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REVIEW

Drug-drug interactions between vitamin K antagonists and statins: a systematic review

Anna E. Engell[1] · Andreas L. O. Svendsen[2] · Bent S. Lind[1,3] · Tore Bjerregaard Stage[4] · Maja Hellfritzsch[4,5] · Anton Pottegård[4]

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Abstract

Purpose Concomitant use of vitamin K antagonists (VKA) and statins is frequent in cardiovascular patients. However, clinical guidelines on this drug combination are divergent. Therefore, we performed a systematic review to evaluate the effect of statin initiation on coagulation among VKA users.

Methods Following the PRISMA guidelines, we applied two broad search strategies for the drug interaction between VKA and statins in both Embase and Pubmed; 8623 unique hits were obtained. In the final sample, eight studies were included.

Results The most frequently used VKA in the studies was warfarin, while simvastatin was the most commonly initiated statin. All included studies showed a minor increase in the anticoagulant effect of VKA following statin initiation during VKA treatment. The reported increases in mean international normalized ratio (INR) ranged from 0.15–0.65.

Conclusion The anticoagulant effect of statin initiation in patients treated with VKA is likely to be of limited clinical relevance but should be evaluated individually.

Keywords Drug interactions · Statins · Anticoagulants · Vitamin K antagonists · Warfarin

Introduction

Vitamin K antagonists (VKA) are used in long-term treatment and prevention of thromboembolic events. They exhibit their anticoagulant effect by interfering with the vitamin K–dependent γ-carboxylation of blood coagulation factors including factors II, VII, and X. The anticoagulant effect is monitored by measurement of one of the following two blood tests: the international normalized ratio (INR) or the prothrombin time (PTT). It is essential to achieve INR levels within the therapeutic range to avoid thromboses as well as bleedings [1, 2]. The use of VKA can be challenging, due to a narrow therapeutic index and substantial interindividual variation in dose response [1]. Furthermore, the anticoagulant effect of VKA can be influenced by drug-drug interactions, certain food, genetic variation, and other factors (e.g., fever) [3].

Warfarin is the most widely prescribed VKA, but acenocoumarol and phenprocoumon are also commonly used, especially in some European countries [4]. VKA are metabolized by the hepatic cytochrome P450 enzymes. CYP2C9 is responsible for the metabolism of S-warfarin, and CYP1A2, CYP2C19, and CYP3A4 are responsible for the metabolism of R-warfarin. Considering that S-warfarin is 3–4 times more pharmacologically active, CYP2C9 is the most important metabolic pathway for the pharmacological efficacy of warfarin [2–4]. Phenprocoumon is primarily metabolized by CYP2C9, while acenocoumarol is metabolized by both CYP2C9 and CYP2C19 [2, 4].

Cholesterol-lowering treatment with HMG-CoA reductase inhibitors (statins) comprises one of the most frequent drug

✉ Anna E. Engell
anna.elise.engell@regionh.dk

1 Department of Clinical Biochemistry, Copenhagen University Hospital Hvidovre, Kettegaard Allé 30, 2650 Hvidovre, Denmark

2 Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark

3 Copenhagen Primary Care Laboratory (CopLab) Database, Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

4 Clinical Pharmacology and Pharmacy, Department of Public health, University of Southern Denmark, Odense, Denmark

5 Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark

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treatments, with more than 200 million statin users worldwide [5]. The metabolism of statins also involves CYP3A4 (simvastatin, atorvastatin, and lovastatin) and CYP2C9 (fluvastatin and rosuvastatin) [6]. Furthermore, the membrane transport protein, organic anion transporting polypeptide 1B1 (OATP1B1), is also involved in the metabolism of the majority of statins [6]. Coadministration of VKA and statins is common with approximately 50% of warfarin users taking statins in Denmark [7].

Despite the widespread concomitant use of statins and VKA and the overlapping metabolic pathways, data about potential drug-drug interactions between the two drug groups are limited and conflicting. Studies have both reported that statin initiation leads to moderate INR increases, potentially associated with increased anticoagulant effects and small INR changes of limited clinical relevance. Nevertheless, it is recommended by commonly used online drug-drug interaction databases to increase the frequency of INR monitoring when initiating or discontinuing statin treatment and following dose changes [8–10]. To assess the clinical relevance of the potential drug-drug interactions between VKA and statins, we conducted a systematic literature review of the collectively available evidence on the effect of statin initiation on the anticoagulant effect of VKAs.

