Received: 15 April 2020 | Revised: 26 May 2020 | Accepted: 3 June 2020

DOI: 10.1111/bcp.14428

SHORT REPORT

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

Anna E. Engell[1] | Andreas L.O. Svendsen[2] | Bent S. Lind[1] | Christen L. Andersen[3,4] | John S. Andersen[5] | Tora G. Willadsen[5] | Frederik Persson[6] | Anton Pottegård[7]

[1]Department of Clinical Biochemistry, Copenhagen University Hospital Hvidovre, 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, Denmark

[4]Department of Hematology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

[5]Research Unit for General Practice, Department of Public Health, Copenhagen University, Copenhagen, Denmark

[6]Steno Diabetes Center Copenhagen, Gentofte, Denmark

[7]Clinical Pharmacology and Pharmacy, Department of Public health, University of Southern Denmark, Odense, Denmark

Correspondence
Anna E. Engell, MD, Department of Clinical Biochemistry, University Hospital Hvidovre, Kettegaard Allé 30 2650, Hvidovre, Denmark.
Email: anna.elise.engell@regionh.dk

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 = 1363), 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.

KEYWORDS

anticoagulants and warfarin, drug interactions, statins

1 | 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 metabolised by the **cytochrome P450** (CYP) liver enzymes, especially **CYP2C9**,[4] which makes it highly susceptible to drug-drug interactions (DDIs).[1,4] Statins are also metabolized by some of the same CYP enzymes and transporters dependent of statin type, eg, **simvastatin** is metabolised by **CYP3A4**, **2C8**, **2D6** and **MRP2**, **atorvastatin** by CYP3A4, 2C8 and OATP1B1, and **rosuvastatin** by CYP2C9, 2C19 and OATP1B1.[5]

Due to several overlaps in indications of use, coadministration of warfarin and statins is common.[6,7] A limited number of generally conflicting studies have reported both that statin initiation leads to moderate INR increases[8–11] and that small INR changes are of limited clinical relevance.[12,13] 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.[14–16] This results in additional consultations and blood testing, burdening both the patient and the healthcare 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.

What is already known about this subject

- Warfarin has a narrow therapeutic window and pharmacological characteristics that render the drug highly susceptible to drug-drug interactions.
- Statins and warfarin are often coprescribed due to convergent clinical indications.

What this study adds

- Initiation of statins in patients treated with warfarin is associated with a minor increase in international normalised ratio (INR), peaking at about 4 weeks after statin initiation.
- The observed association was similar for high- and low-dose simvastatin.
- The increase in INR is probably of limited clinical relevance.

2 | METHODS

2.1 | 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 healthcare patients in the Copenhagen area of Denmark from 2000 to 2015.[17,18] During this period the primary healthcare doctors in the Copenhagen area were served by the Elective Laboratory of the Capital Region (ELCR). ELCR covers approximately 1.2 million inhabitants and provides 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[19] as well as hospital diagnoses from the Danish National Patient Registry (NPR).[20] Data linkage was done using the unique Danish Civil Registration Number assigned to all Danish residents.[21]

2.2 | 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 180 days before statin initiation and those aged <18 years at the time of statin initiation.

2.3 | 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 10th and 90th percentiles 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 weeks 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 high- (≥40 mg) and low-dose (<40 mg) simvastatin in secondary analyses. Finally, we calculated the proportion of patients with an INR above the therapeutic interval (for most patients INR between 2 and 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 anonymised register data neither approval from the Ethics Committee nor collection of informed consent was needed.

2.4 | Supplementary and sensitivity analyses

To assess the potential impact from other drugs interacting with warfarin, the main analysis was repeated excluding patients with a prescription for other potentially interacting drugs 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.[11]

Furthermore, the main analysis was repeated excluding patients with a mechanical heart valve, identified through the NPR,[22] to assess the potential influence of this patient group with target INR ranges other than 2-3.[23]

Finally, some INR measurements were labelled 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 where these INR measurements were discarded.

2.5 | 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.

3 | RESULTS

For the analyses, we included 1363, 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 patients with INR > 5 increased from 1.3% before initiation of statin treatment to 3.2% after ($P < 0.01$).

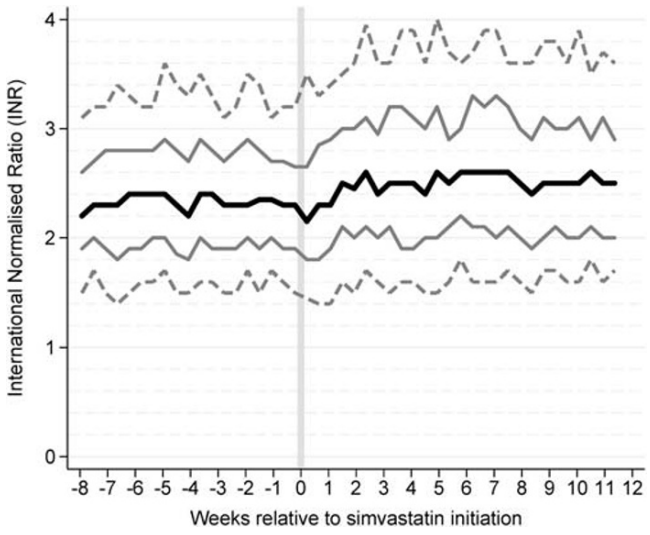

FIGURE 1 Median INR from 8 weeks before and 12 weeks after initiation of simvastatin treatment. Grey and dashed lines illustrate the 10th, 25th, 75th and 90th percentiles, respectively. INR values are summarised in 3-day intervals

