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The BALKAN-AF survey

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Treatment implications of renal disease in patients with atrial fibrillation: The BALKAN-AF survey

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Abstract

Background: Atrial fibrillation (AF) often co-exists with renal function (RF) impairment. We investigated the characteristics and management of AF patients across creatinine clearance strata and potential changes in the use of nonvitamin K oral anticoagulants (NOAC) according to different equations for estimation of RF.

Methods: In this post hoc analysis of the BALKAN-AF survey, patients were classified according to RF (Cockcroft-Gault formula) as: preserved/mildly depressed RF (P-RF) ≥50 mL/min, moderately depressed RF (MD-RF) 30-49 mL/min, and severely depressed RF (SD-RF) <30 mL/min.

Results: Of 2712 enrolled patients, 2062 (76.0%) had data on RF. Patients with SD-RF and MD-RF were older, had higher mean value of European Heart Rhythm Association score, stroke and bleeding risk scores, and more comorbidities than patients with P-RF (all $P < .05$). They received oral anticoagulants (OAC), AF catheter ablation, and electrical

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cardioversion less often than those with P-RF (all $P < .05$). Rate control, no OAC, single-antiplatelet therapy (SAPT) alone, and loop diuretics were more prevalent in patients with SD-RF and MD-RF than in subjects with P-RF (all $P < .005$). An important change in NOAC therapy could appear in <1% of patients (Modification of Diet in Renal Disease formula) and in <1% of patients (Chronic Kidney Disease Epidemiology Collaboration group formula).

Conclusions: Patients with SD-RF and MD-RF were older, more symptomatic, had higher stroke and bleeding risk and more comorbidities than those with P-RF. They were less likely to receive OAC and more likely to use rate control strategy, SAPT alone, and no OAC than subjects with P-RF.

KEYWORDS

atrial fibrillation, BALKAN-AF survey, creatinine clearance, oral anticoagulant therapy, renal function

1 | INTRODUCTION

Atrial fibrillation (AF) is often accompanied by renal function (RF) impairment of various degree[1], coexisting with chronic kidney disease (CKD) in about 15%-20% of patients[2], especially among the elderly and those with concomitant risk factors such as, for example, diabetes mellitus (DM), hypertension or obesity.[3]

Kidney damage (ie, albuminuria) or impaired kidney function (ie, glomerular filtration rate [GFR] <60 mL/min/1.73 m^2) for 3 months or more is defined as CKD.[4] Estimated GFR (eGFR) may be calculated from the serum creatinine using various equations[1,5], and the Kidney Disease: Improving Global Outcomes (KIDIGO) group endorsed Chronic Kidney Disease Epidemiology Collaboration group (CKD-EPI) equation.[5] The CKD-EPI equation is less biased and more precise in GFR estimation than Cockcroft-Gault (CG) or MDRD (Modification of Diet in Renal Disease).[1] In case of management with nonvitamin K oral anticoagulants (NOACs), RF should be assessed by calculating creatinine clearance (CrCl) using the CG method as in most NOAC trials.[6] Patients are eligible for NOACs if CrCl is ≥30 mL/min in case of dabigatran or CrCl is ≥15 mL/min in case of rivaroxaban, apixaban, and edoxaban. Importantly, NOAC dose should be selected as per the drug label.[6,7]

There is a bidirectional interaction between AF and CKD. AF facilitates the development or progression of CKD, whereas decreased RF is associated with increased prevalence and incidence of AF. AF and CKD share common abnormal molecular signaling pathways contributing to their pathogenesis. There is a well-established interrelationship between heart and the kidney, thus dysfunction of one organ negatively affects the other.[8-10] Both nonend-stage CKD and the disease requiring renal-replacement therapy are independently associated with higher risk of stroke, bleeding, myocardial infarction, and mortality in patients with AF.[11,12] Assessment of RF is crucial for adequate NOACs dose selection in patients with AF.[6]

Reportedly, the adherence to AF guidelines in the Balkan region is low[13,14], and data on the management of patients with AF across the RF strata are lacking. Given the differences in socioeconomic and healthcare system-related features between the Balkan region and Western Europe, describing patterns of AF management in clinical practice in the Balkans may identify region-specific knowledge gaps and inform strategies for optimizing the management of patients with AF in the participating Balkan countries.[15]

The aims of this study were to: (a) investigate the baseline characteristics of patients with AF across CrCl strata, (b) determine "real-world" management of AF patients according to their RF, and (c) assess potential changes in decision making on the use of NOACs according to different equations for estimation of RF.

