Therapeutics Initiative

Better prescribing. Better health.

THE UNIVERSITY OF BRITISH COLUMBIA

Comparative effectiveness and safety of direct oral anticoagulants in patients with nonvalvular atrial fibrillation

A systematic review and meta-analysis of observational studies

February 2024

1. Background

Nonvalvular atrial fibrillation (NVAF) affects about 1-2% of all Canadians, but prevalence increases dramatically with age (< 1.0% up to 50 years of age, 4% at 65 years, and 12% above age 80).[1] NVAF is independently associated with a 1.5- to 4-fold increased risk of mortality, predominantly due to thromboembolic events and ventricular dysfunction. Compared with people who are anticoagulated, non-anticoagulated AF patients have a 3- to 5-fold increased risk of stroke, although absolute risks depend on many other factors.[2]

However, anticoagulated patients risk serious morbidity and mortality from hemorrhage. In the United States from 2007 through 2009, bleeding attributed to warfarin caused one-third of the nearly 100,000 emergency hospitalizations for an adverse drug event in people age 65 or older.[3] A similar analysis in older people Ontario from 2006 through 2008 found anticoagulants (then limited to Vitamin K antagonists) responsible for 15% of adverse drug events assessed in emergency departments.[4]

The decision to provide anti-coagulant therapy depends on multiple clinical factors, including the anticipated risk of stroke, bleeding history, kidney and liver function, prior drug experience, and patient goals and preferences.

1.1 Warfarin

Warfarin is a low-cost and effective therapy used since the 1950's to reduce the risk of stroke in NVAF patients. But it requires regular blood tests to maintain INR (international normalized ratio) within the target therapeutic range. Numerous drug and food interactions affect warfarin's efficacy and safety.

1.2 Direct oral anticoagulants (DOACs)

In 2010 Health Canada approved dabigatran (PRADAXA®) as the first direct oral anticoagulant (DOAC) for stroke prevention in patients with NVAF, inhibiting thrombin (Factor IIa). Approval was based mainly on one large randomized controlled trial (RCT). The RE-LY trial compared dabigatran with warfarin, but it was not double blinded. Therapeutics Letter 80 analysed the RE-LY trial and concluded that licensing of dabigatran at 150mg BID was *"premature, pharmacologically irrational and unsafe for many patients."*[5] However, dabigatran quickly became a popular alternative to warfarin because of its major convenience advantage that blood tests to adjust dose are neither required nor practical.

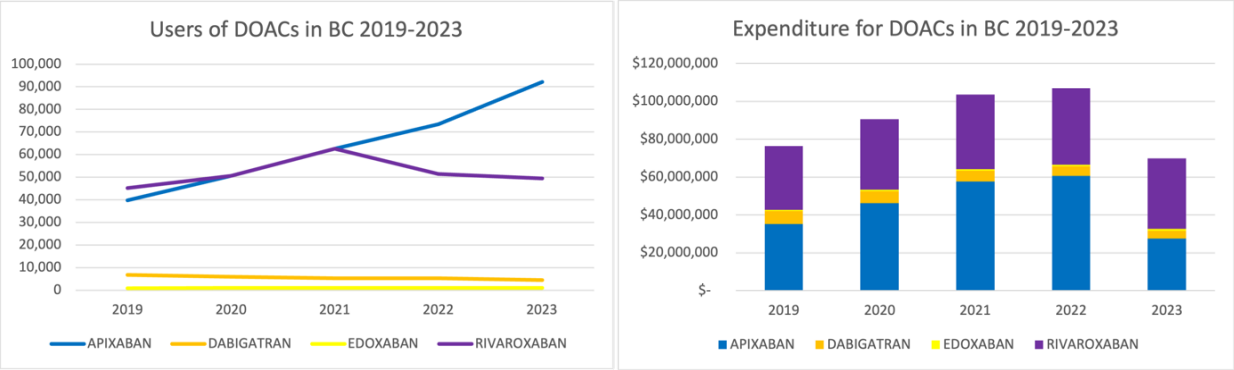
Between 2012 and 2016, Health Canada also approved the Factor Xa (prothrombinase) inhibitor DOACs: apixaban, rivaroxaban and edoxaban for treatment of NVAF (Table 1).

Table 1: DOACs approved in Canada for NVAF – year approved, usual dose, daily costs

Chemical name	Brand name	Approved	Usual dose	Daily ingredient cost (generic)	Daily ingredient cost (brand)
Dabigatran	PRADAXA	2010	150 mg BID	2.71	3.61
Apixaban	ELIQUIS	2012	5 mg BID	0.88	3.53
Rivaroxaban	XARELTO	2012	20 mg OD	0.77	3.07
Edoxaban	LIXIANA	2016	60 mg OD	Not available	3.17

Randomized controlled trials found DOACs to be at least as safe and effective as warfarin,[6] and they are now recommended as first-line therapy in NVAF patients for whom anticoagulation is indicated.[1] Apixaban and rivaroxaban are the most commonly prescribed DOACs for NVAF. In BC, apixaban and rivaroxaban dominate prescriptions and total costs in 2023 were $27,600,000 and $37,400,000, respectively.[7] Since generic formulations of apixaban, dabigatran, and rivaroxaban became available in Canada during 2023, annualized ingredient costs have dropped by 75% for both apixaban and rivaroxaban, versus 25% for dabigatran. Figure 1 shows changes in utilization of DOACs in BC and total drug ingredient costs (public and private, not including dispensing fees) since 2019.

Figure 1: Utilization of DOACs and total ingredient costs in BC (2019-2023)



1.3 Choosing a DOAC for NVAF

Randomized clinical trials directly comparing the DOACs for atrial fibrillation were never conducted, making it impossible to choose a superior DOAC based on direct evidence.[8] Indirect evidence is available from network meta-analyses of the large pre-approval RCTs that compared different DOACs with warfarin. But it is compromised by marked differences between these RCTs in the populations studied, in blinding strategies, and in the quality of warfarin management.[8]

However, comparative effectiveness research using large administrative databases, and increasingly sophisticated study methodology, provide a growing body of scientific evidence from which to compare the observed benefits and harms of the four DOACs licensed in Canada.

The BC Ministry of Health and Therapeutics Initiative seek to understand the direct evidence between the four DOACs apixaban, dabigatran, edoxaban and rivaroxaban for effectiveness and safety outcomes.

2. Research Question

In observational studies, what is the comparative effectiveness and safety of apixaban compared with other DOACs (dabigatran, edoxaban and rivaroxaban) in patients with nonvalvular atrial fibrillation (NVAF)?

3. Methods

We conducted a systematic review of observational studies that compare directly the effectiveness and safety of apixaban with other DOACs for treatment of NVAF patients (Table 2).

Table 2: PICOS and study inclusion criteria

Population	Patients with NVAF aged ≥18 years, treated for stroke prevention
Intervention	Apixaban
Comparators	Dabigatran, edoxaban, rivaroxaban
Outcomes	• Total mortality • Stroke/systemic embolism • Ischemic stroke • Intracranial hemorrhage • Major bleeds
Eligible studies	Prospective and retrospective cohort studies
Databases searched	Medline, Embase, CENTRAL up to September 5, 2023

3.1 Search strategy

We searched Ovid MEDLINE (1946-September 5, 2023), Embase (1974-September 5, 2023) and Cochrane Central Register of Controlled Trials (CENTRAL) September 2023 for observational studies directly comparing DOACs to each other in patients with NVAF. We also scanned the bibliographies of the included articles and relevant reviews for further references.

3.2 Inclusion and exclusion criteria

Studies eligible for inclusion were prospective or retrospective cohort studies comparing DOACs (apixaban, dabigatran, edoxaban or rivaroxaban) to each other in patients with NVAF. Conference abstracts of cohort studies were excluded since they contain insufficient information to adequately assess risk of bias.

3.3 Study selection

Two independent reviewers (BSH and SA) performed study selection. Titles and abstracts were screened to identify potentially relevant studies and duplicate publications; Full-text articles of potentially relevant studies were retrieved for review. Full-texts were independently assessed by the reviewers (BSH and SA) for study inclusion. Discrepancies were resolved by consensus.

3.4 Data collection and analysis

Two reviewers (BSH and SA) independently extracted data from the included studies. We used clinical outcomes as defined in the observational studies. While these studies define some outcomes differently, the events are obviously clinically important.

Pooled effect estimates were calculated using Review Manager 5.4 software of the Cochrane Collaboration. The meta-analysis is limited to included studies that reported number of events and total sample size. Results are presented as relative risks (RR) with 95% confidence intervals (Cis). Random-effects models were used to meta-analyze data.

Pooled effect estimates are presented for the comparisons of apixaban versus dabigatran, apixaban versus edoxaban, and apixaban versus rivaroxaban if there were sufficient data. For those studies that reported measures of interest as hazard ratios (HR) or odds ratios (OR) with 95% confidence intervals (CIs), we summarized their findings in summary tables.

3.5 Risk of bias assessment

Two independent reviewers (BSH and SA) assessed the included studies for risk of bias using the Risk Of Bias In Non-Randomized Studies—of Interventions (ROBINS-I) tool. Seven domains were assessed: bias due to confounding; bias in the selection of study participants; bias in the classification of interventions; bias due to departure from intended interventions; bias due to missing data; bias in the measurement of outcomes; and bias in the selection of the reported results. Based on the assessment of each domain, an overall risk of bias was assigned as low, moderate, serious, or critical, with the overall risk determined by the highest risk assigned in any individual domain.

4. Results

4.1 Search Findings

We identified 42 retrospective cohort studies (N=2,936,126). Of these, we could meta-analyze 27 studies (N=2,135,415) that reported the total number of events during the study periods.[12] The remaining 15 studies (N=800,711) reported HR, OR or incidence rates for clinical outcomes, precluding meta-analysis.

4.2 Description of included studies

The included studies were published between 2009 and 2023. Study duration ranged from 3 to 46 months. Mean/median patient age ranged from 62 to 86 years, and the proportion of females ranged between 18% and 66%. Of the 42 included studies, 21 were conducted in the USA, 12 in Europe, 4 in the UK, 3 in Asia and 1 in Canada. One study included data from Canada, the USA and the UK.

All studies were judged to have a moderate risk of bias except for one study that was judged to be at serious risk of bias (Noseworthy 2017). The risk of bias of all included studies was elevated due to confounding, an intrinsic limitation of observational studies.

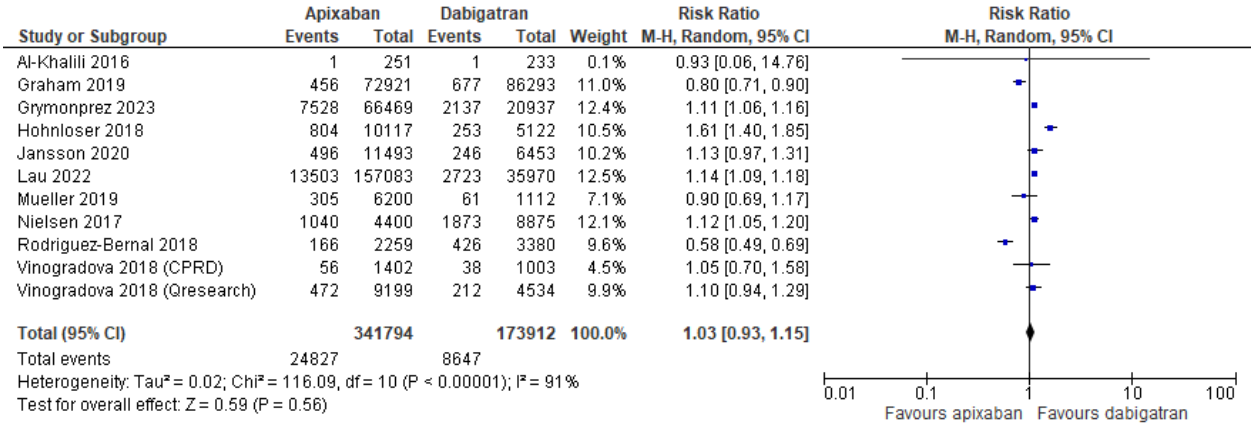
4.3 Outcomes reported

4.3.1 Apixaban vs. Dabigatran or Rivaroxaban

Based on 11 studies (n = 515,706) there was no difference in total mortality between apixaban and dabigatran (RR 1.03, 95% CI 0.93 to 1.10) (Figure 2A). Apixaban was associated with lower total mortality as compared to rivaroxaban (RR 0.86, 95% CI 0.79–0.95) in 13 studies (n=1,267,040) (Figure 2B).

