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Buckley, BJR, Lane, DA, Calvert, P, Zhang, J, Gent, D, Mullins, CD, Dorian, P, Kohsaka, S, Hohnloser, SH and Lip, GYH (2022) Effectiveness and Safety of Apixaban in over 3.9 Million People with Atrial Fibrillation: A Systematic Review and Meta-Analysis. Journal of Clinical Medicine. 113. ISSN 2077-

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Systematic Review

Effectiveness and Safety of Apixaban in over 3.9 Million People with Atrial Fibrillation: A Systematic Review and Meta-Analysis

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Abstract: Background: There is a plethora of real-world data on the safety and effectiveness of direct-acting oral anticoagulants (DOACs); however, study heterogeneity has contributed to inconsistent findings. We compared the effectiveness and safety of apixaban with those of other direct-acting oral anticoagulants (DOACs) and vitamin K antagonists (VKA e.g., warfarin). Methods: A systematic review and meta-analysis was conducted retrieving data from PubMed, SCOPUS and Web of Science from January 2009 to December 2021. Studies that evaluated apixaban (intervention) prescribed for adults (aged 18 years or older) with AF for stroke prevention compared to other DOACs or VKAs were identified. Primary outcomes included stroke/systemic embolism (SE), all-cause mortality, and major bleeding. Secondary outcomes were intracranial haemorrhage (ICH) and ischaemic stroke. Randomised controlled trials and non-randomised trials were considered for inclusion. Results: In total, 67 studies were included, and 38 studies were metaanalysed. Participants taking apixaban had significantly lower stroke/SE compared to patients taking VKAs (relative risk (RR) 0.77, 95% confidence interval (CI) 0.64-0.93, I²=94%) and dabigatran (RR 0.84, 95% CI 0.74–0.95, I²=66%), but not to patients administered rivaroxaban. There was no statistical difference in mortality between apixaban and VKAs or apixaban and dabigatran. Compared to patients administered rivaroxaban, participants taking apixaban had lower mortality rates (RR 0.83, 95% CI 0.71–0.96, I²=96%). Apixaban was associated with a significantly lower risk of major bleeding compared to VKAs (RR 0.58, 95% CI 0.52–0.65, I²=90%), dabigatran (RR 0.79, 95% CI 0.70–0.88, I²=78%) and rivaroxaban (RR 0.61, 95% CI 0.53–0.70, I²=87%). Conclusions: Apixaban was associated with a better overall safety and effectiveness profile compared to VKAs and other DOACs.

Keywords: apixaban; atrial fibrillation; stroke; major bleeding; anticoagulant; secondary prevention

Citation: Buckley, B.J.R.; Lane, D.A.; Calvert, P.; Zhang, J.; Gent, D.; Mullins, D.; Dorian, P.; Kohsaka, S.; Hohnloser, S.H.; Lip, G.Y.H. Effectiveness and Safety of Apixaban in over 3.9 Million People with Atrial Fibrillation: A Systematic Review and Meta-Analysis. *J. Clin. Med.* 2022, *11*, 3788. https://doi.org/ 10.3390/jcm11133788

Academic Editor: Ugo Limbruno

Received: 6 June 2022 Accepted: 24 June 2022 Published: 30 June 2022

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1. Introduction

Anticoagulation is the fundamental priority for the prevention of stroke in people diagnosed with atrial fibrillation (AF) and is one of the pillars of guideline-recommended AF management [1,2]. The efficacy of direct-acting oral anticoagulants (DOACs) versus warfarin has received considerable attention in the last decade. DOACs have generally [3,4], although not always [5], demonstrated favourable outcomes for stroke and mortality. Typically, DOACs are now favoured over warfarin for stroke prevention in AF due to their superior safety profile regarding intracranial haemorrhage (all DOACs) and major bleeding (some DOACs) [1,6]. However, agreement on the most favourable DOAC in terms of effectiveness and safety is challenging, particularly given that there are no head-to-head comparison trials.

There is a plethora of real-world data on the safety, and to a lesser extent, the effectiveness of DOACs, but the disparity in study populations, inclusion and exclusion criteria, and statistical analyses, has resulted in inconsistent findings and several unanswered questions. Further, our understanding of the potential impact of geographical region, study design and age on such outcomes is lacking. Addressing these gaps in the current evidence base will allow clinicians and patients to make better, evidence-informed decisions when selecting a DOAC to prevent stroke in people with AF.

Given apixaban is the most commonly used DOAC [7], the aims of this systematic review and meta-analysis were to compare the effectiveness and safety of apixaban with those of other DOACs and vitamin K antagonists (VKA e.g., warfarin). First, we sought to determine if apixaban was more effective (reduced stroke and mortality) and safer (reduced major bleeding) than dabigatran, rivaroxaban, edoxaban, and VKAs for patients with AF. Second, we investigated how geographical region (Asia, Europe, North America) and age (\geq 75/<75 years of age) may impact the effectiveness and safety of apixaban.

2. Methods

This systematic review was registered in the International Prospective Register of Systematic Reviews—PROSPERO (CRD42021236826) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [8].

2.1. Study Inclusion Criteria

We included studies carried out in any setting that evaluated apixaban (intervention) prescribed for adults (aged 18 years or older) with AF for stroke prevention compared to other DOACs or VKAs (e.g., warfarin). Primary outcomes included stroke or any thromboembolic event (stroke/SE composite), all-cause mortality, and major bleeding. Secondary outcomes included intracranial haemorrhage (ICH) and ischaemic stroke. Definitions used for each outcome were employed by the primary trials and may not be consistent between studies. All randomised controlled trials and non-randomised studies, pre–post studies and interrupted time series were considered for inclusion. Crosssectional studies, case reports and qualitative studies were excluded.

2.2. Search Strategy

The search strategy was developed by the review team who selected all key terms. Medical subject headings (MesH) terms and synonyms for the different terms such as "atrial fibrillation", "apixaban" and "stroke" were used and combined with Boolean operators, proximity operators, truncations and wildcards. PubMed, SCOPUS and Web of Science were searched from 1 January 2009 to 21 December 2021 for relevant studies (refer to Supplement S1 for full search strategies). Database searches were initiated from 2009 rather than inception, because the first DOAC trial (RE-LY) was published in 2009 [9]. There were no language restrictions; however, availability of the full text was a requirement for inclusion. Search results were managed using EndNote X9.3.3.

