ORIGINAL RESEARCH

Estimated Thresholds of Minimum Necessary Adherence for Effective Treatment with Direct Oral Anticoagulants – A Retrospective Cohort Study in Health Insurance Claims Data

Lucas Wirbka
Walter Emil Haefeli [ID]
Andreas Daniel Meid [ID]

On behalf of ARMIN Study Group

Department of Clinical Pharmacology and Pharmacoepidemiology, University of Heidelberg, Heidelberg, 69120, Germany

Background: An essential contribution regarding the prevention of thromboembolic events in patients with (non-valvular) atrial fibrillation (AF) is good adherence to direct oral anticoagulants (DOACs). However, it is an open question what "good" adherence means for DOACs or below which threshold non-adherence is clinically relevant for AF patients. Ultimately, such a classification could prevent strokes and associated costs through adjusted treatment regimens or supportive measures.

Methods: We selected 10,092 AF patients from health insurance claims data between 2014 and 2018 who were issued a majority (at least half of the number) of maximum approved strength prescriptions of one of the following DOACs, namely rivaroxaban, apixaban, or dabigatran. Due to the limited sample size, the prescriptions of dabigatran had to be finally excluded for the cut-off analysis. DOAC adherence was calculated as the proportion of days covered (PDC) by dividing the days of theoretical use (days covered) of the drug by the duration in days of the observation interval. PDC cut-off values were derived from stroke risk as a function of continuous PDC values in time-to-event analyses and corresponding dose-response models. The influence of adherence-promoting interventions (targeted and untargeted) on the occurrence of strokes and related costs was then projected, considering intervention costs per patient.

Results: The population had a mean age of 74.5 years and 50% were female. The median PDC was 0.79 ± 0.28 with a median follow-up time of 1218 days, in which 2% of all DOAC patients had a stroke. The adherence cut-offs for good adherence were identified at 0.78 for rivaroxaban and 0.8 for apixaban. Targeted interventions appeared to be far more cost-effective than untargeted interventions.

Conclusion: Clear adherence cut-offs enable healthcare professionals to identify patients with clinically relevant non-adherence. Interventions based on these cut-offs appear to be a promising means to optimize DOAC treatment.

Keywords: DOAC, atrial fibrillation, adherence, pharmacoepidemiology, cut-off, claims data

Correspondence: Andreas Daniel Meid
Department of Clinical Pharmacology and Pharmacoepidemiology, University of Heidelberg, Im Neuenheimer Feld 410, Heidelberg, 69120, Germany
Tel +49 6221 56 37113
Fax +49 6221 56 4642
Email Andreas.Meid@med.uni-Heidelberg.de

Introduction

Adherence is a necessary prerequisite for a drug to work, either prophylactically, therapeutically, or palliatively.[1–3] This is also true for direct oral anticoagulants (DOACs), which aim to prevent serious medical consequences such as thromboembolic events in patients with (non-valvular) atrial fibrillation (AF).[1,4,5] Adherence is a continuum and achieving and consistently maintaining 100% adherence over

a long period of time is difficult. Indeed, the cost of keeping adherence rates high increases with the level of intended adherence.[6] Therefore, the obvious question is how much adherence is necessary and how much is enough? Often, general cut-off values that define "good" adherence have been arbitrarily and conventionally set at 80%.[5,7–10] However, this is unlikely to be true for all medicines and may not apply to DOACs. Sufficient adherence may be a critical factor in clinical practice, depending on the expected benefits of the medicine and the consequences of underuse. A drug-specific adherence cut-off for DOACs may help to classify patients at substantially higher risk and to offer supportive interventions.

Medication adherence can be readily estimated from routine claims data that contain information on drug purchases and dispensed package sizes and thus allow investigating the relationship between adherence, clinical outcomes, and associated costs.[1–3] In addition to a continuous adherence metric, the use of adherence thresholds is common, dividing patients into "good" and "poor" adherence groups by a cut-off, which can help clinicians to identify patients in need of support.[2,11,12] Such adherence cut-off values can be established by relating them to clinical outcomes. Taking binary outcome definitions as an example, one can maximize their sensitivity and specificity, and for time-to-event analyses, one can maximize the test statistic for the group comparison between "high" and "low" adherence, separated by a cut-off value.[2,11,12] Because the effect of DOACs on clinical endpoints is concentration-dependent as well as dose-dependent (and non-adherence is in fact a dose reduction), a pharmacologically more intuitive approach would be to apply (sigmoid) dose-response analyses to choose a cut-off value and to thus achieve a certain percentage of maximum effect. Regardless of the method chosen, the adherence model allows to project the impact of adherence-increasing interventions on the number of (averted) clinical outcomes and thus equally addresses health economic aspects.[5] Given the disastrous clinical consequences of strokes[13,14] and the immense costs associated with them,[15–17] it seems imperative to define an adherence threshold that identifies patients at risk of treatment failure while considering the potential benefits in terms of averted events and costs.

In this study, we explored claims data from a large German statutory health insurance fund to determine adherence cut-offs for the DOACs rivaroxaban and apixaban in AF patients; the data were generated as a preparatory step for the evaluation of the ARMIN ("Arzneimittelinitiative Sachsen-Thüringen") program, a quality initiative to improve medication quality and safety. Therefore, we analyzed the association between continuous adherence and stroke risk as a dose-response relationship to derive clinically meaningful adherence cut-offs for optimum stroke risk reduction after DOAC initiation. A secondary aim was to compare adherence patterns and cut-offs of DOACs with different dosing schedules, such as once-daily regimens for rivaroxaban and twice-daily for apixaban. Finally, we predicted the potential impact of supportive interventions on avoided events as a function of adherence cut-off values.

