Boehringer Ingelheim

Protocol for observational studies based on existing data

	Doc. No.: c02790280-01
BI Study No.:	1160.177
Products:	PRADAXA (dabigatran)
Title:	A description of warfarin and NOAC utilization patterns including initiation, switching, and discontinuation (Phase 3 of the BI/BWH Pradaxa study program)
Team Member Epidemiology:	
Status, Version:	Final Protocol, Version 2.0
Date of Protocol:	**31 July 2014**
Study Sponsor:	**Boehringer Ingelheim GmbH**
Planned Dates of Study:	**Jun 2012 – Jun 2017**

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OBSERVATIONAL STUDY PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim GmbH			
Name of product: PRADAXA®			
Name of active ingredient: dabigatran			
Protocol date 31 July 2014	**Study number** 1160.177	**Planned study period** Jun 2012 – Jun 2017	
Title of study:	A description of warfarin and NOAC utilization patterns including initiation, switching, and discontinuation		
Team Member Epidemiology:			
Project Team:			
Study data source:	UnitedHealth 2009 through 2015 MarketScan 2009 through 2015		
Objectives:	The objective of this study is to provide a description of patients with non-valvular atrial fibrillation at risk for stroke initiating oral anticoagulants and a description of existing utilization patterns for warfarin and for the new oral anticoagulant (NOAC) medications as they become available over time.		
Methodology/Study design:	Observational cohort study		
Expected number of patients:	~ 200,000 (estimated size of the unmatched cohort including warfarin, dabigatran, and other NOACs)		

Main criteria for inclusion:	A recorded diagnosis of atrial fibrillation. Initiation of oral anticoagulant medication. At least 18 years of age on the date of anticoagulant initiation CHA_2DS_2-VASc score ≥ 1

Name of company: Boehringer Ingelheim GmbH			
Name of product: PRADAXA®			
Name of active ingredient: dabigatran			
Protocol date 31 July 2014	**Study number** 1160.177	**Planned study period** Jun 2012 – Jun 2017	
Main criteria for exclusion:	Patients with less than 12 months enrolment in the UnitedHealth Research Database or MarketScan database preceding the date of first dispensing will be excluded. Also excluded will be patients with missing or ambiguous age or sex information. Patients with documented evidence of valvular disease. Patients with prior use of any oral anticoagulant		
Study product:	PRADAXA (dabigatran)		
Comparison group:	Warfarin, and other new oral anticoagulants as they become available		
Expected duration of exposure:	Until treatment discontinuation as observed in the data source; the study objective is to describe observed utilization		
Outcomes:	This study will describe the patient population with non-valvular atrial fibrillation initiating oral anticoagulants and anticoagulants utilization patterns. Utilization measures include: • Number/proportion of patients initiated on specific anticoagulants and anticoagulant doses • Time until treatment discontinuation (gap > 30 days) • Time until treatment switch		

Data Analysis Methods:	Analyses are inherently descriptive in nature. Utilization patterns will be examined overall The initial analyses will be based on currently available data from Jan 2009 – Jun 2012. Subsequent analyses will include additional data in 6-month increments (Jul 2012 – Dec 2015).

PROTOCOL CHANGES

Informed by the first two analyses (Interim Report 1 and 2), the analyses were streamlined to remove redundant information and focus on the main outcomes of interest. The specific changes are documented in the table below.

Date	Version	Type of Change	Comments
31 July 2014	V 2.0	Addition of MarketScan data throughout the document	Added to increase the population size (Synopsis, Study design, Data Sources 3.1)
31 July 2014	V 2.0	Treatment gap to define end of follow-up changed from 6 months to 30 days	Many patients will be censored for administrative reasons before they reach a 6-month treatment gap, reducing the opportunity to observe between-treatment differences. Treatment discontinuation will therefore be evaluated using a 30 day treatment gap instead in the main analysis,
31 July 2014	V 2.0	Prevalence of use was changed to treatment initiation rates	Change implemented to streamline the analyses and focus on the main outcomes of interest (Main analyses 3.6.1)
31 July 2014	V 2.0		
31 July 2014	V 2.0	Persistence over time is considered a secondary outcome	Informed by the first analyses, persistence over time is considered of high importance to describe anticoagulant utilization (Outcomes 3.4 and Main analyses 3.6.1)
31 July 2014	V 2.0	12-month covariate	The covariate assessment period was changed from 6 months to one year for

		assessment period	consistency with the comparative safety protocol (Covariates 3.5)
31 July 2014	V 2.0	Utilization measures are examined in a propensity-matched cohort	To ensure a valid comparison of utilization measures, these measures are examined in a propensity-score matched cohort, rather than in the overall study population (Main analyses 3.6.1)
31 July 2014	V 2.0		
31 July 2014	V 2.0		

