

BRIEF REPORT

Initiation of glucose-lowering treatment decreases international normalized ratio levels among users of vitamin K antagonists: a self-controlled register study

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Essentials

- It is not known if initiation of glucose-lowering drugs alters the efficacy of vitamin K antagonists (VKA).
- We examined if glucose-lowering drugs affected international normalized ratio (INR) in VKA-treated patients.
- Upon initiating glucose-lowering drugs, 51% of patients had INR values below the therapeutic window.
- Monitoring of INR levels should be intensified upon initiation of glucose-lowering drugs.

Summary. *Background:* It is not known whether initiation of antidiabetic treatment affects the effect of vitamin K antagonists (VKAs). It was previously shown that metformin affects the effect of one VKA, phenprocoumon. *Objectives:* The aim of this study was to determine if initiation of glucose-lowering treatment affects the international normalized ratio (INR) and dose requirements of the anticoagulant VKAs warfarin and phenprocoumon. *Patients/methods:* We performed a self-controlled retrospective register-based study. A total of 118 patients commencing glucose-lowering treatment while being treated with warfarin or phenprocoumon were included in the study. We compared INR, dose/INR and proportion

of patients with at least one sub-therapeutic INR measurement before and after initiation of glucose-lowering treatment. *Results:* Initiation of glucose-lowering treatment caused mean INR to decrease from 2.5 to 2.2 (decrease of -0.3 [95% CI: -0.1 ; -0.5]) and led to more than half of the patients having at least one sub-therapeutic INR measurement. Six to 12 weeks later, the VKA dose/INR was increased by 11%, indicating a weakened effect of the VKA. *Conclusion:* Initiation of glucose-lowering treatment reduces the anticoagulant effect of VKAs to an extent that is likely to be clinically relevant. This finding needs confirmation and mechanistic explanation.

Keywords: antidiabetic drugs; drug interactions; pharmacoepidemiology; phenprocoumon; warfarin.

Introduction

Vitamin K antagonists (VKAs) are the mainstay drugs in the prevention and treatment of venous thromboembolisms. While VKAs are cheap and effective, the anticoagulant effect in the individual patient is, to some extent, unpredictable. This is caused by several factors such as diet, genetic polymorphisms and drug–drug interactions (DDIs) [1].

Metformin is the most commonly used oral pharmacological treatment of type 2 diabetes. In recent years there has been an increasing focus on DDI with metformin [2]. Despite this, the role of metformin as a perpetrator of DDIs is much less explored [3,4]. Two reports have suggested a clinically relevant DDI between the VKA phenprocoumon and metformin. The first report on a putative interaction between a VKA and metformin was a small observational study ($n = 13$) from 1983 that showed that

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a higher dose of phenprocoumon was used in patients with type 2 diabetes treated with a high vs. a low dose of metformin [3]. More recently, a database study based on 27 patients with type 2 diabetes, showed that initiation of metformin treatment resulted in an 18% increase in the dose of phenprocoumon [4], due to a lower effect of phenprocoumon as observed from international normalized ratio (INR) values. It appears plausible that an interaction between metformin and phenprocoumon would pertain to warfarin as well, as the mechanism of action and metabolism of warfarin is similar to that of phenprocoumon.

We performed a registry-based self-controlled study on the effect of initiating treatment with metformin on the INR and dose of VKA in patients from a clinical setting.

Methods

Data sources

The data used in this study have previously been described in detail [5]. Briefly, we linked Thrombbase with the population-based prescription database Odense University Pharmacoepidemiological Database (OPED). Thrombbase is a clinical database that contains INR measurements, type of VKA, treatment indication and doses for patients treated at three outpatient clinics at Odense University Hospital and 50 general practitioners in Funen (population approximately 450 000). OPED contains prescription data for all drugs that are reimbursed by the Danish healthcare system for all residents in Funen since 1989 [6]. Flawless linkage was achieved using the civil registration number, which is a unique identifier given to every Danish resident [7]. We used OPED to identify VKA users in Thrombbase who were exposed to glucose-lowering drugs (metformin, sulphonylureas and insulin) within the study period and identified concomitant use of other medications.

