Observational Study Protocol CV185266

RISK OF STROKE AND OTHER CARDIOVASCULAR EVENTS AMONG WARFARIN-TREATED ATRIAL FIBRILLATION PATIENTS- A NATIONWIDE COHORT STUDY IN FINLAND

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SYNOPSIS

Observational Study Protocol CV185266

Protocol Title: Risk of stroke and other cardiovascular events among warfarin-treated atrial fibrillation patients – a nationwide cohort study in Finland

Department: BMS Medical, Finland

Objective(s):

Primary objectives:

1) To investigate and compare risk of stroke, systemic thromboembolism, and myocardial infarction among atrial fibrillation (AF) patients in relation to International Normalized Ratio (INR) levels: under 2.0, 2.0-3.0, and over 3.0.
2) To investigate and compare risk of bleeding events among AF patients in relation to INR levels: under 2.0, 2.0-3.0, and over 3.0.
3) To investigate and compare mortality risk among AF patients in relation to INR levels: under 2.0, 2.0-3.0, and over 3.0.

Secondary objectives

1) To investigate risk of stroke, systemic thromboembolism, myocardial infarction, and bleeding events among AF patients during the first 90 days after initiation of warfarin treatment.
2) To investigate risk of stroke, systemic thromboembolism, myocardial infarction, and bleeding events among AF patients in relation to time from AF diagnosis to time of initiation of warfarin treatment.
3) To investigate risk of stroke, systemic thromboembolism, myocardial infarction, and bleeding events among AF patients who have stopped using warfarin.

Study Design: The study is conducted as a nationwide retrospective register-based linkage study using data obtained from the Finnish health care registers. The study population consists of all AF patients using warfarin with INR measurements in selected hospital district areas in Finland between 01-Jan-2007 and 31-Dec-2009 with up to 5 years follow-up.

Study Population:

Inclusion criteria: Patients who:

- have purchased warfarin (ATC code B01AA03) between 01-Jan-2007 and 31-Dec-2009,
- have at least one INR measurement between 01-Jan-2007 and 31-Dec-2009, and
- have ICD-10 diagnosis I48 for AF between 01-Jan-2005 and 31-Dec-2009.

Exclusion criteria: Permanent residence in Finland less than 12 months prior to index date. Age below 18 years at index date.

Data Collection Methods:

This is a fully register-based study and patients will not be contacted in any phase of the study.

- Patients with warfarin exposure will be identified by Kela, who then will convert the patient IDs to study IDs (SIDs). Kela will then send the IDs and the SIDs to other register holders: Statistics Finland, National Institute for Health and Welfare, Statistics Finland, Population Register Center, Finnish Cancer Registry, and central hospital laboratories included in the study.

- EPID Research will receive unidentifiable data including SIDs only.
- All patient data are then anonymous which ensures full data protection of the patients.
- Approval of Ethical Review Board of Hospital District of Helsinki and Uusimaa (HUS) will be requested to cover the nationwide study.
- Data permits will be requested from each registry holder based on the study protocol and ethical approval.
- Index date is defined as the date of first purchase of warfarin after 01-Jan-2007. Follow-up of the patients starts on the index date, and ends on 31-Dec-2011, at time of death or at time of emigration whichever occurs first. Treatment and comorbidity history is gathered from the period 01-Jan-2005 and 31-Dec-2006.

Data Analyses: Stratified incidence rates with 95% CIs will be estimated for each endpoint within the strata of the INR levels, time in therapeutic INR range (TTR) categories, and other covariates.

The crude and adjusted hazard ratio (HR) estimates with 95% CIs and P-values will be estimated within the INR levels and TTR categories using the conventional Cox's proportional hazards model adjusting for other covariates. For INR the category 2.0–3.0 will be used as the reference category. Similarly for TTR the category ≥ 60% of time will be used as the reference category.

Sample Size/Power: According to the power calculations we are able to detect 10-20% differences in the main endpoints with sufficient power of approximately 80% or higher.

Limitations/Strengths:

- No exact prescribed dosages are available. Warfarin exposure is assumed based on the information of purchases and package sizes with defined daily doses (DDDs).
- Fully reliable information on eg, acetylsalicylic acid use is not available because the data of the prescription register exclude relatively inexpensive packages and over the counter medications which are not reimbursed.
- Medications used during hospitalizations are not available. However, based on the hospital care register the hospitalization periods can be taken into account to define gaps in the drug treatment periods.
- The laboratory data are collected from separate local central laboratories. Changes in places of domicile may affect the follow-up of the patients. On the other hand, previous published surveys on the subject have not included INR follow-up to this extent.

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1 INTRODUCTION

1.1 Study Rationale

Atrial fibrillation (AF) resulting in an increased risk of stroke and systemic thromboembolism is the most common indication for warfarin treatment. Anticoagulant treatment, while decreasing the risk of embolic events, increases the risk of bleeding complications.

The benefits of a Vitamin K antagonist (VKA), such as warfarin, depend on maintaining the International Normalized Ratio (INR) within a relatively narrow range. It has been shown that the optimal INR target range is between 2.0 and 3.0 for AF patients.[1] This range has been implemented into common clinical practice in Finland from 2000 onwards. Considering INR data at the time of the event, an INR below 2.0 decreases the benefit of VKA for prevention of strokes, whereas an INR above 3.0 increases the risk for serious bleeding complications. Due to the pharmacokinetic variability of warfarin and its interactions with many drugs and foods, as well as inter individual differences among patients, it may be difficult to maintain the INR in this therapeutic range.[2,3] It has been described that only about 63% of AF patients receive appropriate anticoagulation treatment,[4] and that even with adequate INR monitoring the time in therapeutic range (TTR) is generally less than 60%.[5] The Social Insurance Institution of Finland considers warfarin treatment balance to be satisfactory if TTR of 60% is reached in steady state.[6] The treatment with other anticoagulants other than warfarin, ie, treatment with new oral anticoagulant treatments (NOACs), is reimbursed only as a second-line treatment if this balance is not achieved. The TTR is generally high in Nordic countries.[7] In Finland, any data of performance of anticoagulation therapy assessed with TTR has not been published, but it has previously been shown in Helsinki area that 63% of all outpatient INR measurements were at the target between 2.0-3.0 and 70% between 1.9–3.5.[8]

The present study is the first nationwide register-based cohort study in Finland focusing on AF. The study provides real world data on current anticoagulation treatment practices, treatment balance, and its consequences in whole Finland. Evidence on TTR through INR monitoring specifically addresses the reimbursement question and the possible unmet medical need for new oral anticoagulation treatment of AF patients.

