PHARMO

ARS TOSCANA
agenzia regionale di sanità

BIPS Leibniz

Study protocol

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

Study protocol

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

PHARMO Institute

January 2019

Grant: Daiichi Sankyo Europe GmbH

Version 2.0 confidential

Contact details

Client:	**Daiichi Sankyo Europe GmbH | Clinical Safety & Pharmacovigilance**
Contact:	Pearl Gumbs, PhD, Director Market Access (HEOR)
Address:	Zielstattstr. 48 81379 Munich, Germany
Tel:	+49-(0)89-7808-256 | +49-(0)176 11 7808 41
E-mail:	pearl.gumbs@daiichi-sankyo.eu
Research:	**PHARMO Institute for Drug Outcomes Research** Lisa Smits, MSc, Research Manager Eline Houben, MSc, Research Manager Jelle Evers, MSc, Researcher Fernie Penning-van Beest, PhD, Senior Research Quality Manager Ron Herings, PharmD, PhD, Scientific Director
Address:	Van Deventerlaan 30-40 3528 AE Utrecht, Netherlands
Tel:	+31 (0)30 7440 800
E-mail:	pharmo@pharmo.nl
	Agenzia regionale di sanità della Toscana database Rosa Gini, MSc, PhD
	Leibniz Institute for Prevention Research and Epidemiology - BIPS Dr. Tania Schink

Contents

Contents of figures and tables

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
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 for (QD) versus BID regimens 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 describes the patient selection and methods, including definitions and analyses for the primary objective of the study.

2. Objectives

The primary objectives of this study are to:

- determine the relationship between adherence and QD vs. BID
- determine the relationship between persistence and QD vs. BID
- determine the relationship between adherence and switchers vs. non-switchers
- determine the relationship between persistence and switchers vs. non-switchers
- compare switching patterns for QD and BID

3. Methods

3.1 Data sources

The study will be 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

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. 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 4 million (25%) residents of a well-defined population in the Netherlands for an average of ten years. 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 will be 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 will be performed.

3.3 Patient selection

The source population will include 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, June 30th, 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 will be 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 4th, 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 will be restricted to adult patients (≥18 years at index date) with at least one year of database history at the index date for selection of new users (i.e. no previous dispensing of DOACs in the year before index date, or multiple different DOACs on the index date). Patients will also be required to have 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 will additionally be 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 5.1 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 will be 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 any other treatment regimen (e.g. dabigatran QD or three times daily) or initiating on both QD and BID at the index date will be excluded. In GePaRD, no prescribed dosage regimen is available; therefore the dosage regimen of Table 3.1 will be used here. PHARMO will share interim results of age and gender distributions among these two groups in order to determine whether matching on relevant characteristics will be performed (in consultation with Daiichi).

Patients will be 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 occurs first.

3.4 Patient characteristics

The following patient characteristics will be determined at index date:

- Gender
- 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 or on the index date; ATC B01AA)
- Co-medication (dispensedin 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 will be defined based on the proportion of days covered (PDC) during the exposure period. The exposure period will be 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 will be assessed. PDC will be 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 will be calculated based on the prescribed dosage regimen. In

GePaRD, this will be estimated based on the defined daily dose (DDD). PDC values will range from 0 to 1, with higher values suggesting higher adherence. Mean ± SD and median (IQR) PDC will be 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 will also be determined during a fixed 12 months follow-up period.

Persistence with treatment will be defined as the time from index date to treatment discontinuation and will be based on DOAC treatment episodes (see Section 3.7). Treatment discontinuation will be 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 will be determined at 3, 6, 9 and 12 months after index date. In addition, persistence will be presented in a Kaplan-Meier persistence curve which will also show the median persistence.

For both the assessment of adherence and persistence, switches within the QD or BID clusters will be allowed. In other words, a patients switching from rivaroxaban to edoxaban will still be considered persistent with and adherent to QD treatment. The exposure period and a treatment episode will end 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), measures of adherence and persistence as described above will be assessed before and after the first dosage regimen switch. The period before the first recorded dosage regimen switch will be equal to the exposure period as defined above. The period after switch will be 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. Adherence and persistence after switch will only be determined among patients with at least one year of follow-up relative to the switch date in all required databases.

3.6 Switching patterns

Switching patterns will be assessed from the day after index date until the end of follow-up based on DOAC treatment episodes. This will be 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 will be 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 will be taken into account. Furthermore, the type of DOAC switched to will be assessed on a drug level.

3.7 Treatment episodes

DOAC dispensings will be converted into treatment episodes of uninterrupted use. The duration of each dispensing will be 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 will be 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 will be considered uninterrupted if the duration of this gap is less than half the duration of the preceding dispensing with a minimum of 7 days. The end date of an episode will be 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 precedes the first dispensing of another DOAC, this indicates a switch of treatment, and the former DOAC episode will be cut short at the start of the next DOAC episode. In other words, concomitant use of different DOACs will not be allowed.

