Comparing DOACs and Warfarin for Secondary Stroke Prevention in Atrial Fibrillation: Insights from a Multicenter Cohort Analysis

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Background: International guidelines recommend **direct oral anticoagulants (DOACs)** over **vitamin K antagonists (VKAs)** for stroke prevention in patients with **atrial fibrillation (AF),** due to their efficacy and safety. However, no head-to-head randomized controlled trials (RCTs) have been conducted to compare individual DOACs in this population. Furthermore, although DOACs are recommended over VKAs for **secondary prevention** after ischemic stroke, there are no RCTs specifically designed to assess their comparative efficacy in this context. **Aim:** To compare the efficacy and safety of apixaban, dabigatran, rivaroxaban, edoxaban and VKAs for secondary prevention of ischemic stroke in patients with AF-related stroke.

	Dabigatran (797)	Apixaban (990)	Rivaroxaban (789)	Edoxaban (145)	Warfarin (702)	P value
Age	74.7 ± 10.3	78.2 ± 9.3	77.7 ± 9.4	79.5 ± 7.6	75.4 ± 8.8	**<0.0001**
Antiplatelet on admission	207 (26.0%)	240 (24.2%)	197 (25.0%)	18 (12.4%)	272 (38.7%)	**<0.0001**
OAT on admission	388 (48.7%)	575 (58.1%)	427 (54.1%)	129 (88.9%)	248 (35.3%)	**<0.0001**
Hyperlipidemia	358 (44.9%)	416 (42.0%)	345 (43.7%)	71 (48.9%)	243 (34.6%)	**0.001**
PAF	356 (44.7%)	518 (52.3%)	387 (49.0%)	68 (46.9%)	280 (39.9%)	**0.003**
History of stroke/TIA	261 (32.7%)	305 (30.8%)	235 (29.8%)	53 (36.5%)	172 (24.5%)	**0.001**
Current smoking	103 (12.9%)	94 (9.5%)	93 (11.8%)	13 (9.0%)	55 (7.8%)	**0.005**
CHF	142 (17.8%)	160 (16.2%)	139 (17.6%)	36 (24.8%)	148 (21.1%)	**0.02**
History of MI/angina	113 (14.2%)	190 (19.2%)	148 (18.7%)	39 (26.9%)	138 (19.6%)	**0.007**
Leukoaraiosis	424 (53.2%)	666 (67.3%)	465 (58.9%)	96 (66.2%)	296 (42.2%)	**<0.0001**
Association with antiplatelets	41 (5.1%)	71 (7.2%)	47 (5.9%)	17 (11.7%)	100 (14.2%)	**<0.0001**
CHADSVASC ≥ 5	563 (70.6%)	829 (83.7%)	660 (83.6%)	128 (88.3%)	561 (79.9%)	**0.005**

Table 1. *Demographic and clinical characteristics.*

Results: 3423 ischemic stroke patients with AF on secondary prevention were initially included in the pooled cohort, 37 lost to follow-up. Demographic and clinical characteristics are summarized in **Table 1.** Univariate analysis showed significant differences in outcome occurrence across treatment groups **(Table 2)** for the combined **(p = 0.002)** and the ischemic endopoints **(p = 0.003),** while no statistically significant differences emerged for hemorrhagic events (p = 0.3). Multivariate logistic regression analysis showed that DOACs were associated with lower risk of both combined and ischemic endpoints compared to warfarin (**Table 3**). Notably, **edoxaban** showed the greatest risk reduction with the lowest odds ratios (OR) for both the combined endpoint (**OR 0.40, 95% CI 0.17–0.96)** and the ischemic endpoint (**OR 0.28, 95% CI 0.08–0.91)**. No significant difference was observed in the risk of hemorrhagic events between treatment groups.

Methods: We conducted a post hoc analysis of pooled data from three international, multicenter, prospective cohort studies (RAF, RAF-NOAC and RENO-EXTEND), including acute ischemic stroke patients with non-valvular AF, secondary stroke prevention with DOACs or VKA and follow-up for 3 months. Primary outcome is a composite of ischemic stroke, systemic embolism, intracranial bleeding, and major extracranial bleeding, while secondary outcomes are ischemic and hemorrhagic events. Demographic and clinical characteristics as well as outcome occurrence were compared using Pearson's chi-square test for categorical variables and Kruskal–Wallis test or ANOVA test for continuous variables according to distribution assessed by Kolmogorov-Smirnov test. A multivariable logistic regression analysis was performed to evaluate the association between the type of oral anticoagulant and outcome events, using warfarin as the reference group.

	Dabigatran (783)	Apixaban (980)	Rivaroxaban (776)	Edoxaban (145)	Warfarin (702)	p value
Combined endopoint	35 (4.5%)	66 (6.7%)	42 (5.4%)	6 (4.1%)	65 (9.2%)	**0.002**
Ischemic endpoint	23 (2.9%)	40 (4.1%)	24 (3.1%)	3 (2.1%)	46 (6.5%)	**0.003**
Hemorragic endpoint	12 (1.5%)	26 (2.6%)	18 (2.3%)	3 (2.1%)	19 (2.7%)	0.3

Table 2. *Univariate analysis.*

Endpoint	Treatment	Odds Ratio (95% CI)	p-value
Combined Endpoint	Warfarin	1 (Reference)	-
	Dabigatran	0.53 (0.34–0.83)	**0.005**
	Apixaban	0.71 (0.48–1.03)	0.07
	Rivaroxaban	0.59 (0.39–0.90)	**0.01**
	Edoxaban	0.40 (0.17–0.96)	**0.04**
Ischemic Endpoint	Warfarin	1 (Reference)	-
	Dabigatran	0.49 (0.29–0.83)	**0.008**
	Apixaban	0.62 (0.39–0.97)	**0.03**
	Rivaroxaban	0.46 (0.27–0.78)	**0.004**
	Edoxaban	0.28 (0.08–0.91)	**0.03**
Hemorrhagic Endpoint	Warfarin	1 (Reference)	-
	Dabigatran	0.70 (0.34–1.44)	0.3
	Apixaban	0.99 (0.53–1.85)	0.9
	Rivaroxaban	0.90 (0.45–1.77)	0.7
	Edoxaban	0.74 (0.21-2.58)	0.6

Table 3. *Multivariate logistic regression analysis.*

Conclusion: Our findings support the use of **DOACs** over warfarin as secondary prevention in AF-related ischemic stroke patients, extending and reinforcing previous evidence coming from RCT subgroups analyses. Moreover, in this setting **edoxaban** may be particularly effective in reducing the risk of recurrent ischemic events without increasing the risk of major bleeding, although this needs to be confirmed in further studies such as larger prospective studies or head-to-head RCTs.

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