Research Square

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Effectiveness and safety of dabigatran compared to vitamin K antagonists in patients with atrial fibrillation: a systematic review and metanalysis.

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Abstract

Purpose: To assess the comparative effectiveness and safety of dabigatran –globally and stratified by dose (110 or 150 mg b.i.d.) compared to vitamin K antagonists (VKA) in patients with non-valvular atrial fibrillation (NVAF) from “real world” studies.

Methods: A systematic review was performed according to Cochrane methodological standards. The results were reported according to the PRISMA statement. The ROBINS-I tool was used to assess risk of bias.

Results: A total of 25 studies, corresponding to 27 articles involving 771.468 participants (490.082 exposed to VKA and 281.386 to dabigatran) were eligible for this review. Dabigatran reduced the risk of ischemic stroke compared to VKA, particularly dabigatran 150 mg, with a 15% risk reduction (HR 0.85, 95%CI 0.74-0.98). Globally, dabigatran reduced the risk of all-cause mortality compared to VKA (HR 0.75, 95%CI 0.67-0.85), with a greater effect observed with dabigatran 150 mg (HR 0.66, 95%CI 0.58-0.74). 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 to VKA (HR 0.74, 95%CI 0.66-0.83), as well as the risk of intracranial bleeding (HR 0.45, 95%CI 0.39-0.52) and fatal bleeding (HR 0.76, 95%CI 0.60-0.95), but with a non-significant trend towards a higher gastrointestinal bleeding risk (HR 1.08, 95%CI 0.99 to 1.18).

Conclusion: Dabigatran has a favourable impact in effectiveness and safety outcomes compared to VKA in real-world populations.

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 AF patients [1]. During decades, vitamin K antagonists (VKA) have been used for thromboembolic prevention in AF patients. However, VKAs exhibit many disadvantages, including the narrow therapeutic window, multiple drug-drug interactions, dietary restrictions, periodic monitoring and multiple dose adjustments in routine practice [4].

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 one that directly inhibits thrombin [7]. In the RE-LY trial, compared to warfarin, dabigatran 150 mg 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 than 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 be always directly translated into real-life patients [9]. In the last years, many database studies have analyzed the use of dabigatran among AF patients 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 patient clinical profile [7].

The aim of this systematic review was to assess the comparative effectiveness and safety of dabigatran globally and stratified by dose (110 or 150 mg b.i.d.), compared to VKA in patients with NVAF from “real world” studies.

Materials And 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 Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement (PRISMA) 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) versus 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).

Inclusion / Exclusion criteria

The inclusion was limited to those studies using as a data source national or regional-wide registers, both administrative or clinical, covering a large population (N > 1,000 patients, restricted to dabigatran and VKA patients). Reanalyses or subgroup analyses from randomized controlled trials, or modelling studies were not included. Studies conducted exclusively in Asian populations were excluded as well as studies that

contained unspecified or lower dose (75 mg) of dabigatran. Studies did not have to overlap with other studies already included. In case of an overlap, for each specific outcome we used data from the most complete report or the biggest sample population.

Search methods

We searched MEDLINE (access via Pubmed) and EMBASE (access through OVID), from inception up to July 2019, using appropriate controlled vocabulary and free search terms (supplementary table I). 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 grey literature.

Study selection and data extraction

Two authors (AA and CR) independently screened the search results based on the title and abstract. It was retrieved a full-text copy of the references 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 [13].

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.

Risk of bias assessment

We used ROBINS-I to assess the risk of bias of the included studies [14]. For each study, two authors independently assessed: 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 (supplementary table II).

All the analyzed outcomes were defined as time to event variables. Accordingly, the effect measure considered for time-to-event outcomes was HR (95% confidence intervals). When feasible we obtained pooled estimates of effect by means of formal meta-analytic technics, applying the inverse-variance method under a random-effects model, using the Review Manager software (v 5.3.5). The heterogeneity across study results was assessed through 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 21–65% were considered moderate; and values of I^2 over 65% were considered highly heterogeneous. When data allowed, subgroup analysis was performed according to sex. Sensitivity analyses were conducted restricted to naive participants and to participants older than 65 years. In addition, a sensitivity analysis was performed restricted to studies using propensity score as a statistical matching tool. Subgroups and sensitivity analyses were only conducted for primary outcomes.

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 5.527 unique references. After completing the screening, we identified a total of 25 studies –corresponding to 27 articles- involving 771.468 participants (490.082 exposed to VKA and 281.386 to dabigatran) that were eligible for the review (supplementary table III) [15–41].

