Original Paper

Is There Association Between Changes in eGFR Value and the Risk of Permanent Type of Atrial Fibrillation? – Analysis of Valvular and Non-Valvular Atrial Fibrillation Population

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Key Words

Valvular atrial fibrillation • Non-valvular atrial fibrillation • Kidney function • Estimated glomerular filtration rate

Abstract

Background/Aims: There are no data concerning renal function in population with valvular and non-valvular atrial fibrillation (AF). To assess renal function in patients with AF, the association between eGFR and AF perpetuation, in-hospital mortality. **Methods:** We studied 1523 patients with AF. Patients with chronic kidney disease (CKD) were compared to population with preserved renal function. **Results:** CKD was more frequently observed in patients with valvular AF ($p=0.009$). In non-valvular AF patients eGFR $<60\text{ml/min./1.73m}^2$ had more often permanent AF ($p<0.0001$). In patients with CKD $\text{CHA}_2\text{DS}_2\text{VASc}$ score was 4.1 ± 1.5 and HAS-BLED score was 2.1 ± 1.2 and it was higher as compared to population with preserved renal function ($p<0.0001$ vs $p<0.0001$). The odds of permanent AF in patients with non-valvular AF and CKD were increased 1.82 times ($\text{OR}=1.82, p<0.0001, 95\%\text{CI}:1.46-2.27$). The odds of permanent AF in patients with valvular AF and CKD were not significantly increased ($\text{OR}=1.46, p=0.2, 95\%\text{CI}:0.86-2.5$). In non-valvular AF, if eGFR decrease by 10ml/min , odds of permanent AF are increased by 10% ($\text{OR}=1.1, p<0.0001, 95\%\text{CI}:1.05-1.15$). In multivariate logistic regression, in non-valvular AF, odds of in-hospital death were higher for patients >75 years old ($\text{OR}=3.70, p=0.01, 95\%\text{CI}:1.33-10.28$), with CKD ($\text{OR}=2.61, p=0.03, 95\%\text{CI}:1.09-6.23$). The type of AF had no significant influence on in-hospital mortality ($\text{OR}=0.71, p=0.45, 95\%\text{CI}:0.30-1.70$). **Conclusions:** CKD is more often observed in patients with valvular AF. In population with non-valvular AF decreased eGFR is associated with permanent type of AF and with higher $\text{CHA}_2\text{DS}_2\text{VASc}$ and HAS-BLED score.

Among valvular AF patients there are no differences in type of AF between patients with and without CKD. There is the correlation between CKD and AF perpetuation but only in non-valvular population.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, occurring in 1%-2% of the general population and is a well-known risk factor of cardiovascular morbidity and mortality [1, 2]. AF frequently occurs in renal failure population and ranges from 19% to 24% rising to 27% in patients with end-stage renal disease [3, 4]. Several studies have implicated AF as a contributing factor in CKD and cardiovascular events [3, 5].

On the other hand there are few studies concerning renal function in population with AF [6, 7]. Moreover influence of renal impairment on in-hospital mortality in patients with valvular and non-valvular AF is not defined. It is worth noting that renal function has not been investigated in patients with valvular atrial fibrillation so far. Although the type of AF does not influence mortality and the risk of stroke in general population with AF, the significance of type AF in population with renal failure is also unknown.

The aim of the present study was to assess renal function in patients with AF, the association between eGFR (estimated glomerular filtration rate) value and the prevalence of certain types of AF in valvular and non-valvular AF patients. We also investigated the influence of renal function on in-hospital mortality in AF population both valvular and non-valvular.

Material and Methods

Study population

We retrospectively studied 1523 patients with the diagnosis of AF hospitalized in the Department of Cardiology and the Department of Invasive Cardiology in years 2012-2014. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the local ethics committee. At the study entry medical history was recorded, all patients underwent physical examination, resting ECG, routine transthoracic echocardiography.

The patients were subsequently divided into two groups according to the presence of valvular or non-valvular atrial fibrillation. Clinical characteristics, type of AF and renal function were compared between the two groups. Patients with chronic kidney disease were compared to population with preserved renal function in each group separately. The primary end-point was in-hospital mortality.

