vitamin K antagonists

3a. Major bleeding.



3b. Intracranial bleeding.

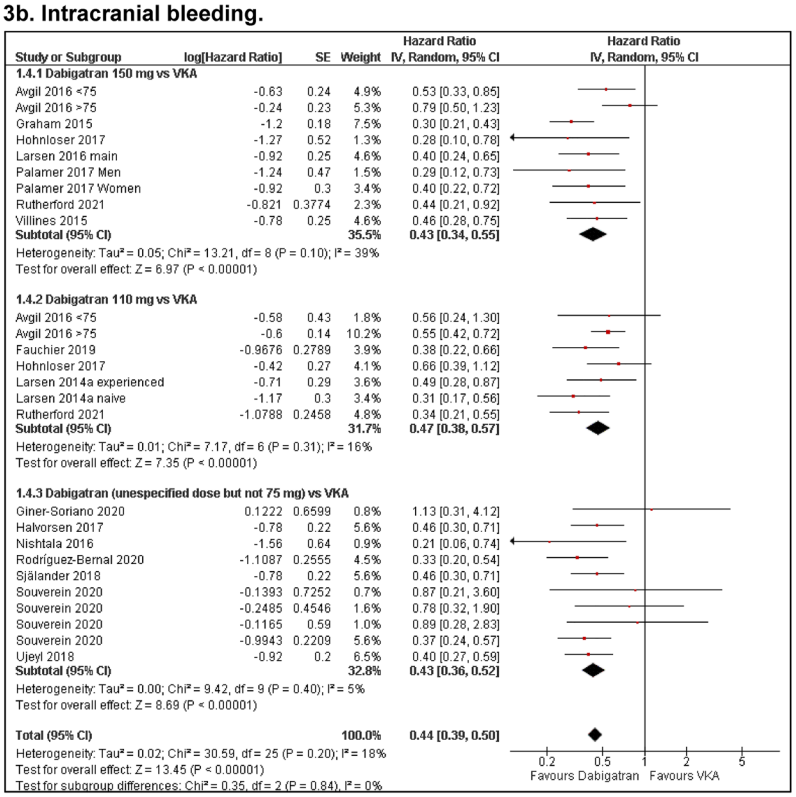
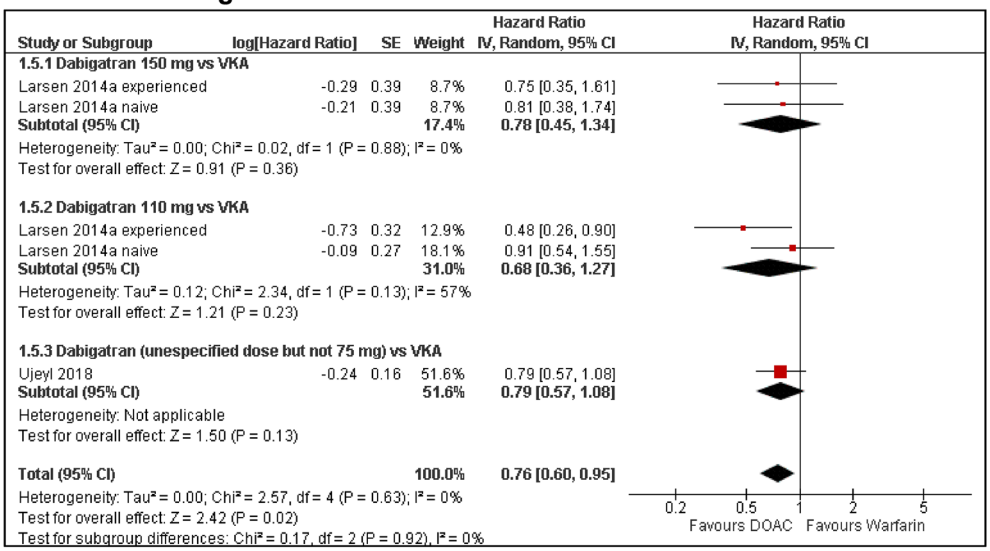


Fig. 3 (continued)

3c. Fatal bleeding.



3d. Gastrointestinal bleeding.

