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Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy

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Using data from the international Dialysis Outcomes and Practice Patterns Study (DOPPS), we determined incidence, prevalence, and outcomes among hemodialysis patients with atrial fibrillation. Cox proportional hazards models, to identify associations with newly diagnosed atrial fibrillation and clinical outcomes, were stratified by country and study phase and adjusted for descriptive characteristics and comorbidities. Of 17,513 randomly sampled patients, 2188 had preexisting atrial fibrillation, with wide variation in prevalence across countries. Advanced age, non-black race, higher facility mean dialysate calcium, prosthetic heart valves, and valvular heart disease were associated with higher risk of new atrial fibrillation. Atrial fibrillation at study enrollment was positively associated with all-cause mortality and stroke. The CHADS2 score identified approximately equal-size groups of hemodialysis patients with atrial fibrillation with low (less than 2) and higher risk (more than 4) for subsequent strokes on a per 100 patient-year basis. Among patients with atrial fibrillation, warfarin use was associated with a significantly higher stroke risk, particularly in those over 75 years of age. Our study shows that atrial fibrillation is common and associated with elevated risk of adverse clinical outcomes, and this risk is even higher among elderly patients prescribed warfarin. The effectiveness and safety of warfarin in hemodialysis patients require additional investigation.

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Atrial fibrillation (AF) is the most common cardiac dysrhythmia requiring clinical attention and is associated with age and cardiovascular morbidity.[1] In the general population, AF is a potent risk factor for stroke (cerebrovascular events)[2] and death.[3] AF is often associated with impaired cardiac performance and lower quality of life.[4] Given the aging populations and associated rising burden of cardiovascular disease in industrialized countries, the prevalence of AF is expected to increase by 2.5-fold over the next five decades.[5]

Decreased glomerular filtration rate and chronic kidney disease are independently associated with cardiovascular events.[6] Older patients with end-stage renal disease (ESRD) are a rapidly growing group; the incidence of ESRD has tripled in the last decade.[7] Cardiovascular prognosis is even worse in patients with coexisting cardiovascular disease and ESRD requiring hemodialysis (HD) therapy.[8] In addition to these patient-based factors associated with AF, the specific pattern of intermittent HD may raise the risk of HD patients developing AF. Differences in the incidence of AF between HD and peritoneal dialysis patients[9] and the occurrence of supraventricular arrhythmias in the last hours of HD[10] point toward an association between HD practice patterns and the development of AF in HD patients.

In the general population, clinical trial data support the use of warfarin for stroke prevention in many patients with non-rheumatic AF; risk stratification according to stroke risk (for example, by the CHADS2 score) now guides recommendations for warfarin use.[11–13] Though warfarin use in dialysis patients with AF is common, there are few, if any, data supporting its efficacy and there are widespread concerns about its safety.[14–16] In the absence of clinical trial data in dialysis patients, evaluation of tools such as the CHADS2 score may provide a useful step toward informed decisions about warfarin use.

This study reports several findings: the prevalence of AF in an international, representative sample of HD patients; the associations of AF with comorbid conditions, laboratory measures, and cardiovascular medications; and the relative risks of adverse outcomes including mortality and strokes

among AF patients. An additional goal of this study was to evaluate the association of anticoagulation therapy with subsequent strokes and to assess the performance of the CHADS2 stroke risk stratification scheme as a means to potentially guide warfarin therapy in HD patients.

RESULTS

Prevalence and incidence of atrial fibrillation

Among the prevalent cross-section of HD patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS), 12.5% (2188 out of 17,513) had pre-existing AF at baseline (range 5.6% in Japan to 24.7% in Belgium, see Table 1). The incidence of newly diagnosed AF during the follow-up period was 1.0 per 100 patient-years (range 0.5 in Japan to 3.0 in Sweden). The prevalence of AF increased with age and was much higher in all age categories than in the general population (Figure 1).

Associations with pre-existing atrial fibrillation

The baseline cross-sectional model showed a substantially higher adjusted odds ratio (OR) of pre-existing AF (that is, with having a known history of AF) with older age (Table 2). There was no significant difference by sex. However, AF was less common in black vs non-black patients. The OR of having AF was higher with more years of HD therapy. AF was associated with many cardiac conditions (listed in Table 2). Patients with cerebrovascular disease were marginally more likely to have AF. AF was significantly associated with left ventricular hypertrophy, though not with a diagnosis of hypertension; patients with higher pre-dialysis systolic blood pressure at the time of study enrollment were less likely to have AF. Dividing systolic blood pressure into categories, only the lowest quintile of the systolic blood pressure (<130 mm Hg) was associated with pre-existing AF (OR = 1.37, 95% CI = 1.18–1.58, $P<0.0001$) compared with the reference category of 143–156 mm Hg.