A total of 142 studies were excluded due to several reasons. See supplementary table IV for details. Additionally, we excluded thirteen studies that reported overlapped data with other included studies (supplementary table V).

Description of the studies

A summary description of included studies is provided in supplementary table III. All the studies reported findings from a cohort study design. Twenty-three studies were retrospective [15–35, 37–39, 41] and two studies were prospective [36, 40]. The source of the data was from an administrative database in thirteen studies [15, 16, 19, 21–23, 25, 30, 34–40] and three used a commercial database [20, 29, 41]. Instead, in nine studies [17, 18, 24, 26–28, 31–33], data were extracted from a national healthcare database.

The studies used different approaches to control for confounding, being the propensity score the method used more frequently in seventeen studies [15–17, 19, 22, 23, 25–27, 30, 31, 33–39, 41]. On the other hand, eight studies performed adjusted analyses according to a Cox analysis [18, 20, 21, 24, 26, 28, 32, 40]. Twenty-five articles provided data about our primary outcome/s, eighteen of which also reported on secondary outcome/s. Two articles [28, 34] provided data only on secondary outcome/s.

Two of the studies (with 9,232 participants) [32, 36] had as an intervention dabigatran only at a dose of 110 mg; fourteen studies (with 154,243 participants) [18–20, 22, 23, 27–31, 34, 35, 39–41] had only dabigatran 150 mg, and six studies [15–17, 21, 25, 26, 33] had both doses (with 38,612 participants at dose of 110mg and 28,098 at dose of 150 mg). Moreover, there were three studies (with 51,201 participants) [24, 37, 38] that provided only unspecified doses (but not 75 mg).

With regard to the comparison group, nineteen of the studies (with 400,060 participants) used warfarin [15, 16, 19–24, 26, 27, 29, 30, 32–37, 39–41] two studies (with 47,477 participants) [25, 38] used phenprocoumon, and in four of the studies (with 47,545 participants) [17, 18, 28, 31] it was not specified which VKA was used.

As for the follow-up, since the vast majority were retrospective analyses, the duration was different for each patient, ranging from 6 months to 3 years on average.

Risk of bias of included studies

All the included studies in the review had an overall moderate risk of bias mainly due to potential confounding (baseline). The risk of bias was summarised at supplementary table VI.

Effects of the intervention

Two effectiveness outcomes were pre-specified as primary outcomes: ischemic stroke and the composite of ischemic stroke/systemic embolism. Dabigatran (either at a dose of 150 mg or 110 mg) may reduce slightly the hazard (or instantaneous risk) to develop an ischemic stroke compared to VKA (8% lower risk at any particular time during the study period as indicated by a HR 0.92, 95% CI 0.84 to 1.02; 19 comparison groups; I^2 65) (Fig. 2a). Of note, there was a subgroup effect suggesting the results are affected by the dose. Thus, the reduction observed with dabigatran at a dose of 150 mg was statistically significant (15% lower risk, HR 0.85, 95% CI 0.74 to 0.98; 11 comparisons; I^2 61), whereas no difference was found with dabigatran at a dose of 110 mg compared to VKA (HR 0.97, 95% CI 0.85 to 1.12; 6 comparisons; I^2 55). Regarding to the composite of ischemic stroke/systemic embolism, dabigatran (either at a dose of 150 mg or 110 mg) may reduce the hazard to develop this outcome compared to VKA (15% lower risk as indicated by a HR 0.85, 95% CI 0.71 to 1.02; 6 comparisons; I^2 52) (Fig. 2b). No subgroup effect related with the dose was observed for this outcome. With regard to myocardial infarction, dabigatran 150 mg may reduce slightly, despite non significantly, the hazard to develop this outcome compared to VKA (HR 0.86, 95% CI 0.71 to 1.04; 10 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 to 1.25; 5 comparisons; I^2 27) (Fig. 2c). Globally, dabigatran also reduced the hazard of all-cause mortality compared to VKA (25% lower risk as indicated by a HR 0.75, 95% CI 0.67 to 0.85; 15 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 (34% lower mortality, HR 0.66, 95% CI 0.58 to 0.74; I^2 71), in relation with dabigatran at a dose of 110 mg (HR 0.91, 95% CI 0.79 to 1.04; I^2 79) (Fig. 2d).

