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The risk of overanticoagulation in patients with heart failure on coumarin anticoagulants

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Summary

Heart failure has been identified as a risk factor for increased coumarin anticoagulant responsiveness in several small-scale experiments. Epidemiological studies quantifying the risk of overanticoagulation by heart failure in a non-selected population on coumarins are scarce. Therefore, we investigated whether patients with heart failure have an increased risk of overanticoagulation and determined the effect of incidental heart failure on coumarin dose requirements. A cohort study of all patients was performed from an outpatient anticoagulation clinic treated with acenocoumarol or phenprocoumon between 1 January 1990 and 1 January 2000. All cohort members were followed until the first occurrence of an international normalized ratio (INR) ≥6·0, the last INR assessment, death, loss to follow-up, or end of the study period. Of the 1077 patients in the cohort, 396 developed an INR ≥6·0. The risk of overanticoagulation was 1·66 [95% confidence interval (CI): 1·33–2·07] for cases of prevalent heart failure and 1·91 (95%CI: 1·31–2·79) for incidental cases. The decrease in dose requirements in patients with incidental heart failure showed a significant trend from the fifth INR measurement preceding the date of incidental heart failure to the third measurement after this date. Heart failure is an independent risk factor for overanticoagulation. Therefore, patients with heart failure should be closely monitored to prevent potential bleeding complications.

Keywords: acenocoumarol, cohort study, heart failure, overanticoagulation, phenprocoumon.

Coumarin anticoagulants are used in the primary and secondary prophylaxis of thromboembolic disease (British Committee for Standards in Haematology, 1998). They inhibit the production of the vitamin K-dependent coagulation factors by the liver (Sadowski *et al*, 1996). Inherent to their mode of action and narrow therapeutic range, haemorrhage is the most common adverse reaction to coumarin anticoagulants. The risk of haemorrhage is strongly associated with the intensity of anticoagulation and sharply increases when the international normalized ratio (INR) ≥6·0 (Cannegieter *et al*, 1995; Van der Meer *et al*, 1996). A number of comorbid conditions are suspected to enhance the response to coumarin anticoagulants (O'Reilly & Aggeler, 1970; Hirsh *et al*, 2001). Heart failure was identified as a risk factor for increased coumarin responsiveness in some small-scale experiments (groups of up to 30 patients) in the late 1940s (Stats & Davison, 1949; Covert, 1952). The mechanism has not been fully elucidated but it is speculated that increases in coumarin responsiveness are associated with hepatic congestion and redistribution of body fluids (Stats & Davison, 1949; Covert, 1952; Killip & Payne, 1960; O'Reilly & Aggeler, 1970; Bachmann & Shapiro, 1977). Epidemiological studies quantifying the risk of overanticoagulation by heart failure in a non-selected population on coumarins are scarce. A recent case–control study suggested that patients with heart failure had an increased risk of an INR ≥6·0 (Penning-van Beest *et al*, 2001). In that study, however, the presence of chronic comorbidities was only based on the diagnoses of general practitioners and no cases of incidental heart failure were included. Therefore, we conducted a follow-up study in a large population-based cohort among outpatients of an anticoagulation clinic on acenocoumarol or phenprocoumon. We studied the association between heart failure and overanticoagulation and determined the effect of heart failure on the coumarin dosage.

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Methods

Setting

Data were obtained from the Rotterdam Study and from the regional outpatient anticoagulation clinic. The Rotterdam Study is a prospective population-based cohort study in 7983 subjects of 55 years and older and has been approved by the Medical Ethics Committee of the Erasmus Medical Centre (Hofman *et al*, 1991). The baseline examination was conducted between 1990 and 1993, during which information was obtained on age, gender, smoking, body mass index (BMI), medication use, blood pressure and verified history of heart failure. Participants have been continuously monitored for major events that occurred during follow-up, including heart failure, through automated linkage with files from general practitioners. Information on vital status was also obtained regularly from municipal health authorities in Rotterdam. Furthermore, all drug prescriptions dispensed to participants by automated pharmacies were routinely stored in the database.

The anticoagulation clinic monitors all inhabitants of Ommoord with an indication for anticoagulant therapy. The choice of anticoagulant was made by the physician. The optimal target range of coumarin anticoagulant therapy, as recommended by the Federation of Dutch Thrombosis Centers, lies between 2·5 and 3·5 INR or between 3·0 and 4·0 INR, depending on the indication for treatment. Some patients are targeted at a level between 2·0 and 2·5 INR because of contraindications. Prothrombin times were monitored at 1–6-week intervals by reference to the INR, dependent on the stability of the anticoagulant level. Doses were adjusted on the basis of the target range of the INR of the patient by computerized dose calculations.

