Effects of clinical practice by exploring national and regional register data. The case of NOAK consumption and patient health.

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Sammanfattning

Denna rapport undersöker effekterna av klinisk praxis på patienthälsan genom att använda sig av datauppgifter från både nationella register och primärvårdsdatabaser från tre regioner, Region Skåne, Västra Götalandsregionen och Region Östergötland. Vi studerar fallet med klinisk praxis för antikoagulantiabehandling av patienter med förmaksflimmer, lungemboli eller djup ventrombos för att förhindra stroke och emboli. Den rekommenderade behandlingen har länge varit warfarin under 2010-talet har den alltmer kommit att ersättas med en ny typ av blodförtunningsmedel, *non–vitamin K antagonist oral anticoagulants* eller NOAK, som kliniska studier har funnit inneha goda egenskaper i term av lägre risk för stroke och mindre behov av uppföljningar inom vården. Med mindre behov av uppföljning kommer också ett större ansvar för patienten att följa behandlingen och det finns risk för att de goda effekterna av NOAK-behandlingen uteblir i ett vardagssammanhang. Vidare är det en empirisk fråga hur snabbt en ny klinisk praxis får fäste hos vårdgivarna och på vilken nivå i ett hälso- och sjukvårdssystem. Är det framförallt på regional nivå, ex. via riktlinjer för läkemedelsbehandling, som spridningen sker eller är det en decentraliserad process på vårdcentralsnivå eller lägre? Det är därför viktigt att studera effekterna av behandlingspraxis utanför kliniskt kontrollerade studier, med hjälp av data från både nationella register och primärvårdsdatabaser.

Vi använder oss av det faktum att regionerna respektive vårdcentraler är olika snabba på att införa nya läkemedel för att studerar effekterna av NOAK-förskrivning med hjälp av regressionsanalys. Förskrivningspraxis mäts på gruppnivå, antingen på region- eller vårdcentralsbasis, med hjälp av data på läkemedelsuttag från Läkemedelsregistret. Effekterna på patienthälsan mäts på individnivå med hjälp av data på sjukhusvård (besök i öppen- eller slutenvård och sjukhusinläggning på grund av

stroke) från Patientregistret, mortalitet (alla dödsorsaker) från Dödsorsaksregistret och primärvård (läkarbesök) från tre primärvårdsdatabaser (Skåne, Västra Götaland och Östergötland). Analysen ger inga indikationer på en bättre hälsa hos patienter som tillhör en region eller vårdcentral med en tidig introduktion av NOAK. Framförallt visar resultaten att individer som använder NOAK i dessa regioner och vårdcentraler löper signifikant större risk för att dö och att behöva mer sjukhusvård. Resultaten kan tolkas som ett tecken på att vårdgivare på både sjukhus- och primärvårdsnivå behöver införa striktare uppföljningar av NOAK-användarna. Skattningsstrategin uppvisar emellertid tydliga brister, vilket gör det omöjlighet att dra några slutsatser om kausala samband. Däremot visar studien på möjligheterna med att använda såväl nationella register som primärvårdsregister för att undersöka klinisk praxis. Studien belyser också de utmaningar som finns i datatillgången. Till exempel finns data på uttag av receptbelagda läkemedel i Läkemedelsregistret men varken där eller i primärvårdsdatabaser finns information om förskrivningarna i sig. Dessutom ger primärvårdsdatabaserna små möjligheter att studera den enskilde läkarens roll för introduktionen och effekterna av nya läkemedel.

Introduction

This report explores Swedish national registers and regional (primary care) databases to analyse the effect on patient health of clinical practice with respect to pharmaceutical treatment. As a case study we choose treatment with anticoagulants (blood thinners) for patients with non-valvular atrial fibrillation (the AF indication) and patients with deep venous thrombosis and pulmonary embolism (the DVT indication) to prevent stroke and system embolism.

Historically, warfarin, a vitamin K antagonist substance, has been the recommended treatment for the AF and DVT indications. Warfarin treatment requires frequent controls of the individual dosage by means of lab tests, administered by specialized anticoagulation clinics or primary care centres.[1] In the 2010s the Swedish Dental and Pharmaceutical Benefits Agency, TLV, granted state subsidization

[1] Compared to other countries, Sweden experiences better treatment results, which may be attributed to the organization of the warfarin treatment and follow-ups (Björck et al, 2015; National Board of Health and Welfare, 2018).

to non–vitamin K antagonist oral anticoagulants, NOACs, for the indications of DVT and AF[2]. Randomized clinical trials on patients with atrial fibrillation show that NOACs decrease the risk of stroke, decrease mortality and the risk of bleeding compared to warfarin (Wallentin, 2018). NOACs treatment also implies easier and less frequent follow-ups for the patients. These traits motivated an update of the national guidelines to recommend NOACs instead of warfarin as the first line of treatment for the AF indication (National Board of Health and Welfare, 2018).

In this report we are interested in the relationship between patient health and clinical practice. The entry of NOACs has implied a considerable change in the anticoagulation treatment for AF and DVT patients and thus provides an interesting case to study. How early a patient can be exposed to a new clinical practice may depend on several factors. For example, the regional pharmaceutical committees may respond with varying speed to new research evidence and update the regional guidelines. In addition, the adoption of new practices may depend on the level of decentralisation of the anticoagulation treatment. For example, a primary care centre with well-established routines for warfarin follow-ups could be less prone to transition to NOAC treatment, indicating that patients at that centre is less or later exposed to new prescription practices compared to patients at other primary care centres. Moreover, with less detailed controls performed by health care providers, a successful anticoagulation treatment using NOAC implies that more responsibility falls on the patient to stay motivated and comply with treatment (Svensson & Själander, 2015). However, referring to a clinical trial where treatment interruptions were found to be more common among NOAC patients than warfarin patients, Forslund et al (2012) observe that compliance rates may be even lower in an everyday care context. On the other hand, Friberg (2015a, 2015b) finds that compliance is higher among patients on NOAC, using data from Swedish national registers. Thus, to analyse the effect of clinical practice on patient health outside the context of randomized controlled trials, access to both national and regional registers may be important.

