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Review Article

Comparison between the different new anti-coagulants for non-valvular atrial fibrillation: network meta-analysis

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ABSTRACT

Background: Atrial fibrillation is associated with high risk of ischaemic stroke which is considered a major fatal complication in atrial fibrillation. That's why, anticoagulants were used to prevent this major complication. However, anticoagulants themselves are associated with their own complications. A systematic search of Embase, Medline and Google scholar were conducted. The included papers were extracted for outcomes related to the complications of each drugs. A Bayesian network meta-analysis based on Markov chain Monte Carlo simulation (MCMC) with 10000 burn-in iterations and 50000 inference iterations. We found eighteen papers that fit our inclusion criteria. Apixaban had the least risk of major bleeding compared to Warfarin [HR = 0.536, 95% (0.448, 0.652)] and the least risk of gastrointestinal hemorrhage. For stroke risk, the Rivaroxaban had the least risk compared to Warfarin [HR = 1.05, 95% (0.98, 1.14)]. For intracranial hemorrhage, dabigatran had the least risk of intracranial haemorrhage compared to Warfarin [HR = 0.46, 95% CrI (0.36, 0.61)]. For the thromboembolism risk, other non-vitamin k antagonist had the least risk of intracranial haemorrhage compared to Warfarin [HR = 0.523, 95% (0.095, 2.85)]. There were no conclusive results about the best anticoagulant drugs for non-valvular atrial fibrillation. Apixaban was the least among them to be associated with major bleeding, while rivaroxaban was ranked the first with least stroke complications. Furthermore, dabigatran was associated with less risk of intracranial haemorrhage compared to other anticoagulants.

Keywords: Anti-coagulant, Atrial fibrillation, Drugs, Non-valvular heart disease

INTRODUCTION

Atrial fibrillation is most common prevalent cardiac arrythmia representing 2.3 million in United States increasing up to 5.6 to 7.56 million by 2050. The higher the age, the higher the incidence of atrial fibrillation reaching up to 18 in 100 patients of 85 aged patients.[1] The atrial fibrillation represents a major public health problem with significant morbidity and mortality. It is a disturbance of electrical activity in the atrial that cause rapid contraction of the ventricles which may be paroxysmal or persistent.[1] The most dangerous complication of atrial fibrillation is systemic embolism. The management of the atrial fibrillation includes anti-arrhythmic and anti-coagulants.[1] The anti-coagulants are used to decrease risk of systemic embolism; it was estimated that in 2003, about 46-53% of patients with atrial fibrillation were receiving a vitamin K antagonist. Still, many complications are reported for anticoagulants.[1-3] Major bleeding, fatal bleeding and intracranial haemorrhage are among many complications reported for vitamin k anti-coagulants.[1] Major bleeding was reported in 20 of 1000 atrial fibrillation patients of which 0.5 to 1 percent has fatal bleeding. Intracranial haemorrhage occurred in about 0.2% of the patients.[1,4] Other bleeding from gastrointestinal tract was reported from warfarin use.[2,5] Warfarin is characterized by narrow therapeutic window and slow

onset.[2,5] This urged the use of the new generation of anti-coagulants. The most investigated new anti-coagulants are apixaban, dabigatran and rivaroxaban. Rivaroxaban and apixaban are factor Xa inhibitors while dabigatran is direct thrombin inhibitors.[3,6] Comparative studies showed apixaban reduced the risk of stroke without increasing the risk of bleeding while rivaroxaban had the same efficacy of the warfarin.[7-12] However, there are heterogenous results of the efficacy of the new oral anti-coagulants compared to vitamin k antagonist. Studies reported that the switching of the patients from warfarin to dabigatran had increased the risk of major bleeding.[13,14] Larsen et al, found that there are higher numbers of the myocardial infarction and major bleeding in patients switched to Warfarin.[9] Dabigatran was found to be associated with wide safety margin while rivaroxaban was found to have better and more potent effect than both dabigatran and apixaban.[15,16] However, there is still contradictory results about the best fit for treatment of atrial fibrillation.

In this network meta-analysis, we are going to compare between rivaroxaban, dabigatran and apixaban regarding its complications.

