SYSTEMATIC REVIEW

Is dabigatran a good alternative to warfarin in patients with atrial fibrillation accompanied by valvular and non-valvular heart diseases? A systematic review and meta-analysis

Le dabigatran est-il une bonne alternative à la warfarine chez les patients atteints de fibrillation atriale accompagnée de maladies cardiaques valvulaires et non valvulaires? Une revue systématique et une méta-analyse

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Abstract

Background: There is ongoing discussion regarding the terminology used when atrial fibrillation (AF) is present alongside either valvular heart disease (VHD) or non-valvular heart disease (NVHD). We conducted this meta-analysis to assess the effectiveness and safety of dabigatran compared to warfarin in AF patients with VHD and NVHD.

Methods and results: Online databases were searched for eligible studies. Ten RCTs (22981 patients) were included. In NVHD subgroup, dabigatran 150 mg showed no statistically significantly difference in stroke (S) and systemic embolism (SE) (risk difference (RD) -0.01,95% confidence interval(CI):-0.01,0.0), and death (RD -0.00,95% CI -0.01,0.00) except for intracranial hemorrhage (ICH) (RD -0.01,95% CI -0.01,-0.01), and major bleeding (RD -0.02,95% CI -0.04,-0.00), similarly ,110 mg showed a low risk of ICH (RD -0.01,95% CI -0.01,-0.01), and no significant differences in S/SE and death compared to warfarin. In VHD subgroup, dabigatran showed no significant differences in S/SE (RD 0.02,95% CI -0.03,0.07), major bleeding (RD 0.01,95% CI -0.02,0.04), and death (RD -0.01,95% CI -0.04,0.01) compared to warfarin. In the catheter ablation subgroup, dabigatran reduced only groin hematoma (RD -0.02,95% CI -0.03,-0.00).

Conclusion: Dabigatran 150 mg and 110 mg was superior to warfarin in AF patients with NVHD in reducing bleeding particularly ICH; However, no significant difference in reducing S/SE, and mortality. In catheter ablation, dabigatran reduced only groin hematoma. In the VHD subgroup, dabigatran did not show superiority or inferiority to warfarin; further studies are needed. “Non-valvular AF” should be replaced with “type II VHD” to distinguish it from other valvular heart diseases.

Keywords: Catheter ablation, Dabigatran, Non-valvular atrial fibrillation, Valvular atrial fibrillation, Warfarin.

Résumé

Introduction : Un débat persiste concernant la terminologie employée lorsque la fibrillation atriale (FA) coexiste avec une maladie cardiaque valvulaire (VHD) ou non valvulaire (NVHD). Cette méta-analyse a été réalisée afin d’évaluer l’efficacité et la sécurité du dabigatran comparativement à la warfarine chez les patients atteints de FA associée à une VHD ou une NVHD.

Méthodes et résultats : Les bases de données électroniques ont été consultées pour identifier les études éligibles. Dix essais cliniques randomisés (ECR) incluant 22 981 patients ont été retenus. Dans le sous-groupe NVHD, le dabigatran 150 mg n’a montré aucune différence statistiquement significative par rapport à la warfarine concernant les accidents vasculaires cérébraux (AVC) et les embolies systémiques (ES) (différence de risque [DR] : –0,01 ; intervalle de confiance [IC] à 95 % : –0,01 à 0,00) ou la mortalité (DR : –0,00 ; IC 95 % : –0,01 à 0,00), à l’exception des hémorragies intracrâniennes (HIC) (DR : –0,01 ; IC 95 % : –0,01 à –0,01) et des saignements majeurs (DR : –0,02 ; IC 95 % : –0,04 à –0,00), significativement réduits sous dabigatran. De même, le dabigatran 110 mg a été associé à un risque plus faible d’HIC (DR : –0,01 ; IC 95 % : –0,01 à –0,01) sans différence significative pour les AVC/ES ou la mortalité, comparativement à la warfarine. Dans le sous-groupe VHD, aucune différence significative n’a été observée entre le dabigatran et la warfarine pour les AVC/ES (DR : 0,02 ; IC 95 % : –0,03 à 0,07), les hémorragies majeures (DR : 0,01 ; IC 95 % : –0,02 à 0,04) ou la mortalité (DR : –0,01 ; IC 95 % : –0,04 à 0,01). Enfin, dans le sous-groupe des patients ayant bénéficié d’une ablation par cathéter, le dabigatran a uniquement réduit la survenue d’hématomes inguinaux (DR : –0,02 ; IC 95 % : –0,03 à –0,00).

Conclusion : Le dabigatran, à la dose de 150 mg ou 110 mg, s’est révélé supérieur à la warfarine chez les patients présentant une FA avec NVHD pour la réduction des saignements, en particulier des HIC. En revanche, aucune différence significative n’a été observée concernant les AVC/ES ou la mortalité. Chez les patients ayant bénéficié d’une ablation par cathéter, le dabigatran a seulement réduit le risque d’hématome de l’aine. Dans le sous-groupe VHD, le dabigatran n’a montré ni supériorité ni infériorité par rapport à la warfarine. Des études supplémentaires sont nécessaires pour confirmer ces résultats. Enfin, le terme « FA non valvulaire » pourrait avantageusement être remplacé par l’appellation « VHD de type II », afin de mieux distinguer cette entité des autres formes de maladies valvulaires cardiaques.

Mots clés: Ablation par cathéter, Dabigatran, Fibrillation atriale non valvulaire, Fibrillation atriale valvulaire, Warfarine.

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What is known?

• Non-vitamin K oral anticoagulants (NOACs) have a safe profile compared to warfarin, particularly in major bleeding and intracranial hemorrhage in atrial fibrillation (AF) patients with non-valvular heart diseases (NVHD).

• NOACs showed a good efficacy profile in reducing stroke and systemic embolism in AF patients with NVHD.

What does this study add?

• To the best of our knowledge, this is the first meta-analysis comparing the safety and efficacy of dabigatran as one of the NOACs to warfarin in AF patients with or without valvular heart disease (VHD) and those undergoing catheter ablation.

• In AF patients with VHD, dabigatran did not show superiority or inferiority to warfarin; further studies are needed. In those who were undergoing catheter ablation, dabigatran only reduced the groin hematoma in comparison to warfarin.

• In AF patients with NVHD, both dosages of dabigatran (150 and 110 mg) showed a decrease in different types of bleeding particularly, intracranial and major bleeding. This suggests it might be a safe alternative to warfarin, assuming no contraindications and good renal function.

• The expression “Non-valvular AF” is outdated and ought to be substituted with “type II VHD” to distinguish it from other valvular heart diseases that AF accompanies.

Introduction

Atrial fibrillation (AF) is characterized by rapid and irregular atrial activation; it is reflected in a surface electrocardiogram (ECG) because of the lack of clearly defined P waves [1].

AF is the most prevalent supraventricular tachyarrhythmia, which is frequently correlated with aging [2] and can lead to major health conditions such as stroke (S), systemic embolism (SE), and heart failure (HF), as well as increased healthcare expenditure, morbidity, and death [2]. Recent estimates suggest that over 33 million people worldwide have AF [1]. Estimates indicate that the number of AF patients in the United States is between 3 and 5 million, with projections indicating an increase to 8 million by 2050 [1]. Since 1990, the global burden of AF has increased steadily, with its prevalence more than doubling (+120.7%) at all socioeconomic levels [2]. AF significantly increases the risk of stroke by 5-fold, which increases mortality rates and sudden death risk [1].

At least 30% of AF patients have some degree of valvular heart disease (VHD) [3], making the term "non-valvular" inaccurate and misleading, as previously mentioned in the ARISTOTLE trial [4]. The controversy between American and European guidelines for managing both VHD and AF confirms the necessity of making a conclusive decision about the best terminology to resolve this debate. Figure 1A [3,5-12] illustrates this.

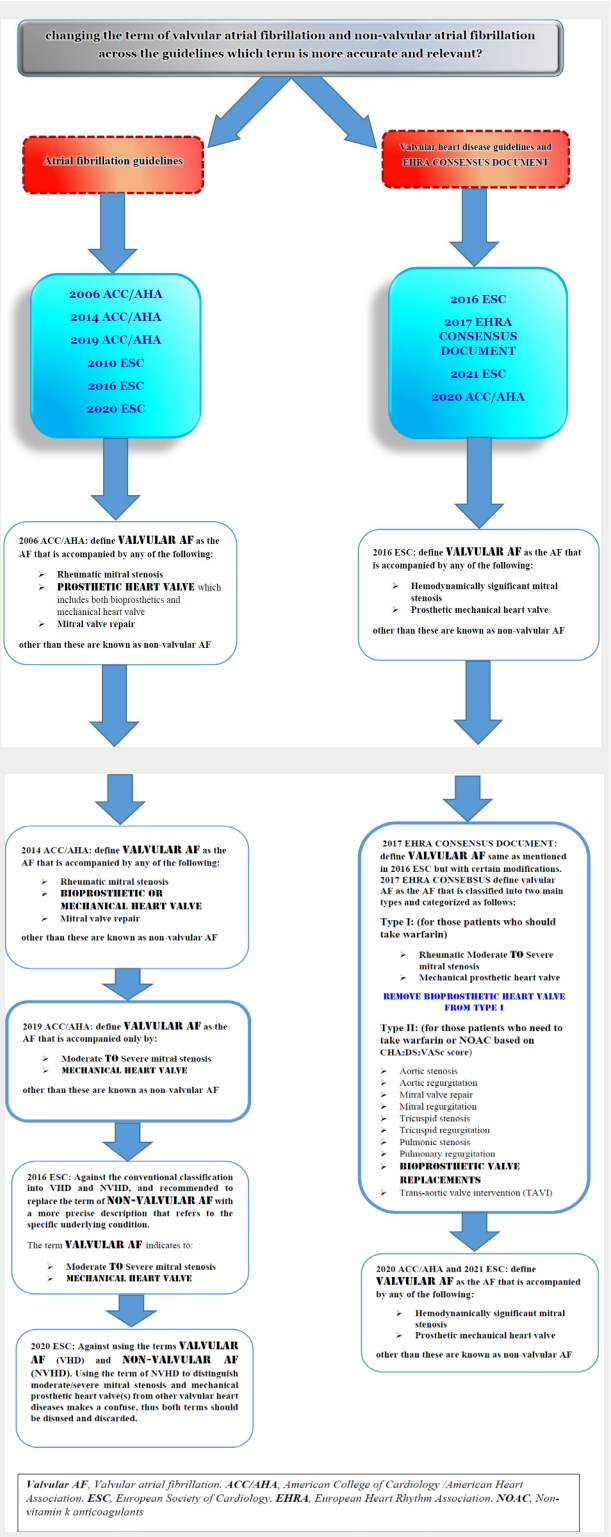


Figure 1. The controversy between ACC/AHA, ESC, and EHRA guidelines for the management of AF and VHD in the terminology of Valvular and non-valvular AF

Given that the incidence of AF-related strokes is greater than that of patients without AF, patients with both AF and VHD should initiate oral anticoagulants (OACs) as prophylaxis against S and SE, considering the CHA_2DS_2-VASc score and the risk of thromboembolic events [13]. For decades, warfarin has been used to prevent thromboembolic incidents in AF patients. Despite its ability to prevent stroke in AF patients, clinicians do

not recommend it as a first-line anticoagulant due to its interactions with foods and other drugs, its pharmacogenetic impact related to VKORC1, its narrow therapeutic index, the need for repeated monitoring of the international normalized ratio (INR), diversity in dose adjustment, and the high risk of intracranial bleeding [14]. The US Food and Drug Administration (FDA) has authorized several non-vitamin K oral anticoagulants (NOACs) to prevent strokes in AF patients; one of these NOACs is dabigatran [14].

