The Effect of Flucloxacillin on Warfarin Anticoagulation: A Swedish Register-Based Nationwide Cohort Study

Buster Mannheimer[1] Tore B. Stage[2] Anton Pottegård[2] Jonatan D. Lindh[3]

[1] Department of Clinical Science and Education at Södersjukhuset, Karolinska Institutet, Stockholm, Sweden
[2] Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark
[3] Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden

Address for correspondence Buster Mannheimer, PhD, Department of Clinical Science and Education at Södersjukhuset, Karolinska Institutet, SE 118 82, Stockholm, Sweden (e-mail: buster.mannheimer@sll.se).

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Abstract

Background Data indicate that codispensing flucloxacillin to patients already on warfarin may result in decreased warfarin efficacy.

Objectives This article investigates the effect of flucloxacillin on warfarin anticoagulation.

Patients and Methods In a retrospective cohort study of warfarin users, using three nationwide registers we included 5,848 patients receiving 10 days flucloxacillin treatment and 201 with $\geq$30 days treatment. To assess the potential for confounding by indication, we also identified 21,430 individuals initiating phenoxymethylpenicillin. International normalized ratio (INR) values and warfarin doses were calculated day-by-day and proportion of patients with a subtherapeutic INR week-by-week during cotreatment.

Results Following initiation of flucloxacillin with a planned treatment duration of 10 days and $\geq$30 days, the mean INR decreased from 2.36 (95% confidence interval [CI] 2.34; 2.37) to 2.20 (95% CI 2.19; 2.21) and from 2.24 (95% CI 2.16; 2.32) to 1.96 (95% CI 1.89; 2.02), respectively. Consequently, for individuals with 10 days treatment the proportion of patients with a subtherapeutic INR of <2 increased from 22% in the week preceding flucloxacillin initiation to 35% in the third week after initiation of flucloxacillin. In patients with 30 days treatment, the proportion increased from 34 to 63% by week 6. In individuals initiating phenoxymethylpenicillin, INR levels did not decrease.

Conclusion One in three patients with 10 days flucloxacillin and almost two in three patients initiating long-term treatment, was exposed to a subsequent subtherapeutic anticoagulant effect. To avoid unnecessary thromboembolic complications, the initiation of flucloxacillin should be accompanied by closer INR monitoring which may be especially important among individuals with lengthy treatments.

Keywords
- flucloxacillin
- cytochrome P-450 CYP2C9
- drug interactions
- international normalized ratio
- warfarin

Introduction

The narrow therapeutic window of vitamin K antagonists (VKAs) makes ensuring stable international normalized ratio (INR) levels, which is one of the key challenges in providing high-quality anticoagulant treatment. Disruption of stable VKA treatment can occur, for example, due to minor noncompliance,[1] dietary changes,[2] or acute illness.[3] Warfarin is administered as a racemic mixture and the *S*-isomer is three times as potent as the *R*-isomer. The *S*-isomer is predominantly metabolized by CYP2C9 and modulating the activity of CYP2C9 can thus lead to drug–drug interactions altering

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the efficacy of warfarin. There are many examples of such effects which assume clinically relevant magnitudes, such as inhibition of CYP2C9 by miconazole[4,5] and amiodarone[6,7] leading to increased anticoagulation or induction by CYP2C9 from use of carbamazepine[8] or rifampicin[9] leading to subtherapeutic INR levels.

Based on a small Danish cohort, we have previously shown that use of dicloxacillin, a isoxazolyl β-lactam penicillin, led to a marked drop in INR levels.[10] Subsequently, we elucidated the underlying mechanism to be induction of CYP2C9 mediated by pregnane X receptor activation.[11] Importantly, in vitro data suggested a similar mechanism, although less pronounced, for flucloxacillin,[11] which is of concern as flucloxacillin in many countries is the most used isoxazolyl β-lactam penicillin.[12,13] To our knowledge, only one study has investigated the clinical impact of flucloxacillin use among patients treated with VKA, showing a decrease in INR levels upon concomitant use.[4] Leveraging registry data from a large sample of Swedish anticoagulant patients, we further assessed whether flucloxacillin affects the anticoagulative effect of warfarin.

