Risk of left atrial appendage thrombus in patients with atrial fibrillation and chronic kidney disease

Monika Budnik¹, Monika Gawalko¹, Iwona Gorczyca²,³, Beata Uziębło-Życzkowska⁴, Pawel Krzesiński⁴, Janusz Kochanowski¹, Piotr Scisło¹, Anna Michalska³, Olga Jelonek², Katarzyna Starzyk²,³, Agnieszka Jurek⁴, Marek Kiliszek⁴, Beata Wożakowska-Kapłon²,³, Grzegorz Gielerak⁴, Krzysztof J. Filipiak¹, Grzegorz Opolski¹, Agnieszka Kapłon-Cieślicka¹

¹¹st Chair and Department of Cardiology, Medical University of Warsaw, Poland
²¹st Clinic of Cardiology and Electrotherapy, Swietokrzyskie Cardiology Center, Kielce, Poland
³Collegium Medicum, The Jan Kochanowski University, Kielce, Poland
⁴Department of Cardiology and Internal Diseases, Military Institute of Medicine, Poland

Abstract

Background: Atrial fibrillation (AF) and chronic kidney disease (CKD) are associated with an increased risk of ischemic stroke. The aim of this study was to compare the clinical characteristics, the incidence of left atrial appendage (LAA) thrombus and its predictors, and spontaneous echo contrast (SEC) in a population of patients with AF depending on estimated glomerular filtration rate (eGFR) values.

Methods: This study included 1962 patients who underwent transesophageal echocardiographic examination prior to cardioversion or ablation in the years 2014–2018 in three cardiac centers.

Results: More than a quarter of AF patients had decreased eGFR (< 60 mL/min/1.73 m²) and were characterized as a high-risk population, with more comorbidities, higher thromboembolic and bleeding risk compared to those with normal renal function. Oral anticoagulation (OAC) was prescribed in 97% and 93% of patients with decreased and normal eGFR, respectively, with a higher prevalence of prescribed non-vitamin K antagonist oral anticoagulants (NOACs). The incidence of LAA thrombus (24%, 9% and 4%) and SEC (25%, 25% and 19%) increases simultaneously with a decrease in eGFR (< 30, 30–59 and ≥ 60 mL/min/1.73 m², respectively). Among patients prescribed reduced doses of NOAC, those with decreased eGFR were more often observed with LAA thrombus (10% vs. 2.5%). Non-paroxysmal AF, heart failure and previous bleeding were predictors of LAA thrombus, irrespective of eGFR value. CKD was the predictor of LAA thrombus in all patients including those with non-paroxysmal AF, males, without diabetes, without hypertension and with CHA2DS2-VASc < 2.

Conclusions: Despite OAC, patients with concomitant AF and CKD remain at high risk for LAA thrombus formation. (Cardiol J 2022; 29, 2: 205–215)

Key words: oral anticoagulation, renal failure, stroke prevention, thromboembolic risk

Introduction

Atrial fibrillation (AF) occurs in approximately 3% adults aged 20 years or older with a greater prevalence in the elderly and patients with greater comorbid burden [1, 2]. It is an important risk factor for ischemic stroke since it associates with a 5-fold higher risk of stroke compared with the general population [3]. Thromboembolic events were identified in about 12% of cases for AF patients [4]. An-
ticoagulation treatment with vitamin K antagonists (VKAs) or non-VKA oral anticoagulants (NOACs), reducing the incidence of stroke and mortality [5]. Chronic kidney disease (CKD) alone is associated with a higher incidence of both strokes and bleeding [6, 7]. Moreover, patients with advanced CKD were excluded in large clinical trials (trials with dabigatran, rivaroxaban, and edoxaban excluded patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m², with apixaban — those with eGFR were < 25 mL/min/1.73 m² or creatinine > 2.5 mg/dL) [8–11]. Kidney function should be regularly monitored in AF patients on oral anticoagulants (OACs) to allow dose adaptation and to estimate risk of complications [12].

Previous studies suggest that the incidence of left atrial appendage (LAA) thrombi or spontaneous echo contrast (SEC) is up to 29% [13].

The aim of the present study was to compare the incidence of the LAA thrombi and SEC in a population of patients with AF who underwent transesophageal echocardiographic (TEE) examination prior to cardioversion or ablation depending on eGFR, a comparison of clinical characteristic of patients according to eGFR and determination of risk factors of LAA thrombi.

Methods

Study population

The study included consecutive patients with AF undergoing TEE before cardioversion or ablation between 2014 and 2018 from three large cardiac centers in Poland (an academic, military and district hospitals). In the academic department, TEE was performed routinely in all patients regardless of the duration of AF and the anticoagulant therapy. In the military and district hospitals, TEE was performed in cases when there was doubt regarding the timing of anticoagulant treatment and patient compliance. All TEE studies were performed by certified echocardiographers (certified with accreditation of the Section of Echocardiography of the Polish Cardiac Society), using EPIQ 7 Ultrasound Machine® (Philips Medical Systems, Andover, Massachusetts, United States), iE33 Ultrasound Machine® (Philips Medical Systems), General Electric Vivid 7 (GE Healthcare, Milwaukee, Wisconsin, United States) or E95 Ultrasound Machine® (GE Healthcare). Written informed consent for TEE was obtained from all patients.

Data on the clinical characteristics of patients, echocardiographic findings, laboratory results were retrospectively retrieved from patients’ medical history. The study protocol was approved by the Bioethics Committee. In addition, due to the retrospective nature of the study and the lack of additional interventions, the Committee waived the requirement to obtain separate consent from each patient to participate in the study.

The current analysis included only patients with data on baseline eGFR. This was estimated based on creatinine measurement at hospital admission (i.e. before TEE), using the Modification of Diet in Renal Disease (MDRD) Study equation. Patients were divided into three groups according to eGFR (< 30 mL/min/1.73 m² — 21 patients, 30–59 mL/min/1.73 m² — 509 patients and ≥ 60 mL/min/1.73 m² — 1432 patients). However, due to the small number of patients in the group with eGFR < 30 mL/min/1.73 m², the multivariate logistic regression analysis of the two groups are included (eGFR ≥ 60 mL/min/1.73 m² and < 60 mL/min/1.73 m²).