2.3. Study Selection

Two reviewers (B.J.R.B., J.Z.), independently and in duplicate, screened the titles and abstracts of the studies retrieved by the databases against the search criteria. The full texts of all potentially relevant articles were retrieved and independently assessed by the reviewers (B.J.R.B., P.C., D.A.L., M.C., D.G.). Any disagreement was resolved through discussion with the first author (B.J.R.B.).

2.4. Data Extraction

Data extraction was conducted independently by five reviewers (B.J.R.B., P.C., D.A.L., M.C., D.G.), with at least 20% checked by (B.J.R.B.) to ensure consistency/accuracy. The following information was extracted: (i) authors, year, country, reference; (ii) study design with inclusion/exclusion criteria; (iii) study aim; (iv) intervention and comparator characteristics (*n*=, age, sex, CHA₂DS₂-VASc, HAS-BLED); (v) outcomes (effectiveness and safety); (vi) follow-up time points; (vii) results; (viii) study conclusions; (ix) risk of bias assessment.

2.5. Risk of Bias Assessment

Five authors (B.J.R.B., P.C., D.A.L., M.C., D.G.) independently assessed the individual studies for risk of bias in duplicate, and any discrepancies were resolved via discussion or referral to a third reviewer, as required. The Cochrane Risk of Bias v.2 (RoB2) tool [10] was used to assess the risk of bias for randomised controlled trials (RCTs). The Risk Of Bias In Non-randomised Studies—of Interventions (ROBINS-I) [11] was used to assess the risk of bias for non-randomised studies.

2.6. Data Synthesis

Meta-analyses were conducted for comparable studies. Primary and secondary outcome effect measures with 95% confidence intervals were pooled using RevMan software [12]. Results are presented visually using Forest plots. For studies where quantitative data were too few or too heterogeneous, a narrative synthesis approach was used. Effect measures for dichotomous outcomes were analysed using the number of events and total sample size as reported in the included studies. Results of the selected studies were combined using the Mantel–Haenszel method. Effect sizes were expressed as relative risk and 95% confidence intervals. Heterogeneity was quantitatively assessed using Higgins's index (I²), with 25%, 50% and 75% considered moderate, substantial and considerable heterogeneity, respectively. Random-effect models were applied allowing for between-study variability by weighting studies using a combination of intra- and inter-study variance.

2.7. Sub-Group and Sensitivity Analyses

Sub-group analyses were conducted (if sufficient data) to explore any impact of cohort age (\geq 75 and <75 years) and geographical region (North America, Asia, Europe) on the safety and effectiveness of apixaban compared to VKAs, dabigatran, and rivaroxaban. Sensitivity analyses were planned to explore the impact of studies deemed as 'serious risk of bias' on the safety and effectiveness of apixaban.

3. Results

The database searches identified 9246 papers. After removal of duplicates, 6644 papers were included in the title and abstract screening, which resulted in 109 papers retrieved for full-text screening against the inclusion/exclusion criteria. Of these, 67 (61%) studies were included in the systematic review, and 38 (35%) studies were included in meta-analyses (Figure 1).



Figure 1. PRISMA Diagram depicting the screening and study selection process.

3.1. Characteristics of the Included Studies

The included studies were published between 2009 and 2021; two of them were randomised controlled trials [13,14], two were prospective cohort studies [15,16], and the remaining 63 were retrospective cohort studies (Supplementary File; Table S1). The sample size for the apixaban-treated cohorts ranged between n = 98 [17] and n = 353,897 patients [18]. The total sample of patients included in the review was 3,911,894, of which, 1,292,620 patients (33%) were taking apixaban. Mean/median patient age ranged from 62 [19] to 86 [20] years, and the proportion of females ranged between 15% [14] and 69% [21]. Of the 67 included studies, 34 were conducted in the U.S.A., 7 in Denmark, 3 each in Sweden, Spain, Norway, Japan, and Germany, 2 each in the UK and South Korea, 1 each in Taiwan, Canada, Thailand, France, and Singapore, 1 was international, with 39 participating countries, and 1 included data from Canada, the U.S.A.

For the two included randomised controlled trials, one was deemed 'low risk of bias' [13], and one was deemed 'some concerns' [14], with the latter due to non-blinded participants. Overall, 64/65 real-world studies were deemed 'moderate risk of bias', with one study deemed to be at serious risk of bias [22]. For all included real-world studies, the risk of bias was elevated due to confounding which was inherent in the study design.

Further study-level detail regarding the risk of bias is reported within the Supplementary File, Table S2 and Figure S1.

3.2. Primary Outcomes

Meta-analyses for stroke/SE (Figure 2), mortality (Figure 3) and major bleeding (Figure 4) are presented below. Each analysis includes all eligible studies and compared apixaban with VKAs, dabigatran and rivaroxaban for each outcome. A comparison of apixaban with edoxaban was not possible due to only one eligible study including data for both drugs [23].

A total of 17 (n = 802,063), 10 (n = 321,486), and 12 (n = 1,146,705) studies compared apixaban to VKAs, dabigatran and rivaroxaban, respectively, and were included in metaanalyses investigating stroke/SE (Figure 2). Compared to VKAs, apixaban was associated with a significantly lower risk of stroke/SE (relative risk (RR) 0.77, 95% confidence interval (CI) 0.64–0.93, I² = 94%). Compared to dabigatran, apixaban was associated with a significantly lower risk of stroke/SE (RR 0.84, 95% CI 0.74–0.95, I² = 66%). There was no statistical difference in risk of stroke/SE between apixaban and rivaroxaban (RR 0.90, 95% CI 0.78–1.03, I² = 88%).

A total of 10 (n = 533,997), 8 (n = 235,247) and 10 (n = 878,520) studies compared apixaban to VKAs, dabigatran and rivaroxaban, respectively, and were included in metaanalyses investigating mortality (Figure 3). There was no statistical difference in mortality between apixaban and VKAs (RR 0.72, 95% CI 0.50–1.00, I² = 99%) or apixaban and dabigatran (RR 1.00, 95% CI 0.82–1.22, I²=93%). Compared to rivaroxaban, apixaban was associated with a significantly lower risk of mortality (RR 0.83, 95% CI 0.71–0.96, I²=96%).