Figure 2: Total mortality

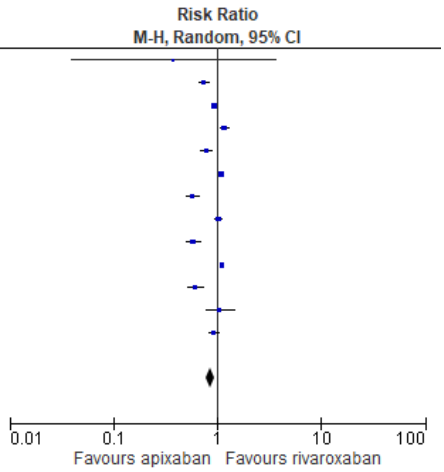
A) Apixaban vs Dabigatran



B) Apixaban vs Rivaroxaban

Study or Subgroup	Apixaban Events	Apixaban Total	Rivaroxaban Events	Rivaroxaban Total	Weight	Risk Ratio M-H, Random, 95% CI
Al-Khalili 2016	1	251	3	282	0.2%	0.37 [0.04, 3.58]
Graham 2019	456	72921	904	106369	8.5%	0.74 [0.66, 0.82]
Grymonprez 2023	7342	65026	7234	59271	9.6%	0.93 [0.90, 0.95]
Hohnloser 2018	804	10117	1509	22143	9.0%	1.17 [1.07, 1.27]
Jansson 2020	496	11493	438	7897	8.3%	0.78 [0.69, 0.88]
Lau 2022	13420	157083	8374	107140	9.6%	1.09 [1.06, 1.12]
Mueller 2019	305	6200	622	7265	8.1%	0.57 [0.50, 0.66]
Nielsen 2017	1040	4400	798	3476	9.0%	1.03 [0.95, 1.12]
Perreault 2021	284	6771	334	4632	7.7%	0.58 [0.50, 0.68]
Ray 2021	12839	353879	7497	227572	9.6%	1.10 [1.07, 1.13]
Rodriguez-Bernal 2018	166	2259	412	3445	7.3%	0.61 [0.52, 0.73]
Vinogradova 2018 (CPRD)	56	1402	112	2950	4.6%	1.05 [0.77, 1.44]
Vinogradova 2018 (Qresearch)	472	9199	757	13597	8.5%	0.92 [0.82, 1.03]
Total (95% CI)		**701001**		**566039**	**100.0%**	**0.86 [0.79, 0.95]**
Total events	37681		28994			

Heterogeneity: Tau² = 0.02; Chi² = 316.00, df = 12 (P < 0.00001); I² = 96%
Test for overall effect: Z = 3.11 (P = 0.002)



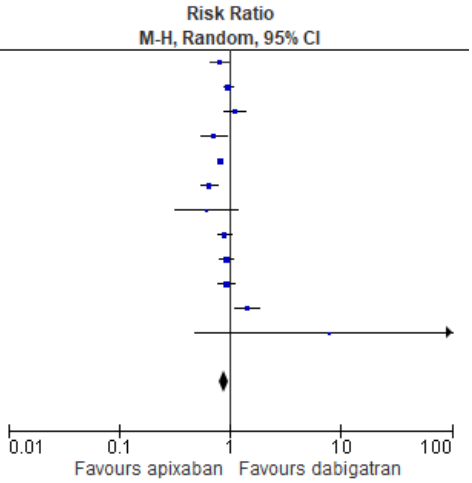
A total of 12 (n = 828,396) and 14 (n = 1,826,473) studies compared apixaban with dabigatran and rivaroxaban, respectively, for stroke/SE (Figure 3A). The difference in risk of stroke/SE was not statistically significant between apixaban and rivaroxaban (RR 0.92, 95% CI 0.85–1.00) (Figure 3B).

Figure 3: Stroke/Systemic embolism

A) Apixaban vs Dabigatran

Study or Subgroup	Apixaban Events	Apixaban Total	Dabigatran Events	Dabigatran Total	Weight	Risk Ratio M-H, Random, 95% CI
Graham 2019	190	72921	279	86293	9.3%	0.81 [0.67, 0.97]
Grymonprez 2023	1938	66469	628	20937	12.5%	0.97 [0.89, 1.06]
Hohnloser 2018	226	10117	104	5122	7.9%	1.10 [0.87, 1.38]
Jansson 2020	115	11493	91	6453	6.7%	0.71 [0.54, 0.93]
Lau 2022	15738	330362	4343	74733	13.7%	0.82 [0.79, 0.85]
Lip 2018	215	37314	333	37314	9.8%	0.65 [0.54, 0.77]
Mitsuntisuk 2021	14	405	25	441	2.0%	0.61 [0.32, 1.16]
Nielsen 2017	236	4400	535	8875	10.5%	0.89 [0.77, 1.03]
Rutherford 2020	335	10413	360	10413	10.6%	0.93 [0.80, 1.08]
Staerk 2017	171	6899	336	12613	9.4%	0.93 [0.78, 1.12]
Staerk 2018	148	7203	102	7078	7.3%	1.43 [1.11, 1.83]
Tiew 2020	12	98	0	30	0.1%	7.83 [0.48, 128.45]
Total (95% CI)		**558094**		**270302**	**100.0%**	**0.89 [0.81, 0.98]**
Total events	19338		7136			

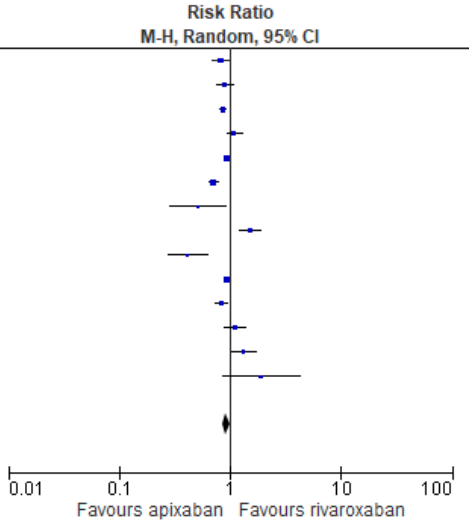
Heterogeneity: Tau² = 0.02; Chi² = 52.80, df = 11 (P < 0.00001); I² = 79%
Test for overall effect: Z = 2.35 (P = 0.02)



B) Apixaban vs Rivaroxaban

Study or Subgroup	Apixaban Events	Apixaban Total	Rivaroxaban Events	Rivaroxaban Total	Weight	Risk Ratio M-H, Random, 95% CI
Fralick 2020	206	39351	251	39351	7.3%	0.82 [0.68, 0.99]
Graham 2019	190	72921	312	106369	7.4%	0.89 [0.74, 1.06]
Grymonprez 2023	1805	65026	1916	59271	11.1%	0.86 [0.81, 0.91]
Hohnloser 2018	226	10117	456	22143	8.1%	1.08 [0.93, 1.27]
Lau 2022	15674	330362	10699	211038	11.8%	0.94 [0.91, 0.96]
Lip 2018	710	107236	1008	107236	10.2%	0.70 [0.64, 0.78]
Mitsuntisuk 2021	14	405	41	604	1.6%	0.51 [0.28, 0.92]
Nielsen 2017	236	4400	124	3476	6.4%	1.50 [1.22, 1.86]
Perreault 2021	37	6771	61	4632	2.9%	0.41 [0.28, 0.62]
Ray 2021	4108	353879	2838	227572	11.4%	0.93 [0.89, 0.98]
Rutherford 2020	452	13699	541	13699	9.3%	0.84 [0.74, 0.94]
Staerk 2017	171	6899	128	5693	6.1%	1.10 [0.88, 1.38]
Staerk 2018	148	7203	107	6868	5.6%	1.32 [1.03, 1.69]
Tiew 2020	12	98	10	154	0.9%	1.89 [0.85, 4.20]
Total (95% CI)		**1018367**		**808106**	**100.0%**	**0.92 [0.85, 1.00]**
Total events	23989		18492			

Heterogeneity: Tau² = 0.01; Chi² = 97.64, df = 13 (P < 0.00001); I² = 87%
Test for overall effect: Z = 2.08 (P = 0.04)



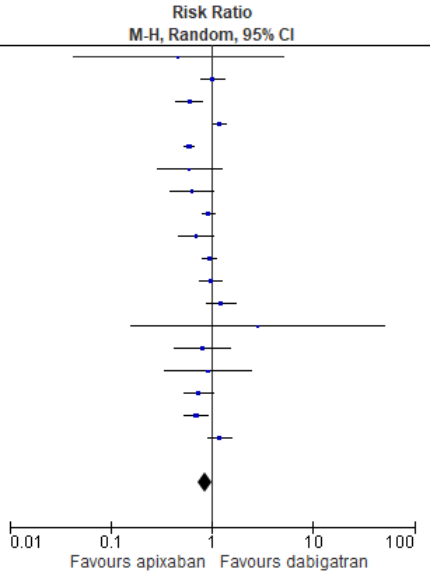
A total of 18 (n = 394,554) and 19 (n = 1,087,791) studies compared apixaban with dabigatran and rivaroxaban, respectively, for ischemic stroke. Apixaban was associated with a significantly lower risk of ischaemic stroke compared with dabigatran (RR 0.85, 95% CI 0.73–0.99) and rivaroxaban (RR 0.75, 95% CI 0.58–0.98). Meta-analyses for this outcome are presented below (Figures 5A and 5B).

Figure 4: Ischemic stroke

A) Apixaban vs Dabigatran

Study or Subgroup	Apixaban Events	Apixaban Total	Dabigatran Events	Dabigatran Total	Weight	Risk Ratio M-H, Random, 95% CI
Al-Khalili 2016	1	251	2	233	0.4%	0.46 [0.04, 5.08]
Hohnloser 2018	165	10117	82	5122	7.1%	1.02 [0.78, 1.32]
Jansson 2020	83	11493	78	6453	6.6%	0.60 [0.44, 0.81]
Lee 2019	385	22177	370	25420	8.3%	1.19 [1.04, 1.37]
Lip 2018	533	100977	895	100977	8.6%	0.60 [0.54, 0.66]
Mitsuntisuk 2021	11	405	20	441	3.0%	0.60 [0.29, 1.23]
Mueller 2019	67	6200	19	1112	4.6%	0.63 [0.38, 1.05]
Nielsen 2017	230	4400	504	8875	8.2%	0.92 [0.79, 1.07]
Rodriguez-Bernal 2018	35	2259	75	3380	5.6%	0.70 [0.47, 1.04]
Rutherford 2020	302	10413	322	10413	8.2%	0.94 [0.80, 1.09]
Staerk 2017	86	6899	163	12613	7.1%	0.96 [0.74, 1.25]
Staerk 2018	75	7203	60	7078	6.3%	1.23 [0.88, 1.72]
Tiew 2020	4	98	0	30	0.3%	2.82 [0.16, 50.90]
Villines 2019	17	4802	21	4802	3.6%	0.81 [0.43, 1.53]
Vinogradova 2018 (CPRD)	9	1402	7	1003	1.9%	0.92 [0.34, 2.46]
Vinogradova 2018 (Qresearch)	86	9199	58	4534	6.3%	0.73 [0.52, 1.02]
Yang 2020 (cohort without stroke)	106	1864	95	1168	7.1%	0.70 [0.54, 0.91]
Yang 2020 (cohort with stroke()	124	494	52	247	6.8%	1.19 [0.90, 1.59]
Total (95% CI)		**200653**		**193901**	**100.0%**	**0.85 [0.73, 0.99]**
Total events	2319		2823			

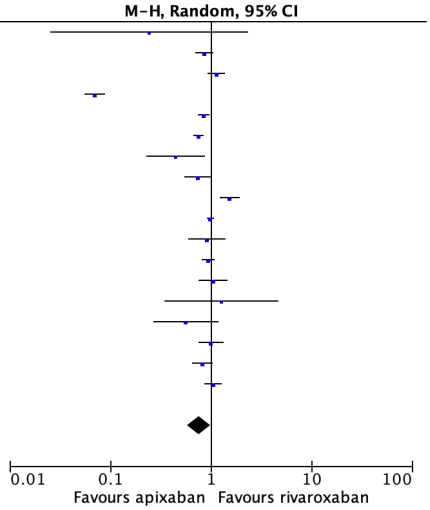
Heterogeneity: Tau² = 0.07; Chi² = 91.53, df = 17 (P < 0.00001); I² = 81%
Test for overall effect: Z = 2.06 (P = 0.04)



