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Citation
Mayer, Flavia, Ursula Kirchmayer, Paola Coletta, Nera Agabiti, Valeria Belleudi, Giovanna Cappai, Mirko Di Martino, Sebastian Schneeweiss, Marina Davoli, and Elisabetta Patorno. 2018. “Safety and Effectiveness of Direct Oral Anticoagulants Versus Vitamin K Antagonists: Pilot Implementation of a Near Real Time Monitoring Program in Italy.” Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease 7 (6): e008034. doi:10.1161/JAHA.117.008034. http://dx.doi.org/10.1161/JAHA.117.008034.

Published Version
doi:10.1161/JAHA.117.008034

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Safety and Effectiveness of Direct Oral Anticoagulants Versus Vitamin K Antagonists: Pilot Implementation of a Near-Real-Time Monitoring Program in Italy

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Background—Real-time monitoring is used to the ends of postmarketing observational research on newly marketed drugs. We implemented a pilot near-real-time monitoring program on the test case of oral anticoagulants. Specifically, we evaluated the safety and effectiveness of direct oral anticoagulants compared to vitamin K antagonists in nonvalvular atrial fibrillation secondary prevention during 2013-2015 in the Lazio Region, Italy.

Methods and Results—A cohort study was conducted using a sequential propensity-score–matched new user parallel-cohort design. Sequential analyses were performed using Cox models. Overall, 10,742 patients contributed to the analyses. Compared with vitamin K antagonists, direct oral anticoagulant use was associated with a reduction of all-cause mortality (0.81; 95% confidence interval [CI] 0.66-0.99), cardiovascular mortality (0.71; 95% CI 0.54-0.93), myocardial infarction (0.67; 95% CI 0.43-1.04), ischemic stroke (0.87; 95% CI 0.52-1.45), hemorrhagic stroke (0.25; 95% CI 0.07-0.88), and with a nonsignificant increase of gastrointestinal bleeding (1.26; 95% CI 0.69-2.30).

Conclusions—The present pilot study is a cornerstone to develop real-time monitoring for new drugs in our region. (J Am Heart Assoc. 2018;7:e008034. DOI: 10.1161/JAHA.117.008034.)

Key Words: anticoagulant • comparative effectiveness • drug therapy • monitoring • pharmacoepidemiology • pilot • real-world • surveillance

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Accompanying Tables S1 through S5 and Figure S1 are available at http://jaha.ahajournals.org/content/7/6/e008034/DC1/embed/inline-supplementary-material-1.pdf

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Received December 6, 2017; accepted January 22, 2018.

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A standardized methodology has been implemented in the context of the Sentinel Program,3,4 which allows monitoring of the safety and effectiveness of newly marketed drugs through aggregation of data from different data sources, as soon as the data become available, using standardized methods.5-12 Postmarketing information is particularly useful for new drugs that have not shown a clear superiority versus the comparator drug in randomized controlled trials in the context of incremental licensing procedures, such as “adaptive licensing.”

Direct oral anticoagulants (DOACs, ie, dabigatran, rivaroxaban, apixaban) offer an alternative to vitamin K antagonists (VKAs, ie, warfarin, acenocoumarol) for the prevention of stroke or systemic embolism and all-cause mortality in patients with nonvalvular atrial fibrillation (AF). The main advantages of using DOACs with respect to VKAs are that there is no need to monitor the international normalized ratio and that they show fewer interactions with food. On the other hand, some DOACs require renal function to be regularly monitored13 and are associated with higher costs.

A meta-analysis, based on randomized controlled trials comparing individual DOACs with warfarin14-16 among nonvalvular AF patients,17 showed a significant reduction in the risk
of total mortality and hemorrhagic stroke and an increased risk for gastrointestinal bleeding associated with the randomization to DOACs. Subsequently, several healthcare database analyses comparing individual DOACs versus warfarin or VKAs have been conducted to answer questions regarding their relative safety and effectiveness in routine care, but results have not been homogeneous among different studies.18–27

In a context of rapidly accumulating postmarketing information, the establishment of a robust framework capable of generating valid, timely information on the safety and effectiveness of new medications to either support or limit evolving observed prescribing changes (Figure S1) is highly valuable. We were interested in the pilot implementation of a medication-monitoring program and chose oral anticoagulants as a test case in response to a request by the regional healthcare government. This request was motivated by the current absence of effectiveness and safety information on these agents as used in routine care in Italy. The ultimate goal is the creation of a monitoring framework that could promptly provide Italian prescribers with relevant clinical information on the safety and effectiveness of newly marketed drugs.

Methods

Study Design

We conducted a sequential propensity score (PS)–matched new user parallel cohort design of DOAC versus VKA initiators and implemented a pilot near-real-time monitoring program in the Lazio Region in central Italy, leveraging population-based healthcare data. This design has many key strengths,28 1 of which is to reduce channeling bias, which may be particularly pronounced in studies of newly marked drugs.

Source of Data

The Lazio Region healthcare assistance file collects demographic and residence information of all residents living in the Lazio Region and registered in the regional health service, accounting for ≈95% of the overall population. This database can be linked with other regional health information systems through an anonymous unique patient identifier, to capture the clinical history of this population. Specifically, information about mortality (date, place, and cause of death coded by International Classification of Diseases 9th Revision [ICD-9] code) was retrieved from the regional Mortality Information System. Information regarding admissions to regional hospitals (eg, primary and secondary diagnoses and procedures recorded at discharge, coded according to ICD-9-CM [Clinical Modification]) was retrieved from the Hospital Information System. Information on specialist visits (eg, visits and exams, prescription codes, and prescription dates) was collected from the Outpatient Specialist Service Information System. Data about emergency room visits (ie, up to 5 diagnoses coded according to ICD-9-CM, patient severity [triage code], and some clinical parameters) were collected from the Healthcare Emergency Information System. Information on drugs reimbursed by the healthcare system and dispensed by public and private pharmacies or by hospital pharmacies at discharge (ie, the national drug register code, which is related to the international ATC [Anatomical Therapeutic Chemical Classification System], claim date, number of pills), was available from the Regional Drug Dispense Registry.

All Information Systems were updated to the end of 2015.

The present study is based on anonymized patient data available in the regional health information system, and the study protocol obtained consensus from the regional ethics committee. The data, analytic methods, and study materials have been and will be made available to other researchers for purposes of reproducing the results or replicating the procedure on request to the corresponding author.

Study Population

Inclusion/Exclusion Criteria

The study population consisted of sequential cohorts of DOAC or VKA new users aged 18 to 100 years between July 1, 2013 and December 31, 2015. In Italy, DOACs were authorized for nonvalvular AF treatment during 2013: the first was dabigatran on June 19, followed by rivaroxaban and apixaban later in September 2013 and January 2014. We considered a period of 11 days as the minimum time gap for physicians to begin to implement the extended indication. Moreover, this choice
allowed us to easily divide the overall study period into 3-month sequential interim periods.

Study participants were patients not prescribed with any oral anticoagulant drugs in the 6 months before the first drug claim for a DOAC or a VKA agent during the study period (index date). We only included drug initiators who were continuously enrolled in the regional healthcare assistance file throughout the 12 months preceding the index date and who had a diagnosis of AF (ICD-9-CM codes 427.31 or 427.32) registered in Hospital Information System or Healthcare Emergency Information System in the 12 months before the index date.

We excluded patients with mitral stenosis or mechanical heart valve in order to select only patients with nonvalvular AF. Patients undergoing dialysis or with a history of renal transplant were also excluded as severe renal impairment is a contraindication for DOAC prescription. Finally, patients with joint replacement were excluded to ensure that DOACs were used for the AF indication only. All exclusion criteria were assessed during the 12 months before the index date (code lists of exclusion criteria are reported in Table S1).

**Exposure**

We compared the overall group of DOACs marketed in Italy during the study period (dabigatran, rivaroxaban, apixaban) with VKAs (warfarin, acenocoumarol). Drugs were identified using ATC codes (rivaroxaban ATC B01AF01, apixaban ATC B01AF02, dabigatran ATC B01AE07, warfarin ATC B01AA03, acenocoumarol ATC B01AA07).

Because information on the exact number of days supplied is not available in the Regional Drug Dispense Registry, patients’ drug use periods were calculated using the defined daily doses (DDD) metric as defined by the World Health Organization. For each prescription the total number of DDDs was translated into the number of days in which the patient was treated, counting 1 DDD per day and distributing all available DDDs to the days of follow-up and allowing for the use of accumulated DDDs over time.