Dabigatran is a direct thrombin inhibitor that offers several advantages over warfarin, including a broad therapeutic index, minimal drug interactions, no food interactions, fast onset of action, unnecessary regular coagulation monitoring, high bioavailability, and consistent pharmacodynamic and pharmacokinetic profiles. Moreover, patients benefit from a fixed dosage schedule due to its broad therapeutic window, which enhances convenience and compliance [15]. However, the missed dabigatran doses significantly reduce anticoagulation compared to warfarin because of its shorter half-life, which offers warfarin an advantage over dabigatran and other direct oral anticoagulants (DOACs). Table S1 illustrates the differences between dabigatran and warfarin. In the era of NOACs and their increasing demand, can we still rely on warfarin as a prophylactic OAC from S/SE in AF patients with or without VHD, or should we retire it and replace it with NOACs such as dabigatran? We performed this systematic review and meta-analysis to investigate dabigatran's efficacy and safety profile compared to warfarin and assess its potential use instead of warfarin in AF patients with VHD or non-valvular heart disease (NVHD).

Methods

This meta-analysis was implemented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [29]. Additionally, we used the Cochrane Handbook of Systematic Reviews and Meta-analysis of Interventions (version 6.3) as a reference [31].

Search strategy and selection criteria

A thorough literature search was performed across CENTRAL (Cochrane Central Register of Controlled Trials), PubMed, Web of Science, and Scopus databases from the beginning to May 2023. The search method utilized a blend of Medical Subject Headings (MeSH) and free text phrases to guarantee thorough coverage. Furthermore, we reviewed the archives of the manufacturer's site of dabigatran for potentially eligible published/unpublished studies and checked recent systematic reviews for any additional published literature. The search strings used were: ((Dabigatran) or (BIBR 1048) or (Pradaxa) or (Dabigatran Etexilate)) AND ((warfarin) or (Apo-warfarin) or (Aldocumar) or (Coumadin) or (Warfant) or (Marevan) or (Tedicumar)) AND ((Atrial Fibrillations) or (Auricular Fibrillations) or (AF) or (valvular atrial fibrillations)) AND (prosthetic heart valve).

Inclusion criteria

We encompassed published or unpublished randomized controlled trials (RCTs) that adhere the following criteria: adults aged 18 years or over with AF and VHD, NVHD, or prosthetic heart valves (mechanical heart valves (MHVs) or bioprosthetic heart valves (BHVs)) who have received dabigatran at various doses (50 mg, 110 mg, 150 mg, 220 mg, 300 mg) q.d, bid, or 75 mg twice daily "in cases of significant renal dysfunction, where creatinine clearance (CrCl) is 15-30 ml/min" in comparison to warfarin at various doses (1 mg, 2 mg, 5 mg, 10 mg) at INR 2- 3 or 2.5-3.5 in case of a MHV.

Exclusion criteria

The exclusion criteria encompassed RCTs that investigated NOACs other than dabigatran, as well as observational studies, reviews, non-randomized controlled trials, case series, animal studies, duplicate studies reporting the same trials, post-hoc-analyses, and studies not written in English.

Outcome measures and endpoints

- **Primary outcomes:**

The primary efficacy outcomes included S and SE reduction. The primary safety event includes major bleeding, according to the International Society of Thrombosis and Haemostasis definition (ISTH) [30].

- **Secondary outcomes:**

The secondary safety endpoints include intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), all-cause mortality, cause-specific mortality, any bleeding, minor bleeding, groin hematoma, pseudoaneurysm, cardiac tamponade, and pericardial effusion in cases of catheter ablation.

Data extraction

A.M. and M.D. indepentently screened titles and abstracts for eligibility. Full-text articles of likely eligible RCTs were reviewed and appraised for inclusion. Any disagreements were resolved by a third investigator (E.Y). The PRISMA flow diagram clarified the selection process.

Data were extracted independently by the investigator (E.Y) via a consistent data collection sheet. The data that were extracted included the following: (i) the characteristics of the included studies (authors, publication year, study design, setting, type of AF with/without VHD, intervention and comparator details (dose, frequency), INR, follow-up duration, and primary and secondary endpoints, including efficacy and safety). (ii) Baseline characteristics of the study population (age, sex, CHA2DS2-VASc score, HAS-BLED score, comorbidities, and risk factors).

Assessment of the risk of prejudice in the selected studies

The risk of bias was evaluated via the Cochrane Risk of Bias Assessment 2.0 Tool (ROB2) [31,32]. E.Y and A.G conducted this assessment autonomously. The following domains were assessed: bias arising from the randomization process, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in measuring the outcome, and bias in selecting the reported result. Every domain was categorized as having low risk, some concerns, or high risk. The quality of studies was assessed as follows: (i) high quality if all domains were assessed as low risk, (ii) moderate quality if one or more domains were assessed as some concerns, and (iii) low quality with substantially diminishing confidence in the outcome if one or more domains were assessed as high risk, or if multiple domains were some concerns.

Data Collection and Statistical Analysis

E.Y. and M.D. performed statistical analyses using RevMan website, and comprehensive Meta-analysis software version 4 to report the plot of prediction interval (PI). A Random-effects DerSimonian-Laird model was used to analyze the outcomes. Although risk difference(RD) is more heterogeneous than risk ratio (RR) and depends on baseline risk, RD and its 95% confidence interval (CI) were used due to zero events in both arms and the imbalance in the sample sizes across studies[33-35]. A P-value < 0.05 was deemed statistically significant. Continuous variables were reported as means with standard deviations.

I^2 indicates the proportion of observed effects variance that is attributable to the true effects variance; however, it does not quantify the magnitude of this variance, except in cases where I^2 equals 0%. Thus, using I^2 is not reliable and is not an absolute measure of heterogeneity [36-38]. In our meta-analysis, heterogeneity was assessed via PI. Using PI is reasonable and reliable because the PI shows the dispersion of true effect sizes across studies. In contrast, the I^2 statistic does not indicate the extent to which the effect size varies; thus, assessing heterogeneity based on I^2 may potentially mislead in many cases [36]. Notably, PI is less reliable when the number of studies is small; ten or more studies are recommended for robust estimates [37-39]. Additionally, PI calculations were not possible for subgroups with fewer than three studies. If all studies shared a common effect size, PI could not be computed, indicating zero/no heterogeneity [37-39]. The sensitivity analysis was performed to evaluate the robustness of the findings by excluding studies that caused heterogeneity.

Results

Outcomes of searching and selection of studies

Our search yielded 10601 records. 3788 duplicates were deleted, and 6781 were eliminated by screening titles and abstracts. The remaining 32 publications were eligible for full-text screening; only 10 RCTs met the meta-analysis criteria. The excluded full-text publications were for the following reasons: they did not relate to the intended interventions, or they aligned with the intended interventions but were observational studies, reviews, non-randomized clinical trials, articles without abstracts, guidelines, or studies written in languages other than English. The PRISMA flow diagram (Figure 2) shows the flow chart of the selected studies

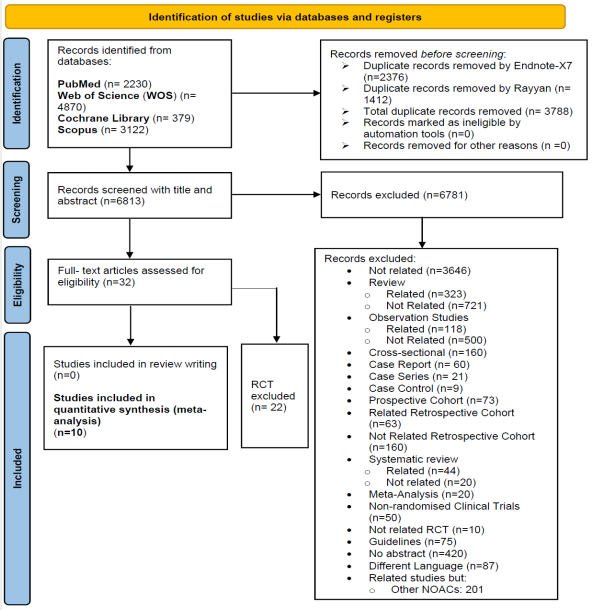


Figure 2. Flowchart of study selection adapted based on PRISMA guidelines [29]

Characteristics of the included studies

All 10 RCTs included 22981 patients. Of these, 14982 were randomly assigned to the intervention arm dabigatran (DAB), and 7824 were assigned to the comparison arm warfarin (WAR). The NVHD subgroup included 7675 patients in the WAR arm and 14740 in the DAB arm, whereas the VHD subgroup included 242 in the DAB arm and 149 in the WAR arm. Tables 1 and 2 show the attributes of the included studies and baseline characteristics.