Methods

Following the PRISMA guidelines for systematic review [11, 12], two medical doctors (AEE and ALS) conducted the literature search. The databases used included PubMed (Medline) and the more drug and pharmacological oriented database Embase (Exerpta Medica, Elsevier; Ovid). The databases were searched from inception to June 2020. We performed two separate literature searches using relevant keywords in MESH terms combined with free text search in PubMed and in Embase.

The specific searches are described in detail in the Appendix section. The two searches in PubMed and EMBASE resulted in 878 and 8450 hits, respectively. All articles were imported to the web-based software platform Covidence.

Study selection and data extraction

The subsequent review and selection process were divided into two rounds. In the first round, articles were screened by their titles and abstracts independently by two reviewers (AEE and ALS), and discrepancies were solved via consensus. Studies were eligible for initial inclusion if they reported original data evaluating a possible drug-drug interaction associated with concomitant use of VKA and statins, as judged via the abstract. Furthermore, we excluded conference proceedings. Lastly, if no abstract was available, the title should indicate that the study concerned concomitant use of VKA and statins.

In the second round, we required studies to meet the same inclusion criteria as mentioned above, as judged by full-text read. Furthermore, we required that (i) the studies presented data from humans, (ii) the statin treatment should be initiated during stable VKA treatment; and (iii) the studies should report an outcome related to degree of coagulation, including changes in INR, PTT, VKA dose adjustments, or the clinical outcomes bleeding or thrombosis. Case reports, reviews, letters to the editor not presenting original data, and publications concerning healthy volunteers were excluded. Furthermore, articles in languages other than English or Scandinavian were excluded.

Lastly, we cross-reference-searched all included original publications for additional original publications meeting the abovementioned inclusion criteria.

Data were extracted from the included publications, by the two reviewers (AEE and ALS), based on a pre-defined data collection form and interpreted and analyzed by the entire author group.

Results

We screened 8623 titles and abstracts and selected 80 studies for full-text screening. Of these, eight studies were included (Fig. 1). The most common reason for excluding studies during full-text screening was due to the studies not concerning newly initiated statin treatment ($n = 30$). A full overview of the included studies can be found in Table 1. Out of the eight included studies, four studies investigated the effect of a specific statin (simvastatin [14, 19], rosuvastatin [18], and atorvastatin [20]), while three studies investigated the effect of more than one statin type [13, 16, 17]. Finally, one study did not specify which statin type the patients were initiating treatment with [15]. Concerning the VKA treatment, seven studies included patients in warfarin treatment only [13–15, 17–20], whereas one study concerned patients in phenprocoumon and acenocoumarol treatment [16]. The size of the included population ranged from 7 to 5637 patients in seven of the studies, while one study did not report the size of the study population [15]. Although all eight studies met our inclusion criteria, only seven studies focused specifically on the effect of initiating statin treatment on coagulation activity [13, 14, 16–20], while one study addressed several drug interactions with warfarin, including statins [15]. Two of the included studies were prospective controlled drug trials, comprising patients in stable warfarin treatment receiving statin treatment only due to the trial, and not due to any known medical condition [18, 20].

The three studies that focused on simvastatin initiation in patients treated with warfarin all reported a small increase in mean INR. The largest study, including data from 5637

Table 1 Characteristics of included studies

Main author	Study design	Statin treatment (*n*)[a]	Primary outcome	Absolute change after initiation of statin treatment[b] (95% CI)
Engell et al. [13]	Cohort study	Simvastatin (1363) Atorvastatin (165) Rosuvastatin (23)	Change in INR (mean)	+0.32 (0.25–0.38)
Andersson et al. [14]	Cohort study	Simvastatin (5637)	Change in INR (mean) Mean daily warfarin dose reduction (%) 1 year after the initiation of statin treatment	+0.15 −6.80%
Hansen et al. [15]	Cohort study	No data	Distribution of change in INR from baseline (1.8>INR<3.2) to one of four groups (%)	Nonevents (2.0<INR<3.0): 67.9% Increasing (INR≥4.0): 7.8% Decreasing (INR≤1.5): 7.1% Residual: 17.3%
Rein et al. [16]	Cohort study	Phenprocoumon Simvastatin (310) Atorvastatin (60) Pravastatin (64) Rosuvastatin (0) Fluvastatin (1) Acenocoumarol Simvastatin (206) Atorvastatin (51) Pravastatin (17) Rosuvastatin (28) Fluvastatin (1)	Mean daily phenprocoumon and acenocoumarol dose reduction (%) 12 weeks after the initiation of statin treatment	−3.00% (−4.00 to −1.00) −2.00% (−5.00 to 1.00)
Schelleman et al. [17]	Case-control study	Fluvastatin (16) Simvastatin (277) Atorvastatin (499) Pravastatin (113)	OR[c] of gastrointestinal bleeding 31–60 days after initiation of statin treatment	1.45 (0.68–3.09) 1.33 (1.00–1.78) 1.29 (1.04–1.61) 0.66 (0.38–1.14)
Simonson et al. [18]	Clinical trial	Rosuvastatin, 10 mg (7) Rosuvastatin, 80 mg (5)	INR>4 in a 14 days period INR>4 in a 14 days period	2 out of 7 patients increased INR>4 4 out of 5 patients increased INR>4
Kamali et al. [19]	Cohort study	Simvastatin (29)	Change in INR (mean) Change in INR (median)	+0.65±0.61 +0.65
Stern et al. [20]	Clinical trial	Atorvastatin, 80 mg (12)	Change in PTT (mean) in a 15-day period	Unchanged[d]