1. BACKGROUND[1]

A number of new oral anticoagulants are being developed and marketed to replace vitamin K antagonists (e.g., warfarin), one of the most important drugs in modern medicine.[P12-08021] Unlike vitamin K antagonists, these new drugs do not require dose titration involving intensive therapeutic monitoring of prothrombin time to achieve target anticoagulation within a narrow therapeutic range. In Phase III studies, these drugs were found to be therapeutically advantageous or non-inferior over warfarin; however, little is known about their efficacy relative to one another.[R11-4190; P09-11669; R11-4223] In the coming years, as many as six new anticoagulants could be on the market and a lack of valid comparative evidence will hinder prescriber and payor decision-making.

To date, these drugs have been studied in pre-marketing clinical trials for three separate indications: (1) prevention of stroke and systemic embolism among patients with atrial fibrillation; (2) prevention of deep venous thromboembolism (DVT) among patients undergoing hip or knee replacement therapy; and (3) treatment of venous thromboembolism (VTE). Phase III clinical trials comparing dabigatran, rivaroxaban, and apixaban to warfarin in patients with non-valvular atrial fibrillation (NVAF) have been completed. [R11-4190; P09-11669; R11-4223]

It was hypothesized that the effectiveness and safety of oral anticoagulants in stroke prevention will strongly depend on their use patterns. [P12-08021] A thorough understanding of (1) the existing utilization patterns for warfarin, and changes in this utilization that occur after the introduction of NOACs; (2) differences in utilization patterns between warfarin and NOACs; and (3) differences between specific NOACs, will help with the design, analysis and interpretation of comparative effectiveness and safety studies for the NOAC.

This protocol is for a series of descriptive analyses starting with the cohort of patients with non-valvular atrial fibrillation identified in the currently available Jan 2009- Jun 2012 data, followed by inclusion of additional cohorts identified in 6-month data increments. Such sequential approach will extend initial analyses by allowing (1) examination of shifts in utilization patterns over time, and (2) inclusion of additional NOACs at they become available.

1 A complete list of all abbreviations used in the protocol is provided in Appendix 4

2. OBJECTIVES

To provide an overview of existing utilization patterns for warfarin and the NOAC medications as they become available in patients with non-valvular atrial fibrillation at risk for stroke. Specifically:

-
- Examine treatment initiation, switching and discontinuation.
-
- Update initial analyses on a 6-month basis.

3. STUDY DESIGN

This study will use a cohort design with descriptive analyses, using data from 2009-2015. It will be conducted within two US-based longitudinal healthcare claims databases (MarketScan and UnitedHealth Research Database, see also section 3.1 for more details). Cohort selection and all analyses will be conducted separately within each data source.

3.1 DATA SOURCES

The data source for this project is a combination of claims data from UnitedHealth, a commercial health insurer, and MarketScan, a research claims database from commercial employer-sponsored health plans both of which provide comprehensive medical coverage for members with active policies.

3.2 STUDY POPULATION

From the UnitedHealth Research Database and MarketScan source data, we will identify patients with a recorded diagnosis of non-valvular atrial fibrillation at risk for stroke who initiated anticoagulant medications between January 2009 and June 2012. Additional increments of data will be added as they become available (in 6 month intervals). Data from the time period before dabigatran was launched will be used to describe the characteristics of warfarin patients before the availability of NOAC, and to evaluate a potential shift in characteristics of warfarin patient over time as NOAC enter the market.

Inclusion criteria[2]:

- Any person within the source data who had a diagnosis of atrial fibrillation recorded (ICD-9 Dx code of 427.31, atrial fibrillation) and received a dispensing of an anticoagulant medication (warfarin and dabigatran for the initial analysis; with others to be added as they become available for stroke prevention in later time intervals) in the timeframe of the study.
- The first dispensing is preceded by at least 12 months continuous enrollment in the study database, defined as <32 days enrollment gap using enrollment and disenrollment dates. The study will thus focus on 'new initiators' defined operationally as no dispensing of any anticoagulant in the prior 12 months. Note that new initiators will turn into prevalent users over time.
- Patients' follow-up will end when there is a treatment gap of ≥30 days. If the same patient re-initiates treatment later on – after a treatment gap of ≥12 months –, (s)he may re-enter the cohort at that time (an indicator variable will be created to identify such patients, known as former users).
- 18 years or older at the time of treatment initiation
- CHA_2DS_2-VASc score[3] ≥ 1

Exclusion criteria:

