

Warfarin in Atrial Fibrillation Patients with Moderate Chronic Kidney Disease

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Summary

Background and objectives The efficacy of adjusted-dose warfarin for prevention of stroke in atrial fibrillation patients with stage 3 chronic kidney disease (CKD) is unknown.

Design, setting, participants, & measurements Patients with stage 3 CKD participating in the Stroke Prevention in Atrial Fibrillation 3 trials were assessed to determine the effect of warfarin anticoagulation on stroke and major hemorrhage, and whether CKD status independently contributed to stroke risk. High-risk participants ($n = 1044$) in the randomized trial were assigned to adjusted-dose warfarin (target international normalized ratio 2 to 3) versus aspirin (325 mg) plus fixed, low-dose warfarin (subsequently shown to be equivalent to aspirin alone). Low-risk participants ($n = 892$) all received 325 mg aspirin daily. The primary outcome was ischemic stroke (96%) or systemic embolism (4%).

Results Among the 1936 participants in the two trials, 42% ($n = 805$) had stage 3 CKD at entry. Considering the 1314 patients not assigned to adjusted-dose warfarin, the primary event rate was double among those with stage 3 CKD (hazard ratio 2.0, 95% CI 1.2, 3.3) versus those with a higher estimated GFR (eGFR). Among the 516 participants with stage 3 CKD included in the randomized trial, ischemic stroke/systemic embolism was reduced 76% (95% CI 42, 90; $P < 0.001$) by adjusted-dose warfarin compared with aspirin/low-dose warfarin; there was no difference in major hemorrhage (5 patients versus 6 patients, respectively).

Conclusions Among atrial fibrillation patients participating in the Stroke Prevention in Atrial Fibrillation III trials, stage 3 CKD was associated with higher rates of ischemic stroke/systemic embolism. Adjusted-dose warfarin markedly reduced ischemic stroke/systemic embolism in high-risk atrial fibrillation patients with stage 3 CKD.

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Introduction

Chronic kidney disease (CKD) affects about 10% of adults and is associated with increased rates of cardiovascular disease (1,2). In a large observational study of outpatients with atrial fibrillation, about one-third had stage 3 or 4 CKD and an estimated GFR (eGFR) of <45 ml/min per 1.73 m², which was found to be an independent predictor of stroke (3). Anticoagulation with adjusted-dose warfarin reduces the risk of stroke in patients with nonvalvular atrial fibrillation by about two-thirds, based on consistent results of several randomized trials (4), but its efficacy in CKD patients with atrial fibrillation has not been specifically established. In hemodialysis patients with atrial fibrillation (excluded from participation in randomized trials to date), recent observational studies have challenged the value of warfarin anticoagulation (5–7), leading to doubts about whether results of randomized trials can be reliably extrapolated to CKD patients (8).

A substantial number of participants with stage 3 CKD were included in the two Stroke Prevention in

Atrial Fibrillation (SPAF) 3 trials (9,10). Here, we analyze whether CKD status contributes to stroke risk stratification and assess the efficacy of adjusted-dose warfarin for stroke prevention in participants with stage 3 CKD.

Materials and Methods

SPAF 3 trials sponsored by the National Institute for Neurologic Disorders and Stroke (R01-NS24224) were carried out between 1993 and 1997 at 20 clinical sites in the United States and Canada; the design and main results have been previously reported (9–11) (Figure 1). Potential participants with atrial fibrillation were stratified as high risk or low risk for stroke based on patient characteristics identified in earlier SPAF trials as predictive of stroke (10). Those categorized as low risk were all placed on aspirin, 325 mg daily, and followed for a mean of 2 years to validate the risk stratification scheme. Those categorized as high risk, and who were deemed eligible to receive warfarin anticoagulation, were entered into a randomized trial comparing adjusted-dose warfarin (tar-

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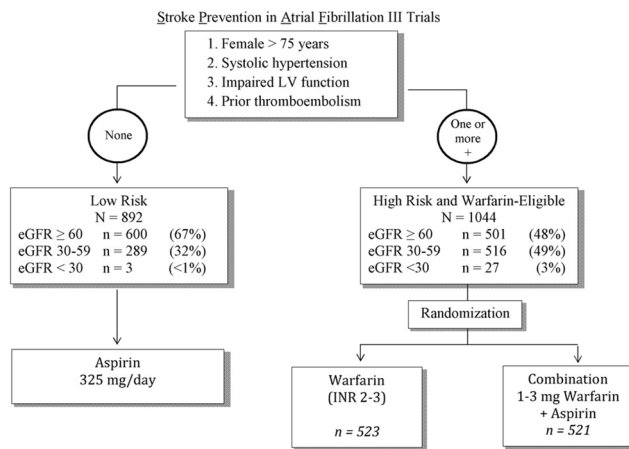