Cohort and outcome definition

The study cohort consisted of all participants of the Rotterdam Study who were treated with acenocoumarol or phenprocoumon in the study period between the baseline visit and 1 January 2000 and for whom INR data were available. If a patient had multiple treatment periods during the study period, only the first period after the baseline examination was considered. The cohort included patients on coumarin anticoagulants without heart failure, patients on coumarins with prevalent heart failure at baseline and patients on coumarins who developed heart failure during the study period (incidental cases). All cohort members were followed-up as of their baseline examination for patients without heart failure and for cases of prevalent heart failure, and from the date of incidental heart failure for incidental cases until the earliest of an INR ≥6·0, death, loss to follow-up, or 1 January 2000. In cases where the date of incidental heart failure was not during a treatment period with coumarins, follow-up started at the first day of the next treatment period and heart failure was classified as prevalent. The index date was defined as the point in time at which one of the endpoints occurred for a participant of this study. The effect of heart failure on the coumarin dosage was determined by calculating the average weekly dosage per INR measurement for the subsequent measurements after start of follow-up. This was carried out separately for prevalent and incidental cases of heart failure and for the rest of the cohort, and for both acenocoumarol and phenprocoumon. For the incidental cases of heart failure, for which the follow-up started at the date of incidental heart failure, we also studied the course of the coumarin dosage from the 10th INR measurement preceding this date.

Heart failure assessment

Assessment of prevalent heart failure at baseline has been described in detail (Mosterd *et al*, 1999). Cases of incidental heart failure were obtained by continuously monitoring participants of the Rotterdam Study for the occurrence of heart failure during follow-up through automated linkage with files from general practitioners. All available data on these events, such as hospital discharge letters and notes from general practitioners, were copied from the medical records. Apart from this systematic follow-up procedure, we used verified hospital discharge diagnoses for case finding, gathered from all hospitals in the Rotterdam area. The definition of heart failure was based on the criteria of the European Society of Cardiology, which include the presence of typical symptoms of heart failure, such as pulmonary crepitations, and objective evidence of cardiac dysfunction (Remme & Swedberg, 2001).

Cofactors

The following baseline patient characteristics were considered as potential determinants for affecting the response of the INR to coumarin anticoagulants: gender, age, CYP2C9 genotype, hepatic dysfunction (defined as serum aminotransferases >2× the upper level of normal), hypoalbuminaemia (≤35 g/l), malignancies, hyperthyroidism, hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or use of antihypertensives) and low dietary intake of vitamin K (<1 μg/kg/d). In addition, we considered the type of anticoagulant, the indication for therapy, the target INR level, the number of visits to the anticoagulation clinic during the follow-up period, and the use of thiazides or non-steroidal anti-inflammatory drugs (NSAIDs) on the index date as potential confounding factors. Separate analyses were performed for prevalent and incidental cases of heart failure.

Statistical analysis

Allele and genotype proportions were tested for deviations from Hardy–Weinberg equilibrium (HWE) by using a chi-squared test. Independent-sample *t*-tests and Pearson's chi-square were used to compare baseline characteristics between

prevalent or incidental heart failure cases and patients without heart failure. Incidence rates of overanticoagulation were calculated by dividing the number of cases of an INR ≥6·0 by the number of days on a coumarin anticoagulant. The association between heart failure and overanticoagulation was evaluated using Cox proportional hazards regression analysis to estimate relative risks (RR) and 95% confidence intervals (95%CI). To adjust for potential confounding, cofactors were included in the model, in addition to age and gender, if the point estimate changed by >5% upon inclusion of the cofactor in the model. For missing data on categorical covariates, we used a missing value indicator, whereas for missing data on continuous covariates, we used the median value of the respective value as calculated from the total sample. To evaluate the effect of incidental heart failure on the coumarin dosage, a trend test was performed using a linear regression model with the mean dosage as outcome variable. For all statistical analyses $P < 0{\cdot}05$ were considered to be statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 11.0.1 (SPSS Inc., Chicago, IL, USA).

Results

A total of 1077 individuals on coumarin anticoagulants were included in our study population (Table I). The mean age of these patients was almost 72 years, and 47·4% of the patients were men. All patients were white people. There were 636 patients (59·1%) with the wild type CYP2C9 genotype (CYP2C9*1/*1 homozygotes), and 323 (30·0%) with a variant genotype (one or two of the mutant alleles CYP2C9*2 or CYP2C9*3). Allele and genotype proportions were in HWE. There were 915 acenocoumarol-treated patients (85·0%), and 162 patients (15·0%) who used phenprocoumon. Twenty-five patients (2·3%) were targeted at an INR between 2·0 and 2·5, 368 patients (34·2%) at an INR between 2·5 and 3·5, and 684 patients (63·5%) at an INR between 3·0 and 4·0. Patients had a median of 29 INR assessments during a median follow-up time of 245 days (0·7 years).