- patients with less than 12 months continuous enrollment in the study database without anticoagulant use before the first dispensing of anticoagulant medication.
- Patients with missing or ambiguous age or sex information.
- Patients with documented evidence of valvular disease defined as at least 1 inpatient or outpatient ICD-9 Dx code of [R11-4334]
  394.x (diseases of mitral valve)
  395.x (diseases of aortic valve)
  396.x (diseases of mitral and aortic valve)
  397.x (diseases of other endocardial structures)
  398.9x (other and unspecified rheumatic heart diseases)
  V42.2 (heart valve replaced by transplant)
  V43.3 (heart valve replaced by a mechanical device/prosthesis)
  OR

2 A full description of all diagnostic and procedure codes included in this protocol is provided in Appendix 3.
3 See Table 7 in section 3.5 for CHA2DS2-VASc components and calculation

ICD-9 procedure code 35.1x (open heart valvuloplasty without replacement), 35.2x (replacement of heart valve) [R03-1232]
OR
one of the following CPT codes:
33660-33665 (atrioventricular valve repair)
33400-33403 (aortic valve valvuloplasty)
33405 (Replacement, aortic valve, with cardiopulmonary bypass; with prosthetic valve other than homograft or stentless valve)
33420-33430 (mitral valve repair/valvuloplasty/replacement)
33460 (valvectomy, tricuspid valve, with cardiopulmonary bypass)
33463-33468 (tricuspid valve repair/valvuloplasty/replacement)
33475 (replacement, pulmonary valve)
33496 (prosthetic valve dysfunction repair)
0257T (implantation of catheter-delivered prosthetic aortic heart valve; open thoracic approach)
0258T (transthoracic cardiac exposure for catheter-delivered aortic valve replacement; without cardiopulmonary bypass)
0259T (transthoracic cardiac exposure for catheter-delivered aortic valve replacement; with cardiopulmonary bypass)
0262T (implantation of catheter-delivered prosthetic pulmonary valve, endovascular approach)

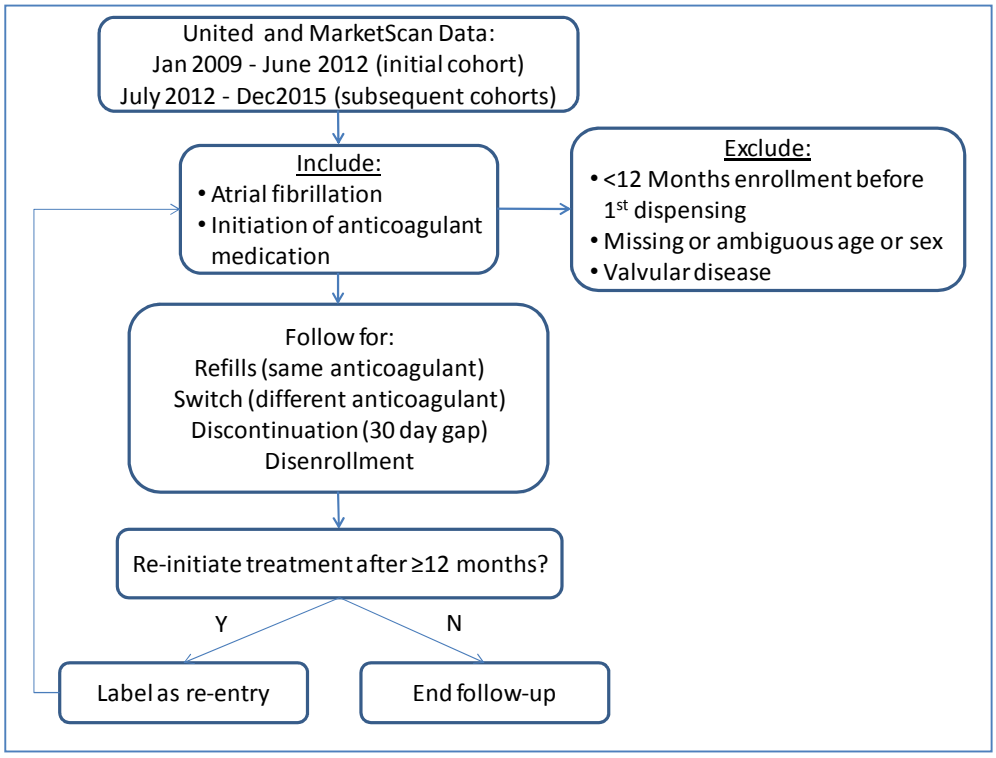


Figure 1 Patient selection flow chart for initial cohort

3.2.1 Study size

This study will be estimating anticoagulant utilization parameters within a sampled population. The precision of these estimates will depend on the numbers of patients on which the estimate is made, and features of the estimate itself. The number of patients receiving anticoagulant medication and meeting study selection criteria is unknown at this stage. However, we assume that between 10,000 and 15,000 patients per year will meet selection criteria as having used warfarin or a newer anticoagulant so that by the end of the study (data from 2009-2015), there will be a total of at least 100,000 patients in each data source. (source: These are projections based on preliminary counts in the available UnitedHealth data)