1.2 Research Question

The aim of this study is to evaluate the incidence and risk of stroke, systemic thromboembolic events, myocardial infarction, bleeding events, and mortality in relation to management of warfarin therapy among AF patients. INR target is defined as 2.0-3.0 according to current care treatment guidelines.[9,10] The risks mentioned above are separately evaluated with different management levels of warfarin therapy. The study population is also characterized according to comorbidity, interactive medications and antiarrhythmic drugs in use. Additional study questions are related to initiation, discontinuation, and duration of warfarin treatment. The incidence of anemia and renal impairment in association with warfarin use will also be studied.

2 OBJECTIVES

2.1 Primary Objectives

1) To investigate and compare risk of stroke, systemic thromboembolic events, and myocardial infarction among AF patients in relation to INR levels: under 2.0, 2.0-3.0, and over 3.0.
2) To investigate and compare risk of bleeding events among AF patients in relation to INR levels: under 2.0, 2.0-3.0, and over 3.0.
3) To investigate and compare mortality risk among AF patients in relation to INR levels: under 2.0, 2.0-3.0, and over 3.0.

The primary objectives are evaluated separately for prevalent users of warfarin and for new users of warfarin.

2.2 Secondary Objectives

1) To investigate risk of stroke, systemic thromboembolic events, myocardial infarction, and bleeding events among AF patients during the first 90 days after initiation of warfarin treatment.
2) To investigate risk of stroke, systemic thromboembolic events, myocardial infarction, and bleeding events among AF patients in relation to time from AF diagnosis to time of initiation of warfarin treatment.
3) To investigate risk of stroke, systemic thromboembolic events, myocardial infarction, and bleeding events among AF patients who have stopped using warfarin.

2.3 Exploratory Objectives

1) To investigate and compare incidence of anemia and renal impairment among AF patients in relation to INR levels: under 2.0, 2.0-3-0, and over 3.0.
2) To investigate risk of stroke, systemic thromboembolic events, myocardial infarction, and bleeding events among AF patients in relation to discontinuation of warfarin treatment due to surgical operations and interventions.
3) To investigate how long it takes to achieve INR target in treatment initiators.
4) To investigate how well the INR target is maintained (TTR level).
5) To characterize the use of antiarrhythmic medication in AF patients at start of warfarin use and during warfarin use.
6) To characterize the use of medications with known interactions with warfarin in AF patients at start of warfarin use and during warfarin use.
7) To characterize comorbidity in AF patients using warfarin.

3 STUDY DESIGN

3.1 Overview of Study Design

The study with cohort design is conducted as a nationwide retrospective register-based linkage study using data obtained from the Finnish health care registers. The study population consists of all AF patients using warfarin with INR measurements in selected hospital district areas in Finland between 01-Jan-2007 and 3-Dec-2009.

Index date: Index date is defined as the date of first purchase of warfarin after 01-Jan-2007.

Follow-up period: Follow-up of the patients starts on the index date, and ends on 31-Dec-2011, at time of death or at time of emigration whichever occurs first.

History period: Treatment and comorbidity history is gathered from the period 01-Jan-2005 through 31-Dec-2006.

The key milestones of the study process are given below (Table 3.1-1). Note that the timelines are estimates only and are subject to change depending on the duration of the data permission processes and actual receipt of the data from the register holders.

Table 3.1-1: Study Timelines

Milestone	Anticipated date
Study protocol approved	4-Mar-2013
Registration in the ENCePP e-Register	30-Apr-2013
Ethics committee approval	30-Apr-2013
Data permit approvals	30-Jun-2013
Receipt of data from register holders	30-Sep-2013
Final study report	30-Dec-2013

3.2 Study Population

The study cohort consists of selected hospital district areas that have INR measurements available for AF patients using warfarin. See also Sections 3.1 and 3.3.

3.2.1 Inclusion Criteria

Patients fulfilling the following criteria are included in the study:

- Patient has purchased warfarin (Anatomical Therapeutic Chemical classification (ATC) code B01AA03) between 01-Jan-2007 and 31-Dec-2009,
- Patient has at least one INR measurement available between 01-Jan-2007 and 31-Dec-2009, and
- Patient has a International Classification of Diseases (ICD-10 version 10) diagnosis code I48 for AF between 01-Jan-2005 and 31-Dec-2009.

3.2.2 Exclusion Criteria

- Patients with permanent residence in Finland less than 12 months prior to index date.
- Patients with age below 18 years at index date.

3.3 Data Source/Data Collection Process

The study timelines are presented in the picture below:

