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BRIEF REPORT

The potential drug–drug interaction between proton pump inhibitors and warfarin

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ABSTRACT

Background Proton pump inhibitors (PPIs) have been suggested to increase the effect of warfarin, and clinical guidelines recommend careful monitoring of international normalized ratio (INR) when initiating PPI among warfarin users. However, this drug–drug interaction is sparsely investigated in a clinical setting. The aim was to assess whether initiation of PPI treatment among users of warfarin leads to increased INR values.

Methods The study was an observational self-controlled study from 1998 to 2012 leveraging data on INR measurements on patients treated with warfarin from primary care and outpatient clinics and their use of prescription drugs. Data were analyzed in 2015.
We assessed INR, warfarin dose, and dose/INR ratio before and after initiating PPI treatment using the paired student's *t*-test.

Results We identified 305 warfarin users initiating treatment with PPIs. The median age was 71 years (interquartile range 63–78 years), and 64% were men. The mean INR in the 70 days prior to PPI initiation was 2.6 (95%CI 2.5–2.8) and 2.6 (95%CI 2.5–2.7) in the period 1–3 weeks after PPI initiation ($p = 0.67$). Further, neither mean warfarin dose nor the dose/INR ratios were significantly different before and after PPI initiation. Sensitivity analyses revealed no differences among individual PPIs.

Conclusions We found no evidence of a clinically meaningful drug–drug interaction between PPIs and warfarin in a Northern European patient population of unselected patients from an everyday outpatient and primary care clinical setting. Thus, we do not support the recommendation to "cautiously monitor" users of warfarin initiating PPI treatment. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—proton pump inhibitors; vitamin K antagonists; drug interactions; adverse drug reactions; pharmacoepidemiology

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INTRODUCTION

A recent consensus paper recommends careful monitoring of international normalized ratio (INR) among users of warfarin when initiating treatment with proton pump inhibitors (PPIs), because of a potential drug–drug interaction.[1] Such clinical recommendations suggesting *careful monitoring* are not trivial to treating physicians as PPIs are among the most commonly prescribed drugs and as the nature of the suggested careful monitoring is not defined.[2]

These recommendations are based on limited evidence. A study from 1976 showed an increased warfarin absorption in rats concomitantly treated with PPI, likely due to the increase in gastric pH.[3] Further, two observational studies have demonstrated a slightly increased risk of excessive anticoagulation among vitamin K antagonist (VKA) patients using PPIs.[4,5] This putative drug–drug interaction might be mediated through inhibition of CYP2C9,[6,7] responsible for the metabolization of warfarin.[8] However, the clinical significance of the potential pharmacokinetic drug–drug interaction between warfarin and PPIs is poorly documented.[7]

We performed a database study to assess whether initiation of treatment with PPIs influenced the INR values and warfarin doses among warfarin users.

METHODS

The study was an observational self-controlled study using two databases assessing the INR, warfarin dose,

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and dose/INR ratio among stable primary care and outpatient warfarin-treated individuals before and after initiation of PPI treatment.

Data sources

The data material has previously been described elsewhere.[9] In short, we linked INR measurement data from a database on anticoagulant use (Thrombobase) to a population-based register on prescription fills (Odense University Pharmacoepidemiological Database).

Thrombobase is a clinical database receiving information from patients treated with VKA from three outpatient clinics at Odense University Hospital and 50 general practitioners in Funen County. The database contains information on the type of VKA, the treatment indication, dose, and INR values for each visit. Thrombobase covered close to 7400 unique patients during the study period (1998–2012).

The Odense University Pharmacoepidemiological Database contains information on reimbursed and redeemed prescriptions of residents of Funen County since 1989.[10]

Data were linked using the unique Danish Civil Registration Number, a personal identification number assigned to all Danish residents.[11]

Participants

Patients 18 years or above receiving warfarin therapy for more than 3 months were eligible for inclusion during the study period. We included individuals initiating treatment with PPI (index PPI) during treatment with warfarin. We excluded patients who had redeemed a prescription for any PPIs within the last 24 months, those who performed INR measurements at home, those with a target INR outside 2–3, and those who changed therapy to another VKA.

Patients were observed from 70 days before to 70 days after PPI initiation. INR measurements were grouped according to the week relative to the PPI initiation. For patients with multiple measurements in rapid succession (≤5 days between measurements), only the first measurement was included.

We identified comorbid conditions, using a validated adaption of the chronic disease score, based on ATC codes.[12] Patients were defined as having the chronic disease if they redeemed a prescription indicating a comorbid conditions within 120 days prior PPI initiation.