The precision of proportion estimates (e.g. prevalence) is a function of the proportion and the number of patients contributing to the proportion (precision = standard error = square root[p(1-p)/n]). As indicated in the table below, across a range of estimates provided, the precision for a prevalence estimate of 10% or 20% is less than 5% even for sample sizes that will likely be present in subgroups described in this study.

Table 1 Precision of estimates for proportion measures

Numerator	Denominator	Prevalence	95% CI	Precision (s.e.)
10	100	10%	4.9%-17.6%	3.0%
100	1,000	10%	8.2%-12.0%	0.9%
1,000	10,000	10%	9.4%-10.6%	0.3%
10,000	100,000	10%	9.8%-10.2%	0.1%
20	100	20%	12.7%-29.2%	4.0%
200	1,000	20%	17.6%-22.6%	1.3%
2,000	10,000	20%	19.2%-20.8%	0.4%
20,000	100,000	20%	19.8%-20.2%	0.1%

For continuous measures such as medication possession ratio ((MPR), see Table 3), the precision depends on the number of subjects on whom the estimate is made and the variability of the measures (precision = standard error = square root[standard deviation^2/n]). As indicated in the table, the precision for a continuous measure is 5% or less even for measures that apply to strata that represent subgroups to be defined in this study.

Table 2 Precision of estimates for continuous measures

Sample Size	Mean	SD	Precision (s.e.)
100	1	0.5	5.0%
1,000	1	0.5	1.6%
10,000	1	0.5	0.5%
100,000	1	0.5	0.2%

By the end of the study, with a projected 100,000 patients meeting selection criteria, the various adherence measures will be estimated with a precision of 1% or less, except within fairly small strata.

3.3 EXPOSURES

- Initiation of oral anticoagulant medication (i.e., no use in the prior 12 months) represents the primary exposure.
- Utilization patterns will be defined by individual oral anticoagulant: warfarin and dabigatran for the initial cohort (Jan 2009-June 2012), as well as rivaroxaban and other NOACs as they enter the market within the study time horizon for subsequent cohorts (July 2012- Dec 2015).

3.4 OUTCOMES

Patterns of anticoagulant medication use will be identified on the basis of a pharmacy dispensing. Pharmacy dispensing is considered the most accurate utilization measure short of electronic pillcounting caps. [R13-0543]

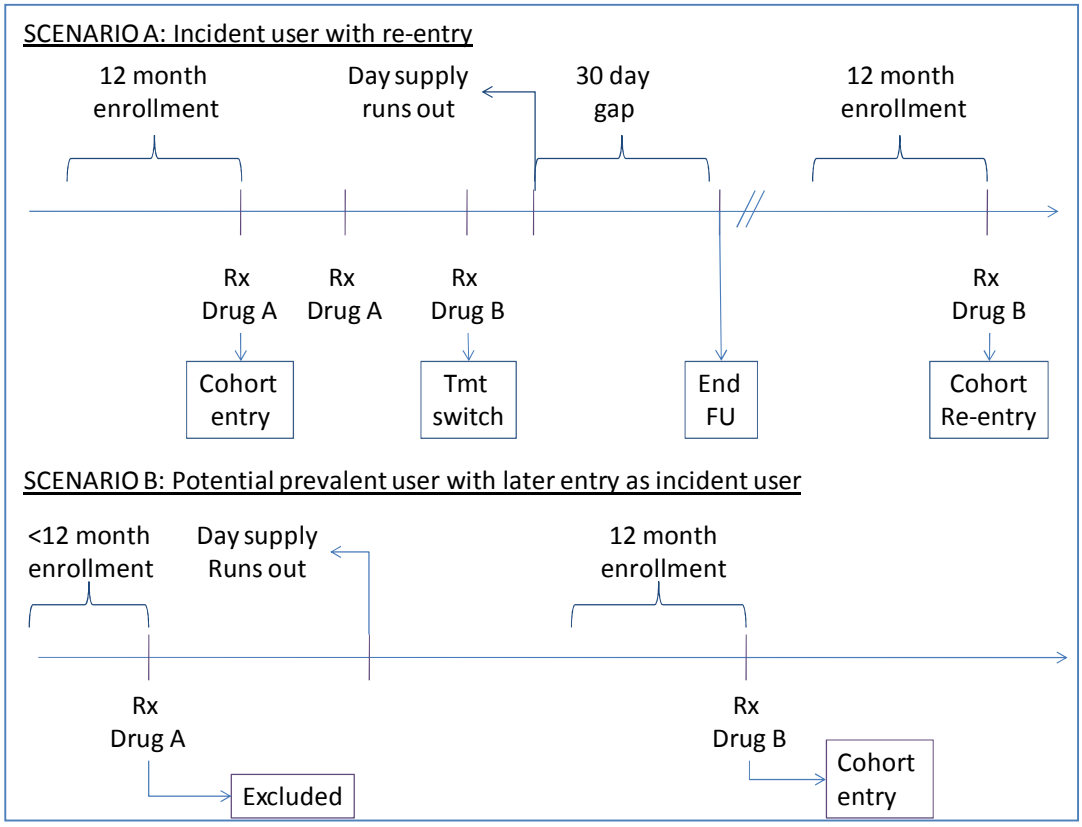
The primary outcomes considered include the proportion of patients dispensed specific anticoagulants and anticoagulant doses (for NOAC), as well as a description of the characteristics of these patients.