2 | METHODS

The design of the BALKAN-AF survey has been previously published.[15] A 14-week prospective, international, multicenter "snapshot" registry of consecutive patients with electrocardiographically documented nonvalvular AF was created by the Serbian Atrial Fibrillation Association (SAFA). The registry was announced to the National Cardiology Societies and Associations or Working Groups in the Balkan countries. The survey was conducted from December 2014 to February 2015 in seven Balkan countries (Albania, Bulgaria, Bosnia & Herzegovina, Croatia, Montenegro, Romania, and Serbia). Individuals were enrolled into the study, irrespective whether AF was the main reason for outpatient visit or inpatient stay in the hospital. Admissions for cardioversion or AF catheter ablation were also included. Patients were treated by a cardiologist or an internal medicine specialist if cardiologist was not available. Patients were recruited by academic and nonuniversity hospitals and outpatient health centers (a total of 49 centers) in Albania, Bosnia & Herzegovina, Bulgaria, Croatia, Montenegro, Romania, and Serbia.

Each country recruited university and nonuniversity hospitals and outpatient health centers situated in different cities or rural areas. The centers were selected by the respective National Coordinator. Those centers had to accurately reflect AF management in particular country in daily clinical practice. A signed patient informed consent form was obtained before enrolment. The study protocol is consistent with the ethical guidelines of the 1975 Declaration of Helsinki.

The exclusion criteria were age <18 years, prosthetic mechanical heart valves or significant valvular disease with indication for surgical repair.

Data were documented using an electronic case report form (eCRF) designed by SAFA. The eCRF included: patient characteristics, patient presentation and healthcare setting, diagnostic procedures for AF within the last 12 months and at enrolment, and AF management at enrolment and at discharge. All the cardiovascular risk factors, diseases, and risk scores were defined based on individual European Society of Cardiology guidelines, other current guidelines, scientific statements, and textbooks presented previously in supplementary information.[13]

Following equations were used for RF assessment: (a) the CG formula for CrCl[16], (b) MDRD[17], and (c) CKD-EPI.[5] Using the CG formula for CrCl patients were categorized to three groups as follows: (a) preserved/ mildly depressed RF (P-RF) ≥50 mL/min, (b) moderately depressed RF (MD-RF) 30-49 mL/min, and (c) severely depressed RF (SD-RF) <30 mL/min. Baseline characteristics and management of patients stratified into three groups according to CG formula for CrCl were performed. The cut-off values were selected according to those used in the landmark NOAC trials.[6] The same cut-offs were chosen for other equations reported in this study. We reported the proportion of patients re-allocated to each class of RF for each specific formula used for RF evaluation. Some differences are present in the number of individuals allocated to each category of RF according to different equations.

Symptoms of AF were classified according to European Heart Rhythm Association (EHRA) symptom score (ie, 1—AF does not cause any symptoms, 2—typical daily activity not affected by symptoms related to AF, 3—typical daily activity affected by AF symptoms, 4—normal daily activity discontinued).[18]

Stroke risk was estimated using the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischemic attack (TIA), vascular disease, age 65-74 years, sex category) score.[19] Bleeding risk was evaluated according to the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio (INR), elderly (>65 years), drugs or alcohol concomitantly) score.[19,20]

Because of relatively short period of the survey systematic monitoring of centers and follow-up visits was not performed. National coordinators and investigators were responsible for verification of the consecutiveness of enrolled patients and data correctness and completeness.

2.1 | Statistical analysis

Univariate analysis was used for both continuous and categorical variables. Categorical variables were reported as absolute frequencies and percentages, and continuous variables as mean value and standard deviation (SD). Comparison of categorical variables among RF categories was calculated using chi-square test. Normal distribution was checked using the Shapiro-Wilk test and a Q-Q plot. Homogeneity of variances was checked using Leven's test. Analysis of variance was performed using one-way ANOVA with post hoc Tukey test. The descriptive analysis included baseline characteristics of patients according to their RF using CG formula and characteristics of AF patients with HF stratified by their RF. The association of patient-, AF-, healthcare system- and management-related variables with the eGFR strata was evaluated using univariate linear regression. The variables with statistically significant association on univariate linear regression analysis were entered into multivariable linear regression model. Results are expressed as odds ratio with 95% confidence interval. A two-sided P value of <.05 was interpreted as statistically significant. All analyses were performed using SAS software version 9.4 (SAS Institute, Inc, Cary, NC, USA).

