Boehringer Ingelheim

Protocol for observational studies based on existing data

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Title:	Sequential Expansion of Comparative Effectiveness of Oral Anticoagulants: A Cohort Study (Phase 2 of the BI/ Pradaxa study program)
Title for lay people:	Comparative effectiveness of oral anticoagulants
Date of last version of protocol:	25 Feb 2014
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Author / Responsible Parties/BI contact person:	All from the
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Version and Date:	Version 1, 25 Feb 2014

PROTOCOL ABSTRACT

Name of company: Boehringer Ingelheim			Boehringer Ingelheim
Name of product: PRADAXA®			
Name of active ingredient: DABIGATRAN ETEXILATE			
Protocol date:	**Study number:**	**Version/Revision:**	**Version/Revision date:**
25 Feb 2014	1160.207	Version 1	25 Feb 2014

Title of study:	Sequential expansion of comparative effectiveness of oral anticoagulants: a cohort study
Team member Epidemiology:	
Project team:	
Rationale and background:	A number of new oral anticoagulants are being developed and marketed to replace vitamin K antagonists. 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. However, their long-term safety and effectiveness have not been characterized in a real-world setting.
Research question and objectives:	This protocol is for a series of comparative effectiveness and safety analyses within periodically updated cohorts of patients initiating dabigatran (compared to warfarin) and other new oral anticoagulants (NOAC) (as they become available), compared to warfarin, followed longitudinally for the occurrence of a variety of health outcomes. Objectives 1) Primarily, to conduct direct comparisons over time between dabigatran and warfarin and quantify the association between anticoagulant choice and the occurrence of specific outcomes of interest **2)** Secondarily, to monitor the number of people initiating other NOAC medications and, when sufficient, to compare study outcomes between other NOAC medications and warfarin
Study design:	Observational sequential cohort study based on existing data

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Population:	Patients with a recorded diagnosis of atrial fibrillation without evidence of valvular etiology who initiate dabigatran (or other NOACs as they become available) compared with warfarin initiators.
Study data source:	This study will be conducted within both UnitedHealth and Marketscan data sources. The first analyses of this study will include data from October 2010 through December 2012 for the cohort formation and data from July 2008 through September 2010 for disease risk score (DRS) calculation. Both data sources will be updated on a 6-month basis through December 2015
Expected study size:	The estimated final study size will be ~ 60,000 dabigatran initiators, matched to ~60,000 warfarin initiators with approximately 24,000 cumulative person-years of observation in each exposure group, and other NOAC initiators (numbers dependent on use) separately matched to a similar number of warfarin initiators. The estimated study size (after PS matching) for interim analyses: Interim report 1 (Apr 2014): ~ 24,000 dabigatran and ~24,000 warfarin initiators with 10,000 PYs of observation in each group Interim report 2 (Jul 2014): ~ 30,000 dabigatran and ~30,000 warfarin initiators with 12,350 PYs of observation in each group Interim report 3 (Nov 2014): ~ 36,000 dabigatran and ~36,000 warfarin initiators with 14,700 PYs of observation in each group Interim report 4 (Mar 2015): ~ 42,000 dabigatran and ~42,000 warfarin initiators with 17,050 PYs of observation in each group Interim report 5 (Sep 2015): ~ 48,000 dabigatran and ~48,000 warfarin initiators with 19,400 PYs of observation in each group Interim report 6 (Mar 2016): ~ 54,000 dabigatran and ~54,000 warfarin initiators with 21,750 PYs of observation in each group Final report (Dec 2016): ~ 60,000 dabigatran and ~60,000 warfarin initiators with 24.100 PYs of observation in each group

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Main criteria for inclusion:	• A recorded diagnosis of atrial fibrillation. • Initiation of anticoagulant medication (dabigatran (or other NOACs as they become available) or warfarin). • At least 18 years of age on the date of anticoagulant initiation. • CHA_2DS_2-VASc score ≥ 1
Main criteria for exclusion:	• Patients with missing or ambiguous age or sex information. • Patients with evidence of valvular disease. • Patients with less than 12 months enrolment preceding the date of anticoagulant initiation • Patients with a dispensing of any oral anticoagulant during the 12 months preceding the date of anticoagulant initiation • Patients with a nursing home stay during baseline
Comparison group:	Warfarin
Expected duration of exposure:	As observed in the data source

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ACCP	American College of Chest Physicians
ACEI	Angiotensin-converting Enzyme Inhibitor
AES	Advanced Encryption Standard
AF	Atrial Fibrillation
ALT	Serum Alanine Aminotransferase
ARB	Angiotensin Receptor Blocker
ASCVD	Atherosclerotic Cardiovascular Disease
BB	Beta Blocker
BI	Boehringer Ingelheim
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
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
DRG	Disease
DRS	Disease Risk Score
DVT	Deep Venous Thromboembolism
Dx	Diagnosis-Related Group
ESC	European Society of Cardiology
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
HbA1c	Hemoglobin A1C
HCPC	Healthcare Common Procedure Coding
hdPS	High-dimensional Propensity Score
HR	Hazard Ratio
ICD-9	International Classification of Diseases, Ninth Revision, Clinical Modification