In addition, a variety of measures will be derived from features of the dispensing data, including: number of dispensings, characteristics of dispensings (dose, and days supplied), along with persistence measures (e.g., proportion with a single dispensing, proportion remaining on therapy over time, time until treatment switch or discontinuation). [R13-0542; R12-3689; P06-11504] Treatment persistence over time constitutes the secondary outcome.

Table 3 Definition of utilization measures

Measure	**Definition**
Days supplied*	Number of days supplied by a dispensing
Dose**	Presumed dose based on # tablets, mg per tablet, and number of days
One dispensing only	Number (and fraction) of first anticoagulant recipients with no second dispensing
Persistence	Fraction of anticoagulant users with continued dispensings. Patients will be classified as persistent if they possess medication at the specified time point. Grace period of 14 days will be allowed to obtain an additional refill.
Anticoagulant switch	Dispensing of another anticoagulant within <30 days of the end of days supplied of the previous medication
Anticoagulant discontinuation	Treatment gap of ≥30 days (i.e., no dispensing of anticoagulant medication within 30 days of the end of days supplied)

*: Days supply likely reflects use patterns in a commercial insurer such as United Health or MarketScan.
**: Estimation of dose will be challenging during the dose titration period for warfarin. We explore warfarin dose over time and assess the feasibility of estimating average dose, seeking to identify maintenance dose (i.e., dose needed for consistent therapeutic INR).
***:



Notes:
Incident user: Patient with no dispensing of an oral anticoagulant in the prior 12 months
(potential) prevalent user: Patients with <12 months enrollment before first observed dispensing. Since these patients could have been treated in the prior 12 months (treatment status during the unobserved time period is unknown), they are considered 'potential' prevalent patients.

Figure 2 Illustration of cohort entry and subsequent treatment patterns

3.6 DATA ANALYSIS

All analyses will be conducted separately within each database.

3.6.1 Main analyses

Analyses in this protocol are inherently descriptive in nature. The analyses described below will initially be conducted for the base cohort (Jan 2009- June 2012 data). Analyses will be updated at 6-month intervals as more data become available for the existing cohort(s) and new users are identified within the additional time period (July 2012- Dec 2015 data). As new data become available, we will characterize the patients newly initiated on treatment during that time period separately, in order to enable characterization of the shift in patient characteristics and use over time. In addition, short and long-term outcomes for the already existing cohorts (i.e., patients identified in previous time periods) will be updated with the newly available information in terms of switches, discontinuations, adherence and persistence.

A 12-month time window of no treatment is used to define a "new" treatment episode (i.e., incident user). Patients who re-initiate treatment after a treatment gap of ≥ 12 months will re-enter the cohort as former users.

Primary outcomes:

Treatment initiation over time:

The yearly anticoagulation initiation rate will be estimated as the proportion of patients who initiated treatment among the source cohort of patients with non-valvular atrial fibrillation who met the study inclusion criteria and were not already on treatment. To identify the

source cohort of treatment candidates in a given calendar time window (i.e., the denominator for the rate), all patients with at least one day eligibility will be identified. A random date within the first eligibility period (if more than one) within the calendar time window will be selected and set as the index date. The cohort inclusion and exclusion criteria will be evaluated using this index date. Patients who were dispensed an anticoagulant before the assigned index date (prevalent users) will be removed from the denominator, unless they are identified as new initiators (i.e., included in the numerator) for that particular time period.