Figure 3.3-1: Study Timelines

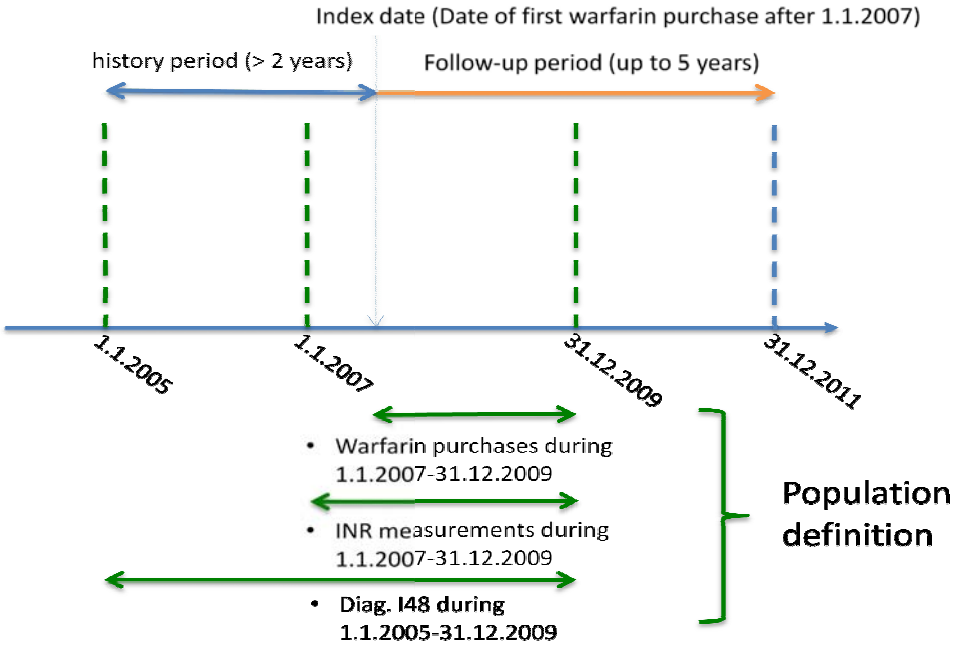

Table 3.3-1: Study Registers

Register	Register Holder	Information obtained
National Prescription Register	Kela – The Social Insurance Institution of Finland	Drug purchases (ATC codes)
National Reimbursement Register	Kela	Reimbursement decisions 207 for chronic arrhythmias (for population characterization)
Finnish Care Register, HILMO	National Institute for Health and Welfare	Diagnoses (ICD10 codes) and date of diagnosis
National Causes of Death Register	Statistics Finland	Time of death and causes of death (ICD-10 codes)
Laboratory databases	HUSLAB + other hospital laboratories	INR measurements and other relevant laboratory values
Finnish Cancer Registry	National Institute for Health and Welfare	Cancer diagnosis (ICD-O-3 codes) and date of diagnosis
Population Register	Population Register Center	Places of domicile 12 months prior to and on index dates.
Social HILMO	National Institute for Health and Welfare	Information (dates) about institutionalization (other than hospitalization)

- Data will be requested from the registry holders (Table 3.3-1) based on the study protocol.
- Data permits will be requested from each registry holder based on the study protocol and ethical approval.
- Approval of Ethical Review Board of Hospital District of Helsinki and Uusimaa (HUS) will be requested to cover the nationwide study.
- This is a fully register-based study and patients will not be contacted in any phase of the study.
- Warfarin exposure will be defined by Kela, who then will convert the patient IDs to study IDs (SIDs). Kela will then send the IDs and the SIDs to other register holders: Statistics Finland, National Institute for Health and Welfare, Statistics Finland, Population Register Center, and central hospital laboratories included in the study.
- EPID Research will receive unidentifiable data including SIDs only. All patient data handled by the researchers are then anonymous which ensures full data protection of the patients.

3.4 Definitions of Study Variables

3.4.1 Outcomes/Endpoint Variables

The studied primary outcomes/endpoint variables of interest are defined through ICD-10 diagnosis codes (hospitalizations and deaths) or ICD-O-3 codes (cancers). See Appendix 1 and 2 for more detail.

The time to event for each primary outcome will be calculated as the time from the index date to the time of the diagnosis of the outcome when such an event occurs during the follow-up.

Index date is defined as the date of first purchase of warfarin after 01-Jan-2007. Follow-up of the patients starts on the index date, and ends on 31-Dec-2011, at time of death or at time of emigration whichever occurs first. Treatment and comorbidity history is gathered from the period 01-Jan-2005 to 31-Dec-2006.

Primary outcomes:

- Stroke
- Other systemic thromboembolic events excluding stroke
- Myocardial infarction
- Bleeding events
- Mortality all-cause
- Mortality (stroke)
- Mortality (myocardial infarction)
- Mortality (systemic thromboembolic events excluding stroke)
- Mortality (bleeding events)

The studied secondary outcomes/endpoint variables of interest are anemia and renal impairment.

Time to anemia is defined as the time from index date to time of first decrement of 20 g/L in haemoglobin or time when haemoglobin is under the reference value.

Time to renal impairment is defined as the time from index date to time when creatinine is under the reference value.

Secondary outcomes

- Anemia
- Renal impairment

In the statistical analysis follow-up for each time to event outcome continues until the time of the event, death, emigration or 31-Dec-2011 whichever comes first.

3.4.2 Exposure/Independent Variables of Interest

- Performance of warfarin therapy
  - INR values under 2.0, 2.0-3.0, and over 3.0
  - time to reach the target INR 2.0–3.0
  - TTR, percentage of time during which the interpolated INR values lie between 2.0 and 3.0[13]
- Exposure to warfarin (ATC B01AA03)
  - new vs. prevalent users (< vs. > 90 days)
  - time since discontinuation
- I48 diagnosis
  - yes/no
  - time from the diagnosis
- Place of domicile 12 months prior to and on the index date
  - if not in Finland, excluded
- Use of antiarrhythmic drugs:
  - yes/no
    - Group C01B: antiarrhythmic drugs, classes I and III (see Appendix 3, Table 1 for details)
    - Group C07: beta blockers / class II antiarrhythmics (see Appendix 3, Table 2 for details)
    - C08DB01: diltiazem (class IV antiarrhythmic)
    - C08DA01: verapamil (class IV antiarrhythmic)
- Use of other anticoagulant or reimbursed antithrombotic therapy:
  - heparins (B01AB01, B01AB51), clopidogrel (B01AC04), dipyridamole (B01AC07), ticlopidine (B01AC05), prasugrel (B01AC22)

3.4.3 Other Covariates/Control Variables

- Reimbursement code 207
  - Yes/no
- Information about hospitalizations and institutionalization (other than hospitalization)

