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Changes in glomerular filtration rate and outcomes in patients with atrial fibrillation

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Key words*:* atrial fibrillation, stroke, renal function

3 tables, 2 figures, 1 supplemental table

Abstract

Background: Patients with kidney disease are more likely to develop atrial fibrillation (AF) than individuals with normal renal function, and more likely to suffer ischemic stroke (IS) /thromboembolism (TE). We investigated the relationship of kidney function evolution to IS/TE, mortality and bleeding in AF patients.

Methods: In a cohort of 8962 AF patients, 2653 had serum creatinine data, with 10894 patient-years of follow-up. Patients were stratified into quartiles of estimated glomerular filtration rate (eGFR) evolution (in ml/min/1.73 m^2/year).

Results: Rates of events (IS/TE, bleeding, mortality) increased with worsening eGFR by quartiles. The risk of events was particularly increased when patients in the 4th quartile were compared to others. Renal impairment *per se* was not an independent predictor of IS/TE but was an independent predictor of bleeding, whilst eGFR *worsening* was an independent predictor both for IS/TE (Hazard Ratio [HR] 1.573, 95%CI 1.160-2.134 for patients in the last quartile) and for bleeding events (HR 1.543, 95%CI 1.157-2.004). Worsening eGFR did not improve the predictive ability of the CHA_2DS_2VASc and HAS-BLED scores for identifying a higher risk of IS/TE or bleeding events, respectively. When the benefit of IS reduction was balanced against the increased risk of bleeding events, the net clinical benefit was positive in favor of OAC use (vs non-use) in patients with worsening eGFR.

Conclusions: Rates of IS/TE, mortality and bleeding increased with worsening eGFR >4.81 ml/min/1.73 m^2. Worsening eGFR was an independent predictor of IS/TE and of bleeding, and a better predictor of IS/TE than renal impairment in AF.

Introduction

Chronic kidney disease (CKD) and atrial fibrillation (AF) are both independently associated with poor cardiovascular outcomes and all-cause mortality, presenting a growing global burden of disease[1-10]. Individuals with CKD are more likely to develop AF, ischemic stroke (IS) and thromboembolism (TE)[11] than patients with normal renal function. In a large study of Danish individuals with AF, CKD was associated with increased risk of IS/TE and bleeding[12], confirming observations of previous smaller studies[13, 14]. Renal failure is included as a dichotomous variable in risk prediction tools for bleeding but is less evident in guideline-recommended risk prediction tools for IS/TE[14-17], and we found that renal impairment and eGFR does not independently improve IS/TE risk prediction[1]. In clinical practice, renal function is quantified by the estimated glomerular filtration rate (eGFR)[18, 19]. Whilst eGFR was a debated independent predictor of IS/TE in several studies with AF patients, some patients are still 'high risk' and regular checks on eGFR are recommended, especially since mild renal impairment at baseline does not preclude some patients deteriorating to severe renal impairment[20].

No prior epidemiologic studies have considered the impact of *changes* in eGFR on *long-term* outcomes in individuals with AF. Therefore the balance between risk of IS/TE and bleeding has not been quantified by worsening in eGFR in a large 'real world' population of individuals with AF. This study investigated the relationship of eGFR evolution to IS/TE, mortality and bleeding in an AF population, unrestricted by age or comorbidity.

Methods

Between January 2000 and December 2010, 8962 patients seen in the Cardiology department in our institution with a diagnosis of AF were identified. [1, 2]. The regional university hospital of Tours serves approximately 400,000 inhabitants and is the only public institution in an area of about 4,000

km². The information for each patient was extracted from computerized data of hospitalization and consultation of our institution. During follow-up, information on outcomes was recorded and we defined major bleeding using the Bleeding Academic Research Consortium (BARC) definitions[21]. VKA therapy was the only form of OAC used during the study period.

Assessment of renal function

Renal impairment at baseline was defined as glomerular filtration rate (GFR) of less than 60 mL/min/1.73m^2 [22]. Baseline eGFR was recorded at the time of the first record of AF (i.e. index date). Creatinine-based GFR estimating equations have greater utility in assessing kidney function compared to creatinine measurement alone [23, 24]. In adults, the most widely-used and validated method for estimating GFR from serum creatinine level is the isotope dilution mass spectrometry (IDMS)-traceable Modification of Diet in Renal Disease (MDRD) Study equation [18, 19]. The MDRD equation was preferred to the "CKD-Epi" equation[25] because there were very few patients age≥75 years in cohorts used to validate this equation whereas the current study population was unrestricted by age. The African population in the present study population was <1% and therefore no correction factor for ethnicity was required in the MDRD calculation of eGFR. Patients with duration between first and last eGFR calculation <180 days were excluded of the analysis. We then estimated change in eGFR by calculating eGFR slope during follow-up, expressed in ml/min/1.73m^2/year and defined as (last eGFR calculation minus first eGFR calculation)/(duration between first and last eGFR calculation). For patients a clinical event, last eGFR was the last eGFR obtained before the first outcome of interest recorded in this study.

Statistical analysis

The study population was stratified into quartiles according to eGFR changes (in ml/min/1.73 m^2/year). Baseline characteristics were determined in the 4 quartiles, and differences were investigated using chi-squared test for categorical covariates and Kruskal-Wallis test for continuous

covariates. Cox-proportional hazards analyses were performed to investigate whether renal impairment and eGFR evolution were independent predictors of events. The risk associated with renal impairment and eGFR evolution were estimated with hazard ratio (HR) in a univariate analysis, as well as a sex- and age-adjusted analysis, and a multivariate analysis adjusted for the risk factors included in the CHA_2DS_2-VASc and HAS-BLED scores and antithrombotic therapy.

