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ORIGINAL ARTICLE

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

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Essentials

- Data on the effect of introducing amiodarone in patients already using warfarin regime are scarce.
- Information on 754 patients was extracted from three nationwide registers in Sweden.
- With amiodaron, 37% of patients had an international normalized ratio (INR) over 3.0
- To avoid bleeding, the initiation of amiodarone should be accompanied by closer INR monitoring.

Summary. *Background:* Data indicate that the interaction between warfarin and amiodarone results in an increased warfarin effect. There are several large, well-performed studies using genetic and clinical factors such as co-medication to predict an adequate starting dose of warfarin. However, longitudinal data on the effect of introducing amiodarone in patients on an ongoing warfarin regime are more scarce. *Objectives:* An investigation of how initiation of amiodarone affects the anticoagulant effect and dosing of warfarin, using data from three nationwide registries. *Patients/Methods:* In a retrospective cohort study including 754 patients, warfarin doses were compared between two 4-week periods, before and 18–21 weeks after initiating co-treatment with amiodarone. In addition, warfarin doses and international normalized ratio (INR) values were calculated week-by-week after the initiation of amiodarone. *Results:* The initiation of amiodarone increased the mean INR from 2.6 to 3.1. The proportion of patients with a supratherapeutic INR over 3.0 and 4.0 increased from 12% to 37% and 0.9% to 5.5%, respectively. The subsequent mean decrease in warfarin dose was 24.6% (95% confidence interval [CI], 23.5, 25.6). The frequency of INR monitoring within 1 and 2 weeks after initiation of amiodarone was 67% and 90%. *Conclusions:* Although warfarin doses in most patients were within the therapeutic range, more than one in three patients initiating co-treatment with amiodarone were exposed to a supratherapeutic anticoagulative effect within 3 weeks. In order to further avoid severe unnecessary bleeding, the initiation of amiodarone should be accompanied by closer INR monitoring, anticipating an average dose reduction of 25%.

Keywords: amiodarone; cytochrome P-450 CYP2C9; drug interactions; International normalized ratio; warfarin.

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Introduction

Warfarin is an anticoagulant well known for its potential to interact with other drugs, sometimes with serious consequences [1,2]. Amiodarone is an effective class III antiarrhythmic agent used in patients with ventricular as well as supraventricular arrhythmias [3,4]. Amiodarone inhibits warfarin hydroxylation in a non-stereo selective manner, potentiating anticoagulation [5–7]. Because warfarin is used in stroke prevention for patients with atrial fibrillation, the drugs are frequently used concomitantly [8], sometimes resulting in severe bleedings [9]. There are several large, well-performed studies using genetic and clinical factors such as co-medication to predict an adequate starting dose of warfarin [10–12]. However, longitudinal data on the effect of introducing amiodarone in patients on an ongoing warfarin regime are more scarce [5,13–16]. The aim of the present study was to investigate how the anticoagulative effect of warfarin is affected by the initiation of amiodarone in a very large patient sample.

Methods

This retrospective cohort study investigated the effect of initiation of amiodarone treatment on international normalized ratio (INR) and warfarin dose requirements. Data on warfarin doses and INR were retrieved from the two warfarin monitoring registers Auricula and Journalia [17,18]. These medical records systems are used in more than 300 Swedish anticoagulation clinics and contain information on daily prescribed warfarin doses and INR values as well as the personal identification number, sex and age of the patients. Both Auricula and Journalia include anticoagulation used for the treatment of atrial fibrillation as well as for other diagnoses. Data on concomitant amiodarone treatment were retrieved from the Swedish Prescribed Drug Register, a nationwide drug dispensation register [19]. Information from the different data sources was linked by the personal identification numbers unique to each individual in Sweden. Patients aged ≥ 18 years, with a documented warfarin dispensation, who had initiated amiodarone treatment were eligible for inclusion. The index date of initiation of co-treatment with warfarin and amiodarone was defined as the date of first dispensation of amiodarone preceded by a period of at least 12 months during which no amiodarone had been dispensed in patients with ongoing warfarin treatment. Ongoing warfarin treatment was defined as the dispensation of warfarin during the period from 4 to 20 weeks preceding the index date. To avoid the inclusion of patients who stopped amiodarone treatment within the study period, a second and third dispensation of amiodarone within 60–120 and 150–210 days of the index date were also required for inclusion (in Sweden, each dispensation typically covers 3 months of drug use).

