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

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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 (TEE) 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 m^2) 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 $\geq$ 60 mL/min/1.73 m^2, 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 CHA_2DS_2-VASc < 2.

Conclusions: Despite OAC, patients with concomitant AF and CKD remain at high risk for LAA thrombus formation.

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]. Tromboembolic events were identified in about 12% of cases for AF patients [4]. Anticoagulation 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 m^2, with apixaban — those with eGFR were < 25 mL/min/1.73 m^2 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 LAA thrombi or SEC is up to 29% [13]. The aim of the present study was to compare the incidence of the left atrial appendage (LAA) thrombi and spontaneous echo contrast (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 m^2, 30–59 mL/min/1.73 m^2 and ≥ 60 mL/min/1.73 m^2 (1432 patients). However, due to the small number of patients in the group with eGFR < 30 mL/min/1.73 m^2, the multivariate logistic regression analysis of the two groups are included (eGFR ≥ 60 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2).

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 chi-squared 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

A total of 1962 patients are included in the study and were divided into three groups: eGFR: < 30 mL/min/1.73 m^2 (21 patients), 30–59 mL/min/1.73 m^2 (509 patients) and $\geq$ 60 mL/min/1.73 m^2 (1432 patients).

Basic characteristic

Compared to other groups, patients with eGFR < 60 mL/min/1.73 m^2 were older, more often suffered from hypertension, diabetes, coronary artery disease, peripheral vascular disease, heart failure, cancer and were more often were female. Moreover, the incidence of previous thromboembolic complications definied as composite of stroke/transient ischemic attack (TIA) 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 m^2 with a higher prevalance 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 m^2 than in those with $\geq$ 60 mL/min/1.73 m^2 (9% vs. 4%, respectively). In a relatively small group of patients with eGFR < 30 mL/min/1.73 m^2 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 m^2 (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 $\geq$ 60 mL/min/1.73 m^2 (Table 4A). In those with eGFR < 60 mL/min/1.73 m^2, 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 CHA_2DS_2-VASc < 2 i.e. groups not included in

classic risk factors (Fig. 1). Among patients with LAA thrombus no differences retaled to OAC treatment were observed between patients with eGFR < 60 mL/min/1.73 m^2 and eGFR ≥ 60 mL/min/1.73 m^2 (Table 5). Among patients on reduced dose of NOAC, LAA thrombus occured more often in patients with eGFR < 60 mL/min/1.73 m^2 than in those with eGFR ≥ 60 mL/min/1.73 m^2 (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 m^2 than in those with eGFR < 60 mL/min/1.73 m^2. Patients with eGFR < 60 mL/min/1.73 m^2 more often had persistent AF and heart failure as compared to those with normal eGFR. Median CHA_2DS_2-VASc score was 2 in patients with eGFR < 60 mL/min/1.73 m^2 and 1 in patients with eGFR ≥ 60 mL/min/1.73 m^2. More than 50% of patients in both groups were found to be at high thromboembolic risk (CHA_2DS_2-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 m^2) 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 m^2). The higher prevalence of prescribed NOAC was observed among patients with eGFR 30–59 mL/min/1.73 m^2. Importantly, among patients prescribed with reduced doses of NOAC, those with eGFR < 60 mL/min/1.73 m^2 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 m^2. 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 CrCl 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 CrCl ≥ 50 mL/min, the primary endpoint 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 m^2 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 m^2 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. In 7409 patients 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 m^2) [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 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 CHA_2DS_2-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 CHA_2DS_2-VASc score could improve its predictive value. Some of studies suggest that the predictive value of CHA_2DS_2-VASc score is not improved by the addition of renal status because the factors within CHA_2DS_2-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. CHA_2DS_2-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 spontaneous echo contrast, 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 (OR 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 function treated with OAC were at moderate or high risk (CHA_2DS_2-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 m^2.

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 m^2, and age, non-paroxysmal AF, heart failure, previous bleeding in those with eGFR ≥ 60 mL/min/1.73 m^2. 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 CHA_2DS_2-VASc < 2 that is in groups which are not included in classic risk factors.

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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/m^2]	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%)	**0.002**
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%)	126 (25%)	263 (18%)	**0.004**