Analysis

Data were analyzed in 2015. Short-term changes in INR were assessed by comparing INR values from 1 to 3 weeks (day 8 to day 21) after PPI initiation with the INR measured closest to the date of PPI exposure within the 70 preceding days, using paired student's *t*-test. Long-term changes were assessed using a marker for a sustained relationship of warfarin, dose/INR ratio. We compared the mean dose/INR 6 to 10 weeks (day 35 to 70) after PPI initiation with the mean dose/INR in the 70 days preceding PPI initiation.

Sensitivity analyses

We performed analyses for each individual PPI drug. Further, we restricted the material to the following: (1) patients with at least one additional PPI prescription within 120 days after the index PPI initiation, indicating a startup of a more chronic use of PPI; (2) patients with a first-ever use of PPI; and (3) patients without recent high INRs prior to initiation with PPIs (no INR measures above 3 within 14 days prior to PPI initiation).

Data protection and ethics

The study was approved by the Danish Data Protection Agency. According to Danish law, ethical approval is not required for registry-based studies.[13]

RESULTS

We identified 305 warfarin users initiating treatment with PPIs, median age 71 years (interquartile range 63–78 years), and 63.9% were men. The most common therapeutic indication for warfarin treatment was atrial fibrillation (56%); and the most commonly used PPI was esomeprazole ($n = 135$). For more details on the demographic characteristics and a flow chart of the study population, see Appendix S1. The distribution of INR measurements, warfarin doses, and dose/INR ratios over time relative to initiation of PPI treatment is displayed in Figure 1.

The mean INR value in the 70 days prior to PPI initiation was 2.6 (95%CI 2.5–2.8) and 2.6 (95%CI 2.5–2.7) 1–3 weeks after PPI initiation, indicating no significant change in INR before and after PPI treatment ($p = 0.67$) (Table 1).

The mean dose of warfarin before PPI initiation (4.4 mg, 95%CI 4.0–4.7 mg) and after PPI initiation (4.4 mg, 95%CI 4.1–4.7 mg) was not statistically significantly different ($p = 0.68$). Further, dose/INR ratio before PPI initiation (1.8, 95%CI 1.7–2.0) and after PPI initiation (1.8, 95%CI 1.7–1.9) was not statistically significantly different either ($p = 0.53$) (Table 1).

In analyses of individual PPIs, no differences were observed compared with the main analysis, with changes

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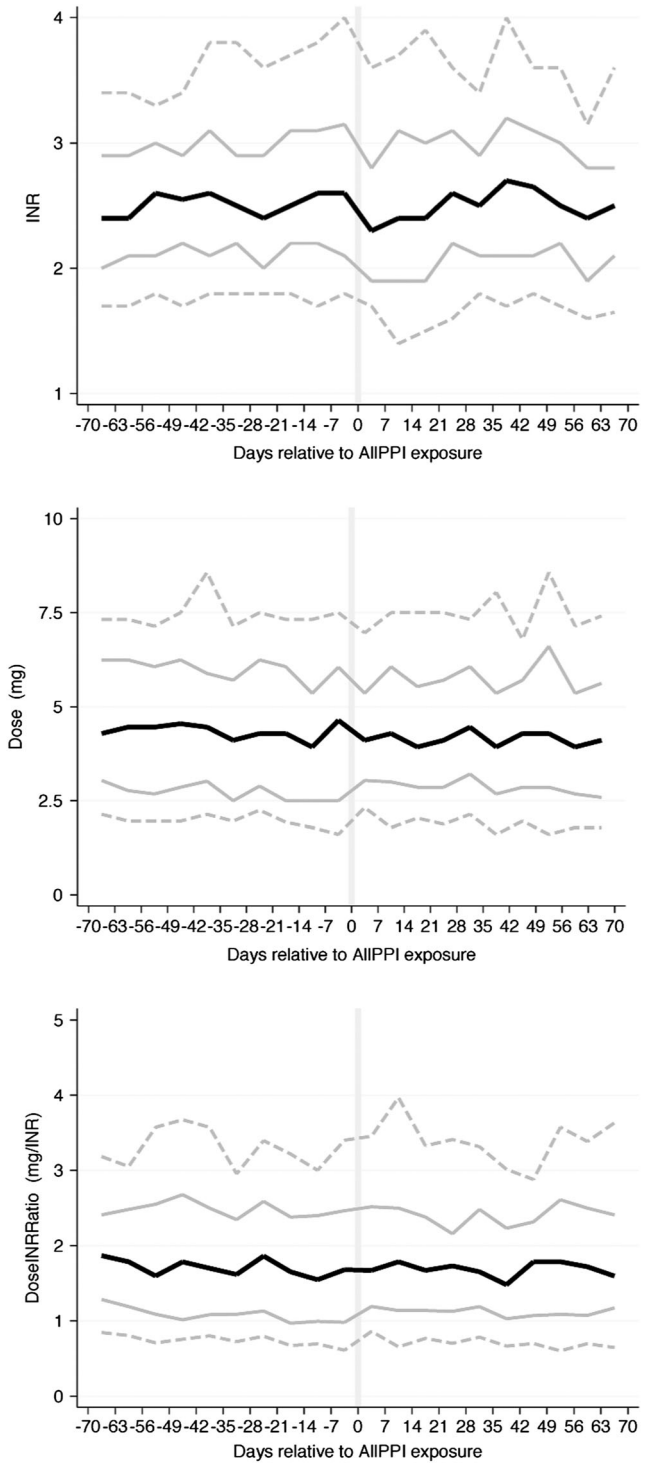