Patients who had been dispensed other interacting drugs concomitantly were excluded. Interacting drugs were defined as drugs that, according to the validated drug–drug interaction database SFINX [20], have a well-documented and clinically relevant effect on warfarin (changes in the INR or the area under the time-plasma concentration curve of warfarin exceeding 10%). Consequentially, patients were excluded if they had been prescribed and dispensed 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. Patients with missing information on dosing and INR values during the period −28 to −1 days before the index date were excluded because this would not allow analysis of the outcome measures. Finally, for individuals with more than one episode of amiodarone treatment fulfilling the inclusion criteria, only the first episode was included in the analysis.

To determine the change in INR after the initiation of amiodarone the Rosendaal interpolation method was used [21]. Values were log transformed and mean INR levels with 95% confidence intervals were calculated for 1 week before until 30 weeks after the index date. For each week the fraction of patients that had an INR > 3 and the fraction of patients with an INR > 4 were calculated.

We analyzed the difference between mean daily dose of warfarin at baseline during a 4-week period immediately prior to the index date (−1 to −28 days) and a 4-week period at a time-point after the index date when the interaction was expected to have had full effect (120–147 days). The change between the two periods in log-transformed dose was calculated and the mean difference was compared with zero (no change) in a two-sided dependent *t*-test. The mean difference was retransformed to provide the dose increase as a relative measure of effect. The impact of amiodarone on warfarin dose and the potential impact of age and sex on the association were further investigated by fitting a multiple linear regression model with change in (log-transformed) warfarin dose as the dependent variable. Age was analyzed in groups ranging between 18–49, 50–59, 60–69, 70–79, 80– 89 and 90–100 years. The inter-individual variability in impact of the interaction was visualized by plotting each individual patient's baseline dose against the corresponding dose recorded after initiation of amiodarone, at 120–147 days.

To create a descriptive analysis of the interaction over time, mean normalized warfarin dose was calculated for each week. In each patient, normalization of the doses was carried out by dividing all doses by the patient's baseline dose. The reason for this normalization was 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) [22]. Calculations of the fraction of patients in whom the warfarin dose decreased by > 10%, > 25% or > 50% from baseline were carried out for each week of the study period (these fractions were calculated separately for each week, not as a cumulative fraction). Patients were also divided into groups with baseline dose of < 33 mg and ≥ 33 mg, respectively. The primary analysis was then repeated for the two groups separately to evaluate whether baseline warfarin dose requirements influenced the relative dose decrease associated with amiodarone exposure. The proportion of patients that had not yet been subject to a follow-up INR measurement at 1, 2 and 3 weeks of concomitant treatment was calculated to give an estimation of prescribers' awareness of the potential interaction effect and consequentially their action to monitor it. *P*-values of < 0.05 were considered statistically significant. Analyses were performed with IBM SPSS STATISTICS 22.0 (SPSS, Chicago, IL, USA) and R version 2.0.3 [23].

Results

In total, 5446 events from the period 1 July 2005 to 31 December 2012 were identified where amiodarone

treatment had been initiated in a patient who had also been dispensed warfarin. Events were excluded where there was no dispensation of warfarin 4–20 weeks before initiation of amiodarone (n = 2328), or where the dispensation of amiodarone was not renewed twice after the index date (n = 1955), or where the patient simultaneously received drugs other than amiodarone that interact with warfarin (n = 252). Furthermore, patients with incomplete warfarin dose data (n = 148) were excluded. Finally, events that constituted repeated episodes of amiodarone initiation were excluded, resulting in a study population of 754 unique individuals to be further analyzed (Fig. 1).

The median age (range) of the included patients was 67 years (23–90 years) and 30.5% were female.

