

Coumarins and survival in incident dialysis patients

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Abstract

Background. The benefit and risk of oral anticoagulation in dialysis patients are debated controversially.

Methods. We prospectively followed 235 dialysis patients of the INVOR Study (Study of Incident Dialysis Patients in Vorarlberg) for up to 7 years and analysed the prevalence and incidence of atrial fibrillation (AF) and the impact of coumarin therapy on survival. Oral anticoagulation was monitored frequently.

Results. A total of 748 person-years were recorded with a median follow-up of 2.84 years. Twelve patients (5.1%) had AF at the start of dialysis. During follow-up, 40 patients (17.0%) developed AF, representing an incidence of 5.85 per 100 person-years. AF was positively associated with mortality ($P = 0.004$). Forty-six (19.6%) of the 235 patients were treated with coumarins. The majority (93.7%) had a clear indication for oral anticoagulation. In 65% of our patients, AF was the indication for coumarins. Patients without coumarins and without AF represented our reference group. The mortality risk of the coumarin-treated patients with AF or an alternative indication for coumarins was slightly lower compared to the reference group [hazard ratio (HR) 95% confidence interval (CI): 0.80 (0.28–2.29), $P = 0.679$ and 0.42 (0.16–1.10), $P = 0.078$, respectively]. No patient under sufficient oral anticoagulation experienced a stroke or a fatal bleeding event. Patients with AF and a contraindication for coumarins had a significantly higher mortality risk compared to the reference group [HR (95% CI): 3.90 (2.16–7.04), $P < 0.001$].

Conclusions. Our data suggest that coumarins might be less harmful than previously anticipated when clearly indicated and closely monitored.

Keywords: atrial fibrillation; coumarins; end-stage renal disease; oral anticoagulation; survival

Introduction

Atrial fibrillation (AF) is associated with increased mortality in the general population [1]. Oral anticoagulation

therapy (OAT) successfully prevents ischaemic stroke [2] and improves survival in AF patients without severe kidney disease [3].

Although AF is a common co-morbidity in dialysis patients [4], prospective randomized data indicating a benefit of OAT for an end-stage renal disease (ESRD) population do not exist. Debate regarding OAT and its hazards and benefits for this subpopulation is ongoing. Increased risk for haemorrhages [5] and the potential to accelerate vascular calcification as an effect of coumarins on vitamin K-dependent calcification inhibitor proteins [6] are put forward as main arguments against oral anticoagulation in dialysis patients.

On the other hand, the prevalence of ischaemic stroke is high in the ESRD population [7] with an excessive risk for new stroke and high mortality after stroke [8]. The United States Renal Data System reported reduced mortality with use of coumarins in patients later hospitalized for AF [9].

We conducted a prospective single-centre observational cohort study to evaluate the association of a closely monitored OAT on all-cause mortality of dialysis patients. Furthermore, we also determined the prevalence and incidence of AF in incident dialysis patients in the Vorarlberg region and investigated the association with incident stroke.

Materials and methods

INVOR Study

The INVOR Study [10] (Study of Incident Dialysis Patients in Vorarlberg) is a single-centre, prospective observational cohort study of incident Caucasian haemodialysis and peritoneal dialysis patients in Vorarlberg, the westernmost province of Austria counting ~400 000 inhabitants. The study was approved by the local ethics committee, and all patients enrolled in the study provided written informed consent.

All incident dialysis patients from this province starting chronic dialysis treatment between 1 May 2000 and 30 April 2006 were consecutively enrolled with the advantage that all patients of this region are treated by the same care provider. During this period of 6 years, a total of 235 patients were included and followed until the study end point was reached or follow-up was censored at 31 December 2007. Four patients were lost to follow-up, three of them regained renal function and the other one moved away. Ten patients with a malignancy at initiation of dialysis were not recruited defined by the exclusion criteria. Patients were treated

according to the European Best Practice Guidelines in place at the time of treatment (<http://www.ndt-educational.org/guidelines.asp>).

Data description

Clinical, laboratory and medication data were collected prospectively starting at the time of initiation of dialysis. These data included age, sex, height, weight, body mass index, diabetes status, primary cause of ESRD, smoking status and time between first nephrological visit and initiation of dialysis. Type of renal replacement therapy (haemodialysis, peritoneal dialysis and kidney transplantation), sinus rhythm (SR) or AF and coumarin treatment status were recorded and deemed time-dependent for data analysis. Vascular access procedures and the type of vascular access (native fistula, graft or central venous catheter) for haemodialysis were also evaluated.