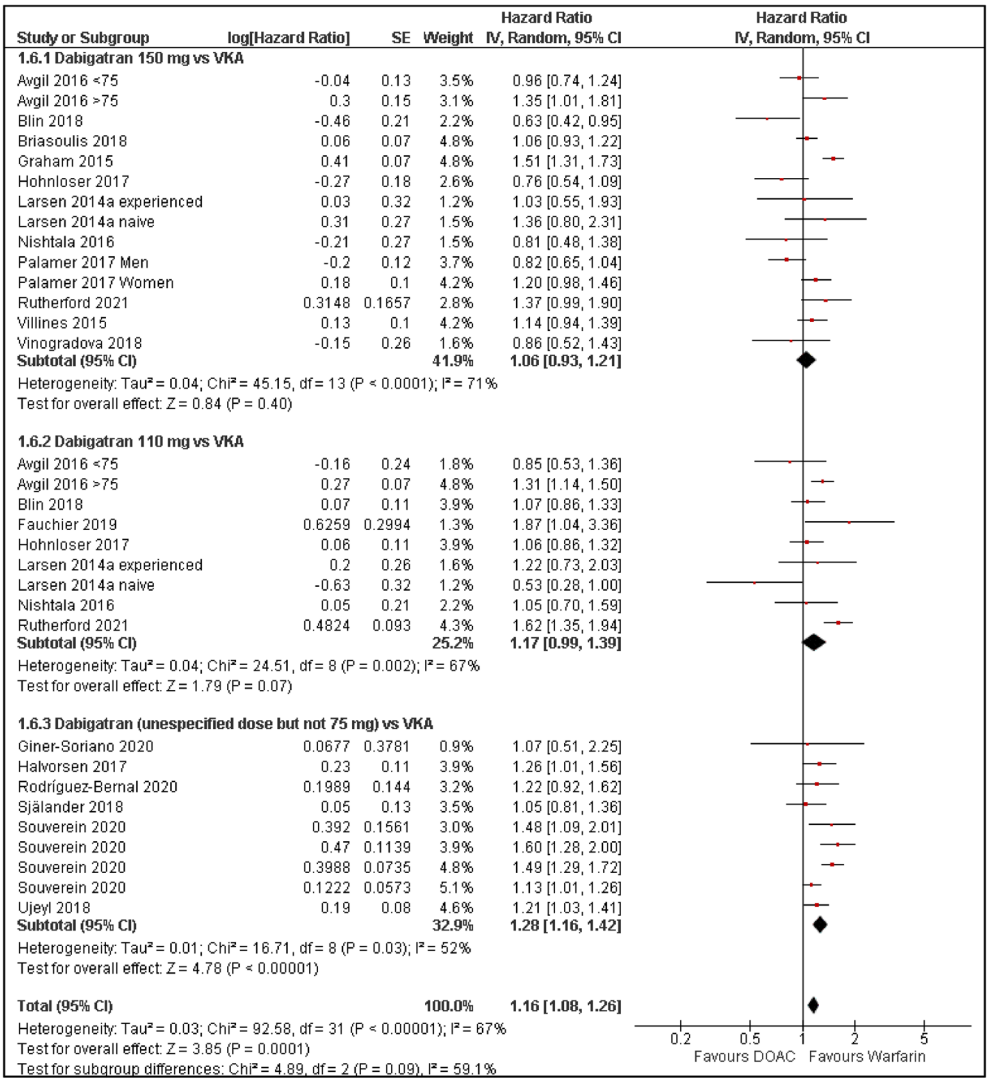


Table 1 Effectiveness and safety summary of the results

	Primary outcomes						Secondary outcomes					
	Ischemic stroke	Ischemic stroke/SE		Major bleeding	Intracranial bleeding	Fatal bleeding	GI bleeding	Systemic embolism	Myocardial infarction	Pulmonary embolism		Mortality
	Efficacy	Efficacy		Safety	Safety	Safety	Safety	Efficacy	Efficacy	Efficacy		
Number of studies	17	8		20	16	5	23	2	16	1		17
Globally	N	Y ↓		Y ↓	Y ↓	Y ↓	Y ↑	Limit ↓	Limit ↓	N		Y ↓
150 mg	Y ↓	Limit ↓		Y ↓	Y ↓	N	Y ↑	N	Limit ↓	N		Y ↓
110 mg	N	Y ↓		Y ↓	Y ↓	N	Limit ↑	Y ↓	N	NA		Limit ↓

GI gastrointestinal, *Limit* no difference but close to statistical significance, *N* no difference, *NA* not assessed, *SE* systemic embolism, *Y* statistically significant difference, ↓ risk reduction, ↑ increased risk

may be higher among those patients with a history of previous gastrointestinal bleeding [56].

In contrast to the other DOACs, in which dose adjustment was performed in the phase III clinical trials, in RE-LY, patients were randomized to receive either dabigatran 150 mg or 110 mg, but no dose adjustment was required [8, 57–59]. A great concern with DOACs is the prescription of inappropriate doses that could translate into more events [60]. However, our study showed that in clinical practice, both doses of dabigatran seem effective and safe. In addition, it has been reported that in daily clinical practice, patients treated with dabigatran exhibit high convenience and satisfaction scores [61].

The main strength of this research is that it was based on a rigorous and systematic review process that allowed us to identify exhaustively a large number of studies that addressed our research question, with a special focus on dose, increasing the validity and generalizability of our results. The review was based on observational studies performed on a more representative population of real-world patients than randomized clinical trials. To avoid the risk of double counting, we carefully detected overlapping studies assessing the same patients. Many published reviews on the same topic fell into the error of not removing overlapping studies.