METHODS

Search strategy

A systematic search was conducted from the January 2010 on EMBASE, Medline and Google Scholar. Search terms used are (apixaban OR apixaban OR rivaroxaban OR rivaroxaban OR “dabigatran etexilate” OR “dabigatran etexilate” OR “novel anticoagulants” OR “new anticoagulants” OR “novel anticoagulant” OR “new anticoagulant” OR “newer anticoagulants” OR “newer anticoagulant” OR “new oral anticoagulant”) AND (("Atrial Fibrillation” OR "Atrial Fibrillation” OR "Atrial Flutter" OR "Atrial Flutter”) OR (nonvalvular OR non-valvular OR nonvalvar)) OR (NVAF OR “nonvalvular atrial fibrillation” OR “non-valvular AF”).

Manual search was conducted by checking relevant papers on PubMed and papers which cited the included studies. We also checked the systematic review and meta-analysis for any relevant studies.

Eligibility criteria

Eligibility criteria were studies that specify that patients had non-valvular atrial fibrillation as other types were associated with other risk factors that bias our analysis, and therefore, specifically exclude patients with valvular conditions (e.g., mitral valvular disorders). Treatments of interest included apixaban, rivaroxaban, edoxaban, or dabigatran of any dose or duration compared to each other or compared to vitamin k antagonist. We only included full-text articles, and only studies reporting relative effect estimates (hazard ratios [HRs], odds ratios [ORs], risk ratios [RRs]) for complications. Observational studies (e.g., prospective and retrospective cohort studies, case-control studies, database/registry studies) were eligible for inclusion. We only included real-world observational studies. RCTs, systematic reviews or meta-analyses, narrative reviews, single-arm studies, case reports, case series and cross-sectional studies were excluded from the analysis.

Data extraction

The standardized template was developed through a pilot extraction with the two most relevant references. The data were extracted into the template. Extracted data included: authors, publication year, baseline characteristics of participants including sample size, age of patients, gender and educational. Risk statistics for each complication were extracted.

Quality assessment of included studies

Authors independently assessed the quality and risk of bias in included studies using the NIH quality assessment tool. It is a 14 questions tool that assess the quality of observational studies, each question had “yes” or “no” answers.[17]

Statistical method

Bayesian contrast based random effect model network based on Markov chain Monte Carlo simulation (MCMC) was employed to indirectly compare different methods of administration using Control as a common comparator and rank the best approach as the best one to produce significant decrease in the anxiety score. The statistical analysis is based on binomial likelihoods with a standardized mean difference (SMD) function. Vague priors were assigned so it was less likely to affect the model results; GeMTC package automatically determines the uniform prior distribution heuristically setting a value for the outcome scale parameter.

We used four chain each with 10000 burn-in iterations and 50000 inference iterations; convergence was assessed via inspecting the Brooks-Gelman-Rubin graphs and the Potential Scale Reduction Factor by which we considered our iterations are enough when it is below 1.05. We also checked the accuracy of our Markov simulation was assessed by density plots and Monte Carlo error. The model fit was assessed using the deviance information criterion (DIC).[18] The heterogeneity in random effect model was assessed by inspecting the heterogeneity in individual studies. The inconsistency of the model was assessed using node splitting model.[18]

The ranking of treatments was performed in each chain of MCMC by counting the proportions of iterations that each type of therapy is the first, the second and so on. Our model results are presented using SMD and 95% credible interval. GeMTC package was used in R 3.3.0 for performing the analyses.

RESULTS

Search results

We had 5562 papers relative to our research terms; only 18 papers were eligible for network meta-analysis. The flow of the search is illustrated in Figure 1.