  - dates
  - will be taken into account when defining the discontinuation of warfarin treatment
- Laboratory parameters for anemia characterizations
  - Blood picture
    - Haemoglobin
      - decrement of 20 g/L
      - being under the reference value
  - See Appendix 2 for details.
- Concomitant use of class D interactive drugs according to SFINX (Swedish, Finnish, INteraction X-referencing, see Appendix 3, Table 3 for complete ATC listing)
  - Concomitant use during the warfarin treatment period assumed by the purchases and exposure (see definition for exposure in Section 4.1).
- Age*
- Gender*
- Hospital district
  - Helsinki, Turku, Tampere, Kuopio, Oulu, Jyväskylä
  - other possible central hospitals
- $CHADS_2$ [11,12]
- CHA_2DS_2-VASc[11,12]
- Comorbidities (more in detail in Appendix 4)
  - Hypertension*
  - Thyrotoxicosis
  - Cardiomyopathy
  - Congestive heart failure*
  - Diabetes*
  - Stroke*
  - Transient ischemic attack*
  - Vascular disease**
  - Cancer
  - Venous thromboembolism

*included in $CHADS_2$ score and in CHA_2DS_2-VASc score
**included in CHA_2DS_2-VASc score.

4 STATISTICAL ANALYSIS

4.1 Statistical Analysis Methods

Data management, tabulations, graphics, and statistical modeling in carried out with R language (http://www.r-project.org). R language is described more detailed in report "R: Regulatory

Compliance and Validation Issues: A Guidance Document for the Use of R in Regulated Clinical Trial Environments" (http://www.r-project.org/doc/R-FDA.pdf)

A separate statistical analysis plan (SAP) including detailed statistical analysis and outputs will be produced by EPID research prior to performing any analysis.

Study population: The study population will be described at baseline (start of follow-up) using by previous drug exposure and other covariates.

Study outcomes: All study outcomes will be summarized by drug exposure and other covariates.

Drug exposure: Drug exposure starts at date of purchase. The length of the exposure period is calculated as DDD/dose × 1.5, where DDD (daily defined dose) is the total amount purchased and "dose" is the amount used daily (one for an average person). For the first purchase "dose=1" and for other purchases the "dose" is calculated from previous use by dividing the previous DDD with the time between the present and the previous purchase.

The impact of the multiplier 1.5 in the construction of drug exposure will be evaluated for the primary objectives in sensitivity analyses by using multiplier values 1.25, 1.5 and 2. We will also perform a sensitivity analysis for the primary objectives by including only those patients with at least two purchases of prescriptions within a clinically meaningful timeframe of 3 months after the index date.

INR levels: Daily INR levels are calculated:

1) As the previous recorded INR measurement
2) By linear interpolation between two consecutive INR measurements. If the gap between the measurements is more than 60 days the previous measurement is applied.

Daily INR estimates are categorized into levels: under 2.0, 2.0-3.0, over 3.0. In addition when appropriate a finer categorization is used: under 1.5, 1.5-2.0, 2.0-3.0, 3.0-4.0, 4.0-5.0, 5.0-9.0, and over 9.0. This finer categorization will be used only in the analysis of the primary objectives.

Time in therapeutic range (TTR): The INR target value for AF patients is 2.0-3.0. In addition for stroke, systemic thromboembolic events, and myocardial infarction INR target above 2.0 is considered and for bleeding events INR target under 3.0 is considered.

TTR will be calculated as

1) the percentage of time during which the interpolated INR values lie between 2.0 and 3.0[13] and this is calculated using INR measurements during the previous 1, 2, 3, 6 and 10 months, and
2) the percentage from previous 5 and 10 INR measurements that are between 2.0 and 3.0.

4.1.1 Primary Objective

Objectives 1-3: Stratified incidence rates with 95% confidence intervals (CIs) will be estimated for each primary endpoint within the strata of the exposure variables (INR levels and TTR categories) and other covariates, including history of AF prior the index date.

The crude and adjusted hazard ratio (HR) estimates with 95% CIs and P-values will be estimated separately within the INR levels and TTR categories using the conventional Cox's proportional hazards model adjusting for other covariates. For INR the category 2.0–3.0 will be used as the reference category. Similarly for TTR the category ≥ 60% of time will be used as the reference category.

The objectives will be evaluated separately for the prevalent warfarin user population and the new warfarin user population. The new warfarin user population consists of those patients who initiate warfarin treatment during the follow-up (01-Jan-2007 to 31-Dec-2009).

A further sensitivity analysis will be performed where the adjusted HRs are estimated stratifying by the history of AF prior to the index date.

4.1.2 Secondary Objectives

Objective 1: Stratified incidence rates with 95% CIs will be estimated for stroke, systemic thromboembolic events, myocardial infarction, and bleeding events within the strata of the exposure variables (INR levels and TTR categories) and other covariates during the first 90 days after initiation of warfarin treatment.

The crude and adjusted hazard ratio (HR) estimates with 95% CIs and P-values will be estimated separately within the INR levels and TTR categories using the conventional Cox's proportional hazards model adjusting for other covariates, including history of AF prior the index date. For INR the category 2.0–3.0 will be used as the reference category. Similarly for TTR the category ≥ 60% of time will be used as the reference category.

Objective 2: Stratified incidence rates with 95% CIs will be estimated for stroke, systemic thromboembolic events, myocardial infarction, and bleeding events within the strata of the exposure variables (INR levels and TTR categories), and time from AF diagnosis to time of initiation of warfarin treatment (categories: under 6 months, 6-12 months, over 12 months). For INR the category 2.0–3.0 will be used as the reference category. Similarly for TTR the category ≥ 60% of time will be used as the reference category.

Also, time from AF diagnosis to time of initiation of warfarin treatment will be added as an additional covariate to the Cox's proportional hazards model.

Objective 3: Stratified incidence rates with 95% CIs will be estimated for stroke, systemic thromboembolic events, myocardial infarction, and bleeding events within the strata of other covariates for warfarin patients after stopping warfarin treatment. Warfarin treatment is considered ended if there is more than 2 months gap since last warfarin exposure and INR measurement. Sensitivity analysis with 1 and 3 months gaps will be performed to study the robustness of the definition.

