Decreased Glomerular Filtration Rate and Markers of Left Atrial Stasis in Patients with Nonvalvular Atrial Fibrillation

Rui Providência a, b, Andreia Fernandes a, Luis Paiva a, Ana Faustino a, Sérgio Barra a, Ana Botelho a, Joana Trigo a, José Nascimento a, António Leitão-Marques a

a Coimbra’s Hospital Centre and University and b Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Key Words
Atrial fibrillation · Stroke · Chronic kidney disease · Estimated glomerular filtration rate · Chronic Kidney Disease Epidemiology Collaboration equation

Abstract
Background: It is currently unknown if the increased risk of stroke in subjects with chronic kidney disease and atrial fibrillation (AF) is due to the presence of left atrial stasis or to any other vascular or systemic conditions. Methods: This was a retrospective study of 372 subjects undergoing evaluation during an AF episode. The following markers of left atrial stasis were sought on transesophageal echocardiogram: left atrial or left atrial appendage thrombus (LAAT), dense spontaneous echocardiographic contrast (DSEC), and low flow velocities (LFV) in the left atrial appendage. Subgroup comparisons were performed according to the level of estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation as follows: ≥90, 45–89.9, and <45 ml/min/1.73 m². Results: LAAT was found in 11.6%, DSEC in 29.0%, and LFV in 14.9% of cases. A significant increase in the prevalence of DSEC was observed in the lower categories of eGFR: 37.8% in eGFR <45 ml/min, 30.7% in eGFR 45–89.9 ml/min, and 17.0% in eGFR ≥90 ml/min (p = 0.009; γ for trend = 0.297, p = 0.002).

Conclusions: Our results suggest an association between compromised renal function as assessed through eGFR and markers of left atrial stasis in patients with AF. The increased risk of stroke in this population may be due to thromboembolism.

Introduction

Chronic kidney disease is highly prevalent in patients with atrial fibrillation (AF), ranging from 7 to 27% of cases, as previously described in the literature [1–4]. According to the 2011 European Society of Cardiology AF guidelines, controlled data assessing a link between renal disease and increased risk of AF-related cardiovascular complications, namely stroke, is sparse [5]. In the
Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) trial, a higher stroke risk was observed in patients with AF and an estimated glomerular filtration rate (eGFR) <45 ml/min when adjusted for other confounding variables. An important limitation that is attributed to this proposed association is the lack of supportive prospective studies [5]. Furthermore, vascular disease is also more severe in this population [6].

In patients with AF, left atrial dysfunction and increased thromboembolic risk can be illustrated by the presence of markers of left atrial stasis. The most well-studied markers of left atrial stasis are left atrial appendage thrombus (LAAT), dense spontaneous echocardiographic contrast (DSEC), and left atrial appendage low flow velocities (LFV) (defined as ≤20 cm/s). The presence of at least one of the previous markers of left atrial stasis is also known as left atrial abnormality (LA ABN). The presence of left atrial stasis and protuberant aortic plaques has been associated with an increased risk of stroke [7]. An annual thromboembolism rate of 12% was found in the SPAF III study in subjects with LA ABN along with protuberant aortic plaques [8]. Bernhardt et al. [9] described a 22% likelihood of cerebral embolism and/or death at 12 months of follow-up despite anticoagulation in patients with AF and DSEC.

It is currently unknown whether the increased risk of stroke in subjects with chronic kidney disease and AF is mainly due to the presence of left atrial stasis or to other vascular or systemic conditions (a thromboembolic vs. atherothrombotic mechanism).

**Purpose**

The purpose of this study was to determine the relation between the eGFR, assessed through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and the prevalence of markers of left atrial stasis on transesophageal echocardiogram during an AF episode.

**Methods**

**Study Population**

This was a cross-sectional study of 504 consecutive patients undergoing transesophageal echocardiogram over a period of 32 months during an AF episode. Laboratory criteria for admission to the study were the following: patients who had been admitted to the emergency department were selected if they had a creatinine measurement in the last 24 h and those performing elective transesophageal echocardiogram were selected only if they had a creatinine measurement in the past 6 months and had been clinically stable during that time window. Among the 479 patients fulfilling the laboratory criteria, 107 with valvular AF (defined as presence of a previous valve repair, a prosthetic valve, rheumatic heart disease, and moderate or severe valve stenosis and/or regurgitation) were excluded from analysis. The remaining 372 patients comprised the study population.

Baseline overall group characterization with demographic, anthropometric, clinical, laboratory, and echocardiographic data, along with information on medication, was obtained for all patients. These data were retrieved from clinical records.

