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COMPARISON OF TREATMENT ADHERENCE AND PERSISTENCE WITH EDOXABAN VERSUS APIXABAN, DABIGATRAN, RIVAROXABAN, AND VITAMIN K ANTAGONIST IN NON-VALVULAR ATRIAL FIBRILLATION PATIENTS IN GERMANY: A PROPENSITY MATCHED COHORT STUDY

Wang R[1], Marston XL[2], Yeh YC[2], Zimmermann L[3], Ye X[1], Gao X[2]
[1.] Daiichi Sankyo Inc., Basking Ridge, NJ; [2.] Pharmerit International, Bethesda, MD; [3.] Gesundheitsforen Leipzig GmbH, Leipzig

BACKGROUND

- Atrial fibrillation (AF) is the most common form of arrythmia. Characterized by an irregular and often rapid heartbeat, AF increases the risk of stroke [1] and mortality compared with age-matched individuals.[2]
- Germany has one of the highest prevalence of AF among European countries at 2.3% in 2014, and an incidence of 0.41 per 1,000 person/year.[3]
- Risk factors of AF include older age, heart disease, high blood pressure, alcohol consumption, and a family history of AF.[4]
- The use of oral anticoagulants was shown to reduce the risk of stroke and therefore is recommended in patients with non-valvular AF (NVAF) by international guidelines.[5,6]
- Compared to vitamin K antagonists (VKA),[7] non-vitamin K antagonist oral anticoagulants (NOACs) have fewer food and drug interactions and do not require monitoring of international normalized ratio (INR).[8-11]
- The 2016 European Society of Cardiology guidelines recommended the use of NOACs over VKA.[5]
- NOACs available in Germany include dabigatran (approved in November 2011), rivaroxaban (approved in December 2011), apixaban (approved in December 2012) and edoxaban (approved in June 2015).[12]
- Because treatment adherence and persistence to anticoagulant therapy may affect patient outcomes, it is important to understand the utilization patterns of anticoagulants in the real-world setting.

OBJECTIVE

To compare treatment adherence and persistence to edoxaban with other NOACs (including apixaban, dabigatran, rivaroxaban) and VKA in NVAF patients in Germany.

METHODS

Data Source: This is a retrospective study using the German analysis database (Gesundheitsforen Leipzig), a representative sample of the total German statutory health insured population.

Study Cohorts

- Eligible patients included individuals:
  - With a pharmacy claim for edoxaban, apixaban, dabigatran, rivaroxaban, or VKA between 2014 and 2017.
  - With an AF diagnosis
    - At least 1 primary or secondary hospital discharge diagnosis of AF (ICD-9 427.31, ICD-10 I48) before or on the index date, or
    - At least 1 outpatient diagnosis of AF before or on the index date, and at least 1 discrete outpatient diagnosis of AF between 12 months before to 3 months after the index date.[13]
  - ≥ 18 years of age on index date.
  - With continuous enrollment in the 12 months before the index date.
- Patients were excluded if they:
  - received any NOAC within 12 months before the index date,
  - received VKA within 12 months before their index VKA claims,
  - received more than 1 NOAC or 1 NOAC plus VKA on the index date, or
  - had valvular AF, deep vein thrombosis, pulmonary embolism, or end-stage renal disease within 12 months before the index date
  - had joint replacement within 6 months before the index date
  - pregnancy within 12 months before the index date or before December 31,2017

Outcomes

- **Medication adherence** was assessed by proportion of days covered (PDC) and medication possession ratio (MPR). Proportion of patients with PDC ≥ 0.8 and proportion of patients with MPR ≥ 0.8 were reported.
  - Six-month PDC
    $$\frac{Number\ of\ days\ covered\ by\ the\ index\ therapy\ in\ 6\ months}{180\ days}$$
  - Six-month MPR
    $$\frac{Number\ of\ days\ supplied\ of\ the\ index\ therapy\ in\ 6\ months}{180\ days}$$
- **Medication persistence** was assessed by time to discontinuation
  - Discontinuation was defined as a supply gap > 90 days of the index therapy.
  - Proportion of patients continuing the index therapy at 6 months was reported.

Propensity Score Matching

- Goal of matching: to control for potential differences between the study cohorts with respect to baseline characteristics [14-17]
- Comparison groups: edoxaban versus one of the other NOAC or VKA
- Matching methods: 1:1 nearest neighbor matching without replacement

Statistical Analysis

- T-tests were used to evaluate the statistical differences in PDC, MPR, and persistence between patients using edoxaban and other NOAC or VKA.
- Multivariable logistic regression was performed to identify factors associated with adherence (MPR ≥ 0.8) and persistence (PDC ≥ 0.8).

