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Secondary adherence to non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation in Sweden and the Netherlands

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Transparancy

Abstract

Objective: There is limited evidence on patients' adherence and the impact of the prescribed dosing regimen in non-vitamin K oral anticoagulants (NOACs). We aimed to assess secondary adherence to NOACs and to determine the impact of the dosing regimen in patients with atrial fibrillation.

Methods: Patients using a NOAC between 2009 and 2013 were identified from the nation-wide Swedish Prescribed Drug Register and the Dutch regional IADB.nl database. Patients using a consistent dosage for at least 180 consecutive days were included. Adherence was calculated using the medication possession ratio (MPR) and adjusted for overlapping dates. Adherence was defined as a MPR ≥0.8. Sensitivity analyses were performed using a MPR ≥0.9. Logistic regression was performed to compare secondary adherence and to explore the influence of the dosing regimen.

Results: A total of 5,254 Swedish and 430 Dutch NOAC users were included. The mean MPR was 96.0% (SD 7.8%) in Sweden and 95.1% (SD 10.1%) in the Netherlands. Multivariable logistic regression analysis showed that a twice-daily regimen had a lower likelihood of being secondary adherent compared to a once-daily regimen in Sweden (odds ratio [OR] 0.21 [95% CI: 0.12-0.35]).

Limitations: The influence of selection bias introduced by the inclusion criterion of ≥ 2 dispensations covering at least 180 days could not be excluded.

Conclusions: This study demonstrated that secondary adherence was high in this specific setting among patients with at least 2 initial dispensations of a NOAC covering a minimum of 180 days. The use of NOACs in a once-daily regimen showed a higher adherence compared to a twice-daily regimen.

Short title
Adherence to non-vitamin K oral anticoagulants.

Introduction

Atrial Fibrillation (AF) is the most common cardiac arrhythmia, affecting 1-3% of the population and expected to rise due to an aging population (1,2). Patients with AF have a five-fold higher risk of stroke, particularly ischemic strokes (3-5). Moreover, AF is associated with valvular heart disease, heart failure, hypertension, diabetes mellitus, and ischemic heart diseases (6). Vitamin K antagonists (VKAs) have been the mainstay for stroke prevention in AF. In 2010 and 2011, the non-vitamin K oral anticoagulants (NOAC) dabigatran, rivaroxaban and apixaban were approved for the prevention of stroke and systemic embolism (SE) in nonvalvular AF patients and later also approved for treatment and prevention of venous thromboembolism (VTE). In 2015, edoxaban was approved by the European Medicines Agency (EMA) for the same indication as the other NOACs. Clinical trials have shown non-inferiority of rivaroxaban and edoxaban and superiority of apixaban and dabigatran compared to warfarin for the prevention of all-cause stroke or systemic embolism in patients with nonvalvular AF (7-10).

Medication adherence is deemed as an important contributor to treatment success. Adherence is a broad term that defines whether a patient's drug-taking behavior corresponds to the prescribed dosing regimen. Adherence consists of three elements: primary adherence (prescription being filled by the patient), secondary adherence (dispensed medication being taken as prescribed) and discontinuation (persistence) (11,12). With regards to AF, non-adherence may lead to a significant disease burden and increased healthcare costs due to a decreased stroke preventive effect (13,14). In order to prevent non-adherence, it is important to understand which variables are related to non-adherence. Polypharmacy, age-associated physiological changes, patients' perspective and comorbidities are major challenges to adherence among (15,16). The number of doses per day has been found to be negatively associated with medication adherence, also in cardiovascular disease (17-22).

The evidence on adherence to NOACs in real-life setting is getting more attention. Population based studies are thought to be more representative for real-world use given its non-controlled setting. Studies exploring adherence in a real-world setting reported lower adherence compared to the clinical trials (23-30). Most studies focused on one or two NOACs, however only a limited number of studies compared the adherence to apixaban, dabigatran and rivaroxaban all three. These studies found that dabigatran users had a significant lower adherence (31-33). Studies have shown that twice-daily dosing of NOACs appears to have a more favourable risk-benefit profile as compared to once-daily dosing (22,34,35). Currently, no studies have focused on the effect of the dosing regimen on NOAC adherence stratified by dosing regimen.

We aimed to assess the secondary adherence to NOACs in patients with atrial fibrillation based on dispensing data from Sweden and the Netherlands, focussing on the impact of the dosing regimen.

Patients and Methods

Data Source

Prescription data of NOACs were extracted from The Swedish Prescribed Drug Register (SPDR) and the Dutch IADB.nl database. The SPDR contains data from dispensed out-patient prescriptions of all Swedish pharmacies from July 1, 2005. The registry covers the entire Swedish population of 10 million inhabitants. The SPDR contains detailed information about each dispensed drug, including information on the exact date of both prescription and dispensation (36). Individual patient data was pseudonymized, and data filtered with regard to information such as age-group and county, by the relevant authority before delivery in order for the data-set to be classified as aggregated volume statistics. The IADB.nl database covers a population of 600,000 people and contains pharmacy-dispensing data from 55 community pharmacies in the Netherlands since 1999. IADB.nl holds information on all prescription refills, including date of prescription, number of days the drug was prescribed and the number of defined daily doses (DDDs) (37). Patients have an opt-out option if they have any objections to being included in the IADB.nl. Each patient has a unique anonymous identifier making it impossible to relate data to individuals and therefore informed consent was not necessary. Due to national regulations, confidentiality was warranted by following the guidelines of disclosure of identities of individual persons. The study protocol was reviewed and approved by the daily management and the supervisory board of IADB.nl. The aggregated dataset was provided by an independent person. Neither SPDR nor IADB.nl contain information on over the counter (OTC) drugs and in-hospital prescriptions. Information on year of birth, patient sex and prescribed and dispensed co-medication were available in both databases. Information on clinical diagnoses were not available. In Sweden, drugs are dispensed for a maximum period of approximately 90 days. In the Netherlands, drugs are dispensed for 14 days at treatment initiation. For every subsequent dispensation, drugs are provided for a maximum period of 90 days.