Materials and Methods
Data Source and Study Population

The study's data source was constituted of claims data of insured persons belonging to a large German health insurance fund (AOK PLUS) in the calendar years 2013–2018. Insured persons were included in the follow-up period between 2014 and 2018 if they received at least one DOAC prescription (rivaroxaban, apixaban, or dabigatran) between 01/JAN/2014 and 31/DEC/2018, were permanently insured in the period from 01/JAN/2013 to 31/DEC/2018, and at least 18 years old in 2013. Thus, the year 2013 served as a run-in period to characterize the population at baseline and ensured that each patient was characterized for at least 12 months prior to individual follow-up. Figure 1 describes the inclusion and exclusion criteria used to form the study population (for a detailed description of underlying billing codes, see Supplementary Table 1). Accordingly, the study applied a retrospective cohort design considering DOAC initiation as individual entry time. We chose a new-user design (also called incident-user design) as study design, meaning that only patients who had not received a DOAC prescription in the year prior to individual study entry (ie, the time of the "first" prescription) were included in the study. Inclusion was restricted to patients with a majority of full-dose prescriptions in order to avoid inclusion of patients who were falsely underdosed, a common phenomenon in clinical practice associated with an increased risk of stroke.[18–21] Hence, the study exclusively considered patients who received at least half of the number (or the same number) of prescriptions with the full dose strength (rivaroxaban 20 mg, apixaban 5 mg, and dabigatran 150 mg) per tablet. This also avoided the consideration of renal function, which cannot be validly extracted from (outpatient and inpatient)
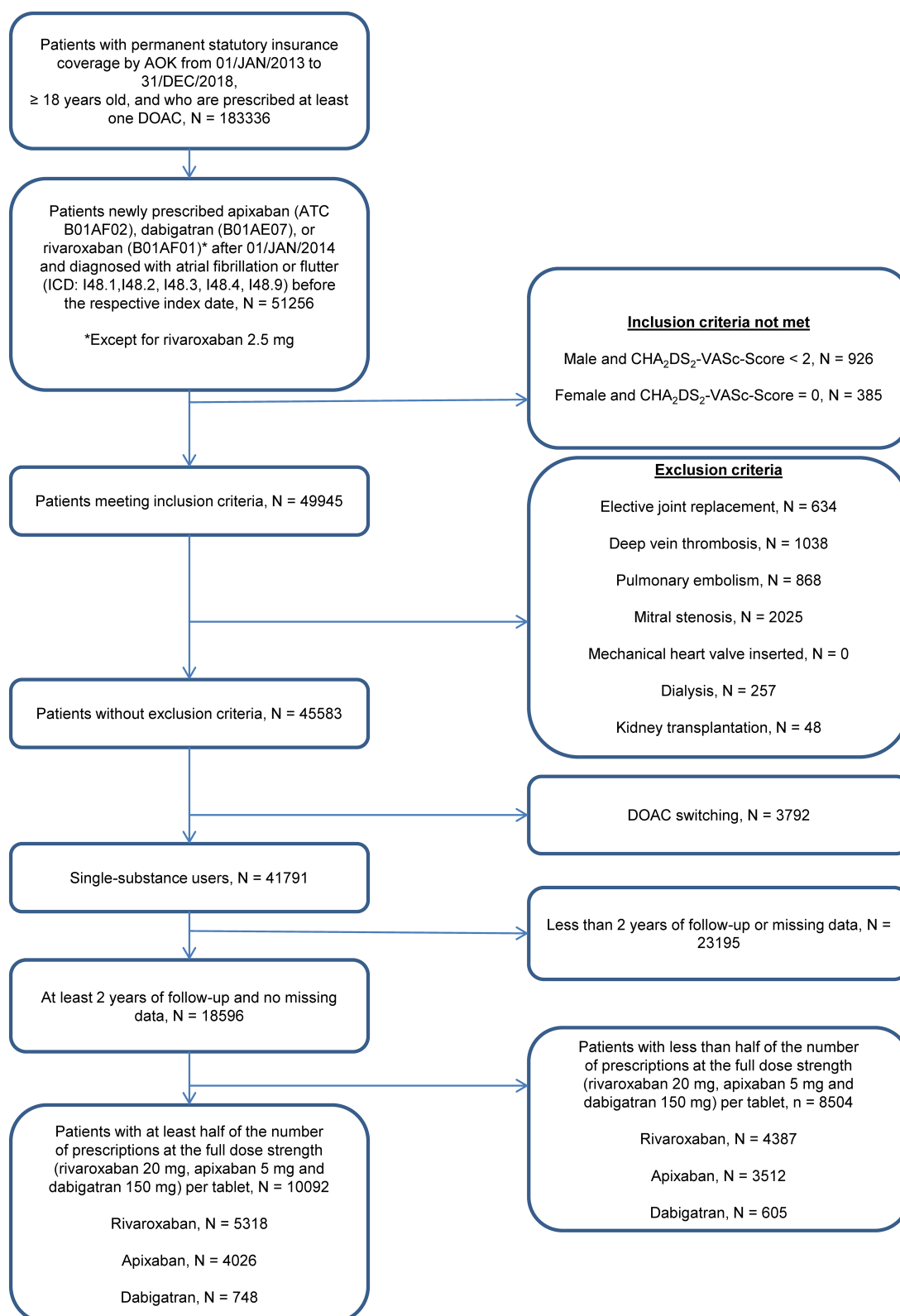
Figure 1 Selection of a patient cohort suffering from atrial fibrillation that are anticoagulated with direct oral anticoagulants as documented in a large health insurance database.

