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Report

Adherence, persistence and switching patterns – once- versus twice-daily direct oral anticoagulants

Report

Adherence, persistence and switching patterns – once- versus twice-daily direct oral anticoagulants

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Contents

1. Background 8
2. Objectives 9
3. Methods 10
   - 3.1 Data sources 10
     - 3.1.1 PHARMO Database Network – the Netherlands 10
     - 3.1.2 Agenzia regionale di sanità della Toscana database (ARS) – Italy 11
     - 3.1.3 German Pharmacoepidemiological Research Database (GePaRD) – Germany .. 11
   - 3.2 Study design 12
   - 3.3 Patient selection 12
   - 3.4 Patient characteristics 13
   - 3.5 Adherence and persistence 13
   - 3.6 Switching patterns 14
   - 3.7 Treatment episodes 15
   - 3.8 Statistical analyses 15
4. Results and interpretations 17
   - 4.1 Patient selection 17
   - 4.2 Patient characteristics 19
   - 4.3 Adherence and persistence 22
   - 4.4 Switching patterns 31
5. References 33
6. Appendix 34
   - 6.1 Code list 34
   - 6.2 Stratified results 35

Contents of figures and tables

Figure 3.1: Model for multi-database common programming and reporting 16
Figure 4.1: Kaplan-Meier curve showing the proportion of patients persistent with the QD and BID dosage regimen for DOACs, stratified by database and index dosage regimen..... 24
Figure 4.2: Kaplan-Meier curve showing the proportion of patients persistent with the QD and BID dosage regimen for DOACs after first dosage regimen switch, stratified by database and type of dosage regimen switch 29
Figure 7.1: Kaplan-Meier curve showing the proportion of patients persistent with the QD and BID dosage regimen for DOACs, stratified by database and index dosage regimen - among patients aged ≥65 years at index date 38
Figure 7.2: Kaplan-Meier curve showing the proportion of patients persistent with the QD and BID dosage regimen for DOACs, stratified by database and index dosage regimen - among patients aged ≥75 years at index date 39
Figure 7.3: Kaplan-Meier curve showing the proportion of patients persistent with the QD and BID dosage regimen for DOACs after first dosage regimen switch, stratified by database and type of dosage regimen switch – among patients aged ≥65 years at index date 42
Figure 7.4: Kaplan-Meier curve showing the proportion of patients persistent with the QD and BID dosage regimen for DOACs after first dosage regimen switch, stratified by database and type of dosage regimen switch – among patients aged ≥75 years at index date 43

Table 3.1: Characteristics of DOACs included in this study 12
Table 4.1: Selection of the study population in PHARMO, ARS and GePaRD 17
Table 4.2: Characteristics of DOAC users at index date, stratified by database and index dosage regimen..... 19
Table 4.3: Adherence and persistence among DOAC users, stratified by database and index dosage regimen 22
Table 4.4: Adherence among DOAC users before and after a dosage regimen switch, stratified by database and type of dosage regimen switch 27
Table 4.5: Sex, age and polypharmacy at index date among patients with a recorded dosage regimen switch, stratified by database and type of dosage regimen switch..... 30
Table 4.6: Type of switches among DOAC users after index date, stratified by database and index dosage regimen 31
Table 4.7: Switching patterns among DOAC users after index date, stratified by database 31
Table 7.1: Diagnostic codes for identification of AF..... 34
Table 7.2: Adherence and persistence among DOAC users, stratified by database and index dosage regimen - among patients aged ≥65 years at index date 35

Table 7.3: Adherence and persistence among DOAC users, stratified by database and index dosage regimen- among patients aged ≥75 years 36
Table 7.4: Adherence among DOAC users before and after a dosage regimen switch, stratified by database and type of dosage regimen switch – among patients aged ≥65 years at index date 40
Table 7.5: Adherence among DOAC users before and after a dosage regimen switch, stratified by database and type of dosage regimen switch – among patients aged ≥75 years at index date 41
Table 7.6: Sex, age and polypharmacy at index date among patients with a recorded dosage regimen switch, stratified by database and type of dosage regimen switch – among patients aged ≥65 years at index date.....44
Table 7.7: Sex, age and polypharmacy at index date among patients with a recorded dosage regimen switch, stratified by database and type of dosage regimen switch – among patients aged ≥75 years at index date.....45

List of used abbreviations

AF	Atrial fibrillation
ARS	Agenzia regionale di sanità della Toscana database
ATC	Anatomical therapeutic chemical
BID	Twice-daily ('bis in die')
BIPS	Leibniz Institute for Prevention Research and Epidemiology
DE	Germany
DSE	Daiichi Sankyo Europe GmbH
DOAC	Direct oral anticoagulant
GePaRD	German Pharmacoepidemiological Research Database
GP	General practitioner
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10	International Classification of Diseases, 10th Revision
ICPC	International Classification of Primary Care
IQR	Interquartile range
IT	Italy
NA	Not applicable
NL	The Netherlands
PDC	Proportion of days covered
PHARMO	PHARMO Database Network
SD	Standard deviation
SHI	Statutory Health Insurers
QD	Once-daily ('quaque die')
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WCIA	Werkgroep Coördinatie Informatisering en Automatisering

1. Background

One of the major challenges for stroke prevention in patients with atrial fibrillation (AF) is medication adherence and persistence to ensure efficacy and safety[1]. A high degree of adherence to direct oral anticoagulants (DOACs) is essential for reducing the risk of ischaemic stroke and systemic embolism in patients with AF, due to the rapid decline in anticoagulation activity when doses are omitted (i.e. rebound effect)[2]. Contrary to treatment with vitamin K antagonists (VKAs), use of DOACs does not require routine coagulation testing. This may influence the adherence and persistence with DOACs compared to VKAs in a real life setting[3].

DOACs are available as once- or twice-daily regimens; edoxaban and rivaroxaban are once-daily (QD) regimens for AF while apixaban and dabigatran are twice-daily (BID) regimens. Studies have shown that there is an association between daily dosing frequency (QD versus BID) and medication adherence[4].

Daiichi Sankyo Europe (DSE) requested the PHARMO Institute to set up a study comparing adherence, persistence and switching patterns between patients using QD and BID DOACs for AF.

The current document gives a description of the methods, including definitions and analyses, and results of a multi-database study in the Netherlands, Germany and Italy.

2. Objectives

The primary objectives of this study were to:

- determine the relationship between adherence and QD vs. BID
- determine the relationship between persistence and QD vs. BID
- compare adherence before and after a dosage regimen switch
- compare persistence after a dosage regimen switch from QD to BID vs. a dosage regimen switch from BID to QD
- compare switching patterns for QD and BID

3. Methods

3.1 Data sources

The study was conducted in three databases: the PHARMO Database Network (PHARMO) from the Netherlands, the Italian Agenzia regionale di sanità della Toscana database (ARS) and the German Pharmacoepidemiological Research Database (GePaRD).

3.1.1 PHARMO Database Network – the Netherlands

Data for the study were obtained from the PHARMO Database Network in the Netherlands. This population-based network of electronic healthcare databases combines data from different primary and secondary healthcare settings in the Netherlands. These different data sources, including data from general practices, in- and out-patient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms. To ensure the privacy of the data in the PHARMO Database Network, the collection, processing, linkage and anonymization of the data is performed by STIZON. STIZON is an independent, ISO/IEC 27001 certified foundation, which acts as a Trusted Third Party (TTP) between the data sources and the PHARMO Institute. Detailed information on the methodology and the validation of the used record linkage method can be found elsewhere.[5,6].

The longitudinal nature of the PHARMO Database Network system enables to follow-up more than 9 million persons of a well-defined population in the Netherlands for an average of twelve years. Currently, the PHARMO Database Network covers over 6 million active persons out of 17 million inhabitants of the Netherlands. Data collection period, catchment area and overlap between data sources differ. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status and mortality. Other available information is dependent on the data source.

To address the primary objective of this study the following PHARMO databases were used:

- General Practitioner Database
- Out-patient Pharmacy Database

A detailed description of these databases is given below.

General Practitioner Database

The General Practitioner (GP) Database comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen,

quantity and route of administration. Drug prescriptions are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System [7]. Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) [8], which can be mapped to ICD codes, but can also be entered as free text. GP data cover a catchment area representing 3.2 million residents.

Out-patient Pharmacy Database

The Out-patient Pharmacy Database comprises GP or specialist prescribed healthcare products dispensed by the out-patient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. Drug dispensings are coded according to the WHO ATC Classification System[7]. Out-patient pharmacy data cover a catchment area representing 4.2 million residents.

3.1.2 Agenzia regionale di sanità della Toscana database (ARS) – Italy

The ARS database includes pseudonymised patient-level information on the utilisation of healthcare services reimbursed by the National Healthcare Service and dispensed to all subjects who are residents and registered with a general practitioner in Tuscany. Dates of admission to reimbursement for specific indications, as imposed by the national regulatory authority (Agenzia Italiana del Farmaco, AIFA) are available in the database.

ARS covers 3.7 million residents in Tuscany. Data is available as of 2003. The database contains demographic data, hospitalisation data (including discharge diagnosis and procedures), emergency visits (including diagnosis and procedures), causes of death, exemptions from co-payment for chronic diseases, pathology registry and outpatient dispensing data both upon specialist and primary care prescription. Specialist visits are recorded if they are reimbursed and, in this case, the specialty of the ward where the visit is performed is available. Drugs that are purchased over the counter are not contained in the database. Medication administered in hospital is not deterministically linkable to patient IDs, although probabilistic record linkage is possible.

3.1.3 German Pharmacoepidemiological Research Database (GePaRD) – Germany

GePaRD is based on claims data from four German statutory health insurance providers and currently includes information on more than 22 million persons who have been insured with one of the participating providers since 2004 or later. Per data year, there is information on approximately 17% of the general population and all geographical regions of Germany are represented. In addition to demographic data, GePaRD contains information on drug dispensations, outpatient and inpatient services and diagnoses. Drugs that are purchased over

the counter are not contained in the database. With a few exceptions the same applies to medication administered in hospital. For data protection reasons information is pseudonymised and coarsened (e.g. instead of a person's birthday only the respective birth year is included). The lag time of the database is approximately two years. Methodological assessment and validation studies have shown the applicability of GePaRD for pharmacoepidemiological research[9-11] and GePaRD has been used for various pharmacoepidemiological studies, inter alia in the area of (oral) anticoagulants[12,13].

3.2 Study design

A cohort study among patients using DOACs for the treatment of AF was performed.

3.3 Patient selection

The source population included all patients receiving DOACs from the date of positive CHMP opinion on the AF indication for each drug (see Table 3.1) until the end of data availability for each database (December 31st, 2017 in PHARMO, December 31st, 2018 in ARS and December 31st, 2016 in GePaRD). During this period the date of first prescription/dispensing (hereafter referred to as 'dispensing') of a DOAC was defined as the index date and the dispensed DOAC as the index drug.

Table 3.1: Characteristics of DOACs included in this study

	Date of positive CHMP opinion on AF indication	Dosage regimen	ATC
DOAC			
Dabigatran[14]	April 14th, 2011	BID	B01AE07
Rivaroxaban[15]	September 22nd, 2011	QD	B01AF01, B01AX06
Apixaban[16]	September 20th, 2012	BID	B01AF02
Edoxaban[17]	April 23rd, 2015	QD	B01AF03

The study population was restricted to adult patients (≥18 years at index date) with at least one year of database history at the index date for selection of eligible new users (i.e. no previous dispensing of DOACs in the year before index date, no multiple different DOACs on the index date and no VKA dispensing on the index date). Patients were also required having at least one year of follow-up relative to the index date in all required databases.