3 | RESULTS

Of 2712 patients enrolled in seven Balkan countries, complete data on RF based on CG formula for CrCl were available for 2062 (76.0%). Of the study cohort, 1677 patients (81.3%) had P-RF, 308 (14.9%) had MD-RF, and 77 (3.8%) had SD-RF, Table 1.

3.1 | Demographic and AF-related characteristics

Patients with SD-RF and MD-RF were older, with higher mean EHRA symptom score, less likely to be smokers, but more likely to have permanent AF than those with P-RF (all $P < .05$), Table 1.

3.2 | Physical findings and comorbidity

Patients with SD-RF and MD-RF were more likely to have various comorbidities, such as prior stroke, coronary artery disease, heart failure (HF), DM, aortic valve disease (aortic regurgitation or stenosis), mitral valve disease (mitral regurgitation or stenosis), hypertrophic cardiomyopathy, chronic obstructive pulmonary disease (COPD), anemia, and malignancy than subjects with P-RF (all $P < .05$), Table 1. There was no significant difference in terms of prior bleeding history across the groups, Table 1.

3.3 | Stroke and bleeding risk factors

Mean CHA_2DS_2-VASc and HAS-BLED score values were higher in patients with SD-RF and MD-RF than in patients with P-RF (all $P < .05$), Table 1. The proportion of patients with CHA_2DS_2-VASc score of ≥2 and HAS-BLED score of ≥3 was higher in patients with SD-RF and MD-RF than in patients with P-RF (both $P < .001$), Table 1.

TABLE 1 Baseline characteristics of patients according to renal function

	CG ≥ 50 mL/min n = 1677 (81.3%)	CG 30-49 mL/min n = 308 (14.9%)	CG < 30 mL/min n = 77 (3.8%)	*P* value (among the three groups)
Age, mean (SD), years	66.8 ± 10.5	78.4 ± 7.2	77.8 ± 8.2	<.001
Age ≥75 years, n (%)	433 (25.8)	230 (74.7)	50 (64.9)	<.001
BMI, mean (SD), kg/m^2	28.2 ± 4.4	25.8 ± 4.0	25.7 ± 4.4	<.001
Male sex, n (%)	1012 (60.3)	105 (34.1)	34 (44.2)	.796
Current smoker, n (%)	253 (15.1)	25 (8.1)	4 (5.2)	<.001
Alcohol abuse[a], n (%)	84 (5.0)	10 (3.2)	1 (1.3)	.147
First-diagnosed AF, n (%)	406 (24.2)	72 (23.4)	22 (28.6)	.634
Paroxysmal AF, n (%)	654 (39.0)	80 (26.0)	31 (40.3)	<.001
Persistent AF, n (%)	252 (15.0)	44 (14.3)	4 (5.2)	.064
Permanent AF, n (%)	616 (36.7)	144 (46.8)	38 (49.4)	.001
EHRA symptom score, mean (SD)	2.1 ± 0.8	2.3 ± 0.8	2.4 ± 0.8	<.001
EHRA I, n (%)	376 (22.4)	53 (17.2)	10 (13.0)	.025
EHRA II, n (%)	800 (47.7)	131 (42.5)	30 (39.0)	.104
EHRA III, n (%)	402 (24.0)	100 (32.5)	30 (39.0)	<.001
EHRA IV, n (%)	99 (5.9)	23 (7.5)	7 (9.1)	.332
Heart rate, mean (SD), beats per minute	90.7 ± 28.2	93.3 ± 29.4	86.6 ± 29.6	.138
SBP, mean (SD), mm Hg	134.5 ± 20.7	136.0 ± 24.9	127.2 ± 27.9	.006
DBP, mean (SD), mm Hg	81.5 ± 11.9	80.5 ± 13.3	75.7 ± 14.2	<.001
Medical history, n (%)				
Hypertension	1298 (77.4)	250 (81.2)	58 (75.3)	.294
Hypertension well controlled[b]	870 (51.9)	161 (52.3)	42 (54.5)	.465
Previous stroke	162 (9.7)	39 (12.7)	14 (18.2)	.022
Previous TIA	50 (3.0)	13 (4.2)	2 (2.6)	.504
CAD	484 (28.9)	107 (34.7)	31 (40.3)	.017
MI	202 (12.0)	53 (17.2)	17 (22.1)	.134
Prior PCI/stenting	154 (9.2)	27 (8.8)	4 (5.2)	.044
Heart failure	594 (35.4)	179 (58.1)	59 (76.6)	<.001
LVEF ≤ 40%	281 (16.8)	81 (26.3)	28 (36.4)	<.001
Diabetes mellitus	396 (23.6)	97 (31.5)	25 (32.5)	.004
Prior bleeding	86 (5.1)	18 (5.8)	4 (5.2)	.869
Aortic valve disease[c]	150 (8.9)	43 (14.0)	12 (15.6)	.006
Mitral valve disease[d]	416 (24.8)	114 (37.0)	29 (37.7)	<.001
DCM	130 (7.8)	22 (7.1)	6 (7.8)	.933
HCM	30 (1.8)	7 (2.3)	8 (10.4)	<.001
RCM	3 (0.2)	1 (0.3)	0 (0.0)	.802
Hyperthyroidism	86 (5.1)	45 (14.6)	7 (9.1)	.060
COPD	216 (12.9)	50 (16.2)	21 (27.3)	.001
PAD	79 (4.7)	13 (4.2)	2 (2.6)	.653
Hypercholesterolemia	704 (42.0)	109 (35.4)	27 (35.1)	.054
Anemia	171 (10.2)	88 (28.6)	28 (36.4)	<.001
Malignancy	64 (3.8)	29 (9.4)	4 (5.2)	<.001
Obesity	415 (24.7)	71 (23.1)	9 (11.7)	.018
Hemoglobin (SD), g/L	137.3 ± 18.4	126.3 ± 19.4	122.0 ± 20.1	<.001

