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

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Abstract

Abstract 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 according to the PRISMA guidelines to evaluate the effect of statin initiation on coagulation among VKA users. Applying two broad search strategies for the drug interaction between VKA and statins in both Embase and Pubmed, 8,623 unique hits were obtained. In the final sample eight studies were included. The most frequent 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 INR ranged from 0.15-0.65. The effect is likely to be of limited clinical relevance but should be evaluated individually.

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 factor 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] The cytochrome P450 enzymes CYP2C9 and CYP3A4 are responsible for the metabolism of S-warfarin and R-warfarin, respectively, with CYP2C9 being the most important metabolic pathway for 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 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 well as 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 AOS) conducted the literature search. The databases used included Pubmed (Medline) and the more drug and pharmacological oriented database Embase (Exerpta Medica, Elsevier; Ovid). Limits 'human' and 'English language' were applied. 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 Appendix X. The two searches in PubMed and EMBASE resulted in 878 and 8,450 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 AOS), 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. Further, 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 and publications concerning healthy volunteers 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 AOS) based on a pre-defined data collection form and interpreted and analyzed by the entire author group.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

Results

We screened 8,623 titles and abstracts and selected 80 studies for full-text screening. Of these, eight studies were included (**Figure 1**). The most common reason for excluding studies during full-text screening was due to the studies not concerning newly initiated statin treatment (n = 29). 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[13, 14], rosuvastatin[15], and atorvastatin[16]), while three studies investigated the effect of more than one statin type.[17-19] Finally, one study did not specify which statin type the patients were initiating treatment with.[20] Concerning the VKA-treatment, seven studies included patients in warfarin treatment only,[13-16],[18-20] whereas one study concerned patients in phenprocoumon and acenocoumarol treatment.[17] The size of the included population ranged from 7 to 5,637 patients in six of the studies, while one study did not report the size of the study population.[20] Although all eight studies met our inclusion criteria, only seven studies focused specifically on the effect of initiating statin treatment on coagulation activity,[13-19] while one study addressed several drug interactions with warfarin, including statins.[20] 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.[15, 16]

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 5,637 warfarin users, found an increase in mean INR from 2.43 at baseline to 2.58, four weeks after initiation of simvastatin treatment.[13] Similarly, another large register-based cohort study including 1,363 patients found an increase in mean INR from 2.40 to 2.71 also peaking approximately four weeks after initiation of simvastatin treatment.[19] 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).[19] A smaller study (n=29) reported an increase in mean INR from 2.50 at baseline to 3.15 after initiation of simvastatin treatment.[14] 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.[14] Two studies reported a mean reduction of the daily warfarin dose following statin initiation of 7% and 9%, respectively.[13, 14] An observational case-control study assessed whether initiation of fibrates or statins in chronic warfarin users increased the risk of hospitalization due to gastrointestinal (GI) bleeding.[13] The study included warfarin patients initiating treatment with fluvastatin (n = 16), simvastatin (n = 277), atorvastatin (n = 499) and pravastatin (n = 113). Each patient case with GI bleeding was matched with up to 50 controls, whom had initiated treatment with the same type of statin as the case, but had not been hospitalized due to GI bleedings. 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), and for atorvastatin the risk of GI bleeding was highest 1-30 days after initiating treatment with an OR of 1.39 (95% CI 1.07-1.81). Concerning fluvastatin treatment, there were too few cases to obtain reliable estimates. No increased risk of GI bleeding was observed, when initiating treatment with the chosen reference drug; pravastatin, as pravastatin is not metabolized by CYP enzymes and therefore was not expected to interact with warfarin.[18]

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 compromised: nonevents (2.0<INR<3.0), increasing (INR[?]4.0), decreasing (INR[?]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.[20] 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 (6-12 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.[17] 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 INR was an increase of 0.1 among phenprocoumon users, while no effect was observed for acenocoumarol. VKA dose was decreased with 0.02 mg/day in phenprocoumon users and 0.04 mg/day in acenocoumarol users within the first six weeks after initiation of statin treatment, and reduced furthermore with 0.07 mg/day

and 0.11 mg/day respectively after 12 weeks of statin treatment.[17]

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. Initiation of treatment with 10 mg rosuvastatin per day in a period of up to 14 days resulted in an INR > 4 in two out of the seven patients. Four out of the remaining five patients experienced an INR > 4 within the next 14 days, when rosuvastatin dosage was increased to 80 mg.[15] A small study with 12 patients in warfarin treatment described the change in mean prothrombin time the first 15 days after initiation of atorvastatin treatment. The mean prothrombin time remained unchanged except for a small yet statistically significant decrease of 1.6 seconds from day 3-5 after initiation of atorvastatin treatment. However, the decrease was not considered therapeutically important.[16]

