Original article

Direct Oral Anticoagulants Versus Vitamin K Antagonists in Real-life Patients With Atrial Fibrillation. A Systematic Review and Meta-analysis



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Article history: Received 27 October 2017 Accepted 2 March 2018 Available online 30 March 2018

Keywords: Apixaban Atrial fibrillation Clinical practice Dabigatran Direct oral anticoagulants Meta-analysis Rivaroxaban Warfarin

Palabras clave: Apixabán Fibrilación auricular Práctica clínica Dabigatrán Anticoagulantes orales directos Metanálisis Rivaroxabán Warfarina

ABSTRACT

Introduction and objectives: To assess the effectiveness of direct oral anticoagulants vs vitamin K antagonists in real-life patients with atrial fibrillation.

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

Results: A total of 27 different studies publishing data in 30 publications were included. In the studies with a follow-up up to 1 year, apixaban (HR, 0.93; 95%CI, 0.71-1.20) and dabigatran (HR, 0.95; 95%CI, 0.80-1.13) did not significantly reduce the risk of ischemic stroke vs warfarin, whereas rivaroxaban significantly reduced this risk (HR, 0.83; 95%CI, 0.73-0.94). Apixaban (HR, 0.66; 95%CI, 0.55-0.80) and dabigatran (HR, 0.83; 95%CI, 0.70-0.97) significantly reduced the major bleeding risk vs warfarin, but not rivaroxaban (HR, 1.02; 95%CI, 0.95-1.10), although with a high statistical heterogeneity among studies. Apixaban (HR, 0.56; 95%CI, 0.42-0.73), dabigatran (HR, 0.45; 95%CI, 0.39-0.51), and rivaroxaban (HR, 0.66; 95%CI, 0.49-0.88) significantly reduced the risk of intracranial bleeding vs warfarin. Reduced doses of direct oral anticoagulants were associated with a slightly better safety profile, but with a marked reduction in stroke prevention effectiveness.

Conclusions: Data from this meta-analysis suggest that, vs warfarin, the stroke prevention effectiveness and bleeding risk of direct oral anticoagulants may differ in real-life patients with atrial fibrillation. © 2018 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

Anticoagulantes orales directos frente a antagonistas de la vitamina K en pacientes con fibrilación auricular de la práctica clínica: revisión sistemática y metanálisis

RESUMEN

Introducción y objetivos: Determinar la efectividad de los anticoagulantes orales directos frente a los antagonistas de la vitamina K en pacientes con fibrilación auricular de la práctica clínica. *Métodos:* Se realizó una revisión sistemática acorde con los estándares metodológicos de Cochrane. Los resultados de la revisión se publicaron según la declaración PRISMA. Se empleó la herramienta ROBINS-I

para determinar el riesgo de sesgos. *Resultados:* Se incluyeron datos de 27 estudios diferentes provenientes de 30 publicaciones. En los estudios con seguimiento hasta 1 año, el apixabán (HR = 0,93; IC95%, 0,71-1,20) y dabigatrán (HR = 0,95; IC95%, 0,80-1,13) no se redujo significativamente el riesgo de ictus isquémico frente a la warfarina, pero sí el rivaroxabán (HR = 0,83; IC95%, 0,73-0,94). Con respecto al riesgo de hemorragias mayores, el apixabán (HR = 0,66; IC95%, 0,55-0,80) y el dabigatrán (HR = 0,83; IC95%, 0,70-0,97) lo redujeron significativamente frente a la warfarina, pero no el rivaroxabán (HR = 1,02, IC95%, 0,95-1,10), aunque con heterogeneidad entre los estudios. El apixabán (HR = 0,56; IC95%, 0,42-0,73), el dabigatrán (HR = 0,45; IC95%, 0,39-0,51) y el rivaroxabán (HR = 0,66; IC95%, 0,49-0,88) redujeron significativamente el riesgo de hemorragia intracraneal frente a la warfarina. El empleo de dosis bajas de anticoagulantes orales directos se asoció con una ligera mejoría del perfil de seguridad, pero con una marcada reducción de la efectividad en la prevención de ictus.

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https://doi.org/10.1016/j.rec.2018.03.009

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Conclusiones: Los resultados de este metanálisis indican que, en comparación con la warfarina, la efectividad para prevenir el riesgo de ictus y de hemorragias de los anticoagulantes orales directos en los pacientes con fibrilación auricular de la práctica clínica real puede ser diferente.

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Abbreviations

AF: atrial fibrillation DOACs: direct oral anticoagulants VKAs: vitamin K antagonists

INTRODUCTION

Atrial fibrillation (AF), the most common arrhythmia in clinical practice,¹ is associated with a markedly increased risk of stroke. AF-associated stroke has a higher risk of death, disability, and recurrence.² A cornerstone in the prevention of thromboembolic complications in patients with AF is anticoagulation.³ Although vitamin K antagonists (VKAs) are associated with a 60% reduction in the risk of stroke in AF patients,⁴ they have many disadvantages that have limited their use in clinical practice, including a narrow therapeutic window, multiple interactions with other drugs and foods, and the need for frequent monitoring of anticoagulant activity and for dosage adjustments.⁵

Direct oral anticoagulants (DOACs) overcome most of these limitations. In addition, a number of phase III clinical trials have shown that DOACs are at least as effective as VKAs for the prevention of stroke or systemic embolism, but have a better safety profile, particularly regarding the risk of intracranial bleeding.^{6–8}

The introduction of DOACs to routine clinical practice has been associated with improved rates of overall oral anticoagulation use in patients with AF.⁹ Due to strict clinical trial inclusion and exclusion criteria and closer patient follow-up, patients with AF participating in clinical trials frequently differ from those in clinical practice. Thus, the information reported in randomized clinical trials is not always valid for real-life patients.^{10,11} In the last few years, many claims database studies have analyzed the use of DOACs in AF in clinical practice. However, discrepancies between data sources, the statistical analysis approach, and patient characteristics can lead to conflicting results. In this context, a comprehensive analysis of all published information on the use of DOACs in patients with AF vs VKAs is of great interest. The aim of this systematic review and meta-analysis was to assess the effectiveness and safety of DOACs (apixaban, dabigatran, and rivaroxaban) vs VKAs in real-life patients with nonvalvular AF.

METHODS

A systematic review was performed according to Cochrane methodological standards.¹² Results were reported according to the PRISMA statement.¹³ The review protocol is detailed in the Methods section of the supplementary material. C. Escobar and J. Martí-Almor selected the articles to be included. If there was disagreement, a third researcher, A. Pérez Cabeza, was consulted. All authors were responsible for data extraction. M.J. Martínez-Zapata was responsible for data analysis. All authors were involved in writing the manuscript.

Eligibility Criteria

We included observational controlled studies in patients diagnosed with nonvalvular AF comparing any DOAC (apixaban, dabigatran, or rivaroxaban; any dose) vs VKAs (focusing on warfarin). Only studies that reported rates and effect measures (hazard ratios [HRs]) were included in this meta-analysis. Inclusion was limited to observational studies (either prospective or retrospective) reporting on any of the abovementioned efficacy and safety outcomes from routinely collected health data. Studies with national or regional registries or registries covering a large population across multiple sites were included. Single-center studies using local registries were excluded unless they had more than 1000 patients. For studies that used the same registry and were conducted in the same period (or with substantial overlap), the most complete publication was selected. Only when the degree of overlap between studies was minimal were all publications included.

Outcomes

The outcomes of interest are detailed in the protocol described in the Methods section of the supplementary material. We prioritized ischemic stroke and the composite end point of stroke/systemic embolism for efficacy and major and intracranial bleeding for safety. All outcomes were assessed according to follow-up duration (up to 1 year, as well as longer) and anticoagulant dose (standard vs reduced).

