NON-INTERVENTIONAL (NI) DRUG STUDY PROTOCOL

POST-APPROVAL SAFETY STUDY (PASS) OF THE UTILIZATION PATTERN OF APIXABAN IN SWEDEN

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Compound Name:	Apixaban
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1. INTRODUCTION

Off-label prescription occurs when a practitioner chooses to prescribe a drug in a manner that is inconsistent with the prescribing information approved by the governing regulatory authority. For medicinal products approved by the European Commission, the licensed indications are documented in the Summary of Product Characteristics (SmPC). Examples of off-label prescribing may include, but are not limited to the administration of the drug in doses, routes of administration or for reasons outside of labeled indications, or use in patients who do not meet age requirements, or other criteria as outlined in the label.

1.1. Background and Rationale

Apixaban is an orally administered anticoagulant that inhibits coagulation factor Xa. It is currently approved for:

1) Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery,

2) Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors,

3) Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

These indications, referred to as knee and hip replacement, NVAF, and treatment of DVT/PE, along with the date of approval are shown in Table 1. Use of apixaban outside these indications is a regulatory and safety concern.

To address this concern, the Sponsor proposes two studies describing the utilization of the product in two countries of the European Union (EU): a drug utilization study focusing on off-label use of apixaban in Sweden, as described herein, and a second study of apixaban drug utilization in the Netherlands, which is described in a separate protocol.

The approved SmPC in Sweden will be used as the single reference safety document for this study.

Table 1. Indications and Dates of EMA Authorisations

	Abbreviated Indication	Indication	Date of EMA Authorisation
1.	THA/TKA	Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery	18 May 2011
2.	NVAF	Prevention of stroke and SE in adult patients with NVAF, with one or more risk factors, such as prior stroke or TIA; age >= 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class >= II).	19 Nov 2012
3.	Treatment of DVT/PE	Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.	28 July 2014

DVT: Deep vein thrombosis
NVAF: Non-valvular atrial fibrillation
NYHA: New York Heart Association
PE: Pulmonary Embolism
SE: Systemic Embolism
TIA: Transient Ischaemic Attack
VTE: Venous Thromboembolic Events

2. STUDY OBJECTIVES AND ENDPOINTS

The overall objective of this study is to describe the utilization pattern of apixaban in Sweden.

Specifically, the study seeks to:

1. ***Estimate*** the proportion of apixaban users in the outpatient settings who receive the drug for the approved indications at the time of the study,

2. ***Describe*** the characteristics of the patients who are prescribed apixaban for on-label and off-label indications.

3. STUDY DESIGN

This will be a descriptive study using retrospectively collected data from electronic health record databases. The study will describe the utilization pattern of apixaban during the first three years after launch for the VTE prevention indication in Sweden (01 Jan 2012 through 31 Dec 2014).

4. STUDY POPULATION

4.1. Inclusion Criteria

All patients identified in the database who have received an apixaban dispensation during the study period (01 Jan 2012 through 31 Dec 2014) will be included in this study.

4.2. Exclusion Criteria

There is no exclusion criterion. All patients identified in the database who have received at least one apixaban dispensation during the study period will be included.

5. STUDY TREATMENT AND DURATION

This is a descriptive study assessing the utilization pattern of apixaban in real-world outpatient settings. There is no study mandated dosing or duration requirement.

6. STUDY PROCEDURES

6.1. Data Source

Patients using apixaban will be identified from the National Prescribed Drug Register (PDR) which contains information on all drugs prescribed in Sweden that are dispensed to patients outside hospitals, including information about patients, drugs by ATC codes, dates, settings of the dispensing, and the specialty of the prescribing physician.

Relevant clinical history for the apixaban users identified from the PDR will be obtained from the National Patient Register (NPR). Patients in the PDR who have used apixaban will be linked to the NPR by a personal identification number (PIN) unique to all Swedish citizens. The NPR contains data from all hospital admissions in Sweden from 1987 to present. At each discharge, information is collected about the patient´s demographics, primary and secondary diagnoses, procedure codes, hospitals and wards of admission, and dates of admission and discharge. Patients who have undergone knee or hip replacement surgery will be identified by applicable procedure codes and relevant ICD-10 diagnostic codes. The ICD-10 classification system was used from 1997 and onwards so data on diagnoses and procedures may extend back to 1997.

