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Original Article

Efficacy and Safety of Apixaban versus Warfarin in Atrial Fibrillation Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

Background : The real-world evidence-based recommendation is still needed to improve Atrial fibrillation (AF) management in anticoagulant administration.
Objectives : This study aimed to disclose apixaban safety and efficacy profile compared with warfarin in a real-world population.
Methods : We collected data from articles worldwide studies comparing apixaban and warfarin in non-valvular atrial fibrillation (NVAF) patients. Data were retrieved from studies published in Embase ProQuest, PubMed, and Cochrane based on inclusion criteria. Data analysis was carried out using Review Manager Version 5.4.1 (Cochrane, Copenhagen, Denmark) using Mantel-Haenszel statistical method for categorical data to measure relative risk (RR) and 95% confidence interval (CI). We used a random-effect analysis model if p for heterogeneity was <0.1 and a fixed-effect analysis model if p for heterogeneity (pHet) was ≥0.1.
Results: Apixaban showed a benefit in preventing ischemic stroke (RR = 0.51; 95% CI=0.40-0.66; p <0.01), ischemic stroke/systemic embolism (RR = 0.63; 95% CI=0.50-0.81; p <0.01), and all-cause mortality (RR = 0.54; 95% CI=0.40-0.74; p <0.01) compared to warfarin. Apixaban also showed benefit to prevent major bleeding (RR = 0.49; 95% CI=0.41-0.58; p <0.01), gastrointestinal (GI) bleeding (RR = 0.46; 95% CI=0.36-0.60; p <0.01), and intracranial hemorrhage (RR = 0.45; 95% CI=0.36-0.57; p <0.01) compared to warfarin.
Conclusion: Apixaban, compared to warfarin, has superior efficacy and safety. Apixaban has a safer profile than warfarin in reducing the risk of major bleeding, GI bleeding, and intracranial hemorrhage in AF patients.

1. Introduction

Atrial fibrillation (AF) is a heart rhythm disorder caused by abnormal electrical activity in the heart, which is characterized by tachyarrhythmias, either paroxysmal or persistent. Older age, higher blood pressure, congenital heart disease, alcohol consumption are the risk factors of AF. Various treatment strategies have been developed to treat AF and reduce complications, one of which is the administration of anticoagulants.[1] Anticoagulant selection should be based on the risk factors, price, tolerance, patient preference, and potential drug interactions.[2] Current guidelines recommend the administration of non-vitamin K antagonist oral anticoagulants (NOAC) to prevent AF complications, such as stroke and thromboembolism.[2-4] Thromboembolism in AF is associated with an increased risk of recurrent stroke and death. The use of appropriate anticoagulant therapy and reasonable control of risk factors can reduce the risk of complications in AF patients.[5]

Warfarin is an anticoagulant that can reduce the risk of stroke in AF patients by about 68%. However, currently, the use of NOACs is more recommended. Clinical trials in previous studies have shown that NOACs were as effective and safe as warfarin.[2,6-8] In other studies, apixaban was reported to have a significantly better safety profile but not efficacy than warfarin.[9] Studies related to the efficacy and safety of apixaban and warfarin were still contradictory from several current research views. Although randomized controlled trial (RCT) studies have good evidence, research limitations remain existed concerning inclusion criteria and the number of samples used. The existing research data in the world can be further analyzed into an additional evidence-based and more selective, and the larger population can be well controlled. We conducted a systematic review and meta-analysis to measure the efficacy and safety of apixaban and warfarin in preventing complications of AF patients.