We assessed the predictive capability of CHA_2DS_2-VASc and HAS-BLED scores using Harrell's c-statistic with 95% CIs as a measure of model performance. The CHA_2DS_2-VASc and HAS-BLED scores were analyzed as categorical risk groups and the effect of adding eGFR worsening as a categorical variable (patients in the 4th quartile of eGFR worsening) to the scores was determined. The value of adding eGFR worsening as a categorical variable to the established risk scores was also evaluated by Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI)[26].

Finally, the net clinical benefit (NCB) of treatment was calculated using the method proposed by Connolly[27] which uses a weighted sum of rate differences ΔR = Rate not treated – Rate treated:

NCB = w1*ΔR ischemic stroke + w2*ΔR ICH + w3*ΔR major bleeding + w4*ΔR MI,

where major bleeding refers to major extracranial bleeding, ICH=intracranial hemorrhage, MI= myocardial infarction and weights w1=1, w2=3.08, w3=0.67, w4=0.95.

The NCB is used by clinicians as a method of balancing risk of ischemic stroke and thromboembolism, against ICH.

Ethics approval

This type of study registered as a clinical audit was approved by the review board of the Pole Coeur Thorax Vaisseaux from the Trousseau University Hospital on December 7, 2010. Ethical review

was therefore not required. Patient consent was not sought. Patient data were utilized only to facilitate the cross referencing of data sources and records were otherwise anonymous. The study was conducted retrospectively, patients were not involved in its conduct, and there was no impact on their care. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

Of 8962 individuals with AF seen in the cardiology department, 2653 had several available serum creatinine data allowing the eGFR (expressed in ml/min/1.73m^2) and eGFR evolution (slope of eGFR, expressed in ml/min/1.73m^2/year) to be calculated (Figure 1). The number of samples with creatinine level assessment was 12±14 per patient (median 7, interquartile range 4-14).

Baseline characteristics are shown in Table 1. The eGFR at baseline in this population was 65.5 ml/min/1.73m^2. Supplemental table 1 shows comparison of baseline characteristics between included patients and patients excluded from the analysis, which were relatively similar in terms of age and CHA_2DS_2-VASc and HAS-BLED scores, although included patients more frequently had coronary artery disease or heart failure. Quartiles based on eGFR slope determined 4 groups of patients with eGFR slope ≥1.56, 1.56 to -1.25, -1.25 to -4.81 and <-4.81 ml/min/1.73m^2/year. Individuals with decreasing eGFR were older, and more likely to have hypertension, diabetes, vascular disease, heart failure, previous bleeding and higher CHA_2DS_2-VASc and HAS-BLED scores. Subjects in the rapid decline group had substantially higher baseline eGFR compared to other groups. Decreasing eGFR during follow-up was not associated with differences in rates of OAC nor antithrombotic therapies.

During a mean follow-up of 1499 days (median 1318, interquartile range 524-2317), the incidence rate of IS/TE was 19.6 per 1000 person-years. Rates of all-cause mortality and of major bleeding were 26.1 and 27.9 per 1000 person-years, respectively. Rates of all events increased with decreasing eGFR, regardless of OAC therapy (table 2).

Figure 2 (top panel) shows the event-free curves for stroke/TE events in the 4 groups based on eGFR slope. There was an increased risk of stroke/TE when worsening in eGFR was more marked (HR 1.226, 95%CI 1.087-1.381 for each change of quartile) and the risk was markedly increased when patients in the 4th quartile were compared to other patients (HR 1.803, 95%CI 1.367-2.378). Figure 2 (lower panel) shows the event-free curves for bleeding events in the 4 groups based on eGFR slope. There was an increased risk of bleeding when worsening in eGFR was more marked (HR 1.184, 95%CI 1.071-1.308 for each change of quartile) and the risk was particularly increased when patients in the 4th quartile were compared to other patients (HR 1.582, 95%CI 1.245-2.010).

Rates of IS/TE and all-cause mortality were lower in individuals on OAC, compared with those individuals not on OAC and the effect was not significantly affected by eGFR worsening quartiles. Bleeding rates were higher in individuals on OAC, compared with non-anticoagulated individuals and the effect was not significantly affected by eGFR worsening quartiles (table 2).

Table 3 shows the results from regression analyses for IS/TE and bleeding events, respectively. As a categorical variable, eGFR worsening (patients in the 4th quartile with eGFR slope <-4.81 ml/min/1.73m^2/year) was an independent predictor for IS/TE after adjustment for age, sex, renal impairment at baseline, CHA_2DS_2VASc risk factors and antithrombotic therapy. Renal function with eGFR at baseline was a predictor of IS/TE in AF in univariate analysis but was not an independent predictor after adjustment for age, sex, and other baseline characteristics. Considering bleeding events, eGFR worsening as a categorical variable, was an independent predictor after

adjustment for age, sex, renal impairment at baseline, HAS-BLED risk factors and antithrombotic therapy. Renal function with eGFR at baseline was also an independent predictor of bleeding after adjustment for age, sex, and other baseline characteristics. eGFR worsening as a categorical variable was also an independent predictor for total mortality (HR 3.192, 95%CI 2.504-4.069). after adjustment for age, sex, renal impairment at baseline, HAS-BLED risk factors and antithrombotic therapy. Renal function with eGFR at baseline was also an independent predictor of mortality after adjustment for age, sex, and other baseline characteristics (HR 0.980, 95%CI 0.974-0.987).

