

## ORIGINAL REPORT

# Generic switching of warfarin and risk of excessive anticoagulation: a Danish nationwide cohort study<sup>†</sup>

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## ABSTRACT

**Purpose** Generic switching of warfarin was recently repealed in Denmark, as adverse drug reaction (ADR) reports suggested risk of excessive anticoagulation following switches from branded to generic warfarin. We investigated this putative association in a formalized pharmacoepidemiological analysis.

**Methods** We conducted a nationwide cohort study based on Danish healthcare registries, including data from the introduction of generic warfarin until the repeal (January 2011–April 2015). We followed Danish warfarin users over time and compared the rate of incident hospitalizations due to excessive anticoagulation (i.e. increased INR or any bleeding requiring hospitalization) in periods following a recent switch to generic warfarin to the rate in periods without a recent switch.

**Results** We included 105 751 warfarin users, filling a total of 1 539 640 prescriptions for warfarin (2.5% for generic warfarin). This constituted 89.0% of all warfarin prescriptions in Denmark during the study period. We observed 19 362 switches to generic warfarin during the study period. The adjusted hazard ratio for excessive anticoagulation following a recent switch from branded to generic warfarin was 1.1 (95%CI, 0.8–1.4). The result was robust within subgroups and several sensitivity analyses.

**Conclusion** Switching from branded to generic warfarin is not associated with an increased risk of hospitalization with excessive anticoagulation. However, a minor excess risk of transient INR increase cannot be excluded. Pharmacoepidemiological studies provide an effective method for swift evaluation of hypotheses generated by ADR-reports. Copyright © 2015 John Wiley & Sons, Ltd.

**KEY WORDS**—oral anticoagulants; warfarin; generic drugs; adverse drug reaction reports; excessive anticoagulation; pharmacoepidemiology; Denmark

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## INTRODUCTION

Warfarin treatment is limited by a narrow therapeutic interval with even minor fluctuations in international normalized ratio (INR) posing a risk for inadequate treatment (i.e. thrombosis) or excessive anticoagulation (i.e. bleeding).<sup>1</sup> For this reason, generic substitution of warfarin, i.e. the automatic substitution of one medical product with another containing the same

active substance without involvement of the prescribing physician, is a delicate matter.

In Denmark, the requirements for bioequivalence of warfarin generics are strict.<sup>2</sup> Even so, the Danish Health and Medicines Authority recently (20 April 2015) repealed automatic generic substitution of branded warfarin to Warfarin “Orion”®, a warfarin generic marketed in late 2010. The reason for this decision was seven adverse drug reaction (ADR) reports of excessive anticoagulation following such switching.<sup>3</sup> Following the repeal, the decision received much public attention, causing insecurity among both patients and treating physicians.

Warfarin is used extensively in the developed world, and it would constitute a major public health issue if the bioequivalence of a warfarin generic, included in

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a group of assumed interchangeable products, was insufficient. The repeal of automatic generic substitution by the Danish health authorities was a precautionary measure because of the potential serious consequences if the reported association was indeed causal. Importantly, no formal analysis was performed prior to the repeal. Based on the present repeal-case, we aimed to provide an example of how the Danish nationwide health registries can be used for rapid evaluation of safety signals produced by spontaneous ADR-reports. We conducted a nationwide cohort study examining the association between generic switching from branded to generic warfarin and risk of hospitalization with excessive anticoagulation.

## MATERIAL AND METHODS

The study was a nationwide retrospective cohort study. In brief, we followed Danish warfarin users over time and compared the rate of admissions due to excessive anticoagulation (i.e. increased INR or bleeding requiring hospitalization) in periods following a switch to generic warfarin to the rate in periods where no recent switch had occurred.

### Data sources

We used data from three Danish nationwide registries: the National Prescription Registry,<sup>4</sup> which captures all dispensed prescriptions, the National Patient Register,<sup>5</sup> and the Civil Registration System.<sup>6</sup> The data sources and definitions of drugs and diseases within these registries are described in detail in Appendix A and B.

