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CLINICAL INVESTIGATIONS

Glomerular filtration rate: A prognostic marker in atrial fibrillation—A subanalysis of the AntiThrombotic Agents Atrial Fibrillation

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Objective: An increased cardiovascular mortality and morbidity has been widely reported in patients with atrial fibrillation (AF). In this study, a subanalysis of the AntiThrombotic Agents Atrial Fibrillation (ATA-AF) is performed with the aim to evaluate estimated glomerular filtration rate (eGFR) as an independent prognostic marker of cardiovascular mortality and morbidity in patients with AF.

Methods and Results: The ATA-AF study enrolled 7148 patients with AF, in 360 Italian centers. The eGFR was calculated from data reported in patient notes or hospital database. This post-hoc analysis included 1097 AF patients with eGFR data available and 1-year clinical follow-up. The endpoint was assessed as cardiovascular mortality and/or hospital admission for cardiovascular causes at follow-up. Patients were also divided in two groups according to the eGFR (<60 and ≥60 mL/min/1.73 m^2). The Kaplan-Meyer curve for the mentioned endpoint showed a higher endpoint incidence in the group of patient with eGFR below 60 mL/min/1.73 m^2 ($P < 0.001$). Using multivariate analysis (Cox regression), a trend toward a higher rate of occurrence of the primary endpoint was observed for eGFR below 60 mL/min/1.73 m^2 without reaching the conventional level of statistical significance (hazard ratio [HR] 1.40; 95% confidence interval [CI] 0.99-1.99; $P = 0.0572$). When eGFR was included in the analysis as continuous variable a significant correlation was observed with the combined endpoint at the Cox regression (HR 0.99, 95% CI 0.98-0.99, $P = 0.04$).

Conclusion: The result of this post-hoc analysis indicates that an impaired eGFR is independently associated with worse prognosis among patients with AF.

KEYWORDS

atrial fibrillation, glomerular filtration rate, mortality

1 | INTRODUCTION

An increased cardiovascular mortality and morbidity not related to stroke, including occurrence of ischemic heart disease, congestive heart failure, and cardiovascular hospitalization, has been widely reported in patients with atrial fibrillation (AF),[1] albeit overshadowed by the risk of thromboembolic events.

Likewise, few studies[2,3] looking at the clinical markers capable of stratifying the long-term prognosis in patients with AF have applied the risk stratification used to determine the CHADS score, although with limited success.

[†]See Appendix S1 for a complete list of participating Centers and Investigators.

In contrast, chronic kidney disease (CKD), which had been not included in the algorithm for thromboembolic risk stratification in patients with AF, is a well-known risk factor for mortality, cardiovascular events, and hospitalization in the general population.[4–6]

In large population from the Danish national registry, Olesen et al[7] reported that CKD is independently associated with stroke and systemic embolism in patients with AF.

More recently, an impaired glomerular filtration rate (GFR) combined with a high CHADS score has been shown to be an effective predictor of cardiovascular event and mortality in patients with AF.[8]

The AntiThrombotic Agents Atrial Fibrillation (ATA-AF) study[9] is a multicenter observational study that assessed the differences in clinical profile and treatment strategies between patients with AF, referred to cardiology and internal medicine units.

A subanalysis on the ATA-AF population is presented with the aim to evaluate the association between estimated glomerular filtration rate (eGFR) and cardiovascular mortality and morbidity in patients with AF.

2 | METHODS

The ATA-AF study has been described somewhere else[9]; briefly from May to July 2010, 7148 patients with AF, of which 4845 with a nonvalvular form, were enrolled in 360 Italian centers. A substudy was run in 64 centers that followed-up a total of 1368 patients for 1 year; among these 1097 patients had data on eGFR and were included in this subanalysis. The clinical and therapeutic management was assessed according to the department of admission, either medicine or cardiology. The only exclusion criterion was AF after acute coronary syndrome or cardiothoracic surgery (within 1 week from symptom onset or surgery).

Information regarding occurrence of major cardiovascular events requiring hospitalization or mortality were collected at follow-up visits or through phone calls to the patients and their relatives.

All patients gave written informed consent. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The eGFR was calculated from data reported in patient notes or hospital database, according to the CKD-EPI Creatinine Equation.

The clinical outcome was assessed as composite endpoint of cardiovascular mortality and/or hospital admission for cardiovascular causes at 1-year follow-up. Occurrence of thromboembolic events, including ischemic and hemorrhagic stroke, pulmonary, or peripheral embolism, was assessed as a secondary endpoint.