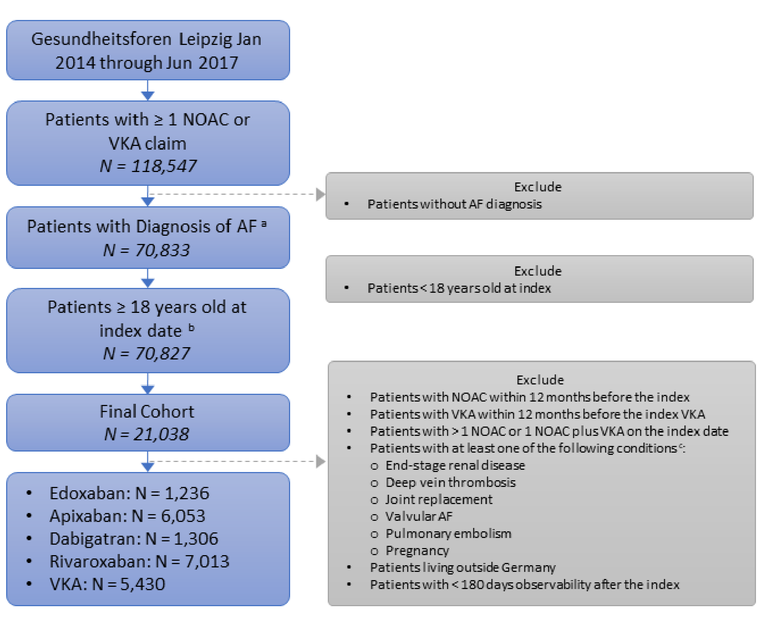

Figure 1. Flowchart of Patient Selection

Note:
[a] Patients are required to have: (1) ≥ 1 primary or secondary hospital discharge diagnosis of AF before or on the index date, or (2) ≥ 1 outpatient diagnosis of AF before or on the index date and ≥ 1 discrete outpatient diagnosis after the index date.
[b] Index claim = first NOAC or VKA claim; Index date = date of the first NOAC or VKA claim.
Abbreviation: NOAC = Non-vitamin K antagonist oral anticoagulant; VKA = Vitamin K antagonist; AF = Atrial fibrillation

RESULTS

- A total of 1,236 edoxaban patients were matched with patients treated with apixaban, dabigatran, rivaroxaban, and VKA (**Figure 1**).
- **Table 1a** and **1b** show the baseline characteristics of the study cohort before and after matching. After matching, the baseline characteristics were well balanced (standardized difference < 10%) between all comparison groups.

Table 1a. Baseline Characteristics before Propensity Score Matching

	Edoxaban	Apixaban	Dabigatran	Rivaroxaban	VKA
N=	1,236	6,053	1,306	7,013	5,430
Age, mean (SD)	72.3 (10.9)	73.9 (11.8)	71.6 (11.6)	70.9 (12.0)	74.3 (10.2)
Female, %	40%	44%	40%	42%	44%
CHA2DS2-VASc, mean (SD)	3.5 (1.7)	4.0 (1.9)	3.8 (1.9)	3.5 (1.8)	4.0 (1.7)
Modified HAS-BLED, mean (SD)	2.3 (1.0)	2.5 (1.1)	2.4 (1.1)	2.3 (1.1)	2.5 (1.0)

Table 1b. Baseline Characteristics after Propensity Score Matching

	Edoxaban	Apixaban	Edoxaban	Dabigatran	Edoxaban	Rivaroxaban	Edoxaban	VKA
N =	1,232		1,006		1,236		1,231	
Age, mean (SD)	72.3 (10.9)	72.3 (11.6)	71.9 (11.3)	72.1 (11.0)	72.3 (10.9)	72.0 (11.0)	72.4 (10.9)	72.2 (10.6)
Female, %	40%	40%	39%	40%	40%	41%	40%	40%
CHA2DS2-VASc, mean (SD)	3.5 (1.7)	3.5 (1.8)	3.6 (1.8)	3.6 (1.8)	3.5 (1.7)	3.5 (1.8)	3.5 (1.7)	3.6 (1.6)
Modified HAS-BLED, mean (SD)	2.3 (1.0)	2.3 (1.1)	2.3 (1.1)	2.3 (1.1)	2.3 (1.0)	2.3 (1.1)	2.3 (1.0)	2.3 (1.0)

Note: Modified HAS-BLED excludes INR. ***Abbreviation:*** VKA, Vitamin K antagonist.