Statistical analysis

Data is presented as a median and interquartile range (IQR) or number of patients and percentages where appropriate. The statistical significance of differences in medians was analyzed using the Kruskal-Wallis test. Frequencies of parameters or events were compared using the χ² test or the Fisher exact test, as appropriate. For all tests, a p value < 0.05 was considered to be statistically significant. To determine predictors of LAA thrombus formation, univariate and multivariate logistic regression analyses were performed. Only variables that were available for more than 88% of patients were included in the logistic regression analysis. Statistical analysis was performed with StatsModels: Statistic in Python — v0.10.1 documentation.

Results

Basic characteristic

Compared to other groups, patients with eGFR < 60 mL/min/1.73 m² were older, more often suffered from hypertension, diabetes, coronary artery disease, peripheral vascular disease, heart failure, cancer and more often were female. Moreover, the incidence of previous thromboembolic complications defined as composite of stroke/transient ischemic attack and/or peripheral embolism as well as hemorrhagic events were higher in patients with the lowest value of eGFR. Detailed clinical characteristics of the groups are presented in Table 1.
Non-vitamin K antagonist oral anticoagulants were least often prescribed in the group with eGFR < 30 mL/min/1.73 m² with a higher prevalence of low-dose NOAC prescription. There were no significant differences in the frequency of antiplatelet therapy or bridging therapy with heparin among all eGFR groups.

**Comparison of LAA thrombi prevalence**

The incidence of LAA thrombi was more than twice as high in patients with eGFR 30–60 mL/min/1.73 m² than in those with ≥ 60 mL/min/1.73 m² (9% vs. 4%, respectively). In a relatively small group of patients with eGFR < 30 mL/min/1.73 m² thrombi were present in almost a quarter of patients (24%). In addition, the lowest LAA emptying velocity were observed in the group of patients with eGFR < 30 mL/min/1.73 m² (31 vs. 42 vs. 50 cm/s, respectively). Detailed therapeutic characteristics and echocardiographic findings of the eGFR groups are presented in Table 2.

**Predictors of LAA thrombus**

On multivariate logistic regression, for the whole study group, eGFR was one of the predictors of LAA thrombus (p = 0.04). The other predictors were age, non-paroxysmal AF, heart failure, previous bleeding (Table 3), similar to patients with eGFR ≥ 60 mL/min/1.73 m² (Table 4A). In those with eGFR < 60 mL/min/1.73 m², non-paroxysmal AF, hypertension, heart failure and previous bleeding were the predictors of LAA thrombus (Table 4B).

Chronic kidney disease was the predictor of LAA thrombus in all patients as well as in those with non-paroxysmal AF (but not with paroxysmal AF), in males (but not in females), without diabetes, without hypertension and with CHA2DS2-VASc < 2 i.e. groups not included in classic risk factors (Fig. 1). Among patients with LAA thrombus no differences related to OAC treatment were observed between patients with eGFR < 60 mL/min/1.73 m² and eGFR ≥ 60 mL/min/1.73 m² (Table 5). Among patients on reduced dose of NOAC, LAA thrombus occurred more often in patients with eGFR < 60 mL/min/1.73 m² than in those with eGFR ≥ 60 mL/min/1.73 m² (Table 6).

**Comparison of patients without OAC**

Analyzing patients who were not treated with OAC (neither VKA nor NOAC) (Table 7), the incidence of LAA thrombus was higher and LAA emptying velocity was lower in patients with eGFR < 60 mL/min/1.73 m² than in those with eGFR < 60 mL/min/1.73 m². Patients with eGFR < 60 mL/min/1.73 m² more often had persistent AF and heart failure as compared to those with normal eGFR. Median CHA2DS2-VASc score was 2 in patients with eGFR < 60 mL/min/1.73 m² and 1 in patients with eGFR ≥ 60 mL/min/1.73 m². More than 50% of patients in both groups were found to be at high thromboembolic risk (CHA2DS2-VASc score ≥ 2).

**Discussion**

The major findings of the present study are as follows. First, more than a quarter of AF patients had decreased eGFR (< 60 mL/min/1.73 m²) and simultaneously were characterized as a high-risk population, with more comorbidities, higher thromboembolic and bleeding risk compared to those with normal renal function. Second, OAC was prescribed in approximately 97% of patients with decreased eGFR (90.5% of patients with eGFR < 30 mL/min/1.73 m²). The higher prevalence of prescribed NOAC was observed among patients with eGFR 30–59 mL/min/1.73 m². Importantly, among patients prescribed with reduced doses of NOAC, those with eGFR < 60 mL/min/1.73 m² were more often observed with LAA thrombus. Third, the most important finding was that CKD was the predictor of LAA thrombus in all patients as well as in the group that are not included in classic risk factors.

Numerous observational studies yielded conflicting results for OAC regarding which of the two types of anticoagulant drug, NOAC vs. VKA, is preferable for patients with decreased eGFR. In the present study, among patients with LAA thrombus, there was no difference reflected to OAC treatment between patients with eGFR < 60 and ≥ 60 mL/min/1.73 m². It is in line with a previous study [14] which proved that none of the OAC regimens predicted LAA thrombus in patients with AF, as well as with other studies focused on thromboembolic risk among AF patients with CKD [15–17]. Pivotal randomized controlled trials have established that NOAC are superior, however without statistical significance, to VKA among patients with CKD in preventing thromboembolic events. The ROCKET AF study indicates that, when compared with warfarin, rivaroxaban was non-inferior in preventing stroke or systemic embolism. Among patients with creatinine clearance 30–49 mL/min, the primary endpoint of stroke or systemic embolism occurred in 2.32 per 100 patient-years with rivaroxaban 15 mg/day vs. 2.77 per 100 patient-years with warfarin, whereas among those with creatinine clearance ≥ 50 mL/min, the primary end-
Table 1. Clinical characteristics in all groups according to eGFR.