Patients and Methods

Study Design

This was a register-based cohort study in patients receiving flucloxacillin or phenoxymethylpenicillin during ongoing treatment with warfarin. In each individual, INR values and warfarin doses registered immediately before initiation of the antibiotic were compared with the corresponding values observed during and after the course of antibiotic treatment.

Data Sources

Information on warfarin doses and INR values were obtained from Auricula[14] and Journalia,[15] two medical record systems used by more than 300 Swedish outpatient clinics. Neither Auricula nor Journalia contain information on INR measurements or warfarin dosing in hospitalized patients. The two systems contain complete day-to-day data on warfarin doses and INR measurements for all patients treated with warfarin in these clinics. Information on coexposure to flucloxacillin, phenoxymethylpenicillin, and other potentially interacting drugs were obtained from the Swedish Prescribed Drug Register (SPDR).[16] This register contains complete, individual-level data on all prescribed drugs dispensed in Sweden from 2005 onwards. The SPDR does not contain information regarding drugs dispensed to hospitalized patients. The information in the SPDR include information on type of drug (Anatomical Therapeutic Chemical code), strength per tablet, and dispensed number of tablets. It also contains a string variable with the dosing instruction text on the prescription written by the physician used to communicate the dosage regimen and planned treatment duration to the patient.

Patients

Inclusion criteria were patients above 18 years old with warfarin treatment documented in Journalia or Auricula. In addition, they had to be dispensed flucloxacillin or phenoxymethylpenicillin at least once in the years 2005 to 2012.

Drug Exposure

Three different drug exposures were analyzed separately: flucloxacillin for 10 days, flucloxacillin for $\geq$30 days, and phenoxymethylpenicillin (regardless of treatment duration). We chose 10 days because this is the most common treatment duration, and therefore the most clinically relevant exposure. For the long-term treatment group, we aimed to select patients with the longest treatment duration possible, but at the same time had to avoid excluding too many patients. Thus, 30 days was chosen to enable inclusion of a reasonably large number of patients while still extending the exposure time enough to investigate the maximum effect on plasma clearance after the start of induction.[17] In the 30-day group, the total treatment length was based on the dispensed number of tablets divided with the prescribed number of tablets per day according to the dosing text. To exclude individuals with poor compliance and those that may have stopped the treatment prematurely due to adverse effects, the $>$ 30 days exposure had to consist of at least two consecutive dispensations. In such a series of dispensations, each prescription was assumed to last for up to 20% longer than intended, to account for missed tablets or short treatment gaps. Phenoxymethylpenicillin was included as a negative control, since this drug has indications similar to flucloxacillin and presumably does not interact with warfarin.[10] The exclusion criteria were identical for all exposures.

Thus, the day of dispensation (or the first in a series of dispensations) was considered the index date, indicating start of coexposure. Each index date had to be preceded by a 1-year washout period without dispensations of the antibiotic (flucloxacillin or phenoxymethylpenicillin). No dispensations of other drugs known to interact with warfarin were allowed between 120 days before the index date until the end of follow-up. Thus, individuals codispensed any drugs that, according to the validated drug–drug interaction database SFINX, have a well-documented, clinically significant pharmacokinetic potential to interact with warfarin (i.e., changes in the INR or the area under the time–plasma concentration curve of warfarin exceeding 10%) were excluded.[18] Consequently, patients were excluded if they had been prescribed and dispensed amiodarone, bosentan, capecitabine, carbamazepine, cimetidine, clofibrate, co-trimoxazole, dabrafenib, darunavir, dasabuvir, disulfiram, dronedarone, enzalutamide, eslicarbazepine, erythromycin, fluconazole, fluorouracil, lopinavir, metronidazole, miconazole, paritaprevir, phenobarbital, primidone, propafenone, rifampicin, ritonavir, sitaxentan, ombitasvir, oritavancin, vemurafenib, voriconazole, or zafirlukast. To assure ongoing warfarin treatment, at least one dispensation of warfarin was required in the period 4 to 20 weeks prior to the index date and warfarin treatment had to be documented for at least 90 days prior to the index date. If more than one potential index date was identified for one of the three exposures, only the first was used in each patient. Patients were followed for 10 weeks after commencing the antibiotic treatment, but if warfarin treatment (as documented in Journalia/Auricula) ended within 10 weeks, follow-up ended on the day of the last INR measurement.