Study design

An observational, retrospective cohort study was performed to assess secondary adherence to NOACs. Patients with at least one initial dispensation of dabigatran (Anatomical Therapeutic Chemical [ATC] Classification (B01AE07)), rivaroxaban (B01AF01) or apixaban (B01AF02) from 2009 through 2013 were eligible for inclusion. The included dosing regimens were apixaban 2.5 mg twice daily (BID), apixaban 5 mg BID, dabigatran 110 mg BID, dabigatran 150 mg BID, rivaroxaban 15 mg once daily (QD) or rivaroxaban 20 mg QD. Edoxaban was not included in this study, because it was not yet approved by EMA during the study period. Guidelines on NOAC use for AF patients in both countries were viewed and used to distinguish AF-patients from patients that used NOACs for other indications. It was decided to include all dosing regimens mentioned above with a minimum treatment period of 180 days to distinguish between the indication AF and VTE. If a NOAC was used for VTE prophylaxis, the treatment period would be 5 weeks maximum and the doses of dabigatran and rivaroxaban differ from the doses used for AF. VTE treatment and AF stroke prevention have an overlap in dosing regimens, though the treatment period for VTE would on average be 3-6 months. Treatment of recurrent VTE is almost indistinguishable from AF since the dosing regimens overlap and treatment is lifelong. The combined criteria of the specific doses and the minimum treatment period made the inclusion criteria most sensitive to AF patients, though inclusion of other indications couldn't be ruled out completely.

Patients were included using the following criteria: (a) filled prescription of a NOAC with at least 180 days between dispensing, (b) ≥18 years at the moment of start and (c) known in the database for 360 days before start. Patients were allowed to switch to another NOAC after the initial 180 days. Patients with two or more separate periods of 180 days with the same dosage of the same NOAC were excluded to avoid double counting of patients. The follow-up time was truncated at the last known dispensation date within the study period, i.e. the last dispensation before 1st of January 2014. Non-adherence after discontinuation beyond the study period therefore was not taken into account.

Baseline characteristics

Daily regimen was stratified in two groups depending on their initial dispensation: a once daily dosing regimen consisting of rivaroxaban 15 mg & 20 mg and a twice daily dosing regimen consisting of apixaban 2.5 mg & 5 mg, dabigatran 110 mg & 150 mg.

Main outcome measure
The main objective was to assess patient secondary adherence based on the Medication Possession Ratio (MPR) for the time period from first dispensation up until, and including, the date of the last recorded dispensation. When an overlap occurred between two dispensations, an adjustment was made (figure 1) to correct for stockpiling. Medication use ongoing after the study period was not included. Patients meeting the inclusion criteria were defined as being secondary adherent with a MPR ≥ 0.8. A threshold of 80% was used to dichotomize between adherent and non-adherent users. The proportion of 80% has been widely used as a threshold in earlier (cardiovascular) research (20,38). A 90% MPR threshold for secondary adherence was used in the sensitivity analyses, since there is no standard value to define adequate adherence and other values should therefore be considered.

Co-medication
The use of co-medication within 180 days prior to the start date was assessed for the following drug groups: vitamin K antagonists (VKA) (B01AA03, B01AA04, B01AA07), antihypertensive agents (C02), diuretics (C03), beta-blockers (C07), calcium-channel blockers (C08C, C08DA02, C08DB, C08E, C08G), renin-angiotensin-aldosterone system (RAAS) inhibitors (C09), verapamil (C08DA01), amiodarone (C01BD01), statins (C10AA, C10BA), other cardiovascular drugs (C01A, C01BA02, C01BA03, C01BA04, C01BA05, C01BA08, C01BA08, C01BB, C01BC, C01BD02, C01BD03, C01BD04, C01BD05, C01BD06, C01BD07, C01BG, C01C, C01D, C04, C05), non-steroidal anti-inflammatory drugs (NSAIDs) (M01AB, M01AE) and medication for diabetes mellitus (A10). The variables were dichotomized in 'used before' or 'not used before'. The number of prescriptions was the number of unique drugs (by ATC code) that a patient used at the start date of a NOAC.

