Drug-drug interaction between warfarin and statins: A Danish cohort study

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April 28, 2020

Abstract

Initiation of statin treatment is suggested to increase the international normalised ratio (INR) among warfarin users. However, available data is limited and conflicting. We conducted a register-based cohort study to evaluate the drug-drug interaction between warfarin and statins. By linking data on INR measurements and filled prescriptions, we identified warfarin users 2000-2015 initiating simvastatin (n=1,363), atorvastatin (n=165), or rosuvastatin (n=23). Simvastatin initiation led to an increase in mean INR from 2.40 to 2.71, with INRs peaking after 4 weeks, corresponding to a mean change of 0.32 (95%CI 0.25-0.38). High-dose and low-dose simvastatin led to comparable changes (mean change 0.33 vs 0.29). Initiation of atorvastatin and rosuvastatin lead to INR increases of 0.27 (95%CI 0.12-0.42) and 0.30 (95%CI -0.09-0.69). In conclusion, initiation of simvastatin, atorvastatin, or rosuvastatin among warfarin users led to a minor increase in INR. The magnitude of this change is for most patients likely of limited clinical relevance.

Introduction

The vitamin K antagonist warfarin is used in the treatment and prevention of thromboembolic events.[1–3] Due to its narrow therapeutic index, use of warfarin requires close monitoring of the international normalised ratio (INR). Warfarin is metabolized by the cytochrome P450 (CYP) liver enzymes, especially CYP2C9,[4] which makes it highly susceptible to drug-drug interactions (DDIs).[1,4]

Due to several overlaps in indications of use, coadministration of warfarin and statins is common.[5,6] A limited number of generally conflicting studies have reported both that statin initiation leads to moderate INR increases,[7–10] as well as, small INR changes of limited clinical relevance.[11,12]Despite limited evidence of a clinically relevant interaction between warfarin and statins, commonly used online DDI guidelines consistently advise clinicians to increase the frequency of INR monitoring and if necessary adjust the warfarin dose, when initiating statin treatment.[13–15] This results in additional consultations and blood testing, burdening both the patient and the health care system.

To provide additional data on this potential DDI between statins and warfarin, we conducted a large register-based study and examined the INR changes in warfarin users following exposure to simvastatin, atorvastatin, and rosuvastatin.

Methods

Base cohort and data sources

A base cohort was established by linking different Danish health registries. The base cohort comprised all patients registered with at least one INR measurement in the Copenhagen Primary Care Laboratory (CopLab) database. The database includes laboratory test results from primary health care patients in the Copenhagen area of Denmark from 2000 to 2015.[16,17] During this period the primary health care doctors in the Copenhagen area were served by the Elective Laboratory of the Capital Region (ELCR). ELCR covered approximately 1.2 million inhabitants and provided a wide range of biochemical, physiological, and cardiac tests. The CopLab database does not include INR point of care testing (POCT) results from general practice. The ELCR was accredited for International Organization for Standardization (ISO) standards ISO17025 and ISO15189. Appendix A provides a detailed description of the INR assay.

For the cohort identified via CopLab, we retrieved data about drug use from the Danish National Prescription Registry[18] as well as hospital diagnoses from the Danish National Patient Registry (NPR).[19] Data linkage was done using the unique Danish Civil Registration Number assigned to all Danish residents.[20]

Study population

From the base cohort (see above) we restricted the dataset to patients with at least two INR measurements, at least one recorded vitamin K antagonist (VKA) dispensing, and at least one statin dispensing. Within this cohort we identified all incident prescriptions for simvastatin, atorvastatin and rosuvastatin, defined as a prescription with no preceding prescription for a statin within the last 2 years. If one individual had two such incident prescriptions for the same statin, only the first was included. We further restricted to those with at least one INR measurement 8 weeks before statin initiation, as well as at least one INR measurement within 12 weeks after statin initiation. Finally, we excluded those with no VKA prescription within 8 weeks before statin initiation and those aged <18 years at the time of statin initiation.

Main analysis

The INR results were measured from 8 weeks before statin initiation to 12 weeks after statin initiation. We graphically depicted the changes in INR values by mapping median, interquartile and $10^{\text{th}}$and 90^{th} percentile during this window. To formally assess the INR changes, we estimated the increase in mean INR by comparing the latest INR result in the before window to the first INR result within week 3-6 after statin initiation (if any), by using a paired t test. We further assessed the median effect by estimating median changes in INR levels for all statin treated patients, as well as those treated with a high- ([?]40mg) and low-dose (<40mg) simvastatin in secondary analyses. Finally, we calculated the proportion of patients with an INR above the therapeutic interval (for most patients INR between 2-3); defined as INR > 4 and > 5 by comparing the proportion of patients 1-4 weeks prior to initiating simvastatin to the proportion 3-6 weeks after.