Associations with newly diagnosed atrial fibrillation

In the longitudinal model evaluating time from enrollment to hospitalization for new AF (patients with previous AF were excluded from the analysis) (Table 2), the likelihood of developing AF was positively associated with older age,

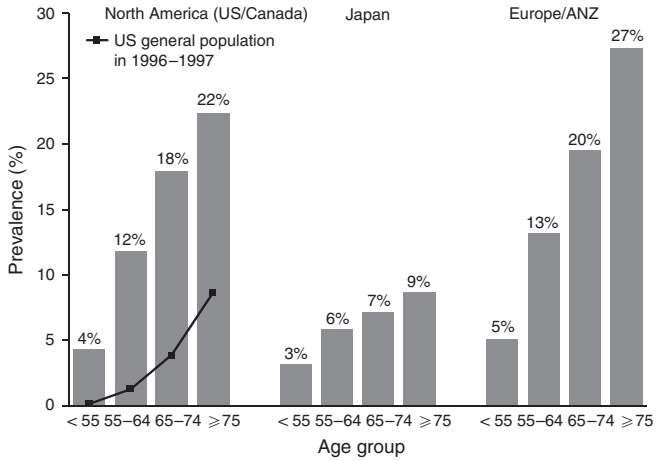


Figure 1 | Prevalence of history of atrial fibrillation (AF) at DOPPS enrollment by region and age in prevalent cross-sections combining DOPPS I (1996–2001) and DOPPS II (2002–2004) ($n = 17,513$). For comparison, the approximate prevalence of AF in the same age categories among 1.89 million adults in the US general population in 1996–1997 is also shown (ref. 5).

Table 1 | Prevalence and incidence of atrial fibrillation by country

	Prevalent (pre-existing) AF[a]			Incident (newly diagnosed) AF[b]		
Country	Total number of patients	Prevalence *n* (%)	OR (95% CI; *P*-value)	Incident cases - *n*	Incidence per 100 patient-years	HR (95% CI, *P*-value)
Belgium	534	132 (24.7)	1.96 (1.39–2.75; $P<0.01$)	27	2.9	2.26 (1.25–4.06; $P<0.01$)
France	1043	191 (18.3)	1.65 (1.27–2.15; $P<0.01$)	27	1.4	1.41 (0.89–2.22; $P=0.14$)
Germany	1064	170 (16.0)	1.62 (1.27–2.07; $P<0.01$)	25	1.2	1.18 (0.71–1.95; $P=0.53$)
Italy	1137	128 (11.3)	1.09 (0.81–1.46; $P=0.57$)	40	1.8	1.70 (1.01–2.86; $P=0.05$)
Spain	1097	163 (14.9)	1.36 (1.01–1.83; $P=0.04$)	30	1.4	1.38 (0.80–2.36; $P=0.25$)
Sweden	535	115 (21.5)	2.04 (1.44–2.89; $P<0.01$)	29	3.0	2.70 (1.54–4.74; $P<0.01$)
United Kingdom	1041	122 (11.7)	1.20 (0.87–1.64; $P=0.26$)	18	1.1	1.17 (0.64–2.11; $P=0.61$)
EUR Overall	*6451*	*1021 (15.8)*	*1.47 (1.23–1.75; $P<0.01$)*	*196*	*1.6*	*1.51 (1.09–2.09; $P=0.01$)*
Australia/New Zealand	507	81 (16.0)	1.29 (0.88–1.89; $P=0.20$)	14	1.6	1.54 (0.63–3.74; $P=0.34$)
Canada	596	113 (19.0)	1.45 (1.00–2.12; $P=0.05$)	16	1.6	1.45 (0.79–2.68; $P=0.23$)
Japan	3935	219 (5.6)	0.67 (0.52–0.87; $P<0.01$)	36	0.5	0.60 (0.38–0.96; $P=0.03$)
United States	6024	754 (12.5)	1.00 (Ref.)	125	0.7	1.00 (Ref.)
Overall	*17,513*	*2188 (12.5)*	—	*387*	*1.0*	—

Combined DOPPS I/II data (1996–2004); logistic and Cox models were adjusted for country, phase, age, sex, black race, time with ESRD, CAD, cancer, cerebrovascular disease, heart failure, diabetes mellitus, GI bleed, HIV/AIDS, hypertension, lung disease, neurological disorder, psychiatric disorder, PVD, and recurrent cellulitis, controlling additionally for effects of facility clustering. France, Germany, Italy, Japan, Spain, UK, and US participated in both DOPPS I and II. Australia/New Zealand, Belgium, Canada, and Sweden were only in DOPPS II.

Abbreviations: CAD, coronary artery disease; DOPPS, Dialysis Outcomes and Practice Patterns Study; ESRD, end-stage renal disease; GI, gastrointestinal, PVD, peripheral vascular disease.

[a]Prevalent (pre-existing) atrial fibrillation (AF) calculated among baseline DOPPS I and II prevalent cross-sections (n=17,513); OR = adjusted odds ratio of having history of AF (yes vs no) before study entry.

[b]Incident (newly diagnosed) AF calculated at follow-up and includes data from all DOPPS I and II patients without a baseline diagnosis of AF (n=25,709); HR = hazard ratio of hospitalization for new AF during study follow-up (n=387 events overall).