We allowed for a renewal grace time (a maximum number of days without any drug supply permitted between 2 consecutive drug claims of the same drug group) of 90 days and a final grace period (extension of the observation period after the last day of exposure) of 90 days.

The duration of the grace periods was chosen on the basis of the distribution of the mean difference between 2 consecutive drug claims observed in the study population and on the basis of a descriptive analysis for a sample of our VKA population for whom we obtained information regarding the individual prescribed doses.

**Follow-up and Outcomes**

Follow-up started on the day following the index date and ended at the occurrence of the first event among a study outcome, death, regional healthcare assistance disenrollment, discontinuation of the index drug treatment (defined as a gap greater than 90 days between the last day covered by a drug claim and the start of the subsequent drug claim of the same drug group; date of discontinuation was defined as the date of last day covered by DDD prescribed plus the grace period of 90 days), switch to the alternative drug group, and end of the study period (December 31, 2015), in an as-treated approach.

The primary study outcome was mortality for any cause; secondary outcomes were cardiovascular mortality, acute myocardial infarction, ischemic and hemorrhagic stroke, and gastrointestinal bleeding (see Table S2 for outcome definitions). Each outcome was evaluated separately. If more than 1 study outcome occurred during the follow-up time, we considered each of them in separate analyses. If patients experienced the same study outcome more than once, only the first outcome was considered.

**Patient Characteristics**

Patient characteristics were measured from the different health information systems during the year before the index date and included demographic information, comorbidities (eg, risk factors for bleeding, ischemic stroke), drug use (eg, oral cardiovascular agents, medications that increase bleeding risk, interacting medications), measures of health service utilization, a combined comorbidity score, adapted for administrative data, for a total of 90 potential confounders (see Table S3 for a complete list of patient characteristics and related ICD-9-CM and ATC codes).

**Statistical Analysis**

*Identification of Sequential PS-Matched Cohorts*

We started the monitoring program on July 1, 2013. After the first monitoring period comprising 6 months (July 2013 through December 2013), we used subsequent monitoring intervals of 3 months for cohort update. In each interval we identified new users of DOACs and VKAs on a periodic basis as data became available. In this pilot phase we identified 9 monitoring periods. In Italy healthcare data are collected for administrative purposes by the regional government, which then grants access to updates with a 6-month delay. In this study we implemented a sequential analysis built on 3-month windows to mimic an ideal situation characterized by 3-month delays between data collection and analysis.

For each monitoring period, we estimated PS models on all eligible initiators during that interval, keeping matches from previous intervals fixed. PS was estimated in a logistic regression model as the probability of being prescribed with a
DOAC versus a VKA conditional on the 90 potential confounders reported in Table S3. DOAC initiators were 1:1 PS-matched to their nearest VKA initiators within a caliper of 0.05 on the PS scale. In each monitoring period, covariate balance between the 2 matched exposure groups was evaluated through absolute standardized differences; values below 0.1 were interpreted as evidence of good balance achievement.

Sequential Analyses
To compare the risk of each outcome of interest between DOAC and VKA new users over time, at the end of each monitoring period we calculated cumulative PS-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) using Cox proportional hazard models stratified by matched set. The proportional hazards assumption was assessed using Schoenfeld residuals.

We decided a priori to continue the monitoring program throughout the entire study period July 2013 through December 2015, so we did not conduct sequential testing at each interim analysis to assess whether the accumulated evidence was sufficient to stop or to continue the monitoring.

To account for the fact that patients may be prescribed therapeutic doses other than the DDD or may not be perfectly adherent to daily drug therapy, we performed an intention-to-treat analysis, in which the follow-up started on the day following the index date and ended at the occurrence of the first event among a study outcome of death, regional healthcare assistance disenrollment, 12 months of follow-up, or end of study period (December 31, 2015), without considering index treatment discontinuation.

Implementation Details
In the first monitoring period (July 2013 through December 2013), all DOAC and VKA users with an index date in this period were enrolled, applying inclusion/exclusion criteria, and the information data related to 90 covariates (retrieved from different health information systems in the year before the index date) were used to build the PS. Then, DOAC and VKA users were matched 1:1, using the nearest-neighbor method. The 2 matched cohorts were followed-up from the day after the index date to the occurrence of the first event among study outcome, death, disenrollment, discontinuation, switching, and end of monitoring period (March 31, 2014). Meanwhile, follow-up time for the DOAC and VKA users cohorts already matched in the first monitoring period were extended until the occurrence of the first event among study outcome, death, disenrollment, discontinuation, switching, and end of the second monitoring period. At this point the second analysis was performed running a crude Cox proportional hazard model to estimate the second updating study outcome HRs. This procedure was then used for the further monitoring periods, following the scheme proposed by Schneeweiss and colleagues.

Analyses were performed using SAS 9.2 (SAS Institute Inc, Cary, NC) and Stata version 12 (Stata Corporation, College Station, TX).

Results
Study Population and Patient Characteristics
During the study period, DOAC use increased steadily, while VKA use sharply dropped until DOACs outweighed VKAs in September 2015 (Figure S1). Overall, 124,684 patients initiated an oral anticoagulant agent during the study period. After the application of the inclusion and exclusion criteria, the study population accounted for 19,201 patients overall, with the following distribution in each of the 9 periods: 4199 patients in the first period (19.7% DOACs), 2351 in the second (30.2% DOACs), 1901 in the third (35.6% DOACs), 1657 in the fourth (41.2% DOACs), 1817 in the fifth (48.4% DOACs), 1990 in the sixth (53.6% DOACs), 1959 in the seventh (55.3% DOACs), 1515 in the eighth (58.8% DOACs), 1815 in the ninth (63.5% DOACs) (Figure 1).

Before PS matching, some covariates were unbalanced across most monitoring periods (data not shown). VKA patients were more likely to have a history of chronic kidney disease, percutaneous coronary intervention, acute myocardial infarction, and other cardiovascular diseases, whereas DOAC patients had a higher prevalence of prior ischemic stroke. VKA patients were also more likely to receive treatment with heparin and diuretics at baseline. After PS matching, all patient characteristics were well balanced, as assessed by absolute standardized differences lower than 0.1 (Table S4 reports patient characteristics and their balance between the 2 groups at the end of the ninth period before and after PS matching).

PS-matched sequential cohorts steadily accumulated over time, starting with 1650 enrollees in the first monitoring period and reaching 10,742 in the ninth period.
Safety and Effectiveness Outcomes

For all outcomes of interest, with increasing numbers of enrollees, power and precision of the effect estimates increased over time (Figures 2 through 7).

Compared with VKAs, DOACs were associated with a decrease in the risk of total mortality, with a broad confidence interval in the first period (HR 0.42; 95% CI 0.16-1.11) and a more precise estimate at the end of the study period (HR 0.81; 95% CI 0.66-0.99) (Figure 2). DOAC use was also associated with a 29% reduction in the risk of cardiovascular mortality (HR 0.71; 95% CI 0.54-0.93, by the end of the study period) compared with VKA use (Figure 3). By the end of the study period, we observed a decrease in risk of acute myocardial infarction associated with the use of DOACs (HR 0.67; 95% CI 0.43-1.04), although effect estimates were imprecise due to the low number of events (Figure 4). DOAC use was also associated with a nonsignificant reduction in the risk of ischemic stroke (HR 0.87; 95% CI 0.52-1.45) and with a meaningful but imprecise reduction in the risk of hemorrhagic stroke (HR 0.25; 95% CI 0.07-0.88) and ischemic stroke (HR 0.87; 95% CI 0.52-1.45) (Figures 5 and 6). Finally, we observed a nonsignificant excess in the risk of gastrointestinal bleeding among DOAC initiators compared with patients initiating VKAs (HR 1.26; 95% CI 0.69-2.30) (Figure 7).

Results from the intention-to-treat analysis mostly confirmed the main findings (Table S5).

Discussion

In this pilot implementation of a near-real-time monitoring program in Italy, patients with nonvalvular AF initiating DOACs had a significant reduction in the risk of all-cause and cardiovascular mortality and in the risk of hemorrhagic stroke compared with VKA initiators with AF. DOACs were also associated with a slightly decreased risk of myocardial infarction and ischemic stroke and with a nonsignificant increased risk of gastrointestinal bleeding. The different outcomes were analyzed independently from each other, and competing risks were not considered.

