ORIGINAL ARTICLE

Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

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ABSTRACT

BACKGROUND

Both atrial fibrillation and chronic kidney disease increase the risk of stroke and systemic thromboembolism. However, these risks, and the effects of antithrombotic treatment, have not been thoroughly investigated in patients with both conditions.

METHODS

Using Danish national registries, we identified all patients discharged from the hospital with a diagnosis of nonvalvular atrial fibrillation between 1997 and 2008. The risk of stroke or systemic thromboembolism and bleeding associated with non–end-stage chronic kidney disease and with end-stage chronic kidney disease (i.e., disease requiring renal-replacement therapy) was estimated with the use of time-dependent Cox regression analyses. In addition, the effects of treatment with warfarin, aspirin, or both in patients with chronic kidney disease were compared with the effects in patients with no renal disease.

RESULTS

Of 132,372 patients included in the analysis, 3587 (2.7%) had non–end-stage chronic kidney disease and 901 (0.7%) required renal-replacement therapy at the time of inclusion. As compared with patients who did not have renal disease, patients with non–end-stage chronic kidney disease had an increased risk of stroke or systemic thromboembolism (hazard ratio, 1.49; 95% confidence interval [CI], 1.38 to 1.59; P<0.001), as did those requiring renal-replacement therapy (hazard ratio, 1.83; 95% CI, 1.57 to 2.14; P<0.001); this risk was significantly decreased for both groups of patients with warfarin but not with aspirin. The risk of bleeding was also increased among patients who had non–end-stage chronic kidney disease or required renal-replacement therapy and was further increased with warfarin, aspirin, or both.

CONCLUSIONS

Chronic kidney disease was associated with an increased risk of stroke or systemic thromboembolism and bleeding among patients with atrial fibrillation. Warfarin treatment was associated with a decreased risk of stroke or systemic thromboembolism among patients with chronic kidney disease, whereas warfarin and aspirin were associated with an increased risk of bleeding. (Funded by the Lundbeck Foundation.)

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The prevalence of both atrial fibrillation and chronic kidney disease increases with age.[1,2] The prevalence of atrial fibrillation is 2.3% among persons 40 years of age or older and 5.9% among those 65 years of age or older,[2] and the prevalence of end-stage renal disease increases from approximately 3.5% among persons 45 to 64 years of age to nearly 6% among those 75 years of age or older.[1] Many patients have both disorders,[3-6] and the number of such patients is increasing, owing in part to the aging population and the improved survival in both diseases.

Atrial fibrillation increases the risk of stroke by a factor of 5,[7] and chronic kidney disease increases the risk of stroke among patients without atrial fibrillation.[1,8] The U.S.-based Renal Data System has reported that chronic kidney disease increases the risk of stroke by a factor of 3.7, and end-stage renal disease (i.e., disease requiring renal-replacement therapy) increases the risk by a factor of 5.8.[1] Chronic kidney disease has also been associated with an increase in the risk of myocardial infarction,[9] as has atrial fibrillation, at least among women.[10]

To reduce the risk of stroke or systemic thromboembolism, patients with atrial fibrillation should be treated with antithrombotic therapy.[11] However, some studies have suggested that the use of warfarin may actually increase the risk of ischemic stroke among patients undergoing dialysis.[3,12,13] Furthermore, the risk of bleeding associated with warfarin treatment is increased among patients with atrial fibrillation who also have chronic kidney disease.[6] Despite the size of this patient group, large randomized trials of antithrombotic therapy in patients with atrial fibrillation have typically excluded those who also have moderate-to-severe chronic kidney disease,[14-16] and the treatment of these patients has been based on data obtained from smaller observational studies.[13]

The objective of this study was to determine the risk of stroke or systemic thromboembolism and bleeding associated with chronic kidney disease among patients with atrial fibrillation and to determine whether the effect of warfarin and aspirin differed between patients with and those without chronic kidney disease.