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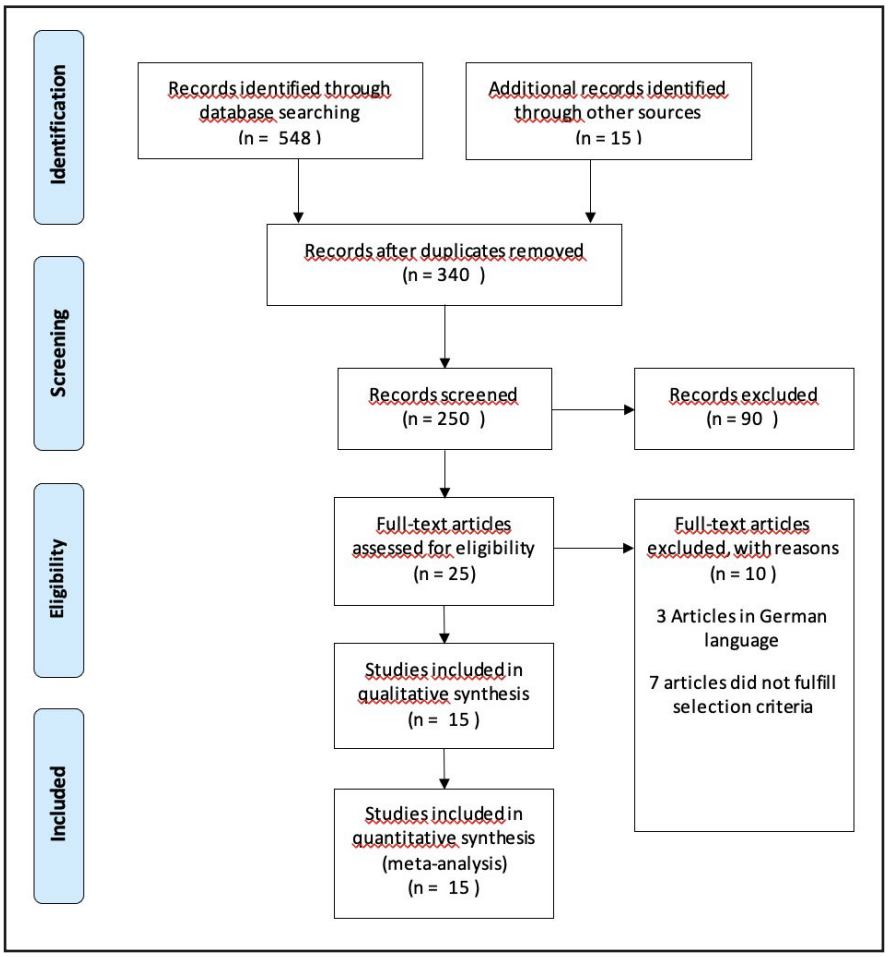


Figure 1. PRISMA flow diagram of the study selection process

2. Method

2.1.Study design and search strategy

We performed a systematic review and meta-analysis study by following the checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in March 2021.[10] We collected data from articles worldwide comparing apixaban and warfarin in non-valvular atrial fibrillation (NVAF) patients, searched from the scientific database such as Embase, ProQuest, PubMed, and Cochrane based on inclusion criteria. Studies-based study selection criteria were involved in the quality assessment of the study. We extracted data from a high-quality article and divided the patients into “apixaban group” and “warfarin group. The keywords used to search articles were “non-valvular atrial fibrillation” AND ”stroke prevention” AND “non-vitamin K antagonist oral anticoagulant” AND “ apixaban” AND “VKA,” AND “Warfarin. We also collected all relevant articles through references from all assessed articles or google scholar. We did not apply language restriction during the data searching process.

2.2. Outcome measures

The stroke risk was our primary outcome. The secondary outcomes included the risk of (1) all-cause mortality, (2) intracranial bleeding, (3) gastrointestinal (GI) bleeding, and (4) major bleeding. The pooled hazard ratio (HR) and 95% confidence interval (CI) were applied in determining the overall effect estimates.

2.3. Study selection

The inclusion criteria were (1) cohort retrospective studies, (2) the age of patients was >18 years, (3) NVAF patients treated with apixaban or warfarin with the minimum follow up period was more than three months or 90 days, (4) the main outcomes were thromboembolic event and/or bleeding events. We excluded articles if the following criteria were found:(1) duplication; (2) non - English; (3) patients with venous thromboembolism (VTE); (4) failure to specify the drug's name; (5) failure to use warfarin as VKA; and (6) failure to report the desired outcome. Two investigators independently reviewed the potential articles. The disagreement was resolved through discussion between the two investigators or consultation with a third investigator.

2.4. Data extraction

The following information was extracted from the articles: (1) name of the first author; (2) date of publication; (3) enrolment period; (4) country; (5) data source; (6) type of anticoagulants; (7) number of participants; (8) gender; (9) CHA2DS2VASc score; (10) HAS-BLEDscore; (10) follow up period duration; (11) primary statistical model; (12) comorbidities; and (13) adjusted HR, and 95% CI of stroke, all-cause mortality, intracranial bleeding, GI bleeding, and major bleeding. Three investigators conducted the data extraction proces