To limit the study population to patients with AF, new users of DOACs were additionally required to meet at least one of the following criteria:

- Have a recorded coded diagnosis, examination or free text indicating AF any time before the index date or up to 30 days after the index date (see Section 6.1 for diagnostic codes);

- the index drug being prescribed by a cardiologist (if recorded in the database), except for rivaroxaban 2.5mg as initial dose which is the indication-specific regimen for acute coronary syndrome.

Patients with AF were included in the QD or BID group based on the prescribed dosage regimen of their index drug (i.e. index dosage regimen) in PHARMO and ARS. In these databases, patients with a deviating treatment regimen (e.g. dabigatran QD or three times daily) or initiating on both QD and BID at the index date were excluded. In GePaRD, no prescribed dosage regimen is available; therefore the dosage regimen of Table 3.1 was used there to group patients.

Patients were followed from index date until end of data collection (i.e. patient moves out of the catchment area), death or end of data availability for the database, whichever occurred first.

3.4 Patient characteristics

The following patient characteristics were determined at index date:

- Sex
- Age (categorised, mean ± standard deviation (SD), median (interquartile range (IQR))
- Year of index date
- Available database follow-up (categorised, mean ± SD, median (IQR))
- Index drug (type of DOAC and associated dosage regimen)
- Prior VKA treatment (dispensed in the year before the index date; ATC B01AA)
- Co-medication (dispensed in the 3 months before or on the index date)
    - Lipid modifying agents (ATC C10)
    - Antihypertensive drugs (ATC C02, C03, C07, C08, C09)
    - Antidiabetic drugs (ATC A10)
    - Antiarrhythmic drugs (ATC C01B)
- Polypharmacy, defined as the number of all different pharmacological subgroups (ATC 3rd level) excluding antithrombotic agents (ATC B01A), dispensed in the 3 months before or on the index date (categorised)

3.5 Adherence and persistence

Adherence to treatment was defined based on the proportion of days covered (PDC) during the exposure period. The exposure period was defined as the number of days between the date of the first drug dispensing (i.e. index date) and that of the last drug dispensing with the index dosage regimen. The number of dispensings per patient within the exposure period was assessed. Among patients with >1 dispensing in the exposure period, PDC was calculated as the

total days of supply of the index dosage regimen during the exposure period divided by the number of days in the exposure period. In PHARMO and ARS, the total days of supply was calculated based on the prescribed dosage regimen. In GePaRD, this was estimated based on the defined daily dose (DDD). PDC values range from 0 to 1, with higher values suggesting higher adherence. Mean ± SD and median (IQR) PDC are presented as well as the proportion of adherent patients defined as those with PDC ≥0.8. Considering the varying length of follow-up within the study population, the PDC was also determined during a fixed 12 months follow-up period.

Persistence with treatment was defined as the time from index date to treatment discontinuation and was based on DOAC treatment episodes (see Section 3.7). Treatment discontinuation was defined as the failure to refill the index dosage regimen within the number of days of supply of the last filled prescription plus the maximum allowed gap. Persistence rates were determined at 3, 6, 9, 12 months after index date and at end of follow-up. In addition, persistence is presented in a Kaplan-Meier persistence curve which also shows the median persistence.

For both the assessment of adherence and persistence, switches within the QD or BID clusters were allowed. In other words, patients switching from e.g. rivaroxaban to edoxaban were still considered persistent with and adherent to QD treatment. The exposure period and a treatment episode ended upon introduction of a DOAC with a dosage regimen other than the index drug.

Among patients with a recorded dosage regimen switch (i.e. from QD to BID or vice versa), PDC was assessed during the exposure period before and after the first recorded dosage regimen switch. The exposure period before the first recorded dosage regimen switch was similar to the exposure period as defined above. The period after switch was defined as the period from the first recorded dosage regimen switch until the end of the treatment episode, according to the methods as defined above. Only patients with >1 dispensing in both exposure periods were included in the analysis to enable the before-after comparison being based on the same patients.
Furthermore, persistence after the first recorded dosage regimen switch from QD to BID or vice versa was assessed. To interpret these results, sex, age and polypharmacy at index date are presented for patients switching from QD to BID and those switching from BID to QD.

3.6 Switching patterns

Switching patterns were assessed from the day after index date until the end of follow-up based on DOAC treatment episodes. This was defined as either the occurrence of a dosage

regimen switch or a BID/QD cluster switch (i.e. to another DOAC with the same dosage regimen). BID/QD cluster switches were assessed relative to the cluster of the index drug. In case of multiple dosage regimen or BID/QD cluster switches, only the first occurring switch per switch type was taken into account. Furthermore, the type of DOAC switched to was assessed on a drug level.

3.7 Treatment episodes

DOAC dispensings were converted into treatment episodes of uninterrupted use. The duration of each dispensing was calculated by dividing the number of tablets dispensed by the number of tablets to be used per day (or the number of DDDs for GePaRD). The dosing instructions were used to determine the number of tablets to be used per day. In case of an interruption between DOAC dispensings, use of the respective DOAC was considered uninterrupted if the duration of this gap was less than half the duration of the preceding dispensing with a minimum of 7 days. The end date of an episode was set at the end of the duration of the last dispensing within that episode, excluding the permissible gap. Patients may have several treatment episodes after index date. If the last dispensing of a DOAC preceded the first dispensing of another DOAC, this indicates a switch of treatment, and the former DOAC episode was cut short at the start of the next DOAC episode. In other words, concomitant use of different DOACs was not allowed.

3.8 Statistical analyses

The patient selection is presented in an attrition table with numbers included and excluded in each subsequent step. Exclusions are reported as absolute numbers as well as percentages of the population size immediately prior to exclusion according to the attrition table. Outcomes are presented stratified by database and index dosage regimen. Continuous data is presented as means with SD and medians with IQR. Categorical data is presented as counts (n) and proportions (%). Persistence over time is additionally presented in a Kaplan-Meier persistence curve, stratified by database and index dosage regimen (for persistence since index date) or type of dosage regimen switch (for persistence since dosage regimen switch). Measures of adherence, persistence and switching patterns were compared between QD and BID DOAC users or between the period before and after dosage regimen switch by means of Chi-square tests for categorical variables and ANOVA tests for continuous variables. At PHARMO, all data were analyzed using SAS programs organized within SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC, USA) and conducted under Windows using SAS version 9.4. At ARS, R was used for data processing and analyses. At BIPS, SAS version 9.4 was available for data processing and analysis.

Due to the different database characteristics and coding schemes it was not possible to use one single data extraction algorithm for all the databases. Therefore, each database extracted data locally and transformed them into a simple common data model, i.e. standardised patient and dispensing files, linkable through a unique patient identifier. The input files – as specified in the common data model – formed the basis for this study. Aggregated data summaries as outlined in Section 4 were created on site for each database using SAS programs shared by PHARMO. Since ARS does not have a SAS license, ARS used the SAS programs shared by PHARMO to create transformation programs in R. These R programs were validated by comparison to the SAS programs using simulated data. PHARMO combined all aggregated data into a report. The general process of data collection, programming and reporting is illustrated in Figure 3.1.

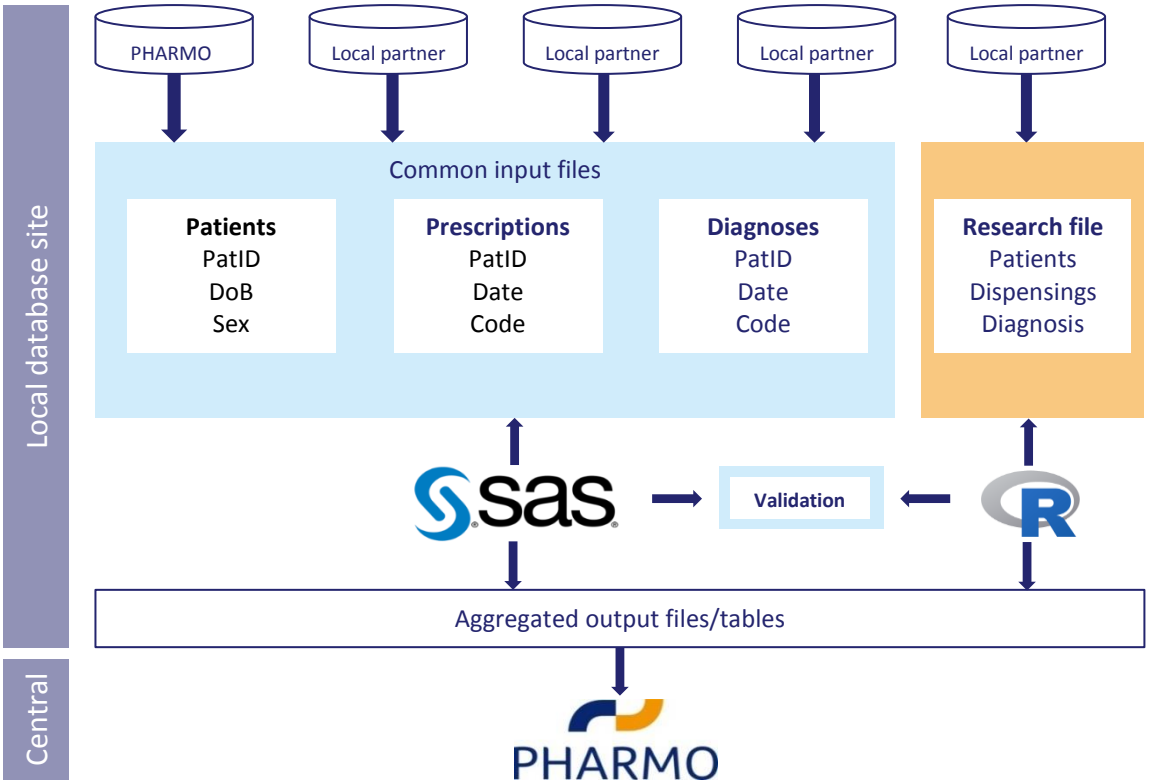


Figure 3.1: Model for multi-database common programming and reporting

4. Results and interpretations

4.1 Patient selection

Table 4.1: Selection of the study population in PHARMO, ARS and GePaRD

	PHARMO (NL)	ARS (IT)	GePaRD (DE)
Patients receiving DOACs during selection period* (N)	**19,947**	**78,614**	**454,018**
Exclude: patients aged <18 years at index date, n (%)	7 (<0.5)	32 (<0.5)	417 (<0.5)
Adult patients (N)	**19,940**	**78,582**	**453,601**
Exclude: less than one year of database history, n (%)	374 (2)	214 (<0.5)	13,500 (3)
With at least 1 year database history (N)	**19,566**	**78,368**	**440,101**
Exclude: less than one year of database follow-up, n (%)	7,617 (39)	22,778 (29)	139,275 (32)
With at least 1 year database follow-up (N)	**11,949**	**55,590**	**300,826**
Exclude: previous dispensing of DOACs in the year before index date, multiple different DOACs or a VKA dispensing on the index date, n (%)	61 (1)	90 (<0.5)	1,021 (<0.5)
Eligible new users of DOACs (N)**	**11,888**	**55,500**	**299,805**
Exclude: patients without AF, n (%)	5,728 (48)	23,240 (42)	132,360 (44)
Patients with AF (N)	**6,160**	**32,260**	**167,445**
Exclude: patients without QD or BID regimen, n (%)	92 (1)	0 (0)	NA
Study population: patients meeting all the inclusion criteria (N)	**6,068**	**32,260**	**167,445**
QD DOAC users, n (%)	1,907 (31)	13,017 (40)	102,422 (61)
BID DOAC users, n (%)	4,161 (69)	19,243 (60)	65,023 (39)

*Selection period: from the date of positive CHMP opinion on the AF indication for each drug (see Table 3.1) until the end of data availability for each database; **No previous dispensing of DOACs in the year before index date, multiple different DOACs on the index date or VKA dispensing on the index date.