Patients’ indications for undergoing transesophageal echocardiogram were: 89.8% (n = 334) for exclusion of LAAT before direct current cardioversion of AF, 7.5% (n = 28) for cardioembolic source evaluation due to recent stroke, and 2.7% (n = 10) before percutaneous left atrial appendage closure.

**Echocardiographic Data**

A GE Vivid 7 echocardiograph was used for transthoracic and transesophageal echocardiogram, along with the following probes: M4S (1.5–4.0 MHz) and a 6T phased array multiplane transesophageal probe (2.9–7.0 MHz). Transesophageal echocardiogram was performed without anesthesia or sedation in more than 97% of patients.

The left atrium volume was measured using the single-plane area length method [10, 11]. The left ventricle ejection fraction (LVEF) was qualitatively assessed and classified as normal or mildly, moderately, or severely depressed using the cutoff values defined in the guidelines [12, 13]. On transesophageal echocardiogram, the left atrium and left atrial appendage were imaged in different tomographic planes to detect the presence of LAAT and spontaneous echocardiographic contrast. Spontaneous echocardiographic contrast was classified according to the classification (1–4+) proposed by Fatkin et al. [14]. Grade 3+ or 4+ was defined as DSEC. Left atrial appendage flow velocities were assessed with a pulsed Doppler sample placed 1 cm from the entry of the left atrial appendage into the body of the left atrium. Maximum emptying and filling velocities were estimated from an average of 5 well-defined emptying and filling waves. Patients with a maximum emptying and filling velocity ≤20 cm/s were classified as having LFV. Aortic plaques ≥4 mm were sought on transesophageal echocardiogram according to the method described by Amarenco et al. [15] and designated as protuberant aortic plaque.

All examinations were performed by two cardiologists with accreditation in transthoracic and transesophageal echocardiography by the European Society of Cardiology and who were blind for the lab results and clinical information (i.e. the level of eGFR, risk factors composing the CHADS2 and CHA2DS2-VASc score, and medication) of the patients other than the fact that they were in AF and their indication for the transesophageal echocardiogram.

Offline analysis was performed using GE Health Care EchoPac Dimension software, PC version 108.1.4. Reporting of data concerning left atrial stasis resulted from mutual agreement between these two cardiologists after reviewing the images.

**Laboratory Data**

Blood samples were collected upon admission in all patients. Creatinine was measured using the CREA VITROS Chemistry Products assay. Values from 4 to 1,238 μmol/l could be detected.
with this assay and normal expected values were 58–110 μmol/l in male patients and 46–92 μmol/l in female patients.

Assessment of Kidney Function

Kidney function was assessed as the level of eGFR. This was calculated using the CKD-EPI equation [16], which has shown a higher performance than the Modification of Diet in Renal Disease (MDRD) equation [16, 17]. The last creatinine measurement before performing transesophageal echocardiogram was used in the formula. Using the eGFR we defined 3 categories based on the defined cutoff value from the ATRIA study for increased risk of stroke in AF patients with renal disease (≤45 ml/min) and the cutoff value for normal eGFR (≥90 ml/min), according to the National Kidney Foundation classification for chronic kidney disease [18, 19]. The other cutoff values for the different stages of chronic kidney disease in this classification were assessed on univariate analysis as predictors of transesophageal echocardiogram changes.

Statistical Analysis

PASW Statistics version 18.0 was used for descriptive and inferential statistical analysis. Comparisons were performed according to the different classes of eGFR. The χ² test was used for nominal variables and ANOVA was used for comparison of continuous variables, where appropriate; equivalent nonparametric tests were used when the Kolmogorov-Smirnov test was in favor of absence of a normal distribution. Post hoc testing of ANOVA tests were used when the χ² test was observed in the three eGFR categories, with patients with eGFR ≤45 ml/min presenting higher values. LVEF levels and the prevalence of DSEC and LA ABN: as the eGFR categories. An inverse relationship was found between eGFR and chronic heart failure and arterial hypertension were increasingly more prevalent as eGFR values decreased. There was an overall increase in CHADS₂ and CHA₂DS₂-VASc scores as eGFR values decreased. In the lower eGFR groups, there was a trend for a progressive increase in the prevalence of female gender individuals. Patients with higher eGFR were younger and had a lower prevalence of previous stroke or transient ischemic attack (TIA) and vascular disease (as defined by the CHA₂DS₂-VASc score).