Quality assessment

For the RCTs included, ROB2 [31,32] revealed that the overall risk-of-bias judgment had "some concerns" about the overall quality of the evidence. Six RCTs had "some concerns" due to randomization bias, three RCTs had high risk due to reporting bias, and one RCT had low risk (Figure 3A &B)

Table 1. Characteristics of included studies

Study ID	Year of publi-cation	Study design	Setting	Intervention	Comparator	Type of AF (VHD or non-VHD)				INR	Follow up	Safety endpoint	Primary efficacy	Dose ad-justment
						Totally in the whole study (%)	DAB 150 mg	DAB 110 mg	Warfarin					
						Non-valvular atrial fibrillation (non-VHD)								
Connolly *et al.* (RE-LY) [40]	2009	phase III, Randomized parallel, Prospective, Non-inferiority controlled Trial, blinded for DAB and open-label for WAR	Multi-center	DAB 150 mg twice daily, DAB 110 mg twice daily	WAR 1,2,3 mg once daily adjusted according to INR	paroxysmal: 32.8 % persistent: 31.96 % permanent: 35.19%	paroxysmal: 32.1 % persistent: 32.4 % permanent: 35.4%	Paroxysmal: 32.6% persistent: 31.4% permanent: 36%	paroxysmal: 33.8% persistent: 32.0% permanent: 34.1%	**2-3**	**24** mos	**Primary safety:** MB: 375 **Secondary safety:** ICH: 36 GIB: 182	S or SE: 134 S: 122 PE: 18	NR
Ezekowitz *et al* (PETRO)[41]	2007	phase II, Randomized parallel, Prospective, Controlled Trial, double-blinded for DAB w/o ASA and open-label with ASA, and for WAR.	Multi-center	DAB 150 mg twice daily	WAR once daily	**Non-valvular atrial fibrillation (non-VHD)** Non-rheumatic atrial fibrillation paroxysmal: 22.9% persistent: 38.8% permanent: 38.2%	NR	NR	NR	**2-3**	**3** mos	**Primary safety:** MB w/o ASA: 0 MB with ASA 81 mg: 0 MB with ASA 325 mg : 0	TEE w/o ASA: 0 TEE with ASA 81 mg: 0 TEE with ASA 325 mg: 0	NR
Cannon *CP et al.* (RE-DUAL PCI) [42]	2017	phase IIIb, prospective Randomised, open-label, blinded endpoint (PROBE), (RE-DUAL PCI)	Multi-center	***110 mg dual therapy group*** = 110 mg DAB twice daily + CLO or ticagrelor ***150 mg dual therapy group*** = 150 mg DAB twice daily + CLO or ticagrelor	warfarin once daily in a triple therapy group (warfarin + ASA+ clopidogrel or ticagrelor)	**Non-valvular atrial fibrillation (non-VHD)** paroxysmal: 49.6 % persistent: 17.8% permanent: 32.6%	***in dual therapy group*** : paroxysmal: 49.8 % persistent: 17.3% permanent: 32.8 %	***in dual therapy group :*** paroxysmal: 49.6 % persistent: 17.7 % permanent: 32.6 %	***in triple therapy group:*** paroxysmal: 49.4% persistent: 18.2% permanent: 32.4%	**2-3**	**14** mos	**Primary safety:** MB: 43 **Secondary safety:** ICH: 1 GIB: NR	TEE: 60 (7.9) S: 9 (1.2)	NR
Chu Min Soo *et al.*[43]	2022	prospective, single-center, open-label, randomized controlled trial	Mono-center	DAB 150 mg twice daily, which may be reduced to DAB 110 mg twice daily when CrCl (30-49) ml/min	WAR once daily)	**Non-valvular atrial fibrillation (non-VHD)** persistent/ permanent: 99 (83%)	persistent/ permanent: 52 (88%)		persistent/ permanent (in the conventional group as a whole WAR + ASA): 47 (78%)	**2-3**	**12** mos	**Primary safety:** MB: 0	SE: 0 S: 0	reduce the dose to 110 mg twice daily in the case of CrCl of 30 to 49 ml/min
						valvular AF Mitral stenosis MS (Moderate to Severe)								
						Moderate MS 43 (36%)	23 (39%)	-	20 (33%)					
						Severe MS 39 (33%)	17 (29%)	-	22 (37%)					
Calkins Hugh *et al.* (RE-CIRCUIT) [44]	2017	phase IV, randomized, open-label, controlled trial	Multi center	DAB 150 mg twice daily	WAR (a combination of 1, 3, and 5 mg)	nonvalvular atrial fibrillation undergoing ablation of atrial fibrillation	Paroxysmal: 213 (67.2) Persistent: 86 (27.1) Long-standing persistent: 18 (5.7)		Paroxysmal: 219 (68.9) Persistent: 81 (25.5) Long-standing persistent: 18 (5.7)	**2-3**	**2** mos	**Primary safety:** MB: 5 **Secondary safety:** ICH: 0 GIB: 1	SE: 0 S:0	**NR**

Table 1. (following) Characteristics of included studies

Study ID	Year of publi-cation	Study design	Setting	Intervention	Comparator	Type of AF (VHD or non-VHD)				INR	Follow up	Safety endpoint	Primary efficacy	Dose ad-justment
						Totally in the whole study (%)	**DAB 150 mg**	**DAB 110 mg**	**Warfarin**					
						Non-valvular atrial fibrillation (non-VHD)								
Nogami *et al.* (ABRIDGE-J)[45]	2019	Prospective Open-label, randomized clinical trial	Multi center (different centers in Japan)	DAB 150 mg twice daily or (110 mg twice daily in moderate renal disorders)	WAR	non-valvular AF undergoing catheter ablation	Paroxysmal 138 (62.7) Persistent 52 (23.6) Long-standing persistent 30 (13.6)	-	Paroxysmal: 219 (68.9) Persistent: 81 (25.5) Long-standing persistent: 18 (5.7)	**2- 3** for patients younger than 70 years and **1.6 - 2.6** for patients 70 years or older.	**3** mos	**Primary safety:** MB event: 3 (1.4)	SE: 0 S: 0	Reduced to 110 mg twice daily in patients with a CrCl rate of 30-50 mL/min
Eikelboom *et al.* (RE-ALIGN) [46]	2013	prospective randomized, phase 2, open-label trial with blinded end-point adjudication.	Multi center	DAB 150 mg twice	WAR 1,3 and 5 mg once daily adjusted by INR	**valvular AF (VHD) "Mechanical heart valve"** **Type of valve-replacement surgery (n=252)**				**2-3** in case of low thrombotic risk **2.5-3.5** in case of inte-rmediate or high thrombotic risk	**3** mos	**Primary safety:** MB: 7(4)	SE: 0 S:9 (5)	(i) 150 mg twice daily in patients with a CrCl of Less than 70 ml/min (ii) 220 mg twice daily in those with a CrCl of 70 to 109 ml/min (iii) 300 mg twice daily in those with a CrCl of 110 ml/ min or more
						Aortic n=172 (68%)	113 (67)	-	59 (70)					
						Mitral n= 71 (28%)	49 (29)	-	22 (26)					
						Aortic and Mitral n= 9 (4%)	6 (4)	-	3 (4)					
						"**NB**: Population A = 199 patients, Postoperative patients who had valve implantation recently (within one week of randomization) (133 DAB, 66 WAR); population B = 53 patients, Postoperative patients who had valve implantation ≥ 3 months ago (35 DAB,18 WAR)». However, in our meta-analysis we included all patients " population A and B"								
Dura˜es *et al.* (DAWA)[47]	2016	Prospective phase II pilot, open-label	Mono center (uni center)	DAB 110 mg BID	WAR adjusted dose	**valvular AF (VHD) "Bioprosthetic heart valve"** **NB.** Bioprosthetic valves Patients with mitral and/ or aortic valve bioprosthesis for at least 3 months postoperatively				**2-3**	**3** mos	bleeding: 1 (6.7)	S or SE: 0	NR
NCT01136408 (BIBR 1048) [48]	2010	phase II, Randomized, parallel, open-label controlled trial	Multi center in japan	DAB 110 mg BID, 150 mg	Dose-adjusted WAR based on target INR values	**non-valvular atrial fibrillation (NVHD)** (paroxysmal, persistent or permanent)				**2-3**	**3** mos	**Primary safety:** MB: 1 (1.7)	S: 0 SE: 0	NR
Nin *et al.*[49]	2012	prospective the randomized, single-center study»	Mono center study	DAB 110 mg BID	A dose-adjusted WAR based on target INR values	**non-valvular atrial fibrillation (non-VHD)**				**1.6-2.5**	**half mos**	NR	S or SE: 0	NR
						non-valvular AF: paroxysmal 66 (73%)	-	**non-valvular AF:** paroxysmal: 76%	**non-valvular AF:** paroxysmal: 71%					
						persistent 23(25%)		persistent: 24%	persistent: 27%					
						long-standing persistent 1 (1%)		long-standing persistent: 0	long-standing persistent: 2%					

Abbreviations: **DAB**: Dabigatran; **WAR**: Warfarin; **CrCl ml/min**: Creatinine Clearance, **MB:** Major bleeding, **S**: stroke, **SE**: systemic embolism, **TEE**: thromboembolic event, **PE**: pulmonary embolism, **GIB**: Gastrointestinal bleeding, **mos**: months, **ASA**: Acetylsalicylic acid, **BID**: twice daily

