REVIEW



Effects of rivaroxaban and warfarin on the risk of gastrointestinal bleeding and intracranial hemorrhage in patients with atrial fibrillation: Systematic review and meta-analysis

Hongcheng Jiang MS¹ | Yue Jiang MS¹ | Haotian Ma BS² | Hesong Zeng PhD¹ | Jiagao Lv PhD¹

¹Division of Cardiology, Department of Internal Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

²The First Clinical School, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Correspondence

Dr. Jiagao Lv, Division of Cardiology, Department of Internal Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 13 Hangkong Road, Wuhan 430030, China. Email: lujiagao@tjh.tjmu.edu.cn

Abstract

To assess the risk of gastrointestinal bleeding and intracranial hemorrhage in patients with atrial fibrillation (AF) after the use of rivaroxaban or warfarin. To investigate the effects of rivaroxaban and warfarin on gastrointestinal and intracranial hemorrhage in patients with AF, we searched PubMed, Embase, and Medline from the establishment of databases up to 2020. We finally included 38 observational studies involving 1 312 609 patients for the assessment of intracranial hemorrhage, and 33 observational studies involving 1 332 956 patients for the assessment of gastrointestinal bleeding. The rates of intracranial hemorrhage were 0.55% in the rivaroxaban group versus 0.91% in the warfarin group (OR 0.59; 95% CI 0.53-0.66; p < .00001, I2 = 78%). The rates of gastrointestinal bleeding were 2.63% in patients with rivaroxaban versus 2.48% in those with warfarin (OR 1.06; 95% CI 0.96–1.17; p < .00001, I2 = 94%). Rivaroxaban could significantly reduce the risk of intracranial hemorrhage in patients with AF than warfarin, but the risk of gastrointestinal bleeding remained controversy due to no statistical significant difference. Notably, a subgroup analysis demonstrated that patients in rivaroxaban group with severe chronic renal diseases or undergoing hemodialysis exposed to less gastrointestinal hemorrhage risk than the group from warfarin.

KEYWORDS

atrial fibrillation, gastrointestinal bleeding, intracranial hemorrhage, rivaroxaban, warfarin

1 | INTRODUCTION

Atrial fibrillation (AF), the most prevalent cardiac arrhythmia in clinical practice, is associated with a dramatically increasing risk of ischemic stroke, causes death and disability five-fold.¹

Vitamin K antagonists (VKAs), represented by warfarin have been the primary oral anticoagulants for ischemic stroke prevention in AF.²

VKAs, vitamin K antagonists. Hongcheng Jiang and Yue Jiang authors contributed equally to this work. the

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2021 The Authors. Clinical Cardiology published by Wiley Periodicals LLC.

Abbreviations: AF, atrial fibrillation; NOACs, nonvitamin K antagonist oral anticoagulants;

Regarding the former reports, AF was associated with a 60% reduction in the risk of stroke, but also have many deficiencies that have restricted their applies in clinical practice, which was associated with a narrow therapeutic window, multiple interactions with other medications, and therefore there is a demand for real time monitoring for efficacy evaluation and dosage adjustments when use VKAs.³

Nowadays non-VKA oral anticoagulants (NOACs), particularly the factor Xa inhibitors, for example rivaroxaban, have drawn lots of attention considering a number of phase III clinical trials have shown that NOACs are confirmed as effective as VKAs as treatments for the prevention of ischemic stroke or systemic embolism, and have a better safety outcome, especially regarding the risk of major bleeding, which was proved by several net meta-analysis.⁴⁻⁶ Although VKAs and NOACs are associated with an obvious reduction in the risk of stroke in AF patients, they have many complications that result in adverse outcomes in clinical practice, including hemorrhage. Several clinical studies have contributed to inquiry of the hemorrhage outcomes in rivaroxaban versus warfarin. Rivaroxaban was the first oral factor Xa inhibitor used to the clinical practice, and provided potential advantages over VKAs, including rapid onset and offset of action, and fewer drug interactions.⁷ It has been already testified for the effect of preventing stroke and systemic embolism. However, the comparative safety outcomes of rivaroxaban and warfarin regimens remain unclear and controversial, especially regarding high-risk patient groups such as suffering from severe renal diseases, or populations in varied geographical distributions, because of the scarcity and inaccuracy of trials. Thus, we collected data of several observational studies to conduct a meta-analysis to compare the differences of safety outcomes between rivaroxaban and warfarin.

2 | METHODS

2.1 | Search strategy

PubMed, Embase, and medline were systematically searched from the establishment of databases up to 2020. The search strategy was edited to each database and included index terms (medical subject headings) [MeSH] and Emtree) and text words related to AF, rivaroxaban, warfarin and hemorrhage. We also scanned the bibliographies of the included articles and relevant reviews for further references.

2.2 | Inclusion and exclusion criteria

Cross-sectional studies, letters to the editor, commentaries/editorials, and previous reviews and meta-analyses were excluded. Conference abstracts were also excluded as their results are primary and they often contain deficient information causing risk of bias. The primary safety outcomes we regarded as inclusion criteria were CLINICAL CARDIOLOGY WILEY 1209

gastrointestinal bleeding and intracranial hemorrhage events. (Figure S1 show in the supplemental material.)