Information on the following clinical events was collected before initiation of dialysis and during the entire observation period thereafter: coronary artery disease (including myocardial infarction, percutaneous transluminal coronary angioplasty and aortocoronary bypass), cardiovascular disease (including myocardial infarction, percutaneous transluminal coronary angioplasty, aortocoronary bypass, angiographically proven coronary stenosis $\geq 50\%$, sudden cardiac death, ischaemic or haemorrhagic cerebral infarction, transient ischaemic attack, carotid stenosis and carotid endarterectomy) and peripheral arterial disease (including significant ultrasound- or angiographically proven vascular stenosis, percutaneous transluminal angioplasty, peripheral bypass and amputation).

Electrocardiograms were taken at study entry and once a year during follow-up or when clinical symptoms of arrhythmia or angina pectoris occurred; 24-h electrocardiograms were taken as needed. Each patient with one documented episode of AF was assigned to the AF group and considered for OAT. We did not differentiate between paroxysmal, persistent and permanent AF.

The contraindications for OAT were bleeding diathesis, active peptic ulcers, proliferative diabetic retinopathy with retinal haemorrhage, severe thrombocytopenia ($< 50\ 000/\mu\text{L}$), non-compliance, frailty with recurrent falls (> 1 in the last year) and severe cognitive impairment.

Strokes were documented by computed tomography or magnetic resonance imaging.

Laboratory parameters were recorded continuously during the study period and measured in a central laboratory. Among others, haemoglobin, creatinine, high-sensitivity C-reactive protein, albumin, calcium, phosphorus, ferritin and erythrocytes were measured.

The entire medication history was documented including all drugs, doses and duration of therapy.

Laboratory parameters were measured in different time intervals. Haemoglobin, erythrocytes, creatinine, calcium and phosphorus were measured twice per month. Albumin, C-reactive protein and ferritin were measured every 3 months. Prothrombin time and the resultant international normalized ratio (INR) of patients on OAT were measured weekly followed by adequate dose adaptation to keep the INR in the target range. INR values were measured in the central laboratory, but partially we used a point of care device (CoaguChek® XS plus F. Hoffmann-La Roche Ltd, Basel, Switzerland). Only values measured in the central laboratory were used for the data analysis since we lack an interface from our point of care device with our database. The values derived from the point of care device were not included in the data analysis but were used for dose adjustment decisions.

Statistical methods

At baseline, data are presented as number (%), mean \pm SD or rate per 100 person-years. Categorical data were compared using Pearson's χ^2 test and continuous variables were analysed using an unpaired *t*-test or the non-parametric Mann-Whitney *U*-test.

To investigate the influence of coumarins on all-cause mortality, a time-dependent Cox-proportional hazards model was used allowing all variables to vary over different measurements during the whole observation time for each patient, i.e. each time-span between two successive measurements enters the model independently. Each covariate that entered the model was updated at the time it was measured and modelled in a time-dependent fashion. If all variables were not measured at a particular time, the missing values were replaced with the values measured at the last observation of the variable ('last observation carried forward'). To account for possible correlation of values within one patient, robust variances were estimated, which were grouped for each patient. The proportional hazards assumption was tested for each model by testing for zero slopes of scaled Schoenfeld residuals.

The Cox model was adjusted for age, sex, diabetes mellitus and the time-dependent variables type of renal replacement therapy, SR or AF and coumarin treatment status, C-reactive protein, albumin and haemoglobin. Adjusted survival curves were plotted for coumarins, holding all covariates fixed at their mean level. We also performed a sensitivity analysis with censoring at the time of transplantation. Rates for stroke and bleeding events are given with 95% confidence intervals (CIs) calculated using the normal approximation of the Poisson distribution. All analyses were conducted in SPSS version 16.0 software (SPSS Inc., Chicago, IL) and in R using the 'survival' package.

Results

Patient characteristics

Table 1 presents the baseline demographic and laboratory characteristics as well as medication and co-morbidities during follow-up of the 235 incident dialysis patients. A total of 748 person-years were recorded. The median follow-up time was 2.84 years, ranging from 25 days to ~ 7.6 years. During this period, 82 patients (34.9%) died, 38 of them due to cardiovascular disease, 22 due to infections and 22 patients due to other causes. All-cause and cardiovascular mortality were higher in patients with AF than in patients with SR. Patients with AF were significantly older, had lower serum creatinine values and lower diastolic blood pressure, but there was no difference in the prevalence of diabetes between the two groups. AF patients were treated less frequently with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or platelet aggregation inhibitors than were patients with SR.