Table 2 | Associations with pre-existing and newly diagnosed atrial fibrillation

Characteristics	Pre-existing AF			Newly diagnosed AF		
	OR[a]	95% CI	*P*-value	HR[b]	95% CI	*P*-value
Demographics						
Age (per 5 years older)	**1.25**	**(1.22–1.28)**	**<0.001**	**1.19**	**(1.14–1.24)**	**<0.001**
Male (vs female)	1.07	(0.96–1.19)	0.231	0.88	(0.72–1.08)	0.228
Black race (vs non-black)	**0.74**	**(0.59–0.93)**	**0.009**	**0.40**	**(0.25–0.63)**	**<0.001**
Time with ESRD (per 1 year)	**1.04**	**(1.03–1.05)**	**<0.001**	1.02	(0.99–1.04)	0.153
Body mass index (per 1 kg/m^2)	**1.01**	**(1.00–1.02)**	**0.007**	1.01	(0.99–1.03)	0.392
Dialysis and laboratory values						
Pre-HD systolic blood pressure (per 10 mm Hg)	**0.94**	**(0.92–0.96)**	**<0.001**	0.99	(0.95–1.04)	0.788
Duration of HD session (per 30 min)	**1.08**	**(1.02–1.14)**	**0.006**	1.01	(0.93–1.09)	0.871
spKt/V (per 0.1)	0.99	(0.96–1.01)	0.248	1.03	(0.99–1.07)	0.154
Serum albumin (per 1 g/dl)	0.92	(0.81–1.04)	0.174	0.90	(0.70–1.16)	0.426
Normalized PCR (per 0.1)	1.00	(0.98–1.03)	0.788	1.02	(0.96–1.08)	0.489
Serum calcium (per 1 mg/dl)	**1.13**	**(1.06–1.20)**	**<0.001**	0.95	(0.83–1.09)	0.499
Serum phosphorus (per 1 mg/dl)	1.02	(0.99–1.06)	0.129	1.05	(0.99–1.11)	0.090
Serum PTH (per 100 pg/ml)	1.00	(0.99–1.02)	0.627	1.03	(0.99–1.07)	0.109
Serum potassium (per 1 mg/dl)	0.94	(0.88–1.01)	0.080	0.96	(0.84–1.09)	0.538
Hemoglobin (per 1 g/dl)	0.99	(0.96–1.03)	0.749	0.95	(0.88–1.02)	0.172
Dialysate calcium (per 1 mEq/l)	1.04	(0.87–1.23)	0.678	1.32	(0.96–1.81)	0.082
Dialysate potassium (per 1 mEq/l)	**1.18**	**(1.06–1.31)**	**0.003**	1.03	(0.84–1.27)	0.787
Facility mean dialysate calcium (per 1 mEq/l)[c]	1.01	(0.76–1.33)	0.955	**1.63**	**(1.04–2.55)**	**0.034**
Facility mean dialysate potassium (per 1 mEq/l)[c]	1.10	(0.86–1.40)	0.436	0.80	(0.55–1.14)	0.554
Summary comorbid conditions (yes vs no)						
Coronary artery disease	**1.56**	**(1.39–1.75)**	**<0.001**	1.12	(0.89–1.41)	0.341
Heart failure	**2.08**	**(1.84–2.35)**	**<0.001**	1.14	(0.90–1.45)	0.283
Cerebrovascular disease	1.11	(0.98–1.25)	0.090	0.87	(0.65–1.18)	0.374
Hypertension	1.08	(0.95–1.23)	0.232	1.19	(0.89–1.58)	0.239
Peripheral vascular disease	1.02	(0.90–1.16)	0.762	1.03	(0.80–1.34)	0.805
Recurrent cellulitis	**1.23**	**(1.04–1.46)**	**0.017**	1.11	(0.70–1.75)	0.665
Diabetes mellitus	0.89	(0.79–1.00)	0.053	0.88	(0.69–1.13)	0.325
GI bleed	1.18	(0.97–1.44)	0.094	0.97	(0.64–1.46)	0.875
Lung disease	1.15	(1.00–1.32)	0.050	1.15	(0.84–1.56)	0.392
Neurological disorder	1.09	(0.93–1.27)	0.281	1.00	(0.68–1.46)	0.997
Psychiatric disorder	**1.15**	**(1.01–1.30)**	**0.031**	1.07	(0.82–1.39)	0.602
Cancer, other than skin	0.96	(0.83–1.11)	0.585	1.09	(0.81–1.45)	0.575
HIV/AIDS	0.70	(0.26–1.88)	0.484		No events	
Other cardiac conditions (yes vs no)						
Permanent pacemaker implanted	**2.36**	**(1.90–2.92)**	**<0.001**	0.97	(0.49–1.92)	0.921
Left ventricular hypertrophy	**1.24**	**(1.11–1.40)**	**<0.001**	1.13	(0.87–1.46)	0.353
Valvular heart disease	**1.65**	**(1.45–1.89)**	**<0.001**	**1.44**	**(1.08–1.93)**	**0.012**
History of cardiac arrest	**2.22**	**(1.72–2.87)**	**<0.001**	0.73	(0.30–1.80)	0.497
Pericarditis	**1.61**	**(1.25–2.07)**	**<0.001**	0.93	(0.52–1.65)	0.799
Prosthetic heart valve	**1.71**	**(1.27–2.32)**	**<0.001**	**1.94**	**(1.08–3.50)**	**0.028**
Current medications (Rx vs no Rx)[d]						
Aspirin	0.95	(0.84–1.08)	0.414	1.06	(0.83–1.35)	0.654
Warfarin	**2.76**	**(2.30–3.30)**	**<0.001**	0.89	(0.51–1.56)	0.692
β-blocking agents	1.08	(0.96–1.22)	0.188	1.11	(0.85–1.46)	0.448
Digoxin	**4.48**	**(3.80–5.27)**	**<0.001**	**1.67**	**(1.08–2.57)**	**0.020**
Angiotensin-converting enzyme inhibitors	0.90	(0.79–1.03)	0.117	1.10	(0.87–1.39)	0.442
Ca channel-blocking agents	**1.65**	**(1.38–1.97)**	**<0.001**	1.25	(0.87–1.80)	0.229