ICH	Intracerebral Hemorrhage
INR	International Normalized Ratio
ITT	Intent-To-Treat
LDL	Low Density Lipoprotein
LOS	Length of Stay
MDRD	Modification of Diet in Renal Disease
MI	Myocardial Infarction
NOAC	New Oral Anticoagulant
NSAID	Non-steroidal Anti-inflammatory Drug
NVAF	Non-valvular Atrial Fibrillation
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PE	Pulmonary Embolism
PGP	P-glycoprotein
PPI	Proton Pump Inhibitor
PPV	Positive Predictive Value
PS	Propensity Score
PTCA	Percutaneous Transluminal Coronary Angioplasty
PVD	Peripheral Vascular Disease
PY	Person-Year
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
RR	Relative Risk
SAH	Subarachnoid Hemorrhage
SCr	Serum Creatinine
SD	Standard Deviation
TIA	Transient Ischemic Attack
US	United States
VTE	Venous Thromboembolism

2. RESPONSIBLE PARTIES

(1)

(1)

(1)

(1)

(1)

3. AMENDMENT AND UPDATES

None

4. MILESTONES

Planned dates for the following milestones:

Date	Phase 2		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*)
Jun, 2012	Contract	0		
	Year 1			
Jun, 2013	Draft Protocol	12		
Year 2				
Jan, 2014	Final Protocol	19		
Apr, 2014	Interim Report 1	22	Data through Dec 2012	Claims through Dec 2012 *Labs through Dec 2012*
Jul, 2014	Interim Report 2	25	Data through Jun 2013 (Update received in Jan 2014)	Claims through Jun 2013 (Update received in Mar 2014) *Labs through Dec 2012* *(Update received in Dec 2013)*
Nov, 2014	Interim Report 3	29	Data through Dec 2013 (Update received in Jul 2014)	Claims through Sep 2013 (Update received in Jun 2014) *Labs through Dec 2012* *(Update received in Dec 2013)*
Year 3				
Mar, 2015	Interim Report 4	32	Data through Jun 2014 (Update received in Jan 2015)	Claims through Dec 2013 (Update received in Dec 2014) *Labs through Dec 2013* *(Update received in Dec 2014)*
Sep, 2015	Interim Report 5	39	Data through Dec 2014 (Update received in Jul 2015)	Claims through Sep 2014 (Update received in Jun 2015) *Labs through Dec 2013* *(Update received in Dec 2014)*
Year 4				
Mar, 2016	Interim Report 6	45	Data through Jun 2015 (Update received in Jan 2016)	Claims through Dec 2014 (Update received in Dec 2015) *Labs through Dec 2014* *(Update received in Dec 2015)*
	Year 4			
Dec, 2016	Final Report	54	Data through Dec 2015 (Update received in Jul 2016)	Claims through Dec 2015 (Update received in Sep 2016) *Labs through Dec 2014* *(Update received in Dec 2054)*

5. RATIONALE AND BACKGROUND

A number of new oral anticoagulants are being developed and marketed to replace vitamin K antagonists, one of the most important drugs in modern medicine. [P11-11875] 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. 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 randomized clinical trials for three separate indications: (1) prevention of stroke and systemic embolism among patients with atrial fibrillation; (2) prevention of deep venous thrombosis (DVT) among patients undergoing hip or knee replacement therapy; and (3) treatment of venous thromboembolism (VTE). Phase III clinical trials comparing dabigatran, rivaroxaban, apixaban, and edoxaban to warfarin in patients with non-valvular atrial fibrillation (NVAF) have been completed. [R11-4190] [P09-11669] [R11-4223] [R13-5082] The objective of this part of the project is to conduct a series of comparative effectiveness and safety studies across the available anticoagulants, starting with warfarin and dabigatran and including additional ones as they become available within data sources available to us at the Division of Pharmacoepidemiology. Such sequential approach will extend Phase I analyses (study protocol 1160.157) by providing greater precision around effect estimates as well as providing an evaluation of their use in actual practice and among subgroups of patients that were not represented in clinical trials. This evaluation will provide a direct assessment of comparative effectiveness and potential adverse events across the anticoagulants that may have eluded the pre-marketing trials.

6. RESEARCH QUESTIONS AND OBJECTIVES

This protocol is for a series of comparative effectiveness and safety analyses within periodically updated cohorts of patients with NVAF at risk for stroke initiating dabigatran or other oral NOAC medications as they become available, compared to warfarin, followed longitudinally for the occurrence of a variety of health outcomes.

Specific objectives of this active surveillance program are:

1) Primarily, to conduct direct comparisons over time between dabigatran and warfarin and quantify the association between anticoagulant choice and the occurrence of specific outcomes of interest
2) Secondarily, to monitor the number of people initiating other NOAC medications as they become available and, when sufficient, to compare study outcomes between other NOAC medications and warfarin.

7. RESEARCH METHODS

7.1 STUDY DESIGN

This study will involve a sequentially built parallel cohort design with propensity score (PS) matching to address potential confounding. Each new data update will provide additional follow-up time on the patients already in the cohort, as well as new initiators who will be matched on PS and calendar quarter of initiation and added to the existing cohort for the cumulative analyses. This study design was selected to facilitate the inclusion of additional subjects and follow-up time as data become available over the course of the study period. The study will be conducted within two US-based longitudinal healthcare claims databases (MarketScan and UnitedHealth Research Database, see also section 6.5 for more details). Cohort selection and all analyses will be performed separately within each database and a combined analysis that pools results from the two databases for the same time periods will be done if appropriate, based on an assessment of homogeneity of treatment effect. Pooling of results across data sources will correspond to a weighted average effect (as in a fixed effects meta-analysis) using the Mantel-Haenszel method. [R97-0509] It is expected that there will be little heterogeneity of treatment effects across the databases since the databases are similar with respect to who is included in the database (employed people and their dependents) and the nature of data captured (health insurance transactions billed on a negotiated fee for service basis). Heterogeneity will be assessed by comparing the treatment effect point estimates across data sources. Assessment of heterogeneity will not rely on a statistical test of heterogeneity, since the large study size may indicate significant heterogeneity ($p<0.05$) even if estimates are similar (i.e. a difference that is not clinically meaningful) and the purpose of this assessment of heterogeneity is intended only for determining whether it is reasonable to combine data sources. If contrary to expectations, there is a difference >30% in the overall effect measure for a primary outcome across the two data sources, we will conduct an additional investigation that assesses treatment effect within levels of protocol-specified subgroups (Section 6.9.2) separately by a database. If treatment effect is different across levels of the subgroup variable within a data source, and the distribution of this subgroup variable differs by data source, then the pooling will be conducted within strata of the subgroup variable or variables across which heterogeneity is observed to account for this heterogeneity.