Comments to Table 4.1:

- Table 4.1 presents the selection of the study population. In PHARMO, 6,068 DOAC users were included in the study population. Among these patients, 1,907 (31%) used a QD dosage regimen, 4,161 (69%) used a BID regimen. 32,260 patients were included in the study population in ARS. 13,017 (40%) used a QD dosage regimen and 19,243 (60%) used a BID regimen. In GePaRD, 167,445 DOAC users were included in the study population, with 102,422 (61%) users with a QD dosage regimen and 65,023 (39%) users with a BID regimen.
- About 30%-40% of the patients were excluded, because less than one year of database follow-up was available. In PHARMO, 91% of these excluded patients had an index date in 2017. There won't be a year of data available for these patients, as the end of database availability is December 31st, 2017 in PHARMO. Presumably, this will be the reason of exclusion in the other databases as well.
- In the PHARMO Database Network, 51% of the study population started with dabigatran (BID regimen) (not shown in this table). In GePaRD, largest part of the

patients (61%) started with rivaroxaban (QD regimen), which explains the difference in dosage regimen use between the databases. In ARS, rivaroxaban, dabigatran and apixaban were used equally frequent (about 30%).

4.2 Patient characteristics

Table 4.2: Characteristics of DOAC users at index date, stratified by database and index dosage regimen

	PHARMO (NL)		ARS (IT)		GePaRD (DE)	
	QD N = 1,907 n (%)	BID N = 4,161 n (%)	QD N = 13,017 n (%)	BID N = 19,243 n (%)	QD N = 102,422 n (%)	BID N = 65,023 n (%)
Sex						
Male	1,135 (60)	2,410 (58)	6,553 (50)	9,632 (50)	52,120 (51)	32,876 (51)
Female	772 (40)	1,751 (42)	6,464 (50)	9,611 (50)	50,302 (49)	32,147 (49)
Age (years)						
18-50	70 (4)	154 (4)	203 (2)	212 (1)	3,302 (3)	1,694 (3)
51-64	398 (21)	846 (20)	1,136 (9)	1,433 (7)	14,694 (14)	8,362 (13)
65-74	827 (43)	1,683 (40)	3,159 (24)	4,867 (25)	31,419 (31)	18,959 (29)
≥75	612 (32)	1,478 (36)	8,519 (65)	12,731 (66)	53,007 (52)	36,008 (55)
Mean ± SD	70 ± 10	70 ± 10	77 ± 10	77 ± 9	74 ± 11	74 ± 10
Median (IQR)	70 (65-76)	71 (65-78)	78 (71-84)	78 (72-84)	75 (68-80)	76 (69-81)
Year of index date						
2011	1 (<0.5)	25 (1)	0 (0)	0 (0)	64 (<0.5)	1,820 (3)
2012	54 (3)	288 (7)	0 (0)	0 (0)	6,518 (6)	3,496 (5)
2013	164 (9)	440 (11)	371 (3)	2,041 (11)	33,019 (32)	13,520 (21)
2014	374 (20)	811 (19)	1,909 (15)	3,352 (17)	31,973 (31)	19,036 (29)
2015	561 (29)	1,099 (26)	2,456 (19)	4,206 (22)	30,847 (30)	27,147 (42)
2016	753 (39)	1,498 (36)	3,073 (24)	5,162 (27)	1 (<0.5)	4 (<0.5)
2017	0 (0)	0 (0)	5,204 (40)	4,478 (23)	0 (0)	0 (0)
Available database follow-up (years)						
1-<2	805 (42)	1,647 (40)	5,609 (43)	5,257 (27)	36,119 (35)	29,890 (46)
2-<3	557 (29)	1,097 (26)	3,188 (24)	5,356 (28)	32,293 (32)	18,773 (29)
≥3	545 (29)	1,417 (34)	4,220 (32)	8,630 (45)	34,010 (33)	16,360 (25)
Mean ± SD	2.4 ± 1.1	2.6 ± 1.3	2.5 ± 1.2	3.0 ± 1.3	2.5 ± 0.9	2.3 ± 1.0
Median (IQR)	2.2 (1.5-3.1)	2.4 (1.6-3.4)	2.2 (1.6-3.4)	2.8 (1.9-3.9)	2.5 (1.7-3.3)	2.1 (1.5-3.0)

	PHARMO (NL)		ARS (IT)		GePaRD (DE)	
	QD N = 1,907 n (%)	BID N = 4,161 n (%)	QD N = 13,017 n (%)	BID N = 19,243 n (%)	QD N = 102,422 n (%)	BID N = 65,023 n (%)
Index drug						
Edoxaban, QD	48 (3)	NA	3,139 (24)	NA	1,028 (1)	NA
Rivaroxaban, QD	1,859 (97)	NA	9,878 (76)	NA	101,394 (99)	NA
Apixaban, BID	NA	1,081 (26)	NA	9,340 (49)	NA	40,843 (63)
Dabigatran, BID	NA	3,080 (74)	NA	9,903 (51)	NA	24,180 (37)
Prior VKA treatment*	642 (34)	1,245 (30)	5,417 (42)	8,700 (45)	25,761 (25)	16,162 (25)
Co-medication†						
Lipid modifying agents	765 (40)	1,774 (43)	4,331 (33)	6,584 (34)	28,559 (28)	21,428 (33)
Antihypertensive drugs	1,675 (88)	3,653 (88)	11,485 (88)	17,241 (90)	91,622 (89)	58,744 (90)
Antidiabetic drugs	247 (13)	588 (14)	2,061 (16)	3,169 (16)	15,067 (15)	9,865 (15)
Antiarrhythmic drugs	244 (13)	530 (13)	3,524 (27)	5,487 (29)	10,925 (11)	7,298 (11)
Polypharmacy†,††						
0-5	1,246 (65)	2,667 (64)	5,629 (43)	8,165 (42)	59,453 (58)	36,632 (56)
6-7	373 (20)	767 (18)	2,825 (22)	4,209 (22)	20,328 (20)	13,401 (21)
≥8	288 (15)	727 (17)	4,563 (35)	6,869 (36)	22,641 (22)	14,990 (23)

*Assessed in the year before the index date; †Assessed in the 3 months before or on the index date; ††the number of all different pharmacological subgroups (ATC 3rd level) excluding antithrombotic agents (ATC B01A).

Comments to Table 4.2:

- In the PHARMO study population, about 75% of the patients was 65 years or older, in ARS this was about 90% and in GePaRD this was about 83%.
- End of data availability in PHARMO was up to December 31st, 2017 and in GePaRD up to December 31st, 2016. Therefore (almost) no patients were included in the year 2017 in PHARMO and in 2016 and 2017 in GePaRD, as one year of database follow-up was required. In ARS, where end of data availability was up to December 31st, 2018, 40% of the QD users and 23% of the BID users were included in the year 2017. Median follow-up (i.e. available database follow-up) was 2.1-2.8 years in all databases.
- In PHARMO and GePaRD, DOACs were seen from the date of positive CHMP opinion on the AF indication for each DOAC. In ARS, DOACs were seen from the date of reimbursement for each drug (dabigatran June 6th, 2013; rivaroxaban August 29th, 2013; apixaban December 19th, 2014 and edoxaban August 25th 2016). Therefore, in ARS the DOAC users were included in later years compared to PHARMO and GePaRD.
- In all databases, rivaroxaban (the first approved DOAC among the QD group) was the most frequently used drug at index date (76-99%) among users in the QD group. In PHARMO and GePaRD, edoxaban was used by only 1%-3% of the patients in the QD group. In ARS this was 24%. Among users in the BID group, dabigatran was the most frequently used drug at index date (74%) in PHARMO; in GePaRD this was apixaban (63%). In ARS, apixaban and dabigatran were used equally frequent.
- In PHARMO, about 31% of the patients did have a previous record of VKA treatment. In ARS this was about 43% and in GePaRD this was about 25% of the patients.
- Most DOAC users used antihypertensive drugs (88%-90% in all databases), 40%-43% of the users in PHARMO, 33%-34% of the users in ARS and 28%-33% of the users in GePaRD used lipid modifying agents. In all databases, 11%-29% of the patients used antidiabetic drugs and/or antiarrhythmic drugs.
- Patient characteristics were equally distributed between the dosage regimen groups.
- Study populations were slightly different between the databases. In PHARMO, the proportion of male patients was higher, patients were slightly younger and there was less polypharmacy compared to patients in GePaRD and ARS. With only hospital diagnoses, ARS had the most severe study population compared with the other databases. This likely explains why there was more polypharmacy in ARS.

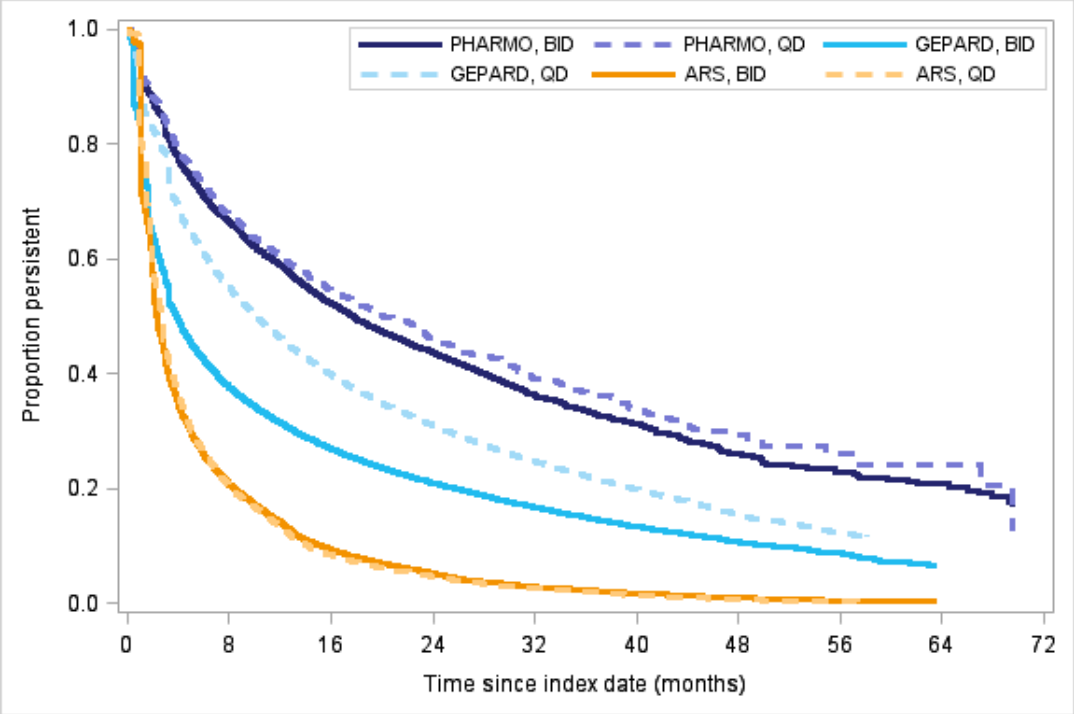
4.3 Adherence and persistence

Table 4.3: Adherence and persistence among DOAC users, stratified by database and index dosage regimen