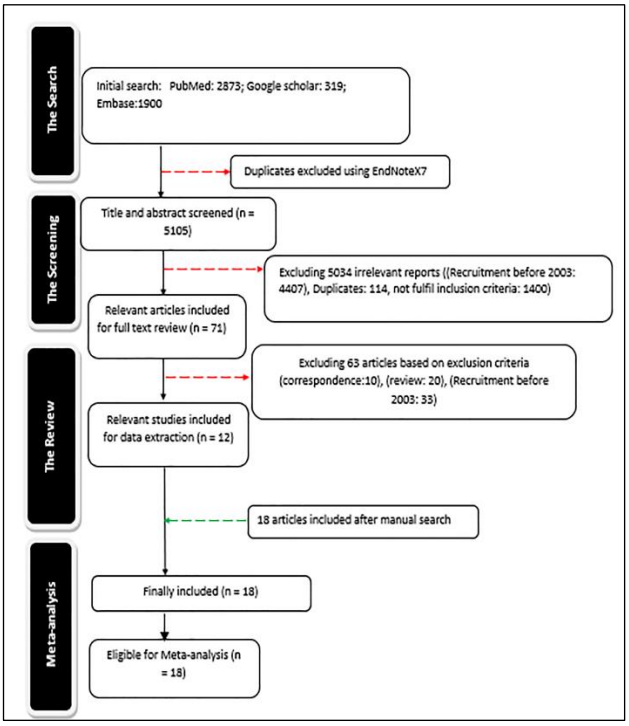

Figure 1: The method for the search, abstract screening, systematic review and meta-analysis.

Study characteristics

We included 18 studies, the study and patients' characteristics are illustrated in Table 1.

Quality assessment

Based on NIH bias tool, twelve studies have a good quality while the rest had a fair quality. Most studies lacked blinding and absence of reference assessment common to all studies. The explanation of assessment of the quality are explained in Supplementary Table 1.

Comparison between different new oral anti-coagulants regarding the major bleeding risk

The network included five arms representing warafarin, Dabigatran, Rivaroxaban, non-vitamin k antagonist and apixaban Figure 2A. Based on the ranking probability Figure 2C, the apixaban had the least risk of bleeding compared to Warfarin [HR = 0.536, 95% (0.448, 0.652)] followed by Dabigatran [HR = 0.726, 95% CI (0.641, 0.859)] Figure 2B.

Unexpectedly, the warfarin surpassed the Rivaroxaban and other non-vitamin K antagonist Figure 2C. The comparison between different new oral anti-coagulants is presented in Table 2.

The network was consistent as evident by the P-value = 0.78; there was no heterogeneity as the standard deviation of the random effect model is less than the effect size and within the pairwise comparisons. The model is considered fit as present in Supplementary Table 2.

Comparison between different new oral anti-coagulants regarding the risk of stroke

The network included four arms representing warafarin, Dabigatran, Rivaroxaban, and apixaban Figure 3A. Based on the ranking probability Figure 3C, the rivaroxaban had the least risk of stroke compared to warfarin [HR = 1.05, 95% (0.98, 1.14)] followed by dabigatran [HR = 1.03, 95% CrI (0.91, 1.04)] Figure 3B. Unexpectedly, the apixaban had the highest risk for the stroke [HR = 1.07, 95% CrI (0.91, 1.26)]. The comparison between different new oral anti-coagulants is presented in Table 3. The network was consistent as evident by the P-value = 0.8; there was no heterogeneity as the standard deviation of the random effect model is less than the effect size (Table 2).

Comparison between different new oral anti-coagulants regarding the risk of intracranial haemorrhage

The network included four arms representing warafarin, Dabigatran, Rivaroxaban, and apixaban Figure 4A. Based on the ranking probability Figure 4C, Dabigatran had the least risk of intracranial haemorrhage compared to Warfarin [HR = 0.46, 95% CrI (0.36, 0.61)] followed by Apixaban [HR = 0.64, 95% CrI (0.36, 1.13)] followed by Rivaroxaban Figure 4B. The comparison between different new oral anti-coagulants is presented in Table 4. The network was consistent as evident by the P-value = 0.63. The model is considered fit as present in Supplementary Table 2.

Comparison between different new oral anti-coagulants regarding the risk of gastrointestinal hemorrhage

The network included four arms representing warafarin, Dabigatran, Rivaroxaban, and apixaban Figure 5A. Based on the ranking probability Figure 5C, Apixaban had the least risk of gastrointestinal haemorrhage compared to Warfarin [HR = 0.756, 95% (0.438, 1.28)] Figure 5B. The other two anti-coagulant had more risk than warfarin to develop gastrointestinal bleeding. The comparison between different new oral anti-coagulants is presented in Table 5. The network was consistent as evident by the P-value = 0.58; there was no heterogeneity as the standard deviation of the random effect model is less than the effect size. The model is considered fit as present in Supplementary Table 2.