Incidence of AF and association with mortality

Twelve patients (5.1%) had AF at commencement of dialysis. During follow-up, 40 patients (17.0%) were newly diagnosed with AF, giving an incidence of 5.85 (95% CI 4.04–7.67) per 100 person-years.

Fifty-five (30.1%) of the 183 patients with SR and 27 (51.9%) of the 52 patients with AF died during the study period ($P = 0.004$).

Incidence of stroke

Twelve patients (5.1%) suffered a stroke during follow-up, 8 of them with SR and 4 of them with AF. This corresponds to 1.35 (95% CI: 0.41–2.28) strokes per 100 person-years for patients with SR and 2.83 (95% CI: 0.06–5.61) per 100 person-years for patients with AF. Ten of the strokes were ischaemic and 2 were haemorrhagic. One stroke occurred in a patient under OAT. At the time of the event, INR was 1.4 and therefore below therapeutic range. No patient with an INR in the therapeutic range experienced a stroke.

Coumarins and mortality

Of the 235 patients, 46 (19.6%) were treated with coumarins. The indications for OAT are shown in Table 2.

We divided the entire cohort into four groups: a reference group without coumarins and without AF, a group with coumarins and AF, a group without AF but an alternative indication for coumarins and a group with AF but a contraindication for coumarins. Survival of the group with AF but a contraindication for coumarins was significantly inferior compared to the reference group [hazard ratio (HR) 95%

Table 1. Differences between patients with sinus rhythm and patients with AF at baseline and during follow-up^a