Regarding the safety outcomes, dabigatran (either at a dose of 150 mg or 110 mg) reduced the hazard to develop a major bleeding compared to VKA (26% lower risk at any particular time during the study period as indicated by a HR 0.74, 95% CI 0.66 to 0.83; 19 comparisons; I^2 80) (Fig. 3a) as well as the hazard of an intracranial bleeding (55% lower risk at any particular time during the study period as indicated by a HR 0.45, 95% CI 0.39 to 0.52; 17 comparisons; I^2 24) (Fig. 3b). No subgroup effect related with the dose was observed for either of these outcomes. In addition, among the secondary outcomes, dabigatran (either at a dose of 150 mg or 110 mg) may reduce the hazard to develop a fatal bleeding compared to VKA (24% lower risk as indicated by a HR 0.76, 95% CI 0.60 to 0.95; I^2 0) (Fig. 3c), based on five comparison groups corresponding to only 3 studies. As for gastrointestinal bleeding, dabigatran (either at a dose of 150 mg or 110 mg) may increase the hazard to develop a gastrointestinal bleeding compared to VKA, although this increase was not significant (HR 1.08, 95% CI 0.99 to 1.18; 23 comparisons; I^2 62) (Fig. 3d). No subgroup effect related with the dose was observed. A summary of the effectiveness and safety results is showed in the Table 1. Other secondary outcomes such as systemic embolism and pulmonary embolism are showed in the supplementary material (e-figure I).

Table 1
Effectiveness and safety summary of the results.

	Primary outcomes					**Secondary outcomes**				
	Ischaemic stroke	**Ischaemic 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*	
Num. of studies	21	6	20	19	5	26	2	16	1	15
Globally	Limit ↓	Limit ↓	**Y ↓**	**Y ↓**	**Y ↓**	**Y ↑**	**Y ↓**	Limit	N	**Y ↓**
150 mg	**Y ↓**	N	**Y ↓**	**Y ↓**	N	N	N	Limit	N	**Y ↓**
110 mg	N	Limit ↓	N	**Y ↓**	N	N	**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

Sensitivity and subgroup analysis

Subgroup analysis related participants older than 65 years, sex and naïve to DOAC / VKA for primary outcomes are reported in the supplementary material (e-figure II). Sensitivity analysis for primary outcomes using propensity scores are also showed in supplementary material (e-figure III). Both subgroup analysis and sensitivity analysis demonstrated no major differences from the main analysis. Nevertheless, the limited number of studies available for some outcomes precludes reaching solid conclusions.

Discussion

This systematic review, based exclusively in real world studies, showed that dabigatran (either at a dose of 150 mg or 110 mg) had a favourable impact in effectiveness and safety outcomes compared to VKA. Subgroup analysis suggests that the magnitude of the effects observed with dabigatran were related with 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 randomised controlled clinical trials.

For a majority of the analyzed outcomes, there were a large number of studies (and participants) available, which allowed detecting differences of small magnitude, 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 which 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 [42]. Our meta-analysis showed that these results can be translated into real-life patients, with a 15% risk reduction of both outcomes with dabigatran 150 mg and a similar effect with dabigatran 110 mg comapred to VKA. Of note, a recent study has shown that the early dabigatran treatment after transient ischemic attack and minor ischemic stroke is safe [43].

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 detailed examination [8, 44]. Our data showhed that in clinical practice, there was inversely a trend towards a lower risk of myocardial infarction with dabigatran compared to warfarin, particularly with dabigatran 150 mg. As a result, it is well demonstrated 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 of death from any cause with dabigatran compared to warfarin [8]. In our study, dabigatran significantly reduced the hazard of all-cause mortality compared to VKA by 25%, with a greater effect of dabigatran 150 mg, with a 34% risk reduction.

With regard to safety outcomes, our study showed that in routine practice, dabigatran reduced the risk of major bleeding, intracranial and fatal bleeding compared to VKA, without a subgroup effect related with the dose. These data are in line with those reported in clinical trials [8, 42]. A non-significative trend towards a higher risk of gastrointestinal bleeding with dabigatran was observed. 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 may be higher among those patients with a history of previous gastrointestinal bleeding [45].

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, 46–48]. A great concern with DOACs is the prescription of inappropriate doses that could translate into more events [49]. 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 [50].

The main strenght 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 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 same patients. Many published reviews on the same topic fell into the error of not removing overlaping studies.