A total of 18 (n = 700,098), 14 (n = 288,057) and 13 (n = 468,097) studies compared apixaban to VKAs, dabigatran and rivaroxaban, respectively, and were included in metaanalyses investigating major bleeding (Figure 4). Apixaban was associated with a significantly lower risk of major bleeding compared to VKAs (RR 0.58, 95% CI 0.52–0.65, $I^2 = 90\%$), dabigatran (RR 0.79, 95% CI 0.70–0.88, $I^2 = 78\%$) and rivaroxaban (RR 0.61, 95% CI 0.53–0.70, $I^2 = 87\%$).



Figure 2. Comparison of apixaban to VKAs (1.1.1), dabigatran (1.1.2) and rivaroxaban (1.1.3) for stroke/SE [17,18,20,24–43].

	Apixa	aban	Comp	arator		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
1.2.1 Apixaban vs VKA								
Alcusky, 2020	554	2881	645	2881	9.8%	0.86 [0.78, 0.95]	-	
Chan, 2018	319	5843	2588	19375	9.8%	0.41 [0.37, 0.46]		
Graham, 2019	456	72921	2234	183003	9.8%	0.51 [0.46, 0.57]		
Hohnloser, 2018	804	10117	1595	23823	9.9%	1.19 [1.09, 1.29]	-	
Larsen, 2016	232	6349	2652	35436	9.8%	0.49 [0.43, 0.56]		
Lip. 2017	19	1470	249	7674	8.5%	0.40 [0.25, 0.63]	·	
Mitsuntisuk, 2021	3	405	4	605	3.6%	1.12 [0.25, 4.98]		
Nielsen, 2017	1040	4400	5366	38893	9.9%	1.71 [1.62, 1.82]	+	
Rodríguez-Bernal, 2018	166	2259	4539	32476	9.7%	0.53 [0.45, 0.61]		
Vinogradova, 2018, (CPRD Database)	56	1402	780	16664	9.4%	0.85 [0.65, 1.11]		
Vinogradova, 2018, (Oresearch Database)	472	9199	3182	53921	9.8%	0.87 [0.79, 0.96]	-	
Subtotal (95% CI)		117246		414751	100.0%	0.72 [0.50, 1.02]		
Total events	4121		23834				-	
Heterogeneity: $Tau^2 = 0.33$: $Chi^2 = 1017.0$	2. df = 10) (P < 0.0	0001) 12	= 99%				
Test for overall effect: $Z = 1.84$ (P = 0.07)	_, 10	0.0		5575				
1000000000000000000000000000000000000								
1.2.2 Apixaban vs Dabigatran								
Al-Khalili, 2016	1	251	1	233	0.5%	0.93 [0.06, 14.76]	· · · · · · · · · · · · · · · · · · ·	
Graham, 2019	456	72921	677	86293	13.4%	0.80 [0.71, 0.90]		
Hohnloser, 2018	804	10117	253	5122	13.2%	1.61 [1.40, 1.85]		
Jansson, 2020	496	11493	246	6453	13.1%	1.13 [0.97, 1.31]		
Mueller, 2019	305	6200	61	1112	11.3%	0.90 [0.69, 1.17]		
Nielsen, 2017	1040	4400	1873	8875	13.9%	1.12 [1.05, 1.20]	-	
Rodríguez-Bernal, 2018	166	2259	426	3380	12.8%	0.58 [0.49, 0.69]	(
Vinogradova, 2018, (CPRD Database)	56	1402	38	1003	8.9%	1.05 [0.70, 1.58]		
Vinogradova, 2018, (Qresearch Database)	472	9199	212	4534	13.0%	1.10 [0.94, 1.29]		
Subtotal (95% CI)		118242		117005	100.0%	1.00 [0.82, 1.22]	•	
Total events	3796		3787					
Heterogeneity: Tau ² = 0.07; Chi ² = 109.61, df = 8 (P < 0.00001); l ² = 93%								
Test for overall effect: $Z = 0.00 (P = 1.00)$								
1.2.3 Apixaban vs Rivaroxaban								
Al-Khalili, 2016	1	251	3	282	0.5%	0.37 [0.04, 3.58]	· · ·	
Graham, 2019	456	72921	904	106369	10.3%	0.74 [0.66, 0.82]		
Hohnloser, 2018	804	10117	1509	22143	10.5%	1.17 [1.07, 1.27]	-	
lansson, 2020	496	11493	438	7897	10.1%	0.78 [0.69, 0.88]		
Mueller, 2019	305	6200	622	7265	10.1%	0.57 [0.50, 0.66]	—	
Nielsen, 2017	1040	4400	798	3476	10.5%	1.03 [0.95, 1.12]		
Perreault, 2021	284	6771	334	4632	9.8%	0.58 [0.50, 0.68]	_ _	
Ray, 2021	12839	353879	7497	227572	10.8%	1.10 [1.07, 1.13]	-	
Rodríguez-Bernal, 2018	166	2259	412	3445	9.6%	0.61 [0.52, 0.73]		
Vinogradova, 2018, (CPRD Database)	56	1402	112	2950	7.5%	1.05 [0.77, 1 44]	_	
Vinogradova, 2018, (Oresearch Database)	472	9199	757	13597	10.3%	0.92 [0.82, 1.03]		
Subtotal (95% CI)	472	478892	, ,,	399628	100.0%	0.83 [0.71, 0.96]	•	
Total events	16919		13386					
Heterogeneity: Tau ² = 0.06; Chi ² = 249.82 Test for overall effect: Z = 2.41 (P = 0.02)	, df = 10	(P < 0.00	001); I ² =	96%				
							0.5 0.7 1 1.5 2	
							Favours Apixaban Favours Comparator	

Figure 3. Comparison of apixaban to VKAs (1.2.1), dabigatran (1.2.2) and rivaroxaban (1.2.3) for mortality [16,18,21,25–27,30,32,34,35,39,44–47].