	All patients, (n = 235)	Sinus rhythm, (n = 183)	AF, (n = 52)	P-value ^b
Age (years)	61.7 ± 14.0	59.6 ± 14.2	69.1 ± 10.6	<0.001
Sex (male/female), n (%)	146/89 (62.1/37.9%)	111/72 (60.7/39.3%)	35/17 (67.3/32.7%)	0.383
Start of dialysis with				
Haemodialysis, n (%)	197 (83.8%)	152 (83.1%)	45 (86.5%)	0.548
<i>Central venous catheter, n (%)</i>	<i>32 (16.25%)</i>	<i>23 (15.1%)</i>	<i>9 (20.0%)</i>	<i>0.437</i>
<i>Native fistula, n (%)</i>	<i>133 (67.5%)</i>	<i>105 (69.1%)</i>	<i>28 (62.2%)</i>	<i>0.388</i>
<i>Graft, n (%)</i>	<i>32 (16.25%)</i>	<i>24 (15.8%)</i>	<i>8 (17.8%)</i>	<i>0.751</i>
Peritoneal dialysis, n (%)	38 (16.2%)	31 (16.9%)	7 (13.5%)	0.548
Systolic blood pressure (mmHg)	154.0 ± 22.7	154.1 ± 22.5	153.6 ± 23.5	0.883
Diastolic blood pressure (mmHg)	83.0 ± 12.3	83.8 ± 12.3	80.1 ± 12.2	0.047
Year of start of dialysis				
2000–2003, n (%)	122 (51.9%)	95 (51.9%)	27 (51.9%)	0.999
2004–2007, n (%)	113 (48.1%)	88 (48.1%)	25 (48.1%)	0.999
Diabetes mellitus, n (%)	82 (34.9%)	63 (34.4%)	19 (36.5%)	0.778
Body mass index (kg/m ²)	26.1 ± 4.5	26.3 ± 4.6	25.3 ± 4.1	0.180
Laboratory parameters at baseline				
Haemoglobin (g/dL)	11.17 ± 1.72	11.24 ± 1.80	10.90 ± 1.38	0.214
Erythrocytes (T/L)	3.73 ± 0.62	3.75 ± 0.65	3.69 ± 0.50	0.596
Creatinine (mg/dL)	7.28 ± 2.64	7.53 ± 2.78	6.43 ± 1.84	0.006
Albumin (g/dL)	3.71 ± 0.65	3.74 ± 0.67	3.60 ± 0.59	0.192
Calcium (mmol/L)	2.12 ± 0.27	2.11 ± 0.28	2.16 ± 0.24	0.287
Phosphorus (mmol/L)	1.98 ± 0.61	2.03 ± 0.61	1.84 ± 0.60	0.071
C-reactive protein (mg/dL)	3.24 ± 5.34	3.23 ± 5.50	3.29 ± 4.77	0.414
Ferritin (ng/mL)	174.3 ± 206.5	165.7 ± 179.9	203.4 ± 278.6	0.910
Follow-up				
Follow-up time (years)	3.18 ± 1.94	3.29 ± 1.92	2.83 ± 1.95	0.132
Dialysis treatment years (years)	2.60 ± 1.66	2.65 ± 1.66	2.44 ± 1.66	0.419
Transplantation, n (%)	58 (24.7%)	51 (27.9%)	7 (13.5%)	0.033
All-cause mortality, n (%)	82 (34.9%)	55 (30.1%)	27 (51.9%)	0.004
<i>CV mortality related to all-cause mortality^c, n (%)</i>	<i>38 (46.3%)</i>	<i>24 (43.6%)</i>	<i>14 (51.9%)</i>	<i>0.017</i>
Medication during follow-up				
Coumarins, n (%)	46 (19.6%)	16 (8.7%)	30 (57.7%)	<0.001
ACE inhibitors, n (%)	141 (60.0%)	113 (61.7%)	28 (53.8%)	0.305
Platelet aggregation inhibitors ^d , n (%)	138 (58.7%)	110 (60.1%)	28 (53.8%)	0.418
Angiotensin receptor blockers, n (%)	45 (19.1%)	38 (20.8%)	7 (13.5%)	0.238
Beta blockers, n (%)	176 (74.9%)	137 (74.9%)	39 (75.0%)	0.984
Co-morbidities during follow-up				
CVD events ^e , n (%)	93 (39.6%)	68 (37.2%)	25 (48.1%)	0.155
CVD event ^e rate per 100 person-years	15.95	14.61	21.25	
Stroke ^f , n (%)	12 (5.1%)	8 (4.4%)	4 (7.7%)	0.337
Stroke ^f rate per 100 person-years	1.63	1.35	2.83	
Bleeding episodes, n (%)	16 (6.8%)	11 (6.0%)	5 (9.6%)	0.363
<i>Platelet aggregation inhibitors in those with bleeding episodes^d, n (%)</i>	<i>11 (68.8%)</i>	<i>7 (63.6%)</i>	<i>4 (80.0%)</i>	<i>0.513</i>
Bleeding rate per 100 person-years	2.21	1.80	3.94	

^aMean ± SD or number (%) or rate per 100 person-years. ACE, angiotensin-converting enzyme inhibitor; CVD, cardiovascular disease. P values <0.05 are printed in bold letters; subgroup analysis printed in italic letters refer to the most previous group printed in normal letters.

^bComparison of patients with SR versus patients with AF (χ^2 test, *t* test or Mann–Whitney *U* test).

^cCardiovascular mortality: myocardial infarction, heart failure, sudden death, ischaemic stroke and haemorrhagic stroke.

^dPlatelet aggregation inhibitors: ASS, Clopidogrel, Ticlopidin, Dipyridamol retard + ASS.

^eCardiovascular disease events: myocardial infarction, percutaneous transluminal coronary angioplasty, aortocoronary bypass, coronary artery stenosis ≥50%, sudden cardiac death, ischaemic or haemorrhagic cerebral infarction, transient ischaemic attack, carotid stenosis and carotid endarterectomy.

^fStroke: ischaemic or haemorrhagic cerebral infarction.

CI: 3.90 (2.16–7.04), *P* < 0.001] (Figure 1 and Table 3). Survival of the two coumarin-treated groups was slightly better than the reference group without reaching statistical significance [HR (95% CI): 0.80 (0.28–2.29), *P* = 0.679 and 0.42 (0.16–1.10), *P* = 0.078, respectively] (Figure 1 and Table 3).

