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Original Articles

Warfarin use, mortality, bleeding and stroke in haemodialysis patients with atrial fibrillation

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ABSTRACT

Background. Oral anticoagulation therapy (OAT) is the choice treatment for thromboembolism prevention in atrial fibrillation (AF), although data about OAT use in haemodialysis (HD) patients with AF are contradictory.

Methods. The effect of OAT on the risk of mortality, stroke and bleeding was prospectively evaluated in a population of HD patients with AF. All the patients of 10 HD Italian centres alive on 31 October 2010 with documented AF episode(s) were recruited and followed-up for 2 years. OAT and antiplatelet intake, age, dialytic age, comorbidities and percentage time in the target international normalized ratio (INR) range (target therapeutic range; TTR) were considered as predictors of hazard of death, thromboembolic and bleeding events.

Results. At recruitment, 134 patients out of 290 were taking OAT. During the follow-up, 115 patients died (4 strokes, 3 haemorrhagic and 1 thromboembolic). Antiplatelet therapy, but not OAT, was associated with increased mortality (HR 1.71, CI 1.10–2.64, P = 0.02). The estimated survival of patients always taking OAT tended to be higher than that of patients who stopped taking (68.6 versus 49.6%, P = 0.07). OAT was not correlated to a significant decreased risk of thromboembolic events (HR 0.12, CI 0.00–3.59, P = 0.20), while it was associated with an increased risk of bleeding (HR 3.96, CI 1.15–13.68, P = 0.03). Higher TTR was associated with a reduced bleeding risk (HR 0.09, CI 0.01–0.76, P = 0.03), while previous haemorrhagic events were associated with higher haemorrhagic risk (HR 2.17, CI 1.09–4.35, P = 0.03).

Conclusions. In our population of HD patients with AF, the mortality is very high. OAT is not associated with increased mortality, while antiplatelet drugs are. OAT seems, on the contrary, associated with a better survival; however, it does not decrease the incidence of ischaemic stroke, whereas it increases the incidence of bleeding. Bleeding risk is lower in subjects in whom the INR is kept within the therapeutic range.

Keywords: atrial fibrillation, bleeding, haemodialysis, mortality, oral anticoagulation therapy, stroke

INTRODUCTION

The prevalence of atrial fibrillation (AF) in patients with end-stage renal disease (ESRD) on haemodialysis (HD) is high [1–4]. The presence of AF increases the risk of thromboembolic stroke in the general population [5] and a similar phenomenon seems to occur in the population of ESRD patients [6, 7]. This is of particular concern given the fact that the risk of stroke in the HD population is already increased by nearly 6-fold, even in the absence of AF [8]. The treatment of choice

for reducing thromboembolic risk in AF patients is oral anticoagulant therapy (OAT) with warfarin [9], but randomized trials showing the beneficial effects of OAT on thromboembolic risk excluded ESRD patients. An increased risk of stroke in ESRD patients taking OAT was described [10, 11]. A Canadian study, performed in elderly patients hospitalized for AF, showed that HD patients did not benefit from warfarin therapy with regard to ischaemic stroke, and that they had an increased haemorrhagic risk [12]. In contrast, a Danish study described a protective effect of warfarin on thromboembolic events in HD patients, without an increment in bleeding [13]. A review of data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) showed that, in patients with AF, OAT was associated with a slightly higher incidence of bleeding than in non-OAT patients, while bleeding episodes rose dramatically in patients with a history of bleeding [14].

At the moment, there are no prospective studies regarding the risk–benefit assessment of the use of warfarin in ESRD patients with AF and the argument is controversial. The purpose of this study was to prospectively evaluate the effect of OAT on the risk of mortality, stroke and bleeding in this population.

MATERIALS AND METHODS

All patients alive and under observation in 10 Italian HD centres on 31 October 2010 were considered ($N = 1529$) and their clinical charts revised for eligibility to the study. All subjects with at least one documented paroxysmal (self-terminating) or persistent (required termination by pharmacological or electrical cardioversion) AF episode, or with permanent AF (arrhythmia that could not be interrupted spontaneously or by pharmacological or electrical cardioversion), were recruited, for a total of 290 patients.

At recruitment, data were collected on the presence of hypertension, diabetes mellitus, dyslipidaemia, peripheral artery disease, ischaemic heart disease, heart failure, previous strokes and major bleeding episodes and on administration of anticoagulants (warfarin and low-molecular-weight heparin) and antiplatelets (aspirin, ticlopidine and clopidogrel) (see Supplementary material for definitions).