Participants

We included patients 18 years or older who received VKA therapy in the period 1998–2012. Incident use of glucose-lowering treatment was defined as the first filling of a prescription for a glucose-lowering drug during VKA therapy (denoted the index date). We excluded users who had redeemed a prescription for any glucose-lowering medication within 24 months before the index date, users who changed VKA treatment and users who measured INR at home. INR and dose of VKA were monitored from 12 weeks before the index date until 12 weeks after. We identified comorbid diseases in the patients using a previously validated adaption of a chronic disease score based on ATC codes [8]. Patients were defined as having a chronic disease if they had redeemed a prescription for

a comorbid condition within the 120 days prior to the index date.

Analysis

We assessed the short- and long-term effects of initiation of glucose-lowering treatment on the INR and dose of VKAs (both phenprocoumon and warfarin).

- 1 A short-term interaction was assessed as a change in INR 1 to 3 weeks after the index date. This was compared with the last INR measurement within 12 weeks preceding the index date.
- 2 We assessed proportion of patients who had at least one INR measurement below the therapeutic range ($\text{INR} < 2$) 1–6 weeks before and 5 weeks after glucose-lowering treatment was initiated.
- 3 The long-term effect of glucose-lowering drugs on the dose of VKA needed to maintain INR was assessed using a marker for the dose-effect relationship of VKAs: dose/INR. This was assessed as the average dose/INR of each patient 6–12 weeks after the incident use of glucose-lowering treatment and compared with the dose/INR of each patient in the 12 weeks preceding the index date.

We also assessed the effect of sulphonylureas and insulin (no users fulfilled inclusion criteria for GLP-1 analogues or DPP-IV inhibitors) and carried out a combined analysis for all three drug classes.

Statistics

Differences in INR or INR/dose before and after use of the incident glucose-lowering drug are compared by the paired *t*-test. Proportions of patients below the lower limit of the therapeutic range ($\text{INR} < 2$) are compared by Fisher's exact test.

Sensitivity analysis

We performed a range of sensitivity analyses as defined below.

- 1 Different definitions of short- and long-term changes in dose or INR, all compared with 12 weeks preceding the index date, were tested.
 - i For short-term exposure, we tested different lengths of the period after the index date: 1–6 weeks, 2–4 weeks and 2–6 weeks.
 - ii For long-term exposure, we tested different lengths of the period after the index date: 4–12 weeks and 8–12 weeks.
- 2 Individuals were required to obtain an additional prescription for glucose-lowering therapy within 6 months after the index date.
- 3 We excluded individuals who had first use of any other drug during the study period in order to avoid bias

caused by co-initiation of other drugs commonly prescribed in type 2 diabetes.

- 4 We carried out a stratified analysis specifically for warfarin and phenprocoumon.

Results and discussion

We identified a total of 205 incident users of glucose-lowering drugs during VKA treatment. Of these, 87 users were excluded due to inclusion and exclusion criteria, which gave a final eligible cohort of 118 patients commencing any glucose-lowering drug (Fig. 1). Their median age was 71 years (interquartile range, 64–78) and 77 (65%) were men. The main indications for VKA use were