| Variable                          | Patients with eGFR < 30 (n = 21) | Patients with eGFR 30–59 (n = 509) | Patients with eGFR ≥ 60 (n = 1432) | P      |
|-----------------------------------|----------------------------------|------------------------------------|------------------------------------|--------|
| **Age [years]**                   | 71 [60–82]                       | 67 [62–72]                         | 61 [54–67]                         | < 0.0001 |
| **Female**                        | 9 (43%)                          | 281 (55%)                         | 424 (30%)                         | < 0.0001 |
| **BMI [kg/m²]**                   | 26 [24–30]; n = 14               | 29 [26–32]; n = 347               | 29 [26–32]; n = 1158              | 0.34   |
| **Obesity**                       | 4 (22%); n = 17                  | 145 (39%); n = 370                | 483 (40%); n = 1204               | 0.49   |
| **Type of AF**                    |                                  |                                    |                                    |        |
| **Paroxysmal AF**                 | 6 (29%)                          | 197 (39%)                         | 740 (52%)                          | < 0.0001 |
| **Persistent AF**                 | 11 (52%)                         | 279 (55%)                         | 622 (43%)                          | < 0.0001 |
| **Permanent/long-standing persistent AF** | 4 (19%)                        | 33 (6.5%)                         | 70 (4.9%)                          | 0.02   |
| **Concomitant diseases**          |                                  |                                    |                                    |        |
| **Hypertension**                  | 17 (81%)                         | 395 (78%)                         | 965 (67%)                          | < 0.0001 |
| **Dyslipidemia**                  | 5 (24%)                          | 180 (35%)                         | 532 (37%)                          | 0.57   |
| **Diabetes**                      | 6 (29%)                          | 114 (22%)                         | 243 (17%)                          | 0.01   |
| **CAD**                           | 6 (29%)                          | 114 (22%)                         | 240 (17%)                          | 0.01   |
| **Previous MI**                   | 5 (24%)                          | 53 (10%)                          | 88 (6.1%)                          | < 0.0001 |
| **Previous PCI/CABG**             | 5 (24%)                          | 55 (11%)                          | 104 (7.3%)                         | 0.0002 |
| **PAD**                           | 2 (11%); n = 18                  | 14 (3.4%); n = 407                | 29 (2.8%); n = 1031               | 0.11   |
| **Vascular disease (CAD and/or PAD)** | 7 (33%); n = 18                 | 126 (25%); n = 407                | 263 (18%); n = 1031               | 0.0004 |
| **Heart failure**                 | 9 (43%)                          | 147 (29%)                         | 250 (18%)                          | < 0.0001 |
| **Previous stroke/TIA/peripheral embolism** | 3 (14%); n = 18                | 49 (9.6%); n = 407                | 85 (5.9%)                          | 0.02   |
| **Chronic respiratory disease**   | 1 (5.6%); n = 18                 | 32 (7.9%); n = 406                | 54 (5.2%); n = 1031               | 0.15   |
| **Liver disease**                 | 1 (5.6%); n = 18                 | 2 (0.5%); n = 407                 | 19 (1.8%); n = 1031               | 0.06   |
| **Malignancy**                    | 1 (6.7%); n = 15                 | 27 (8.7%); n = 309                | 39 (4.5%); n = 869                | 0.018  |
| **Previous bleeding**             | 4 (19%); n = 18                  | 41 (8.1%); n = 309                | 56 (3.9%); n = 869                | < 0.0001 |
| **Labile INR**                    | 0 (0%); n = 18                   | 9 (2.2%); n = 407                 | 9 (0.9%); n = 1031                | 0.10   |
| **Smoking**                       | 2 (13%); n = 18                  | 95 (31%); n = 309                 | 282 (33%); n = 1031               | 0.30   |
| **Thromboembolic risk**           |                                  |                                    |                                    |        |
| **CHADS² score**                  | 2.2 ± 1.3                        | 1.6 ± 1.2                         | 1.2 ± 1.0                         | < 0.0001 |
|                                  | 2 [1–3]                          | 1 [1–2]                           | 1 [0–2]                           |        |
| **CHA²DS₂-VASc score**            | 3.7 ± 2.0                        | 3.1 ± 1.7                         | 2.0 ± 1.5                         | < 0.0001 |
|                                  | 3 [3–5]                          | 3 [2–4]                           | 2 [1–3]                           |        |
| **CHA²DS₂-VASc score**            |                                  |                                    |                                    |        |
| = 0                              | 0 (0%)                           | 15 (2.9%)                         | 231 (16%)                         | < 0.0001 |
| = 1                              | 3 (14.3%)                        | 77 (15%)                          | 384 (27%)                         | < 0.0001 |
| ≥ 2                              | 2 (9.5%)                         | 115 (23%)                         | 344 (24%)                         | 0.28   |
| ≥ 3                              | 16 (76%)                         | 302 (59%)                         | 473 (33%)                         | < 0.0001 |
| **HAS-BLED score**                | 2.8 ± 1.0                        | 1.8 ± 1.0                         | 1.1 ± 0.9                         | < 0.0001 |
|                                  | 3 [2–3]; n = 18                  | 2 [1–2]; n = 407                  | 1 [0–2]; n = 1038                 |        |
| **HAS-BLED score**                |                                  |                                    |                                    |        |
| = 0                              | 0 (0%)                           | 34 (8.4%)                         | 336 (26%)                         | < 0.0001 |
| = 1                              | 1 (5.6%)                         | 150 (30%)                         | 623 (44%)                         | < 0.0001 |
| = 2                              | 7 (39%)                          | 175 (34%)                         | 404 (28%)                         | < 0.0001 |
| ≥ 3                              | 10 (56%)                         | 146 (29%)                         | 69 (4.8%)                         | < 0.0001 |
Table 1 (cont.). Clinical characteristics in all groups according to eGFR.