Stroke risk

The CHA$_2$DS$_2$-VASc score (Congestive heart failure, Hypertension, Age 65-75, Age ≥ 75 years [doubled], Diabetes, Stroke [doubled], Vascular disease, and Sex category [female]) is a validated risk assessment tool to stratify the stroke risk and refines the identification of patients at low risk (CHA$_2$DS$_2$-VASc = 0) (39,40). Estimated CHA$_2$DS$_2$-VASc scores were used to assess stroke risk as a possible explanatory variable for the extent of adherence. Only partial scores could be calculated with the help of proxies, since no indications were available and the stroke risk factors could otherwise not be handled in a straightforward manner. CHA$_2$DS$_2$-VASc was calculated in scores of 0, 1 and ≥2 by using ATC-codes as a proxy for co-morbidity. CHA$_2$DS$_2$-VASc scores ≥2 were truncated at 2. Diabetes medication (A10) was used as a proxy for diabetes. Diuretics (C03), RAAS-inhibitors (C09) or other antihypertensive agents (C02) were a proxy for congestive heart failure or hypertension. Age and gender could be scored with the demographic data that was available in the prescription databases.

Statistical analysis

Patient baseline characteristics were summarized using the mean plus the standard deviation (SD). Baseline characteristics of groups based on their dosing regimen were compared using student's t tests for continuous variables and chi-square tests for categorical variables (both p<0.05). Logistic regression analyses were performed (p<0.05) to determine the factors that could influence non-adherence. Multivariable logistic regression analyses were used to correct for covariates that showed trends (p<0.10) towards non-adherence. Results are presented as odds ratios (ORs) and corresponding 95% confidence interval (95% CI). All calculations were performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Baseline patients characteristics of the included Swedish and Dutch NOAC users are summarized in Table 1 and Supplementary Table S1. A total of 5,254 Swedish and 430 Dutch NOAC users met the inclusion criteria. In both populations the majority of the patients were using a twice-daily dosing regimen (71.6% in the Swedish population vs. 85.8% in the Dutch population) and the majority had an estimated CHA$_2$DS$_2$-VASc score of 2 or higher (79.2% in Swedish population vs. 82.6% in Dutch population). Dabigatran was used by 6.6% and 21.3% of the patients before being switched to rivaroxaban in Sweden and the Netherlands respectively. The percentages of patients starting rivaroxaban and switching to apixaban or dabigatran were 0.4% in Sweden and 0% in the Netherlands.

Secondary adherence vs. non-adherence

In Sweden, the mean MPR of an once-daily regimen was 97.8% (SD 4.9%) and 95.2% (SD 8.6%) for a twice-daily regimen. Median follow up was 254 days (range 181-581 days) for the once daily regimen and 350 days (range 181-820 days) for the twice-daily regimen (Table S1). Using the 80% cut-off criterion, 4,965 Swedish NOAC users (94.5%) were adherent (Table 1). In unadjusted analysis (Figure 2), patients with a twice daily regimen were less adherent than patients with a once daily regimen (OR 0.24 [95% CI 0.16-0.36]). Patients aged 65-74 years old were more adherent (OR 1.74 [95% CI 1.27-2.37]) compared to patients <65 years old. Patients using dabigatran 110 mg were less adherent than patients using dabigatran 150 mg (OR 0.52 [95% CI 0.41-0.68]). Patients on treatment with 15 and 20 mg rivaroxaban were more adherent than dabigatran 150 mg users (OR 3.57 [95%CI 2.23-5.72] and OR 2.55 [95%CI: 1.12-5.84] respectively). Multivariable analysis (Figure 3) for all variables with P-values lower than 0.1 showed that secondary adherence of patients using a twice-daily regimen was lower compared to a once-daily regimen (OR 0.21 [95%CI 0.12-0.35]). Patients' age (64-74 years) was associated with good adherence (OR 2.00 [95%CI: 1.45-2.74]).

In the Netherlands, the mean MPR of an once-daily regimen or a twice-daily regimen were respectively 98.7% (SD 2.0%) and 94.4% (SD 10.8%). Median follow up was 306 days (range 180-622 days) for the once daily regimen and 384 days (range 180-1521 days) for the twice-daily regimen (Table S1). Using the 80% cut-off criterion, 398 Dutch NOAC users (92.6%) were adherent (Table 1). Unadjusted analysis showed that patients' age (75-84 years) was associated with good adherence (OR 2.99 [95%CI 1.08-8.29] and the CHA_2DS_2-Vasc score 1 category was associated with lower adherence (OR 0.349 [95% CI 0.15-0.81] (Figure 4). Multivariable analysis was not possible for dosing regimen due too small sample size. Other variables included in the multivariable analysis showed no significant effect on adherence (Figure 5).

Sensitivity analyses

Using the 90% cut-off criterion, 4,551 (86.6%) Swedish NOAC users were secondary adherent (Table S2). Unadjusted analysis showed a significant association with twice-daily dosing regimen (OR 0.41 [95%CI 0.33-0.51]). Furthermore, patients were more adherent when 65-74 years old or using dabigatran 150 mg. The CHA_2DS_2-VASc score of 0 was negatively associated with good adherence. Adjusted analysis showed significant influence of a twice-daily dosing regimen (OR 0.45 [95%CI: 0.34-0.59]), the age group 65-74 years and estimated CHA_2DS_2-VASc score.

In The Netherlands, 375 users (87.2%) were found to be adherent (Table S3) using the 90% cut-off criterion. Patients were more adherent if they were 75-84 years old or when they used dabigatran 110 mg. All patients with a once-daily regimen were adherent. Multivariable analysis showed that dabigatran 110 mg users had a higher likelihood of being adherence (OR 1.98 [95%CI 1.01-3.82]). Adjustment for dosing regimen was not possible due to a too small sample size.