4.1.3 Exploratory Objectives

Objective 1: Stratified incidence rates with 95% CIs will be estimated for anemia as endpoint within the strata of the exposure variables (INR levels and TTR categories) and other covariates.

The crude and adjusted hazard ratio (HR) estimates with 95% CIs and P-values will be estimated separately within the INR levels and TTR categories using the conventional Cox's proportional hazards model adjusting for other covariates. For INR the category 2.0–3.0 will be used as the reference category. Similarly for TTR the category ≥ 60% of time will be used as the reference category.

Objective 2: Discontinuity period of warfarin treatment due to a surgical operation or intervention is identified as starting two weeks before and ending two weeks after such procedure.

Stratified incidence rates with 95% CIs will be estimated for stroke, systemic thromboembolic events, myocardial infarction, and bleeding events in the strata of other covariates within periods of warfarin discontinuity. Also, an indicator variable of the discontinuity period will be added to the Cox's proportional hazards model.

Sensitivity analysis will be done to study the robustness of the discontinuity period definition.

Objective 3: The distribution of days taken to achieve INR target in the new warfarin user population will be provided. Stable INR-target is considered achieved after 3 consecutive INR measurements are within the target 2.0-3.0.

Objective 4: For the new warfarin user population the distribution of TTR at 1, 6, and 12 months after start of warfarin treatment stratified by other covariates. For the prevalent warfarin user population the distribution of TTR at the end of 2010 and 2011 stratified by other covariates.

Objective 5: Warfarin users will be tabulated by use of antiarrhythmic medication (yes/no) at start of follow-up and during follow-up. During follow-up users will also be stratified by the INR and the TTR levels.

Objective 6: Warfarin users will be tabulated by use of interaction medication (yes/no) at start of follow-up and during follow-up. During follow-up users will also be stratified by the INR and the TTR levels.

Objective 7: Warfarin users will be tabulated by comorbidities.

4.2 Power/Sample Size

Statistical hypothesis

With regard to the stroke incidence the formal statistical hypothesis between any two groups is as follows:

H_0 : HR = Incidence_1 / Incidence_2 = 1

against the alternative,

H_1 : HR = Incidence_1 / $\text{Incidence}_2 \neq 1$

Where HR denotes the hazard ratio, Incidence_1 is the stroke incidence rate for example in the treatment group 1 (eg, INR level below 2.0) and Incidence_2 is the stroke incidence rate in the treatment group 2 (INR level 2.0-3.0 used as the reference group).

Similar hypotheses apply for the comparisons between the other outcomes and INR targets and the TTR levels.

Power calculations

According to Wallentin[14] for AF patients using warfarin the incidence rates for "stroke and systemic embolism" vary from 1.34 to 2.06 events per 100 patient years depending on the mean TTR values in different centers. For "major bleeding" events the incidence ranges from 3.11 to 4.13 and for "total bleeding" from 16.56 to 18.96. For "total death" the incidence rates vary from 3.04 to 5.72 per 100 patient years. Thus we perform power calculations for incidence rates 1.5, 3, and 6 and consider differences from of 5 % to 50% by 5% increments or equivalently relative risks from 1.05 to 1.50.

The population size in the areas participating in the study is about 3 million. About 1.6 % of the population are warfarin users and out of these about 67% are AF patients[15] resulting in a study population of size 32 000. Assuming a 3-year mean follow-up time this results in 96 000 person years. According to Helin *et al.*[8] the proportion on INR measurements in the categories: under 2.0, 2.0-3.0, and over 3.0 are 21.7 %, 63.6 % and 14.7 % respectively. In person time this means 21000 (INR under 2.0), 61000 (INR 2.0-3.0) and 14000 (INR over 3.0) person years. The power calculations are performed for the comparisons between the INR categories 2.0–3.0 as the reference group against the INR category below 2.0. Because some of the patients may not have INR measurements available we also repeat the calculations for a 20% smaller study population size. The resulting calculations are given in Table 4.2-1.

Table 4.2-1: Power (%) for comparisons between group 1 (INR below 2.0) and group 2 (INR values 2.0-3.0 used as the reference group) for different relative risk values, incidence rates and study population sizes.

Relative risk	**Incidence rate per 100 patient years**		
Study population size = 32 000			
	1.5	3.0	6.0
1.05	11.7	19.0	35.0
1.10	30.8	55.2	86.2
1.15	56.5	86.1	99.3
1.20	78.6	97.6	100
1.25	91.7	99.8	100
1.30	97.4	100	100
Study population size = 80% × 32 000 = 25 600			
	1.5	3.0	6.0
1.05	10.3	16.1	29.1

Table 4.2-1: Power (%) for comparisons between group 1 (INR below 2.0) and group 2 (INR values 2.0-3.0 used as the reference group) for different relative risk values, incidence rates and study population sizes.

Relative risk	Incidence rate per 100 patient years		
1.10	25.6	46.4	77.8
1.15	47.6	77.7	97.8
1.20	69.2	94.1	99.0
1.25	84.9	99.0	100
1.30	93.8	99.9	100

According to the power calculations the current study will be able to detect 20%, 15% and 10% differences in endpoints with incidences rates of 1.5, 3.0 and 6.0 per 100 person years with sufficient power of about80% or higher, respectively.

5 STUDY LIMITATIONS/STRENGTHS

Finland has a well-developed population register system with tens of years of longitudinal follow-up data. The persons are identified in the registers with a unique personal identification number enabling linkage between different registers. These data has not been collected for study purposes, which may affect the quality of the data. However, these registers have been considered reliable for scientific research purposes.

Only those citizens that have been living in Finland for 12 months prior to index date will be included in the study.

No exact prescribed dosing information is available. Dosing is assumed based on the information of purchases and package sizes with defined daily doses (DDDs).

Coverage of the Prescription Register containing reimbursement information of all permanent residents of Finland is about 97%. Missing data includes relatively inexpensive packages which are not reimbursed. Fully reliable information on eg, acetylsalicylic acid use is then not available.