2.3 | Study selection

Two individual reviewers performed study selection. When two individual's screening results are inconsistent, a third person makes the judgment. Titles and abstracts were screened to identify potentially relevant studies and duplicates; all studies identified as potentially relevant by either reviewer proceeded to full-text review. All the discrepancies were settled by getting through full texture to reach consensus.

2.4 | Data analysis

Meta-analytic results were present as adjusted ORs with 95% CIs. The heterogeneity was present with estimation using the I^2 statistic. All analyses were conducted using Review Manager 5.3.

3 | RESULTS

A total of 1778 articles were identified in the initial search. We excluded 122 duplicates and removed 1448 studies not meeting inclusion criteria, and 208 full-text studies were evaluated in a closer inspection. After 161 articles (three changed drugs during the observational studies, 73 data unavailable, 30 NOAC but not rivaroxaban, five observational studies included patients not only suffered from AF, 50 were only major bleeding and not mentioned gastrointestinal bleeding and intracranial hemorrhage) were discarded, a total of 47 studies were finally included in the analysis. Thirty eight observational studies were included in our review for intracranial hemorrhage, a total of 1 312 609 patients diagnosed with nonvalvular AF, with sample sizes from 353 to 166 014 patients, while 33 observational studies were included in our review for gastrointestinal bleeding, a total of 1 391 923 patients diagnosed with nonvalvular AF, with sample sizes from 353 to 166 014 patients. Figures below (Figure 1 and Figure 2) summarize the main outcomes of the two group of included trials.

3.1 | Safety outcomes of intracranial hemorrhage between rivaroxaban and warfarin

Data were collected from 38 studies including 632 513 patients in the rivaroxaban group and 680 096 patients in the warfarin group. The rates of intracranial hemorrhage were 0.55% in the rivaroxaban group versus 0.91% in the warfarin group. As is demonstrated in the Figure 1, the risk of intracranial hemorrhage in the rivaroxaban group was significantly lower when compared with the group of warfarin (OR 0.59; 95% CI 0.53–0.66; p < .00001, I2 = 78%) However the

1210 WILEY CLINICAL

	rivarox			arin	10-1 B	Odds Ratio	Odds Ratio
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Alpesh Amin 2017	315	52476	441	52476	4.0%	0.71 [0.62, 0.82]	+
Alpesh Amin 2019	110	15712	189	15712	3.6X	0.58 [0.46, 0.73]	
Alpesh Amin 2019	277	55359	400	55359	4.0%	0.69 [0.59, 0.81]	+
Blin 2019	209	54485	321	54485	3.9X	0.65 [0.55, 0.77]	+
Brandon 2019	9	3418	12	3418	1.1%	0.75 [0.32, 1.78]	
Brandon K. Martinez 2018	10	2635	20	2635	1.3×	0.50 [0.23, 1.07]	
Cappato 2014	2	966	1	499	0.2%	1.01 [0.09, 11.17]	
Coleman 2019	9	2604	23	2604	1.3×	0.39 [0.18, 0.84]	
Coleman 2017	13	5517	22	5517	1.5%	0.59 [0.30, 1.17]	——————————————————————————————————————
Coleman 2016	1	3319	7	3319	0.2%	0.14 [0.02, 1.16]	· · · · · · · · · · · · · · · · · · ·
Coleman 2019	2	1896	14	4848	0.4%	0.36 [0.08, 1.61]	
Diepen 2013	55	7111	84	5676	3.0X	0.52 [0.37, 0.73]	
Faye L. Norby 2018	46	32495	124	45496	3.0%	0.52 [0.37, 0.73]	
Franc, ols Laliberte 2014	66	3654	219	14616	3.3×	1.21 [0.92, 1.60]	+
Gboyega Adeboyeje 2017	46	6396	338	23431	3.2%	0.38 [0.28, 0.51]	- -
Gregory 2018	329	83007	519	83007	4.1%	0.63 [0.55, 0.73]	+
Gregory 2020	266	44412	489	44412	4.0%	0.54 [0.47, 0.63]	+
Hsin-Fu Lee 2016	258	26000	305	16000	3.9X	0.52 [0.44, 0.61]	+
onathan L. Halperin 2014	36	7111	53	7125	2.5%	0.66 [0.44, 1.04]	
Kevin E. Chan 2016	0	244	121	8064	0.1%	0.13 [0.01, 2.16]	• • • • •
Kiran Gupta 2019	52	8226	91	8226	3.0%	0.57 [0.40, 0.80]	
Lars J. Kjerpesethi 2019	20	7851	48	6435	2.1%	0.34 [0.20, 0.57]	
Lizheng Mao 2014	1	177	3	176	0.2%	0.33 [0.03, 3.18]	
Martin H. Ellis 2016	7	2709	66	9564	1.3×	0.36 [0.17, 0.79]	
Min Soo Cho 2019	93	21000	54	10409	3.0%	0.85 [0.61, 1.19]	
Palamaner 2017	37	18649	61	18159	2.6%	0.59 [0.39, 0.89]	
Renato D. Lopes 2016	207	7071	259	7133	3.6%	0.80 [0.66, 0.96]	
Sameer Bansilal 2016	55	7071	84	7133	3.0%	0.66 [0.47, 0.93]	
Sara Själander 2018	59	8323	72	8323	3.0%	0.82 [0.58, 1.16]	
Sigrun Halvorsen 2017	63	6817	90	11427	3.1×	1.17 [0.85, 1.62]	+
So-Ryoung Lee 2019	195	35965	191	25420	3.6%	0.72 [0.59, 0.88]	-
So-Ryoung Lee 2019	105	13569	353	13569	3.7%	0.29 [0.23, 0.36]	-
Steve Deltelzweig 2020	66	22053	176	22053	3.5%	0.50 [0.39, 0.64]	
Torben 2016	23	7192	190	35436	2.5%	0.60 [0.39, 0.92]	
Washam 2017	72	7131	82	7133	3.1%	0.88 [0.64, 1.21]	
Klaoxi Yao 2017	71	16175	128	16175	3.3%	0.55 [0.41, 0.74]	
Yi-Hsin Chan 2016	30	3916	130	5251	2.7%	0.30 [0.20, 0.45]	
ri-Hsin Chan 2018	272	27777	378	19375	4.0%	0.50 [0.42, 0.58]	+
Fotal (95% CI)		632513		680096	100.0%	0.59 [0.53, 0.66]	•
Fotal events	3509		6160				
leterogeneity: Tau ² = 0.06;	$Cht^2 = 16$	i4.58, df	= 37 (P	< 0.0000	1); i ² = 7	6 %	0.01 0.1 1 10 1
est for overall effect: Z = 9	.87 (P < 0	00001					Favours rivaroxaban Favours warfarin