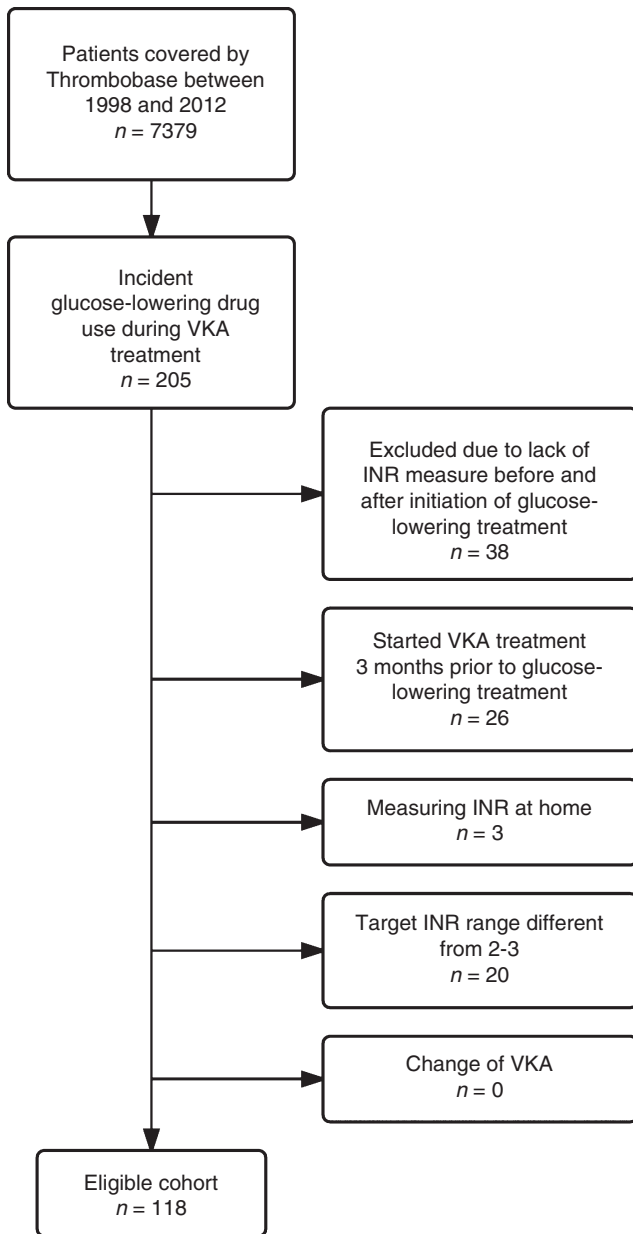


Fig. 1. Flowchart showing exclusion of patients.

Table 1 Demographics of included patients (n = 118)

Age, years (median (IQR))	71 (64–78)
Male, n (%)	77 (65.3%)
VKA indication, n (%)	
Atrial fibrillation	75 (63.6%)
Heart valve disorder	26 (22.0%)
Other	17 (14.4%)
Comorbid conditions n (%)	
Hypertension	43 (36.4%)
Congestive heart failure	92 (78.0%)
Thyroid disorders	9 (7.6%)
Depression or psychotic illness	17 (14.4%)

IQR, interquartile range; VKA, vitamin K antagonist.

atrial fibrillation (64%) and heart valve disorder (22%). Eighteen (15%) of the patients with VKAs used phenprocoumon and the remaining patients used warfarin. The most prevalent comorbid conditions were congestive heart failure (78%) and hypertension (36%) (Table 1).

From the final cohort, 89 patients were eligible for the INR analysis (short-term interaction), 104 were eligible for determining the proportion of patients with at least one INR measurement < 2 (below therapeutic range) and 108 were eligible for the dose/INR analysis (long-term interaction). Mean values for INR, dose/INR and the proportion of patients with at least one INR measurement < 2 are shown in Table 2. Briefly, the mean INR fell from 2.5 to 2.2 (decrease of -0.3 [95% confidence interval (CI), -0.1 to -0.5], $P = 0.001$) within 1–3 weeks after glucose-lowering treatment was initiated (Fig. 2). This led to more than half of the patients having at least one INR measurement below the therapeutic interval (29% before vs. 51% after, $P < 0.001$) within 5 weeks. Six to 12 weeks after initiation of glucose-lowering treatment the patients needed a higher dose of VKA to maintain INR in response to this (1.8 mg/INR before vs. 2.0 mg/INR after; increase of 0.3 [95% CI, 0.1 – 0.4], $P < 0.001$).

Sensitivity analyses did not reveal any changes to the results of the main analysis (data not shown).

This study, surprisingly, demonstrates that initiation of treatment with metformin results in a statistically significant and probably clinically relevant lower effect of VKAs. This increases the VKA dose needed to maintain sufficient anticoagulant effect. A similar trend was observed for sulfonylureas and insulin. The proportion of patients with at least one measurement of sub-therapeutic INR (< 2) before and after initiation of glucose-lowering treatment increased from 29% to 51%. These changes are not trivial, even if the dose of VKA is adjusted following routine INR measurements. Sub-therapeutic INR levels, even for a shorter period of time, confer an increased risk of thromboembolic events [9].

