

Faut-il anticoaguler les patients hémodialysés avec FA chronique?

PD Dr P. Saudan, Service de Néphrologie HUG juin 2010

FA, Hémodialyse et Anticoagulation: quelques faits

- FA chez patients en IRT:
- prévalence 11-27%
- Risque annuel d'AVC chez patients en IRT: 1-12%
- Risque hémorragique chez patients en IRT: 3x > pop générale
- Risque hémorragique chez patients en IRT et sous ACO:
- 2x que patients en IRT sans ACO

- Ne pas oublier augmentation calcifications ectopiques sous antivit K

AC individualisée selon le niveau de risque

TABLE 1. Risk of stroke in National Registry of Atrial Fibrillation participants not treated with warfarin or aspirin, stratified by CHADS₂

CHADS ₂ score	Predicted annualized stroke rate (95% CI)
0	1.9 (1.2–3.0)
1	2.8 (2.0–3.8)
2	4.0 (3.1–5.1)
3	5.9 (4.6–7.3)
4	8.5 (6.3–11.1)
5	12.5 (8.2–17.5)
6	18.2 (10.5–27.4)

CHADS₂ score: one point is assigned for each of the following stroke risk factors: CHF, hypertension, age >75, diabetes mellitus, and two points are assigned for stroke or TIA (34).

TABLE 2. Risk of major bleeding in National Registry of Atrial Fibrillation participants prescribed warfarin, stratified by HEMORR₂HAGES score

HEMORR ₂ HAGES score	Predicted annualized major bleeding rate (95% CI)
0	1.9 (0.6–4.4)
1	2.5 (1.3–4.3)
2	5.3 (3.4–8.1)
3	8.4 (4.9–13.6)
4	10.4 (5.1–18.9)
≥5	12.3 (5.8–23.1)

HEMORR₂HAGES score: one point is assigned for each of the following bleeding risk factors: hepatic or renal disease, ethanol abuse, malignancy, older age (age > 75 years), reduced platelet count or function, rebleeding risk (two points), hypertension (uncontrolled), anemia, genetic factors, excessive fall risk, and stroke (37).

Warfarin Use Associates with Increased Risk for Stroke in Hemodialysis Patients with Atrial Fibrillation

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Etude rétrospective

1671 incident hemodialysis patients with preexisting atrial fibrillation.

Follow-up: from the time of initiation of dialysis for an average of 1.6 yr

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Table 1. Baseline patient characteristics

Characteristic	Warfarin Only	Clopidogrel Only	Aspirin Only	≥2 Drugs ^a	None	p-value ^b
No. of patients	508	43	304	336	480	
Age (yr)	72.6 (0.4)	74.1 (1.0)	72.9 (0.6)	72.3 (0.5)	71.3 (0.6)	0.21
Male gender (%)	57.8 (2)	46.5 (8)	51.6 (3)	65.5 (3)	54.4 (2)	0.02
Race (%)						
white	82.2 (2)	86.0 (5)	77.0 (2)	82.4 (2)	78.5 (2)	0.35
black	12.8 (1)	7.0 (4)	17.4 (2)	11.6 (2)	15.8 (2)	
other	4.9 (1)	7.0 (4)	5.6 (1)	6.0 (1)	5.6 (1)	
Cause of ESRD (%)						
diabetes	40.6 (1)	53.5(8)	43.8 (3)	50.0 (3)	34.4 (2)	0.002
hypertension	32.9 (2)	27.9 (7)	32.2 (3)	30.1 (3)	35.8 (2)	
glomerulonephritis	7.3 (1)	9.3 (4)	4.9 (1)	2.7 (1)	7.3 (1)	
other	19.3 (2)	9.3 (4)	19.1 (2)	17.3 (2)	22.5 (2)	
Pre-HD SBP (mmHg)	134.9 (1)	147.4 (4)	139.7 (1)	136.2 (1)	139.7 (1)	<0.0001
Pre-HD DBP (mmHg)	67.6 (0.5)	70.0 (2)	68.7 (0.6)	67.8 (0.6)	70.0 (0.5)	0.006
Heparin (1000 IU per session)	4.2 (0.1)	4.4 (0.4)	4.5 (0.2)	4.4 (0.2)	4.6 (0.2)	0.48
Facility SMR	0.97 (0.02)	0.96 (0.06)	0.98 (0.03)	0.93 (0.02)	0.99 (0.02)	0.49
Access (%)						
fistula	16.5 (2)	9.3 (4)	18.1 (2)	21.7 (2)	14.6 (2)	0.28
graft	18.5 (2)	20.9 (6)	13.8 (2)	15.2 (2)	15.4 (2)	
catheter	59.3 (2)	62.8 (7)	62.8 (3)	58.3 (3)	65.2 (2)	
unknown	5.7 (1)	7.0 (4)	5.3 (1)	4.8 (1)	4.8 (1)	
CAD (%)	41.7 (2)	62.8 (7)	49.0 (3)	53.6 (3)	32.3 (2)	<0.0001
Myocardial infarction (%)	12.2 (1)	18.6 (6)	17.1 (2)	22.3 (2)	11.3 (1)	<0.0001
Stroke (%)	14.4 (2)	20.9 (6)	9.9 (2)	15.5 (2)	11.9 (1)	0.09
Hypertension (%)	79.7 (2)	88.4 (5)	78.9 (2)	78.3 (2)	79.8 (2)	0.65
CHF (%)	58.3 (2)	55.8 (8)	55.3 (3)	50.9 (3)	52.9 (2)	0.26
Charlson comorbidity index	5.46 (0.1)	5.88 (0.3)	5.34 (0.1)	5.68 (0.1)	5.35 (0.1)	0.08
CHADS ₂ index	2.75 (0.05)	3.12 (0.10)	2.59 (0.06)	2.74 (0.07)	2.58 (0.06)	0.01
Digoxin use (%)	30.5 (2)	18.6 (6)	19.4 (2)	21.1 (2)	13.5 (2)	<0.0001