Notes: CHA_2DS_2-VASc score components include congestive heart failure (1 point), hypertension (1 point), age (≥ 75 years: 2 points; 65–74 years: 1 point), diabetes mellitus (1 point), prior stroke (2 points), vascular disease (1 point), and female sex (1 point).

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification System; ICD, International Classification of Diseases, 10th revision.

claims data and can be a reason for dose reduction. Patients were followed up to the first clinical event (stroke), or to a censoring event. This could be either death, switching to a vitamin K antagonist, or end of follow-up. Because all data were completely anonymous to the analysts, this research project did not require ethical approval. All analyses strictly followed the STROBE statement (Strengthening the Reporting of Observational studies in Epidemiology, see Supplementary Table 3).[22]

Outcome

To identify patients with stroke as an outcome, validated and previously applied code sets of the main and secondary diagnoses of inpatient admissions were used (for a detailed list of codes, see Supplementary Table 2).[23,24]

Exposure

The exposure variable was defined by DOAC adherence, which was obtained by a form of proportion of days covered (PDC). The PDC is a numeric proportion between 0 and 1 that is calculated by dividing the days of theoretical use (number of days covered by medication) by the number of (outpatient) days in the follow-up window.[25] Formula 1 below describes how the PDC is calculated:

$$PDC = \frac{\text{Number of days of theoretical use}}{\text{Index date to end of follow up}} \quad (1)$$

The algorithm used (CMA6 function from the AdhereR package[25]) first determines the number of days without medication (the so-called gap days are derived from the prescription durations of the packs) in the follow-up period. In the next step, these are subtracted from the total number of days in the follow-up period to determine the number of days with theoretical use. DOAC prescription records were used to determine the date of prescription and the quantity and strength of tablets prescribed. From this, a prescription duration was determined for each pack based on the patient's dose. According to patient selection, the usual doses of 10 mg per day for apixaban, 20 mg per day for rivaroxaban, and 300 mg per day for dabigatran were assumed. The prescription duration (PD) was calculated for each pack according to formula 2:

$$PD = \frac{\text{Quantity} * \text{Number} * \text{Strength}}{\text{Dose}} \quad (2)$$

Quantity denotes quantity of tablets per package, Number corresponds to the number of packages prescribed, Strength denotes the amount of active ingredient of one solid oral dosage form of the package and Dose denotes the standard dose (full-dose) per day of the corresponding DOAC. If patients were hospitalized within the prescription duration of a package, the length of the hospital stay was added to the prescription duration of the package because during hospitalization, provision of all drugs by the hospital is mandatory. PDC was calculated using the R package AdhereR as an averaged value over a patient's entire observation period (see Supplementary Material 1 for functional parameters).[25]

Potential Confounders

Potential confounding variables were defined by clinical expertise considering 18 variables as extracted from prior publications.[4] These variables originated from different areas such as demographics (sex and age), comorbidities (hypertension, heart failure, diabetes mellitus, prior stroke, prior myocardial infarction, renal disease, chronic liver disease, peripheral vascular disease, depression, alcohol abuse, and drug abuse), scores for individual prognosis (CHA_2DS_2-VASc Score for thromboembolic events),[26] comedication (use of antiplatelets or vitamin K antagonist), and healthcare utilization (number of hospitalizations and number of medications co-prescribed). We assessed which of the individual conditions mentioned in the Charlson and Elixhauser scores were predictors of non-adherence and used these to adjust the model.[27,28] Overall, their covariates were derived from the prescription data, the medically-confirmed outpatient diagnoses by the general practitioner, the hospital admission diagnoses, and the main diagnoses of hospital stays in the year before the patient's index date.[4] A complete list of potential confounders and their definitions is provided in Supplementary Table 4.

Sample Size

With our study design, the total number of patients for all three DOAC cohorts was 10,092 (Figure 1). Of these, 4026 patients (39.9%) were treated with apixaban and 5318 patients (52.7%) with rivaroxaban. Only rivaroxaban initiators and apixaban initiators were used for adherence-response modeling, while the cohort of 748 (7.4%) dabigatran initiators was too limited for either statistical inferences or modeling and was thus only used for an exploratory comparison with an external reference.[4] Because enrollment was restricted to patients with complete data sets, no values were missing.

Statistical Analyses

The cohort was described by statistics summarizing their distributional location parameters for continuous and proportions for categorical variables. Inferential tests on descriptive characteristics of the study population were chosen in accordance with the variable scale and variable distribution.

Association of DOAC Adherence with Stroke

To describe the association between DOAC adherence and stroke risk, we adopted the procedure proposed by Shore et al.[4] Cox proportional hazards regression[4] was applied to all three DOAC cohorts in order to analyze event times for each patient starting at the index date and ending with the event of stroke or censoring time due to premature death, switching to a vitamin K antagonist, or end of follow-up (31/DEC/2018). In addition to the list of potential confounders, the continuous adherence measure of each patient was chosen as independent variable of interest. To facilitate a comparison with the external reference by Shore and colleagues, hazard ratios (HR) with 95% confidence intervals (CI) were determined for each 10% decrease in adherence to the respective DOAC regimen.[4] The fully adjusted Cox models were also used for a general group comparison between rivaroxaban and apixaban. In a further analysis, the stroke event frequency of the study population was compared with a population that switched between the different DOAC agents.