Outcomes

The main outcome was day-by-day INR values. Secondary outcomes were the week-by-week proportion of patients who exhibited one or more subtherapeutic (< 2) INR values and day-by-day warfarin doses. In each patient, warfarin doses were normalized by dividing them by the baseline dose (mean dose during the 4 weeks preceding the index date). Hence, doses below 100% would indicate a decrease compared with baseline and doses above 100% an increase. Since INR is typically not measured daily, missing values were imputed using linear interpolation, as described by Rosendaal et al.[19]

Statistical Methods

For each day, from 4 weeks before until 10 weeks after the index date, means and 95% confidence intervals (CIs) of log-transformed INR values were calculated. Means and 95% CIs of warfarin doses were calculated in a similar fashion, starting at the index date. All values were retransformed before presentation. The 4-week preindex INR observation period was included to enable detection of INR trends indicative of, for example, confounding by indication or misclassification of index dates. For each of the 10 weeks (7 days periods) following the index date, the percentage of patients with at least one INR value below 2 was calculated. All analyses were performed with R version 3.3.2.[20]

Results

In total, 66,682 warfarin-treated patients recorded in the Auricula and Journalia databases had been dispensed flucloxacillin on at least one occasion between July 1, 2005 and December 31, 2012. Of these patients, 48,135 were excluded because the flucloxacillin treatment did not coincide with warfarin treatment, or because other interacting drugs had been codispensed. To investigate the effect of a 10 days' treatment period, we excluded individuals not explicitly treated for 10 days being evident from the dosing text. Thus, individuals whose treatment duration explicitly lasted for a period of time other than 10 days ($n = 10{,}950$), or whose treatment length was not being specified ($n = 1{,}098$) were excluded. In addition, individuals without ongoing warfarin treatment ($n = 651$) were excluded leaving 5,848 patients. To investigate the effect of a treatment period of 30 days or more, individuals with shorter treatment ($n = 18{,}232$), without ongoing warfarin treatment ($n = 35$), and those where data during the treatment period could not be assessed ($n = 79$) were excluded, leaving 201 patients (►**Fig. 1**). To rule out confounding by indication as an alternative explanation for the observed effects of flucloxacillin, we also investigated the effect after initiation of phenoxymethylpenicillin, a drug that does not interact with warfarin ($n = 21{,}430$).

Baseline characteristics of the study population is shown in ►**Table 1**. The median age ranged between 74 and 76 years in the three groups and the proportion of women between 27 and 38%.

International Normalized Ratio

Following initiation of flucloxacillin with a planned treatment duration of 10 days, the mean INR rapidly decreased from 2.36 (95% CI 2.34; 2.37) to 2.20 (95% CI 2.19; 2.21) after 14 days and then turning upwards to again reach baseline after about a month. In individuals with a planned treatment duration of 30 days, mean INR rapidly decreased from 2.24 (95% CI 2.16; 2.32) to 1.96 (95% CI 1.89; 2.02) after 5 weeks of cotreatment. On the contrary, in individuals initiating treatment with phenoxymethylpenicillin, INR levels instead increased slightly from 2.49 (95% CI 2.48; 2.50) at baseline to 2.52 (95% CI 2.51; 2.53) during the first week (►**Fig. 2**).

Because of the decline in the INR, the proportion of patients exposed to subtherapeutic INR levels increased. Consequently, for individuals with 10 days treatment the proportion of patients with a subtherapeutic INR < 2 increased from 22% in the week preceding flucloxacillin initiation to 35% in the third week after initiation of flucloxacillin. In patients with 30 days treatment, the proportion increased from 34 to 63% by week 6. In individuals initiating phenoxymethylpenicillin, the fraction of patients with an INR below 2.0 remained stable at approximately 15% (►**Fig. 3**).

Warfarin Dose

►**Fig. 4** shows the relative changes in relative warfarin doses among the three groups, individuals dispensed flucloxacillin or phenoxymethylpenicillin. After 2 weeks' cotreatment, individuals with 10 days treatment with flucloxacillin reached a maximum of 2% increase in doses. In patients with 30 days treatment duration, the warfarin doses increased by 13% after approximately 10 weeks. In contrast, warfarin doses decreased by approximately 1% in patients with phenoxymethylpenicillin treatment.