Definition of Valvular Atrial Fibrillation

We define valvular atrial fibrillation according to recent 2014 AHA/ACC/HRS Guidelines for the Management of Patients with Atrial Fibrillation [8] as AF in rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve or valve repair. We also consider as valvular AF patients with aortic stenosis or insufficiency and mitral insufficiency who need a surgical procedure, as in three major AF trials (RE-LY, ROCKET AF, and ARISTOTLE trials) [9-11].

Assessment of renal function

Baseline laboratory values were obtained on admission. Renal function was assessed using glomerular filtration rate (GFR) estimated by MDRD equation: estimated GFR = $186 \times (\text{serum creatinine level in mg/dl})^{-1.154} \times \text{age (in years)}^{-0.203}$. For women the product of this equation was multiplied by a correction factor of 0.742 [12, 13]. The cut off value of eGFR was 60 ml/min/1.73m².

Echocardiographic analysis

Left ventricular ejection fraction (LVEF) was assessed in transthoracic echocardiography using the modified biplane Simpson's method (Philips Ultrasound System Sonos 5500, equipped for harmonic imaging with a 3.6 MHz transducer) and was derived in accordance with the recommendations of the European Society of Echocardiography [14].

Statistical analysis

Data are expressed as means and standard deviations (SD). Relative frequencies are used to present categorical variables. The Student's t test, the Wilcoxon rank-sum test and chi-square test was used for statistical analysis where applicable. Logistic regression was used to test associations between variables and outcomes. Multinomial logistic regression was used to evaluate the association between variables and in-hospital mortality. A p value of less than 0.05 was considered as statistically significant. The statistic software, StataIC (data analysis of statistical software) version 13, was used.

Results

Baseline characteristics

A total of 1523 patients with AF (668 women, 45%; mean age 71 ± 11 years) were included in the analysis. Paroxysmal AF was present in 43% (n=656), persistent in 16% (n=249), permanent in 40% (n=616) of the patients. Valvular AF was observed in 16% (n=237) and among them aortic valvular disease in 33% (n=78) and mitral valve disease in 45% (n=107). Hypertension was present in 73% (n=1119), diabetes in 27% (n=408), CKD in 31% (n=475), ischemic heart disease (IHD) in 46% (n=693) and chronic heart failure (CHF) in 57% (n=875) of the patients. The mean LVEF assessed by echocardiography was $46 \pm 14\%$, mean left atrium diameter was 46 ± 8 mm.

CHA₂DS₂VASc score in the population with non-valvular AF was 3.5 ± 1.7 and HAS-BLED score was 1.8 ± 1.1 .

In the study population the in-hospital mortality was 2% (n=31). Clinical characteristics of the population is shown in Table 1.

Comparison of patients with valvular and non-valvular atrial fibrillation

Patients with valvular AF were more frequently females (p=0.01) and had more often permanent AF (p<0.0001), heart failure (p<0.0001) and anaemia (p=0.0004).

The mean eGFR evaluated by MDRD formula was 74 ± 26 ml/min./1,73m² in patients with non-valvular AF and 72 ± 27 ml/min./1,73m² in patients with valvular AF. Chronic kidney disease was more frequently observed in patients with valvular AF (p=0.009). Previous stroke/TIA was observed with similar frequency (p=0.89). Comparison between the two groups is shown in Table 1.

Non-valvular AF and chronic kidney disease

In population with non-valvular AF patients with moderately and severely decreased eGFR (<60ml/min./1,73m²) tended to be older (p<0.0001), they were more frequently females (p=0.001) and had more often permanent AF (p<0.0001), CHF (p=0.002), diabetes (p=0.0004), anaemia (p<0.0001), history of myocardial infarction (MI) (p=0.005) and CABG (p=0.01). Previous stroke/TIA and IHD was observed with similar frequency (p=0.13, p=0.57, respectively).