Adherence Cut-off Estimation

To analyze the dose-response relationship and derive an adherence cut-off, we applied the time-to-event approach with continuous PDC estimates in Cox proportional hazards models for stroke risk.[29] As a preliminary step, non-linearity in the effects of apixaban and rivaroxaban was ruled out by inferential tests based on model comparisons with multifractional polynomials.[30] Because empirically no evidence for non-linearity was present, we applied linear Cox models of adherence to predict probabilities of stroke and used them as the (continuous) dependent variable in dose-response analyses with adherence as the independent variable. In particular, 4-fold logistic (growth) models were used to derive a cut-off value from the common effective dose exerting 80% of the maximum effect (ie, ED_{80} value corresponding to the estimated PDC inducing 80% of the maximum effect).[31] In these

models, the effect sizes (hazard ratios) were scaled to 100% by dividing each value by the maximum value (ie, estimate at the point of zero adherence). Sensitivity analyses included a cut-off determination based on the Youden index to maximize sensitivity and specificity[32] and a derivation of the cut-off from the receiver operating characteristic (ROC) curve as the point with the smallest distance from the upper left corner (0/1).[11]

Impact of Supportive Interventions on Averted Events

We considered two settings to examine the impact of adherence-increasing interventions on stroke incidence. In the first setting, we considered offering a complex adherence-increasing intervention to the entire study population regardless of the adherence score of the individual patient (untargeted intervention), whereas the second setting foresaw a targeted adherence-increasing intervention for the group below the previously determined cut-off value. Untargeted and targeted interventions differ in whether all patients participate in the intervention or only a predefined (eg, presumably poorly adherent) proportion of patients. Possible interventions for both groups include a mobile app or phone calls that remind patients to take their anticoagulant. Other possibilities are patient education about the value of good adherence and ways to reach adherence rates $\geq$ 80% or refill activities to promote uninterrupted drug supply.[33–36] To consider the interventional impact independently from our modeling data, we chose a DOAC adherence distribution from an external reference.[4] The assumed effect estimate for the untargeted intervention in the first setting was adopted from unpublished data as an odds ratio of 1.08 for an increased probability for adherence improvement by a complex intervention. We applied formula 3:

$$\text{PDC}^* = \frac{OR_{AI}*\text{PDC}}{1 + (OR_{AI}*\text{PDC}) - \text{PDC}} \tag{3}$$

where OR_{AI} denotes the odds ratio for adherence improvement. First, baseline adherence (PDC) from the reference distribution was randomly assigned to our patients in order to predict the baseline number of strokes from the aforementioned adjusted Cox models. Second, improved adherence (PDC*) was derived from the formula to predict the number of strokes after an intervention. This procedure was repeated a thousand times and median numbers of strokes across iterations were extracted to calculate the number of avoided events.

The assumed effect estimates for the targeted intervention in the second setting related to probabilities for improving a patient's adherence to a value above the cut-off yielding 80% efficacy. We considered the meta-analytically pooled odds ratio of 1.57 for achieving "good" adherence.[37] First, each patient was randomly assigned an adherence according to the reference distribution. Then, we randomly sampled 57% of the patients below the cut-off, assigned the cut-off value to their adherence estimate, and predicted the number of events depending on the new adherence values. This procedure was repeated a thousand times to obtain a median number of avoided events across all iterations. Finally, we averaged the number of averted events across all samples. For both types of intervention, we then calculated the costs that could be saved with each intervention through reduced events. Costs of 43,129 Euros were assumed for each case of stroke.[17]

In general, statistical tests were two-sided, and 95% CI were calculated according to an alpha level of 0.05. All analyses were conducted using the R software environment in version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results
Study Population

Table 1 shows the baseline characteristics of the three cohorts selected by our inclusion and exclusion criteria. The mean age of the 10,092 eligible patients was 74.5 ± 9.7 years and 50% were female. During follow-up, 210 (2% of all patients) strokes were recorded with a median follow-up time of 1218 days (Figure 1). The median CHA_2DS_2-VASc Score of the study population was 4. Comorbidities were frequent, with nearly all patients being diagnosed for hypertension (95%) and nearly half of the patients being diagnosed for heart failure (53%), and diabetes (46%). Antiplatelets were used by 18% of patients and 30% of patients had a prescription for a vitamin K antagonist in the year before the first DOAC prescription. Apixaban patients were older than patients receiving rivaroxaban. They had shorter median times to stroke, on average more comorbidities, and were more frequently prescribed antiplatelets or anticoagulants before participating in the study. They equally had higher CHA_2DS_2-VASc scores. A detailed presentation of the cohort subdivided into age groups can be found in Supplementary Tables 6 and 7.

Association of DOAC Adherence and Stroke

In our study cohorts mean adherence (PDC) during follow-up was 0.79 ± 0.28 in total, while highest PDC was observed for apixaban users (0.81 ± 0.27) followed by rivaroxaban (0.80 ± 0.29) and dabigatran users (0.70 ± 0.33). Adherence distributions were quite similar between different DOACs and dosing regimens (Figure 2). A 10% reduction in adherence was associated with a 2% increase in stroke risk in the dabigatran cohort (adjusted HR 1.02, 95% CI [0.9–1.15]), a 5% increase of the rivaroxaban cohort (adjusted HR 1.05, 95% CI [0.98–1.12]), and a 3% increase in the apixaban cohort (adjusted HR 1.03 95% CI [0.95–1.11]). In a sensitivity analysis, the stroke incidence of patients who were a priori excluded because they switched between DOACs (n = 3792) was substantially greater (12.5%) than in our main study population, where patients did not switch between DOACs (1.9%). Moreover, in patients who switched twice (n = 106), stroke rate was 18.9%, ie, 50% larger than in patients switching only once (12.3%). In the follow-up period, 94 patients (1% of all enrolled patients) switched to a vitamin K antagonist.