Monitoring of anticoagulation management

In total, we followed 3768 coumarin treatment weeks with 2878 INR values available in our database. The number of INR measurements used for dose adjustment was markedly

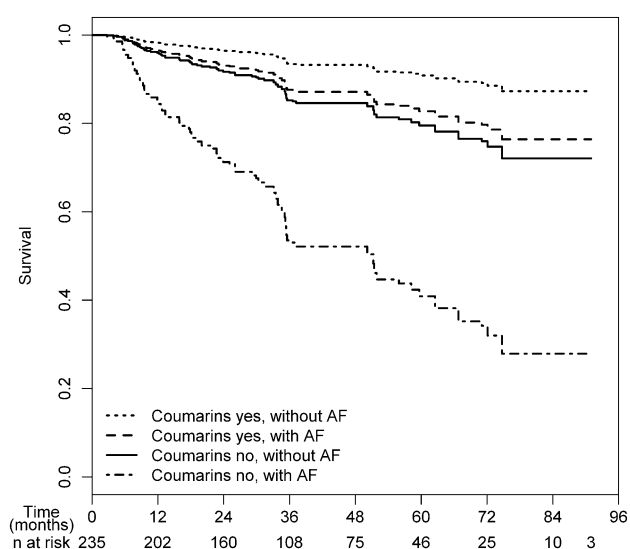
higher since not all values were computerized (see Materials and methods section). Figure 2 provides the distribution of INR values with a median of 2.1 and a mean ± SD of 2.4 ± 1.1. Forty-two per cent of the INR values were between 2 and 3, 61% between 1.8 and 3.5 and 59% between 1.5 and 2.5.

Bleeding events

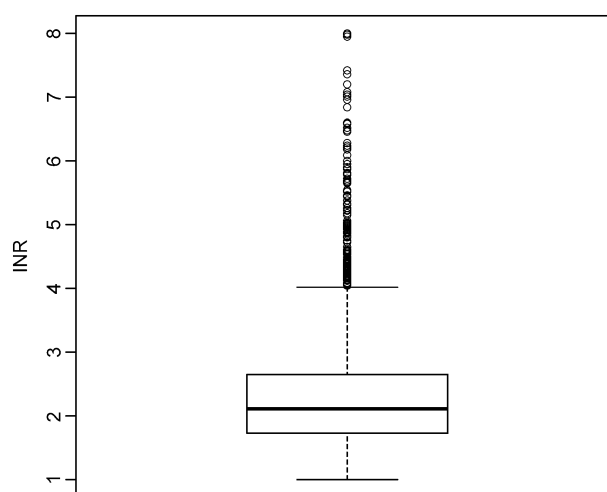
Overall, we observed 16 (6.8%) major bleeding episodes, corresponding to 2.21 (95% CI: 1.13–3.30) bleeding episodes per 100 person-years. Four bleeding episodes occurred in the coumarin group. One of these patients

Table 2. Indication for oral anticoagulation in 46 patients

Indication	n (%)
AF	30 (65.2)
Deep vein thrombosis and pulmonary embolism	6 (13.0)
Recurrent arteriovenous graft thrombosis	3 (6.5)
Left ventricular aneurysm	2 (4.3)
Prosthetic mechanical valve	2 (4.3)
Femoropopliteal bypass	1 (2.2)
Antiphospholipid syndrome	2 (4.3)

**Fig. 1.** Survival curves for all-cause mortality adjusted for age, sex, diabetes mellitus and the time-dependent variables type of renal replacement therapy, SR or AF, coumarin treatment status, C-reactive protein, albumin and haemoglobin for the entire cohort. The number of patients at risk for each year of observation is given with the last observation time at 91 months.**Table 3.** The association of coumarins as time-dependent variable with all-cause mortality adjusted for different parameters using time-dependent Cox-proportional hazards models^a

	All patients		
	HR	95% CI	P-value
Age (years)	1.04	(1.02–1.07)	0.001
Sex (0 = female, 1 = male)	1.08	(0.65–1.79)	0.774
Type of renal replacement therapy			
1 = haemodialysis	Ref.		
2 = peritoneal dialysis	0.57	(0.23–1.43)	0.231
3 = transplantation	0.79	(0.29–2.19)	0.656
Diabetes mellitus	1.48	(0.93–2.37)	0.100
Coumarins			
1 = no, without AF (n = 167)	Ref.		
2 = yes, without AF (n = 16)	0.42	(0.16–1.10)	0.078
3 = yes, with AF (n = 30)	0.80	(0.28–2.29)	0.679
4 = no, with AF (n = 22)	3.90	(2.16–7.04)	<0.001
C-reactive protein (mg/dL)	1.13	(1.10–1.17)	<0.001
Albumin (g/dL)	0.29	(0.19–0.45)	<0.001
Haemoglobin (g/dL)	1.02	(0.86–1.21)	0.816