4.1 Limitations

Compared to clinical trials, observational studies are at an increased risk of bias as treatment allocation was not randomly decided. However, these were predominantly broad retrospective cohorts, which used databases or registries suitable for this type of analysis and where robust adjustment methods were used to match groups of patients. However, although the measurement of exposure to treatment and of the ocurrence of the events of interest present limitations in this type of study, the methods and algorithms related to this specific topic have been used extensively, thus we believe that they did not introduce a differential bias in the results. In some comparisons, statistical heterogeneity was high among studies, limiting the validity and the generalizability of the results.

5 Conclusions

This meta-analysis showed that in clinical practice, dabigatran may reduce the risk of ischemic stroke and all-cause mortality compared with VKA, particularly with dabigatran 150 mg. The dose of dabigatran 110 mg may reduce the risk of ischemic stroke/embolism compared with VKA. In addition, there was a trend towards a lower risk of myocardial infarction with dabigatran 150 mg. Regarding safety

outcomes, both doses of dabigatran reduced the risk of major, intracranial, and fatal bleeding compared with VKA, with a slightly increased risk of gastrointestinal bleeding. In summary, dabigatran has a favorable impact on effectiveness and safety outcomes compared with VKA in non-Asian real-world patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40261-021-01091-w.

Acknowledgements Medical writing support was provided by Jordi Galera BSc (TFS Health Science). Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

Declarations

Funding This meta-analysis has been funded by Boehringer Ingelheim Spain. The authors did not receive compensation related to the development of the manuscript.

Conflicts of interest Carlos Escobar has received fees for oral presentations and consultancies from Bayer, BMS/Pfizer, Boehringer Ingelheim, and Daiichi Sankyo. Vivencio Barrios has received fees for oral presentations and consultancies from Bayer, BMS/Pfizer, Boehringer Ingelheim, and Daiichi Sankyo. Gregory Y.H. Lip has been a consultant for Bayer/Janssen, BMS/Pfizer, Boehringer Ingelheim, Verseon, and Daiichi-Sankyo and a speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. Alpesh Amin reported serving as a principal investigator or co-principal investigator of clinical trials of NIH/NIAID, NeuroRx Pharma, Pulmotect, Blade Therapeutics, Novartis, Takeda, Humanigen, Eli-Lilly, PTC Therapeutics, OctaPharma, Fulcrum Therapeutics, and Alexion. He has served as a speaker or consultant for BMS, Pfizer, BI, Portola, Sunovion, Mylan, Salix, Alexion, AstraZeneca, Novartis, Nabriva, Paratek, Bayer, Tetraphase, Achogen, LaJolla, Millenium, Ferring, Seres, PeraHealth, HeartRite, Asepticscope, and Sprightly.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The datasets and analysis are available from the corresponding author on reasonable request.

Code availability Not applicable.

Author contributions All authors have contributed to the study design, result review, manuscript preparation, and final approval of the manuscript.

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Clinical Drug Investigation
https://doi.org/10.1007/s40261-022-01126-w

CORRECTION

Correction to: Effectiveness and Safety of Dabigatran Compared to Vitamin K Antagonists in Non-Asian Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis

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Correction to: Clinical Drug Investigation
https://doi.org/10.1007/s40261-021-01091-w

The original version of this article unfortunately contained a mistake. Page 950, Table 1: row 3 in column 7—GI bleeding, which previously read Y ↑ should read Limit ↑.

Corrected Table 1 is given in the following page.

The original article can be found online at https://doi.org/10.1007/s40261-021-01091-w.

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Published online: 14 February 2022

Table 1 Effectiveness and safety summary of the results

	Primary outcomes					Secondary outcomes				
	Ischemic stroke	Ischemic stroke/SE	Major bleeding	Intracranial bleeding	Fatal bleeding	GI bleeding	Systemic embolism	Myocardial infarction	Pulmonary embolism	Mortality
	Efficacy	Efficacy	Safety	Safety	Safety	Safety	Efficacy	Efficacy	Efficacy	
Number of studies	17	8	20	16	5	23	2	16	1	17
Globally	N	Y ↓	Y ↓	Y ↓	Y ↓	Y ↑	Limit ↓	Limit ↓	N	Y ↓
150 mg	Y ↓	Limit ↓	Y ↓	Y ↓	N	Limit ↑	N	Limit ↓	N	Y ↓
110 mg	N	Y ↓	Y ↓	Y ↓	N	Limit ↑	Y ↓	N	NA	Limit ↓

GI gastrointestinal, *Limit* no difference but close to statistical significance, *N* no difference, *NA* not assessed, *SE* systemic embolism, *Y* statistically significant difference, ↓ risk reduction, ↑ increased risk