Results are displayed as mean (standard error).

CAD, coronary artery disease; CHF, congestive heart failure; DBP, diastolic BP; SBP systolic BP; SMR, standardized mortality ratio.

^aPatient on any two of warfarin, clopidogrel, or aspirin.

^bFive-way ANOVA among warfarin, clopidogrel, aspirin, two or more drugs, and no drug group.

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Kevin E. Chan,* J. Michael Lazarus,* Ravi Thadhani,[†] and Raymond M. Hakim*

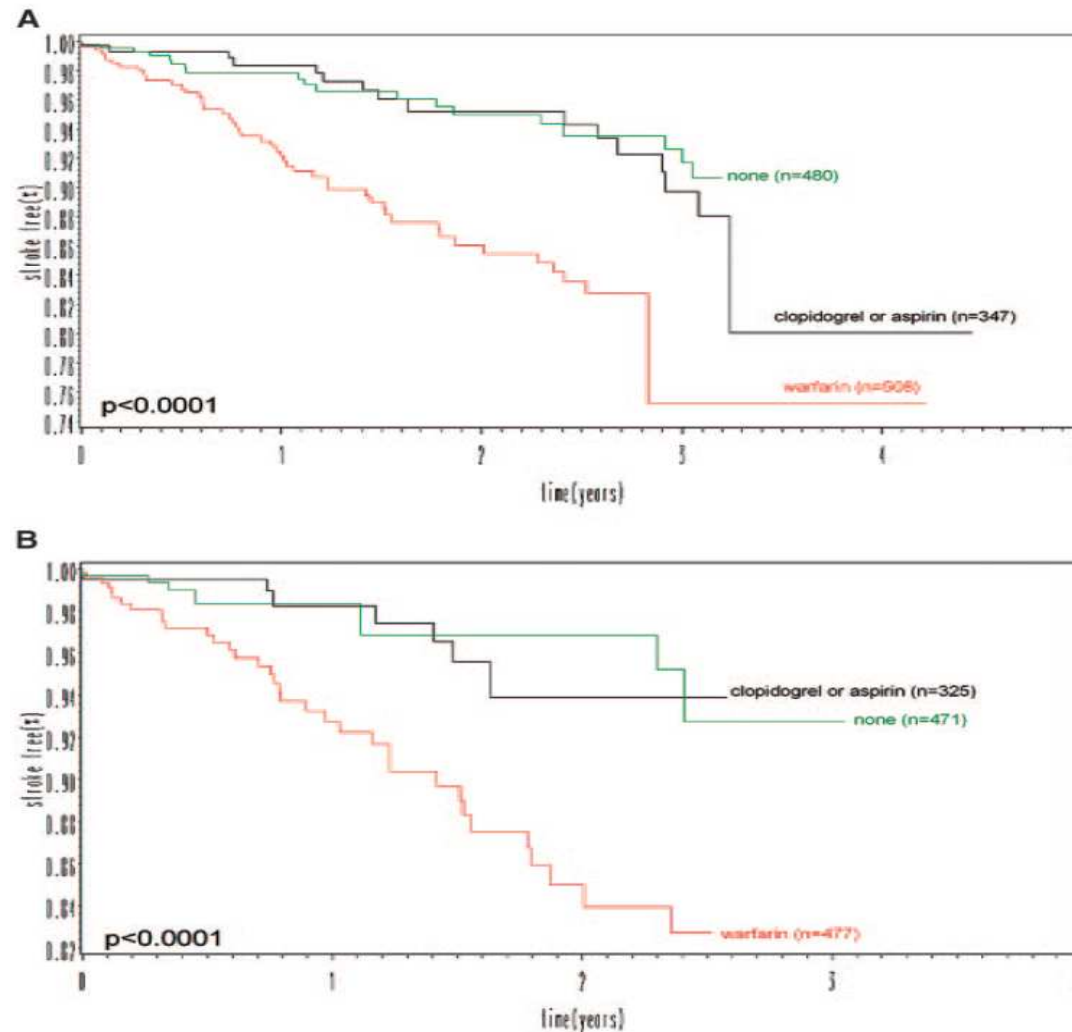


Figure 1. Crude stroke curves by drug exposure. (A) Under an intention-to-treat assumption, increased incidence of new stroke was associated with patients who were on warfarin. (B) Similar results were noted when patients were censored when they changed their warfarin, clopidogrel, or aspirin prescription after study enrollment.

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Table 2. HRs for stroke by drug therapy

Parameter	n	Warfarin (HR [95% CI])	Clopidogrel (HR [95% CI])	Aspirin (HR [95% CI])
HR for stroke (intention to treat)				
unadjusted model	1671	2.00 (1.34 to 2.99)	0.67 (0.31 to 1.47)	0.87 (0.57 to 1.33)
covariate ^a adjusted model	1671	1.93 (1.29 to 2.90)	0.66 (0.30 to 1.46)	0.86 (0.56 to 1.32)
covariate ^a and propensity score adjusted model ^b	1400	1.74 (1.11 to 2.72)	0.61 (0.25 to 1.50)	0.98 (0.58 to 1.63)
HR for stroke (patients censored on drug status change)				
