

# The bidirectional relationship between chronic kidney disease and atrial fibrillation does not occur in elderly female outpatients

## *Dwukierunkowa zależność pomiędzy przewlekłą chorobą nerek a migotaniem przedsionków nie występuje u seniorów leczonych ambulatoryjnie*

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**Key words:** hypertension, chronic kidney disease, atrial fibrillation, type 2 diabetes, end-stage renal failure.

**Słowa kluczowe:** nadciśnienie tętnicze, przewlekła choroba nerek, migotanie przedsionków, cukrzyca typu 2, schyłkowa niewydolność nerek.

### Abstract

**Introduction:** The relationship between atrial fibrillation (AF) and chronic kidney disease (CKD) is bidirectional. Both diseases are characterised by high prevalence, additionally increasing with age. CKD, especially with glomerular filtration rate (GFR) < 60 ml/min/1.73 m<sup>2</sup> is a well-known independent risk factor of AF. However, this relationship was inadequately evaluated in elderly patients, especially females.

**Aim of the research:** To evaluate whether there is a relationship between CKD and AF and if it is bidirectional in elderly females.

**Material and methods:** The data was obtained from 336 female outpatients, aged 70 to 84 years, suffering from CKD.

**Results:** Out of 336 females outpatients aged over 70 years suffering from CKD (10.12% with GFR < 60 ml/min/1.73 m<sup>2</sup>) selected to the study, 8.63% were diagnosed with AF, 21.13% with diabetes, and 63.99% with hypertension. 4.46% underwent a myocardial infarction, and 2.68% underwent a stroke. No relationship between CKD and AF was found (neither depending on stage of CKD, nor in multivariate analysis). AF correlated with diabetes and stroke but not with renal function parameters.

**Conclusions:** In elderly females CKD does not influence on prevalence of AF, suggesting different pathogenesis of AF in this group. Further studies are required to establish this pathogenesis and potential risk factors of AF in this group of patients.

### Streszczenie

**Wprowadzenie:** Zależność pomiędzy migotaniem przedsionków (AF) a przewlekłą chorobą nerek (CKD) jest dwukierunkowa. Obie choroby charakteryzują się dużą częstością występowania, zwiększającą się z wiekiem. Przewlekła choroba nerek, zwłaszcza przy współczynniku przesączania kłębuszkowego (GFR) poniżej 60 ml/min/1,73 m<sup>2</sup>, jest uznanym niezależnym czynnikiem ryzyka AF. Jednak ich wzajemna relacja nie została jeszcze dokładnie zbadana u chorych w podeszłym wieku, szczególnie starszych kobiet.

**Cel pracy:** Ocena, czy u kobiet w podeszłym wieku występuje zależność pomiędzy CKD a AF i czy jest ona dwukierunkowa.

**Materiał i metody:** Dane pochodziły z grupy 336 kobiet w wieku od 70 do 84 lat leczonych ambulatoryjnie z powodu CKD.

**Wyniki:** Spośród 336 pacjentek w wieku powyżej 70 lat leczonych ambulatoryjnie z powodu CKD (10,12% miało GFR < 60 ml/min/1,73 m<sup>2</sup>) włączonych do badania u 8,63% rozpoznano AF, u 21,3% cukrzycę, u 63,99% nadciśnienie tętnicze, natomiast 4,46% przeżyło zawał serca, a 2,68% udar mózgu. Nie wykazano żadnego związku pomiędzy CKD a AF zarówno ze względu na stopień CKD, jak i w analizie wieloczynnikowej. Migotanie przedsionków korelowało jedynie z cukrzycą oraz udarem mózgu, ale nie z parametrami funkcji nerek.

**Wnioski:** Choroba przewlekła nerek u kobiet w podeszłym wieku nie wpływała na występowanie AF, co sugeruje inny patomechanizm AF w tej grupie. Potrzebne są dalsze badania w celu ustalenia, w jakim mechanizmie AF rozwija się w tej grupie, oraz wyznaczenia potencjalnych czynników ryzyka.

## Introduction

There is a bidirectional relationship between atrial fibrillation (AF) and chronic kidney disease (CKD). Both diseases are characterised by high prevalence, additionally increasing with age. AF is the most common cardiac arrhythmia globally [1–7] with a prevalence of 1–2% in the general population [1, 2, 8] and even higher among the elderly (7% in patients above 65 years old and 15–20% aged 80 or above) [1, 8]. Lifetime risk of occurrence of AF is one in six in patients  $\geq 40$  years old [5]. Chronic kidney disease is estimated to affect 10–15% of the general population and 22–25% of people aged 65 years or above [9, 10].