Virtually all medical care in Denmark is reimbursed by the national health authorities, allowing true population-based register-linkage studies covering all inhabitants of Denmark. Data were linked using the personal identification number, a unique identifier assigned to all Danish residents since 1968.<sup>6</sup>

### Cohort of warfarin users

We followed Danish warfarin users from 1 January 2011 (as Warfarin “Orion”® was marketed in December 2010) through 19 April 2015 (i.e. the day prior to the repeal). Acknowledging the increased rate of complications during early warfarin therapy,<sup>7,8</sup> we did not consider warfarin users eligible for cohort entry until filling their third consecutive prescription within one year (also considering prescriptions prior to the study period). We further required that warfarin users were more than 18 years old when entering the cohort and had no history of the main study outcome (see below) or mechanical mitral valve replacement (a rare indication requiring more

intensive anticoagulant treatment). Baseline characteristics (Table 1) were assessed at the date of cohort entry. Indications for warfarin treatment and comorbidities (discharge diagnoses and filled prescriptions for drugs used as proxies for disease) registered within five years before cohort entry were identified in the Patient Registry and the Prescription Registry. Prescriptions for relevant co-medication filled within 180 days of cohort entry were identified in the Prescription Registry. Individuals were followed until the end of the study period, occurrence of a study outcome, filling a prescription for a new oral anticoagulant (NOAC), or until 180 days had passed without filling a prescription for warfarin. The latter was subjected to a sensitivity analysis as described below.

Table 1. Baseline characteristics of warfarin users

	Cohort (n = 105 751)
Age, median (IQR, years)	72 (63–79)
Males	62 301 (58.9%)
Duration of follow-up, median (IQR, months)	22 (9–47)
Presumed indication for warfarin treatment <sup>*,†</sup>	
Atrial fibrillation <sup>‡</sup>	62 232 (58.8%)
Venous thromboembolism	23 929 (22.6%)
Artificial heart valve	6181 (5.8%)
Unknown	13 409 (12.7%)
Co-morbidity <sup>†</sup>	
Alcohol abuse	2719 (2.6%)
Cancer (except non-melanoma skin cancer)	9298 (8.8%)
Congestive heart failure	16 535 (15.6%)
Chronic renal failure	3862 (3.7%)
Diabetes mellitus	16 981 (16.1%)
Hypertension	75 997 (71.9%)
Ischemic stroke/TIA	10 758 (10.2%)
Liver failure	376 (0.4%)
Myocardial infarction	4824 (4.6%)
Thyroid disease	9383 (8.9%)
Co-medication <sup>†</sup>	
Platelet inhibitors <sup>§</sup>	31 028 (29.3%)
NSAID	10 877 (10.3%)
SSRI	8912 (8.4%)
Hospital admissions in the year prior to cohort entry	
0	48 736 (46.1%)
1	30 459 (28.8%)
≥2	26 556 (25.1%)

Abbreviations: IQR = interquartile range, TIA = transient ischemic attack, NSAID = non-steroidal anti-inflammatory drugs, SSRI = selective serotonin re-uptake inhibitors.

\*If a subject had more than one diagnosis, only one diagnosis was given. The priority of the diagnoses was: heart valves > venous thromboembolism > atrial fibrillation.

†Comorbidities (including indications for warfarin treatment) diagnosed at any time before cohort entry were searched in the Patient Registry, and prescriptions for relevant co-medication filled within 180 days of cohort entry were identified in the Prescription Registry.

‡3.1% of atrial fibrillation patients were identified through prescription data only.

§Aspirin, dipyridamole, ADP-receptor blockers (clopidogrel, prasugrel, ticagrelor).