Concerning antithrombotic medication and antiplatelet agents, no differences were found among the 3 eGFR classes. Patients with values ≥90 ml/min were less frequently on statins and ACEi/ARB-II. Patients with eGFR <45 presented with lower hemoglobin levels. No differences were found in what relates to international normalized ratio values.

A gradual and significant increase in left atrial volume was observed in the three eGFR categories, with patients in the lower eGFR group presenting higher values. LVEF >55% was more frequent in patients with eGFR ≥90 ml/min. The prevalence of LAAT was similar in the 3 eGFR categories. An inverse relationship was found between eGFR levels and the prevalence of DSEC and LA ABN: as the levels of eGFR declined, the prevalence of DSEC and LA ABN significantly rose. The prevalence of protuberant aortic plaque was lower in the ≥90 ml/min category than in the 45–89.9 ml/min category (10.2 vs. 19.8%; p < 0.05).

Predictors of Left Atrial Stasis and Proteruberant Plaques

Among the clinical risk factors that compose CHADS₂ and CHA₂DS₂-VASc along with eGFR and chronic hemodialysis, only congestive heart failure and previous stroke or TIA were predictors of LAAT on univariate analysis (OR = 2.14, p = 0.02, and OR = 5.01, p < 0.001, respectively) (table 2). These remained the only independent predictors of LAAT on multivariate logistic regression (table 4).

As far as DSEC is concerned, congestive heart failure (OR = 3.10; p < 0.001), arterial hypertension (OR = 2.01; p = 0.04), diabetes mellitus (OR = 1.63; p = 0.05), stroke/
Table 1. Population characterization overall and according to the different levels of eGFR

<table>
<thead>
<tr>
<th>Overall (n = 372)</th>
<th>eGFR using the CKD-EPI equation (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;45 (n = 82)</td>
</tr>
<tr>
<td>Age, years</td>
<td>67.08 ± 11.04</td>
</tr>
<tr>
<td>Female gender</td>
<td>28.5 (106)</td>
</tr>
<tr>
<td>BMI</td>
<td>28.72 ± 5.42</td>
</tr>
<tr>
<td>Estimated AF episode duration &lt;1 week</td>
<td>21.8 (81)</td>
</tr>
<tr>
<td>Estimated AF episode duration &gt;1 month</td>
<td>38.7 (144)</td>
</tr>
<tr>
<td>Chronic dialysis</td>
<td>1.6 (6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>46.2 (172)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82.5 (307)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>26.3 (98)</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>14.8 (55)</td>
</tr>
<tr>
<td>Vascular disease&lt;sup&gt;e&lt;/sup&gt;</td>
<td>46.2 (172)</td>
</tr>
<tr>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt;</td>
<td>2.08 ± 1.24</td>
</tr>
<tr>
<td>CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc</td>
<td>3.51 ± 1.74</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>48.5 (180)</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>34.7 (129)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>29.3 (109)</td>
</tr>
<tr>
<td>ACEi/ARB-II</td>
<td>70.7 (263)</td>
</tr>
<tr>
<td>Statin</td>
<td>41.1 (153)</td>
</tr>
<tr>
<td>eGFR using the CKD-EPI, ml/min/1.73 m²</td>
<td>67.96 ± 25.85</td>
</tr>
<tr>
<td>Creatinine, μmol/l</td>
<td>108.80 ± 83.88</td>
</tr>
<tr>
<td>Blood urea nitrogen, mmol/l</td>
<td>8.77 ± 5.18</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>1.43 ± 0.70</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>13.87 ± 1.94</td>
</tr>
<tr>
<td>INR ≥2.0</td>
<td>19.1 (71)</td>
</tr>
<tr>
<td>Left atrium volume, ml/m²</td>
<td>59.92 ± 24.53</td>
</tr>
<tr>
<td>LVEF &lt;55%</td>
<td>22.3 (83)</td>
</tr>
<tr>
<td>LVEF ≤35%</td>
<td>9.1 (34)</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD or percents (n). Subgroup comparisons according to eGFR: <sup>a</sup>< 45 vs. 45–89.9, p < 0.05; <sup>b</sup> <45 vs. ≥90, p < 0.05; <sup>c</sup> 45–89.9 vs. ≥90, p < 0.05. ACEi = Angiotensin converting enzyme inhibitor; ARB-II = angiotensin II receptor blocker.