Table 1: The characteristics table of the included studies.

Author, year	Study Design/ Source of data	Region	Enrolled Period	Follow-Up	Quality judgement
Abraham et al[10]	retrospective cohort	USA	November 2010 to September 2013	NA	Good quality
Avgil-Tsadok et al[19]	retrospective cohort	Canada	1999-2013	14 years	Good quality
Bouillon et al[20]	retrospective cohort	France	January 2011 to November 2012	8 months	Fair quality
Chan et al[21]	retrospective cohort	Taiwan	February 2013 to December 2013	1 y	Good quality
Colemn et al[22]	retrospective cohort	Germany	January 2012 to October 2013	6 months	Good quality
Graham et al[8]	Prospective cohort	USA	October 2010 and December 2012	2 years and 2 months	Fair quality
Gorst-Rasmussen et al[23]	Registry	Denmark	February 2012 to July 2014	2 years and five months	Fair quality
Halvorsen et al[7]	Registry	Norway	January 2013 to June 2015	six months	Fair quality
Hernandez et al[24]	retrospective cohort	USA	October 1, 2010, through October 31, 2011,	One year	Fair quality
Lalibert et al[25]	retrospective cohort	USA	May 2011 to July 2012	1 year and two months	Fair quality
Larsen et al[9]	retrospective cohort	Denmark	August 2011 to October 2015	4 years and two months	Good quality
Lauffenburger et al[26]	large US database of commercial and Medicare supplement claims	USA	October 2010 to December 2012	Two years	Fair quality
Lip et al[15]	retrospective cohort	USA	January 2012 to December 2014	six months	Good quality
Maura et al[2]	retrospective cohort	France	July to November 2012	five months	Fair quality
Noseworthy et al[12]	data from Optum Labs Data Warehouse (OLDW)	USA	October 1st, 2010 and February 28th, 2015	five years	Fair quality
Seeger et al[13]	two commercial health insurance databases (MarketScan, Truven and Clinformatics, Optum)	USA	October 2010 to December 2012		Good quality
Staerk et al[14]	Registry	Denmark	2011–2015	4 years	Fair quality
Villines et al[11]	US Department of Defense Database	USA	October 2009 to July 2013	3 years and five months	Fair quality
Yao et al[27]	retrospective cohort	USA	October 2010 to June 2015	4 years and six months	Good quality

Comparison between different new oral anti-coagulants regarding the risk of thromboembolism

The network included four arms representing warafarin, Dabigatran, Rivaroxaban, and non-vitamin k antagonist Figure 6A.

Based on the ranking probability Figure 6C, non-vitamin k antagonist had the least risk of intracranial haemorrhage compared to Warfarin [HR = 0.523, 95% (0.095, 2.85)] followed by Dabigatran [HR = 0.0.54, 95% CrI (0.11, 2.52)] followed by Rivaroxaban [HR = 1.823, 95% (0.37, 9.28)] Figure 6B.

The comparison between different new oral anti-coagulants is presented in Table 6. The network was consistent as evident by the P-value = 0.9; there was no heterogeneity as the standard deviation of the random effect model is less than the effect size. The model is considered fit as present in Supplementary Table 7.

Table 2: Comparison of the included interventions for the risk of major bleeding: hazard ratio (95% CrI).

Intervention column 1	Intervention column 2	Intervention column 3	Intervention column 4	Intervention column 5
Rivaroxaban	0.995 (0.875, 1.113)	0.533 (0.444, 0.648)	0.722 (0.653, 0.824)	0.889 (0.641, 1.254)
	Warfarin	0.536 (0.448, 0.652)	0.726 (0.641, 0.859)	0.896 (0.639, 1.278)
		Apixaban	1.357 (1.124, 1.662)	1.668 (1.155, 2.428)
			Dabigatran	1.229 (0.887, 1.693)
				Nonvitamin K antagonist