Adherence Cut-off Estimation

Using our study design the determined adherence cut-offs for 80% efficacy (ED_{80}) were 0.78 for rivaroxaban and 0.8 for apixaban (Figure 2B and D; other estimated doses and the corresponding PDC values can be found in Supplementary Table 5). Alternative methods in sensitivity analyses yielded an optimal cut-off for rivaroxaban of 0.84 and 0.94 (determined by the Youden index/ROC 0/1 method) and an optimal cut-off for apixaban of 0.83 and 0.83, respectively (determined by the Youden index/ROC 0/1 method). Based on our design of the study the maximum achievable plateau effect within the separate cohorts was estimated to be greater for rivaroxaban than for apixaban (Figure 2A and C). The apparently stronger relationship between adherence and stroke risk is consistent with the group effect for the comparison rivaroxaban versus apixaban in our cohorts (adjusted hazard ratio 0.93, 95% CI [0.75–1.14]). While a 10% reduction in adherence in the pooled cohort resulted in a 4% increase of stroke risk, this adherence effect was higher in the rivaroxaban cohort by additional 2% (adjusted HR 1.02, 95% CI [0.99–1.05]). Both DOACs differed only slightly in their PDC distribution, with patients in the rivaroxaban cohort having higher mean and identical median adherence scores as patients in the apixaban cohort (Figure 2A and C, Table 1). Based on

Table 1 Baseline Characteristics of the Study Cohorts

	Dabigatran	Rivaroxaban	Apixaban	Total	Comparison Rivaroxaban vs Apixaban (p-value)	Comparison Rivaroxaban vs Apixaban (Standardized Difference)
Number of patients, N Age in years, mean ± SD	748 73.3 ± 10.5	5318 74.0 ± 9.7	4026 75.3 ± 9.4	10,092 74.5 ± 9.7	$P_{ttest} < 0.001$	0.083
Female sex, N (%)	340 (45)	2619 (49)	2098 (52)	5057 (50)	$P_{\chi^2} = 0.035$	0.034
Outcome stroke, N (%)	32 (4)	93 (2)	85 (2)	210 (2)	$P_{\chi^2} = 0.355$	0.016

Proportion of days covered (PDC)
  Mean ± SD
  Median (IQR)
	0.70 ± 0.33
	0.84 (0.47,0.98)
		0.80 ± 0.29
		0.95 (0.69,1.00)
			0.81 ± 0.27
			0.95 (0.71,1.00)
				0.79 ± 0.28
				0.95 (0.68,1.00)
					$P_{ttest} = 0.004$	0.017

Median follow-up time, median in days (IQR)	1382 (1056, 1628)	1281 (1027, 1532)	1124 (914, 1372)	1218 (971, 1487)	$P_{ttest} < 0.001$	0.237

Comorbidities
  Hypertension, N (%)
  Heart failure, N (%)
  Diabetes, N (%)
  Prior stroke, N (%)
  Prior myocardial infarction, N (%)
  Renal disease, N (%)
  Chronic liver disease, N (%)
  Peripheral vascular disease, N (%)
  Depression, N (%)
  Alcohol abuse, N (%)
  Drug abuse, N (%)
	
	722 (97)
	392 (52)
	345 (46)
	152 (20)
	71 (9)
	150 (20)
	105 (14)
	166 (22)
	116 (16)
	45 (6)
	7 (1)
		
		5,012 (94)
		2693 (51)
		2382 (45)
		519 (10)
		474 (9)
		1146 (22)
		762 (14)
		1081 (20)
		994 (19)
		240 (5)
		48 (1)
			
			3,877 (96)
			2284 (57)
			1949 (48)
			683 (17)
			419 (10)
			1300 (32)
			633 (16)
			1012 (25)
			798 (20)
			170 (4)
			39 (1)
				
				9611 (95)
				5369 (53)
				4676 (46)
				1354 (13)
				964 (10)
				2596 (26)
				1500 (15)
				2259 (22)
				1908 (19)
				455 (5)
				94 (1)
					
					$P_{\chi^2} < 0.001$
					$P_{\chi^2} < 0.001$
					$P_{\chi^2} = 0.007$
					$P_{\chi^2} < 0.001$
					$P_{\chi^2} = 0.063$
					$P_{\chi^2} < 0.001$
					$P_{\chi^2} = 0.153$
					$P_{\chi^2} < 0.001$
					$P_{\chi^2} = 0.296$
					$P_{\chi^2} = 0.626$
					$P_{\chi^2} = 0.864$
						
						0.056
						0.074
						0.044
						0.134
						0.031
						0.150
						0.024
						0.070
						0.017
						0.009
						0.004

Comedication
  Antiplatelet before, N (%)
  Vitamin K antagonist before, N (%)
	
	140 (19)
	201 (27)
		
		866 (16)
		1568 (29)
			
			784 (19)
			1284 (32)
				
				1790 (18)
				3053 (30)
					