Abbreviation: HD, hemodialysis.
[a]Combined DOPPS I and II data (1996–2004), among respective phase-specific prevalent cross-sections (n=17,513 overall); OR = Adjusted odds ratio of history of atrial fibrillation (AF) (n=2,188); multivariable model adjusted for all covariates listed (except as below) and country, and controlling for effects of facility clustering.
[b]Combined DOPPS I and II data (1996–2004), among all patients without a baseline diagnosis of AF (n=25,709 overall); HR = adjusted hazard ratio of hospitalization for new AF (n=387 events); multivariate model adjusted for all covariates listed (except as below) in addition to phase and country, and controlling for effects of facility clustering.
[c]Facility dialysate variables were run in separate multivariable models from the patient-level dialysate variables.
[d]Medications were each run individually in separate multivariable models.

non-black race, and higher facility mean dialysate calcium. Other cardiac conditions positively associated with new AF included valvular heart disease and prosthetic heart valves.

Medication use in patients with atrial fibrillation

As shown in Table 3, aspirin was the most frequently prescribed cardiac-related medication (31%) in patients with pre-existing AF. The relatively frequent prescription (23%) in

Table 3 | Medication use among patients according to atrial fibrillation status, by region

	Medication (% use)													
	Aspirin		Warfarin		β-Blocking agents		Calcium channel-blocking agents		ACE inhibitors		Digoxin		Amiodarone	
Country/region	AF	No AF	AF	No AF	AF	No AF	AF	No AF	AF	No AF	AF	No AF	AF	No AF
Belgium	33	31	7	3	31	30	2	2	19	23	3	2	25	3
France	27	20	5	1	18	21	9	6	20	20	11	1	46	6
Germany	37	31	2	2	34	34	12	8	37	30	4	0	7	1
Italy	24	21	14	5	7	9	7	5	13	16	24	6	29	2
Spain	25	17	4	0	11	13	9	4	15	14	25	2	22	2
Sweden	39	36	16	3	57	51	3	2	15	18	21	2	2	0
United Kingdom	46	35	24	11	31	23	2	4	21	24	21	2	22	1
EUR Overall	*32*	*26*	*9*	*4*	*26*	*23*	*7*	*5*	*21*	*20*	*15*	*2*	*23*	*2*
Australia/New Zealand	33	41	25	4	26	26	12	9	22	28	27	3	14	2
Canada	40	38	37	17	42	47	8	8	28	39	18	2	9	2
Japan	17	10	5	1	13	9	14	8	13	18	17	3	0	0
United States	30	25	26	8	31	30	17	9	22	24	33	8	8	1
Overall	*31*	*23*	*16*	*5*	*27*	*23*	*11*	*7*	*21*	*22*	*22*	*4*	*15*	*1*

Combined DOPPS I/II data (1996–2004); among baseline DOPPS I and II prevalent cross-sections (n=17,220). Patients with AF had 'history of atrial fibrillation' at DOPPS enrollment.

patients without a history of dysrhythmia indicates that the proportion of aspirin prescription for specific anticoagulation effects in AF is small. Though prescribed less frequently than aspirin, prescription of warfarin (16%) was three times more frequent in patients with pre-existing AF than those without AF. There was an 18-fold difference between countries in the frequency of prescribing warfarin to AF patients, with the lowest usage in Germany (2%) and the highest in Canada (37%). The overall prevalence of medications used for AF frequency control among patients with pre-existing AF was 22% for digoxin, 27% for beta-blockers, 21% for ACE inhibitors, and 11% for calcium channel blockers. Use of anti-arrhythmic agents among AF patients was 15% overall for amiodarone and $\leqslant$1.1% for other agents. Digoxin was more frequently prescribed to patients with (vs without) pre-existing AF in all countries, as were amiodarone and calcium channel-blocking agents in most countries. Use of amiodarone in AF was extremely variable among countries: in France nearly 50% were treated with this Class 3 anti-arrhythmic, but its use in Japan and Sweden was nearly absent. Beta-blocker and ACE inhibitor use did not substantially vary by AF status in most countries. In keeping with the findings in Table 3, prescription of warfarin (OR = 2.76, $P<0.001$), digoxin (OR = 4.48, $P<0.001$), and calcium channel-blocking agents (OR = 1.65, $P<0.001$) were significantly associated with pre-existing AF in multivariable models (Table 2).

Mortality and hospitalization

Pre-existing AF at DOPPS enrollment was positively associated with all-cause mortality (HR = 1.16, 95% CI = 1.08–1.25, $P<0.001$) and hospitalization or death because of a stroke/cerebrovascular event (HR = 1.28, 95% CI = 1.01–1.63; $P=0.048$) after adjusting for sex, black race, years of ESRD, age, 14 summary comorbidities, and excluding patients with a prosthetic heart valve. Pre-existing AF was also positively associated with cardiac mortality (HR = 1.10, 95% CI = 0.98–1.23; $P=0.09$) whereas no association was observed with all-cause hospitalization (HR = 1.02, 95% CI = 0.96–1.07; $P=0.59$).