There was no statistically significant improvement in either the CHA_2DS_2VASc or HAS-BLED scoring systems by the addition of eGFR worsening for identifying the risk of IS/TE and bleeding events, respectively. The c-statistic was neither improved when adding eGFR worsening to CHA_2DS_2VASc score (c-statistic 0.558 95%CI 0.534-0.583 for CHA_2DS_2VASc score, 0.556 95%0.525-0.587 when adding eGFR worsening in the 4th quartile) nor to HAS-BLED score (c-statistic 0.547 95%CI 0.523-0.571 for HAS-BLED score, 0.538 95%0.510-0.567 when adding eGFR worsening in the 4^{th} quartile). The NRI and IDI were not significantly different by adding eGFR worsening to CHA_2DS_2VASc (NRI -0.092, IDI 0.088, relative IDI 16%). The NRI and IDI were neither improved for bleeding by adding eGFR worsening to HAS-BLED (NRI -0.093, IDI 0.378, relative IDI -66%).

When the benefit of ischemic stroke reduction was balanced against the increased risk of bleeding event amongst AF patients with worsening eGFR, the net clinical benefit (NCB) remained positive in favor of VKA use. In individuals with eGFR slope >-4.81 ml/min/1.73m^2/year), NCB was 1.46(95%CI 0.32-2.67), whilst in those with eGFR slope <-4.81 ml/min/1.73m^2/year), NCB was 3.95(95%CI 0.81-7.48).

Discussion

In this large series of AF patients, our principal findings are as follows: (i) incidence rates of IS/TE, mortality and bleeding increased with worsening eGFR; (ii) worsening eGFR was an independent predictor of IS/TE and of bleeding, and a better predictor of IS/TE than renal function at baseline; (iii) worsening eGFR did not improve the predictive ability of the CHA_2DS_2VASc and HAS-BLED scores for identifying a higher risk of IS/TE or bleeding events; and (iv) when the benefit of IS reduction was balanced against the increased risk of bleeding event, the NCB was positive in favour of OAC use in patients with worsening eGFR.

This is the first comprehensive assessment of eGFR evolution in AF patients on IS/TE or bleeding risk, and the NCB of antithrombotic therapy. We have previously shown that eGFR does not add incremental value to risk prediction in IS/TE[1]. Since renal impairment is commonly associated with many of the individual components of CHA_2DS_2-VASc score, our observation that low eGFR was not an independent predictor of IS/TE in AF is unsurprising.

Our observations also confirm the high bleeding risk associated with increasing renal impairment. The present study extends prior observations by showing that worsening eGFR was an independent predictor for bleeding events. Indeed, the latter may have implications for future risk stratification schemes for major bleeding which currently classify (baseline) renal failure as a dichotomous variable[14, 16, 17]. Actually, both low eGFR at baseline and falling eGFR over time were combining for optimal risk prediction of bleeding events.

The observation that worsening eGFR confers a worse prognosis is perhaps unsurprising since risk does not remain static, especially in the elderly AF population with multiple comorbidities and polypharmacy. A previous study has shown that approximately 1 in 5 patients with AF demonstrate

mean eGFR decrease of >10 ml/min/1.73 m^2, and that normal or mild renal dysfunction at baseline did not exclude the subsequent development of severe renal dysfunction during the follow-up period[20]. In another smaller study, an absolute decrease in eGFR ≥25 ml/min/1.73 m^2 on MDRD, or a relative reduction (≥25%) in eGFR, independently predicted the risk for stroke or death in AF patients[28]. Since it is a time dependent variable, eGFR slope is not available at baseline. Several years of follow-up (after baseline GFR) were needed to define "GFR slope", which makes our concept uneasy to translate into clinical use. Since worsening eGFR is globally a linear function,[29-31] the clinician might instead consider a reasonable approach looking at GFR slope during a landmark period (e.g. 1 year) and then predict risk using this landmark view. This may have implications for regular monitoring of renal function, and use of particular therapies that may be associated with less deterioration of renal function[32]. eGFR slope might also refine risk prediction during follow-up, as soon as its estimation seems reliable. This may be a new type of tool for risk stratification, which has to be used a bit differently than others (available at baseline) for risk prediction of future events in AF patients. This would be in line with the opinion that the risks of different events are dynamic processes in AF patients and need to be regularly re-evaluated.

Importantly, the cut-off value defining the 4thquartile in our study (≥5 ml/min/year) has a special meaning for nephrologists and corresponds to the so-called "rapid progression of renal disease"[19]. Moreover, predictors of rapid progression include (among other parameters) older age, elevated blood pressure, hyperglycemia and history of cardiovascular disease[19]. Despite the fact that true baseline renal impairment was infrequent in subjects from the present cohort, subjects in the 4th quartile were indeed older, more often had hypertension, diabetes and history of cardiovascular disease, confirming the value of these parameters even in a low renal risk population. Of note, these subjects in the rapid decline group had substantially higher baseline eGFR compared to other groups. This further emphasizes the point that a single baseline creatinine by itself does not provide full information on kidney status for AF patients. It may seem counterintuitive that these patients

initially had a better renal function. However, significant worsening in eGFR is probably more likely to be seen in patients with relatively preserved eGFR at baseline, whilst patients with lower or very low eGFR at baseline are unlikely to have a marked additional decrease in eGFR.