INR

After the initiation of amiodarone (index date) mean INR increased markedly, peaking 3 weeks after initiation of amiodarone therapy at 3.07 (95% CI, 3.01–3.13). During the subsequent weeks INR gradually declined and

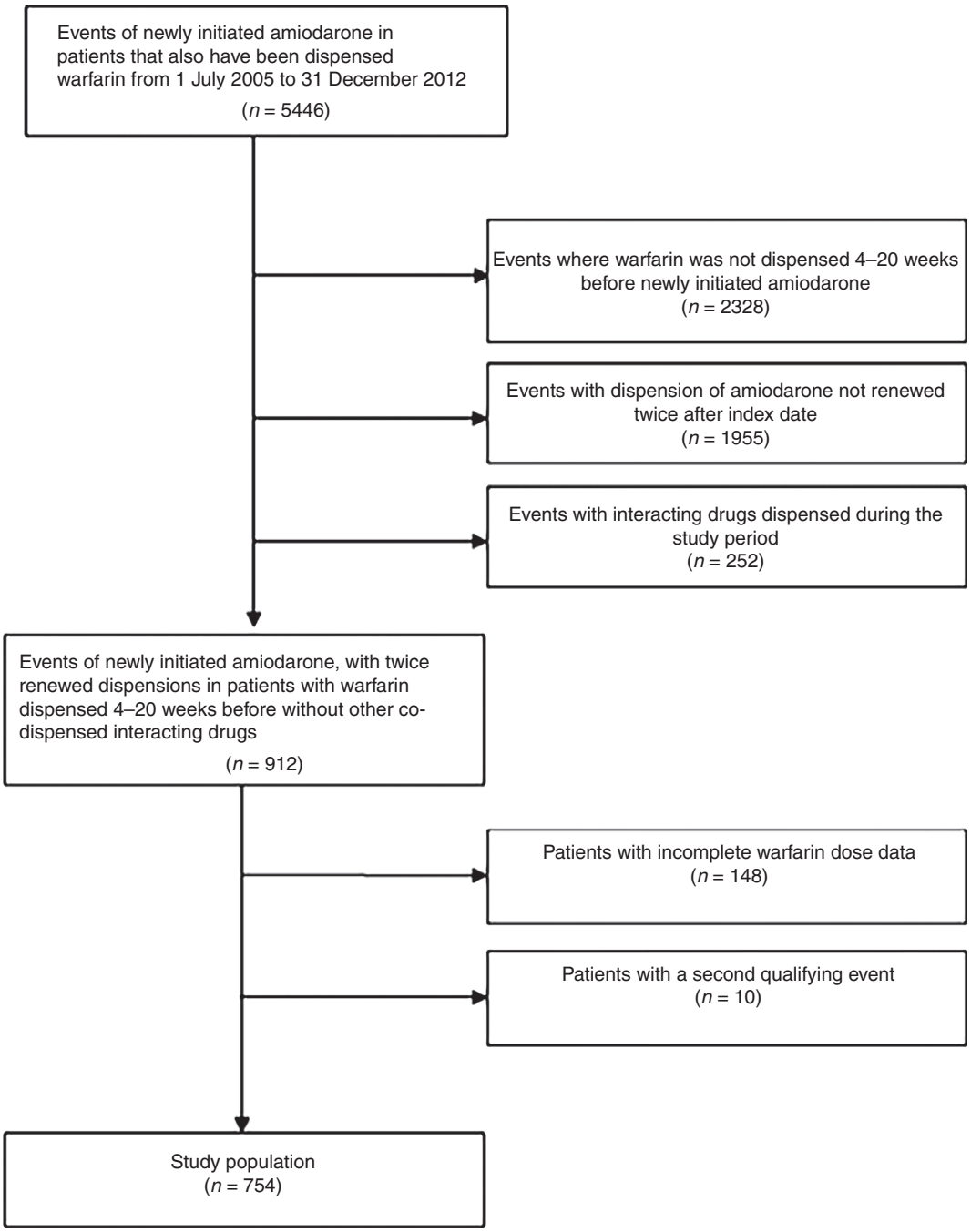

Fig. 1. Patient flow diagram.