Our findings are in line with results of 3 meta-analyses of randomized clinical trials comparing DOACs versus VKAs. Specifically, the reduced risk among DOAC users to experience all-cause mortality, hemorrhagic stroke, and ischemic outcomes is comparable across studies. Also, our nonsignificant finding of an increased risk of gastrointestinal bleeding is confirmed by 2 of the meta-analyses. Similarly, our results are in line with findings from previous observational studies that compared single DOACs versus warfarin.

At the time we started monitoring, evidence on the comparative effectiveness of DOACs versus VKAs was still
not conclusive, especially regarding the real-world setting. Therefore, our regional health policy makers committed to this study. As mentioned above, we believe this is still a relevant clinical question in the context of local settings where specific patterns of use of medications may play an important role toward their overall safety and effectiveness. This relevant question is embedded within the first pilot implementation of a monitoring framework in Italy and, to our knowledge, in Europe. This system could be used to promptly monitor new drugs nationwide with the ultimate goal to provide stakeholders with information for rapid decision making.

In this pilot monitoring program the sequential accrual of the data was simulated to conduct sequential analyses. As new medications enter the market, this monitoring framework will promptly provide Italian prescribers with relevant clinical information on the safety and effectiveness of new agents in “near”-real-time, which comes from the fact that there is generally a lag between when the drug is delivered to a patient and when the data become available for analysis.28,39 This occurs in temporal updates, which we refer to as “monitoring periods” in the current article. This is a peculiarity of claims data in general and, thus, of postmarketing surveillance programs based on claims data, including the

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**Figure 2.** Mortality—sequential analysis of new users of DOACs vs VKAs—HR and 95% CI. CI indicates confidence interval; DOAC, direct oral anticoagulants; HR, hazard ratio; PS, propensity score; VKA, vitamin K antagonists.

**Figure 3.** Cardiovascular mortality—sequential analysis of new users of DOACs vs VKAs—HR and 95% CI. CI indicates confidence interval; DOAC, direct oral anticoagulants; HR, hazard ratio; PS, propensity score; VKA, vitamin K antagonists.
US Sentinel program. In Italy, healthcare data are collected for administrative purposes by the regional government, which then grants access to updates with a 6-month delay. In this study we implemented a sequential analysis built on 3-month windows to mimic an ideal situation characterized by 3-month delays between data collection and analysis. The usefulness of a real-time monitoring system as demonstrated by this pilot study may drive the process of accelerating data access in Italy.

As in the majority of observational studies based on administrative databases, confounding is a challenge. We tried to rule out measurable confounding as much as possible using specific techniques in the design and in the analysis. To this end, we excluded patients with hospital and/or specialist care codes for chronic dialysis and those with kidney replaced by transplant (Table S1). In the propensity score we accounted for over 90 potential confounders, which included chronic kidney disease, percutaneous coronary intervention, and the use of antiplatelets (Table S3).

In studying newly authorized drugs, confounding by indication is a potential risk. In a monitoring program it is fundamental to account for the potential temporal changes in prescribing patterns. As shown in Figure S1, prescribing
patterns of DOACs and VKAs rapidly changed over time: in the first month after authorization, DOACs accounted for about 10% of newly prescribed anticoagulants in AF patients, whereas at the end of our observation period, DOACs had become the first anticoagulant choice. To account for these rapid changes, we PS-matched patients within 3-month monitoring periods.

Another critical issue may come from socioeconomic differences in access to treatment and risk of the outcome, but a previous investigation on secondary prevention after myocardial infarction in a similar population in the same region showed that in our healthcare system, where chronic drug treatment is equally accessible to all residents, this is not an issue.40

A strength of our population-based observational study is that we were able to enroll all patients treated with the study drugs in a real-world setting, independently of older ages, comedications, comorbidities, and so forth. Consequently, our population is older and sicker than those included in clinical trials and is representative of patients actually treated. In order to guarantee internal validity, we applied some exclusion criteria, such as renal disorders, and therefore, our results may not be transferrable to special populations such as patients with chronic kidney disease.

Figure 6. Hemorrhagic stroke—sequential analysis of new users of DOACs vs VKAs—HR and 95% CI. CI indicates confidence interval; DOAC, direct oral anticoagulants; HR, hazard ratio; PS, propensity score; VKA, vitamin K antagonists.

Figure 7. Gastrointestinal bleeding—sequential analysis of new users of DOACs vs VKAs—HR and 95% CI. CI indicates confidence interval; DOAC, direct oral anticoagulants; HR, hazard ratio; PS, propensity score; VKA, vitamin K antagonists.
Our study has several limitations, one of which is the risk of residual confounding. We accounted for 90 potential confounders available in our data, but we did not have any detailed clinical information, which might play an important role. In particular, we built proxies of CHA2DS2-VASc and HAS-BLED scores, but as values of creatinine clearance were not available, we used the number of creatinine tests instead. Moreover, our data lack important sociodemographic information such as body mass index, smoking, and socioeconomic status. For a subset of the study population, receiving care at an anticoagulant center of the Lazio Region, some clinical variables recorded during ambulatory visits, which are not captured in administrative databases (such as type and dosage of anticoagulant drugs, exact HAS-BLED and CHA2DS2-VASc score, international normalized ratio value, creatinine clearance, and others), will become available for subsequent monitoring periods. This information will allow us to evaluate the balance of these potential unmeasured confounders between exposure groups within this subset and to possibly use that balance for adjustment purposes.

Another limitation of this study was the adherence calculation using the DDD to approximate the days supplied, especially for VKAs, as physicians frequently need to adapt individual prescribed doses according to periodic international normalized ratio measurements, and our data provide neither individual doses nor results of the international normalized ratio measurements. We addressed this limitation by applying a grace period of 90 days in the main analysis and by performing sensitivity analyses with an intention-to-treat approach, which produced consistent results to the main findings.

Weaknesses related to study power, unmeasured confounding, and generalizability will be addressed in a next step, extending the study population to other Italian regions and performing external adjustment using detailed clinical information available for a subsample of the Lazio cohort. A larger sample size will also allow for comparing single DOACs versus single VKAs and performing intraclass comparisons among individual DOAC agents to test the potential differences in safety and effectiveness among the different DOACs highlighted previously.

Conclusions
The present study describes the pilot implementation of a monitoring program for newly marketed medications in the Lazio region and demonstrates the feasibility of such a framework to produce timely and valid evidence on the comparative safety and effectiveness of new drugs. In Italy, all healthcare–related data are routinely collected for administrative purposes, and the access does not imply any extra costs. Using these data for postmarketing surveillance is actually an added value, which requests an investment in human resources but not in data acquisition. Thus, a system based on routinely collected data is much more cost-effective than any active data collection for monitoring purposes. Although active pharmacovigilance is based on cases reported by healthcare providers and thus depends on their awareness and willingness to actively feed the system, a system based on routine data can identify a much larger range of outcomes. A fully developed monitoring system will be a useful instrument for clinicians and healthcare decision makers, defining the net incremental value of new agents.

Sources of Funding
This work was supported by a grant from the regional Pharmacovigilance call 2014 with grants from the Italian Medicine Agency.

Disclosures
None.

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SUPPLEMENTAL MATERIAL
Table S1. Exclusion criteria.

| DESCRIPTION                                      | CODE TYPE AND CODE*                                                                 | EXCLUSION PERIOD                      |
|-------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------|
| Codes Suggestive of Chronic Dialysis             | ICD9(D): 792.5, V56, V45.1                                                         | 1 year before index date              |
|                                                 | ICD9(P): 39.95, 54.98, 38.95                                                        |                                       |
|                                                 | OSSIS: 38.95, 39.95.1, 39.95.2, 39.95.3, 39.95.4, 39.95.5, 39.95.6, 39.95.7, 39.95.8, 39.95.9, 39.99.1, 54.93, 54.98.1, 54.98.2, 96.57, 97.29.1, 97.82 |                                       |
| Kidney replaced by transplant                    | ICD9(D): V42.0, 996.81                                                              | 1 year before index date              |
|                                                 | ICD9(P): 55.6                                                                       |                                       |
| Mitral/Aortic stenosis or mechanical heart valve | ICD9(D): 394.0, 394.2, 395.0, 395.2, 396.0, 396.1, 746.3, 746.5, 996.02, 996.71   | 1 year before index date              |
|                                                 | ICD9(P): 35.20-35.24                                                                |                                       |
| Recent joint replacement/arthroplasty surgery     | ICD9(P): 00.70 - 00.77, 00.80 - 00.87, 81.51-81.55                                | 1 year before index date              |