Table 2. Detected transesophageal endpoints according to the different levels of eGFR

<table>
<thead>
<tr>
<th>Overall (n = 372)</th>
<th>eGFR using the CKD-EPI equation (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;45 (n = 82)</td>
</tr>
<tr>
<td>LAAT</td>
<td>11.6 (43)</td>
</tr>
<tr>
<td>DSEC</td>
<td>29.0 (108)</td>
</tr>
<tr>
<td>LFV</td>
<td>14.9 (46)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>LA ABN</td>
<td>32.5 (121)</td>
</tr>
<tr>
<td>PP</td>
<td>17.5 (65)</td>
</tr>
</tbody>
</table>

Values are presented as percentages (n). Subgroup comparisons according to eGFR: <sup>a</sup> <45 vs. 45–89.9, p < 0.05; <sup>b</sup> <45 vs. ≥90, p < 0.05; <sup>c</sup> 45–89.9 vs. ≥90, p < 0.05. ACEi = Angiotensin converting enzyme inhibitor; ARB-II = angiotensin II receptor blocker.

<sup>e</sup> Only 309 of the patients had LAA flow velocities measured (see Discussion).
Decreased Glomerular Filtration Rate in Nonvalvular AF

TIA (OR = 2.35; p < 0.001), vascular disease (OR = 1.89; p < 0.001), and eGFR < 30 ml/min (OR = 2.71; p = 0.005), eGFR < 45 ml/min (OR = 1.68; p = 0.047), and eGFR < 90 ml/min (OR = 2.37; p = 0.005) were predictors on univariate analysis. Nonetheless, on multivariate logistic regression only congestive heart failure, stroke or TIA, vascular disease, and eGFR < 30 ml/min were included in a model to predict DSEC.

Female gender, vascular disease, and eGFR < 30 ml/min were predictors of LFV on both univariate and multivariate analyses.

Congestive heart failure (OR = 3.37; p < 0.001), diabetes mellitus (OR = 1.85; p = 0.01), stroke/TIA (OR = 2.09; p = 0.01), vascular disease (OR = 1.76; p = 0.01), eGFR < 30 ml/min (OR = 2.57; p = 0.008), eGFR < 45 ml/min (OR = 1.65; p = 0.05), and eGFR < 90 ml/min (OR = 1.88; p = 0.03) were predictors of LA ABN on univariate analysis. Age ≥ 65 years and arterial hypertension also displayed a trend for predicting this transesophageal echocardiogram endpoint. On multivariate logistic regression only congestive heart failure, diabetes mellitus, stroke/TIA, and eGFR < 30/min were independent predictors of LA ABN.

On univariate analysis, arterial hypertension (OR = 3.78; p = 0.008), age ≥ 65 years (OR = 2.23; p = 0.01), age ≥ 75 years (OR = 3.32; p = 0.04), chronic dialysis (OR = 4.90; p = 0.03), and eGFR < 90 ml/min (OR = 2.16; p = 0.04) were predictors of protuberant aortic plaque. The only independent predictors of protuberant aortic plaque on multivariate logistic regression were arterial hypertension, age ≥ 75 years, and chronic dialysis.

The power of our sample for predicting a 50% increase in the risk of LAA T in patients with clearance < 45 ml/min/1.73 m² was 0.81, with an estimated effect size of w = 0.13 (>0.80, the standard for adequacy). Similar results were found for the remaining and more prevalent left atrial stasis endpoints.

**Discussion**

We found evidence supporting a possible relation between compromised renal function and an increased prevalence of markers of left atrial stasis in our sample composed of patients undergoing transesophageal echocardiogram during an AF episode. This may be explained by the increased levels of endothelium-related factors, abnormalities in coagulations factor levels and activity and inflammation [3] that lead to a prothrombotic and inflammatory state in patients with chronic hemodialysis.
Extrapolating this data, we wonder if these can also be observed, at least to some degree, in patients with mild to moderate kidney disease. Moreover, these parameters of renal function added predictive power to the traditional clinical risk factors that compose the CHADS$_2$ and CHA$_2$ DS$_2$-VASc.

As eGFR decreased, a higher estimated clinical risk as assessed by CHADS$_2$ and CHA$_2$ DS$_2$-VASc along with a significant increase in the prevalence of transesophageal echocardiogram markers of left atrial stasis (i.e. DSEC and LA ABN) was observed on univariate analysis. Therefore, we are led to think that the increased risk of stroke in patients with chronic kidney disease observed in the ATRIA study [3] is possibly due to thromboembolism rather than atherothrombosis. Since thrombi in AF are mainly composed of fibrin, resembling those found in venous thromboembolic disease [3], the theoretical benefit of anticoagulation in these subjects is reinforced by our results.