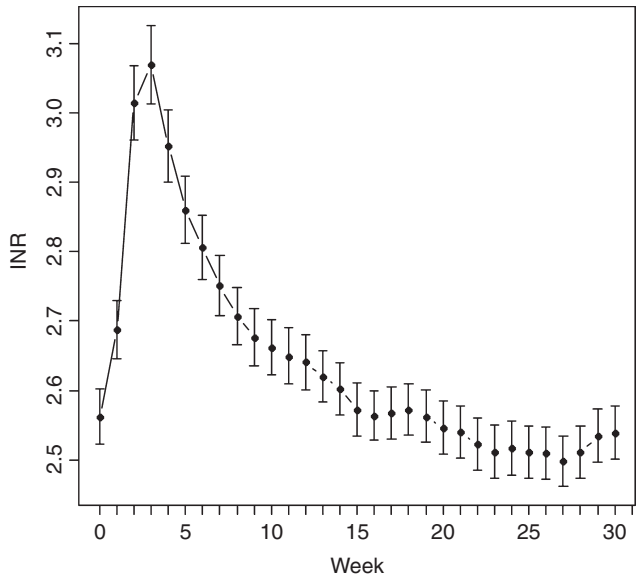

Fig. 2. Weekly mean international normalized ratio (INR) during co-treatment with warfarin and amiodarone. The INR was interpolated to allow inclusion of weekly values for all patients. Brackets denote 95% confidence intervals.

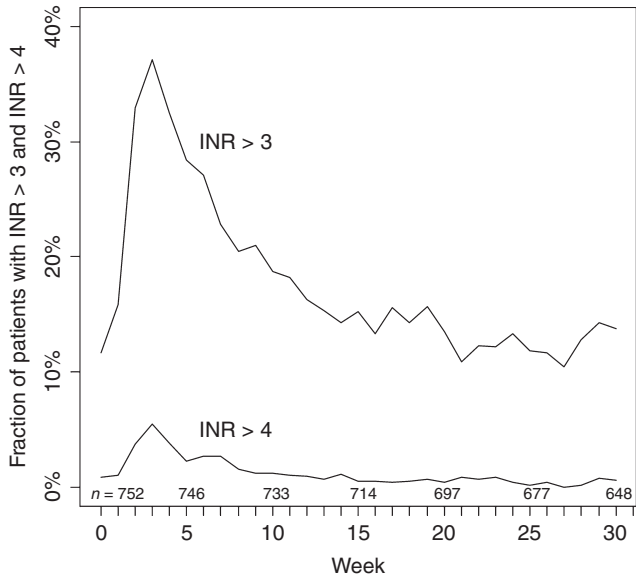

Fig. 3. Fraction of patients with an international normalized ratio (INR) over 3.0 following amiodarone initiation. The numbers at the bottom of the graph indicate the number of patients remaining in the study (i.e. still co-treated with warfarin and amiodarone) at different time-points.

returned to baseline after approximately 25 weeks (Fig. 2). The fraction of patients exposed to an INR above the therapeutic interval increased from 11.7% at the index date to a maximum level of 37.1% during the third week and then slowly decreased. At weeks 15–20 the fraction of patients exposed to INR above the therapeutic interval had returned close to baseline (Fig. 3). In parallel, the fraction of patients exposed to INR levels above 4 increased from 0.9% at baseline to 5.5% during the third week and returned to baseline levels by week 12. The proportion of patients in whom INR had been measured within 1, 2 and 3 weeks after initiation of amiodarone was 67%, 90% and 96%, respectively.

Warfarin dose

The mean baseline warfarin dose per week was 34.6 mg. During the 4-week period 120–147 days after the start of concomitant treatment the warfarin dose was 24.6% (95% CI, 23.5–25.6%; $P < 0.001$) lower than the baseline dose ($n = 712$). In a multivariable regression model, the effect of amiodarone on warfarin dose requirements did

Table 1 Warfarin dose decreases associated with amiodarone co-treatment

Group	*n*	Dose decrease (95% CI)
< 65 years	284	23.0% (21.5, 24.6)
≥ 65 years	428	25.6% (24.2, 26.9)
Men	497	24.4% (23.2, 25.5)
Women	215	25.1% (23.0, 27.1)
All patients	712	24.6% (23.5, 25.6)