Methods

Registry Data Sources

In this Danish cohort study, we linked individual-level data from national registries, using the personal registration number provided to all Danish residents. The data were obtained from the Central Population Registry, the National Patient Registry, the Registry of Medicinal Product Statistics, the National Registry on Regular Dialysis and Transplantation, and the National Registry of Causes of Death.[17-22] The details of the information contained in each of these registries, as well as the diagnoses, surgical procedures, and pharmacotherapy used for defining the study population, coexisting conditions, and outcomes, are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The Lundbeck Foundation provided grant support but had no role in the conduct of the study. The study was approved by the Danish Data Protection Agency. Approval by an ethics committee and written informed consent are not required for retrospective registry studies in Denmark. The first author vouches for the integrity of the data and the accuracy of the data analysis.

Study Population

We identified all patients discharged from the hospital with a diagnosis of nonvalvular atrial fibrillation during the study period, from 1997 through 2008.[17,19] Pharmacotherapy was determined by means of filled prescriptions and, because treatment may have been changed or intensified during or immediately after hospitalization, the baseline assessment and follow-up period began 7 days after discharge. Patients were excluded if they died, had a thromboembolic event, or had major bleeding during the 7 days before the baseline assessment (Fig. 1).[17-19]

Chronic Kidney Disease and Renal-Replacement Therapy

Patients with chronic kidney disease who did not require renal-replacement therapy (i.e., who had non–end-stage chronic kidney disease) were identified from the National Patient Registry. Patients requiring renal-replacement therapy (those who were undergoing maintenance dialysis or who

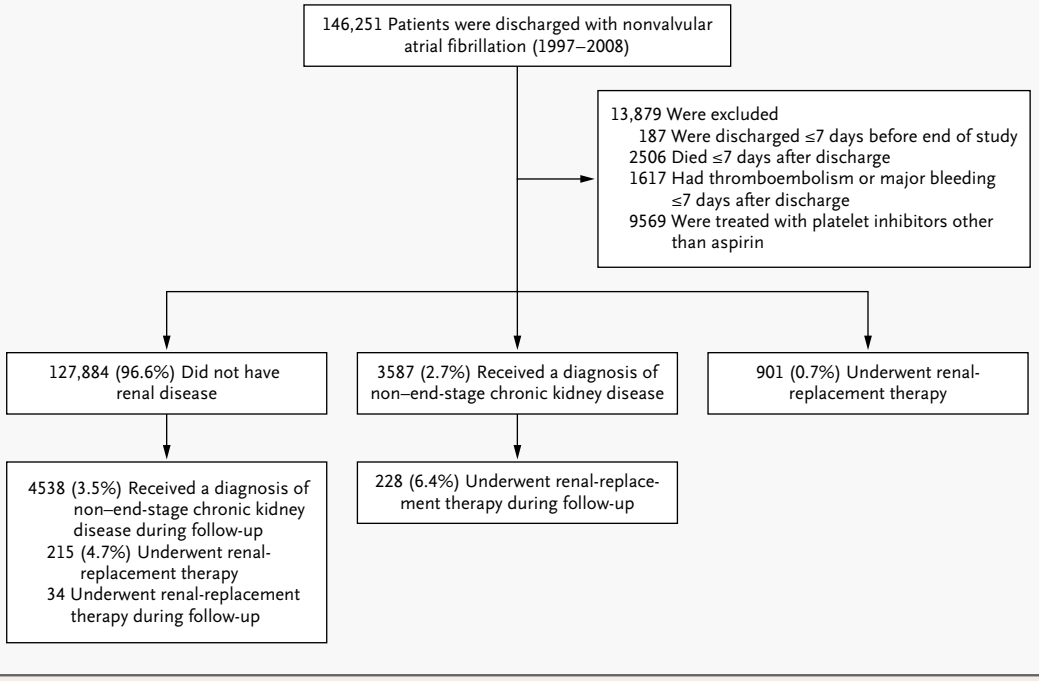

Figure 1. Study Population, According to Status with Respect to Renal Disease.

Of the 132,372 patients who were discharged from the hospital with a diagnosis of nonvalvular atrial fibrillation during the study period and who were included in the study, 4488 had renal disease at baseline. The majority of the study population had no renal disease at baseline, although non–end-stage chronic kidney disease or a disorder necessitating renal-replacement therapy developed in 4572 patients during follow-up.

had received a kidney transplant) were identified from the National Registry on Regular Dialysis and Transplantation. Renal status was determined at baseline and could be modified during follow-up (Fig. 1). The renal status of patients who were initially classified as having no chronic kidney disease could change to non–end-stage chronic kidney disease and could subsequently change to disease requiring renal-replacement therapy. The status of patients with non–end-stage chronic kidney disease initially could change to disease requiring renal-replacement therapy. The status of patients who initially had disease requiring renal-replacement therapy could not change during follow-up. Data were not censored in relation to change in renal status; patients remained in the analysis until an event occurred or until the end of follow-up. Thus, patients were analyzed according to their current renal status.