Table 1. Baseline characteristics of the studies

Study	**Data source**	**Country**	**Cohort Size**	Study	Enrollment Period	Treatment
Adeboyeje et al.,2017 [14]	Regional Database	United States	44057	Adeboyeje et al.,2017 [14]	November 2009 to January 2016	Warfarin, Dabigatran, Apixaban, Rivaroxaban
Cha et al., 2017 [15]	National Insurance Database	Korean	34833	Cha et al., 2017 [15]	January 2014 to December 2015	Warfarin, Dabigatran, Apixaban, Rivaroxaban
Chan et al., 2018 [16]	National Insurance Database	Taiwan	73074	Chan et al., 2018 [16]	June 2012 to December 2016	Warfarin, Dabigatran, Apixaban, Rivaroxaban
Cho et al., 2019 [17]	National Insurance Database	Korea	56504	Cho et al., 2019 [17]	July 2015 to December 2016	Warfarin, Dabigatran, Apixaban, Rivaroxaban
Graham et al., 2019 [18]	National Insurance Database	United States	448944	Graham et al., 2019 [18]	October 2010 to September 2015	Warfarin, Dabigatran, Apixaban, Rivaroxaban
Halvorsen et al., 2017 [19]	Nationwide Registries	Norway	32675	Halvorsen et al., 2017 [19]	January 2013 to June 2015	Warfarin, Dabigatran, Apixaban, Rivaroxaban
Kjerpeseth et al., 2019 [20]	Nationwide Registries	Norway	30820	Kjerpeseth et al., 2019 [20]	July 2013 to December 2015	Warfarin, Dabigatran, Apixaban, Rivaroxaban
Koshaka et al., 2020 [21]	Regional Database	Japan	73989	Koshaka et al., 2020 [21]	March 2011 to July 2018	Warfarin, Dabigatran, Apixaban, Edoxaban, Rivaroxaban
Lamberts et al., 2016 [22]	Nationwide Registries	Denmark	54321	Lamberts et al., 2016 [22]	August 2011 to December 2015	Warfarin, Dabigatran, Apixaban, Rivaroxaban
Larsen et al., 2016 [23]	Nationwide Registries	Denmark	61678	Larsen et al., 2016 [23]	August 2011 to October 2015	Warfarin, Dabigatran, Apixaban, Rivaroxaban
Lee et al., 2019 [24]	National Insurance Database	Korea	24974	Lee et al., 2019 [24]	January 2014 to December 2016	Warfarin, Dabigatran, Apixaban, Edoxaban, Rivaroxaban
Li et al., 2017 [25]	Insurance Database	United States	76940	Li et al., 2017 [25]	January 2012 to September 2015	Warfarin, Apixaban
Mitsuntisuk et al., 2020 [26]	Hospital Database	Thailand	2055	Mitsuntisuk et al., 2020 [26]	January 2012 to April 2019	Warfarin, Dabigatran, Apixaban, Rivaroxaban
Rutherford et al., 2020 [27]	Nationwide Registries	Norway	65563	Rutherford et al., 2020 [27]	January 2013 to December 2017	Warfarin, Dabigatran, Apixaban, Rivaroxaban
Staerk et al., 2016 [28]	Nationwide Registries	Denmark	43299	Staerk et al., 2016 [28]	August 2011 to December 2015	Warfarin, Dabigatran, Apixaban, Rivaroxaban

Table 2. Baseline characteristics of the patients.