Patients were prospectively followed-up for 2 years (until 31 October 2012 or death), with updates at each dialysis session. The fresh onset of permanent AF, stroke (ischaemic or haemorrhagic), bleeding, cardiovascular events (ischaemic and heart failure episodes), antiplatelet and anticoagulant treatment modifications were recorded.

In patients taking OAT, the international normalized ratio (INR) values were assessed at least once a month. To determine the achieved intensity of anticoagulation and to assess INR variability, the percentage time in the target INR range (target therapeutic range; TTR) and its variance growth rate (VGR; according to the Cannegieter formula) were also calculated [15, 16].

Thromboembolic and haemorrhagic risk were calculated using the $CHA_2DS_2VAS_c$ and the HASBLED scores ([17], see Supplementary material for definitions). Procedures were performed according to the Helsinki declaration for ethical treatment of human subjects and approved by the local ethical committee. Informed consent was obtained from the enrolled subjects.

Statistical analysis

All data were centrally revised by clinical and statistical reviewers. Patients were considered under OAT at recruitment if taking OAT on 31 October 2010 (or starting OAT within 2 weeks following recruitment).

The association between demographic and clinical features according to OAT administration at recruitment was evaluated using the Pearson's χ^2 and Fisher's test, where appropriate. The rate of thromboembolic and haemorrhagic events was computed as total number of events divided by the total person years at risk.

The Cox regression model was applied to assess the effect of OAT administration at recruitment on different relevant end points. For mortality and mortality due to cardiovascular causes, the models were adjusted for the following potential confounders: age and dialytic age, gender, antiplatelet therapy and hypertension status at recruitment, permanent AF and bleedings/haemorrhagic strokes as time-dependent covariates (i.e. updated during follow-up). Other variables that were considered and selected by a backward approach (criteria for exclusion: $P > 0.1$) were diabetes mellitus, ischaemic stroke, ischaemic heart disease and heart failure (the last three as time-dependent covariates). The variable bleeding/haemorrhagic stroke was also considered fixed at the value reported at recruitment, when explicity notified.

The analyses of OAT effect on the hazard of thromboembolic events or on the hazard of haemorrhagic events (first event) during follow-up were all adjusted by antiplatelet therapy administration at recruitment while a backward strategy was adopted on all other variables (criteria for exclusion: $P > 0.1$). Two additional covariates were considered in the backward strategy, namely TTR and log(sqrt-VGR) (because of the skewed distribution), as calculated on the follow-up time elapsed from recruitment until the occurrence of the first outcome event. Results of the Cox models are expressed in terms of estimated hazard ratios (HR), 95% confidence intervals ($CI_{95}\%$) and P-values.

A sensitivity analysis was performed to assess the effect of confounding by indication of OAT treatment at recruitment by a propensity score analysis. In particular, propensity scores were estimated by a logistic regression model with OAT at recruitment as the outcome and all potential confounding variables as explanatory variables (antiplatelet therapy, age, dialytic age, gender, permanent AF, hypertension, heart failure, bleeding/haemorrhagic stroke). Patients were then grouped into 10 categories based on quintiles of the estimated propensity scores, and a Cox regression model was applied to evaluate the effect of OAT on mortality adjusting by these categories.

The Kaplan–Meier estimator was used to describe survival in four subgroups defined according to use of OAT at recruitment and therapy shifts during follow-up, and the log-rank test was used for comparisons of interest. TTR and sqrt-VGR distributions were described by means of median, interquartile range and box-plot and whiskers. Analyses were carried out by

means of the statistical software SAS v.9.2 (SAS Institute Inc., Cary, NC, USA), while figures were made by the freeware R statistical software v.2.12.2 (http://www.r-project.org).

RESULTS

At recruitment, 134 patients out of 290 were taking warfarin and their characteristics are described in Table 1. Patients with permanent AF were more likely on OAT (P < 0.001), while those with previous bleeding (P < 0.001), higher HASBLED score (P = 0.04) and presence of hypertension (P = 0.05) were associated with a lower frequency of warfarin prescription. Patients taking antiplatelet were less likely on OAT (P < 0.001) and showed higher ischaemic heart disease prevalence (81/139 = 58% versus 59/151 = 39%, P = 0.001).