| Variable                  | Patients with eGFR < 30 (n = 21) | Patients with eGFR 30–59 (n = 509) | Patients with eGFR ≥ 60 (n = 1432) | P     |
|---------------------------|----------------------------------|-------------------------------------|------------------------------------|-------|
| **Laboratory parameters** |                                   |                                     |                                    |       |
| Hemoglobin [g/dL]         | 13 [12–14]; n = 21               | 14 [13–15]; n = 490                 | 15 [14–15]; n = 1418               | < 0.0001 |
| Hematocrit [%]            | 39 [35–42]; n = 18               | 42 [39–45]; n = 391                 | 43 [40–46]; n = 1233               | < 0.0001 |
| Platelet count [K/μL]     | 175 [156–199]; n = 21            | 217 [179–253]; n = 488              | 216 [182–252]; n = 1414            | 0.01  |
| Creatinine [mg]           | 2.4 [2.0–5.4]; n = 18            | 1.3 [1.1–1.4]; n = 391              | 1.0 [0.9–1.1]; n = 1233            | < 0.0001 |
| GFR [mL/min/1.73 m²]      | 23 [11–28]                      | 53 [46–57]; n = 371                 | 84 [71–90]; n = 1031               | < 0.0001 |
| INR (for patients on VKA) | 2.1 [2.0–2.4]; n = 9             | 2.3 [1.8–2.9]; n = 147              | 2.3 [1.8–2.9]; n = 461             | 0.63  |
| INR (for patients on VKA) | < 2.0                            | 4 (44%); n = 54 (37%)               | 139 (30%); n = 147                 | 0.37  |
|                           | 2.0–3.0                          | 4 (44%); n = 61 (41%)               | 225 (49%); n = 147                 | 0.35  |
|                           | > 3.0                            | 1 (11%); n = 32 (22%)               | 97 (21%); n = 147                  | 0.82  |
| APTT [s]                  | 34 [32–48]; n = 17               | 37 [32–45]; n = 371                 | 35 [30–42]; n = 1171               | < 0.0001 |

AF — atrial fibrillation; APTT — activated partial thromboplastin time; BMI — body mass index; CABG — coronary artery bypass graft; CAD — coronary artery disease; MI — myocardial infarction; eGFR — estimated glomerular filtration rate; INR — international normalized ratio; PAD — peripheral artery disease; PCI — percutaneous coronary intervention; TIA — transient ischemic attack; VKA — vitamin K antagonists

Table 2. Therapeutic characteristics and echocardiography findings in all groups according to eGFR.

| Variable                  | Patients with eGFR < 30 (n = 21) | Patients with eGFR 30–59 (n = 509) | Patients with eGFR ≥ 60 (n = 1432) | P     |
|---------------------------|----------------------------------|-------------------------------------|------------------------------------|-------|
| **Type of procedure planned** |                                   |                                     |                                    |       |
| Cardioversion             | 9 (43%)                          | 246 (48%)                          | 479 (33%); n = 953 (67%)          | < 0.0001 |
| Ablation                  | 12 (57%)                         | 263 (52%)                          | 953 (67%)                         | < 0.0001 |
| **Antithrombotic treatment** |                                   |                                     |                                    |       |
| No OAC                    | 2 (9.5%); n = 18                  | 13 (2.6%); n = 216                  | 102 (7.1%); n = 1031              | 0.001  |
| VKA                       | 9 (43%); n = 165                  | 168 (33%); n = 303                 | 503 (35%); n = 393                | 0.44  |
| NOAC                      | 10 (48%); n = 24                  | 328 (64%); n = 216                  | 827 (58%); n = 216                | 0.01  |
| dabigatran                | 5 (24%); n = 12                   | 157 (31%); n = 216                  | 387 (27%); n = 216                | 0.29  |
| rivaroxaban               | 3 (14%); n = 12                   | 160 (32%); n = 216                  | 431 (30%); n = 216                | 0.18  |
| apixaban                  | 2 (9.5%); n = 12                   | 11 (2.2%); n = 216                  | 9 (0.6%); n = 216                 | < 0.0001 |
| Reduced dose of NOAC      | 5 (24%); n = 12                   | 53 (10%); n = 216                   | 40 (2.8%); n = 216                | < 0.0001 |
| Bridging therapy with heparin | 1 (5.6%); n = 18                  | 14 (3.4%); n = 216                  | 70 (6.7%); n = 216                 | 0.05  |
| Antiplatelets             | 1 (5.6%); n = 18                   | 19 (4.7%); n = 216                  | 62 (6.0%); n = 216                 | 0.63  |
| **Transthoracic echocardiography** |                                   |                                     |                                    |       |
| Ejection fraction [%]     | 50 [25–55]; n = 5                 | 55 [50–60]; n = 211                 | 58 [50–60]; n = 607               | 0.04  |
| Left atrial diameter [cm] | 49 [48–52]; n = 6                  | 45 [42–48]; n = 216                 | 45 [41–48]; n = 664               | 0.26  |
| **Transepophageal echocardiography** |                                   |                                     |                                    |       |
| Thrombus                  | 5 (24%); n = 12                   | 46 (9.0%); n = 216                  | 57 (4.0%); n = 216                 | < 0.0001 |
| LAA emptying velocity [cm/s] | 31 [25–55]; n = 7               | 42 [29–64]; n = 332                | 50 [32–74]; n = 1130              | < 0.0001 |
| SEC                       | 5 (25%); n = 18                   | 97 (25%); n = 392                  | 237 (19%); n = 1233               | 0.08  |

*Performed during index hospitalization. eGFR — estimated glomerular filtration rate; LAA — left atrial appendage; OAC — oral anticoagulants; NOAC — non-vitamin K antagonist oral anticoagulants; SEC — spontaneous echo contrast; VKA — vitamin K antagonists
point of stroke or systemic embolism occurred in 1.57 per 100 patient-years with rivaroxaban 20 mg/day vs. 2.00 per 100 patient-years with warfarin [18]. The ARISTOTLE study shows that apixaban at doses of 5 mg twice daily in eGFR categories > 80, > 50 to 80, ≤ 50 mL/min/1.73 m² was generally superior in preventing thromboembolic events with no significant interaction between the treatment effect [19]. According to the RE-LY study, the annual rates of thromboembolic events among patient eGFR categories > 80, 50 to < 80, < 50 mL/min/1.73 m² were lower with dabigatran 150 mg and similar with 110 mg twice daily compared with warfarin without significant heterogeneity in subgroups defined by renal function (interaction [20]. However, another sub-analysis of the RE-LY trial data showed a significantly faster rate of decline in renal function in patients on VKA compared with those on dabigatran [21]. Using data from the IMS Disease Analyzer Germany study, Posch et al. [22] proved that exposure to VKA is associated with accelerated eGFR decline.