CI, confidence interval.

not differ between men and women, or between different age groups. Changes in dose requirements for men, women and for different age groups are shown in Table 1. A visualization of the inter-individual variability of the impact on dose requirements is given in Fig. 4. The vast majority had a reduction of the warfarin dose between 0 and 50%. Figure 5 illustrates how the normalized warfarin dose changed week by week after initiation of amiodarone treatment. A marked dose reduction was seen during the first 5 to 10 weeks and after 15 weeks a new stable dose had been achieved in most patients. Figure 6 shows the fraction of patients who had a > 50%, > 25% and > 10% dose decrease; 3.1%, 55.1% and 87.1% of patients, respectively (peak values during follow-up). A high and low baseline warfarin dose (≥ 33 mg week-1) were associated with similar dose reductions after initiation of amiodarone treatment. Patients with a high and low baseline dose requirement had 25.5% (95% CI, 24.1–26.8%) and 23.7% (95% CI, 22.1–25.3%) reduction in warfarin dose associated with initiation of amiodarone treatment, respectively.

Discussion

In the present study, involving 754 patients, we found that the initiation of amiodarone transiently increased the mean INR from 2.6 to 3.1. The proportion of patients with a supratherapeutic INR over 3 increased 3-fold from 12% to 37%. The proportion with an INR > 4 increased even more (6-fold), from 0.9% to 5.5%. The subsequent mean decrease in warfarin dose was 25%.

There are several well-performed studies using genetic and clinical factors such as co-medication to predict an adequate starting dose of warfarin [10–12]. However, longitudinal data on the effect of introducing amiodarone in patients on a stable warfarin regime are scarce. Sanoski *et al.* investigated the initiation of different maintenance doses of amiodarone in 43 patients on warfarin. However, because of the prospective design and explicit efforts to keep INR stable within the study frame, contrasting to our retrospective and naturalistic approach, no effect with regard to changes in INR was noted during the follow-up [14]. Lu *et al.* investigated 70 patients on concurrent warfarin and amiodarone treatment retrospectively. The study showed a relative risk for individuals on combined

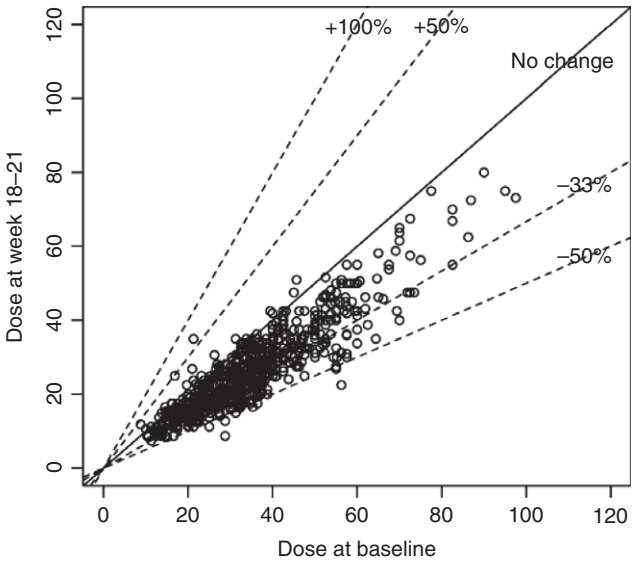

Fig. 4. Individual warfarin doses at baseline (1–4 weeks prior to amiodarone initiation) and during weeks 18–21 of co-treatment with warfarin and amiodarone. Lines indicate no change in warfarin dose, dose increases by 50% and 100%, and corresponding dose reductions by 33% and 50%.