Mortality

During the 2-year follow-up, 115 patients died (39.6%), 51 with and 64 without OAT at recruitment, with a 2-year estimated mortality of 37.9% (SE = 4.2) and 41.7% (SE = 4.0), respectively (log-rank test: P = 0.6). Death was due to cardiovascular causes in 36 patients (17 with and 19 without OAT at recruitment). All causes of death are summarized in Table 2.

As summarized in Table 3, in the multivariate analysis, patients with or without OAT at recruitment did not differ either in the hazard of death for any cause (HR = 0.96, CI 0.59–1.56, P = 0.9), or for cardiovascular death (HR = 1.08, CI 0.47–2.51, P = 0.9), akin to the results obtained in the univariate analysis. Among possible confounders, antiplatelet therapy (HR 1.71, CI 1.10–2.64, P = 0.02) and higher age (≥75 years, 2.08, CI 1.39–3.11, P < 0.001) at recruitment, presence of permanent AF (HR 2.05, 1.35–3.13, P < 0.001), heart failure (HR 2.06, CI 1.40–3.03, P < 0.001) and bleeding episodes (HR 1.68, CI 1.10–2.57, P = 0.02) were significantly associated with an increased risk of death, while only heart failure was significantly associated with an increased hazard of cardiovascular death (HR 3.52, CI 1.67–7.42, P < 0.001, Table 2). When bleedings indicated only previous haemorrhagic episodes reported at recruitment, the variable was not associated with increased mortality and the relationship between OAT and death was again not significant (HR = 0.88, CI 0.55–1.44, P = 0.6). The sensitivity analysis confirmed the absence of association between OAT at recruitment and death (HR = 0.92 CI 0.56–1.52, P = 0.9) and cardiovascular death (HR = 1.04 CI 0.44–2.44, P = 0.9).

We found no significant association between OAT at recruitment and age classes; among <75-year-old patients, the HR of total mortality for OAT at recruitment was 1.66 (CI 0.77–3.58), P = 0.2, while among >75-year-old patients HR was 0.71 (CI 0.37–1.39), P = 0.32.

Patients continuously taking OAT had an estimated 2-year survival of 68.6% (SE = 5.0), higher, but not significantly, than patients who discontinued OAT during follow-up (49.6%, SE = 7.4, P = 0.07) or who were never exposed to OAT (56.2%, SE = 4.3, P = 0.1) (Figure 1).

Table 1. Patient characteristics by OAT at recruitment

Patient characteristics	Total, *N* (%)	OAT at recruitment		P-value
		No, *N* (%)	Yes, *N* (%)	
Total	290	156	134	
Gender				
Female	116 (40.0)	68 (43.6)	48 (35.8)	0.2
Male	174 (60.0)	88 (56.4)	86 (64.2)	
Age (years)				
<65	60 (20.7)	36 (23.1)	24 (17.9)	0.2
65	75 (25.9)	34 (21.8)	41 (30.6)	
≥75	155 (53.4)	86 (55.1)	69 (51.5)	
Dialytic age (years)				
<3	118 (40.7)	64 (41.0)	54 (40.3)	0.9
≥3	172 (59.3)	92 (59.0)	80 (59.7)	
Hypertension				
Yes	235 (81.0)	133 (85.3)	102 (76.1)	0.05
No	55 (19.0)	23 (14.74)	32 (23.9)	
Diabetes mellitus				
Yes	91 (31.4)	52 (33.3)	39 (29.1)	0.4
No	199 (68.6)	104 (66.7)	95 (70.9)	
Dyslipidaemia				
Yes	93 (32.1)	44 (28.2)	49 (36.6)	0.1
No	197 (67.9)	112 (71.8)	85 (63.4)	
Peripheral artery disease				
Yes	201 (69.3)	106 (68.0)	95 (70.9)	0.6
No	89 (30.7)	50 (32.0)	39 (29.1)	
Ischaemic heart disease				
Yes	140 (48.3)	79 (50.6)	61 (45.5)	0.4
No	150 (51.7)	77 (49.4)	73 (54.5)	
Heart failure				
Yes	115 (39.7)	57 (36.5)	58 (43. 3)	0.2
No	175 (60.3)	99 (63.5)	76 (56.7)	
Ischaemic stroke				
Yes	43 (14.8)	22 (14.1)	21 (15.7)	0.7
No	247 (85.2)	134 (85.9)	113 (84.3)	
Bleeding/Haemorrhagic stroke				
Yes	57 (19.7)	41 (26.3)	16 (11.9)	0.002
No	233 (80.3)	115 (73.7)	118 (88.1)	
Atrial fibrillation				
Paroxysmal	59 (20.4)	46 (29.5)	13 (9.7)	<0.001
Persistent	130 (44.8)	77 (49.4)	53 (39.6)	
Permanent	101 (34.8)	33 (21.1)	68 (50.7)	
Thromboembolic pulmonary disease				
Yes	8 (2.8)	5 (3.2)	3 (2.2)	0.7[a]
No	282 (97.2)	151 (96.8)	131 (97.8)	
Antiplatelet therapy				
Yes	139 (47.9)	112 (71.8)	27 (20.2)	<0.001
No	151 (52.1)	44 (28.2)	107 (79.8)	
Low-molecular-weight heparin				
Yes	12 (4.1)	7 (4.5)	5 (3.7)	0.7
No	278 (95.9)	149 (95.5)	129 (96.3)	
$CHA_2DS_2VASC_S$				
0–1	12 (4.1)	9 (5.8)	3 (2.2)	0.08
2–4	149 (51.4)	72 (46.1)	77 (57.5)	
5–9	129 (44.5)	75 (48.1)	54 (40.3)	
HASBLED[b]				
0–1	3 (1.0)	1 (0.6)	2 (1.5)	0.04[a]
2–3	96 (33.1)	43 (27.6)	53 (39.5)	
4–9	191 (65.9)	112 (71.8)	79 (59.0)	