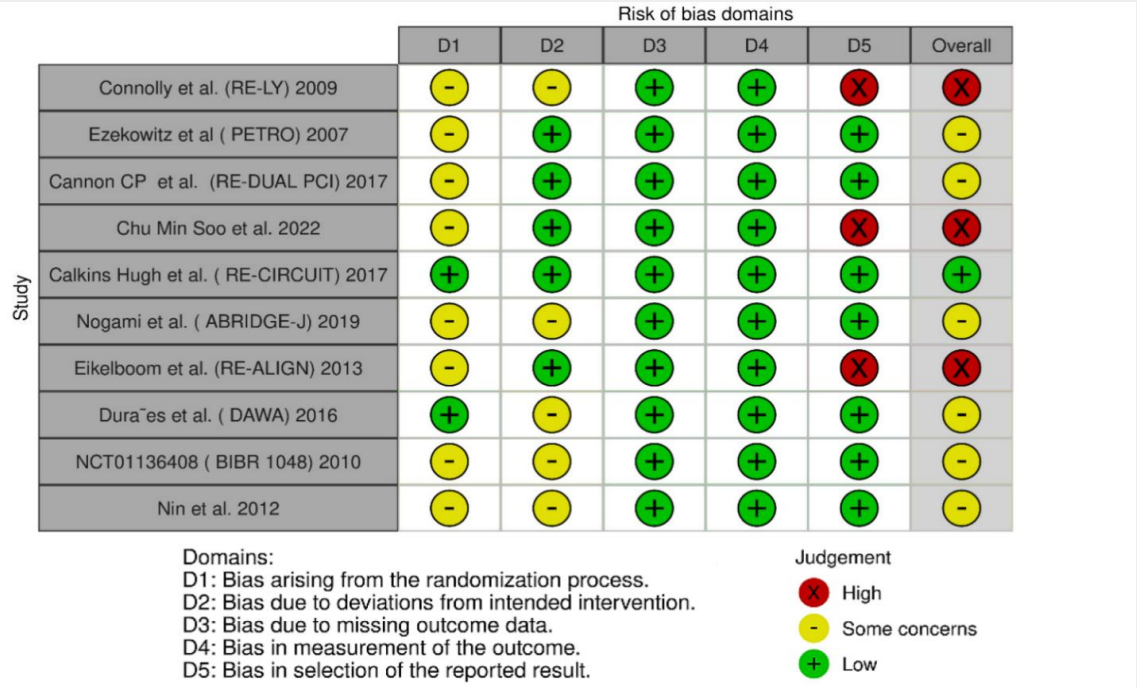
Table 2. Baseline characteristics

Study	Sample size T.I.S & DAB VS. WAR	Mean age	Sex (M/F) n (%) T.I.S & DAB VS. WAR"	Mean CHA2DS2-VASc	Mean HAS-BLED	Comorbidities and risk factor n (%)	Medications n (%)
Connolly *et al.* (RE-LY) 2009	**18113** ***DAB 150: 6076*** ***DAB 110: 6015*** ***WAR: 6022***	**DAB 150: 71.4 ± 8.6** **DAB 110:** 71.5 ± 8.8 **WAR:** 71.6 ± 8.6	**T.I.S:** **M: 11514 (63.5%)** **F: 6599 (36%)** **DAB 150:** M = 3865 (64%), F = 2202 (36%) **DAB 110:** M = 3840 (63%), F = 2175 (36%) **WAR:** M = 3809 (63%), F=2213 (36.7)	**DAB 150:** 2.1±1.1 **DAB 110:** 2.2±1.2 **WAR:** 2.1±1.1	NR	***DAB 150 vs DAB 110 vs. WAR:*** • % Previous stroke or TIA: 19.9 vs 20.3 vs.19.8. • Prior MI: 16.8 vs. 16.9 vs. 16.1% • HF: 32.2 vs. 31.8 vs. 31.9% • DM: 23.4 vs. 23.1 vs. 23.4 % • HTN: 78.8 vs. 78.9 vs. 78.9 %	***DAB 150 vs. DAB 110 vs. WAR:*** • Aspirin; 40% vs. 38.7% vs. 40.6 % • ARB or ACEI; 66.3 vs. 66.7 vs. 65.5 % • BB; 62.9 vs. 63.7 vs. 61.8% • Amiodarone; 10.4 vs. 10.9 vs 10.7 % • Long-term VKA therapy: 50.1 vs 50.2 vs 48.6 %
Ezekowitz *et al*502 (PETRO) 2007	***DAB 150: 100*** ***WAR: 70***	**DAB 150:** 70 ± 8.1 **WAR:** 69 ± 8.3	**T.I.S:** **M: 441 (81.9%)** **F: 91 (18%)** **DAB 150:** M= 135 (81.3%), F= 31 (18.7%) **WAR:** M=59 (84.3%), F = 11 (15.7%)	NR	NR	***DAB 150 vs. WAR:*** • Previous stroke or TIA; 17.5 vs. 18.6 % • HF: 27 vs. 34.3% • DM; 27 vs. 21.4 • HTN; 71% vs. 70 % • CAD: 31.3 VS 60 %	***DAB 150 vs. WAR:*** • ARBs or ACEI; 69.8 vs. 81.4% • BB ;73 vs. 70 % • Amiodarone; 5.4 vs. 8.5 % • CCB; 18.7 vs. 20 % • Digoxin; 45 vs. 45.7 • % diuretics 53.6 vs 63 %
Cannon CP *et al.* (RE-DUAL PCI) 2017	**2725** ***DAB 150: 763*** ***DAB 110: 981*** ***WAR: 981***	**DAB 150:** 68.6 ± 7.7 **DAB 110:** 71.5 ± 8.9 **WAR:** 71.7 ± 8.9	**T.I.S:** **M: 2070 (75.96%)** **F: 655 (24%)** **DAB 150:** **M**: 592 (78%) **F:** 171 (22%) **DAB 110:** M: 728 (74.2) **WAR:** **M :** 750 (6%) **F :** 231 (24%)	**DAB 150:** 3.3 ± 1.5 **DAB 110:** 3.7±1.6 **WAR:** 3.8±1.5 ***CHA2DS2-VASC SCORE > 2 , n (%):*** **DAB 150:** 751 (76.6) **DAB 110**: 516 (67.6) **WAR:** 788 (80.3) ***CHA2DS2-VASC SCORE ≤ 2, n (%):*** **DAB 150:** 230 (23.4) **DAB 110:** 247 (32.4) **WAR:** 193 (19.7)	**DAB 150:** 2.6±0.7 **DAB 110:** 2.7±0.7 **WAR**: 2.8±0.8 ***HAS-BLED <3, n (%):*** **DAB 150**: 336 (34.3) **DAB 110:** 316 (41.4) **WAR:** 291 (29.7) ***HAS-BLED ≥ 3, n (%):*** **DAB 150:** 645 (65.7) **DAB 110:** 447 (58.6) **WAR:** 690 (70.3)	***DAB 150 vs DAB 110 vs. WAR:*** • Previous stroke or TIA; 6.8 vs 7.5 vs. 10.2% • Prior MI; 16.8 vs. 16.9 vs. 16.1% • DM; 34.1 vs. 36.9 vs. 37.9 % • % Previous CABG: 10.4 vs 9.9 vs. 11.3%	***DAB 150:*** Use of aspirin or clopidogrel after surgery — no. (%): • One agent or both: 51 (30) • Both agents :3 (2)
Chu Min Soo *et al. (2022)*	**119** ***DAB 150:*** 59 (only **40** MS *was taken DAB)* ***WAR:*** *53 (only **42** MS was taken WAR)*	**DAB 150**: 61.1 ± 8.3 **WAR:** 61.3 ± 9.8	**T.I.S:** **M: 82 (69%)** **F:37(33%)** **DAB 150:** **M**: 41 (70%), **F:** 18 (30%) **WAR:** **M**: 41 (68%), **F**: 19 (32%)	***CHA2DS2-VASc score:*** Totally: 2.1 ± 1.2 **DAB 150**: 2.0 ± 1.1 **WAR:** 2.2±1.2 ***CHA2DS2-VASc score: ≥2, n (%):*** Totally: 68 (57%) **DAB 150 mg:** 32 (54%) **WAR**: 36 (60%)	NR	***DAB 150 vs. WAR:*** • Previous stroke or TIA: 12 vs. 13 % • HF: 15 vs. 13 % • DM; 7 vs. 13 % • HTN: 46 vs. 52 % • CKD: 5 vs. 33 %	***DAB 150 vs. WAR:*** • ARBs or ACEI; 32 vs. 32 BB; %53 vs. 58 % • CCB; 17 vs. 19 % • Digitalis; 34 vs. 28 % • Diuretics; 59 vs 45% • Antiplatelet 15 vs. 13 %
Calkins Hugh *et al.* (RE-CIRCUIT) 2017	**635** ***DAB 150: 317*** ***WAR: 318***	**DAB 150:** 59.1±10.4 **WAR:** 59.3±10.3	**T.I.S:** **M: 475 (75%)** **F: 160 (25%)** **DAB 150:** **M:** 230 (72.6), **F:** 87 (27%) **WAR:** **M**: 245 (77.0), **F**: 73 (22.9%)	***Mean CHA2DS2-VASc score;*** **DAB:** 2.0 **WAR:** 2.2	NR	***DAB 150 vs. WAR:*** • Previous stroke or TIA; 3.2 vs. 2.8 % • HF: 9.8 vs. 10.7 % • DM: 9.5 VS. 10.7% • HTN: 52.4 vs. 55.7% • Renal disease; 2.2 VS 4.4 % • CAD; 10.1 vs 15.1% • Previous MI: 3.2 vs 4.7 %	***DAB 150 vs. WAR:*** • BB 57.7 vs. 60.4 % • NSAIDs; 19.5 vs. 23.1 • Statins: 31.4% VS. 29.9% • Vitamin K antagonist: 28.1 vs 25.4 • PPIs: 21.6% VS. 23.4%

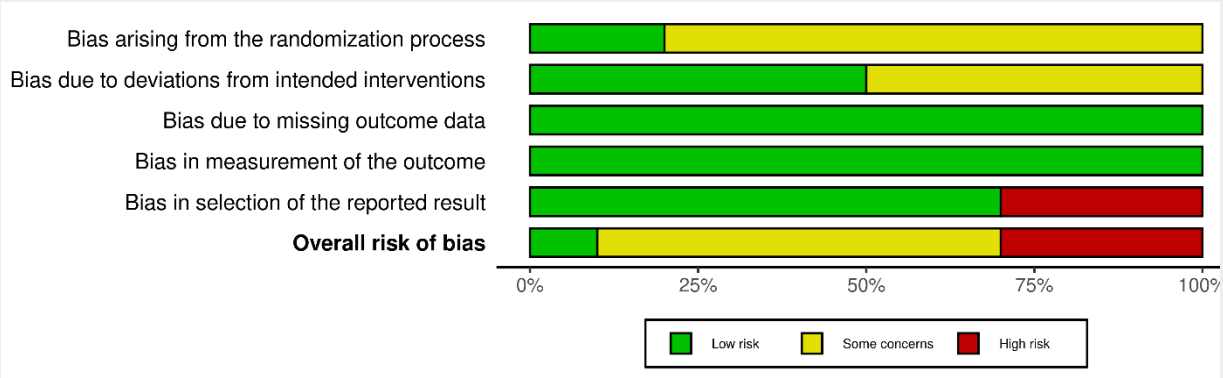
Table 2. (following) Baseline characteristics