Treatment with warfarin is implicit unless other is specified

INR international normalized ratio, *CI* confidence interval, *OR* odds ratio

[a] Number of patients taking VKA and statins

[b] Range of absolute change after initiation of statin treatment and dosage of statin treatment are specified if reported

[c] OR for chronic warfarin users

[d] Except for a − 1.6-s decrease in PTT from days three to five

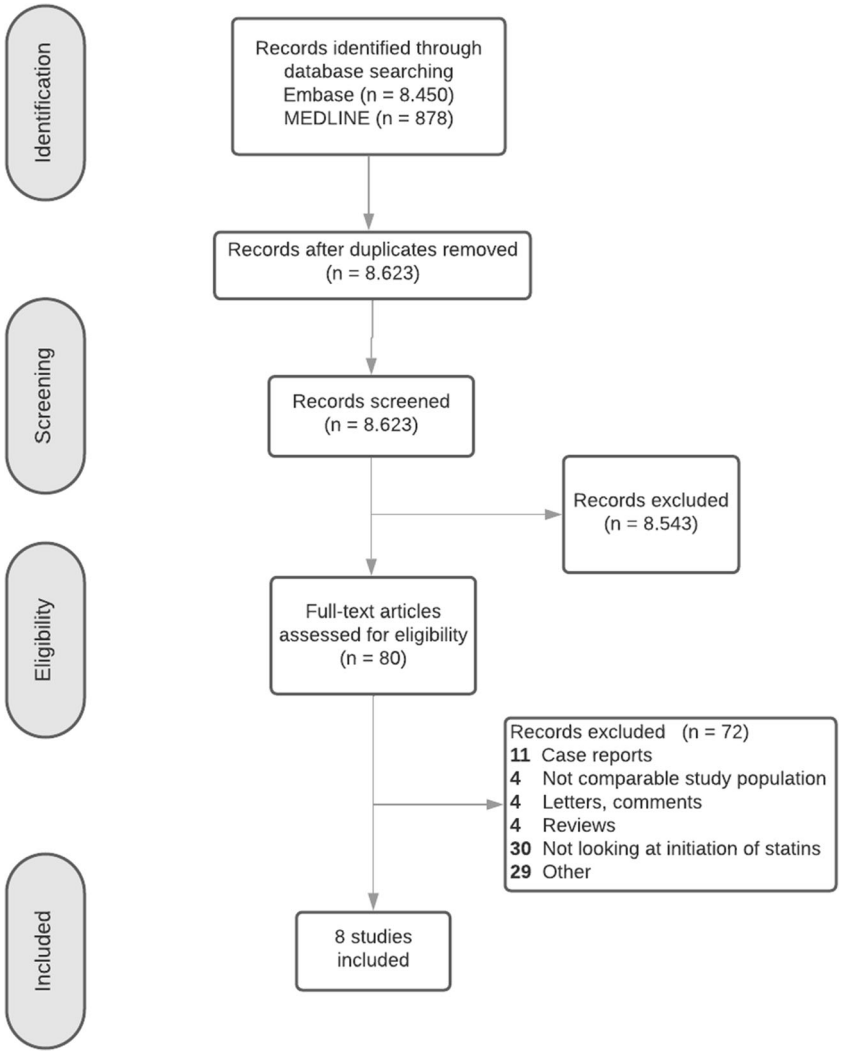

Fig. 1 PRISMA flow diagram

warfarin users, found an increase in mean INR from 2.43 at baseline to 2.58, 4 weeks after initiation of simvastatin treatment [14]. Similarly, another large register-based cohort study including 1363 patients found an increase in mean INR from 2.40 to 2.71 also peaking approximately 4 weeks after initiation of simvastatin treatment [13]. Furthermore, it was shown that high-dose (> 40 mg) and low-dose simvastatin (< 40 mg) led to comparable changes in INR (increase of 0.33 vs 0.29) [13]. A smaller study ($n = 29$) reported an increase in mean INR from 2.50 at baseline to 3.15 after initiation of simvastatin treatment [19]. In this study, the INR values were obtained from the patient's visit to the anticoagulation clinic prior to initiating simvastatin treatment and from the subsequent clinic visit after simvastatin had been initiated, with no information about the number of days/weeks in between [19]. Two studies reported a mean reduction of the daily warfarin dose following statin initiation of 7% and 9%, respectively [14, 19]. An observational case-control study assessed whether initiation of fibrates or statins in warfarin users increased the risk of hospitalization due to gastrointestinal (GI) bleeding [17]. Cases were warfarin users hospitalized with GI bleeding, whom were matched to 50 controls based on date and state. The study included 12,193 cases and 606,650 controls. Patients in the case group were initiating treatment with fluvastatin ($n = 16$), simvastatin ($n = 277$), atorvastatin ($n = 499$), and pravastatin ($n = 113$). In chronic warfarin users, the risk of GI bleeding was highest 31–60 days after simvastatin initiation with an odds ratio (OR) of 1.60 (95% CI 1.07–2.39) compared to no simvastatin initiation. For atorvastatin, the risk of GI bleeding was the highest 1–30 days after initiating treatment with an OR of 1.39 (95% CI 1.07–1.81) compared to no initiation of atorvastatin. Concerning fluvastatin treatment, there were too few cases to obtain reliable estimates. No increased risk of GI bleeding was observed, when initiating treatment with pravastatin [17].

A pilot study of warfarin-associated drug interactions did not find any changes in INR related to initiation of statin treatment, when patients with INR > 1.8 and < 3.2 in the period of 60 days prior to initiation of statin treatment were categorized in four groups according to the