^aAdjusted for age, sex, diabetes mellitus, time-dependent type of renal replacement therapy, CRP, albumin and haemoglobin.**Fig. 2.** The 2878 INR measurements of 46 patients receiving treatment with coumarins. The bottom and the top of the box are the 25th and 75th percentile and the band in the box indicates the 50th percentile (median). The ends of the whiskers represent the lowest and highest values still within 1.5 times the inter-quartile range (range of the middle two quartiles). The circles represent outlier INR values.

experienced a bleeding from the fistula requiring surgical intervention as a consequence of over-anticoagulation (INR > 8). One gastrointestinal bleeding under OAT occurred in the course of a peptic ulcer at an INR of 1.3. Two of the patients were not anti-coagulated at the time of the event but treated with coumarins later and therefore included in the coumarin group.

Two bleeding episodes occurred in the group without antiplatelet therapy or coumarins and 10 in the patients with antiplatelet agents only once in the follow-up. This corresponds to 1.09 (95% CI: 0–3.22) bleeding episodes per 100 person-years with coumarins and 5.91 (95% CI: 0–12.60) bleeding episodes per 100 person-years without coumarins, which was statistically not significant. The two haemorrhagic strokes occurred with acetylsalicylic acid therapy.

Sensitivity analysis

It is possible that some considerable bias to the data analysis could be introduced when a patient is selected for transplantation and follow-up time is censored at the time of transplantation. For this reason, the main analyses were performed by a time-dependent modelling of the renal replacement therapy status as discussed earlier [11, 12]. To exclude the possibility that this procedure could have influenced our main findings, we performed a sensitivity analysis with classical censoring at the time of transplantation which, however, did not reveal any substantial differences in HRs compared to the primary analysis (data not shown).

Discussion

The present study focuses on two questions: the frequency of AF and stroke and the effect of oral anticoagulation on survival in an incident dialysis population from a defined geographical region with complete recruitment of all patients.

Prevalence and incidence of AF and stroke

In comparison with the previous literature, our study shows a rather low prevalence and a relatively high incidence of AF in dialysis patients [4, 8, 13–15]. As in the general population, the occurrence of AF increased with age [16, 17] and was associated with mortality. The age difference of almost a decade between patients with AF or SR may explain the higher mortality in the AF group. Significantly lower serum creatinine values may indicate malnutrition, another well-known contribution to excess mortality. The incidence of stroke (1.35 per 100 person-years with SR and 2.83 per 100 person-years with AF) was comparable with recently published studies in ESRD patients [4, 8, 16]. However, due to the small absolute number of strokes in our cohort, the difference was not statistically significant. The higher incidence of stroke in patients with AF is consistent with data from the DOPPS cohort [15] and contrasts with previous studies that found no elevation in stroke risk [18, 19]. The fact that only 10 of the 12 strokes were ischaemic leads to a further decrease in the risk for ischaemic stroke. The resulting small absolute number of ischaemic strokes is remarkable and potentially related to the high percentage of AF patients on coumarins (57%) in our study as compared to the DOPPS cohort (16%) [15] or the Fresenius US cohort (21.7%) [20].

Effect of oral anticoagulation on survival

To minimize confounding by indication, we divided the entire cohort into four groups: a reference group of the relatively healthy patients without coumarins and without AF, a second group with coumarins because of AF, a third group with coumarins because of an alternative indication for OAT and a group of the relatively sickest with AF but a contraindication for coumarins (Figure 1). The most important finding of our study was that the overall mortality of coumarin-treated dialysis patients irrespective of the indication for OAT (AF or an alternative indication) was not worse than of patients without coumarins and without AF. This is of interest as every indication for OAT poses a mortality risk by itself. Additionally, vitamin K deficiency is thought to be a risk factor for vascular calcification [21] and vitamin K inhibition by coumarins may accelerate calcification [22, 23] by inhibiting γ -carboxylation and also activation of matrix Gla protein [24].