Compared with patients without AF at DOPPS enrollment, those with AF had a significantly higher rate of subsequent stroke/cerebrovascular events (hospitalization or death because of cerebrovascular causes) during follow-up (3.4 vs 1.9 events per 100 patient-years; adjusted HR = 1.28, 95% CI = 1.01–1.62 for AF vs no AF, $P=0.048$).

Stroke risk stratification

To evaluate the performance of CHADS2 as a stroke risk stratification score to potentially guide anticoagulation decisions, stroke rates according to CHADS2 score for patients with AF at DOPPS enrollment are provided in Table 4. Patients with a prosthetic heart valve ($n=177$) were excluded, as use of warfarin is required in these patients. Findings are presented for all other AF patients ($n=3250$), as well as restricted to AF patients ($n=643$) without valvular heart disease and taking acetylsalicylic acid (ASA, aspirin) but not warfarin (as used for CHADS2 development).[13] The table shows that the cerebrovascular event rate for patients with CHADS2 = 0 was <1 per 100 patient-years, and that the event rate increased monotonically with rising CHADS2 scores (to 12–19 per 100 patient-years at the maximum CHADS2 score). In a multivariable model, three of the five CHADS2 variables (history of previous stroke, diabetes, and older age) were significantly associated with subsequent stroke, but the other two (hypertension and heart failure) were not (data not shown).

Warfarin use and stroke risk

As shown in Figure 2, warfarin use among patients with pre-existing AF was associated with elevated stroke risk in older patients, with HR = 1.29 (95% CI = 0.45–3.68; $P=0.63$) for patients $\leqslant$65 years, 1.35 (95% CI = 0.69–2.63; $P=0.39$) for patients 66–75 years, and 2.17 (95% CI = 1.04–4.53, $P=0.04$)

Table 4 | Stroke rates among HD patients with history of atrial fibrillation, by CHADS2 score[a]

CHADS2 score[c]	(A) Patients with history of non-valvular AF—prescribed aspirin but not warfarin[b]			(B) All patients with history of non-valvular AF[b]		
	Patients (*n*)	Stroke events (*n*)	Stroke rate per 100 patient-years[d]	Patients (*n*)	Stroke events (*n*)	Stroke rate per 100 patient-years[d]
0	16	0	0.0	141	1	0.5
1	114	1	0.6	568	18	2.1
2	174	6	2.3	875	23	1.9
3	167	8	3.8	882	45	3.9
4	92	6	5.6	403	27	6.0
5	70	6	6.1	311	25	6.5
6	10	2	19.0	70	9	12.7
Overall	*643*	*29*	*3.3*	*3250*	*148*	*3.4*

[a]Stroke rates during DOPPS follow-up among patients with history of atrial fibrillation (AF) at DOPPS enrollment, excluding 177 patients with mechanical heart valves.
[b]Column A includes dialysis patients generally comparable with those used to evaluate CHADS2 in the general population; 27 patients on heparin between dialysis sessions but not warfarin were also excluded; column B includes all AF patients without a mechanical heart valve.
[c]Based on stroke risk according to CHADS2 score in the general population: 0=low, 1 or 1–2=moderate, and ⩾2 or 3=high risk. Among a non-dialysis Medicare population with non-valvular AF and not receiving warfarin, stroke rates for CHADS2 score=0, 1–2, and ⩾3 were 0.8, 2.7, and 5.3 per 100 patient-years, respectively (refs. 11–13).
[d]Column A=891 patient-years; column B=4348 patient-years.

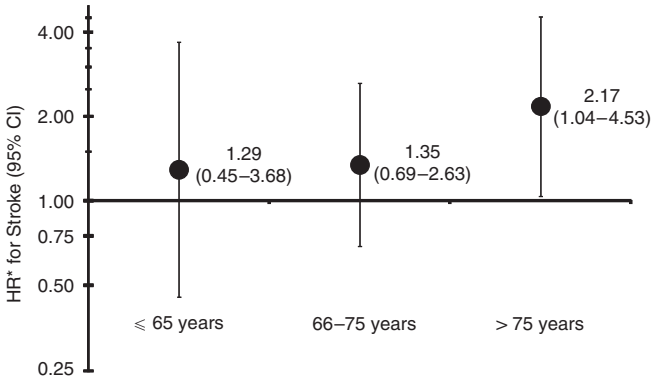


Figure 2 | Hazard ratio (HR) for stroke according to warfarin use, by age categories among patients with a diagnosis of atrial fibrillation at DOPPS enrollment. The numbers of patients (strokes) were 1001 (35), 1137 (61), and 1107 (49) for age groups ⩽65, 66 to 75, and >75 years, respectively. The numbers (%) of patients on warfarin were 146 (15%), 192 (17%), and 171 (15%) for age groups ⩽65, 66 to 75, and >75 years, respectively. Patients with prosthetic heart valves ($N=177$) were excluded. Separate Cox models for each age category were used to estimate the hazard ratio and 95% confidence interval (whiskers) of first stroke after study entry, adjusted for age within the restricted category, sex, black race, years with ESRD, study phase, history of stroke, comorbid conditions as listed in Table 2, permanent pacemaker implanted, previous history of cardiac arrest, left ventricular hypertrophy, and valvular heart disease, stratified by region and study phase and accounting for effects of facility clustering. In addition to warfarin use, the following variables were statistically significant ($P<0.05$) in a model including all age categories: neurologic disease ($P=0.02$), diabetes ($P=0.03$), and previous history of stroke ($P=0.002$).