To investigate the risk associated with the severity of non–end-stage chronic kidney disease, patients were stratified in a time-dependent manner according to the treatment dose of loop diuretics, because high doses are frequently used in patients with severe renal failure or the nephrotic syndrome. We studied the influence of the underlying renal disease in non–end-stage chronic kidney disease by comparing the following diagnostic groups: autosomal dominant polycystic kidney disease, chronic glomerulonephritis, diabetic nephropathy, chronic tubulointerstitial nephropathy, hypertensive nephropathy, and other causes.

PHARMACOLOGIC TREATMENT

Baseline pharmacologic treatment with all drugs other than warfarin and aspirin was determined on the basis of prescriptions filled from 180 days before discharge to 7 days after discharge, and

patients receiving antiplatelet drugs other than aspirin (i.e., clopidogrel or dipyridamole) were excluded from the study population (Fig. 1).[19] Periods during which each patient was treated with warfarin, aspirin, or both were determined throughout follow-up.[19-21,23]

STROKE AND BLEEDING RISK ASSESSMENT

The predicted risk of stroke or systemic thromboembolism for all patients was assessed with the use of the CHA_2DS_2-VASc score,[17,24] which reflects the risk of stroke among patients with atrial fibrillation who are not receiving anticoagulant therapy, with values ranging from 0 to 9 and with higher scores indicating greater risk (see Table 1 in the Supplementary Appendix). The predicted risk of bleeding was assessed with the use of the HAS-BLED score,[18,25] which reflects the risk of major bleeding among patients with atrial fibrillation who are receiving anticoagulant therapy, with values ranging from 0 to 9 and with higher scores indicating greater risk (see Table 2 in the Supplementary Appendix). Two risk factors typically included in the HAS-BLED score were not included in this analysis: abnormal renal function (since chronic kidney disease was the subject of the study) and labile international normalized ratios (because these data were not available).

STUDY OUTCOMES

Outcomes under investigation were hospitalization or death from stroke or systemic thromboembolism (peripheral-artery embolism, ischemic stroke, and transient ischemic attack),[17,26] bleeding (gastrointestinal, intracranial, urinary tract, and airway bleeding),[20,21] myocardial infarction,[27] and death from any cause. A secondary analysis of the risk of stroke or systemic thromboembolism excluded transient ischemic attack.

STATISTICAL ANALYSIS

Comparisons of characteristics among patients who had no renal disease, those who had non–end-stage chronic kidney disease, and those requiring renal-replacement therapy at baseline were performed with the use of the chi-square test for categorical covariates and the Kruskal–Wallis test or Student's t-test for continuous covariates. Event rates for the four study outcomes were calculated according to renal status; the renal status of each patient was updated during follow-up if renal function worsened.

The risk of stroke or systemic thromboembolism associated with non–end-stage chronic kidney disease or disease requiring renal-replacement therapy was estimated by means of time-dependent Cox proportional-hazards models, with adjustment for changes in renal status or antithrombotic treatment during follow-up. Cox analyses were adjusted for risk factors in the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age >75 years, diabetes mellitus, history of stroke or thromboembolism, vascular disease, age 65 to 74 years, female sex), antithrombotic treatment, and year of inclusion. The total study population was included in the initial analysis, and subsequent analyses were restricted to patients with non–end-stage chronic kidney disease and to those requiring renal-replacement therapy.

Similar analyses were conducted to assess the risk of bleeding, with the use of the HAS-BLED risk factors (hypertension, abnormal liver function, history of stroke or thromboembolism, history of bleeding, age ≥65 years, use of nonsteroidal antiinflammatory drugs, and unhealthy alcohol use). Finally, the risks of stroke or systemic thromboembolism, bleeding, myocardial infarction, and death from any cause were estimated by means of time-dependent Cox proportional-hazards models, with adjustment for all baseline characteristics.