D=Diagnoses (primary or secondary); P=procedures (primary or secondary)
Table S2. Outcomes of interest.

| OUTCOME                | CODES                                      |
|------------------------|--------------------------------------------|
| Total mortality        | 001-999 (ICD9 codes)                       |
| Cardiovascular mortality| 390-459 (ICD9 codes)                       |
| AMI                    | Mortality: 410-414 (ICD9 codes) or         |
|                        | Hospital admission: Primary diagnosis of   |
|                        | acute myocardial infarction (ICD-9-CM 410.0, 410.x1) |
| Ischemic stroke        | Mortality 433, 434, 436 (ICD9 codes) or    |
|                        | Hospital admission: Primary diagnosis of   |
|                        | Ischemic stroke (ICD-9-CM 433.x1, 434.x1, 436) |
| Hemorrhagic stroke     | Mortality 430, 431 (ICD9 codes) or         |
|                        | Hospital admission: Primary diagnosis of   |
|                        | hemorrhagic stroke (ICD-9-CM 430, 431)     |
| GI bleeding            | 455.2, 455.5, 455.8, 456.0, 456.20, 503.93, 530.7, 530.82, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.0, 578.1, 578.9 (ICD-9-CM codes, primary diagnosis) |
Table S3. Potential confounders included in the PS – part 1.

| BROAD CATEGORIES OF CONFOUNDERS | DESCRIPTION | ICD9-CM CODES |
|---------------------------------|-------------|---------------|
| Sex                             |             |               |
| Age                             | deciles     |               |
| Enrollment period               | Enrollment period | from 1 to 9 |
| Measures of overall health status | Number of distinct active agents (tertiles) | distinct ATC at 5<sup>th</sup> level |
|                                 | Number of prior hospitalizations (yes/no) | from HIS |
|                                 | Number of prior outpatient visits (quintiles) | from OSSIS |
|                                 | Presence of hospitalization with at least 1 major surgical procedure | from HIS |
|                                 | Number of prior emergency room visits (0, 1, >1) | from HEIS |
| Combined comorbidity score (tertiles) | Reference 30 |
| CHA2DS2-VASc score (tertiles)   | Reference 31 |
| HAS-BLED score (tertiles)       | Reference 31 |
| Frailty indicator (at least one condition among: septicemia, sepsis, accidental falls, Osteoporotic fracture, urinary incontinence, oxygen, decubitus ulcers) | septicemia 038, sepsis 995.91, 995.92, accidental falls E880-E888, Osteoporotic fracture V13.51, urinary incontinence 788.3, 788.91, 625.6, oxygen V46.2, decubitus ulcers 707 |
| Prior Hemorrhagic stroke        | 430, 431    |
| Risk factors for | Major haemorrhagic event |  |
|-----------------|--------------------------|------------------|
| GI bleeding     | 455.2, 455.5, 455.8, 456.0, 456.20, 503.93, 530.7, 530.82, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.0, 578.1, 578.9, 535.71, 537.84, 569.86 |
| Other bleed     | 432, 853.0 Prior intracranial bleed without open intracranial wound, 286.5 Hemorrhagic disorder due to intrinsic circulating anticoagulants, 530.21 Ulcer of esophagus with bleeding, 719.1 hemoartroses, 459.0 Hemorrhage, unspecified, Epistaxis 784.7, Haemorrhhalmos except current injury 360.43, Choroidal haemorrhage, unspecified 363.61, Hyphema 364.41, Conjunctival haemorrhage 372.72, Vitreous haemorrhage 379.32, Haemoptysis 786.3, Haemorrhage or hematoma complicating a procedure 998.1, 568.81, 782.7, 596.7, 599.7, 626.5, 626.6, 626.9, 627.0, 627.1, 784.8, 423.0 |
| Upper GI disease without mention of hemorrhage | 531.1, 531.3, 531.5, 531.7-531.9, 532.1, 532.3, 532.5, 532.7-532.9, V12.71, 533.1, 533.3, 533.5, 533.7-533.9, 534.1, 534.3, 534.5, 534.7-534.9, 535.00, 535.10, 535.20, 535.30, 535.40, 535.50, 535.60, 535.70, 456.1, 456.21 |
| Hypertension    | 401–405 |
| Anemia          | 280-285 |
| Chronic Kidney Disease (CKD) | Chronic Renal Insufficiency 582, 583, 585, 586, 587, Diabetic Nephropathy 250.4, 250.40, 250.41, 250.42, 250.43, Hypertensive nephropathy 403.xx, 404.xx, Acute Renal Failure 572.4, 580.xx, 584.xx, 580.0, 580.4, 580.89, 580.9, 582.4, 791.2, 791.3, Miscellaneous other renal disease 274.10, 440.1, 442.1, 453.3, 581.xx, 593.xx, 753.0, 753.3, 866.00, 866.01, 866.1 |
| Chronic liver disease and cirrhosis | 571, 570, 572, 573 (except 573.0), 070 |
| Prior ischemic stroke | 433.x1, 434.x1, 436 |
| Risk factors for Major ischemic event | Sistemic Embolism (SE) | 444 |
|--------------------------------------|------------------------|-----|
|                                      | Transient ischemic attack (TIA) | 435 |
|                                      | Other cerebrovascular disease | 433 (except 433.x1), 434 (except 434.x1), 437, V12.54, 438 |
|                                      | Prior percutaneous coronary intervention (PCI) | ICD9(D): V45.81, V45.82, 996.03 |
|                                      |                                      | ICD9(P): 0.66, 17.55, 36.01-36.09, 37.22, 37.23, 88.5x, 36.1X, 36.2 |
|                                      | Peripheral vascular disease | 093.0, 440-448 (except 444), 557 |
|                                      | Venous thromboembolism (VTE) | 453.xx (other venous embolism and thrombosis); 451.xx (phlebitis and thrombophlebitis); 415.1x (pulmonary embolism and infarction) |
|                                      | Heart failure | 428 |
|                                      | Cardiac dysrhythmias except Atrial Fibrillation | 427.0, 427.1, 427.2, 427.4, 427.5, 427.6, 427.8, 427.9 |
|                                      | Other cardiovascular disease | 425, 426, 745, V15.1, V42.2, V43.2, V43.3, V45.0, 394-396, 397.0 424, 746, 84.10-84.17, 39.25, 39.29, 38.18, 38.19 |
|                                      | Diabetes | 250 |
|                                      | Hyperlipidemia | 272.0, 272.1, 272.2, 272.4 |
|                                      | Ischemic heart Disease | 410-414 |
|                                      | ● Acute myocardial infarction | 410 |
|                                      | ● Unstable Angina | 411 |
|                                      | ● Old myocardial infarction | 412 |
|                                      | ● Angina pectoris | 413 |
|                                      | ● Other forms of chronic ischemic heart disease | 414 |
|                                      | Cardioablation | 37.34 Excision or destruction of other lesion or tissue of heart, endovascular approach (Modified maze procedure, percutaneous approach) |
| Other risk factors | Cardioversion | 99.61 Atrial cardioversion |
|-------------------|---------------|---------------------------|
| Overweight and obesity | ICD9 (P): 44.93, 44.94, 44.68, 44.95, 44.96, 44.97, 44.98 IC9 (D): 278.0, V45.86, V65.3, V85.23, V85.24, V85.25, V85.3, V85.4 |
| Chronic Obstructive Lung Disease (asthma/Chronic obstructive pulmonary disease COPD) | 491, 492, 493, 494, 496 |
| Psychiatric condition (Psychosis, Depression) | 293.8, 295-298, 299.1, 300.4, 301.12, 309.0, 309.1, 311 |
| Dementias/Alzheimer | 290.0-290.4, 294.1, 331.0 |
| Malignant neoplasm | 140.0-208.9, V10 |
| Pneumonia | 480-486, 507, 021.2, 039.1, 052.1, 055.1, 073.0, 112.4, 114.0, 130.4, 136.3, 487.0, 003.22, 115.05, 115.15, 115.95 |
| **Outpatients visits (OSSIS codes)** | Number of INR tests (tertiles) | 90.75.4 |
| | Other exams related to blood coagulation | 90.64.3, 99.06.1, 90.64.5, 90.65.1, 90.75.5, 90.76.1, 90.76.2 |
| | Exams relative to renal function | P585A, P585B, P592, 38.95, 55.92, 59.8, 98.51.1, 98.51.2, 98.51.3, 90.40.2, 90.51.5 |
| | Number of creatinine tests (tertiles) | 90.16.3, 90.16.4 |
| | Exams related to lipids (tertiles) | 90.14.1, 90.14.2, 90.14.3, 90.43.2 |
| | Number of blood pressure measurements | 89.61.1 |
| | Number of haemoglobin measurements | 90.62.1, 90.66.2, 90.66.3 |
| | Visits/exams relative to heart failure or to ejection fraction measurement | P428, 92.05.3, 92.05.4, 88.72.2, 88.72.3, 88.72.4, 92.05.1, 92.05.2, 90.05.3, 90.05.4, 92.09.1, 92.09.2, 92.09.3 |
Table S3. Potential confounders included in the PS – part 2: ATC code for medications.