Study	Participant, n		Male, %		Age, mead ± SD		CHA2DS2VASc, mean±SD		HAS-BLED, mean ± SD		Comorbidities							
											Diabetes, %		Hypertension, %		CAD, %		Stroke/TIA, %	
	W	A	W	A	W	A	W	A	W	A	W	A	W	A	W	A	W	A
Adeboyeje et al.,2017 [14]	23431	3689	59.1	59.5	70 ± 12.	70 ± 12.6	3.3 ± 1.8	3.3 ± 1.9	2.2 ± 1.4	2.2 ± 1.4	28.4	29.4	59.8	60	36.2	36.6	15.9	15.6
Cha et al., 2017 [15]	23222	2189	56.9	54.4	68.82 ± 11.1	70.3 ± 10	3.57 ± 1.31	3.57 ± 1.29	NA	NA	26.1	23.6	76.9	76.9	5.2	5.3	NA	NA
Chan et al., 2018 [16]	19375	5843	58	55	71.0 ± 13.0	76.0 ± 10.0	3.26 ± 1.81	3.89 ± 1.56	2.64 ± 1.29	2.96 ± 1.12	36	41	78	87	11	13	15	20
Cho et al., 2019 [17]	10409	12502	54	47.7	70.8 ± 11.0	74.3 ± 8.9	3.5 ± 1.2	3.7 ± 1.2	2.6 ± 1.0	2.5 ± 0.9	48.4	45.3	86.7	85.9	1.3	1.2	27.3	24
Graham et al., 2019 [18]	183318	73039	52	52.3	75.8	75.2	NA	NA	NA	NA	34.2	33.9	86.3	87.6	NA	NA	NA	NA
Halvorsen et al., 2017 [19]	11427	6506	59	55	74.6 ± 11.9	74.5 ± 11.1	3.09	2.93	NA	NA	14.7	12.3	67	65.4	35.9	27.6	11.6	13.9
Kjerpeseth et al., 2019 [20]	6435	10550	59	54	73.6 ± 11.9	74.2 ± 11.0	3.5 ± 1.8	3.5 ± 1.7	2.6 ± 1.2	2.5 ± 1.1	18	15	71	72	23	16	14	18
Koshaka et al., 2020 [21]	15902	22336	60.7	59.1	78.4 ± 9.7	77.0 ± 10.1	4.1 ± 1.8	3.9 ± 1.9	NA	NA	31.4	29.8	57.9	55.5	26.3	25.9	NA	NA
Lamberts et al., 2016 [22]	24230	7963	58.4	50.8	72.1 + 11.3	75.4 + 11.10	2.91 + 1.66	3.15 + 1.62	2.18 + 1.22	2.25 + 1.20	13.8	12.9	48.3	43.5	NA	NA	14.8	21.2
Larsen et al., 2016 [23]	35436	6349	58.8	60.3	72.4 (64.7-79.8)	71.3 (65.8-77.2)	2.8 ± 1.7	2.8 ± 1.6	2.2 ± 1.2	2.3 ± 1.2	15.6	15.8	50.6	48.8	NA	NA	14.8	21.1
Lee et al., 2019 [24]	988	3365	63.2	63.9	66.1 + 11.5	65.6 + 11.3	3 ± 1.9	3 ± 1.6	NA	NA	21.7	20.8	67.4	66.7	NA	NA	NA	NA
Li et al., 2017 [25]	38470	38470	59.8	59.7	70.9 ± 11.9	70.9 ± 12	3.2 ± 1.7	3.2 ± 1.8	2.6 ± 1.3	2.6 ± 1.4	32	32	82.3	82.5	NA	NA	9.9	10.2
Mitsuntisuk et al., 2020 [26]	605	405	49.75	50.37	68.40 ± 11.40	73.89 ± 10.24	3.28 ± 1.75	3.86 ± 1.72	1.27 ± 0.91	1.65 ± 1	30.74	28.89	65.45	63	16.69	16.54	22.48	28.34
Rutherford et al., 2020 [27]	13087	28363	60.5	56	73.4 ± 12.1	73.76 ± 11.3	3.4 ± 1.8	3.3 ± 1.7	2.5 ± 1.1	2.3 ± 1.1	17.4	14.8	70.5	67.8	34.8	24.6	13.1	13.5
Staerk et al., 2016 [28]	18094	6899	56.7	49.8	73 (65–80)	76 (68–84)	1.54 ± 1.24	1.66 ± 1.26	2.16 ± 1.22	2.2 ± 1.19	13.5	12.8	46.8	42.8	25.9	21.1	14.6	20.7

All data were presented by mean SD; A = apixaban, CAD = coronary artery disease, CHA2DS2VAS = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or TIA, vascular disease, age 65 to 74 years, sex category, HASBLED = hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile INR, elderly, drug/alcohol usage, INR = international normalized ratio; SD = standard deviation, TIA = transient ischemic attack, W = warfarin.