Search Strategy

To retrieve studies of interest, a MEDLINE (via PubMed) and EMBASE (via Ovid) search was performed up to March 2017. Search algorithms adapted to the requirements of each database were designed; these algorithms included a combination of controlled vocabulary search terms and filters to retrieve clinical trials and cohort studies (Table 1 of the supplementary material). In addition, the bibliography sections of the retrieved eligible studies were further used to identify additional relevant studies. No temporal or linguistic limitations were applied to the searches.

For the study selection, search results were screened based on the title and abstract independently. Full-text versions of the articles deemed to be eligible were retrieved and eligibility was independently confirmed based on the inclusion criteria. Disagreements were resolved by reaching consensus or by consulting a third researcher. Results were imported into a PRISMA flowchart. For data collection, relevant data from eligible studies were extracted and crosschecked for accuracy.

Risk of Bias Assessment

The ROBINS-I tool was used to assess the risk of bias of the included studies.¹⁴ For each study, the confounding bias was assessed regarding the selection, measurement interventions, deviations from intended interventions, missing data, outcome assessment, and selection of reported results. The original ROBINS-I tool was adapted to fit the design and specificities of the included studies (Table 2 of the supplementary material).

Data Analysis and Summary of Findings

When feasible, a pooled analysis was conducted by applying the Cochran-Mantel-Haenszel method under a random-effects model using Review Manager Software (version 5.3.5). Heterogeneity and sources of variation between studies were assessed through the l^2 statistic. Findings were reported according to a narrative synthesis for each outcome of interest and its effect estimate.

RESULTS

The PRISMA flowchart is shown in Figure 1. A total of 4244 references were obtained from MEDLINE and EMBASE searches. After duplicate elimination, 3391 unique references were screened. Of the 3391 unique references, 3312 were excluded based on their title or abstract because they had no relationship with the outcomes of this systematic review. Of these, full texts were obtained for 79 studies. After a detailed assessment of the full texts, 49 studies were excluded. Finally, 27 different studies with published data in 30 publications were included (3 studies published relevant data in 2 separate articles).^{15–45} The characteristics of the included studies are summarized in Table 3 of the supplementary material.

Data from AF patients treated with DOACs vs VKAs up to about 1 year are shown in Figure 2.

Ischemic Stroke

Apixaban and dabigatran did not reduce the risk of ischemic stroke vs warfarin (HR, 0.93; 95% confidence interval [95%CI],

0.71-1.20; HR, 0.95; 95%CI, 0.80-1.13; respectively). Statistical heterogeneity was high among studies. In contrast, rivaroxaban significantly reduced the risk of ischemic stroke vs warfarin (HR, 0.83; 95%CI, 0.73-0.94). This finding was highly consistent among studies (Figure 2A).

Ischemic Stroke Plus Systemic Embolism

Apixaban did not reduce the risk of an ischemic event (stroke/ systemic embolism) vs warfarin (HR, 0.88; 95%CI, 0.64-1.21). Statistical heterogeneity was high among studies yielding conflicting results. Dabigatran did not reduce the risk of an ischemic event (stroke/systemic embolism) vs warfarin (HR, 0.92; 95%CI, 0.76-1.11). Rivaroxaban significantly reduced the risk of an ischemic event vs warfarin (HR, 0.80; 95%CI, 0.69-0.93), a finding consistent among studies. Overall, only 1 small study compared DOACs with warfarin with regard to ischemic events, with no significant differences between the 2 groups (HR, 0.44; 95%CI, 0.09-2.04) (Figure 2B).

Major Bleeding

A risk reduction was observed in major bleeding with apixaban and dabigatran vs warfarin (HR, 0.66; 95%CI, 0.55-0.80; HR, 0.83; 95%CI, 0.70-0.97; respectively), but statistical heterogeneity was



Figure 1. PRISMA eligibility flowchart.

high among studies. Rivaroxaban did not show a reduction in the risk of major bleeding vs warfarin (HR, 1.02; 95%CI, 0.95-1.10) (Figure 2C).

Intracranial Hemorrhage

Apixaban, dabigatran, and rivaroxaban (HR, 0.56; 95%CI, 0.42-0.73; HR, 0.45; 95%CI, 0.39-0.51; HR, 0.66; 95%CI, 0.49-0.88; respectively) significantly reduced the risk of intracranial bleeding vs warfarin (Figure 2D).

Only 4 studies reported results from more than 1 year (Larsen et al.,³⁶ Nielsen et al.,³⁹ Li et al.,³⁷ Avgil-Tsadok et al.¹⁶). Larsen et al.³⁶ and Nielsen et al.³⁹ reported data on all of the above outcomes but Li et al.³⁷ and Avgil-Tsadok et al.¹⁶ only considered some of them. Compared with studies up to about 1 year of follow-up, the results were unchanged except for apixaban in the outcome "intracranial hemorrhage" and for dabigatran in the outcome "major bleeding"; in these instances, the initially observed significant risk reduction was lost (Figure of the supplementary material).