This exercise uses the different speed at which regions and primary care centers transition from warfarin to NOAC treatments to attempt an identification of the effect of early exposure to NOAC on patient health. National registers on secondary care and regional primary care databases are used to construct health outcomes as well as individual covariates of medical and morbidity history. Among

[2] For the AF indication TLV approved Pradaxa® (dabigatran) in 2011, Xarelto® (rivaroxaban**)** in 2012, Eliquis® (apixaban**)** in 2013 and Lixiana® (edoxaban) in 2016. For the DVT indication, Pradaxa® is part of the subsidisation system since 2008, Xarelto® since 2009, Eliquis since 2011 and Lixiana® since 2016.

other things, we find that primary care patients with AF or DVT diagnosis, tend to be older and have higher risk for stroke compared to secondary care patients. The limitations of the analysis allow only cautious interpretations of the results. For both care levels, regression analyses imply that early exposure to NOAC practices associates with greater health risk, a result pointing to the importance of treatment compliance on health outcomes. To better understand the differences between patients on warfarin or NOAC, the report identifies a need for access to registers containing more detailed information about clinical practice.

Data

The study uses data from several national registers, spanning from 2005 to 2017. From the registers of the National Board of Welfare (Socialstyrelsen) we collect data on dispenses of prescription pharmaceuticals (Pharmaceutical Register), use of secondary (inpatient and outpatient) care (Patient Register) and incidences of death (Cause of Death Register). From registers of Statistics Sweden (Income and tax statistics, IoT and Total population register, RTB) we extract individual background information such as age, marital status, and educational attainment. In addition to national registers, the study also uses regional primary care data on visits to general practitioners, GPs, from three regions Skåne, Västra Götaland and Östergötland, in the period 2005-2017.

The study contains two analyses. The first analysis investigates the effect of prescription practices measured on the regional level and consistently uses data from national registers. The second analysis investigates the effect of prescription practices measured on the primary care level and uses data from both primary care registers and national registers. In both analyses we study individuals who i) collect prescriptions of warfarin or NOACs (comprising dispenses of Pradaxa®, Xarelto®, Lixiana® and Eliquis®) from ii) prescribing health care providers located in the same region, iii) comply with treatment (less than 6 months between dispenses) and iv) receive health care due to (main and secondary) diagnoses of atrial fibrillation (ICD-10 code I48) , deep venous thrombosis (DVT, ICD-10 code I80) or pulmonary embolism (PE, ICD-10 code I26.0 , I126.9) in the study period. In the analysis based on national registers only, the diagnoses refer to registration in secondary care (inpatient and outpatient care). Thus, we restrict the analysis to individuals with diagnoses indicating both warfarin and NOAC treatments on a long-term basis and who collect prescriptions from the same region. If there is a consistent prescription policy with respect to warfarin or NOAC for AF and DVT for all providers in the region, this group of individuals is likely to be the most exposed to the regional

practice. In the analysis of clinical practices in primary care, we further restrict our attention to individuals with warfarin or NOAC dispenses of primary care origin coming from the same prescribing primary care unit. We make this restriction to ensure to the extent possible, that the patients are exposed to only one type of prescription practice. However, we do not exclude individuals who have collected prescriptions from different providers. Thus, a patient collecting all his or her primary care warfarin or NOAC prescriptions from the same unit may also collect prescriptions from e.g. a hospital. In the analysis using primary care data, patients' AF or DVT indications refer to diagnoses registered for visits to general practitioners, GPs.

We can link the drug dispenses to a specific region and to the type of prescribing health care provider by means of information in the Pharmaceutical register. The variable "workplace code" (*arbetsplatskod*) connects the dispenses to the unique, but unidentified, unit (hospital, primary care center etc.) from which the prescriptions originate. The first digits of the workplace code also indicate the region where the unit is located. Furthermore, the Pharmaceutical register contains an "activity code" (verksamhetskod) categorizing the type of activity of the prescribing unit and allowing us to ascertain whether dispenses come from primary care units (using the activity code for *distriktsläkarvård*).

Without a decryption of the workplace code, which can only be provided by the regions respectively, it is a challenge to link drug dispenses to the actual prescribing unit. Focusing for example on primary care, it is possible to compare the date of contact in registers of primary care (which generally do not contain the workplace code but other codes to identify primary care centers) with the date of prescription in the Pharmaceutical register[3] to track dispenses to primary care centers. However, a complete mapping of dispenses and primary care centers requires more information than what is available for this report. It is worth noting that Pharmaceutical register contains information about dispensed prescriptions but not the actual prescriptions. To our knowledge, primary care databases do not contain prescription data. To observe what the GPs prescribe access to journal systems is necessary. . It is also worth noting that we cannot observe actual consumption. We can only assume that the compliant behaviour in terms of dispenses reflects compliant behaviour in terms of treatment. In addition, we are able to study GP visits but GPs may extend prescriptions in connection with other types of contacts e.g. telephone contacts

[3] The Pharmaceutical register contains the prescription date as well as the dispense date of all dispensed prescription pharmaceuticals.