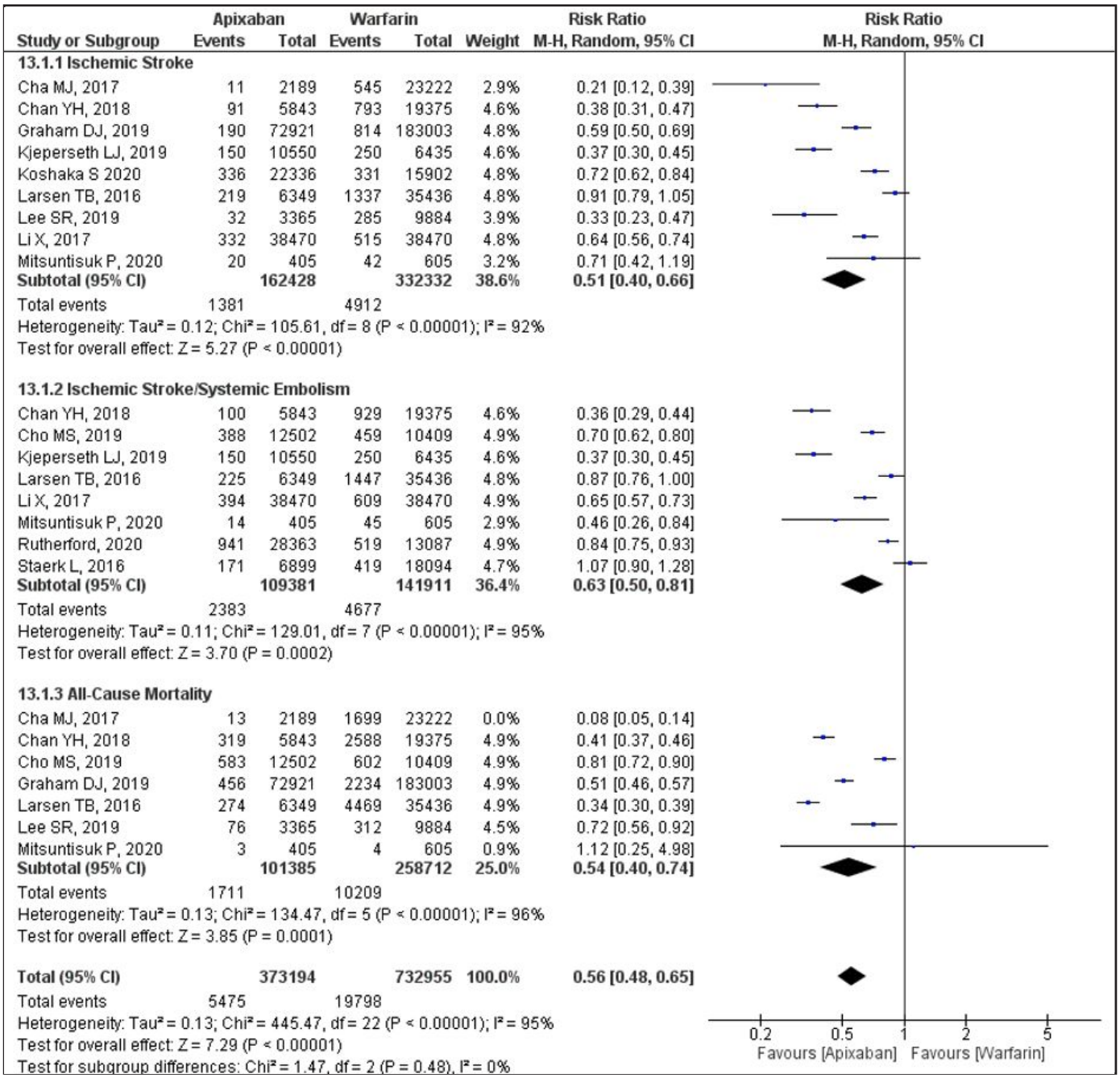


Figure 3. Forest plot of safety comparison between apixaban and warfarin.

