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

ORIGINAL RESEARCH

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

Efficacy and safety of new drugs are typically evaluated in randomized controlled trials, but clinical trials may not always be sufficiently informative. Major limitations of randomized controlled trials are the small and selected study populations, the short observation time, and the well-monitored adherence, all of which do not reflect real-world conditions.[1] Postmarketing observational studies are needed to complement the results of clinical trials.[2]

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 monitored[13] and are associated with higher costs.

A meta-analysis, based on randomized controlled trials comparing individual DOACs with warfarin[14-16] among nonvalvular AF patients,[17] showed a significant reduction in the risk

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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.

Clinical Perspective

What Is New?

- This is the first pilot of a near-real-time monitoring program of newly marketed drugs in Italy.
- Administrative health claims data were used to provide near-real-time evidence for the safety and effectiveness of newly marketed direct oral anticoagulants.

What Are the Clinical Implications?

- In this study on secondary prevention in patients affected by nonvalvular atrial fibrillation, use of new direct oral anticoagulants compared with vitamin K antagonists was associated with a lower risk of all-cause and cardiovascular mortality, hemorrhagic stroke, myocardial infarction, and ischemic stroke, although the risk of gastrointestinal bleeding was increased.
- This pilot program lays the basis for the implementation of real-time monitoring of new drugs in our region and elsewhere.

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, apixabam 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.[29] 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,[30] CHA_2DS_2-VASc and HAS-BLED scores,[31] 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.[32] 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.[33]

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[34-36] 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 first monitoring period (December 31, 2013). At this point the first analysis was performed running a Cox proportional hazard model stratified by match set to estimate the HRs for the study outcomes. In the second monitoring period (January 2014 through March 2014), all DOAC and VKA users with an index date in this period were enrolled, and the information related to 90 covariates was used to build the PS and to match them 1:1. 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 second 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.[28]

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.