Medications used during hospitalizations are not available. However, based on the hospital care register the hospitalization periods can be taken into account to define gaps in the drug treatment periods.

No nationwide database about laboratory measurements is available. The laboratory data is then collected from separate local central laboratories. All laboratory values for particular patients may then not be available. Also changes in places of domicile may affect the follow-up of the patients. On the other hand, previous published surveys on the subject have not included INR follow-up to this extend.

To avoid selection bias, the cohort time (years 2007 to 2009) was chosen to avoid complication of patients switching from warfarin to newer anticoagulant medications eg, dabigatran.

6 STUDY CONDUCT

This study will be conducted in accordance with International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and applicable regulatory requirements.

The study protocol is written by following the Code of Conduct by the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP), a project led by the European Medicines Agency to further strengthen the post-authorization monitoring of medicinal products in Europe by facilitating the conduct of multi-centre, independent, post-authorization studies focusing on safety and on benefit/risk. The parties involved in this study commit to adhere to the rules of the ENCePP Code of Conduct in their entirety.

All the information used in the study will be obtained without any potential harm to the patients. This study will be carried out as a retrospective register-based survey and the patients will not be contacted in any phase of the study. The study does not affect the treatment of the patients.

6.1 Ethics Committee Review and Informed Consent

6.1.1 Ethics Committee Review

The investigator must ensure that the required approvals from Ethics Committees, Independent Review Committees, Regulatory Authorities, and/or other local governance bodies are obtained before study initiation at the site.

Approval of Ethical Review Board of Hospital District of Helsinki and Uusimaa (HUS) will be requested to cover this nationwide study. Data permits will be requested from each registry holder based on the study protocol and ethical approval. (See also Section 3.3)

6.1.2 Informed Consent

This study does not require that informed consent is obtained from patients.

This study will be carried out as a retrospective register-based survey and the patients will not be contacted in any phase of the study. The study does not affect the treatment of the patients.

6.2 Responsibilities within the Study

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by BMS.

For this particular study, BMS has deputed EPID Research to prepare and update the protocol. However, the versions of the protocol are approved by BMS.

6.2.1 Sponsor Roles and Responsibilities

Responsibilities are described in detail in the research agreement. The sponsor is in charge of reviewing and validating the protocol and the final statistical report.

6.2.2 CRO Roles and Responsibilities

The present survey is conducted by EPID Research. Only EPID Research (not BMS) will have access to the study data. Responsibilities are described in detail in the research agreement.

The principal investigator from EPID Research and co-investigators will write the study report. This report will be sent to BMS. Based on these results the investigators and medical steering committee with possible other co-authors (see Section 6.2.3) will prepare (a) scientific manuscript(s) for publication. BMS is entitled to view the final results and interpretations thereof prior to submission for publication and to comment in advance of submission as agreed in the research agreement and without unjustifiably delaying the publication.

A summary of the main results of the study, whether positive or negative, including results from prematurely terminated studies, will always be made available to the public. An abstract of the study findings will be provided through the ENCePP E-register of studies within three months following the final study report. The principal investigator may ask the ENCePP Secretariat to delay the publication of this abstract for a limited period pending response to peer-review comments. The outcome of a study will always be presented in an objective and truthful manner providing a comprehensive and accurate description of the findings. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial or personal interests.

6.2.3 External Advisory/Steering Committee

An external medical steering committee of external medical experts on the field has been established to guarantee scientific integrity and high medical impact of the study. The members of this medical steering committee will review (the versions of) the protocol and attend scientific publication writing. In addition to the investigators from EPID Research and members of medical steering committee some other academic collaborators may be invited to be a co-author of the publication(s).

6.3 Confidentiality of Study Data

The confidentiality of records that could identify patients within the database must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

All patient data handled by the investigators will be anonymous ensuring the full data protection of patients. EPID Research will receive unidentifiable data including patient study IDs only. See Section 3.3 for details.

6.4 Quality Control

The study will be conducted as specified in this protocol. All revisions to the protocol shall be properly documented as protocol amendments.

The study protocol has been written by following the Code of Conduct by the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP 2011) that provides a set of rules and principles for post-authorization studies with regard to the best practices and

transparency, thereby promoting scientific independence of such studies. The study protocol also follows the key element of the Guideline for Good Pharmacoepidemiology Practices by International Society for Pharmacoepidemiology (ISPE 2008) and the recent draft Guidance for Industry and FDA Staff (2011) "Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets".

Due to the study type (register study) on-site monitoring will not be performed.

6.5 Database Retention and Archiving of Study Documents

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study. Location of database and supporting documentation will be outlined in the final observational study report.

All study data (unidentifiable patient data) with supporting documents will be retained by EPID Research for a minimum of 5 years after the publication of results. Secure archives will be maintained for the orderly storage and retrieval of all study related material. An index shall be prepared to identify the archived contents to identify their location. Access to the archives will be controlled and limited to authorized personnel only.

6.6 Registration of Study on Public Website

The study will be registered on the ENCePP's E-register. The results will also be published on the same site (http://www.encepp.eu/encepp/studiesDatabase.jsp). According to the ENCePP Code of Conduct, the principal investigator is responsible of publication of the results.

7 ADVERSE EVENT REPORTING

This study does not meet the criteria for adverse event reporting.