In our analysis, an eGFR of 60 mL/min/1.73 m^2, was used as cutoff point to assign patients into two groups; equal and above (preserved eGFR), or below the cutoff point (impaired eGFR). In order to evaluate the effect of eGFR on the clinical outcome we also considered eGFR both as a continuous variable and in three groups <30 mL/min/1.73 m^2, from 30 to 59 mL/min/1.73 m^2, and ≥60 mL/min/1.73 m^2.

2.1 | Statistical analysis

Continuous variable are expressed as mean and SDs, and were compared by Mann-Whitney *U* test. Categorical variables are reported as number and percentages, and were compared by χ^2 test. A multivariable analysis (Cox regression) was used to determine the independent predictors of the combined endpoint of cardiovascular mortality and/or hospitalization for cardiovascular causes at 1 year follow-up, using the variables that were statistically significant at univariate analysis (eGFR among these), and gender and age, even though not significant. Three models were performed, the first with eGFR in two classes (<60; ≥60 mL/min/1.73 m^2), the second with eGFR in three classes (<30; 30-59; ≥60 mL/min/1.73 m^2, with the latter as reference group), and the last with eGFR as continuous. Kaplan-Meier curves for the combined outcome were produced by eGFR (preserved vs impaired), and compared by log-rank test. For the eGFR the linearity of the risk was evaluated by restricted cubic splines. A P value <0.05 was considered statistically significant. All analyses were performed with SAS system software (SAS Institute Inc, Cary, NC, USA), version 9.2.

3 | RESULTS

3.1 | Baseline characteristics

In the ATA-AF study population, data on GFR were available in 5681 of 7148 enrolled patients (79.5%). Baseline clinical characteristics of patients with and without data on eGFR are shown in Supporting Information Table S1. Patients with data on GFR were older and had a higher $CHADS_2$ score and a lower body mass index (BMI). Cognitive deficit, dementia, heart failure, ischemic cardiomyopathy, diabetes, transient ischemic attack (TIA), cancer, and anemia were significantly higher among patients with data on eGFR.

Among the 5681 patients with data on GFR, 1-year clinical follow-up was available for 1097 patients in 67 of the 360 centers participating in the substudy.

The clinical characteristics of the patients with and without follow-up are reported and compared in Table S2. Patients with an eGFR and 1-year clinical follow-up were younger, more likely to be admitted in a cardiology department, and had a lower $CHADS_2$ and CHA_2D_2SVasc score. Prevalence of cognitive deficit and dementia, stroke, peripheral vascular disease, cancer, anemia, and chronic obstructive pulmonary disease (COPD) was significantly lower among patients with eGFR and clinical follow-up. Persistent AF was more prevalent among patients with follow-up while paroxysmal and permanent AF were more prevalent among patients without. Finally, patients with clinical follow-up were more likely to be on oral anticoagulants (OAC) and propafenone, and less on ASA.

Among the 1097 patients with eGFR and 1-year follow-up data, 459 (42%) had eGFR <60 mL/min/1.73 m^2, while 638 (58%) had eGFR ≥60 mL/min/1.73 m^2. A comparison between the baseline characteristics of patients with 1-year follow-up divided in the two groups according to eGFR is reported in Table 1. Patients with an eGFR <60 mL/min/1.73 m^2 were older, less likely to be admitted in a cardiology department, predominantly female and not smokers, and had a higher $CHADS_2$ and CHA_2D_2SVasc score. In this subgroup, the prevalence of cognitive deficit, heart failure, hypertension, diabetes and TIA, peripheral vascular disease, cancer, anemia, and COPD was significantly higher.

TABLE 1 Baseline characteristics and therapy at enrollment of the patients with 1-year follow up divided in the two groups with eGFR below or equal and above 60 mL/min/1.73 m^2

