Letters

RESEARCH LETTER

Change in International Normalized Ratio Among Patients Treated With Dicloxacillin and Vitamin K Antagonists

A challenge in the use of vitamin K antagonists (VKAs) is the potential for drug-drug interactions, resulting in insufficient or excessive anticoagulation. Solid data are lacking for most alleged interactions. In case reports,[1-3] the commonly used antibiotic dicloxacillin has been reported to lower the anticoagulant effect of warfarin, the most used VKA.

Methods | Patients currently taking warfarin were identified via the anticoagulant database Thrombobase, a clinical database of all VKA-treated patients (N ≈ 7400) followed up by 3 outpatient clinics and 50 general practitioners in Funen, Denmark. All international normalized ratios (INRs) are recorded.

We included all patients who filled a prescription for dicloxacillin while receiving warfarin therapy between March 1998 and November 2012 (as ascertained via the population-based prescription register Odense Pharmacoepidemiological Database). Registry-based studies are exempt from ethical review in Denmark.

Measures of INR were grouped by the week relative to dicloxacillin exposure. For individuals with multiple measurements in rapid succession (≤5 days between measurements), only the first measurement was included.

We compared the last INR measurement before dicloxacillin exposure with the first measurement within weeks 2 to 4 after dicloxacillin exposure. To retain the paired nature of the data, we excluded individuals without an INR measurement within this postexposure period and the analysis was performed using a paired *t* test.

Furthermore, we assessed the use of dicloxacillin among patients taking another VKA, phenprocoumon. To assess the potential for confounding by indication, we performed similar analyses among patients taking warfarin and phenoxymethylpenicillin or amoxicillin.

A 2-sided *P* value of <.05 was considered statistically significant. Analyses were performed using Stata version 13.1 (StataCorp).

Results | Of 519 patients taking warfarin and initiating treatment with dicloxacillin (**Figure 1**), 236 met inclusion criteria. Patients most commonly filled prescriptions for 30 dicloxacillin tablets (89%; range, 30-100 tablets). The median age was 68 years (interquartile range, 59-77 years) and 61% were male. The main indications for anticoagulant treatment were atrial fibrillation (56%) and heart valve replacement (22%).

Median INR levels with corresponding percentiles over time relative to dicloxacillin exposure are displayed in **Figure 2**.

Figure 1. Patients Treated With a Vitamin K Antagonist in Denmark

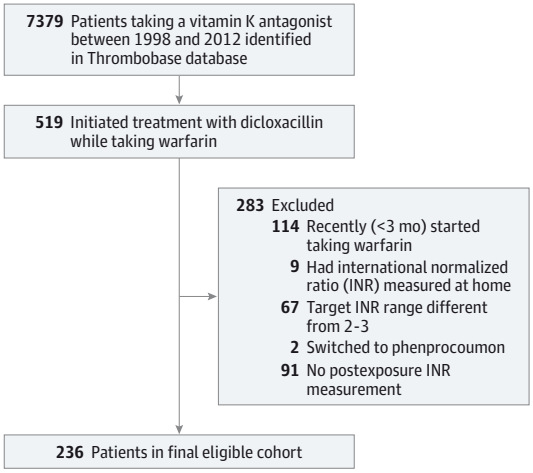
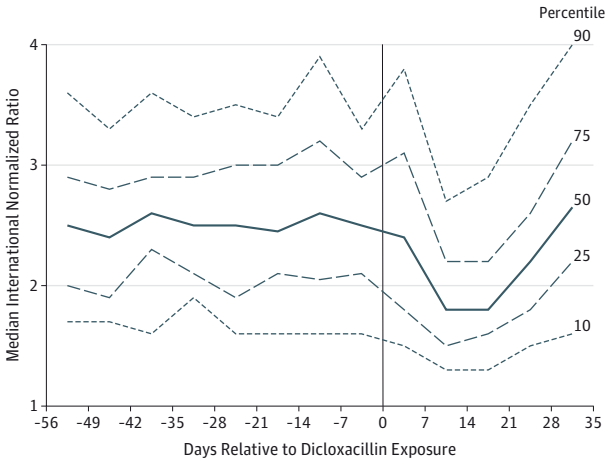


Figure 2. Median International Normalized Ratio Levels Over Time Among Users of Warfarin Exposed to Dicloxacillin



The mean INR level prior to dicloxacillin exposure was 2.59 (95% CI, 2.50-2.68) compared with 1.97 (95% CI, 1.90-2.05) 2 to 4 weeks after dicloxacillin exposure, a mean decrease of 0.62 (95% CI, 0.50-0.74; $P < .001$). In total, 61% (n = 144) experienced subtherapeutic INR levels (<2.0) within 2 to 4 weeks after dicloxacillin treatment.