A two-sided P value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with the use of SAS software, version 9.2 (SAS Institute), and Stata software, version 11.0 (StataCorp).

RESULTS

STUDY POPULATION

During the 12-year study period, 132,372 patients with nonvalvular atrial fibrillation were included in the cohort (Fig. 1). Of these, 127,884 patients (96.6%) had no renal disease at baseline, 3587 (2.7%) had non–end-stage chronic kidney disease, and 901 (0.7%) required renal-replacement therapy. Baseline characteristics of each group are shown in Table 1; medications at baseline other than antithrombotic agents are shown in Table 3 in the Supplementary Appendix.

Among the patients who had no renal disease initially, non–end-stage chronic kidney disease developed in 4538 patients (3.5%) after a median of 893 days (interquartile range, 313 to 1715), and renal-replacement therapy was required in 477 pa-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	No Renal Disease (N=127,884)	Non–End-Stage Chronic Kidney Disease (N=3587)	Disease Requiring Renal-Replacement Therapy (N=901)	P Value
Age — yr	73.2±12.9	76.5±11.0	66.8±11.7	<0.001
Risk factors for stroke or thromboembolism — no. (%)				
Congestive heart failure	22,073 (17.3)	1284 (35.8)	171 (19.0)	<0.001
Hypertension	53,917 (42.2)	1952 (54.4)	486 (53.9)	<0.001
Age				
≥75 yr	66,675 (52.1)	2277 (63.5)	267 (29.6)	<0.001
65–74 yr	31,245 (24.4)	809 (22.6)	293 (32.5)	<0.001
Diabetes mellitus	10,920 (8.5)	885 (24.7)	129 (14.3)	<0.001
History of stroke or systemic thromboembolism	17,928 (14.0)	644 (18.0)	133 (14.8)	<0.001
Vascular disease	18,174 (14.2)	1034 (28.8)	248 (27.5)	<0.001
Female sex	59,930 (46.9)	1472 (41.0)	303 (33.6)	<0.001
Risk factors for bleeding — no. (%)				
Hypertension	53,917 (42.2)	1952 (54.4)	486 (53.9)	<0.001
Abnormal liver function	2,070 (1.6)	106 (3.0)	36 (4.0)	<0.001
History of stroke or systemic thromboembolism	17,928 (14.0)	644 (18.0)	133 (14.8)	<0.001
History of bleeding	8,969 (7.0)	584 (16.3)	137 (15.2)	<0.001
Age ≥65 yr	95,418 (74.6)	3035 (84.6)	533 (59.2)	<0.001
Use of NSAIDs	26,592 (20.8)	843 (23.5)	99 (11.0)	<0.001
Alcohol abuse	4,552 (3.6)	145 (4.0)	43 (4.8)	0.05
Antithrombotic medication — no. (%)				
Warfarin only	36,638 (28.6)	609 (17.0)	178 (19.8)	<0.001
Aspirin only	23,952 (18.7)	879 (24.5)	153 (17.0)	<0.001
Warfarin and aspirin	10,745 (8.4)	290 (8.1)	45 (5.0)	<0.001
CHA_2DS_2-VASc score†				<0.001
0	11,720 (9.2)	70 (2.0)	42 (4.7)	
1	16,926 (13.2)	251 (7.0)	165 (18.3)	
≥2	99,238 (77.6)	3266 (91.1)	694 (77.0)	
HAS-BLED score‡				<0.001
0 or 1	51,262 (40.1)	883 (24.6)	390 (43.3)	
2	46,159 (36.1)	1336 (37.2)	312 (34.6)	
≥3	30,463 (23.8)	1368 (38.1)	199 (22.1)	

* Plus–minus values are means ±SD. NSAIDs denotes nonsteroidal antiinflammatory drugs.
† Scores on the CHA_2DS_2-VASc,[17,24] which reflect the risk of stroke in patients with atrial fibrillation who are not receiving anticoagulant therapy, range from 0 to 9; a score of 0 indicates low risk, a score of 1 intermediate risk, and a score of 2 or more high risk (Table 1 in the Supplementary Appendix).
‡ Scores on the HAS-BLED,[18,25] which reflect the risk of major bleeding in patients with atrial fibrillation who are receiving anticoagulant therapy, range from 0 to 9; a score of 0 or 1 indicates low risk, a score of 2 intermediate risk, and a score of 3 or more high risk (Table 2 in the Supplementary Appendix).