We use the workplace code and the activity code in the Pharmaceutical register to categorize dispenses as originating from prescriptions in primary care. However, the workplace codes are adapted to administrative purposes in the regions, not to research purposes. Thus, it is not guaranteed that codes are consistently linked to the same primary care centers over time, nor that there is a one-to-one correspondence between the workplace codes and the actual primary care centres. In the three regions included in this study we probably encounter different administrative routines. Let us assume that the primary care units in the Pharmaceutial register correspond to primary care centres. In the period 2005-2017, including all dispenses made by individuals who collect all their warfarin and NOAC prescriptions in the same region but without our requirement of compliance, we have nearly 500 unique primary care centres in Östergötland and Västra Götaland, respectively, and over 350 unique primary care units in Skåne These figures can be related to recent information provided by the national health care site 1177.se, stating that Östergötland has 67 centres, Västra Götaland 261 centres and Skåne 188 centres, including evening and night practices.[4] Requiring treatment compliance and that individuals collect prescriptions from the same prescribing primary care unit, we are left with almost 200 primary care centers in Östergötland, nearly 400 in Västra Götaland and over 250 in Skåne. We further restrict our focus to "established" primary care centers, in total 228 units with non-zero annual dispenses of warfarin or NOACs (or both) in 2009 or earlier until the end of the study period.[5] Narrowing down the sample to patients with AF- or DVT-indications registered in primary care, we lose 7 centers and then another 24 centers after the propensity score matching process. Of the remaining 197 units (in 2009), 21 are located in Östergötland, 85 in Västra Götaland and 91 in Skåne. Due to death or migration, in the study period we observe some variation in the number of primary care units; in 2015 179 units are represented.

Outcome variables

For the analysis using national registers, we consider the individual's use of hospital care and mortality by investigating three outcome variables. The variable *hospital visit* takes the value one if the individual has used inpatient or outpatient secondary care for all causes during a year and zero otherwise. We use this variable as a measure of general frailty. We also consider *hospitalization due to stroke*, a variable which takes the value one if the individual has used inpatient care during a year

[4] www.1177.se/hitta-vard/. Information extracted 2020-12-13.

[5] We also require that the primary care centers keep their status as early NOAC adopters (an annual ratio of NOACs to warfarin dispenses at or above 20 percent) "switched on" once that threshold has been passed (two primary care centers are excluded due to this requirement).

with diagnoses with ICD-10 code I64, I63.9, I61.9, G45.9. The outcome variable *mortality* takes the value one if the individual dies, irrespective of underlying cause,in the current year). For the analysis of primary care, we also investigate three outcome variables. The variable *GP visit* takes the value one if the individual has visited a GP during a year and zero otherwise. The variable *GP visit due to stroke* takes the value one if the individual has visited a GP due to stroke-related issues according to diagnoses with diagnoses ICD-10 code I64, I63.9, I61.9, G45.9 during a year and zero otherwise. The third outcome variable in the primary care analysis is all-cause *mortality*.

Independent variables

Early exposure to NOAC prescription practices

Of particular interest among our independent variables is the variable we construct to identify individuals with early exposure to NOAC prescription practices, the "treated" as opposed to the "control" individuals with late exposure to NOAC prescription practices. Categorization into early exposure/late exposure and treatment/control does not refer to the individual's own prescriptions but to prescriptions on an aggregate level. Individuals with early exposure are those collecting their prescriptions either in a region that is early to take on board NOACs (regional analysis) or from a primary care center that is an early NOAC adopter (primary care analysis).

Focusing first on regional prescription practices, we observe that the number of NOAC prescriptions per region has steadily increased from single digit levels early in the study period to a level where NOACs are the dominant pharmaceutical compared to warfarin by the end of the study period. This development takes place in virtually all regions but with varying speed. There are (more or less) early, and (more or less) late "adopters" among the regions but late regions tend to catch up over time.

We use data on all dispenses, not only by the individuals selected for our analysis, aggregated by region and year to define NOAC exposure , the annual share of NOAC dispenses in relation warfarin dispenses in the region at or above 20 percent. [6][7] The variable *EarlyExposure* categorises individuals as belonging to the treated group (taking the value one) or to the control group (taking the value zero) and does not change over time. Individuals with dispenses in eight regions are treated

[6] Annual n.o. NOAC dispenses/annual n.o. warfarin dispenses≥20 %
[7] We have tried shares of 10-40 percent with similar results.

according to the definition of *EarlyExposure* , see Table 1. Table 1 also shows the year in which treated and control regions reach 20 percent NOAC dispenses in relation to warfarin dispenses. The two regions of Halland and Västmanland reach the 20 percent threshold in 2013. Another six regions follow in 2014. By 2015, 20 out of 21 regions have an annual ratio of NOACs to warfarin dispenses at or above 20 percent. The control group consists of individuals living in those 13 regions, which until 2015 have not reached the threshold. For our estimations, we create a dummy variable *Post* that takes the value one for all subsequent years when treated regions reach/exceed the level of 20 percent of NOAC (i.e. it "switches on" in 2013 for individuals in two regions and in 2014 for individuals in six regions), and the value zero for all previous years when treated regions have not reached the level of 20 percent of NOAC. For individuals in control regions or control primary care centers, this variable is consistently zero for all years included in the analysis.

Table 1. First year of NOAC exposure for treated and control regions.

	Year				
Region	2013	2014	2015	2016	Treated/control
Halland	x				T
Västmanland	x				T
Stockholm		x			T
Uppsala		x			T
Kronoberg		x			T
Västra Götaland		x			T
Värmland		x			T
Södermanland			x		C
Östergötland			x		C
Jönköping			x		C
Kalmar			x		C
Gotland			x		C
Blekinge			x		C
Skåne			x		C
Örebro			x		C
Gävleborg			x		C
Jämtland			x		C
Västerbotten			x		C
Norrbotten			x		C
Västernorrland				x	C

The table shows the first year in which NOAC dispenses as compared to warfarin dispenses reach/exceed 20% in the treated/control region.