	PHARMO (NL)			ARS (IT)			GePaRD (DE)		
	QD N = 1,907	BID N = 4,161	*p* value QD vs. BID	QD N = 13,017	BID N = 19,243	*p* value QD vs. BID	QD N = 102,422	BID N = 65,023	*p* value QD vs. BID
Number of dispensings per patient*, n (%)			0.0464			<.0001			<.0001
1	122 (6)	231 (6)		484 (4)	647 (3)		14,059 (14)	6,669 (10)	
2-5	264 (14)	659 (16)		976 (7)	1,263 (7)		24,350 (24)	13,292 (20)	
6-9	522 (27)	1,044 (25)		855 (7)	880 (5)		27,724 (27)	17,247 (27)	
≥10	999 (52)	2,227 (54)		10,702 (82)	16,453 (86)		36,289 (35)	27,815 (43)	
Persistence, n (%)									
At 3 months	1,606 (84)	3,466 (83)	0.3697	5,836 (45)	8,242 (43)	0.0004	80,320 (78)	36,593 (56)	<.0001
At 6 months	1,377 (72)	2,942 (71)	0.2300	3,428 (26)	4,990 (26)	0.4184	62,289 (61)	27,195 (42)	<.0001
At 9 months	1,251 (66)	2,667 (64)	0.2551	2,390 (18)	3,648 (19)	0.1775	53,584 (52)	22,997 (35)	<.0001
At 12 months	1,151 (60)	2,444 (59)	0.2330	1,752 (13)	2,736 (14)	0.0533	47,248 (46)	20,177 (31)	<.0001
At end of follow-up	825 (43)	1,624 (39)	0.0018	460 (4)	487 (3)	<.0001	27,729 (27)	12,835 (20)	<.0001
Patients for whom PDC is determined, n (%)**	**1,785 (94)**	**3,930 (94)**		**12,533 (96)**	**18,596 (97)**		**88,363 (86)**	**58,354 (90)**	
Exposure period (months)**									
Mean ± SD	23 ± 14	25 ± 16	0.0014	25 ± 15	29 ± 17	<.0001	23 ± 13	21 ± 13	<.0001
Median (IQR)	21 (13-33)	21 (13-34)		21 (14-35)	28 (17-41)		22 (13-33)	19 (13-29)	
PDC during exposure period**									
Mean ± SD	0.96 ± 0.11	0.94 ± 0.15	<.0001	0.94 ± 0.15	0.93 ± 0.14	<.0001	0.89 ± 0.19	0.78 ± 0.24	<.0001
Median (IQR)	1.00 (0.98-1.00)	1.00 (0.95-1.00)		1.00 (0.95-1.00)	1.00 (0.93-1.00)		0.99 (0.82-1.00)	0.90 (0.53-1.00)	
n (%) adherent (PDC ≥0.8)	1,667 (93)	3,540 (90)	<.0001	11,421 (88)	16,566 (86)	<.0001	68,331 (77)	33,932 (58)	<.0001

	PHARMO (NL)			ARS (IT)			GePaRD (DE)		
	QD N = 1,907	BID N = 4,161	*p* value QD vs. BID	QD N = 13,017	BID N = 19,243	*p* value QD vs. BID	QD N = 102,422	BID N = 65,023	*p* value QD vs. BID
PDC during 12 months of follow-up**									
Mean ± SD	0.96 ± 0.10	0.95 ± 0.13	<.0001	0.95 ± 0.13	0.95 ± 0.12	0.0088	0.91 ± 0.16	0.80 ± 0.23	<.0001
Median (IQR)	1.00 (0.99-1.00)	1.00 (0.97-1.00)		1.00 (0.98-1.00)	1.00 (0.97-1.00)		1.00 (0.88-1.00)	0.93 (0.56-1.00)	
n (%) adherent (PDC ≥0.8)	1,670 (94)	3,559 (91)	0.0005	11,610 (89)	16,971 (88)	0.0001	71,320 (82)	35,521 (62)	<.0001

*Assessed within the exposure period; **Assessed among patients with >1 dispensing in the exposure period.



Months	0	8	16	24	32	40	48	56	64	72
$N_{at\ risk}$	1,907	1,286	862	519	288	130	54	15	7	-
$N_{at\ risk}$	4,161	2,752	1,845	1,120	652	344	158	98	41	-
$N_{at\ risk}$	13,017	2,677	979	416	180	63	20	4	-	-
$N_{at\ risk}$	19,243	4,000	1,712	842	391	181	79	28	3	-
Nat risk	102,422	55,988	35,900	20,915	11,562	5,135	921	155	-	-
Nat risk	65,023	24,112	14,495	7,330	3,577	1,432	291	95	-	-

Figure 4.1: Kaplan-Meier curve showing the proportion of patients persistent with the QD and BID dosage regimen for DOACs, stratified by database and index dosage regimen

Comments to Table 4.3 and Figure 4.1:

- During the exposure period (i.e. the period between the index date and that of the last drug dispensing with the index dosage regimen), most of the patients had ≥10 DOACs dispensings: in PHARMO 52%-54%, in ARS 82%-86% and in GePaRD 35%-43%. QD users had slightly less DOAC dispensings compared to BID users in all databases.
- Persistence rates were highest in PHARMO and lowest in ARS. Patients in ARS had the highest number of dispensings. The duration of these dispensings was shorter compared to the dispensings in the other databases (not shown in this table). Consequently, the permissible gap between dispensings might be too short for ARS, resulting in a shorter persistence in ARS.
- In PHARMO, 84% of the QD users and 83% of the BID users were still using the initial dosage regimen after 3 months of follow-up. After 12 months, this was 60% and 59% respectively. The Kaplan-Meier curve (Figure 4.1) shows a slightly higher proportion of persistent users among the QD group from 16 months of follow-up and onwards. At end of follow-up, 43% of the QD users was still on their index dosage regimen treatment; which is slightly, but significantly higher ($p<0.05$) compared to the BID users (39%). This difference in persistence cannot be explained by a difference in frequency of dosage regimen switches (see Table 4.6). This difference can also not be explained by time to switch, which was longer among BID users compared to QD users (see Table 4.4).
- Although QD users were slightly more persistent, BID users had a longer exposure period, which includes gaps in treatment.
- In ARS, 45% of the QD users and 43% of the BID users were still using the initial dosage regimen after 3 months of follow-up. After 12 months, this was 13% and 14% respectively. The Kaplan-Meier curve (Figure 4.1) shows no difference in proportion of persistent users among the QD group and BID group during follow-up. At end of follow-up, only 4% of the QD users and 3% of the BID users were still on their index dosage regimen treatment.
- In GePaRD, 78% of the QD users and 56% of the BID users were still using the initial dosage regimen after 3 months of follow-up. After 12 months, this was 46% and 31% respectively. Persistence rates at all time points were significantly higher among QD users compared to BID users ($p<0.05$). The Kaplan-Meier curve illustrates this difference (Figure 4.1). At end of follow-up, 27% of the QD users was still on their index dosage regimen treatment; which is significantly higher ($p<0.05$) compared to the BID users (20%). This difference in persistence cannot be explained by a difference in frequency of dosage regimen switches, as patients with a QD regimen switched more often compared to patients with a BID regimen (see Table 4.6). However, the time to switch was longer among QD users compared to BID users (see Table 4.4).

- In PHARMO, 93%-94% of the QD users was adherent to treatment, either when assessed during the first 12 months of follow-up as well as during the total exposure period. These proportions were slightly, but significantly lower among BID users (90%-91%) ($p<0.05$). In ARS, 88%-89% of the QD users was adherent to treatment, which was also slightly but significantly lower among BID users (86%-88%) ($p<0.05$). In GePaRD, 77%-82% of the QD users was adherent to treatment, which was significantly lower among BID users (58%-62%) ($p<0.05$).
- Similar adherence and persistence results were observed among older patients (Table 6.2, Table 6.3, Figure 6.1 and Figure 6.2).

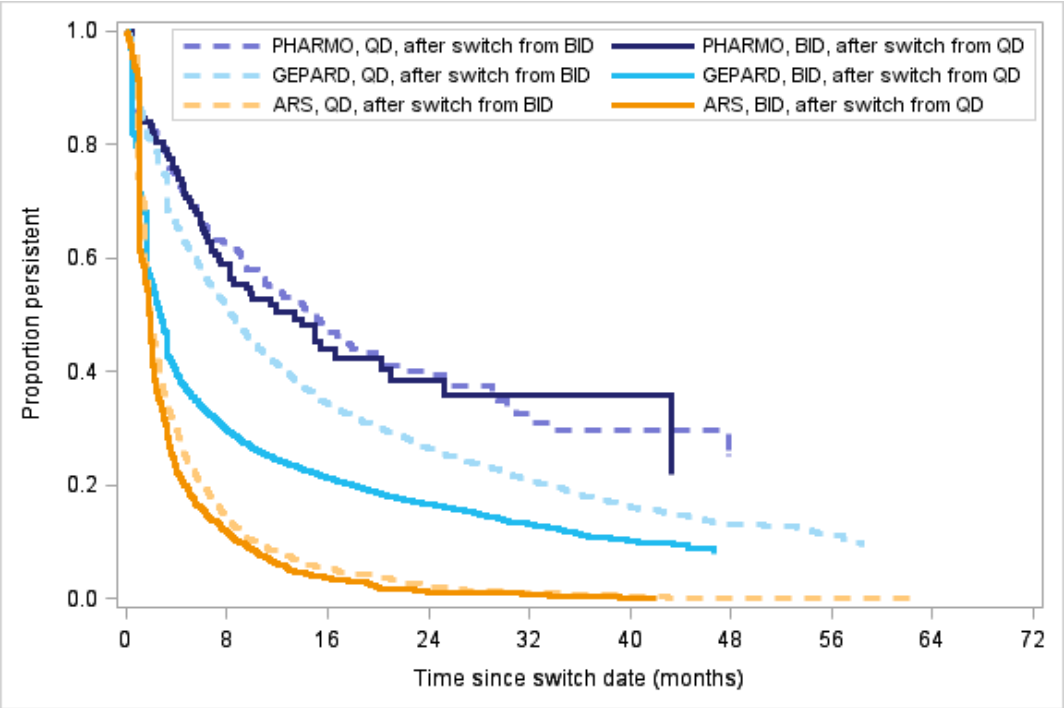
Table 4.4: Adherence among DOAC users before and after a dosage regimen switch, stratified by database and type of dosage regimen switch