| BROAD CATEGORIES OF CONFOUNDERS | DESCRIPTION                                                                                                                                                                                                 | ATC CODES |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Drug therapy                    | **Cardiovascular and antidiabetic agents**                                                                                                                                                                  |           |
|                                 | Statins                                                                                                                                                                                                       | C10AA, C10B |
|                                 | Non-statin lipid lowering agents                                                                                                                                                                           | C10AB, C10AC, C10AD, C10AX |
|                                 | Digitalis glycosides                                                                                                                                                                                          | C01AA     |
|                                 | Nitrates                                                                                                                                                                                                     | C01DA     |
|                                 | Oral antidiabetic agents (Biguanides, Sulfonylureas, Sulphonamides (heterocyclic), Combinations of oral blood glucose lowering drugs, Alpha glucosidase inhibitors, Thiazolidinediones, Dipeptidyl peptidase 4 (DPP-4) inhibitors, Other blood glucose lowering drugs, excl. insulins) |           |
|                                 | Insulin                                                                                                                                                                                                       | A10A      |
|                                 | ACE inhibitors                                                                                                                                                                                                | C09A, C09B |
|                                 | Angiotensin receptor blockers (ARBs)                                                                                                                                                                           | C09C, C09D |
|                                 | Aldosterone receptor antagonists                                                                                                                                                                             | C03DA     |
|                                 | Beta blockers                                                                                                                                                                                                  | C07       |
|                                 | Calcium channel blockers                                                                                                                                                                                      | C08       |
|                                 | **Diuretics**                                                                                                                                                                                                  |           |
|                                 | ● Loop-diuretics                                                                                                                                                                                              | C03C      |
|                                 | ● Others                                                                                                                                                                                                       | C03B, C03D, C03E, C03X, C03A |
|                                 | **Other antihypertensives**                                                                                                                                                                                    |           |
|                                 | Antiarrhythmics                                                                                                                                                                                                | C01BA, C01BB, C01BC, C01BD, C01BG |
|                                 | **Antifibrinolytics**                                                                                                                                                                                           |           |
|                                 | **Glucocorticoids (Oral corticosteroids)**                                                                                                                                                                     |           |
|                                 | **Antiepileptics**                                                                                                                                                                                              |           |
|                                 |                                                                                                                                                                                                              |           |
### Antipsychotics

| Medications that increase bleeding risk: | N05A |
|-----------------------------------------|------|
| • Nonsteroidal anti-inflammatory drugs (NSAIDs) | M01A |
| Coxibs | M01AH |
| Others NSAIDs | M01AB, M01AC, M01AE, M01AX |
| • Antidepressant | N06AB |
| Selective serotonin receptor inhibitors (SSRIs) | N06AX16, N06AX21 |
| Serotonin and noradrenaline reuptake inhibitors (SNRIs) | N06AA, N06AX12, N06AA21, N06AX05, N06AX11 |
| Others | |
| • Antiplatelet agents | |
| Aspirin (to the extent captured) | B01AC06, B01AC56 |
| Clopidogrel | B01AC04 |
| Others | B01AC02, B01AC03, B01AC05, B01AC09, B01AC10, B01AC11, B01AC13, B01AC16, B01AC17, B01AC18, B01AC21, B01AC22, B01AC23, B01AC24, B01AC30, B01AC49 |
| • Injectable anticoagulants | |
| Heparin | B01AB01 |
| Fondaparinux | B01AX05 |
| Low molecular weight heparin | B01AB04, B01AB05, B01AB06, B01AB07, B01AB08, B01AB10, B01AB11, B01AB12 |
| Medications that may protect from bleeding: | |
| H2 antagonists | A02BA |
| Proton pump inhibitors (PPIs) | A02BC |
| Medications listed on label as having a potential interaction with anticoagulant drugs (not already listed above): | |
| Medicine          | Code(s)                          |
|-------------------|----------------------------------|
| Diclofenac        | A01AD11, D11AX18, M01AB05, M02AA15, S01BC03, M01AB55 |
| Antacids          | A02A                             |
| Clarithromycin    | J01FA09                          |
| Ciprofloxazin     | J01MA02, S01AE03, S02AA15        |
| Allopurinol       | M04AA01                          |
Table S4. Baseline characteristics for the overall population before PS-matching and for the sequential cohort after PS matching in each monitoring periods.