FIGURE 1 Forest plot of studies assessing the risk of intracranial hemorrhage among patients in the rivaroxaban and warfarin group

statistical heterogeneity was high among studies. Thus, we next conducted subgroup analysis.

3.2 | Subgroup analysis

Considering the situation that different patients from varied racial distributions may lead to different outcomes, we conducted subgroup analyses based on 27 trials and divided the data into three subgroups, including 218 604 Asian patients, 788 871 American patients and 158 146 European patients. The rates of intracranial hemorrhage in the rivaroxaban group are 0.74%, 0.50%, 0.45%, respectively. Compared with patients in group rivaroxaban,the rates of warfarin groups are 1.57%, 0.74%, 0.66%, respectively. As was shown in the Figure 3, every subgroup indicated that patients in the rivaroxaban group exposed to obviously lower risk of intracranial hemorrhage than the patients from warfarin group.(Asian: OR 0.49; 95% CI 0.37–0.65; p<.00001,I2 = 88%; Europe: OR 0.70;95% CI 0.48–1.04; p = .0003,I2 = 84%; USA: OR

0.63;95% CI 0.58-0.69; *p* = .03,I2 = 44%; total: OR 0.60; 95% CI 0.53-0.67; *p*<.00001, I2 = 79%).

3.3 | Safety Outcomes of gastrointestinal bleeding between rivaroxaban and warfarin

The Figure 2 shows the overall results of the gastrointestinal bleeding outcomes. Data regarding the occurrence of gastrointestinal bleeding are available from 33 trials, 646 118 patients in the group of rivaroxaban and 745 805 patients in the group of warfarin. The rates of gastrointestinal bleeding were 2.63% in patients with rivaroxaban versus 2.48% in those with warfarin. Interestingly, the group of rivaroxaban was associated with similar risk of gastrointestinal bleeding, when compared with the group of warfarin, but the statistical heterogeneity was high among studies. Thus, we next conducted subgroup analysis. (OR 1.06; 95% CI 0.96–1.17; p = 0.26, I2 = 94%).