By contrast, some patients had some improvement in eGFR. These patients in the first quartile had an initial eGFR which was a bit (but not dramatically) lower than other patients and a follow-up duration which was bit lower than in the 2nd and 3rd quartiles. We would thus consider that these patients had a stabilization of kidney function on a mid-term follow-up, possibly starting from a moderate alteration of kidney function, rather than a marked improvement on a fully normal function, which would be difficult to understand. This relatively good clinical response may be part of the holistic management of AF, since rate control, rhythm control, management of heart failure (whether it is with reduced or preserved ejection fraction), and cardiovascular drugs *per se* (e.g. RAAS blockade) might improve cardiac output and renal perfusion.

Study limitations

This study is based on a 'real world' registry with its inherent limitations, as previously reported[1, 2]. In this retrospective analysis, the slope of eGFR over time may depend on the number of samples taken in the individual patients and we did not exclude those with only two draws, in whom slope may be less accurate compared to multiple sampling. Patients who experienced severe adverse events and early death did not have 2nd measurement of creatinine, and the slope of renal function was therefore not assessed. Non-inclusion of patients due to missing data may be related to the fact that eGFR may be measured in patients with different comorbidities and the relation with IS/TE may be mediated by unmeasured confounders/mediators as opposed to renal deterioration *per se*. It may also be simplistic to assume that renal deterioration is a linear function. In several situations, acute kidney injury leads to an abrupt reduction in renal function that does not return to baseline. Other biomarkers such as proteinuria and cystatin c values were not available in these patients.

Bleeding and thromboembolic events often happen in relation to acute decompensation, which can relate to acute renal failure as opposed to CKD progression, and this may not be reflected in overall slope. We used a categorical variable analysis for eGFR evolution as this would be more useful in terms of being incorporated into a risk prediction score; there was no appreciable difference with eGFR slope analyzed as a continuous variable. Despite stratification and adjustment for several risk factors, the non-randomized design leaves a risk of residual confounding factors, but the majority of randomized trials in AF patients has excluded analyses of the effect of renal function. The study population was hospital-based and therefore may not be representative of all patients with AF. The study was not ethnically diverse and our findings may not be generalizable to other populations. The data regarding OAC use were only regarding baseline therapy and do not reflect any changes in prescribed therapy or adherence to therapy. Also, data regarding compliance and the "time in therapeutic range" are not available for our study population. Finally, lack of inclusion of patients treated with non-vitamin K OACs, which are commonly prescribed and variably cleared by the kidneys, is another limitation.

Conclusions

Worsening renal function (rather than renal impairment) is associated with poor outcomes in individuals with AF across the whole range of renal function, as measured by eGFR. Incidence rates of IS/TE, mortality and bleeding substantially increased with worsening eGFR. Worsening eGFR was an independent predictor of IS/TE and of bleeding, and a better predictor of IS/TE than baseline renal impairment. These observations may have implications for future risk prediction tools of outcomes in AF as well as future clinical trials.

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FIGURE LEGENDS

Figure 1. Study population by stage of renal function worsening

Figure 2. Top: Kaplan-Meier estimates of the percentages of patients remaining free of stroke and/or thromboembolic events by quartile of renal function worsening. Bottom: Kaplan-Meier estimates of the percentages of patients remaining free of major bleeding by quartile of renal function worsening.

Table 1: Characteristics of patients with atrial fibrillation in relation to degree of renal function worsening by quartiles