Figure 1. Graphical representation of the mean INR, mean warfarin dose, and mean warfarin dose/INR over time ($n = 305$). PPI, proton pump inhibitor; INR, international normalized ratio

in mean INR ranging from −0.1 (esomeprazole) to +0.2 (lansoprazole), neither reaching statistical significance. These analyses are presented in full in Table 1.

Table 1. Short-term effect of internationalized normalized ratio (INR) and long-term effect of dose and dose/INR in patients treated with warfarin before and after initiation of proton pump inhibitors (PPIs)

	Before*	After*	P**
All PPIs ($n = 229$)			
INR	2.6 (2.5–2.8)	2.6 (2.5–2.7)	0.67
Dose (mg)	4.4 (4.0–4.7)	4.4 (4.1–4.7)	0.68
Dose/INR ratio	1.8 (1.7–2.0)	1.8 (1.7–1.9)	0.53
Omeprazole ($n = 50$)			
INR	2.5 (2.3–2.7)	2.5 (2.2–2.7)	0.79
Dose (mg)	4.5 (3.9–5.0)	4.3 (3.9–4.9)	0.55
Dose/INR ratio	1.9 (1.6–2.2)	1.9 (1.7–2.1)	0.79
Pantoprazole ($n = 24$)			
INR	2.4 (2.1–2.9)	2.3 (2.1–2.6)	0.66
Dose (mg)	4.4 (3.6–5.3)	4.5 (2.0–5.4)	0.43
Dose/INR ratio	2.0 (1.5–2.4)	1.8 (1.5–2.1)	0.31
Lansoprazole ($n = 65$)			
INR	2.5 (2.4–2.7)	2.7 (2.5–2.9)	0.24
Dose (mg)	4.6 (3.8–5.4)	4.5 (3.8–5.2)	0.17
Dose/INR ratio	1.9 (1.6–2.2)	1.8 (1.6–2.1)	0.51
Esomeprazole ($n = 106$)			
INR	2.8 (2.6–3.0)	2.7 (2.4–2.9)	0.52
Dose (mg)	4.2 (3.7–4.6)	4.3 (3.9–4.7)	0.48
Dose/INR ratio	1.8 (1.6–2.0)	1.8 (1.6–2.0)	0.97

*Mean and 95% confidence interval.
**Paired student's *t*-test.

All other sensitivity analyses returned results similar to that of the main analysis (data not shown).

DISCUSSION

In this study on the potential drug–drug interaction between PPIs and warfarin in a primary care and outpatient clinical setting, we found no evidence that initiation of PPI treatment affected INR values. This finding was persistent across all individual PPIs and patient subgroups.

The main strength of our study is a large sampling of unselected patients from an everyday clinical setting with routine monitoring of INR. Further, we have previously used this setup to identify a drug–drug interaction between dicloxacillin and warfarin,[14] which indicates that the analytical setup is capable of identifying signals. The study is also prone to some limitations. If the treating physician contemplates a drug–drug interaction, it may result in an intensified monitoring of the patient, potentially leading to surveillance bias. As this would inflate the potential signal, this further strengthens our confidence in our findings. Also, as the study population consisted primarily of Caucasians, the results might not be generalizable to other ethnicities because of ethnic variations in genetic polymorphisms in liver enzymes such as CYP2C.

Our findings substantiate the results from clinical drug–drug interaction studies, which do not suggest a clinically meaningful drug–drug interaction between

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warfarin and PPIs.[7] Pharmacokinetic studies of PPIs have shown that the inhibitory potency on CYP2C9, the enzyme responsible for metabolization of the most potent stereoisomer S-warfarin,[8] varies markedly across PPIs, with pantoprazole being markedly more potent than the other PPIs.[6] In the present study, we did not find a difference in INR, warfarin dose or dose/INR ratio of the different types of PPIs suggesting that these *in vitro* results do not translate into a clinically meaningful difference. This corresponds well with a single-dose warfarin study in healthy volunteers, where pantoprazole did not alter the pharmacokinetics or pharmacodynamics of warfarin.[15]

CONCLUSIONS

We found no evidence of a clinically meaningful drug–drug interaction between PPIs and warfarin in a Northern European patient population of unselected patients from an everyday outpatient and primary care clinical setting. As such, we do not support the recommendation to "cautiously monitor" patients receiving warfarin who initiate treatment with PPIs within this population.

