Journal of Thrombosis and Haemostasis, **14**: 765–771 DOI: 10.1111/jth.13268

ORIGINAL ARTICLE

The effect of carbamazepine on warfarin anticoagulation: a register-based nationwide cohort study involving the Swedish population

B. MANNHEIMER,* M. L. ANDERSSON,† H. JÄRNBERT-PETTERSSON* and J. D. LINDH†
Department of Clinical Science and Education at Södersjukhuset, Karolinska Institutet; and †Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden

To cite this article: Mannheimer B, Andersson ML, Järnbert-pettersson H, Lindh JD. The effect of carbamazepine on warfarin anticoagulation: a register-based nationwide cohort study involving the Swedish population. *J Thromb Haemost* 2016; **14**: 765–71.

Essentials

- The clinical impact of the carbamazepine-warfarin drug interaction is largely unknown.
- We studied the interaction in 166 patients, using data from three nationwide registries.
- Co-treatment with carbamazepine increased warfarin dose requirements by 49%.
- International normalized ratio remained reduced for months, indicating poor control.

Summary. *Background:* There are data indicating that the interaction between warfarin and carbamazepine results in decreased warfarin efficacy. However, the evidence on the magnitude of and interindividual differences in susceptibility to this interaction has remained scarce. *Objectives:* To investigate the effect of carbamazepine on warfarin anticoagulation and warfarin maintenance doses by the use of data from three nationwide registries. *Patients/Methods:* In a retrospective cohort study including 166 patients, warfarin doses were compared 2–4 weeks before and 10–13 weeks after initiation of cotreatment with carbamazepine. In addition, warfarin doses and International Normalized Ratio (INR) values were calculated week-by-week during cotreatment. Data on prescribed warfarin doses and INR measurements were obtained from two large Swedish warfarin registers. Data on carbamazepine use were retrieved from the Swedish Prescribed Drug Register. *Results:* The average warfarin doses were 49% (95% confidence interval 43–56) higher during carbamazepine treatment. The INR decreased upon carbamazepine initiation, and subtherapeutic INR levels were observed in 79% of all patients during the fifth week of cotreatment. Warfarin maintenance dose increases exceeding 50% and 100% were observed in 59% and 17% of patients, respectively. *Conclusions:* Four of five warfarin-treated patients in whom cotreatment with carbamazepine was initiated experienced subtherapeutic anticoagulative effect within 3–5 weeks. The warfarin dose was subsequently increased by 49%, a change that differed widely between patients. In order to avoid thrombosis and ischemic stroke, carbamazepine initiation should be accompanied by close INR monitoring to better meet the anticipated increase in dose demand.

Keywords: carbamazepine; cytochrome P450 (CYP2C9); drug interactions; International Normalized Ratio; warfarin.

Correspondence: Marine L. Andersson, Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet, Karolinska University Hospital, Huddinge, SE 141 86 Stockholm, Sweden.
Tel.: + 46 8 585 810 64; fax: + 46 8 585 810 70.
E-mail: marine.andersson@karolinska.se

Received 9 October 2015
Manuscript handled by: M. Cushman
Final decision: F. R. Rosendaal, 7 January 2016

Introduction

The anticoagulant warfarin is the drug most frequently associated with severe adverse drug reactions [1,2]. The main reason is its narrow therapeutic window, and even small changes in warfarin sensitivity may lead to both subtherapeutic and supratherapeutic responses, resulting in an increased risk for thrombosis or severe bleeding [2]. In clinical practice, such changes in warfarin sensitivity are often caused by drug–drug interactions. Carbamazepine is an antiepileptic drug that presumably enhances the metabolism of warfarin, thereby increasing the warfarin dose required to keep the International Normalized Ratio (INR) within the therapeutic range. Although this is one of the most well established drug–drug interactions, the empirical evidence is scarce [3–8]. The aim of the present study was to investigate how

carbamazepine affects the anticoagulative effect of warfarin in a large patient sample.

Methods

We analyzed changes in warfarin dose requirements during cotreatment with carbamazepine in a retrospective cohort study based on data from two widely used warfarin-monitoring registers and the Swedish Prescribed Drug Register, a nationwide register of drug dispensation [9]. Auricula and Journalia are medical record systems used in > 300 anticoagulation clinics in Sweden [10,11]. They include individual-level information on sex, age and day-to-day data on prescribed warfarin doses adjusted to maintain the INR within therapeutic levels (typically 2–3). By linking and matching Journalia and Auricula with the Swedish Prescribed Drug Register, we compared individual patients' warfarin doses before and after carbamazepine initiation.