	rivaro	kaban	warf	arin		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% CI
Algesh Amin 2017	1866	52476	1401	52476	3.5%	1.35 [1.25, 1.44]	
Alpesh Amin 2019	1367	55359	1126	55359	3.5%	1.22 [1.13, 1.32]	
Alpesh Amin 2019	864	15712	550	15712	3.4%	1.60 [1.44, 1.79]	
Amgad Mentias 2016	533	23177	2597	101715	3.5%	0.90 [0.82, 0.99]	_
Blin 2019	590	54485	567	54485	3.4%	1.04 [0.93, 1.17]	_
Brandon K. Martinez 2018	113	2635	66	2635	2.7%	1.30 [0.98, 1.72]	
Chen 2018	217	7111	134	7124	3.0%	1.64 [1.32, 2.04]	
Coleman 2018	113	5517	121	5517	2.9%	0.93 [0.72, 1.21]	
Coleman 2019	25	3319	33	3319	1.6%	0.76 [0.45, 1.27]	· · · · · · · · · · · · · · · · · · ·
Coleman2 2019	64	1896	219	4646	2.6%	0.74 [0.56, 0.98]	
Faye L. Norby 2018	492	32495	717	45496	3.4%	0.96 [0.86, 1.08]	+
Franc, ois Laliberte 2014	348	3654	1023	14616	3.4%	1.40 [1.23, 1.59]	
Gboyega Adeboyeje 2017	92	8398	649	23431	3.0%	0.39 [0.31, 0.48]	•
Gregory 2018	1813	83007	1460	83007	3.5%	1.23 [1.15, 1.32]	
Gregory 2020	1821	44412	1511	44412	3.5%	1.21 [1.13, 1.30]	
Hsin–Fu Lee 2018	368	26000	315	16000	3.3%	0.71 [0.61, 0.83]	
Kevin E. Chan 2016	15	244	826	8064	1.6%	0.57 [0.34, 0.97]	·
Kiran Gupta 2019	301	8226	236	8226	3.2%	1.29 [1.08, 1.53]	
Lars J. Kjerpesethi 2019	121	7851	124	6435	2.9%	0.60 [0.62, 1.03]	
Lizheng Mao 2014	6	177	1	176	0.2%	8.28 [1.03, 66.95]	→
Martin H. Ellis 2016	65	2709	160	9564	2.7%	1.28 [0.96, 1.71]	
Min Soo Cho 2019	995	21000	475	10409	3.4%	1.04 [0.93, 1.16]	_
Palamaner 2017	450	18649	369	18159	3.3×	1.19 [1.04, 1.37]	
Renato D. Lopes 2016	1321	25903	907	25903	3.5×	1.48 [1.36, 1.61]	
Sara Själander 2016	132	8323	112	8323	2.9%	1.18 [0.92, 1.52]	
Sigrun Halvorsen 2017	175	6817	199	11427	3.1×	1.49 [1.21, 1.83]	
Simon Mantha 2014	224	7111	154	7125	3.1×	1.47 [1.20, 1.81]	
So-Ryoung Lee 2019	451	35965	366	25420	3.3×	0.82 [0.71, 0.94]	
So-Ryoung Lee2 2019	179	13569	373	13569	3.2%	0.47 [0.40, 0.57]	<u>←</u>
Steve Deitelzweig 2020	860	22053	664	22053	3.4%	1.27 [1.14, 1.40]	
Xlaoxi Yao 2017	527	16175	409	16175	3.4%	1.30 [1.14, 1.48]	
YI-Hsin Chan 2016	105	3916	96	5251	2.6%	1.48 [1.12, 1.96]	· · · · · · · · · · · · · · · · · · ·
YI-Hsin Chan 2018	394	27777	444	19374	3.3×	0.61 [0.53, 0.70]	
Total (95% CI)		646118		745805	100.0%	1.06 [0.96, 1.17]	•
Total events	17011		18508				
Heterogeneity: Tau ² = 0.07;			= 32 (P	< 0.0000	1); i ² = 94	176	0.5 0.7 1 1.5 2
Test for overall effect: $Z = 1$.12 (P = ().26)					Favours [rivaroxaban] Favours [warfarin]

FIGURE 2 Forest plot of studies assessing the risk of gastrointestinal bleeding among patients in the rivaroxaban and warfarin group

3.4 | Subgroup analysis

Based on the situation that different patients are under varied healthy conditions and medical treatments, we conducted subgroup analyses on account of chronic renal diseases or undergoing hemodialysis, and racial distribution.

The outcomes based on two trials showed that the patients from rivaroxaban group suffering from severe chronic renal diseases or undergoing hemodialysis exposed to less gastrointestinal hemorrhage risk than the group from warfarin, including 2140 patients in group rivaroxaban and 12 912 patients in group warfarin, 3.69% versus 8.09%. (OR 0.70; 95% CI 0.54–0.90; p = .005, I2 = 0%)(Figure 4).

The outcomes based on 30 trials showed the specific features of patients from varied ethnicities, including Asian, American and European. The data of was collected from 218 603 Asian patients, 951 858 American patients and 158 146 European patients. The rates of gastrointestinal bleeding in the rivaroxaban group are 1.95%, 3.10%, and 1.31%, respectively. Compared with rivaroxaban, the rates of warfarin groups are 2.32%, 2.73%, and 1.24%, respectively. Only data collected from American patients appeared to have the difference of gastrointestinal bleeding risk, between rivaroxaban and warfarin, with 19 studies reporting, demonstrating warfarin results in less gastrointestinal hemorrhage. (USA: OR 1.12; 95% CI1.01–1.24; p = .04, I2 = 93%) However it

remained uncertain whether the risk of gastrointestinal bleeding between racial variety showed discrepancy since no statistic differences of total events with high statistical heterogeneity. (Asian: OR 0.82; 95% CI 0.63–1.07; p < .00001, I2 = 94%; Europe: OR 1.10;95% CI 0.88–1.38; p = .001,I2 = 81%; total: OR 1.03; 95% CI 0.92–1.14; p = 0.56, I2 = 95%)(Figure 5).