Discussion

Main findings

This study used a database that covered patients drugs' dispenses from 55 Dutch pharmacies. By using a second real world nationwide Swedish database covering all patients drugs' dispenses from pharmacies and hospitals, the findings from The Netherlands could be validated. This enabled us to confirm the observed patterns. The low patient number from the Dutch database reduced the ability to find any significant results for the Netherlands. We demonstrated that in this specific setting where patients already had at least 2 dispensations with a minimal coverage of 180 days, secondary adherence was high. A total of 94% Swedish and 93% Dutch patients were considered adherent using a 80% MPR criterion. The CHA_2DS_2-VASc score was not different in the adherent vs. non-adherent group for both countries, based on partial scores calculated from proxies. This study showed a higher likelihood of non-adherence for patient in our population using a twice-daily dosing but the result might be influenced by confounding and biases. Data from Sweden suggest that patients who used a twice-daily dosing regimen had a significantly lower likelihood of secondary adherence compared to patients prescribed a once-daily regimen. In addition, all Dutch patient being prescribed a once-daily regimen were adherent compared to 91% of patients being prescribed a twice daily regimen.

Our findings indicate that a once daily regimen was associated with higher secondary adherence to NOACs in persistent patients. However, numbers of apixaban users were low in both countries, making it predominantly a comparison between dabigatran and rivaroxaban. Other studies showed that adherence was lowest for dabigatran and that there is a difference in adherence to apixaban compared to rivaroxaban adherence (31,32,33). Differences in adherence may be due to different side effects profiles of dabigatran or rivaroxaban. In the RE-LY study dabigatran patients reported dyspepsia as a frequent side effect, though in a small retrospective cohort study dyspepsia was not found as the main reason for discontinuation therapy (9,30). Another reason for a higher rate of discontinuation of dabigatran could be the contraindication in patients with renal impairment. Patients switching between NOACs were identified by taking into account the medication use in the period before the study period. A small number of patients switched from apixaban or dabigatran to rivaroxaban, or vice versa. Reasons of switching NOACs however, could not be identified based on the available data, since reasons for discontinuation are not available in the databases.

Despite methodological differences, our results are in line with the findings of other studies. The MPR is a recommended measure for compliance. Another often used method is the proportion of days covered (PDC) which is the total number of days' supply dispensed during specified observation period divided by number of days in patient's observation period. The PDC and MPR should give similar results when looking at a single drug in the same observation period (41,42). A retrospective database analysis by Beyer-Westendorf et al. showed that significantly more rivaroxaban users were adherent (MPR ≥ 0.80) compared to dabigatran users, and mean MPR of rivaroxaban was significantly higher than dabigatran (28). McHorney et al. reported that the likelihood of being adherent for apixaban was significantly lower

compared to rivaroxaban, but significantly higher compared to dabigatran with a PDC of ≥ 0.8 (31). In comparison to other studies assessing adherence to NOACs, our mean MPR and numbers of adherent patients were high (23,26,27,43). Tsai et al. reported a mean PDC of 0.674 for dabigatran users that did not receive warfarin before (43). However, the mean PDC of the persistent users (56.5%) was 0.935. Differences found may be due to our inclusion criterion of a minimum NOAC use of 180 days, which makes the inclusion most sensitive to the indication AF. Exclusion of patients with life-long VTE treatment could not be ruled out. All patients that discontinued use of a NOAC before 180 days were excluded, which may lead to an overestimation of secondary adherence because of implicit selection of primary adherent patients. Other studies have shown that the non-adherence in the first period is generally around 20-25%, though non-persistence was found to be 42% for dabigatran after 180 days (26,28,31,44).

Implication of the findings

Switching non-adherent patients from twice-daily regimens to once-daily regimens to enhance adherence is faulty, because effectiveness as well as pharmacokinetic and pharmacodynamic effects should also be considered. A meta-analysis concluded that NOACs with twice-daily dosing regimens have a more balanced risk-benefit profile for prevention of strokes and intracranial bleedings (34). Comté et al. mentioned in their study, which compared adherence between once-daily and twice-daily protease inhibitor regimens, that it is likely that taking two pills per day to maintain drug concentrations within a therapeutically desirable range is superior to one pill per day (21). Missing one dose in a once daily regimen is the pharmacokinetic equivalent of missing two to three doses in a row in a twice daily regimen. The chance of missing two to three doses in a row is half the probability of missing one dose. This principle may also be applied to NOACs, because they have a relatively narrow therapeutic range. Missing a single dose in a once daily regimen may be more harmful compared to missing a single dose in a twice daily regimen (22).

It is important for prescribers to understand the reasons for patient non-adherence. Different reasons require different approaches to enhance adherence. Some patients have a preference to take medications twice-daily instead of once-daily, as with asthma or COPD patients (45). Long-term treatment should be initiated in a shared-decision making process with the patient and tailored to their needs and preferences. Because of a presumably more balanced risk-benefit profile with an twice daily regimen and the unknown reasons of patient non-adherence, more research should be done before making a statement on improving adherence in relation to dosing regimen.