Eligible for inclusion were patients aged ≥ 18 years with warfarin treatment documented in Auricula or Journalia, who had started carbamazepine therapy during ongoing treatment with warfarin. Initiation of carbamazepine treatment was defined as dispensation of carbamazepine preceded by a period of at least 12 months during which no carbamazepine dispensations had been made. The date of this first dispensation was used as the index date (start of warfarin–carbamazepine cotreatment). To avoid including patients who stopped carbamazepine treatment shortly after the index date, we also required a second dispensation of carbamazepine within 60–120 days after the index date (in Sweden, each dispensation typically covers 3 months). In addition, warfarin treatment had to be documented from 4 weeks prior to the index date until 11 weeks after the index date, and at least one dispensation of warfarin had to be recorded in the period 4–20 weeks prior to the index date, to avoid including patients who had started warfarin treatment but who had not yet achieved a stable warfarin dose when carbamazepine was introduced. Individuals codispensed any drugs that, according to the validated drug–drug interaction database SFINX, have a well-documented clinically significant pharmacokinetic potential to interact with warfarin (i.e. changes in the INR or the area under the time–plasma concentration curve of warfarin exceeding 10%) were excluded [12]. Thus, patients were excluded if they had received amiodarone, bosentan, capecitabine, cimetidine, clofibrate, co-trimoxazole, dabrafenib, darunavir, dasabuvir, disulfram, dronedarone, enzalutamide, eslicarbazepine, erythromycin, fluconazole, fluorouracil, lopinavir, metronidazole, miconazole, paritaprevir, phenobarbital, primidone, propafenone, rifampicin, ritonavir, sitaxentan, ombitasvir, oritavancin, vemurafenib, voriconazole, or zafirlukast.

To determine whether cotreatment with carbamazepine altered the warfarin dose requirements, the mean daily warfarin dose over a 4-week period (70–97 days after the index date) was compared with a baseline dose recorded during a 4-week period before the index date. In patients abandoning warfarin treatment between day 70 and day 97, all available doses during this period were used for calculation of the warfarin dose during cotreatment with carbamazepine.

In each patient, the change in log-transformed dose between the two periods was calculated, and the mean difference was compared against zero (no change) in a two-sided dependent *t*-test. Retransformation of the mean difference provided a relative effect measure, i.e. the relative dose increase. The potential influence of age and sex on the drug–drug interaction was investigated in a multiple linear regression model with change in (log-transformed) warfarin dose as the dependent variable. In this model, age was coded as 18–49, 50–59, 60–69, 70–79, 80–89 and 90–100 years. To visualize the interindividual variability in the impact of the drug–drug interaction, each patient's baseline dose was plotted against the corresponding dose recorded after 10–13 weeks of carbamazepine treatment.

To investigate the temporal aspects of the drug–drug interaction in further detail, we calculated mean warfarin doses separately for each week. In this secondary analysis, each patient's doses were normalized by dividing them by the patient's baseline dose. This normalization procedure was justified by the assumption that the relative effect (percentage dose change) of altered drug clearance would be more uniform among patients than the absolute effect (mg $week^{-1}$). In addition, we performed week-by-week calculations of the fraction of patients in whom the warfarin dose had increased by > 25%, > 50% or > 100% from baseline. These time-dependent analyses covered 21 weeks, starting from the index date. To determine whether the baseline warfarin dose requirements influenced the relative dose increase associated with carbamazepine exposure, we divided the patients into those with a baseline dose of < 30 mg $week^{-1}$ and those with a baseline dose of ≥ 30 mg. We then repeated the analyses separately for each of the two groups.

Theoretically, the proposed drug interaction could cause a temporary drop in the INR before the warfarin dose has been successfully increased to match the induced drug elimination. This would be of clinical importance, as a period of subtherapeutic INR levels following carbamazepine initiation would expose the patients to an increased risk of thrombosis. To determine whether the INR dropped during the early phases of cotreatment with warfarin and carbamazepine, we calculated daily INR values with the Rosendaal interpolation method [13]. After log transformation of these values, mean INR levels with 95% confidence intervals (CIs) were calculated week-by-week, from 1 week before until 21 weeks after carbamazepine initiation. For each week, we also

calculated the fraction of patients who were exposed to an INR of < 2, which is typically the lower limit of the target INR interval.