Characteristics of anticoagulant users:

The analyses will describe the proportion of patients treated with various oral anticoagulants, as well as the characteristics of these patients. For the NOACs, the starting dose will also be considered. Analyses will be conducted

as well for the combined cohort of incident and former users. Characteristics for the combined cohort will be presented in the core set of tables;

Data prior to the launch of dabigatran in October 2010 will be used to characterize warfarin patients before the NOACs became available, and to evaluate the potential shift in patient characteristics over time. A comparison of patient characteristics across treatment groups will only be conducted within a common time window.

Secondary outcomes:

Utilization measures: Non-persistence

To ensure a valid comparison of utilization measures (Table 3), patients exposed to the various NOACs will be matched to warfarin on an exposure propensity score (PS) in a 1:1 fixed ratio using a nearest neighbor technique and a caliper of 0.05. In addition, the patients

will be matched within calendar quarters (3 month periods).

Briefly, all covariates listed in will be included in a logistic regression propensity score (PS) model without further variable selection. In addition to demographic information, variables included in the PS were identified based on the a-priori expectation that they might be both associated with choice of anticoagulant and risk factors for study outcomes so that they represent likely confounding variables in a comparative safety and effectiveness analysis. The underlying assumption is that these variables capture the most important predictors of treatment persistence.

Balance of baseline characteristics in the matched cohorts will be evaluated. The utilization measures included in Table 3 will be described for the PS-matched cohort. To properly account for differential follow-up, survival type analyses (i.e., Kaplan-Meier) will be used to describe time from treatment initiation to non-persistence (discontinuation or switch). Number of patients at risk for this treatment outcome will be provided at 3-month intervals.

The various analyses are summarized below:

Analysis	**Population**	**Outcome measure**	**Outcome type**
Treatment initiation over time	Source population	Yearly initiation rate	Primary
Characteristics of anticoagulant users	Treatment cohort - Unmatched - Matched	Baseline characteristics	Primary
Utilization measures	Matched treatment cohort	- Treatment non-persistence (KM)	Secondary

4. STUDY LIMITATIONS

As an observational study, there are inherent limitations with respect to potential for alternate explanations for any observed association.

The source claims data include limitations with respect to certainty of the capture of exposure, covariates, and outcomes. As a comprehensive insurance database, essentially all billable medical services will result in claims for reimbursement, so that the certainty of capture is tied to likelihood of a claim being submitted to the insurer.

Although duration of atrial fibrillation may represent a risk factor for study outcomes, this covariate will be incompletely captured since the patient history in the dataset is relatively short (at least 12 months, and an average of approximately 2 years), and a first claim within the database may not represent atrial fibrillation onset since the condition is typically not diagnosed at its onset.

Dosing of warfarin in clinical practice is complicated, and estimating dose and duration of exposure based on healthcare utilization data is therefore challenging. The "days' supply" field is expected to be most meaningful, but the potential for misclassification exists.

New initiators are operationally defined as patients with no use in the prior 12 months. This does not ensure, however, that patients have never used anticoagulants; the possibility remains that these patients were treated at some prior time point before they enrolled in United or insurance plans that are part of the MarketScan database.

Medication use in United Healthcare and MarketScan data - as in all administrative healthcare databases - is restricted to prescription drug medication. Consequently, the use of over-the-counter (OTC) medications (e.g., OTC aspirin) is not captured. In addition, exposure is assessed based on prescription pick-up at a pharmacy and might be misclassified in "as treated" analysis if patients do not take their medications. However, misclassification of prescription drug exposure is generally considered less than in other exposure assessment

approaches, including physician prescribing records and patient self-reporting. [P13-03077; P13-03078]

6. QUALITY ASSURANCE AND CONTROL

All aspects of data analysis will be conducted according to standard procedures of the . Programming for this project will be conducted by a primary analyst and validated by a separate analyst (validation analyst). For all data processing and analysis steps, the validation analyst will review the program along with input and output data sets, and for select steps of the project will employ double programming techniques to reduce the potential for programming errors.