B) Apixaban vs Rivaroxaban

Study or Subgroup	Apixaban Events	Apixaban Total	Rivaroxaban Events	Rivaroxaban Total	Weight	Risk Ratio M-H, Random, 95% CI
Al-Khalili 2016	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]
Mueller 2019	67	6200	106	7265	6.0%	0.74 [0.55, 1.00]
Nielsen 2017	230	4400	119	3476	6.3%	1.53 [1.23, 1.90]
Ray 2021	2196	353879	1447	227572	6.5%	0.98 [0.91, 1.04]
Rodriguez-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]
Tiew 2020	4	98	5	154	2.6%	1.26 [0.35, 4.57]
Vinogradova 2018 (CPRD)	9	1402	34	2950	4.4%	0.56 [0.27, 1.16]
Vinogradova 2018 (Qresearch)	86	9199	128	13597	6.1%	0.99 [0.76, 1.30]
Yang 2020 (cohort without stroke)	106	1864	281	4035	6.3%	0.82 [0.66, 1.01]
Yang 2020 (cohort with stroke()	124	494	265	1104	6.3%	1.05 [0.87, 1.26]
Total (95% CI)		**591423**		**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 < 0.00001); $I^2 = 97\%$
Test for overall effect: Z = 2.09 (P = 0.04)



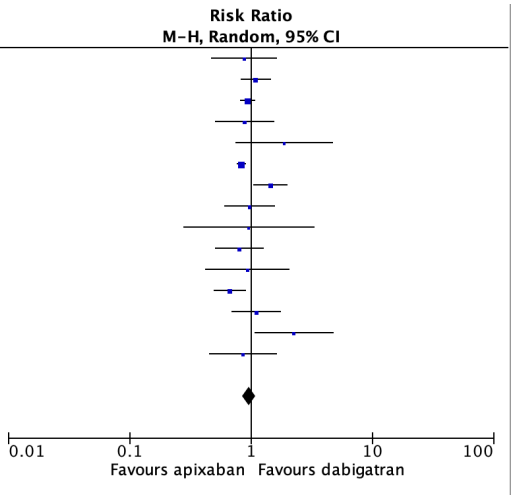
A total of 15 studies (n = 922,271) compared apixaban with dabigatran and were included in meta-analysis of intracranial hemorrhage (ICH). There was no difference in ICH between apixaban and dabigatran (RR 0.96, 95% CI 0.85–1.10) (Figure 5A). As compared to rivaroxaban (18 studies; n = 1,973,314), apixaban was associated with a lower risk of ICH (Figure 5B).

Figure 5: Intracranial Haemorrhage

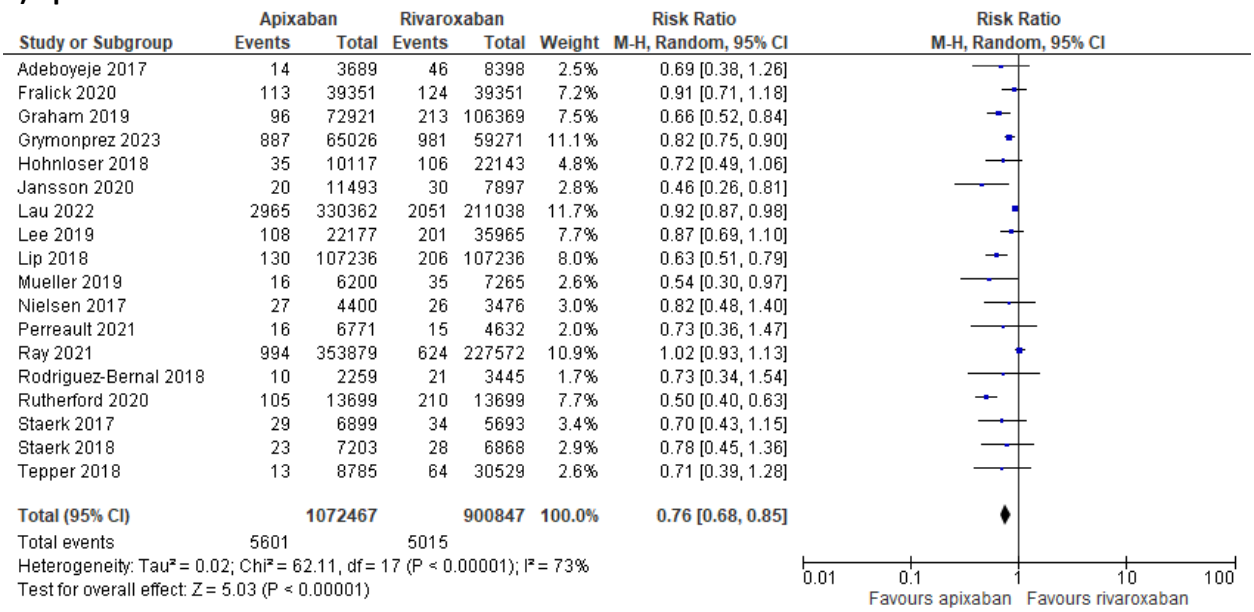
A) Apixaban vs Dabigatran

Study or Subgroup	Apixaban Events	Apixaban Total	Dabigatran Events	Dabigatran Total	Weight	Risk Ratio M-H, Random, 95% CI
Adeboyeje 2017	14	3689	37	8539	3.5%	0.88 [0.47, 1.62]
Graham 2019	96	72921	104	86293	10.3%	1.09 [0.83, 1.44]
Grymonprez 2023	904	66469	305	20937	16.6%	0.93 [0.82, 1.06]
Hohnloser 2018	35	10117	20	5122	4.2%	0.89 [0.51, 1.53]
Jansson 2020	20	11493	6	6453	1.8%	1.87 [0.75, 4.66]
Lau 2022	2974	330362	808	74733	18.7%	0.83 [0.77, 0.90]
Lee 2019	112	22177	62	17745	9.2%	1.45 [1.06, 1.97]
Lip 2018	34	37314	35	37314	5.3%	0.97 [0.61, 1.56]
Mueller 2019	16	6200	3	1112	1.0%	0.96 [0.28, 3.28]
Nielsen 2017	27	4400	68	8875	5.8%	0.80 [0.51, 1.25]
Rodriguez-Bernal 2018	10	2259	16	3380	2.3%	0.94 [0.43, 2.06]
Rutherford 2020	74	10413	111	10413	9.7%	0.67 [0.50, 0.89]
Staerk 2017	29	6899	48	12613	5.5%	1.10 [0.70, 1.75]
Staerk 2018	23	7203	10	7078	2.6%	2.26 [1.08, 4.74]
Tepper 2018	13	8785	36	20963	3.4%	0.86 [0.46, 1.62]
Total (95% CI)		**600701**		**321570**	**100.0%**	**0.96 [0.85, 1.10]**
Total events	4381		1669			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 28.51$, df = 14 (P = 0.01); $I^2 = 51\%$
Test for overall effect: Z = 0.55 (P = 0.58)



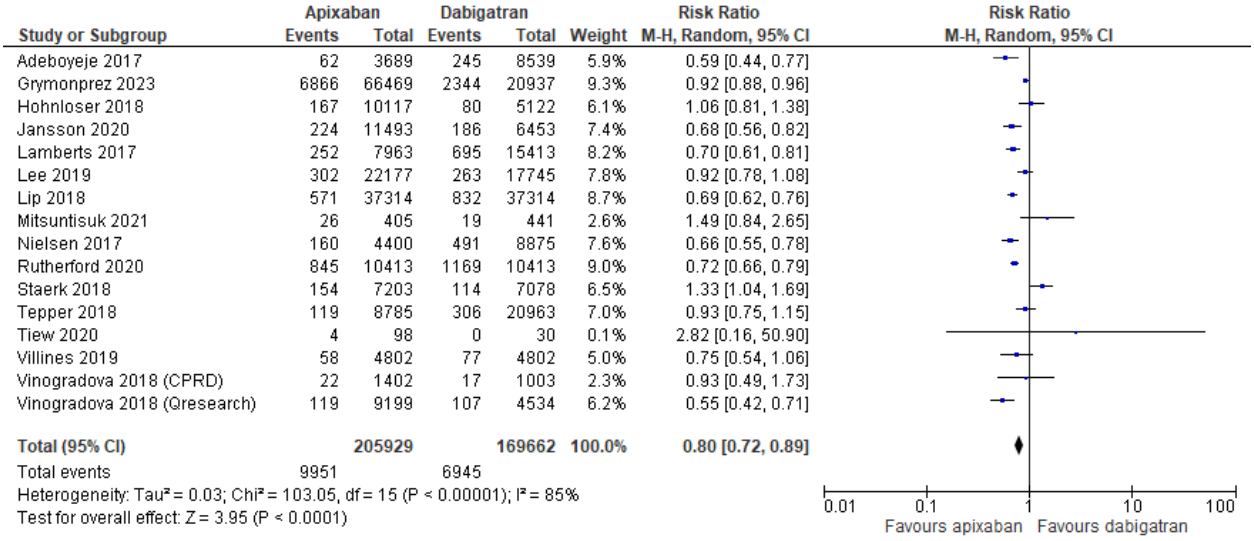
B) Apixaban vs Rivaroxaban



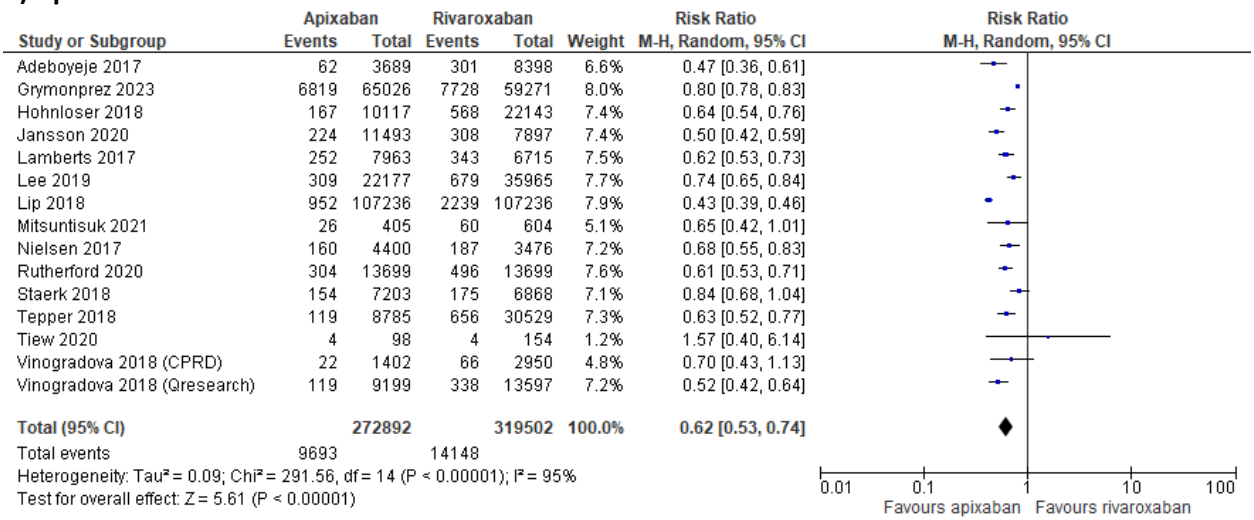
A total of 16 (n = 375,591) and 15 (n = 592,394) studies compared apixaban with dabigatran and rivaroxaban, respectively, for major bleeds. Apixaban was associated with a significantly lower risk of major bleeds compared with dabigatran (RR 0.80, 95% CI 0.72–0.89) (Figure 6A) and rivaroxaban (RR 0.62, 95% CI 0.53–0.74) (Figure 6B).

Figure 6: Major bleeds

A) Apixaban vs Dabigatran



B) Apixaban vs Rivaroxaban



4.3.2 Apixaban vs. Edoxaban

Only 3 included studies compared apixaban with edoxaban. Findings of 3 published observational studies comparing apixaban with edoxaban are summarized in Table 3.