The main weakness of our study is the lack of data on clinical outcomes, such as death, thromboembolic events or major bleeding. Further, the patients were included

Table 2 INR, dose and dose/INR in patients treated with VKAs before and after incident use of glucose-lowering drugs

Drug	Endpoint*	n	Before initiation Mean (95% CI)	After initiation Mean (95% CI)	Difference Mean (95% CI)	P†
All glucose-lowering drugs	INR	89	2.5 (2.3; 2.6)	2.2 (2.1; 2.3)	-0.3 (-0.1; -0.5)	0.001
	Proportion with INR < 2	104	29%	51%	-	< 0.001
	Dose/INR (mg/INR)	108	1.8 (1.6; 2.0)	2.0 (1.8; 2.3)	0.3 (0.1; 0.4)	< 0.001
Metformin	INR	54	2.5 (2.3; 2.6)	2.2 (2.1; 2.4)	-0.2 (-0.2; -0.5)	0.04
	Proportion with INR < 2	61	30%	52%	-	0.02
	Dose/INR (mg/INR)	62	1.9 (1.6; 2.1)	2.2 (1.9; 2.6)	0.4 (0.1-0.6)	0.003
Sulfonylureas	INR	24	2.5 (2.2; 2.8)	2.2 (2.0; 2.4)	-0.3 (0.0; -0.7)	0.06
	Proportion with INR < 2	32	25%	41%	-	0.29
	Dose/INR (mg/INR)	34	1.6 (1.2; 1.9)	1.6 (1.3; 2.0)	0.1 (-0.1; 0.2)	0.33
Insulin	INR	12	2.4 (2.1; 2.8)	2.1 (1.8; 2.4)	-0.4 (0.1; -0.8)	0.10
	Proportion with INR < 2	12	25%	58%	-	0.21
	Dose/INR (mg/INR)	13	1.6 (1.2; 2.0)	1.9 (1.4; 2.4)	0.3 (0.0; 0.6)	0.04

INR, international normalized ratio; CI, confidence interval; VKA, vitamin K antagonists. *INR was determined 1–3 weeks after the incident use of a glucose-lowering drug. Dose/INR was determined 6–12 weeks after incident use of a glucose-lowering drug. The proportion of patients with INR < 2 was determined in the 1–6 weeks preceding initiation of treatment with a glucose-lowering drug and compared with the proportion in the 5 weeks after. †Statistical significance was assessed using the paired *t*-test for INR and dose/INR and Fisher's exact test for proportion with INR < 2.

based on redeeming a prescription at a primary pharmacy. There is no measure of when the included patients actually started taking their glucose-lowering medication and thus no measure of non-compliance. However, such behavior would result in a conservative bias towards a null effect. Another limitation of the study is that while a substantial proportion of patients reach sub-therapeutic INR levels, our dataset is too sparse to allow for estimation of time spent in therapeutic range or other more accurate measures. Patients with acute disease could initiate glucose-lowering treatment in response to this and thus other factors could affect INR levels besides initiation of glucose-lowering therapy. Finally, we excluded 58% of the initial sample, which may limit the generalization of the study findings to all users of VKAs.

The main strength of the study is the high number of VKA-treated patients that commenced taking glucose-lowering drugs within an everyday clinical setting. As the data are of a paired nature, the observed signals are not affected by inter-individual variability, such as body weight and age, which are known to affect the response to VKAs [1].

Previous studies have focused on the possible drug–drug interaction between phenprocoumon and metformin [3,4]. The results of both these studies are in agreement with those observed in this study: there is a requirement for a higher dose of VKA due to a weakened effect. Sensitivity analysis excluding patients commencing treatment with additional drugs besides the glucose-lowering drug did not affect the results of the main analysis. This notion supports the hypothesis that the weakened effect of VKAs is a result of the glucose-lowering drugs or the subsequent effect on blood glucose homeostasis.