				NA/			
Study or Subgroup	log[HR]	SE	Total	Warfarir : Total		HR IV, Random, 95%C	HR I IV, Random, 95%CI
Apixaban							
Coleman et al. ²²	0.122	0.42	4083	4083	6.8%	1.13 [0.49-2.61]	
Forslund et al. ²⁴	-0.186	0.19	3587	12919	15.8%	0.83 [0.57-1.21]	
Larsen et al. ³⁶	0.100	0.08	6349	35436		1.11 [0.94-1.31]	+=-
Li et al. ³⁷	-0.400	0.07	38470	38470		0.67 [0.58-0.77]	
Nielsen et al. ³⁹	0.173	0.07	4400	38893		1.19 [0.95-1.49]	
Yao et al. ⁴⁵	-0.183		15390	51390	13.8%	0.83 [0.53-1.30]	_
Subtotal (95%CI)	-0.105	0.22		181191		0.93 [0.71-1.20]	\sim
Heterogeneity: Tau ² =	= 0 07 [.] chi-sa	are = 2					Ť
Test for overall effect			0.55, ui ·	- 5 (7	0001), 7 -	- 05 /0	
	Z = 0.59 (F	50)					
Dabigatran							
Bengtson et al. ¹⁷	0.182	0.12	13937	63460	9.1%	1.20 [0.95-1.52]	+
Bengtson et al. ¹⁷	-0.430	0.11	18891	37707	9.2%	0.65 [0.52-0.81]	
Chan et al. ¹⁹	-0.342	0.15	5921	5251	8.3%	0.71 [0.53-0.95]	
Forslund et al. ²⁴	-0.174	0.17	3322	12919	7.7%	0.84 [0.60-1.18]	
Graham et al. ²⁶	-0.223		67207	67207	9.8%	0.80 [0.67-0.96]	
Larsen et al. rdcd ³⁵	0.548	0.18	412	1918	7.4%	1.73 [1.21-2.47]	
Larsen et al. stnd ³⁵	0.582	0.21	547	1918	6.6%	1.79 [1.18-2.72]	
Larsen et al. ³⁶	0.215	0.14	12701	35436	8.5%	1.24 [0.94-1.64]	
Nielsen et al. ³⁹	-0.083	0.07	8875	38893	10.1%	0.92 [0.79-1.07]	
Seeger et al. ⁴²	-0.597	0.20	15529	15529	6.9%	0.55 [0.37-0.82]	F
Villines et al. ⁴⁴	-0.174		12793	12793	8.1%	0.84 [0.62-1.14]	e
Yao et al. ⁴⁵	0.058		28614	28614	8.3%	1.06 [0.79-1.42]	
Subtotal (95%CI)	0.000		188749			• •	\rightarrow
						0 95 10 80-1 131	
Heterogeneity: Tau ² =	= 0 07 [.] chi-sa					0.95 [0.80-1.13] l ² = 80%	Ĭ
Heterogeneity: Tau ² = Test for overall effect		uare = 5					
Test for overall effect		uare = 5					
Test for overall effect Rivaroxaban	:: Z = 0.56 (P	uare = 5 = .57)	3.92, df	= 11 (<i>P</i> <	.00001);	<i>f</i> ² = 80%	Ĭ
Test for overall effect Rivaroxaban Chan et al. ¹⁹	: Z = 0.56 (P -0.562	uare = 5 = .57) 0.20	3.92, df 3916	= 11 (<i>P</i> < 5251	.00001); 8.5%	ť = 80% 0.57 [0.38-0.85]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²²	: Z = 0.56 (P -0.562 -0.342	uare = 5 = .57)	3.92, df	= 11 (<i>P</i> <	8.5% 8.2%	f [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴	-0.562 -0.342 -0.356	uare = 5 = .57) 0.20	3.92, df 3916	= 11 (<i>P</i> < 5251	.00001); 8.5%	ť = 80% 0.57 [0.38-0.85]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³	: Z = 0.56 (P -0.562 -0.342	uare = 5 = .57) 0.20 0.21	3.92, df 3916 11411	= 11 (<i>P</i> < 5251 11411	8.5% 8.2%	f [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³ Larsen et al. ³⁶	-0.562 -0.342 -0.356	uare = 5 = .57) 0.20 0.21 0.21	3.92, df 3916 11411 2370	= 11 (<i>P</i> < 5251 11411 12919	8.5% 8.2% 8.0%	<i>f</i> [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07] 0.70 [0.46-1.07]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³ Larsen et al. ³⁶ Nielsen et al. ³⁹	-0.562 -0.342 -0.356 -0.212	uare = 5 = .57) 0.20 0.21 0.21 0.18	3.92, df 3916 11411 2370 3654	= 11 (<i>P</i> < 5251 11411 12919 14616	8.5% 8.2% 8.0% 11.0%	f [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07] 0.70 [0.46-1.07] 0.81 [0.57-1.15]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³ Larsen et al. ³⁶	-0.562 -0.342 -0.356 -0.212 -0.150	uare = 5 = .57) 0.20 0.21 0.21 0.21 0.18 0.09	3.92, df 3916 11411 2370 3654 7192	= 11 (<i>P</i> < 5251 11411 12919 14616 35436	8.5% 8.2% 8.0% 11.0% 32.4%	f [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07] 0.70 [0.46-1.07] 0.81 [0.57-1.15] 0.86 [0.72-1.03]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³ Larsen et al. ³⁶ Nielsen et al. ³⁹	-0.562 -0.342 -0.356 -0.212 -0.150 -0.072	uare = 5 = .57) 0.20 0.21 0.21 0.21 0.18 0.09 0.14	3.92, df 3916 11411 2370 3654 7192 3476 32350	= 11 (<i>P</i> < 5251 11411 12919 14616 35436 38893	8.5% 8.2% 8.0% 11.0% 32.4% 17.3% 14.7%	f [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07] 0.70 [0.46-1.07] 0.81 [0.57-1.15] 0.86 [0.72-1.03] 0.93 [0.71-1.22]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³ Larsen et al. ³⁶ Nielsen et al. ³⁹ Yao et al. ⁴⁵	-0.562 -0.342 -0.356 -0.212 -0.150 -0.072 0.010	uare = 5 = .57) 0.20 0.21 0.21 0.18 0.09 0.14 0.15	3.92, df 3916 11411 2370 3654 7192 3476 32350 64369	= 11 (<i>P</i> < 5251 11411 12919 14616 35436 38893 32350 150876	8.5% 8.2% 8.0% 11.0% 32.4% 17.3% 14.7% 100.0%	f [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07] 0.70 [0.46-1.07] 0.81 [0.57-1.15] 0.86 [0.72-1.03] 0.93 [0.71-1.22] 1.01 [0.75-1.36] 0.83 [0.73-0.94]	
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Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³ Larsen et al. ³⁶ Nielsen et al. ³⁹ Yao et al. ⁴⁵ Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect:	-0.562 -0.342 -0.356 -0.212 -0.150 -0.072 0.010 = 0.00; chi-squ	uare = 5 = .57) 0.20 0.21 0.21 0.18 0.09 0.14 0.15 uare = 6	3.92, df 3916 11411 2370 3654 7192 3476 32350 64369	= 11 (<i>P</i> < 5251 11411 12919 14616 35436 38893 32350 150876	8.5% 8.2% 8.0% 11.0% 32.4% 17.3% 14.7% 100.0%	f [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07] 0.70 [0.46-1.07] 0.81 [0.57-1.15] 0.86 [0.72-1.03] 0.93 [0.71-1.22] 1.01 [0.75-1.36] 0.83 [0.73-0.94]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³ Larsen et al. ³⁶ Nielsen et al. ³⁹ Yao et al. ⁴⁵ Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: All DOAC	: Z = 0.56 (P -0.562 -0.342 -0.356 -0.212 -0.150 -0.072 0.010 = 0.00; chi-squ Z = 2.97 (P =	Jare = 5 = .57) 0.20 0.21 0.21 0.18 0.09 0.14 0.15 Jare = 6 = .003)	3.92, df 3916 11411 2370 3654 7192 3476 32350 64369 .99, df =	= 11 (<i>P</i> < 5251 11411 12919 14616 35436 38893 32350 150876 6 (<i>P</i> = .3	.00001); 8.5% 8.2% 8.0% 11.0% 32.4% 17.3% 14.7% 100.0% 2); f = 14	f [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07] 0.70 [0.46-1.07] 0.81 [0.57-1.15] 0.86 [0.72-1.03] 0.93 [0.71-1.22] 1.01 [0.75-1.36] 0.83 [0.73-0.94]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³ Larsen et al. ³⁶ Nielsen et al. ³⁹ Yao et al. ⁴⁵ Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: All DOAC Forslund et al. ²⁴	Z = 0.56 (P) -0.562 -0.342 -0.356 -0.212 -0.150 -0.072 0.010 = 0.00; chi-squ Z = 2.97 (P) = -0.210	Jare = 5 = .57) 0.20 0.21 0.21 0.21 0.18 0.09 0.14 0.15 Jare = 6 = .003) 0.12	3.92, df 3916 11411 2370 3654 7192 3476 32350 64369 .99, df = 9272	= 11 (<i>P</i> < 5251 11411 12919 14616 35436 38893 32350 150876 6 (<i>P</i> = .3	.00001); 8.5% 8.2% 8.0% 11.0% 32.4% 14.7% 100.0% 2); f = 14 73.6%	f [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07] 0.70 [0.46-1.07] 0.81 [0.57-1.15] 0.86 [0.72-1.03] 0.93 [0.71-1.22] 1.01 [0.75-1.36] 0.83 [0.73-0.94] !