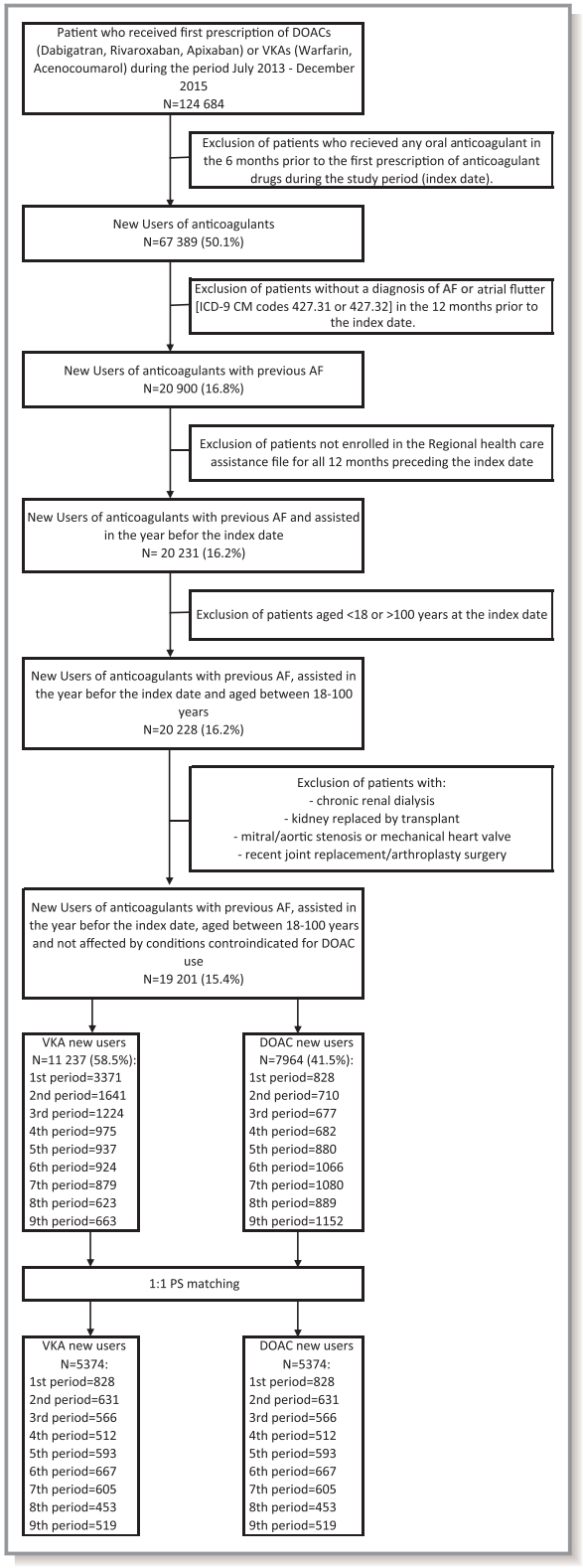


Figure 1. Cohort selection. AF indicates atrial fibrillation; DOAC, direct oral anticoagulants; *ICD-9-CM*, the *International Classification of Diseases, 9th Revision, Clinical Modification*; PS, propensity score; VKA, vitamin K antagonists.

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).

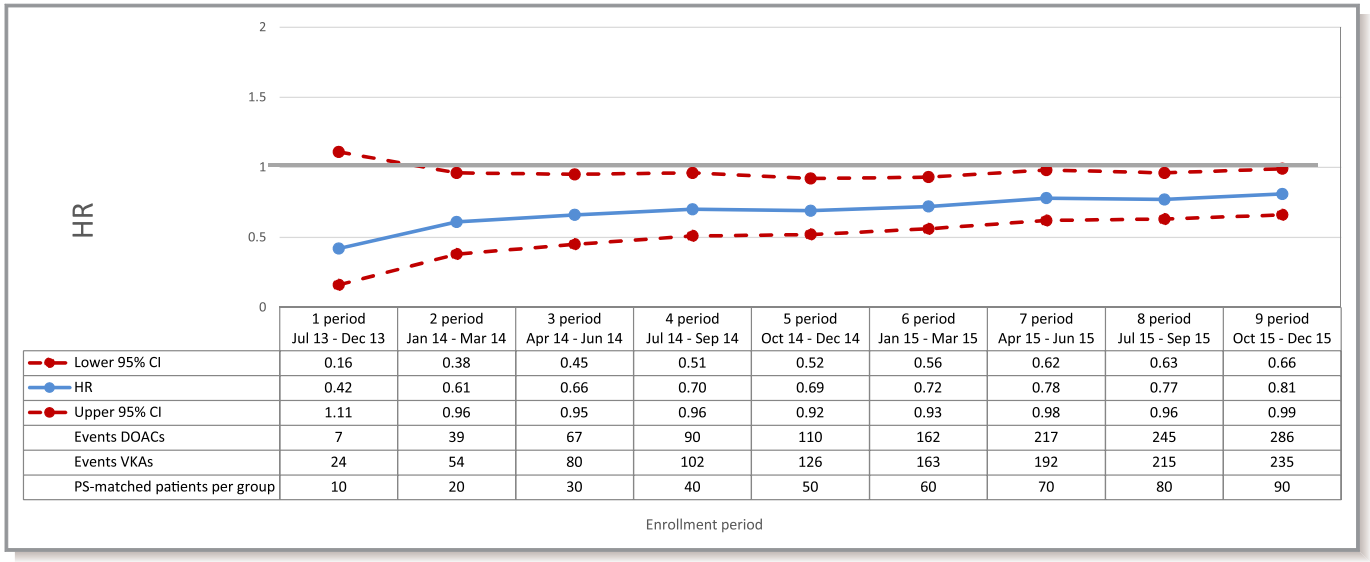
Results from the intention-to-treat analysis mostly confirmed the main findings (Table S5).

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.[17,37,38] 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.[17,37] Similarly, our results are in line with findings from previous observational studies[18-21,23-25] that compared single DOACs versus warfarin.