| Baseline characteristics                      | All eligible patients (unmatched) | Overall sequential PS-matched cohorts |
|-----------------------------------------------|-----------------------------------|---------------------------------------|
|                                               | VKAs N=11237                       | DOACs N=7964                          | VKAs N=5371 | DOACs N=5371 |
|                                               | N  | %    | N    | %    | N  | %    | N    | %    | Absolute standardized differences | Absolute standardized differences |
| Sex (women)                                   | 5628 | 50.08 | 4121 | 51.75 | 0.0 | 2698 | 50.23 | 2698 | 50.23 | 0.0 |
| Age (deciles)                                 |              |              |              |              |              |              |              |              |              |
| <=62                                          | 1194 | 10.63 | 824  | 10.35 | 0.0 | 599  | 11.15 | 546  | 10.17 | 0.0 |
| 63-68                                         | 1204 | 10.71 | 951  | 11.94 | 0.0 | 630  | 11.73 | 615  | 11.45 | 0.0 |
| 69-71                                         | 852  | 7.58  | 621  | 7.80  | 0.0 | 429  | 7.99  | 431  | 8.02  | 0.0 |
| 72-74                                         | 1150 | 10.23 | 781  | 9.81  | 0.0 | 536  | 9.98  | 531  | 9.89  | 0.0 |
| 75-77                                         | 1425 | 12.68 | 954  | 11.98 | 0.0 | 658  | 12.25 | 657  | 12.23 | 0.0 |
| 78-79                                         | 971  | 8.64  | 680  | 8.54  | 0.0 | 453  | 8.43  | 460  | 8.56  | 0.0 |
| 80-81                                         | 983  | 8.75  | 706  | 8.86  | 0.0 | 457  | 8.51  | 478  | 8.90  | 0.0 |
| 82-84                                         | 1445 | 12.86 | 953  | 11.97 | 0.0 | 652  | 12.14 | 652  | 12.14 | 0.0 |
| 85-87                                         | 1081 | 9.62  | 726  | 9.12  | 0.0 | 495  | 9.22  | 495  | 9.22  | 0.0 |
| >=88                                          | 932  | 8.29  | 768  | 9.64  | 0.0 | 462  | 8.60  | 506  | 9.42  | 0.0 |
| Frailty indicator                              | 182  | 1.62  | 105  | 1.32  | 0.0 | 70   | 1.30  | 72   | 1.34  | 0.0 |
| Prior Hemorrhagic stroke                      | 25   | 0.22  | 33   | 0.41  | 0.0 | 11   | 0.20  | 15   | 0.28  | 0.0 |
| Prior GI bleeding                             | 133  | 1.18  | 76   | 0.95  | 0.0 | 43   | 0.80  | 47   | 0.88  | 0.0 |
| Other bleed                                   | 180  | 1.60  | 104  | 1.31  | 0.0 | 75   | 1.40  | 68   | 1.27  | 0.0 |
| Upper GI disease without mention of hemorrhage| 101  | 0.90  | 70   | 0.88  | 0.0 | 42   | 0.78  | 42   | 0.78  | 0.0 |
| Chronic Kidney Disease (CKD)                  | 1401 | 12.47 | 520  | 6.53  | 0.2 | 474  | 8.83  | 448  | 8.34  | 0.0 |
| Chronic liver disease and cirrhosis           | 167  | 1.49  | 87   | 1.09  | 0.0 | 71   | 1.32  | 67   | 1.25  | 0.0 |
| Prior ischemic stroke                         | 545  | 4.85  | 710  | 8.92  | 0.2 | 363  | 6.76  | 348  | 6.48  | 0.0 |
| Prior Sistemic Embolism (SE)                  | 100  | 0.89  | 39   | 0.49  | 0.0 | 37   | 0.69  | 31   | 0.58  | 0.0 |
| Condition                                                                 | Value1 | Value2 | Value3 | Value4 | Value5 | Value6 | Value7 | Value8 | Value9 | Value10 |
|---------------------------------------------------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|
| Transient ischemic attack (TIA)                                           | 245    | 2.18   | 274    | 3.44   | 0.08   | 143    | 2.66   | 150    | 2.79   | 0.0     |
| Other cerebrovascular disease                                             | 1044   | 9.29   | 866    | 10.87  | 0.05   | 526    | 9.79   | 522    | 9.72   | 0.0     |
| Prior percutaneous coronary intervention (PCI)                            | 1569   | 13.96  | 671    | 8.43   | 0.2    | 526    | 9.79   | 541    | 10.07  | 0.0     |
| Peripheral vascular disease                                               | 487    | 4.33   | 311    | 3.91   | 0.0    | 212    | 3.95   | 226    | 4.21   | 0.0     |
| Venous thromboembolism (VTE)                                              | 196    | 1.74   | 104    | 1.31   | 0.0    | 82     | 1.53   | 75     | 1.40   | 0.0     |
| Heart failure                                                             | 2946   | 26.22  | 1782   | 22.38  | 0.09   | 1289   | 24.00  | 1270   | 23.65  | 0.0     |
| Other cardiovascular disease                                              | 2300   | 20.47  | 1170   | 14.69  | 0.2    | 896    | 16.68  | 912    | 16.98  | 0.0     |
| Hypertension                                                              | 4415   | 39.29  | 3289   | 41.30  | 0.0    | 2139   | 39.82  | 2132   | 39.69  | 0.0     |
| Diabetes                                                                  | 1672   | 14.88  | 988    | 12.41  | 0.07   | 699    | 13.01  | 675    | 12.57  | 0.0     |
| Anemia                                                                    | 637    | 5.67   | 326    | 4.09   | 0.07   | 226    | 4.21   | 231    | 4.30   | 0.0     |
| Hyperlipidemia                                                            | 775    | 6.90   | 546    | 6.86   | 0.0    | 386    | 7.19   | 361    | 6.72   | 0.0     |
| **Ischemic heart Disease**                                                |        |        |        |        |        |        |        |        |        |         |
| - Acute myocardial infarction                                             | 576    | 5.13   | 173    | 2.17   | 0.2    | 143    | 2.66   | 155    | 2.89   | 0.0     |
| - Unstable Angina                                                         | 211    | 1.88   | 99     | 1.24   | 0.05   | 78     | 1.45   | 81     | 1.51   | 0.0     |
| - Old myocardial infarction                                               | 398    | 3.54   | 177    | 2.22   | 0.08   | 141    | 2.63   | 138    | 2.57   | 0.0     |
| - Angina pectoris                                                         | 118    | 1.05   | 60     | 0.75   | 0.0    | 52     | 0.97   | 46     | 0.86   | 0.0     |
| - Other forms of chronic ischemic heart disease                          | 1477   | 13.14  | 805    | 10.11  | 0.095  | 589    | 10.97  | 562    | 10.46  | 0.0     |
| Cardioablation                                                           | 263    | 2.34   | 118    | 1.48   | 0.06   | 96     | 1.79   | 93     | 1.73   | 0.0     |
| Cardioversion                                                            | 892    | 7.94   | 558    | 7.01   | 0.0    | 404    | 7.52   | 410    | 7.63   | 0.0     |
| Overweight and obesity                                                   | 349    | 3.11   | 214    | 2.69   | 0.0    | 172    | 3.20   | 156    | 2.90   | 0.0     |
| Chronic Obstructive Lung Disease                                         | 1347   | 11.99  | 799    | 10.03  | 0.06   | 572    | 10.65  | 572    | 10.65  | 0.0     |
| Psychiatric condition                                                    | 125    | 1.11   | 96     | 1.21   | 0.0    | 62     | 1.15   | 62     | 1.15   | 0.0     |
| Dementias/Alzheimer                                                      | 167    | 1.49   | 150    | 1.88   | 0.0    | 76     | 1.42   | 97     | 1.81   | 0.0     |
| Malignant neoplasm                                                       | 675    | 6.01   | 333    | 4.18   | 0.08   | 270    | 5.03   | 247    | 4.60   | 0.0     |
| Pneumonia                                                                | 744    | 6.62   | 421    | 5.29   | 0.06   | 313    | 5.83   | 306    | 5.70   | 0.0     |
| Cardiovascular and antidiabetic agents | 5008 | 44.57 | 3389 | 42.55 | 0.0 | 2339 | 43.55 | 2310 | 43.01 | 0.0 |
|--------------------------------------|------|-------|------|-------|-----|------|-------|------|-------|-----|
| Statins                              | 956  | 8.51  | 578  | 7.26  | 0.0 | 419  | 7.80  | 414  | 7.71  | 0.0 |
| Non-statin lipid lowering agent      | 2186 | 19.45 | 1046 | 13.13 | 0.2 | 801  | 14.91 | 792  | 14.75 | 0.0 |
| Digitalis glycosides                 | 1828 | 16.27 | 1039 | 13.05 | 0.09| 712  | 13.26 | 768  | 14.30 | 0.0 |
| Oral antidiabetic agents             | 2297 | 20.44 | 1518 | 19.06 | 0.0 | 1043 | 19.42 | 1039 | 19.34 | 0.0 |
| Insulin                              | 854  | 7.60  | 435  | 5.46  | 0.0 | 328  | 6.11  | 322  | 6.00  | 0.0 |
| ACE inhibitors                       | 5414 | 48.18 | 3492 | 43.85 | 0.0 | 2419 | 45.04 | 2430 | 45.24 | 0.0 |
| ARBs                                 | 4935 | 43.92 | 3589 | 45.07 | 0.0 | 2428 | 45.21 | 2397 | 44.63 | 0.0 |
| Aldosterone receptor antagonators    | 2662 | 23.69 | 1360 | 17.08 | 0.2 | 1032 | 19.21 | 1046 | 19.47 | 0.0 |
| Beta blockers                        | 7752 | 68.99 | 5346 | 67.13 | 0.0 | 3642 | 67.81 | 3610 | 67.21 | 0.0 |
| Calcium channel blockers             | 4456 | 39.65 | 2836 | 35.61 | 0.08| 2091 | 38.93 | 2019 | 37.59 | 0.03|