%	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³ Larsen et al. ³⁶ Nielsen et al. ³⁹ Yao et al. ⁴⁵ Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: All DOAC Forslund et al. ²⁴ Gieling et al. ²⁵	: Z = 0.56 (P -0.562 -0.342 -0.356 -0.212 -0.150 -0.072 0.010 = 0.00; chi-squ Z = 2.97 (P =	Jare = 5 = .57) 0.20 0.21 0.21 0.21 0.18 0.09 0.14 0.15 Jare = 6 = .003) 0.12	3.92, df 3916 11411 2370 3654 7192 3476 32350 64369 .99, df = 9272 1306	= 11 (<i>P</i> < 5251 11411 12919 14616 35436 38893 32350 150876 6 (<i>P</i> = .3 12919 13643	.00001); 8.5% 8.2% 8.0% 11.0% 32.4% 14.7% 100.0% 2); f = 14 73.6% 26.4%	f [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07] 0.70 [0.46-1.07] 0.81 [0.57-1.15] 0.86 [0.72-1.03] 0.93 [0.71-1.22] 1.01 [0.75-1.36] 0.83 [0.73-0.94] !% 0.81 [0.64-1.03] 1.22 [0.67-2.22]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³ Larsen et al. ³⁶ Nielsen et al. ³⁹ Yao et al. ⁴⁵ Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: All DOAC Forslund et al. ²⁴ Gieling et al. ²⁵ Subtotal (95%CI)	Z = 0.56 (P) -0.562 -0.342 -0.356 -0.212 -0.150 -0.072 0.010 = 0.00; chi-squ Z = 2.97 (P) = -0.210 0.198	Jare = 5 = .57) 0.20 0.21 0.21 0.18 0.09 0.14 0.15 Jare = 6 = .003) 0.12 0.30	3.92, df 3916 11411 2370 3654 7192 3476 32350 64369 .99, df = 9272 1306 10578	= 11 (<i>P</i> < 5251 11411 12919 14616 35436 38893 32350 150876 6 (<i>P</i> = .3 12919 13643 26562	.00001); 8.5% 8.2% 8.0% 11.0% 32.4% 17.3% 14.7% 100.0% 2); f = 14 73.6% 26.4% 100.0%	f [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07] 0.70 [0.46-1.07] 0.81 [0.57-1.15] 0.86 [0.72-1.03] 0.93 [0.71-1.22] 1.01 [0.75-1.36] 0.83 [0.73-0.94] 1.22 [0.64-1.03] 1.22 [0.67-2.22] 0.90 [0.63-1.29]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³ Larsen et al. ³⁶ Nielsen et al. ³⁹ Yao et al. ⁴⁵ Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: All DOAC Forslund et al. ²⁴ Gieling et al. ²⁵ Subtotal (95%CI) Heterogeneity: Tau ² =	Z = 0.56 (P) -0.562 -0.342 -0.356 -0.212 -0.150 -0.072 0.010 = 0.00; chi-squ Z = 2.97 (P) -0.210 0.198 = 0.03; chi-squ	Jare = 5 = .57) 0.20 0.21 0.21 0.18 0.09 0.14 0.15 Jare = 6 = .003) 0.12 0.30 Jare = 1	3.92, df 3916 11411 2370 3654 7192 3476 32350 64369 .99, df = 9272 1306 10578	= 11 (<i>P</i> < 5251 11411 12919 14616 35436 38893 32350 150876 6 (<i>P</i> = .3 12919 13643 26562	.00001); 8.5% 8.2% 8.0% 11.0% 32.4% 17.3% 14.7% 100.0% 2); f = 14 73.6% 26.4% 100.0%	f [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07] 0.70 [0.46-1.07] 0.81 [0.57-1.15] 0.86 [0.72-1.03] 0.93 [0.71-1.22] 1.01 [0.75-1.36] 0.83 [0.73-0.94] 1.22 [0.64-1.03] 1.22 [0.67-2.22] 0.90 [0.63-1.29]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³ Larsen et al. ³⁶ Nielsen et al. ³⁹ Yao et al. ⁴⁵ Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: All DOAC Forslund et al. ²⁴ Gieling et al. ²⁵ Subtotal (95%CI)	Z = 0.56 (P) -0.562 -0.342 -0.356 -0.212 -0.150 -0.072 0.010 = 0.00; chi-squ Z = 2.97 (P) -0.210 0.198 = 0.03; chi-squ	Jare = 5 = .57) 0.20 0.21 0.21 0.18 0.09 0.14 0.15 Jare = 6 = .003) 0.12 0.30 Jare = 1	3.92, df 3916 11411 2370 3654 7192 3476 32350 64369 .99, df = 9272 1306 10578	= 11 (<i>P</i> < 5251 11411 12919 14616 35436 38893 32350 150876 6 (<i>P</i> = .3 12919 13643 26562	.00001); 8.5% 8.2% 8.0% 11.0% 32.4% 17.3% 14.7% 100.0% 2); f = 14 73.6% 26.4% 100.0%	f [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07] 0.70 [0.46-1.07] 0.81 [0.57-1.15] 0.86 [0.72-1.03] 0.93 [0.71-1.22] 1.01 [0.75-1.36] 0.83 [0.73-0.94] 1.22 [0.64-1.03] 1.22 [0.67-2.22] 0.90 [0.63-1.29]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³ Larsen et al. ³⁶ Nielsen et al. ³⁹ Yao et al. ⁴⁵ Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: All DOAC Forslund et al. ²⁴ Gieling et al. ²⁵ Subtotal (95%CI) Heterogeneity: Tau ² =	Z = 0.56 (P) -0.562 -0.342 -0.356 -0.212 -0.150 -0.072 0.010 = 0.00; chi-squ Z = 2.97 (P) -0.210 0.198 = 0.03; chi-squ	Jare = 5 = .57) 0.20 0.21 0.21 0.18 0.09 0.14 0.15 Jare = 6 = .003) 0.12 0.30 Jare = 1	3.92, df 3916 11411 2370 3654 7192 3476 32350 64369 .99, df = 9272 1306 10578	= 11 (<i>P</i> < 5251 11411 12919 14616 35436 38893 32350 150876 6 (<i>P</i> = .3 12919 13643 26562	.00001); 8.5% 8.2% 8.0% 11.0% 32.4% 17.3% 14.7% 100.0% 2); f = 14 73.6% 26.4% 100.0%	f [*] = 80% 0.57 [0.38-0.85] 0.71 [0.47-1.07] 0.70 [0.46-1.07] 0.81 [0.57-1.15] 0.86 [0.72-1.03] 0.93 [0.71-1.22] 1.01 [0.75-1.36] 0.83 [0.73-0.94] 1.22 [0.64-1.03] 1.22 [0.67-2.22] 0.90 [0.63-1.29]	
Test for overall effect Rivaroxaban Chan et al. ¹⁹ Coleman et al. ²² Forslund et al. ²⁴ Laliberté et al. ³³ Larsen et al. ³⁶ Nielsen et al. ³⁹ Yao et al. ⁴⁵ Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: All DOAC Forslund et al. ²⁴ Gieling et al. ²⁵ Subtotal (95%CI) Heterogeneity: Tau ² =	Z = 0.56 (P) -0.562 -0.342 -0.356 -0.212 -0.150 -0.072 0.010 = 0.00; chi-squ Z = 2.97 (P) -0.210 0.198 = 0.03; chi-squ Z = 0.57 (P)	Jare = 5 = .57) 0.20 0.21 0.21 0.18 0.09 0.14 0.15 Jare = 6 = .003) 0.12 0.30 Jare = 1 = .57)	3.92, df 3916 11411 2370 3654 7192 3476 32350 64369 .99, df = 9272 1306 10578 .55, df =	= 11 (<i>P</i> < 5251 11411 12919 14616 35436 38893 32350 150876 6 (<i>P</i> = .3 12919 13643 26562 1 (<i>P</i> = .2	.00001); 8.5% 8.2% 8.0% 11.0% 32.4% 14.7% 100.0% 2); f = 14 73.6% 26.4% 100.0% 1); f = 36	$f^{*} = 80\%$ 0.57 [0.38-0.85] 0.71 [0.47-1.07] 0.70 [0.46-1.07] 0.81 [0.57-1.15] 0.86 [0.72-1.03] 0.93 [0.71-1.22] 1.01 [0.75-1.36] 0.83 [0.73-0.94] 1.22 [0.67-2.22] 0.90 [0.63-1.29] 3%	0.5 1 2 DOAC Favors Warfa