4 | DISCUSSION

Our meta-analysis included 38 observational studies involving 1 312 609 patients (632 513 used rivaroxaban and 680 096 used warfarin) with AF, in order to assess the risk of intracranial hemorrhage after warfarin and rivaroxaban use, and 33 observational studies involving 1 391 923 patients (646 118 used rivaroxaban and 745 805 used warfarin) with AF, in order to assess the risk of gastrointestinal bleeding after warfarin and rivaroxaban use.

In our meta-analysis, we found that anticoagulant therapy with rivaroxaban could significantly reduce the risk of intracranial hemorrhage in patients with AF, which was statistically significant, and partially increased the risk of gastrointestinal bleeding among different ethnic groups of patients, but there was no statistical significance. The reason why rivaroxaban reduces intracranial hemorrhage is not

	rivaro		warf			Odds Ratio	Odds Ratio
Study or Subgroup	Events	lotal	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
L.2.1 Asian							
Isin-Fu Lee 2018	258	26000	305	16000	5.1%	0.52 [0.44, 0.61]	+
Izheng Mao 2014	1	177	3	176	0.2%	0.33 [0.03, 3.18]	
Win Soo Cho 2019	93	21000	54	10409	3.6%	0.85 [0.61, 1.19]	
io-Ryoung Lee 2019	195	35965	191	25420	4.9%	0.72 [0.59, 0.88]	
io-Ryoung Lee 2019	105	13569	353	13569	4.7%	0.29 [0.23, 0.36]	+
'i-Hsin Chan 2016	30	3916	130	5251	3.4%	0.30 [0.20, 0.45]	
7—Hsin Chan 2018 Subtotal (95% CI)	272	27777 128404	378	19375 90200	5.2X 27.4%	0.50 [0.42, 0.58] 0.49 [0.37, 0.65]	•
fotal events	954		1414				
Heterogeneity: $Tau^2 = 0.11$; Fest for overall effect: $Z = 4$			6 (P < 1	0.00001);	l ² = 66%		
1.2.2 Europe							
Slin 2019	209	54485	321	54485	5.1%	0.65 [0.55, 0.77]	+
ars J. Kjerpesethi 2019	20	7851	48	6435	2.6%	0.34 [0.20, 0.57]	<u> </u>
Sara Själander 2018	59	8323	72	8323	3.7%	0.82 [0.58, 1.16]	-+-
Sigrun Halvorsen 2017	63	6817	90	11427	3.9%	1.17 [0.85, 1.62]	+
Subtotal (95% CI)		77476		80670	15.3%	0.70 [0.48, 1.04]	◆
Fotal events	351		531				
leterogeneity: Tau ² = 0.13; lest for overall effect: Z = 1			3 (P = 1	0.0003); f	² = 64%		
1.2.3 USA							
Alpesh Amin 2017	315	52476	441	52476	5.3%	0.71 [0.62, 0.82]	+
Alpesh Amin 2019	110	15712	189	15712	4.6%	0.58 [0.46, 0.73]	-
Alpesh Amin 2019	277	55359	400	55359	5.2%	0.69 [0.59, 0.81]	+
Srandon 2019	9	3418	12	3418	1.3%	0.75 [0.32, 1.78]	
Srandon K. Martinez 2018	10	2635	20	2635	1.6%	0.50 [0.23, 1.07]	
Coleman 2019	1	3319	7	3319	0.3%	0.14 [0.02, 1.16]	
Coleman 2019	2	1896	14	4646	0.5%	0.36 [0.08, 1.61]	
aye L. Norby 2018	46	32495	124	45496	3.6%	0.52 [0.37, 0.73]	
Gregory 2018	329	83007	519	83007	5.3%	0.63 [0.55, 0.73]	+
Gregory 2020	266	44412	489	44412	5.2%	0.54 [0.47, 0.63]	+
Ciran Gupta 2019	52	8226	91	8226	3.6%	0.57 [0.40, 0.80]	
tenato D. Lopes 2018	207	25903	259	25903	5.0%	0.80 [0.66, 0.96]	+
ameer Bansilal 2016	55	7071	84	7133	3.6%	0.66 [0.47, 0.93]	
iteve Deltelzweig 2020	66	22053	176	22053	4.5%	0.50 [0.39, 0.64]	-
Forben 2016	23	7192	190	35436	3.1×	0.60 [0.39, 0.92]	
Washam 2017	72	7131	82	7133	4.0%	0.88 [0.64, 1.21]	
Subtotal (95% CI)		372305		416566	57.3%	0.63 [0.58, 0.69]	•
Fotal events	1862		3097	A A 33. R			
Heterogeneity: Tau ² = 0.01; Fest for overall effect: Z = 9			. 12 (6 =	0.03); F	= 44%		
Fotal (95% CI)		578185		587436	100.0%	0.60 [0.53, 0.67]	•
iotal events	3167		5042				
Heterogeneity: Tau ² = 0.06;			= 26 (P	< 0.0000	1);	9 %	0.01 0.1 1 10 1
lest for overall effect: $Z = B$	Ar /n + /	(10000					A'AT A'T TA TA TA