Finally, we calculated the delay between carbamazepine initiation and the first follow-up INR measurement, as an indicator of the prescribers' awareness of the potential drug–drug interaction. This delay was expressed as the proportion of patients who had not yet been subjected to INR monitoring after 1, 2 and 3 weeks of cotreatment.

In all analyses, *P*-values of < 0.05 were considered to be statistically significant. All analyses were performed with IBM SPSS STATISTICS 22.0 (SPSS, Chicago, IL, USA) and R version 2.0.3 [14].

Results

In total, 1733 warfarin-treated patients recorded in the Auricula and Journalia databases had been dispensed carbamazepine on at least one occasion between 1 July 2005 and 31 December 2012. Of these patients, 1473 were excluded because the carbamazepine treatment did not coincide with warfarin treatment, or because other interacting drugs had been codispensed. Of the remaining 260 patients, 94 were excluded because a 4-week warfarin baseline dose could not be calculated, leaving 166 individuals for inclusion in the study (Fig. 1). The median age (interquartile range) of the included patients was 74 years (66–80 years), and 42% were women. At baseline, i.e. immediately before carbamazepine initiation, the median warfarin dose (interquartile range) was 30.0 mg week^{-1} (20.0–37.5 mg week^{-1}).

INR

Following carbamazepine initiation, the mean INR rapidly decreased from 2.26 (95% CI 2.18–2.34) and reached a subtherapeutic level of 1.78 (95% CI 1.75–1.85) after 4 weeks of cotreatment (Fig. 2). From 6 weeks onwards, the INR increased slowly, but it did not return to baseline levels until 18–20 weeks after carbamazepine initiation .

As a consequence of the decline in the INR, the proportion of patients exposed to subtherapeutic INR levels was more than doubled, from 35% in the week preceding carbamazepine initiation to 79% in the fifth week of cotreatment (Fig. 3). The increased frequency of subtherapeutic INRs returned to baseline levels after 13 weeks of cotreatment.

After 1 week of cotreatment with carbamazepine and warfarin, 46% of the patients had not yet had a follow-up INR measurement performed. After 2 weeks and 3 weeks, the corresponding proportions were 21% and 11%, respectively.

To investigate the impact of warfarin dose on subsequent changes in INR values, we divided patients into those with a low (< 30 mg week^{-1}) and those with a high (≥ 30 mg week^{-1}) warfarin dose at baseline. Patients with a low dose had an INR of 1.74 after 4 weeks, returning to baseline levels by week 13. In the high-dose group, the INR was very similar, i.e. 1.82 after 4 weeks, but the INR did not return to baseline levels until week 18.

Warfarin dose

When we compared the daily dose of warfarin 28 days immediately before and 70–97 days after carbamazepine initiation, carbamazepine increased the warfarin dose requirements by 49.2% (95% CI 42.8–55.9).

The corresponding changes among men and women and in different age groups are shown in Table 1. The warfarin dose increase associated with carbamazepine treatment was evident in all subgroups, and, in the multivariable regression model, neither sex nor age was a significant modifier of the drug–drug interaction effect. The warfarin dose increase seen after carbamazepine initiation did not end until after approximately 15–17 weeks of cotreatment (Fig. 4).

Figure 5 shows the distribution of changes in warfarin dose requirements over 21 weeks of cotreatment. During this follow-up period, 82%, 59% and 17% of the patients experienced dose increases exceeding 25%, 50% and 100%, respectively.

The change in warfarin dose associated with carbamazepine exposure varied widely between individuals, but, in most patients, the dose increased by between 0% (i.e. no change) and 100% (Fig. 6). After patients had been divided into those with a low (< 30 mg week^{-1}) and those with a high (≥ 30 mg week^{-1}) warfarin dose at baseline, it was evident that carbamazepine treatment was associated with greater dose increases in the former group. Among patients with a low warfarin dose requirement, the dose increased by 61.4% (95% CI 52.1–71.3), as compared with 37.7% (95% Ci 29.6–46.4) in the high-dose group. The proportion of patients requiring dose increases by 100% or more was almost five times higher in the low-dose group (29% [20/70]) than in the low-dose group (6% [4/68]).

Discussion

In this study encompassing 166 patients, we found that carbamazepine initiation transiently increased the proportion of patients with a subtherapeutic INR below 2.0 from 35% to 79%. The subsequent increase in warfarin dose was highly variable, but amounted to a mean of 49%. Among patients with a low warfarin dose requirement, the dose was increased even more. Stable warfarin doses were not reached until 15–17 weeks after carbamazepine initiation.