| Variable                        | Univariate analysis | Multivariate analysis | P     |
|---------------------------------|---------------------|-----------------------|-------|
| Age                             | < 0.0001            | 1.02                  | 1.00–1.05 | 0.03 |
| Non-paroxysmal AF (vs. paroxysmal AF) | < 0.0001            | 5.62                  | 3.10–10.17 | < 0.0001 |
| Dyslipidemia                    | 0.02                | 0.72                  | 0.45–1.15 | 0.16 |
| Diabetes                        | 0.001               | 1.40                  | 0.87–2.25 | 0.16 |
| Coronary artery disease         | 0.02                | 5.47                  | 0.40–75.39 | 0.20 |
| Vascular disease                | 0.045               | 0.14                  | 0.01–1.93 | 0.14 |
| Myocardial infarction           | 0.03                | 1.09                  | 0.48–2.50 | 0.83 |
| Heart failure                   | < 0.0001            | 2.22                  | 1.42–3.47 | < 0.0001 |
| Previous bleeding               | < 0.0001            | 2.97                  | 1.56–5.65 | 0.001 |
| eGFR                            | 0.001               | 0.9888                | 0.9782–0.9996 | 0.04 |

AF — atrial fibrillation; CI — confidence intervals; eGFR — estimated glomerular filtration rate; OR — odds ratio

### Table 3. Logistic regression analyses of predictors of left atrial thrombus in the whole group of patients.

| Variable                        | Univariate analysis | Multivariate analysis | P     |
|---------------------------------|---------------------|-----------------------|-------|
| Age                             | 0.001               | 1.03                  | 1.00–1.06 | 0.047 |
| Non-paroxysmal AF (vs. paroxysmal AF) | < 0.0001            | 4.49                  | 2.12–9.48 | < 0.0001 |
| Diabetes                        | < 0.0001            | 1.66                  | 0.90–3.04 | 0.10 |
| Heart failure                   | < 0.0001            | 2.35                  | 1.31–4.23 | 0.004 |
| Previous bleeding               | 0.002               | 3.64                  | 1.49–8.92 | 0.005 |

### Table 4. Logistic regression analyses of predictors of left atrial thrombus.

| Variable                        | Univariate analysis | Multivariate analysis | P     |
|---------------------------------|---------------------|-----------------------|-------|
| Non-paroxysmal AF (vs. paroxysmal AF) | < 0.0001            | 6.72                  | 2.49–18.17 | < 0.0001 |
| Hypertension                    | 0.048               | 0.46                  | 0.23–0.91 | 0.03 |
| Dyslipidemia                    | 0.04                | 0.65                  | 0.31–1.36 | 0.25 |
| Heart failure                   | 0.002               | 2.25                  | 1.18–4.27 | 0.01 |
| Previous bleeding               | 0.02                | 2.84                  | 1.16–6.99 | 0.02 |

AF — atrial fibrillation; CI — confidence intervals; OR — odds ratio; eGFR — estimated glomerular filtration rate
with VKA exposure, real failure progression was significantly faster compared to patients without VKA exposure (5-year absolute eGFR loss from baseline: 6.0 vs. 4.5 mL/min/1.73 m²) [22]. It has been suggested that VKA may lead to decreased renal function via repeated subclinical glomerular hemorrhages or through accelerated tissue or vascular calcification [23].

There is no conclusive research that has determined the superiority of one of the NOAC drugs. Noteworthy, all NOAC are at least partly eliminated by the kidneys. In contrast to dabigatran (80%) and rivaroxaban (35%), apixaban is less dependent on renal elimination (27%) and is labeled for use in end-stage kidney disease. It may explain results from a Falissard et al. [24] study, in
Table 7. Comparison of patients without oral anticoagulation according to glomerular filtration rate.