Table 3: TI Summary of observational studies comparing apixaban vs. edoxaban

Outcome HR (95% C()	Lee 2019 (n = 37,673)	Lau 2022 (n = 218,780)	Grymonprez 2023 (n =)
Total mortality	NR	0.83, 95% CI 0.59, 1.17	1.17, 95% CI 1.09, 1.25
Stroke/systemic embolism	NR	NR	0.97, 95% CI 0.85, 1.10
Ischemic stroke	0.92, 95% CI 0.77, 1.09	NR	"no significant diff" Data NR
Intracranial hemorrhage	0.56, 95% CI 0.38, 0.82	0.91, 95% CI 0.56, 1.47	1.06, 95% CI 0.88, 1.28
Major bleeds	0.97, 95% CI 0.80, 1.18	NR	0.79, 95% CI 0.72, 1.28

4.4 Summary of findings

Table 4 shows that apixaban was associated with lower risks of major bleeds, compared with dabigatran and rivaroxaban. Despite similar stroke or systemic embolism risks, apixaban was associated with a lower risk of total mortality, ischemic stroke and intracranial hemorrhage compared with rivaroxaban. Apixaban and dabigatran were associated with similar risks of death and intracranial hemorrhage; but apixaban was associated with a lower risk of stroke or systemic embolism and of ischemic stroke, compared with dabigatran.

Table 4: TI Meta-analysis of DOAC observational studies

Outcome	Comparison	Number of studies (N)	Pooled Relative Risk (95% CI)
Total mortality	apixaban vs. dabigatran	11 (515,706)	1.03 (0.93, 1.15)
	apixaban vs. rivaroxaban	13 (1,267,040)	0.86 (0.79, 0.95)
Stroke/systemic embolism	apixaban vs. dabigatran	12 (828,396)	0.89 (0.81, 0.98)
	apixaban vs. rivaroxaban	14 (1,826,473)	0.92 (0.85, 1.00)
Ischemic stroke	apixaban vs. dabigatran	18 (394,554)	0.85 (0.73, 0.99)
	apixaban vs. rivaroxaban	19 (1,087,791)	0.75 (0.58, 0.98)
Intracranial hemorrhage	apixaban vs. dabigatran	15 (922,271)	0.96 (0.85, 1.10)
	apixaban vs. rivaroxaban	18 (1,973,314)	0.76 (0.68, 0.85)
Major bleeds	apixaban vs. dabigatran	16 (375,591)	0.80 (0.72, 0.89)
	apixaban vs. rivaroxaban	15 (592,394)	0.62 (0.53, 0.74)

5. Discussion

The retrospective design of administrative database studies has inherent limitations that preclude establishing causal relationships as confidently as one can assert from randomized clinical trials.

Except for one study judged to be at serious risk of bias (Noseworthy 2017), all studies were judged to have a moderate risk of bias. Due to the non-randomized nature of the evidence, we cannot exclude the possibility of residual confounding and other biases, even with the use of innovative statistical methods.[8]

In this instance the research studies on comparative effectiveness are large, methodologically sound, and remarkably consistent. This provides useful guidance for physicians to choose the most appropriate DOAC for their patients. In support of this position, previous systematic reviews found that the results of many large, well-designed observational studies of DOACs versus warfarin were consistent with the findings from RCTs.[11,12]

6. Conclusions

- Observational studies of comparative effectiveness provide consistent scientific evidence to inform the choice of a direct oral anticoagulant (DOAC) for non-valvular atrial fibrillation (NVAF).
- For patients with NVAF, apixaban is associated with a lower risk of major bleeds than rivaroxaban or dabigatran, and is similar to rivaroxaban but more effective than dabigatran for prevention of stroke and systemic embolism.
- Compared with rivaroxaban, apixaban use is associated with a lower risk of premature death or intracerebral bleeds.

7. References

Trial ID	Citation
Abraham 2017	Abraham, N.S.; Noseworthy, P.A.; Yao, X.; Sangaralingham, L.R.; Shah, N.D. Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study. Gastroenterology **2017**, 152, 1014–1022.e1.
Adeboyeje 2017	Adeboyeje, G.; Sylwestrzak, G.; Barron, J.J.; White, J.; Rosenberg, A.; Abarca, J.; Crawford, G.; Redberg, R. Major Bleeding Risk during Anticoagulation with Warfarin, Dabigatran, Apixaban, or Rivaroxaban in Patients with Nonvalvular Atrial Fibrillation. J. Manag. Care Spéc. Pharm. **2017**, 23, 968–978
Al-Khalili 2016	Al-Khalili, F.; Lindström, C.; Benson, L. The safety and persistence of non-vitamin-K-antagonist oral anticoagulants in atrial fibrillation patients treated in a well structured atrial fibrillation clinic. Curr. Med. Res. Opin. **2016**, 32, 779–785
Amin 2018	Amin, A.; Keshishian, A.; Vo, L.; Zhang, Q.; Dina, O.; Patel, C.; Odell, K.; Trocio, J. Real-world comparison of all-cause hospitalizations, hospitalizations due to stroke and major bleeding, and costs for non-valvular atrial fibrillation patients prescribed oral anticoagulants in a US health plan. J. Med. Econ. **2017**, 21, 244–253.
Amin 2019a	Amin, A.; Keshishian, A.; Dina, O.; Dhamane, A.; Nadkarni, A.; Carda, E.; Russ, C.; Rosenblatt, L.; Mardekian, J.; Yuce, H.; et al. Comparative clinical outcomes between direct oral anticoagulants and warfarin among elderly patients with non-valvular atrial fibrillation in the CMS medicare population. J. Thromb. Thrombolysis **2019**, 48, 240–249.
Amin 2019b	Amin, A.; Reeves, A.G.; Li, X.; Dhamane, A.; Luo, X.; Di Fusco, M.; Nadkarni, A.; Friend, K.; Rosenblatt, L.; Mardekian, J.; et al. Effectiveness and safety of oral anticoagulants in older adults with non-valvular atrial fibrillation and heart failure. PLoS ONE **2019**, 14, e0213614.
Andersson 2018	Andersson, N.W.; Svanström, H.; Lund, M.; Pasternak, B.; Melbye, M. Comparative effectiveness and safety of apixaban, dabigatran, and rivaroxaban in patients with non-valvular atrial fibrillation. Int. J. Cardiol. **2018**, 268, 113–119.
Deitelzweig 2016	Deitelzweig, S.; Bruno, A.; Trocio, J.; Tate, N.; Gupta, K.; Lin, J.; Lingohr-Smith, M. An early evaluation of bleeding-related hospital readmissions among hospitalized patients with nonvalvular atrial fibrillation treated with direct oral anticoagulants. Curr. Med. Res. Opin. **2016**, 32, 573–582
Deitelzweig 2017	Deitelzweig, S.; Luo, X.; Gupta, K.; Trocio, J.; Mardekian, J.; Curtice, T.; Lingohr-Smith, M.; Menges, B.; Lin, J. Comparison of effectiveness and safety of treatment with apixaban vs. other oral anticoagulants among elderly nonvalvular atrial fibrillation patients. Curr. Med. Res. Opin. **2017**, 33, 1745–1754
Durand 2020	Durand, M.; Schnitzer, M.E.; Pang, M.; Carney, G.; Eltonsy, S.; Filion, K.B.; Fisher, A.; Jun, M.; Kuo, I.F.; Matteau, A.; et al. Effectiveness and safety among direct oral anticoagulants in nonvalvular atrial fibrillation: A multi-database cohort study with meta-analysis. Br. J. Clin. Pharmacol. **2020**, 87, 2589–2601.
Fralick 2020	Fralick, M.; Colacci, M.; Schneeweiss, S.; Huybrechts, K.F.; Lin, K.J.; Gagne, J.J. Effectiveness and Safety of Apixaban Compared with Rivaroxaban for Patients with Atrial Fibrillation in Routine Practice. Ann. Intern. Med. **2020**, 172, 463.
Graham 2019	Graham, D.J.; Baro, E.; Zhang, R.; Liao, J.; Wernecke, M.; Reichman, M.E.; Hu, M.; Illoh, O.; Wei, Y.; Goulding, M.R.; et al.

	Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation. Am. J. Med. **2019**, 132, 596–604.e11.
Grymonprez 2023	Grymonprez M, Petrovic M, De Backer TL, Steurbaut S, Lahousse L. Clinical outcomes in patients with atrial fibrillation and a history of falls using non-vitamin K antagonist oral anticoagulants: A nationwide cohort study. International Journal of Cardiology. Heart & Vasculature. 2013 47:101223.
Hernandez 2017	Hernandez, I.; Zhang, Y.; Saba, S. Comparison of the Effectiveness and Safety of Apixaban, Dabigatran, Rivaroxaban, and Warfarin in Newly Diagnosed Atrial Fibrillation. Am. J. Cardiol. **2017**, 120, 1813–1819.
Hohnloser 2017	Hohnloser, S.H.; Basic, E.; Nabauer, M. Comparative risk of major bleeding with new oral anticoagulants (NOACs) and phenprocoumon in patients with atrial fibrillation: A post-marketing surveillance study. Clin. Res. Cardiol. **2017**, 15, 486–628.
Hohnloser 2018	Hohnloser, S.H.; Basic, E.; Hohmann, C.; Nabauer, M. Effectiveness and Safety of Non–Vitamin K Oral Anticoagulants in Comparison to Phenprocoumon: Data from 61,000 Patients with Atrial Fibrillation. Thromb. Haemost. **2018**, 118, 526–538.
Jansson 2020	Jansson, M.; Själander, S.; Sjögren, V.; Renlund, H.; Norrving, B.; Själander, A. Direct comparisons of effectiveness and safety of treatment with Apixaban, Dabigatran and Rivaroxaban in atrial fibrillation. Thromb. Res. **2020**, 185, 135–141.
Lamberts 2017	Lamberts, M.; Staerk, L.; Olesen, J.B.; Fosbøl, E.L.; Hansen, M.L.; Harboe, L.; Lefevre, C.; Evans, D.; Gislason, G.H. Major Bleeding Complications and Persistence with Oral Anticoagulation in Non-Valvular Atrial Fibrillation: Contemporary Findings in Real-Life Danish Patients. J. Am. Heart Assoc. **2017**, 6, e004517.
Lau 2022	Lau WCY, Torre CO, Man KKC, Stewart HM, Seager S, Van Zandt M, Reich C, Li J, Brewster J, Lip GYH, Hingorani AD, Wei L, Wong ICK. Comparative Effectiveness and Safety Between Apixaban, Dabigatran, Edoxaban, and Rivaroxaban Among Patients With Atrial Fibrillation : A Multinational Population-Based Cohort Study. 2022, Annals of Internal Medicine. 175(11):1515-1524
Lee 2019	Lee, S.-R.; Choi, E.-K.; Kwon, S.; Han, K.-D.; Jung, J.-H.; Cha, M.-J.; Oh, S.; Lip, G.Y. Effectiveness and Safety of Contemporary Oral Anticoagulants Among Asians with Nonvalvular Atrial Fibrillation. Stroke **2019**, 50, 2245–2249.
Lin 2017	Lin, J.; Trocio, J.; Gupta, K.; Mardekian, J.; Lingohr-Smith, M.; Menges, B.; You, M.; Nadkarni, A. Major bleeding risk and healthcare economic outcomes of non-valvular atrial fibrillation patients newly-initiated with oral anticoagulant therapy in the real-world setting. J. Med. Econ. **2017**, 20, 952–961.
Lip 2016	Lip, G.Y.H.; Keshishian, A.; Kamble, S.; Pan, X.; Mardekian, J.; Horblyuk, R.; Hamilton, M. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. Thromb. Haemost. **2016**, 116, 975–986.
Lip 2018	Lip, G.Y.; Keshishian, A.; Li, X.; Hamilton, M.; Masseria, C.; Gupta, K.; Luo, X.; Mardekian, J.; Friend, K.; Nadkarni, A.; et al. Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients. Stroke **2018**, 49, 2933–2944.
Lip 2020	Lip, G.Y.H.; Keshishian, A.; Kang, A.; Dhamane, A.D.; Luo, X.; Klem, C.; Rosenblatt, L.; Mardekian, J.; Jiang, J.; Yuce, H.; et al. Effectiveness and safety of oral anticoagulants among non-valvular atrial fibrillation patients with polypharmacy. Eur. Heart J. -Cardiovasc. Pharmacother. **2020**, 7, 405–414
Mentias 2020	Mentias, A.; Heller, E.; Sarrazin, M.V. Comparative Effectiveness of Rivaroxaban, Apixaban, andWarfarin in Atrial Fibrillation Patients with Polypharmacy. Stroke **2020**, 51, 2076–2086.