unadjusted model	1671	2.94 (1.60 to 5.40)	0.63 (0.15 to 2.64)	0.73 (0.37 to 1.41)
covariate ^a adjusted model	1671	2.75 (1.49 to 5.08)	0.59 (0.14 to 2.49)	1.20 (0.96 to 1.49)
covariate ^a and propensity score adjusted model ^b	1400	1.95 (0.99 to 3.84)	0.31 (0.04 to 2.45)	0.70 (0.31 to 1.59)

^aAdjusted for CHADS₂ score, gender, race, Charlson comorbidity index, entry date, access, body mass index, facility standardized mortality ratio, cardiovascular drugs, dialysis adequacy, baseline laboratory values (albumin, hemoglobin, creatinine, ferritin, and white blood cell count), heparin dosage (units per treatment), and heparin regimen (bolus versus continuous versus unknown).

^bParameters used to calculate the propensity score: CHADS₂ score, gender, race, entry date, access, body mass index, facility standardized mortality ratio, cardiovascular drugs, dialysis adequacy, baseline laboratory values (albumin, hemoglobin, creatinine, ferritin, and white blood cell count), heparin dosage (units per treatment), heparin regimen (bolus versus continuous versus unknown), stroke, myocardial infarction, hypertension, peptic ulcer disease, AIDS, peripheral vascular disease, coronary artery disease, dementia, chronic obstructive pulmonary disease, hemiplegia, diabetes, cancer, liver disease, arterial clot, deep vein thrombosis, mechanical heart valve, pulmonary embolism, and hypercoagulable state.