	eGFR < 60	eGFR ≥ 60	*P*-value
Number of patients, n (%)	459 (41.8)	638 (58.2)	
Cardiology department of admission, n (%)	254 (55.3)	415 (65.1)	0.001
Male, n (%)	199 (43.4)	387 (60.7)	<0.0001
Age (SD)	79 (8.0)	71 (11.0)	<0.0001
BMI (SD)	26.7 (4.2)	27.0 (4.5)	0.28
Smoke, n (%)	14 (3.1)	57 (8.9)	<0.0001
Hypercholesterolemia, n (%)	138 (30.1)	196 (30.7)	0.82
Cognitive deficit, n (%)	29 (6.3)	19 (3.0)	0.008
Dementia, n (%)	10 (2.2)	10 (1.6)	0.46
Heart failure, n (%)	180 (39.2)	146 (22.9)	<0.0001
Diabetes, n (%)	142 (30.9)	123 (19.3)	<0.0001
Hypertension, n (%)	375 (81.7)	457 (71.6)	0.0001
TIA, n (%)	46 (10.0)	33 (5.2)	0.002
Stroke, n (%)	35 (7.6)	40 (6.3)	0.38
Ischemic CMP, n (%)	112 (24.4)	105 (16.5)	0.001
Dilated CMP, n (%)	69 (15.0)	65 (10.2)	0.02
Hypertensive CMP, n (%)	227 (49.5)	277 (43.4)	0.048
Hypertrophic CMP (%)	15 (3.3)	9 (1.4)	0.04
Other CMP, n (%)	34 (7.4)	39 (6.1)	0.40
Valvular CMP, n (%)	153 (33.3)	170 (26.7)	0.02
$CHADS_2$ score (SD)	2.5 (1.3)	1.7 (1.2)	<0.0001
CHA_2D_2vasc score (SD)	4.3 (1.5)	3.0 (1.7)	<0.0001
Prior PM, n (%)	61 (13.3)	48 (7.5)	0.002
Prior ICD, n (%)	18 (3.9)	17 (2.7)	0.24
Hyperthyroidism, n (%)	14 (3.1)	41 (6.4)	0.01
Hypothyroidism, n (%)	46 (10.0)	35 (5.5)	0.005
Peripheral vascular disease, n (%)	60 (13.1)	33 (5.2)	<0.0001
Renal failure, n (%)	186 (40.5)	16 (2.5)	<0.0001
COPD, n (%)	91 (19.8)	97 (15.2)	0.045
Sleep apnea, n (%)	7 (1.5)	6 (0.9)	0.38
Anemia, n (%)	85 (18.5)	51 (8.0)	<0.0001
Cancer, n (%)	52 (11.3)	39 (6.1)	0.002
Type of AF			<0.0001
Paroxysmal, n (%)	79 (17.2)	165 (25.8)	
Permanent, n (%)	274 (59.7)	254 (39.8)	
Persistent, n (%)	89 (19.4)	200 (31.4)	
Other AF, n (%)	17 (3.7)	19 (3.0)	
EF[a] % (SD)	50.0 (12.0)	53.2 (11.2)	<0.0001
Hemoglobin g/dL (SD)	12.4 (1.8)	13.5 (1.9)	<0.0001
Creatinine mg/dL (SD)	1.5 (0.8)	0.9 (0.2)	<0.0001
GFR-EPI mL/min/1.73 m^2 (SD)	42.6 (12.5)	79.3 (13.0)	<0.0001
Therapy prescribed at enrollment			
OAC, n (%)	315 (68.6)	416 (65.2)	0.24
ASA, n (%)	108 (23.5)	154 (24.1)	0.82
Anti-arrhythmic therapy			
Amiodarone, n (%)	72 (15.7)	118 (18.5)	0.23
Propafenone, n (%)	11 (2.4)	42 (6.6)	0.001
Sotalol, n (%)	3 (0.7)	26 (4.1)	0.0005
Flecainide, n (%)	11 (2.4)	32 (5.0)	0.03
Beta-blockers, n (%)	228 (49.7)	289 (45.3)	0.15

TABLE 1 (Continued)

	eGFR < 60	eGFR ≥ 60	*P*-value
ACE-inhibitors, n (%)	178 (38.8)	257 (40.3)	0.62
Sartans, n (%)	134 (29.2)	163 (25.6)	0.18
Diuretics, n (%)	336 (73.2)	328 (51.4)	<0.0001
Anti-aldosterone, n (%)	66 (14.4)	93 (14.6)	0.93
Oral hypoglycaemic, n (%)	63 (13.7)	77 (12.1)	0.42
Insulin, n (%)	43 (9.4)	22 (3.5)	<0.0001
Digoxin, n (%)	114 (24.8)	141 (22.1)	0.29

Abbreviations: ACE, angiotensin converting enzyme; AF, atrial fibrillation; ASA, acetylsalicylic acid BMI, body mass index; CHADs2, congestive heart failure, Hypertension, Age (>=65=1point, >=75=2points), Diabetes and Stroke/TIA (2 points); CMP, (documented) cardiomyopathy; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; EPI, epidemiology; eGFR, estimated Glomerular Filtration Rate; ICD, implantable cardiac defibrillator; OAC, oral anticoagulants; PM, pacemaker; TIA, transient ischemic attack.
[a] EF available for 856 patients.