Table 2. Event Rates, According to Status with Respect to Renal Disease.*

Event	No. of Person-yr	No. of Events	Event Rate per 100 Person-yr (95% CI)
Stroke or thromboembolism			
No renal disease	461,734	16,648	3.61 (3.55–3.66)
Non–end-stage CKD	13,078	842	6.44 (6.02–6.89)
Disease requiring renal-replacement therapy	2,922	164	5.61 (4.82–6.54)
Bleeding			
No renal disease	457,605	16,195	3.54 (3.48–3.59)
Non–end-stage CKD	12,515	1,097	8.77 (8.26–9.30)
Disease requiring renal-replacement therapy	2,734	243	8.89 (7.84–10.08)
Myocardial infarction			
No renal disease	480,745	9,037	1.88 (1.84–1.92)
Non–end-stage CKD	13,500	784	5.81 (5.41–6.23)
Disease requiring renal-replacement therapy	2,925	175	5.98 (5.16–6.94)
Death			
No renal disease	493,305	55,297	11.21 (11.12–11.30)
Non–end-stage CKD	14,052	5,431	38.65 (37.63–39.69)
Disease requiring renal-replacement therapy	3,114	914	29.35 (27.51–31.32)

* A patient's renal status could change during follow-up. CI denotes confidence interval, and CKD chronic kidney disease.

tients (0.4%) after a median of 217 days (interquartile range, 33 to 681). Of the 1378 patients requiring renal-replacement therapy during the study period, 1074 (77.9%) were receiving hemodialysis, 212 (15.4%) were receiving peritoneal dialysis, and 92 (6.7%) underwent kidney transplantation. The outcomes did not differ significantly according to the type of renal-replacement therapy.

Rates of stroke or systemic thromboembolism, bleeding, myocardial infarction, and death from any cause are shown according to renal status in Table 2. All event rates were markedly increased in both groups of patients with renal disease. The distribution between the three types of stroke or thromboembolic outcomes and the four types of bleeding outcomes is shown in Table 4 in the Supplementary Appendix.

RISK OF STROKE OR THROMBOEMBOLISM

Table 3 shows the results from Cox regression models of the risk of stroke or systemic thromboembolism, with adjustment for CHA_2DS_2-VASc risk factors, antithrombotic therapy, and year of inclusion. As compared with patients who did not have renal disease, the risk of stroke or systemic thromboembolism was increased among patients with non–end-stage chronic kidney disease (hazard ratio, 1.49; 95% confidence interval [CI], 1.38 to 1.59; P<0.001) and among those requiring renal-replacement therapy (hazard ratio, 1.83; 95% CI, 1.57 to 2.14; P<0.001). The results were similar in a sensitivity analysis for the outcome of stroke or systemic thromboembolism that excluded transient ischemic attack (Table 5 in the Supplementary Appendix). Among patients with non–end-stage chronic kidney disease, no significant association between the risk of stroke or systemic thromboembolism and dose of loop diuretics was found (Table 6 in the Supplementary Appendix). Among the diagnostic groups analyzed, the risk of stroke or systemic thromboembolism was increased to the greatest degree among patients with hypertensive nephropathy and to the lowest degree among those with chronic tubulointerstitial nephropathy (for whom the increase in risk was not significant; see Table 6 in the Supplementary Appendix).

Warfarin treatment was associated with a significantly decreased risk of stroke or systemic thromboembolism overall and among patients requiring renal-replacement therapy, and with a nonsignificantly decreased risk among patients with non–end-stage chronic kidney disease (Table 3). In an analysis that compared all patients who had any renal disease with those who had no renal disease, warfarin decreased the risk of stroke or systemic thromboembolism (hazard ratio, 0.76; 95% CI, 0.64 to 0.91; P=0.003), as did warfarin plus aspirin (hazard ratio, 0.74; 95% CI, 0.56 to 0.98; P=0.04). Aspirin was associated with an increased risk of stroke or systemic thromboembolism overall (Table 3) and among patients who had any renal disease, as compared with those who had no renal disease (hazard ratio, 1.17; 95% CI, 1.01 to 1.35; P=0.04). The risk of stroke or systemic thromboembolism in association with chronic kidney disease was of the same magnitude in multivariate Cox regression models that were adjusted for all baseline characteristics (Fig. 1 in the Supplementary Appendix).