Medication Adherence within 6 Months (Table 2)

- **PDC**
  - After matching, the proportion of patients with PDC ≥ 80% was significantly higher for edoxaban versus apixaban (63.0% versus 52.0%), dabigatran (62.0% versus 41.4%), and VKA (62.9% versus 45.2%) (all $p < 0.05$).
  - The proportion of patients with PDC ≥ 80% was comparable between edoxaban and rivaroxaban (63.0% versus 66.6%, $p = 0.07$).
  - Multivariable logistic regressions show that edoxaban was associated with increased likelihood of having PDC ≥ 0.8 compared to apixaban (odds ratio [OR], 95% CI: 1.64, 1.39-1.94), dabigatran (OR, 95% CI: 2.40, 1.99-2.88), and VKA (OR, 95% CI: 2.17, 1.84-2.57).
- **MPR**
  - The proportion of patients with MPR ≥ 80% was significantly higher for edoxaban versus apixaban (66.2% versus 55.5%), dabigatran (65.4% versus 45.7%), and VKA (66.1% versus 47.3%) (all $p < 0.05$).
  - The proportion of patients with MPR ≥ 80% was lower for edoxaban than rivaroxaban(66.3% versus 71.0%, $p < 0.05$).
  - Multivariable logistic regressions show that edoxaban was associated with increased likelihood of having MRP ≥ 0.8 compared to apixaban (OR, 95% CI: 1.63, 1.38-1.93), dabigatran (OR, 95% CI: 2.32, 1.93-2.79), and VKA (OR, 95% CI: 2.29, 1.94-2.72).

Medication Persistence within 6 Months (Table 2)

- Six-month persistence was significantly higher for edoxaban versus dabigatran (75.8% versus 66.3%), rivaroxaban (77.4% versus 73.1%) and VKA (77.4% versus 58.6%) (all $p < 0.05$).
- Persistence was numerically higher in edoxaban group compared to apixaban (77.4% versus 75.8%, $p = 0.37$).

Table 2. Medication Adherence and Persistence within 6 Months by Index Anticoagulant (After Propensity Score Matching)

	Edoxaban	Apixaban	Edoxaban	Dabigatran	Edoxaban	Rivaroxaban	Edoxaban	VKA
N =	1,232		1,006		1,236		1,231	
Adherence								
PDC								
PDC, mean	***0.7928***	***0.7292***	***0.7854***	***0.6847***	0.7930	0.7843	***0.7924***	***0.7445***
PDC ≥ 80%, n (%)	***776 (63.0)***	***640 (52.0)***	***624 (62.0)***	***416 (41.4)***	779 (63.0)	823 (66.6)	***774 (62.9)***	***556 (45.2)***
OR (95% CI [a])	***1.64 (1.39-1.94)***		***2.40 (1.99-2.88)***		0.86 (0.73-1.02)		***2.17 (1.84-2.57)***	
MPR								
MPR, mean	***0.8146***	***0.7521***	***0.8078***	***0.7112***	0.8150	0.8105	***0.8144***	***0.7561***
MPR ≥ 80%, n (%)	***816 (66.2)***	***684 (55.5)***	***658 (65.4)***	***460 (45.7)***	***819 (66.3)***	***877 (71.0)***	***814 (66.1)***	***582 (47.3)***
OR (95% CI [a])	***1.63 (1.38-1.93)***		***2.32 (1.93-2.79)***		***0.81 (0.68-0.97)***		***2.29 (1.94-2.72)***	
Persistence								
Patients continuing the index therapy, n (%)	954 (77.4)	934 (75.8)	***763 (75.8)***	***667 (66.3)***	***957 (77.4)***	***904 (73.1)***	***953 (77.4)***	***721 (58.6)***

Abbreviation: VKA, vitamin K antagonist; PDC, proportion of days covered; MPR, medication possession ratio.
Note: Bold italic text indicates $p < 0.05$.
[a] Key variables controlled in the models included age, gender, region, Charlson comorbidities, and concomitant medications.

CONCLUSIONS

- Edoxaban was associated with significantly higher adherence in NVAF patients compared to apixaban, dabigatran, and VKA. A possible explanation is that edoxaban is dosed once rather than twice daily and does not require routine blood tests.
- Edoxaban patients also had higher persistence compared to dabigatran, rivaroxaban, and VKA.
- Adherence and persistence should be considered in treatment selection to improve patient care.

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