7. ETHICAL/SCIENTIFIC APPROVAL

This study will be submitted to the Institutional Review Board (IRB)

8. STUDY MILESTONES AND RESPONSIBILITIES

Date	**Phase 3**		**Data Source**	
	Milestone	**Month**	**United** Claims and lab data are released every 6 months in Jan and Jul (6-month lag time)	**MarketScan** Claims data are released quarterly in Mar, Jun, Sept, and Dec (9-month lag time) *Lab data are released yearly in Dec (12-month lag time*)
	Year 1			
Jun, 2012	Contract	0		
Jul, 2012	Draft Protocol	1		
Mar, 2013	Protocol finalization	9		
Year 2				
Jun, 2013	Draft Interim Report*	12	Jun, 2012	
Aug, 2013	Interim Report	14	Jun, 2012	
Dec, 2013	Interim Report	15	Dec, 2012	
Oct, 2014	Interim Report	20	Jun, 2013	Claims through Mar 2013 Labs through Dec 2012
	Year 3			
Mar,2015	Interim Report	27	Dec, 2013	Claims through Sep 2013 Labs through Dec 2012
Aug, 2015	Interim Report	32	Jun, 2014	Claims through Mar 2014 Labs through Dec 2013
	Year 4			
Mar, 2016	Interim Report	39	Dec, 2014	Claims through Sep 2014 Labs through Dec 2013
Aug, 2016	Interim Report	44	Jun, 2015	Claims through Mar 2015 Labs through Dec 2014
	Year 5			
Jun, 2017	Final Report	54	Dec, 2015	Claims through Dec 2015 Labs through Dec 2014

The reports will include a core set of analyses with corresponding tables and figures that repeat with updated data in each of the 6 monthly blocks.

The interim reports along with the draft and final reports will consist of a description of the methods, including patient selection and variable definitions. This description will be followed by tables for each of the anticoagulant medications, follow-up characteristics (including adherence) and the utilization measures of interest. The tables will be descriptive of all included medications and not include explicit comparisons. The tabular results will be followed by an interpretive summary along with a discussion of the findings and implications.

9. DISTRIBUTION OF RESULTS

Manuscripts describing this work will be submitted for publication in peer-review journals. Findings may also be submitted for presentation at scientific conferences.

10. FUNDING

Boehringer Ingelheim GmbH

11. APPENDICES

11.1 APPENDIX 1: LIST OF FIGURES AND TABLES

List of Core Tables

These tables will be generated separately for United and MarketScan; and will be presented only for incident and former users combined, unless meaningful differences between characteristics of incident and former users are observed.

Table 1 Treatment initiation over time

Table 2 Characteristics of Anticoagulation Users: all time periods combined

Table 3 Characteristics of Anticoagulation users: latest time period

Table 4 Adherence metrics for Anticoagulation users: all time periods combined

Table 5 Adherence metrics for Anticoagulation users: latest time period

Table 6

Table 7 Characteristics of continuers, switchers (combined and by treatment switched to), and discontinuers **at 3 months**: characteristics measured during the 12-months **preceding treatment initiation**.

Table 8 Characteristics of continuers, switchers, and discontinuers at 3 months: characteristics measured during the 3-months immediately **preceding the event** (day of switch, day of discontinuation, day 90 for continuers).

Table 9 Characteristics of continuers, switchers, and discontinuers **at 6 months**: characteristics measured during the 12-months **preceding treatment initiation**.

Table 10 Characteristics of continuers, switchers, and discontinuers at 6 months: characteristics measured during the 3-months immediately **preceding the event** (day of switch, day of discontinuation, day 180 for continuers).

Table 11 Characteristics of continuers, switchers, and discontinuers **at 12 months**: characteristics measured during the 12-months **preceding treatment initiation**.

Table 12 Characteristics of continuers, switchers, and discontinuers at 12 months: characteristics measured during the 3-months immediately **preceding the event** (day of switch, day of discontinuation, day 360 for continuers).