	PHARMO (NL)			ARS (IT)			GePaRD (DE)		
	Before†	**After‡**	***p* value before vs. after**	**Before†**	**After‡**	***p* value before vs. after**	**Before†**	**After‡**	***p* value before vs. after**
Patients with a switch from QD to BID (N)*	**105**	**105**		**541**	**541**		**7,851**	**7,851**	
Exposure period (months)									
Mean ± SD	8 ± 9	14 ± 12	0.0001	12 ± 12	15 ± 13	0.0009	12 ± 11	13 ± 10	<.0001
Median (IQR)	5 (2-12)	10 (5-22)		9 (3-18)	12 (4-23)		9 (3-19)	11 (5-19)	
PDC during exposure period									
Mean ± SD	0.96 ± 0.12	0.96 ± 0.11	0.9346	0.95 ± 0.13	0.94 ± 0.13	0.2136	0.89 ± 0.19	0.73 ± 0.25	<.0001
Median (IQR)	1.00 (0.98-1.00)	1.00 (0.97-1.00)		1.00 (0.97-1.00)	1.00 (0.95-1.00)		1.00 (0.83-1.00)	0.75 (0.50-1.00)	
n (%) adherent (PDC ≥0.8)	97 (92)	97 (92)	>0.99	505 (93)	493 (91)	0.1731	6,117 (78)	3,725 (47)	<.0001
Patients with a switch from BID to QD (N)*	**230**	**230**		**939**	**939**		**3,457**	**3,457**	
Exposure period (months)									
Mean ± SD	12 ± 13	16 ± 14	0.0028	16 ± 15	17 ± 15	0.4800	9 ± 10	18 ± 14	<.0001
Median (IQR)	6 (3-17)	12 (5-21)		12 (4-24)	13 (5-24)		6 (2-13)	13 (6-28)	
PDC during exposure period									
Mean ± SD	0.92 ± 0.18	0.94 ± 0.15	0.1203	0.93 ± 0.15	0.95 ± 0.13	0.0002	0.83 ± 0.22	0.89 ± 0.18	<.0001
Median (IQR)	1.00 (0.94-1.00)	1.00 (0.97-1.00)		1.00 (0.94-1.00)	1.00 (0.98-1.00)		0.95 (0.70-1.00)	0.99 (0.80-1.00)	
n (%) adherent (PDC ≥0.8)	196 (85)	210 (91)	0.0426	836 (89)	879 (94)	0.0004	2,298 (66)	2,618 (76)	<.0001

†Before first recorded switch; ‡From the first recorded switch until end of the treatment episode; *Among patients with >1 dispensing in both exposure periods of interest (i.e. before and after switch).

Comments to Table 4.4:

- Table 4.4 shows the adherence among DOAC users before and after a dosage regimen switch.
- Among patients with a switch from a QD to a BID dosage regimen, the mean exposure time to switch was 8 months in PHARMO. Before as well as after the switch 92% of these users was adherent to treatment. Also among older patients switching from a QD to a BID dosage regimen, adherence was similar before and after switch (Table 6.4-Table 6.5). In ARS and GePaRD, the mean exposure time to switch from QD to BID was 12 months. In ARS, before as well as after switch about 92% was adherent to treatment. Also among older patients switching from a QD to a BID dosage regimen, adherence was similar before and after switch (Table 6.4-Table 6.5). In GePaRD, before switching from QD to BID 78% of the users was adherent to treatment; after switch this was significantly lower (47% of the patients was adherent). Among patients older than 75 years the difference in the proportion of adherent patients before and after switch was slightly larger compared with all patients (Table 6.5).
- Among patients with a switch from a BID to a QD dosage regimen, the mean exposure time to switch was 12 months in PHARMO. Before switch, 85% of the patients was adherent to treatment, which was slightly, but significantly ($p<0.05$) higher after switch (91%). Among patients older than 75 years, this difference was not significant anymore (Table 6.5). In ARS, the mean exposure time to switch from BID to QD was 16 months. Before switch 89% of the patients was adherent to treatment, which was slightly but significantly higher after switch (94% of the patients was adherent). These results were similar among older patients (Table 6.4-Table 6.5). In GePaRD, the mean exposure time to switch from BID to QD was 9 months. Before switch 66% of the patients was adherent to treatment, which was significantly higher after switch (76% of the patients was adherent). These results were similar among older patients (Table 6.4-Table 6.5).



Months	0	8	16	24	32	40	48	56	64	72
Nat risk	308	159	84	44	24	13	-	-	-	-
Nat risk	147	70	31	17	9	5	-	-	-	-
$N_{at\ risk}$	1,155	181	62	32	9	3	1	-	-	-
$N_{at\ risk}$	694	85	21	6	2	0	0	-	-	-
$N_{at\ risk}$	6,282	2,705	1,384	813	474	223	72	25	-	-
$N_{at\ risk}$	13,065	2,916	1,385	635	253	61	6	-	-	-

Figure 4.2: Kaplan-Meier curve showing the proportion of patients persistent with the QD and BID dosage regimen for DOACs after first dosage regimen switch, stratified by database and type of dosage regimen switch

Table 4.5: Sex, age and polypharmacy at index date among patients with a recorded dosage regimen switch, stratified by database and type of dosage regimen switch

	PHARMO (NL)		ARS (IT)		GePaRD (DE)	
	Switch from QD to BID N = 147 n (%)	Switch from BID to QD N = 308 n (%)	Switch from QD to BID N = 694 n (%)	Switch from BID to QD N = 1,155 n (%)	Switch from QD to BID N = 13,065 n (%)	Switch from BID to QD N = 6,282 n (%)
Sex						
Male	81 (55)	152 (49)	331 (48)	565 (49)	6,146 (47)	2,912 (46)
Female	66 (45)	156 (51)	363 (52)	590 (51)	6,919 (53)	3,370 (54)
Age (years)						
18-50	10 (7)	11 (4)	9 (1)	12 (1)	273 (2)	136 (2)
51-64	29 (20)	51 (17)	42 (6)	74 (6)	1,450 (11)	713 (11)
65-74	66 (45)	129 (42)	191 (28)	314 (27)	3,978 (30)	2,012 (32)
≥75	42 (29)	117 (38)	452 (65)	755 (65)	7,364 (56)	3,421 (54)
Mean ± SD	69 ± 9	71 ± 9	77 ± 9	77 ± 9	75 ± 10	74 ± 10
Median (IQR)	70 (64-76)	71 (66-78)	78 (72-83)	78 (72-83)	76 (70-81)	75 (70-81)
Polypharmacy†,††						
0-5	98 (67)	189 (61)	264 (38)	487 (42)	7,096 (54)	3,612 (57)
6-7	23 (16)	58 (19)	150 (22)	239 (21)	2,707 (21)	1,231 (20)
≥8	26 (18)	61 (20)	280 (40)	429 (37)	3,262 (25)	1,439 (23)

†Assessed in the 3 months before or on the index date; ††the number of all different pharmacological subgroups (ATC 3rd level) excluding antithrombotic agents (ATC B01A).

Comments to Figure 4.2 and Table 4.5:

- In PHARMO, after a switch from a BID to QD dosage regimen patients were slightly more persistent from approximately 6 months after switch onwards compared to patients switching from a QD to BID dosage regimen. Among patients older than 75 years, this difference was slightly larger (see Figure 6.4).
- In ARS, there was no difference in proportion of persistent users among the QD group and BID group after a dosage regimen switch. Among patients older than 75 years, after a switch from a BID to QD dosage regimen patients were slightly more persistent compared to patients switching from a QD to a BID dosage regimen (see Figure 6.4).
- In GePaRD, after a switch from a BID to QD dosage regimen patients were clearly more persistent compared to patients switching from a QD to a BID dosage regimen. Among older patients, this difference was slightly larger (see Figure 6.3 and Figure 6.4).
- General characteristics did not largely differ between patients switching from a BID to a QD dosage regimen compared to patients switching form a QD to a BID dosage regimen. This was similar among older patients (Table 6.6 and Table 6.7).

4.4 Switching patterns

Table 4.6: Type of switches among DOAC users after index date, stratified by database and index dosage regimen

	PHARMO (NL) QD N = 1,907 n (%)	PHARMO (NL) BID N = 4,161 n (%)	*p* value QD vs. BID	ARS (IT) QD N = 13,017 n (%)	ARS (IT) BID N = 19,243 n (%)	*p* value QD vs. BID	GePaRD (DE) QD N = 102,422 n (%)	GePaRD (DE) BID N = 65,023 n (%)	*p* value QD vs. BID
Dosage regimen switch	147 (8)	308 (7)	0.6740	694 (5)	1,155 (6)	0.0110	13,065 (13)	6,282 (10)	<.0001
BID/QD cluster switch[†]	1 (<0.5)	5 (<0.5)	0.4358	12 (<0.5)	43 (<0.5)	0.0005	70 (<0.5)	173 (<0.5)	<.0001
No switch	1,760 (92)	3,853 (93)	0.6740	12,323 (95)	18,088 (94)	0.0110	89,357 (87)	58,741 (90)	<.0001

[†]BID/QD cluster switches were assessed relative to the cluster of the index drug.

Table 4.7: Switching patterns among DOAC users after index date, stratified by database

	PHARMO (NL)					ARS (IT)					GePaRD (DE)				
Index drug	**N**	Edoxaban, QD **n (%)**	Rivaroxaban, QD **n (%)**	Apixaban, BID **n (%)**	Dabigatran, BID **n (%)**	**N**	Edoxaban, QD **n (%)**	Rivaroxaban, QD **n (%)**	Apixaban, BID **n (%)**	Dabigatran, BID **n (%)**	**N**	Edoxaban, QD **n (%)**	Rivaroxaban, QD **n (%)**	Apixaban, BID **n (%)**	Dabigatran, BID **n (%)**
Edoxaban, QD	48	-	1 (2)	3 (6)	1 (2)	3,139	-	2 (<0.5)	63 (2)	50 (2)	1,028	-	2 (<0.5)	63 (6)	10 (1)
Rivaroxaban, QD	1,859	0 (0)	-	58 (3)	85 (5)	9,878	10 (<0.5)	-	398 (4)	183 (2)	101,394	68 (<0.5)	-	10,281 (10)	2,712 (3)
Apixaban, BID	1,081	7 (1)	34 (3)	-	2 (<0.5)	9,340	139 (1)	145 (2)	-	9 (<0.5)	40,843	480 (1)	1,649 (4)	-	59 (<0.5)
Dabigatran, BID	3,080	21 (1)	246 (8)	3 (<0.5)	-	9,903	297 (3)	574 (6)	34 (<0.5)	-	24,180	409 (2)	3,744 (15)	114 (<0.5)	-

Note: switches highlighted in blue and orange represent BID/QD cluster and dosage regimen switches, respectively. In case of multiple dosage regimen or BID/QD cluster switches during follow-up, only the first per switch type is presented.

Comments to Table 4.6 and Table 4.7:

- In all databases, the majority of patients (about 90%) did not switch during follow-up.
- In PHARMO, switches from QD to BID occurred equally frequent as switches from BID to QD (8% and 7% of the patients respectively). Dabigatran and apixaban users mostly switched to rivaroxaban. Rivaroxaban users mostly switched to dabigatran; edoxaban users mostly switched to apixaban.
- In ARS, 5% of the QD users and 6% of the BID users switched from dosage regimen. Dabigatran users mostly switched to rivaroxaban here as well. Apixaban users switched equally often to edoxaban as to rivaroxaban. RIvaroxaban users mostly switched to apixaban; and edoxaban users switched equally often to apixaban as to dabigatran.
- In GePaRD, 13% of the QD users and 10% of the BID users switched from dosage regimen. Dabigatran and apixaban users mostly switched to rivaroxaban here as well. Edoxaban and rivaroxaban users mostly switched to apixaban.
- In all databases, only very few patients (<0.5%) switched within QD or BID clusters.