	GFR slope (in ml/min/1.73 m^2/year)				
n (%)	**Q1 (≥1.56) n=661**	**Q2 (1.56 to -1.25) n=662**	**Q3 (-1.25 to -4.81) n=666**	**Q4 (<-4.81) n=664**	**p-value**
Mean age (SD)	68(14)	68(14)	70(13)	71(14)	<0.0001
Female	211(31)	241(36)	217(32)	216(32)	0.29
Baseline eGFR, ml/min/1.73m² (SD)	60(21)	62(18)	65(17)	71(50)	<0.0001
Mean follow-up, months (SD)	44(35)	62(38)	57(38)	34(30)	<0.0001
Type of AF					
Paroxysmal	362(55)	377(57)	357(54)	378(57)	0.20
Permanent	261(39)	232(35)	256(38)	250(38)	
Persistent	38(6)	53(8)	53(8)	36(5)	
Comorbidities					
Hypertension	227(34)	231(35)	253(38)	287(43)	0.003
Diabetes	82(12)	72(11)	110(17)	139(21)	<0.0001
Previous stroke	45(7)	57(9)	55(8)	44(7)	0.41
Coronary artery disease	208(32)	219(33)	241(36)	260(39)	0.02
Vascular disease	147(22)	156(24)	165(25)	200(30)	0.006
Heart failure	328(50)	321(49)	375(56)	437(66)	<0.0001
Renal impairment	43(7)	40(6)	48(7)	63(10)	0.08
Liver impairment	3(1)	1(0)	1(0)	4(1)	0.39
Dyslipidaemia	129(20)	139(21)	136(20)	145(22)	0.76
Smoking	88(13)	84(13)	87(13)	92(14)	0.94
Pacemaker/ICD	116(18)	168(25)	194(29)	144(22)	<0.0001
Bleeding risk factors					
Previous bleeding	32(5)	33(5)	52(8)	67(10)	0.0002
Labile INR	13(2)	22(3)	21(3)	19(3)	0.45
Anaemia	5(1)	6(1)	9(1)	6(1)	0.71
NSAIDs	1(0)	0(0)	4(1)	0(0)	0.04
Drugs	124(19)	142(22)	142(21)	144(22)	0.52
Cancer	20(3)	15(2)	8(1)	15(2)	0.30
Excessive risk of falls	12(2)	4(1)	5(1)	11(2)	0.10
Thrombocytopenia	1(0)	0(0)	1(0)	0(0)	0.57
Antithrombotic agents					
Vitamin K antagonist	391(64)	380(62)	410(68)	409(67)	0.15
Antiplatelet	191(32)	209(35)	199(34)	204(34)	0.80
Any antithrombotic	502(84)	506(84)	511(86)	516(85)	0.75
Other therapies					
ACEI	225(35)	265(41)	275(42)	298(46)	0.0006
Beta-blocker	320(49)	324(49)	360(54)	374(57)	0.008
Digoxin	144(22)	154(23)	162(24)	141(21)	0.51
Diuretic	38(13)	438(16)	679(25)	96(33)	<0.001
Antiarrhythmic agent	281(43)	283(43)	274(41)	288(44)	0.87
Calcium channel blocker	18(14)	39(21)	25(14)	22(23)	0.11
CHA_2DS_2-VASc score (SD)	2.6(1.7)	2.7(1.7)	3.0(1.7)	3.3(1.7)	<0.0001
Low(score<2 in males, 3 in females)	219(33)	213(32)	158(24)	136(20)	<0.0001
High(score≥2 in males, 3 in females)	442(67)	449(68)	508(76)	528(80)	
HAS-BLED score	1.4 (1.1)	1.5(1.1)	1.6(1.1)	1.7(1.1)	<0.0001
Low(score=0)	158(24)	146(22)	123(19)	99(15)	
Moderate(score=1-2)	408(62)	402(61)	419(63)	423(64)	0.0002
High(score≥3)	95(14)	114(17)	123(19)	142(21)	

SD: standard deviation; AF: atrial fibrillation; ICD: implantable cardiac defibrillator; INR: international normalised ratio; CHA_2DS_2-VASc (1 point for heart failure, hypertension, diabetes, vascular disease, age 65-74, and female gender; 2 points for prior stroke or thromboembolism and age ≥75); HAS-BLED (Hypertension, Abnormal renal and/or liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio (INR), Elderly (> 65 years).

Table 2. Event rates (95% confidence interval) per 1000 person years in patients with atrial fibrillation by quartiles of renal function worsening

	Slope of Estimated glomerular filtration rate(in ml/min/1.73 m^2/year)								
	Q1 n=661		Q2 n=662		Q3 n=666		Q4 n=664		P
	Events	Event rate	Events	Event rate	Events	Event rate	Events	Event rate	
Ischaemic Stroke/TE									
Total	52	2.23(1.70-2.92)	66	2.04(1.60-2.59)	72	2.38(1.89-3.00)	71	4.06(3.21-5.11)	0.0003
No VKA	18	2.51(1.58-3.94)	27	2.58(1.77-3.74)	21	2.38(1.55-3.62)	17	3.42(2.12-5.43)	0.65
VKA	31	2.17(1.52-3.07)	38	1.98(1.44-2.71)	45	2.43(1.82-3.25)	46	4.19(3.13-5.57)	0.005
Relative risk(VKA vs No VKA)		0.86(0.48-1.53)		0.77(0.47-1.25)		1.03(0.62-1.74)		1.24(0.71-2.16)	0.61*
Ischaemic Stroke/TE/Mortality									
Total	105	4.51(3.72-5.45)	113	3.48(2.90-4.18)	113	3.74(3.11-4.49)	178	10.18(8.77-11.76)	<0.0001
No VKA	46	6.40(4.78-8.49)	46	4.40(3.29-5.84)	44	4.98(3.70-6.66)	53	10.65(8.09-13.82)	<0.0001
VKA	49	3.43(2.59-4.51)	63	3.28(2.56-4.19)	77	4.16(3.33-5.19)	104	9.48(7.80-11.44)	<0.0001
Relative risk(VKA vs No VKA)		0.54(0.36-0.81)		0.74(0.50-1.08)		0.85(0.58-1.23)		0.89(0.64-1.24)	0.27*
Major bleeding									
Total	72	3.12(2.48-3.92)	99	3.15(2.58-3.82)	103	3.49(2.87-4.22)	92	5.33(4.34-6.52)	0.002
No VKA	22	3.08(2.02-4.63)	29	2.75(1.91-3.94)	18	2.04(1.28-3.20)	25	5.32(3.58-7.79)	0.03
VKA	47	3.36(2.52-4.45)	63	3.45(2.70-4.41)	77	4.30(3.44-5.36)	57	5.11(3.93-6.59)	0.11
Relative risk(VKA vs No VKA)		1.08(0.65-1.80)		1.26(0.81-1.96)		2.11(1.26-3.53)		0.98(0.61-1.56)	0.15*
All-cause mortality									
Total	69	2.84(2.24-3.59)	62	1.82(1.42-2.32)	90	2.83(2.30-3.47)	133	7.13(6.01-8.43)	<0.0001
No VKA	33	4.40(3.12-6.14)	24	2.13(1.43-3.16)	29	3.12(2.16-4.45)	44	8.38(6.20-11.16)	<0.0001
VKA	28	1.89(1.30-2.72)	35	1.74(1.25-2.42)	50	2.56(1.94-3.37)	74	6.28(4.99-7.85)	<0.0001
Relative risk(VKA vs No VKA)		0.44(0.27-0.73)		0.80(0.47-1.34)		0.83(0.53-1.32)		0.75(0.52-1.09)	0.24*