The primary analyses will involve dabigatran initiators compared to warfarin initiators; as other NOAC medications become available for stroke prevention, we will form additional cohorts of other NOAC medications and separately compare them to warfarin in the secondary analyses once sufficient number of initiators will have accrued. The same (as described below for dabigatran) inclusion/exclusion criteria will apply and a similar set of analyses will be conducted.

7.2 SETTING

Initiators of dabigatran and warfarin from two US data sources: (1) UnitedHealth Research Database and (2) MarketScan Commercial Claims and Encounters database and Medicare supplement between October 2010 and December 2012, with 6-month updates through December 2015. Initiators of other NOAC medications will be added as these medications become available for stroke prevention in NVAF. Data from July 2008 through September 2010 will be used for disease risk score (DRS) calculation.

7.3 SUBJECTS

Patient Selection:

- The main cohort will consist of patients with NVAF at risk for stroke initiating an oral anticoagulant medication in the timeframe of the study
    - warfarin and dabigatran for the primary analysis
    - other NOACs to be added separately in the secondary analysis as they become available for stroke prevention in later time intervals

- Warfarin initiators between January 2009 and September 2010 will be used for estimation of disease risk scores.

Inclusion criteria:

- Initiation of an oral anticoagulant is defined by a dispensing of an anticoagulant medication (warfarin or a NOAC medication) in the source data, with no dispensing of any oral anticoagulant in the prior 12 months. The date of that dispensing will be defined as the index date for that initiation.
- At least one ICD-9 diagnosis code of 427.31 (atrial fibrillation) at any time prior to and including the index date
- At least 12 months (365 days) continuous enrollment, defined as ≤32 days enrollment gap using enrollment and disenrollment dates, preceding the index date
- 18 years of age and older at index date
- CHA_2DS_2-VASc score ≥ 1

Exclusion criteria:

- Patients with missing or ambiguous age or sex information
- Patients with a nursing home stay during baseline
- Patients with a dispensing of any oral anticoagulant during the 12 months preceding and including the index date
- 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
  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)
  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)

  at any time prior to and including the index date.

We will balance baseline covariates among patients initiating each drug by means of a multivariate confounder summary score (by matching on the exposure propensity score, with confounder balance assessed by the disease risk score). [R12-1912]

Cohort formation

We will receive new data as they become available on a periodic basis (every 6 months) and we will update the study cohorts through December 2015. Initiators of oral anticoagulants identified in each data cut, as previously described, will form sequential cohorts.

In each sequential cohort we will balance baseline covariates among patients initiating each drug by matching on the exposure propensity score and calendar quarter of initiation. Patients' follow-up will end when there is a treatment gap of ≥14 days from the end of calculated days supplied. Patients will be allowed to contribute only once.

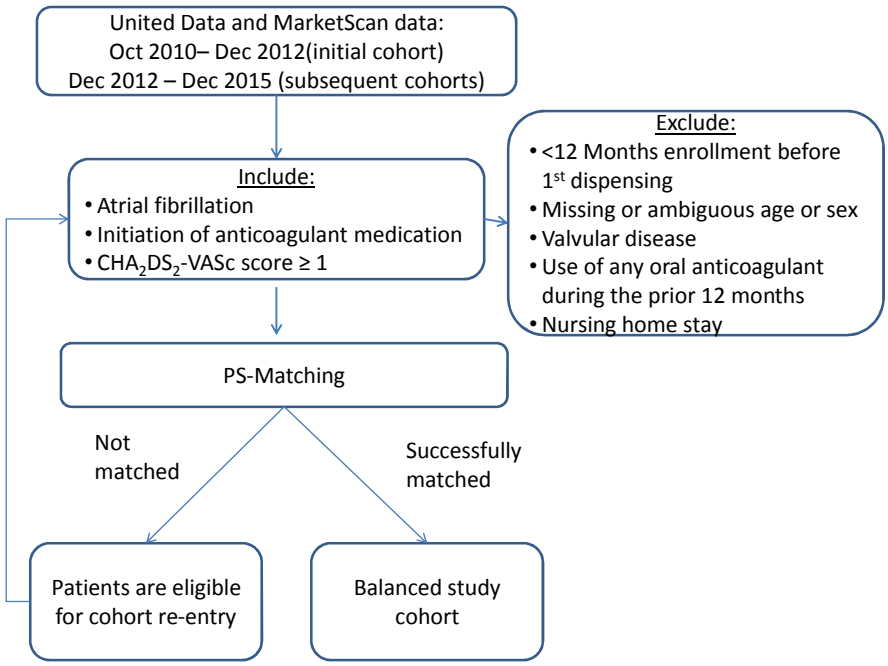

Figure 1 Patient Selection Flow

7.4 VARIABLES

7.4.1 EXPOSURES

Table 1 Market availability for the treatments of interest

Class	Drug	FDA approved*	FDA approved for stroke prevention in patients with non-valvular atrial fibrillation at risk for stroke
Direct thrombin inhibitors	Dabigatran	19 October 2010	19 October 2010
Direct Xa inhibitors	Rivaroxaban	1 July 2011	4 November 2011
	Apixaban	28 December 2012	28 December 2012

Table 1 (con't) Market availability for the treatments of interest

Edoxaban	Phase III	N/A
Otamixaban	Phase III	N/A
Betrixaban	Phase II	N/A

*as of December2013

The primary contrast of interest is between new initiators of warfarin and new initiators of dabigatran, defined as no anticoagulation with *any oral anticoagulant* in the 12 months before the index prescription.