5. References

1. Raparelli V, Proietti M, Cangemi R, Lip GY, Lane DA, Basili S. Adherence to oral anticoagulant therapy in patients with atrial fibrillation. Focus on non-vitamin K antagonist oral anticoagulants. *Thrombosis and haemostasis* 2017; **117**(2): 209-18.
2. Alberts MJ, Peacock WF, Fields LE, et al. Association between once- and twice-daily direct oral anticoagulant adherence in nonvalvular atrial fibrillation patients and rates of ischemic stroke. *International journal of cardiology* 2016; **215**: 11-3.
3. Forslund T, Wettermark B, Hjemdahl P. Comparison of treatment persistence with different oral anticoagulants in patients with atrial fibrillation. *European journal of clinical pharmacology* 2016; **72**(3): 329-38.
4. Laliberté F, Bookhart BK, Nelson WW, et al. Impact of once-daily versus twice-daily dosing frequency on adherence to chronic medications among patients with venous thromboembolism. *The patient* 2013; **6**(3): 213-24.
5. Herings R, Pedersen L. Pharmacy-based Medical Record Linkage Systems. In: Strom B, Kimmel S, Hennessy S, eds. Pharmacoepidemiology. 5 ed: John Wiley & Sons, Ltd.; 2012: 270-86.
6. van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, et al. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. *Eur J Cancer* 2010; **46**(2): 395-404.
7. WHO Anatomical Therapeutic Chemical Classification System [www.whocc.no/atc_ddd_index].
8. International Classification of Primary Care [https://www.nhg.org/themas/artikelen/icpc].
9. Czwikla J, Jobski K, Schink T. The impact of the lookback period and definition of confirmatory events on the identification of incident cancer cases in administrative data. *BMC medical research methodology* 2017; **17**(1): 122.
10. Ohlmeier C, Langner I, Garbe E, Riedel O. Validating mortality in the German Pharmacoepidemiological Research Database (GePaRD) against a mortality registry. *Pharmacoepidemiology and drug safety* 2016; **25**(7): 778-84.
11. Ohlmeier C, Langner I, Hillebrand K, et al. Mortality in the German Pharmacoepidemiological Research Database (GePaRD) compared to national data in Germany: results from a validation study. *BMC public health* 2015; **15**: 570.
12. Jobski K, Behr S, Garbe E. Drug interactions with phenprocoumon and the risk of serious haemorrhage: a nested case-control study in a large population-based German database. *European journal of clinical pharmacology* 2011; **67**(9): 941-51.
13. Jobski K, Enders D, Amann U, et al. Use of rivaroxaban in Germany: a database drug utilization study of a drug started in hospital. *European journal of clinical pharmacology* 2014; **70**(8): 975-81.
14. CHMP. Summary of positive opinion (post authorisation) on Pradaxa (dabigatran etexilate mesilate). 2011.
15. CHMP. Summary of positive opinion (post authorisation) on Xarelto (rivaroxaban). 2011.
16. CHMP. Summary of positive opinion (post authorisation) on Eliquis (apixaban). 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/002148/WC500132869.pdf.
17. CHMP. Summary of positive opinion (initial authorisation) on Lixiana (edoxaban). 2015.

6. Appendix

6.1 Code list

Table 6.1: Diagnostic codes for identification of AF

Coding system	Code	Description
ICD-9-CM	427.31	Atrial fibrillation
	427.32	Atrial 'flutter'
ICD-10	I48	Atrial fibrillation and flutter
ICPC	K78	Atrial fibrillation/flutter
WCIA*	3451	Main treating physician for atrial fibrillation
	3452	Check-up frequency atrial fibrillation
	3656	Type of atrial fibrillation
	3838	Participation in atrial fibrillation managed care program
Free text	N.A.	Search terms: “fibri”, “atrium”, “flutt”, “fladd”, “AF”.†

*According to http://aut.nhg.org/labcodeviewer; †Extended or refined search terms were applied based on data findings.

6.2 Stratified results

Table 6.2: Adherence and persistence among DOAC users, stratified by database and index dosage regimen - among patients aged ≥65 years at index date

	PHARMO (NL)			ARS (IT)			GePaRD (DE)		
	QD N = 1,439	**BID N = 3,161**	***p* value QD vs. BID**	**QD N = 11,678**	**BID N = 17,598**	***p* value QD vs. BID**	**QD N = 84,426**	**BID N = 54,967**	***p* value QD vs. BID**
Number of dispensings per patient*, n (%)			0.1368			<.0001			<.0001
1	86 (6)	170 (5)		433 (4)	585 (3)		10,470 (12)	5,111 (9)	
2-5	179 (12)	423 (13)		832 (7)	1,099 (6)		19,014 (23)	10,519 (19)	
6-9	403 (28)	795 (25)		735 (6)	778 (4)		23,533 (28)	14,869 (27)	
≥10	771 (54)	1,773 (56)		9,678 (83)	15,136 (86)		31,409 (37)	24,468 (45)	
Persistence, n (%)									
At 3 months	1,223 (85)	2,670 (84)	0.6486	5,308 (45)	7,529 (43)	0.0004	67,049 (79)	30,336 (55)	<.0001
At 6 months	1,068 (74)	2,330 (74)	0.7165	3,142 (27)	4,601 (26)	0.4184	52,895 (63)	22,891 (42)	<.0001
At 9 months	970 (67)	2,128 (67)	0.9532	2,203 (19)	3,370 (19)	0.1775	45,677 (54)	19,423 (35)	<.0001
At 12 months	890 (62)	1,954 (62)	0.9832	1,626 (14)	2,531 (14)	0.0533	40,341 (48)	17,057 (31)	<.0001
At end of follow-up	655 (46)	1,307 (41)	0.0080	433 (4)	446 (3)	<.0001	23,623 (28)	10,863 (20)	<.0001
Patients for whom PDC is determined, n (%)**	**1,353 (94)**	**2,991 (95)**		**11,245 (96)**	**17,013 (97)**		**73,956 (88)**	**49,856 (91)**	
Exposure period (months)**									
Mean ± SD	24 ± 14	25 ± 16	0.0018	25 ± 15	29 ± 16	<.0001	23 ± 13	22 ± 13	<.0001
Median (IQR)	21 (13-33)	22 (14-35)		22 (14-35)	28 (17-41)		22 (13-33)	20 (13-30)	
PDC during exposure period**									
Mean ± SD	0.96 ± 0.11	0.95 ± 0.13	0.0004	1 ± 0	1 ± 0	<.0001	0.89 ± 0.18	0.77 ± 0.24	<.0001
Median (IQR)	1.00 (0.98-1.00)	1.00 (0.96-1.00)		1.00 (0.95-1.00)	1.00 (0.93-1.00)		0.99 (0.82-1.00)	0.88 (0.52-1.00)	

	PHARMO (NL)			ARS (IT)			GePaRD (DE)		
	QD N = 1,439	BID N = 3,161	*p* value QD vs. BID	QD N = 11,678	BID N = 17,598	*p* value QD vs. BID	QD N = 84,426	BID N = 54,967	*p* value QD vs. BID
n (%) adherent (PDC ≥0.8)	1,274 (94)	2,755 (92)	0.0158	10,307 (88)	15,215 (86)	<.0001	57,044 (77)	28,069 (56)	<.0001
PDC during 12 months of follow-up**									
Mean ± SD	0.97 ± 0.09	0.96 ± 0.11	0.0002	0.95 ± 0.13	0.95 ± 0.12	0.0088	0.91 ± 0.16	0.79 ± 0.24	<.0001
Median (IQR)	1.00 (0.99-1.00)	1.00 (0.98-1.00)		1.00 (0.98-1.00)	1.00 (0.97-1.00)		1.00 (0.87-1.00)	0.92 (0.54-1.00)	
n (%) adherent (PDC ≥0.8)	1,277 (95)	2,753 (93)	0.0085	10,425 (89)	15,545 (88)	0.0001	59,599 (82)	29,415 (60)	<.0001

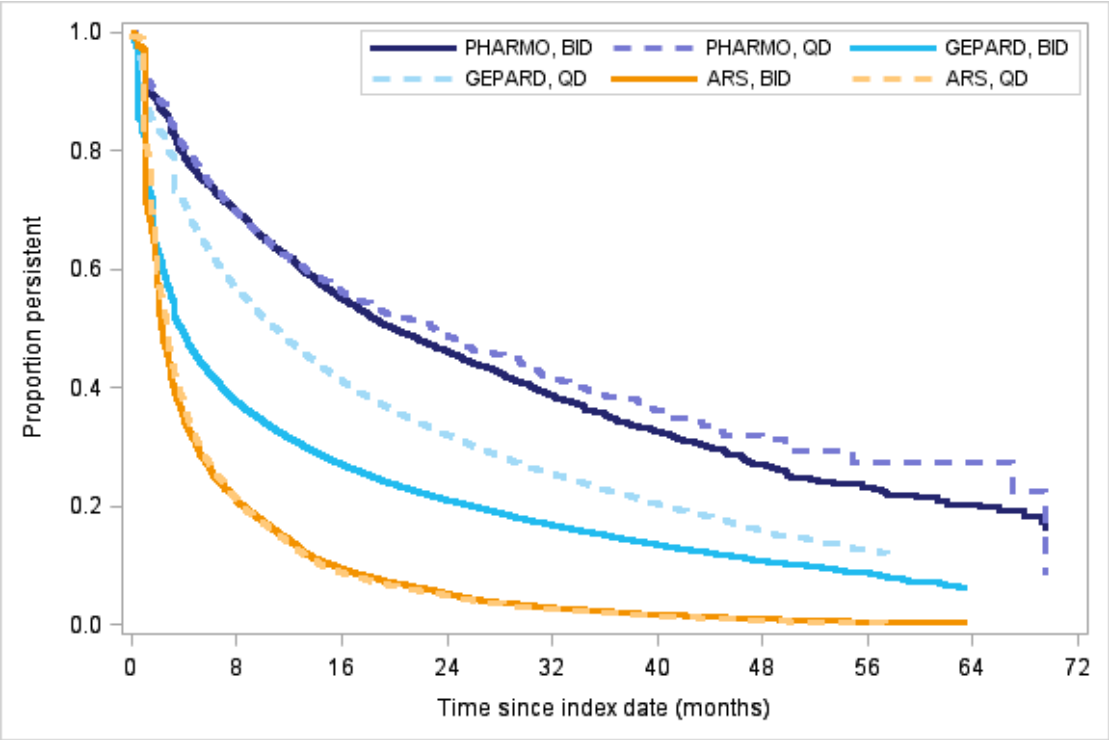
*Assessed within the exposure period; **Assessed among patients with >1 dispensing in the exposure period.