Our finding stands in contrast to the data of Chan *et al.* [20] who reported an increased risk for mortality in a large cohort of coumarin-treated patients at Fresenius Medical Care clinics in the USA. To interpret these diverging results, two points deserve closer attention. The first refers to the indication for oral anticoagulation. Nearly all of our patients (93.7%) had a clear indication for anticoagulation (Table 2). AF was the indication for anticoagulation in 65.2% of our patients as compared to only 21.7% in the study by Chan *et al.* [20]. Of the Fresenius cohort, 69.6% of patients had no identifiable clear indication for oral anticoagulation. The authors suggested that prevention of access thrombosis may have been the main reason for coumarin use in these patients. In contrast, only three (6.5%) of our patients were treated with coumarins for that indication. Coumarin use, however, is associated with worse primary graft patency

[25, 26] and causes more bleeding episodes [27] when given for that indication. The second point relates to drug monitoring. One advantage of the dialysis setting is the feasibility of weekly INR monitoring. Maintaining INR values in the therapeutic range is crucial for efficacy and safety of anticoagulation [28]. Anticoagulation status was monitored weekly and followed by dose adjustments in all our patients when needed. In contrast, in the Fresenius cohort, 30% of coumarin users had no INR monitoring at all, exposing them to a greater risk of bleeding or ineffective anticoagulation. The latter would, of course, preclude any positive effect on cardiovascular mortality or stroke prevention.

Quality of anticoagulation control was comparable to data from large-scale meta-analyses with a high proportion of patients treated in clinical trials and with a target range between 1.8 and 3.5 [29, 30]. In the meta-analysis of Baker *et al.* [29], the subcohort of patients not treated within a prospective trial showed worse anticoagulation control with only 51% of time in the target range versus 61% in our cohort. Forty-two per cent of the INR values of our patients were between 2 and 3 compared to a Canadian study in dialysis patients, where the thrice weekly and the daily coumarin administration group hit that INR goal in 56.9% and 49.3%, respectively [31]. With a median INR of 2.1, our patients were in the lower target range and despite that none of our AF patients under OAT suffered a stroke. Haemodialysis patients have impaired platelet function and receive intravenous heparin thrice weekly. Therefore, it may be wise to lower the INR target compared to the general population. However, this hypothesis has to be addressed in future controlled trials.

Bleeding episodes

Bleeding remains a major concern when using coumarins in dialysis patients. The rate of major bleedings in our study was consistent with data from Holden [32] and Biggers [33] and similar to bleeding rates in a non-uraemic population. Bleeding risk is much higher on antiplatelet therapy than with oral anticoagulation, possibly due to the exaggerated effect of acetylsalicylic acid on bleeding time in chronic kidney disease patients [27]. We did not observe a higher bleeding risk in patients treated with coumarins, but the low number of bleeding events in our population limits statistical validity. We suggest, however, that close weekly INR monitoring with an INR target even in the lower therapeutic range, as done in our study population, can effectively reduce the risk of bleeding.

Holden *et al.* [32] suggest that almost 50% of major bleeding episodes occur in dialysis patients taking medication for prevention of access thrombosis, which is no clear indication for coumarins [33, 34]. Therefore, many bleeding episodes might be prevented by avoiding this practice [19, 20, 34].

Strengths and limitations of the study

Our study has some notable strengths. It is a single-centre inception cohort with complete recruitment of all suitable patients, frequent laboratory measurements and complete collection of all events over a period of up to 7 years. Furthermore, anticoagulation monitoring followed standardized criteria with a weekly measurement of INR values followed by dose adjustment.

A limitation of this study is the lack of a control group as only AF patients with contraindications were excluded from OAT. Another limitation is the relatively small sample size. Thus, our observations should stimulate further controlled large-scale prospective studies investigating the impact of coumarins on survival, especially in AF patients in the dialysis population.

Conclusions

Our study made the following three important observations: (i) Dialysis patients have a high incidence and prevalence of AF. (ii) Mortality in AF patients is significantly higher. (iii) Coumarin therapy in closely INR-monitored patients is not associated with an increased mortality risk, both in patients with AF and with SR and other indications for OAT. The fact that no patient under sufficient OAT experienced a stroke or a fatal bleeding event underlines the efficacy and safety of OAT in dialysis patients.

The main differences to studies that reported increased mortality risk with oral anticoagulation in dialysis patients were clear indications and frequent INR monitoring in our study population. We therefore suggest that coumarins might be less harmful in dialysis patients than previously anticipated when clearly indicated and closely monitored.

Acknowledgements. This study was supported by a grant from Hans Drexel to the Vorarlberg Institute for Vascular Investigation and Treatment.

Conflict of interest statement. None declared.

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Received for publication: 9.10.10; Accepted in revised form: 16.5.11