p-value for 2-sided chi-squared test. TE: thromboembolism. * p-value for interaction. VKA: Vitamin K antagonist. HAS-BLED (Hypertension, Abnormal renal and/or liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio (INR), Elderly (> 65 years)

Table 3. Renal function, renal function worsening and risk of ischaemic stroke/thromboembolism or bleeding events: Results from Cox regression analyses

Ischaemic Stroke/Thromboembolism	**Hazard Ratio (CI)**	**Bleeding Events**	**Hazard Ratio (CI)**
Univariate analysis		*Univariate analysis*	
Baseline GFR	0.985(0.981-0.989)	Baseline GFR	0.986(0.983-0.990)
GFR slope (categorical variable)	1.803(1.367-2.378)	GFR slope (categorical variable)	1.582(1.245-2.010)
Adjusted for sex and age		*Adjusted for sex and age*	
Baseline GFR	0.994(0.986-1.001)	Baseline GFR	0.990(0.983-0.996)
GFR slope (categorical variable)	1.825(1.369-2.431)	GFR slope (categorical variable)	1.644(1.285-2.104)
Female gender	1.142(0.885-1.474)	Female gender	0.753(0.599-0.947)
Age per 10-y increase	1.289(1.166-1.414)	Age per 10-y increase	1.216(1.113-1.319)
Adjusted for CHA_2DS_2VASc risk factors		*Adjusted for HAS-BLED risk factors*	
Baseline GFR	0.996(0.988-1.003)	Baseline GFR	0.991(0.985-0.997)
GFR slope (categorical variable)	1.760(1.314-2.357)	GFR slope (categorical variable)	1.578(1.231-2.024)
Heart failure	1.362(1.055-1.761)	Hypertension	1.108(0.895-1.374)
Hypertension	1.073(0.829-1.389)	Liver impairment	0.684(0.095-4.902)
Age per 10-y increase	1.252(1.126-1.379)	Previous stroke	0.934(0.632-1.383)
Diabetes mellitus	1.186(0.853-1.650)	Previous bleeding	1.957(1.410-2.717)
Previous stroke/thromboembolism	3.584(2.632-4.878)	Labile INR	1.543(0.976-2.439)
Vascular disease	1.258(0.958-1.653)	Age per 10-y increase	1.183(1.069-1.309)
Female gender	1.181(0.909-1.535)	Drugs	1.305(1.025-1.664)
Adjusted for CHA_2DS_2VASc score and antithrombotic therapy		*Adjusted for HAS-BLED score and antithrombotic therapy*	
Baseline GFR	0.994(0.986-1.002)	Baseline GFR	0.991(0.984-0.997)
GFR slope (categorical variable)	1.573(1.160-2.134)	GFR slope (categorical variable)	1.543(1.187-2.004)
CHA_2DS_2VASc score	1.336(1.234-1.447)	HAS-BLED score	1.265(1.132-1.414)
Vitamin K antagonist use	1.174(0.868-1.587)	Vitamin K antagonist use	1.420(1.087-1.855)
Antiplatelet use	1.401(1.042-1.880)	Antiplatelet use	1.198(0.912-1.570)

*adjusted for Table 1 risk factors and including age as a continuous covariate, the result is only displayed for renal impairment and renal function worsening. GFR slope as categorical variable defined as GFR slope in the 4th quartile (<-4.81 ml/min/1.73m^2/year.