Study	Sample size T.I.S & DAB VS. WAR	Mean age	Sex (M/F) n (%) T.I.S & DAB VS. WAR"	Mean CHA2DS2-VASc	Mean HAS-BLED	Comorbidities and risk factor n (%)	Medications n (%)
Nogami *et al.* (ABRIDGE-J) 2019	**442** ***DAB 150: 220*** ***WAR: 222***	**DAB 150**: 65 ± 8.95 **WAR:** 65.33 ± 8.95	**T.I.S:** **M: 331 (65%)** **F: 111 (25%)** **DAB 150:** **M**: 171 (77.7), **F:** 49 (22%) **WAR:** **M**:160 (72.1), **F:** 62 (28%)	**DAB:** 2± 1.49 **WAR:** 2 ± 1.49	**DAB:** 1 ± 1.49 **WAR:** 1.33 ± 0.75	***DAB 150 vs. WAR:*** • Previous stroke or TIA; 6.8 vs. 5.4% • CHF; 3.6 vs. 6.3 % • DM: 16.4 vs. 15.3% • HTN; 55.9 vs. 56.8 % • CKD; 6.8% vs. 7.2% • CAD; 3.2 vs 6.3% • Previous MI: 0.9 vs 2.7 % • Previous GIT bleeding; 0 vs. 1.4 % *Renal function "CrCl (ml/ min)": 79.86 ± 21.42 vs. 79.86 ± 24.33*	***DAB 150 vs. WAR:*** • Aspirin; 5.9 vs 6.3 % • Clopidogrel bisulfate: 1.4 vs.1.4% • Ticlopidine hydrochloride: 0 vs.0 • Cilostazol: 0 vs.0.5% • Eicosapentaenoic acid: 1.4 vs. 0.9% • NSAID: 0.5 vs. 3.2% • Rivaroxaban 15.5 vs. 15.8% • Apixaban; 11.8 vs. 10.8%
Eikelboom *et al*. (RE-ALIGN) 2013	**252** ***DAB 150: 168*** ***WAR: 84***	**DAB 150:** 56.0±9.4 **WAR:** 55.7±10.4	**T.I.S:** **M: 163 (37%)** **F: 89 (35%)** **DAB 150:** **M:** 107 (64) **F:** 61 (36%) **WAR:** **M:** 56 (67) **F**: 28 (33%)	NR	NR	***DAB 150 vs. WAR***: • Previous stroke; 3 vs. 6 % • DM; 16 vs. 15 % • HTN: 60 vs. 63 %; • CAD; 23 vs 29 % • Previous MI; 5 vs 8 % Atrial fibrillation:22 vs. 26 % • Atrial flutter: 4 vs. 6 % *Renal function "CrCl ml/ min": 107.8±39.9 vs. 106.4±34.4*	**DAB 150:** Use of aspirin or clopidogrel after surgery: • One agent or both: 51 (30) • Both agents: 3 (2) **WAR:** Use of aspirin or clopidogrel after surgery One agent or both: 25 (30) Both agents: 1 (1)
Dura˜es *et al.* (DAWA) 2016	**27** ***DAB 110: 15*** ***WAR: 12***	**DAB:** 48.8 ± 10.5 **WAR:** 45.7 ± 7	**T.I.S:** **M: 10 (37%)** **F: 17 (63%)** **DAB:** **M:** 5 (33.3) **F:** 10 (67%) **WAR:** **M**: 5 (41.7) **F**: 7 (58%)	NR	**DAB:** 0.33 ± 0.82, **WAR:** 0.33 ± 0.85	***DAB 150 vs. WAR:*** • Previous stroke or TIA; 26.7 vs. 33.3% • DM: 7.1 vs. 0% • HTN: 46.7 vs. 50 % • NYHA (III–IV): 27.3 vs. 27.3%	NR
NCT01136408 (BIBR 1048) 2010	**166** ***DAB 150: 58*** ***DAB 110: 46*** ***WAR: 62***	**DAB 150:** 68.3 ± 9.1 **DAB 110**: 69.9 ± 7.5 **WAR:** 67.4 ± 8.8	**T.I.S:** **M: 146 (88%)** **F: 20 (12%)** **DAB 150:** **M:** 53 (91.4%), **F**: 5 (8.6%) **DAB 110:** **M:** 36 (78.3%), **F**: 10 (21.7%) **WAR:** **M**: 57 (91.9%), **F:** 5(8.1%)	NR	NR	NR	NR
Nin *et al.* 2012	**90** ***DAB 110: 45*** ***WAR: 45***	**DAB 110:** 61 ± 11 **WAR:** 61 ± 6	**T.I.S:** **M: 74 (82%)** **F: 16 (18%)** **DAB 110:** **M:** 38 (84%), **F**: 7 (16%) **WAR:** **M**: 36 (80%) **F**: 9 (20%)	***CHADS2 score for DAB, n (%):*** **0–1:** 37 (82%) **2:** 5 (11%) **3–6:** 3 (7%) ***CHADS2 score for WAR, n (%):*** **0–1**: 36 (80%) **2:** 6 (13%) **3–6:** 3 (7%)	NR	***DAB 110 vs. WAR:*** • Previous stroke or TIA: 4 vs. 11 %; • HF; 4 vs. 7 % • DM; 11 vs. 11 % • HTN: 44 vs. 49 % *Serum creatinine (mg/dL) 0.94 ± 0.21 vs. 0.94 ± 0.20*	**DAB 110:** PPIs: 15 (33%) **WAR:** PPIs: 9 (20%)

Abbreviations: **T.I.S**: Total in the study, DAB 150/110: Dabigatran 150 mg and 110 mg. **WAR**: Warfarin, **M**: Males, **F**: Females, **MI**: myocardial infarction, **HF**: Heart failure, **TIA**: transient ischemic stroke, **HTN**: Hypertension, **DM**: Diabetes mellitus, **CHADS2 VAS score**: congestive heart failure, hypertension, Age ≥75, Diabetes, Stroke (TIA, thromboembolism), Vascular disease history, "prior MI, peripheral artery disease, or aortic plaque", Age 65-74, Sex category "female". **HAS-BLED**: Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/ alcohol usage. **ACE**; Angiotensin-converting enzyme, ARBs: Angiotensin receptor blockers, **CCB**: calcium channel blockers, **BB**: Beta-blockers, **NYHA**: New York Heart Association, **PPIs**: proton pump inhibitors. **CrCl**: creatinine clearance. ** All continuous variables are presented in mean and standard deviation (mean ± SD), and the dichotomous variables in number and percentage n (%).



(A) Risk of Bias Tool 2.0 for Randomized Controlled Trials [31]



(B) Summary of risk of bias assessment

Figure 3. Risk of bias assessment of the included studies

Results of the Subgroup Analysis

We entered four subgroups (DAB vs. WAR in AF patients with NVHD and VHD, DAB 150 &110 mg vs. WAR in non-valvular AF (NVAF), DAB vs. WAR in valvular AF (VAF), and DAB 150 mg vs. WAR in AF patients undergoing catheter ablation) into the meta-analysis via the random effects DerSimonian and Laird model. The results in Figures 4A, B, and C revealed no statistically significant overall differences in S+ SE (RD -0.00, 95% confidence interval (CI):[-0.01,0.01], Prediction interval (PI): [-0.01,0.01] and death (RD -0.00,95% CI: [-0.01, 0.00],PI:[-0.01,0.00]), respectively, between DAB and WAR in VAF and NVAF groups.Conversely, a statistically significant overall difference in major bleeding (RD -0.02,95% CI: [-0.03, -0.00], PI:[-0.05,0.01]) between DAB and WAR in the VAF and NVAF groups.

(i) Dabigatran 150 mg VS. warfarin in non-valvular AF:
Efficacy: Pooling outcomes from the included trials revealed that the overall S and S+SE between DAB group and WAR group were not statistically significant (RD -0.00,95% CI: [-0.01, 0.00], *p*-value = 0.07,PI:[-0.02,0.01]), and (RD -0.01, 95% CI: [-0.01, 0.00], *p*-value = 0.06,PI:[-0.02,0.01]), respectively and with no heterogeneity. (Figures 5A,5B,S1 and S3)
Safety: The major bleeding outcomes were considerably lower in DAB than with WAR, but there was low heterogeneity(RD = -0.02,95% CI:[-0.04, -0.00], *p*-value = 0.02, PI:[-0.08,0.03]). (Figure 5C, S5)

Valvular heart disease vs. non-valvular heart disease

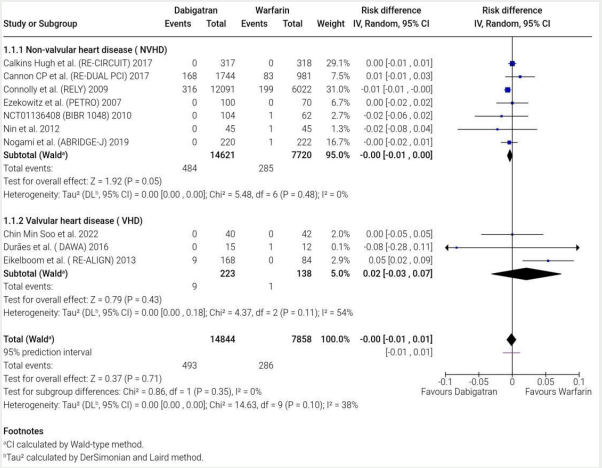


Figure 4A. forestplot showing risk of stroke + systemic embolism in VHD versus NVHD

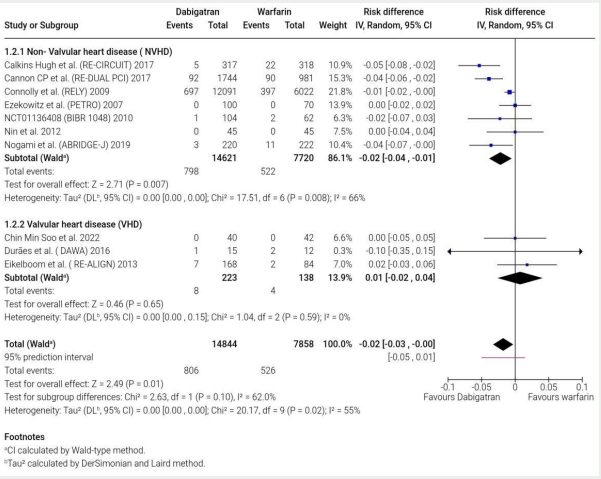


Figure 4B. Forest plot showing risk of major bleeding in VHD versus NVHD

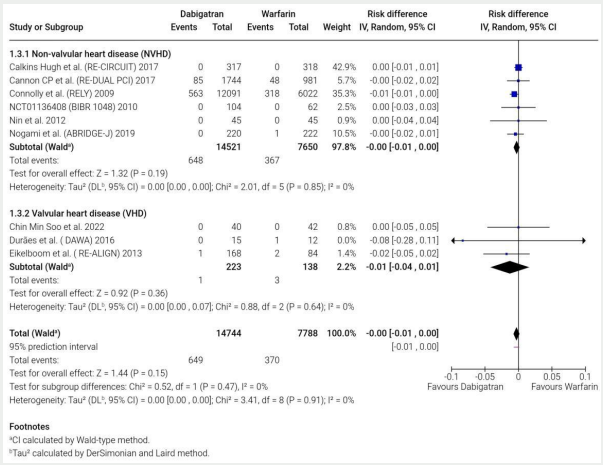


Figure 4C. Forestplot showing risk of death in VHD versus NVHD

Dabigatran 150 mg and 110 mg Versus Warfarin in NVHD

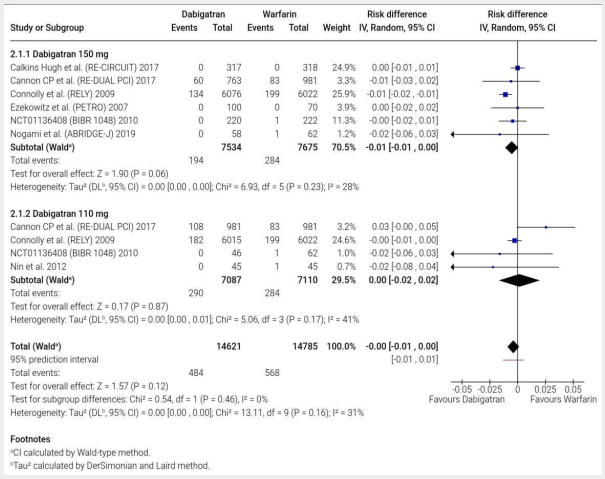


Figure 5A. forestplot showing the risk of stroke and systemic embolism (Thromboembolic event) associated with dabigatran 150 mg VS. dabigatran 110 mg VS. warfarin in NVHD