for patients >75 years. Warfarin use (compared with non-use) was also associated with elevated stroke risk in patients with high (⩾3) but not lower CHADS2 scores. However, this finding was explained by age (Figure 2), not the other CHADS2 variables. AF was not associated with elevated risk of hospitalization because of gastrointestinal bleeding, and this relationship was not influenced by the use of aspirin, warfarin, or other anticoagulation medications (data not shown).

DISCUSSION

Epidemiology of atrial fibrillation

This international study confirms that AF is common in the HD population, with prevalence several times higher than in the general population.[2,5] In support of our findings, the prevalence of AF among HD patients in previous smaller studies was 14 to 27%,[17–22] and the incidence of AF in the US-DOPPS population was almost identical to that reported in the United States Renal Data System for a cohort of dialysis patients hospitalized for AF.[9]

There was a more than threefold variation in reported AF between DOPPS countries (Table 1). This may represent, in part, differences in the detection of AF between countries. The DOPPS medical questionnaire asks if the patient has a history of AF (yes or no), but does not require ECG documentation. On the other hand, the much lower prevalence of AF in Japan than in other countries may be largely due to true differences in prevalence. This possibility is consistent with the lower prevalence of cerebrovascular disease in Japanese HD patients than elsewhere.[23,24]

Atrial fibrillation and associated conditions

As in the general population,[5,25] the incidence and prevalence of AF in the HD population was higher in older patients and in non-black compared with black patients (Table 2 and Figure 1). Greater duration of ESRD was also associated with higher incidence and prevalence of AF. Numerous cardiovascular conditions were associated with pre-existing AF, which is very comparable with associations observed in the general population[1,3,25] and described for dialysis patients in Italy, Turkey, New Zealand, Spain, and the United States.[9,18–20,22]

The association between pre-existing AF and lower blood pressures (Table 2) is also notable. Dividing systolic blood pressure (SBP) into categories, only the lowest quintile of the SBP range (<130 mm Hg) was associated with pre-existing AF (HR = 1.37, 95% CI = 1.18–1.58, $P<0.0001$). The longitudinal model of the occurrence of new AF detected no such associations with low blood pressure. Taken together, these data are consistent with the possibility that low blood pressure is a sequela, not a cause, of AF and/or associated comorbidities.

Many other cardiac conditions studied (heart failure, valvular heart disease, permanent pacemaker, and others) were associated with pre-existing AF, as expected (Table 2). In contrast to the associations with pre-existing AF, only valvular heart disease and prosthetic heart valves were associated with newly diagnosed AF. In addition, patients using digoxin were more likely to develop AF, probably because cardiovascular abnormalities that are indications for digoxin therapy also raise the risk of developing AF. The absence of anticipated associations of some cardiac conditions with new AF may be due to the relatively rare occurrence, or reporting, of new AF. Reports have shown that progression of renal failure and time on ESRD therapy are associated with multiple cardiovascular alterations, such as the easily detectable progression of left ventricular hypertrophy and cardiac atrial diameters;[26,27] overt or masked calcifications of cardiac valves, myocardium, and media of vessels;[28–30] and the progressive increase in cardiac fibrosis.[31,32] Many of these alterations escape clinical detection (and therefore are not captured in the DOPPS) despite the fact that left atrial enlargement—which is prevalent in 40% of HD patients[27]—is a powerful predictor of AF.[33] In a study from northern Italy, which prospectively followed by ECG 349 hospital-based HD patients over 3 years, 35 had new onset AF, and in a multivariable analysis there was a significant association with left ventricular hypertrophy.[34]

Pharmacological intervention to achieve heart rate control is a primary therapeutic approach for recurrent and persistent AF.[35–37] In the AFFIRM study,[35] digoxin (71%), β-blockers (47%), and nondihydropyridine calcium channel antagonists (40%) were commonly used in AF patients. If these data in cardiac patients are applied as standards for HD patients with AF, then these three classes of drugs were underused by a factor of approximately 2.5 in the DOPPS (Table 3). The large international variability in amiodarone use may be explained by different opinions about risk-benefit assessment in the absence of long-term effectiveness, safety, and outcomes data in dialysis patients. Although the drug is effective in achieving and maintaining sinus rhythm in non-renal patients with AF,[38] concerns about long-term toxicity and interactions with drugs like statins, digoxin, and warfarin may cause some providers to be reluctant to prescribe the drug to dialysis patients.

Atrial fibrillation and clinical events

In the general population, the risk of death or stroke attributed to AF without overt structural heart disease is low below the age of 60 years.[1,3,39] However, older patients with AF and arterial hypertension have an increased complication rate. The possibility that AF in HD patients might be a marker for other undetected cardiovascular disease is supported by the independent association of years on dialysis with AF, as more years on dialysis is generally associated with increased prevalence of cardiovascular disease.