RISK OF BLEEDING

The risk of bleeding was higher among patients with non–end-stage chronic kidney disease and among those requiring renal-replacement thera-

Table 3. Hazard Ratios for Stroke or Systemic Thromboembolism.*

Characteristic	Total Population (N=132,372)		No Renal Disease (N=127,884)†		Non–End-Stage Chronic Kidney Disease (N=3587)†		Disease Requiring Renal-Replacement Therapy (N=901)†	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants			1.00		1.49 (1.38–1.59)	<0.001	1.83 (1.57–2.14)	<0.001
Antithrombotic therapy								
None	1.00		1.00		1.00		1.00	
Warfarin	0.59 (0.57–0.62)	<0.001	0.59 (0.56–0.61)	<0.001	0.84 (0.69–1.01)	0.07	0.44 (0.26–0.74)	0.002
Aspirin	1.11 (1.07–1.15)	<0.001	1.10 (1.06–1.14)	<0.001	1.25 (1.07–1.47)	0.01	0.88 (0.59–1.32)	0.54
Warfarin and aspirin	0.70 (0.65–0.75)	<0.001	0.69 (0.64–0.74)	<0.001	0.76 (0.56–1.03)	0.08	0.82 (0.37–1.80)	0.62
Risk factors for thromboembolism‡								
Congestive heart failure	1.03 (0.99–1.07)	0.18	1.03 (0.99–1.08)	0.11	0.98 (0.84–1.14)	0.78	0.96 (0.64–1.43)	0.84
Hypertension	1.06 (1.03–1.09)	<0.001	1.05 (1.02–1.09)	0.002	1.13 (0.98–1.30)	0.10	1.05 (0.76–1.45)	0.78
Age								
≥75 yr	3.48 (3.31–3.66)	<0.001	3.56 (3.38–3.76)	<0.001	1.87 (1.48–2.36)	<0.001	2.46 (1.60–3.79)	<0.001
65–74 yr	2.02 (1.91–2.14)	<0.001	2.03 (1.92–2.16)	<0.001	1.52 (1.18–1.94)	0.001	2.18 (1.46–3.24)	<0.001
Diabetes	1.32 (1.26–1.38)	<0.001	1.32 (1.25–1.39)	<0.001	1.16 (0.99–1.36)	0.07	1.41 (0.95–2.10)	0.09
History of stroke or systemic thromboembolism	3.20 (3.10–3.31)	<0.001	3.24 (3.14–3.35)	<0.001	2.71 (2.34–3.15)	<0.001	1.99 (1.36–2.91)	<0.001
Vascular disease	1.10 (1.06–1.15)	<0.001	1.12 (1.07–1.16)	<0.001	0.89 (0.76–1.05)	0.17	1.11 (0.78–1.58)	0.57
Female sex	1.12 (1.08–1.15)	<0.001	1.12 (1.08–1.15)	<0.001	1.06 (0.92–1.22)	0.44	1.34 (0.97–1.85)	0.08

* Results from the time-dependent Cox regression analyses were adjusted for year of inclusion.
† Numbers of patients are from baseline data. Because the analyses were time-dependent, these numbers changed during follow-up.
‡ The reference group for the hazard ratio for each thromboembolism risk factor is the group of all patients in the study without that risk factor.

py than among patients without renal disease, and treatment with warfarin, aspirin, or both incrementally increased this risk (Table 4). Among all patients who had any renal disease, as compared with those who had no renal disease, there was an increased risk of bleeding with warfarin (hazard ratio, 1.33; 95% CI, 1.16 to 1.53; P<0.001), aspirin (hazard ratio, 1.17; 95% CI, 1.02 to 1.34; P=0.03), and warfarin plus aspirin (hazard ratio, 1.61; 95% CI, 1.32 to 1.96; P<0.001). Among patients with non–end-stage chronic kidney disease, the risk of bleeding increased with a higher dose of loop diuretics (Table 6 in the Supplementary Appendix). The risk of bleeding was highest among patients with chronic glomerulonephritis and lowest among those with chronic tubulointerstitial nephropathy (Table 6 in the Supplementary Appendix). The risk of bleeding among patients with chronic kidney disease was of similar magnitude in the multivariate Cox regression model (Fig. 1 in the Supplementary Appendix).