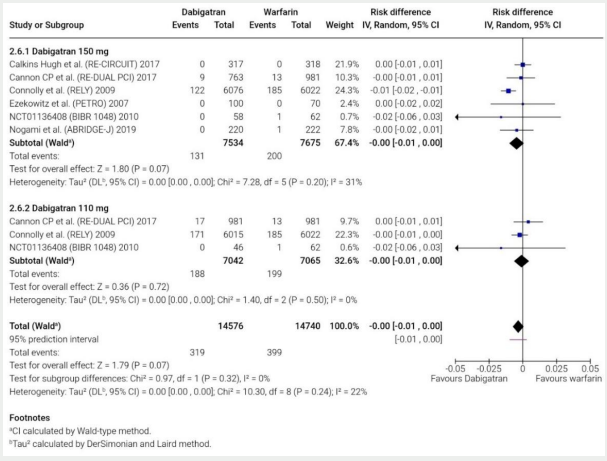


Figure 5B. forestplot showing the risk of Stroke only associated with dabigatran 150 mg and 110 mg VS. warfarin in NVHD

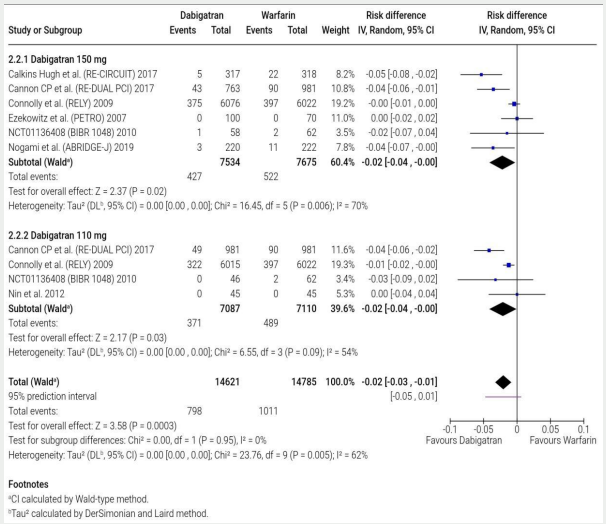


Figure 5C. forest plot showing the risk of major bleeding associated with dabigatran 150 mg VS dabigatran 110 mg VS. warfarin in NVHD

DAB 150 was associated with a significantly lower risk of ICH (RD -0.01, 95% CI: [-0.01, -0.01], p-value <0.00001,PI:[Not calculated]), with no significant reduction in minor bleeding (RD= -0.01,95% CI = [-0.04,0.02], P-value = 0.52,PI:[-0.1,0.09]), and death (RD -0.00, 95% CI: [-0.01, 0.00], p-value = 0.12,PI:[Not calculated] compared to WAR respectively. Additionally, RD of GIB demonstrated no statistically significant difference between DAB 150 mg and WAR (RD 0.00 ,95%CI:[-0.01,0.02],p-value=0.51,PI:[Not calculated]). However, the overall GIB event using RR (RR 1.49, 95% CI:[1.19,1.87],p-value= 0.0006) was considerably greater with DAB than with WAR. This discrepancy reflects the differing sensitivities of RR and RD to baseline risk, particularly when the outcome has a low event rate. No heterogeneity was observed in ICH and death, except for minor bleeding, which showed moderate heterogeneity. (Figures 5D, E, F,G,H, S7,S8, and S10)

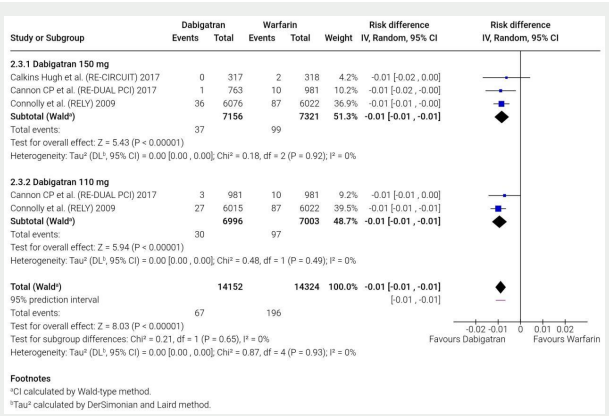


Figure 5D. forest plot of intracranial bleeding in dabigatran 150 mg VS. dabigatran 110 mg VS. warfarin in NVHD

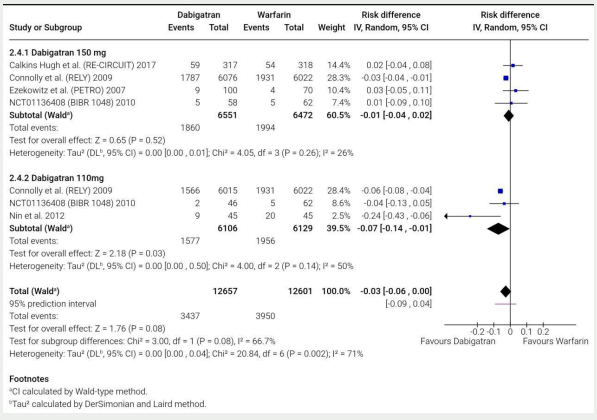


Figure 5E. forest plot showing minor bleeding in dabigatran 150 mg VS. dabigatran 110 mg VS. warfarin in NVHD

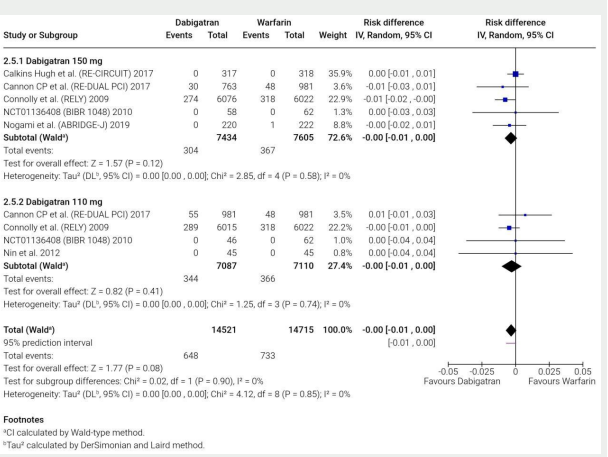


Figure 5F. Forestplot showing the risk of death associated with dabigatran 150 mg VS. dabigatran110 mg VS. warfarin in NVHD

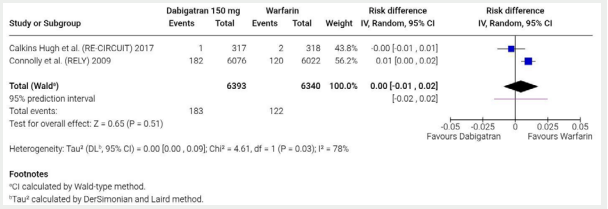


Figure 5G. Forestplot showing the risk of gastrointestinal bleeding associated with dabigatran 150 mg VS. warfarin in NVHD. Effect size measured by RD which showing no statistically significant difference between DAB 150 mg and WAR

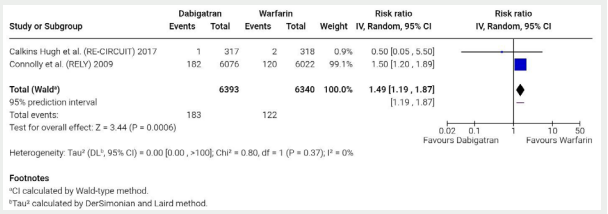


Figure 5H. forestplot showing risk of gastrointestinal bleeding associated with dabigatran 150 mg VS. warfarin in NVHD by using risk ratio (RR) which showing statistically significant difference between DAB 150mg and WAR due to low baseline risk.

(ii) Dabigatran 110 mg VS. warfarin in non-valvular AF:

Efficacy: The overall difference between the DAB and WAR groups in S and S + SE was not significant (RD -0.00, 95% CI: [-0.01,0.00], p-value = 0.72,PI: [Not calculated], and (RD 0.00,95%CI:[-0.02,0.02], p-value = 0.87,PI:[-0.06,0.06]),with no and moderate heterogeneity respectively. (Figures 5A,5B,S2,and S4)

Safety: DAB 110 showed a considerably lower risk of major bleeding (RD -0.02, 95% CI: [-0.04,-0.00], p-value = 0.03, PI:[-0.09,0.05]), minor bleeding (RD -0.07, 95% CI:[-0.14, -0.01], p-value = 0.03,PI:[-0.75,0.61]), and ICH (RD -0.01, 95% CI: [-0.01,-0.01], p-value < 0.00001,PI:[Not calculated]) compared to WAR, respectively with moderate heterogeneity for major bleeding and substantial heterogeneity for minor bleeding . There was no substantial difference in death events between the groups (RD -0.00,95% CI: [-0.01,0.00], p-value =0.41,PI:[Not calculated, all studies share common effect size]) with no heterogeneity. (Figures 5C,D, E, F,S6,S7,S9and S10).

(iii) Dabigatran VS. warfarin in valvular AF:

Efficacy: The overall S + SE events were similar across both groups (RD 0.02, 95% CI: [-0.03, 0.07], p-value = 0.43,PI:[-0.51,0.55]). PI suggested substantial heterogeneity. (Figure 6A)

Safety: The overall major bleeding (RD 0.01, 95% CI: [-0.02, 0.04], p-value = 0.65,PI: [Not calculated]), death (RD -0.01, 95% CI: [-0.04, 0.01], p-value = 0.36,PI:[Not calculated]), and all bleeding events (RD 0.04, 95% CI:[-0.09, 0.18], p-value=0.53,PI:[-1.54,1.63]) showed no remarkable difference between DAB and WAR with substantial heterogeneity in all bleeding outcome. (Figures 6A,B, C, D, S11,S12,S13,and S14)

Notably ,wide PI for the S/SE, and all bleeding outcomes, suggesting substantial uncertainty about the true effect size.