We have also observed a progressive dilatation of the left atrium (volume) along with deterioration of renal function. Since we have excluded all patients with valvular disease, we think that this may be due to the higher prevalence of congestive heart failure and arterial hypertension in those eGFR classes. Other biomarkers like NTproBNP [20], cardiac troponin I [21], and C reactive protein [22] have shown a strong association to the presence of markers of left atrial stasis like LAAT [20–22], DSEC [20–22], LFV [21], and LA ABN [21] and have inclusively shown additive prognostic power when added to the CHADS$_2$ [21, 22] and CHA$_2$ DS$_2$ VASc classifications [20, 21]. Transthoracic echocardiographic parameters like left atrial size and LVEF have also been shown to be associated with markers of left atrial stasis and able to refine the currently available clinical risk schemes [23].

Despite this, extrapolation of these data into clinical endpoints is sometimes difficult, since these markers of
left atrial stasis are only surrogates of an increased risk of thromboembolic events. Furthermore, transesophageal echocardiogram takes only one ‘picture’ of the left atrium and left atrial appendage. Patients without left atrial stasis in one isolated evaluation may present an LA ABN at a different time.

The impact of compromised renal function in the presence of markers of left atrial stasis in subjects with AF had not been previously assessed in other investigations. Most of the knowledge concerning the association of compromised renal function with stroke in patients with AF resulted from the ATRIA study. Besides this data, evidence is controversial. Some studies are in favor of an association [24, 25], while others fail to confirm it [26, 27].

Concerning patients with chronic kidney disease as a whole, instead of analyzing only those with AF, there seems to be some contradiction concerning this association as well. There is evidence that points towards a positive association of chronic kidney disease with stroke [28, 29] but some studies have also failed to confirm the association [30, 31].

Marinigh et al. [32] recently proposed that the ‘c’ from CHA2DS2-Vasc could be eventually used as a surrogate for ‘creatinine clearance’ if future evidence confirms the association between chronic kidney disease and increased thromboembolism in AF patients. Our findings seem to support this hypothesis.

Nevertheless, chronic kidney disease is a marker of bleeding risk in patients with AF and has been included in the HAS-BLED score [33]. Thus, the use of oral anticoagulation in these patients must be carefully addressed.

Limitations

Proteinuria was not assessed in this cohort. Because the majority of patients were admitted to the emergency department and this data was retrospectively assessed, almost none had this measurement since it is not common practice to assess proteinuria in this type of patients.

Some biases were present in our population. First, it was mainly composed of white Caucasians. Therefore, these results may not be extrapolated to other populations composed by different ethnic groups. Second, our patients were mostly subjects referred for cardioversion and may therefore not be representative of the general AF population. Last of all, patients on chronic dialysis were also underrepresented.

In our cohort, age over 75 years displayed a trend for a protective role on univariate analysis as far as LFV was concerned. Conversely, it was associated with a higher prevalence of protuberant aortic plaques. This may be explained by the fact that we only selected elderly patients who were very symptomatic and had a preserved biological age for the transesophageal echocardiogram and subsequent cardioversion strategy. Most of the times, frail elderly are either not so symptomatic or are directly referred to rate control strategy. This may cause a selection bias of healthier elderly individuals, without as many comorbidities as expected, and the observed trend for a lower prevalence of some markers of left atrial stasis in the transesophageal echocardiogram plus rhythm control strategy.

In a subset of patients (63 out of 372; 16.9%) echocardiographic data was not available regarding left atrial appendage flow velocities. Some patients were classified as unsuitable for accurate assessment of this parameter while others did not tolerate the probe. Still, in all of these subjects, the presence or absence of LAAT and DSEC could be excluded right away.

This study was not sufficiently powered to demonstrate increases of less than 50% in any of the endpoints. This may, in part, account for the observed lack of association between eGFR and the less prevalent transesophageal echocardiogram changes, like LAAT, LFV, and protuberant aortic plaques.

Besides the presented clinical data that leads to hypothesis generation concerning a link between compromised kidney function and prothrombotic status in patients with AF, further studies will be needed to assess its biological plausibility and eventually confirm and clarify the underlying mechanisms behind this association.

Conclusions

Our results suggest an association between compromised renal function as assessed through the eGFR and markers of left atrial stasis in patients with AF. Moreover, the eGFR was able to increase the predictive ability of clinical parameters from CHADS2 and CHA2DS2-VASc scores.

The observed increase in the prevalence of stroke in patients with AF and chronic kidney disease is possibly due to thromboembolism rather than atherothrombosis.

Conflict of Interest

None.
References


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