| Diuretics                            |      |       |      |       |     |      |       |      |       |     |
| - Loop-diuretics                     | 6532 | 58.13 | 3666 | 46.03 | 0.2 | 2724 | 50.72 | 2743 | 51.07 | 0.0 |
| - Others                             | 3234 | 28.78 | 1752 | 22.00 | 0.2 | 1296 | 24.13 | 1303 | 24.26 | 0.0 |
| Other antihypertensives              | 986  | 8.77  | 667  | 8.38  | 0.0 | 475  | 8.84  | 472  | 8.79  | 0.0 |
| Antiarrhythmics                      | 4404 | 39.19 | 3373 | 42.35 | 0.06| 2248 | 41.85 | 2253 | 41.95 | 0.0 |
| Antifibrinolytics                    | 142  | 1.26  | 77   | 0.97  | 0.0 | 52   | 0.97  | 60   | 1.12  | 0.0 |
| Glucocorticoids                      | 2783 | 24.77 | 1823 | 22.89 | 0.0 | 1275 | 23.74 | 1300 | 24.20 | 0.0 |
| Drugs that may increase bleeding risk|      |       |      |       |     |      |       |      |       |     |
| NSAIDs                               | 0.00 | 0.00  |      |       |     |      |       |      |       |     |
| Coxibs                               | 1266 | 11.27 | 868  | 10.90 | 0.0 | 594  | 11.06 | 578  | 10.76 | 0.0 |
| Others NSAIDs                        | 4927 | 43.85 | 3328 | 41.79 | 0.0 | 2321 | 43.21 | 2297 | 42.77 | 0.0 |
| Antidepressant                       |      |       |      |       |     |      |       |      |       |     |
| - SSRIs                              | 1255 | 11.17 | 930  | 11.68 | 0.4 | 576  | 10.72 | 595  | 11.08 | 0.0 |
| - SNRIs                              | 293  | 2.61  | 247  | 3.10  | 0.0 | 155  | 2.89  | 154  | 2.87  | 0.0 |
|                                | No. | %    | No. | %    | No. | %    | No. | %    | No. | %    | No. | %    |
|--------------------------------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|
| - Others                       | 314 | 2.79 | 268 | 3.37 | 0.3 | 163 | 3.03 | 181 | 3.37 | 0.0 |
| Antiepileptics                 | 1096| 9.75 | 751 | 9.43 | 0.0 | 498 | 9.27 | 503 | 9.37 | 0.0 |
| Antipsychotics                 | 402 | 3.58 | 262 | 3.29 | 0.0 | 193 | 3.59 | 164 | 3.05 | 0.0 |
| **Antiplatelet agents**        |     |      |     |      |     |     |      |     |      |      |
| - Aspirin                      | 5320| 47.34| 3828| 48.07| 0.0 | 2625| 48.87| 2591| 48.24| 0.0 |
| - Clopidogrel                  | 1509| 13.43| 1103| 13.85| 0.0 | 718 | 13.37| 736 | 13.70| 0.0 |
| - Others                       | 1097| 9.76 | 745 | 9.35 | 0.0 | 551 | 10.26| 541 | 10.07| 0.0 |
| **Injectable anticoagulants**  |     |      |     |      |     |     |      |     |      |      |
| Heparin                        | 250 | 2.22 | 39  | 0.49 | 0.2 | 39  | 0.73 | 36  | 0.67 | 0.0 |
| Fondaparinux                   | 181 | 1.61 | 129 | 1.62 | 0.0 | 89  | 1.66 | 81  | 1.51 | 0.0 |
| Low molecular weight heparin   | 5538| 49.28| 3228| 40.53| 0.2 | 2495| 46.45| 2495| 46.45| 0.0 |
| **Drugs that may protect from bleeding** |    |      |     |      |     |     |      |     |      |      |
| - H2 antagonists               | 479 | 4.26 | 345 | 4.33 | 0.0 | 227 | 4.23 | 223 | 4.15 | 0.0 |
| - PPIs                         | 9383| 83.50| 6400| 80.36| 0.08| 4407| 82.05| 4385| 81.64| 0.0 |
| **Drugs listed on label as having a potential interaction with anticoagulant drugs (not already listed above):** |     |      |     |      |     |     |      |     |      |      |
| Diclofenac                     | 1519| 13.52| 1019| 12.80| 0.02| 739 | 13.76| 726 | 13.52| 0.0 |
| Antacids                       | 651 | 5.79 | 548 | 6.88 | 0.04| 365 | 6.80 | 346 | 6.44 | 0.0 |
| Clarithromycin                 | 877 | 7.80 | 672 | 8.44 | 0.02| 435 | 8.10 | 425 | 7.91 | 0.0 |
| Ciprofloxazin                  | 2053| 18.27| 1410| 17.70| 0.0 | 978 | 18.21| 975 | 18.15| 0.0 |
| Allopurinol                    | 2135| 19.00| 1055| 13.25| 0.2 | 810 | 15.08| 820 | 15.27| 0.0 |
| **Number of INR tests (tertiles)** |     |      |     |      |     |     |      |     |      |      |
| 0                              | 6291| 55.98| 6071| 76.23| 0.4 | 3870| 72.05| 3837| 71.44| 0.0 |
| 1                              | 2053| 18.27| 1176| 14.77| 0.09| 859 | 15.99| 871 | 16.22| 0.0 |
| >1                             | 2893| 25.75| 717 | 9.00 | 0.5 | 642 | 11.95| 663 | 12.34| 0.0 |
| **Other exams related to blood coagulation** |     |      |     |      |     |     |      |     |      |      |
|                                | 2108| 18.76| 1570| 19.71| 0.0 | 1055| 19.64| 1061| 19.75| 0.0 |
| Exams relative to renal function | 51 | 0.45 | 30 | 0.38 | 0.0 | 27 | 0.50 | 20 | 0.37 | 0.0 |
|----------------------------------|----|------|----|------|-----|----|------|----|------|-----|
| Number of creatinine tests       |    |      |    |      |     |    |      |    |      |     |
| <=0                              | 3748 | 33.35 | 2686 | 33.73 | 0.0 | 1789 | 33.31 | 1799 | 33.49 | 0.0 |
| 1-2                              | 5459 | 48.58 | 4083 | 51.27 | 0.05 | 2700 | 50.27 | 2701 | 50.29 | 0.0 |
| >2                               | 2030 | 18.07 | 1195 | 15.01 | 0.08 | 882  | 16.42 | 871  | 16.22 | 0.0 |
| Exams related to lipids          |    |      |    |      |     |    |      |    |      |     |
| <=0                              | 4248 | 37.80 | 3008 | 37.77 | 0.0 | 2017 | 37.55 | 2017 | 37.55 | 0.0 |
| 1-4                              | 4180 | 37.20 | 3115 | 39.11 | 0.0 | 2082 | 38.76 | 2072 | 38.58 | 0.0 |
| >4                               | 2809 | 25.00 | 1841 | 23.12 | 0.0 | 1272 | 23.68 | 1282 | 23.87 | 0.0 |
| Number of blood pressure         | 177 | 1.58 | 135 | 1.70 | 0.0 | 93  | 1.73 | 92  | 1.71 | 0.0 |
| measurements                     |    |      |    |      |     |    |      |    |      |     |
| Number of haemoglobin            | 61  | 0.54 | 33  | 0.41 | 0.0 | 23  | 0.43 | 25  | 0.47 | 0.0 |
| measurements                     |    |      |    |      |     |    |      |    |      |     |
| Visits/exams relative to heart    | 1516 | 13.49 | 963  | 12.09 | 0.0 | 677 | 12.60 | 683 | 12.72 | 0.0 |
| failure or to ejection fraction   |    |      |    |      |     |    |      |    |      |     |
| measurement                      |    |      |    |      |     |    |      |    |      |     |
| Major surgical procedures        | 2617 | 23.29 | 1368 | 17.18 | 0.2 | 1016 | 18.92 | 1041 | 19.38 | 0.0 |
| Number of emergency room visits  |    |      |    |      |     |    |      |    |      |     |
| 0                                | 1071 | 9.53 | 774  | 9.72 | 0.0 | 516 | 9.61 | 538 | 10.02 | 0.0 |
| 1                                | 5484 | 48.80 | 3998 | 50.20 | 0.0 | 2701 | 50.29 | 2658 | 49.49 | 0.0 |
| >1                               | 4682 | 41.67 | 3192 | 40.08 | 0.0 | 2154 | 40.10 | 2175 | 40.50 | 0.0 |
| Number of patients with at least  | 9303 | 82.79 | 6434 | 80.79 | 0.05 | 4324 | 80.51 | 4318 | 80.39 | 0.0 |
| one hospitalization              |    |      |    |      |     |    |      |    |      |     |
| Number of different active       |    |      |    |      |     |    |      |    |      |     |
| agents (tertiles)                |    |      |    |      |     |    |      |    |      |     |
| <=11                             | 4514 | 40.17 | 3743 | 47.00 | 0.1 | 2361 | 43.96 | 2370 | 44.13 | 0.0 |
| 12-17                            | 4337 | 38.60 | 2940 | 36.92 | 0.0 | 2020 | 37.61 | 2028 | 37.76 | 0.0 |
| >=18                             | 2386 | 21.23 | 1281 | 16.08 | 0.1 | 990  | 18.43 | 973  | 18.12 | 0.0 |
| Number of specialist visits      |    |      |    |      |     |    |      |    |      |     |
| (quintiles)                      |    |      |    |      |     |    |      |    |      |     |
| Group | Chads2Vasc2 score (tertiles) | HAS BLED score (tertiles) | Combined Comorbidity Score (tertiles) | Enrollment period |
|-------|-----------------------------|---------------------------|--------------------------------------|------------------|
| <=8   |                             |                           |                                      |                  |
| 9-23  |                             |                           |                                      |                  |
| 24-37 |                             |                           |                                      |                  |
| 38-59 |                             |                           |                                      |                  |
| >=60  |                             |                           |                                      |                  |
|       | 2293 20.41 1981 24.87 0.1 |                           | 1273 23.70 1272 23.68 0.0          |                  |
|       | 2102 18.71 1474 18.51 0.0 |                           | 993 18.49 1009 18.79 0.0           |                  |
|       | 2117 18.84 1624 20.39 0.0 |                           | 1095 20.39 1063 19.79 0.0          |                  |
|       | 2239 19.93 1561 19.60 0.0 |                           | 1040 19.36 1057 19.68 0.0          |                  |
|       | 2486 22.12 1324 16.62 0.1 |                           | 970 18.06 970 18.06 0.0           |                  |