Since 2001, it is also possible to collect the same information from visits to hospital outpatient offices. Information about other diagnoses (eg, atrial fibrillation) in patients admitted to the hospitals without knee or hip replacement or visiting hospital outpatient offices will also be retrieved. The register is updated annually and data from the previous year is usually available for analyses in November each year after completion of data quality checks.

The databases cover the whole Swedish population of 9.3 million inhabitants. In 2008, about 14,500 knee and hip replacement surgeries and 4,600 hemi-hip arthroplasties were performed; 78% of the procedures were performed for primary arthrosis. The number of primary TKA was 10,600 in 2008. In addition, re-operations and revisions were also performed. Following an average hospital stay of 4 days, 25% of the patients are discharged to rehabilitation centers or nursing homes and 75% of the patients are discharged to home. The total number of hip arthroplasties increased by 10% from 2008 to 2010.

Inpatient and outpatient hospital data are available through the NPR, but the register does not include information from primary care visits. To address the missing primary care data, a sensitivity analysis will examine primary care records for apixaban users in Västra Götaland County (1.6 million, available from 2006). These regional data will supplement the nationwide data with greater detail for patients in Västra Götaland County, as well as provide an insight into the effect of missing primary care data. At this time, Västra Götaland is the only region in Sweden where primary care data are available. These records are based on patient contacts to primary care centers and collected in the health administrative databases.

The total number of persons diagnosed with atrial fibrillation and flutter in inpatient settings in 2010 was 25,672 (0.3%) according to national Swedish health statistics. The overall prevalence of atrial fibrillation has been studied in a geographically well-defined area of northern Sweden using data from a quality register of anticoagulant treatment and was found to be 2.5% in 2010 (Andersson, Londahl et al. 2012).[1]

6.2. Data Compilation Procedure

Patients who received a dispensation for apixaban (identified by ambulatory prescriptions by general practitioner or specialist physician) will be identified. The personal identification numbers of these patients will be used to link to their hospital records.

Hip and knee replacement and other surgeries will be identified via appropriate procedure codes and ICD-10 codes from hospital discharge diagnoses. The following algorithm will be used to identify the patients who have undergone the elective hip or knee replacement surgery:

- First, procedure codes will be used to identify all patients who have undergone hip or knee replacement surgery within 30 days before apixaban prescription (including total and partial replacement procedures).
- Second, hospital discharge diagnoses (both primary and secondary) will be used to see if these included hip or knee fracture diagnostic codes.
    - If yes, then the hip or knee replacement surgery will be considered non-elective and apixaban prescription off-label.

If the primary or secondary discharge diagnoses do not include hip or knee fracture, then surgery will be considered elective and apixaban prescription on-label.

NVAF and treatment of DVT/PE will be identified by ICD-10 diagnosis codes in the main or secondary discharge diagnoses as well as in hospital outpatient visits and, where available, the primary care diagnoses.