Carbamazepine is an inducer of several cytochrome P450 enzymes [15,16], and it induces its own metabolism [17]. Although there are several case reports

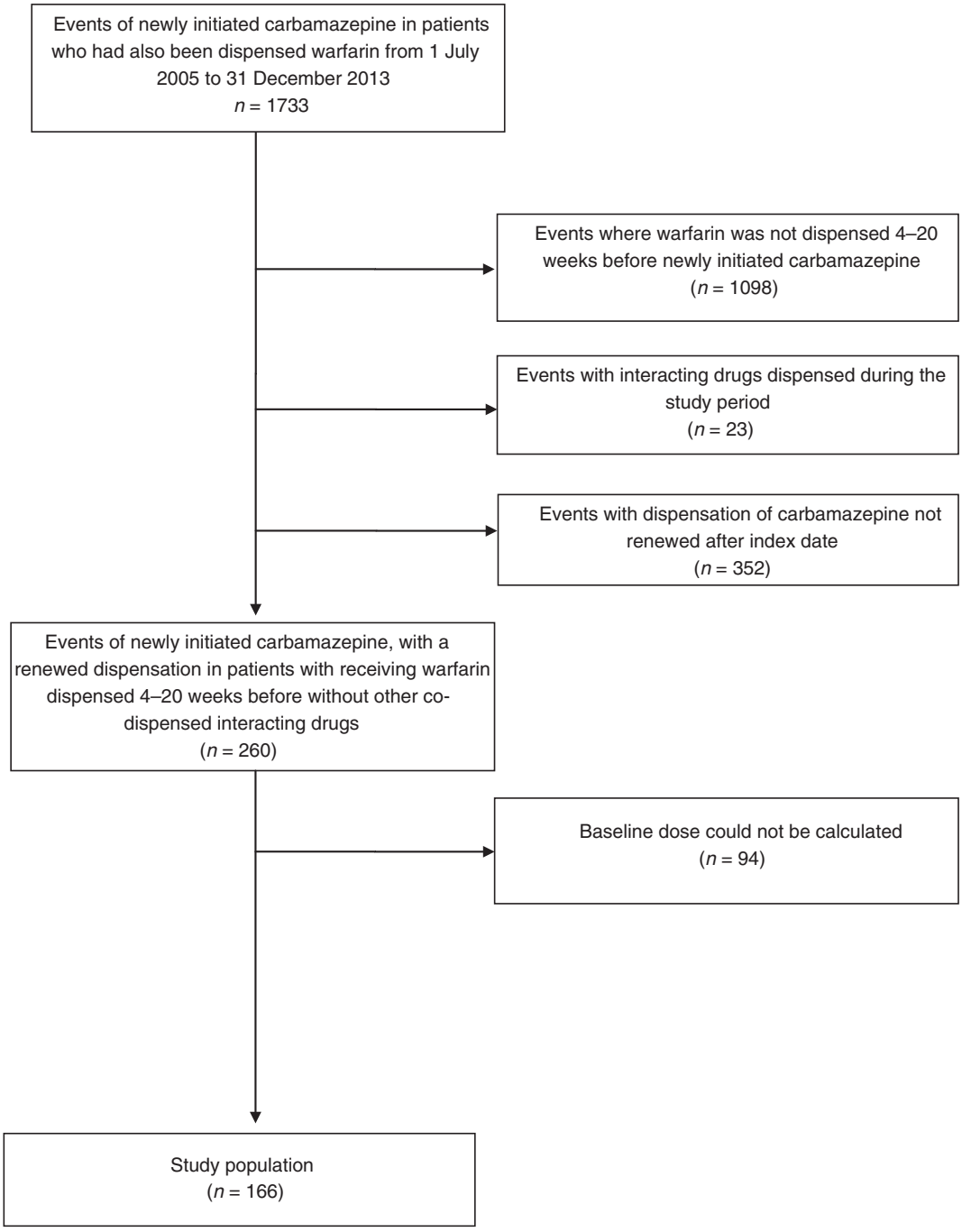

Fig. 1. Patient flow diagram.

on carbamazepine decreasing serum warfarin levels and shortening warfarin's half-life [3–6], more structured studies are scarce [7,8]. Herman *et al*. studied 82 patients receiving warfarin, with different cotreatments. The warfarin doses in five patients who were codispensed carbamazepine ranged from 6.2 mg day^{-1} to 12.0 mg day^{-1}, as compared with a median dose of 3.9 mg day^{-1} in patients receiving no interacting drugs [7]. By analyzing data from the Swedish Prescribed Drug Register, we recently suggested that the dispensed volumes of warfarin were increased by 37% in 1125 patients who were codispensed carbamazepine [8].