To investigate prescription practices of primary care centers in Skåne, Västergötland and Östergötland, we use dispense data aggregated by primary care center and year. In similarity with the dispense data at the regional level, we observe a pattern of early and late adopters among the primary care centers and late adopters catching up. The treatment definition is constructed in a similar fashion: Individuals are treated if their prescribing primary care center has an annual rate of NOACs to warfarin dispenses at or above 20 percent. In 2009 the number of primary care centers in the working sample are 197 units; 45 belonging to the control group and 152 units categorized as treated. Due to migration or death, in 2015 there are 40 units in the control group (7 in Östergötland, 13 in Västergötland and 20 in Skåne) and 139 units in the treatment group (13 in Östergötland, 58 in Västergötland and 68 in Skåne). Table 2 shows that treated primary care centers reach 20 percent NOAC in 2014 or 2105, implying that these are the years when *Post* switches on for individuals belonging to these centers. The control group consists of individuals getting his or her prescriptions from 40 primary care centers, which up until 2016 have not reached the NOACs-warfarin rate of 20 percent.

Table 2. First year of NOAC exposure for treated and control primary care centers

	Year	
number of primary care centers	2014	2015
Treated		
25	x	
114		x
Control		
40		

The table shows the first year in which NOAC dispenses as compared to warfarin dispenses reach/exceed 20% for the primary care center.

Covariates

We consider individual age, sex (indicator taking the value one for women, otherwise zero) and marital status (indicator taking the value one for married individuals, otherwise zero). We use a categorical variable describing the highest educational attainment (primary school takes the value one, …, PhD degree the value seven). In addition, we consider the individual history of medical treatment and thromboembolic risk. The CHA_2DS_2VASc score is used to estimate the risk of stroke for

patients with atrial fibrillation. As shown in Table 3, older female persons run a greater risk of suffering from a stroke. Earlier events of heart failure, stroke as well as a history of hypertension, vascular disease and diabetes also increases the risk. With a CHA_2DS_2VASc score above 2, treatment using warfarin or NOACs is recommended. Our model specifications also include information about the individual's medical history, based on data from the Pharmaceutical register. We use two indicators signalling treatment with blood thinners: dispenses of warfarin and dispenses of low dosage acetylsalicylic acid, ASA (Trombyl), in any previous year, respectively. ASA has a long history as an alternative to anticoagulant treatment in preventing stroke for patients with atrial fibrillation. However, treatment recommendations for this indication have changed as recent studies find that anticoagulants perform better (National Board of Health and Welfare, 2018). In the primary care analysis, the thromboembolic risk score is based on diagnoses registered for GP visits while the indicators of medical history are based on dispenses categorised as primary care prescriptions in the Pharmaceutical register.

Table 3: Dimensions of the CHA_2DS_2VASc score.

Age	<65 years, score: 0	65-74 years, score: 1	>=75 years score: 2
Female	No, score: 0	Yes, score: 1	
Congestive heart failure history	No, score: 0	Yes, score: 1	
Hypertension history	No, score: 0	Yes, score: 1	
Stroke/TIA/thromboembolism history	No, score: 0	Yes, score: 1	
Vascular disease history	No, score: 0	Yes, score: 1	
Diabetes history	No, score: 0	Yes, score: 1	

Estimation strategy

We aim to estimate the effect of exposure to early NOAC prescription practices on patient health by comparing the outcomes for the individuals belonging to the treated group with the outcomes for the individuals in the control group and how the outcomes of the groups change over time. This estimation strategy is called difference-in-difference strategy because we consider changes between

groups and changes over time . Table 1 and Table 2 show that patients are exposed to treatment at different points in time depending on the prescribing region (Table 1) or, in the case of the primary care analysis, depending on the prescribing primary care center (Table 2). We will use this information to compare the effects of early with late NOAC exposure and apply a staggered difference-in-difference estimation strategy. In the analysis we estimate this model

$$y_{it} = \alpha + \beta Exposure_p * Post_{pt} + X_{it}\delta + \mu_i + \theta_t + \varepsilon_{ipt}$$

where y_{ipt} is one of three outcomes *y* per analysis level (hospital or GP visit for all causes, hospitalization or GP visit due to stroke and mortality) for of individual *i* in region/primary care center *p* in year *t*. The interaction term, $EarlyExposure_p * Post_{pt}$, is our main variable of interest, indicating the effect of early exposure to NOAC prescription practices. The dummy variable $EarlyExposure_p$ takes the value one for individuals belonging to a prescribing region or a prescribing primary care center *p* with a ratio of NOACs dispenses to warfarin dispenses at or over 20 percent, according to categorization in Table 1 or Table 2, and zero otherwise. The dummy variable $Post_{pt}$ takes the value one in all years *t* after the first year when the share of NOAC dispenses to warfarin dispenses reaches 20 percent, for the treated prescribing region or treated primary care center *p*. $EarlyExposure_p$ is time-invariant and drops out of the equation because we include individual-specific fixed effects, captured by μ_i. By including individual-specific fixed effects our analysis takes into account individual characteristics, observable and unobservable, that are stable over time (for example gender or ability) and instead focuses on observable variables that vary over time for the individual. X_{it} is a vector of time-varying covariates, describing the medical history and stroke risk of the individual. The year effects are θ_t and the parameters to be estimated are β and vector δ. α is the intercept and ε is the residual term. We use robust standard errors, clustered at the region or primary care center.