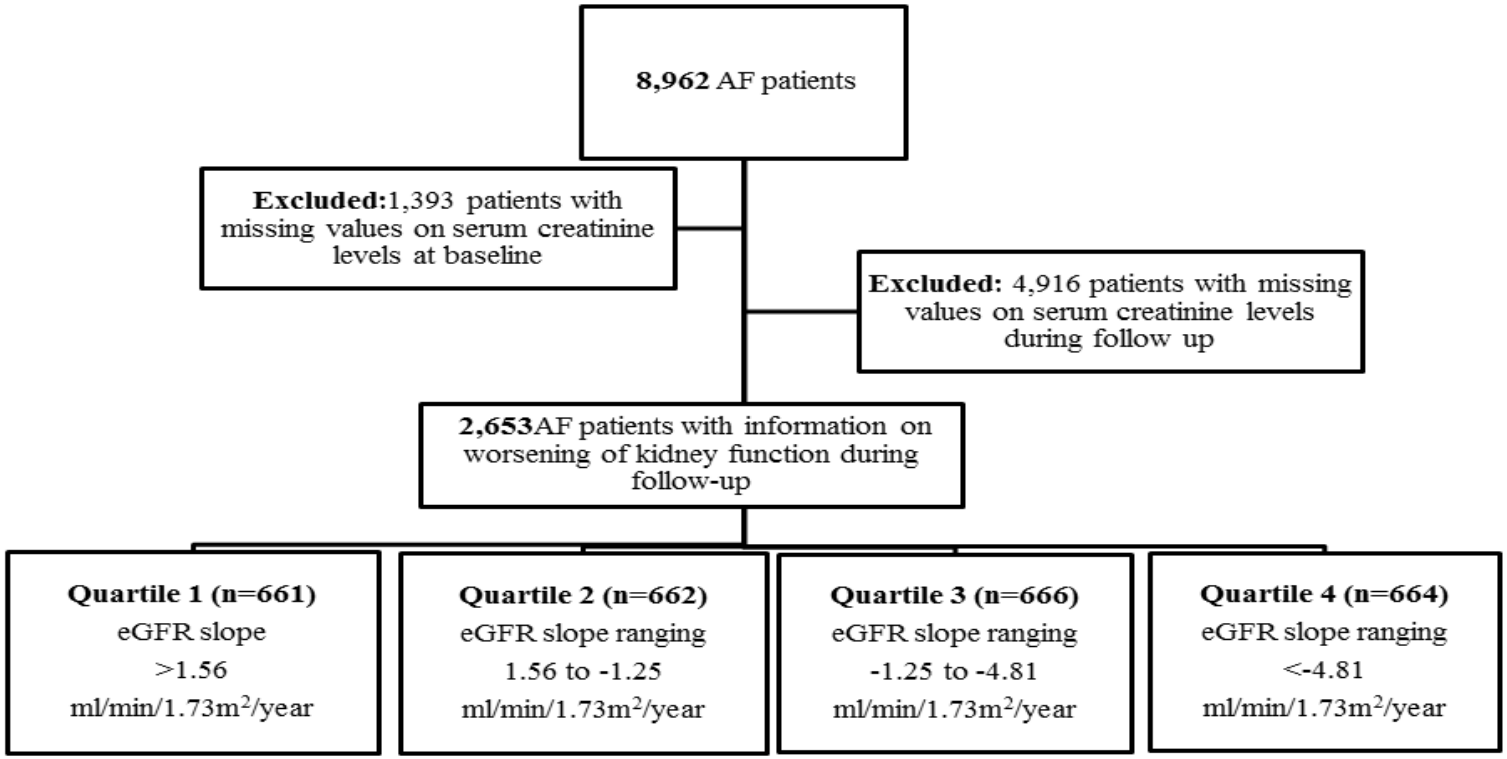


Figure 1

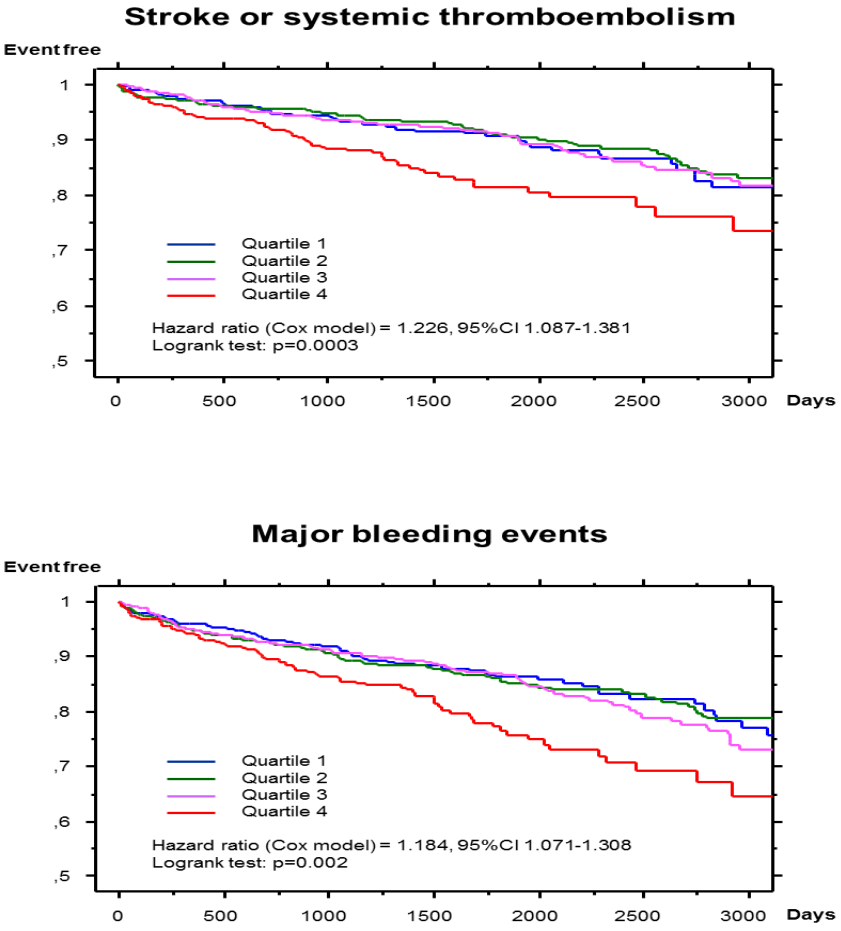


Figure 2

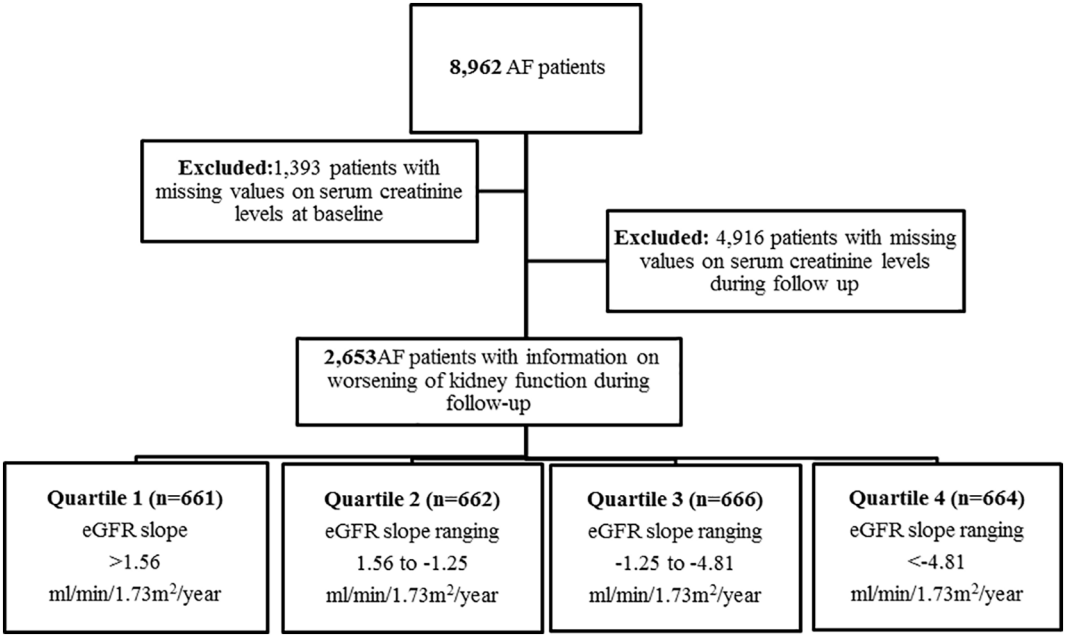
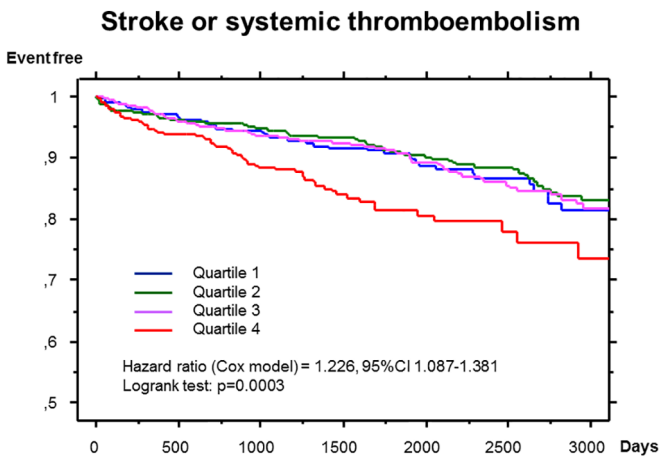

8,962 AF patients
Excluded:1,393 patients with missing values on serum creatinine levels at baseline
Excluded: 4,916 patients with missing values on serum creatinine levels during follow up
2,653AF patients with information on worsening of kidney function during follow-up
Quartile 1 (n=661)
eGFR slope
>1.56
ml/min/1.73m2/year
Quartile 2 (n=662)
eGFR slope ranging
1.56 to -1.25
ml/min/1.73m2/year
Quartile 3 (n=666)