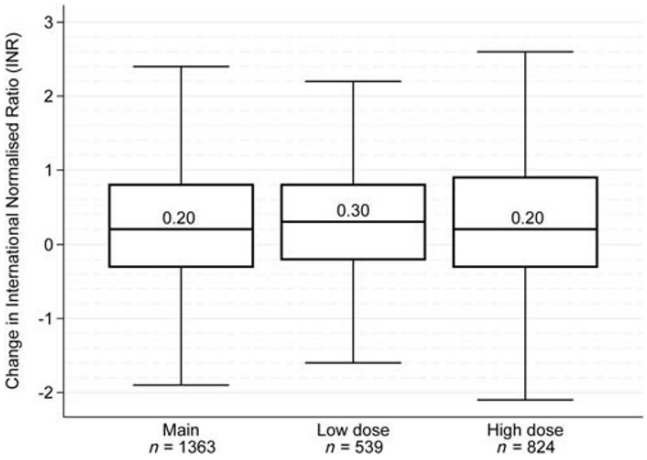

FIGURE 2 Box and whisker plot showing median change in the INR for all patients treated with simvastatin, low dose (<40 mg) and high dose (≥40 mg). Upper and lower box borders illustrate the 75th and 25th percentiles of observed change in INR, while upper and lower whiskers illustrate the 10th and 90th percentiles

When stratifying by simvastatin dosage, we found that initiation of both high-dose (≥40 mg) simvastatin (0.33, 95%CI 0.25-0.42) and low-dose (<40 mg) simvastatin (0.29, 95%CI 0.20-0.38) was 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 it 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), patients with a mechanical heart valve (n = 110), and INR measurements labelled as potentially imprecise (n = 81 patients with no alternative measurements) yielded virtually unchanged estimates (data not shown).

4 | DISCUSSION

In this register-based study based on a primary healthcare 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. We observed a similar response in patients initiating treatment with atorvastatin and rosuvastatin, although it failed to reach statistical significance. Sufficient data to allow analyses was not available for other statins.

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 the 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 minimise the effect on the change in INR.[24] Also, we had no available information about other factors that might impact the INR level, eg lifestyle factors and herbal medications as well as relevant diagnoses diagnosed solely in primary health care, but due to the within-person comparison most of these factors can reasonably be assumed to be constant. Furthermore, we do not report clinical outcomes. However, increases in INR are well known to increase the risk of severe bleeding.[1,25,26] This is supported by a study that found initiation of statins to increase the risk of gastrointestinal bleeding in chronic warfarin users.[27] 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 scrutinising 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.

Finally, our study was limited to simvastatin, atorvastatin and rosuvastatin. Limited use of other statins and other cholesterol lowering therapy, eg the cholesterol absorption inhibitor ezetimibe, were not included in the present study. One study reported a possible drug interaction between warfarin and **ezetimibe**, which was enhanced in patients taking both ezetimibe and statins with an increase in INR (0.06 ± 0.36 for ezetimibe and 0.34 ± 0.54 for ezetimibe and statins, $P = 0.03$).[28]

Our findings from primary health care in the Copenhagen area support the recent findings from specialised 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.[11] A more pronounced increase in INR was found in a small study in which INR increased from 2.5 at baseline to 3.2 after simvastatin initiation in 29 patients in stable warfarin treatment.[8]

Despite relying on different CYP enzymes and transporters, we found a similar increase in INR values with use of simvastatin, atorvastatin and rosuvastatin. This suggests that non-CYP effects might play a role in this drug-drug interaction. Also, the latency in the INR increase, peaking after 4 weeks of concomitant treatment, is surprising. Of note, a similar course was seen in the study by Andersson et al.[11] 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, eg, as 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.

COMPETING INTERESTS

F.P. reports having received a research grant from AstraZeneca, Novo Nordisk and Novartis and lecture fees from MSD, AstraZeneca, Novo Nordisk, Novartis, Eli Lilly and Boehringer Ingelheim, and has 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.

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.