Limitations

Compared to clinical trials, observational studies are at 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 analyses and where robust adjustment methods were used to match groups of patients. On the other hand, although the measurement of exposure to treatment and of the

ocurrence of the events of interest present limitations in this type of study, however, the methods and algorithms related to this specific topic have been used extensively, so 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.

Conclusions

This meta-analysis showed that in clinical practice, dabigatran may reduce the risk of ischemic stroke, and all-cause mortality compared to VKA, particularly with dabigatran 150 mg. In addition, there was a trend towards a lower risk of myocardial infaction with dabigatran 150 mg. Regarding safety outcomes, dabigatran reduced the risk of major, intracranial and fatal bleedings compared to VKA, with a non-significative trend towards an increased risk of gastrointestinal bleeding. In summary, dabigatran has a favourable impact in effective and safety outcomes compared to VKA in real-world patients.

Declarations

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Disclosures

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.

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Alpesh Amin reported serving as PI or co-I of clinical trials of NIH/NIAID, NeuroRx Pharma, Pulmotect, Blade Therapeutics, Novartis, Takeda, Humanigen, Eli-Lilly, PTC Therapeutics, OctaPharma, Fulcrum Therapeutics, Alexion. He has served as speaker or consultant for BMS, Pfizer, BI, Portola, Sunovion, Mylan, Salix, Alexion, AstraZeneca, Novartis, Nabriva, Paratek, Bayer, Tetraphase, Achogen, LaJolla, Millenium, Ferring, PeraHealth, HeartRite, Aseptiscope, Sprightly.

Availability of data and material

The datasets and analysis are available from the corresponding author on reasonable request.

Authors' contributions

CE, VB, AA and CR had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and wrote the manuscript. GYHL and ANA contributed substantially to the interpretation and the writing of the manuscrit. All authors reviewed the results and approved the final version of the manuscript.