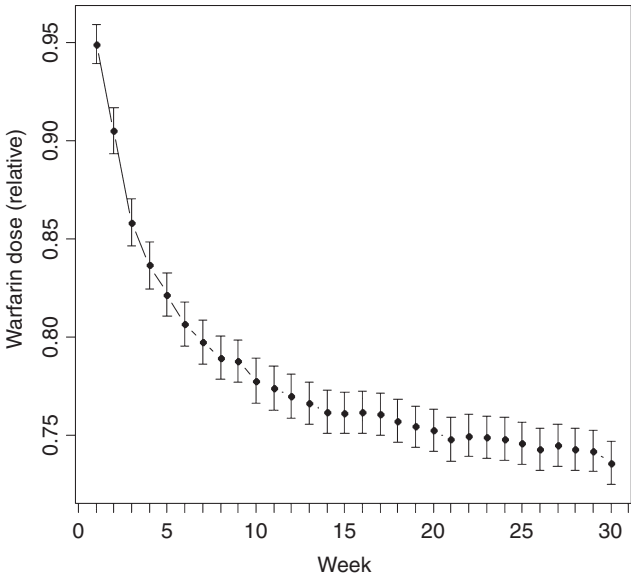

Fig. 5. Changes in dispensed warfarin dose during concomitant amiodarone treatment (means and 95% confidence intervals).

treatment of 1.36 for reaching a supratherapeutic INR of > 5 as compared with individuals on warfarin alone. Although the study showed that the risk was most pronounced during the first 12 weeks of amiodarone treatment it was not possible to stratify the risk within this time period [13].

The present investigation of the Swedish population confirms an elevated risk of supratherapeutic INR values during the first 12 weeks and, importantly, indicates that

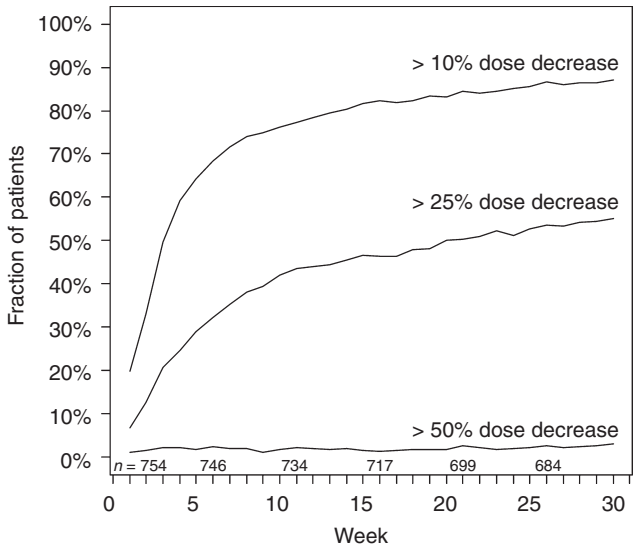

Fig. 6. Fraction of patients with warfarin dose decreases of > 10%, > 25% and > 50% during co-treatment with amiodarone. The numbers at the bottom of the graph indicate the number of patients remaining in the study (i.e. still co-treated with warfarin and amiodarone) at different time-points.

this risk peaks 3 weeks after initiation of amiodarone (Fig. 3). This illustrates the importance of close monitoring of INR after initiating amiodarone in patients on warfarin. With the intent to describe monitoring of anticoagulation we investigated the proportion of patients that had their INR checked during the first few weeks following initiation of amiodarone. One-third of the patients did not have INR measured within a week of amiodarone initiation, and one out of 10 patients had not yet had their INR monitored after 2 weeks of treatment with the potentially interacting drug. Although indicating a fair degree of monitoring, these results suggest that some prescribers' awareness of the interaction may be limited, exposing patients to an unnecessary risk of adverse bleedings.

In the present study, the mean reduction in warfarin dose, 25 weeks after the initiation of amiodarone, was 25%. Our results are roughly in accordance with some previous studies [5,11,14] but not all [15,16,24]. The divergence may be explained by various factors, such as differences in study design, local traditions of clinical monitoring and maintenance doses of amiodarone. Furthermore, some of the variation may be a result of chance as a few of the above studies were rather small. The prospective study by Sanoski *et al.* is interesting as the decrease in warfarin dose was 44% after only 7 weeks. After 12 months, the decrease in warfarin dose compared with baseline was only 19%. The substantially larger initial interaction effect is remarkable but may reflect the use of a rather large loading dose of amiodarone of approximately 900 mg/day, and a subsequent prompt increase in warfarin dose, followed by a more modest maintenance dose below 250 mg day^{-1}. Decreased compliance with the prescribed amiodarone may be another explanation [14]. Although the levels of warfarin doses were not quantified in the paper by Lu *et al.*, it interestingly indicates a similar pattern [13]. The opposite progression seen in our study with warfarin doses that continues to decrease throughout the study period may in part reflect a delay in response to the elevated INR seen in the corresponding time period.