Figure 1. | Design of the Stroke Prevention in Atrial Fibrillation (SPAF) III trials. LV, left ventricular.

get international normalized ratio [INR] 2 to 3, mean achieved INR 2.4) with fixed, low-dose warfarin (1 to 3 mg daily, mean achieved INR 1.3) plus 325 mg of aspirin daily, administered open-label (*i.e.*, the trial was unblinded). The fixed, low dose of warfarin was that which initially prolonged the INR to 1.2 to 1.5 on two measurements done 1 week apart, limited to a maximum dose of 3 mg per day. The median warfarin dose was 2.0 mg/d yielding a mean (SD) INR during follow-up of 1.3 (0.8). For those assigned adjusted-dose warfarin, the initial dose was based on age, and patients underwent weekly INR measurements until stable in the target range of 2.0 and 3.0, and subsequently monitored at least monthly. The mean (SD) warfarin dose was 3.8 (1.9) mg/d, yielding a mean INR of 2.4. Sixty-one percent of INR measurements were between 2.0 and 3.0, 25% were below this range, and 76% were within the range of 1.8 to 3.2. The randomized trial was terminated at the first interim analysis, after a mean follow-up of 1.1 year, due to the clear superiority of adjusted-dose warfarin (8).

The primary outcome of both studies was all ischemic stroke and systemic (*i.e.*, non-central nervous system CNS) emboli; 96% of primary events were ischemic strokes. Ischemic strokes required a focal neurologic deficit of sudden onset persisting for more than 24 hour; 93% of ischemic strokes had neuroimaging acutely to confirm the absence of brain hemorrhage. Systemic embolism required abrupt vascular insufficiency related to proven arterial occlusion without previous evidence of obstructive atherosclerosis. A central event adjudication committee verified primary events and major hemorrhage by review of source documents from which information relevant to antithrombotic therapy was purged. Major hemorrhage was defined as clinically overt bleeding that was fatal, life threatening (serious permanent injury or surgery to stop bleeding), potentially life threatening (requiring two of the following: >3 units of blood loss, hypotension to systolic BP of <90 mmHg, drop in hematocrit to ≤20%), or acute/subacute bleeding (<7 days) combined with >2 units of blood loss (12).

CKD stages were based on the eGFR, calculated using the serum creatinine at study entry and the Chronic Kidney Disease Epidemiology Collaboration equation (13). Se-

rum creatinine was measured at local laboratories at the 20 clinical sites. Patients with CKD stage 3 were those with an eGFR of 30 to 59 ml/min per 1.73 m², while stage 4 patients had an eGFR of 15 to 29 ml/min per 1.73 m² (14). Patients with a serum creatinine >3 mg/dl were ineligible for participation in either trial.

To investigate whether CKD stage adds to risk stratification for the primary outcome, all participants not assigned to adjusted-dose warfarin were included in the analysis, *i.e.*, all participants in the aspirin trial for low-risk patients were combined with those randomized to combination therapy in the randomized trial for high-risk patients. The achieved intensity of anticoagulation with the fixed, low-dose warfarin regimen was below that associated with substantial protection against stroke, and hence this treatment arm was treated as equivalent to aspirin alone (15,16). Patient characteristics independently predictive of stroke among those assigned aspirin in the SPAF I to III trials have been previously reported (17). The most widely used stroke risk stratification score for atrial fibrillation patients is currently the CHADS2 scheme. CHADS2 uses a point system, with one point given for each of Congestive heart failure, Hypertension, Age ≥75 years, and Diabetes mellitus, and 2 points for prior Stroke/transient ischemic attack (18).

All analyses followed intention-to-treat principles. Patient characteristics were compared between groups using a chi-squared test for categorical variables and a *t* test for continuous measures. Follow-up was censored after 2 years to increase the likelihood that the stage of renal disease classified at entry would be present during the follow-up interval. Two-year event rates were computed by fitting Kaplan–Meier curves and compared using the log rank statistic. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported as a measure of relative risk, with relative risk reductions calculated as 1 minus the HR. Cox proportional hazards models adjusted for individual CHADS2 risk factors were fit to assess the independent contribution of stage 3 CKD to stroke risk stratification. All statistical tests were two-sided, and statistical significance was accepted at the 0.05 level. Statistical analyses were accomplished using SPSS Statistics 18.0 and MedCalc 11.5.0.