In previous studies of dialysis patients, overall mortality was elevated by as much as 1.7–3.8 times among patients with vs without AF.[18,34] In this study, the magnitude of the excess risk of all-cause mortality in HD patients with AF was smaller (adjusted HR = 1.17, 95% CI = 1.08–1.24, $P<0.01$). Our findings are generally comparable with the magnitude of the adjusted HR of mortality from AF (1.31) in long-term observational studies in the general population.[1,3,39] The relative risk of cardiovascular death in HD patients with AF was also elevated (adjusted HR = 1.16, 95% CI = 1.08–1.24, $P=0.009$), which underlines the association of AF with coexisting cardiovascular disease.[9,18–20,40]

There is an excessive stroke risk in the ESRD population, and mortality after stroke is very high.[41–43] In the general population, AF is associated with a sixfold increased risk for stroke,[44] with the mechanism considered to be embolism originating as thrombus in the fibrillating atrial appendage.[45] In our study, HD patients with AF had a higher rate of subsequent stroke than those without AF (3.4 vs 1.9 events per 100 patient-years; HR = 1.79, $P=0.003$). This difference is directionally similar to that for AF patients in the general population, although the magnitude is notably smaller. Our finding contrasts with some previous smaller studies of AF among HD patients, which found no elevation of stroke risk.[17,34] However, in another study, the rate of ischemic stroke was higher in dialysis patients with AF (3 of 40 patients) compared with those without AF (3 of 115 patients).[21]

Stroke risk and warfarin therapy in AF

Risk-benefit assessment with respect to anticoagulation therapy for stroke prophylaxis is crucially dependent on the magnitude of stroke risk, as well as the effectiveness and safety of anticoagulation therapy.[13] With regard to the former, risk stratification can help guide informed clinical decision making.[46] The CHADS2 score (an acronym for congestive heart failure, hypertension, age >75 years, diabetic status, and history of stroke or transient ischemic attack) was developed to predict the risk of subsequent stroke (and therefore to help guide anticoagulation therapy) among patients with AF in the general population.[13] CHADS2 has been adapted in a clinical practice guideline for AF patients, and it was recently endorsed in the United States as part of a clinical performance measure for management of AF.[11,12] Using DOPPS data, this study has found that in dialysis patients CHADS2 effectively identified approximately

equal-sized patient groups at low and higher risk for subsequent stroke (rates <2 and >4 per 100 patient-years, respectively) (Table 4). CHADS2 performance was comparable in (A) patients without valvular heart disease and not prescribed warfarin (as used for CHADS2 validation in the general population) and (B) for a less restricted group of patients. Notably, CHADS2 scores were higher in this study than in the general population (by 0.6 for mean and 1.0 for median), and thus the proportion at higher risk was somewhat greater.[47]

The absolute stroke rate among patients in the low-risk group in our study (<2 per 100 patient-years) is approximately equal to the rate below which anticoagulation is not recommended in the general population with AF.[11–13] In conjunction with data validating CHADS2 for the identification of low-risk patients in the general population, these findings may support the decision to not anticoagulate dialysis patients with AF and a low CHADS2 score, in the absence of other indications for anticoagulation.

On the other hand, several CHADS2 components (hypertension, heart failure) in our dialysis population were not independently associated with stroke. Hypertension may not predict stroke in dialysis patients because its epidemiological associations differ from those in the general population: most ($>80\%$ of) HD patients have a history of hypertension, and patients with high blood pressure paradoxically survive longer, due in part to better health status. The explanation for the finding for heart failure is less evident. Regardless of the reason, our data indicate that CHADS2 may misclassify some low-risk HD patients as having higher stroke risk than they actually have. Modifications to CHADS2 (for example, dropping hypertension and heart failure) might strengthen its ability to discriminate low vs higher risk patients. However, these possible modifications are speculative and require validation in other data sets.

With respect to the effectiveness and safety of anticoagulation therapy, the risk of hemorrhagic stroke is elevated in HD patients.[41,42,48,49] Rigorous clinical data evaluating anticoagulation in dialysis patients are sparse. However, routine warfarin use has been questioned because it (1) further increases risk of bleeding and (2) may promote vascular calcification (by inhibiting vitamin K-dependent γ-carboxylation).[15,16,50] In addition, recent observational data have linked warfarin use to higher mortality rates in patients with or without AF.[14] These observations raise the important possibility that the strategy of anticoagulation for AF may not be safe for certain dialysis patients. Underscoring this possibility is our finding that anticoagulation with warfarin in HD patients with AF was not associated with the desired effect—fewer cerebrovascular events. In contrast, there was a strong tendency to more frequent events, especially among older patients (Figure 2). Although this observation may be confounded (patients receive warfarin because they have elevated risk of thromboembolic stroke) or causal (anticoagulation leads to elevated rates of hemorrhagic stroke) or both, the finding underscores the need for caution when prescribing anticoagulation to these patients.

In summary, CHADS2 appears to effectively identify groups of dialysis patients with AF who are at low risk for subsequent stroke, though it may misclassify some patients (for example, those with hypertension or heart failure) as having higher stroke risk than they actually have. For patients identified by CHADS2 as having low stroke risk, this provides further evidence against anticoagulation therapy. For some patients at higher stroke risk (especially older patients), the risks of anticoagulation may still outweigh the benefits. Treatment decisions need to be individualized, and further studies including randomized trials of anticoagulation therapy (possibly including future factor Xa antagonists) in dialysis patients are needed.