In the secondary analysis and as they become available for stroke prevention in NVAF patients, other NOAC medications will be compared to warfarin. The same definitions and inclusion/exclusion criteria will be applied.

Concomitant therapy with medications that are not cohort-defining medications (defined as simultaneous use on the day of dabigatran or warfarin initiation) will be accounted for in the study analyses as a covariate and used for balancing or stratification.

Study follow-up

We will follow patients for each of the outcomes of interest in a prospective manner and we will estimate measures of effect using person-time based analyses.

The primary analyses will use an 'as treated' approach. Follow-up will start the day after cohort inclusion, which is the day of treatment initiation, and will end at the time of disenrollment, end of the observation period (available data), death, admission to a nursing home, discontinuation of the index study exposure, or switch to a different anticoagulant whichever comes first. Exposure will be considered discontinued if there is a treatment gap ≥14 days from the end of calculated days supplied. Warfarin therapy involves dose titration following initiation before a stable therapeutic INR is obtained. We will use the reported days' supply as a proxy for duration of exposure following a dispensing as it may more adequately reflect the use pattern within a commercial health insurer database represented by UnitedHealth and MarketScan. This approach involves a potential mismatch between the presumed exposure derived from dispensing data and actual exposure. The utilization study (described in study protocol 1160.177) will inform the sensitivity analyses around this assumption and seek to clarify how sensitive results are to variations in the exposure assumption. Switchers will be censored in the as-treated approach on the day of the dispensing of the alternative medication. If switching was the consequence of a side effect of a drug, most likely the index drug was discontinued for some time before the new drug was initiated. Any clinical event therefore was most likely recorded during that period and will be

attributed to the index drug.

7.4.2 OUTCOME(S)

The primary outcomes of interest include stroke (hemorrhagic, ischemic, uncertain classification) and major bleeding. Secondary outcomes are: stroke or systemic embolism, , transient ischemic attack (TIA), myocardial infarction (MI), venous thromboembolism (VTE), deep vein thrombosis (DVT), pulmonary embolism (PE).
Systemic embolism (defined as an acute vascular occlusion of the extremities or any organ, such as kidneys, mesenteric arteries, spleen, retina or grafts), ischemic stroke, hemorrhagic stroke, stroke of uncertain classifications, major intracranial bleeding, major extracranial bleeding, major gastrointestinal (GI) bleeding, major upper GI bleeding, major lower GI bleeding, major urogenital bleeding, major other bleeding. Further outcomes include hepatotoxicity and all-cause mortality.

As mortality data in the commercial databases is currently limited to inpatient deaths, we will seek to improve the ascertainment of the death outcome through external linkage, such as with the Social Security Death Master File.

Table 2 Outcome Definitions

Outcome	Hospital Discharge Code(s)	Comments
Primary Outcomes		
Stroke	As primary ICD-9 discharge diagnosis (Dx): 431.x Intracerebral hemorrhage (ICH) 433.x1 Occlusion and stenosis of precerebral arteries with cerebral infarction 434.x1 Occlusion and stenosis of cerebral arteries with cerebral infarction 436.x Acute, but ill-defined cerebrovascular events	See Mini-Sentinel report for PPV for individual codes or other algorithms [R14-0052]
Major hemorrhage	Major intracranial bleeding, major extracranial bleed (for codes see component outcomes below)	
Secondary outcomes		
Stroke or systemic embolism	Stroke or systemic embolism (for codes see component outcomes below)	

Table 2 (con't) Outcome Definitions

Outcome	Hospital Discharge Code(s)	Comments
Systemic embolism	ICD-9 Diagnoses: 444.x Arterial embolism	No validation studies available. Codes are thought to be specific because of the substantial clinical symptomatic and required therapy.

Table 2 (con't) Outcome Definitions

Ischemic stroke	As primary ICD-9 discharge diagnosis (Dx): ICD-9 Dx 433.x1 Occlusion and stenosis of precerebral arteries with cerebral infarction ICD-9 Dx 434.x1 Occlusion and stenosis of cerebral arteries with cerebral infarction	PPV 95.5% in commercially-insured population for the codes in any position [R11-4887] Use of codes in the primary position generally increases the PPVs [R14-0052]
Hemorrhagic stroke	As primary ICD-9 discharge diagnosis (Dx): 431.x Intracerebral hemorrhage (ICH)	Median PPV 96% (86% if all discharge diagnoses) for ICH based on 2 validation studies [R14-0052]
Stroke uncertain classification	As primary ICD-9 discharge diagnosis (Dx): ICD-9 Dx code 436.x (acute, but ill-defined cerebrovascular disease)	Mini-Sentinel report: Median PPV of 81% for the code of 436 [R14-0052]
Transient Ischemic Attack (TIA)	ICD-9 Dx code 435.xx (transient cerebral ischemia) as the principal (primary) discharge diagnosis	PPV of 89% (primary Dx) and 77% (primary and secondary) in 1992 study [R13-0519] and 70% (primary only in Canadian database) [R13-0520] have been reported. Median PPV is 79% (72 if all discharge Dx) [R14-0052]
Myocardial infarction (MI)	ICD-9 Dx 410.X (acute myocardial infarction) excluding 410.x2 (subsequent episode of care), as the principal (primary) or the next (secondary) diagnosis AND a length of stay (LOS) between 3-180 days, or death if LOS is < 3 days	PPV 94% in Medicare claims data [R11-4316] PPV 88.4% in commercially-insured population [R11-4887]
Venous Thromboembolism (VTE)	DVT or PE (for codes see component outcomes below)	