To interpret β as a causal effect the assumption of parallel trends must hold. This assumption implies that the development of the outcome variable over time would be parallel for treated and untreated individuals if the treatment had not existed. It is a counterfactual situation which we cannot test directly. For this exercise we assume that the assumption holds.

To be able to interpret the estimates as an effect of the treatment, we want to make the treatment and control groups as similar as possible regarding background characteristics. Therefore, we perform the regressions on a matched sample of individuals. We obtain the matching weights by applying the propensity score matching technique. An individual propensity score for treatment

exposure is retrieved from a regression of the treatment indicator on the individual background variables sex, age, marital status, educational attainment and CHA_2DS_2VASc score in 2009, a pre-treatment year. Based on the propensity scores individuals in the treatment group are matched with individuals in the control group. We apply matching with the (one) nearest neighbour with caliper, setting the maximum distance between two individuals that may match to 0.25 standard deviation of the propensity score. We allow individuals in the control group to serve as a match several times (replacement) and require matching between comparable individuals (common support).

We estimate the treatment effect on the entire sample which comprises individuals with different types of pharmaceutical treatments. We identify three categories: individuals who only collect dispenses of warfarin, individuals who switch between dispenses of warfarin and NOACs and individuals who only collect prescriptions of NOACs. We run estimations on smaller samples, focusing on those switching between treatments and on those using only NOACs. The estimations were computed in Stata, version 16. [8]

Results

Analysis of regional prescription practices

Descriptives

Table 3 shows the descriptive statistics for the matched dataset based on national registers. Almost 93 percent of the individuals have sought hospital care for AF and 10 percent for DVT (there are no patient with PE in the working sample). We use both main and secondary diagnoses to categorize the health care use. However, there may be systematic differences in the coverage of secondary diagnoses between regions depending on the system of diagnosis-related groups (DRG) (see e.g. Serdén et al., 2003). Patients from regions with systems promoting generous registration practices may be overrepresented in our dataset. Nearly 30 percent collect warfarin prescriptions exclusively at some point in the study period, over 50 percent make NOACs dispenses exclusively, while 20 percent have experience from both warfarin and NOAC treatments. 62 percent of the individuals make at least one hospital visit (both outpatient and inpatient visit) annually but only 0.09 percent receive inpatient care due to stroke. The mortality rate is about 2 percent. The mean age is 72 years and a mean CHA_2DS_2VASc score of 2.6. Less than half of the group is women.

[8] Stata Statistical Software: Release 16

Table 4. Descriptive statistics for the regional analysis, using national registers.

	mean	sd	min	max
Treatment indication				
patient w AF	0.922	0.267	0	1
patient w DVT	0.107	0.309	0	1
patient w PE	0	0	0	0
Pharmaceutical treatment				
ever use only warfarin	0.296	0.457	0	1
ever use only NOAC	0.519	0.500	0	1
ever use warfarin and NOAC	0.185	0.388	0	1
Dependent variables				
hospital visit, all causes	0.620	0.485	0	1
hospitalization, stroke	0.001	0.030	0	1
mortality, all causes	0.021	0.144	0	1
Background and control variables				
CHA_2DS_2VASc, current year	2.610	1.723	0	9
female	0.443	0.497	0	1
age	71.994	10.959	16	103
educational attainment	3.063	1.757	1	7
married	0.535	0.499	0	1
CHA_2DS_2VASc, previous year	2.385	1.641	0	9
previous warfarin use	0.192	0.394	0	1
previous ASA use	0.395	0.489	0	1

Data from national registers. Matched sample based on propensity score matching (860 770 matched obs., 456 478 raw obs., 79 932 ind.)

Effect of early NOAC prescription practices in regions: NOAC users at risk?

Table 5 presents the estimation results from the difference-in-difference analysis of warfarin and NOAC users belonging to regions with early NOAC prescription practices compared to those who belong to regions with late adoption. Panel A shows the estimates for warfarin users, Panel B for a sample only containing individuals who switch pharmaceutical treatments during the study period and Panel C for a hospital visit (all-causes) (column 1), hospitalization due to stroke (column 2) and death (column 3). According to Panel A, warfarin users are less likely to visit the hospital (column 1) or get hospitalized (column 2) if they belong to a region with early NOAC prescription practices.

However, the estimates are statistically insignificant. In contrast, compared to late exposure, early exposure to NOAC practices increases the risk of death for warfarin users significantly (significant at 1 percent) (column 3): they face a risk increase by over 3 percentage points, or 155% in relation to the mean. The estimates for individuals switching medication are positive insignificant (Panel B) while those for NOAC users are positive significant (at 5 percent in columns 1 and 3, at 10 percent in column 2) (see Panel C). Thus, NOAC users who belong to regions with early adoption of NOAC prescription practices are more likely to need hospital care and to die than NOAC users who belong to regions with late adoption. The probability of a hospital visit is 2.6 percentage point higher (4 percent higher compared to the mean), the estimate for hospitalization due to stroke implies an over-risk by 35 percent compared to the mean and the over-risk of dying is 14 percent compared to the mean.

Table 5. The effect on patient health of early exposure to regional NOAC prescription practice. Analysis of individuals complying with treatment.