List of Core Figures

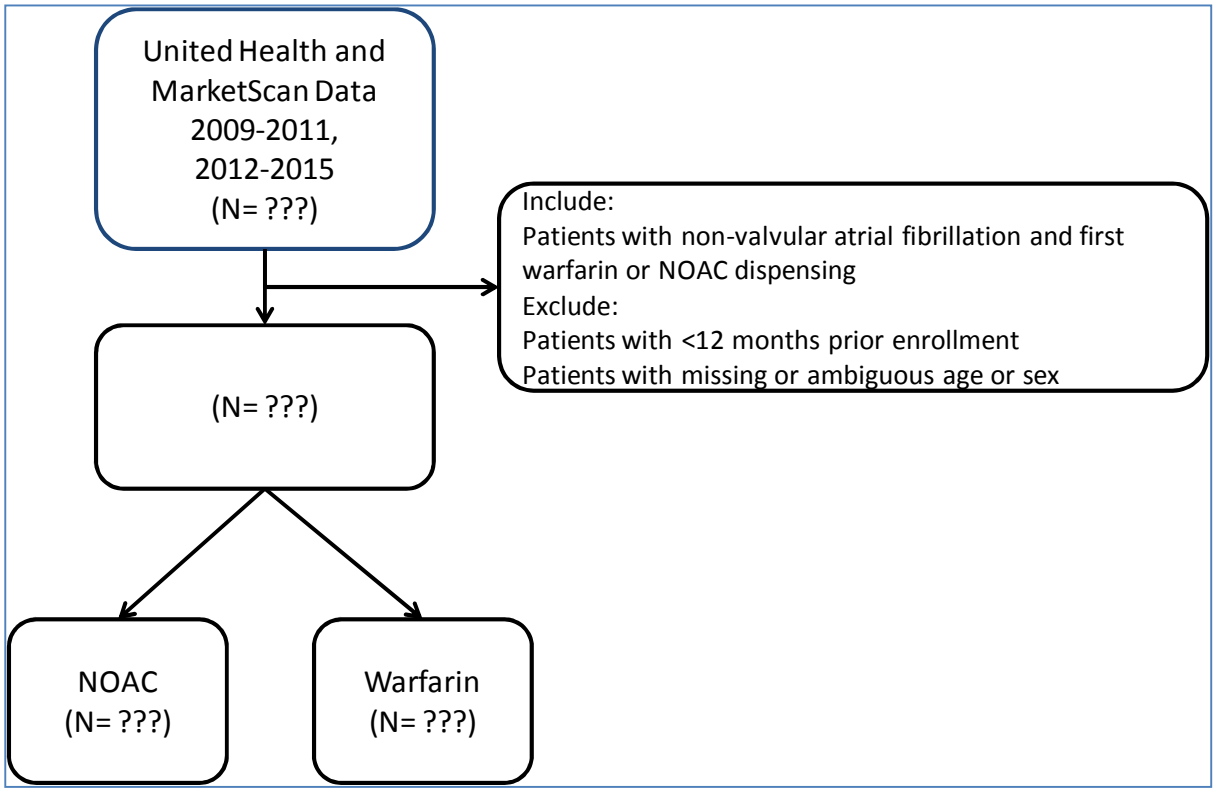
These figures will be generated separately for United and MarketScan

Figure 1: Cumulative incidence of treatment switches - 30 day gap

Figure 2: Cumulative incidence of treatment discontinuation – 30 day gap

Figure 3: Cumulative incidence of treatment switches or discontinuation – 30 day gap

11.2 APPENDIX 2: STUDY FIGURES



NOAC: New Oral Anticoagulant

Figure A1 Patient selection flow diagram (CONSORT Style)

11.4 APPENDIX 4: LIST OF ALL ABBREVIATIONS INCLUDED IN THE PROTOCOL

ACCP	American College of Chest Physicians
ACEI	Angiotensin-converting Enzyme Inhibitor
AES	Advanced Encryption Standard
AF	Atrial Fibrillation
ARB	Angiotensin Receptor Blocker
ASCVD	Atherosclerotic Cardiovascular Disease
BB	Beta Blocker
BI	Boehringer Ingelheim
BMI	Body Mass Index
CAD	Coronary Artery Disease
CCB	Calcium Channel Blocker
CHA_2DS_2-VASc	Congestive Heart Failure, Hypertension, Age > 75, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack, Vascular Disease, Age 65-74, Sex Category
$CHADS_2$	Congestive Heart Failure, Hypertension, Age> 75, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack
CHF	Congestive Heart Failure
CI	Confidence Interval
CONSORT	Consolidated Standards for Reporting Trials
CPT	Current Procedural Terminology
Cr	Creatinine
DM	Diabetes Mellitus
DVT	Deep Venous Thromboembolism
Dx	Diagnosis-Related Group
ESC	European Society of Cardiology
FU	Follow Up
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
H2 Receptor	Histamine H2 Receptor

HAS-BLED	Hypertension, Abnormal Liver/Renal function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (Age >65), Drugs-Alcohol usage
HCPC	Healthcare Common Procedure Coding
ICD-9	International Classification of Diseases, Ninth Revision
INR	International Normalized Ratio
ITT	Intent-To-Treat
MI	Myocardial Infarction
MPR	Medication Possession Ratio
NOAC	New Oral Anticoagulant
NSAID	Non-steroidal Anti-inflammatory Drug
NVAF	Non-valvular Atrial Fibrillation
PAD	Peripheral Artery Disease
PDC	Proportion of Days Covered
PE	Pulmonary Embolism
PPI	Proton Pump Inhibitor
PPV	Positive Predictive Value
PS	Propensity Score
PVD	Peripheral Vascular Disease
PY	Person-Year
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
Rx	Prescription
SCr	Serum Creatinine
SD	Standard Deviation
s.e.	Standard Error
TIA	Trans-Ischemic Attack
US	United States
VTE	Venous Thromboembolism

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