Patients with eGFR <60 mL/min/1.73 m^2 had more likely permanent AF while those with eGFR ≥60 mL/min/1.73 m^2 a paroxysmal and persistent form. The latter were in a larger proportion on antiarrhythmic therapy with class Ic drugs. Finally, no significant differences between the groups were detected on the proportion of patients on OAC and antiplatelet.

3.2 | Clinical outcome

Table 2 displays the major causes for hospital admission and mortality; death for cardiovascular causes was significantly higher ($P < 0.0001$) in the group with eGFR <60 mL/min/1.73 m^2. Hospital admissions were comparable between the two groups.

At 1-year follow-up, 210 patients (19%) presented a major cardiovascular event (death or hospital admission) and at univariate analysis, a statistically significant higher occurrence of the composite endpoint was observed in the group with eGFR below 60 ($\chi^2 = 9.8$, $P = 0.002$) (Table 2).

Accordingly, the Kaplan-Meyer curve for the composite endpoint of cardiovascular mortality and/or hospitalization for cardiovascular causes at 1-year follow-up showed a higher incidence of new events in the group of patients with eGFR below 60 mL/min/1.73 m^2 (*P*-value long-rank <0.001) (Figure 1).

Over the 1-year follow-up, 20 thromboembolic events have been reported including fatal and nonfatal cases. Sixteen occurred in the group with eGFR <60 mL/min/1.73 m^2 and four in the group with eGFR ≥60 mL/min/1.73 m^2 ($P = 0.0005$).

3.3 | Multivariable analyses

3.3.1 | Model with eGFR divided in two groups (<60 or ≥60 mL/min/1.73 m^2)

At multivariate analysis only the type of center (internal medicine vs cardiology, adjusted hazard ratio [HR] 1.83, 95% confidence interval [CI] 1.33-2.52), the presence of congestive heart failure (adjusted HR 1.52, 95% CI 1.10-2.09), hypothyroidism (adjusted HR 1.75, 95% CI 1.12-2.74), and the presence of previous implantable cardiac defibrillator (ICD) (adjusted HR 2.24 95% CI 1.24-4.06) were significantly associated with the combined endpoint of cardiovascular mortality and/or hospitalization for cardiovascular causes at 1-year follow-up; the presence of an impaired renal function (eGFR below 60 mL/min/1.73 m^2) showed a trend toward a positive association with a higher rate of occurrence of the primary outcome measure, but the conventional level of statistical significance was not reached (HR 1.40, 95% CI 0.99-1.99, $P = 0.0572$) (Table 3A).

3.3.2 | Model with eGFR divided in three groups (<30, 30-59, ≥60 mL/min/1.73 m^2)

In this analysis, patients were divided in three groups according to the eGFR (<30, 30-59, ≥60 mL/min/1.73 m^2) and assessed on the combined outcome (mortality/hospital admissions for CV causes). The results of the adjusted analysis including the other clinical variables are shown in Table 3B. The group with preserved eGFR (≥60 mL/min/1.73 m^2) was used as the comparison group. A statistically significant difference was detected between the group with eGFR <30 mL/

TABLE 2 Major causes for hospital admission and mortality[a]

	eGFR < 60 (n = 459)	eGFR ≥ 60 (n = 638)	*P*-value
Number of death, n (%)	87 (19.0)	39 (6.1)	<0.001
Deaths for CV causes, n (%)	44 (9.6)	12 (1.9)	<0.0001
Deaths non-CV causes, n (%)	21 (4.6)	13 (2.0)	0.02
Not known, n (%)	22 (4.8)	14 (2.2)	0.02
Hospital admissions, n (%)	123 (26.8)	136 (21.3)	0.035
Hospital admission CV causes, n (%)	81 (17.7)	95 (14.9)	0.22
Hospital admission non-CV causes, n (%)	51 (11.1)	46 (7.2)	0.02
Deaths for CV causes/hospital admission CV causes, n (%)	108 (23.5)	102 (16.0)	0.002

Abbreviations: CV, cardiovascular; eGFR, estimated Glomerular Filtration Rate.
[a] 1097 patients with 1 year-follow-up available.