Figure 2. HRs with 95%CIs for ischemic stroke (A), ischemic stroke plus systemic embolism (B), major bleeding (C), and intracranial hemorrhage (D) in patients with AF treated with DOACs vs VKAs up to about 1 year. 95%CI, 95% confidence interval; AF, atrial fibrillation; DOACs, direct oral anticoagulants; HR, hazard ratio; IV, interval variable; SE, systemic embolism.

В **DOAC** Warfarin HR HR Study or Subgroup log[HR] SE Total Total Weight IV, Random, 95%CI IV, Random, 95%CI Apixaban Larsen et al.36 1.08 [0.91-1.28] 0.076 0.08 7192 35436 26.6% Li et al.37 -0.400 0.06 17801 15461 27.6% 0.67 [0.59-0.76] Nielsen et al.39 0.173 0.11 4400 38893 25.2% 1.19 [0.95-1.49] Yao et al.45 -0.400 0.19 32350 32350 20.6% 0.67 [0.46-0.98] Subtotal (95%CI) 61743 122140 100.0% 0.88 [0.64-1.21] Heterogeneity: Tau² = 0.09; chi-square = 30.99, df = 3 (P < .00001); $l^2 = 90\%$ Test for overall effect: Z = 0.79 (P = .43)Dabigatran Bouillon et al.¹⁸ 10705 11.5% 0.095 0.23 4370 1.10 [0.70-1.73] Chan et al.¹⁹ -0.446 0.13 5251 20.1% 0.64 [0.49-0.84] 5921 Larsen et al.36 0.157 12701 35436 19.7% 1.17 [0.89-1.54] 0.14 Nielsen et al.39 -0.116 0.07 8875 38893 27.9% 0.89 [0.77-1.03] Yao et al.45 -0.020 0.13 28614 28614 20.8% 0.98 [0.76-1.26] Subtotal (95%CI) 60481 118899 100.0% 0.92 [0.76-1.11] Heterogeneity: Tau² = 0.03; chi-square = 11.00, df = 4 (P = .03); l^2 = 64% Test for overall effect: Z = 0.87 (P = .38)Rivaroxaban Bouillon et al.18 4.7% -0.2871 0.34 2335 10705 0.75 [0.39-1.44] Chan et al.19 -0.673 0 19 3916 5251 12.0% 0.51 [0.35-0.74] Laliberté et al.33 3654 -0.261 0 17 14616 14.2% 0.77 [0.55-1.08] Larsen et al.³⁶ -0.186 35436 28.4% 0.09 7192 0.83 [0.69-1.00] Nielsen et al.39 -0.116 0.13 3476 38893 20.4% 0.89 [0.69-1.15] Yao et al.45 -0.072 0.13 32350 32350 20.3% 0.93 [0.72-1.20] Subtotal (95%CI) 52923 137251 100.0% 0.80 [0.69-0.93] Heterogeneity: Tau² = 0.01; chi-square = 7.65, df = 5 (P = .18); l^2 = 35% Test for overall effect: Z = 2.92 (P = .003)All DOAC Arihiro et al.15 -0.821 0.78 475 662 100.0% 0.44 [0.09-2.04] Subtotal (95%CI) 475 662 100.0% 0.44 [0.09-2.04] Heterogeneity: Not applicable Test for overall effect: Z = 1.05 (P = .29) 0.05 0.2 20 5 Favors DOAC Favors Warfarin Test for subgroup differences: chi-square = 2.02, df = 3 (P = .57), l^2 = 0%



Data on ischemic stroke, major bleeding, and intracranial hemorrhage in patients with AF and treated with DOACs vs VKAs are shown in Figure 3 according to DOAC dose (standard and reduced).

Ischemic Stroke

Standard Dose

Compared with warfarin, treatment with standard doses of apixaban did not reduce the risk of ischemic stroke (HR, 1.11; 95%CI, 0.94-1.31). In addition, treatment with standard doses of dabigatran did not reduce the risk of ischemic stroke (HR, 0.97; 95%CI, 0.68-1.38). However, statistical heterogeneity was high among studies. Treatment with standard doses of rivaroxaban reduced the risk of ischemic stroke vs warfarin (HR, 0.86; 95%CI, 0.72-1.03) (Figure 3A).

Reduced Dose

Compared with warfarin, reduced doses of apixaban, dabigatran, or rivaroxaban did not decrease the risk of ischemic stroke (HR, 1.19; 95%Cl, 0.95-1.49; HR, 0.94; 95%Cl, 0.66-1.36; HR, 0.93; 95%Cl, 0.71-1.22; respectively) (Figure 3A).

Major Bleeding

Standard Dose

Compared with warfarin, standard doses of apixaban reduced the risk of major bleeding (HR, 0.55; 95%CI, 0.45-0.66). Treatment with standard doses of dabigatran and rivaroxaban did not reduce the risk of major bleeding (HR, 0.85; 95%CI, 0.61-1.19; HR, 1.02; 95%CI, 0.92-1.12; respectively) (Figure 3B).

Reduced Dose

Compared with warfarin, reduced doses of apixaban did not reduce the risk of major bleeding (HR, 0.75; 95%CI, 0.49-1.15). However, statistical heterogeneity was high among studies. Reduced doses of dabigatran did not diminish the risk of major bleeding (HR, 0.96; 95%CI, 0.78-1.17). No risk reduction in С

			DOAO				
Study or Subgroup	log[HR]	SE	Total	Warfarir Total		HR IV, Random, 95%CI	HR IV, Random, 95%CI
Apixaban	log[HK]	3E	TOLA	TULAI	weight	TV, Rahuom, 95/601	IV, Randoni, 93 /8Ci
					40.00/		
Forslund et al. ²⁴ Halvorsen et al. ²⁸	0.048	0.12	3587	12919	12.9%	1.05 [0.82-1.34]	
	-0.579	0.17	6506	11427	10.8%	0.56 [0.40-0.78]	
Hohnloser et al. ³¹	-0.385	0.15	3633	16179	12.0%	0.68 [0.51-0.91]	
Larsen et al. ³⁶	-0.494	0.11	6349	35436	13.5%	0.61 [0.49-0.76]	
Li et al. ³⁷	-0.510	0.05	38470	38470	15.8%	0.60 [0.54-0.67]	
Lip et al. ³⁸	-0.634	0.16	7438	15461	11.5%	0.53 [0.39-0.72]	•
Nielsen et al. ³⁹	0.039	0.16	4400	38893	11.3%	1.04 [0.76-1.42]	
Yao et al. ⁴⁵	-0.798	0.14	15390	51390	12.1%	0.45 [0.34-0.60]	
Subtotal (95%CI)				220175		0.66 [0.55-0.80]	\sim
Heterogeneity: Tau ² = 0			.52, df = 7	(P < .00	(01); T = 8	30%	
Test for overall effect: Z	2 = 4.34 (P <	.0001)					
Dabigatran							
-							
Forslund et al. ²⁴	-0.040	0.11	3322	12919	7.1%	0.96 [0.77-1.20]	1
Graham et al. ²⁶	-0.030	0.05	67207	67207	7.9%	0.97 [0.88-1.07]]
Halvorsen et al. ²⁸	-0.400	0.13	7925	11427	6.8%	0.67 [0.52-0.86]	•
Hernandez et al. ²⁹	0.457	0.07	1302	8102	7.6%	1.58 [1.36-1.84]	•
Hohnloser et al. ³¹	-0.274	0.15	3138	16179	6.5%	0.76 [0.57-1.01]	•
Larsen et al. rdcd ³⁴	0.157	0.14	2038	8504	6.6%	1.17 [0.89-1.54]	
Larsen et al. stnd ³⁴	-0.150	0.15	2214	8504	6.4%	0.86 [0.64-1.16]	
Larsen et al. ³⁶	-0.544	0.11	12701	35436	7.2%	0.58 [0.47-0.72]	-
Lip et al. ³⁸	-0.371	0.16	4661	15461	6.2%	0.69 [0.50-0.95]	
Nielsen et al. ³⁹	-0.139	0.07	8875	38893	7.6%	0.87 [0.75-1.01]	
Nishtala et al.40	-0.798	0.09	2153	4835	7.3%	0.45 [0.37-0.55]	
Seeger et al.42	-0.223	0.08	15529	15529	7.6%	0.80 [0.68-0.94]	Ŧ
Villineset al.44	-0.139	0.08	12793	12793	7.6%	0.87 [0.74-1.02]	
Yao et al. ⁴⁵	-0.235	0.08	28614	28614	7.5%	0.79 [0.67-0.93]	
Subtotal (95%CI)				284403		0.83 [0.70-0.97]	\checkmark
Heterogeneity: Tau ² = 0			7.96, df =	13 (<i>P</i> < .	00001); /	² = 91%	
Test for overall effect: Z	2 = 2.31 (<i>P</i> =	.02)					
Diversity							
Rivaroxaban							
Forslund et al. ²⁴	0.048	0.12	2370	12919	9.0%	1.05 [0.83-1.33]	-
Halvorsen et al. ²⁸	-0.150	0.12	6817	11427	9.1%	0.86 [0.68-1.09]	-#-
Hohnloser et al. ³¹	-0.062	0.15	12063	16179	5.2%	0.94 [0.69-1.28]	
Laliberté et al.33	0.076	0.21	3654	14616	2.8%	1.08 [0.71-1.64]	
Larsen et al. ³⁶	0.058	0.07	7192	35436	21.4%	1.06 [0.91-1.23]	I
Lip et al. ³⁸	-0.020	0.08	17801	15461	18.1%	0.98 [0.83-1.16]	T_
Nielsen et al. ³⁹	0.157	0.11	3476	38893	10.4%	1.17 [0.94-1.46]	
Yao et al. ⁴⁵	0.039	0.07	32350	32350	23.9%	1.04 [0.90-1.20]	T
Subtotal (95%CI)				177281		1.02 [0.95-1.10]	Y
Heterogeneity: Tau ² = 0			46, df = 7	(<i>P</i> = .73);	<i>I</i> ² = 0%		
Test for overall effect: Z	2 = 0.67 (<i>P</i> =	.50)					
All DOAC				_			_
Arihiro et al. ¹⁵	-0.462	0.61	475	662	16.3%	0.63 [0.19-2.09]	
Forslund et al. ²⁴	0.009	0.07	9272	12919	47.1%	1.01 [0.87-1.17]	₹_
Gieling et al. ²⁵	0.732	0.24	1306	13643	36.6%	2.08 [1.28-3.38]	
Subtotal (95%CI)			11053		100.0%	1.22 [0.67-2.20]	
Heterogeneity: Tau ² = 0			52, df = 2	(<i>P</i> = .01);	<i>I</i> ² = 77%		
Test for overall effect: Z	2 = 0.65 (<i>P</i> =	.51)					
						1	
						0.05	0.2 1 5 20
Test for subgroup differ	ences: chi-s	quare =	22.42, df	= 3 (<i>P</i> < .	0001), l²		