8 GLOSSARY OF TERMS AND LIST OF ABBREVIATIONS

8.1 Glossary of Terms

Not Applicable

8.2 List of Abbreviations

Term	Definition
AF	Atrial fibrillation
ATC	Anatomical Therapeutic Chemical classification
CI	Confidence interval
DDD	Defined daily dose
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
ID	Personal identification number
HR	Hazard ratio
HUS	Hospital District of Helsinki and Uusimaa
ICD-10	International Classification of Diseases version 10
INR	International Normalized Ratio
Kela	The Social Insurance Institution of Finland
NOAC	New oral anticoagulant
SAP	Statistical analysis plan
SFINX	Swedish, Finnish, INteraction X-referencing
SID	Study identification number
TTR	Time in therapeutic range
VKA	Vitamin K antagonist

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APPENDIX 1 OUTCOMES/ENDPOINT VARIABLES AND ICD-10 CODES

Studied outcomes (Endpoint variables of interest)

Variable	Definition (ICD-10)
Stroke/Transient ischemic attack	I63, I64, I693-I698, G45
Myocardial infarction	I21, I22
Pulmonary embolism	I26
Other systemic thromboembolic event	I65, I66, I74, H34, K550, N280, I80, I82
Bleeding events	D68.3, I60-I62, I690-I692, J942, K221, K223, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K274, K276, K280, K282, K284, K286, K290, K631, K633, K920-K922, R04, R31, S064-S066, S068
Mortality: all-cause	
Mortality: stroke	ICD codes as above
Mortality: myocardial infarction	ICD codes as above
Mortality: other embolic event	ICD codes as above
Mortality: bleeding events	ICD codes as above
Anemia	See Appendix 2

ICD=International Classification of Diseases and Related Health Problems.

APPENDIX 2 ICT NUMBERS AND REFERENCE VALUES FOR LABORATORY PARAMETERS

The ICT numbers for the laboratory variables with the reference values valid in adults in Finland in 2013

Test name	Test abbreviation	ICT number (HUS)		Lower target	Upper target	Unit
International Normalized Ratio	P-INR	4520		2.0	3.0	
Blood picture	B-PVKT	2474				
	B-PVK+TKD	2475				
	B-PVK+Ne	8370				
Hemoglobin	B-Hb	1552	women	117	155	g/L
			men	134	167	g/L
Hematocrit	B-HCT		women	35	46	%
			men	39	50	%
Leukocyte count	fB-Leuk			3.4	8.2	E9/L
erythrocyte count	B-Eryt		women	3.90	5.20	E12/L
			men	4.25	5.70	E12/L
mean corpuscular haemoglobin	E-MCH			27	33	pg/cell
mean corpuscular volume	E-MCV			82	98	fL
platelet count	B-Trom			150	360	E9/L
Creatinine	P-Crea	4600	women	50	90	µmol/L
			men	60	100	µmol/L
Alanine aminotransferase	P-ALAT	1024	women	10	45	U/L
			men	10	70	U/L

Source: Laboratory of Helsinki University Central Hospital. Available at: http://huslab.fi/cgi-bin/ohjekirja/tt_show.exe?assay=2475&terms=pvk. Accessed February 25, 2013.

Note: The ICT numbers may not be the ones mentioned above if the laboratory is using some data system other than Hospital District of Helsinki and Uusimaa (HUS).

APPENDIX 3 ATCS INCLUDED IN THE STUDY

Possible changes in the ATC code during the study period are taken into account by Kela – The Social Insurance Institution of Finland.

B01AA03: warfarin

Antiarrhythmics:

Group C01B: antiarrhythmics, classes I and III (listed in detail in Table 1)

Group C07: beta blockers / class II antiarrhythmics (listed detail in Table 2)

C08DB01: diltiazem (class IV antiarrhythmic)

C08DA01: verapamil (class IV antiarrhythmic)

C01EB10: adenosine (other type antiarrhythmic)

Table 1: C01B ANTIARRHYTHMICS, CLASS I AND III

C01BA Antiarrhythmics, class Ia	
C01BA01	quinidine
C01BA02	procainamide
C01BA03	disopyramide
C01BA04	sparteine
C01BA05	ajmaline
C01BA08	prajmaline
C01BA12	lorajmine
C01BA51	quinidine, combinations excl. psycholeptics
C01BA71	quinidine, combinations with psycholeptics
C01BB Antiarrhythmics, class Ib	
C01BB01	lidocaine
C01BB02	mexiletine
C01BB03	tocainide
C01BB04	aprindine
C01BC Antiarrhythmics, class Ic	
C01BC03	propafenone
C01BC04	flecainide
C01BC07	lorcainide
C01BC08	encainide
C01BD Antiarrhythmics, class III	
C01BD01	amiodarone
C01BD02	bretylium tosilate
C01BD03	bunaftine
C01BD04	dofetilide
C01BD05	ibutilide
C01BD06	tedisamil
C01BD07	dronedarone
C01BG Other antiarrhythmics, class I and III	
C01BG01	moracizine
C01BG07	cibenzoline
C01BG11	vernakalant

Table 2: C07A BETA BLOCKING AGENTS

C07AA Beta blocking agents, non-selective	
C07AA01	alprenolol
C07AA02	oxprenolol
C07AA03	pindolol
C07AA05	propranolol
C07AA06	timolol
C07AA07	sotalol
C07AA12	nadolol
C07AA14	mepindolol
C07AA15	carteolol
C07AA16	tertatolol
C07AA17	bopindolol
C07AA19	bupranolol
C07AA23	penbutolol
C07AA27	cloranolol
C07AA57	sotalol, combinations
C07AB Beta blocking agents, selective	
C07AB01	practolol
C07AB02	metoprolol
C07AB03	atenolol
C07AB04	acebutolol
C07AB05	betaxolol
C07AB06	bevantolol
C07AB07	bisoprolol
C07AB08	celiprolol
C07AB09	esmolol
C07AB10	epanolol
C07AB11	s-atenolol
C07AB12	nebivolol
C07AB13	talinolol
C07AB52	metoprolol, combinations
C07AB57	bisoprolol, combinations
C07AG Alpha and beta blocking agents	
C07AG01	labetalol
C07AG02	carvedilol
C07B BETA BLOCKING AGENTS AND THIAZIDES	
C07BA Beta blocking agents, non-selective, and thiazides	
C07BA02	oxprenolol and thiazides
C07BA05	propranolol and thiazides
C07BA06	timolol and thiazides
C07BA07	sotalol and thiazides
C07BA12	nadolol and thiazides
C07BA68	metipranolol and thiazides, combinations
C07BB Beta blocking agents, selective, and thiazides	
C07BB02	metoprolol and thiazides
C07BB03	atenolol and thiazides
C07BB04	acebutolol and thiazides
C07BB06	bevantolol and thiazides
C07BB07	bisoprolol and thiazides
C07BB12	nebivolol and thiazides
C07BB52	metoprolol and thiazides, combinations
CC07BG Alpha and beta blocking agents and thiazides	
C07BG01	labetalol and thiazides