Panel A. Warfarin users			
	1	2	3
	all cause hospital visit	hospitalization d.t. stroke	mortality
EarlyExposure x Post	-0.00790	-0.00166	0.0326***
	(0.0188)	(0.00177)	(0.0110)
Observations	253,087	251,657	254,780
R-squared	0.042	0.003	0.106
Number of lopnr	24,648	24,648	24,648
Panel B. Switchers between warfarin and NOAC			
	1	2	3
	all cause hospital visit	hospitalization d.t. stroke	mortality
EarlyExposure x Post	0.00749	0.000213	0.00220
	(0.0119)	(0.00138)	(0.00158)
Observations	159,053	159,036	159,069
R-squared	0.043	0.008	0.009
Number of lopnr	14,580	14,580	14,580
Panel C. NOAC users			
	1	2	3

	all cause hospital visit	hospitalization d.t. stroke	mortality
EarlyExposure x Post	0.0263***	0.000354*	0.00284***
	(0.00730)	(0.000198)	(0.000594)
Observations	446,727	446,705	446,760
R-squared	0.016	0.003	0.003
Number of lopnr	40,704	40,704	40,704

Difference-in-difference model. The estimated coefficient shows the average effect on individuals in regions with early adoption of NOAC prescription practices. Standard errors, clustered at the regional level, in parentheses. All model specifications include controls for the CHA_2DS_2VASc score from the previous year, previous warfarin use (if applicable) and previous use of acetylsalicylic acid (Trombyl), year fixed effects , and individual fixed effects. *** p<0.01, ** p<0.05, * p<0.1

Table 5. The effect on patient health of early exposure to regional NOAC prescription practice. Analysis of individuals complying with treatment.

Panel A. Warfarin users

	1 all cause hospital visit	2 hospitalization d.t. stroke	3 mortality
EarlyExposure x Post	-0.00790	-0.00166	0.0326***
	(0.0188)	(0.00177)	(0.0110)
Observations	253,087	251,657	254,780
R-squared	0.042	0.003	0.106
Number of lopnr	24,648	24,648	24,648

Panel B. Switchers between warfarin and NOAC

	1 all cause hospital visit	2 hospitalization d.t. stroke	3 mortality
EarlyExposure x Post	0.00749	0.000213	0.00220
	(0.0119)	(0.00138)	(0.00158)
Observations	159,053	159,036	159,069
R-squared	0.043	0.008	0.009
Number of lopnr	14,580	14,580	14,580

Panel C. NOAC users

	1	2	3

	all cause hospital visit	hospitalization d.t. stroke	mortality
EarlyExposure x Post	0.0263***	0.000354*	0.00284***
	(0.00730)	(0.000198)	(0.000594)
Observations	446,727	446,705	446,760
R-squared	0.016	0.003	0.003
Number of lopnr	40,704	40,704	40,704

Difference-in-difference model. The estimated coefficient shows the average effect of early regional exposure of NOAC on the treated, who comply with warfarin or NOAC treatment. Robust standard errors in parentheses. All model specifications include controls for the CHA_2DS_2VASc score from the previous year, previous warfarin use (if applicable) and previous use of acetylsalicylic acid (Trombyl), year fixed effects , and individual fixed effects. *** p<0.01, ** p<0.05, * p<0.1

Analysis of primary care prescription practices

Descriptives

Table 6 shows the descriptive statistics of the matched primary care sample, consisting of individuals who comply with warfarin or NOAC treatment (not more than six months between any dispenses) and whose dispensed primary care prescriptions come from the same primary care unit. Nearly 96 percent of the individuals has a registration of AF in the primary care register and 9 percent has a DVT diagnosis (while no PE is registered). Since the introduction of patient choice reforms in primary care, regions have implemented the instrument of adjusted clinical groups (ACG), linking diagnosis registration to payment. The ACG system promotes the registration of more diagnoses in general but research has also found that registration practices of primary care centres depend on competitive pressure (Dackehag and Ellegård, 2019). Thus, we cannot rule out that patients from primary care units with relatively generous diagnosis registration practices are overrepresented. Based on primary care prescriptions, 58 percent of the individuals uses only warfarin, nearly 39 percent uses only NOACs and 3 percent switches between pharmaceutical treatments. 78 percent use of ASA (Trombyl). 82 percent makes at least one GP visit per year and over 1.5 percent of the individuals makes at least one annual GP visit for which stroke is registered as the main diagnosis. The mortality rate is 3.5 percent and the mean thromboembolic risk of primary care patients 3.7. The mean age is 79.

Table 6. Descriptive statistics, primary care, 2009-2015

	mean	sd	min	max
Treatment indication				
patient w AF	0.957	0.204	0	1
patient w DVT	0.094	0.291	0	1
patient w PE	0	0	0	0
Pharmaceutical treatment				
ever used only warfarin	0.578	0.494	0	1
ever used only NOAC	0.390	0.488	0	1
ever used warfarin and NOAC	0.031	0.174	0	1
Dependent variables				
GP visit, all causes	0.822	0.382	0	1
GP visit, stroke	0.015	0.123	0	1
mortality, all causes	0.036	0.185	0	1
Background and control variables				
CHADSVASc	3.747	1.547	0	9
female	0.462	0.499	0	1
age	78.51	8.22	38	101
educational attainment	2.400	1.596	1	7
married	0.503	0.500	0	1
lag_CHADSVASc	3.447	1.638	0	9
previous warfarin use	0.333	0.471	0	1
previous ASA use	0.782	0.413	0	1

Data for regions Östergötland, Västra Götaland, Skåne. Matched sample using propensity score matching (20 389 matched obs., 12 630 raw obs., 2 183 ind.)

Effect of early NOAC prescription practices in primary care centers: NOAC users at some risk?