At the time we started monitoring, evidence on the comparative effectiveness of DOACs versus VKAs was still



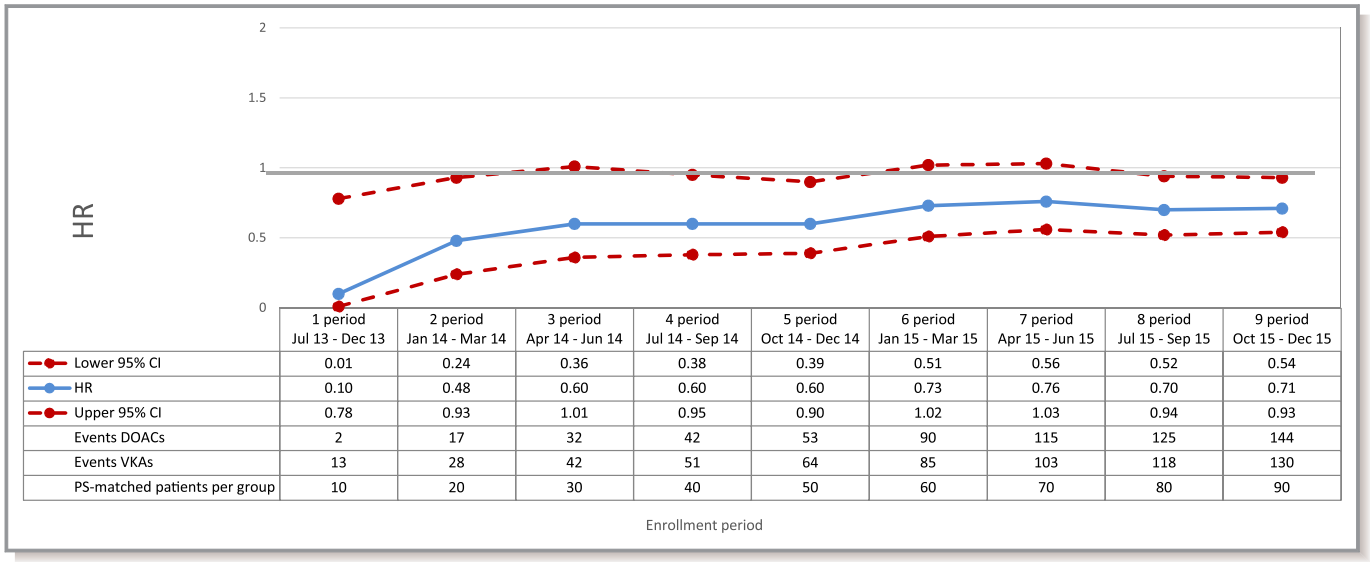
	1 period Jul 13 - Dec 13	2 period Jan 14 - Mar 14	3 period Apr 14 - Jun 14	4 period Jul 14 - Sep 14	5 period Oct 14 - Dec 14	6 period Jan 15 - Mar 15	7 period Apr 15 - Jun 15	8 period Jul 15 - Sep 15	9 period Oct 15 - Dec 15
Lower 95% CI	0.16	0.38	0.45	0.51	0.52	0.56	0.62	0.63	0.66
HR	0.42	0.61	0.66	0.70	0.69	0.72	0.78	0.77	0.81
Upper 95% CI	1.11	0.96	0.95	0.96	0.92	0.93	0.98	0.96	0.99
Events DOACs	7	39	67	90	110	162	217	245	286
Events VKAs	24	54	80	102	126	163	192	215	235
PS-matched patients per group	10	20	30	40	50	60	70	80	90

Enrollment period

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.