eGFR slope ranging
-1.25 to -4.81
ml/min/1.73m2/year
Quartile 4 (n=664)
eGFR slope ranging
<-4.81
ml/min/1.73m2/year

Figure 1


Stroke or systemic thromboembolism
Event free
1
,9
,8
,7
,6
,5
Quartile 1
Quartile 2
Quartile 3
Quartile 4
Hazard ratio (Cox model) = 1.226, 95%CI 1.087-1.381
Logrank test: p=0.0003
0
500
1000
1500
2000
2500
3000
Days

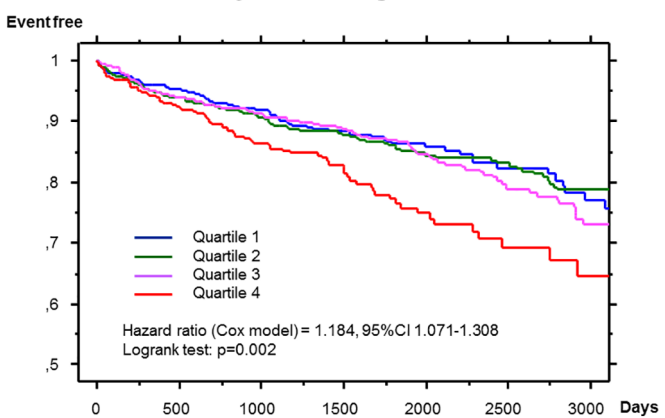

Major bleeding events
Event free
1
,9
,8
,7
,6
,5
Quartile 1
Quartile 2
Quartile 3
Quartile 4
Hazard ratio (Cox model) = 1.184, 95%CI 1.071-1.308
Logrank test: p=0.002
0
500
1000
1500
2000
2500
3000
Days

Figure 2