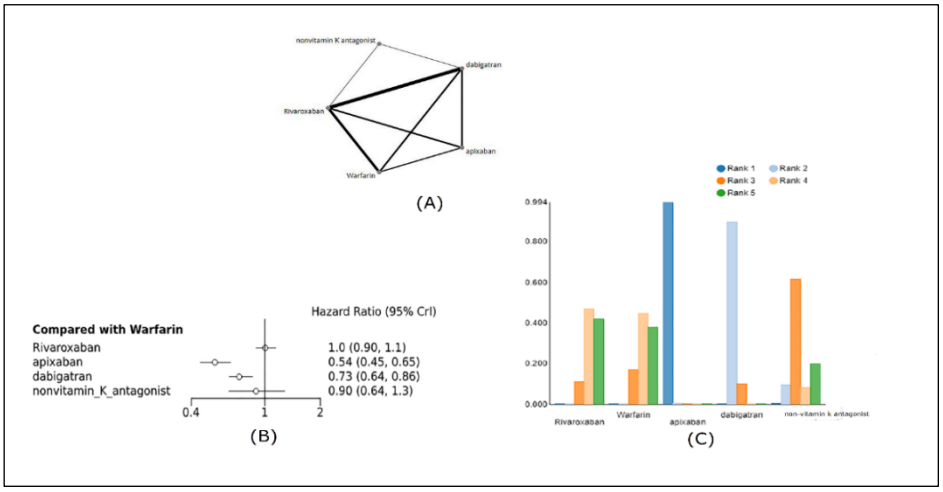

Figure 2: Network of treatments included in the network meta-analysis of risk for bleeding, A) The network graph, B) The random effect model forest plot showing the risk of bleeding for each type compared to warfarin, and C) The ranking probability for the risk of bleeding of different types of anticoagulants.

Table 3: Comparison of the included interventions for the risk of stroke: hazard ratio (95% CrI).

Intervention column 1	Intervention column 2	Intervention column 3	Intervention column 4
Rivaroxaban	1.058 (0.983, 1.144)	1.134 (0.951, 1.346)	1.025 (0.944, 1.116)
	Warfarin	1.070 (0.906, 1.263)	0.969 (0.905, 1.036)
		Apixaban	0.905 (0.765, 1.076)
			Dabigatran

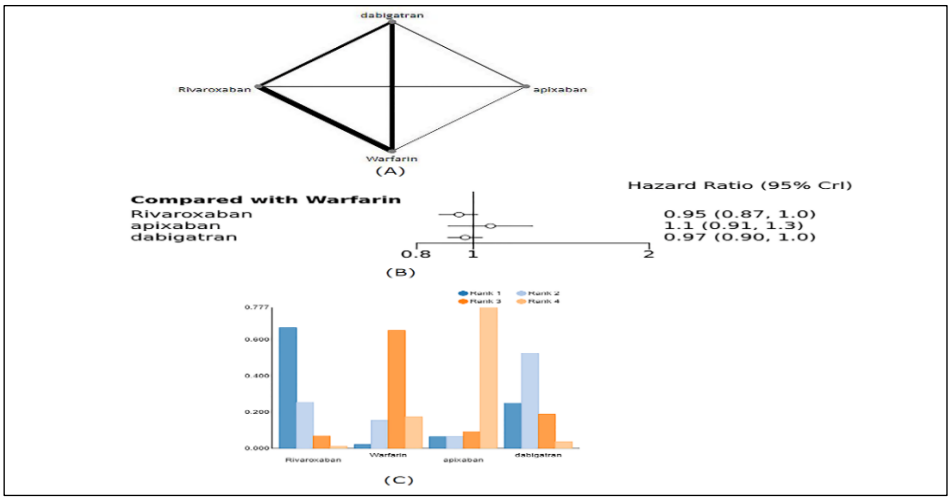

Figure 3: Network of treatments included in the network meta-analysis of risk for stroke, A) The network graph, B) The random effect model forest plot showing the risk of stroke for each type compared to warfarin, and C) The ranking probability for the risk of stroke of different types of anticoagulants.

Table 4: Comparison of included interventions for the risk of intracranial hemorrhage: hazard ratio (95% CrI).