Table 2 (con't) Outcome Definitions

Deep vein thrombosis (DVT)	Validated algorithm: ICD-9 451.1x (Phlebitis and thrombophlebitis of deep vessels of lower extremities) ICD-9 451.2x (of lower extremities, unspecified) ICD-9 451.81 (of Iliac vein) ICD-9 451.9x (of unspecified site) ICD-9 453.1x (thrombophlebitis migrans) ICD-9 453.2x (venous embolism and thrombosis of vena cava) ICD-9 453.8x (venous embolism and thrombosis of other specified veins) ICD-9 453.9x (venous embolism and thrombosis of unspecified site) Not in the validated algorithm but will be included following Mini-Sentinel recommendation for VTE outcome: ICD-9 453.40 (Venous embolism and thrombosis of unspecified deep vessels of lower extremity (includes DVT) ICD-9 453.41 (Venous embolism and thrombosis of deep vessels of proximal lower extremity (includes femoral, iliac, popliteal, thigh, and upper leg) ICD-9 453.42 (Venous embolism and thrombosis of deep vessels of distal lower extremity (includes calf, lower leg, peroneal, and tibia) ICD-9 453.0 (Hepatic vein thrombosis)	Algorithm for Deep vein thrombosis (DVT): ICD-9 codes of 451.1, 451.2, 451.81, 451.9, 453.1, 453.2, 453.8, 453.9 [hospital discharge, any position] had PPV of 0.72 and specificity > 0.99 in Medicare population [R11-4334] Mini-Sentinel: while using ICD-9 codes 415.x (PE), 451.x and 453.x (DVT) as a VTE event yielded the highest PPV, for a specific event (DVT or PE) PPV was lower; therefore, the performance of algorithms depends on a population studied [R13-0522]
Pulmonary Embolism (PE)	ICD-9 415.1x (pulmonary embolism and infarction)	PPV of 72% in a community sample (45 YO and older) [R05-0358]
Major intracranial bleeding	ICD-9 diagnosis: 430.x (Subarachnoid hemorrhage (SAH)) 431.x (Intracerebral hemorrhage (ICH)) 432.x (other and unspecified intracranial hemorrhage, including 432.1x – subdural hemorrhage)	PPV 77% or higher reported [R14-0052]
Major extracranial bleeding	Major upper GI bleed, major lower and unspecified GI bleed, major urogenital bleed, major other bleed (for codes see component outcomes below)	No validation studies available for this outcome
Major GI bleeding	Major upper GI bleeding, major lower/unspecified GI bleeding (for codes see component outcomes below)	No validation studies available for this outcome

Table 2 (con't) Outcome Definitions

Major upper GI bleed	ICD-9 diagnoses: 531.0x (acute gastric ulcer with hemorrhage with/without obstruction) 531.2x (with hemorrhage and perforation with/without obstruction) 531.4x (chronic or unspecified gastric ulcer with hemorrhage with/without obstruction) 531.6x (with hemorrhage and perforation with/without obstruction) 532.0x (acute duodenal ulcer with hemorrhage with/without obstruction) 532.2x (with hemorrhage and perforation with/without obstruction) 532.4x (chronic or unspecified duodenal ulcer with hemorrhage with/without obstruction) 532.6x (with hemorrhage and perforation with/without obstruction) 533.0x (acute peptic ulcer of unspecified site with hemorrhage with/without obstruction) 533.2x (with hemorrhage and perforation with/without obstruction) 533.4x (chronic or unspecified peptic ulcer of unspecified site with hemorrhage with/without obstruction) 533.6x (with hemorrhage and perforation with/without obstruction), 534.0x (acute gastrojejunal ulcer with hemorrhage with/without obstruction) 534.2x (with hemorrhage and perforation with/without obstruction) 534.4x (chronic or unspecified gastrojejunal ulcer with hemorrhage with/without obstruction) 534.6x (with hemorrhage and perforation with/without obstruction) 578.0 (hematemesis) OR ICD-9 procedure code 44.43 (endoscopic control of gastric or duodenal bleeding) OR CPT code 43255 (upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate with control of bleeding, any method)	PPV of 87.8% in commercially-insured population [R11-4887]
Major lower GI bleeding	Lower GI/unspecified GI site bleeds [R11-2274]: Diverticulosis of small intestine with hemorrhage: 562.02 Diverticulitis of small intestine with hemorrhage: 562.03 Diverticulosis of colon with hemorrhage: 562.12 Diverticulitis of colon with hemorrhage: 562.13 Hemorrhage of rectum and anus: 569.3x Angiodysplasia of intestine with hemorrhage: 569.85 Blood in stool: 578.1x Hemorrhage of GI tract, unspecified: 578.9	PPVs for individual codes [R11-2274]: 562.12 – 91.7% 562.13 – 66.7% 569.3 - 71.4% 569.85 – 100% 578.1 - 81.8% 578.9 -88.2%