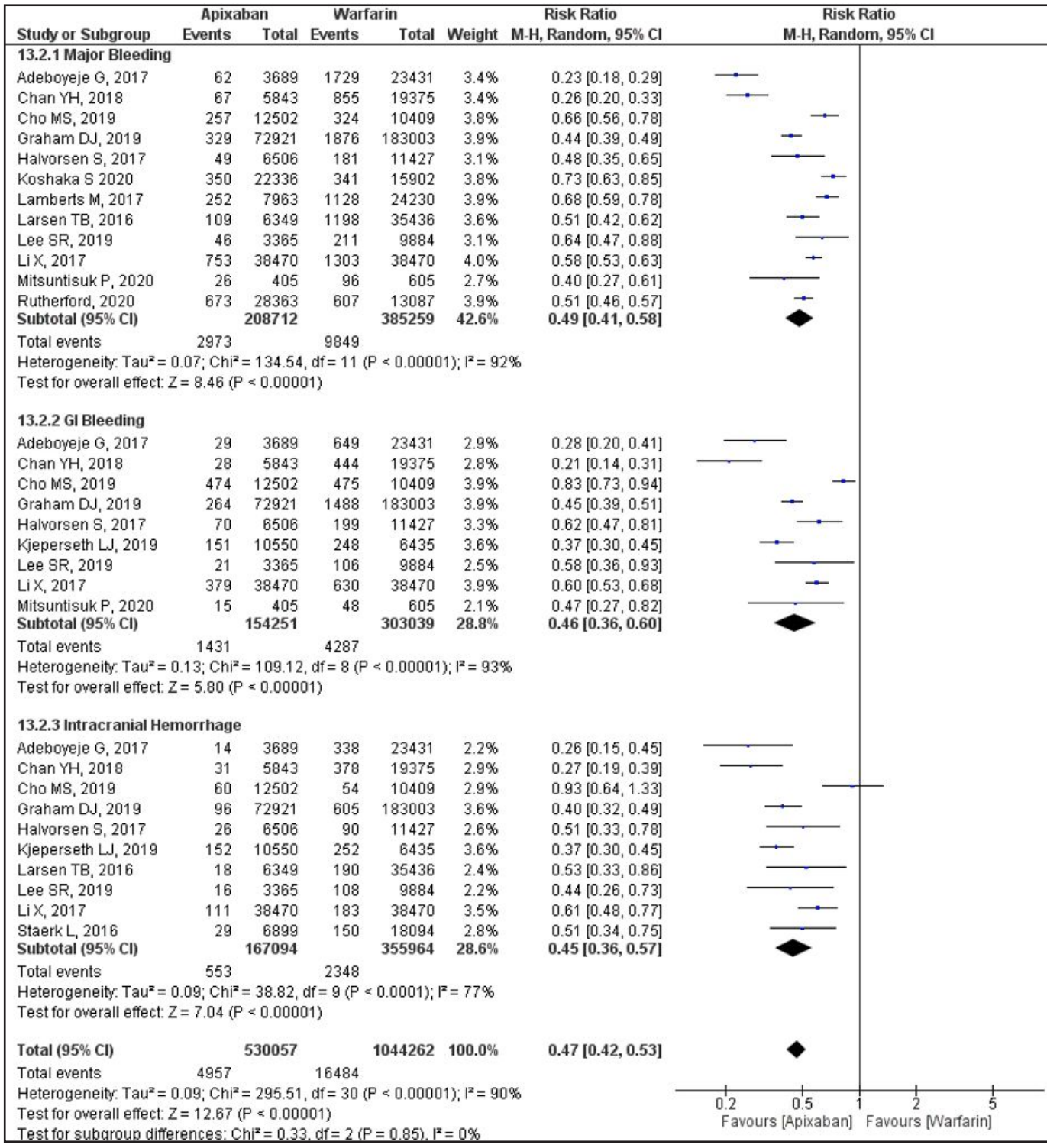
2.5. Data synthesis and risk for bias assessment

Data analysis was carried out using Review Manager Version 5.4.1 (Cochrane, Copenhagen, Denmark) using Mantel-Haenszel statistical method for categorical data to measure relative risk (RR) and 95% confidence interval (CI). We used a random-effect analysis model if P for heterogeneity was <0.1 and a fixed-effect analysis model if p for heterogeneity (pHet) ≥0.1.[11] We used the funnel plot and Egger test to measure publication bias using Comprehensive Meta-Analysis version 3.0 (CMA, New Jersey, US).[12] Significant publication bias was detected if p for Egger Test <0.05.[13]

3. Result

3.1.Study selection

We included a PRISMA flow diagram (Figure 1) for the details of study selection. There were 548 potential articles identified through Embase, ProQuest, PubMed, and Cochrane, while 15 others were identified through other sources. We removed 340 duplicated articles. We assessed 25 full articles for eligibility. Ten articles were excluded because three were found in the German language, and 7 articles did not meet the selection criteria. Finally, 15 articles were selected to perform a meta-analysis and systematic review.



Note, data were presented in mean ±SD or n (%)

3.2. Study characteristics

There were 42,4429 patients treated with apixaban and 228,468 patients treated with warfarin from 15 studies.[14-28] All studies were retrospective cohort studies that were published between 2016 to 2020. Of them, 6 studies were retrieved from Nationwide Registries, 5 from National Insurance Database, 1 from Regional Database, and 1 from Hospital Database. 6 studies were conducted in Europe, 6 studies from Asia, and 3 studies from the United States.

Most of the studies compared all four NOAC and warfarin, while Kosaka et al.[21] and Lee et al.[24] studies also added edoxaban as a comparator, and the only study from Li et al.[25] only compared apixaban directly with warfarin (Table 1).