Limitations of the study

Though this is the largest international study, to date, to describe AF and anticoagulation in AF patients among HD patients, there are several limitations. First, as in any observational study, the associations found may not be causal, and the possibility of bias due to unmeasured confounding cannot be excluded. Second, DOPPS questionnaires do not distinguish ischemic from hemorrhagic stroke. As noted above, the excess stroke risk for patients receiving warfarin may be due to an excess of ischemic and/or hemorrhagic stroke. As a corollary, INR data are not available in the DOPPS, and thus neither inadequate nor excessive anticoagulation among warfarin-treated patients can be excluded. As patients on warfarin often receive the same dose of heparin during dialysis as patients not receiving warfarin, excessive anticoagulation, even if transient, might constitute a possibly modifiable risk.

Third, because the DOPPS relies exclusively on data collection by questionnaires, misclassification of AF is likely, as ECG confirmation is not obligatory and some AF may escape clinical detection. In occasional cases, patients with transient (for example, post-operative) AF might be classified as having AF, even though anticoagulation decisions may be unnecessary in these patients. DOPPS data also do not differentiate between paroxysmal, persistent, or permanent AF. Current guidelines for AF patients in the general population recommend that some management decisions (for example, selection of antithrombotic therapy) be irrespective of AF type, whereas others (for example, rate vs rhythm control) depend in part on AF type.[12] Some misclassification of valvular heart disease (yes/no) is probable, and the DOPPS does not differentiate between location of (for example, mitral vs aortic) valvular disease. However, these limitations are unlikely to substantially influence our findings with respect to the predictive value of CHADS2 because performance was similar in patients with and without diagnosed valvular heart disease (Table 4). Patients with a prosthetic heart valve are identified in the DOPPS, and these patients were appropriately excluded from the analyses of CHADS2 as a predictive tool.

CONCLUSIONS

Results of this large, multinational study clearly indicate wide variations in the diagnosis of AF in different countries and variations among several factors associated with AF. New AF is associated with higher age, greater overall time on dialysis, and coexisting cardiovascular disease. Previous diagnosis of AF is associated with an elevated risk of mortality, cardiovascular mortality, stroke, and hospitalizations. Beta-blockers or calcium antagonists appear to be underused for rate control. The risks and benefits of anticoagulation have to be carefully weighed on an individual basis. To this end, the CHADS2 score can be used to identify low vs higher stroke risk. Additional clinical studies to evaluate the safety and efficacy of treatments for dialysis patients with AF are indicated.

MATERIALS AND METHODS

Data were combined from the first and second phases of the Dialysis Outcomes and Practice Patterns Study (DOPPS I and DOPPS II, respectively), an international, observational study of HD practices and outcomes in countries with large populations of dialysis patients. The study design has been described previously.[51] IRB approval and informed patient consent were obtained as required in each country. A representative sample of HD facilities was selected in each country within DOPPS I and II (countries in both DOPPS I and II are France, Germany, Italy, Spain, and the United Kingdom, $n = 40$ each; Japan, $n = 125$; the United States, $n = 222$; countries in DOPPS II only are Australia/New Zealand, Belgium, Canada, Sweden, $n = 20$ each). Patients were entered into DOPPS I from 1996 to 2001 in the United States, from 1998 to 2000 in Europe, and from 1999 to 2000 in Japan. All patients in DOPPS II were enrolled from 2002 to 2004. A random sample of patients was selected from each facility at the start of both phases, representing a prevalent cross-section ($n = 17{,}513$). The initial cross-sectional sample of prevalent patients was used to describe patient characteristics, whereas the entire sample of 29,873 patients was used for statistical modelling.

Patients were classified as having 'pre-existing' (that is, a history of) AF at DOPPS enrollment based on a response of 'yes' or 'suspected' AF on the medical questionnaire. Patients who did not have pre-existing AF at enrollment but were subsequently hospitalized with the diagnosis 'atrial fibrillation' were classified as developing 'newly diagnosed' AF during the study. Patients were classified as having a cerebrovascular event during the study if they were hospitalized for stroke or if they died with cause of death listed as 'cerebrovascular accident (including intracranial hemorrhage).'

Standard descriptive statistics were used to describe the cross-sectional sample of patients. For patients with pre-existing AF at DOPPS enrollment, CHADS2 score (an acronym for congestive heart failure, hypertension, age >75 years, diabetes mellitus, and previous stroke or TIA) was calculated as sum of two points for previous stroke or TIA, and one point for each other factor (range 0–6).[13] Multivariable logistic regression models, adjusted for country, phase, and the variables listed in Table 2 and accounting for facility-clustering effects, were used to determine the associations with patients with pre-existing AF. Multivariable cox proportional hazard models were used to study associations with (1) time to hospital admissions for newly diagnosed AF, and (2) time to mortality, stroke, or hospitalizations among patients with AF. Cox models were stratified by country and phase, adjusted for the variables listed in Table 2, and accounted for facility-clustering effects using robust standard estimates based on the sandwich estimator. Statistical analyses were performed using SAS software, version 9.1 (SAS Institute; Cary, NC, USA).

DISCLOSURE

None of the authors of this paper have had involvements (financial or otherwise) that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated.

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