Mitsuntisuk 2021	Mitsuntisuk, P.; Nathisuwan, S.; Junpanichjaroen, A.; Wongcharoen, W.; Phrommintikul, A.; Wattanaruengchai, P.; Rattanavipanon, W.; Chulavatnatol, S.; Chaiyakunapruk, N.; Likittanasombat, K.; et al. Real-World Comparative Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants vs. Warfarin in a Developing Country. Clin. Pharmacol. Ther. **2020**, 109, 1282–1292.
Mueller 2019	Mueller, T.; Alvarez-Madrazo, S.; Robertson, C.; Wu, O.; Bennie, M. Comparative safety and effectiveness of direct oral anticoagulants in patients with atrial fibrillation in clinical practice in Scotland. Br. J. Clin. Pharmacol. **2018**, 85, 422–431.
Nielsen 2017	Nielsen, P.B.; Skjøth, F.; Søgaard, M.; Kjældgaard, J.N.; Lip, G.Y.H.; Larsen, T.B. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: Propensity weighted nationwide cohort study. BMJ **2017**, 356, j510.
Noseworthy 2016	Noseworthy, P.A.; Yao, X.; Abraham, N.S.; Sangaralingham, L.R.; McBane, R.; Shah, N.D. Direct Comparison of Dabigatran, Rivaroxaban, and Apixaban for Effectiveness and Safety in Nonvalvular Atrial Fibrillation. Chest **2016**, 150, 1302–1312.
Noseworthy 2017	Noseworthy, P.A.; Yao, X.; Gersh, B.J.; Hargraves, I.; Shah, N.D.; Montori, V.M. Long-term stroke and bleeding risk in patients with atrial fibrillation treated with oral anticoagulants in contemporary practice: Providing evidence for shared decision-making. Int. J. Cardiol. **2017**, 245, 174–177.
Perreault 2021	Perreault, S.; Dragomir, A.; Côté, R.; Lenglet, A.; White-Guay, B.; de Denus, S.; Schnitzer, M.E.; Dubé, M.; Brophy, J.M.; Dorais, M.; et al. Comparative effectiveness and safety of high-dose rivaroxaban and apixaban for atrial fibrillation: A propensity score-matched cohort study. Pharmacother. J. Hum. Pharmacol. Drug Ther. **2021**, 41, 379–393.
Ray 2021	Ray,W.A.; Chung, C.P.; Stein, C.M.; Smalley,W.; Zimmerman, E.; Dupont,W.D.; Hung, A.M.; Daugherty, J.R.; Dickson, A.; Murray, K.T. Association of Rivaroxaban vs Apixaban with Major Ischemic or Hemorrhagic Events in Patients with Atrial Fibrillation. JAMA **2021**, 326, 2395–2404.
Rodriguez-Bernal 2018	Rodríguez-Bernal, C.L.; Santa-Ana-Téllez, Y.; García-Sempere, A.; Hurtado, I.; Peiró, S.; Sanfélix-Gimeno, G. Clinical outcomes of nonvitamin K oral anticoagulants and acenocoumarol for stroke prevention in contemporary practice: A population-based propensity-weighted cohort study. Br. J. Clin. Pharmacol. **2020**, 87, 632–643.
Rutherford 2020	Rutherford, O.-C.W.; Jonasson, C.; Ghanima, W.; Söderdahl, F.; Halvorsen, S. Comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in atrial fibrillation: A nationwide cohort study. Eur. Heart J.-Cardiovasc. Pharmacother. **2020**, 6, 75–85.
Staerk 2017	Staerk, L.; Fosbøl, E.; Lip, G.Y.; Lamberts, M.; Bonde, A.N.; Torp-Pedersen, C.; Ozenne, B.; Gerds, T.A.; Gislason, G.H.; Olesen, J.B. Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: A nationwide cohort study. Eur. Heart J. **2016**, 38, 907–915.
Staerk 2018	Staerk, L.; Gerds, T.A.; Lip, G.Y.H.; Ozenne, B.; Bonde, A.N.; Lamberts, M.; Fosbøl, E.; Torp-Pedersen, C.; Gislason, G.; Olesen, J.B. Standard and reduced doses of dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation: A nationwide cohort study. J. Intern. Med. **2017**, 283, 45–55.
Tepper 2018	Tepper, P.G.; Mardekian, J.; Masseria, C.; Phatak, H.; Kamble, S.; Abdulsattar, Y.; Petkun, W.; Lip, G.Y.H. Real-world comparison

	of bleeding risks among non-valvular atrial fibrillation patients prescribed apixaban, dabigatran, or rivaroxaban. PLoS ONE **2018**, 13, e0205989.
Tiew 2020	Tiew, W.J.; Wong, V.L.; Tan, V.H.; Tan, Y.C.; Lee, E.M. A Real-world Experience of the Safety and Efficacy of Non-vitamin K Oral Anticoagulants Versus Warfarin in Patients with Non-valvular Atrial Fibrillation—A Single-centre Retrospective Cohort Study in Singapore. Ann. Acad. Med. Singap. **2020**, 49, 838–847.
Van Ganse 2020	Van Ganse, E.; Danchin, N.; Mahé, I.; Hanon, O.; Jacoud, F.; Nolin, M.; Dalon, F.; Lefevre, C.; Cotté, F.-E.; Gollety, S.; et al. Comparative Safety and Effectiveness of Oral Anticoagulants in Nonvalvular Atrial Fibrillation. Stroke **2020**, 51, 2066–2075.
Villines 2019	Villines, T.C.; Ahmad, A.; Petrini, M.; Tang,W.; Evans, A.; Rush, T.; Thompson, D.; Oh, K.; Schwartzman, E. Comparative safety and effectiveness of dabigatran vs. rivaroxaban and apixaban in patients with non-valvular atrial fibrillation: A retrospective study from a large healthcare system. Eur. Heart J.-Cardiovasc. Pharmacother. **2018**, 5, 80–90.
Vinogradova 2018	Vinogradova, Y.; Coupland, C.; Hill, T.; Hippisley-Cox, J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: Cohort study in primary care. BMJ **2018**, 362, k2505.
Yang 2020	Yang, L.; Brooks, M.M.; Glynn, N.W.; Zhang, Y.; Saba, S.; Hernandez, I. Real-World Direct Comparison of the Effectiveness and Safety of Apixaban, Dabigatran, Rivaroxaban, and Warfarin in Medicare Beneficiaries with Atrial Fibrillation. Am. J. Cardiol. **2020**, 126, 29–36.

8. Appendix

Table S1: Characteristics of included studies

First author, Year, country **Study design**	**Apixaban** *n=participants* mean (±SD) Age (years) % Female/Male Charlson comorbidity index CHA DS -VASc score HAS-BLED score	**Comparator(s)** *n=patients* mean (±SD) Age (years) % Female/Male Charlson comorbidity index CHA DS -VASc score HAS-BLED score	**Outcomes**	**Follow-up**
Abraham, 2017, USA	6,542 AF patients on Apixaban Mean age 72.2 (±11.1) 46% Female 6,565 AF patients on Apixaban Mean age 72.3 (±11.1) 46% Female	6,542 AF patients on Dabigatran Mean age 72.1 (±10.5) 46% Female 6,565 AF patients on Rivaroxaban Mean age 72.1 (±11.2) 46% Female	GI bleed	Apixaban = 89 days Dabigatran = 120 days Apixaban = 89 days Rivaroxaban = 106 days
Adeboyeje, 2017, USA Retrospective cohort study	3,689 AF patients on Apixaban Mean age 69 41% Female	23,431 AF patients on Warfarin Mean age 73 44% Female 8,539 AF patients on Dabigatran Mean age 66 35% Female 8,398 AF patients on Rivaroxaban Mean age 67 39% Female	Time to first major bleeding-related hospitalisation. Major GI bleeding Major Intracranial bleeding	Apixaban = 139 days Warfarin = 285 days Dabigatran = 212 days Rivaroxaban = 169 days
Al-Khalili, 2016, Sweden Retrospective cohort study	251 AF patients on Apixaban Mean age 73 (±8) 49% Female	233 AF patients on Dabigatran Mean age 72 (±8) 49% Female 282 AF patients on Rivaroxaban Mean age 73 (±8) 50% Female	Arterial thromboembolic events All-cause mortality Major bleed	Apixaban = 348 days (IQR 267-419) Dabigatran = 367 days (IQR 183-493) Rivaroxaban = 432 days (IQR 255-546)
Amin, 2018, USA Retrospective with PSM	8,328 Apixaban-warfarin pairs: Apixaban: Mean age 73.5 (±10.7) 45% Female Mean Charlson 2.4 (±2.3) Mean CHA DS -VASc 3.9 (±1.8) Mean HAS-BLED 2.81 (±1.31) 3,557 Apixaban-Dabigatran pairs. Apixaban: Mean age 70.9 (±11.4) 39% Female	8,328 Apixaban-warfarin pairs: Warfarin: Mean age 73.4 (±10.4) 46% Female Mean Charlson 2.36 (±2.33) Mean CHA DS -VASc 3.9 (±1.8) Mean HAS-BLED 2.8 (±1.3) 3,557 Apixaban-Dabigatran pairs. Dabigatran: Mean age 70.7 (±11.2) 30% Female	All-cause hospitalisation Hospitalisations due to stroke and major bleeding	12-months

	Mean Charlson 2.0 (±2.2) Mean CHA DS -VASc 3.5 (±1.8) Mean HAS-BLED 2.56 (±1.28) 8,440 apixaban-rivaroxaban pairs. Apixaban: Mean age 72.8 (±11.1) 44% Female Mean Charlson 2.3 (±2.3) Mean CHA DS -VASc 3.8 (±1.8) Mean HAS-BLED 2.75 (±1.30)	Mean Charlson 2.0 (±2.1) Mean CHA DS -VASc 3.5 (±1.8) Mean HAS-BLED 2.6 (±1.3) 8,440 apixaban-rivaroxaban pairs. Rivaroxaban: Mean age 72.5 (±10.8) 44% Female Mean Charlson 2.3 (±2.3) Mean CHA DS -VASc 3.8 (±1.8) Mean HAS-BLED 2.7 (±1.3)		
Amin, 2019b, USA Retrospective with PSM	Apixaban vs Warfarin 10,570 patients on Apixaban Mean age 80.4 54% Female Mean CHA DS -VASC 5.4 Mean HAS-BLED 3.7 Mean Charlson 5.7 Apixaban vs Dabigatran 4,263 patients on Apixaban Mean age 78.7 52% Female Mean CHA DS -VASC 5.2 Mean HAS-BLED 3.5 Mean Charlson 5.2 Apixaban vs Rivaroxaban 10,477 patients on Apixaban Mean age 80.4 54% Female Mean CHA DS -VASC 5.4 Mean HAS-BLED 3.7 Mean Charlson 5.7	Apixaban vs Warfarin 10,570 patients on Warfarin Mean age 80.4 54% Female Mean CHA DS -VASC 5.4 Mean HAS-BLED 3.7 Mean Charlson 5.7 Apixaban vs Dabigatran 4,263 patients on Dabigatran Mean age 78.8 51% Female Mean CHA DS -VASC 5.2 Mean HAS-BLED 3.5 Mean Charlson 5.3 Apixaban vs Rivaroxaban 10,477 patients on Rivaroxaban Mean age 80.3 54% Female Mean CHA DS -VASC 5.4 Mean HAS-BLED 3.7 Mean Charlson 5.7	Stroke / SE Ischaemic stroke Haemorrhagic stroke Major bleeding GI bleeding Intracranial haemorrhage Other bleeding Major adverse cardiac event (MACE) Myocardial infarction All-cause mortality	Mean 6-8 months across all cohorts
Andersson, 2018, Denmark Retrospective with PSM	Apixaban vs Dabigatran 3,235 patients on Apixaban 63% Male Mean age 67.6 (±8.2) Apixaban vs Rivaroxaban 3,676 patients on Apixaban 56% Male Mean age 71.9 (±9.1)	Apixaban vs Dabigatran 3,235 patients on Dabigatran 64% Male Mean age 67.5 (±7.3) Apixaban vs Rivaroxaban 3,676 patients on Rivaroxban 56% Male Mean age 72.0 (±9.8)	Stroke / SE Major bleeding	Apixaban vs Dabigatran: Apixaban mean 210 days Dabigatran mean 241 days Apixaban vs Rivaroxaban Apixaban mean 212 days Rivaroxaban mean 201 days