Limitations

Indications of dispensed drugs was lacking and therefore a period of 180 days was chosen to make the inclusion of NOAC users most sensitive for the indication AF and least sensitive for the indication VTE prophylaxis or treatment Also, in Sweden it is recommended to prescribe drugs for chronic diseases for

three months, at least one large package size (180 tablets for dabigatran BID and 98 or 100 tablets for rivaroxaban QD) was used to select patients with atrial fibrillation in the Swedish population. The minimal treatment period of 180 days may have introduced bias since only patients with an initial high primary adherence were included. The secondary adherence could lead to an overestimation since the proportion of patients, around 2-3% in Sweden, who never initiated therapy or patients who did not obtain a refill were excluded (46,47). The dosing regimen could be seen as another limitation if a twice-daily dosing regimen is associated with a lower tendency to be adherent and inclusion criteria could therefore not be met to the same extent as for once-daily regimen.

The different drugs, and thus the different dosage regimens, were not introduced on the market at the same time. Compliance varies over time and this together with the definition of MPR (from first up until last recorded dispensation) may have introduced time-length bias in our analysis, possibly favoring higher compliance for drugs introduced later during the study period. However, the drug with a once-daily dosage regimen, rivaroxaban, was introduced almost the same time as dabigatran while apixaban was introduced considerably later and used only to a small extent, making time-length bias less likely to have influenced our results. The follow up was different for the once-daily vs twice-daily regimen, both in Sweden and the Netherlands, when comparing median follow up. Median follow up for the adherent vs non-adherent group was not statistically different in both countries.

Since indications were not available in both databases, ATC-codes of drugs were used as proxies for estimating CHA_2DS_2-VASc scores. This method may have a good specificity, but less sensitivity for patients with an estimated score of >0. Another limitation is that only concomitant cardiovascular drugs were identified. Neither the IADB.nl database nor the SPDR have any information about OTC drugs and drugs dispensed in hospitals. The total number of drugs and their dosing regimen may also have impacted patients' adherence.

The use of pharmacy-based databases has some limitations. The IADB.nl does not cover the complete Dutch population, but it is validated as a representative sample of the Dutch population (48). The Swedish database contains information about the amount of drugs dispensed (in size and number of packages per dispensation) and the prescribed dose. The latter is however is in a free text format and are not available for research studies performed with pseudonymized data. A limitation of the calculation of adherence based on dispensation data is the lack of confirmation that patients actually took their medication. However, validation studies have shown a good correlation between prescription claims and actual drug use (49).

Future research

Prescribing of NOACs should not be limited based on adherence. Choosing a suitable dosing regimen should be well-considered, with careful consideration of a patients' preferences since tailored interventions are expected to lead to more optimized treatment. Further research is needed to understand why patients are non-adherent to NOACs, for example by focusing on compliance without a time-length inclusion criterion that could bias the results. One of the priorities is to identify those

patients that may benefit from switching from a twice-daily regimen to a once-daily regimen or vice versa.

Conclusion

This large real-world study of AF patients with at least two dispensations of NOAC covering at least 180 days had a high secondary adherence after the two initial dispensations in this specific setting. The influence of selection bias introduced by the inclusion criterion of ≥ 2 dispensations covering at least 180 days could not be excluded. Multivariable logistic regression showed that a once-daily dosing regimen of NOACs was associated with a higher likelihood of a higher secondary adherence compared to a twice-daily regime. The inclusion criterion demanding at least two dispensations introduced a selection bias towards patients with higher primary and secondary adherence, thus restricting the external validity of the findings. Future research should focus on the effect of the dosing regimen on adherence and persistence to NOACs.

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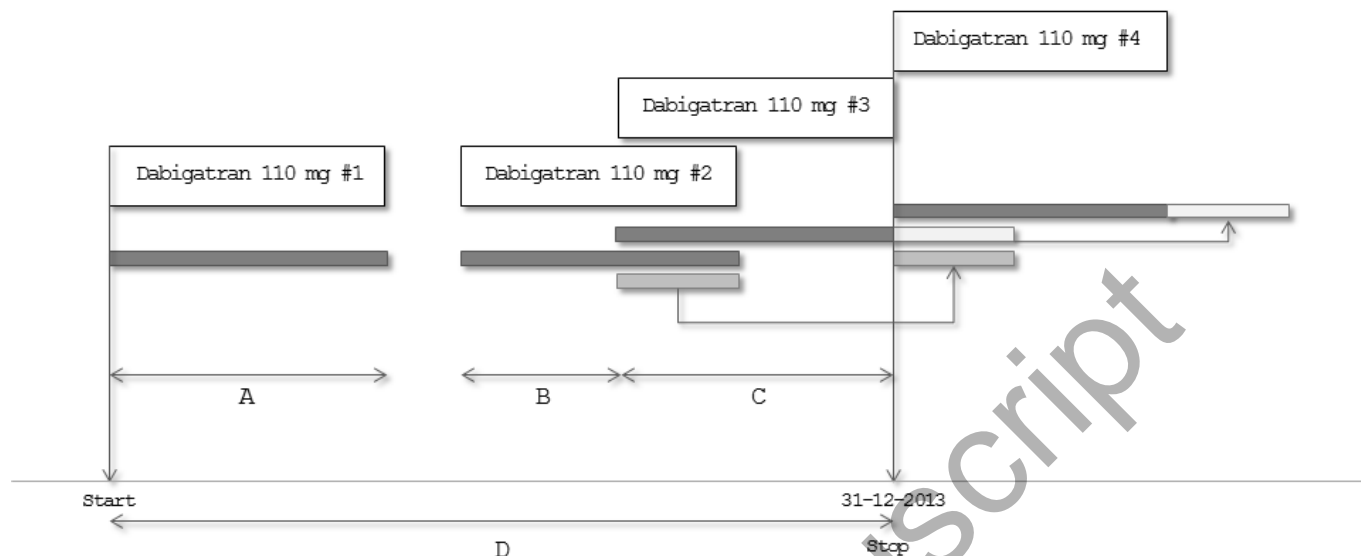
Figure 1 Pictorial determination of start- and stop date and Medication Possession Ratio calculation. White frames indicates dispensations in time. Light grey frames are adjusted dispensations. Time periods A, B and C represent the time that the patient received a NOAC. Time period D is the total time between the start- and stop date.