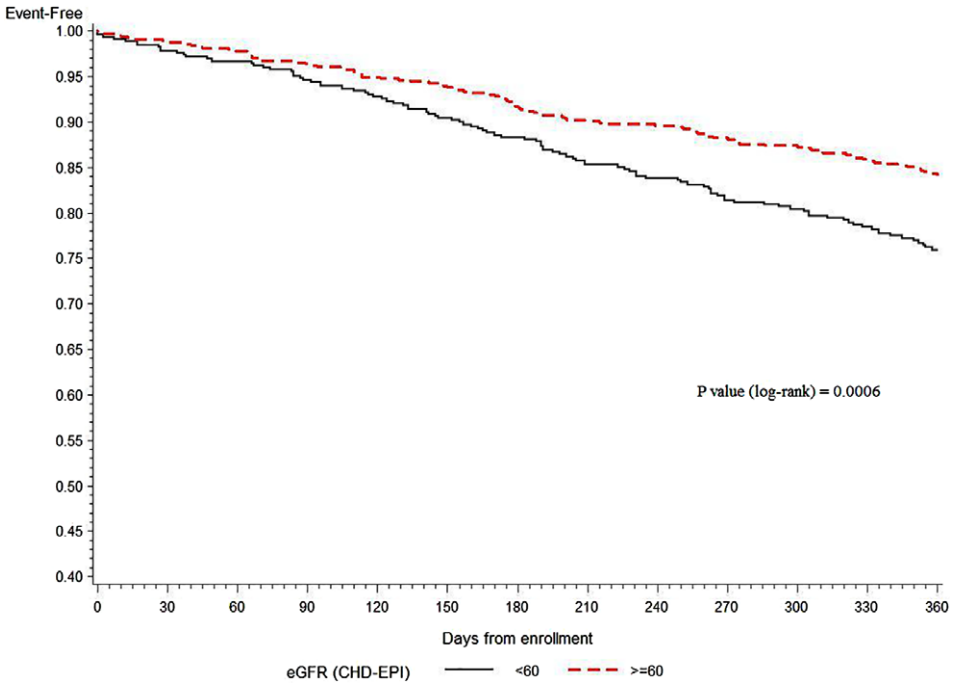

FIGURE 1 Kaplan-Meyer curve showing free-events survival on the composite endpoint of cardiovascular mortality and/or hospitalization for cardiovascular causes at 1-year follow-up in the group the two groups with eGFR < or ≥60 mL/min/1.73 m^2 (*P*-value long-rank < 0.001). eGFR, estimated glomerular filtration rate

min/1.73 m^2 and ≥60 mL/min/1.73 m^2 (HR 2.62, 95% CI 1.43, 4.79, *P* = 0.0017). Conversely, no statistically significant difference was detected between the group with eGFR 30-59 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2 (HR 1.37, 95% CI 0.96-1.95, *P* = 0.0825).

3.3.3 | Model with eGFR as continuous variable

In the third analysis, the eGFR was considered as a continuous variable. Univariate Cox regression assessing the association between the composite endpoint (mortality/hospital admission for CV causes) and the eGFR showed a significant inverse correlation (HR 0.987, 95% CI 0.981-0.993, *P* < 0.0001). In the adjusted analysis that included the other clinical variables the association between level of eGFR and clinical endpoints was also statistically significant (HR 0.99, 95% CI 0.98-0.99, *P* = 0.04) (Table 3C).

4 | DISCUSSION

The results of our post-hoc analysis performed on the data of the ATA-AF study shows that eGFR is independently associated with worse prognosis in patients with AF. An impaired eGFR heralds a higher risk for cardiovascular morbidity and mortality among patients with AF.

The association between mortality and AF has recently become more apparent; three epidemiological studies[10–12] from different countries analyzing death certificates have consistently described a relevant association between mortality and AF. In addition, several cohort studies in patients with AF have shown an independent association with mortality with a relative risk of death reported ranging from 1.5 to 2.5.[1] A recent meta-analysis, that included 104 studies and 587 867 patients, reported an absolute risk in cardiovascular mortality associated to AF of 2.6 events/1000 cases per year. In the same analysis, the pooled relative risk of congestive heart failure and ischemic heart events was reported around 4.99 (95% CI 3.04-8.22) and 1.61 (95% CI 1.38-1.87), respectively.[1]

Although the strength of the evidence cannot support direct causality, as for stroke, it identifies an increased cardiovascular mortality and morbidity in patients with AF, independent from thromboembolic events. This mortality risk needs to be adequately evaluated and addressed by clinicians.