[a]Fisher's test.
[b]It does not include the score related to labile INR, because unavailable at recruitment.

INR and VGR in patients taking OAT

Repeated INR evaluations were available for 149/155 patients treated with OAT during follow-up. The overall median

TTR was 54% (IQR 41–67%). Patients taking OAT without discontinuation had the highest TTR (median = 60%, IQR 45–71%), while those who discontinued therapy and those who started OAT during follow-up had similar TTR distributions (Figure 2).

Overall, INR variability (estimated according to standard deviation, i.e. square root of VGR, sqrt-VGR) results were not normally distributed with the median equal to 0.92 (IQR: 0.61–1.60). Patients treated with OAT during the whole follow-up had a median sqrt-VGR equal to 0.77 (IQR: 0.55–1.07), while those who did not take OAT continuously had a more spread VGR (Figure 2).

Thromboembolic events

During follow-up, 17 thromboembolic events occurred in 15 patients (16 ischaemic strokes and 1 thromboembolic pulmonary disease). Six events (35.3%) occurred in patients currently assuming OAT: INR was <2 in four cases (66.7%) and between 2 and 3 in the other two cases (33.3%). OAT was not associated with a significant decrease in the risk of thromboembolic events in the multivariate model (HR = 0.12, CI 0.00–3.59, P = 0.2). The only factor feebly associated with thromboembolic events was higher age (≥75 years) (HR 3.01, CI 0.81–11.18, P = 0.1).

Table 2. Causes of death stratified by OAT at recruitment

	Total, *N* (%)	OAT at recruitment	
		No (*n* = 156), *N* (%)	Yes (*n*= 134), *N* (%)
Alive	175 (60.3)	92 (59)	83 (62)
Dead	115 (39.7)	64 (41)	51 (38)
Cause of death			
Sudden cardiac death	17 (5.9)	7 (4.5)	10 (7.5)
Acute pulmonary oedema	1 (0.3)	1 (0.6)	0 (0)
Cardiogenic shock	13 (4.5)	8 (5.1)	5 (3.7)
Ischaemic stroke	1 (0.3)	1 (0.6)	0 (0)
Haemorrhagic stroke	3 (1)	1 (0.6)	2 (1.5)
Sepsis	25 (8.6)	14 (9)	11 (8.2)
Neoplasia	8 (2.8)	6 (3.9)	2 (1.5)
Cachexia	32 (11)	16 (10.3)	16 (11.9)
Other causes	15 (5.2)	10 (6.4)	5 (3.7)

Haemorrhagic events

During follow-up, 67 events occurred in 42 patients and 24 of them (57.1%) experienced bleeding when taking OAT. Of the three haemorrhagic strokes, one occurred in a patient taking antiplatelet therapy, one in a patient treated with low-molecular-weight heparin and one in a patient treated with both drugs. Out of 42 patients with haemorrhagic events during follow-up, 14 had other bleeding episodes before recruitment.