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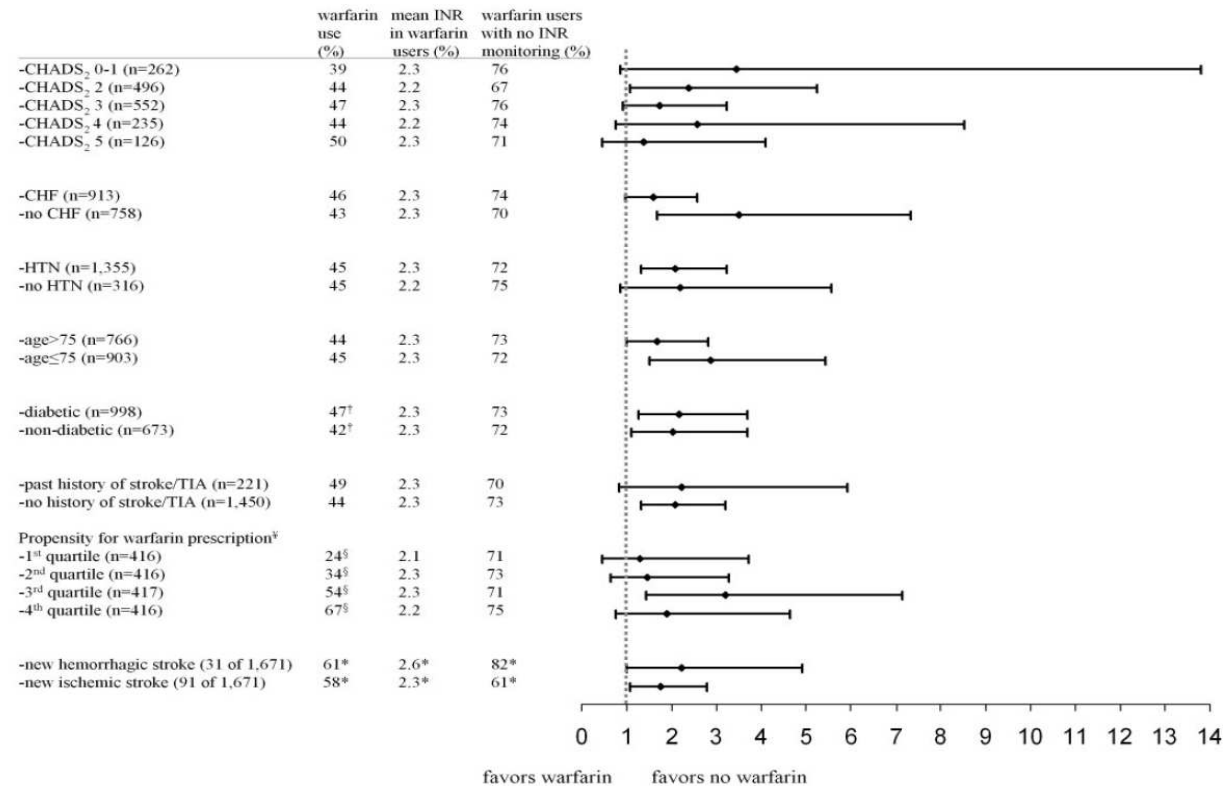


Figure 2. Stratified analysis. Patients at higher risk for future stroke (higher CHADS₂ score) had better risk-benefit profiles (warfarin*CHADS₂ = 0.84; *P* = 0.31 for interaction) with warfarin use when compared with nonusers. With the exception of diabetes, there were no statistical differences in the prevalence of warfarin use, INR level, or INR monitoring with increasing risk for stroke (CHADS₂ score) and by five well-established risk factors for future stroke in atrial fibrillation.³⁸ The crude ischemic stroke rate in warfarin users was 5.8 strokes per 100 patient-years (95% CI 4.6 to 7.4) versus 2.3 strokes per 100 patient-years in nonusers (95% CI 1.5 to 3.6). The crude hemorrhagic stroke rate in warfarin users was 1.2 strokes per 100 patient-years (95% CI 0.7 to 2.1) versus 0.5 strokes per 100 patient-years in nonusers (95% CI 0.2 to 1.4).

[†]Statistically significant difference (*P* = 0.03) in prevalence of warfarin use in diabetic versus nondiabetic incident dialysis patients with atrial fibrillation.

[§]As expected, patients with a higher propensity for warfarin prescription had a higher prevalence of warfarin use.

[¶]After matching, the caliper width of the propensity score between the two groups was found to be ±0.6 SD.

*Values reported only for patients who had a stroke outcome.

CHF, congestive heart failure; HTN, hypertension.

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Analysis using international normalized ratio (INR) suggested a dose-response relationship between the degree of anticoagulation and new stroke in patients on warfarin ($P = 0.02$ for trend). Warfarin users who received no INR monitoring in the first 90 d of dialysis had the highest risk for stroke compared with nonusers (hazard ratio 2.79; 95% confidence interval 1.65 to 4.70). Warfarin use did not associate with statistically significant increases in all-cause mortality or hospitalization. In conclusion, warfarin use among patients with both ESRD and atrial fibrillation associates with an increased risk for stroke. The risk is greatest in warfarin users who do not receive in-facility INR monitoring.