Chronic kidney disease, especially with glomerular filtration rate (GFR)  $< 60$  ml/min/1.73 m<sup>2</sup>, is a well-known independent risk factor of cardiovascular diseases (CVD), including AF [8, 10, 11]. Patients with CKD, especially end-stage renal disease (ESRD), are 2–3-fold more often affected by AF [3, 4, 6, 7], and the prevalence of AF in this group ranges from 7 to 27% [2, 8]. Moreover, due to the increasing age of patients suffering from ESRD and their susceptibility to comorbid illnesses, the incidence of AF is expected to increase [12]. CKD and AF share a number of risk factors, including age, hypertension, obesity, diabetes (type 2), metabolic syndrome, and CVD [5, 8]. Suffering from AF increases the chances of developing CKD and vice versa [8]. CKD was proved to increase the risk of new-onset AF [13], thromboembolic incidents [4, 6, 14] and bleeding due to anticoagulation [4]. It is also associated with higher cardiovascular morbidity and mortality [15].

However, the relationship between CKD and AF was inadequately evaluated in elderly patients, especially females, because not only are males burdened with higher risk of CVD [16–20], such as AF, but also they comprise the majority of most of the examined groups. Some side results of performed studies referring to the AF-CKD dependence suggest that this relationship may differ in this group of patients [15–19]. Given that the population of elderly women is constantly increasing, it is important to establish the AF-CKD relationship in this group, because it may suggest the need to adjust diagnostic and therapeutic options within it.

## Aim of the research

Thus, the aim of this study is to evaluate whether the relationship between CKD and AF occurs and if it is bidirectional within the group of elderly females.

## Material and methods

A total of 336 female outpatients over 70 years diagnosed with CKD (10.12% had GFR  $< 60$  ml/min/1.73 m<sup>2</sup>) were selected for the study from a larger group of patients staying under the care of general practice in the years 2015–2016. CKD was recogni-

sed according to KDIGO 2012 guidelines (creatinine concentration was marked two times in the interval of 3 months) [21]. To avoid the potential influence of comorbid diseases on both AF and CKD, the excluding criteria were: age under 70 years, NYHA IV heart failure, cancer, severe liver damage, steroid therapy, chronic inflammatory diseases, disorders of the thyroid function, and cachexia.

The minimal age criterion of 70 years was established in relation to age compartments selected in previous studies about the relationship of CKD and AF. There was no maximal age limitation.

The following biochemistry parameters were evaluated with standard tests: GFR was estimated with the CKD-EPI formula and LDL with Friedewald's formula. The intima/media ratio was examined with use of a B-mode presentation using the ultrasound system GE LOGIQ 500 with a 6–12 MHz linear transducer. Intima-media thickness measurements were performed bilaterally in plaque-free arterial segments on the far wall of the common carotid arteries and internal carotid arteries, in the diastolic phase of the heart cycle.

## Statistical analysis

Because the compared variables did not meet the criteria of normal distribution (checked with Shapiro-Wilk test), further analysis was performed using non-parametric tests. Differences in the number of occurrences of concomitant diseases in patients with and without AF were compared with Fischer's exact test. To compare the prevalence of AF for each CKD stage, the Kruskal-Wallis ANOVA was used. To estimate the correlation between variables, Spearman's regression was used. To compare values of variables the Mann-Whitney *U* test was used. To perform statistical analysis the TIBCO Software Inc. (2017) Statistica data analysis software system, version 13 <http://statistica.io> was used.

## Results

### Characteristics of the examined group

Out of 336 female outpatients suffering from CKD (10.12% with GFR  $< 60$  ml/min/1.73 m<sup>2</sup>) selected to the study, 8.63% were diagnosed with AF, 21.13% with diabetes, and 63.99% with hypertension. 4.46% underwent a myocardial infarction, and 2.68% underwent a stroke. 38.69% of them had GFR  $> 90$  ml/min/1.73 m<sup>2</sup>, 51.19% had GFR in the range 60–90 ml/min/1.73 m<sup>2</sup>, and 10.12% had GFR  $< 60$  ml/min/1.73 m<sup>2</sup>. Table 1 presents detailed characteristics of the group, including comparison of the subgroups with GFR  $\geq 60$  and  $< 60$  ml/min/1.73 m<sup>2</sup>.