Results

Among all 1936 SPAF 3 participants, the mean age was 70 years, and the frequency of stage 3 CKD at entry was 42% (805 of 1936), with an additional 2% (*n* = 30) categorized as stage 4 CKD. The frequency of stage 3 CKD was 32% (289 of 892) among those categorized at study entry as low risk for stroke (mean age = 67 years) and treated with aspirin, and was 49% (516 of 1044) among the high-risk patients (mean age = 72 years) in the randomized trial (Table 1, Figure 1). Considering participants not assigned to adjusted-dose warfarin, patients with stage 3 CKD (mean eGFR = 50 ml/min per 1.73 m²) were older (*P* < 0.001), more often women (*P* = 0.02), and had higher frequencies of hypertension (*P* < 0.001), diabetes (*P* = 0.03), heart failure (*P* = 0.001), and prior stroke/transient ischemic attack (*P* < 0.001) than those with an eGFR ≥60 ml/min per 1.73 m² (mean eGFR = 76 ml/min per 1.73 m²) (Table 1).

Table 1. Features of SPAF III trial participants according to eGFR^a

Feature	All SPAF III Participants Not Assigned to Adjusted-Dose Warfarin			High-Risk Randomized Trial Participants ^b		
	eGFR ≥60 (n = 859)	eGFR 30 to 59 (n = 538)	P	eGFR ≥60 (n = 501)	eGFR 30 to 59 (n = 516)	P
Age, mean (years)	67	73	<0.01	70	74	<0.01
Male (%)	75	69	0.02	63	59	0.20
Race (%)			0.56			0.66
Caucasian	93	94		92	92	
African American	3	2		5	5	
Hispanic	3	2		3	2	
Other	1	2		1	1	
Hypertension (%)	49	62	<0.01	64	73	0.02
Diabetes (%)	12	17	0.03	16	20	0.14
Heart failure (%)	18	26	0.01	41	46	0.14
Coronary artery disease (%)	17	30	<0.01	27	37	<0.01
Prior stroke/TIA (%)	11	19	<0.01	37	39	0.54
Paroxysmal AF (%)	25	20	0.03	19	15	0.10
CHADS2 score (%)			<0.01			<0.01
0	32	17		4	3	
1	36	31		27	16	
2+	32	52		68	81	
Serum creatinine, mean (mg/dl)	1.0	1.3	<0.001	1.0	1.3	<0.01
Mean eGFR (ml/min per 1.73 m ²)	76	50	—	74	49	—

SPAF, Stroke Prevention in Atrial Fibrillation; eGFR, estimated GFR in ml/min per 1.73 m² (13); TIA, transient ischemic attack; AF, atrial fibrillation.

^a30 participants with eGFR<30 ml/min per 1.73 m² are not considered.

^bThere were no significant differences in patient features between randomized treatment arms in stage 3 chronic kidney disease (CKD) patients (see Supplementary Table 1).

Stage 3 CKD and Stroke Risk among Non-anticoagulated Patients

Among participants who were not assigned adjusted-dose warfarin, the 2-year primary event rates were higher for those with stage 3 CKD (HR 2.0, 95% CI 1.2, 3.3) (Table 2). For those with stage 3 CKD, the CHADS2 score (0 versus 1 versus ≥ 2) stratified stroke risk (P = 0.001) but with similar event rates for CHADS2 scores of 0 and 1 (Table 2, Figure 2). Lower eGFR as a continuous measure (HR 1.2 per 10 ml decrease, 95% CI 1.0, 1.4, P = 0.04) was independently predictive of primary events after adjusting indi-

vidually for CHADS2 risk factors in a multivariate model; however, stage 3 CKD was not (adjusted HR 1.4, 95% CI 0.8, 2.3, P = 0.2).