As summarized in Table 4, OAT is seen to be associated with an increased risk of haemorrhagic events (HR 3.96, CI 1.15–13.68, P = 0.03) after adjustment for possible confounders. Patients who experienced bleeding before recruitment had a higher risk of new haemorrhagic events (HR 2.17, CI 1.09–4.35, P = 0.03), so the higher the TTR, the lower the haemorrhagic risk (HR 0.09, CI 0.01–0.76, P = 0.03). In the 228 patients who had not experienced bleeding before recruitment, the increased haemorrhagic risk during follow-up due to OAT was confirmed (HR = 4.81, CI 1.08–21.35, P = 0.04), such as the protective effect of higher TTR (HR = 0.07, CI 0.01–0.80, P = 0.03). In the 56 patients who had haemorrhagic events before recruitment, none of the previous factors seemed to affect the risk of onset of new haemorrhagic events.

Predictive ability of thromboembolic and haemorrhagic risk scores

The rate of thromboembolic events increased with $CHA_2DS_2VAS_c$ score and patients with low $CHA_2DS_2VAS_c$ (0–1) had no events. An increment of the rate of major bleeding with increasing HASBLED was also observed (Table 5).

DISCUSSION

In a cohort of chronic HD patients with AF, OAT is not associated with total mortality, while antiplatelet agents are associated with an increased risk of death of ~70% more. The continuous use of warfarin tends to be associated with improved survival as compared with individuals who discontinued the medication during follow-up, but the incidence of thromboembolic events is not different in OAT subjects as compared with those who do not take it. Moreover, bleeding

Table 3. Cox model on the death risk for any cause and on cardiovascular death risk adjusted by relevant covariates

	Death for any cause			Cardiovascular death		
	HR	$CI_{95\%}$	P-value	HR	$CI_{95\%}$	P-value
OAT: yes versus no	0.96[a]	0.59–1.56	0.9	1.08[b]	0.47–2.51	0.9
Antiplatelet therapy: yes versus no	1.71	1.10–2.64	0.02	1.77	0.83–3.78	0.1
Age ≥75 years versus <75 years	2.08	1.39–3.11	<0.001	1.51	0.76–3.02	0.2
Dialytic age ≥3 years versus <3 years	0.9	0.61–1.31	0.6	1.27	0.64–2.53	0.5
Gender: female versus male	0.71	0.49–1.04	0.08	0.85	0.43–1.71	0.7
Permanent AF versus other AF	2.05	1.35–3.13	<0.001	1.78	0.84–3.77	0.1
Hypertension: yes versus no	1.26	0.77–2.07	0.4	1.14	0.49–2.67	0.8
Heart failure: yes versus no	2.06	1.40–3.03	<0.001	3.52	1.67–7.42	<0.001
Bleeding/haemorrhagic stroke: yes versus no	1.68	1.10–2.57	0.02	1.57	0.74–3.32	0.2

OAT, oral anticoagulant therapy; AF, atrial fibrillation.
[a]The corresponding estimated HR in a model without adjustment by other covariates was HR = 0.90 (P-value = 0.6).
[b]The corresponding estimated HR in a model without adjustment by other covariates was HR = 1.01 (P-value = 0.9).

events are more frequent in patients taking warfarin, although the maintenance over time of an INR in the therapeutic range wards against the risk of bleeding.

Studies regarding OAT use in AF patients with ESRD are relatively few and they do not reach conclusive results. Some studies are based on large databases, but they also draw conclusions from retrospectively collected and analysed registry data [10, 12, 13] or from a *post hoc* analyses made on the results of trials designed for other purposes [11, 14].

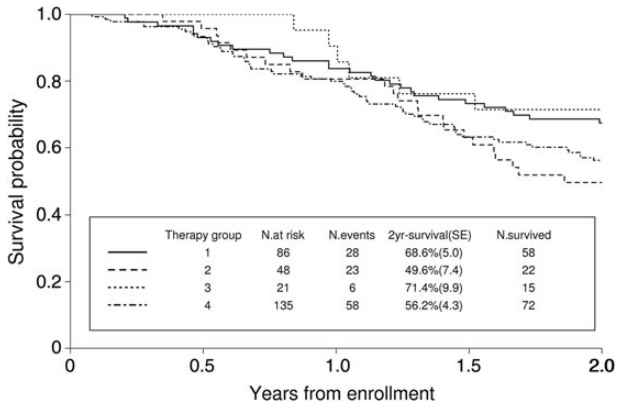

FIGURE 1: Kaplan–Meier curves for survival according to oral anticoagulant therapy (OAT) accounting for therapy shift during the 2 years of follow-up. Therapy group: 1 = OAT at recruitment and during the whole follow-up; 2 = OAT at recruitment, but interrupted during the follow-up; 3 = no OAT at recruitment, but taken during the follow-up; 4 = neither OAT at recruitment nor during the whole follow-up. Log-rank test P-value between couples of therapy group: 1 versus 2 = 0.07; 1 versus 4 = 0.1.