Deitelzweig, 2016, USA Retrospective with multivariate regression	4,138 AF patients on Apixaban Mean age 73.6 (±11.6) 51% Female Mean Charlson 2.1 (±1.2) Mean CHA DS -VASc 3.7 (±1.6) HAS-BLED mean 2.4 (±1.0)	37,754 AF patients on rivaroxaban Mean age 72.3 (±11.8) 49% Female Mean Charlson 2.1 (±1.1) Mean CHA DS -VASc 3.7 (±1.6) Mean HAS-BLED 2.4 (±1.0) 32,838 AF patients on dabigatran Mean age 71.9 (±11.8) 46% Female Mean Charlson 2.1 (±1.9) Mean CHA DS -VASc 3.7 (±1.6) Mean HAS-BLED 2.3 (±1.0)	Bleeding-related hospital readmission All-cause hospital readmission	1-month
Deitelzweig, 2017, USA Retrospective with PSM	6,810 AF patients on Apixaban Mean age 77.1 (±8.0) 48% Female Mean Charlson 2.8 (±2.3) Mean CHA DS -VASc 4.4 (±1.6) Mean HAS-BLED 2.9 (±1.1)	Apixaban vs Rivaroxaban After PSM, 6,810 AF patients were in each cohort. Mean ages (77.1 vs. 77.0 years), Charlson (2.8 vs. 2.7), CHA DS -VASc (4.4 vs. 4.4), HAS-BLED (2.9 vs. 2.9). Apixaban vs Dabigatran After PSM, 2,327 AF patients were in each cohort. Mean ages (77.3 vs. 76.9 years), Charlson (2.6 vs. 2.6), CHA DS -VASc (4.6 vs. 4.3), HAS-BLED (2.9 vs. 2.9). Apixaban vs Warfarin After PSM, 7,107 AF patients were in each cohort. Mean ages (78.2 vs. 78.1 years), Charlson (3.0 vs. 3.0), CHA DS -VASc (4.6 vs. 4.6), HAS-BLED (3.0 vs. 3.1).	Stroke/SE Ischaemic stroke Haemorrhagic stroke SE Major bleeding GI bleeding	6-months
Durand, 2020, Canada, USA, UK Retrospective with PSM	Apixaban Vs Dabigatran 49,058 pairs Mean age 75.3 54% Male Apixaban Vs Rivaroxaban 54,276 pairs Mean age 75.5 54% Male	NA	Ischaemic stroke or SE Major bleeding MI Intracranial bleeding GI bleeding All-cause mortality	12-months
Fralick, 2020, USA Retrospective with PSM	39,351 AF patients on Apixaban Mean age 69.4 (±10.5) 40% Female	39,351 AF patients on Rivaroxaban Mean age 69.3 (±10.6) 40% Female	Stroke SE GI bleeding ICH	Apixaban = Mean follow-up 288 days

				Rivaroxaban = Mean follow-up 291 days
Graham, 2019, USA Retrospective with Inverse Probability of Treatment Weighting	72,921 AF patients on Apixaban Mean age 75.1 47% Female 80% had CHA DS - VASc >3 45% had HAS-BLED >3	183,003 AF patients on Warfarin Mean age 75.2 47% Female 80% had CHA DS - VASc >3 45% had HAS-BLED >3 86,293 AF patients on Dabigatran Mean age 75.1 47% Female 80% had CHA DS - VASc >3 45% had HAS-BLED >3 106,369 AF patients on Dabigatran Mean age 75.1 47% Female 81% had CHA DS - VASc >3 45% had HAS-BLED >3	Thromboembolic stroke ICH All-cause mortality	A total of 448,944 anticoagulant initiators contributed 159,927 person-years of on-treatment follow-up (mean duration 130 days).
Hernandez, 2017, USA Retrospective	2,358 AF patients on Apixaban Mean age 77.4 ±8.6 43% Male CHA DS -VASc 4.7 (±1.7) HAS-BLED 3.7 (±0.9)	1,415 AF patients on Dabigatran Mean age 74.9 (±8.7) 47% Male CHA DS -VASc 4.3 (±1.7) HAS-BLED 3.5 (±0.9) 5,139 AF patients on Rivaroxaban Mean age 76.4 (±8.6) 44% Male CHA DS -VASc 4.6 (±1.8) HAS-BLED 3.7 (±1.0)	Ischaemic stroke All-cause mortality Any bleeding event Intracranial bleeding GI bleeding	Apixaban = 185 days Dabigatran = 294 days Rivaroxaban = 255 days Warfarin = 274 days
Hohnloser, 2018, Germany Retrospective with adjusted HRs	10,117 AF patients on Apixaban Mean age 74.5 (±11.4) years 51% Male Charlson 3.4 (±2.7) CHA DS -VASc 4.0 (±1.8) HAS-BLED 2.8 (±1.2)	23,823 AF patients on Phenprocoumon Mean age 75.2 (±9.5) years 53% Male Charlson 3.4 (±2.6) CHA DS -VASc 4.0 (±1.6) HAS-BLED 2.8 (±1.1) 5,122 AF patients on Dabigatran Mean age 71.7 (±11.6) years 55% Male Charlson 2.9 (±2.5) CHA DS -VASc 3.7 (±1.8) HAS-BLED 2.6 (±1.2) 22,143 AF patients on Rivaroxaban Mean age 72.1 (11.8) years 55% Male Charlson 2.9 (±2.5) CHA DS -VASc 3.5 (±1.8) HAS-BLED 2.5 (±1.2)	Stroke Ischaemic stroke Haemorrhagic stroke All-cause mortality Major bleeding Intracranial bleeding GI bleeding	Phenprocoumon = 362 days Apixaban = 306 Dabigatran = 339 days Rivaroxaban = 340 days

Jansson, 2020, Sweden Retrospective Cohort with full optimal matching	11,493 AF patients on Apixaban Mean age 73.5 (±10.3) 57% Male	6,453 AF patients on Dabigatran Mean age 72.3 (±9.8) 58% Male 7,897 AF patients on Rivaroxaban Mean age 73.5 ± 10.3 57% Male	Ischaemic stroke Combined all cause stroke + SE Myocardial infarction All-cause mortality Haemorrhagic stroke Major bleeding	Apixaban - Median 205 days (IQR 83-381) Dabigatran - Median 352 days (IQR 111-750) Rivaroxaban - Median 267 (IQR 102-532)
Lamberts, 2017, Denmark Retrospective cohort with adjusted HRs	7,963 AF patients on Apixaban Mean age 75.4 (±11.1) 51% Male Mean CHA DS -VASC 3.2 (±1.6) Mean HAS-BLED 2.3 (±1.2)	6,715 AF patients on Rivaroxaban Mean age 74.4 (± 11.0) 52% Male Mean CHA DS -VASC 3.0 (±1.6) Mean HAS-BLED 2.2 (±1.2) 15,413 AF patients on Dabigatran Mean age 71.5 (±11.0) 57% Male Mean CHA DS -VASC 2.7 (±1.6) Mean HAS-BLED 2.1 (±1.2) 24,230 AF patients on Warfarin Mean age 72.1 (±11.3) 58% Male Mean CHA DS -VASC 2.9 (±1.7) Mean HAS-BLED 2.2 (±1.2)	Major bleeding (total) Major bleeding (30 day)	Apixaban = 268.1 days Rivaroxaban = 348.5 days Dabigatran = 511.4 days Warfarin = 398.0 days Overall mean = 403 days
Lee, 2019, Korea Retrospective cohort with Inverse Probability of Treatment Weighting	Apixaban vs Warfarin: 22,177 AF patients on Apixaban Mean age 70.9 (±11.0) 56% Male Mean CHA DS -VASC 3.6 (±1.4) Mean HAS-BLED 2.7 (±1.1) Mean Charlson 3.8 (±2.3) Apixaban vs Rivaroxaban: 22,177 AF patients on Apixaban Mean age 72.3 (±10.1) 53% Male Mean CHA DS -VASC 3.7 (±1.4) Mean HAS-BLED 2.8 (±1.0) Mean Charlson 3.8 (±2.3) Apixaban vs Dabigatran: 22,177 AF patients on Apixaban Mean age 71.8 (±10.3) 54% Male Mean CHA DS -VASC 3.7 (±1.4) Mean HAS-BLED	Apixaban vs Warfarin: 25,420 AF patients on Warfarin Mean age 71.2 (±11.1) 55% Male Mean CHA DS -VASC 3.6 (±1.6) Mean HAS-BLED 2.7 (±1.1) Mean Charlson 3.82 ± 2.39 Apixaban vs Rivaroxaban: 35,965 AF patients on Rivaroxaban Mean age 72.3 (±10.0) 53% Male Mean CHA DS -VASC 3.7 (± 1.4) Mean HAS-BLED 2.8 (±1.0) Mean Charlson 3.8 (±2.3) Apixaban vs Dabigatran: 17,745 AF patients on Dabigatran Mean age 71.8 (±9.9) 54% Male Mean CHA DS -VASC 3.7 (±1.38) Mean HAS-BLED	Ischaemic stroke Intracranial haemorrhage GI bleeding Major bleeding	Apixaban = 0.80 years Rivaroxaban = 0.87 years Dabigatran = 0.87 years Edoxaban = 0.57 years Warfarin = 0.82 years

	2.7 (±1.03) Mean Charlson 3.8 (±2.3) Apixaban vs Edoxaban: 22,177 AF patients on Apixaban Mean age 72.3 (±10.3) 53% Male Mean CHA DS -VASC 3.7 (±1.4) Mean HAS-BLED 2.7 (±1.0) Mean Charlson 3.8 (±2.3)	2.71 ± 1.02 Mean Charlson 3.8 (±2.3) Apixaban vs Edoxaban: 15,496 AF patients on Edoxaban Mean age 72.3 (±9.8) 53% Male Mean CHA DS -VASC 3.7 (±1.40) Mean HAS-BLED 2.7 (±1.0) Mean Charlson 3.8 (±2.4)		
Lin, 2017, USA Retrospective cohort with PSM	Apixaban vs Rivaroxaban 4,062 AF patients on Apixaban Mean age 62.0 (±8.5) 29% Female Mean CHA DS -VASC 2.1 (±1.4) Mean HAS-BLED 2.2 (±0.9) Mean Charlson 1.2 (±1.6) Apixaban vs Dabigatran 2,684 AF patients on Apixaban Mean age 63.0 (±9.2) 28% Female Mean CHA DS -VASC 2.1 (±1.5) Mean HAS-BLED 2.1 (±0.9) Mean Charlson 1.2 (±1.6) Apixaban vs Warfarin 4,847 AF patients on Apixaban Mean age 63.9 (±9.5) 32% Female Mean CHA DS -VASC 2.3 (±1.6) Mean HAS-BLED 2.2 (±1.0) Mean Charlson 1.4 (±1.8)	Apixaban vs Rivaroxaban 4,062 AF patients on Rivaroxaban Mean age 62.0 (±8.4) 30% Female Mean CHA DS -VASC 2.1 (±1.4) Mean HAS-BLED 2.2 (±0.9) Mean Charlson 1.2 (±1.6) Apixaban vs Dabigatran 2,684 AF patients on Dabigatran Mean age 63.0 (±9.3) 28% Female Mean CHA DS -VASC 2.1 (±1.5) Mean HAS-BLED 2.1 (±0.9) Mean Charlson 1.2 (±1.6) Apixaban vs Warfarin 4,847 AF patients on Warfarin Mean age 64.0 (±9.4) 31% Female Mean CHA DS -VASC 2.3 (±1.7) Mean HAS-BLED 2.2 (±1.1) Mean Charlson 1.4 (±1.8)	1) Hospitalisations 2) Major bleeding	Matched cohorts (mean months ± SD) Apixaban vs Rivaroxaban Apixaban 4.5 ± 4.3 Rivaroxaban 4.5 ± 4.5 Apixaban vs Dabigatran Apixaban 5.2 ± 5.1 Dabigatran 5.0 ± 5.2 Apixaban vs Warfarin Apixaban 4.9 ± 4.9 Warfarin 4.8 ± 4.8
Lip, 2016a, USA Retrospective Cohort with PSM	vs Warfarin cohort: 6,964 AF patients on Apixaban Mean age 69.1 (±12.3) 39% Female Mean CHA DS -VASC 2.9 (±1.7) Mean HAS-BLED 2.2 (±1.3) Mean Deyo-Charlson 1.9 (±2.0) vs Dabigatran cohort: 4,407 AF patients on Apixaban Mean age 67 (±12.3) 36% Female	vs Warfarin cohort: 6,964 AF patients on Warfarin Mean age 69.0 (±12.3) 38% Female Mean CHA DS -VASC 2.8 (±1.6) Mean HAS-BLED 2.2 (±1.2) Mean Deyo-Charlson 1.8 (±2.0) vs Dabigatran cohort: 4,407 AF patients on Dabigatran Mean age 66.9 (±12.2) 36%	Major bleeding requiring hospitalisation	Apixaban vs Warfarin cohort: Apixaban 148.1 days Warfarin 161.6 days Apixaban vs Dabigatran cohort: Apixaban 145.6 days Dabigatran 179.0 days Apixaban vs Rivaroxaban cohort: Apixaban