Figure 2. (Continued).

major bleeding was observed between reduced doses of rivaroxaban and warfarin (HR, 1.16; 95%CI, 0.98-1.38) (Figure 3B).

Intracranial Hemorrhage

Standard Dose

No differences in the risk reduction of intracranial bleeding were observed between standard doses of apixaban and warfarin (HR, 0.72; 95%CI, 0.42-1.23). Standard doses of dabigatran (HR, 0.39; 95%CI, 0.30-0.52) and rivaroxaban (HR, 0.56; 95%CI, 0.34-0.92) did reduce the risk of intracranial bleeding over time (Figure 3C).

Reduced Dose

No studies compared the incidences of intracranial bleeding between reduced doses of apixaban and warfarin. Reduced doses of

			DOAC	Warfarin		HR	HR
Study or Subgroup	log[HR]	SE					%CI_IV, Random, 95%CI
Apixaban							
Coleman et al. ²²	-0.967	0.41	4083	4083	8.9%	0.38 [0.17-0.85	51 —
Forslund et al. ²⁴	-0.287				16.4%	0.75 [0.45-1.25	-
Halvorsen et al. ²⁸	-0.579				19.1%		
Larsen et al. ³⁶	-0.328				15.4%		-
Li et al. ³⁷	-0.446			15461		0.64 [0.50-0.82	
Yao et al. ⁴⁵				32350		0.24 [0.12-0.48	-
Subtotal (95%CI)	1.721	0.00		111676		0.56 [0.42-0.73	-
Heterogeneity: $Tau^2 = 0.0$	05. chi-sc	iliare :				•	, 1 .
Test for overall effect: Z =					.00), 1	4170	
Dabigatran							
Avgil-Tsadok et al. < 75 ¹⁶	-0.634	0.22	6370	14262	7.1%	0.53 [0.34-0.83	3] —
Avgil-Tsadok et al. > 75 ¹⁶	-0.510				15.6%	•	-
Bengtson et al. ¹⁷	-0.867			37707	4.3%	0.42 [0.23-0.77	-
Bengtson et al. ¹⁷				63460	4.1%	0.37 [0.20-0.68	31
Chan et al. ¹⁹	-0.821			5251	6.9%		
Forslund et al. ²⁴	-0.653			12919	6.1%	0.52 [0.32-0.85	5
Graham et al. ²⁶				67207		0.34 [0.26-0.44	4j •
Halvorsen et al. ²⁸	-0.776			11427	7.5%	0.46 [0.30-0.71	nj 📲
Hernandez et al. ²⁹	-1.140			8102	6.5%	0.32 [0.20-0.51	
Larsen et al. rdcd ³⁴	-0.371	0.29		8504	4.7%	0.69 [0.39-1.22	21
Larsen et al. stnd ³⁴	-0.693			8504	2.7%		
Larsen et al. ³⁶	-0.916			35436	6.5%		4j —
Nishtala et al.40	-1.560			4835		0.21 [0.06-0.74	
Villines et al. ⁴⁴				12793	6.0%		
Yao et al. ⁴⁵	-1.021				7.0%	0.36 0.23-0.56	51 -
Subtotal (95%CI)			194936	351951	100.0%	0.45 [0.39-0.51	
Heterogeneity: Tau ² = 0.0	01; chi-sc	uare =	= 17.83,	df = 14	(P = .21)	; <i>I</i> ² = 21%	-
Test for overall effect: Z =	11.90 (F	°< .00	001)				
Rivaroxaban							
Chan et al. ²⁰	-1.204	0.35	3916	5251	10.0%	0.30 [0.15-0.60	on <u> </u>
Coleman et al. ²²	-0.634			11411		0.53 0.35-0.80	
Forslund et al. ²⁴	-0.116				14.8%		
Halvorsen et al. ²⁸	-0.072				17.5%	•	
Laliberté et al.33	0.157				12.2%		-
Larsen et al. ³⁶	-0.579				13.6%		-
				32350		•	
Yao et al. ⁴⁵	-0.673	0.19			10.470	0.51 [0.35-0.74	·]
Yao et al. ⁴⁵ Subtotal (95%CI)	-0.673	0.19				•	-
Subtotal (95%CI)			67710	123410	100.0%	0.66 [0.49-0.88	-
	10; chi-sc	quare =	67710 = 17.92 ,	123410	100.0%	0.66 [0.49-0.88	-
Subtotal (95%Cl) Heterogeneity: Tau ² = 0. Test for overall effect: Z = All DOAC	10; chi-sc	quare =	67710 = 17.92 ,	123410	100.0%	0.66 [0.49-0.88	-
Subtotal (95%Cl) Heterogeneity: Tau ² = 0. Test for overall effect: Z = All DOAC Arihiro et al. ¹⁵	10; chi-sc	quare = = .006)	67710 = 17.92 ,	123410	100.0%	0.66 [0.49-0.88 ; <i>f</i> = 67%	s]
Subtotal (95%Cl) Heterogeneity: Tau ² = 0. Test for overall effect: Z = All DOAC Arihiro et al. ¹⁵ Forslund et al. ²⁴	10; chi-sc 2.77 (P	quare = = .006)	67710 = 17.92,) 475	123410 df = 6 (<i>H</i> 662	100.0% P = .006)	0.66 [0.49-0.88 ; <i>f</i> = 67% 0.15 [0.01-2.25	5] • _
Subtotal (95%Cl) Heterogeneity: Tau ² = 0. Test for overall effect: Z = All DOAC Arihiro et al. ¹⁵	10; chi-sc 2.77 (P -1.897	quare = = .006j 1.38	67710 = 17.92,) 475 9272	123410 df = 6 (<i>H</i> 662	100.0% P = .006) 5.6% 64.1%	0.66 [0.49-0.88 ; <i>f</i> = 67% 0.15 [0.01-2.25	5] •
Subtotal (95%Cl) Heterogeneity: Tau ² = 0. Test for overall effect: Z = All DOAC Arihiro et al. ¹⁵ Forslund et al. ²⁴ Gieling et al. ²⁵ Subtotal (95%Cl)	10; chi-sc 2.77 (P -1.897 -0.371 0.350	1.38 0.15 0.47	67710 = 17.92,) 475 9272 1306 11053	123410 df = 6 (<i>H</i> 662 12919 13643 27224	100.0% P = .006) 5.6% 64.1% 30.3% 100.0%	0.66 [0.49-0.88 ; <i>f</i> = 67% 0.15 [0.01-2.25 0.69 [0.51-0.93 1.42 [0.56-3.60 0.79 [0.40-1.54	
Subtotal (95%Cl) Heterogeneity: Tau ² = 0. Test for overall effect: Z = All DOAC Arihiro et al. ¹⁵ Forslund et al. ²⁴ Gieling et al. ²⁵ Subtotal (95%Cl) Heterogeneity: Tau ² = 0.	10; chi-sc 2.77 (P -1.897 -0.371 0.350 16; chi-sc	quare = = .006 1.38 0.15 0.47 quare =	67710 = 17.92,) 475 9272 1306 11053	123410 df = 6 (<i>H</i> 662 12919 13643 27224	100.0% P = .006) 5.6% 64.1% 30.3% 100.0%	0.66 [0.49-0.88 ; <i>f</i> = 67% 0.15 [0.01-2.25 0.69 [0.51-0.93 1.42 [0.56-3.60 0.79 [0.40-1.54	
Subtotal (95%Cl) Heterogeneity: Tau ² = 0. Test for overall effect: Z = All DOAC Arihiro et al. ¹⁵ Forslund et al. ²⁴ Gieling et al. ²⁵ Subtotal (95%Cl)	10; chi-sc 2.77 (P -1.897 -0.371 0.350 16; chi-sc	quare = = .006 1.38 0.15 0.47 quare =	67710 = 17.92,) 475 9272 1306 11053	123410 df = 6 (<i>H</i> 662 12919 13643 27224	100.0% P = .006) 5.6% 64.1% 30.3% 100.0%	0.66 [0.49-0.88 ; <i>f</i> = 67% 0.15 [0.01-2.25 0.69 [0.51-0.93 1.42 [0.56-3.60 0.79 [0.40-1.54	
Subtotal (95%Cl) Heterogeneity: Tau ² = 0. Test for overall effect: Z = All DOAC Arihiro et al. ¹⁵ Forslund et al. ²⁴ Gieling et al. ²⁵ Subtotal (95%Cl) Heterogeneity: Tau ² = 0.	10; chi-sc 2.77 (P -1.897 -0.371 0.350 16; chi-sc	quare = = .006 1.38 0.15 0.47 quare =	67710 = 17.92,) 475 9272 1306 11053	123410 df = 6 (<i>H</i> 662 12919 13643 27224	100.0% P = .006) 5.6% 64.1% 30.3% 100.0%	0.66 [0.49-0.88 ; <i>f</i> = 67% 0.15 [0.01-2.25 0.69 [0.51-0.93 1.42 [0.56-3.60 0.79 [0.40-1.54	