Our prospective study suggests a reduction in the mortality risk in HD patients with documented AF on OAT therapy. This result contrasts with Chan's data, showing an increased mortality in a population of ESRD patients treated with warfarin [18]. However even in this study, the analysis, restricted solely to AF patients receiving OAT, does not show any increase in deaths [10]. A revision of data from the DOPPS shows an excess of mortality in patients treated with warfarin or ticlopidine, but a mortality analysis on the subpopulation of patients with AF is lacking [14]. In our population, warfarin is not associated with a higher death risk, even though subjects with permanent AF most frequently take OAT, and permanent AF represents an important mortality predictor. Moreover, patients who continue to take OAT have lower mortality as compared with those who suspend it during the follow-up, often due to a bleeding. The latter is a factor independently associated with increased mortality and thus our data suggest an advantage in terms of survival for those patients who are able to continue taking the medication with no side effects. It is possible that our patients taking OAT, particularly those who have taken it for the entire follow-up, were healthier at recruitment and thus the improved prognosis was not due to the effect of warfarin treatment alone. However, results similar to ours have recently been found in a population of chronic kidney disease patients with AF [19]. Unlike warfarin, antiplatelet agents are associated with an increased risk of mortality, confirming what had been observed in other ESRD populations [14, 18]. However, this could be due not only to antiplatelet agents *per se* but to the higher prevalence of ischaemic heart disease in this group of patients, which could make them more vulnerable.

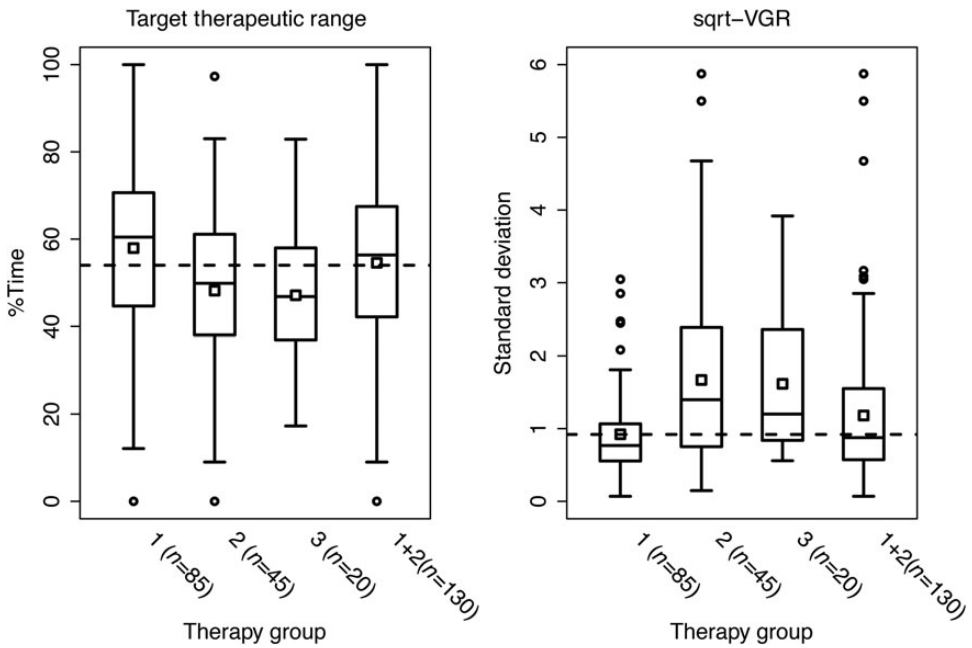

FIGURE 2: TTR and the squared root of VGR distributions by OAT administration during follow-up. The box represents the first and third quartile, the central line the median, the white square the mean and the whiskers are located at the maximum and minimum observation (outside observations indicated with dots are those out of the 1.5× interquartile range); the dashed line represents the overall median. Therapy group: 1 = OAT at recruitment and during the whole follow-up; 2 = OAT at recruitment, but interrupted during the follow-up; 3 = no OAT at recruitment, but assumed during the follow-up 1 + 2 = OAT at recruitment (intention to treat).