Abbreviations: D110 = Dabigatran 110mg; D150 = Dabigatran 150mg; NOAC = non-vitamin K antagonist oral anticoagulant
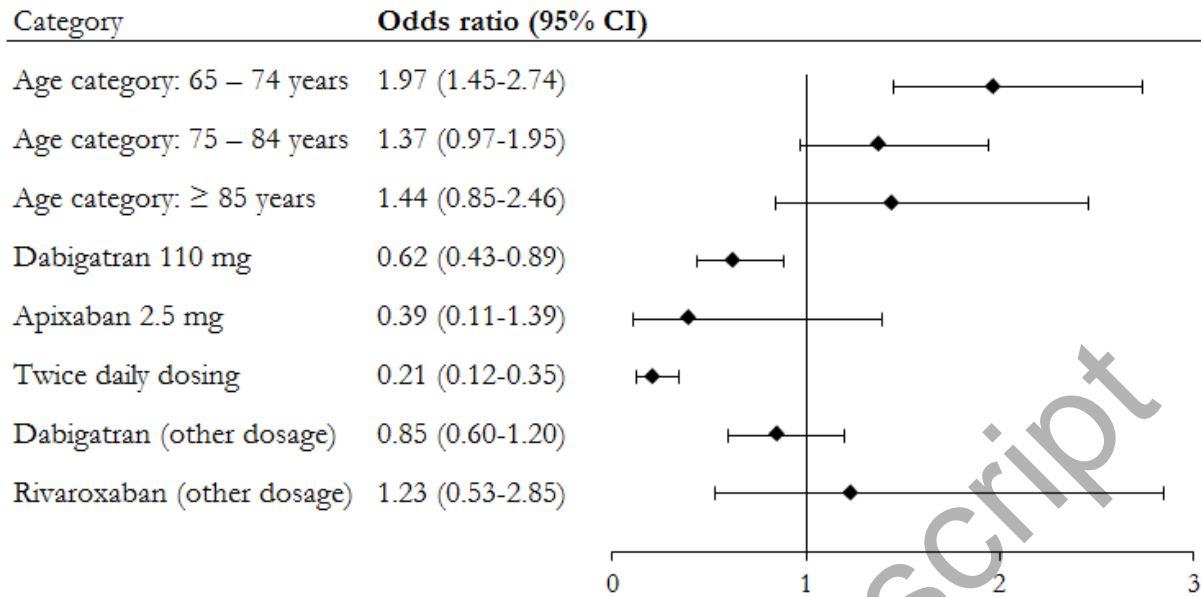
Table 1: Baseline characteristics for the adherent versus non-adherent group of Swedish (N=5,254) and Dutch (N=430) NOAC users

	Sweden			Netherlands		
	Adherent N (%)	**Non-adherent** N (%)	**P-value**	**Adherent** N (%)	**Non-adherent** N (%)	**P-value**
All patients	4,965 (94.5)	289 (5.5)		398 (92.6)	32 (7.4)	
Gender						
Male	3,014 (60.7)	187 (64.7)	REF	216 (54.3)	21 (65.6)	REF
Female	1,951 (39.3)	102 (35.3)	0.176	182 (45.7)	11 (34.4)	0.218
Age category						
18–64 year, N (%)	1,064 (21.4)	77 (26.6)	REF	79 (19.8)	12 (37.5)	REF
65–74 year, N (%)	2,185 (44.0)	91 (31.5)	**0.001**	178 (44.7)	12 (37.5)	0.059
75–84 year, N (%)	1,389 (28.0)	96 (33.2)	0.771	118 (29.6)	6 (18.8)	**0.036**
≥ 85 year, N (%)	327 (6.6)	25 (8.7)	0.818	23 (5.8)	2 (6.3)	0.485
NOAC						
Dabigatran 150mg	2,468 (49.7)	146 (50.5)	REF	152 (38.1)	19 (59.4)	REF
Dabigatran 110mg	1,010 (20.3)	114 (39.4)	**<0.001**	184 (46.1)	13 (40.6)	0.129
Rivaroxaban 20mg	1,206 (24.3)	20 (6.9)	**<0.001**	50 (12.6)	-	NA