In contrast to previous studies, the longitudinal approach of the present nationwide investigation gave us excellent statistical power that enabled us to study the variability of the drug–drug interaction in the general population in more detail, as well as in different subsets of the population. The mean increase in warfarin dose was 49%, and large dose increases exceeding 100% were seen in 17% of the patients.

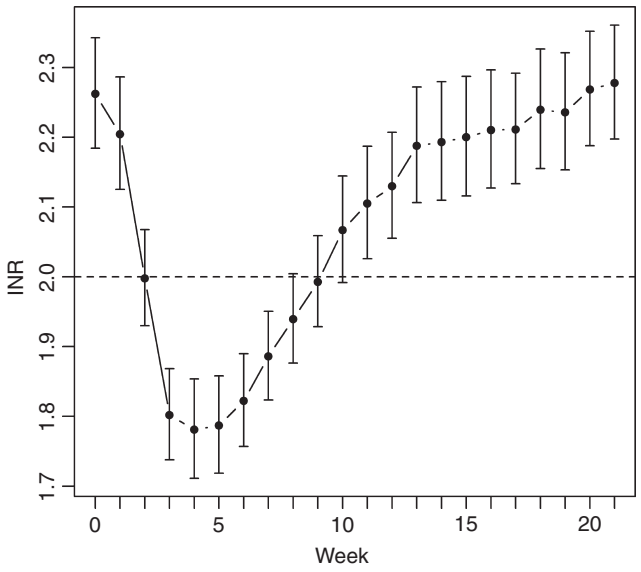

Fig. 2. Weekly mean International Normalized Ratio (INR) during cotreatment with warfarin and carbamazepine. The INR was interpolated to allow inclusion of weekly values for all patients. Brackets denote 95% confidence intervals.

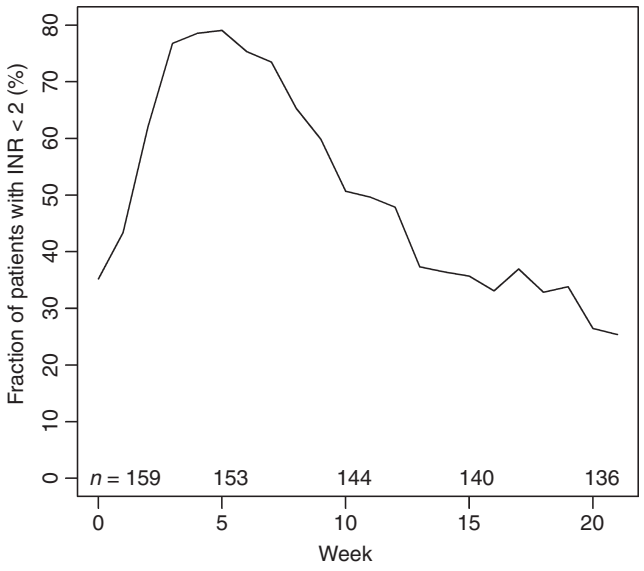

Fig. 3. Fraction of warfarin-treated patients with an International Normalized Ratio (INR) below 2.0 following carbamazepine initiation. The numbers at the bottom of graph indicate the number of patients remaining in the study (i.e. still cotreated with warfarin and carbamazepine) at different time points.

The relative increase in warfarin dose was largest in patients with a low baseline warfarin dose (< 30 mg week^{-1}). Theoretically, this could reflect increased inducibility of low-active cytochrome P450 2C9 (CYP2C9) variants predisposing to a low warfarin dose requirement, or a larger contribution of inducible enzyme pathways in patients with low drug clearance. There is no empirical evidence for these mechanisms, but a genotype-dependent drug interaction has previously been described for the CYP2C9*3 variant. In this case, codispensed simvastatin lowered warfarin dose requirements more effectively in individuals carrying the CYP2C9*3 allele [18].