Chads2Vasc2 score (tertiles)

| Group | <=2 | 3-4 | >=5 |          |          |
|-------|-----|-----|-----|----------|----------|
|       | 4545 40.45 3294 41.36 0.0 | 4502 40.06 2925 36.73 0.07 | 2190 19.49 1745 21.91 0.06 |          |          |
|       | 2261 42.10 2261 42.10 0.0 | 2070 38.54 2057 38.30 0.0 | 1040 19.36 1053 19.61 0.0 |          |          |

HAS BLED score (tertiles)

| Group | <=2 | 3 | >=4 |          |          |
|-------|-----|---|-----|----------|----------|
|       | 6338 56.40 4482 56.28 0.0 | 3558 31.66 2458 30.86 0.0 | 1341 11.93 1024 12.86 0.0 |          |          |
|       | 3079 57.33 3088 57.49 0.0 | 1661 30.93 1650 30.72 0.0 | 631 11.75 633 11.79 0.0 |          |          |

Combined Comorbidity Score (tertiles)

| Group | 0 | 1-2 | >2 |          |          |
|-------|---|-----|----|----------|----------|
|       | 4179 37.19 3349 42.05 0.1 | 3944 35.10 2765 34.72 0.0 | 3114 27.71 1850 23.23 0.1 |          |          |
|       | 2200 40.96 2216 41.26 0.0 | 1798 33.48 1821 33.90 0.0 | 1373 25.56 1334 24.84 0.0 |          |          |

Enrollment period

| Group                  | 1 (July 2013 - December 2013) | 2 (January 2014 - March 2014) | 3 (April 2014 - June 2014) | 4 (July 2014 - September 2014) | 5 (October 2014 - December 2014) | 6 (January 2015 - March 2015) | 7 (April 2015 - June 2015) | 8 (July 2015 - September 2015) |
|------------------------|-------------------------------|-------------------------------|---------------------------|-------------------------------|----------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Enrollment period      | 3371 30.00 828 10.40 0.5     | 1641 14.60 710 8.92 0.2      | 1224 10.89 677 8.50 0.08   | 975 8.68 682 8.56 0.0         | 937 8.34 880 11.05 0.09       | 924 8.22 1066 13.39 0.2    | 879 7.82 1080 13.56 0.2     | 623 5.54 889 11.16 0.2      |
| 9 (October 2015 - December 2015) | 663 | 5.90 | 1152 | 14.47 | 0.3 | 519 | 9.66 | 519 | 9.66 | 0.0 |
| Intention to treat analysis | matched patients | Total mortality | Cardiovascular mortality | Acute Myocardial Infarction | Ischemic Stroke | Haemorrhagic Stroke | Gastrointestinal bleeding |
|----------------------------|------------------|----------------|-------------------------|-----------------------------|----------------|--------------------|--------------------------|
|                            | Events | HR  | 95%CI  | Events | HR  | 95%CI | Events | HR  | 95%CI | Events | HR  | 95%CI | Events | HR  | 95%CI |
| 1 period                   | AVK    | 825 | 28  | 1.00 | - | - | 14 | 1.00 | - | - | 5 | 1.00 | - | - | 3 | 1.00 | - |
| (july 2013 - dec 2013)     | DOAC   | 825 | 7   | 0.3  | 0.13 - 0.68 | 2 | 0.16 | 0.03 - 0.73 | 2 | 0.46 | 0.08 - 2.37 | 2 | 0.8 | 0.13 - 4.80 | 0 | - | 2 | 2.46 | 0.22 - 27.17 |
| 2 period                   | AVK    | 1456 | 68  | 1.00 | - | - | 34 | 1.00 | - | - | 13 | 1.00 | - | - | 10 | 1.00 | - |
| (jan 2014 - mar 2014)      | DOAC   | 1456 | 41  | 0.62 | 0.42 - 0.92 | 19 | 0.57 | 0.32 - 1.01 | 13 | 1.05 | 0.48 - 2.26 | 8 | 0.86 | 0.34 - 2.19 | 0 | - | 7 | 1.27 | 0.42 - 3.79 |
| 3 period                   | AVK    | 2022 | 114 | 1.00 | - | - | 56 | 1.00 | - | - | 27 | 1.00 | - | - | 14 | 1.00 | - |
| (apr 2014 - jun 2014)      | DOAC   | 2022 | 73  | 0.64 | 0.48 - 0.87 | 36 | 0.64 | 0.42 - 0.98 | 19 | 0.7 | 0.39 - 1.26 | 14 | 1.02 | 0.48 - 2.14 | 0 | - | 10 | 1.01 | 0.42 - 2.45 |
| 4 period                   | AVK    | 2534 | 159 | 1.00 | - | - | 78 | 1.00 | - | - | 37 | 1.00 | - | - | 18 | 1.00 | - |
| (jul 2014 - sep 2014)      | DOAC   | 2534 | 107 | 0.66 | 0.52 - 0.85 | 53 | 0.67 | 0.47 - 0.95 | 21 | 0.56 | 0.33 - 0.96 | 20 | 1.10 | 0.58 - 2.08 | 0 | - | 15 | 1.15 | 0.55 - 2.43 |
| 5 period                   | AVK    | 3127 | 214 | 1.00 | - | - | 106 | 1.00 | - | - | 47 | 1.00 | - | - | 27 | 1.00 | - |
| (oct 2014 - dec 2014)      | DOAC   | 3127 | 138 | 0.63 | 0.51 - 0.79 | 67 | 0.62 | 0.46 - 0.85 | 27 | 0.56 | 0.35 - 0.91 | 26 | 0.95 | 0.55 - 1.63 | 1 | 0.07 | 0.009 - 0.57 | 18 | 0.99 | 0.51 - 1.90 |
| 6 period                   | AVK    | 3794 | 273 | 1.00 | - | - | 135 | 1.00 | - | - | 54 | 1.00 | - | - | 33 | 1.00 | - |
| (jun 2015 - mar 2015)      | DOAC   | 3794 | 213 | 0.77 | 0.64 - 0.9 | 118 | 0.86 | 0.67 - 1.10 | 42 | 0.77 | 0.51 - 1.15 | 39 | 1.17 | 0.73 - 1.86 | 4 | 0.26 | 0.08 - 0.78 | 23 | 1.08 | 0.59 - 1.95 |
| 7 period                   | AVK    | 4399 | 391 | 1.00 | - | - | 171 | 1.00 | - | - | 66 | 1.00 | - | - | 45 | 1.00 | - |
| (apr 2015 - jun 2015)      | DOAC   | 4399 | 284 | 0.84 | 0.72 - 0.99 | 154 | 0.89 | 0.71 - 1.10 | 54 | 0.81 | 0.56 - 1.16 | 45 | 0.99 | 0.65 - 1.49 | 7 | 0.38 | 0.16 - 0.91 | 34 | 1.40 | 0.83 - 2.36 |
| 8 period                   | AVK    | 4852 | 379 | 1.00 | - | - | 199 | 1.00 | - | - | 75 | 1.00 | - | - | 52 | 1.00 | - |
| (jul 2015 - sep 2015)      | DOAC   | 4852 | 316 | 0.82 | 0.71 - 0.95 | 166 | 0.82 | 0.67 - 1.01 | 58 | 0.76 | 0.54 - 1.07 | 53 | 1.01 | 0.68 - 1.48 | 8 | 0.39 | 0.17 - 0.89 | 41 | 1.40 | 0.87 - 2.25 |
| 9 period                   | AVK    | 5371 | 427 | 1.00 | - | - | 227 | 1.00 | - | - | 88 | 1.00 | - | - | 59 | 1.00 | - |
| (oct 2015 - dec 2015)      | DOAC   | 5371 | 371 | 0.86 | 0.74 - 0.98 | 193 | 0.84 | 0.69 - 1.02 | 70 | 0.78 | 0.57 - 1.07 | 57 | 0.95 | 0.66 - 1.37 | 9 | 0.38 | 0.17 - 0.83 | 43 | 1.33 | 0.84 - 2.11 |
Fig. A1 New users of anticoagulant drugs: time trend

![Graph showing the number of new users of anticoagulant drugs over time. The graph compares VKAs and DOACs.](image-url)