CONFLICTS OF INTEREST

Mr. Hansen reports grants from Menarini paid to his institution, outside the submitted work. Mr. Stage reports personal fees from Astellas Pharma, Orifarm A/S, Eisai, and Novartis, outside the submitted work. Mr. Pottegård reports grants from AstraZeneca paid to his institution, outside the submitted work. Mr. Henriksen, Ms. Rasmussen, and Mr. Damkier have nothing to disclose.

KEY POINTS

- A putative drug–drug interaction between warfarin and proton pump inhibitors (PPIs) might be mediated through inhibition of CYP2C9.
- Clinical guidelines recommend careful monitoring of internationalized normalized ratio (INR) when initiating PPIs among warfarin users.
- The present study showed no evidence that initiation of proton pump inhibitors affected INR values. This finding was persistent across individual PPIs and patient subgroups.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

AUTHOR CONTRIBUTIONS

D. P. Henriksen, T. B. Stage, M. R. Hansen, L. Rasmussen, P. Damkier, and A. Pottegård designed the research, interpreted the analysis, and revised the paper. T. B. Stage and A. Pottegård extracted information from electronic data sources and performed the statistical analysis. D. P. Henriksen, T. B. Stage, P. Damkier, and A. Pottegård drafted the initial version of the paper. D. P. Henriksen, T. B. Stage, M. R. Hansen, L. Rasmussen, P. Damkier, and A. Pottegård contributed to as well as read and approved the final version of the paper.

REFERENCES

1. Agewall S, Cattaneo M, Collet JP, *et al.* Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. *Eur Heart J* 2013; **34**: 1708–1713. doi:10.1093/eurheartj/eht042.
2. Shaheen NJ, Hansen RA, Morgan DR, *et al.* The burden of gastrointestinal and liver diseases, 2006. *Am J Gastroenterol* 2006; **101**: 2128–2138. doi:10.1111/j.1572-0241.2006.00723.x.
3. Julkunen RJ. The absorption of warfarin from the rat stomach *in situ*. *Med Biol* 1976; **54**: 260–263.
4. Cadiou G, Varin R, Levesque H, *et al.* Risk factors of vitamin K antagonist overcoagulation. A case–control study in unselected patients referred to an emergency department. *Thromb Haemost* 2008; **100**: 685–692.
5. Teichert M, van Noord C, Uitterlinden AG, *et al.* Proton pump inhibitors and the risk of overanticoagulation during acenocoumarol maintenance treatment: interaction between proton pump inhibitors and acenocoumarol. *Br J Haematol* 2011; **153**: 379–385. doi:10.1111/j.1365-2141.2011.08633.x.
6. Li X-Q, Andersson TB, Ahlström M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. *Drug Metab Dispos* 2004; **32**: 821–827.
7. Blume H, Donath F, Warnke A, Schug BS. Pharmacokinetic drug interaction profiles of proton pump inhibitors. *Drug Saf* 2006; **29**: 769–784.
8. Limdi NA, Veenstra DL. Warfarin pharmacogenetics. *Pharmacotherapy* 2008; **28**: 1084–1097. doi:10.1592/phco.28.9.1084.
9. Pottegård A, dePont CR, Wang SV, Gagne JJ, Larsen TB, Hallas J. Pharmacoepidemiological assessment of drug interactions with vitamin K antagonists: drug interactions with vitamin K antagonists. *Pharmacoepidemiol Drug Saf* 2014; **23**: 1160–1167. doi:10.1002/pds.3714.
10. Hallas J. Conducting pharmacoepidemiologic research in Denmark. *Pharmacoepidemiol Drug Saf* 2001; **10**: 619. doi:10.1002/pds.638.
11. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011; **39**: 22–25. doi:10.1177/1403494810387965.
12. Kuo RN, Dong Y-H, Liu J-P, Chang C-H, Shau W-Y, Lai M-S. Predicting healthcare utilization using a pharmacy-based metric with the WHO's anatomic therapeutic chemical algorithm. *Med Care* 2011; **49**: 1031–1039.
13. Thygesen LC, Daasnes C, Thaulow I, Bronnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health* 2011; **39**: 12–16. doi:10.1177/1403494811399956.
14. Pottegård A, Henriksen DP, Madsen KG, Hellfritzsch M, Damkier P, Stage TB. Change in international normalized ratio among patients treated with dicloxacillin and vitamin K antagonists. *JAMA* 2015; **314**: 296. doi:10.1001/jama.2015.6669.
15. Duursema L, Muller FO, Schall R, *et al.* Lack of effect of pantoprazole on the pharmacodynamics and pharmacokinetics of warfarin [see comments]. *Br J Clin Pharmacol* 1995; **39**: 700–703.

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