Rivaroxaban 15mg	259 (5.2)	6 (2.1)	**0.026**	11 (2.8)	-	NA
Apixaban 5mg	7 (0.1)	-	NA	1 (0.3)	-	NA
Apixaban 2.5mg	15 (0.3)	3 (1.0)	0.056	NA	NA	
Dosing regimen on start date						
Once daily	1,465 (29.5)	26 (9.0)	REF	61 (15.3)	-	NA
Twice daily	3,500 (70.5)	263 (91.0)	**<0.001**	337 (84.7)	32 (100.0)	REF
Prior anticoagulans use						
VKA	1,580 (31.8)	85 (29.4)	0.392	132 (33.2)	10 (31.3)	0.825
Dabigatran (other dose)	762 (15.3)	76 (26.3)	**<0.001**	48 (12.1)	4 (12.5)	0.941
Rivaroxaban (other dose)	390 (7.9)	7 (2.4)	**0.001**	-	-	NA
CHA$_2$DS$_2$-Vasc score						
0	238 (4.8)	17 (5.9)	0.372	14 (3.5)	2 (6.3)	0.298
1	788 (15.9)	49 (17.0)	0.564	50 (12.6)	9 (28.1)	**0.014**
≥2	3,939 (79.3)	223 (77.2)	REF	334 (83.9)	21 (65.6)	REF
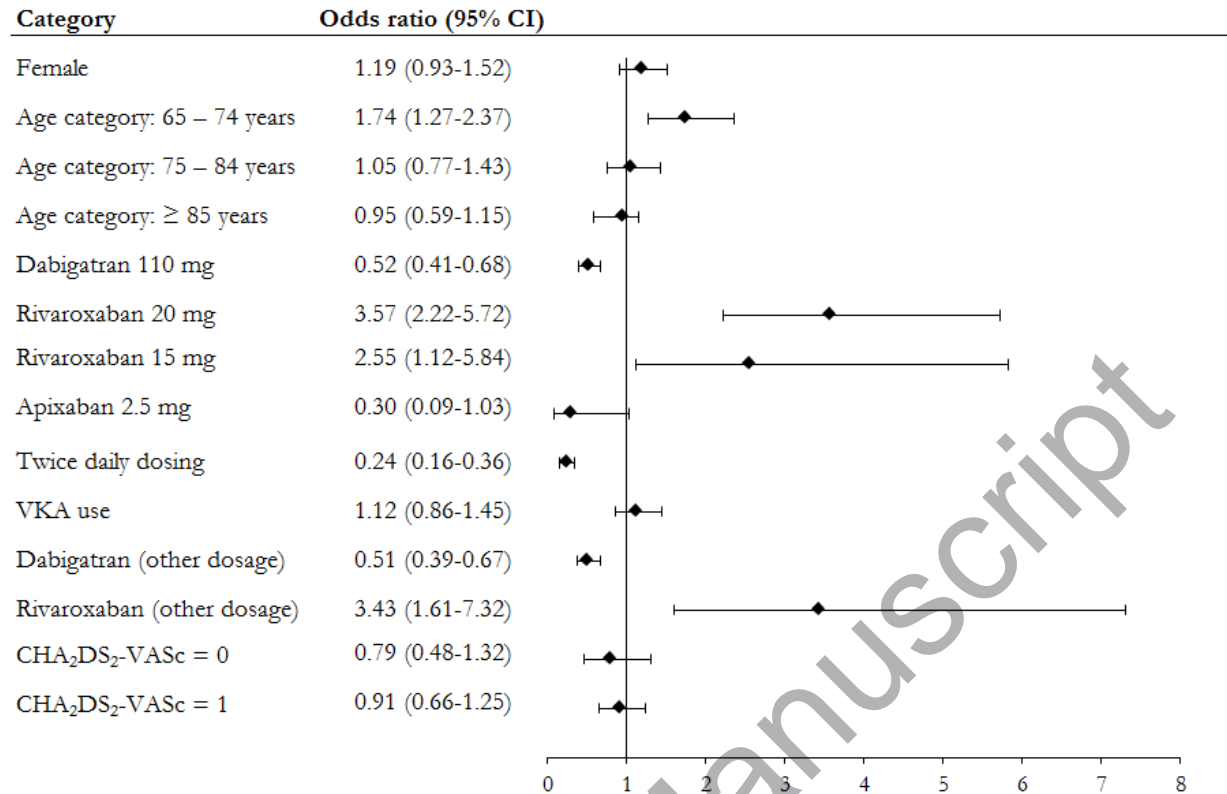
Figure 2: Univariate analysis of factors influencing adherence in Swedish NOAC users (N=5,254). The reference categories were, in descending order: Male, Age 18-64 years (x3), Dabigatran 150 mg (x4), Once daily dosing, Not used a priori (x3), CHA2DS2-VASc ≥ 2 (2x).

Category	Odds ratio (95% CI)
Age category: 65 – 74 years	1.97 (1.45-2.74)
Age category: 75 – 84 years	1.37 (0.97-1.95)
Age category: ≥ 85 years	1.44 (0.85-2.46)
Dabigatran 110 mg	0.62 (0.43-0.89)
Apixaban 2.5 mg	0.39 (0.11-1.39)
Twice daily dosing	0.21 (0.12-0.35)
Dabigatran (other dosage)	0.85 (0.60-1.20)
Rivaroxaban (other dosage)	1.23 (0.53-2.85)

Figure 3: Multivariable analysis of factors influencing adherence in Swedish NOAC users (N=5,254). The reference categories were, in descending order: Male, Age 18-64 years (x3), Dabigatran 150 mg (x2), Once daily dosing, Not used a priori (x2).