					$P_{\chi^2} = 0.002$
					$P_{\chi^2} = 0.054$
						
						0.051
						0.032

CHA$_2$DS$_2$-VASc Score, median (IQR)	4 (3,5)	4 (3,5)	4 (3,5)	4 (3,5)	$P_{Wilcox} < 0.001$	0.106

Healthcare Utilization
  Median number of hospitalizations (IQR)
  Median number of ATC codes (IQR)
	
	4 (3,8)
	21 (15,28)
		
		4 (2,7)
		21 (15,29)
			
			5 (3,7)
			22 (16,30)
				
				4 (2,7)
				22 (16, 29)
					
					$P_{ttest} < 0.001$
					$P_{ttest} < 0.001$
						
						0.055
						0.064

Notes: CHA$_2$DS$_2$-VASc score components include congestive heart failure (1 point), hypertension (1 point), age (≥75 years: 2 points; 65–74 years: 1 point), diabetes mellitus (1 point), prior stroke (2 points), vascular disease (1 point), and female sex (1 point); Because adherence cut-off values were determined only for apixaban and rivaroxaban (and due to the small case numbers for dabigatran), only these groups are reported in the table.
Abbreviations: IQR, interquartile range; SD, standard deviation; N, number.

these cut-off values, approximately 30% of rivaroxaban patients and 32% of the apixaban patients were classified as poorly adherent. Numerous patient characteristics were associated with poor adherence according to these adherence cut-off values in adjusted logistic models (Supplementary Figure 1).

Impact of Supportive Interventions on Averted Events

Figure 3 shows that a targeted intervention to improve patient adherence was significantly superior to a non-targeted intervention offered to all patients. Accordingly, a non-targeted intervention ceased to be cost-effective, whereas a targeted intervention allows for intervention costs of more than 500 Euros per patient. Of note, the saved costs were directly proportional to the events prevented. Thus, the general intervention potentially prevented a mean of 0.04 strokes per 1000 patient-years (combined from the simulation of rivaroxaban and apixaban), whereas the targeted intervention potentially prevented a mean of 27.8 strokes per 1000 patient-years (combined from the simulation of rivaroxaban and apixaban).
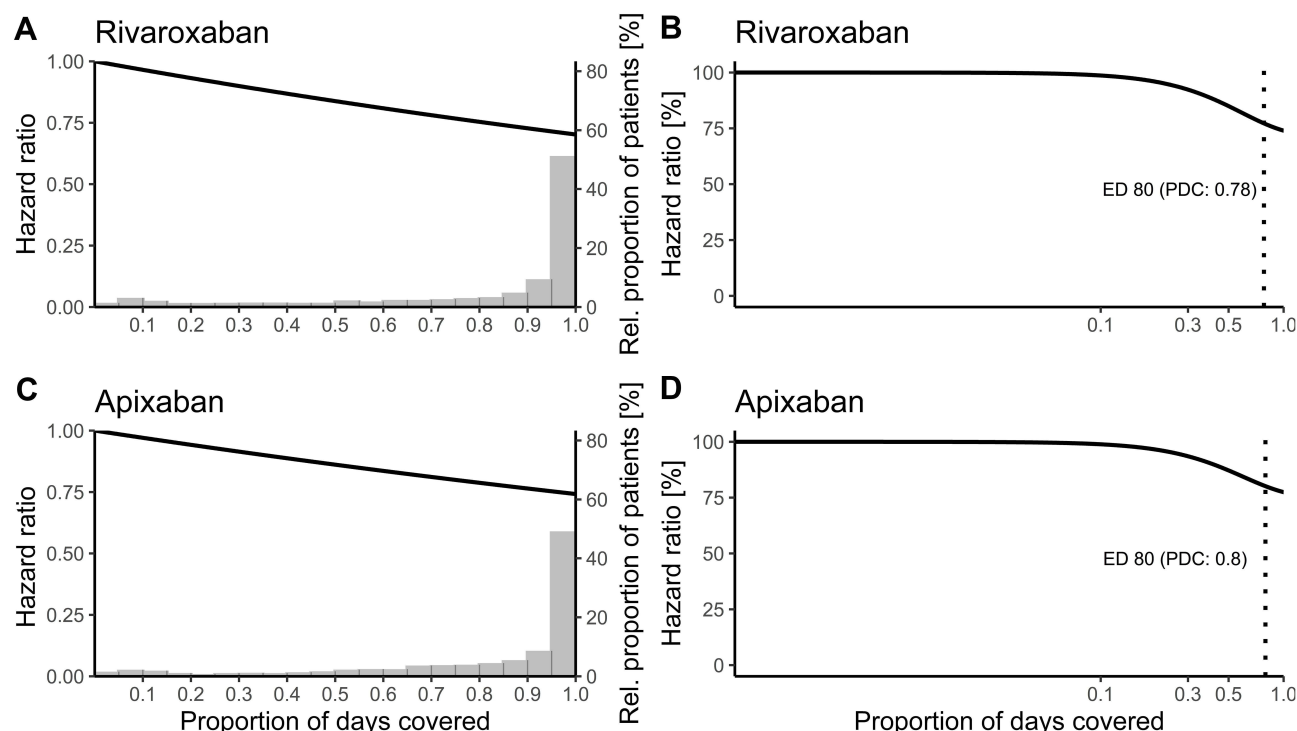
Figure 2 Adherence cut-off estimation of apixaban and rivaroxaban with Cox models (**A** and **C**) and 4-parameter logistic dose-response models (**B** and **D**).
Notes: Adherence patterns (as proportion of days covered, PDC) are shown as histograms (**A** and **C**) with superimposed relationships between adherence values and fitted hazard ratios (HR). Dose-response analyses (**B** and **D**) were based on four-parameter logistic models to obtain adherence values at 80% of maximum predicted effectiveness (ED 80). The hazard ratios were scaled by dividing each hazard ratio by the maximum hazard ratio.