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

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Etude DOPPS prospective interventionnelle
2188 patients avec FA

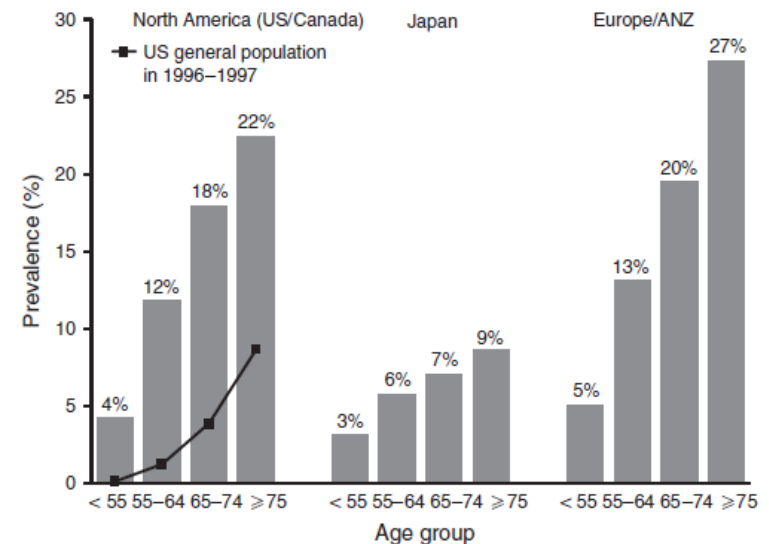


Figure 1 | Prevalence of history of atrial fibrillation (AF) at DOPPS enrollment by region and age in prevalent cross-sections combining DOPPS I (1996-2001) and DOPPS II (2002-2004) ($n = 17,513$). For comparison, the approximate prevalence of AF in the same age categories among 1.89 million adults in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

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

Country/region	Medication (% use)													
	Aspirin		Warfarin		β-Blocking agents		Calcium channel-blocking agents		ACE inhibitors		Digoxin		Amiodarone	
	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
<i>EUR Overall</i>	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
<i>Overall</i>	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.

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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
<i>Overall</i>	<i>643</i>	<i>29</i>	<i>3.3</i>	<i>3250</i>	<i>148</i>	<i>3.4</i>

^aStroke rates during DOPPS follow-up among patients with history of atrial fibrillation (AF) at DOPPS enrollment, excluding 177 patients with mechanical heart valves.

^bColumn 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.

^cBased 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).

^dColumn A=891 patient-years; column B=4348 patient-years.

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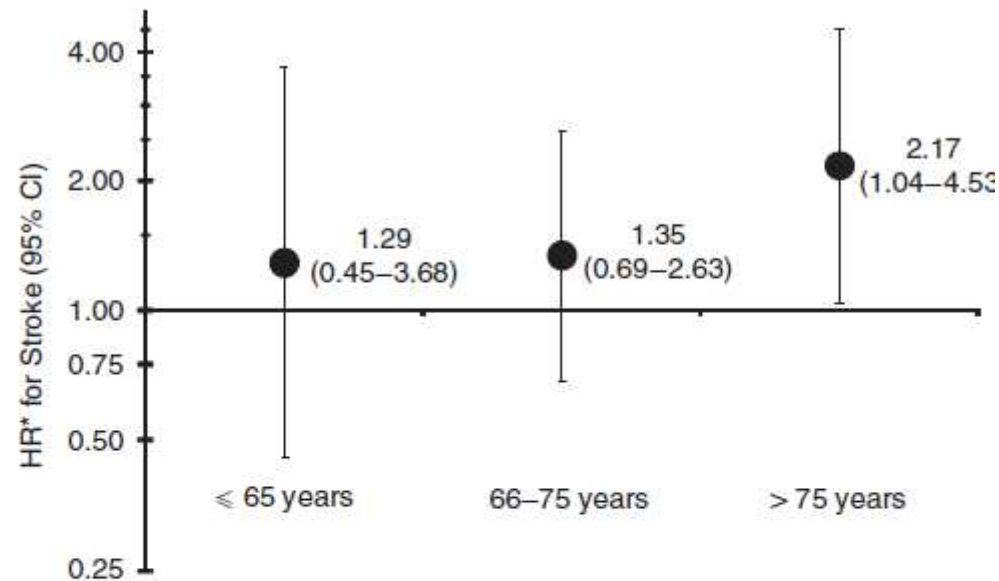


Figure 2 | Hazard ratio (HR) for stroke according to warfarin use, by age categories among patients with a diagnosis of atrial fibrillation at DOPPS enrollment. The numbers of patients (strokes) were 1001 (35), 1137 (61), and 1107 (49) for age groups ≤65, 66 to 75, and >75 years, respectively. The numbers (%) 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

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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.

Faut-il anticoaguler les patients hémodialysés avec FA chronique?

- Patients avec FA et > 75 ans en HD: 0 ACO
- Patients avec FA et < 75 ans. En fonction du risque thrombo-embolique