Table 1 Warfarin dose increases associated with carbamazepine cotreatment

Group	*n*	Dose increase, % (95% CI)
< 65 years	38	41.0 (28.7–54.4)
≥ 65 years	128	51.9 (44.4–59.7)
Men	96	46.5 (39.0–54.3)
Women	70	53.0 (41.7–65.3)
All patients	166	49.2 (42.8–55.9)

CI, confidence interval.

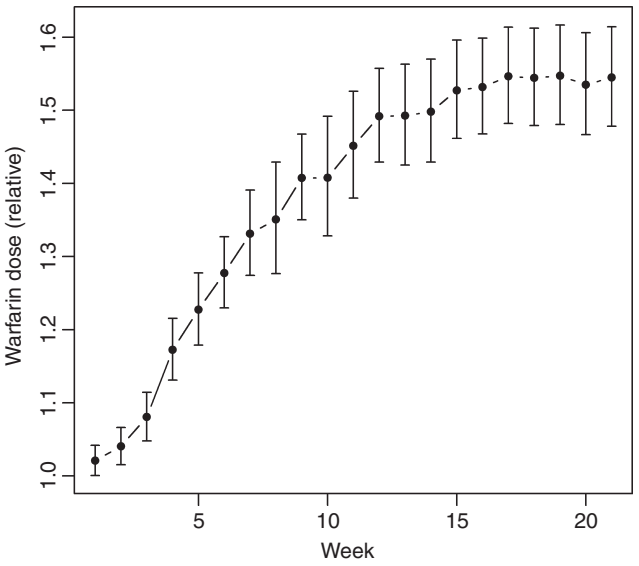

Fig. 4. Changes in prescribed warfarin dose during concomitant carbamazepine treatment (means and 95% confidence intervals).

The ability to address intraindividual rather than interindividual changes is an important strength of the current study. Not only does it improve the statistical power, but it also reduces the risk of confounding, as each individual was used as his or her own control. For example, although ethnicity may differ between two study subjects [19], it obviously remains constant within the same individual before and after carbamazepine initiation. Similarly, although body weight and body surface area may affect warfarin doses [7,20–24], they are likely to remain stable during the relatively short study period.

The study has a few potential weaknesses. The most important limitation concerns the register-based approach, which limits the information on other factors influencing the warfarin dose. Most importantly, the observational design makes it hard to control for confounding by indication, i.e. a situation where the indication for carbamazepine in itself has an influence on the warfarin dose requirements. Although the data have the

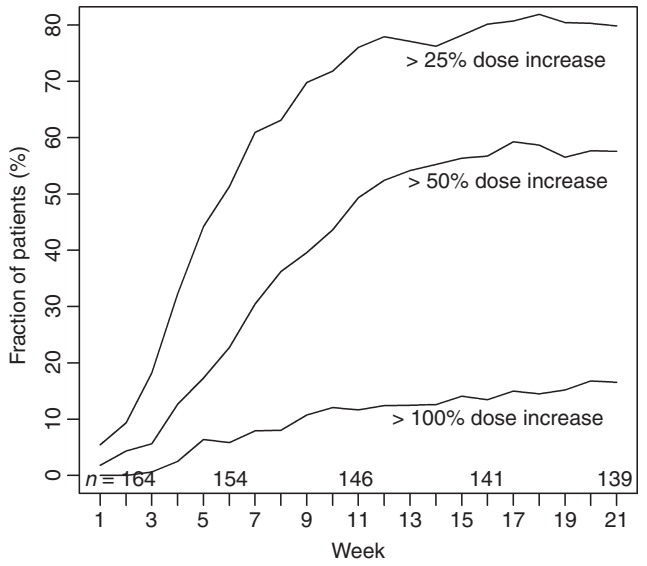

Fig. 5. Fraction of patients with warfarin dose increments of 25%, 50% and 100% during cotreatment with carbamazepine. The numbers at the bottom of graph indicate the number of patients remaining in the study (i.e. still cotreated with warfarin and carbamazepine) at different time points.