| Variable                                | No OAC | GFR < 60 (n = 15) | GFR ≥ 60 (n = 102) | P       |
|-----------------------------------------|--------|-------------------|-------------------|---------|
| Age [years]                             |        | 63 [58–71]        | 53 [38–60]        | 0.007   |
| Female                                  |        | 7 (47%)           | 28 (28%)          | 0.14    |
| BMI [kg/m²]                             |        | 29 [27–31]; n = 12| 27 [25–31]; n = 97| 0.39    |
| Obesity                                 |        | 4 (27%)           | 31 (30%)          | 1.00    |
| **Type of AF**                           |        |                   |                   |         |
| Paroxysmal AF                           |        | 8 (53%)           | 89 (87%)          | 0.004   |
| Persistent AF                           |        | 5 (33%)           | 11 (11%)          | 0.03    |
| Permanent/long-standing persistent AF   |        | 2 (13%)           | 2 (2.0%)          | 0.08    |
| **Type of procedure planned**           |        |                   |                   |         |
| Cardioversion                           |        | 6 (40%)           | 17 (17%)          | 0.07    |
| Ablation                                |        | 9 (60%)           | 85 (83%)          | 0.07    |
| **Concomitant diseases**                |        |                   |                   |         |
| Hypertension                            |        | 8 (53%)           | 40 (39%)          | 0.40    |
| Dyslipidemia                            |        | 1 (6.7%)          | 31 (30%)          | 0.07    |
| Diabetes                                |        | 2 (13%)           | 3 (2.9%)          | 0.12    |
| CAD                                     |        | 3 (20%)           | 8 (7.8%)          | 0.15    |
| Previous myocardial infarction          |        | 2 (13%)           | 6 (5.9%)          | 0.27    |
| Previous CABG/PCI                       |        | 2 (13%)           | 5 (4.9%)          | 0.22    |
| PAD                                     |        | 2 (13%)           | 1 (1.0%)          | 0.04    |
| Vascular disease (CAD and/or PAD)       |        | 3 (20%)           | 9 (8.8%)          | 0.18    |
| Heart failure                           |        | 5 (33%)           | 10 (9.8%)         | 0.02    |
| Previous ischemic stroke/TIA            |        | 2 (13%)           | 2 (2.0%)          | 0.08    |
| Previous ischemic stroke/TIA/peripheral embolism | | 2 (13%) | 2 (2.0%) | 0.08 |
| Chronic respiratory disease             |        | 1 (6.7%)          | 2 (2.0%)          | 0.34    |
| Liver disease                           |        | 0 (0%)            | 0 (0%)            | 1.00    |
| Hyperthyroidism                         |        | 1 (6.7%)          | 3 (2.9%)          | 0.43    |
| Hypothyroidism                          |        | 3 (20%)           | 8 (7.8%)          | 0.15    |
| Malignancy                              |        | 0 (0%)            | 1 (1.0%)          | 1.00    |
| Previous bleeding                       |        | 4 (27%)           | 4 (3.9%)          | 0.009   |
| Smoking                                 |        | 5 (33%)           | 34 (33%)          | 1.00    |
| **Thromboembolic risk**                 |        |                   |                   |         |
| CHADS₂ score                            |        | 1 [0.5–2]         | 0 [0–1]           | 0.007   |
| CHA₂DS₂-VASc score                     |        | 2 [1–3]           | 1 [0–2]           | 0.01    |
| CHA₂DS₂-VASc score = 0                  |        | 0 (0%)            | 24 (24%)          | 0.04    |
| CHA₂DS₂-VASc score = 1                  |        | 6 (40%)           | 23 (23%)          | 0.20    |
| CHA₂DS₂-VASc score ≥ 3                  |        | 4 (27%)           | 25 (25%)          | 1.00    |
| HAS-BLED score                          |        | 1 [1–3]           | 1 [0–1.8]         | 0.02    |
| HAS-BLED score = 0                      |        | 2 (13%)           | 27 (27%)          | 0.35    |
| HAS-BLED score = 1                      |        | 3 (20%)           | 36 (35%)          | 0.38    |
| HAS-BLED score ≥ 3                      |        | 7 (47%)           | 24 (24%)          | 0.07    |
| HAS-BLED score ≥ 3                      |        | 3 (20%)           | 15 (15%)          | 0.70    |
which apixaban was more likely to be prescribed than other NOACs in patients with decreased renal function. Based on online an survey created to analyze the opinion of the role of OAC in various clinical settings, edoxaban and apixaban were the favorites for patients with AF and moderate CKD [25]. In the present study, apixaban was prescribed more often in patients with kidney failure than in patients with normal kidney function. However, the prevalence of apixaban therapy was the lowest among all NOACs.

Recent publications have demonstrated the limitation of the CHA2DS2-VASc score for predicting future strokes in patients with AF [26]. There are conflicting data as to whether the integration of renal function parameters into CHA2DS2-VASc score could improve its predictive value. Some of studies suggest that the predictive value of CHA2DS2-VASc score is not improved by the addition of renal status because the factors within CHA2DS2-VASc are themselves related to renal dysfunction [27]. On the other hand, previous results from Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) registry shows that moderate/severe CKD is independently associated with a higher risk of stroke/systemic embolism [28]. These findings are consistent with a previous study evaluating new thromboembolic risk score i.e. CHA2DS2-VASc-RAF score included two additional parameters i.e. renal dysfunction and AF type. Both variables proved strong, independent predictors of LAA thrombus on TEE and improve thromboembolic risk stratification [29]. Moreover, an inverse correlation between eGFR values and LAA thrombus occurrence were observed among patients included in the current study (24%, 9% and 4% of patients with eGFR < 30, 30–59 and ≥ 60 mL/min/1.73 m$^2$, respectively). This is in line with study by Kizawa et al. [30], that examined 581 AF patients with CKD stages 1–4. The prevalence of thrombogenic milieu (LA thrombus, dense SEC, or LAA a velocity ≤ 25 cm/s) increased with decreasing eGFR (4%, 18%, 36%, and 86% for each group, p < 0.001). Moreover, multivariate logistic regression analysis revealed that every 10 mL/min/1.73 m$^2$ decrement in eGFR was a significant independent correlate of thrombogenic milieu (odds ratio 0.80, p = 0.005) [30].

It is unclear, whether patients with decreased renal function and AF benefit from OAC to the same extent as those with normal kidney function. Current evidence suggests that patients with AF who have CKD with eGFR > 15 mL/min/1.73 m$^2$ should be treated with OAC if they have an at least an intermediate risk of embolization, as assessed with the CHA2DS2-VASc score [31]. In the present study, 98% of patients with decreased renal func-

| Variable | No OAC | GFR < 60 (n = 15) | GFR ≥ 60 (n = 102) | P |
|----------|--------|-------------------|-------------------|---|
| **Laboratory parameters** | | | | |
| Hemoglobin [g/dL] | | 13 [12–15] | 15 [14–15] | 0.005 |
| Hematocrit [%] | | 41 [38–43] | 44 [42–46] | 0.003 |
| WBC [K/μL] | | 7.4 [6.6–8.6] | 7.1 [6.1–8.8] | 0.73 |
| Platelet count [K/μL] | | 254 [196–284] | 228 [199–256] | 0.41 |
| AST | | 25 [20–39]; n = 14 | 22 [19–27]; n = 93 | 0.27 |
| ALT | | 31 [21–46]; n = 14 | 32 [23–38]; n = 94 | 0.88 |
| **Transthoracic echocardiography** | | | | |
| Ejection fraction [%] | | 50 ± 0; n = 1 | 60 [55–62]; n = 17 | 0.29 |
| Left atrial diameter [cm] | | 44 [43–47]; n = 4 | 43 [40–45]; n = 44 | 0.71 |
| **Transesophageal echocardiography** | | | | |
| Thrombus | | 3 (20%) | 3 (2.9%) | 0.03 |
| LAA emptying velocity [cm/s] | | 56 [42–68]; n = 15 | 70 [49–87]; n = 99 | 0.04 |
| SEC | | 2 (13%) | 7 (6.9%) | 0.32 |