	Apixa	aban	Compa	arator		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	
2.1.1 Apixaban vs VKA								
Adeboyeje, 2017	245	3689	1729	23431	6.3%	0.90 [0.79, 1.02]		
Bang, 2020	432	10548	466	8648	6.3%	0.76 [0.67, 0.86]	· · · ·	
Chan, 2018	67	5843	855	19375	5.1%	0.26 [0.20, 0.33]	← ···	
Hohnloser, 2018	167	10117	692	23823	5.9%	0.57 [0.48, 0.67]		
Kjerpeseth, 2019	446	10550	490	6435	6.3%	0.56 [0.49, 0.63]		
Kohsaka, 2018	99	11972	134	11972	5.0%	0.74 [0.57, 0.96]		
Lamberts, 2017	252	7963	1128	24230	6.2%	0.68 [0.59, 0.78]		
Larsen, 2016	90	6349	725	35436	5.4%	0.69 [0.56, 0.86]		
Lee, 2019	290	221//	1202	25420	6.2%	0.58 [0.51, 0.67]	<u> </u>	
LI, 2017	1003	38470	1303	38470	0.0%	0.58 [0.53, 0.63]		
LIP, 2018 Martinez, 2018	1902	1202	5770	1202	0.7%	0.50 [0.46, 0.55]		
Mitcupticule 2021	44	1592	06	1592	3.0% 3 E0/	0.76 [0.52, 1.11]		
Nielson 2017	160	405	2126	20002	5.5%	0.40 [0.27, 0.01]		
Ramagonalan 2019	52	2160	100	2160	4 3%	0.52 [0.37, 0.78]		
Tiew 2020	4	2100	100	157	0.8%	0.80 [0.25, 2.59]		
Vinogradova, 2018, (CPRD Database)	22	1402	515	16664	3 4%	0.51 [0.33 0.78]		
Vinogradova, 2018, (Oresearch Database)	119	9199	1813	53921	5.8%	0.38 [0.32, 0.46]		
Wanat, 2019	600	10189	887	10189	6.5%	0.68 [0.61. 0.75]		
Subtotal (95% CI)	000	257900	007	442198	100.0%	0.58 [0.52, 0.65]	◆	
Total events	5770		17474				•	
Heterogeneity: Tau ² = 0.05; Chi ² = 176.95.	df = 18	(P < 0.000	$(001); I^2 =$	90%				
Test for overall effect: $Z = 9.51 (P < 0.0000)$	1)							
	-							
2.1.2 Apixaban vs Dabigatran								
Adeboyeje, 2017	62	3689	245	8539	6.5%	0.59 [0.44, 0.77]		
Hohnloser, 2018	167	10117	80	5122	6.7%	1.06 [0.81, 1.38]		
Jansson, 2020	224	11493	186	6453	8.1%	0.68 [0.56, 0.82]	_ _	
Lamberts, 2017	252	7963	695	15413	9.1%	0.70 [0.61, 0.81]		
Lee, 2019	302	22177	263	17745	8.7%	0.92 [0.78, 1.08]		
Lip, 2018	571	37314	832	37314	9.8%	0.69 [0.62, 0.76]	-	
Mitsuntisuk, 2021	26	405	19	441	2.8%	1.49 [0.84, 2.65]		
Nielsen, 2017	160	4400	491	8875	8.5%	0.66 [0.55, 0.78]		
Rutherford, 2020	845	10413	1169	10413	10.1%	0.72 [0.66, 0.79]	-	
Staerk, 2018	154	7203	114	7078	7.2%	1.33 [1.04, 1.69]		
Tepper, 2018	119	8785	306	20963	7.8%	0.93 [0.75, 1.15]		
Tiew, 2020	4	98	-0	30	E 40/	Not estimable		
Villines, 2019	58	4802	17	4802	5.4%	0.75 [0.54, 1.06]		
Vinogradova, 2018, (CPRD Database)	110	1402	107	1003	2.5%	0.93 [0.49, 1.73]		
Subtotal (95% CI)	119	139362	107	148695	100.0%	0.79 [0.70, 0.88]	•	
Total events	3081	199905	4601	1.0000	1001070	011 0 [011 0] 0100]	•	
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 60.23$.	df = 13 (F	< 0.0000	(1001)	78%				
Test for overall effect: $Z = 4.19 (P < 0.0001)$.)							
2.1.3 Apixaban vs Rivaroxaban								
Adeboyeje, 2017	62	3689	301	8398	6.9%	0.47 [0.36, 0.61]		
Hohnloser, 2018	167	10117	568	22143	8.3%	0.64 [0.54, 0.76]	- -	
Jansson, 2020	224	11493	308	7897	8.3%	0.50 [0.42, 0.59]		
Lamberts, 2017	252	7963	343	6715	8.4%	0.62 [0.53, 0.73]		
Lee, 2019	309	22177	679	35965	8.7%	0.74 [0.65, 0.84]		
Lip, 2018	952	107236	2239	107236	9.2%	0.43 [0.39, 0.46]	-	
Mitsuntisuk, 2021	26	405	60	604	4.8%	0.65 [0.42, 1.01]		
Nielsen, 2017	160	4400	187	3476	7.8%	0.68 [0.55, 0.83]		
Rutherford, 2020	304	13699	496	13699	8.6%	0.61 [0.53, 0.71]		
Staerк, 2018	154	7203	175	6868	7.7%	0.84 [0.68, 1.04]		
Tiepper, 2018	119	8785	656	30529	8.0%	0.63 [0.52, 0.77]		
Hew, 2020	4	98	4	154	0.9%	1.57 [0.40, 6.14]		
Vinogradova, 2018, (CPRD Database)	22	1402	66	2950	4.4%	0.70 [0.43, 1.13]		
vinogradova, 2018, (Qresearch Database) Subtotal (95% CI)	119	207866	338	260231	100.0%	0.52 [0.42, 0.64]		
Total events	2071	207000	6420	200231	100.0/0	0.01 [0.33, 0.70]	▼	
Heterogeneity: $Tau^2 = 0.05$: $Ch^2 = 98.50$, $df = 13 (P < 0.0001)$; $l^2 = 87\%$								
Test for overall effect: $7 - 7.00 (P < 0.000)$	ai — 15 (f 11)	~ 0.0000	, i), i = .	07/0				
1000000000000000000000000000000000000	-)							
							U.5 U.7 1 1.5 2 Eavours Anivahan Eavours Comparator	

Figure 4. Comparison of apixaban to VKAs (2.1.1), dabigatran (2.1.2) and rivaroxaban (2.1.3) for major bleeding [16,17,20,23–25,27–31,33–36,38–41,48–51].