Efficacy and Bleeding Risk of Adjusted-Dose Warfarin

Treatment with adjusted-dose warfarin reduced the risk of primary events relative to fixed/low-dose warfarin plus aspirin by 76% (95% CI 42, 90, P < 0.001) among high-risk atrial fibrillation patients with stage 3 CKD (Table 3). The relative risk reduction by warfarin was not different from

Table 2. Primary event rates according to CHADS2 score and CKD status in participants not assigned to adjusted-dose warfarin^a

Risk Group	eGFR >60 ml min per 1.73 m ²			Stage 3 CKD eGFR 30 to 59 ml/min per 1.73 m ²		
	n	No. of Events	2-year Rate (%)	n	No. of Events	2-year Rate (%)
All participants	859	28	4.1	538	36	9.2 ^b
CHADS2 = 0	275	3	1.5	89	3	4.6
CHADS2 = 1	306	8	3.3	168	5	3.8
CHADS2 = 2	161	6	4.3	140	13	14.1
CHADS2 = 3	75	7	11.4	77	4	6.7
CHADS2 ≥ 4	42	4	15.2	64	11	24.9

^aSPAF III participants assigned to aspirin or to aspirin plus fixed, low-dose warfarin (see Materials and Methods); 16 patients with stage 4 chronic kidney disease (CKD) were excluded; were 96% of primary events were ischemic strokes. For the CHADS2 score, one point is given for each of Congestive heart failure, Hypertension, Age ≥75, and Diabetes mellitus, and 2 points for prior Stroke/transient ischemic attack.(18)

^bP = 0.004 compared with those with estimated GFR (GFR) ≥60 ml/min per 1.73 m²; 95% confidence intervals for the rates are shown in Figure 2.

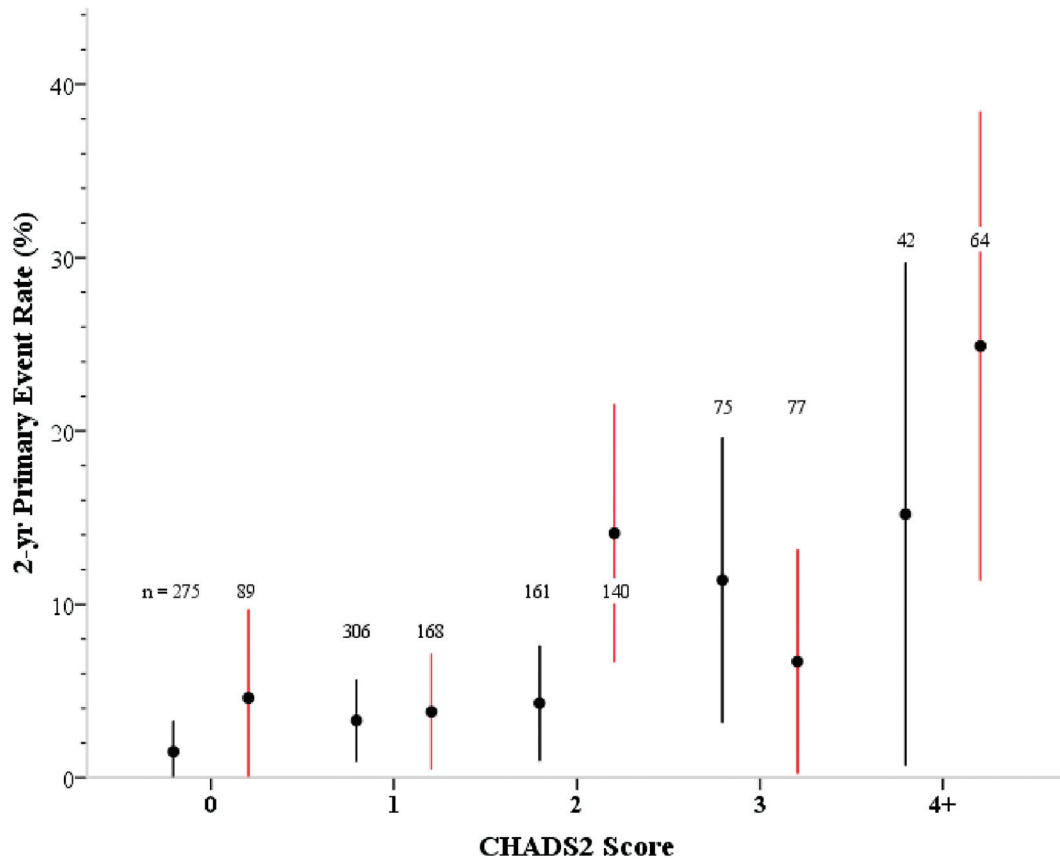


Figure 2. | Rate of primary events by CHADS2 score (18) among non-anticoagulated patients with atrial fibrillation according to chronic kidney disease status. Stage 3 CKD = red; eGFR>60 = black.