In patients with chronic kidney disease CHA₂DS₂VASc score was 4.1 ± 1.5 and HAS-BLED score was 2.1 ± 1.2 and it was significantly higher as compared to population with preserved renal function (p<0.0001, p<0.0001, respectively). The use of oral anticoagulation did not differ between the two groups (p=0.08).

Table 1. Clinical characteristics of the population and comparison between valvular and non-valvular atrial fibrillation

	All patients n=1523	Valvular AF n=237	Non- valvular AF n=1286	p-value
Females (%)	685 (45)	126 (53)	566 (44)	0.01
Age (years)	71±11	72±9	71±11	0.2
Age ≥ 75 years (%)	655 (43)	107 (45)	540 (42)	0.4
Body mass index (kg/m ²)	29±5	27±4	29±5	<0.0001
Heart rate (beats /min)	81±25	83±24	81±24	0.2
Systolic blood pressure (mmHg)	130±23	127±25	130±22	0.008
eGFR (ml/min/1.73m ²)	74±26	72±27	74±26	0.3
Left atrial diameter (mm)	46±8	50±8	45±7	<0.0001
Ejection fraction (%)	46±14	42±15	46±14	<0.0001
CHA2-DS2-VASc score *			3.5±1.7	
HAS-BLED score *			2.4±1.1	
Valvular AF (%)	244 (16)			
<i>Type of AF</i>				
Paroxysmal (%)	655 (43)	69 (29)	592 (46)	<0.0001
Persistent (%)	244 (16)	33 (14)	180 (14)	0.4
Permanent (%)	609 (40)	135 (57)	476 (37)	<0.0001
Hypertension (%)	1112 (73)	154 (65)	964 (75)	<0.0001
Diabetes mellitus (%)	411 (27)	59 (25)	347 (27)	0.4
Coronary artery disease (%)	701 (46)	90 (38)	604 (47)	0.007
Chronic heart failure (%)	868 (57)	182 (77)	694 (54)	<0.0001
Chronic kidney disease (%)	472 (31)	69 (29)	231 (18)	0.0003
COPD (%)	107 (7)	19 (8)	90 (7)	0.4
Anaemia (%)	442 (29)	90 (38)	347 (27)	0.0004
Previous myocardial infarction (%)	274 (18)	28 (12)	244 (19)	0.01
Previous TIA/stroke (%)	152 (10)	24 (10)	129 (10)	0.9
Previous PCI (%)	137 (9)	12 (5)	129 (10)	0.02
Previous CABG (%)	91 (6)	26 (11)	64 (5)	<0.0001
In-hospital mortality (%)	30 (2)	7 (3)	26 (2)	0.1
AF – Atrial Fibrillation; COPD - Chronic obstructive pulmonary disease; eGFR - estimated glomerular filtration rate; TIA - Transient Ischemic Attack; PCI - percutaneous coronary interventions; CABG - Coronary Artery Bypass Graft ; ICD - implantable cardioverter defibrillator; CRT - Implanted cardiac resynchronization device.				

Valvular AF and chronic kidney disease

Patients with valvular AF and moderately and severely decreased eGFR (<60ml/min./1.73m²) tended to be older (p=0.03). There were no significant differences between patients with and without CKD.

Differences in frequency between valvular and non-valvular AF according to the stage of CKD are shown on Figure 1.

Renal function and type of atrial fibrillation in valvular and non-valvular AF

The odds of permanent AF in patients with non-valvular AF and CKD were increased 1.82 times as compared to patients with preserved renal function (OR=1.82, p<0.0001, 95% CI: 1.46-2.27). The odds of permanent AF in patients with valvular AF and CKD were not significantly increased as compared to patients with preserved renal function (OR=1.46, p=0.2, 95% CI: 0.86-2.5).

In non-valvular AF patients, if eGFR decrease by 10ml/min, odds of permanent AF are increased by 10% (OR= 1.1, p<0.0001, 95% CI 1.05- 1.15).

Fig. 1. Differences in frequency between valvular and non-valvular AF according to the stage of CKD.