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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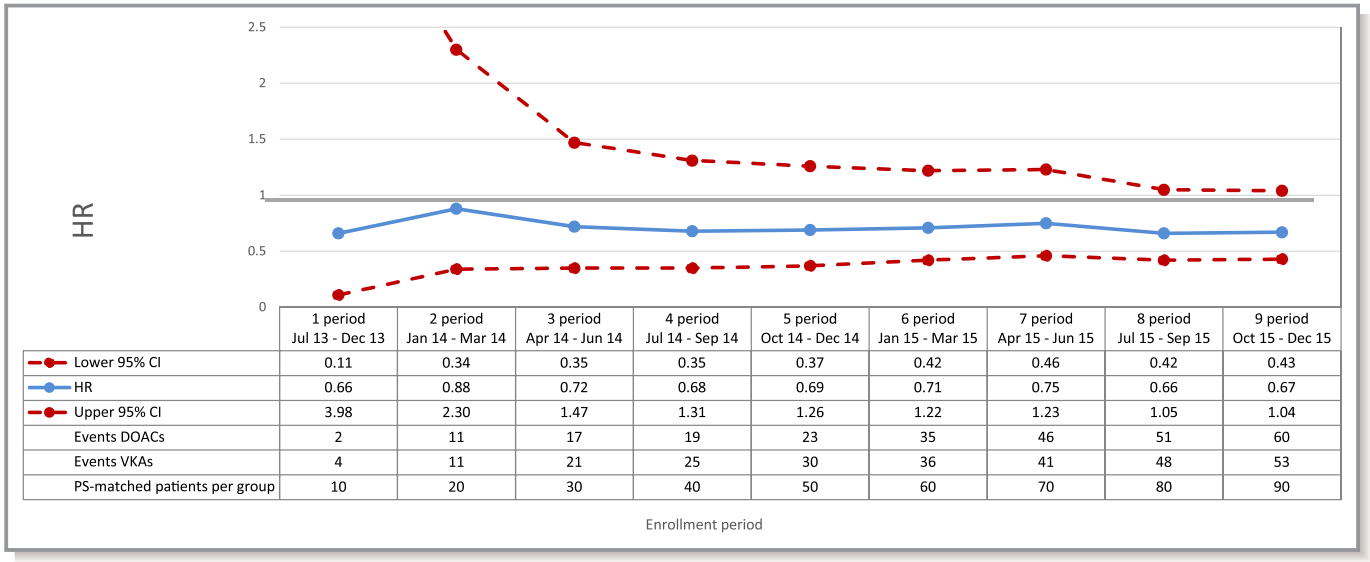
Lower 95% CI	0.01	0.24	0.36	0.38	0.39	0.51	0.56	0.52	0.54
HR	0.10	0.48	0.60	0.60	0.60	0.73	0.76	0.70	0.71
Upper 95% CI	0.78	0.93	1.01	0.95	0.90	1.02	1.03	0.94	0.93
Events DOACs	2	17	32	42	53	90	115	125	144
Events VKAs	13	28	42	51	64	85	103	118	130
PS-matched patients per group	10	20	30	40	50	60	70	80	90

Enrollment period

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.



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Lower 95% CI	0.11	0.34	0.35	0.35	0.37	0.42	0.46	0.42	0.43
HR	0.66	0.88	0.72	0.68	0.69	0.71	0.75	0.66	0.67
Upper 95% CI	3.98	2.30	1.47	1.31	1.26	1.22	1.23	1.05	1.04
Events DOACs	2	11	17	19	23	35	46	51	60
Events VKAs	4	11	21	25	30	36	41	48	53
PS-matched patients per group	10	20	30	40	50	60	70	80	90