According to Table 7, compared to warfarin users who belong to primary care centers with late adoption of NOAC, warfarin users with early NOAC exposure are more likely to visit the GP in general, but less likely to need care due to stroke and or to die (Panel A). However, the differences are statistically insignificant. The estimates for individuals switching between medications are also insignificant but the sample is very small, only 62 individuals (Panel B). NOAC users in primary care centers with early NOAC prescription practices are less likely to visit a GP in general but more likely to make a visit due to stroke (Panel C). This is the opposite relationship compared to the warfarin users but also in this case the estimates are insignificant. However, NOAC users with early NOAC exposure face an increase in the risk of death by 3 percentage points or 9 percent compared to the mean .

Table 7. The effect on patient health of early exposure to primary care NOAC prescription practice. Analysis of individuals with complying warfarin or NOAC use and whose dispenses of all primary care prescriptions of warfarin or NOAK come from the same primare care centers.

Panel A. Warfarin users			
	1	2	3
	all cause GP visit	GP visit d.t. stroke	mortality
EarlyExposure x Post	0.000972	-0.00333	-0.0142
	(0.0353)	(0.00880)	(0.0252)
Observations	11,794	11,794	11,794
R-squared	0.009	0.003	0.081
Number of lopnr	1,272	1,272	1,272
Panel B. Switchers between warfarin and NOAC			
	1	2	3
	all cause GP visit	GP visit d.t. stroke	mortality
EarlyExposure x Post	-0.0883	0.0162	0.0194
	(0.0608)	(0.0323)	(0.0190)
Observations	639	639	639
R-squared	0.102	0.009	0.037
Number of lopnr	62	62	62
Panel C. NOAC users			
	1	2	3
	all cause GP visit	GP visit d.t. stroke	mortality
EarlyExposure x Post	-0.0473	0.0332	0.00320*
	(0.0339)	(0.0235)	(0.00189)
Observations	7,956	7,956	7,956
R-squared	0.011	0.017	0.003
Number of lopnr	849	849	849

Difference-in-difference model. The estimated coefficient shows the average effect on inviduals belonging to a primary care center that adopted NOAC prescription practices (at least 20 percent NOAC to warfarin dispenses at prescribing primary care unit) early . Standard errors, clustered at primary care center level, in parentheses. All model specifications include controls for the CHA2DS2VASc score from last year (t-1) based on diagnoses registered in primary care; previous warfarin use (not applicable in analysis presented in Panel C) and previous use of acetylsalicylic acid, both based on dispenses originating from primary care; year fixed effects and individual fixed effects. *** p<0.01, ** p<0.05, * p<0.1

Discussion

In this report we explore both national registers on secondary care and primary care registers to study the effect of clinical practice on patient health in terms of healthcare use (at secondary and primary care levels) and mortality. The clinical practice concerns the use of anticoagulants warfarin and NOACs, for patients with atrial fibrillation (AF indication), deep venous thrombosis and pulmonary embolism (DVT indication). We exploit the varying speed at which regions and primary care centres adopt new practices in the anticoagulation treatment by applying a staggered difference-in-difference estimation strategy on data where patients belonging to early adopters among regions or primary care centers are matched to patients belonging to late adopters.

We use of different data sources, both national registers and primary care registers to investigate the effect of prescription practices. The outcomes of patient health are based on national registers (hospital care from the Patient register and mortality from the Death register) and primary care registers (GP visits from primary care databases of regions Skåne, Västergötland and Östergötland). We measure prescription practices using dispenses of prescribed warfarin and NOAC from the Pharmaceutical register. The dispenses are aggregated at the regional level and the primary care center level. Thus, in the first case we include dispensed prescriptions from all types of healthcare providers; hospitals, primary care centers etc. In the second case we hone in on dispensed primary care prescriptions.

Based on the development of NOAC and warfarin prescriptions over time, we observe that regions and primary care centers show different responsiveness to new information and recommendations. For example, Table 1 shows that, compared to the “earliest adopters” it takes three years for the last

region to reach the level of 20 percent NOACs dispenses to warfarin dispenses, our chosen definition of (early) NOAC prescription practices. We also find a general pattern of late adopters catching up over time when it comes to the share of NOAC prescriptions. When comparing descriptive statistics of the two samples used for the analyses of regional and primary care prescription practices, we find more warfarin users and fewer NOAC users, as well as more previous use of ASA, in primary care. Compared to the regional sample, the mean thromboembolic risk of primary care patients is higher, over 3.7. This relationship is at least partly related to the fact that primary care patients are generally older, the mean age is 79. In addition, primary care patients are more likely to seek health care. However, one should note that ailments leading to GP visits are probably less severe than ailments requiring hospital care. The statistics may reflect the follow-up visits at the GP's after an incident requiring hospital care and treatment.

The estimations using the difference-in-difference approach provide no significant indication that patients belonging to regions or primary care centers that adopt NOAC prescription practices early, experience better health. In fact, rather the opposite. Early NOAC exposure at the regional level seems to significantly increase the need for hospital care and the risk of death for NOAC users. NOAC users in primary care centers with early NOAC adoption also run a significantly higher risk of dying. The excess mortality for NOAC users that our analysis finds may be caused by differences in treatment compliance between warfarin and NOAC users. Patients using warfarin are checked regularly, which may have a positive effect on compliance. One possible implication of our results is that healthcare providers in general should take more responsibility in monitoring the treatment and health status of NOAC patients. For example, it may be the case that primary care centers mainly take over the responsibility for treating a patient who received his or her first NOAC prescription at the hospital and lack routines or commitment. It is possible that we find support for that interpretation in our primary care findings. Although statistically insignificant the estimates indicate that NOAC users belonging to primary care centers with early adoption NOAC are less likely to visit a GP in general but are more likely to visit a GP for stroke-related issues. This potential lack of follow-ups at the primary care level, may in turn lead to the higher need for hospital care observed in Table 5. The observation that warfarin users in primary care centers with early NOAC prescription practices run a lower mortality risk and a lower risk of visiting the GP due to stroke, while making more GP visits in general, may support that interpretation (although the estimates are insignificant). However, we also find that warfarin users in regions with early adoption of NOAC prescription practices experience a marked increase in the risk of death compared to warfarin users in regions with late adoption. This finding could speak against the interpretation that warfarin users are in better health