The frequency of INR monitoring within the first and second week after initiation of amiodarone was 67% and 90%. The results are in contrast to our recently published data on anticoagulation after initiating carbamazepine, another drug with a large potential to interact with warfarin, where the corresponding figures were 54% and 79% [22]. The results may therefore indicate a greater awareness of the risk of initiating amiodarone, decreasing the proportion of patients exposed to increased anticoagulation in the Swedish population. However, a considerable proportion of patients is still exposed to supratherapeutic INR and there is a clear need for closer monitoring and timely dose adjustment after the initiation of amiodarone. The optimal frequency of monitoring has not been determined but may, based on our clinical experience, come close to once every 3 to 4 days until INR values are stabilized. During this adaptation period, prescribers should expect a need for warfarin dose decreases. Preemptive decreases in doses of between 25% and 65% have been suggested [14–16]. Although, keeping the large inter-individual variability in mind, it may be difficult to state a fixed dose adjustment, the present data suggest a mean reduction of 25%.

The large size of the study is an advantage resulting in higher precision with narrow confidence intervals and a clear description of the longitudinal progression of INRs and warfarin doses. The ability to address intra- rather than inter-individual changes is an important strength of the current study. Not only does this improve statistical power, it also reduces the risk of confounding as each individual was used as his/her own control. For example, although ethnicity may differ *between* two study subjects [10], it obviously remains constant for each individual and does not influence analyses.

There are some relevant limitations to consider. Using register data limits the amount of information available for each patient. For example, although the utilized drug register has the advantage of providing data on dispensed rather than prescribed drugs, the actual level of adherence to the medication cannot be determined. However, by including only patients with a second and third dispensation of amiodarone we believe that the level of adherence in the analyzed cohort is markedly increased. Furthermore, information on amiodarone dose could not be included in the analysis, which is a limitation of this study to some extent. Other studies have shown amiodarone dose to be inversely correlated with warfarin dose [14,24].

However, the initiation of amiodarone in Sweden is strictly standardized. Thus, for orally administrated amiodarone, used for most individuals with atrial fibrillation (the indication for the majority of individuals co-medicating with amiodarone), in the first and second week, daily loading doses of 600 and 400 mg are recommended. From week three a maintenance dose of 200 mg a day is dispensed to the vast majority of patients [25]. Consequently, the initial progression of INR and dose levels is likely to reflect the effect of the loading dose, whereas the subsequent decrease in warfarin dose at 25 weeks mirrors that of a maintenance dose of about 200 mg of amiodarone. To ensure only the inclusion of stable warfarin users with a new initiation of amiodarone who were not dispensed other potentially interacting drugs, a relatively small proportion of the originally screened population (754 of 5446) was included in the analysis. Although this loss is methodologically justified, a selection bias cannot be excluded. For example, some patients may possibly have quit amiodarone treatment because of a more severe interaction between amiodarone and warfarin. If this is the case, the magnitude of the interaction could theoretically have been underestimated.

Finally, the databases used in the study did not include information on bleeding events in the cohort and consequentially we could not analyze the clinical impact of the interaction effect (see Fig. 1). However, it is reasonable to assume that exposure to an INR above the therapeutic interval entails an increased risk of bleeding, and indeed the concomitant use of warfarin and amiodarone has been associated with an increased risk of bleeding-related hospitalizations [9].

In conclusion, although warfarin doses in most patients were adequately adjusted, more than one in three patients initiating co-treatment with amiodarone was exposed to a supratherapeutic anticoagulant effect within 3 weeks. In order to further avoid unnecessary severe bleedings, the initiation of amiodarone should be accompanied by closer INR monitoring, anticipating an average dose reduction of 25%.

Addendum

All authors contributed to the study design and the writing of the manuscript. B. Mannheimer and J. Lindh were responsible for the analysis of data.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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