3.3. Secondary Outcomes

Meta-analyses for ischaemic stroke (Figure 5) and ICH (Figure 6) are presented below. Each analysis included all eligible studies and compared apixaban with VKAs, dabigatran and rivaroxaban for each outcome.

A total of 19 (n = 777,182), 16 (n = 380,145) and 17 (n = 1,087,791) studies compared apixaban to VKAs, dabigatran and rivaroxaban, respectively, and were included in metaanalyses investigating ischaemic stroke (Figure 5). Apixaban was associated with a significantly lower risk of ischaemic stroke compared to VKAs (RR 0.81, 95% CI 0.68–0.96, I² = 92%), dabigatran (RR 0.83, 95% CI 0.70–0.97, I² = 82%) and rivaroxaban (RR 0.75, 95% CI 0.58–0.98, I² = 97%). A total of 17 (n = 1,002,726), 13 (n = 415,489) and 16 (n = 1,293,546) studies compared apixaban to VKAs, dabigatran and rivaroxaban, respectively, and were included in meta-analyses investigating ICH (Figure 6). Apixaban was associated with a significantly lower rates of ICH compared to VKAs (RR 0.49, 95% CI 0.41–0.59, I²=81%) and rivaroxaban (RR 0.71, 95% CI 0.61–0.84, I²=74%), but not dabigatran (RR 0.98, 95% CI 0.83–1.16, I²=34%).

	Apixa	aban	Compa	arator		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M–H, Random, 95% Cl		
Alcusty 2020	24	2881	13	2881	3 4%	1 85 [0 94 3 62]			
Bradley, 2020	108	55038	226	55038	6.0%	0.48 [0.38, 0.60]			
Hohnloser, 2018	196	10117	510	23823	6.3%	0.90 [0.77, 1.07]	-		
Huybrechts, 2020	65	19588	79	19588	5.4%	0.82 [0.59, 1.14]			
Kjerpeseth, 2019	141	10550	84	6435	5.7%	1.02 [0.78, 1.34]	+		
Larsen, 2016	204	6349	920	35436	6.3%	1.24 [1.07, 1.44]			
Lee, 2019	370	38470	515	25420	6.4%	0.67 [0.59, 0.76]	÷		
Lip. 2018	533	100977	895	100977	6.5%	0.60 [0.54, 0.66]	-		
Martinez, 2018	20	1392	27	1392	3.9%	0.74 [0.42, 1.31]			
Mitsuntisuk, 2021	11	405	42	605	3.5%	0.39 [0.20, 0.75]			
Nielsen, 2017	198	4400	1059	38893	6.3%	1.65 [1.42, 1.92]	-		
Rodriguez-Bernal, 2018	35	2259	627	32476	5.3%	0.80 [0.57, 1.12]	<u> </u>		
Tiew 2020	80 4	0899	219	18094	5.9%	3 20 [0.60, 1.32]			
Vinogradova, 2018, (CPRD Database)	9	1402	225	16664	3.4%	0.48 [0.24, 0.92]			
Vinogradova, 2018, (Qresearch Database)	86	9199	794	53921	6.0%	0.63 [0.51, 0.79]			
Yang, 2020, (Cohort without stroke)	106	1864	787	9271	6.1%	0.67 [0.55, 0.82]	-		
Yang, 2020, (Cohort with stroke)	124	494	942	3082	6.3%	0.82 [0.70, 0.97]	-		
Subtotal (95% CI)		294559		482623	100.0%	0.81 [0.68, 0.96]	•		
Total events	2652	(D - 0 00)	8599	0.2%					
Test for overall effect: $Z = 2.39 (P = 0.02)$	df = 18	(P < 0.00)	JU1); I [_] =	92%					
1.3.2 Apixaban vs Dabigatran									
Al-Khalili, 2016	1	251	2	233	0.4%	0.46 [0.04, 5.08]	· · · · · · · · · · · · · · · · · · ·		
Hohnloser, 2018	165	10117	82	5122	7.6%	1.02 [0.78, 1.32]	+		
Jansson, 2020	83	11493	78	6453	7.1%	0.60 [0.44, 0.81]			
Lee, 2019	385	22177	370	25420	8.9%	1.19 [1.04, 1.37]	-		
Lip, 2018	533	100977	895	100977	9.2%	0.60 [0.54, 0.66]	<u>+</u>		
Musurusuk, 2021 Mueller, 2019	67	6200	20	1112	3.2% 1 Q%	0.60 [0.29, 1.25]	-		
Nielsen, 2017	230	4400	504	8875	8.8%	0.92 [0.79, 1.07]	-		
Rodríguez-Bernal, 2018	35	2259	75	3380	6.0%	0.70 [0.47, 1.04]			
Rutherford, 2020	302	10413	322	10413	8.8%	0.94 [0.80, 1.09]	-		
Staerk, 2017	86	6899	163	12613	7.6%	0.96 [0.74, 1.25]			
Staerk, 2018	75	7203	60	7078		Not estimable			
Tiew, 2020	4	98	0	30	2.00/	Not estimable			
Villines, 2019 Vingeradova, 2018 (CRRD Database)	17	4802	21	4802	3.8%	0.81 [0.43, 1.53]			
Vinogradova, 2018, (Crkb Database)	86	9199	58	4534	6.8%	0.92 [0.54, 2.40]			
Yang, 2020. (Cohort without stroke)	106	1864	95	1168	7.5%	0.70 [0.54, 0.91]			
Yang, 2020, (Cohort with stroke)	124	494	52	247	7.3%	1.19 [0.90, 1.59]			
Subtotal (95% CI)		193352		186793	100.0%	0.83 [0.70, 0.97]	•		
Total events	2240		2763						
Heterogeneity: Tau ² = 0.07; Chi ² = 85.70, df = 15 (P < 0.00001); $i^2 = 82\%$ Test for overall effect: Z = 2.35 (P = 0.02)									
133 Aniyahan ya Piyaroyahan									
	1	251	3	182	1 1%	0 24 [0 03 2 30]	•		
Fralick 2020	198	39351	232	39351	6.3%	0.85 [0.71 1.03]	·		
Hohnloser, 2018	165	10117	322	22143	6.3%	1.12 [0.93, 1.35]			
Jansson, 2020	83	11493	818	7897	6.2%	0.07 [0.06, 0.09]			
Lee, 2019	393	22177	761	35965	6.4%	0.84 [0.74, 0.94]	-		
Lip, 2018	559	107236	749	107236	6.5%	0.75 [0.67, 0.83]	-		
Mitsuntisuk, 2021	11	405	37	604	4.6%	0.44 [0.23, 0.86]			
Nielcon 2017	220	6200	106	2476	6.0%	0.74 [0.55, 1.00]			
Ray 2021	2196	353879	1447	227572	6.5%	0.98[0.91, 1.04]			
Rodríguez-Bernal, 2018	35	2259	59	3445	5.6%	0.90 [0.60, 1.37]			
Rutherford, 2020	394	13699	421	13699	6.4%	0.94 [0.82, 1.07]	-		
Staerk, 2017	86	6899	68	5693	6.0%	1.04 [0.76, 1.43]			
Staerk, 2018	75	7203	57	7078		Not estimable			
Tiew, 2020	4	98	5	154	2.6%	1.26 [0.35, 4.57]			
Vinogradova, 2018, (CPRD Database)	9	1402	34	2950	4.4% 6.1%	0.56 [0.27, 1.16]			
Yang 2020 (Cohort without stroke)	106	1864	281	4035	0.1%	0.99 [0.76, 1.30]	-		
Yang, 2020, (Cohort with stroke)	124	494	265	1104	6.3%	1.05 [0.87, 1.26]	—		
Subtotal (95% CI)		591423	205	496368	100.0%	0.75 [0.58, 0.98]	•		
Total events	4747		5855						
Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 574.42$,	df = 17	(P < 0.00)	$(001); I^2 =$	97%					
Test for overall effect: $Z = 2.09 (P = 0.04)$									
							<u></u>		
							0.1 0.2 0.5 1 2 5 10 Favours Apixaban Favours Comparator		