Discussion

In the present study on 5,848 individuals with stable warfarin treatment, initiation of 10 days treatment with flucloxacillin, resulted in an increase of the subtherapeutic INR from 22 to 35%. In 201 patients with at least 30 days flucloxacillin treatment, the proportion of patients with subtherapeutic INR increased from 34 to 63%.

Pottegård et al showed that initiation of dicloxacillin, another isoxazolyl β-lactam penicillin, resulted in a mean drop from an INR level of 2.59 (95% CI 2.50–2.68) to 1.97 (95% CI, 190–2.05), 2 to 4 weeks after initiation in 236 patients with warfarin. In total, 61% were exposed for a subtherapeutic INR.[10] To our knowledge, only one study has investigated the clinical impact of flucloxacillin use among patients treated with warfarin. Martín-Pérez et al conducted a real-world data approach investigating INR values before and after the initiation of potentially interacting drugs in over 120,000 warfarin users. Although well conducted, the paper focuses on 16 potentially interacting drugs which hampers the ability to present all aspects of respective interaction and limits the ability to control for some relevant factors that may have biased the results. In contrast, the present paper focusing on flucloxacillin only, provides a temporal dimension with regard

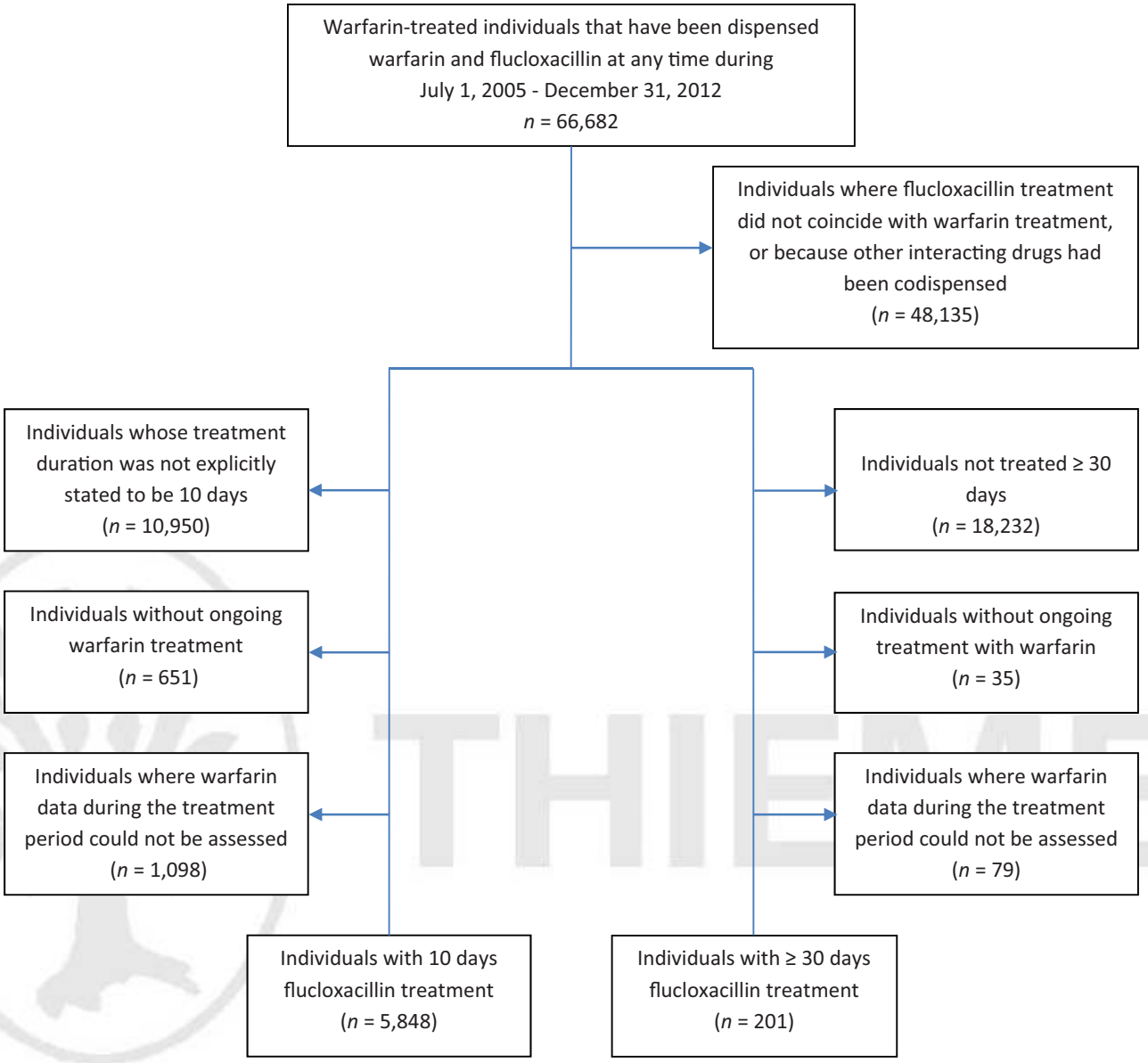