DATA AVAILABILITY STATEMENT

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

ORCID

Anna E. Engell https://orcid.org/0000-0003-4123-0753
Andreas L.O. Svendsen https://orcid.org/0000-0001-8050-6447
Anton Pottegård https://orcid.org/0000-0001-9314-5679

REFERENCES

1. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy - antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012; 141(2):e44S-e88S.
2. Huisman MV, Rothman KJ, Paquette M, et al. Antithrombotic treatment patterns in patients with newly diagnosed nonvalvular atrial fibrillation: the GLORIA-AF registry, phase II. *Am J Med*. 2015; 128(12):1306-1313. e1
3. Adelborg K, Grove EL, Sundbøll J, Laursen M, Schmidt M. Sixteen-year nationwide trends in antithrombotic drug use in Denmark and its correlation with landmark studies. *Heart*. 2016;102(23):1883-1889.
4. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med*. 2005; 165(10):1095-1106.
5. Sirtori CR. The pharmacology of statins. *Pharmacol Res*. 2014;88:3-11.
6. Neuvonen PJ, Niemi M, Backman JT. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. *Clin Pharmacol Ther*. 2006;80(6):565-581.
7. Hellfritzsch M, Rathe J, Stage TB, et al. Generic switching of warfarin and risk of excessive anticoagulation: a Danish nationwide cohort study. *Pharmacoepidemiol Drug Saf*. 2016;25(3):336-343.
8. Kamali F, Hickmott H, Wynne H. The effect of simvastatin co-medication on warfarin anticoagulation response and dose requirements. *Thromb Haemost*. 2003;89:949-950.

9. Lin JC, Ito MK, Stolley SN, Morreale AP, Marcus DB. The effect of converting from pravastatin to simvastatin on the pharmacodynamics of warfarin. *J Clin Pharmacol*. 1999;39(1):86-90.
10. Simonson SG, Martin PD, Mitchell PD, Lasseter K, Gibson G, Schneck DW. Effect of rosuvastatin on warfarin pharmacodynamics and pharmacokinetics. *J Clin Pharmacol*. 2005;45(8):927-934.
11. Andersson ML, Mannheimer B, Lindh JD. The effect of simvastatin on warfarin anticoagulation: a Swedish register-based nationwide cohort study. *Eur J Clin Pharmacol*. 2019;75(10):1387-1392.
12. Stern A, Gibson L. Atorvastatin anticoagulant. *J Clin Pharmacol*. 1997; 37(11):1062-1064.
13. Jindal D, Tandon M, Sharma S, Pillai KK. Pharmacodynamic evaluation of warfarin and rosuvastatin co-administration in healthy subjects. *Eur J Clin Pharmacol*. 2005;61(9):621-625.
14. Lexicomp® drug interactions - UpToDate. https://www.uptodate.com/drug-interactions/?source=responsive_home#di-document. Accessed January 28, 2020.
15. Drug interactions search - MICROMEDEX. https://www.micromedexsolutions.com/micromedex2/librarian/CS/DFE440/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/A7EB49/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert. FindDrugInteractions?navitem=topInteractions&isToolPage=true. Accessed January 28, 2020.
16. Interaktionsdatabasen.Dk. http://www.interaktionsdatabasen.dk/. Accessed January 29, 2020.
17. The Copenhagen primary care laboratory database. https://publichealth.ku.dk/research/databases-for-collaboration/coplab/. Accessed April 1, 2020.
18. Medici BB, Nygaard B, La Cour JL, et al. Changes in prescription routines for treating hypothyroidism between 2001 and 2015: an observational study of 929,684 primary care patients in Copenhagen. *Thyroid*. 2019;29(7):910-919.
19. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: the Danish national prescription registry. *Int J Epidemiol*. 2017;46(3):798-798f.
20. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7: 449-490.
21. Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8): 541-549.
22. Keeling DM, Baglin T, Tait C, et al. Guidelines on oral anticoagulation with warfarin - fourth edition. *Br J Haematol*. 2011;154(3):311-324.
23. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2):e576S-e600S.
24. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. *Eur Heart J*. 2016;37(11):908-916.
25. Nelson WW, Wang L, Baser O, Damaraju CV, Schein JR. Out-of-range INR values and outcomes among new warfarin patients with non-valvular atrial fibrillation. *Int J Clin Pharmacol*. 2014;37:53-59.
26. Wan Y, Heneghan C, Perera R, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ Cardiovasc Qual Outcomes*. 2008;1(2):84-91.
27. Schelleman H, Bilker WB, Brensinger CM, Wan F, Yang YX, Hennessy S. Fibrate/statin initiation in warfarin users and gastrointestinal bleeding risk. *Am J Med*. 2010;123(2):151-157.
28. Hashikata T, Yamaoka-Tojo M, Kakizaki R, et al. Ezetimibe enhances and stabilizes anticoagulant effect of warfarin. *Heart Vessels*. 2017; 32(1):47-54.
29. Venkatakrishnan K, Von Moltke LL, Greenblatt DJ. Effects of the antifungal agents on oxidative drug metabolism. Clinical relevance. *Clin Pharmacokinet*. 2000;38(2):111-180.

How to cite this article: Engell AE, Svendsen ALO, Lind BS, et al. Drug-drug interaction between warfarin and statins: A Danish cohort study. *Br J Clin Pharmacol*. 2020;1–6. https://doi.org/10.1111/bcp.14428

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-stabilised plasma by Stago Prothombin-complex assay (Diagnostica Stago, Asnières, 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 8 December 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 five distributions annually. Each distribution comprised four 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.