RISKS OF MYOCARDIAL INFARCTION AND DEATH FROM ANY CAUSE

On the basis of multivariate Cox regression models, non–end-stage chronic kidney disease and disease requiring renal-replacement therapy were both associated with an increased risk of myocardial infarction, as compared with no renal disease (hazard ratio with non–end-stage chronic kidney disease, 2.00; 95% CI, 1.86 to 2.16; P<0.001; hazard ratio with disease requiring renal-replacement therapy, 3.00; 95% CI, 2.58 to 3.50; P<0.001). Both categories of renal disease were also associated with an increased risk of death from any cause (hazard ratio with non–end-stage chronic kidney disease, 2.37; 95% CI, 2.30 to 2.44; P<0.001; hazard ratio with disease requiring renal-replacement therapy, 3.35; 95% CI, 3.13 to 3.58; P<0.001) (Fig. 1 in the Supplementary Appendix).

DISCUSSION

In a large cohort study, we found that among patients with atrial fibrillation, non–end-stage chronic kidney disease and disease requiring renal-replacement therapy were both associated with increased risks of stroke or systemic thromboembolism and bleeding. Among patients with non–end-stage chronic kidney disease, the risk of stroke or systemic thromboembolism was not influenced by the severity of the renal disease (as determined by the intensity of treatment with loop diuretics), whereas the risk of bleeding was associated with the dose of loop diuretics and with the cause of the chronic kidney disease. The risks of myocardial infarction and death from any cause were also increased among patients with atrial fibrillation who had chronic kidney disease, as compared with those who had no renal disease. In addition, we found that warfarin reduced the risk of stroke or systemic thromboembolism in the whole study population and among patients with chronic kidney disease, whereas aspirin did not reduce this risk. Both warfarin and aspirin increased the risk of bleeding.

The most effective treatment for stroke thromboprophylaxis in patients with atrial fibrillation is oral anticoagulant therapy.[28] However, clinical trials of thromboprophylaxis in atrial fibrillation have largely excluded patients with kidney disease. Indeed, given the predominantly renal excretion of some of the new oral anticoagulant agents, only patients with a creatinine clearance of 30 ml per minute or more have been studied, with some trials adjusting the dose of the study drug for those patients with moderate chronic kidney disease.[14,15] We found that warfarin therapy was associated with a significant reduction in the risk of stroke or thromboembolism among patients with chronic kidney disease but that the risk of bleeding among such patients was significantly increased. Thus, the net clinical effect of warfarin treatment requires careful assessment in patients with chronic kidney disease,[16] and the data do not provide clear guidance regarding indications for anticoagulant therapy in patients with both atrial fibrillation and chronic kidney disease. Certainly, close monitoring of the international normalized ratio is required when warfarin is administered. Ideally, the role of warfarin (or of other, newer anticoagulant agents) in patients with atrial fibrillation who have chronic kidney disease should be evaluated in a clinical trial.

Our study is limited by its observational cohort design, and there may be residual confounding, although we attempted to adjust the analysis for baseline clinical characteristics. The frequencies of risk factors in the study population may also be underestimated, since we identified patients with heart failure, hypertension, and diabetes on the basis of filled prescriptions and thus were not able to identify patients who were treated with diet and lifestyle interventions alone. Al-