change in INR. The four groups comprised the following: nonevents ($2.0 < \text{INR} < 3.0$), increasing ($\text{INR} \geq 4.0$), decreasing ($\text{INR} \leq 1.5$), and residual. Most patients were in the nonevent group (67.9%), while 7.8% and 7.1% experienced increased and decreased INR levels, respectively, and 17.3% patients were in the residual group in between the other three groups [15]. No specification of the type of the included statins was stated, and neither were the size of the exposed population of warfarin users; therefore, this study was considered to have lesser relevance to the evaluation of the effect of initiation of statin treatment on level of coagulation.

In another study, the immediate (on average 1 week after initiation of statin treatment) and long-term (6 and 12 weeks after initiation of statin treatment) effects of statins on INR in 435 patients in phenprocoumon treatment and 303 patients in acenocoumarol treatment were studied [16]. The patients treated with phenprocoumon ($n = 435$) and acenocoumarol ($n = 303$), respectively, initiated treatment with the statins simvastatin, atorvastatin, pravastatin, rosuvastatin, or fluvastatin. For all statins, the immediate effect on mean INR was an increase of 0.1 among phenprocoumon users, while no effect was observed for acenocoumarol. The VKA dose was decreased with 1% in phenprocoumon users and 2% in acenocoumarol users 6 weeks after initiation of statin treatment. After 12 weeks of statin treatment, the statin dose was reduced with 3% in phenprocoumon users, whereas the dose remained unchanged with a 2% reduction in acenocoumarol users. The greatest dose reduction of 4% was observed in acenocoumarol users imitating simvastatin treatment after 6 weeks of treatment [16].

Finally, two prospective clinical studies investigated the potential drug interaction between rosuvastatin and warfarin and atorvastatin and warfarin, respectively. One study investigated the effect of initiation and dosage increasement of rosuvastatin in seven patients in stable warfarin treatment for at least 1 month. Their mean baseline INR value was between 2 and 3 (determined from the mean of 3 values assessed during the screening period). Initiation of treatment with 10-mg rosuvastatin per day in a period of up to 14 days resulted in an $\text{INR} > 4$ in two out of the seven patients. Four out of the remaining five patients experienced an $\text{INR} > 4$ within the next 14 days, when rosuvastatin dosage was increased to 80 mg [18]. A small study with 12 patients in warfarin treatment described the change in mean prothrombin time the first 15 days after the initiation of atorvastatin treatment. The mean prothrombin time remained unchanged except for a small yet statistically significant decrease of 1.6 s from day 3–5 after initiation of atorvastatin treatment. However, the decrease was not considered therapeutically important [20].