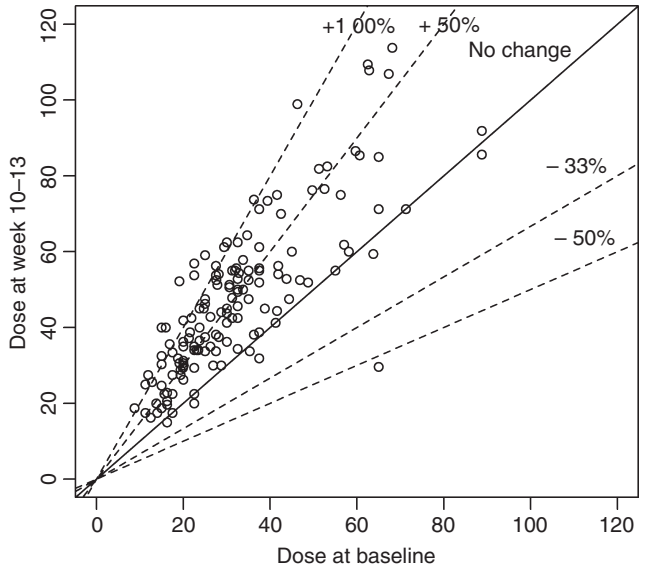

Fig. 6. Individual warfarin doses at baseline (1–4 weeks prior to carbamazepine initiation) and during weeks 10–13 of cotreatment with warfarin and carbamazepine. Lines indicate no change in warfarin dose, dose increases by 50% and 100%, and corresponding dose reductions by 33% and 50%.

advantage of representing dispensed rather than prescribed drugs, it was not possible to ascertain whether the medication was actually consumed through the whole study period. However, because of the inclusion of patients with a second dispensation of carbamazepine 60–120 days after the index date, we believe this bias to be small.

To ensure the inclusion of stable warfarin users with newly initiated carbamazepine who were not dispensed other potentially interacting drugs, only a relatively small percentage (166/1733) of the originally screened population was included in the analysis. Although this loss is methodologically justified, a selection bias cannot be excluded (Fig. 1). Furthermore, it is reasonable to believe that the amount of carbamazepine consumed probably affects the interaction with warfarin. However, in the present study, information on carbamazepine doses was unfortunately not accessible, and could therefore not be controlled for. Similarily, we did not have access to data on thromboses. Hence, the clinical impact of the drug–drug interaction could not be addressed directly, although it it is reasonable to assume that subtherapeutic INR levels would translate into an increased risk of thrombosis.

Full autoinduction is reached ~ 1 week after initiation or dose increase of carbamazepine [17]. Carbamazepine doses are usually increased for at least 2 weeks, and it may therefore take several weeks to reach a new warfarin steady-state concentration after carbamazepine initiation. However, the 15–17 weeks required to achieve stable warfarin doses in the current study was an unexpectedly long period. In addition, only approximately half of the patients had an INR measurement performed within a week of carbamazepine initiation, and one of 10 patients had not yet been monitored after 3 weeks of treatment with the potentially interacting drug. Together with the slow adaptation to increased dose requirements, these figures indicate that the prescribers' awareness of the drug–drug interaction is limited, exposing the patients to a significantly increased risk for thrombotic events [25]. As the enzyme induction increases gradually and the impact on the drug–drug interaction varies widely between individuals, it is not recommended to routinely increase the warfarin dose in patients starting cotreatment with carbamazepine. However, to adequately compensate for the anticipated increase in warfarin dose, the INR should clearly be monitored more closely than is currently the case. The optimal frequency has not been determined, but should – on the basis of our clinical experience – not fall short of once every 3–4 days during a period of at least 4–5 weeks or until INR values are stabilized. In patients whose INRs historically have been known to fluctuate more, and in individuals with a low baseline warfarin dose, even closer monitoring may be justified.

During this adaptation period, the prescribers should anticipate a need for warfarin dose increases. Consequently, they should not react to INR decreases with expectancy, but rather with prompt dose adjustments.

In conclusion, almost 80% of warfarin-treated patients starting cotreatment with carbamazepine experienced subtherapeutic anticoagulative effect within 3–5 weeks. The warfarin dose was subsequently increased by 49%, a

change that differed widely between different groups of patients. In order to avoid thrombosis and ischemic stroke, carbamazepine initiation should be accompanied by close INR monitoring to better meet the anticipated increase in dose demand.

Addendum

All authors contributed to study design and manuscript writing. B. Mannheimer, J. D. Lindh, and H. Järnbert-Pettersson were responsible for the analysis of data.