Intervention column 1	Intervention column 2	Intervention column 3	Intervention column 4
Rivaroxaban	1.299 (0.769, 2.230)	0.828 (0.431, 1.626)	0.607 (0.352, 1.053)
	Warfarin	0.635 (0.363, 1.133)	0.467 (0.357, 0.609)
		Apixaban	0.734 (0.405, 1.301)
			Dabigatran

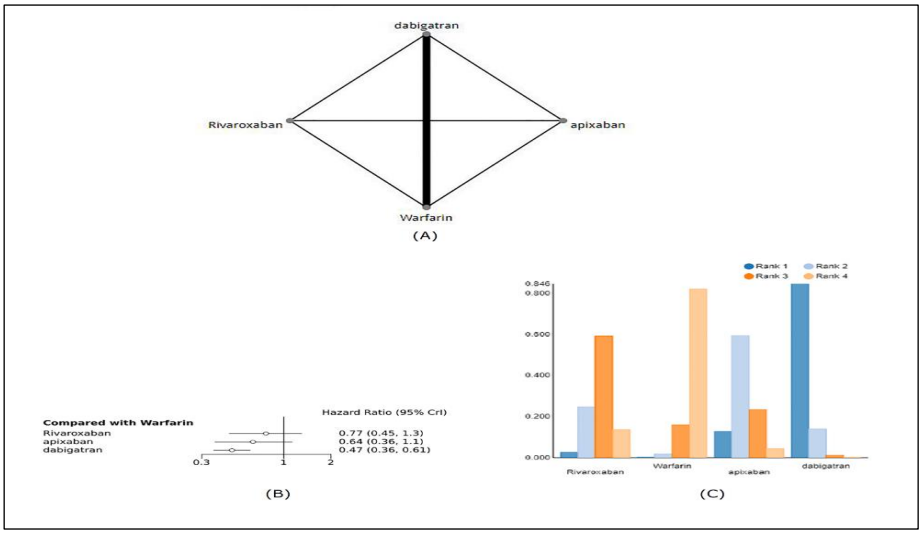

Figure 4: Network of treatments included in the network meta-analysis of risk for intracranial hemorrhage, A) Network graph, B) The random effect model forest plot of risk of intracranial hemorrhage for each type compared to warfarin, C) Ranking probability for the risk of intracranial hemorrhage of different types of anticoagulants.

Table 5: Comparison of included interventions for risk of gastrointestinal hemorrhage: hazard ratio (95% CrI).

Intervention column 1	Intervention column 2	Intervention column 3	Intervention column 4
Rivaroxaban	0.748 (0.453, 1.258)	0.567 (0.307, 1.046)	0.894 (0.538, 1.512)
	Warfarin	0.756 (0.438, 1.280)	1.195 (0.986, 1.424)
		Apixaban	1.579 (0.921, 2.725)
			Dabigatran

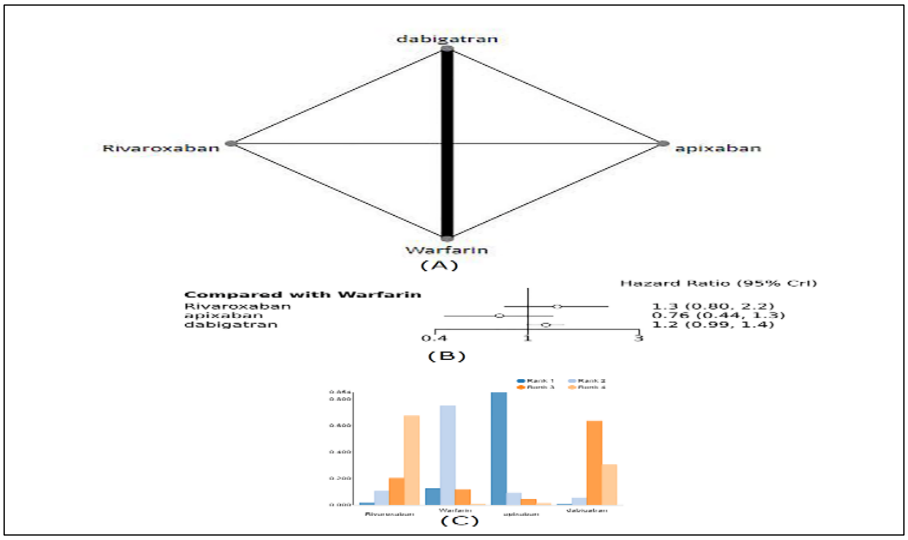

Figure 5: Network of treatments included in the network meta-analysis of risk for gastrointestinal haemorrhage, A) Network graph, B) Random effect model forest plot of risk of gastrointestinal haemorrhage for each type compared to warfarin, and C) Ranking probability for the risk of gastrointestinal haemorrhage of different anticoagulants.