Fig. 1 Patient flow diagram.

Table 1 Baseline characteristics among individuals initiating flucloxacillin treatment with a duration of 10 days ($n = 5{,}898$) and 30 days ($n = 206$) and among individuals initiating phenoxymethylpenicillin treatment ($n = 21{,}626$)

	Individuals with 10 days flucloxacillin treatment	Individuals with ≥ 30 days flucloxacillin treatment	Individuals with phenoxymethylpenicillin treatment
Age median (interquartile range)	76 (68; 82)	74 (67; 80)	74 (65; 80)
Women (%)	36.5	26.2	38.5
Median (interquartile range) warfarin doses in mg/wk before initiation of study drugs	30 (21.3; 40.0)	28.8 (22.0; 40.0)	31.3 (22.5; 40.9)

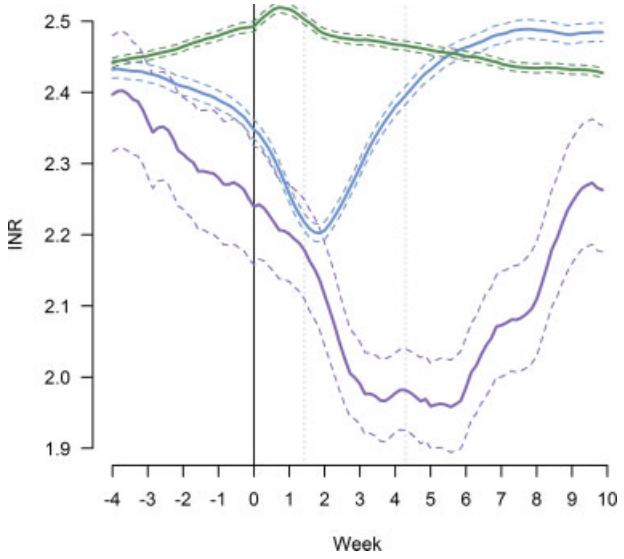

Fig. 2 Mean international normalized ratio (INR) before and during cotreatment with warfarin and flucloxacillin. The progression subsequent to 10 and 30 days flucloxacillin treatment and phenoxymethylpenicillin treatment are illustrated in blue, purple, and green. The INR was interpolated to allow inclusion of daily values for all patients. Dashed lines denote 95% confidence intervals.

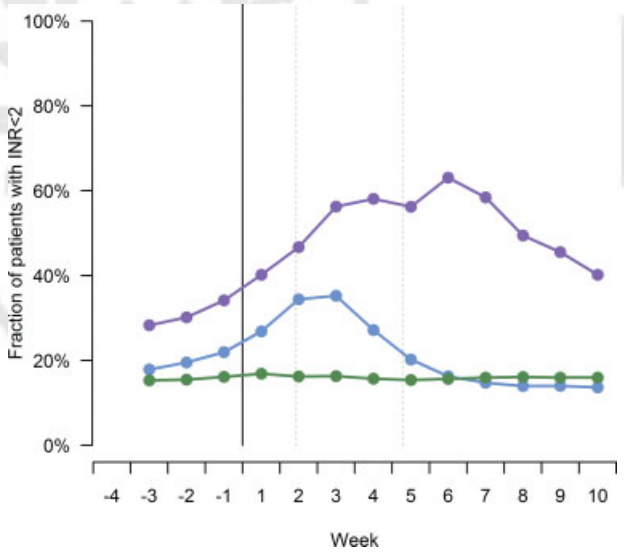

Fig. 3 Fraction of patients with at least one international normalized ratio (INR) below 2.0 per week. The progression subsequent to 10 and 30 days flucloxacillin treatment and phenoxymethylpenicillin treatment are illustrated in blue, purple, and green.