All analyses were performed using STATA Release 14.1 (Stata- Corp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency. Since data is based on anonymized register data neither approval from Ethics Committee nor collection of informed consent was needed.

Supplementary and sensitivity analyses

To assess the potential impact from other drugs interacting with warfarin, the main analysis was repeated excluding patients filling of a prescription for other potentially interacting drug in the observation period (8 weeks before to 12 weeks after the date of statin initiation). These drugs included specific antifungals, macrolides, quinolones, metronidazole and amiodarone as described in Appendix B.[10]

Furthermore, the main analysis was repeated excluding patients with a mechanical heart valve, identified through the NPR [21]to assess the potential influence of this patient group with other target INR ranges than 2-3.[22]

Finally, some INR measurements were labeled as imprecise (up to 5-7% higher than actual values) due to prolonged storage of the blood sample before analysis of INR. We therefore conducted an analysis were these

INR measurements were discarded.

Results

For the analyses, we included 1,363, 165, and 23 warfarin users who had been exposed to simvastatin, atorvastatin, and rosuvastatin, respectively, between 2000 and 2015.

For patients treated with simvastatin, atorvastatin and rosuvastatin, the median ages were 72 years (interquartile range (IQR) 64-79 years), 70 years (IQR 63-76), and 74 years (IQR 64-80), while the proportion of males were 58%, 62%, and 47%, respectively.

INR values increased slightly after initiation of simvastatin treatment with a peak after about 4 weeks (Figure 1). Initiation of simvastatin was associated with an increase in mean INR from 2.40 to 2.71, corresponding to an increase of 0.32 (95%CI: 0.25-0.38, p<0.001) while the median INR change was 0.2 (IQR -0.3-0.8) (Figure 2). During a time window of 1-4 weeks before initiation of statin treatment, 3.4% of patients had at least one INR measurement above 4. This proportion increased to 9.0% during 3-6 weeks after initiation of statin treatment (p<0.01). Similarly, the proportion of the patients with an INR > 5 increased from 1.3% before initiation of statin treatment to 3.2% after (p<0.01).

When stratifying by simvastatin dosage, we found that initiation of both high-dose ([?]40mg) simvastatin (0.33, 95%CI 0.25-0.42) and low-dose (<40mg) simvastatin (0.29, 95%CI 0.20-0.38) were associated with a similar modest increase in mean INR. The median change in INR was 0.2 (IQR -0.3-0.9) and 0.3 (IQR -0.2-0.8) for patients receiving high and low simvastatin dose, respectively (Figure 2).

Considering atorvastatin, initiation of treatment was associated with an increase in mean INR from 2.42 to 2.69 (change 0.27, 95%CI 0.12-0.42, p<0.01), while for rosuvastatin was associated with a corresponding increase from 2.31 to 2.61 (change 0.30, 95%CI -0.09-0.69, p=0.121). Analyses of high dose vs. low dose were prohibited by low statistical power for both atorvastatin and rosuvastatin.

Sensitivity analyses excluding patients filling prescriptions for other potentially interacting drugs (n=77), and patients with a mechanical heart valve (n=110), and INR measurements labeled as potentially imprecise (n=81 patients with no alternative measurements) yielded virtually unchanged estimates (data not shown).

Discussion

In this register-based study based on a primary health care population, we found that initiation of simvastatin was associated with a minor, but statistically significant increase in INR of 0.32 (95%CI: 0.25-0.38, p<0.001), peaking approximately 4 weeks after initiation. A similar increase in INR was observed with atorvastatin and rosuvastatin initiation, although failing to reach statistical significance.

The main strength of this study is the use of data obtained from daily routine work in primary health care with limited risk of selection bias. One limitation of this study is the assessment of drug use by prescription data alone. The level of adherence to statin therapy cannot be determined and neither can the precise date of initiation of statin treatment. Early discontinuation of statins due to side effects could minimize the effect on the change in INR.[23]Furthermore, we had no available information about other factors that might impact the INR level e.g. lifestyle factors, herbal medications as well as relevant diagnoses diagnosed solely in primary health care, however, due to the within-person comparison, most of such factors can reasonably be assumed constant. Finally, we do not report clinical outcomes. However, increases in INR are well known to increase the risk of severe bleeding.[1,26,27] This is supported by a study that found initiation of statins to increase the risk of gastrointestinal bleeding in chronic warfarin users.[28]In our study the proportion of patients with INR > 5 increased from 1.3 to 3.2% after statin treatment was initiated. Importantly, however, when scrutinizing the INR changes at the level of the individual, this increase reflected a small overall increase and not a pronounced increase in a subset of patients.