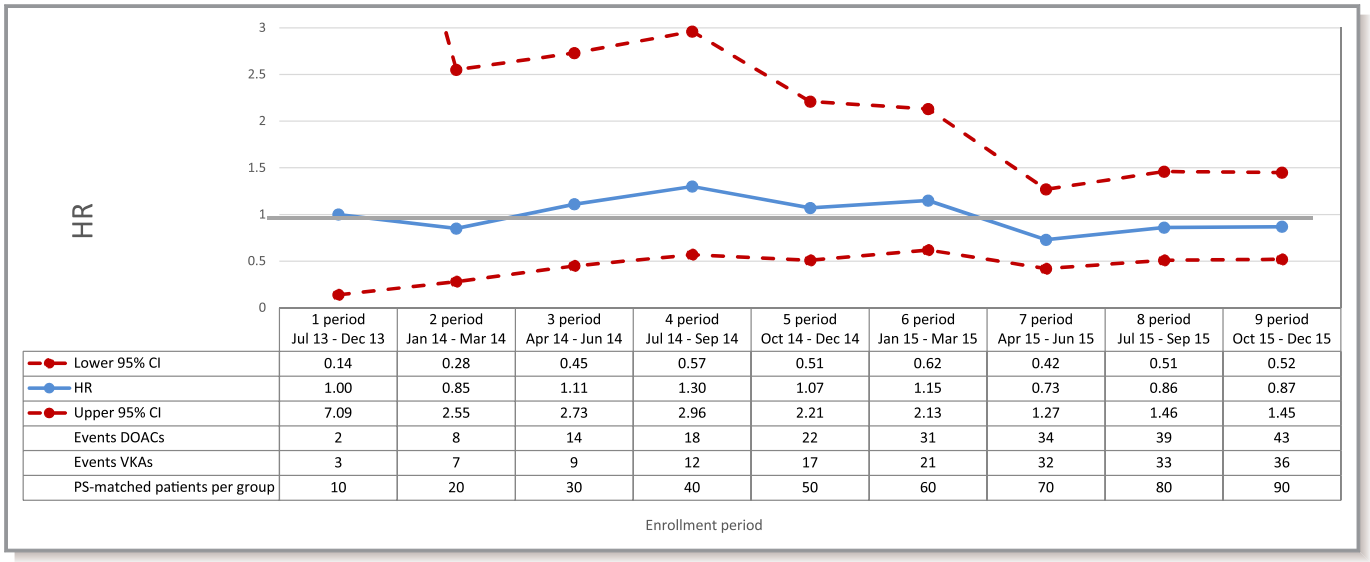
Enrollment period

Figure 4. Acute myocardial infarction—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



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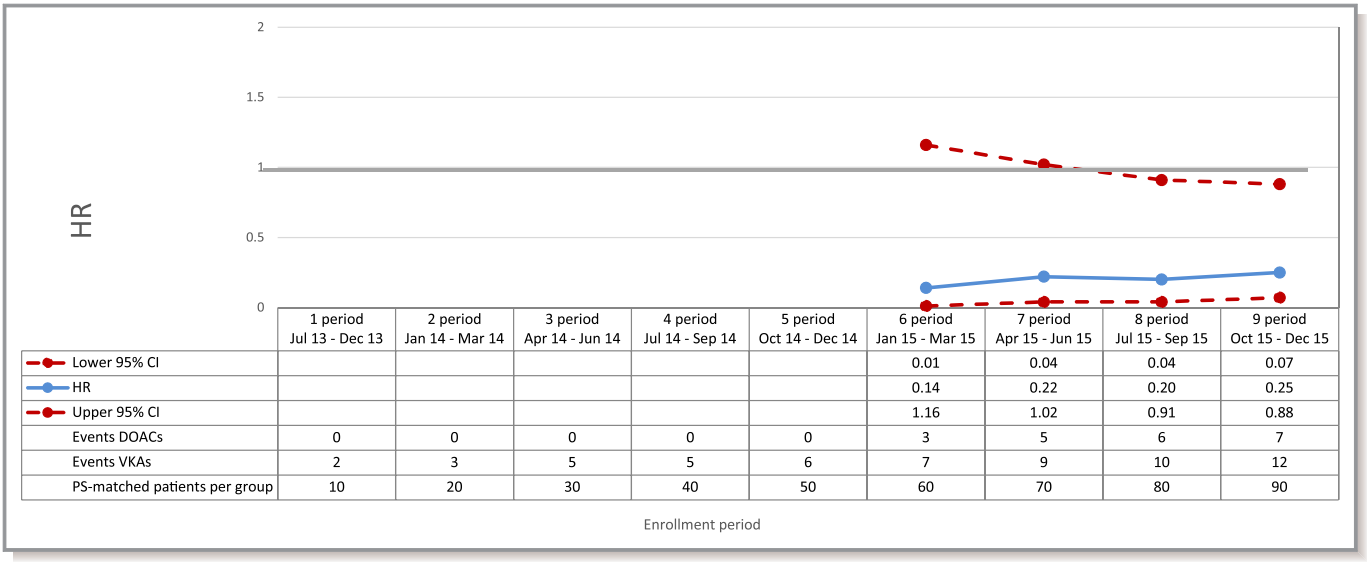
Lower 95% CI	0.14	0.28	0.45	0.57	0.51	0.62	0.42	0.51	0.52
HR	1.00	0.85	1.11	1.30	1.07	1.15	0.73	0.86	0.87
Upper 95% CI	7.09	2.55	2.73	2.96	2.21	2.13	1.27	1.46	1.45
Events DOACs	2	8	14	18	22	31	34	39	43
Events VKAs	3	7	9	12	17	21	32	33	36
PS-matched patients per group	10	20	30	40	50	60	70	80	90

