Effectiveness and Safety of Factor Xa Inhibitors in Atrial Fibrillation: A Systematic Literature Review of Real-World Evidence in Europe

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Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, characterized by an irregular heartbeat due to abnormal electrical activity within the heart[1,2]. Prevalence rates have been on the rise in the last decade, particularly in European countries[3].

In Europe, Vitamin K antagonists (VKAs), such as warfarin, phenprocoumon, acenocoumarin, have been commonly used in routine clinical settings over several decades[4,5]. However, VKAs are limited by a narrow therapeutic range, the need for regular International normalized ratio (INR) monitoring, frequent dose adjustments[6], and an elevated risk of major bleeding[7].

In recent years, factor Xa inhibitors (FXa) have largely replaced VKAs as the standard of care for ischemic stroke prevention in patients with AF[8]. Given their broad adoption, there is growing interest in assessing their effectiveness and safety in real-world clinical practice. Summarizing the latest independent evidence – minimizing potential manufacturer bias – is essential to understanding their impact on patient outcomes.

Objective

The study aims to investigate the effectiveness and safety of FXa prescribed for AF in routine clinical settings across Europe through a systematic literature review of independent research conducted from 2022 to 2024.

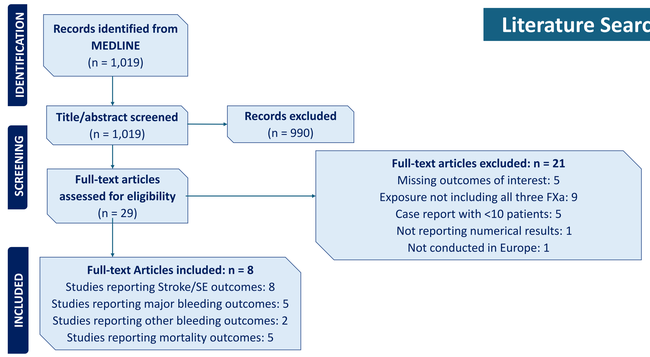
Methods

- Investigators conducted a systematic search in MEDLINE, focusing on English-language publications from the specified period. Independent research (IR) was defined as studies without financial sponsorship (except for unconditional grant) from pharmaceutical companies based on the financial disclosure in the publication. In addition, articles with any co-authors affiliated with pharmaceutical companies were excluded.
- IR studies included real-world data that reported on effectiveness outcome (stroke and systemic embolism), or safety outcome (major bleeding), or mortality. IR studies that included with adult patients with AF who were treated with FXa were selected.
- Evidence was summarized descriptively by two independent reviewers. Discrepancies were resolved by a third reviewer. The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

MEDLINE Query

#1	**("atrial fibrillation"** OR **"atrial flutter"** OR **"nonvalvular"** OR **"nvaf"** OR **"non-valvular")**
#2	**apixaban** OR **warfarin** OR **phenprocoumon** OR **edoxaban** OR **rivaroxaban** OR **"factor xa inhibitor"** OR **"fxa inhibitor"** OR **"direct thrombin inhibitor"** OR **"novel anticoagulant"** OR **"new anticoagulant"** OR **"newer anticoagulant"** OR **"new oral anticoagulant"** OR **NOACs** OR **"direct oral anticoagulant"** OR **DOACs**
#3	**"case control"** OR **cohort** OR **longitudinal** OR **retrospective** OR **"cross-sectional"** OR **comparative** OR **"prevalence study"** OR **registry** OR **"electronic medical record"** OR **"electronic health record"** OR **followup** OR **"follow-up"** OR **observational** OR **"control group"** OR **"propensity score"** OR **"propensity scoring"** OR **"Cox regression"** OR **claims** OR **database** OR **"real-world"** OR **"real world"**
#4	**editorial[pt]** OR **letter[pt]** OR **lecture[pt]** OR **review[pt]** OR **case reports[pt]** OR **practice guideline[pt]**
#5	(#1 AND #2 AND #3) NOT #4
Filters	**English** AND (**"2022/12/06"**[Date - Publication]: **"2024/07/16"**[Date - Publication])