### *Classification of follow-up*

Follow-up (person-time) of the overall cohort of warfarin users was classified into four mutually exclusive categories:

- (1) Continuous use of branded warfarin (from the date of filling a second prescription for branded warfarin in a row until the time of filling the next prescription)
- (2) Continuous use of generic warfarin (from the date of filling a second prescription for generic warfarin in a row until the time of filling the next prescription)
- (3) Recent switch TO generic warfarin (the first 60 days from the day of filling a prescription for generic warfarin and having filled branded warfarin as the last prior prescription)
- (4) Recent switch FROM generic warfarin (the first 60 days from the day of filling a prescription for branded warfarin and having filled generic warfarin as the last prior prescription)

The division by exposure thus pertains to person-time and not the single individual. As an example, if an individual uses branded warfarin for two years and then switches to generic warfarin, he will contribute two person-years to the “continuous use of branded warfarin” cohort, 60 days to the “switched to generic” cohort and, once he fills the second prescription for generic warfarin, he will contribute to the “continuous use of generic warfarin”.

In all analyses, continuous use of branded warfarin served as the reference. This classification of follow-up was subjected to sensitivity analyses as described below. Follow-up not falling into any of the four categories, e.g. time from 61 days after a switch until a new prescription, was not included in the analysis, as this follow-up included time where any events were unlikely to be attributed to the recent switch but also unsuited to serve as a reference.

### *Outcome events*

The main study outcome was incident hospital admission with a primary diagnosis indicating excessive anticoagulation: a composite of “increased INR-levels” and “any bleeding requiring hospitalization”. The diagnoses have not been validated in previous studies; however, the overall quality and accuracy of data in the Patient Registry have been estimated to be high.<sup>5</sup> Secondary outcomes were “increased INR-levels” or “bleeding requiring hospitalization” analysed individually, thromboembolic complications (defined as either venous thromboembolism or ischemic stroke), and fatal cases of excessive anticoagulation (defined as death

within 30 days following admission). All codes are supplied in Appendix B.

### *Main analysis*

The main analysis compared the rate of excessive anticoagulation during follow-up classified as “recent switch TO generic warfarin” to follow-up classified as “continuous use of branded warfarin”. The analysis was performed using cox regression, adjusting for age (at cohort entry, in categories of 5 years), sex, and baseline characteristics (indication for warfarin treatment, comorbidity, co-medication, and number of hospital admissions in the year preceding cohort entry; see Table 1).

Additional analyses were conducted comparing follow-up classified as “recent switch FROM generic warfarin” and “continuous use of generic warfarin” to that of “continuous use of branded warfarin”.

### *Sensitivity and supplementary analyses*

We performed a number of pre-planned sub-analyses and sensitivity analyses.

- First, we restricted the analysis to individuals using warfarin for atrial fibrillation. We achieved this by only including individuals with (i) a diagnosis of atrial fibrillation or (ii) use of an antiarrhythmic drugs almost exclusively used in atrial fibrillation (digoxin or verapamil), while at the same time having no history of venous thromboembolism or mechanical heart valve replacement.
- Second, we excluded follow-up within 30 days for a prescription for any antibiotic, both antibacterials and antimycotics. While unlikely to be associated with switch among generics, both infection and antibiotics are known to affect INR values.<sup>9,10</sup>
- Third, we redefined the time period classified as “recent switch” from the 60 days following a switch between generics used in the main analysis to 30, 45, and 90 days, respectively.

Further, we performed two post-hoc analyses.

- Fourth, we redefined the study period to 13 January 2015–19 April 2015, i.e. the period where the automatic generic substitution of warfarin products in Denmark included Warfarin “Orion” ®.
- Last, we redid the main analysis censoring individuals who had a gap of 120 days or more with no warfarin prescription fills (down from 180 days in the main analysis).

### Other

All analyses were performed using Stata Release 13.0 (StataCorp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency.

## RESULTS

We identified 117 374 individuals with continuous use of warfarin within the study period. After excluding 228 individuals below 18 years of age, 973 with a history of mitral valve replacement, and 10 422 with a previous study outcome we ended up including 105 751 eligible individuals. The median age was 72 years and 59% were male. The majority used warfarin because of atrial fibrillation (Table 1). Individuals who experienced a switch from branded to generic warfarin had longer duration of follow-up and were more often treated for atrial fibrillation compared to the entire cohort as longer warfarin treatment increases the likelihood of experiencing a generic switch (Supporting Information I). Compared to the entire cohort, individuals experiencing a primary outcome were older and had more comorbid conditions (Supporting Information I).