FIGURE 3 Forrest plot of subgroup analysis assessing the risk of intracranial hemorrhage based on racial distribution

	rivarox	aban	warfa	arin		Odds Ratio		Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M	M-H, Random, 95% CI		
1.2.1 chronic kidney	disease	or unde	rgoing h	nemodia	lysis					
Coleman2 2019	64	1896	219	4646	77.6%	0.74 [0.56, 0.98]		-		
Kevin E. Chan 2016 Subtotal (95% CI)	15	244 2140	826	8064 12912	22.4% 100.0%	0.57 [0.34, 0.97] 0.70 [0.54, 0.90]		•		
Total events	79		1045							
Heterogeneity: Tau ² =	- 0.00: Cl	$t^2 = 0.6$	i8. df = 1	$1 \langle \mathbf{P} = 0 \rangle$	41): $f^2 = 1$	0%				
Test for overall effect										
Total (95% CI)		2140		12912	100.0%	0.70 [0.54, 0.90]		•		
Total events	79		1045							
Heterogeneity: Tau ² =	= 0.00; Ch	$h^2 = 0.6$	68, df = 1	1 (P = 0.	41); i ² = 1	0%				
Test for overall effect							0.01 0.1	roxaban] Favou	10 re lucretarial	10
Test for subgroup dif							ravours (rivar	uxabanj Favou	rs (warrarin)	

FIGURE 4 Forrest plot of subgroup analysis assessing the risk of gastrointestinal bleeding considering severe chronic renal diseases or hemodialysis



rivaroxa	ijan	warf			Odds Ratio	
	Total			Woight		Odds Ratio
Events	TOTAL	Events	Total	weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
				0.000		
			-			
				-		
		444				
	128404		90199	21.5%	0.82 [0.63, 1.07]	
	-	6 (P < ().00001);	r = 94%		
1868	52476	1401	52476	3.6%	1.35 [1.25, 1.44]	—
864	15712	550	15712	3.6%	1.60 [1.44, 1.79]	│
1367	55359	1126	55359	3.6%	1.22 [1.13, 1.32]	
533	23177	-		3.6%	and an and the second se	
113	2635	88	2635	3.0%		+
-						
-						
-						
				-		←
-						
					and the line working the line of	
•		-				
-						
	-		-			
-						
		-				
		409				
	+11709		540089	05.0%	1.12 [1.01, 1.24]	-
	36 00 0	-			-	
		= 10 (F	< 0.0000.	1); = 93	57 4	
590	54485	567	54485	3.7%	1.04 [0.93, 1.17]	-+
121	7851	124	6435	3.2%	0.80 [0.62, 1.03]	
132	8323	112	8323	3.2%	1.18 [0.92, 1.52]	
175	6817	199	11427	3.4%	1.49 [1.21, 1.83]	
	77476		80670	13.5%	1.10 [0.88, 1.38]	
1018		1002				
Cht ² = 15.	66, df =	3 (P = 0).001); P	61%		
65 (P = 0.4	40)					
6	517649		710958	100.0%	1.03 [0.93, 1.14]	+
16279		17825				
	1.74, df		< 0.00003	1);	¥	0.5 0.7 1 1.5 2
		2 (P =	0.10). ř =	55.7%		Favours [rivaroxaban] Favours [warfarin]
	2500 Chi ² = 93. 46 ($P = 0$. 1866 864 1367 533 113 113 25 64 492 346 92 1813 1621 1321 224 860 527 12761 Chi ² = 241 06 ($P = 0$. 590 121 132 175 1018 Chi ² = 15. 85 ($P = 0$. (16279 Chi ² = 53. 58 ($P = 0$.	$\begin{array}{c} 8 & 177 \\ 995 & 21000 \\ 451 & 35965 \\ 179 & 13569 \\ 105 & 3916 \\ 394 & 27777 \\ 128404 \\ 2500 \\ Chi^2 = 93.67, df - 46 (P = 0.14) \\ \hline \\ 1868 & 52476 \\ 864 & 15712 \\ 1367 & 55359 \\ 533 & 23177 \\ 113 & 2635 \\ 113 & 5517 \\ 25 & 3319 \\ 64 & 1896 \\ 492 & 32495 \\ 348 & 3654 \\ 92 & 8398 \\ 1813 & 83007 \\ 1821 & 44412 \\ 15 & 244 \\ 301 & 8226 \\ 1321 & 25903 \\ 224 & 7111 \\ 860 & 22053 \\ 227 & 16175 \\ 411769 \\ 12761 \\ Chi^2 = 248.98, df \\ 06 (P = 0.04) \\ \hline \\ 590 & 54485 \\ 121 & 7651 \\ 132 & 8323 \\ 175 & 6817 \\ 77476 \\ 1018 \\ Chi^2 = 15.68, df - 85 (P = 0.40) \\ \hline \\ 617649 \\ 16279 \\ Chi^2 = 531.74, df \\ 58 (P = 0.56) \\ \hline \end{array}$		8 177 1 176 995 21000 475 10409 451 35965 368 25420 179 13569 373 13569 105 3916 96 5251 394 27777 444 19374 128404 90199 2500 2092 Chi ² = 93.67, df = 6 (P < 0.00001);	8 177 1 176 0.2% 995 21000 475 10409 3.7% 451 35965 388 25420 3.7% 179 13569 373 13569 3.5% 105 3916 96 5251 3.1% 394 27777 444 19374 3.7% 128404 90199 21.5% 2500 2092 Chr = 93.67, df = 6 (P < 0.00001); r = 94%	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$