3.8 Statistical analyses

The patient selection will be presented in an attrition table with numbers included and excluded in each subsequent step. Exclusions will be reported as absolute numbers as well as percentages of the population size immediately prior to exclusion according to the attrition table. Outcomes will be presented stratified by database and index dosage regimen. Continuous data will be presented as means with SD and median with interquartile range (IQR). Categorical data will be presented as counts (n) and proportions (%). Persistence over time will additionally be 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 will be 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 Student's *t* tests for continuous variables. If deemed appropriate based on distributions, age- and gender-adjusted analyses will be performed in case of unmatched QD and BID DOAC cohorts. At PHARMO, all data will be analyzed using SAS programs organised 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 is used for data processing and analyses. At BIPS, SAS version 9.4 is available for data processing and analysis.

Due to the different database characteristics and coding schemes it is not possible to use one single data extraction algorithm for all the databases. Therefore, each database extracts data locally and transforms them into a simple common data model, i.e. standardised patient and dispensing files, linkable through a unique patient identifier, as defined in a common data

model. The input files – as specified in the common data model – will form the basis for this study. Aggregated data summaries as outlined in Section **Error! Reference source not found.** will be created on site for each database using SAS programs shared by PHARMO. Since ARS does not have a SAS license, ARS will use the SAS programs shared by PHARMO to create transformation programs in R. These R programs will be validated by comparison to the SAS programs using simulated data. PHARMO will combine all aggregated data into a report. The general process of data collection, programming and reporting is illustrated in Figure 3.1.

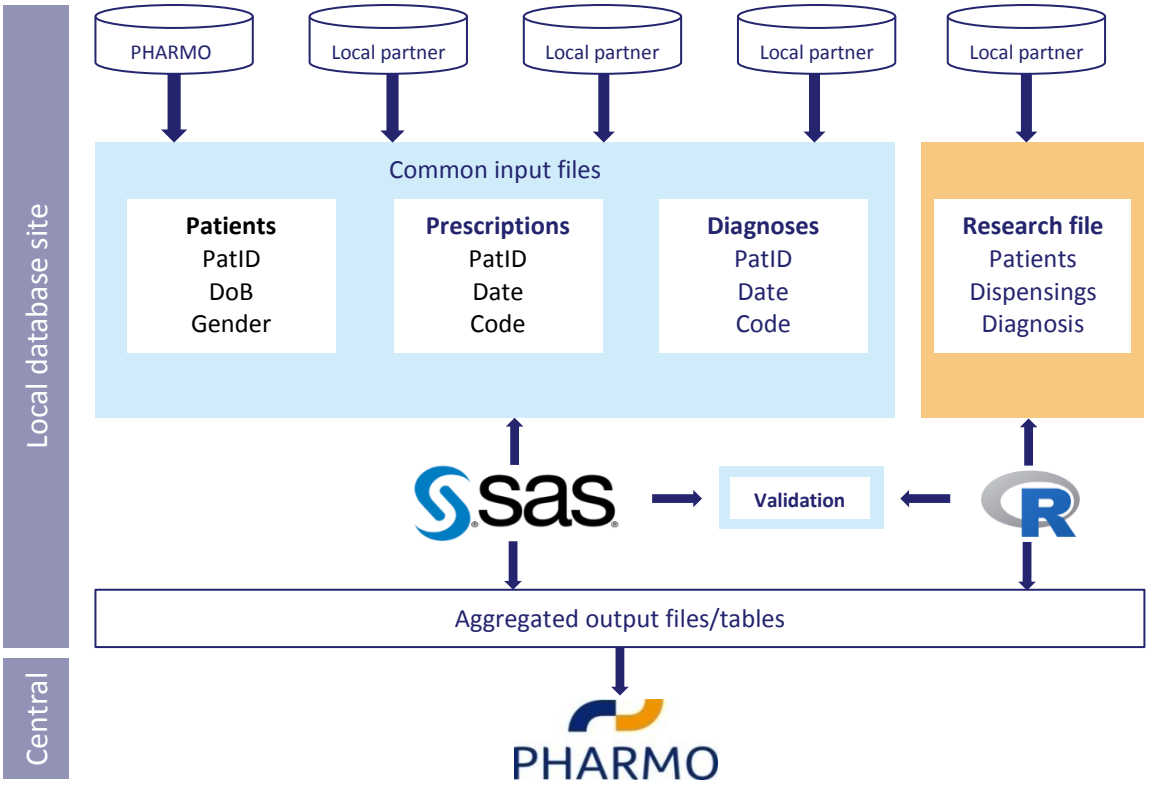

Figure 3.1: Model for multi-database common programming and reporting

4. 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.

5. Appendix

5.1 Code list

Table 5.1: 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 will be applied based on data findings.