Table 4. Cox model results on hazard of haemorrhagic events

	Haemorrhagic events								
	Total population, number of patients = 284, number of events = 40			No before recruitment, number of patients = 228, number of events = 27			Yes before recruitment, number patients = 56, number of events = 13		
	HR	$CI_{95\%}$	P	HR	$CI_{95\%}$	P	HR	$CI_{95\%}$	P
OAT: yes versus no	3.96	1.15–13.68	0.03	4.81	1.08–21.35	0.04	2.21	0.17–28.73	0.5
Antiplatelet therapy: yes versus no	0.86	0.41–1.80	0.7	0.75	0.29–1.96	0.6	1.09	0.33–3.61	0.9
TTR	0.09	0.01–0.76	0.03	0.07	0.01–0.80	0.03	0.2	0.00–18.04	0.5
Bleeding/haemorrhagic stroke: yes versus no	2.17	1.09–4.35	0.03						

OAT, oral anticoagulant therapy; TTR, target therapeutic range.

Table 5. Rate per 100 patients-years of thromboembolic and haemorrhagic events during follow-up according to $CHA_2DS_2VAS_c$ and HASBLED scores and OAT at recruitment

Thromboembolic events	$CHA_2DS_2VAS_c$											
	0–1 ($N = 12$)			2–4 ($N = 149$)			5–9 ($N = 129$)			Overall ($N = 290$)		
	Number of patients	Number of events	Rate	Number of patients	Number of events	Rate	Number of patients	Number of events	Rate	Number of patients	Number of events	Rate
Overall	12	0	0	149	6	2.4	129	11	5.8	290	17	3.7
OAT yes	3	0	0	77	3	2.3	54	5	6.4	134	8	3.7
OAT no	9	0	0	72	3	2.6	75	6	5.3	156	9	3.7
Haemorrhagic events	**HASBLED**											
	0–1 ($N = 3$)			2–3 ($N = 97$)			4–9 ($N = 190$)			Overall ($N = 290$)		
	Number of patients	Number of events	Rate	Number of patients	Number of events	Rate	Number of patients	Number of events	Rate	Number of patients	Number of events	Rate
Overall	3	0	0	97	20	12.6	190	47	15.9	290	67	14.5
OAT yes	2	0	0	60	18	17.8	72	20	18	134	38	17.6
OAT no	1	0	0	37	2	3.5	118	27	14.6	156	29	11.8

The majority of deaths in our patients are not due to stroke and are often non-cardiac deaths, as previously observed in other populations of AF patients with and without ESRD [20–22]. These results emphasize the need to identify effective interventions that go beyond anticoagulation to reduce further high mortality in the AF population.

In our study, patients taking warfarin show a slight, non-significant, reduction of thromboembolic events. Some authors described an increased risk of strokes in HD patients with AF taking warfarin [10, 11], while others see no effect [12] and Olesen *et al.* [13] reported a reduction of thromboembolic events. In these studies, unlike in our study, the ischaemic or haemorrhagic nature of the cerebrovascular episodes is not always documented. In our patients, the thromboembolic event rate was 3.7%, not higher than expected according to the calculated $CHA_2DS_2VAS_c$ score and similar in subjects both taking and not taking OAT. These data are comparable with those previously reported by Wizemann *et al.* [11]. Possibly in HD patients the presence of platelet dysfunction could reduce thromboembolic risk, even in subjects who are not taking OAT. Another possible protective factor is the use of heparin during dialysis, with an anticoagulant effect that may extend for several hours after the dialysis session. However, the fact that although half of the population did not take warfarin, the time of INR in the therapeutic range among treated patients is ~50% and almost all patients experiencing a thromboembolic event were either not on OAT or had an INR <2, which does not allow us to understand whether proper warfarin administration has a role in preventing thromboembolic events in patients with ESRD and AF.

Even in our population, as already reported [12, 23, 24], OAT is associated with an increased haemorrhagic risk. This seems to be a good enough reason to discourage the nephrologist from using warfarin, even when there is an indication for prescription [25]. However, our data show that patients maintaining INR in the therapeutic range are protected from bleeding complications. Hence, the increased haemorrhagic risk does not seem to be so much due to the warfarin *per se* as to the difficulties encountered in maintaining a proper therapeutic INR range. However, a high TTR does not seem to be protective in patients with previous bleeding. Our findings confirm that HD patients are at high risk for both thrombosis and bleeding, and that any OAT treatment needs to be performed with great care. In particular, warfarin should not be

administered in patients with previous bleeding episodes occurring in the presence or even in the absence of OAT. In these subjects, particularly when the $CHA_2DS_2VAS_c$ score is high, alternative hypotheses for the prevention of thromboembolism, recently proposed in cardiology, i.e. the closure of the left atrial appendage [26], could be evaluated.