Both warfarin and phenprocoumon are primarily metabolized by CYP2C9 [1] and the activity of CYP2C9 is an important predictor of the anticoagulant effect

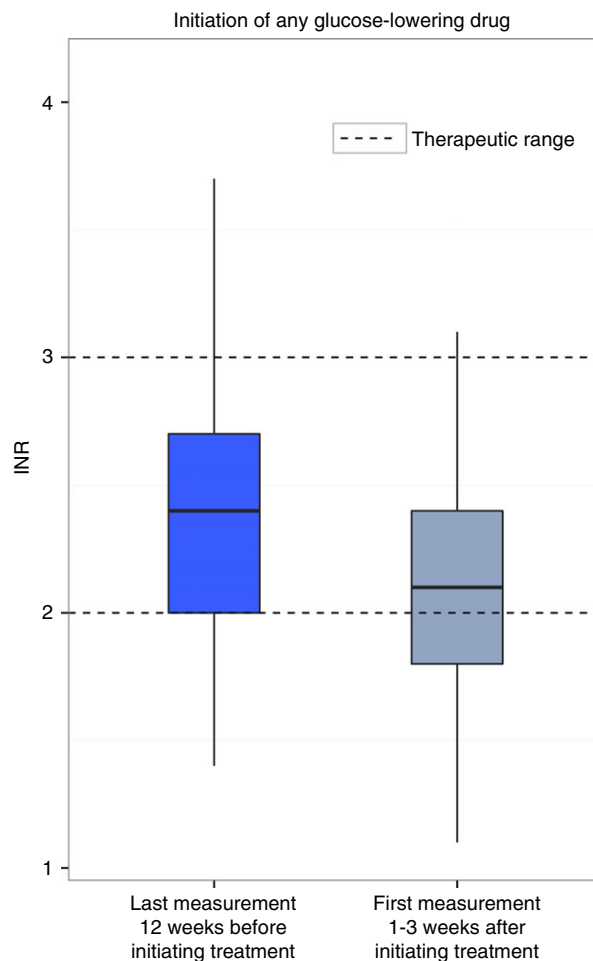


Fig. 2. Box plot of internationalized normalized ratio (INR) in patients treated with vitamin K antagonists before and after initiation of first glucose-lowering drug ($n = 89$). The boxes represent median INR with 25th–75th percentiles, whereas the whiskers represent the range (excluding outliers).

[10,11]. It was recently shown that the expression of CYP2C9 is down-regulated by microRNA-130b [12], which is up-regulated in cholestasis [13]. Hyperinsulinemia as a consequence of type 2 diabetes has been linked to increased proinflammatory cytokines in the liver [14,15]. It may be hypothesized that treatment of increased plasma glucose levels leads to lower insulin levels, which lowers hepatic inflammation, resulting in higher expression of cytochrome P450 enzymes, in this particular case CYP2C9. A higher expression of CYP2C9 would lead to increased metabolism of VKAs and lower plasma concentrations. This could explain the lower effect of VKAs after glucose-lowering treatment is initiated. Other explanations include changes in vitamin K-metabolizing gut microbiota in response to glucose-lowering treatment [16], increased absorption or intake of vitamin K or increased production of coagulation factors in response to lower hepatic inflammation.

In conclusion, initiation of treatment with glucose-lowering drugs in patients treated with VKAs results in a statistically significant and probably clinically relevant reduction of INR levels. Future studies should seek to confirm this association in an independent setting and explore possible mechanisms.

Addendum

T. B. Stage and P. Damkier wrote the manuscript. All the authors helped design the research. A. Pottegård and T. B. Stage performed the research. T. B. Stage, A. Pottegård and P. Damkier analyzed the data. All authors revised and approved the manuscript.

Disclosure of Conflict of Interests

T. B. Stage has been given unrelated paid lectures for Eisai, Orifarm, Novartis and Astellas-Pharma. A. Pottegård has received funding from Servier, Boehringer-Ingelheim, Astellas, Astra-Zeneca, Almirall and Alcon, all of which were paid to the institution where he was employed.

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