Enrollment period

Figure 5. Ischemic 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.



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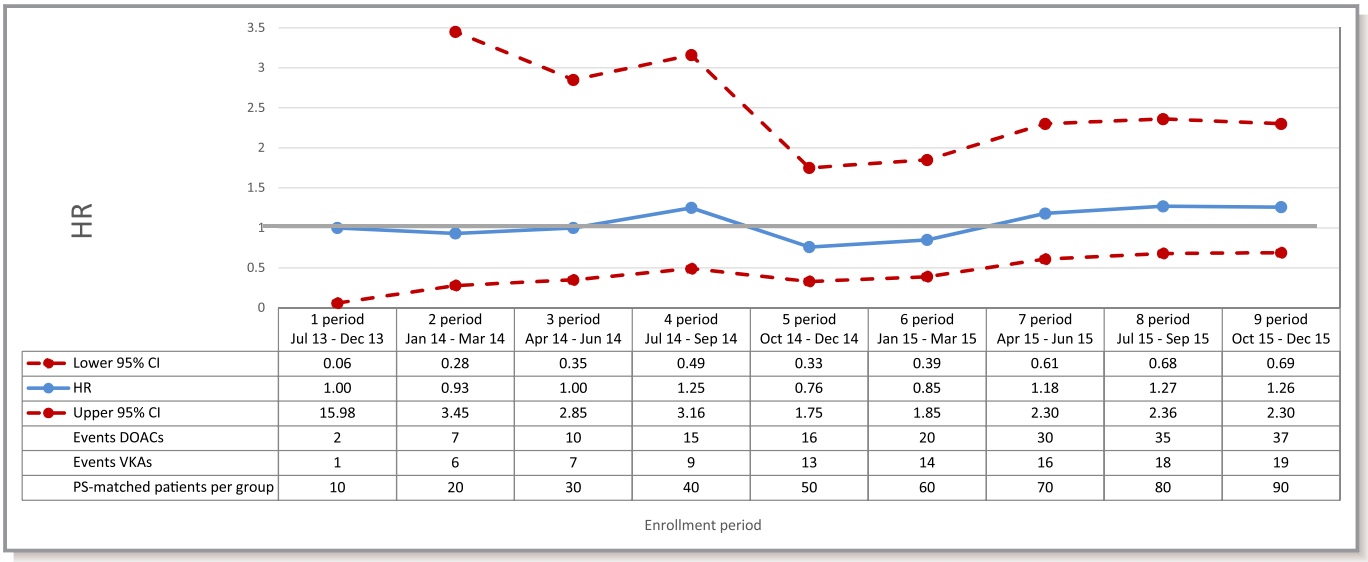
Lower 95% CI						0.01	0.04	0.04	0.07
HR						0.14	0.22	0.20	0.25
Upper 95% CI						1.16	1.02	0.91	0.88
Events DOACs	0	0	0	0	0	3	5	6	7
Events VKAs	2	3	5	5	6	7	9	10	12
PS-matched patients per group	10	20	30	40	50	60	70	80	90

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.

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.