Figure 5. Comparison of apixaban to VKAs (1.3.1), dabigatran (1.3.2) and rivaroxaban (1.3.3) for ischaemic stroke [16–18,20,21,23,27,28,30,31,33–35,37–42,44–46,52–54].

	Apixa	aban	Compa	arator		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl		
2.2.1 Apixaban vs VKA									
Adeboveje, 2017	14	3689	338	23431	4.8%	0.26 [0.15, 0.45]	← → ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓		
Bang, 2020	76	10548	73	8648	6.7%	0.85 [0.62, 1.18]	_ _		
Bradley, 2020	71	55038	171	55038	7.1%	0.42 [0.31, 0.55]			
Chan. 2018	31	5843	378	19375	6.3%	0.27 [0.19, 0.39]			
Graham, 2019	96	72921	605	183003	7.6%	0.40 [0.32, 0.49]			
Hohnloser, 2018	25	10117	119	23823	5.7%	0.49 [0.32, 0.76]			
Huybrechts, 2020	336	19588	497	19588	8.2%	0.68 [0.59, 0.78]			
Kierpeseth, 2019	37	10550	48	6435	5.7%	0.47 [0.31, 0.72]			
Larsen 2016	15	6349	118	35436	4.8%	0 71 [0 41 1 21]			
Lee 2019	108	22177	388	25420	7 7%	0.32 [0.26 0.39]			
Li 2017	111	38470	183	38470	7 5%	0.61 [0.48 0.77]	_ _		
Lip 2018	264	100977	588	100977	8 1%	0 45 [0 39 0 52]			
Martinez 2018	5	1392	500	1392	1.6%	1 00 [0 29 3 45]			
Mitsuntisuk 2021	7	405	7	605	2.1%	1 49 [0 53 4 23]			
Nielsen 2017	27	4400	336	38893	6.0%	0.71 [0.48 1.05]			
Rodríguez-Bernal 2018	10	2250	430	32476	4 1%	0.33 [0.18, 0.62]			
Stoork 2017	20	6800	150	18004	6.0%	0.55 [0.10, 0.02]			
Subtotal (95% CI)	29	371622	100	631104	100.0%	0.49 [0.41 0.59]			
Total events	1262	571022	1121	031101	100.070	0115 [0111, 0155]	•		
Hotorogonaity: $Tau^2 = 0.0$	$0. Chi^2 -$	06 27 de	F = 16 (D	< 0.0000	1), 1 ² – 9	10/			
Heterogeneity. Tau = 0.0	= 7.02 (P)	60.57, ui	I = 10 (P)	< 0.0000	1), 1 = 0	170			
lest for overall effect: Z =	7.92 (P ·	< 0.00001	L)						
2.2.2 Anivahan ve Dahiga	tran								
		2000		0500	c	0.00.00.17.1.001			
Adeboyeje, 2017	14	3689	37	8539	6.0%	0.88 [0.47, 1.62]			
Granam, 2019	96	72921	104	86293	15.7%	1.09 [0.83, 1.44]			
Hohnloser, 2018	35	10117	20	5122	7.1%	0.89 [0.51, 1.53]			
Jansson, 2020	20	11493	6	6453	3.1%	1.87 [0.75, 4.66]			
Lee, 2019	112	22177	62	17745	14.3%	1.45 [1.06, 1.97]			
Lip, 2018	34	37314	35	37314	8.8%	0.97 [0.61, 1.56]			
Mueller, 2019	16	6200	3	1112	1.8%	0.96 [0.28, 3.28]			
Nielsen, 2017	27	4400	68	8875	9.5%	0.80 [0.51, 1.25]			
Rodríguez-Bernal, 2018	10	2259	16	3380	4.0%	0.94 [0.43, 2.06]			
Rutherford, 2020	74	10413	111	10413	15.0%	0.67 [0.50, 0.89]	_ _		
Staerk, 2017	29	6899	48	12613	9.1%	1.10 [0.70, 1.75]			
Staerk, 2018	23	7203	10	7078		Not estimable			
Tepper, 2018	13	8785	36	20963	5.7%	0.86 [0.46, 1.62]			
Subtotal (95% CI)		196667		218822	100.0%	0.98 [0.83, 1.16]	+		
Total events	480		546						
Heterogeneity: Tau ² = 0.0	3; Chi ² =	16.71, di	f = 11 (P	= 0.12); I	² = 34%				
Test for overall effect: Z =	0.21 (P =	= 0.83)							
2.2.3 Apixaban vs Rivaro	xaban								
Adeboyeje, 2017	14	3689	46	8398	4.5%	0.69 [0.38, 1.26]			
Fralick, 2020	113	39351	124	39351	8.9%	0.91 [0.71, 1.18]			
Graham, 2019	96	72921	213	106369	9.1%	0.66 [0.52, 0.84]	_ -		
Hohnloser, 2018	35	10117	106	22143	7.0%	0.72 [0.49, 1.06]			
Jansson, 2020	20	11493	30	7897	4.8%	0.46 [0.26, 0.81]			
Lee, 2019	108	22177	201	35965	9.2%	0.87 [0.69, 1.10]			
Lip, 2018	130	107236	206	107236	9.4%	0.63 [0.51, 0.79]	_ -		
Mueller, 2019	16	6200	35	7265	4.6%	0.54 [0.30, 0.97]			
Nielsen, 2017	27	4400	26	3476	5.1%	0.82 [0.48, 1.40]			
Perreault, 2021	16	6771	15	4632	3.7%	0.73 [0.36, 1.47]			
Ray, 2021	994	353879	624	227572	10.9%	1.02 [0.93, 1.13]	+		
Rodríguez-Bernal, 2018	10	2259	21	3445	3.4%	0.73 [0.34, 1.54]			
Rutherford, 2020	105	13699	210	13699	9.2%	0.50 [0.40, 0.63]	_ -		
Staerk, 2017	29	6899	34	5693	5.6%	0.70 [0.43, 1.15]			
Staerk, 2018	23	7203	28	6868		Not estimable			
Tepper, 2018	13	8785	64	30529	4.5%	0.71 [0.39, 1.28]	_		
Subtotal (95% CI)		669876		623670	100.0%	0.71 [0.61, 0.84]	◆		
Total events	1726		1955						
Heterogeneity: $Tau^2 = 0.0$	6; Chi ² =	53.61, di	f = 14 (P	< 0.0000	1); $I^2 = 7$	4%			
Test for overall effect: Z =	4.03 (P -	< 0.0001)							
		_,							
							Favours Apixaban Favours Comparator		