FIGURE 5 Forrest plot of subgroup analysis assessing the risk of gastrointestinal bleeding based on racial distribution

fully understood. A possible explanation could be the disturbance of the hemostasis by inhibition of coagulation factor VIIa, which is highly expressed in brain vessels, forms complexes with tissue factor and is a key initiator of the coagulation cascade,⁸ and rivaroxaban works by inhibiting clotting factor Xa, which is different from warfarin. However, whether rivaroxaban increases gastrointestinal bleeding or not is unclear yet. The reason that rivaroxaban is partially eliminated through the intestine and is a substrate for the P-glycoprotein transport system could possibly explain why there is a subtle upward trend with no statistic difference.⁹ This system actively pumps drugs into the gastrointestinal tract, allowing it to maintain a higher concentration of the active agent.¹⁰ In contrast, Warfarin is highly bioavailable and is almost entirely absorbed in the intestinal tract, whereas Warfarin is not bioactive when it is not absorbed.¹¹ Anyway, to distinguish the difference of gastrointestinal bleeding risk between two drugs requires more clinical data.

To further investigate the effects of rivaroxaban and Warfarin on bleeding in patients with AF, we performed subgroup analyses based on ethnicity. Not surprisingly, we found that rivaroxaban could significantly reduce the risk of intracranial hemorrhage in patients with AF, regardless of race, although the benefit was more pronounced in Asians. Interestingly, we found that rivaroxaban had a different effect on gastrointestinal bleeding in patients with AF among different ethnic groups, because we found that rivaroxaban could slightly reduce the risk of gastrointestinal bleeding in Asians and slightly increase the risk of gastrointestinal bleeding in Europeans and Americans, but CLINICAL

these results were not statistically significant. Thus, to explain the reason for those weak tendency, more data should be collected for further study in order to rule out individual variety. The reason for this phenomenon may be due to the fact that in Asian countries, safety concerns because of the generally lower body mass index of the population^{12,13} in addition to differential bleeding tendencies have resulted in a preference for the underdosed rivaroxaban.¹³

Previous meta-analysis have shown that rivaroxaban could significantly reduce ischemic events in patients with AF compared to warfarin.¹⁴ and in our meta-analysis, we found that rivaroxaban could reduce the risk of intracranial hemorrhage. Meanwhile, rivaroxaban have a more stable INR levels compared with warfarin because it has lower dose-response variability and less interactions.¹⁵ Besides. Patients with AF may have a better adherence to rivaroxaban than warfarin, likely due to the fact that rivaroxaban do not need constant blood monitoring.¹⁶ Despite these benefits, it is important to note that rivaroxaban may possibly increase the risk of gastrointestinal bleeding, especially in Europeans and Americans. Even though there is no statistic significance to compare gastrointestinal hemorrhage in varied ethnic groups, but we should regard it with caution to figure out whether this trend makes sense. Moreover, unlike warfarin, rivaroxaban do not currently have a widely available reversal agent and are not routinely monitored with laboratory testing,⁷ which also increase the risk of using rivaroxaban.

Our meta-analysis also has certain limitation. First of all, we initially intend to analyze the risk of major bleeding, but due to the distinction of different research in the definition of major bleeding, some on the basis of International Society of Thrombosis and Hemostasis, some on the basis of Cunningham algorithm to identify bleeding resulting in the need for hospitalization as a proxy for major bleeding. some did not mention the standard of major bleeding, so we finally analyze and intracranial hemorrhage and gastrointestinal bleeding, which is not controversial in terms of definition. Secondly, our metaanalysis included observational studies rather than randomized controlled trials, which inevitably led to heterogeneity. At the same time, the enrolled patients in each study are also different in terms of the basic characteristics (gender, age, etc.), basic diseases, basic medication, and AF scores, which may influence the clinic relevant bleeding risk. For instance, patients with cancer are often at an increasing risk for bleeding due to tumor invasion, frequent procedural interventions, endothelial dysfunction,¹⁷ and elderly patients generally have a higher prevalence of comorbidities and polypharmacy, and a higher risk of bleeding, but lower mobility for frequent laboratory monitoring, ^{18,19} It is to be noted that renal impairment is an independent risk factor for bleeding in AF patients.^{20,21} As shown in Figure 4, patients in rivaroxaban group with severe chronic renal diseases or undergoing hemodialysis exposed to less gastrointestinal hemorrhage risk than the group from warfarin. It has to be mentioned half of the rivaroxaban in the body need to be metabolized by kidney. Normal renal function could help the body to minimize the accumulation of rivaroxaban and reduce the side effect of drugs. However, cumulative medication toxicity could not be cleared by body who suffering from renal dysfunction which accounts for elevated hemorrhage rick. But

warfarin is different because of its metabolic pathway, which mostly depends on hepatic metabolism. Finally, the dose of rivaroxaban in different studies is not completely the same. Some studies may use 20 mg, some studies use 15 mg due to renal insufficiency of the included patients, and some experiments do not mention the dose of rivaroxaban, which may also affect the results of the experiments.