There were 234 cases of prevalent and 66 cases of incidental heart failure identified during the study period. Patients with prevalent heart failure were significantly older and more likely to be male than patients without heart failure. They were more often treated with phenprocoumon, were more often targeted at the highest INR level and had their INR more frequently measured. Patients with incidental heart failure were significantly older, were more often targeted at the highest INR level and were more likely to have hypoalbuminaemia than patients without heart failure. Patients without heart failure used coumarins more often for prophylaxis and treatment of venous thrombosis, while patients with prevalent and incidental heart failure had more often an arterial indication for coumarin anticoagulant therapy.

During the study period, 396 of the 1077 individuals (37%) had an INR ≥6·0. Of the 234 prevalent cases of heart failure, 131 individuals (56%) experienced an INR ≥6·0, and of the 66 incidental heart failure cases 32 individuals (48%) were overanticoagulated. Table II presents relative risk estimates for the association between prevalent and incidental heart failure and overanticoagulation. Prevalent and incidental heart failure were both univariately, and after adjustment for confounding factors, associated with an increased risk of overanticoagulation.

Figure 1 shows the mean weekly dosage of acenocoumarol for the subsequent INR measurements after the start of the follow-up. Patients with prevalent and incidental heart failure used lower dosages than patients without heart failure, in spite of the higher target INR levels for patients with heart failure. Patients with incidental heart failure had even lower acenocoumarol dose requirements than patients with prevalent heart failure. As this difference did not disappear in the course of time, this probably reflects the difference in indication and target INR level. Similar features were identified for

Table I. Characteristics of the study population.

Variable	Number of patients ($n = 1077$)
Gender	
Male	511 (47·4%)
Female	566 (52·6%)
Age [average (SD)] (years)	71·8 (7·9)
CYP2C9 genotype*	
Wild type genotype†	636 (59·1%)
Variant genotype‡	323 (30·0%)
Type of anticoagulant	
Acenocoumarol	915 (85·0%)
Phenprocoumon	162 (15·0%)
Indication	
Prophylaxis venous thrombosis	227 (21·1%)
Treatment of venous thrombosis	368 (14·0%)
Treatment or prophylaxis of arterial thrombosis	673 (62·4%)
Prosthetic heart valves	25 (2·3%)
Target INR level	
2·0–2·5	25 (2·3%)
2·5–3·5	368 (34·2%)
3·0–4·0	684 (63·5%)
Time between visits (d ± SD)	11·9 ± 16·3
Hepatic dysfunction	12 (1·1%)
Hypoalbuminaemia	2 (0·2%)
Malignancies	123 (11·4%)
Hyperthyroidism	37 (3·4%)
Hypertension	422 (39·2%)
Low intake of vitamin K	16 (1·5%)
Use of thiazides§	4 (0·4%)

*Totals do not add up to 100% because of missing genotypes.
†CYP2C9*1/*1 homozygotes.
‡Patients with one or more of the variant alleles CYP2C9*2 or CYP2C9*3.
§Assessed by reference to the index date.

	No.	Events (*n*)	IR*	RR_{crude} (95%CI)	$RR_{adj.}$† (95%CI)
Patients without heart failure	777	233	5·19	1·00 (reference)	1·00 (reference)
Prevalent heart failure	234	131	9·82	1·84 (1·48–2·28)	1·66 (1·33–2·07)
Incidental heart failure	66	32	11·78	1·97 (1·36–2·86)	1·91 (1·31–2·79)

Table II. Relative risks for the association between heart failure and overanticoagulation.

*The incidence rate is expressed as the number of cases of overanticoagulation per 10 000 d on a coumarin anticoagulant.

†Adjusted for gender, age and target INR level.