Figure 6. Comparison of apixaban to VKAs (2.2.1), dabigatran (2.2.2) and rivaroxaban (2.2.3) for ICH [18,20,23–28,30,31,33–35,37,39–42,44,46–48,50,52,53].

3.4. Sub-Group and Sensitivity Analyses

Sub-group meta-analyses exploring the impact of participants' age (≥75 and <75 years) were not possible due to insufficient sub-group data stratified by consistent age boundaries within the primary trials. Sub-group analyses for the impact of geographic region (North America, Asia, Europe) on the safety and effectiveness of apixaban are presented in Figures S2–S4 (Supplement S3). Meta-analyses are presented for the primary outcomes stroke/SE, mortality and major bleeding comparing apixaban to VKAs, apixaban to dabigatran and apixaban to rivaroxaban stratified by geographic region.

3.5. Stratification by Geographic Region

Regarding the apixaban vs VKA comparisons, the relative risk of stroke/SE was significantly lower with apixaban in North America, but not in Asia or Europe. There was no difference in the relative risk of mortality across the geographic sub-groups, and the relative risk of major bleeding was lower with apixaban across all geographic sub-groups (Figure S2; Supplement S4). For the apixaban vs dabigatran comparisons, the relative risk of stroke/SE and mortality were significantly lower with apixaban in North America only. The relative risk of major bleeding was significantly lower with apixaban vs rivaroxaban comparisons, the relative risk of stroke/SE was significantly lower with apixaban vs rivaroxaban comparisons, the relative risk of stroke/SE was significantly lower with apixaban in North America only. The relative risk of stroke/SE was significantly lower with apixaban in North America only. The relative risk for mortality was significantly lower with apixaban in North America only. The relative risk for mortality was significantly lower with apixaban in North America only. The relative risk for mortality was significantly lower with apixaban in North America only. The relative risk for mortality was significantly lower with apixaban in Sorth America and Europe and could not be estimated in Asia (due to no eligible studies). The relative risk for major bleeding was significantly lower with apixaban across all geographic subgroups (Figure S4; Supplement S4).

Sensitivity analyses were not necessary to explore the impact of studies deemed 'serious risk of bias' on the safety and effectiveness of apixaban, as no studies with 'serious risk of bias' were included in the meta-analyses.

4. Discussion

Our systematic review and meta-analyses show that the use of apixaban was associated with improved effectiveness (reduced stroke/SE and ischaemic stroke) and safety profile (major bleeding and ICH) when compared with the use of VKAs. Compared with dabigatran, apixaban was associated with significantly lower stroke or systemic embolism, major bleeding events and ischaemic stroke but not mortality or ICH. Compared to rivaroxaban, apixaban was associated with significantly lower mortality, major bleeding, ischaemic stroke, and ICH but not stroke/SE. Some results varied when stratified by geographic region.

In the ARISTOTLE randomised controlled trial (*n* = 18,201 people with AF), apixaban was superior to warfarin for the prevention of stroke or systemic embolism [13]. A phase II randomised controlled trial, ARISTOTLE-J, showed that in Japanese patients with AF, apixaban was well tolerated, with lower rates of major bleeding than warfarin over 12 weeks. However, to determine the effectiveness and safety of apixaban with those of OACs other than VKAs (i.e., warfarin), namely, dabigatran, rivaroxaban and edoxaban, real-world studies are needed.