Table 6: Comparison of the included interventions for the risk of thromboembolism: hazard ratio (95% CrI).

Intervention column 1	Intervention column 2	Intervention column 3	Intervention column 4
Rivaroxaban	1.824 (0.373, 9.276)	0.977 (0.650, 1.571)	0.956 (0.486, 1.903)
	Warfarin	0.543 (0.114, 2.524)	0.523 (0.095, 2.852)
		Dabigatran	0.967 (0.470, 1.950)

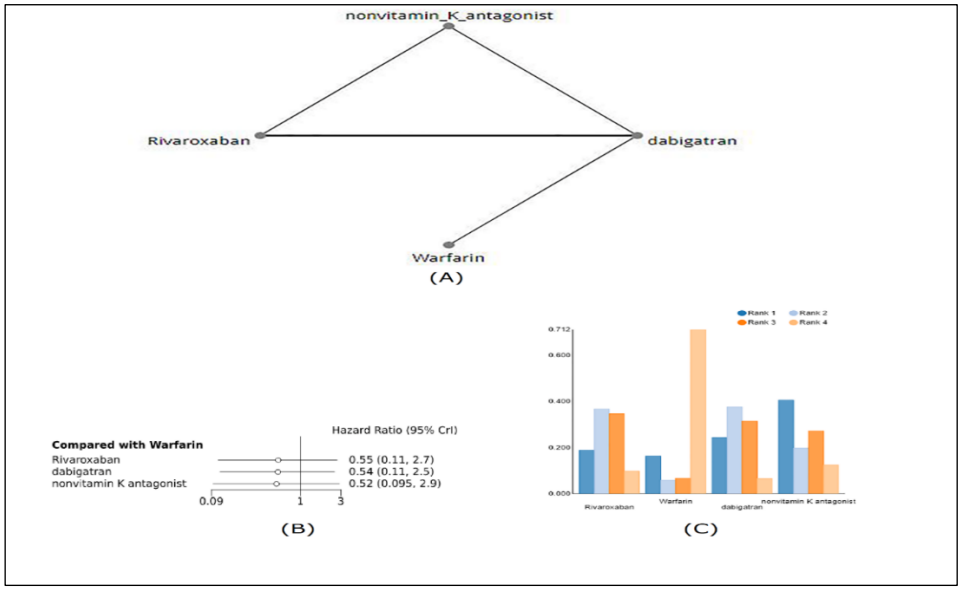

Figure 6: Network of treatments included in the network meta-analysis of risk for thromboembolism, A) Network graph, B) Random effect model forest plot showing the risk of thromboembolism for each type compared to warfarin, and C) Ranking probability for the risk of thromboembolism of different types of anticoagulants.

DISCUSSION

This study is set out to compare between the best anti-coagulant treatment for non-valvular atrial fibrillation with the least complication. Despite the inconclusive results, we found that. Apixaban had the least risk of major bleeding compared to Warfarin [HR = 0.536, 95% (0.448, 0.652)] and the least risk of gastrointestinal hemorrhage. For stroke risk, the Rivaroxaban had the least risk compared to Warfarin [HR = 1.05, 95% (0.98, 1.14)]. For intracranial hemorrhage, Dabigatran had the least risk of intracranial haemorrhage compared to Warfarin [HR = 0.46, 95% CrI (0.36, 0.61)]. For the thromboembolism risk, other non-vitamin k antagonist had the least risk of intracranial haemorrhage compared to Warfarin [HR = 0.523, 95% (0.095, 2.85)].