	Mean CHA DS -VASC 2.5 (±1.6) Mean HAS-BLED 2.0 (±1.2) Mean Deyo-Charlson 1.6 (±1.9) vs Rivaroxaban cohort: 7,399 AF patients on Apixaban Mean age 68.4 (±12.4) 39% Female Mean CHA DS -VASC 2.8 (±1.6) Mean HAS-BLED 2.2 (±1.2) Mean Deyo-Charlson 1.8 (±2.0)	Female Mean CHA DS -VASC 2.6 (±1.7) Mean HAS-BLED 2.0 (±1.2) Mean Deyo-Charlson 1.6 (±1.9) vs Rivaroxaban cohort: 7,399 AF patients on Rivaroxaban Mean age 68.3 (±12.2) 39% Female Mean CHA DS -VASC 2.8 (±1.7) Mean HAS-BLED 2.1 (±1.2) Mean Deyo-Charlson 1.7 (±2.0)		147.6 days Rivaroxaban 182.1 days
Lip, 2016b, USA Retrospective cohort with adjusted HRs	2,402 AF patients on Apixaban Mean age 69.3 (±12.3) 37% Female Mean CHA DS -VASC 2.8 (±1.6) Mean Charlson 1.9 (±2.0)	4,173 AF patients on Dabigatran Mean age 66.8 (±12.8) 34% Female Mean CHA DS -VASC 2.6 (±1.7) Mean Charlson 1.7 (±2.0) 10,050 AF patients on Rivaroxaban Mean age 67.3 (±12.3) 37% Female Mean CHA DS -VASC 2.6 (±1.7) Mean Charlson 1.8 (±2.0) 12,713 AF patients on Warfarin Mean age 72.5 (±11.9) 39% Female Mean CHA DS -VASC 3.2 (±1.7) Mean Charlson 2.4 (±2.3)	Major bleeding	Apixaban = 90.4 days Dabigatran = 126.7 = days Rivaroxaban = 117.7 days Warfarin = 127.6 days
Lip, 2018, USA Retrospective with PSM	100,977 AF patients on Apixaban Mean age 76.1 49% Female Mean CHA DS -VASC 3.9 Mean HAS-BLED 3.1 37,314 AF patients on Apixaban Mean age 73.2 Mean CHA DS -VASC 3.5 Mean HAS-BLED 2.8 107,236 AF patients on Apixaban Mean age 75.2 48% Female Mean CHA DS -VASC 3.8 Mean HAS-BLED 3.0	100,977 AF patients on Warfarin Mean age 76.0 49% Female Mean CHA DS -VASC 3.9 Mean HAS-BLED 3.0 37,314 AF patients on Dabigatran Mean age 73.0 Mean CHA DS -VASC 3.5 Mean HAS-BLED 2.8 107,236 AF patients on Rivaroxaban Mean age 75.1 48.5% Female Mean CHA DS -VASC 3.7 Mean HAS-BLED 3.0	Stroke / SE Ischaemic stroke Haemorrhagic stroke SE Major bleeding GI bleeding Intracranial haemorrhage Other bleeding	Mean follow-up in days Apixaban vs Warfarin: Apixaban = 187.6 Warfarin = 242.3 Apixaban vs Dabigatran Apixaban = 186.0 Dabigatran = 226.3 Apixaban vs Rivaroxaban Apixaban = 187.2 Rivaroxaban = 230.3
Lip, 2020, USA	41,662 AF patients on Apixaban Mean age	41,662 AF patients on Warfarin Mean age	Stroke / SE Ischaemic stroke	Mean follow-up in days

Retrospective with PSM	76.9 (±8.9) 51% Female Mean CHA DS -VASC 4.4 (±1.6) Mean HAS-BLED 3.5 (±1.3) Mean Charlson 3.9 (±2.8) 13,969 AF patients on Apixaban Mean age 74.6 (±9.2) 48.6% Female Mean CHA DS -VASC 4.1 (±1.6) Mean HAS-BLED 3.2 (±1.3) Mean Charlson 3.4 (±2.7) 43,250 AF patients on Apixaban Mean age 76.2 (±9.2) 51.1% Female Mean CHA DS -VASC 4.3 (±1.6) Mean HAS-BLED 3.4 (±1.3) Mean Charlson 3.7 (±2.8)	76.9 (±8.8) 52% Female Mean CHA DS -VASC 4.4 (±1.5) Mean HAS-BLED 3.5 (±1.3) Mean Charlson 3.9 (±2.8) 13,969 AF patients on Dabigatran Mean age 74.6 (±9.1) 48% Female Mean CHA DS -VASC 4.1 (±1.6) Mean HAS-BLED 3.2 (±1.3) Mean Charlson 3.5 (±2.7) 43,250 AF patients on Rivaroxaban Mean age 76.1 (±9.2) 51% Female Mean CHA DS -VASC 4.3 (±1.6) Mean HAS-BLED 3.4 (±1.3) Mean Charlson 3.7 (±2.8)	Haemorrhagic stroke SE Major bleeding GI bleeding Intracranial haemorrhage Other bleeding	Apixaban vs Warfarin: Apixaban = 186.8 Warfarin = 238.4 Apixaban vs Dabigatran Apixaban = 191.0 Dabigatran = 233.6 Apixaban vs Rivaroxaban Apixaban = 187.7 Rivaroxaban = 229.9
Mentias, 2020, USA Retrospective with PSM	Propensity matched cohorts based on degree of polypharmacy High polypharmacy (>8 meds): 723 AF patients on Apixaban Mean age 74.8 (±6.6) 53% Female Mean CHA DS -VASC 5.1 (±1.6) Mean HAS-BLED 3.13 (±1.0) Medium polypharmacy (4-8 meds): 1,487 AF patients on Apixaban Mean age 75.3 (±6.4) 50% Female Mean CHA DS -VASC 4.5 (±1.6) Mean HAS-BLED 2.8 (±1.0) Low polypharmacy (<=3 meds): 1,219 AF patients on Apixaban Mean age 76.0 (±6.4) 47% Female Mean CHA DS -VASC 4.2 (±1.6) Mean HAS-BLED 2.5 (±0.9)	Propensity matched cohorts based on degree of polypharmacy High polypharmacy (>8 meds): 723 AF patients on Rivaroxaban Mean age 74.5 (±6.5) 51% Female Mean CHA DS -VASC 5.0 (±1.7) Mean HAS-BLED 3.2 (±1.1) 723 AF patients on Warfarin Mean age 74.4 (±6.6) 54% Female Mean CHA DS -VASC 5.1 (±1.7) Mean HAS-BLED 3.1 (±1.1) Medium polypharmacy (4-8 meds): 1,487 AF patients on Rivaroxaban Mean age 75.2 (±6.5) 48% Female Mean CHA DS -VASC 4.5 (±1.6) Mean HAS-BLED 2.7 (±1.0) 1,487 AF patients on Warfarin Mean age 75.3 (±6.7) 50% Female Mean CHA DS -VASC 4.6 (±1.6) Mean HAS-BLED 2.8 (±1.0) Low	Ischaemic stroke Bleeding GI bleeding Intracranial bleeding All-cause mortality	Not clearly stated - they reported crude rates as per 100 patient years but the paper does not appear to clarify average follow-up duration per drug

		polypharmacy (<=3 meds): 1,219 AF patients on Rivaroxaban Mean age 75.7 ± 6.4 46% Female Mean CHA DS -VASC 4.14 ± 1.60 Mean HAS-BLED 2.47 ± 0.91 1,219 AF patients on Warfarin Mean age 76.0 ± 6.6		
Mitsuntisuk, 2021, Thailand Retrospective with PSM	Unadjusted cohort (PSM used but matched cohort data not given) 405 AF patients on Apixaban Mean age 73.9 (±10.2) 50% Female Mean CHA DS -VASC 3.9 (±1.7) Mean HAS-BLED 1.7 (±1.0)	Unadjusted cohort (PSM used but matched cohort data not given) 605 AF patients on Warfarin Mean age 68.4 (±11.4) 50% Female Mean CHA DS -VASC 3.3 (±1.8) Mean HAS-BLED 1.3 (±0.9)	Stroke / SE Ischaemic stroke Haemorrhagic stroke Major bleeding Intracranial haemorrhage GI bleeding Other sites major bleeding	Apixaban = 1.90 years Warfarin = 2.82 years Followed until first occurrence of any outcome or end of study period.
Mueller, 2019, UK Retrospective with adjusted HRs	6,200 AF patients on Apixaban Mean age 73.7 (±11.5) 47% Female Mean CHA DS -VASC 2.9 (±1.7) Mean HAS-BLED 2.1 (±1.2) Mean Charlson 1.4 (±1.7)	1,112 AF patients on Dabigatran Mean age 71.1 (±12.0) 37% Female Mean CHA DS -VASC 2.5 (±1.8) Mean HAS-BLED 1.9 (±1.2) Mean Charlson 1.1 ±1.5) 7,265 AF patients on Rivaroxaban Mean age 74.8 (±11.0) 46% Female Mean CHA DS -VASC 3.0 (±1.7) Mean HAS-BLED 2.0 (±1.2) Mean Charlson 1.3 (±1.7)	Ischaemic stroke SE Cardiovascular death Pulmonary embolism TIA Myocardial infarction All-cause mortality Haemorrhagic stroke GI bleeding Other major bleeds	Apixaban = 188 days Dabigatran = 216 days
Noseworthy, 2016, USA Retrospective with PSM (DP of Abraham)	Propensity matched cohorts: Apixaban vs Dabigatran: 6,542 AF patients on Apixaban Median age 73 (IQR 65-81) 54% Male Median CHA DS -VASC 4 (IQR 3-5) Median HAS-BLED 2 (IQR 2-3) Median Charlson 2 (IQR 1-4) Apixaban vs Rivaroxban: 6,565 AF patients on Apixaban Median age 73 (IQR 65-81) 54% Male Median CHA DS -VASC 4 (IQR 3-5) Median HAS-BLED 2	Propensity matched cohorts: Apixaban vs Dabigatran: 6,542 AF patients on Dabigatran Median age 73 (IQR 65-81) 54% Male Median CHA DS -VASC 4 (IQR 3-5) Median HAS-BLED 2 (IQR 2-3) Median Charlson 2 (IQR 1-4) Apixaban vs Rivaroxban: 6,565 AF patients on Rivaroxaban Median age 73 (IQR 65-81) 54% Male Median CHA DS -VASC 4 (IQR 3-5) Median HAS-BLED 2 (IQR 2-3)	Stroke / SE Ischaemic stroke Haemorrhagic stroke Major bleeding Intracranial bleeding	Follow-up per cohort NR. Results presented as event rates /100 PY. Sensitivity analysis by censoring at 6 months was reportedly not significantly different to overall outcome.