*Performed during index hospitalization. AST — aspartate transaminase; AF – atrial fibrillation; ALT — alanine transaminase; BMI — body mass index; CABG — coronary artery bypass grafting; CAD — coronary artery disease; GFR — glomerular filtration rate; LAA — left atrial appendage; OAC — oral anticoagulants; PAD — peripheral artery disease; PCI — percutaneous coronary intervention; SEC — spontaneous echo contrast; TIA — transient ischemic attack; WBC — white blood cells

Table 7 (cont.). Comparison of patients without oral anticoagulation according to glomerular filtration rate.
tion treated with OAC were at moderate or high risk (CHA2DS2-VASc score ≥ 2). Among high risk patients in whom OAC are recommended, thrombus was more frequent in patients with lower eGFR. Moreover, among patients who were not treated with OAC LAA thrombus occurred more often in patients with eGFR < 60 mL/min/1.73 m².

Independent predictors for LAA thrombus formation included the following clinical risk factors — non-paroxysmal AF, hypertension, heart failure, previous bleeding in patients with eGFR < 60 mL/min/1.73 m², and age, non-paroxysmal AF, heart failure, previous bleeding in those with eGFR ≥ 60 mL/min/1.73 m². This is consistent with the high risk associated with such comorbidities in AF patients [32–34].

Based on previous meta-analysis by Wang et al. [35], patients eligible for a reduced dose of NOAC are at elevated risk of thromboembolic complications when compared to those eligible for full dose of NOAC (2.70% vs. 4.35%, respectively). In the current study it was confirmed that patients with reduced NOAC a prevalence of LAA thrombus is higher in patients with lower eGFR.

Therefore, there is a particular need to use adequate OAC treatment in patients with CKD.

Conclusions

The incidence of LAA thrombi was higher in patients with lower eGFR. eGFR was one of the predictors of LAA thrombus. CKD was the predictor of LAA thrombus in all patients as well as in patients with non-paroxysmal AF, in males, without diabetes, without hypertension and with CHA2DS2-VASc < 2 that is in groups which are not included in classic risk factors.

Acknowledgments

The authors thank Paweł Pilkowski for his assistance in the statistical analysis, and students: Aldona Babiarz, Aleksandra Bodys, Robert Uliński, and Maciej Żochowski for their assistance in data collection.

Conflict of interest: Iwona Gorczyca — Honoraire for lectures from Bayer, Boehringer Ingelheim; Beata Wożakowska-Kapłon — Honoraire for lectures from Bayer, Boehringer Ingelheim, Pfeizer; Krzysztof J. Filipiak — Honoraire for lectures from Bayer, Boehringer Ingelheim, MSD, Pfeizer; Grzegorz Opolski — Honoraire for lectures from Bayer, Boehringer Ingelheim, Pfeizer; Agnieszka Kapłon-Cieślicka — Honoraire for lectures/travel grants from Bayer, Boehringer Ingelheim, MSD, Pfeizer.

References

1. Chugh SS, Havmoeller R, Narayan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014; 129(8): 837–847, doi: 10.1161/CIRCULATIONAHA.113.055119, indexed in Pubmed: 24343599.

2. Haim M, Hoshen M, Reges O, et al. Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation. J Am Heart Assoc. 2015; 4(1): e001486, doi: 10.1161/ Jaha.114.001486, indexed in Pubmed: 25669415.

3. Kannel WB, Wolf PA, Benjamin EJ, et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol. 1998; 82(8A): 2N–9N, doi: 10.1016/s0002-9149(98)00583-9, indexed in Pubmed: 9809895.

4. Gorczyca I, Michalska A, Chrapek M, et al. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation in secondary stroke and systemic embolism prevention. Cardiol J. 2019 [Epub ahead of print], doi: 10.5603/CJ.a2019.0069, indexed in Pubmed: 31312376.

5. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014; 383(9921): 955–962, doi: 10.1016/S0140-6736(13)65234-0, indexed in Pubmed: 24315724.

6. Olesen J, Lip G, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med. 2012; 367(7): 625–635, doi: 10.1056/nejmoa1105594.

7. Albertsen I, Rasmussen L, Overvad T, et al. Risk of stroke or systemic embolism in atrial fibrillation patients treated with warfarin. Stroke. 2013; 44(5): 1329–1336, doi: 10.1161/strokea-ha.113.00883.

8. Connolly S, Ezekowitz M, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361(12): 1139–1151, doi: 10.1056/nejmoa0905561.

9. Granger CB, Alexander JH, McMurray JJV, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365(11): 981–992, doi: 10.1056/NEJMoa1107039, indexed in Pubmed: 21870978.

10. Patel M, Mahaffy K, Garg J, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med. 2011; 365(10): 883–891, doi: 10.1056/nejmoa1096638.

11. Giugliano RP, Ruff CT, Braunwald E, et al. ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013; 369(22): 2093–2104, doi: 10.1056/NEJMoa1310907, indexed in Pubmed: 24251359.

12. Heidbuchel H, Verhamme P, Alings M, et al. ESC Scientific Document Group. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015; 17(10): 1467–1507, doi: 10.1093/europace/euv009, indexed in Pubmed: 26324838.

13. Kosmalska K, Rzymań M, Miękus P, et al. Usefulness of trans-esophageal echocardiography before cardioversion in atrial arrhythmias. Cardiol J. 2019 [Epub ahead of print], doi: 10.5603/CJ.a2019.0056, indexed in Pubmed: 31225630.

14. Gawalko M, Kapłon-Cieślicka A, Budnik M, et al. Comparison of different oral anticoagulant regimens in patients with atrial fibrillation undergoing ablation or cardioversion. Pol Arch Intern
Monika Budnik et al., *Atrial fibrillation and chronic kidney disease* Med. 2017; 127(12): 823–831, doi: 10.20452/jamw.4117, indexed in Pubmed: 29072957.