Consequently, the identification of clinical markers capable of stratifying the long-term prognosis in patients with AF may become clinically relevant. However, only a few studies have evaluated the possible predictors of death and cardiovascular events in patients with AF. Most of these studies applied the thromboembolic risk stratification used to calculate the $CHADS_2$ score with limited results.

Nakagawa et al[8] in a cohort of 387 patients with nonvalvular AF followed-up for 5.6 years, has found that a decrease in the eGFR below 60 mL/min/1.73 m^2 combined with a $CHADS_2$ score greater than 2, were robust forecasters of cardiovascular events and mortality.[8] Previously, Guo et al[13] had shown that in patients with AF, the deterioration in renal function increases the risk of death. Lin et al[14] has shown that in the presence of a low CHA_2D_2Svasc between 1 and 2, an impaired renal function (<60 mL/min/1.73 m^2) identifies patients at higher risk for cardiovascular morbidity and ischemic events.

More recently, Kodani et al[15] in the post-hoc analysis of the J-Rhythm registry have reported that even a moderate renal impairment (CrCl 30-49.9 mL/min) carries increased risk for all-cause and cardiovascular mortality in patients with AF. It is worth mentioning that the authors used creatinine clearance for the assessment of the renal

TABLE 3 Multivariable analyses on the combined end-point cardiovascular mortality and/or hospitalization for cardiovascular causes

	HR	95% CI
(A) Model with eGFR divided in two groups (<60, ≥60 mL/min/1.73 m^2)		
Internal medicine vs cardiology admission	1.83	1.33-2.52
Female vs male	0.89	0.65-1.22
Age	0.99	0.97-1.01
DBP	0.99	0.97-1.00
Fall	1.91	0.96-3.81
Heart failure	1.52	1.10-2.09
Diabetes	1.28	0.95-1.74
Ischemic CM	1.27	0.92-1.77
Dilated CM	0.83	0.53-1.29
Smoke	0.51	0.24-1.11
Prior ICD	2.24	1.24-4.06
Hypothyroidism	1.75	1.12-2.74
Peripheral vascular disease	1.01	0.65-1.59
Renal failure	0.88	0.58-1.32
COPD	1.24	0.88-1.76
Anemia	0.98	0.62-1.54
Permanent/other/not detectable AF vs paroxysmal AF	1.21	0.83-1.78
Persistent AF vs paroxysmal AF	1.19	0.76-1.87
Hemoglobin<12 g/dL	0.87	0.61-1.25
eGFR<60 mL/min/1.73 m^2	1.40	0.99-1.99
(B) Model with eGFR divided in three groups (<30, 30-59, ≥60 mL/min/1.73 m^2)		
Internal medicine vs cardiology admission	1.84	1.39-2.54
Female vs male	0.86	0.63-1.78
Age	0.99	0.97-1.00
DBP	0.99	0.97-1.00
Fall	2.02	1.01-4.02
Heart failure	1.50	1.08-2.09
Diabetes	1.28	0.94-1.73
Ischemic CM	1.22	0.87-1.69
Dilated CM	0.83	0.53-1.30
Smoker	0.49	0.23-1.08
Prior ICD	2.24	1.24-4.05
Hypothyroidism	1.74	1.11-2.72
Peripheral vascular disease	0.95	0.60-1.49
Renal failure	0.70	0.44-1.18
COPD	1.29	0.90-1.83
Anemia	0.91	0.57-1.45
Permanent/other/not detectable AF vs paroxysmal AF	1.20	0.81-1.76
Persistent AF vs paroxysmal AF	1.19	0.76-1.87
Hemoglobin <12 g/dL	1.26	0.89-1.78
eGFR <30 mL/min/1.73 m^2	2.62	1.43-4.79
eGFR 30-59 mL/min/1.73 m^2	1.36	0.96-1.95
(C) Model with eGFR as continuous variable		
Internal medicine vs cardiology admission	1.871	1.35-2.57
Female vs male	0.84	0.62-1.15
Age	0.98	0.96-1.00
DBP	0.98	0.97-1.00
Fall	2.12	1.06-4.25
Heart failure	1.51	1.09-2.09
Diabetes	1.27	0.93-1.72
Ischemic CM	1.26	0.91-1.75
Dilated CM	0.81	0.51-1.26
Smoker	0.49	0.23-1.08
Prior ICD	2.15	1.19-3.90
Hypothyroidism	1.77	1.13-2.76
Peripheral vascular disease	0.98	0.63-1.55
Renal failure	0.74	0.48-1.15
COPD	1.26	0.89-1.79
Anemia	0.93	0.59-1.48
Permanent/other/not detectable AF vs paroxysmal AF	1.86	0.8-1.74
Persistent AF vs paroxysmal AF	1.16	0.74-1.82
Hemoglobin<12 g/dL	1.25	0.88-1.77
eGFR	0.98	0.97-0.99