Literature Search FlowChart



Results

- A total of eight studies met the inclusion and exclusion criteria and were included in the final evidence summary. Only three studies conducted direct comparisons among FXa.
- Edoxaban showed numerically lower incidence of stroke/systemic embolism and major bleeding but higher mortality in Italy compared to apixaban and rivaroxaban (See Table 1,2 and 3). However, no statistical comparison was conducted among FXa in this observational study[9].
- In the Spain study, edoxaban showed numerically lowest adjusted hazard ratio (AHR) of stroke/systemic embolism versus no treatment among all three FXa. However, no direct comparisons were conducted among FXa[13].
- In the Belgium study, edoxaban showed numerically lowest AHR of stroke/systemic embolism versus VKA among all three FXa. No direct comparisons were conducted among FXa[14].
- In the German study, all three FXa had statistically lower major bleeding risk compared to phenprocoumon, but showed no statistically significant differences in mortality or stroke/systemic embolism risks. No direct comparisons were conducted among FXa[15].
- In the UK study, apixaban had statistically significantly higher risk of stroke compared to no treatment while rivaroxaban demonstrated statistically significant lower risk of stroke/systemic embolism. Both apixaban and edoxaban had statistically significantly lower risk of mortality compared to no treatment[16].
- Edoxaban demonstrated no statistically significant difference in the risk of stroke/systemic embolism compared to apixaban or rivaroxaban[10-12]. However, rivaroxaban showed a statistically significantly lower risk compared to apixaban in the Denmark and Portugal studies[10,12].
- In studies directly comparing FXa, one found no statistically significant differences in major bleeding risk, while another showed apixaban had a lower risk compared to rivaroxaban[10,11]. In the Belgium study, edoxaban had a lower risk of all-cause mortality compared to rivaroxaban[11].

Table 1. Effectiveness (stroke/systemic embolism)

Outcome Effect Measurements	Reference Group	Apixaban	Edoxaban	Rivaroxaban	Country
Number of incidence cases over 6.5 years: N (%)	_____	45 (10.2%)	3 (3.6%)	29 (6.6%)	Italy[9]
Adjusted Hazard Ratios (95% CIs)	Apixaban	_____	0.65 (0.27–1.59)	0.75 (0.58–0.97)	Denmark[10]
	Rivaroxaban	0.96 (0.86–1.06)	0.93 (0.73–1.18)	_____	Belgium[11]
	No treatment	0.29 (0.19–0.47)	0.17 (0.05–0.36)	0.29 (0.17–0.42)	Spain[13]
	VKA	0.65 (0.60–0.71)	0.61 (0.50–0.74)	0.73 (0.68–0.78)	Belgium[14]
	Phenprocoumon	1.08 (0.94–1.25)	1.14 (0.93–1.40)	1.16 (0.99–1.35)	Germany[15]
Adjusted Odds Ratios (95% CIs)	Rivaroxaban	1.32 (1.16–1.50)	1.31 (0.97–1.76)	_____	Portugal[12]
	No treatment	2.07 (1.95–2.19)	0.95 (0.71–1.27)	0.47 (0.45–0.50)	UK[16]

Table 2. Safety (major bleeding)

Outcome Effect Measurements	Reference Group	Apixaban	Edoxaban	Rivaroxaban	Country
Number of incidence cases over 6.5 year: N (%)	_____	5 (1.1%)	0	5 (1.1%)	Italy[9]
Adjusted Hazard Ratios (95% CIs)	Apixaban	_____	1.15 (0.56–2.36)	1.37 (1.07–1.76)	Denmark[10]
	Rivaroxaban	0.78 (0.72–0.84)	0.99 (0.85–1.15)	_____	Belgium[11]
	VKA	0.87 (0.83–0.91)	0.86 (0.78–0.95)	1.00 (0.96–1.04)	Belgium[14]
	Phenprocoumon	0.54 (0.46–0.63)	0.75 (0.60–0.92)	0.83 (0.72–0.97)	Germany[15]

Table 3. All-cause Mortality

Outcome Effect Measurements	Reference Group	Apixaban	Edoxaban	Rivaroxaban	Country
Number of incidence cases over 6.5 years: N (%)	_____	46 (10.4%)	14 (16.9%)	34 (7.8%)	Italy[9]
Adjusted Hazard Ratios (95% CIs)	Rivaroxaban	1.04 (0.99–1.08)	0.85 (0.77–0.94)	_____	Belgium[11]
	VKA	0.82 (0.78–0.85)	0.60 (0.54–0.68)	0.83 (0.79–0.86)	Belgium[14]
	Phenprocoumon	0.95 (0.87–1.05)	0.87 (0.75–1.02)	1.21 (1.10–1.34)	Germany[15]
	No treatment	0.88 (0.84–0.91)	0.43 (0.34–0.53)	1.10 (1.06–1.15)	UK[16]

Note: Ischemic stroke was reported as an effectiveness outcome in the studies in Spain[13] and the UK[16]. Major bleeding or clinically relevant non-major bleeding was reported as safety outcome in the study in Belgium[14].

Conclusion

- The number of independent research identified in the literature was limited, and only a few conducted direct comparative analyses among factor Xa inhibitors.
- Compared with no treatment or VKA, all factor Xa inhibitors demonstrated lower risk of stroke/systemic embolism.
- There is no increased risk of major bleeding of edoxaban compared with apixaban and rivaroxaban identified in this literature review.

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