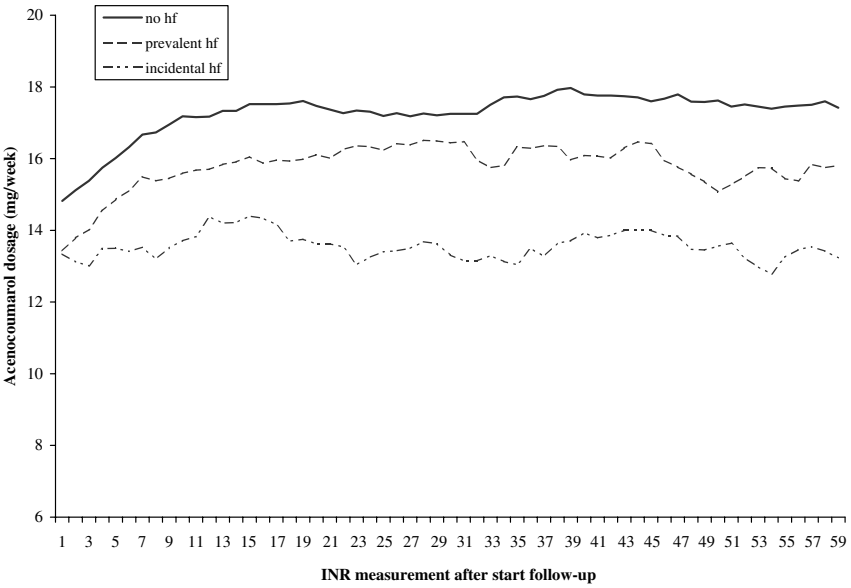

Fig 1. Course of the mean weekly acenocoumarol dosage over time. hf, heart failure.

phenprocoumon. For patients with incidental heart failure the decrease in dosage started, on average, at the fifth INR measurement preceding the incident date and lasted until the third INR measurement after the incident date. A trend test revealed a significant dosage decrease between the subsequent INR measurements of 0·23 mg/week for acenocoumarol (P for trend <0·001) and 0·34 mg per week for phenprocoumon (P for trend <0·001).

Discussion

The current study identified heart failure as an independent risk factor for excessive anticoagulation under everyday circumstances. Patients with heart failure had a 1·5-fold to twofold increased risk of an INR ≥6·0. Our results are in accordance with the study of Penning-van Beest *et al* (2001), who found an OR of 1·6 (95%CI: 1·04–2·6) in stable condition and an OR of 3·0 (95%CI: 0·8–12·0) in case of a relapse.

This increased coumarin responsiveness is assumed to be the result of an impairment of liver function resulting from congestion (Stats & Davison, 1949; Covert, 1952; Killip & Payne, 1960; O'Reilly & Aggeler, 1970). Patients with heart failure were noted to have an increased response as hepatic congestion developed (Killip & Payne, 1960; O'Reilly & Aggeler, 1970), and the responsiveness decreased on relief of the congestion by corrective cardiac surgery (Storm & Hansen, 1955) or use of diuretics (Verstraete & Verwilghen, 1980). Our data also indicate that coumarin responsiveness was already slowly increasing during the weeks preceding the incidental heart failure date, probably because of increasing hepatic congestion. It is speculated that the determinants of increased coumarin responsiveness might chiefly be pharmacodynamic (associated with impaired clotting factor synthesis) rather than pharmacokinetic (associated with decreased hepatic coumarin clearance) (Bachmann & Shapiro, 1977; Verstraete & Verwilghen, 1980). The hypothrombinaemic effect will be even larger because of the redistribution of body water in heart failure patients and consequent accumulation of unbound coumarin anticoagulant in the vicinity of hepatic receptor sites (Bachmann & Shapiro, 1977).

The clinical implication of these findings lies in the possibility of prevention or early detection of excessive anticoagulation, and thus of haemorrhagic complications, by paying special attention to this risk factor when monitoring anticoagulant therapy. Patients with heart failure should therefore be closely monitored for signs of excess anticoagulation and fluid overload and it should be noted whether patients are

taking any drugs associated with fluid retention (e.g. vasodilators, NSAIDs).

In our study, selection bias was probably negligible as we identified all users of oral anticoagulants in a defined population and because regular INR monitoring makes it unlikely that cases were missed. In addition, information bias is not likely as all data on heart failure and coumarin anticoagulant dosages were recorded similarly without prior knowledge of our study hypothesis. Potential confounding by gender, age, CYP2C9 genotype, hepatic dysfunction, hypoalbuminaemia, malignancies, hyperthyroidism, hypertension, low dietary intake of vitamin K, type of anticoagulant, indication for therapy, target INR level, time between the INR measurements, and use of thiazides and NSAIDs was dealt with in the multivariate analyses. Use of thiazide diuretics on the index date was taken into consideration because current use of these drugs was found to increase the bleeding risk of oral anticoagulant therapy by 5·2% (Launbjerg *et al*, 1991).

In conclusion, heart failure is an independent risk factor for overanticoagulation. Patients with heart failure should therefore be closely monitored for signs of excess anticoagulation and fluid overload to prevent potential bleeding complications.

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