COMPARATIVE SAFETY AND EFFECTIVENESS OF NON-VITAMIN-K ORAL ANTICOAGULANTS VS PHENPROCOUMON IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION AND RENAL DISEASE - RESULTS FROM THE RELOADED STUDY

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BACKGROUND

Supplementary to randomized controlled trials, the generation of real-world evidence is important to reinforce safety perceptions and gaining knowledge on differences between treatments used in routine clinical practice. Existing real-world studies have provided evidence that non-vitamin K oral anticoagulants (NOACs) are more effective and at least as safe as vitamin K antagonists in non-valvular atrial fibrillation (NVAF). However, clinicians often hesitate to prescribe NOACs to patients with renal insufficiency. Therefore, it is important to investigate effectiveness and safety of rivaroxaban and other NOACs compared to vitamin-K antagonists in NVAF patients with renal insufficiency in a real life setting.

OBJECTIVES

The objective of the study was to describe the risk of ischemic stroke (IS)/systemic embolism (SE), intracranial hemorrhage (ICH), end-stage renal disease (ESRD) or dialysis, acute kidney injury (AKI) and fatal bleeding in patients with NVAF overall and with renal disease initiating treatment with individual NOACs (rivaroxaban, apixaban and edoxaban) compared to phenprocoumon.

METHODS

A new-user cohort study was conducted in patients with non-valvular atrial fibrillation overall and with renal disease based on German claims data between January 1st, 2013 and June 30th, 2017[1]. A multiple Cox-regression was performed to calculate confounder-adjusted hazard ratios (HRs) and related 95% confidence intervals. Treatment naïve users of each NOAC (rivaroxaban, apixaban and edoxaban) were compared to treatment naïve users of phenprocoumon. Sensitivity analyses comprised a propensity score matching and inverse probability of treatment weight (IPTW) approach.

As no laboratory values were available in the dataset renal disease in this study was defined by the following ICD-10 codes in a patient’s baseline medical history: D63.1, E10.2, E11.2, E13.2, I12, I13, N02, N03, N04, N05, N07, N08, N14, N18.1-N18.4, N18.9, N19, Q61[2,3]

RESULTS

Patient characteristics (not exhaustive)

	Rivaroxaban		Apixaban		Edoxaban		Phenprocoumon	
	Overall N=22,339	Renal N=5,121	Overall N=16,201	Renal N=4,750	Overall N=2,828	Renal N=682	Overall N=23,552	Renal N=7,289
Mean age (SD)	70.7 (12.0)	75.9 (9.4)	73.6 (11.6)	78.5 (9.1)	72.1 (11.4)	77.0 (9.2)	74.1 (9.9)	77.2 (8.4)
Women	41.9%	40.4%	43.9%	44.1%	40.0%	38.3%	41.9%	39.8%
Reduced dose	24.5%	43.4%	33.4%	52.8%	23.0%	42.8%	NA	NA
Mean CHA ₂ DS ₂ -VASc (SD)	3.6 (1.9)	4.6 (1.7)	4.1 (1.9)	5.1 (1.7)	3.7 (1.8)	4.6 (1.6)	4.1 (1.7)	4.9 (1.6)
Mean modified HAS-BLED (SD)	2.5 (1.2)	3.6 (0.9)	2.8 (1.2)	3.8 (0.9)	2.6 (1.2)	3.6 (0.8)	2.8 (1.1)	3.7 (0.8)
Diabetes mellitus	31.3%	48.2%	33.6%	49.1%	30.6%	48.7%	36.3%	50.3%
Chronic heart disease	37.0%	51.3%	39.4%	51.9%	34.7%	47.7%	46.5	59.2%
History of IS/TIA/SE	13.4%	18.5%	21.1%	27.2%	11.8%	15.8%	15.6%	19.7%
History of major bleeding	3.6%	6.6%	4.3%	7.3%	2.8%	5.3%	4.3%	6.8%
Malignant diseases	15.2%	20.6%	16.6%	22.0%	15.3%	21.7%	16.0%	20.2%

	Event rates , % per year (95% confidence interval)			
	Phenprocoumon	Rivaroxaban	Apixaban	Edoxaban
IS/SE	1.19 (1.07- 1.32)	1.11 (0.98- 1.25)	1.59 (1.41- 1.8)	1.22 (0.8- 1.77)
IS/SE renal	1.72 (1.44- 2.04)	1.67 (1.35- 2.05)	2.04 (1.65- 2.5)	N<5
ICH	0.55 (0.46- 0.64)	0.31 (0.24- 0.39)	0.28 (0.21- 0.38)	N<5
ICH renal	0.65 (0.48- 0.86)	0.41 (0.26- 0.62)	0.34 (0.19- 0.55)	N<5
Fatal Bleed	0.48 (0.4- 0.56)	0.36 (0.29- 0.44)	0.29 (0.21- 0.38)	0.27 (0.1- 0.59)
Fatal Bleed renal	1.06 (0.85- 1.32)	0.61 (0.42- 0.85)	0.51 (0.33- 0.76)	N<5
ESRD/Dialysis	0.52 (0.44- 0.61)	0.12 (0.08- 0.17)	0.34 (0.26- 0.44)	N<5
ESRD/Dialysis renal	1.75 (1.47- 2.08)	0.34 (0.21- 0.53)	0.72 (0.5- 1.01)	N<5
AKI	0.8 (0.7- 0.91)	0.58 (0.48- 0.68)	0.89 (0.75- 1.05)	0.59 (0.31- 1.01)
AKI renal	2.03 (1.72- 2.38)	1.43 (1.13- 1.78)	1.97 (1.59- 2.42)	1.89 (0.91- 3.47)

Cox Proportional-Hazard Regression Analysis – adjusted for more than 100 selected baseline covariates

CONCLUSION

This study confirms recommendations by ESC guidelines 2016: “When oral anticoagulation is initiated in a patient with NVAF who is eligible for a NOAC, a NOAC is recommended in preference to a Vitamin-K antagonist.” It is the first Real-World comparative effectiveness study of Factor Xa inhibitors vs. phenprocoumon in Germany with a focus on renal preservation outcomes. Rivaroxaban and apixaban showed a benefit in safety and renal preservation surrogate outcomes as well as a comparable effectiveness when compared to phenprocoumon. Only rivaroxaban showed a benefit in acute kidney injury compared to phenprocoumon. As only limited data were available for edoxaban, not all planned analyses were conducted.

REFERENCES

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DISCLAIMER

This study was sponsored by Bayer AG and S. Kloss is employee of Bayer AG. All authors contributed to the study design and interpretation of the results. Data analyses were conducted independently by WIG2 and InGef.