Dabigatran Versus Warfarin in Atrial Fibrillation with Valvular heart disease (VHD)

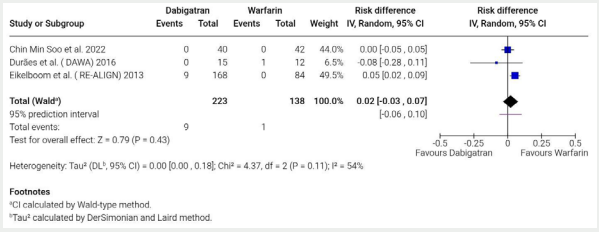


Figure 6A .forestplot showing risk of stroke and systemic embolism (S+SE) events associated with dabigatran VS. warfarin in VHD

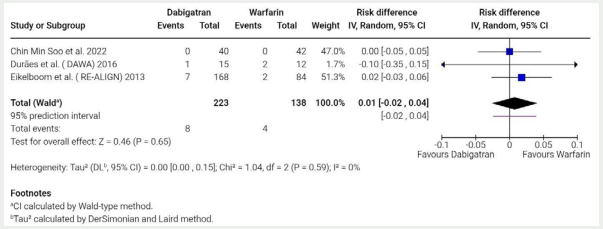


Figure 6B. forestplot showing risk of major bleeding endpoint associated with dabigatran VS. warfarin in VHD

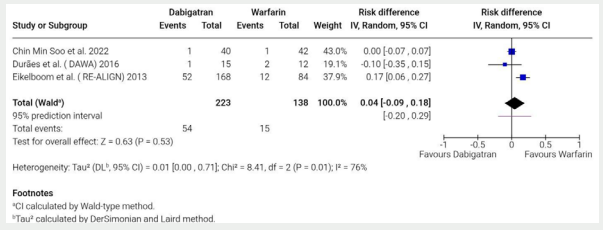


Figure 6C. forestplot showing risk of all bleeding events associated with dabigatran VS. warfarin in VHD

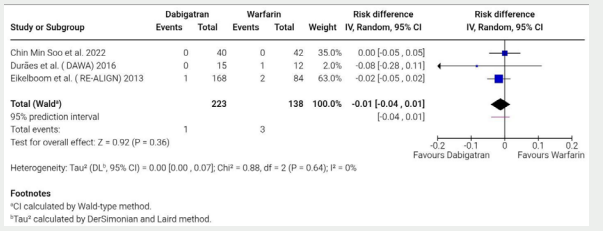


Figure 6D. Forestplot showing the risk of death (mortality) associated with dabigatran VS. warfarin in VHD

(iv) Dabigatran 150 mg VS. warfarin in AF patients undergoing catheter ablation:

The overall groin hematoma events were substantially lower with DAB than with WAR (RD -0.02, 95% CI: [-0.03 to -0.00], p-value = 0.008). However, all the other events—cardiac tamponade (RD -0.01, 95% CI: [-0.02 to 0.00], p-value = 0.09), pseudoaneurysm (RD -0.00, 95% CI:[-0.01 to 0.00], p-value = 0.32), and pericardial effusion (RD 0.00, 95% CI:[-0.00 to 0.01], p-value = 0.32) were not markedly different. (Figure7)

Dabigatran Versus Warfarin in atrial fibrillation patients accompanied with NVHD and undergoing catheter ablation

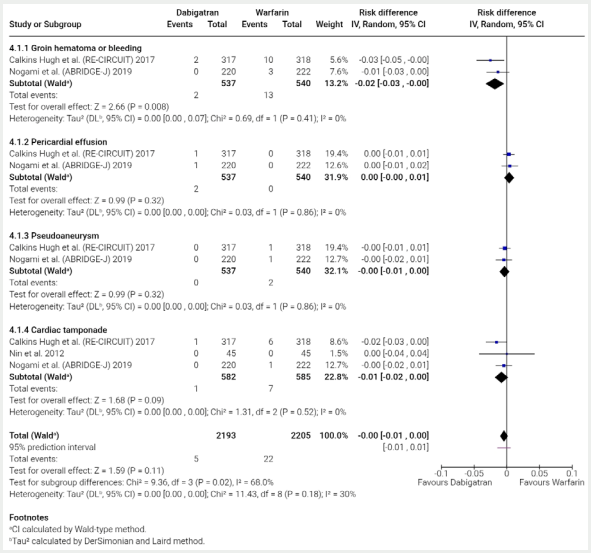


Figure 7A. forestplot showing risk of pericardial effusion, pseudoaneurysm, groin hematoma, and cardiac tamponade endpoints associated with dabigatran Versus warfarin in AF patients undergoing catheter ablation

Sensitivity analysis and heterogeneity resolving

To resolve the moderate and substantial heterogeneity of the major and minor bleeding endpoints of the subgroup comparing DAB 150 and DAB 110 to WAR in AF patients with NVHD, we conducted a sensitivity analysis. The heterogeneity was resolved by excluding the Connolly et al. and Ezekowitz et al. studies for DAB 150 mg, and the Cannon CP et al. for DAB 110mg in case of major bleeding, and Connolly et al.for DAB 150 mg and Nin et al. for DAB 110 mg in case of minor bleeding . Similarly, for S + SE and all bleeding endpoints of the VHD subgroup, comparing DAB to WAR, after excluding the Eikelboom et al. study, the substantial heterogeneity was resolved. (Figure 8A,B,C, D,S15,S16,S17,S18,S19, and S20)

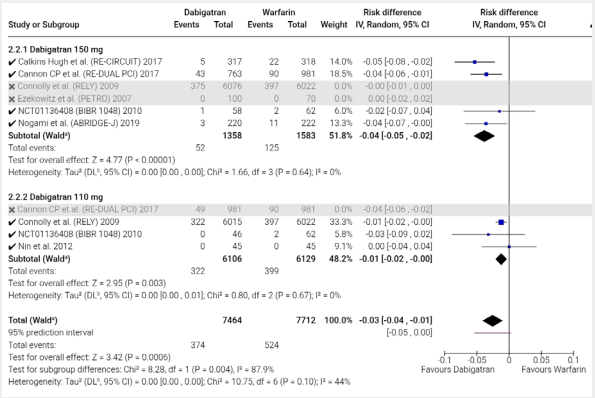


Figure 8A. shows sensitivity test of major bleeding risk associated with dabigatran 150 mg and 110 mg vs warfarin in NVHD

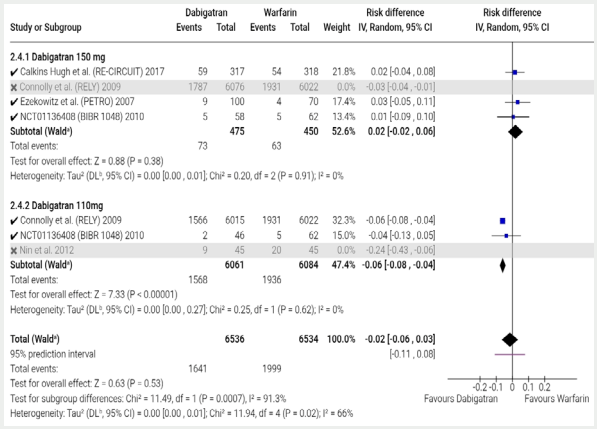


Figure 8B. shows sensitivity test of minor bleeding risk associated with dabigatran 150 mg and 110 mg vs warfarin in NVHD

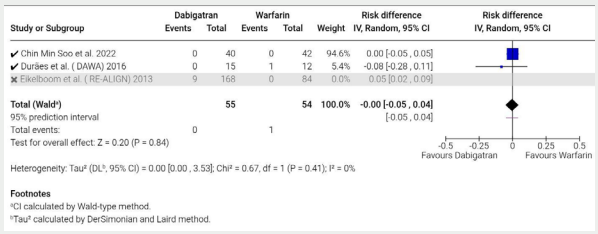


Figure 8C. shows sensitivity test of stroke + systemic embolism risk associated with dabigatran vs warfarin in VHD

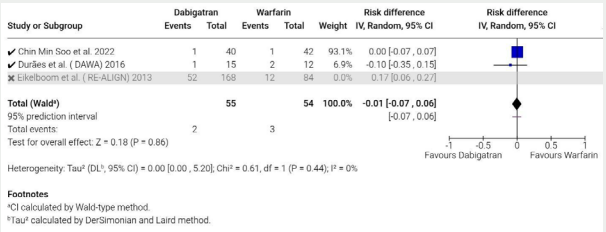


Figure 8D. shows sensitivity test of all bleeding risk associated with dabigatran vs warfarin in VHD

Discussion

Previous studies and meta-analyses compared all NOACs with WAR in NVAF and VHD patients. In the case of VHD patients, these meta-analyses consider aortic stenosis (AS), aortic regurgitation (AR), mitral regurgitation (MR), tricuspid regurgitation (TR), and mild rheumatic mitral stenosis as examples of VHD. This is according to a post hoc analysis of the RE-LY trial, which eliminated patients with severe mitral stenosis (MS) and prosthetic heart valves and included other types of VHD [50]. These meta-analyses concluded that NOACs, including DAB, are preferable over WAR in NVAF patients, particularly those with frailty, polypharmacy, poor anticoagulant adherence, poor time in the therapeutic range (TTR), and poor targeted INR achievement [51-54]. However, none of these meta-analyses compared DAB to WAR in AF patients accompanied by VHD and NVHD, except for YU et al., who compared DAB to WAR in NVHD and excluded prostheses and severe MS [55].

As far as we know, this is the first meta-analysis to compare the safety profile and efficacy of DAB to WAR in AF patients across three subgroups: those with VHD (including BHV, MHV, and severe MS), those with NVHD, and those undergoing catheter ablation. We conducted this study to assess the likelihood of DAB replacing WAR in AF patients with or without VHD.

Elderly individuals and those with comorbidities such as coronary artery disease, VHD, HF, or chronic kidney disease are more likely to experience AF, which often occurs concurrently with VHD [3,56].

Patients with VHD, especially those with prostheses and MS, are at higher risk of thromboembolic events[57]. Additionally, the coexistence of MS with AF markedly elevates the risk of stroke by more than 20 times[58]. The low quality of anticoagulation can hinder the effectiveness of WAR in preventing SE in MS patients with AF[58]. Given these concerns, it is crucial to evaluate the efficacy of NOACs, such as DAB, in individuals with concomitant VHD, especially MS and AF. Many physicians lack a clear understanding of the term “NVAF”. Consequently, some of them resort to off-label use of NOACs in patients with MS, particularly when WAR causes side effects[58]. Clarifying VAF and NVAF terminology helps select the best OACs for AF patients with or without VHD. For that reason, DAB was chosen as one of the NOACs to compare its effectiveness and safety to WAR in AF patients with or without VHD, emphasizing VHD, including BHV, moderate to severe MS, and MHV. We also reviewed all guidelines terminology related to NVAF and VAF to find the best term that clarifies the differences and gives clinicians confidence when prescribing NOACs to AF patients with VHD.

WAR is effective in preventing thromboembolic incidents in AF patients; however, its use is limited to AF patients who have rheumatic, moderate to severe mitral valve disease and/or MHV who are more prone to thromboembolic incidents than those with other types of VHD. Even if AF patients reach an adequate TTR[3], its narrow therapeutic window, repeated INR monitoring, food and drug interactions, and age-related bleeding risk limit its use [56,59]. Otherwise, DAB is preferred over WAR in patients with co-morbidities who cannot achieve a well-controlled INR, such as uncontrolled left ventricular failure. Because elderly patients are more vulnerable to bleeding than younger patients, NOACs, including DAB, are considered the OACs of choice over WAR in AF patients who have a

CHA_2DS_2-VASc score of two or more in men and three or more in women.