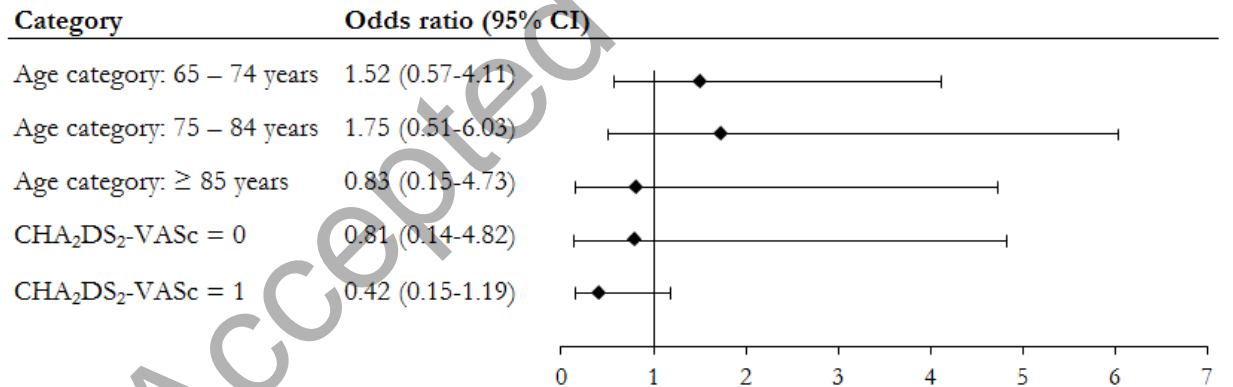| Category	Odds ratio (95% CI)	
Female	1.61 (0.76-3.43)	
Age category: 65 – 74 years	2.25 (0.97-5.23)	
Age category: 75 – 84 years	2.99 (1.08-8.29)	
Age category: ≥ 85 years	1.75 (0.36-8.37)	
Dabigatran 110 mg	1.77 (0.85-3.70)	
VKA use	1.09 (0.50-2.37)	
Dabigatran (other dosage)	0.96 (0.32-2.86)	
CHA_2DS_2-VASc = 0	0.44 (0.09-2.07)	
CHA_2DS_2-VASc = 1	0.35 (0.15-0.81)	
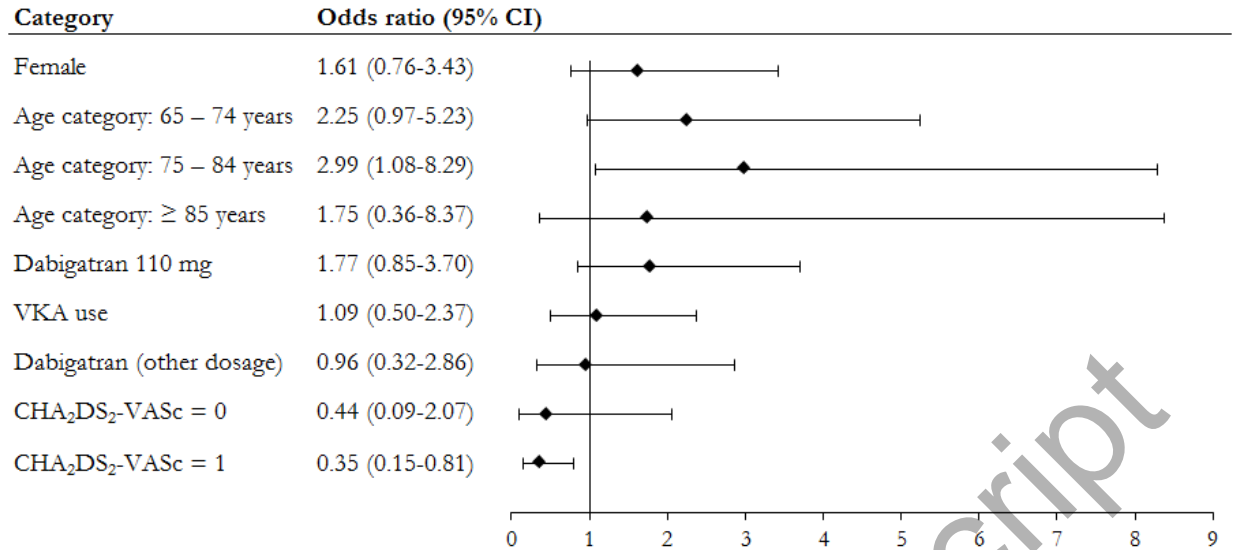
Figure 4: Univariate analysis of factors influencing adherence in Dutch NOAC users (N=430). The reference categories were, in descending order: Male, Age 18-64 years (x3), Dabigatran 150 mg, Not used a priori (x2), CHA2DS2-VASc ≥ 2 (x2).

Category	Odds ratio (95% CI)	
Age category: 65 – 74 years	1.52 (0.57-4.11)	
Age category: 75 – 84 years	1.75 (0.51-6.03)	
Age category: ≥ 85 years	0.83 (0.15-4.73)	
CHA_2DS_2-VASc = 0	0.81 (0.14-4.82)	
CHA_2DS_2-VASc = 1	0.42 (0.15-1.19)	

Figure 5: Multivariable analysis of factors influencing adherence in Dutch NOAC users (N=430). The reference categories were, in descending order: Age 18-64 years (x3) and CHA2DS2-VASc ≥ 2 (x2).