Table 2 (con't) Outcome Definitions

Major urogenital bleed	ICD-9 diagnoses: Hematuria: ICD-9 Dx: 599.7 Excessive/frequent menstruation: ICD-9 Dx 626.2x and secondary diagnosis indicating acute bleeding: anemia (280.0, 285.1, 285.9), [R11-2274]	PPVs for individual codes [R11-2274]: 599.7 - 75.0% 626.2 – 100% (2 cases) [R11-2274]
Other major bleeds	Other major bleeds [R11-2274]: Hemathrosis: 719.1x Hemopericardium: 423.0x Hemoptysis: 786.3x Epistaxis: 784.7x Hemorrhage not specified 459.0x Acute posthemorrhagic anemia 285.1x	PPVs for individual codes [R11-2274]: 719.1x – 100% 786.3x – 80% 784.7x – 100% 459.0x – 100% 285.1x – 100%

7.5 DATA SOURCES

The data source for this project will be a combination of claims data from United Healthcare, a large national commercial health insurer, and MarketScan, a research claims database from commercial employer-sponsored health plans from July 2008 through December 2012 for the first interim report, with 6-month updates through December 2015. Data from July 2008 through September 2010 will be used for DRS estimation (see Main Analysis Section (6.9.1) for more details) while data from October 2010 will be used for cohort formation and analysis. Because of a 6-month time lag before data become available for United and 9-month time lag for MarketScan, we will not have access to any information beyond December 2012 for the first interim report.

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We have obtained the following preliminary estimates from the UnitedHealth and MarketScan databases regarding the number of patients initiating dabigatran or warfarin (new users) and meeting the main study selection criteria in the period October 2010 – June 2012.

Table 7 **UnitedHealth and MarketScan databases, estimated numbers of dabigatran and warfarin with non-valvular atrial fibrillation diagnosis, in the period October 2010 – June 2012**

Medication	United Healthcare	MarketScan	Total
Dabigatran	4,150	20,000	24,150
Warfarin	7,720	40,000	47,720

7.6 BIAS

Various design and analysis methods will be implemented to reduce the potential for bias in the study. We will employ new-user cohorts of NOAC medications and warfarin in order to address differences that might arise in the comparison of newer and older treatments, such as survivor bias and attrition of susceptibles. The comparator cohort will be formed from warfarin initiators with similar clinical profiles to dabigatran and other NOAC medications initiators to reduce confounding by indication. We will employ propensity score matching of NOAC/dabigatran and warfarin cohorts in order to improve the balance of the cohorts with respect to numerous variables and will further assess the balance across the matched cohorts on the basis of disease risk scores for the primary outcomes. We will use established

algorithms for outcome identification and only outcomes expected to be ascertained well in insurance claims.

7.7 STUDY SIZE

The ability of this research program to detect a given risk increase depends on the incidence of the outcome as well as the number of cohort entrants and duration of follow-up. The study size will depend on the number of dabigatran (or other NOAC medications) and warfarin initiators who meet the study inclusion and exclusion criteria and are successfully matched into cohorts. On the basis of the outcome incidence rate observed in the comparison group in the pilot phase of this project (Phase 1) and the cumulative person-time of observation over the study period, we estimated the minimum relative rate that can be detected with 80% power for dabigatran-warfarin comparison.. During the period October 2010 – June 2012, among patients with a minimum of 12 months baseline history, no prior use of any anticoagulants, and a diagnosis of non-valvular atrial fibrillation, there are 4,158 dabigatran incident users in the UnitedHealth database and approximately 20,000 dabigatran users in MarketScan database. These dabigatran users will be matched to a similar number of warfarin incident users. Assuming that approximately 70% or patients will be matched, an average follow-up of 5 months (both based on the preliminary results from Phase 1 of the BI/ Pradaxa project) and the additional users who initiated dabigatran during July-December 2012 period, there should be slightly more 10,000 person-years of dabigatran follow-up for the initial analysis. As this project expands in 6 month increments, the person-time, along with outcomes and the ability to detect a particular relative risk will increase.

The table below provides estimates of the minimum relative rates that can be detected with 80% power for the major study outcomes under specific assumptions regarding their incidence in the comparator group (labeled “base rate”) and the accrual of person-time. The base case incidence rates are the rates observed in warfarin initiators who were calendar quarter- and PS- matched to dabigatran initiators during the October 2010-June 2012 period in the UnitedHealth database (Phase 1 of the project). We conservatively assumed that the number of patients initiating dabigatran each month during July 2012 – December 2015 is equal to the average monthly number of initiators during the first half of 2012, that at least 2/3 of these patients are matched 1:1 to comparator patients, and that each patient contributes 0.41 years of follow-up time.