5 | CONCLUSION

Rivaroxaban could significantly reduce the risk of intracranial hemorrhage in patients with AF, but the risk of gastrointestinal bleeding remained controversy due to no statistical significant difference. Notably, a subgroup analysis demonstrated that patients in rivaroxaban group with severe chronic renal diseases or undergoing hemodialysis exposed to less gastrointestinal hemorrhage risk than the group from warfarin.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

All data included in this study are available upon request by contact with the corresponding author.

ORCID

Hongcheng Jiang b https://orcid.org/0000-0001-9382-847X

REFERENCE

- 1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke*. 1991;22(8): 983-988.
- Ufer M. Comparative pharmacokinetics of vitamin K antagonists: warfarin, phenprocoumon and acenocoumarol. *Clin Pharmacokinet*. 2005; 44(12):1227-1246.
- Barrios V, Escobar C, Calderón A, Rodríguez Roca GC, Llisterri JL, Polo García J. Use of antithrombotic therapy according to CHA2DS2-VASc score in patients with atrial fibrillation in primary care. *Rev Esp Cardiol (Engl Ed)*. 2014;67(2):150-151.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-1151.
- Szczerba E, Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10): 883-891.
- Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11): 981-992.
- Cuker A, Siegal DM, Crowther MA, Garcia DA. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. J Am Coll Cardiol. 2014;64(11):1128-1139.
- Mackman N. The role of tissue factor and factor VIIa in hemostasis. Anesth Analg. 2009;108(5):1447-1452.
- 9. Scaglione F. New oral anticoagulants: comparative pharmacology with vitamin K antagonists. *Clin Pharmacokinet*. 2013;52(2):69-82.
- Sherwood MW, Nessel CC, Hellkamp AS, et al. Gastrointestinal bleeding in patients with atrial fibrillation treated with rivaroxaban or

warfarin: ROCKET AF trial. J Am Coll Cardiol. 2015;66(21):2271-2281.

- 11. Weitz JI. New oral anticoagulants: a view from the laboratory. *Am J Hematol.* 2012;87(Suppl 1):S133-S136.
- 12. Chan YH, Yen KC, See LC, et al. Cardiovascular, bleeding, and mortality risks of Dabigatran in Asians with nonvalvular atrial fibrillation. *Stroke*. 2016;47(2):441-449.
- Chan YH, Kuo CT, Yeh YH, et al. Thromboembolic, bleeding, and mortality risks of rivaroxaban and Dabigatran in Asians with Nonvalvular atrial fibrillation. J Am Coll Cardiol. 2016;68(13):1389-1401.
- 14. Escobar C et al. Direct Oral anticoagulants versus vitamin K antagonists in real-life patients with atrial fibrillation. A systematic review and meta-analysis. *Rev Esp Cardiol (Engl Ed)*. 2019;72(4):305-316.
- Gong IY, Kim RB. Importance of pharmacokinetic profile and variability as determinants of dose and response to dabigatran, rivaroxaban, and apixaban. *Can J Cardiol.* 2013;29(7):S24-S33.
- Di Lullo L, Ronco C, Cozzolino M, et al. Nonvitamin K-dependent oral anticoagulants (NOACs) in chronic kidney disease patients with atrial fibrillation. *Thromb Res.* 2017;155:38-47.
- 17. Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. J Am Coll Cardiol. 2014;63(10):945-953.
- Halperin JL, Hankey GJ, Wojdyla DM, et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the rivaroxaban once daily, Oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Circulation*. 2014;130(2):138-146.

- Lavan AH, Gallagher PF, O'Mahony D. Methods to reduce prescribing errors in elderly patients with multimorbidity. *Clin Interv Aging*. 2016; 11:857-866.
- Go AS, Fang MC, Udaltsova N, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation*. 2009;119(10):1363-1369.
- 21. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish atrial fibrillation cohort study. *Eur Heart J*. 2012;33(12):1500-1510.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Jiang H, Jiang Y, Ma H, Zeng H, Lv J. Effects of rivaroxaban and warfarin on the risk of gastrointestinal bleeding and intracranial hemorrhage in patients with atrial fibrillation: Systematic review and metaanalysis. *Clin Cardiol.* 2021;44(9):1208-1215. <u>https://doi.org/</u> 10.1002/clc.23690