### The analysis of dependences of AF

Spearman's regression showed significant ( $p < 0.05$ ) correlation between AF and the following variables:

**Table 1.** Characteristics of the examined group (mean (minimum–maximum))

Variable	Overall group (N = 336)	Patients with GFR $\geq$ 60 ml/min/1.73 m <sup>2</sup> (n = 302)	Patients with GFR < 60 ml/min/1.73 m <sup>2</sup> (n = 34)	Comparison of the groups with GFR $\geq$ 60 and < 60 ml/min/1.73 m <sup>2</sup> (p-value of U test)
Age	76.13 (70–84)	75.86 (70–84)	78.53 (73–82)	<b>&lt; 0.0001</b>
Intima/media – L mean	0.91 (0.62–1.65)	0.9 (0.62–1.65)	0.94 (0.71–1.27)	0.0800
Intima/media – R mean	0.89 (0.61–1.53)	0.89 (0.61–1.53)	0.88 (0.68–1.21)	0.4519
Intima/media – L max.	1.01 (0.65–2.04)	1.01 (0.65–2.04)	1.03 (0.75–1.53)	0.2532
Intima/media – R max.	0.99 (0.23–1.88)	0.99 (0.23–1.88)	0.98 (0.75–1.6)	0.7585
Total cholesterol [mg/dl]	215.92 (91.28–441.4)	217.67 (91.28–441.4)	199.87 (134.3–319.7)	<b>0.0276</b>
LDL [mg/dl]	125.86 (34.76–350.93)	127.49 (34.76–350.93)	110.71 (47.9–208.16)	<b>0.0346</b>
HDL [mg/dl]	65.72 (32.4–140.97)	65.88 (36.3–136.6)	64.11 (32.4–140.97)	0.2409
Triglycerides [mg/dl]	129.05 (40.5–739.9)	129.05 (40.5–739.9)	129.01 (74.4–282.2)	0.4655
Glucose [mg/dl]	108.89 (71–246.44)	108.85 (71–246.44)	109.26 (76.64–190.56)	0.5510
Creatinine [mg/dl]	0.73 (0–1.74)	0.69 (0.1–0.98)	1.1 (0.7–1.74)	<b>&lt; 0.0001</b>
GFR (CKD-EPI) [ml/min/1.73 m <sup>2</sup> ]	82.8 (0–177.08)	86.22 (60.72–177.08)	49.4 (28.6–59.88)	<b>&lt; 0.0001</b>
SBP [mm Hg]	83.2 (58–123)	83.52 (58–123)	80.35 (60–108)	0.6493
DBP [mm Hg]	148.81 (88–215)	148.88 (88–215)	148.15 (110–215)	0.0770

GFR – estimated glomerular filtration rate, CKD-EPI – chronic kidney disease epidemiology collaboration, SBP – systolic blood pressure, DBP – diastolic blood pressure.

stroke, diabetes, intima/media index, and inverted correlation with: total cholesterol level, low-density lipoprotein (LDL), triglycerides, systolic blood pressure (SBP), and diastolic blood pressure (DBP). Renal function parameters, such as creatinine, estimated glomerular filtration rate (GFR) (estimated with chronic kidney disease epidemiology collaboration (CKD-EPI), and CKD stage, did not correlate with AF ( $R < 0.05$ ,  $p > 0.05$ ).

From the variables correlating with AF, the following showed significant differences in groups with and without AF: intima/media index (left and right mean, right max), total cholesterol, LDL, triglycerides, SBP, and DBP.

Nevertheless, significant differences between groups with and without AF were demonstrated with the use of Fischer's exact test for stroke ( $p = 0.0342$ ) and diabetes ( $p = 0.003$ ). In the AF group, stroke occurred 5.29 times more frequently and diabetes occurred 2.37 times more frequently than in the non-AF group.

Additionally, patients with total cholesterol below 190 mg/dl, SBP below 140 mm Hg, and DBP below 90 mm Hg suffered from AF significantly more often.

#### The analysis of dependences of CKD

ANOVA showed no significant difference in prevalence of AF for each CKD stage ( $p = 0.68$ ). Additionally, because renal failure is considered to be a risk factor of AF, the examined patients were divided into two groups for comparison using Fischer's exact test. The first group consisted of patients with GFR  $\geq$  60 ml/min/1.73 m<sup>2</sup>, while the second group of patients with GFR < 60 ml/min/1.73 m<sup>2</sup>. The prevalence of AF in these groups did not differ significantly ( $p = 0.58$ ).

The only significant correlation ( $p < 0.05$ ) with CKD stages was the correlation with hypertension. Fischer's exact test also confirmed this dependence ( $p = 0.025$ ). Hypertension occurred 1.38 times more frequently in the group with GFR < 60 ml/min/1.73 m<sup>2</sup>. Additionally, Fischer's exact test showed that

in the group with  $\text{GFR} < 60 \text{ ml/min/1.73 m}^2$ , significantly more patients suffered from hypertension from at least 15 years ( $p = 0.0018$ ).