Table 6.3: Adherence and persistence among DOAC users, stratified by database and index dosage regimen- among patients aged ≥75 years

	PHARMO (NL)			ARS (IT)			GePaRD (DE)		
	QD N = 612	BID N = 1,478	*p* value QD vs. BID	QD N = 8,519	BID N = 12,731	*p* value QD vs. BID	QD N = 53,007	BID N = 36,008	*p* value QD vs. BID
Number of dispensings per patient*, n (%)			0.2298			<.0001			<.0001
1	38 (6)	83 (6)		331 (4)	468 (4)		6,380 (12)	3,223 (9)	
2-5	67 (11)	211 (14)		664 (8)	868 (7)		11,956 (23)	6,735 (19)	
6-9	158 (26)	375 (25)		602 (7)	603 (5)		15,307 (29)	9,832 (27)	
≥10	349 (57)	809 (55)		6,922 (81)	10,792 (85)		19,364 (37)	16,218 (45)	
Persistence, n (%)									
At 3 months	519 (85)	1,233 (83)	0.4354	3,932 (46)	5,304 (42)	0.0004	41,640 (79)	17,920 (50)	<.0001
At 6 months	458 (75)	1,066 (72)	0.2042	2,322 (27)	3,194 (25)	0.4184	32,723 (62)	13,385 (37)	<.0001
At 9 months	409 (67)	975 (66)	0.7044	1,625 (19)	2,303 (18)	0.1775	28,022 (53)	11,312 (31)	<.0001
At 12 months	374 (61)	897 (61)	0.8576	1,191 (14)	1,733 (14)	0.0533	24,532 (46)	9,846 (27)	<.0001
At end of follow-up	266 (43)	588 (40)	0.1193	307 (4)	324 (3)	<.0001	14,016 (26)	6,055 (17)	<.0001
Patients for whom PDC is determined, n (%)**	**574 (94)**	**1,395 (94)**		**8,188 (96)**	**12,263 (96)**		**46,627 (88)**	**32,785 (91)**	

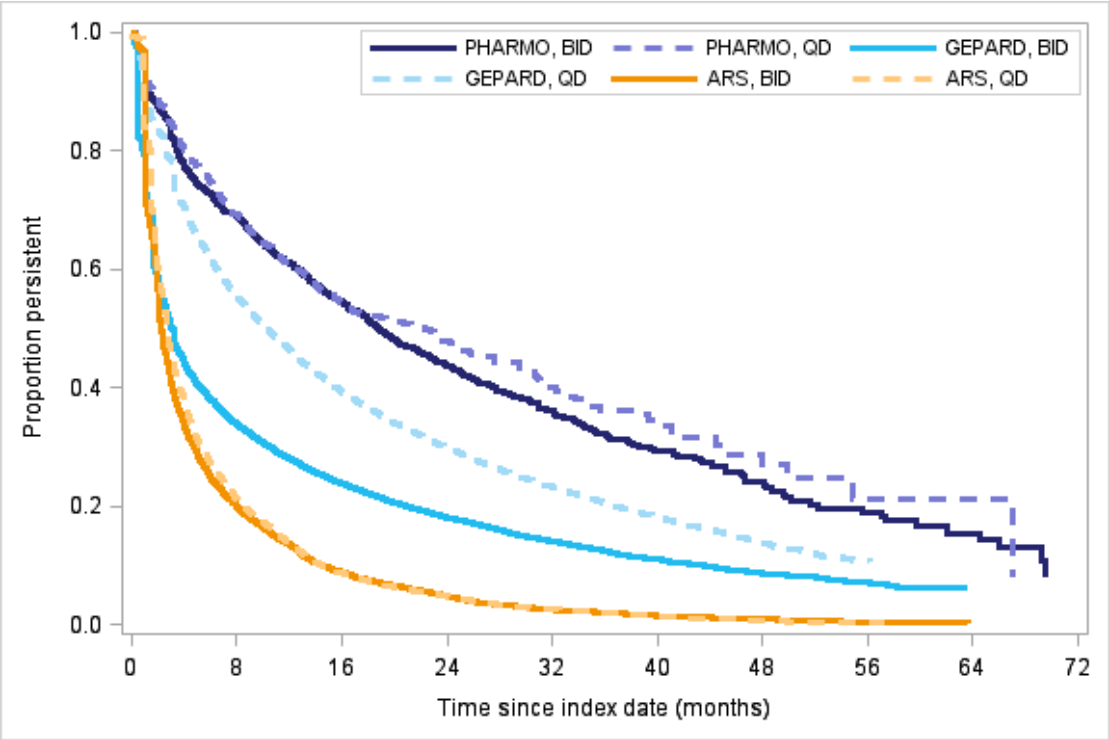
	PHARMO (NL)			ARS (IT)			GePaRD (DE)		
	QD N = 612	BID N = 1,478	*p* value QD vs. BID	QD N = 8,519	BID N = 12,731	*p* value QD vs. BID	QD N = 53,007	BID N = 36,008	*p* value QD vs. BID
Exposure period (months)**									
Mean ± SD	23 ± 14	23 ± 15	0.7332	24 ± 15	28 ± 16	<.0001	22 ± 13	21 ± 12	<.0001
Median (IQR)	21 (14-31)	20 (13-31)		21 (13-34)	26 (16-39)		21 (13-32)	19 (13-28)	
PDC during exposure period**									
Mean ± SD	0.97 ± 0.10	0.95 ± 0.13	0.0009	0.94 ± 0.15	0.93 ± 0.14	<.0001	0.88 ± 0.18	0.74 ± 0.25	<.0001
Median (IQR)	1.00 (0.98-1.00)	1.00 (0.96-1.00)		1.00 (0.95-1.00)	1.00 (0.93-1.00)		0.98 (0.79-1.00)	0.81 (0.50-1.00)	
n (%) adherent (PDC ≥0.8)	549 (96)	1,279 (92)	0.0020	7,472 (88)	10,892 (86)	<.0001	34,573 (74)	16,553 (50)	<.0001
PDC during 12 months of follow-up**									
Mean ± SD	0.97 ± 0.08	0.95 ± 0.12	0.0025	0.95 ± 0.14	0.95 ± 0.12	0.0088	0.90 ± 0.16	0.76 ± 0.25	<.0001
Median (IQR)	1.00 (0.99-1.00)	1.00 (0.98-1.00)		1.00 (0.98-1.00)	1.00 (0.96-1.00)		1.00 (0.83-1.00)	0.86 (0.51-1.00)	
n (%) adherent (PDC ≥0.8)	544 (95)	1,280 (92)	0.0197	7,559 (89)	11,113 (87)	0.0001	36,456 (79)	17,441 (54)	<.0001

*Assessed within the exposure period; **Assessed among patients with >1 dispensing in the exposure period.



Months	0	8	16	24	32	40	48	56	64	72
Nat risk	1,439	1,000	673	409	224	103	41	11	5	-
Nat risk	3,161	2,195	1,479	871	508	265	118	71	33	-
$N_{at\ risk}$	11,678	2,470	919	392	168	60	20	4	0	-
$N_{at\ risk}$	17,598	3,693	1,582	774	357	158	70	23	3	-
$N_{at\ risk}$	84,426	47,724	30,709	17,817	9,841	4,371	769	129	-	-
$N_{at\ risk}$	54,967	20,349	12,277	6,214	3,068	1,231	247	83	-	-

Figure 6.1: Kaplan-Meier curve showing the proportion of patients persistent with the QD and BID dosage regimen for DOACs, stratified by database and index dosage regimen - among patients aged ≥65 years at index date



Months	0	8	16	24	32	40	48	56	64	72
Nat risk	612	424	283	177	86	37	16	-	-	-
Nat risk	1,478	1,010	671	363	197	98	47	26	13	-
$N_{at\ risk}$	8,519	1,817	663	274	120	42	15	4	0	-
$N_{at\ risk}$	12,731	2,542	1,068	508	218	94	43	13	1	-
$N_{at\ risk}$	53,007	29,391	18,276	10,061	5,344	2,284	344	54	-	-
$N_{at\ risk}$	36,008	11,872	7,049	3,420	1,650	679	136	43	-	-

Figure 6.2: Kaplan-Meier curve showing the proportion of patients persistent with the QD and BID dosage regimen for DOACs, stratified by database and index dosage regimen - among patients aged ≥75 years at index date

Table 6.4: Adherence among DOAC users before and after a dosage regimen switch, stratified by database and type of dosage regimen switch – among patients aged ≥65 years at index date

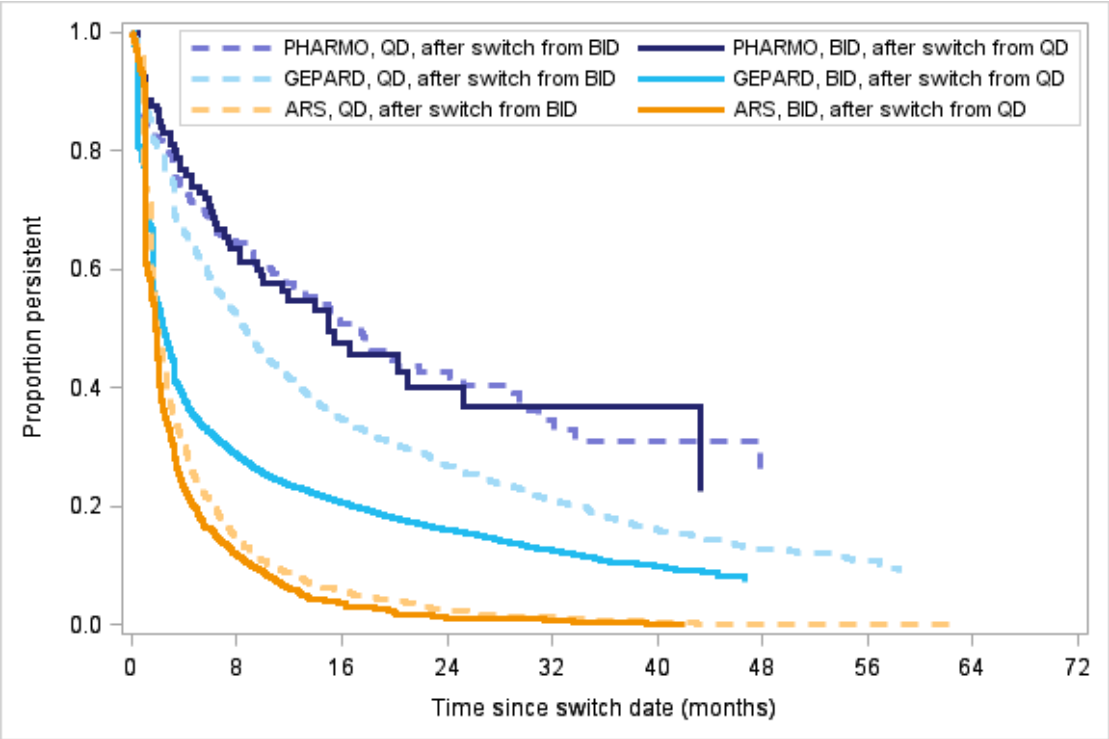
	PHARMO (NL)			ARS (IT)			GePaRD (DE)		
	Before[†]	**After**[‡]	***p* value before vs. after**	**Before**[†]	**After**[‡]	***p* value before vs. after**	**Before**[†]	**After**[‡]	***p* value before vs. after**
Patients with a switch from QD to BID (N)*	**80**	**80**		**498**	**498**		**6,965**	**6,965**	
Exposure period (months)									
Mean ± SD	9 ± 10	16 ± 13	0.0002	12 ± 12	15 ± 13	0.0006	12 ± 11	13 ± 10	<.0001
Median (IQR)	5 (1-14)	12 (6-23)		9 (3-18)	12 (4-24)		9 (3-19)	11 (5-20)	
PDC during exposure period									
Mean ± SD	0.95 ± 0.13	0.96 ± 0.11	0.6896	0.95 ± 0.13	0.94 ± 0.13	0.2884	0.89 ± 0.19	0.71 ± 0.25	<.0001
Median (IQR)	1.00 (0.98-1.00)	1.00 (0.97-1.00)		1.00 (0.97-1.00)	1.00 (0.96-1.00)		1.00 (0.83-1.00)	0.71 (0.50-0.99)	
n (%) adherent (PDC ≥0.8)	74 (93)	76 (95)	0.5136	465 (93)	454 (91)	0.1923	5,427 (78)	3,125 (45)	<.0001
Patients with a switch from BID to QD (N)*	**176**	**176**		**872**	**872**		**3,016**	**3,016**	
Exposure period (months)									
Mean ± SD	12 ± 14	15 ± 14	0.0122	16 ± 15	17 ± 15	0.6538	9 ± 10	18 ± 14	<.0001
Median (IQR)	7 (2-16)	12 (5-21)		12 (4-25)	13 (5-24)		6 (2-13)	13 (6-28)	
PDC during exposure period									
Mean ± SD	0.92 ± 0.18	0.94 ± 0.15	0.2259	0.94 ± 0.14	0.96 ± 0.13	0.0022	0.83 ± 0.22	0.88 ± 0.18	<.0001
Median (IQR)	1.00 (0.96-1.00)	1.00 (0.99-1.00)		1(0.94-1.00)	1.00 (0.98-1.00)		0.95 (0.70-1.00)	0.99 (0.79-1.00)	
n (%) adherent (PDC ≥0.8)	152 (86)	163 (93)	0.0559	789 (90)	820 (94)	0.0055	1,998 (66)	2,258 (75)	<.0001

[†]Before first recorded switch; [‡]From the first recorded switch until end of the treatment episode; *Among patients with >1 dispensing in both exposure periods of interest (i.e. before and after switch).