From baseline characteristics of the patients, with a duration of follow-up ranging from 130 to 1029 days, 49.75 to 63.9 % of the studies population were male, with mean age among studies ranging from 65 to 78 years old. CHA2DS2VAS score ranged from 1 to 4, and

HAS-BLED score ranged from 1 to 4. The summary of the baseline characteristic of the patients is shown in Table 2.

3.3. Heterogeneity and publication bias

We used a random-effect model to measure the correlation because there was heterogeneity in our meta-analysis data (pHet <0.1). There is no significant publication bias detected in our analysis. The summary of heterogeneity and publication bias is outlined in Table 3.

3.4. Outcomes

From the analysis, compared to warfarin, apixaban showed a benefit in preventing ischemic stroke (RR = 0.51; 95% CI=0.40-0.66; p <0.01), ischemic stroke/systemic embolism (RR = 0.63; 95% CI=0.50-0.81; p <0.01), and all-cause mortality (RR = 0.54; 95% CI=0.40-0.74; p <0.01). Apixaban also showed a benefit to prevent major bleeding (RR = 0.49; 95% CI=0.41-0.58; p <0.01), GI bleeding (RR = 0.46; 95% CI=0.36-0.60; p <0.01), and intracranial hemorrhage (RR = 0.45; 95% CI=0.36-0.57; p <0.01) compared to warfarin.

4. Discussion

Our study showed that apixaban had better efficacy in preventing ischemic stroke, ischemic stroke/systemic embolism, and all-cause mortality. Our study was consistent with NOACs versus warfarin RCT, ARISTOTLE's study, that apixaban was superior to warfarin in preventing stroke or systemic embolism. Furthermore, from 9 of included studies, six studies showed a significant difference that apixaban had the lowest incidence of ischemic stroke than warfarin,[16,18,21,24–26] while three studies showed only a small difference between apixaban and warfarin to prevent ischemic stroke.[15,20,23]

Only one study showed that apixaban's incidence of ischemic stroke in NVAF patients was higher than warfarin.[28] In the ischemic stroke/systemic embolism group, 5 from 8 studies showed a significant difference that apixaban had the lowest incidence of ischemic stroke/systemic embolism than warfarin.[16,17,21,25,26] In comparison, two studies showed that apixaban was not statistically significant in preventing ischemic stroke/systemic embolism compared to warfarin.[20,23] Only one study showed that apixaban's ischemic stroke/systemic embolism incidence in NVAF patients was higher than warfarin.[28] On the other hand, a study from Rutherford et al. showed that apixaban had a higher incidence of ischemic stroke/Systemic embolism than dabigatran, but there was no significant difference compared to rivaroxaban.[27] All studies showed a significant difference in the all-cause mortality group that apixaban has the lowest incidence of all-cause mortality compared to warfarin.[14–28]

Besides, six studies also divided apixaban treatment into subgroups: standard dose and low dose apixaban. Five studies showed no difference between a standard dose and a low dose of apixaban to prevent ischemic stroke/systemic embolism.[15,16,20,25,26] On the other hand, both Cha et al. and Cho et al. showed a significant difference that low dose apixaban had lower all-cause mortality,[15,17] and in Chan et al. showed that standard dose apixaban had lower all-cause mortality.[16] Apixaban also showed better efficacy in patients with older age, higher CHA2DS2VAS score, higher HAS-BLED score, lower body mass index or <60 kgs, no prior of stroke, and renal disease with creatinine clearance >95 ml/minute.[15–17,21,24,25] A lower dose of apixaban was recommended for elderly patients with comorbidities, a higher CHA2DS2VAS score, and a higher HAS-BLED score, but it was not significant in reducing all-cause mortality.[16]

The efficacy endpoints of this study were stroke ischemic, ischemic stroke/systemic embolism, and all-cause mortality. Our result showed that apixaban significantly reduced the risk of stroke compared to warfarin. According to the ARISTOTLE trial and other meta-analysis studies, our finding was consistent with prior studies.[16,18,19,21,24] Apixaban exhibited a significant effect in reducing the stroke/systemic embolism regardless of the estimated glomerular filtration rate range and age group.[19] A previous real-world study on apixaban compared to warfarin by Li et al. showed that apixaban treatment was associated with significant stroke/systemic embolism risk reduction.[25] In the subgroup analysis of the previous study, together with other direct oral anticoagulants such as dabigatran and rivaroxaban, apixaban showed a significant risk reduction of all-cause mortality.[16,18,24] Consistent with those previous studies, our study also revealed a significant reduction of all-cause mortality risk of apixaban compared to warfarin. Apixaban has better efficacy than warfarin in reducing the risk of ischemic stroke, stroke/systemic embolism, and all-cause mortality.