(Continues)

TABLE 1 (Continued)

	CG ≥ 50 mL/min n = 1677 (81.3%)	CG 30-49 mL/min n = 308 (14.9%)	CG < 30 mL/min n = 77 (3.8%)	*P* value (among the three groups)
CHA_2DS_2-VASc, mean (SD)	3.0 ± 1.8	4.7 ± 1.4	4.6 ± 1.7	<.001
CHA_2DS_2-VASc ≥ 2	1371 (81.8)	302 (98.1)	76 (98.7)	<.001
HAS-BLED, mean (SD)	1.8 ± 1.2	2.7 ± 1.2	3.1 ± 1.0	<.001
HAS-BLED ≥ 3	408 (24.3)	171 (55.5)	56 (72.7)	<.001

Abbreviations: AF, atrial fibrillation; beats per minute. CAD, coronary artery disease; BMI, body mass index; bpm; CHA2DS2-VASc: congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category, COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly (age > 65 years), drugs or alcohol concomitantly, HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCM, restrictive cardiomyopathy; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischemic attack.

[a]>4 units of alcohol per day.

[b]Well-controlled hypertension—an average systolic blood pressure <140 mm Hg or an average diastolic blood pressure <90 mm Hg, among patients with hypertension.

[c]Aortic regurgitation or stenosis.

[d]Mitral regurgitation or stenosis.

3.4 | AF management settings

In AF patients with SD-RF and MD-RF, the arrythmia was less often the main reason for hospitalization at enrolling visit than in those with P-RF ($P < .001$); the former were more likely to be hospitalized for HF than those with P-RF ($P < .001$), Table 2. Most patients were managed by a cardiologist in an academic healthcare facility and in hospital-based center, Table 2.

3.5 | Diagnostic assessment

Patients with SD-RF and MD-RF were less likely to have thyroid hormones assessment, transthoracic echocardiography, exercise stress testing, and Holter monitoring at enrolling visit than those with P-RF (all $P < .05$), Table 2.

3.6 | The multivariate predictors of decreasing CrCl according to subgroups based on CG formula at baseline

Decreasing CrCl according to subgroups based on CG formula was significantly associated with HF, anemia, mean CHA2DS2-VASc score, mean HAS-BLED score and the use of loop diuretics on multivariable analysis, (all $P < .001$) Table S1. It was also significantly negatively associated with the use of rhythm control strategy, beta-blockers, and angiotensin-converting enzyme inhibitors (ACE-I) on multivariable analysis (all $P < .001$), Table S1.

3.7 | Stroke prevention strategies

Patients with SD-RF and MD-RF were less likely to receive oral anticoagulant therapy (OAC) alone or in combination with antiplatelet drug(s), and more likely to use no antithrombotic therapy or single-antiplatelet therapy (SAPT) alone than patients with P-RF (all $P < .05$), Table 2.

Patients with SD-RF and MD-RF with HAS-BLED score value of ≥3 were more likely to receive single-antiplatelet therapy (SAPT) alone or no anticoagulation compared to their P-RF counterparts. Of SD-RF patients with a CHA_2DS_2-VASc of ≥2, only 58.4% received OAC, and 41.6% were treated with SAPT alone or received no antithrombotic therapy, Figure 1.