to the effects under study that regard not only the week-by-week development of INR levels but also warfarin doses on two specific treatment periods (10 and 30+ days). Moreover, instead of contrasting the results against a cohort free from interacting drugs, the present paper used phenoxymethylpenicillin, a drug with a similar therapeutic range, as a negative control to control for confounding by indication. Finally, by excluding individuals dispensed any of the 32 drugs mentioned above with a documented effect on warfarin anticoagulation, we ensured that the shown effects were not biased by other interacting drugs.

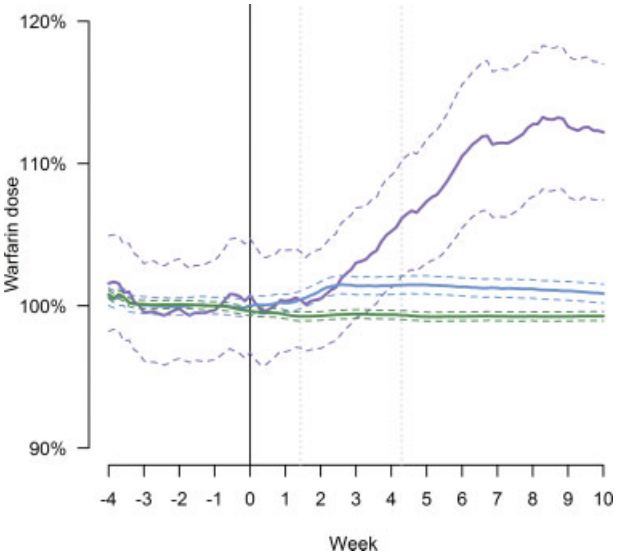

Fig. 4 Prescribed warfarin dose before and during concomitant flucloxacillin treatment (means and 95% confidence intervals). The progression subsequent to 10 and 30 days flucloxacillin treatment and phenoxymethylpenicillin treatment are illustrated in blue, purple, and green.

Martín-Pérez et al showed that initiation of flucloxacillin in 3,138 individuals resulted in a mean decrease in INR from 2.46 (95% CI, 2.45–2.47) to 2.20 (95% CI, 2.18–2-23). The proportion of individuals with subtherapeutic INR increased from 22 to 39%.[4]

The results of the present investigation with regard to changes in INR are in line with the study by Martín-Pérez et al showing a drop from 2.4 to 2.2 with regard to individuals treated with flucloxacillin for 10 days. Martín-Pérez et al investigated proportions of individuals below rather than outside the therapeutic window, which is why the results were not quite comparable with ours. However, the proportions of patients below the therapeutic window among the general population versus in patients initiated flucloxacillin treatment were 22 and 38% pointing toward an effect similar to ours. The primary strength of this study is the presentation of the progression of INR values and doses over time. As evident in ►**Fig. 2**, the decrease in INR among individuals started already a month before initiation of flucloxacillin. We do not know the reason for this but speculate that a proportion of individuals may have been treated with cloxacillin, a isoxazolyl β-lactam penicillin, for parenteral use primarily in hospitalized patients. Unfortunately, exclusively being based on drugs dispensed at pharmacies, this notion could not be investigated further. An alternative explanation could have been an underlying confounder independent of the study drug such as the underlying infection. However, infections have on the contrary been reported to increase INR[3] which is supported by the present study showing a slight increase in INR after the initiation of phenoxymethylpenicillin (►**Fig. 2**). Thus, such an effect would bias the results in the opposite direction of that observed for flucloxacillin.

Another strength of the current investigation was the investigation of the effects in patients with different

treatment durations. Interestingly, among 201 individuals with at least 30 days flucloxacillin treatment, the mean INR dropped below the therapeutic window decreasing from 2.2 to 1.9 and the proportion subtherapeutic individuals increased to a maximum of 65%.