A total of 1 539 640 prescriptions for warfarin were filled by the study population, which constituted 89.0% of all warfarin prescriptions filled in Denmark within the study period. The vast majority (97.5%) was for branded warfarin, while generic warfarin constituted 2.5% of the prescriptions. We observed 19 362 switches to generic warfarin among 18 593 individuals. In the main analysis, 104 265 unique individuals contributed follow-up to the “continuous use of branded warfarin”-group while 18 105 contributed to the “recent switch to generic warfarin”-group. The corresponding numbers for the “continuous use of generic warfarin” and the “recent switch from generic warfarin”-groups were 3304 and 3458, respectively. Among all cohort members, 83.1% contributed follow-up to only one exposure group, which almost exclusively (98.8%) was to the “continuous use of branded warfarin”-group. A total of 12.2% of individuals contributed to two exposure groups, 4.3% to three groups, and 0.5% contributed follow-up to all four exposure groups.

The primary outcome, excessive anticoagulation, occurred 5765 times during the study period (Table 2). Fifty-three (0.9%) of these were in timely relation to a switch from branded to generic warfarin, yielding a crude and adjusted hazard ratio (HR) for excessive anticoagulation in the time following such switch of 1.1 (95% confidence interval (CI), 0.8–1.5) and 1.1 (95%CI, 0.8–1.4), respectively. Separation of the

combined endpoint did not change the association; adjusted HRs of increased INR and bleeding requiring hospitalization were 1.2 (95%CI, 0.7–2.0) and 1.0 (95%CI, 0.7–1.4), respectively.

In the secondary analysis, we found a statistically significant increased adjusted HR of 2.3 (95%CI, 1.0–5.1,  $p < 0.05$ ) between recent switch from generic warfarin and increased INR (Table 2). No similar association was found between recent switch from generic warfarin and the overall outcome of excessive anticoagulation (adjusted HR 1.2; 95%CI, 0.7–2.2). Similarly, the adjusted HR of thromboembolism associated with continuous use of generic warfarin reached 2.4 (95%CI, 1.7–3.2).

The results did not change significantly when restricting the analysis to pre-specified subgroups (Table 3).

Restriction to the period where Warfarin “Orion”® was automatically interchangeable with other warfarin products resulted in a crude and adjusted HR for excessive anticoagulation of 1.1 (95%CI, 0.8–1.5) and 1.0 (95%CI, 0.7–1.4), respectively (Supporting Information II). In this period, 29.6% of warfarin prescriptions were on generic warfarin.

Changing the period after a switch to generic warfarin considered as “time at risk” did not change the adjusted HR noticeably; from 1.3 (95%CI, 0.9–1.8) with a time window of 30 days to 1.1 (95%CI, 0.8–1.4) with a time window of 90 days (Supporting Information III).

Adjusting for confounders generally had little impact on the associations. Test for proportional hazards yielded acceptable results ( $p = 0.07$  for main comparison for Schoenfeld’s residuals), although with some uncertainty likely attributable to the low number of events within person-time classified as related to switching (for graphical illustration, see Supporting Information IV).

Reduction of the allowed gap between warfarin redemptions to 120 days led to results similar to the main analysis (Supporting Information V).

## DISCUSSION

In this nationwide cohort study, we did not find evidence of a clinically significant association between switching from branded warfarin to generic warfarin (Warfarin “Orion”®) and risk of excessive anticoagulation. This finding was robust within different patient subgroups and when using different definitions of time at risk. Overall, our results do not support a causal relationship between the spontaneous ADR-reports of increased INR and generic substitution of warfarin.