	1 period Jul 13 - Dec 13	2 period Jan 14 - Mar 14	3 period Apr 14 - Jun 14	4 period Jul 14 - Sep 14	5 period Oct 14 - Dec 14	6 period Jan 15 - Mar 15	7 period Apr 15 - Jun 15	8 period Jul 15 - Sep 15	9 period Oct 15 - Dec 15
Lower 95% CI	0.06	0.28	0.35	0.49	0.33	0.39	0.61	0.68	0.69
HR	1.00	0.93	1.00	1.25	0.76	0.85	1.18	1.27	1.26
Upper 95% CI	15.98	3.45	2.85	3.16	1.75	1.85	2.30	2.36	2.30
Events DOACs	2	7	10	15	16	20	30	35	37
Events VKAs	1	6	7	9	13	14	16	18	19
PS-matched patients per group	10	20	30	40	50	60	70	80	90

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 CHA_2DS_2-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 CHA_2DS_2-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.[22]

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 ICD9(P): 39.95, 54.98, 38.95	1 year before index date
	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 ICD9(P): 55.6	1 year before index date
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 ICD9(P): 35.20-35.24	1 year before index date
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.x0, 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	
Enrollmenment period	Enrollment period	from 1 to 9
Measures of overall health status	Number of distinct active agents (tertiles)	distinct ATC at 5th 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, Haemophthalmos 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 Desease (CKD)	Chronic Renal Insufficiency 582, 583, 585, 586, 587, Diabetic Nephropathy 250.4, 250.40, 250.41, 250.42, 250.43, Hypertensive nephropaphy 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 desease	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)

	Cardioversion	99.61 Atrial cardioversion
Other risk factors	Overweight and obesity	ICD9 (P): 44.93, 44.94, 44.68, 44.95, 44.96, 44.97, 44.98 ICD9 (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, Sulfonamides (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)	A10BA, A10BB, A10BC, A10BD, A10BF, A10BG, A10BH, A10BX
	Insulin	A10A
	ACE inhibitors	C09A, C09B
	Angiotensin receptor blockers (ARBs)	C09C, C09D
	Aldosterone receptor antagonists	C03DA
	Beta blockers	C07
	Calcium channel blockers	C08
	Diuretics	C03
	● Loop-diuretics	C03C
	● Others	C03B, C03D, C03E, C03X, C03A
	Other antihypertensives	C02
	Antiarrhythmics	C01BA, C01BB, C01BC, C01BD, C01BG
	Antifibrinolytics	B02A
	Glucocorticoids (Oral corticosteroids)	H02AB
	Antiepileptics	N03

	Antipsychotics	N05A
	Medications that increase bleeding risk:	
	● Nonsteroidal anti-inflammatory drugs (NSAIDs)	M01A
	Coxibs	M01AH
	Others NSAIDs	M01AB, M01AC, M01AE, M01AX
	● Antideptressant	
	Selective serotonin receptor inhibitors (SSRIs)	N06AB
	Serotonin and noradrenaline reuptake inhibitors (SNRIs)	N06AX16, N06AX21
	Others	N06AA, N06AX12, N06AA21, N06AX05, N06AX11
	● 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):	

	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 elegible patients (unmatched)					Overall sequential PS-matched cohorts				
	VKAs N=11237		DOACs N=7964		Absolute standardized differences	VKAs N=5371		DOACs N=5371		Absolute standardized differences
	N	%	N	%		N	%	N	%	
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 indicatator	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
Cronic Kidney Desease (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

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
Cardiac dysrhythmias except Atrial Fibrillation	693	6.17	468	5.88	0.0	292	5.44	323	6.01	0.0
Other cardiovascular desease	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										
Statins	5008	44.57	3389	42.55	0.0	2339	43.55	2310	43.01	0.0
Non-statin lipid lowering agent	956	8.51	578	7.26	0.0	419	7.80	414	7.71	0.0
Digitalis glycosides	2186	19.45	1046	13.13	**0.2**	801	14.91	792	14.75	0.0
Nitrates	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	0.09	328	6.11	322	6.00	0.0
ACE inhibitors	5414	48.18	3492	43.85	0.09	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 antagonists	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
Antideptressant										
- 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