There are some relevant limitations to consider. Using register data limits the amount of information available for each patient. For example, although the utilized drug register has the advantage of providing data on dispensed rather than prescribed drugs, the actual level of adherence to the medication cannot be determined. Finally, we did not have access to data on thromboembolic events in the cohort and could not analyze the clinical impact of the interaction effect. However, substantial evidence shows that an INR of 2.0 or greater decreases not only the frequency of ischemic stroke and its severity,[21,22] but other thromboembolic events as well.[23]

The typical package size for warfarin and most other drugs are aimed to cover 90 days which is based on the maximum number of daily doses that can be subsidized at one dispensation. The rationale for requiring a warfarin dispensation 4 to 20 weeks from the index date was to include patients that had reached steady state and at the same time to allow for a certain amount of oversupply from previous dispensations. However, some proportion of patients may theoretically have stopped the treatment. In practice, this may not be a big problem as INR measurements or warfarin doses regarding these patients would not appear after index date. Following the finding that dicloxacillin decreased the INR in warfarin-treated patients, the underlying mechanism is induction of CYP2C9 mediated by pregnane X receptor activation.[11] Importantly, in vitro data suggested a similar mechanism with regard to flucloxacillin, though the effect was less pronounced.[11] This may explain the relatively moderate effect on INR following short-term treatment with flucloxacillin as seen in the present study (mean INR decreasing from 2.4 to 2.2) compared with previous data on the initiation of dicloxacillin (mean INR decreasing from 2.6 to 2.0).[10] Despite a lower effect of flucloxacillin, a substantial proportion of patients were exposed to subtherapeutic INR levels highlighting the clinical relevance of a drug–drug interaction between flucloxacillin and warfarin. This proportion was considerably increased among the subpopulation exposed for a longer treatment duration. This indicates that the maximum induction caused by flucloxacillin is not reached with 10 days treatment, but instead needs 3 weeks treatment before reaching maximum induction.

So, what may the clinical impact of combining flucloxacillin and warfarin on a population level be? Based on the present study, including approximately 80% of Swedish warfarin users, approximately 600 patients a year were also codispensed flucloxacillin. However, the decrease in INR in patients with 10 days treatment which account for the vast majority of the exposure was modest and occurring during a relatively short period of time. Although data regarding the risk with regard to thromboembolic events are lacking, the number of individuals actually affected may therefore be low. Nevertheless, prescribers should include this information when facing a patient initiating treatment with flucloxacillin. Initiation of flucloxacillin should be accompanied by closer INR monitoring. Furthermore, in individuals with INR levels already close to the lower range of the therapeutic interval, a preemptive dose increase may be considered. This is more important among individuals planned for longer treatment periods.

In conclusion, more than one in three patients with 10 days flucloxacillin and almost two in three patients initiating long-term treatment, was exposed to a subsequent subtherapeutic anticoagulant effect within 4 weeks. To avoid unnecessary thromboembolic complications, the initiation of flucloxacillin should be accompanied by closer INR monitoring which may be especially important among individuals with lengthy treatments.

What is known about this topic?

- Flucloxacillin is in many countries the most used isoxazolyl β-lactam penicillin.
- Data indicate that codispensing flucloxacillin to patients already on warfarin may result in decreased warfarin efficacy.

What does this paper add?

- One in three patients dispensed 10 days flucloxacillin and almost two in three patients initiating long-term treatment, was exposed to a subsequent subtherapeutic anticoagulant effect.
- To avoid unnecessary thromboembolic complications, the initiation of flucloxacillin should be accompanied by closer INR monitoring which may be especially important among individuals with lengthy treatments.

Authors' Contributions

All authors contributed to study design and the writing of manuscript. J.L. was responsible for the analysis of data.

Conflict of Interest

T.B.S. reports personal fees from Pfizer, Eisai, and Astellas Pharma, outside the submitted work. T.B.S. has done consulting and paid lectures for Pfizer and paid lectures for Eisai and Astellas Pharma unrelated to this work. A.P. reports grants from Alcon, Almirall, Astellas, AstraZeneca, Boehringer-Ingelheim, Novo Nordisk, Servier, LEO Pharma, outside the submitted work. None of the other authors report any conflicts of interest.

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