Among patients taking phenprocoumon (n = 64), mean INR levels were 2.61 (95% CI, 2.46-2.76) before exposure to dicloxacillin compared with 2.30 (95% CI, 2.12- 2.48) after exposure, a mean decrease of 0.31 (95% CI, 0.11-0.51; $P = .003$). The proportion with subtherapeutic INR levels after dicloxacillin exposure was 41% (n = 26).

Analyses for phenoxymethylpenicillin among patients taking warfarin (n = 539) showed mean INR levels of 2.52 (95% CI, 2.46-2.58) before exposure compared with 2.62 (95% CI, 2.54- 2.69) after exposure, a mean increase of 0.10 (95% CI, 0.01-0.19; P = .03). Corresponding INR levels for amoxicillin (n = 266) were 2.58 (95% CI, 2.50-2.66) compared with 2.72 (95% CI, 2.62-2.81), a mean increase of 0.14 (95% CI, 0.03-0.26; P = .01).

Discussion | We found an association between dicloxacillin treatment and a decrease in INR levels among patients taking either warfarin or phenprocoumon.

The principal strength of this study is the large number of patients taking warfarin and exposed to dicloxacillin, representing nonselected patients from everyday clinical settings.

The main weakness is the lack of data on the underlying infection. In Denmark, dicloxacillin is primarily used against impetigo, soft tissue, and skin infections due to *Staphylococcus aureus*. Infections have been reported to increase INR,[4] which is supported by our results for phenoxymethylpenicillin and amoxicillin. Such an effect would bias our results in the opposite direction of that observed for dicloxacillin.

Other limitations include the potential lack of representativeness of the population from 1 Danish region and the lack of data on clinical outcomes.

A biologically plausible rationale for the finding is through dicloxacillin activation of pregnane X receptor, resulting in induction of CYP3A4[5] and probably CYP2C9,[6] which catalyze the metabolism of warfarin.

Physicians should be aware that dicloxacillin treatment may cause a significant decrease in INR levels among patients taking VKAs.

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Author Contributions: Dr Pottegård had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Additional Contributions: We thank Jesper Hallas, MD, Kim Brøsen, MD, and Henrik Horneberg, BA (all with Clinical Pharmacology, University of Southern Denmark), for valuable comments on the manuscript. No financial compensation was provided.

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COMMENT & RESPONSE

Single-Gene Genotyping and Personalized Preventive Care

To the Editor Dr Nan and colleagues[1] demonstrated that the risk reduction for colorectal cancer afforded by regular use of aspirin (or other nonsteroidal anti-inflammatory drugs [NSAIDs]) was significantly associated with a single-nucleotide polymorphism (SNP) located on chromosome 12p12.3.

They concluded that validation in "additional populations may facilitate targeted colorectal cancer prevention strategies." The accompanying Editorial[2] goes further, citing the study as evidence that SNP (DNA analysis) testing can guide individualized prescription of long-term advice aimed at preventing disease. There are several caveats to these interpretations.

Nan and colleagues[1] provided evidence of an association (rs2965667) but no direct evidence that this SNP modulates the expression or activity of the closest gene, an important issue if the observation is to affect drug discovery efforts. A greater concern is that the 4% of the study population that had the TA or AA genotype, along with the adverse response to aspirin (1.3-2.8 increased risk of colorectal cancer), may be a chance observation.

It would have been informative to build an empirical distribution of relative risk values for repeated small random samples (n = 722 for each). A lack of demographic information for the 4% leaves open the possibility that other factors explain the study observation.

However, my major concern is the suggestion that this study provides direct evidence that single-gene genotyping can underpin personalized medicine.[2] Although the study is an interesting molecular epidemiological analysis that may shed light on colorectal disease, it does not provide evidence for a diagnostic that could guide long-term primary prevention advice for individual patients.

Regular use of aspirin and related compounds has been variably associated with a number of positive health benefits. Nan and colleagues estimated 16.6 fewer cases of colorectal cancer per 100 000. If physicians were to use this type of genotyping evidence to judge if a patient should take aspirin, they would first need to assess the potential benefits for each disease, by prevalence, that aspirin affects (eg, aspirin may