The Danish requirements for bioequivalence of warfarin generics are strict; the 90% confidence interval

Table 2. Rates and adjusted<sup>†</sup> hazard ratios for primary and secondary outcomes, comparing continuous use of warfarin with different regimes of switch between branded and generic warfarin

Outcome measure	Events	Follow-up (PY)	Rate (/1000 PY)	Crude HR (95%CI)	Adjusted HR (95%CI)
<i>Excessive anticoagulation</i> <sup>‡</sup>					
Cont. use of branded	5665	224 282	25	1.0 (ref.)	1.0 (ref.)
Cont. use of generic	36	1349	27	1.1 (0.8–1.5)	1.1 (0.8–1.5)
Switch TO generic	53	1940	27	1.1 (0.8–1.5)	1.1 (0.8–1.4)
Switch FROM generic	11	375	29	1.2 (0.7–2.2)	1.2 (0.7–2.2)
<i>Increased INR</i> <sup>‡</sup>					
Cont. use of branded	1581	228 430	7	1.0 (ref.)	1.0 (ref.)
Cont. use of generic	12	1376	9	1.3 (0.7–2.2)	1.3 (0.7–2.3)
Switch TO generic	17	1995	9	1.2 (0.7–2.0)	1.2 (0.7–2.0)
Switch FROM generic	6	384	16	2.3 (1.0–5.0)*	2.3 (1.0–5.1)*
<i>Bleeding</i> <sup>‡</sup>					
Cont. use of branded	4232	225 627	19	1.0 (ref.)	1.0 (ref.)
Cont. use of generic	26	1363	19	1.0 (0.7–1.5)	1.0 (0.7–1.5)
Switch TO generic	37	1958	19	1.0 (0.8–1.5)	1.0 (0.7–1.4)
Switch FROM generic	5	378	13	0.7 (0.3–1.7)	0.7 (0.3–1.8)
<i>Excessive anticoagulation, fatal</i>					
Cont. use of branded	773	229 615	3	1.0 (ref.)	1.0 (ref.)
Cont. use of generic	<i>n</i> < 5 <sup>§</sup>	1390	2	0.6 (0.2–2.0)	0.7 (0.2–2.0)
Switch TO generic	7	2014	3	1.1 (0.5–2.3)	1.0 (0.5–2.2)
Switch FROM generic	<i>n</i> < 5 <sup>§</sup>	388	3	0.8 (0.1–5.6)	0.8 (0.1–6.0)
<i>Thromboembolism</i>					
Cont. use of branded	2585	227 047	11	1.0 (ref.)	1.0 (ref.)
Cont. use of generic	39	1354	29	2.5 (1.8–3.5)*	2.4 (1.7–3.2)*
Switch TO generic	20	1971	10	0.9 (0.6–1.5)	1.0 (0.6–1.5)
Switch FROM generic	<i>n</i> < 5 <sup>§</sup>	379	8	0.7 (0.2–2.2)	0.7 (0.2–2.2)

Abbreviations: PY = person years; HR = hazard ratio; CI = confidence interval; INR = international normalized ratio.

\**p*-Value < 0.05.

<sup>†</sup>Adjusted for age, sex, co-morbidity (alcohol abuse, cancer, diabetes, heart failure, hypertension, ischemic stroke/transient ischemic attack, liver failure, myocardial infarction, renal failure, thyroid disease), and co-medication (platelet inhibitors, non-steroidal anti-inflammatory drugs, selective serotonin re-uptake inhibitors).

<sup>‡</sup>Excessive anticoagulation is a combined endpoint of increased INR and bleeding. When a subject was diagnosed with both secondary events (increased INR and bleeding) at the same time, it was counted towards each of the secondary outcomes but only as one primary event.

<sup>§</sup>To ensure anonymization, cells with numbers lower than five are not reported.

Table 3. Rates and adjusted<sup>†</sup> hazard ratios for excessive anticoagulation, comparing continuous use of warfarin with different regimes of switch between branded and generic warfarin, by subgroup