Discussion

In our work, we determined the minimum adherence threshold above which the DOACs rivaroxaban and apixaban achieve at least 80% efficacy. The adherence cut-offs we obtained are slightly below the conventional limit of 0.8. Using adjusted adherence risk models, we were able to extrapolate the intervention effect on adherence improvement. This extrapolation not only verified our analysis but may also be an interesting approach for future interventions.

In our population, we noticed similar adherence PDC distributions for the studied DOACs, with the median of the dabigatran cohort achieving the lowest estimate. This appears to be in line with the previous literature, where dabigatran predominantly showed lower median adherence values compared to rivaroxaban and apixaban.[38–40] In contrast to other populations, patients in our cohorts were old aged.[4,38–40] Additionally, differences between cohorts in the literature and our population existed with regard to comorbidities. For example, hypertension, diabetes, and renal failure occurred slightly more frequently in our population.[4,38–40] Moreover, we observed higher CHA_2DS_2-VASc scores on average.[39] With regard to the potential inter-relationship between patient characteristics and adherence, these small differences may partly explain the difference in the adherence estimates in our population compared with previous work.[4]

To ensure that the effect size of our results compared with those measured in clinical trials was plausible, we compared them with the results of randomized controlled clinical trials. The adherence-risk relationships (Figure 2A and C) observed in our study appear plausible when compared with concentration-stroke relationships from pivotal DOAC trials that also found an exponential decrease and a comparable reduction in stroke risk with increasing DOAC exposure.[41,42] Although our curves decreased exponentially, they did not flatten as much at high adherence values as in previous studies, which may be due to the calculation of our adherence measure. The PDC by definition truncates any value above the full maximum daily dose and sets it to the maximum. Higher dose ranges are thus fixed at 100%. As a consequence, it is possible that we did not reach the plateau in our dose-response curves. This is a natural consequence of PDC, which must be seen as a substitute for the actually ingested dose or resulting exposure, with this exposure-response
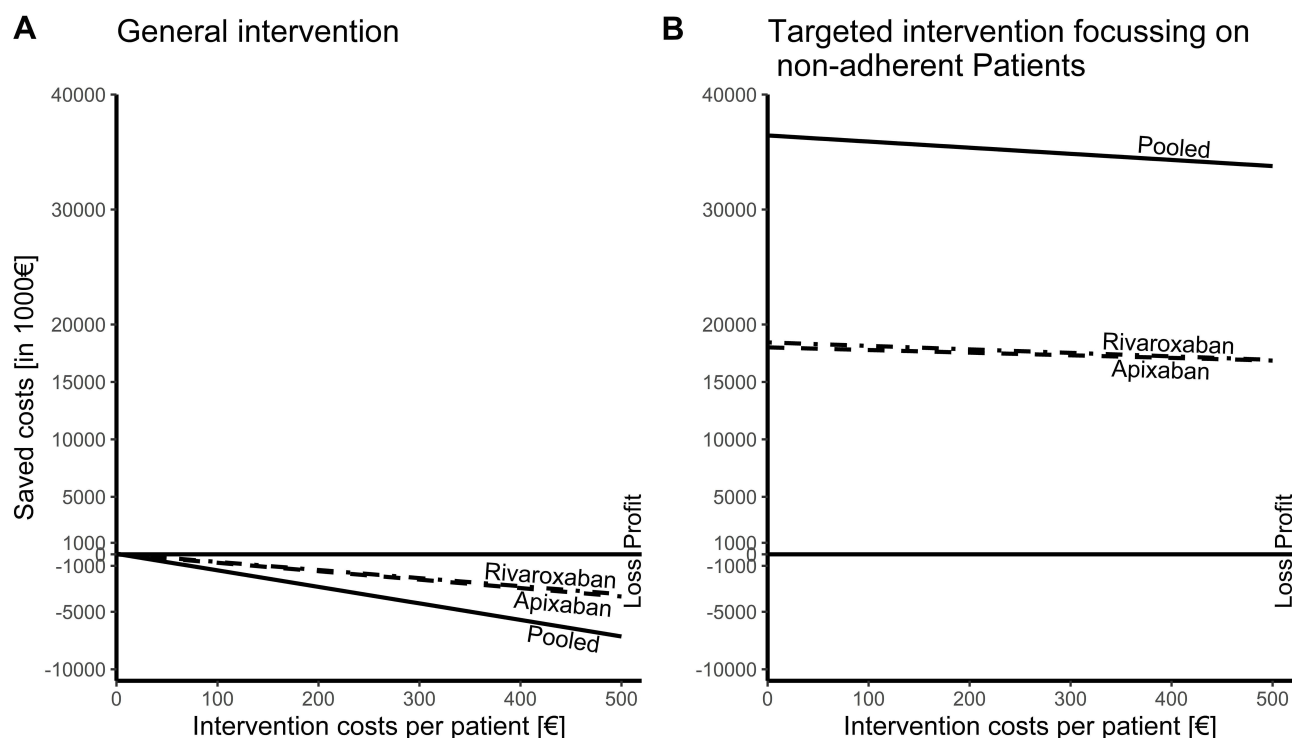
A   General intervention

B   Targeted intervention focussing on non-adherent Patients

Figure 3 Effect of supportive interventions on stroke events in atrial fibrillation and net cost per patient receiving such an intervention.
Notes: Part A shows the predicted savings stratified by the used direct oral anticoagulant (DOAC) if all patients received the intervention irrespective of their actual adherence. Likewise, part B shows the predicted savings when selected patients below the adherence cut-off benefit from a targeted intervention.

relationship being the gold standard. Using our study design, the estimated net pharmacological effect of apixaban and rivaroxaban was within the expected range,[43,44] and group differences were small, possibly reflecting baseline differences in CHA_2DS_2-VASc scores between treatment cohorts (Figure 2).