Table 6.5: Adherence among DOAC users before and after a dosage regimen switch, stratified by database and type of dosage regimen switch – among patients aged ≥75 years at index date

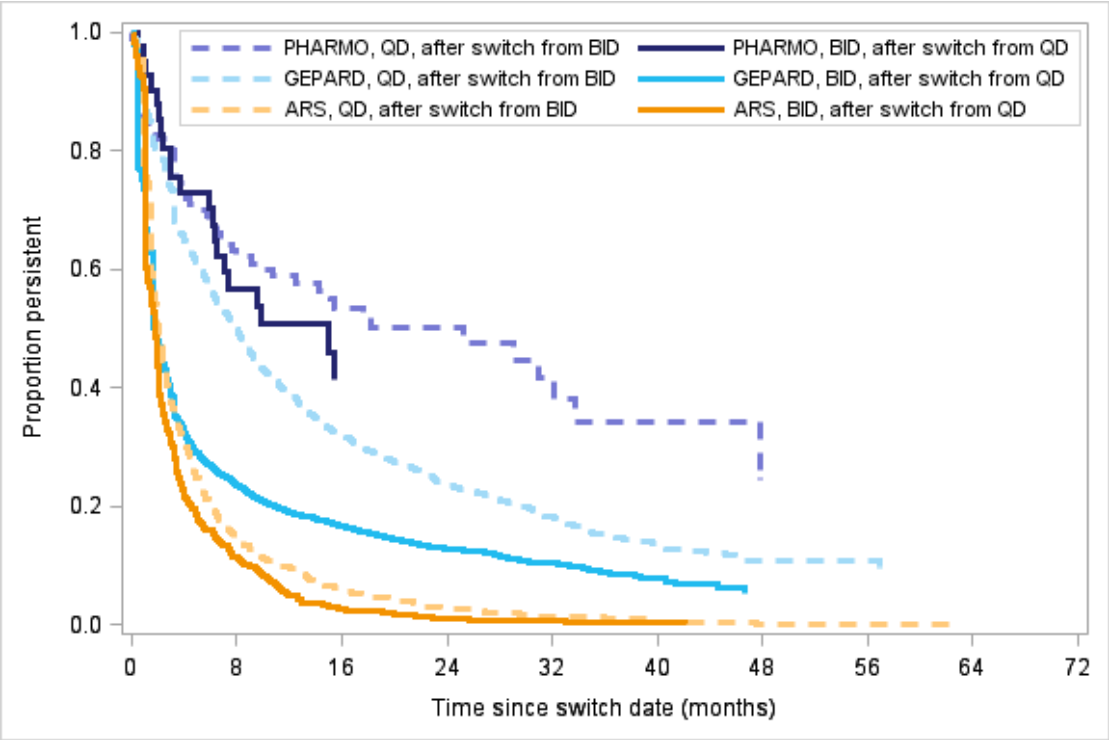
	PHARMO (NL)			ARS (IT)			GePaRD (DE)		
	Before[†]	After[‡]	*p* value before vs. after	Before[†]	After[‡]	*p* value before vs. after	Before[†]	After[‡]	*p* value before vs. after
Patients with a switch from QD to BID (N)*	**32**	**32**		**349**	**349**		**4,532**	**4,532**	
Exposure period (months)									
Mean ± SD	10 ± 11	13 ± 10	0.2409	12 ± 12	15 ± 13	0.0117	12 ± 10	13 ± 10	0.0019
Median (IQR)	5 (1-14)	11 (4-20)		9 (3-18)	12 (4-24)		9 (3-19)	11 (5-19)	
PDC during exposure period									
Mean ± SD	0.95 ± 0.13	0.97 ± 0.07	0.4623	0.95 ± 0.12	0.94 ± 0.14	0.0714	0.89 ± 0.18	0.67 ± 0.25	<.0001
Median (IQR)	1.00 (0.98-1.00)	1.00 (0.99-1.00)		1.00 (0.97-1.00)	1.00 (0.94-1.00)		1.00 (0.82-1.00)	0.57 (0.48-0.96)	
n (%) adherent (PDC ≥0.8)	30 (94)	31 (97)	0.5543	326 (93)	313 (90)	0.0771	3,493 (77)	1,675 (37)	<.0001
Patients with a switch from BID to QD (N)*	**78**	**78**		**612**	**612**		**1,906**	**1,906**	
Exposure period (months)									
Mean ± SD	12 ± 13	14 ± 12	0.2267	16 ± 15	16 ± 14	0.8991	9 ± 10	17 ± 14	<.0001
Median (IQR)	7 (2-17)	12 (5-18)		11 (3-24)	12 (4-22)		6 (2-13)	13 (5-26)	
PDC during exposure period									
Mean ± SD	0.93 ± 0.16	0.97 ± 0.10	0.0636	0.93 ± 0.15	0.96 ± 0.12	0.0008	0.83 ± 0.23	0.88 ± 0.18	<.0001
Median (IQR)	1.00 (0.96-1.00)	1.00 (1.00-1.00)		1.00 (0.94-1.00)	1.00 (0.99-1.00)		0.95 (0.68-1.00)	0.98 (0.78-1.00)	
n (%) adherent (PDC ≥0.8)	70 (90)	75 (96)	0.1179	556 (91)	580 (95)	0.0079	1,280 (67)	1,393 (73)	<.0001

[†]Before first recorded switch; [‡]From the first recorded switch until end of the treatment episode; *Among patients with >1 dispensing in both exposure periods of interest (i.e. before and after switch).



Months	0	8	16	24	32	40	48	56	64	72
Nat risk	246	133	75	39	21	11	5	-	-	-
Nat risk	108	57	25	13	7	-	-	-	-	-
$N_{at\ risk}$	1,069	171	60	30	9	3	1	-	-	-
$N_{at\ risk}$	643	80	21	6	2	0	0	-	-	-
$N_{at\ risk}$	5,433	2,374	1,217	723	423	184	61	22	-	-
$N_{at\ risk}$	11,342	2,427	1,177	542	221	54	6	-	-	-

Figure 6.3: Kaplan-Meier curve showing the proportion of patients persistent with the QD and BID dosage regimen for DOACs after first dosage regimen switch, stratified by database and type of dosage regimen switch – among patients aged ≥65 years at index date



Months	0	8	16	24	32	40	48	56	64	72
Nat risk	117	59	37	20	12	6	-	-	-	-
Nat risk	42	20	8	-	-	-	-	-	-	-
$N_{at\ risk}$	755	109	35	18	3	1	-	-	-	-
$N_{at\ risk}$	452	61	18	5	2	-	-	-	-	-
$N_{at\ risk}$	3,421	1,418	685	382	208	79	23	11	-	-
$N_{at\ risk}$	7,364	1,272	605	281	118	34	-	-	-	-

Figure 6.4: Kaplan-Meier curve showing the proportion of patients persistent with the QD and BID dosage regimen for DOACs after first dosage regimen switch, stratified by database and type of dosage regimen switch – among patients aged ≥75 years at index date

Table 6.6: Sex, age and polypharmacy at index date among patients with a recorded dosage regimen switch, stratified by database and type of dosage regimen switch – among patients aged ≥65 years at index date

	PHARMO (NL)		ARS (IT)		GePaRD (DE)	
	Switch from QD to BID N = 108 n (%)	Switch from BID to QD N = 246 n (%)	Switch from BID to QD N = 643 n (%)	Switch from BID to QD N = 1,069 n (%)	Switch from BID to QD N = 11,342 n (%)	Switch from BID to QD N = 5,433 n (%)
Sex						
Male	56 (52)	113 (46)	295 (46)	502 (47)	5,092 (45)	2,343 (43)
Female	52 (48)	133 (54)	348 (54)	567 (53)	6,250 (55)	3,090 (57)
Age (years)						
Mean ± SD	73 ± 6	75 ± 6	79 ± 7	78 ± 7	77 ± 7	77 ± 7
Median (IQR)	72 (69-77)	74 (69-79)	79 (73-84)	78 (73-83)	77 (73-82)	77 (73-82)
Polypharmacy[†,††]						
0-5	72 (67)	140 (57)	230 (36)	434 (41)	5,945 (52)	3,014 (55)
6-7	16 (15)	49 (20)	146 (23)	224 (21)	2,416 (21)	1,096 (20)
≥8	20 (19)	57 (23)	267 (42)	411 (38)	2,981 (26)	1,323 (24)

[†]Assessed in the 3 months before or on the index date; [††]the number of all different pharmacological subgroups (ATC 3rd level) excluding antithrombotic agents (ATC B01A).

Table 6.7: Sex, age and polypharmacy at index date among patients with a recorded dosage regimen switch, stratified by database and type of dosage regimen switch – among patients aged ≥75 years at index date

	PHARMO (NL)		ARS (IT)		GePaRD (DE)	
	Switch from QD to BID N = 42 n (%)	Switch from BID to QD N = 117 n (%)	Switch from BID to QD N = 452 n (%)	Switch from BID to QD N = 755 n (%)	Switch from BID to QD N = 7,364 n (%)	Switch from BID to QD N = 3,421 n (%)
Sex						
Male	20 (48)	52 (44)	186 (41)	319 (42)	3,084 (42)	1,367 (40)
Female	22 (52)	65 (56)	266 (59)	436 (58)	4,280 (58)	2,054 (60)
Age (years)						
Mean ± SD	80 ± 4	80 ± 4	82 ± 5	82 ± 5	81 ± 5	81 ± 5
Median (IQR)	79 (77-82)	79 (77-83)	82 (79-86)	81 (78-85)	80 (77-85)	80 (77-84)
Polypharmacy†,††						
0-5	26 (62)	57 (49)	145 (32)	279 (37)	3,623 (49)	1,751 (51)
6-7	6 (14)	25 (21)	104 (23)	152 (20)	1,662 (23)	748 (22)
≥8	10 (24)	35 (30)	203 (45)	324 (43)	2,079 (28)	922 (27)

†Assessed in the 3 months before or on the index date; ††the number of all different pharmacological subgroups (ATC 3rd level) excluding antithrombotic agents (ATC B01A).