Stroke is a major complication of atrial fibrillation; usual anti-coagulants are used to prevent this complication.[1,2] However, with the high side effects of the vitamin K antagonist, search for new anti-coagulants with less side effects was initiated.[5] This group included apixaban, Rivaroxaban and Dabigatran which are used for nowadays as alternative for usual anti-coagulants. Still, with contradicting results, the choice of the best one of them is not easy due to the risk of complications for each one.[13,28,29]

Regarding major bleeding, our results were consistent with previous meta-analyses that apixaban was the best approach with less risk of major bleeding.[30] A multi-centre, multinational, double-blind, randomized trial that compared apixaban with warfarin found that apixaban had less risk of bleeding compared to warfarin.[7,12,16] Dabigatran was compared to warfarin and was found to has no difference to it regarding the major bleeding but was significantly associated with decreased rate intracranial haemorrhage.[19,30] This supports our results as Dabigatran was the least among them to have intracranial haemorrhage. For major bleeding, the dabigatran was the second after apixaban to be less associated with risk of major bleeding which contradict these studies as it was superior to warfarin. The same was found for rivaroxaban, two randomized clinical trial found that rivaroxaban was equivalent to warfarin regarding the risk for bleeding and better regarding the risk of stroke, embolism and intracranial haemorrhage.[8,31] Our results support these trials as rivaroxaban had more risk than warfarin for major bleeding and gastrointestinal bleeding. Rivaroxaban's risk of thromboembolism and bleeding was more than other new anticoagulant drugs. Apixaban was considered in other studies is superior to other new oral anticoagulants.[32]

A study found that apixaban was associated with survival benefit compared to warfarin. Comparison between apixaban and rivaroxaban found that the apixaban had less risk of bleeding than rivaroxaban.[32] Dabigitran was found to be superior than rivaroxaban regarding the risk of bleeding and intracranial haemorrhage.[12] This is like our results which supports the concept that rivaroxaban is less than other new anticoagulants. That study also found that rivaroxaban was also associated with more risk of stroke and ischaemic stroke than dabigatran.[12]

Table 7: Model fit statistics of bleeding risk.

Residual deviance (D_{res})	**25.5**
Leverage (p_D)	9.9
DIC	35.4
Number of data points	19
Model fit statistics of stroke risk	
Residual deviance (Dres)	14.5
Leverage (pD)	4.9
DIC	19.4
Number of data points	21
Model fit statistics of intracranial haemorrhage (ICH) risk	
Residual deviance (Dres)	14.8
Leverage (pD)	10
DIC	24.9
Number of data points	13
Model fit Statistics of gastrointestinal bleeding risk	
Residual deviance (Dres)	11.1
Leverage (pD)	10.1
DIC	21.2
Number of data points	11
Model fit statistics of thromboembolism risk	
Residual deviance (Dres)	4.7
Leverage (pD)	4.2
DIC	9
Number of data points	5

Lip et al, found that there was no significant difference between the three new oral anti-coagulants to each other even with different doses.[15,16] Another study suggested that the apibaxan is the best and most superior to all other anticoagulants.[29] Another study found that there was no difference in the efficacy between the three new oral anti-coagulants. In addition, they found that dabigatran was associated with less risk of stroke and bleeding.[33] This was also proved by another study which was also found that the three drugs had the same efficacy, but rivaroxaban had the highest risk of bleeding.[12] Another study found that patients switching to non-vitamin k antagonist had less risk of bleeding. It was only present in thromboembolism outcome in our study and was considered the least ones associated with the thromboembolic complications.[20] Another study with Asian patients found that the rivaroxaban and dabigatran were associated with less risk of bleeding, stroke and intracranial haemorrhage.[21] Nationwide cohort study in atrial fibrillation patients apixaban and dabigatran were associated with a lower risk of major bleeding and higher risk of gastrointestinal bleeding compared with warfarin.[7]

We recommend head to head clinical trials to stand on the best treatment for atrial fibrillation with no significant risk of bleeding and other side effects.

Our results are more reliable than trials or studies that reviewed and analysed clinical trials as the population in clinical trial usually of younger age and limited to specific included populations. In addition, observational and cohort studies usually represent real life patients.

CONCLUSION

Apixaban was the least among them to be associated with major bleeding, while rivaroxaban was ranked the first with least stroke complications. Furthermore, dabigatran was associated with less risk of intracranial haemorrhage compared to other anticoagulants.

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