dabigatran (HR, 0.47; 95%CI, 0.39-0.56) and rivaroxaban (HR, 0.33; 95%CI, 0.16-0.68) significantly reduced the risk of intracranial bleeding vs warfarin (Figure 3C).

DISCUSSION

The results provided by this meta-analysis aid in the understanding of the effectiveness and safety of DOACs in reallife patients. Unlike noncomparative studies, which only include absolute rates,⁴⁶ this study allows determination of the relative effectiveness and safety of DOACs vs VKAs.

The RE-LY study⁶ showed that, after a median follow-up of 2.0 years, 150 mg dabigatran was associated with a lower risk of stroke or systemic embolism vs warfarin, with a similar risk of major bleeding, whereas 110 mg dabigatran was associated with a similar risk of stroke or systemic embolism, but with a lower risk of

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Chan et al.20

Nielsen et al.³⁹ Subtotal (95%CI)

Rivaroxaban Nielsen et al.³⁹

Subtotal (95%CI)

Heterogeneity: Not applicable Test for overall effect: Z = 0.53 (P = .60)

Graham et al.26

Larsen et al. switch rdcd³

Heterogeneity: Tau² = 0.12; chi-square = 28.57, df = 3 (F

Test for overall effect: Z = 0.31 (P = .76)

Α		log[HR]		DOAC	Warfarin		HR	HR
(a)	Study or Subgroup	log[HK]	SE	Tota	Total	Weight	IV, Random, 95%CI	IV, Random, 95%CI
(a)	Apixaban 36							
	Larsen et al ³⁶ Subtotal (95%CI)	0.104	0.08	6349 6349	35436 35436	100.0% 100.0%	1.11 [0.94-1.31] 1.11 [0.94-1.31]	
	Heterogeneity: Not applicable			0040	00100	100.070	1.11[0.04 1.01]	
	Test for overall effect: $Z = 1.23$ ($P = .22$)							
	Dabigatran							
	Chan et al. ²⁰	-0.494	0.25	1168	9913	16.6%	0.61 [0.37-1.01]	
	Graham et al. ²⁶	-0.357	0.10	10522	67207	23.0%	0.70 [0.57-0.86]	
	Larsen et al. switch stnd ³⁵	0.582	0.21	412	1918	18.5%	1.79 [1.18-2.72]	
	Larsen et al. ³⁶	0.215	0.14	12701	35436	21.6%	1.24 [0.94-1.64]	
	Villines et al. ⁴⁴ Subtotal (95%CI)	-0.116	0.18	11212 36015	12793 127267	20.2% 100.0%	0.89 [0.63-1.26] 0.97 [0.68-1.38]	
	Heterogeneity: $Tau^2 = 0.13$; chi-square = 2 Test for overall effect: Z = 0.19 (P = .85)	23.66, df = 4 (<i>P</i> ·	< .0001); /	= 83%				
	Rivaroxaban							
	Larsen et al. ³⁶ Subtotal (95%CI)	-0.151	0.09	7192 7192	35436 35436	100.0% 100.0%	0.86 [0.72-1.03] 0.86 [0.72-1.03]	
	Heterogeneity: Not applicable Test for overall effect: Z = 1.66 (<i>P</i> = .10)							
	,							
	Test for subgroup differences: chi-square	= 4.24, df = 2 (<i>F</i>	= .12), <i>Î</i>	= 52.8%				0.5 0.7 1 1.5 2 Favors DOAC Favors Warfarin
				DOAC	Warfarin		HR	HR
	Study or Subgroup	log[HR]	SE	Tota	Total	Weight	IV, Random, 95%CI	IV, Random, 95%CI
(b)	Apixaban							
	Nielsen et al ³⁹ Subtotal (95%CI)	0.174	0.11	4400 4400	38893 38893	100.0% 100.0%	1.19 [0.95-1.49] 1.19 [0.95-1.49]	
	Heterogeneity: Not applicable Test for overall effect: Z = 1.51 (P = .13)							
	Dabigatran							

0.62 [0.52-0.74]

0.88 [0.60-1.29]

1.73 [1.21-2.47]

0 92 [0 79-1 07]

0.94 [0.66-1.36]

0.93 [0.71-1.22]