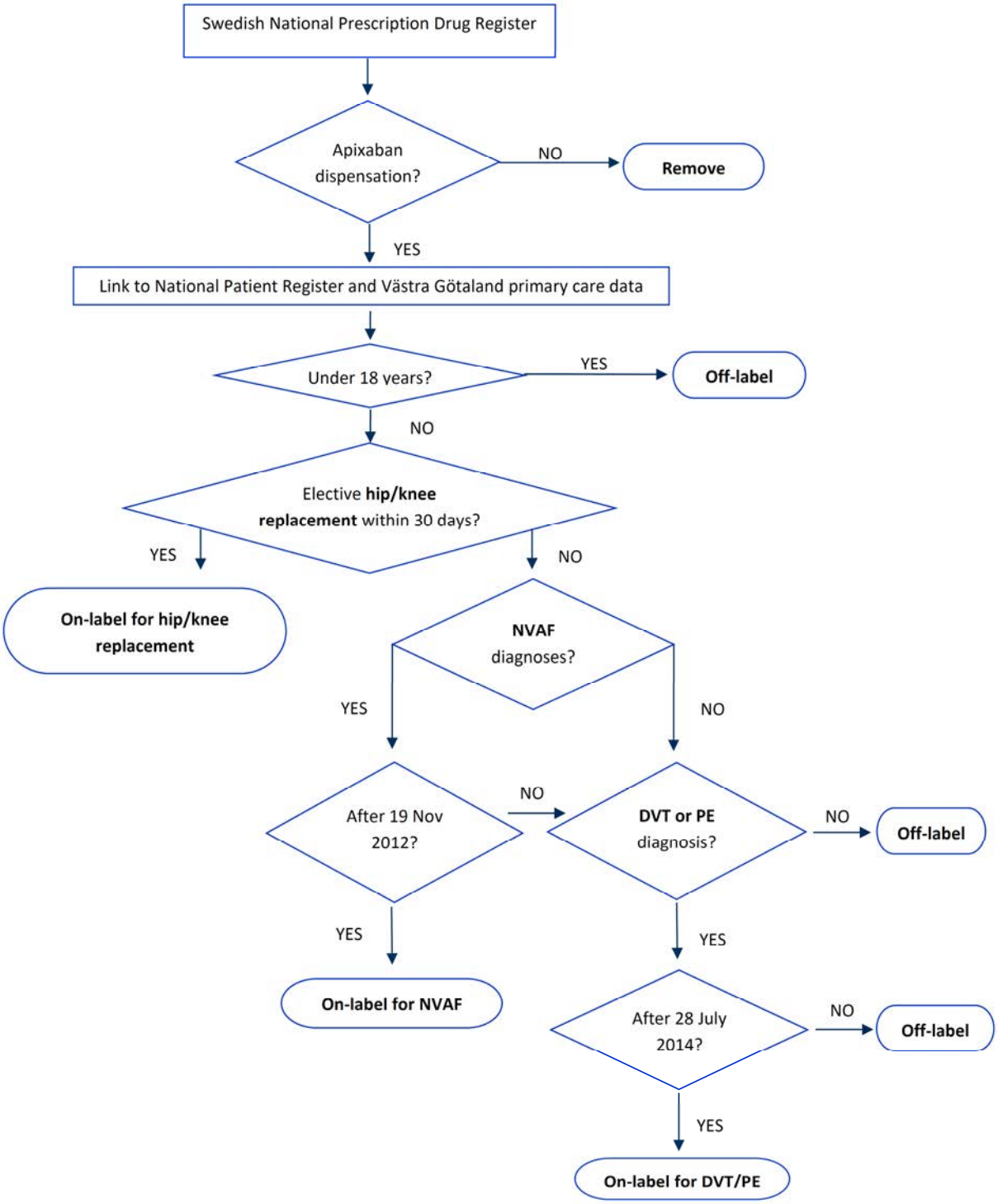
6.3. Decision Rule for Defining On- and Off-label Use

For the purpose of this study, apixaban prescriptions for the NVAF and treatment of DVT/PE indications will be considered off-label up to and including the date that apixaban received approval for those uses in the EU. Apixaban prescriptions for the NVAF and the treatment of DVT/PE indications will be classified as on-label starting on the day after regulatory approval and continuing through the end of the study.

On-label use of apixaban will be defined as a dispensation of the drug to:

1. An adult (ie, 18 years of age or older) and
2. A patient whose hospital records include:
    a) An elective hip or knee replacement within 30 days before the apixaban prescription, or,
    b) An apixaban prescription after 19 November 2012 and a diagnosis of NVAF before that apixaban prescription, or,
    c) An apixaban prescription after 28 July 2014 and a diagnosis of DVT or PE before the apixaban prescription (Figure 1).

Figure 1: Flow Chart for Record linkage and On and Off-label Classification.



If during the study apixaban receives approval for any other condition in Sweden, the new indication will be considered on-label use following the date of approval.