Outcome measure	Events	Follow-up (PY)	Rate (/1000 PY)	Crude HR (95%CI)	Adjusted HR (95%CI)
<i>Only atrial fibrillation</i>					
Cont. use of branded	3685	139 708	26	1.0 (ref.)	1.0 (ref.)
Cont. use of generic	18	796	23	0.9 (0.5–1.4)	0.9 (0.5–1.4)
Switch TO generic	40	1187	34	1.3 (1.0–1.9)	1.3 (1.0–1.8)
Switch FROM generic	5	222	23	0.9 (0.4–2.1)	0.9 (0.4–2.2)
<i>Excluding follow-up exposed to antibiotics</i>					
Cont. use of branded	4348	206 773	21	1.0 (ref.)	1.0 (ref.)
Cont. use of generic	27	1240	22	1.0 (0.7–1.5)	1.0 (0.7–1.5)
Switch TO generic	42	1773	24	1.1 (0.8–1.6)	1.1 (0.8–1.5)
Switch FROM generic	8	339	24	1.1 (0.6–2.2)	1.1 (0.6–2.3)

Abbreviations: PY = person years; HR = hazard ratio; CI = confidence interval; INR = international normalized ratio, EA = excessive anticoagulation.

<sup>†</sup>Adjusted for age, sex, co-morbidity (alcohol abuse, cancer, diabetes, heart failure, hypertension, ischemic stroke/transient ischemic attack, liver failure, myocardial infarction, renal failure, thyroid disease), and co-medication (platelet inhibitors, non-steroidal anti-inflammatory drugs, selective serotonin re-uptake inhibitors).

for the ratios (generic vs. brand name reference) for extent of absorption ( $C_{max}$  and AUC) must be within 90–111%, which is in line with the European Medicines Agency's recommendations.<sup>2,12</sup> Additionally, the 90% confidence interval must specifically include equity in

Denmark.<sup>2</sup> The clinical equivalence of different generic warfarin products and branded warfarin has been assessed in several randomized trials and observational studies.<sup>13,14</sup> In accordance with our findings, these studies find generic warfarin as safe as branded warfarin. To

our knowledge, no prior studies have tested the clinical equivalence of Warfarin “Orion”® and branded warfarin. In the pre-approval bioequivalence study of Warfarin “Orion”®, the pharmacokinetic parameters AUC and  $C_{max}$  were found to be slightly increased compared to branded warfarin.<sup>15</sup> This supports the hypothesis raised by the spontaneous ADR-reports, i.e. that switching from branded warfarin to Warfarin “Orion”® may result in increased INR-levels despite unchanged dosing regimens. We cannot rule out a minor transient increased risk associated with a switch from branded warfarin to Warfarin “Orion”®, as the upper bound in the confidence interval reached 1.4 in the main analysis. Some individuals, with variant genotypes of CYP2C9 (primary metabolizing enzyme) or VKORC1 (target enzyme) or other phenotypic outliers, may be more sensitive to altered warfarin exposure.<sup>16</sup> However, our results did not indicate that the anticoagulant effect of Warfarin “Orion”®, from a clinical point of view, is markedly stronger than branded warfarin.

Surprisingly, we found statistically significant associations between continuous use of generic warfarin and thromboembolism, and switch from generic to branded warfarin and excessive anticoagulation and increased INR. Importantly, these findings do not correspond to any pre-specified hypotheses, and we are not aware of any data or biological rationale supporting them. The first result, we consider to be a chance finding; it is not biologically plausible that continuous use of one anticoagulant drug should increase the risk of thromboembolism compared to continuous use of a bioequivalent anticoagulant drug. The second result also seems counterintuitive, although it, with the overall hypothesis in mind, could be interpreted as a reflection of “overcompensation” of a drop in INR following a switch, if Warfarin “Orion”® was indeed superior in terms of anticoagulant effect to branded warfarin. We did not find a similar association between this particular switch and risk of bleeding, which do not support this interpretation of data.