Heart failure	9 (43%)	147 (29%)	250 (18%)	< **0.0001**
Previous stroke/TIA/peripheral embolism	3 (14%)	49 (9.6%)	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%)	41 (8.1%)	56 (3.9%)	< **0.0001**
Labile INR	0 (0%); n = 18	9 (2.2%); n = 407	9 (0.9%); n = 1031	0.10
Smoking	2 (13%); n = 15	95 (31%); n = 309	282 (33%); n = 869	0.30
Thromboembolic risk				
$CHADS_2$ score	2.2 ± 1.3 2 [1–3]	1.6 ± 1.2 1 [1–2]	1.2 ± 1.0 1 [0–2]	< **0.0001**
CHA_2DS_2-VASc score	3.7 ± 2.0 3 [3–5]	3.1 ± 1.7 3 [2–4]	2.0 ± 1.5 2 [1–3]	< **0.0001**
CHA_2DS_2-VASc score = 0 = 1 = 2 ≥ 3	 0 (0%) 3 (14.3%) 2 (9.5%) 16 (76%)	 15 (2.9%) 77 (15%) 115 (23%) 302 (59%)	 231(16%) 384 (27%) 344 (24%) 473 (33%)	 < **0.0001** < **0.0001** 0.28 < **0.0001**
HAS-BLED score	2.8 ± 1.0 3 [2–3]; n = 18	1.8 ± 1.0 2 [1–2]; n = 407	1.1 ± 0.9 1 [0–2]; n = 1038	< **0.0001**

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**
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]	1.3 [1.1–1.4]	1.0 [0.9–1.1]	< **0.0001**
GFR [mL/min/1.73 m^2]	23 [11–28]	53 [46–57]	84 [71–90]	< **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%)	54 (37%)	139 (30%)	0.37
- 2.0–3.0	4 (44%)	61 (41%)	225 (49%)	0.35
- > 3.0	1 (11%)	32 (22%)	97 (21%)	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%)	**<0.0001**
Ablation	12 (57%)	263 (52%)	953 (67%)	**<0.0001**
Antithrombotic treatment				
No OAC	2 (9.5%)	13 (2.6%)	102 (7.1%)	**0.001**
VKA	9 (43%)	168 (33%)	503 (35%)	0.44
NOAC	10 (48%)	328 (64%)	827 (58%)	**0.01**
dabigatran rivaroxaban apixaban	5 (24%) 3 (14%) 2 (9.5%)	157 (31%) 160 (32%) 11 (2.2%)	387 (27%) 431 (30%) 9 (0.6%)	0.29 0.18 **< 0.0001**
Reduced dose of NOAC	5 (24%)	53 (10%)	40 (2.8%)	**< 0.0001**
Bridging therapy with heparin	1 (5.6%); n = 18	14 (3.4%); n = 407	70 (6.7%); n = 1031	**0.05**
Antiplatelets	1 (5.6%); n = 18	19 (4.7%); n = 407	62 (6.0%); n = 1031	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
Transesophageal echocardiography*				
Thrombus	5 (24%)	46 (9.0%)	57 (4.0%)	**< 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

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

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

Variable	**Univariate analysis**	**Multivariate analysis**		
		OR	**95% CI**	**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 infraction	**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; CABG — coronary artery bypass graft; CI — confidence intervals; eGFR — estimated glomerular filtration rate; PCI — percutaneous coronary intervention; OR — odd ratio; TIA — transient ischemic attack; VKA — vitamin K antagonist

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

A. Predictors of left atrial thrombus in the group of patients with eGFR 60 mL/min/1.73 m^2 or more				
Variable	**Univariate analysis**	**Multivariate analysis**		
		OR	**95% CI**	**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**
B. Predictors of left atrial thrombus in the group of patients with eGFR of less than 60 mL/min/1.73 m^2				
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

Table 5. The distribution of anticoagulation treatment in patients with left atrial appendage (LAA) thrombus glomerular filtration rate less than 60 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2 and more.

Variable	**Patients with LAA thrombus**		
	GFR < 60 (n = 51)	**GFR ≥ 60 (n = 57)**	**P**
No OAC	3 (5.9%)	3 (5.3%)	1.00
VKA	23 (45%)	28 (49%)	0.85
NOAC	25 (49%)	26 (46%)	0.85
dabigatran	14 (46%)	14 (25%)	0.52
rivaroxaban	12 (21%)	12 (21%)	0.64
apixaban	0 (0%)	0 (0%)	1.00

GFR — glomerular filtration rate; NOAC — non-vitamin K antagonist oral anticoagulants; OAC — oral anticoagulants; VKA — vitamin K antagonists

Table 6. The distribution of left atrial appendage (LAA) thrombus in patients with reduced non-vitamin K antagonist oral anticoagulants according to glomerular filtration rate.

Variable	Patients with reduced NOAC			
	GFR < 30 (n = 5)	GFR 30–59 (n = 53)	GFR ≥ 60 (n = 40)	P
LAA thrombus	1 (20%)	5 (9.4%)	1 (2.5%)	**0.001**

GFR — glomerular filtration rate; NOAC — non-vitamin K antagonist oral anticoagulants

Table 7. Comparison of patients without oral anticoagulation according to glomerular filtration rate.