due to the more frequent follow-ups (even though the estimates of hospital care are negative insignificant, indicating perhaps a better health status). It is also unlikely that the early NOAC exposure has shifted some focus in the regions from warfarin users towards NOAC users, as we see an overall risk increase for the latter in the regional analysis. Another suggestion would be that warfarin users stay warfarin users because they are older and therefore are more likely to die in regions with early adoption. That suggestion would indicate that the matching process did not succeed. However, running a couple regressions without matching as a test, we do not see any marked differences in our results. Although we consider the age and the medical history, measured by previous medications and thromboembolic risk, we cannot rule out that our analysis suffers from omitted variable bias. Overall, the significant excess mortality for warfarin users in the regional analysis may be seen as an indication that the analysis provides results that are not connected to the early prescription practices but to something else. We should also be aware of the risk of making incorrect inferences when using clustered standard errors when the number of clusters is small, as in this case where there are 21 regions (Angrist & Pischke, 2009).

Moreover, it is not advisable to draw any strong conclusions from a comparison between the regional and the primary care analysis. First because that the primary care sample is considerably smaller, slightly more than 2000 individuals compared to 79 000 individuals in regional sample. The analysis would benefit from information from more primary care databases. Second because the primary care sample is based on a particular selection of primary care centers. They are "established" in terms of having non-zero annual dispenses of warfarin or NOACs (or both) in 2009 or earlier until the end of the study period. Thus, we do not consider new centers that have entered the primary care market after 2009 or centers with fluctuating prescription levels due to few AF or DVT patients. The patient population for those types of centers may have other traits and treatment requirements, than the primary care centers studied here. Furthermore, it is uncertain if we capture the prescription practices of actual primary care centers. Our definition of centers is based on the workplace code included in the Pharmaceutical register and not on codes for primary care centers used in primary care databases by regional health care organizations.

It is worth mentioning again that this report uses dispenses of prescription pharmaceuticals to analyse clinical practice. Thus, we cannot say anything about what has actually been prescribed by doctors in secondary and primary care other than what the patients collect at the pharmacies. Moreover, registered dispenses cannot be directly translated into actual consumption. However,

what we see in our data is the behaviour of the most "well-behaved" patients, in terms of dispensed pharmaceuticals. We apply a rather strict definition of compliance, implying that only individuals with less than 6 months between dispenses are included in the analysis. Observations of individuals with a temporary lapse lasting longer than 6 months, fall out of the sample. With a more generous definition of compliance the analysis could be based on more observations but also on a more heterogeneous patient population. The impact of treatment compliance on the relationship between prescription practices and patient health is a question for further research. Another indicator of treatment compliance for NOAC patients, is a laboratory test of the NOAC concentration which can be performed if it is suspected that they are not adhering to treatment.[9] However, we cannot investigate the use of laboratory tests without more treatment information. In a future analysis might be relevant to explore the care measure codes (åtgärdskoder or KVÅ-koder) and their registration in the national Patient register and in the primary care databases.

Availability of data is also an issue in other respects. The question what "early exposure" means, applies particularly to the primary care analysis. The treatment definition is based on individual dispenses and does not say anything about the underlying mechanism. Early adoption of NOACs could be the result of a conscious decision taken by the management of the primary care center but it could also by driven by individual GPs or by patients, who may receive their first NOAC treatment at a hospital and return for continued treatment at the primary care center. It would be interesting to identify where the patient initiated his or her NOAC treatment, at the primary care or the secondary care level, but that would require pharmaceutical data that link dispenses to the prescribing healthcare providers in a correct and consistent way over time. Moreover, to our knowledge, there are very limited possibilities to explore the role of the GP by means of the information available in primary care databases.

Nevertheless, with the data at hand it is possible to make interesting observations of the prescription practices and their potential effects at both primary care level and regional level. In this study we study regional prescription patterns in relation to the use of hospital care and primary care prescription patterns in relation to the use of primary care. However, patients may move between secondary care and primary care, for example from secondary to primary care when the patient is transferred to primary care for continued treatment after a medical event requiring hospital care, or from primary to secondary care because the follow-ups in primary care have been insufficient and

increased the risk of stroke. As an expansion with the available data, the analysis could consider the risk of needing hospital care for patients with AF or DVT receiving medical treatment at a primary care center with or without early adoption of NOAC. It is also possible to consider the likelihood of using primary care after getting/starting anticoagulant treatment at the hospital. However, make confident interpretations in those scenarios, where we use information on prescription source, the workplace and activity codes in the Pharmaceutical register must be consistently and correctly registered.

The use of the NOAC-warfarin ratio to define early or late exposure to NOAC treatment does not provide a sharp and obvious boundary between treated and control groups. We have taken measures to reduce problems of endogeneity but whether it is a viable treatment definition for analyses of clinical practice and patient health is far from guaranteed. We have also mentioned the uncertainty regarding the identity of the primary care centers, based on information in the Pharmaceutical register. The analysis is primarily a first attempt to showcase how different sources of data can be used to explore effects of prescription practices. As an exercise to reveal causal relationships, however, there are considerable limitations. The results presented in this report should therefore be interpreted with great care. For a future study of clinical practice and patient health, other estimation strategies may be explored together with more and more detailed data, particularly for primary care, both at centre level and GP level.

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