15. Loo SY, Coulombe J, Dell’Aniello S, et al. Comparative effectiveness of novel oral anticoagulants in UK patients with non-valvular atrial fibrillation and chronic kidney disease: a matched cohort study. BMJ Open. 2018; 8(1): e019638, doi: 10.1136/bmjopen-2017-019638, indexed in Pubmed: 29371284.

16. Kimachi M, Furukawa TA, Kimachi K, et al. Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. Cochrane Database Syst Rev. 2017; 11: CD011373, doi: 10.1002/14651858.CD011373.pub2, indexed in Pubmed: 29105079.

17. Shin JI, Secora A, Alexander GC, et al. Risks and Benefits of Direct Oral Anticoagulants across the Spectrum of GFR among Incident and Prevalent Patients with Atrial Fibrillation. Clin J Am Soc Nephrol. 2018; 13(8): 1144–1152, doi: 10.2215/CJN.13811217, indexed in Pubmed: 30002224.

18. Fox KAA, Fecchin JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J. 2011; 32(19): 2387–2394, doi: 10.1093/eurheartj/ehr342, indexed in Pubmed: 21873070.

19. Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J. 2012; 33(22): 2821–2830, doi: 10.1093/eurheartj/ehs274, indexed in Pubmed: 22930567.

20. Hijazi Z, Hohnloser SH, Oldgren J, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. Circulation. 2014; 129(9): 961–970, doi: 10.1161/CIRCULATIONAHA.113.003628, indexed in Pubmed: 24323795.

21. Böhm M, Ezekowitz MD, Connolly SJ, et al. Changes in renal function in patients with atrial fibrillation: an analysis from the RE-LY trial. J Am Coll Cardiol. 2015; 65(23): 2481–2493, doi: 10.1016/j.jacc.2015.03.577, indexed in Pubmed: 26069896.

22. Posch F, Ayy C, Stöger H, et al. Exposure to vitamin K antagonists and kidney function decline in patients with atrial fibrillation and chronic kidney disease. Res Pract Thermon. Haemost. 2019; 3(2): 207–216, doi: 10.1002/rth2.12189, indexed in Pubmed: 31011765.

23. Zaragatski E, Gronmes J, Schurgers LJ, et al. Vitamin K antagonism aggravates chronic kidney disease-induced neointimal hyperplasia and calcification in arterioleal veins: role of vitamin K treatment? Kidney Int. 2016; 89(3): 601–611, doi: 10.1038/ki.2015.298, indexed in Pubmed: 26466318.

24. Falissard B, Picard F, Mahe I, et al. Apixaban for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation in France: The PAROS cross-sectional study of routine clinical practice. Arch Cardiovasc Dis. 2019; 112(6-7): 400–409, doi: 10.1016/j.acvd.2019.02.003, indexed in Pubmed: 31014991.

25. Chueca Fernández E, López Granados A, Zuazola Martinez MD, et al. Consensus in cardiology on non-vitamin-K oral anticoagulants for patients with atrial fibrillation. Curr Med Res Opin. 2019; 35(9): 1571–1582, doi: 10.1080/03007995.2019.1605049, indexed in Pubmed: 30957564.

26. Quinn GR, Severdija ON, Chang Y, et al. Wide variation in reported rates of stroke across cohorts of patients with atrial fibrillation. Circulation. 2017; 135(3): 208–219, doi: 10.1161/CIRCULATIONAHA.116.024057, indexed in Pubmed: 27799272.

27. Roldán V, Marín F, Manzano-Fernandez S, et al. Does chronic kidney disease improve the predictive value of the CHADS2 and CHA2DS2-VASc stroke stratification risk scores for atrial fibrillation? Thromb Haemost. 2013; 109(5): 956–960, doi: 10.1160/TH13-01-0054, indexed in Pubmed: 23572113.

28. Goto S, Anghaisuksiri F, Bassand JP, et al. GARFIELD-AF Investigators. Management and 1-Year Outcomes of Patients With Newly Diagnosed Atrial Fibrillation and Chronic Kidney Disease: Results From the Prospective GARFIELD – AF Registry. J Am Heart Assoc. 2019; 8(3): e010510, doi: 10.1161/JAHA.118.010510, indexed in Pubmed: 30717616.

29. Kaplon-Cieslicka A, Budnik M, Gavalko M, et al. Atrial fibrillation type and renal dysfunction as important predictors of left atrial thrombus. Heart. 2019; 105(17): 1310–1315, doi: 10.1136/heartjnl-2018-314492, indexed in Pubmed: 31040170.

30. Kizawa S, Ito T, Akamatsu K, et al. Chronic kidney disease as a possible predictor of left atrial thrombogenic milieu among patients with nonvalvular atrial fibrillation. Am J Cardiol. 2018; 122(12): 2962–2967, doi: 10.1016/j.amjcard.2018.08.058, indexed in Pubmed: 30293657.

31. Heine GH, Brandenburg V, Schirmer SH. Oral anticoagulation in chronic kidney disease and atrial fibrillation. Dtsch Arztebl Int. 2018; 115: 287–294.

32. Pang H, Han B, Fu Q, et al. Severity of hypertension correlates with risk of thromboembolic stroke. J Cardiovasc Transl Res. 2017; 10(4): 368–373, doi: 10.1007/s12265-017-9754-0, indexed in Pubmed: 28567670.

33. Olesen J, Lip G, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med. 2012; 367(7): 625–635, doi: 10.1056/nejmoa1105594.

34. Lau YC, Lane DA, Lip GYH. Atrial fibrillation and heart failure: a bad combination. Am J Cardiol. 2014; 113(7): 1196–1197, doi: 10.1016/j.amjcard.2014.01.002, indexed in Pubmed: 24530002.

35. Wang KL, Lopes RD, Patel MR, et al. Efficacy and safety of reduced-dose non-vitamin-K oral anticoagulants in patients with atrial fibrillation: a meta-analysis of randomized controlled trials. Eur Heart J. 2019; 40(19): 1492–1500, doi: 10.1093/eurheartj/ehy802, indexed in Pubmed: 30590440.