Fig. 2. Odds of permanent AF according to the stage of CKD in patients with valvular and non-valvular AF.

Odds of permanent AF according to the stage of CKD in patients with valvular and non-valvular AF are shown on Figure 2.

Among patients who received NOAC, 13% had reduced dose of NOAC, 3% were given NOAC despite eGFR <30ml/min/1.73m².

In-hospital mortality

The in-hospital mortality did not significantly differ between patients with valvular and non-valvular AF (p=0.1).

In the logistic regression model odds of in-hospital death for patients with non-valvular AF were 2.7 times higher for patients with CKD than for patients with preserved renal function (p=0.06, 95% CI: 1.34-5.61). In valvular AF patients impaired renal function did not increase odds of in-hospital death (p=0.96, 95% CI: 0.22-4.12). The type of AF had no significant influence on in-hospital mortality in both valvular AF and non-valvular AF (OR=1.27, p=0.8, 95%CI 0.29-5.43, OR=1.21, p=0.6, 95%CI 0.59-2.49, respectively).

When stratified by eGFR (<60ml/min./1.73m² and > 60ml/min./1.73m²), in population with CKD the type of AF had also no impact on in-hospital mortality in both valvular AF and non-valvular AF (OR= 0.28, p=0.32, 95%CI 0.02-3.27, OR=0.81, p=0.7, 95%CI 0.278-2.40, respectively).

In multivariate logistic regression, in non-valvular AF patients, odds of in-hospital death were higher for patients >75 years old (OR=3.70, p=0.01, 95%CI 1.33-10.28), with

Table 2. Multivariate logistic regression model

Odds of in-hospital death in non-valvular AF patients	OR	95% CI	p value
Age ≥ 75 years	3.70	1.33-10.28	0.01
Chronic kidney disease	2.61	1.09-6.23	0.03
Chronic heart failure	2.74	1.01-7.46	0.049
Type of AF	0.71	0.30-1.70	0.45
Odds of in-hospital death in valvular AF patients	OR	95% CI	p value
Age ≥ 75 years	9.75	1.16-82.16	0.04
Chronic kidney disease	0.71	0.16-3.19	0.66
Chronic heart failure	2.54	0.29-21.88	0.4
Type of AF	0.95	0.21-4.18	0.94
OR – Odds ratio; CI – confidence interval.			

CKD (OR=2.61, p=0.03, 95%CI 1.09-6.23) and CHF (OR=2.74, p=0.049, 95%CI 1.01-7.46). The type of AF had no significant influence on in-hospital mortality (OR=0.71, p=0.45, 95%CI 0.30-1.70) (Table 2).

In multivariate logistic regression, in valvular AF patients, odds of in-hospital death were higher for patients >75 years old (OR=9.75, p=0.04, 95%CI 1.16-82.16). The type of AF, CKD and CHF had no significant influence on in-hospital mortality (OR=0.95, p=0.94, 95%CI 0.21-4.18, OR=0.71, p=0.66, 95%CI 0.16-3.19, OR=2.54, p=0.4, 95%CI 0.29-21.88, respectively) (Table 2).

Discussion

The current study is a one of few studies on renal function in AF patients and the first one which refers to valvular AF population. We showed that CKD is diagnosed in almost every third patient with AF and is significantly more frequently observed in patients with valvular AF.

Chronic kidney disease has well-established link with AF. The prevalence of AF in CKD patients was even 15 times higher than in population from the Framingham Heart Study [15]. Recent population-based studies demonstrated the relationship between frequency of AF and the stage of CKD [16-19]. In the Atherosclerosis Risk in Communities study (ARIC) hazard ratio of developing new onset AF was 3.2 times higher in patients with severely impaired renal function. Moreover, the increased risk of AF was observed even in patients with relatively preserved renal function (eGFR 60-90ml/min) [17]. Similar data was observed in population-based study of U.S. adults - REGARDS, where regardless of severity, CKD was associated with an increased prevalence of AF [16]. Interestingly, the ARIC study reported 2-fold increase in risk of AF in patients with microalbuminuria [17].