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CM, (documented) cardiomyopathy; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated Glomerular Filtration Rate; HR, hazard ratio; ICD, implantable cardiac defibrillator.

function. It is well known that the creatinine clearance tends to overestimate the eGFR, which may partially explain the difference in survival they detected even for mild renal insufficiency. Conversely, in our analysis a worse clinical outcome is significantly associated with a severe impairment in eGFR (<30 mL/min/1.73 m^2). In addition, eGFR was calculated in our study according to the CKD-EPI Creatinine Equation, which has been shown by Boriani et al[16] in the data of EORP-AF registry to have better precision than the other available formulas for eGFR calculation in identifying class of AF patients with renal impairment at increased risk of CVE.

Of note our ancillary analysis of the ATA-AF registry shows that an eGFR <60 mL/min/1.73 m^2 is associated with a higher rate of occurrence of CV mortality and hospitalization, but, after adjusted analysis, this association was not confirmed. These results are in line with the findings by Banerjee et al,[17] in the Loire Valley AF project; the authors reported that eGFR as a categorical variable was an independent predictor of CVE but it lost its predictability when adjustment for other confounding variables. It is worth mentioning that in the Loire Valley AF project the eGFR was calculated according to the MDRD (modification of diet in renal disease) equation.

It has been clearly demonstrated that CKD and AF share the same pathophysiological mechanisms.[18] For instance, Watanabe et al[19] in a community-based prospective study including 231 818 subjects, reported a bidirectional risk between patients with CKD and AF. Specifically, the authors reported a 77% increase in the risk of developing CKD in patients with AF. Hence, it may be hypothesized that renal impairment can act in conferring poor prognosis in patients with AF as progressive eGFR deterioration that fails to be detected as dichotomous discriminator.

The bidirectional link between AF and renal function is further confirmed by studies conducted in patients who underwent catheter ablation; evidence from a recent meta-analysis showed a higher

incidence of AF recurrence after catheter ablation in patients with CKD.[20] In addition, more recently, a decline of eGFR has been shown to be associated with episodes of AF recurrence after ablation.[21] An improvement in eGFR has been detected in patients with mild and moderate renal impairment who were free of arrhythmia recurrence after catheter ablation.[22] Conversely, patients with AF and normal renal function or mild renal dysfunctions treated medically experience a decline in eGFR that is associated with increased thromboembolic events and mortality.[23]

In support of this finding, our results show a significant association between eGFR levels and the primary combined endpoint of the analysis.

Finally, our analysis detected a significantly higher incidence of thromboembolic events in patients with an impaired renal function. This finding is in line with recent evidences that suggest impaired renal function as a potential predictor of thromboembolic events.[24]

4.1 | Limitations

The main limitation of this study is that it represents a post-hoc analysis of a study originally designed with a different aim. Furthermore, only a small subset of the ATA-AF population had data on eGFR and 1-year follow-up and could be included in the analysis. Finally, our results are limited at 1-year follow-up and do not provide long-term follow-up.

5 | CONCLUSION

The result of this post-hoc analysis indicates that an impaired eGFR is independently associated with a worse prognosis among patients with AF.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interest.

Author contribution

Riccardo Proietti, Ahmed AlTurki, Vincenzo Russo, Mauro Lencioni provided substantial contribution to interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be submitted. Giovanni Pizzimenti, Antonietta Ledda, and Pietro Sanna provided substantial contribution to acquisition of data. Lucio Gonzini provided substantial contribution to analysis and interpretation of data. These 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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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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