Discussion

This systematic review identified eight studies exploring the effect of statin initiation on the degree of anticoagulation in VKA users. Overall, the initiation of simvastatin treatment in warfarin users lead to a slight increase in mean INR ranging from 0.15 to 0.65, which seemingly peaks about 4 weeks after initiation [13, 14, 19]. For the other studied statins (atorvastatin, rosuvastatin, and fluvastatin), the same tendency of slightly increased anticoagulation was also present, described as INR increases, reduced doses of VKA, and increased risk of hospitalization with GI bleeding.

The primary strength of our study is the multiple broad systematic search strategies designed to include original data. All literature was assessed by two persons, ensuring validity of the literature selection.

While all the included studies concerned patients in VKA treatment initiating treatment with statins, the studies showed considerable heterogeneity, with regard to the type of statin and statin dose. Furthermore, the included studies concerned patients in VKA treatment with warfarin, phenprocomarol, and acenocoumarol treatment. Finally, the patient population in the included studies also differed. While most studies excluded patients taking other medication that could interact with VKA and coagulation [13, 14, 16, 17, 19, 20], two studies did not report whether these patients were excluded or not [15, 18]. In the two included clinical trials, treatment with rosuvastatin and atorvastatin was initiated in patients without any known clinical indication requiring cholesterol-lowering therapy [18, 20].

Furthermore, for some studies, the lack of information regarding the type of statin [15] and the use of statins in the control group [17] result in difficulties, when interpreting the findings of the studies. Among the six studies where outcome was a change in INR/PTT, only half provided any analytical characterization of the INR/PTT tests used in the studies [13, 18, 20]. This missing laboratory information might explain at least in part the differences in the observed increases in INR [21]. Due to the heterogeneity of the studies, a direct comparison by meta-analysis was not considered feasible.

In the study selection process, we restricted to studies reported in English or a Scandinavian language. However, this criterion only led to the exclusion of a single study. Finally, we also excluded studies involving healthy volunteers, which could have contributed more data [22–25]. However, differences in target INR levels and treatment duration and doses of warfarin and statins between healthy volunteers and patients would make inference from such studies to clinical practice very difficult.

The pharmacological mechanism of the potential interaction between VKA and statins is, to our knowledge, not fully described. In vitro data suggests that statins have the potential to enhance the pharmacological activity of warfarin by

competitively inhibiting its CYP-dependent metabolism [19]. However, considering the substantial delay in the drug-drug interaction (~4 weeks) and the unspecific effect of several statins on warfarin effectiveness, this drug-drug interaction might not be mediated through cytochrome P450 inhibition, which would be expected to lead to a faster onset of INR increase, as, e.g., seen for azole antifungals [26]. An alternative explanation for the observed associations could be related to the effect of changes in cholesterol levels on warfarin metabolism. Cholesterol levels stabilize about 4 weeks after the initiation of statins [27, 28] coinciding with the maximum impact of statin initiation on INR among patients treated with VKA. However, further data is required to support this hypothesis. Finally, the two included studies concerning pravastatin, which is reported not to be metabolized by CYP enzymes [29], did not report an effect on coagulation [16, 17] which to some extent speaks against an interaction mediated solely through cholesterol.

Conclusion

Knowledge on the effects of statin treatment initiating on anticoagulation in stable VKA treatment is limited. Despite different types of VKA and statins, a tendency of an increased anticoagulant effect following statin treatment, when initiated while in VKA treatment, was observed in the included studies. Considering the initiation of simvastatin treatment in patients treated with warfarin, the reported increase in anticoagulation is minimal and overall considered to be of limited clinical relevance. The anticoagulant effect of initiation of other statins varies. In clinical settings, it will always be recommended to monitor INR more closely in the period after the initiation of a new drug regardless of whether a drug-drug interaction is expected or not [1, 30]. Depending on the specific drug, it can then be discussed how frequent this increased INR monitoring should be. For statins, the findings in our study support a recommendation of a slight increase in INR monitoring when statin treatment is initiated.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-020-03074-w.

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Authors' contributions All authors contributed to the study and design. The literature search was performed by Andreas L. O. Svendsen. Data was selected and extracted by Andreas L. O. Svendsen and Anna E. Engell. The first draft of the manuscript was written by Anna E. Engell and Anton Pottegård supervised the work. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

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Data availability All data generated or analyzed during this study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Code availability Not applicable

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