6.4. Data Elements

- Patient demographics: Age and Gender.
- Information on prescription for apixaban: dispensing date, dose, amount dispensed, duration of use based on amount of drug prescribed, refill date, and repeat prescription.
- Hospital admission information: dates of hospital admission and discharges, ICD-10 diagnosis codes in discharge diagnoses, surgical procedure codes.
- Outpatient hospital office visit information: date of visit, ICD-10 diagnosis codes, department type.
- Primary care records in Västra Götaland County (see above): date of contact, contact type (visit, telephone), ICD-10 diagnosis codes.
- Other recently dispensed drugs: ATC code, dispensing date, dose, amount dispensed, use at the time of apixaban dispensing based on amount of drug prescribed.

The operational definitions and coding scheme of the variables will be described in the statistical analysis plan.

7. DATA ANALYSIS/STATISTICAL METHODS

The variables to be collected in this study will be documented in a Statistical Analysis Plan. This document may modify the plans outlined in the protocol; however, any major modifications will be reflected in a protocol amendment.

7.1. Sample Size Calculation

This is a descriptive study of drug usage without any pre-defined hypothesis to be tested. Therefore, no power calculation was performed. All individual patients identified to have received apixaban in the database in the study period will be included in the study without any sampling procedure.

Based on the Sponsor's projection of the number of patients using apixaban in 2012-2014 for prevention of VTE following a hip or knee replacement it is expected that approximately 600 patients will be included in the study. It is projected that up to 13,000 patients with atrial fibrillation (AF) may be included in the study.

As shown in the table below, 19,000 apixaban patients with any indication will provide sufficiently precise estimates of on-label use. For instance, if 25% of patients use apixaban off label, the width of the 95% CI for the off-label use percent will be 1.2 percent (Table 2).

Table 2: Precision Around the Off Label Use Proportion Estimates Assuming a Total Sample Size of 19,000 Patients

Off label use (%)	Width of 95% CI for off label use (%)
5	0.6
15	1.0
25	1.2
35	1.4
45	1.4

7.2. Data Analyses

Descriptive analyses of patient level data will be conducted. Patients will be classified as on-label or off-label apixaban users based on their first prescription for apixaban. The demographic and clinical characteristics of patients identified to have received an apixaban dispensation will be described. The proportion of patients receiving the drug for indications within and outside the approved label in each of the study years will be estimated and any trend over time will be described. From the hospital discharge records, the comorbidities and clinical procedures (e.g., surgeries) at the time of or within 30 days prior to the off-label use will be tabulated as the possible indications for the off-label use. If discharge records during this period do not provide possible indications, information from previous discharges will also be tabulated according to the most recent diagnosis. Furthermore, possible switching from other antithrombotic treatment will be investigated based on dispensed prescriptions during the past year. The dose and duration of prescriptions will be summarized where available.

Stratified descriptive analyses by indication will be performed as described below. As the first step, the study will estimate the proportions of all patients in Swedish databases over the 3-years post-launch period who received apixaban for:

1. VTE prevention following elective hip and knee replacement surgery (on-label indication).

2. NVAF (off-label indication before the approval, and on-label following the approval).

3. Treatment of DVT/PE (off-label indication before the approval, and on-label following the approval).

4. Any other conditions from a list of pre-defined off-label indications, including other types of surgery and history of other diseases (off-label indications). These may include but will not be limited to hip fracture surgeries, general surgeries, gynaecologic and abdominal surgeries, and diagnoses such as cancer, myocardial infarctions, other cardiac conditions, and other hypercoaguable states in which apixaban could be used off-label.

5. Patients who have no evidence of the conditions for on-label use and who cannot be assigned to the list of pre-defined off-label uses will be classified as off-label and unknown.

The only available primary data is from patients in Västra Götaland County. Primary care data may contain information on the conditions that are used to classify on-label or off-label apixaban use. A sensitivity analysis will compare the proportion of on-label users based on both primary care and hospital data to the proportion of on-label use when only the hospital data is used among those in Västra Götaland County. This assumes that the availability of GP data is not related to the ratio of on-label or off-label use and that Västra Götaland County is representative of all of Sweden.