Our results demonstrated the superior safety profile of DAB over WAR. This aligns with the Delphi consensus recommendations, which advocate for switching to NOACs, including DAB, even if patients have a well-stabilized TTR and INR with WAR owing to its superior safety [51]. Additionally, the Turkish AFTER-2 study, which concluded that NVAF patients in Turkey could not achieve an excellent TTR, underscores the necessity of switching NVAF patients to NOACs [60]. Furthermore, our meta-analysis revealed that DAB exhibited a considerable safety profile compared to WAR in AF patients without VHD and those with VHD, except for those with BHV and MHV, because of the limited number of RCTs. Otherwise, the American Geriatrics Society Beers Criteria (AGS) recommended that WAR should not be used as a first choice for elderly patients with NVAF unless NOACs are not suitable due to contraindications or significant side effects, such as antiphospholipid syndrome[25,61], history or high risk of GIB [28] and renal impairments particularly those with CrCl< 15 ml/min [25]. The AGS also recommended that elderly individuals >75 years old who are stabilized on WAR for a long time with well-managed INRs and no adverse effects may continue taking it. For those naïve to anticoagulants, NOACs should be initiated, and avoid DAB and rivaroxaban in the long-term owing to the high risk of GIB and kidney function complications or use DAB cautiously. Consequently, DAB 150 mg is not preferred over 75 years of age; DAB 110 mg is preferable; nevertheless, there is a significant preference for using anti-factor Xa drugs except rivaroxaban because it increases the risk of GIB according to the Beers list and Lip GYH et al. [28,62,63]. These results align with our meta-analysis, which revealed a high risk of GIB with DAB 150 mg compared to WAR and the superiority of DAB 110 mg to WAR regarding safety outcomes. Additionally, these findings align with the RELY-ABLE study [64], which showed no significant change in S or mortality after 2.3 years of continuous DAB use. However, DAB 150 mg caused a higher incidence of major bleeding than DAB 110 mg, which exhibited a good safety profile after 2.3 years of follow-up. The low dose of DAB (110 mg) in NVAF patients reduces ICH, hemorrhagic stroke, minor bleeding, and other types of bleeding compared to WAR while maintaining a good TTR (>70 %) and well-controlled INR. However, no differences were observed between a well-controlled WAR and a reduced dose of DAB in S and SE [65], which was consistent with our meta-analysis, which found that DAB 110 mg did not show any significant difference in S/SE compared to WAR and showed a significant reduction only in major bleeding, minor bleeding, and ICH.

It is thought that the first three months after valve repair, especially for the mitral valve, are the most likely times for thromboembolism. This necessitates the use of OACs, regardless of whether the valve is MHV or BHV; however, there are not enough RCTs to determine which OACs reduce thromboembolic events and bleeding the most when AF coexists with VHD, especially the BHV. There was a discrepancy in the class of recommendation (COR) and quality of evidence (QOE) between the 2020 ACC/AHA and the 2021 ESC/EACTS Guidelines for managing VHD [9,11]. Both guidelines appear to be similar, with only slight differences in COR and QOE regarding the use of OACs within 3 months after BHV implantation. ESC recommended that NOACs may be considered over WAR within 3 months after BHV surgery in the mitral position (COR: IIb,QOE: C) and WAR should be considered over NOACs within 3 months after BHV surgery in mitral or tricuspid valve position (COR: IIa,QOE: B). Meanwhile, ACC/AHA recommended that WAR is reasonable if a new onset of AF occurs within 3 months or less after BHV surgery (COR IIa,QOE: B-NR). Moreover, the use of OACs three months after BHV surgery seems contradictory; the 2020 ACC/AHA recommended NOACs as an effective alternative to WAR for patients who had BHV for >3 months, based on the CHA2-DS-2VASc score (COR:I,QOE:A). On the other hand, ESC/EACTS stated that NOACs should be considered over WAR after 3 months following BHV surgery (COR: IIa, QOE: B). However, after retrieving all studies that supported the ACC/AHA recommendation, we found a lack of data and RCTs about using DAB in BHVs, and these studies did not meet the quality of evidence (A) criteria. Furthermore, according to the manufacturer's Pradaxa® (Dabigatran) pamphlet [25], no studies or recommendations exist for using DAB in the presence of BHV. Thus, clinicians should follow the 2021 ESC/EACTS recommendation since it is more accurate than the 2020 American guidelines. We included the DAWA and RE-ALIGN trials in our meta-analysis. DAWA evaluated the safety and effectiveness of DAB in comparison to WAR in a BHV[47], whereas RE-ALIGN dealt with MHV[46]. However, the small sample size (27 patients) of DAWA and the higher thromboembolic incidents in the DAB arm relative to the WAR arm of RE-ALIGN resulted in the cessation of both trials. The RE-ALIGN trial showed that WAR reduces thromboembolism risk better than DAB in patients with MHV. The variation in thrombus formation pathogenesis between mechanical valves and AF[46] may explain this discrepancy. Other causes include the following: (i) Different mechanisms of action of DAB and WAR make WAR more effective than DAB in preventing coagulation activation because WAR inhibits coagulation factors (II, VII, IX, and X), whereas DAB suppresses only thrombin, resulting in valve blood clots and thromboembolic events. (ii) Although blood DAB levels were subtherapeutic at 50 ng/ml, the plasma and trough levels could not accurately predict thromboembolic events [46]. (iii) Exceeding a trough level of DAB to a level greater than that used in the RE-LY trial (50 ng/ml) may not guarantee a high plasma DAB level without severe bleeding[46]. (iv) DAB's safety and efficacy were assessed within 7 days of valve replacement surgery, the highest period of thrombosis after valve repair surgery, which requires a strong thrombolytic inhibitory effect that DAB cannot provide[46].

We found that all studies that supported DAB versus WAR guidelines recommendations in BHV were retrospective observational. Some have compared all NOACs to WAR without mentioning the results of DAB. Although all NOACs reduce S, SE, and severe bleeding [66,67], the other studies have shown that DAB reduced composite bleeding risk with a similar thromboembolic event risk reduction to

WAR [68]. All studies lacked renal impairment and dialysis data. Moreover, Myllykangas et al. and Mentias et al. reported that NOACs increased ischemic stroke risk and decreased major bleeding and mortality [69,70]. Yadlapati et al. reported that NOACs increased bleeding in patients with BHV without specifying the bleeding rate in the DAB arm [71]. Attena E et al. reported a lower annual rate of thromboembolism and major bleeding when NOACs were used [72]. Although Kim JY et al. included patients with AF and MS as a type of VHD and did not specify the endpoints for each NOAC, the results showed that NOACs, including DAB, significantly reduced thromboembolic rate and mortality per year but not ICH [58]. Yamaji et al. reported no significant difference between DAB and WAR in thromboembolic events and rates of bleeding in AF patients undergoing catheter ablation, which is consistent with our results and supports the need for further studies to assess DAB's effectiveness and safety in AF patients undergoing catheter ablation [73].

Valvular versus non-valvular nomenclature is contentious. NVAF is disingenuous because it implies that AF patients do not have VHD; nevertheless, the secondary analysis of the RE-LY trial indicated that a significant proportion of participants had VHD linked to AF [55]. VHD includes all types of heart valve diseases, including AS, AR, TR, MS, MR, mitral or aortic valve repair surgery, and implantation with biological or mechanical prosthetic heart valves. Thus, the NVAF term should be replaced by new classifications, including type I VHD and type II VHD. Type I VHD pertains to moderate to severe MS, prosthetic heart valves (BHV or MHV), hemodynamically significant MS, and rheumatic moderate to severe MS. On the other hand, type II VHD encompasses the other VHDs.

Limitations of our meta-analysis

Unfortunately, our meta-analysis lacked data concerning the safety profile of DAB versus WAR in elderly patients over 75 years of age who are more susceptible to bleeding since the mean age of AF patients in our meta-analysis of NVHD and VHD was ~67 years and 55 years, respectively. Moreover, owing to the lack of RCTs in the literature for both AF patients undergoing catheter ablation and those with VHD, including BHV, MS, and MHV (whether the locations of heart valves were aortic and mitral valves), our meta-analysis included an insufficient number of RCTs in VHD and catheter ablation subgroups. This makes it challenging to evaluate the effectiveness and safety of DAB at various doses versus WAR for each type and location of VHD.

DAB has a better safety profile than WAR, but renal function monitoring at least annually is needed in patients with renal insufficiencies since 80% of DAB is renally eliminated. Any functional changes in the kidney will affect efficacy, safety, and drug exposure, so renal function monitoring in all patients before and during treatment is necessary to avoid subtherapeutic or supratherapeutic levels. Patients with normal or supernormal kidney filtration may cause a suboptimal effective dose, which leads to suboptimal thromboembolic prophylaxis. Some real clinical evidence suggests that DAB is less effective than WAR in patients with CrCl > 90 mL/min [59]. Our meta-analysis cannot assess dabigatran's renal function safety because most RCTs except Nogami et al. and Eikelboom et al. lack CrCl data.

Authors' conclusion

DAB 150 mg and 110 mg were superior to WAR in terms of safety among AF patients with NVHD in reducing the risk of ICH and major bleeding, with no pronounced differences in reducing S/SE and death compared to WAR. However, the safety of DAB 150 mg regarding GIB was questionable; RR showed increased GIB risk compared to WAR, while RD showed no significant difference —likely due to the sensitivity of RD and RR to baseline risk and the small number of included studies. Therefore, further studies are needed to confirm the high risk of GIB with DAB. DAB 110 mg was superior to WAR in reducing minor bleeding. Overall, in AF patients with high risk of thromboembolic events and minimal risk of bleeding, DAB 150 mg is the best choice, while 110 mg suits those with moderate thromboembolic risk , moderate renal dysfunction, high bleeding risk, or a history of GIB.

In AF patients with NVHD and undergoing catheter ablation, DAB reduced groin hematoma with no difference in thromboembolic prevention compared to WAR. In AF patients with VHD, DAB showed neither superiority nor inferiority versus WAR in effectiveness and safety. Nonetheless, DAB cannot permanently replace WAR due to cost issues (depending on insurance), questionable GIB risk, and unsuitability for patients with CrCl < 15 ml/min or on dialysis. Thus, warfarin still holds a place in preventing S/SE in certain AF patients. Further large RCTs and extended follow-ups are necessary to establish DAB's safety and effectiveness as an acceptable alternative to WAR in VHD patients and those undergoing catheter ablation. We should replace the outdated term "non-valvular AF" with "type II VHD" to distinguish it from other types of VHD that accompany AF.

Figures S1–S20 and Table S1 are published as supplementary data on the website.

Abbreviations
WAR: warfarin
S: Stroke
DAB: dabigatran
SE: systemic embolism
NVHD: non-valvular heart disease
VHD: valvular heart disease
NVAF: non-valvular AF
VAF: valvular AF
COR: class of recommendation
QOE: quality of evidence

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