Table 3. Effect of adjusted-dose warfarin in patients with stage 3 CKD^a

	Adjusted-Dose Warfarin			Fixed, Low-Dose Warfarin + Aspirin			Relative Risk Reduction ^c (%) (95% CI); <i>P</i>
	<i>n</i>	No. of Events	2-year Rate (%)	<i>n</i>	No. of Events	2-year Rate (%)	
Ischemic stroke/systemic embolism ^b							
eGFR ≥60 ml/min per 1.73 m ²	242	5	5.1	259	16	8.5	67 (10, 88); <i>P</i> = 0.02
Stage 3 CKD	267	6	2.9	249	23	14.1	76 (42, 90); <i>P</i> < 0.01
All major bleeds							
eGFR ≥60 ml/min per 1.73 m ²	242	5	6.3	259	7	6.3	21 (-151, 75); <i>P</i> = 0.69
Stage 3 CKD	267	5	2.5	249	6	3.6	24 (-150, 77); <i>P</i> = 0.65
Deaths							
eGFR ≥60 ml/min per 1.73 m ²	242	10	7.9	259	15	10.1	26 (-64, 67); <i>P</i> = 0.45
Stage 3 CKD	267	21	13.7	249	22	17.7	15 (-55, 53); <i>P</i> = 0.60

See Methods for definitions of stages of CKD. Features of stage 3 CKD participants did not differ significantly by treatment arm (see Supplementary Table 1). CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated GFR.

^a27 participants with stage 4 CKD are excluded.

^bAlmost all (96%) were ischemic strokes.

^cRelative risk reduction estimated as 1 minus the hazard ratio.

that seen in those with eGFR ≥60 ml/min per 1.73 m² (67%, 95% CI 10, 88, *P* = 0.4, for interaction term). In the subset of stage 3 CKD participants with eGFR 30 to 44 ml/min per 1.73 m² (*n* = 147), the 2-year primary event rates were 9.2% (four events) for adjusted-dose warfarin

versus 11.7% (seven events) for aspirin/low-dose warfarin (relative risk reduction 34%, *P* = 0.50).

The frequency of major hemorrhage in patients with stage 3 CKD was similar for the two treatment groups and was not increased over those with higher eGFRs, although

few major hemorrhages occurred (Table 3). For the five major hemorrhages in those with stage 3 CKD assigned to adjusted-dose warfarin, one occurred in an inactive patient receiving aspirin, while four occurred while active on warfarin. Four were gastrointestinal (including the inactive patient on aspirin), while one was retroperitoneal following a pelvic fracture. INRs at the time of presentation with major hemorrhage were 2.7, 2.6, 2.8, and 4.6. For the six major hemorrhages among those with stage 3 CKD assigned to fixed, low-dose warfarin plus aspirin, two patients were inactive (one given adjusted-dose warfarin with an INR of 1.2 at the time of gastrointestinal bleeding due to a gastric ulcer) and four were on assigned treatment. Of the four on assigned treatment, the INR at the time of presentation with major hemorrhage was <1.4 in three (traumatic intracerebral bleed, bladder hemorrhage after cystoscopy, and spontaneous subdural hematoma) and was 4.9 in one (bladder hemorrhage; antibiotic use suspected to have contributed to the prolonged INR).

Discussion

While generally assumed to apply to patients with stage 3 CKD, the efficacy of adjusted-dose warfarin has not previously been defined by data from randomized trials for atrial fibrillation patients with stage 3 CKD. These results show that atrial fibrillation patients with stage 3 CKD have high rates of ischemic stroke, and that adjusted-dose warfarin has similar efficacy for prevention of ischemic stroke in patients with stage 3 CKD as in patients with a higher eGFR. There were too few major bleeding events to meaningfully characterize the relative rates of bleeding during warfarin anticoagulation according to CKD status.