Second, descriptive analyses will be performed in each of the indication strata to summarize:

1. Demographic characteristics of patients and prescriber specialty.

2. Estimated duration of apixaban treatment and dosages used.

3. Concomitant medication use, with the focus on contra-indicated medications.

4. History of treatment with other anticoagulants.

5. Select co-morbid conditions/medical history, such as renal impairment, severe hepatic impairment, congenital or acquired bleeding disorders.

For off-label indication strata, distribution of surgical procedures and diagnoses that patients had prior to receiving apixaban to infer possible indications that apixaban was used for. For instance, counts and proportions of patients who had other orthopaedic surgery (eg, hip fracture), within 30 days of apixaban prescription will be reported.

7.3. Interim Analysis

The analysis will be conducted annually for three years. Interim reports will include all data available at the time of the analysis and may not include all the analyses that will be conducted in the final report.

8. DATA COLLECTION AND DATA MANAGEMENT

The details of data collection procedures have been described in Section 6.

8.1. Access to Data

The Sponsor will not have access to health register records at the level of the individual patient but only to tables with aggregated data. In case of an audit from a regulatory authority or Pfizer, the investigator will be able to document the data processing and statistical analysis and thus verify the reported results.

8.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9. ADVERSE EVENT REPORTING AND SERIOUS ADVERSE EVENT REPORTING

This study includes unstructured data (eg, narrative fields in the database) that will be converted to structured (ie, coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (ie, identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual AE reports.

10. STRENGTHS AND LIMITATIONS

10.1. Strengths:

- The study will use an established database that routinely collects information on the variables required to fulfill the objectives. There are strong linkage systems that utilize the unique national identifier of the patients to link different data sources. This database has been used for many pharmacoepidemiologic studies, including those looking at atrial fibrillation and orthopedic surgery populations (Weiss, Stark et al. 2006; Andersson, Londahl et al. 2012).[2,1]

- The database has coverage of all age groups.
- The database has coverage of all hospital admission and discharge diagnoses.
- By repeating the annual analysis over a three-year period after launch of apixaban, the study will provide data on changing trends, if any.

10.2. Limitations:

- The study is based on outpatient prescriptions. Therefore patients who receive apixaban only during hospital stay (either for the approved indication or for any off-label indication) and do not refill following discharge will not be included. This limitation will be addressed by the Netherlands study where inpatient medication use data are available from the inpatient pharmacy database covering a population of over 1 million patients from a representative sample of hospital pharmacies.
- Diagnoses are retrieved from hospital discharge records (nationwide), outpatient clinic contacts (nationwide) and primary care records (available for one county only, see above). Therefore, information on possible indications may in some cases be missing.
- Validation of the data in the database by reviewing individual patients' original medical records will not be possible.
- This study is based on medical records data being collected by the relevant government agencies and county health administrations in Sweden and then accessed by the investigators for analyses. As a result, any unforeseen delay in the collection and compilation of data by one or more of the agencies is beyond the control of the Sponsor and may affect the study timeline.

11. QUALITY CONTROL AND QUALITY ASSURANCE

Investigators are responsible for following their standard institutional procedures to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, and description of available data.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and other relevant documents from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices such as Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), EMA ENCePP Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment.

12.3. Subject Information and Consent

This is a retrospective study of de-identified data from existing databases without any direct enrollment of subjects. Therefore, no informed consent is applicable.

13. COMMUNICATION AND PUBLICATION OF STUDY RESULTS

13.1. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

For all publications relating to the Study, Investigator will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

14. REFERENCES

1. Andersson, P., M. Londahl, et al. (2012). "The prevalence of atrial fibrillation in a geographically well-defined population in Northern Sweden: implications for anticoagulation prophylaxis." J Intern Med.

2. Weiss, R. J., A. Stark, et al. (2006). "Orthopaedic surgery of the lower limbs in 49,802 rheumatoid arthritis patients: results from the Swedish National Inpatient Registry during 1987 to 2001." Ann Rheum Dis **65**(3): 335-341.

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