## Discussion

The key result of our study is that the bidirectional relationship between AF and CKD described in the younger population does not occur within female outpatients over 70 years old, no matter the renal function parameter or the stage of CKD.

Our major observation seems to be consistent with outcomes of the large retrospective cohort study performed by Nelson *et al.* on American patients, among whom almost 60,000 suffered from CKD. The results of this analysis showed that the risk of AF is not increased in patients with CKD aged over 85 years old [18]. A similar conclusion was drawn in an American study performed on a similar population of 392 patients but with the main difference in the mean age of the subjects (approximately 70 years). Significant differences between the prevalence of AF depending on the CKD stage were not proven [16]. Another study performed on a population similar to that mentioned above, but consisting of 3138 subjects, showed a significant difference in the prevalence of AF; however, it decreased parallel with the increase of the CKD stage [15]. The study on nearly 25,000 subjects aged above 55 years (the percentage of CKD and diabetes or hypertension comorbidity was smaller than in our examined population) performed by Sandhu *et al.* also did not show a significant correlation between AF and CKD [17]. Also, a study performed on 234 Polish patients aged over 75 years old showed no difference in prevalence of AF depending on renal function ( $\text{eGFR} \geq 60 \text{ ml/min/1.73 m}^2$  vs.  $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$ ) [19].

Laukkanen *et al.* in their study on 1840 patients aged around 70 years showed increased risk of AF parallel to the increasing CKD stage. The frequency of diabetes and hypertension were close to ours [20]. A study on a group of 223,877 subjects, 68% of them female, aged around 61 years, showed a correlation between CKD and AF. Despite the fact that the risk of AF increasing parallel to the increasing stage of CKD was not statistically significant (apart from CKD stage 3), CKD was diagnosed three times more often within patients already suffering from AF. Of note, these correlations between AF and CKD took place both in patients with diabetes or hypertension as well as in patients without them [5].

A study by Bansal *et al.* performed on 3091 patients showed a significant correlation between AF and CKD stage 5. However, it should be noted that the examined group was significantly different than ours (mean age around 60 years, much higher prevalence of diabetes and hypertension) [6]. Further studies by Bansal *et al.* proved that the coincidence of AF and CKD promotes the decrease of renal function and

increases risk of death [3, 7]. A study on 79 Japanese patients (mostly males with mean age of 75 years) showed that the coincidence of AF and CKD increases the risk of stroke [14]. The analysis of over 1 million patients from the USA showed that the number of hospitalisations caused by AF in patients with CKD stage 5 has doubled since 2003 [4].

A metaanalysis of 25 studies and over 20,000 patients with mean age of 62 years showed a correlation between AF and CKD stage 5 and an increased risk of death among patients with concomitant AF and CKD. However, the prevalence of AF in the analysed studies was higher than in ours (11.6% vs. 8.63%) [12]. The difference in prevalence of AF may be a result of comparing outpatients (our group) with hospital patients.

It is also significant that in the mentioned studies AF, as well as other CVD, occurred more frequently in males than in females suffering from CKD, which may indicate different pathogenesis of AF depending on sex [16, 20]. This observation seems to be consistent with our outcome that in elderly women correlation between AF and CKD does not occur.

According to a variety of obtained results, further studies focused on the bidirectional relationship between AF and CKD, as well as how factors such as age, sex, comorbid illnesses (diabetes, hypertension) and others, yet to be discovered, influencing this dependence, should be performed.

Atherosclerosis (as intima/media indexes) and diabetes were important determined risk factors for AF. Moreover, the concentrations under the reference level of total cholesterol, LDL, and triglycerides correlated with greater occurrence of AF, but this can be explained as the effect of cardiological preventive treatment in these patients. Also, psychosomatic cause of AF should be considered, especially if the organic cause cannot be diagnosed [22]. Similar outcomes to ours can be found in some other studies [4, 15, 16, 23]. It should also be remembered that cardiovascular treatment, including the prevention of AF, can be more difficult in patients with concomitant CKD, for example. The use of oral anticoagulants (especially vitamin K antagonists) in the group of CKD patients is questionable because their risks and benefits are uncertain and in some cases their dosages should be decreased [24, 25].

## Conclusions

In elderly females, CKD does not influence the prevalence of AF, suggesting a different pathogenesis of AF in this group. Further studies are required to establish this pathogenesis and potential risk factors of AF in this group of patients.

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### Conflict of interest

The authors declare no conflict of interest.

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