	(IQR 2-3) Median Charlson 2 (IQR 1-4)	Median Charlson 2 (IQR 1-4)		
Noseworthy, 2017, USA Retrospective	12,949 AF patients on Apixaban Median age 74 (IQR 67 - 81) 48% Female CHA DS -VASc </= 3 42% CHA DS -VASc 4 22% CHA DS -VASc >/= 5 35.9% HAS-BLED 0,1 19.5% HAS-BLED 2 36.3% HAS-BLED 3 27.3% HAS-BLED >/=4 16.8%	68,804 AF patients on Warfarin Median age 73 (IQR 64-80) 42.7% Female CHA DS -VASc </= 3 41.4% CHA DS -VASc 4 21.1% CHA DS -VASc >/= 5 37.4% HAS-BLED 0,1 21.5% HAS-BLED 2 34.2% HAS-BLED 3 27.3% HAS-BLED >/=4 17.1% 9,412 AF patients on Dabigatran Median age 69 (IQR 61-77) 38.7% Female CHA DS -VASc </= 3 56.4% CHA DS -VASc 4 19.6% CHA DS -VASc >/= 5 23.9% HAS-BLED 0,1 31.6% HAS-BLED 2 36.3% HAS-BLED 3 21.9% HAS-BLED >/=4 10.2% 68,804 AF patients on Rivaroxaban Median age 71 (IQR 63-78) 41.2% Female CHA DS -VASc </= 3 52.4% CHA DS -VASc 4 20.6% CHA DS -VASc >/= 5 27% HAS-BLED 0,1 26.8% HAS-BLED 2 37.1%	Stroke Major bleeding	12-months
Perreault, 2021, Canada Retrospective with PSM	6,771 patients on Apixaban Mean age 76.3 (±8.5) 51% Male Mean CHA DS -VASc 3.4 (±1.4) Mean HAS-BLED 2.9 (±1.3) Mean Charlson 4.4 (±3.4)	4,632 patients on Rivaroxaban Age mean 73.2 (±9.1) Male 55% Mean CHA DS -VASc 3.0 (±1.4) Mean HAS-BLED 2.5 (±1.3) Mean Charlson 3.6 (±3.2)	Primary: (i) Composite of ischaemic stroke/SE, acute MI, all-cause mortality. (ii) composite of major bleeding (ICH, GI and major from other sites). Secondary: Stroke/SE/death Stroke/SE Death Acute MI Bleeding outcomes	12-months

Ray, 2021, USA Retrospective with Inverse Probability of Treatment Weighting	353,879 patients on Apixaban Mean age 77 (±7) 50% Male Mean CHA DS -VASc 4.3	227,572 patients on Rivaroxaban Mean age 77 (±7) 50% Male Mean CHA DS -VASc 4.3	Major ischaemic or haemorrhagic events Mortality Ischaemic stroke ICH	4-years
Rodríguez-Bernal, 2018, Spain Retrospective with Inverse Probability of Treatment Weighting	32,476 patients on Acenocoumarol Mean age 74.8 (±9.6) 48% Female Mean CHA DS -VASc 3.8 (±1.65) Mean HAS-BLED 2.9 (±1.2)	2,259 patients on Apixaban Mean age 75.0 (±10.7) 48% Female Mean CHA DS -VASc 3.9 (±1.8) Mean HAS-BLED 3.0 (±1.3)	Mortality Ischaemic stroke TIA GI bleed ICH	Average follow-up of 1.8 years
Rutherford, 2020, Norway Retrospective with PSM	Dabigatran-apixaban PSM 10,413 patients on Apixaban Mean age 70.6 (±11.7) 62% Male Mean CHA DS -VASc 2.94 (±1.72) Mean HAS-BLED 2.3 (±1.2) Apixaban-rivaroxaban PSM 13,699 patients on Apixaban Age 72.7 (±11.7) 58% Male Mean CHA DS -VASc 3.2 (±1.7) Mean HAS-BLED 2.4 (±1.2)	Dabigatran-apixaban PSM 10,413 patients on Dabigatran Age 70.6 (±11.2) 62% Male Mean CHA DS -VASc 2.7 (±1.7) Mean HAS-BLED 2.3 (±1.2) Apixaban-rivaroxaban PSM 13,699 patients on Rivaroxaban Mean age 72.7 (±11.1) 58% Male Mean CHA DS -VASc 3.2 (±1.7) Mean HAS-BLED 2.4 (±1.1)	Stroke Embolism, time to first ischaemic stroke. Time to first major bleed, clinically relevant non-major bleeding (CRNM), major or CRNM bleeding, GI bleeding, intracranial haemorrhage.	12 months
Staerk, 2017, Denmark Retrospective with adjusted HRs	6,899 patients on Apixaban Age 76 (68-84) 50% Male CHA DS -VASc 3.1 (±1.6) HAS-BLED 2.2 (±1.2)	18,094 patients on VKA Age 73 (65-80) 58% Male CHA DS -VASc 2.9 (±1.6) HAS-BLED 2.2 (±1.2)	Stroke/SE Intracranial bleeding (ICH, SAH, traumatic subdural, traumatic epidural)	Study period = 2 years. Drug specific follow up duration (medians) VKA = 252 days Dabigatran = 386 days Rivaroxaban = 208 days Apixaban = 204 days
Staerk, 2018, Denmark Retrospective with adjusted HRs	7,203 patients on Apixaban 58% Male Median age 71 (65, 77) Median CHA DS -VASc 3 (2, 4) Median HAS-BLED 2 (1, 3)	7,078 patients on Dabigatran 64% Male Median age 67 (61, 71) Median CHA DS -VASc 2 (1, 3) Median HAS-BLED 2 (1, 2) 6,868 patients on Rivaroxaban 55% Male Median age 71 (65, 78) Median CHA DS -VASc 3 (2,4) Median HAS-BLED 2 (1,3)	Stroke/SE Ischaemic stroke Major bleeding Intracranial bleeding GI bleeding	Study period = 2 years. Average duration of each cohort follow-up NR.

Tepper, 2018, USA Retrospective with adjusted HRs	8,785 patients on Apixaban Mean age 70 (±12) 37% Female Mean Charlson = 1.8 (±2) Mean CHA DS -VASc 2.5 (±1.5) Mean HAS-BLED 1.9 (±1.2)	20,963 patients on Dabigatran Mean age 71 (±11) 35% Female Mean Charlson 1.6 (±1.9) Mean CHA DS -VASc 2.4 (±1.4) Mean HAS-BLED 1.8 (±1.2) 30,529 patients on Rivaroxaban Mean age = 68 (±12) 37% Female Mean Charlson 1.8 (±2.2) Mean CHA DS -VASc 2.4 (±1.5) Mean HAS-BLED 1.8 (±1.2)	Any bleeding CRNM bleeding Inpatient major bleeding total Intracranial Haemorrhage GI bleeding Other	Apixaban = 184 days Dabigatran = 553 days Rivaroxaban = 300 days
Tiew, 2020, Singapore Retrospective with adjusted HRs	98 patients on Apixaban Mean age 72.9 (±10.6) 46% Female Median CHA DS - VASc 3 (2-4) Median HAS-BLED 1 (1-2)	157 patients on Warfarin Mean age 70.4 (±10.8) 66% Female Median CHA DS - VASc 3 (2-4) Median HAS-BLED 1 (1-2) 154 patients on Rivaroxaban Mean age 70.5 (±11.1) 66% Female Median CHA DS - VASc 3 (2-4) Median HAS-BLED 1 (1-2) 30 patients on Dabigatran Mean age 67.4 (±11.4) 13% Female Median CHA DS - VASc 2 (1-4) Median HAS-BLED 1 (1-2)	Primary: Major bleeding and stroke. Secondary: Overall bleeding (major bleeding and clinically relevant non-major bleeding) Thromboembolic events (stroke, TIA and SE).	Warfarin = 691.7 days Rivaroxaban = 690.5 days Apixaban = 684.5 days Dabigatran = 609.8 days
Van Ganse, 2020, France Retrospective with PSM and adjusted effect measures	87,565 AF patients on Apixaban Mean age 74.7 (±11.5) 51% Male Mean CHA DS -VASC 3.1 (±1.7) Mean HAS-BLED 2.2 (±1.0) Mean Charlson 4.5 (±2.3)	112,628 AF patients on VKA Mean age 78.5 (±11.1) 49% Male Mean CHA DS -VASC 3.9 (±1.7) Mean HAS-BLED 2.6 (±1.1) Mean Charlson 5.9 (±2.6) 100,063 AF patients on Rivaroxaban Mean age 72.0 (±12.0) 55% Male Mean CHA DS -VASC	All-cause mortality Stroke/SE Major bleeding	Mean follow-up duration was 316 days For those receiving apixaban, rivaroxaban, and dabigatran, the mean follow-up duration was 286, 318, and

		2.7 (±1.7) Mean HAS-BLED 2.0 (±1.0) Mean Charlson 4.0 (±2.2) 21,245 AF patients on Dabigatran Mean age 72.7 (±11.8) 54% Male Mean CHA DS -VASC 2.8 (±1.7) Mean HAS-BLED 2.1 (±1.0) Mean Charlson 4.1 (±2.2)		329 days, respectively.
Villines, 2019, USA Retrospective with PSM	4,802 AF patients on Apixaban Mean age 70.2 (±10.0) 63% Male Mean CHA DS -VASC 3.0 (±1.6) Mean HAS-BLED 2.3 (±1.2) Mean Charlson 4.2 (±2.4)	4,802 AF patients on Dabigatran Mean age 70.2 (±10.2) 63% Male Mean CHA DS -VASC 3.0 (±1.7) Mean HAS-BLED 2.3 (±1.2) Mean Charlson 4.2 (±2.5)	Stroke Major bleeding	Dabigatran = 349.5 days Apixaban = 357.7 days
Vinogradova, 2018, UK (Qresearch Database) Prospective Cohort	9,199 AF patients on Apixaban 76.5 (10.9) 52% Male	53,921 AF patients on Warfarin 74.8 (10.4) 56% Male 4,534 AF patients on Dabigatran 74.7 (10.7) 58% Male 13,597 AF patients on Rivaroxaban 75.8 (10.9) 54% Male	All-cause mortality Ischaemic stroke Major bleeding GI bleed Intracranial bleed	Median Days of treatment Apixaban 248 Warfarin 344 Dabigatran 271 Rivaroxaban 265
Vinogradova, 2018, UK (CPRD Database) Prospective with adjusted effect measures	1,402 AF patients on Apixaban 76.6 (10.9) 55% Male	16,664 AF patients on Wafarin 74.8 (10.3) 56% Male 1,003 AF patients on Dabigatran 74.4 (10.8) 62% Male 2,950 AF patients on Rivaroxaban 75.9 (10.8) 54% Male	All-cause mortality Ischaemic stroke Major bleeding GI bleed Intracranial bleed	Median Days of treatment Apixaban 143 Warfarin 286 Dabigatran 214 Rivaroxaban 163
Yang, 2020, USA Retrospective with adjusted HRs	494 post-stroke AF patients on Apixaban Mean age 80.3 (8.3) 35% Male Mean CHA DS -VASC 6.8 (±1.3) Mean HAS-BLED 4.7 (±0.8)	247 post-stroke AF patients on Dabigatran Mean age 78.3 (8.4) 37% Male Mean CHA DS -VASC 6.6 (±1.3) Mean HAS-BLED 4.6 (±0.8) 1,104 post-stroke AF patients on Rivaroxaban Mean age 78.8 (8.6) 44% Male Mean CHA DS -VASC 6.7 (±1.3) Mean HAS-BLED 4.7 (±0.8) 3,082 post-stroke AF patients on Warfarin Mean age 77.9 (10.0) 39% Male Mean CHA DS -VASC 6.8 (±1.3) Mean HAS-BLED 4.7 (±0.8)	Ischaemic stroke Any bleeding event GI bleeding	Apixaban 178 days Dabigatran 271 days Rivaroxaban 256 days Warfarin 267 days

Lau, 2022, Hong Kong, UK Population-based cohort study	Across the 5 databases, the proportion of patients aged 65 years or older ranged from 77% to 87% for apixaban The proportions of women were 42% to 50% for apixaban The mean CHA2DS2-VASc score ranged from 2.8 to 3.9 for apixaban	Across the 5 databases, the proportion of patients aged 65 years or older ranged from 75% to 83% for dabigatran, 79% to 86% for edoxaban, and 73% to 83% for rivaroxaban. The proportions of women were 40% to 47% for dabigatran, 43% to 48% for edoxaban, and 38% to 47% for rivaroxaban. The mean CHA_2DS_2-VASc score ranged from 2.6 to 3.7 for dabigatran, 2.5 to 3.6 for rivaroxaban, and 2.9 to 3.8 for edoxaban across the 5 databases	Ischemic stroke or systemic embolism events, deaths	Apixaban 534-1136 days Dabigatran 726-1612 days Edoxaban 592-1283 days Rivaroxaban 613-1400 days
Grymonprez, 2023, Belgium, The Netherlands Nationwide cohort study	Baseline characteristics of the 15,271 NOAC users 6536 apixaban users with a history of falls before weighting are summarized in Table 1 and eTable 4. After weighting, covariate balance was achieved (Table 1, eFigure 3).	Baseline characteristics of the 15,271 NOAC users 1705 dabigatran 58.3% female, 4896 rivaroxaban 60.9% female, 2134 edoxaban 56.8% female, apixaban 60.4% female and 3676 VKA 55.5% female users with a history of falls before weighting are summarized in Table 1 and eTable 4. After weighting, covariate balance was achieved (Table 1, eFigure 3).	Stroke/systemic embolism, ischemic stroke, all-cause mortality, major bleeding, intracranial bleeding, gastrointestinal bleeding and falls	Dabigatran: 1.1 years Rivaroxaban: 1.1 years Apixaban: 0.9 years Edoxaban: 0.6 years