- 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								0.00		0.00	
- 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 measurements	177	1.58	135	1.70	0.0		93	1.73	92	1.71	0.0
Number of haemoglobin measurements	61	0.54	33	0.41	0.0		23	0.43	25	0.47	0.0
Visits/exams relative to heart failure or to ejection fraction measurement	1516	13.49	963	12.09	0.0		677	12.60	683	12.72	0.0
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 one hospitalization	9303	82.79	6434	80.79	0.05		4324	80.51	4318	80.39	0.0
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)											

<=8	2293	20.41	1981	24.87	**0.1**	1273	23.70	1272	23.68	0.0
9-23	2102	18.71	1474	18.51	0.0	993	18.49	1009	18.79	0.0
24-37	2117	18.84	1624	20.39	0.0	1095	20.39	1063	19.79	0.0
38-59	2239	19.93	1561	19.60	0.0	1040	19.36	1057	19.68	0.0
>=60	2486	22.12	1324	16.62	**0.1**	970	18.06	970	18.06	0.0
Chads2Vasc2 score (tertiles)										
<=2	4545	40.45	3294	41.36	0.0	2261	42.10	2261	42.10	0.0
3-4	4502	40.06	2925	36.73	0.07	2070	38.54	2057	38.30	0.0
>=5	2190	19.49	1745	21.91	0.06	1040	19.36	1053	19.61	0.0
HAS BLED score (tertiles)										
<=2	6338	56.40	4482	56.28	0.0	3079	57.33	3088	57.49	0.0
3	3558	31.66	2458	30.86	0.0	1661	30.93	1650	30.72	0.0
>=4	1341	11.93	1024	12.86	0.0	631	11.75	633	11.79	0.0
Combined Comorbidity Score (tertiles)										
0	4179	37.19	3349	42.05	**0.1**	2200	40.96	2216	41.26	0.0
1-2	3944	35.10	2765	34.72	0.0	1798	33.48	1821	33.90	0.0
>2	3114	27.71	1850	23.23	**0.1**	1373	25.56	1334	24.84	0.0
Enrollment period										
1 (July 2013- December 2013)	3371	30.00	828	10.40	**0.5**	825	15.36	825	15.36	0.0
2 (January 2014 - March 2014)	1641	14.60	710	8.92	**0.2**	631	11.75	631	11.75	0.0
3 (April 2014 - June 2014)	1224	10.89	677	8.50	0.08	566	10.54	566	10.54	0.0
4 (July 2014 - September 2014)	975	8.68	682	8.56	0.0	512	9.53	512	9.53	0.0
5 (October 2014 - December 2014)	937	8.34	880	11.05	0.09	593	11.04	593	11.04	0.0
6 (January 2015 - March 2015)	924	8.22	1066	13.39	**0.2**	667	12.42	667	12.42	0.0
7 (April 2015 - June 2015)	879	7.82	1080	13.56	**0.2**	605	11.26	605	11.26	0.0
8 (July 2015 - September 2015)	623	5.54	889	11.16	**0.2**	453	8.43	453	8.43	0.0

9 (October 2015 - December 2015)	663	5.90	1152	14.47	**0.3**		519	9.66	519	9.66	0.0

Tab. A5 Sequential analysis of study outcomes – Intention to treat analysis.

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	Events	HR	95%CI
1 period	**AVK**	825	28	1.00	-	14	1.00	-	5	1.00	-	3	1.00	-	2	1.00	-	1	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	-	3	1.00	-	6	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	-	7	1.00	-	10	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	-	7	1.00	-	13	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	-	13	1.00	-	18	1.00	-
(oct 2014 - dec2014)	**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	-	15	1.00	-	21	1.00	-
(jan 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	331	1.00	-	171	1.00	-	66	1.00	-	45	1.00	-	18	1.00	-	24	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	-	20	1.00	-	29	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	-	23	1.00	-	32	1.00	-
(oct 2015 - dec2015)	**DOAC**	5371	371	**0.86**	**0.74 - 0.98**	193	**0.84**	**0.69 - 1.02**	70	**0.787**	**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