Table 8 Projected minimum detectable relative rates* by reporting period

	Phase 1 (NOAC Cohort)	Interim report 1	Interim report 2	Interim report 3	Interim report 4	Interim report 5	Interim report 6	Final report
Report Date		Apr, 2014	Jul, 2014	Nov, 2014	Mar, 2015	Sep, 2015	Mar, 2016	Dec, 2016

Table 8 (con't) Projected minimum detectable relative rates* by reporting period

Data through (MarketScan/ United)	Jun, 2012	Dec, 2012	Jun, 2013	Sep/Dec, 2013	Dec 2013/Jun, 2014	Sept/Dec, 2014	Dec 2014/Jun, 2015	Dec, 2015
Estimated number of matched patients		24,000	30,000	36,000	42,000	48,000	54,000	60,000
Cumulative person-time of observation		10,000	12,350	14,700	17,050	19,400	21,750	24,100
Outcome	**Base rate †**	**Minimum detectable relative rate**						
Stroke	31.59	1.24	1.21	1.19	1.18	1.17	1.16	1.15
Major Hemorrhage	66.72	1.16	1.14	1.13	1.12	1.11	1.11	1.10
Ischemic stroke	32.71	1.23	1.21	1.19	1.17	1.16	1.15	1.15
Hemorrhagic stroke	2.09	1.87	1.77	1.70	1.64	1.60	1.56	1.53
MI	14.73	1.35	1.32	1.29	1.27	1.25	1.23	1.22
Major GI bleeding	31.63	1.24	1.21	1.19	1.18	1.17	1.16	1.15
Hepatotoxicity	4.20	1.70	1.62	1.57	1.52	1.49	1.46	1.43

* This table reports the minimum relative rate that can be detected with 80% power assuming an alpha level of 0.05 and a 2-sided test.
† Base rate is incidence rate per 1,000 Person-Years observed in warfarin initiators matched to dabigatran during the October 2010-June 2012 period in the UnitedHealth database

7.9 DATA ANALYSIS

All analysis will be performed with SAS Inc, Version 9.3.

7.9.1 MAIN ANALYSIS

All analyses will be conducted in both data sources and may be combined in pooled analyses if appropriate, based on homogeneity of treatment effect. Pooling of results across data sources will correspond to a weighted average effect (as in a fixed effects meta-analysis) using the Mantel-Haenszel method. [R97-0509] Heterogeneity will be assessed by comparing the treatment effect point estimates across data sources. If there is a difference >30% in the overall effect measure for a primary outcome across the two data sources, we will conduct an additional investigation that assesses treatment effect within levels of protocol-specified subgroups (Section 6.9.2) separately by a database. If treatment effect is different across levels of the subgroup variable within a data source, and the distribution of this subgroup variable differs by data source, then the pooling will be conducted within strata of the subgroup variable or variables across which heterogeneity is observed to account for this heterogeneity (see Section 6.2 for more details). In each data source, we will compare distributions of socio-demographic, clinical and utilization characteristics among initiators of different anticoagulant agents, and calculate event rates during follow-up for each of the specified outcomes.
Unadjusted and adjusted relative risks (hazard ratios) and rate differences will be estimated. In adjusted analyses, we will use propensity score (PS) matching to balance potential confounders. [R13-1120] [R12-1912] PS will be derived from predicted probabilities of treatment initiation, given all measured covariates. We will estimate the primary propensity score for each patient using a logistic regression model that includes all pre-defined covariates (from Section 6.4.3). The propensity score will be used to match dabigatran initiators to initiators of warfarin on a 1:1 fixed ratio basis using a nearest-neighbor algorithm and a caliper of 0.05. In addition, patients will be matched on calendar quarter of initiation. Individual covariates will be further tabulated and compared across matched cohorts. If substantial covariate imbalance between dabigatran and warfarin is noted as assessed by a standardized difference >0.1, then we will further adjust the outcome models for HAS-BLED and CHA_2DS_2-VASc score as Cohort Phase 1 results indicated that these scores include all the variables typically imbalanced.

We will plot post-PS-matching Kaplan-Meier curves for event-free survival as a function of the duration of use of the index anticoagulant agent to evaluate the proportionality of hazards.

The secondary analyses will involve other NOAC medications as compared to warfarin. Other NOACs will include rivaroxaban, apixaban and others once they become available for stroke prevention in NVAF patients. We will monitor the number of patients initiating other NOACs and provide these numbers along with power calculations for primary outcomes at each interim report. Once sufficient numbers have accrued, and sufficient follow up time is available, these other NOAC initiators will be separately matched to warfarin initiators and primary analyses (and further/sensitivity analyses if numbers allow) as described above for dabigatran-warfarin comparison will be done.

7.10 QUALITY CONTROL

All aspects of data analysis will be conducted according to standard procedures of the Division of Pharmacoepidemiology. 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.

7.11 LIMITATIONS OF THE RESEARCH METHODS

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

Given the characteristics of the UnitedHealth data (commercial health insurer), patients older than 65 years will be under-represented in the data. Only approximately 35% of incident dabigatran users during the 2010-2011 period were 65 years of age and older. As NVAF also predominately affects older population, it will be under-represented in the data as well.

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 6 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.

There are a number of covariates, such as the type of atrial fibrillation, cause-specific mortality, BMI, smoking, that are not directly assessed in a health insurer database. Information on formulary and reimbursement is not available for MarketScan data. Further, some covariates that can be directly assessed through diagnosis and procedure codes (such as renal dysfunction) have uncertain sensitivity, specificity, and predictive value. Estimation of creatinine clearance even in the subgroup of patients with laboratory values present is not feasible as information on height and weight is not available. A modified MDRD equation is going to be used (see Further Analysis section), which - although found to accurately estimate GFR from serum creatinine measurements - is not used for dosing. In our study, however, we will only use it to assess balance between exposure cohorts.

In addition, medication use in United Healthcare data 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]

7.12 OTHER ASPECTS

Any other aspect of the research method not covered by the previous sections.

8. PROTECTION OF HUMAN SUBJECTS

Data analysis personnel will have access to patients protected health information (PHI) while linking databases and constructing study variables. After data linkage and variable construction is completed, the subjects' PHI will be deleted from the study database, therefore posing minimal risk to patients' privacy.