Discussion

This systematic review identified eight studies exploring the effect of statin initiation on the degree of anticoagulation in VKA users. Overall, initiation of simvastatin treatment in warfarin users lead to a slight increase in mean INR ranging from 0.15-0.65, which seemingly peaks about 4 weeks after initiation.[13, 14],[19] For the other studied statins (atorvastatin, pravastatin, 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 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],[16-19] two studies did not report whether these patients were excluded or not.[15, 20] In the two included clinical trials, treatment with rosuvastatin and atorvastatin was initiated in patients without any clinical indication requiring cholesterol lowering therapy.[15, 16] It is possible that the pharmacological response to statins and the interaction with VKA in patients with normal cholesterol levels differs from patients with elevated cholesterol levels. Further, for some studies, the lack of information regarding the type of statin[20] and the possible use of statins in the control group[18] result in difficulties, when interpreting the findings of the studies. Among the six studies where outcome was change in INR/PTT,[20] only half provided any analytical characterization of the INR/PTT tests used in the studies.[15, 16, 19] 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.

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.[14] However, considering the substantial delay in the drug-drug interaction (˜four 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.[22] 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 four weeks after initiation of statins [23, 24] coinciding with the maximum impact of statin initiation on INR among patients treated with VKA. However, further data is required to support this hypothesis.

Conclusion

Knowledge on the effects of statin treatment initiating on anticoagulation in stable VKA treatment is lim-

ited. 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 initiation of simvastatin treatment in patients treated with warfarin, the reported increase in anticoagulation is limited and overall considered to be without clinical relevance. The anticoagulant effect of initiation of other statins vary, and it should be evaluated individually, if the frequency of INR monitoring should be increased during the first period of concomitant treatment.

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Contributors

A.E. was the principal author and reviewer together with AOS, who also conducted the literature search. A.P. supervised the work. A.E. prepared he first draft manuscript. All authors read and approved the final manuscript.

Competing interests

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.

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he was employed (no personal fees) and with no relation to the work reported in this paper.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure legends

Figure 1. Flowchart of literature search

Appendix X

The databases PubMed and Embase were searched from inception until February 13, 2020. Eligible studies included human subjects, presented data on vitamin K antagonist use and new statin use, and reported outcomes of changes in INR or proxies herefore. We imposed no restrictions regarding language or publication date on the search. Abstracts, conference proceedings, and unpublished work were not included. Besides original studies, reviews were eligible for full-text screening to identify additional references. Titles and abstracts were screened by two medical doctors (AEE and ALS) independently. Disagreements were resolved by consensus. We searched references in all publications selected for full-text screening to detect relevant potential publications not identified by our search strategy. Furthermore, the interaction databases of the Danish Medicines Agency (www.interaktionsdatabasen.dk), Stockleys Interaction Checker, and Lexicomp/Uptodate.com were reviewed for additional references.

Example of the full search strategy in EMBASE

1. exp hydroxymethylglutaryl coenzyme A reductase inhibitor/

2. (statin or statins).mp.

3. atorvastatin.mp.

4. cerivastatin.mp.

5. fluvastatin.mp.

6. lovastatin.mp.

7. pravastatin.mp.

8. simvastatin.mp.

9. lipitor.mp.

10. baycol.mp.

11. lescol.mp.

12. mevacor.mp.

13. altocor.mp.

14. pravachol.mp.

15. lipostat.mp.

16. zocor.mp.

17. mevinolin.mp.

18. compactin.mp.

19. fluindostatin.mp.

20. rosuvastatin.mp.

21. hydroxymethylglutaryl*.mp.

22. HMG-CoA*.mp.

23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

24. exp coumarin anticoagulant/

25. exp antivitamin K/

26. coumarin derivative/ or 4 hydroxycoumarin/ or 4 hydroxycoumarin derivative/

27. (Vitamin K antagonist$ or VKA or VKAs).mp.

28. (4-hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or fluindione or difenacoum or coumatetralyl).mp.

29. (coumarin$ or cumarin$ or phenprocoum$ or phenprocum$ or dicoumar$ or dicumar$ or acenocoumar$ or acenocumar$ or coumadin$ or fluindione dionor phenindione or clorindione or diphenadione).mp.

30. (adoisine or aldocumar or athrombin$ k or carfin or coumafene or coumaphene or jantoven or kumatox or lawarin or marevan or panwarfarin or panwarfin or prothromadin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin).mp.

31. international normalized ratio/

32. international normalised ratio.mp.

33. international normalized ratio.mp.

34. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33

35. 23 and 34

36. limit 35 to (animals and animal studies)

37. 35 not 36

38. limit 37 to conference abstract

39. 37 not 38

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