0.93 [0.71-1.22]

Test for subgroup differences: chi-square = 2.29, df = 2 (*P* = .32), f = 12.7% Figure 3. HRs with 95% confidence intervals for ischemic stroke, major bleeding, and intracranial hemorrhage in patients with AF treated with DOACs vs VKAs according to the DOAC dosage (standard/reduced) used in each study. A: ischemic stroke (Aa: Standard dose; Ab: Reduced dose); B: major bleeding (Ba: standard dose; Bb: reduced dose); and C: intracranial bleeding (Ca: standard dose; Cb: reduced dose). 95%Cl, 95% confidence interval; AF, atrial fibrillation; DOACs, direct oral anticoagulants; HR, hazard ratio; IV, interval variable; SE, systemic embolism.

maior bleeding. In the ROCKET-AF trial,⁷ after a median follow-up of 707 days, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism, with a similar risk of major bleeding and a lower risk of intracranial and fatal bleeding. In the ARISTOTLE trial, after a median follow-up of 1.8 years. apixaban was superior to warfarin in preventing stroke or systemic embolism, with less bleeding.⁸ Although these 3 studies were head-to-head with warfarin, the patient populations included were different; thus, no direct comparisons can be made. The characteristics of the included studies are summarized in Table 3 of the supplementary material. As shown in Table 3 of the supplementary material, there were some relevant differences in the clinical characteristics of the patients included in these studies, not only among them, but also among the pivotal clinical trials. As a result, the information provided by this meta-analysis is relevant because it allows determination of the relative effectiveness and safety of DOACs vs VKAs in the full spectrum of real-life patients.

-0.478

-0.128

0.548

-0.083

-0.072

0.09

0.19

0.18

0.08

< 00001):

0.14

1168

547

8875

3476

3476

67166

89%

56576

9913

67207

1918

38893

38893

38893

117931

27.4%

22.1%

22.8%

27.8%

100.0%

100.0%

100.0%

This meta-analysis showed that apixaban and dabigatran did not reduce the risk of ischemic stroke vs warfarin in retrospective claims database studies with a follow-up up to 1 year or with longer-term data. However, rivaroxaban significantly reduced this risk vs warfarin. This significant reduction also occurred with the composite variable of ischemic stroke and systemic embolism. Apixaban and dabigatran significantly reduced major bleeding risk vs warfarin, but not vs rivaroxaban. Notably, statistical heterogeneity was high among studies. However, apixaban, dabigatran, and rivaroxaban significantly reduced the risk of intracranial bleeding vs warfarin. The main objective of anticoagulation in AF patients is to prevent stroke with an acceptable bleeding risk.³ Our data showed that, vs warfarin, the most effective drug to reduce the risk of stroke in clinical practice was rivaroxaban, with a similar risk of major bleeding.

0.5

07

Favors DOAC

1.5 2

Favors Warfarin

One of the main advantages of DOACs vs warfarin is that DOACs do not require continuous dosage adjustments. DOAC dosages are adjusted according to specific clinical conditions that differ markedly among each drug.^{6–8} In our meta-analysis, the effective-ness and safety of DOACs was specifically analyzed according to dosage. Standard doses of dabigatran and particularly rivaroxaban, but not apixaban, tended to reduce the risk of ischemic stroke,

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Figure 3. (Continued).

whereas reduced doses of all DOACs did not decrease the risk of stroke. Reduced doses of DOACs tended to be safer than standard doses in terms of bleeding risk. The main limitation of the observational studies that reported the DOAC doses is that the information regarding the dosage adequacy according to patients' clinical characteristics was not reported. Our meta-analysis showed that, overall, DOACs at reduced doses were associated with a slightly better safety profile, but with a marked reduction in the effectiveness of stroke prevention. In fact, the prescription of inadequate doses of DOACs is associated with worse safety and no benefit in effectiveness.^{39,47} This suggests that reduced doses of DOACs should only be used when indicated according to drug labeling and not when physicians perceive an increased risk of bleeding. Unfortunately, inappropriate drug use is reportedly frequent.^{48–50}

A meta-analysis of the effectiveness and safety of DOACs vs VKAs for stroke prevention in AF was recently published.⁵¹ However, there are important differences between our systematic review and that published by Ntaios et al.⁵¹ Our work included a greater number of studies and a higher number of patients. In addition, the inclusion/exclusion criteria were stricter in our systematic review. Indeed, in our systematic review, studies that exhibited a substantial overlap were excluded. In addition, when data were duplicated, the most recent studies or those with the highest number of patients were selected. Moreover, our search was more up-to-date and we included 11 additional studies vs Ntaios et al.⁵¹ Importantly, specific analyses according to follow-up time and DOAC dosage were performed, increasing the validity and generalizability of our results. Accordingly, our systematic review is more complete and exhaustive and has a higher statistical power. For example, due to its higher statistical power and in contrast to the study by Ntaios et al.,⁵¹ our work found that dabigatran significantly reduced the risk of major bleeding vs warfarin and that rivaroxaban decreased the risk of ischemic stroke and systemic embolism.

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Figure 3. (Continued).

Limitations

Some limitations should be mentioned. Observational studies have a higher risk of bias than clinical trials. We found a moderate risk of bias with the ROBINS-I tool. Vitamin K antagonists were the key comparator arm. However, time in therapeutic range and data adjusted according to this parameter were not disclosed in any studies. Analyses were limited to some outcomes, such as stroke, major bleeding, or intracranial bleeding, but not others. In some comparisons, statistical heterogeneity was high among studies, limiting the validity and the generalizability of the results. No significant clinical information was available for edoxaban.

CONCLUSIONS

In conclusion, in studies with a follow-up up to 1 year or with longer-term data, rivaroxaban significantly reduced the risk of ischemic stroke vs warfarin, unlike apixaban and dabigatran. Apixaban and dabigatran significantly reduced the risk of major bleeding, whereas rivaroxaban showed similar risk to warfarin. Compared with warfarin, DOACs significantly reduced the risk of intracranial bleeding. Reduced doses of DOACs were associated with a marked reduction in the effectiveness of stroke prevention and with a slightly better safety profile. Data from this meta-analysis suggest that, vs warfarin, the effectiveness and safety of some DOACs may differ in real-life AF patients.

ACKNOWLEDGMENTS

Editorial assistance was provided by Content Ed Net, Madrid, Spain.

FUNDING

Bayer Hispania S.L.

CONFLICTS OF INTEREST

C. Escobar reports personal fees from Bayer, Boehringer, Bristol-Myers Squibb, Daiichi-Sankyo, and Pfizer outside the submitted work. J. Martí-Almor reports personal fees from Bayer, Daiichi-Sankyo, Pfizer, and Boehringer outside the submitted work. A. Pérez Cabeza reports personal fees from Bayer and Daiichi-Sankyo outside the submitted work. M.J. Martínez-Zapata has nothing to disclose.

WHAT IS KNOWN ABOUT THE TOPIC?

- Data from clinical trials are not always valid for real-life patients.
- In recent years, many studies with different designs, analyses, and patient characteristics have analyzed the use of DOACs in AF patients in clinical practice.
- This systematic review assessed the effectiveness of DOACs vs VKAs in nonvalvular AF patients.

WHAT DOES THIS STUDY ADD?

- In contrast to apixaban and dabigatran, rivaroxaban significantly reduced the risk of ischemic stroke vs warfarin.
- Apixaban and dabigatran significantly reduced the risk of major bleeding vs warfarin, unlike rivaroxaban, but with a high statistical heterogeneity among studies. All DOACs significantly reduced the risk of intracranial bleeding vs warfarin.
- Reduced doses of DOACs were associated with a slightly better safety profile, but with a marked reduction in effectiveness for stroke prevention.

SUPPLEMENTARY MATERIAL



Supplementary material associated with this article can be found in the online version available at https://doi.org/ 10.1016/j.rec.2018.03.009.

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