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

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9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This will be a retrospective observational study; all patient data will be de-identified and analyzed in aggregate. Individual patient safety related information will not be captured during this study. Thus, individual safety reporting is not applicable for this study.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The interim and final reports will consist of a description of the methods, including patient selection and variable definitions along with tabular summaries of cohort characteristics, numbers of patients receiving each anticoagulant and associated follow-up time. Counts of outcomes and corresponding rates and measures of association will be presented. The tabular results will be followed by an interpretive summary along with a discussion of the findings and implications.

The scheduling of communication of interim results will be specified in a separate document.

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

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12. FUNDING

Boehringer Ingelheim GmbH

13. ANNEX

ANNEX 1: LIST OF STAND-ALONE DOCUMENTS

None

Table A3 Follow-up and outcomes among matched cohorts

Group	Size	Follow-up (P-Y)	Outcome events	Incidence Rate	HR	95% CI
Dabigatran	N					
Warfarin	N					

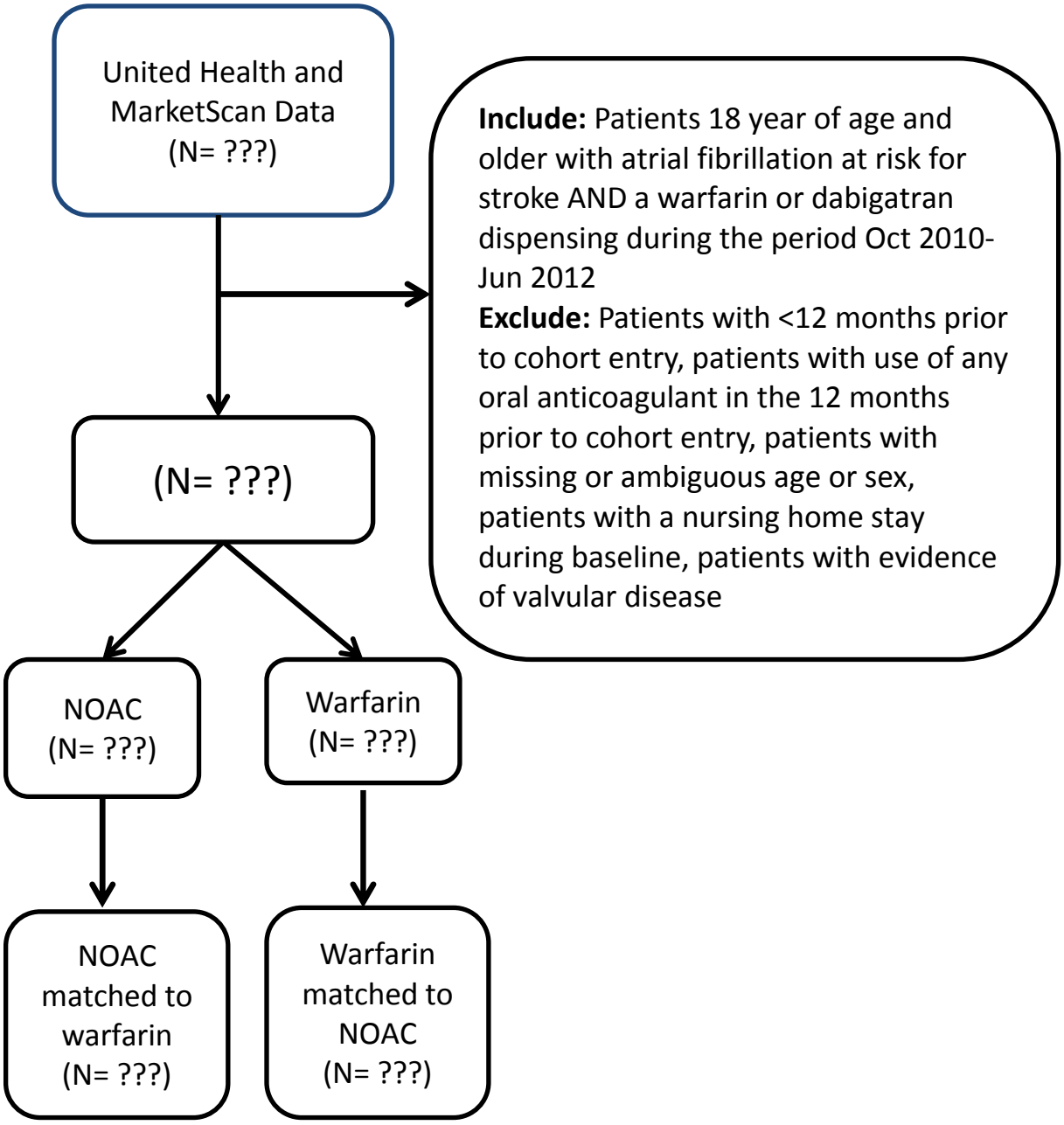
This table will be repeated for each of the outcomes

Table A4 Follow-up and distribution of reasons for discontinuation

Group	Size	Follow-up (years)			Reasons for discontinuation (N, %)					
		Mean	Median	Max	Discontinue	Switch	Event	Disenrollment	Death	Nursing home admission
Dabigatran	N									
Warfarin	N									

This table will be repeated for each of the outcomes.

ANNEX 4 STUDY FIGURES



NOAC: New Oral Anticoagulant

Figure A1 Patient Selection Flow Diagram (CONSORT Style)

This figure will be produced for each interim report and the final report

Figure A2 Survival curves (time to event)

Separate figures to be created for each of the study outcomes. These figures will be produced for each interim report and the final report and displayed in the respective report.

APPROVAL / SIGNATURE PAGE

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