Table 2: C07A BETA BLOCKING AGENTS

C07AA Beta blocking agents, non-selective	
C07C BETA BLOCKING AGENTS AND OTHER DIURETICS	
C07CA Beta blocking agents, non-selective, and other diuretics	
C07CA02	oxprenolol and other diuretics
C07CA03	pindolol and other diuretics
C07CA17	bopindolol and other diuretics
C07CA23	penbutolol and other diuretics
C07CB Beta blocking agents, selective, and other diuretics	
C07CB02	metoprolol and other diuretics
C07CB03	atenolol and other diuretics
C07CB53	atenolol and other diuretics, combinations
C07CB Beta blocking agents, selective, and other diuretics	
C07CB02	metoprolol and other diuretics
C07CB03	atenolol and other diuretics
C07CB53	atenolol and other diuretics, combinations
C07CG Alpha and beta blocking agents and other diuretics	
C07CG01	labetalol and other diuretics
C07D BETA BLOCKING AGENTS, THIAZIDES AND OTHER DIURETICS	
C07DA Beta blocking agents, non-selective, thiazides and other diuretics	
C07DA06	timolol, thiazides and other diuretics
C07DB Beta blocking agents, selective, thiazides and other diuretics	
C07DB01	atenolol, thiazides and other diuretics
C07E BETA BLOCKING AGENTS AND VASODILATORS	
C07EA Beta blocking agents, non-selective, and vasodilators	
C07EB Beta blocking agents, selective, and vasodilators	
C07F BETA BLOCKING AGENTS AND OTHER ANTIHYPERTENSIVES	
C07FA Beta blocking agents, non-selective, and other antihypertensives	
C07FA05	propranolol and other antihypertensives
C07FB Beta blocking agents, selective, and other antihypertensives	
C07FB02	metoprolol and other antihypertensives
C07FB03	atenolol and other antihypertensives
C07FB07	bisoprolol and other antihypertensives

Source: WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index. December 2012. Available at: http://www.whocc.no/atc_ddd_index/?code=C&showdescription=yes.

Class D interactive drugs according to SFINX

Excluding etofenomate with topical ATC only; ATCs only for systemic exposure with an exception of econazole are listed in Table 3.

Table 3: Class D interactive drugs according to SFINX

Drugs increasing bleeding risk without affecting warfarin exposure or INR			
ticlopidine	B01AC05		
NSAIDs:			
dexibuprofen	M01AE14		
dexketoprofen	M01AE17		
diclofenac	M01AB05	M01AB55	
etodolac	M01AB08		
flurbiprofen	M01AE09		
ibuprofen	M01AE01	M01AE51	C01EB16
indometacin	M01AB01	M01AB51	C01EB03
ketoprofen	M01AE03	M01AE53	
ketorolac	M01AB15		
lornoxicam	M01AC05		
meclofenamic acid	M01AG04		
mefenamic acid	M01AG01		
meloxicam	M01AC06	M01AC56	
nabumetone	M01AX01		
naprokseeni	M01AE02	M01AE52	M01AE56
niflumic acid	M01AX02		
niesulide	M01AX17		
phenylbutazone	M01AA01	M01BA01	
piroxicam	M01AC01		
sulindac	M01AB02		
tenoxicam	M01AC02		
tiaprofenic acid	M01AE11		
tolfenamic acid	M01AG02		
Coxibs:			
celecoxib	M01AH01	L01XX33	
etoricoxib	M01AH05		
lumiracoxib	M01AH06		
rofecoxib	M01AH02		
parecoxib	M01AH04		
valdecoxib	M01AH03		
Other analgetics:			

Table 3: Class D interactive drugs according to SFINX

acetylsalicylic acid	B01AC06	M01BA03	N02BA01	N02BA51	N02BA71	
diflunisal	N02BA11					
Drugs raising bleeding risk by increasing warfarin exposure (and INR):						
Antifungals:						
ekonatsoli	D01AC03	G01AF05				
fluconazole	J02AC01					
metronidazole	A02BD01	A02BD02	A02BD03	A02BD08	J01XD01	P01AB01
miconazole	A07AC01	J02AB01				
sulfamethoxazole	J01EC01	J01EE01				
Miscellaneous:						
cimetidine	A02BA01	A02BA51				
clofibrate	C10AB01	C10AB03				
fluvoxamine	N06AB08					
noscapine	R05DA07					
silymarin	A05BA03					
tramadol	N02AX02	N02AX52				
Drugs increasing the risk of embolism by decreasing warfarin exposure (and INR):						
colestyramine	C10AC01					
mitotane	L01XX23					

ATC=Anatomical Therapeutic Chemical; INR=international normalized ratio; NSAIDs=non-steroidal anti-inflammatory drugs.

Source: 1.) SFINX Drug database. Class D interactive drugs. Accessed February 18, 2013. Available at: http://www.medbase.fi/sfinx/whatis_finx.htm. and 2.) WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index. December 2012. Available at: http://www.whocc.no/atc_ddd_index.

APPENDIX 4 COMORBIDITIES

Variable	Definition (ICD-10)
Hypertension	I10-I15
Thyreotoxicosis	E05
Cardiomyopathy	I420-I422, I429
Congestive heart failure	I50
Diabetes	E10-E14
Stroke	I63, I64, I693-I698
Transient ischemic attack*	G45
Vascular disease	I20-I25, I65-I66, I672, I70
Cancer	C00-C97, D00-D09
Pulmonary embolism	I26
Other venous thromboembolism	I80-183

ICD=International Statistical Classification of Diseases and Related Health Problems.