Overall, our results are consistent with findings of previous studies that used comparable approaches to quantify the adherence effect on stroke risk.[45–50] For example, Shore et al[4] observed a 13% increase in the hazard of stroke for every 10% reduction in dabigatran adherence (adjusted HR 1.13, 95% CI [0.97–1.33]). This is statistically comparable to the 2% risk increase (in the hazard of stroke) for every 10% reduction in dabigatran adherence we observed with our study design (adjusted HR 1.02, 95% CI [0.9–1.15]). Borne et al[51] found an increased stroke risk of 7% with each 10% decrease in rivaroxaban adherence (adjusted HR 1.07, 95% CI [0.89–1.28]), which is statistically comparable to the 5% increase found in our analysis (adjusted HR 1.05, 95% CI [0.98–1.12]) using our study design. One possible explanation regarding the similar relationship between non-adherence and stroke risk in our cohort and in previously published cohorts is probably the comparability

of covariates. All cohorts were generated from real-world data, used relatively similar inclusion and exclusion criteria, and were similar in many summary statistics,[4,51] limiting the impact of small variations in a few covariates (eg, age). Finally, it is plausible that underdosing was also associated with an increased risk of stroke because, like poor adherence, it leads to lower DOAC exposure.[20,21,52]

Using these adherence-stroke relationships in economic projections revealed that a targeted intervention is more efficient than a general intervention offered to all patients regardless of their adherence value (Figure 3). Overall, there are several conceivable factors modulating the success of an adherence intervention that equally reduce clinical events and costs. The maximum achievable effect depends on baseline adherence distribution and on the compound's efficacy. Concerning the latter, the absolute effectiveness of the substance determines the maximum achievable effect, while the slope of the relationship determines the individual benefit from an adherence increase. Finally, the nature of the intervention itself is decisive as it may improve adherence significantly in some patients while being ineffective in others. In our example of a steep adherence-response relationship with

an early beginning at low adherence values, an intervention would have a particularly large influence on costs when targeted at a group below the adherence cut-off (assuming a large unexploited benefit and thus an opportunity to generate large responses with small improvements).

When interpreting the results of this study, the following limitations need to be considered. The first limitation relates to the data source and calculation of adherence: limitations of data generated for billing purposes are well known[53] and concern, for example, the correctness of the codes. This has been addressed as far as possible by using established and validated code sets to select the population and to define outcomes and covariates (internal validity) and by aligning the study design with previous work (external reference as a surrogate for external validity). On the other hand, the adherence measure of PDC derived from billing data is itself an approximation. As previously shown by Steiner et al, the refill compliance is considered a good marker of adherence in health insurance systems[54] but the actual adherence behavior within prescription episodes, such as the temporal pattern of omitted doses, remains unclear. It may well make a difference whether one single dose is omitted from a twice-daily regimen, whether both single doses are omitted sporadically, or whether a drug holiday is taken. In this context, it is also important to note that our data source does not distinguish between planned episodes of treatment discontinuation (eg, after a bleeding event) and non-adherence. However, the proportion of patients admitted for bleeding episodes was low (2.3%) and their in-hospital stay was short (median: 6 days), suggesting that intentional pausing of DOACs did not significantly affect these results. Another important limitation is the sample size and the number of events; this was especially obvious as no adherence-stroke relationship could be reasonably modelled for dabigatran. A limiting factor regarding the events of interest is that only patients hospitalized with a stroke can be considered as having an outcome. Patients who died of a stroke without being hospitalized are lost in our database because the causes of death are not coded. However, this loss of information in the follow-up period can be considered as uninformative with regard to the adherence effect because we consider that drug intake patterns do not determine whether a patient is admitted to hospital or dies in the outpatient sector. Thus, we only expect a reduced number of events, but this reduced event frequency may have nevertheless influenced the statistical power of the study.

Conclusion

Using health insurance data as a data source and PDC estimates as a marker for individual patient adherence, the present analysis provided critical threshold values for poor adherence with the two most frequently prescribed DOACs in Germany, rivaroxaban and apixaban. The cut-off-values of rivaroxaban (PDC: 0.78) and apixaban (PDC: 0.8) are only slightly different from the conventional cut-off value (PDC: 0.8), which is reassuring because no substantial misclassification will result from further use of this value (especially when calculated from data sources other than ours). These adherence cut-offs can be applied in prospective studies to investigate whether such a categorization can help clinicians to develop promising adherence measures. They can equally be used in predictive models that detect patients at a higher risk for poor adherence. Given that effective interventions exist, our projections of interventional impact suggest that targeted interventions for patients with poor adherence identified by our cut-off values could substantially contribute to treatment success.

Acknowledgments

Disclosure

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