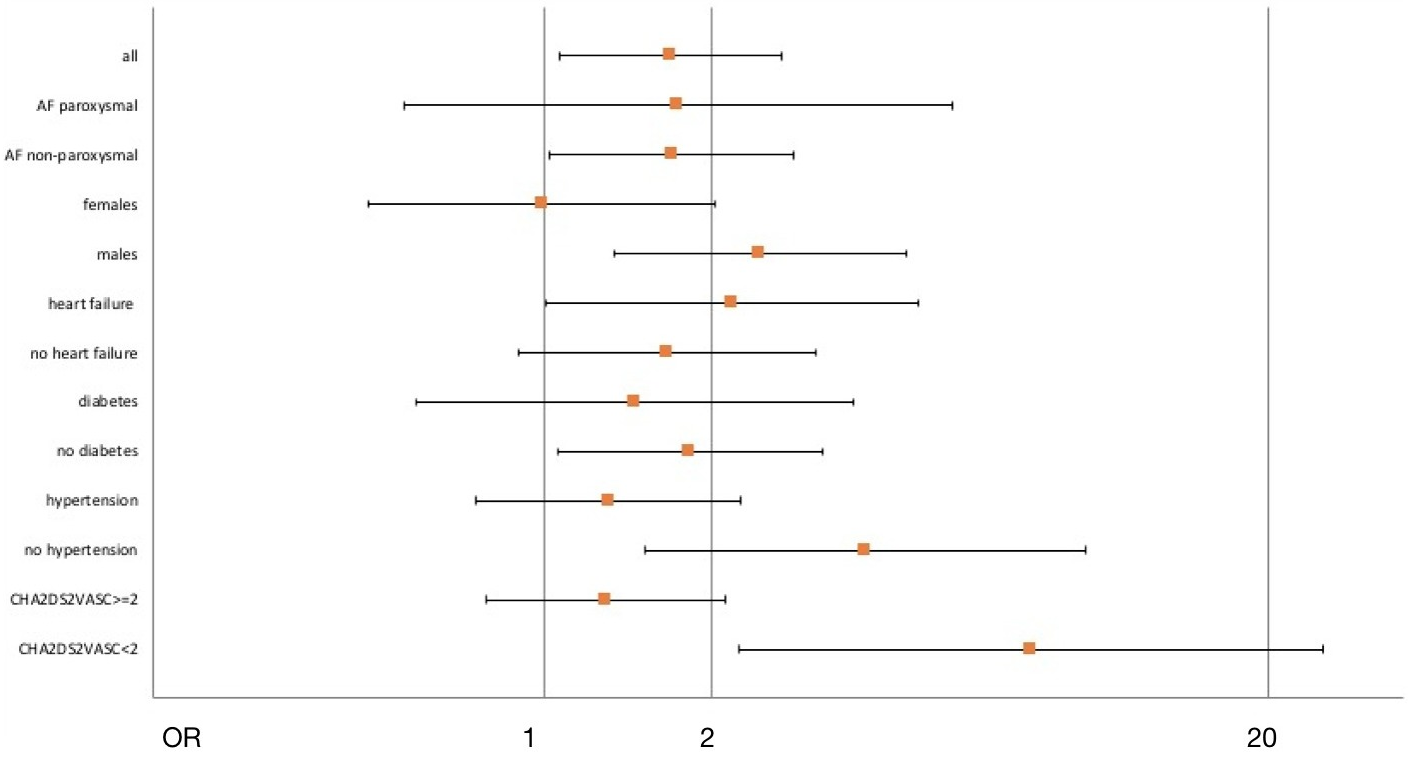
Variable	No OAC		
	GFR < 60 (n = 15)	GFR ≥ 60 (n = 102)	P
Age [years]	63 [58–71]	53 [38–60]	**0.007**
Female	7 (47%)	28 (28%)	0.14
BMI [kg/m^2]	29 [27–31]; n = 12	27 [25–31]; n = 97	0.39
Obesity	4 (27%)	31 (30%)	1.00
Type of AF			
Paroxysmal AF	8 (53%)	89 (87%)	**0.004**
Persistent AF	5 (33%)	11 (11%)	**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			
$CHADS_2$ score	1 [0.5–2]	0 [0–1]	**0.007**
CHA_2DS_2-VASc score	2 [1–3]	1 [0–2]	**0.01**
CHA_2DS_2-VASc score:			
= 0	0 (0%)	24 (24%)	**0.04**
= 1	6 (40%)	23 (23%)	0.20
= 2	4 (27%)	25 (25%)	1.00
$\geq$ 3	5 (33%)	30 (29%)	0.77

HAS-BLED score	1 [1–3]	1 [0–1.8]	**0.02**
HAS-BLED score:			
= 0	2 (13%)	27 (27%)	0.35
= 1	3 (20%)	36 (35%)	0.38
= 2	7 (47%)	24 (24%)	0.07
≥ 3	3 (20%)	15 (15%)	0.70
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

Figure 1. Forest plot of chronic kidney disease as predictor of left atrial appendage thrombus in atrial fibrillation patients depending on additional risk factors.


all
AF paroxysmal
AF non-paroxysmal
females
males
heart failure
no heart failure
diabetes
no diabetes
hypertension
no hypertension
CHA2DS2VASC>=2
CHA2DS2VASC<2
OR
1
2
20