According to the literature CKD is present in 10% -15% of AF patients [20]. Renal failure may increase the risk of AF-related cardiovascular complications [20]. In the multicenter randomized AMADEUS trial, that compare renal function and outcomes in anticoagulated patients with non-valvular AF, patients with CKD were older, they were more frequently females, had more often chronic heart failure, coronary artery disease, history of stroke/TIA, and higher CHA₂DS₂VASc and HAS-BLED score [6]. In our population with non-valvular AF decreased eGFR was associated with chronic heart failure, diabetes, anaemia, higher CHA₂DS₂VASc and HAS-BLED score. We did not observe more frequently coronary artery disease and history of stroke/TIA in patients with CKD. However, they had more often history of MI and CABG.

So far in most of the studies the association between AF and renal function has been investigated in patients with non-valvular AF. The current study is the first one which refers

to valvular AF patients. We showed that CKD is more often observed in this population. However, among valvular AF patients there were no significant differences in clinical characteristics and type of AF between patients with and without CKD. Furthermore, the in-hospital mortality was similar in both groups.

The explanation of these findings is unclear. Valvular AF is connected with completely different, usually severely ill population than non-valvular AF. Although valvular AF is less common in industrialized countries than non-valvular type we are of interest in this field because valvular AF is still relatively frequent and valve problems lead to progressive heart failure and often requires surgical or transcatheter intervention [21, 22].

Decision-making for intervention is complex, since valve disease is often seen at an older age and, as a consequence, there is a higher frequency of comorbidity, contributing to increased risk of intervention [23].

Whether renal impairment influence the development of different types of AF (paroxysmal, persistent, permanent) is also unclear. Furthermore, there is no data demonstrating this relationship in non-valvular as well as valvular AF patients. The observations from our study showed that impaired renal function is associated with permanent type of AF only in non-valvular AF patients. The odds of permanent AF in patients with CKD were increased 1.82 times as compared to patients with preserved renal function. The reduction of eGFR by 10ml/min increased the odds of permanent AF by 10%. However, in valvular AF patients there were no differences in the type of AF between patients with CKD and those with preserved renal function. Therefore the influence of renal disease on AF perpetuation should be assessed in a prospective study in the future.

There is an increase in cardiovascular mortality as kidney function declines. Anavekar et al. reported that each 10 unit reduction of eGFR was associated with a 10% increase in the relative risk of death or non-fatal cardiovascular complications [24]. Several studies have implicated AF as a contributing factor in CKD and cardiovascular events. Nakagawa et al. reported that long-term mortality, cardiac events and stroke risk were 8 times higher in non-valvular AF patients with decreased eGFR ($<60\text{ml/min./1.73m}^2$) [25]. Furthermore a strong association between AF and mortality has been found in patients with end-stage renal disease. Genovesi et al. reported data from 5 dialysis centers in Italy where AF was independently associated with 65% increase in mortality [26]. However, whether renal impairment has different influence on in-hospital mortality in patients with valvular and non-valvular AF is less well defined. In our study the in-hospital mortality was significantly higher only in non-valvular AF patients with CKD. In valvular AF patients there was no significant difference in in-hospital mortality between CKD patients and those with preserved renal function.

Limitations

We have no current data on treatment strategies for the prevention of AF. Out-patient centers did not contribute for this registry and patients cared for by general practitioners were not included. This has to be taken into account when extrapolating from these data to the general population.

Conclusions

CKD is a frequent diagnosis in patients with AF and is significantly more often observed in patients with valvular AF. In population with non-valvular AF decreased eGFR is associated with permanent type of AF and with many accompanying diseases which are reflected by higher CHA₂DS₂VASc and HAS-BLED score. While among valvular AF patients there are no significant differences in clinical characteristics and type of AF between patients with and without CKD. There is the correlation between CKD and AF perpetuation but only in non-valvular population. The in-hospital mortality is similar in both groups.

Disclosure Statement

None of the authors identify any conflict of interests.

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