Our findings from primary health care in the Copenhagen area support the recent findings from specialized anticoagulation clinics in Sweden presented by Andersson et al, which found an increase in INR from 2.43 to 2.58 in 5637 patients on warfarin treatment initiating simvastatin, also peaking about 4 weeks after

simvastatin initiation.[10] A more pronounced increase in INR was found in a small study, where INR increased from 2.5 at baseline to 3.2 after simvastatin initiation in 29 patients in stable warfarin treatment.[7]

The latency in the INR increase, peaking after four weeks of concomitant treatment is surprising. Of note, a similar course was seen in the study by Andersson et al.[10] This does not correspond to statins directly inhibiting the CYP enzymes responsible for the metabolism of warfarin, as this would lead to a faster onset of the INR increase, as e.g. seen for azole antinfungals.[29] To our knowledge, no alternative mechanisms have been proposed. As such, additional work identifying the mechanism through which statin use potentiates the effect of warfarin is warranted.

In conclusion, initiation of simvastatin, atorvastatin, and rosuvastatin led to a minor increase in INR in patients treated with warfarin, peaking about 4 weeks after statin initiation. The magnitude of the change in INR is for most patients likely to be of limited clinical relevance. Individual risk stratification including age, use of medication and other diseases should be applied, when deciding if increased INR monitoring should be performed during the initiation of statin treatment.

ACKNOWLEDGEMENTS

The authors acknowledge Martin T. Ernst for help with data management and Maja Hellfritszch for valuable input to the presentation of the findings.

CONTRIBUTORS

A.E. was the principal author and investigator. A.P. carried out data collection and data analysis. A.P. supervised the work. A.E. prepared the first draft manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTST

F.P. reports having received research grant from AstraZeneca, Novo Nordisk, Novartis and lecture fees from MSD, AstraZeneca, Novo Nordisk, Novartis, Eli Lilly and Boehringer Ingelheim and have served as a consultant for AstraZeneca, Novo Nordisk, Amgen, and MSD.

A.P. reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all with funds paid to the institution where 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. Median international normalised ratio (INR), from 8 weeks before and 12 weeks after initiation of simvastatin treatment. Grey and dashed lines illustrate the 10, 25, 75 and 90 percentiles, respectively. INR-values were summarized in 3-day intervals.

Figure 2. Box and whisker plot showing median change in the international normalised ratio (INR) for all patients treated with simvastatin, low dose (<40mg) and high dose ([?]40mg) treated patients. Upper and lower box borders illustrate the 75^{th} and 25^{th}percentiles, while upper and lower whiskers illustrate the 10^{th} and 90^{th} percentile change in INR observed.

Appendix A – The International Normalised Ratio assay

Coagulation, tissue factor-induced; rel.time (actual/norm; INR); IRP 67/40; proc.) was determined in sodium-citrate-stabilized plasma by Stago Prothombin-complex Assay (Diagnostica Stago, Asnieres, France) on Thrombolyzer (Behnk Elektronik, Norderstedt, Germany) and on STA-R (Diagnostica Stago). For the Thrombolyzer assay the interserial coefficient of variation percentage (CV%) was 2,4 % (at INR level 1,0) and 2,9 % (at INR level 2,3). For the STAR assay the interserial CV% was 2,1 % (at level INR 1,00) and 2,1 % (at INR level 2,2). The results from the two platforms were comparable as documented by parallel analysis of 90 human plasma samples during a period of 6 days in December 2001 to May 2002. The equation from the parallel analysis was STAR = 1,0186*Thrombolyzer -0,0305. The STA-R platform was used after December 8, 2003. The INR assay was subject to external quality control through participation in the Danish quality assessment service DEKS (Glostrup, Denmark). The assessment schemes included 5 distributions annually. Each distribution comprised 4 samples. The results from DEKS confirmed the reliability of the assays, and the results from ELCR (from 2002 to 2015) deviated less than 5% from the method mean in 89 % of the results (n=231). The mean deviation from the method mean was - 1,8 % (n=196).

Appendix B – Codes and definitions

Study drugs

Warfarin ATC B01AA03

Statins ATC C10AA

Simvastatin ATC C10AA01

Rosuvastatin ATC C10AA07

Atorvastain ATC C10AA05

Other drug use

Amiodarone ATC C01BD01

Fluconazole ATC J02AC01

Miconazole ATC D01AC02

Erythromycin ATC J01FA01

Ciprofloxacin ATC J01MA02

Metronidazol ATC D06BX01

Factors affecting therapeutic interval of INR

Presence of prosthetic heart valve ICD-10 Z95.2

International Classification of Diseases Tenth Revision (ICD–10),

ATC: Anatomical Therapeutic Chemical Classification System