Stage 3 or 4 CKD (eGFR 15 to 45 ml/min per 1.73 m²) was previously found to be an independent predictor of ischemic stroke in atrial fibrillation patients in a large cohort study (3). The relative risk conferred by an eGFR of <45 ml/min per 1.73 m² was 1.4 (95% CI 1.1, 1.7) in this study involving 10,908 atrial fibrillation patients. This magnitude was similar to the point estimate from our data for stage 3 CKD (adjusted HR 1.4, 95% CI 0.8, 2.3), albeit not statistically significant, and the absence of significant association may reflect lack of statistical power, difference in the eGFR equation used, or our exclusion of patients with an eGFR <30 ml/min per 1.73 m² from our analysis. The mechanism(s) underlying the increased stroke risk conferred by stage 3 CKD status are not entirely clear and may be multiple, including prothrombotic diatheses (3). In addition, stage 3 CKD may be a marker for end-organ damage from hypertension and diabetes, adding predictive information that is not captured by considering the simple prevalence of vascular risk factors (but not their severity, duration, or treatment). If confirmed by other studies to be an independent risk factor for stroke, the strength of association between stage 3 CKD status and stroke risk appears to be in the range seen with several of the other predictors used in the CHADS2 scheme (19), and, consequently, CKD status might be clinically useful for stratifying stroke risk for decision making about antithrombotic prophylaxis.

A potential limitation of this study was the use of serum creatinine determinations from 20 local laboratories in the

United States and Canada in the 1990s, when laboratory procedures varied (20,21). Estimation of the GFR is very sensitive to differences in creatinine values, and hence even small random variations between laboratories could contribute to misclassification of an uncertain portion of patients with stage 3 CKD (20). For example, in a 75-year-old Caucasian woman, a difference in serum creatinine of 0.8 mg/dl to 1.0 mg/dl would shift the eGFR from 72 ml/min per 1.73 m² to 55 ml/min per 1.73 m². Another potential limitation is the termination of the randomized trial at interim analysis due to an unexpectedly high degree of efficacy, which is accepted to potentially exaggerate the point estimate of treatment effect to an uncertain degree. Finally, the observed rate of major hemorrhage during warfarin anticoagulation of stage 3 CKD patients was relatively low (2.5% after 2 years) (22) and could be explained by our criteria for major hemorrhage (12), careful warfarin management in a clinical trial, or the play of chance due to the small number of events (*n* = 5). Furthermore, over half of high-risk participants in the randomized trial were taking adjusted-dose warfarin before entry, biasing toward lower bleeding rates (23). Consequently, the observed major hemorrhage rate among stage 3 CKD participants assigned to adjusted-dose warfarin in SPAF III may be lower than can be expected in clinical practice. Our results, however, are consistent with the cohort analysis finding that stage 3 CKD was not an independent predictor of major or minor hemorrhage during warfarin anticoagulation (22).

Novel oral anticoagulants that have recently been tested in atrial fibrillation patients are eliminated, to varying degrees, by renal excretion (24,25). Hypothetically, due to the reduced elimination of both dabigatran (a direct thrombin inhibitor, about 80% renal excretion) and apixaban (a factor Xa inhibitor, about 25% renal excretion) in CKD patients, the antithrombotic effects on stroke prevention and on major bleeding should be higher in CKD patients if treated with the same dosage as patients without CKD. Consequently, in our view, their efficacy and safety must be separately considered in CKD patients. From available data, apixaban is more efficacious (about 67% relative risk reduction, *P* < 0.01) than aspirin for prevention of stroke and systemic embolism in atrial fibrillation patients deemed unsuitable for adjusted-dose warfarin and estimated creatinine clearance (estimated by Cockcroft-Gault method [26]) of 25 to 50 ml/min per 1.73 m² (25) (Supplementary Table 2). Dabigatran, in a dose of 150 mg twice daily, was superior to adjusted-dose warfarin (about a 42% relative risk reduction, *P* = 0.01) in atrial fibrillation patients with estimated creatinine clearance (Cockcroft-Gault method) of 30 to 50 ml/min per 1.73 m² (24) (Supplementary Table 2). In 2010, the U.S. Food and Drug Administration approved dabigatran, 150 mg twice daily, for prevention of stroke in atrial fibrillation, including those with stage 3 CKD, and a lower dosage of 75 mg twice daily for atrial fibrillation patients with stage 4 CKD.

Conclusions

Moderate CKD is an independent predictor of stroke in atrial fibrillation patients. Adjusted-dose warfarin mark-

edly reduces ischemic stroke/systemic embolism in high-risk atrial fibrillation patients with stage 3 CKD. These data serve as a benchmark for interpretation of trials comparing novel oral anticoagulants with adjusted-dose warfarin in patients with moderate CKD.

Disclosures

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