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Figures

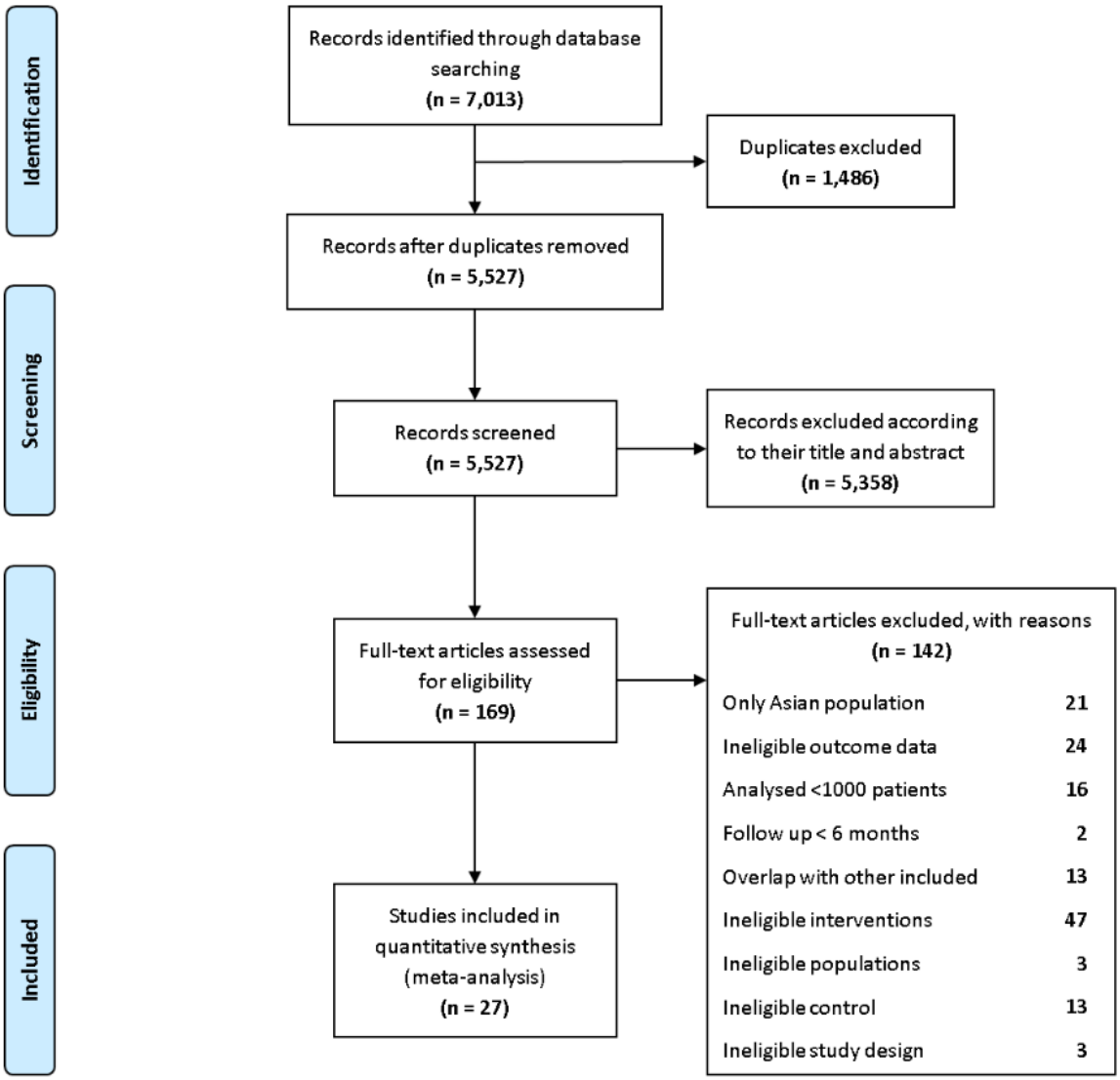


Figure 1

Eligibility PRISMA flowchart.

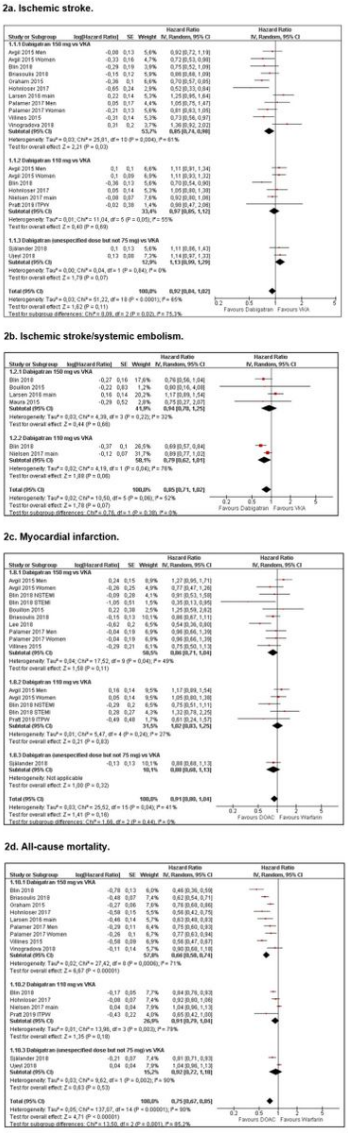
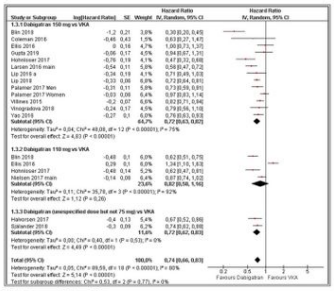


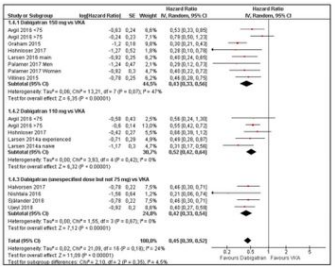
Figure 2

Effectiveness endpoints: ischemic stroke (2a), composite of ischemic stroke/systemic embolism (2b), myocardial infarction (2c), all-cause mortality (2d).

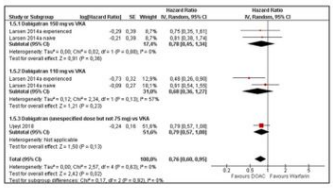
3a. Major bleeding.



3b. Intracranial bleeding.



3c. Fatal bleeding.



3d. Gastrointestinal bleeding.

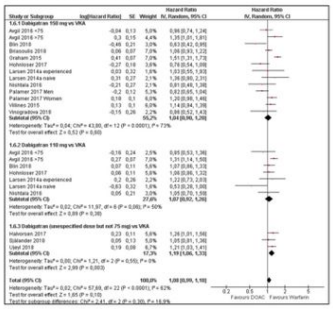


Figure 3

Safety endpoints: major bleeding (3a), intracranial bleeding (3b), fatal bleeding (3c), gastrointestinal bleeding (3d).

Supplementary Files

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- MetaanalysisDabigatranv4FINAL20210301CDTsuppl.docx