Our study revealed that apixaban was associated with a lower risk of major bleeding, GI bleeding, and intracranial hemorrhage than warfarin. Our findings supported the ARISTOTLE trial that demonstrated that apixaban could reduce the risk of major bleeding, total bleeding, and intracranial hemorrhage in the all-age group of AF patients.[29] Besides, other previous studies also supported our findings.[2,9,30] In subgroup analysis, apixaban also showed a safer profile in reducing the risk of major bleeding among AF patients than warfarin and rivaroxaban in real-world study.[31] Another study also found that apixaban had a lower risk of major bleeding than warfarin and rivaroxaban and a lower risk of major GI bleeding than dabigatran.[14] These studies were consistent with our results. Apixaban has a safer profile in reducing the risk of bleeding, particularly major bleeding, GI bleeding, and intracranial hemorrhage among AF patients.

NOAC is recommended over vitamin K antagonists regarding anticoagulants in daily clinical practice. Although some patients still require adjustment of the anticoagulant dose.[32] Many studies used real-world data comparing NOAC and warfarin, including apixaban and warfarin. Those studies revealed that apixaban had better safety than warfarin but had almost the same effect.[9,33] However, our study, which used big real-world data comparing apixaban and warfarin, found other evidence that apixaban was better in efficacy and safety with the specific bleeding risk profile. Its significantly decreased stroke risk was already known as the benefit of apixaban over warfarin in efficacy profile. This study result was consistent with other previous studies.[9,27] The use of apixaban as a direct oral anticoagulant over warfarin as a vitamin K antagonist anticoagulant was superior in food interaction and drug interaction. The anticoagulant effect of warfarin can be affected by the amount of Vitamin K, which includes dietary issues and requires dietary restriction. The restriction was not needed for the use of apixaban. As well as dietary interaction, apixaban use has fewer drugs interaction. Moreover, the plasma concentration of apixaban was relatively stable, and therefore, the bleeding complication was fewer as it has a higher safety profile. Apixaban does not need any frequent laboratory monitoring compared to warfarin which keeps the international normalized ratio (INR) under a close monitor.[27,34] Although routine monitoring was not required, laboratory measurement of drug level and its anticoagulant effect may be helpful for specific circumstances in apixaban-treated patients.[33,35] Moreover, the plasma concentration of apixaban was relatively stable, and therefore, the bleeding complication was fewer as it has a higher safety profile. Apixaban does not need any frequent laboratory monitoring compared to warfarin which keeps the INR closely monitored.

Besides the benefits, apixaban has some pitfalls compared to warfarin, including cost issues and the apixaban Reversal Agent or Antidote, which still needs to be developed.[32] Those factors might explain why warfarin was still used as an anticoagulant for AF patients in developing countries. The lack of a specific reversal agent for a novel anticoagulant such as apixaban also becomes a critical point of research interest.[32,36,37] However, we suggested apixaban as an anticoagulant of choice for AF patients because of its safety and efficacy profile.

Our systematic and meta-analysis study had several limitations. First, anticoagulant control quality data was lacking, either participant compliance or persistence data from all the involved studies. Second, the data was obtained from the health insurance database, and therefore, the limitation associated with the detailed data cannot be avoided. Third, we only compared apixaban and warfarin in standard dose settings and did not perform subgroup analyses with the adjusting

dose group due to a lack of resources. Fourth, the range of time to follow the participants was different across the studies.

5. Conclusion

Apixaban has a superior profile over warfarin in efficacy and safety. Apixaban is associated with decreased stroke risk and is safer in reducing the risk of major bleeding, GI bleeding, and intracranial hemorrhage in AF patients.

6. Declarations

6.1. Ethics Approval and Consent to participate
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involvement in the study.

6.2. Consent for publication
Not applicable.

6.3. Availability of data and materials
Data used in our study were presented in the main text.

6.4. Competing interests
Not applicable.

6.5. Funding source
Not applicable.

6.6. Authors contributions
Idea/concept: MFRS. Design: MFRS/YW. Control/supervision: YW/AR. Literature search: MFRS/IFDF/NEE/KCY. Study quality assessment: MFRS/YW/AR. Data extraction: MFRS/IFDF/NEE/KCY. Statistical analysis: MFRS/IFDF/NEE. Results interpretation: MFRS/YW/AR. Critical review/discussion: MFRS/YW/AR. Writing the article: MFRS/YW/AR/IFDF/NEE/KCY. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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