Acknowledgements

The study was supported by the Swedish Society for Medical Research and Bengt Ihres fond. J. D. Lindh was supported by the Stockholm County Council (clinical postdoctoral appointment). In addition, we wish to thank M. Fahlén and A. Odén for important advice regarding the use of the anticoagulation register Journalia.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

References

1 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK, Breckenridge AM. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; **329**: 15–19.
2 Fitzmaurice DA, Blann AD, Lip GY. Bleeding risks of antithrombotic therapy. *BMJ* 2002; **325**: 828–31.
3 Kendall AG, Boivin M. Warfarin–carbamazepine interaction. *Ann Intern Med* 1981; **94**: 280.
4 Hansen JM, Siersboek-Nielsen K, Skovsted L. Carbamazepine-induced acceleration of diphenylhydantoin and warfarin metabolism in man. *Clin Pharmacol Ther* 1971; **12**: 539–43.
5 Denbow CE, Fraser HS. Clinically significant hemorrhage due to warfarin–carbamazepine interaction. *South Med J* 1990; **83**: 981.
6 Massey EW. Effect of carbamazepine on coumadin metabolism. *Ann Neurol* 1983; **13**: 691–2.
7 Herman D, Locatelli I, Grabnar I, Peternel P, Stegnar M, Lainscak M, Mrhar A, Breskvar K, Dolzan V. The influence of co-treatment with carbamazepine, amiodarone and statins on warfarin metabolism and maintenance dose. *Eur J Clin Pharmacol* 2006; **62**: 291–6.
8 Andersson ML, Lindh JD, Mannheimer B. The impact of interacting drugs on dispensed doses of warfarin in the Swedish population: a novel use of population based drug registers. *J Clin Pharmacol* 2013; **53**: 1322–7.
9 Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, Persson I, Sundstrom A, Westerholm B, Rosen M. The new Swedish Prescribed Drug Register – opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007; **16**: 726–35.
10 Auricula. http://www.ucr.uu.se/auricula/ [cited 2015 September].
11 Journalia. http://www.journalia.se/ [cited 2015 September].
12 Bottiger Y, Laine K, Andersson ML, Korhonen T, Molin B, Ovesjo ML, Tirkkonen T, Rane A, Gustafsson LL, Eiermann B. SFINX – a drug–drug interaction database designed for clinical decision support systems. *Eur J Clin Pharmacol* 2009; **65**: 627–33.
13 Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993; **69**: 236–9.
14 R Core team. R: A language and enviroment for statistical computing, 2013. http://www.R-project.org/. Accessed 23 December 2015.
15 Jerling M, Lindstrom L, Bondesson U, Bertilsson L. Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. *Ther Drug Monit* 1994; **16**: 368–74.
16 Bertilsson L, Tybring G, Widen J, Chang M, Tomson T. Carbamazepine treatment induces the CYP3A4 catalysed sulphoxidation of omeprazole, but has no or less effect on hydroxylation via CYP2C19. *Br J Clin Pharmacol* 1997; **44**: 186–9.
17 Kudriakova TB, Sirota LA, Rozova GI, Gorkov VA. Autoinduction and steady-state pharmacokinetics of carbamazepine and its major metabolites. *Br J Clin Pharmacol* 1992; **33**: 611–15.
18 Andersson ML, Eliasson E, Lindh JD. A clinically significant interaction between warfarin and simvastatin is unique to carriers of the CYP2C9*3 allele. *Pharmacogenomics* 2012; **13**: 757–62.
19 Klein TE, Altman RB, Eriksson N, Gage BF, Kimmel SE, Lee MT, Limdi NA, Page D, Roden DM, Wagner MJ, Caldwell MD, Johnson JA. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 2009; **360**: 753–64.
20 Gurwitz JH, Avorn J, Ross-Degnan D, Choodnovskiy I, Ansell J. Aging and the anticoagulant response to warfarin therapy. *Ann Intern Med* 1992; **116**: 901–4.
21 James AH, Britt RP, Raskino CL, Thompson SG. Factors affecting the maintenance dose of warfarin. *J Clin Pathol* 1992; **45**: 704–6.
22 Hillman MA, Wilke RA, Caldwell MD, Berg RL, Glurich I, Burmester JK. Relative impact of covariates in prescribing warfarin according to CYP2C9 genotype. *Pharmacogenetics* 2004; **14**: 539–47.
23 Absher RK, Moore ME, Parker MH. Patient-specific factors predictive of warfarin dosage requirements. *Ann Pharmacother* 2002; **36**: 1512–17.
24 Dobrzanski S, Duncan SE, Harkiss A, Wardlaw A. Age and weight as determinants of warfarin requirements. *J Clin Hosp Pharm* 1983; **8**: 75–7.
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 Pharm* 2015; **37**: 53–9.