Our findings extend those of a previous systematic review and meta-analysis (16 studies with up to n = 266,598 people with AF included in the meta-analysis), which showed that the use of apixaban in cohort studies was associated with an overall similar effectiveness in reducing stroke and any thromboembolic events when compared with the use of warfarin (odds ratio 0.92, 95% CI 0.72-1.10) [4]. However, the previous review demonstrated a better safety profile for apixaban compared to warfarin, dabigatran, and rivaroxaban. A more recent systematic review and network meta-analysis (21 studies with 605,771 people with AF) [55] found that apixaban was associated with a lower risk of major bleeding compared to rivaroxaban (hazard ratio 1.8, 95% CI 1.6–2.1) and dabigatran (hazard ratio 1.4, 95% CI 1.2-1.6), which is in agreement with the findings of the present study. Menichelli et al. [55] did, however, showed a higher risk of stroke or systemic embolism with rivaroxaban compared to apixaban (hazard ratio 1.4, 95% CI 1.00-1.80) but not with dabigatran compared with apixaban, which is contrary to our findings, although their work included fewer studies and participants. The authors also did not find a mortality benefit for apixaban, whereas the present study found a mortality benefit for apixaban vs. rivaroxaban. Thus, the analysis of randomised controlled trials and cohort studies demonstrated differing (and not yet established) effectiveness and safety profiles in DOAC–DOAC comparisons.

A recent retrospective cohort study (published after the searches for this systematic review), including >580,000 US Medicare beneficiaries, found that rivaroxaban was associated with a higher adjusted risk for ischaemic or haemorrhagic events (hazard ratio 1.18 95% CI 1.12–1.24) compared to apixaban [18]. This present study was updated to include this work in the appropriate meta-analyses. The findings in the present review demonstrate an overall beneficial association for apixaban over rivaroxaban for stroke/SE, mortality, major bleeding, ischaemic stroke and ICH. These findings add to the body of evidence suggesting that apixaban is associated with a lower bleeding risk and greater thromboembolic protection compared with rivaroxaban. Further and more broadly, our findings provide evidence that, although apixaban was not associated with an improvement in all outcomes across all DOAC comparisons, none of the outcomes we investigated favoured either dabigatran or rivaroxaban when compared to apixaban.

Limitations

The generally high heterogeneity in several meta-analyses makes it challenging to ascertain definitive conclusions. Furthermore, there was insufficient evidence from realworld studies to compare edoxaban with other commonly used DOACs. Other factors may have also influenced our findings, including inappropriate DOAC dosing and individual patient OAC adherence and associated comorbidities. Similarly, we did not investigate differences in DOAC dosage and associated study outcomes within this systematic review. Despite the reduced data on the number of participants receiving the standard or a lower dose apixaban, Proietti et al. previously demonstrated that the standard dose may be superior to a reduced dose of apixaban for the reduction of any thromboembolic event [4]. Indeed, OAC is only one aspect of holistic or integrated care management of AF [2], whereby adherence to such an approach and appropriate characterisation of AF patients have been associated with improved clinical outcomes [56,57]. Further, the addition of statin therapy to OAC has been shown to improve inhospital prognosis of patients with acute ischaemic stroke [43] and reduce long-term major adverse cardiovascular events in patients with embolic stroke of undetermined source [58]. This is also important when considering the use of apixaban, given the need for twice-daily dosing compared to once-daily dosing for rivaroxaban, for example, and should be considered on a patient-by-patient and shared decision-making process. Finally, most real-world studies included in this review were of a retrospective cohort design, with innate and well-known limitations, although, adjusted effect measures or propensity score matched populations were used where possible.

5. Conclusions

In this systematic review and meta-analysis combining data from clinical trials and real-world studies with >3.9 million participants, apixaban was associated with a better overall safety and effectiveness profile compared to VKAs and other DOACs. Despite the use of random-effect models to estimate overall effect estimates, considerable heterogeneity was present in most meta-analyses, and this should be considered when interpreting the results.

Supplemental Material: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Supplement S1. Full search strategies. Supplement S2. Characteristics of the included studies. Supplement S3. Risk of bias of the included studies. Supplement S4. Sub-group meta-analyses. References [59–84] are cited in Supplementary Materials.

Author Contributions: Conceptualization, B.J.R.B., D.A.L. and G.Y.H.L.; formal analysis, B.J.R.B.; investigation, B.J.R.B., D.A.L., J.Z., P.C. and D.G.; data curation, B.J.R.B., D.A.L., J.Z., P.C. and D.G.; writing – original draft preparation, B.J.R.B.; writing – review and editing, B.J.R.B., D.A.L., P.C., J.Z., D.G., C.D.M., P.D., S.K., S.H.H. and G.Y.H.L., visualization, B.J.R.B. and P.C.; supervision, B.J.R.B., D.A.L. and G.Y.H.L.; funding acquisition, B.J.R.B., D.A.L. and G.Y.H.L. All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded by a research grant from Pfizer Inc and Bristol-Myers Squibb.

Institutional Review Board Statement: Ethical review and approval were waived for this study due to it being a systematic review and meta-analysis of published data.

Informed Consent Statement: Not applicable as a systematic review and meta-analysis of published data.

Data Availability Statement: Not applicable as data is already published.

Conflicts of Interest: B.J.R.B. has received research funding from Bristol Myers Squibb (BMS)/Pfizer. D.A.L. has received investigator-initiated educational grants from BMS, has been a speaker for Boehringer Ingeheim, and BMS/Pfizer and has consulted for BMS, Boehringer Ingelheim, and Daiichi-Sankyo. C.D.M.: Consultant for AstraZeneca, Bayer Pharmaceuticals, Incyte, Merck, Pfizer, Sanofi, and Takeda and grant funding from Merck. P.D.: Honoraria and consulting fees and research support from Bayer, BMS, Pfizer, and Servier. S.K.: investigator-initiated grants from Novartis and Bristol-Myers Squibb (BMS), and has been a speaker for BMS/Pfizer. S.H.H.: consulting fees from Bayer Healthcare, BI, BMS, Boston Scientific, Daiichi Sankyo, Gilead, Johnson & Johnson, Medtronic, Pfizer, Sanofi Aventis, Servier, Zoll and lecture fees from Bayer Healthcare, BI, BMS, Daiichi Sankyo, Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally.

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