In our study, low $CHA_2DS_2VAS_c$ and HASBLED scores identify patients at lower thromboembolic or haemorrhagic risk confirming that these scores, even in subjects with ESRD, may provide consistent data [11, 12]. A better performance of the $CHADS_2$ score when two points were added in patients with a glomerular filtration rate <45 mL/min has been shown [27]. Studies that lead to a modification of the thromboembolic scores based on the presence of renal disease are warranted and careful evaluation of the HASBLED score before embarking on an OAT in a patient with ESRD definitely remains of paramount clinical importance.

The strengths of this study are that cerebrovascular events were always defined as ischaemic or haemorrhagic by computed tomographic scan or nuclear magnetic resonance, and that the INR was carefully monitored. A limitation is the fact that this was not a randomized study and the nephrologist was left to choose the therapeutic prescription without reservation: OAT, antiplatelet therapy or nothing.

In conclusion, to our knowledge, this is the first prospective study designed to assess the effects of warfarin on both mortality and cerebrovascular events in HD population. In our study, OAT is not associated with increased mortality; although it is not related to a significant decreased incidence of ischaemic stroke, it increases the incidence of bleeding. However, in our population, the risk of bleeding is reduced in subjects in whom INR is constantly kept within the therapeutic range. Moreover, the thromboembolic (CHA2DS2VASc) and haemorrhagic (HASBLED) scores are capable of identifying low-risk patients, but this population represents a minority of the subjects being examined. Many of our findings may be useful with regard to the controversial issue of anticoagulation in HD patients with AF. Larger prospective studies and randomized trials are greatly needed to provide nephrologists with additional elements concerning how to treat HD patients with AF in order to prevent the thromboembolic complications of the arrhythmia avoiding the haemorrhagic risk related to OAT in these patients with such a high risk of bleeding.

SUPPLEMENTARY MATERIAL

Supplementary material is available online at http://ndt.oxfordjournals.org.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Szummer and Carrero. Warfarin therapy for atrial fibrillation in haemodialysis patients: mind the (evidence) gap. *Nephrol Dial Transplant* 2015; 30: 337–339.)

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ORIGINAL ARTICLE

Prescription of potentially inappropriate medications to elderly hemodialysis patients: prevalence and predictors

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ABSTRACT

Background. In elderly hemodialysis (HD) patients, the risk of medication-related problems is particularly high. Thus, certain medications should generally not be prescribed to those patients. The Beers criteria for potentially inappropriate medications (PIMs) have been publicized. Still, with regard to elderly HD patients, the prevalence and risk factors for prescription of PIMs are unknown.

Methods. This was a cross-sectional study of data from the Japan Dialysis Outcomes and Practice Patterns Study (2002–08). Patients were included if they were 65 years old or older and were currently receiving HD treatment at a hospital or clinic. We counted the number of patients who were prescribed at least one PIM, as defined by the modified Beers criteria. We used multiple logistic regression analysis to determine which patient characteristics and facility characteristics were associated with prescription of PIMs.

Results. Data from 1367 elderly patients were analyzed. More than half of the patients (57%) had been prescribed a PIM. The three most frequently prescribed PIMs were H2 blockers (33%), antiplatelet agents (19%) and α-blockers (13%). PIM prescriptions were less likely at facilities that conducted multidisciplinary rounds {adjusted odds ratio (AOR): 0.67 [95% confidence interval (CI): 0.48–0.93]} and at teaching hospitals [AOR: 0.59 (95% CI, 0.39–0.90)]. PIM prescriptions are more likely if more than one physician has clearance to alter the HD regimen [AOR: 1.65 (95% CI, 1.12–2.44)].

Conclusions. PIMs were prescribed to many elderly HD patients in Japan. Nephrologists should become more aware of PIMs. Multidisciplinary rounds could benefit patients by reducing the prescription of PIMs.

Keywords: adverse drug events, DOPPS, elderly patients, hemodialysis, potentially inappropriate medication

INTRODUCTION

Issues associated with medication administration remain a major healthcare concern, particularly among elderly patients. A 2005