Information on a product safety is usually limited at the time of authorization, and ADR-reports from healthcare professionals and patients are one of the basic tools in routine post-marketing pharmacovigilance. However, ADR-reports do not allow an evaluation of associations let alone causality and should therefore only be considered “safety signals” identifying a need for further scientific investigation. Bleeding events during warfarin treatment are common and well known among physicians, therefore, underreporting of such episodes for brand-named drugs could be an issue.<sup>17</sup> On the other hand, both patients and doctors

may be more alert when it comes to generic substitutions for a high-risk drug as warfarin,<sup>18</sup> and this may result in less underreporting or even stimulated reporting among users of generic warfarin.<sup>19</sup> Our study confirms that spontaneous ADR-reports are not sufficient as the sole basis for regulatory decisions. We acknowledge that the formal pharmacovigilance process may be cumbersome and lengthy,<sup>20</sup> thereby forcing regulators to react solely based on ADR-reports in order to best preserve the interest of public health. In countries like Denmark, the evaluation of “safety signals” can be performed swiftly through pharmacoepidemiological studies based on population-based registries of high quality.<sup>11</sup> This minimizes the time at potential risk of further harm, and the risk of unnecessary concern caused by unwarranted precautionary measures.

Although Warfarin “Orion”® was marketed in December 2010 as a bioequivalent and, at least in periods, cheaper alternative to branded warfarin, the market share of the product was minimal until inclusion in the automatic generic substitution of warfarin products in January 2015.

The principle strengths of our study are the sample size and the fact that we included the majority of warfarin users in Denmark during the period where generic warfarin has been available (2011–2015). Further, the completeness of the registry on drug use is very high.<sup>4</sup>

Our study has some limitations. Most importantly, we did not have access to patient-specific INR-values. Accordingly, we cannot rule out transient fluctuations in INR in relation to switching. However, if such fluctuations should occur, they do not seem to cause complications requiring hospitalizations, at least not in a setting of high-quality warfarin-treatment like Denmark.<sup>21</sup> The diagnoses of “increased INR” and “any bleeding requiring hospitalization” in the Patient Register have not been validated. However, it seems unlikely that misclassification of the diagnoses contained in “excessive anticoagulation” would be unequally distributed between warfarin users with different exposure status. Finally, we assumed the date of redemption of a different type of warfarin to be identical to the date of the switch and counted time at risk from this date. If the prescription had been redeemed “in advance”, exposure misclassification could be introduced. Importantly, this was generally not indicated by the sensitivity analyses.

In conclusion, we did not find evidence supporting an increased risk of hospitalization with excessive anticoagulation following switch from branded to generic warfarin (Warfarin “Orion”®) as could be hypothesized from spontaneous ADR-reports. However, a minor

excess risk of transient INR increase cannot be excluded. As exemplified by our study, pharmacoepidemiological studies can be an effective method for swift evaluation of hypotheses generated by ADR-reports.

## CONFLICT OF INTEREST

Steffen Thirstrup is a full-time employee of the pharmaceutical consulting company NDA Regulatory Services. He has never consulted for or in relation to the product studied in this publication.

## KEY POINTS

- Generic substitution of warfarin was recently repealed by the Danish health authorities as adverse drug reaction reports suggested a risk of excessive anticoagulation when switching from branded to generic warfarin
- In this nationwide cohort study, switching from branded to generic warfarin was not associated with a markedly increased risk of hospitalization due to bleeding or increased international normalized ratio
- Pharmacoepidemiological studies based on large healthcare databases are useful in the evaluation of hypotheses generated by adverse drug reaction reports

## ETHICS STATEMENT

According to Danish law, studies based solely on register data do not require approval from an ethics review board.<sup>11</sup>

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.

Supporting Information I Baseline characteristics of all warfarin users in the cohort, users with a history of switching from branded to generic warfarin, and users experiencing an outcome.

Supporting Information II Rates and adjusted hazard ratios for excessive anticoagulation, comparing continuous use of warfarin with different regimes of switch between branded and generic warfarin, study period 13 January–19 April 2015.

Supporting Information III Rates and adjusted hazard ratios for excessive anticoagulation, comparing continuous use of warfarin with different regimes of switch

between branded and generic warfarin, by different cut-offs for recent shift.

Supporting Information IV Test of model assumptions –log-rank plot for proportional hazards.

Supporting Information V Rates and adjusted hazard ratios for primary and secondary outcomes,

comparing continuous use of warfarin with different regimes of switch between branded and generic warfarin. \Allowed gap between warfarin redemptions: 120 days.

Appendix A–Data sources.

Appendix B–Definitions of drugs and diseases.