Table 4. Hazard Ratios for Bleeding.*

Characteristic	Total Population (N=132,372)		No Renal Disease (N=127,884)†		Non–End-Stage Chronic Kidney Disease (N=3587)†		Disease Requiring Renal-Replacement Therapy (N=901)†	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants			1.00		2.24 (2.10–2.38)	<0.001	2.70 (2.38–3.07)	<0.001
Antithrombotic therapy								
None	1.00		1.00		1.00		1.00	
Warfarin	1.28 (1.23–1.33)	<0.001	1.28 (1.23–1.33)	<0.001	1.36 (1.17–1.59)	<0.001	1.27 (0.91–1.77)	0.15
Aspirin	1.21 (1.16–1.26)	<0.001	1.21 (1.16–1.26)	<0.001	1.12 (0.96–1.30)	0.14	1.63 (1.18–2.26)	0.003
Warfarin and aspirin	2.15 (2.04–2.26)	<0.001	2.18 (2.07–2.30)	<0.001	1.63 (1.32–2.02)	<0.001	1.71 (0.98–2.99)	0.06
Risk factors for bleeding‡								
Hypertension	1.01 (0.98–1.04)	0.52	1.01 (0.98–1.04)	0.58	0.99 (0.87–1.11)	0.81	0.92 (0.71–1.20)	0.55
Abnormal liver function	1.37 (1.23–1.52)	<0.001	1.40 (1.25–1.57)	<0.001	1.31 (0.90–1.91)	0.16	0.74 (0.34–1.64)	0.46
History of stroke or systemic thromboembolism	1.23 (1.18–1.28)	<0.001	1.24 (1.19–1.30)	<0.001	1.04 (0.89–1.22)	0.62	0.93 (0.63–1.36)	0.70
History of bleeding	2.44 (2.33–2.55)	<0.001	2.54 (2.42–2.67)	<0.001	1.70 (1.45–1.99)	<0.001	2.09 (1.50–2.91)	<0.001
Age ≥65 yr	2.09 (2.00–2.17)	<0.001	2.12 (2.03–2.20)	<0.001	1.61 (1.35–1.92)	<0.001	1.36 (1.03–1.80)	0.03
Use of NSAIDs	1.12 (1.08–1.16)	<0.001	1.12 (1.08–1.17)	<0.001	1.10 (0.96–1.26)	0.19	0.91 (0.62–1.33)	0.63
Alcohol abuse	1.40 (1.30–1.52)	<0.001	1.43 (1.32–1.56)	<0.001	1.01 (0.73–1.39)	0.97	1.33 (0.70–2.54)	0.39

* Results from the time-dependent Cox regression analyses were adjusted for year of inclusion. NSAIDs denotes nonsteroidal antiinflammatory drugs.
† Numbers of patients are from baseline data. Because the analyses were time-dependent, these numbers changed during follow-up.
‡ The reference group for the hazard ratio for each bleeding risk factor is the group of all patients in the study without that risk factor.

The New England Journal of Medicine

though the positive predictive value of the diagnosis of atrial fibrillation is very high (99%),[29] the inclusion of only hospitalized patients with atrial fibrillation is likely to have resulted in an overestimate of the proportion of patients who were at increased risk for thromboembolism and bleeding. The bleeding outcome was restricted to hospitalization or death related to gastrointestinal bleeding, intracranial bleeding, bleeding from the urinary tract, and airway bleeding, and the results cannot be applied to the risk of other types of bleeding.[20,21] The outcomes of stroke or systemic thromboembolism and myocardial infarction are well validated, and the information on all-cause mortality is accurate,[26,27] as is the information on renal-replacement therapy.[22] Since we did not have brain-imaging data for the patients in the study, some strokes that were reported as ischemic may actually have been hemorrhagic, but Krarup and colleagues did not find this potential bias to be of importance.[26] Despite the accuracy of filled prescriptions as a measure of medication use,[30] aspirin can also be bought over the counter in Denmark, and the use of aspirin may therefore be underestimated. It is also possible that the increased risk of stroke or systemic thromboembolism that was associated with aspirin in our analysis was due to confounding by indication. Finally, some of the dialysis centers in Denmark have reported that they provide warfarin without the use of prescriptions for patients who require renal-replacement therapy (primarily those receiving hemodialysis).

In conclusion, in a large cohort study, we found that non–end-stage chronic kidney disease and disease requiring renal-replacement therapy were independently associated with increased risks of stroke or systemic thromboembolism, bleeding, myocardial infarction, and death among patients with atrial fibrillation. The effect of warfarin was similar among patients with atrial fibrillation and those without chronic kidney disease, reducing the risk of stroke or systemic thromboembolism and increasing the risk of bleeding. In contrast, aspirin was not associated with a reduced risk of stroke or systemic thromboembolism but was associated with an increased risk of bleeding.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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