3.8 | Arrhythmia-directed management strategies

Patients with SD-RF and MD-RF were less likely to receive rhythm control strategy, AF catheter ablation, electrical cardioversion (ECV), propafenone, and beta-blockers, and more likely to receive rate control strategy than those with P-RF (all $P < .05$), Table 2.

3.9 | Other therapies

Patients with SD-RF and MD-RF are less likely to be medicated with ACE-I and statins, and more likely to be treated with loop diuretics than patients with P-RF, (all $P < .05$), Table 2. Interestingly, there was no significant difference in AT1 receptor inhibitors use across the groups, Table 2.

3.10 | Patients re-allocated to a different RF category

Using the MDRD formula, seven patients (0.3%) were reclassified to another RF category and, with CKD-EPI formula, a change in RF category occurred in 17 patients (0.8%), Table 3.

TABLE 2 Atrial fibrillation management according to renal function

	CG ≥ 50 mL/min n = 1677 (81.3%)	CG 30-49 mL/min n = 308 (14.9%)	CG < 30 mL/min n = 77 (3.8%)	*P*-value (among the three eGFR groups)
AF management settings, n (%) (at enrolling visit)				
AF was the main reason for the hospitalization	921 (54.9)	121 (39.3)	20 (26.0)	<.001
ACS was the main reason for the hospitalization	124 (7.4)	27 (8.8)	6 (7.8)	.705
Hypertension was the main reason for the hospitalization	36 (2.1)	10 (3.2)	0 (0.0)	.195
HF was the main reason for the hospitalization	331 (19.7)	96 (31.2)	36 (46.8)	<.001
Healthcare facility in capital city	886 (52.8)	156 (50.6)	25 (32.5)	.002
Hospital-based center	1531 (91.3)	276 (89.6)	71 (92.2)	.597
Outpatient visit	146 (8.7)	32 (10.4)	6 (7.8)	.597
Academic healthcare facility	1324 (79.0)	239 (77.6)	59 (76.6)	.715
AF managed by a cardiologist	1371 (81.8)	241 (78.2)	58 (75.3)	.154
Diagnostic assessment, n (%) (at enrolling visit)				
Routine biochemistry	1675 (99.9)	308 (100.0)	76 (98.7)	.574
Thyroid hormones measurement	725 (43.2)	98 (31.8)	18 (23.4)	<.001
Transthoracic echocardiography	1518 (90.5)	274 (89.0)	62 (80.5)	.010
Holter monitoring (rhythm)	539 (32.1)	62 (20.1)	9 (11.7)	<.001
Exercise stress testing	148 (8.8)	7 (2.3)	2 (2.6)	<.001
Stroke prevention (at enrolling visit), n (%)				
No antithrombotic therapy	159 (9.1)	31 (10.1)	15 (19.5)	.016
Overall OAC	1266 (75.5)	205 (66.6)	45 (58.4)	<.001
OAC alone	1060 (63.2)	175 (56.8)	37 (48.1)	.005
VKA	1010 (60.2)	164 (53.2)	41 (53.2)	.041
TTR ≥65%	166 (16.4)	23 (14.0)	0 (0.0)	.823
Acenocoumarol	653 (38.9)	105 (34.1)	20 (26.0)	.025
Warfarin	357 (21.3)	59 (19.2)	21 (27.3)	.290
Phenprocoumon	0 (0.0)	0 (0.0)	0 (0.0)	
NOAC	256 (15.3)	41 (13.3)	4 (5.2)	.039
Dabigatran 150 mg BID	86 (5.1)	0 (0.0)	0 (0.0)	<.001
Dabigatran 110 mg BID	51 (3.0)	18 (5.8)	1 (1.3)	<.001
Rivaroxaban	80 (4.8)	14 (4.5)	3 (3.9)	.929
Apixaban	36 (2.1)	9 (2.9)	0 (0.0)	.285
Single-antiplatelet therapy alone	175 (10.4)	54 (17.5)	14 (18.2)	<.001
Aspirin (alone or with OAC)	421 (25.1)	93 (30.2)	23 (29.9)	.130
Clopidogrel or ticlopidine (alone or with OAC)	164 (9.8)	34 (11.0)	7 (9.1)	.771
Prasugrel or ticagrelor (alone or with OAC)	5 (0.2)	0 (0.0)	0 (0.0)	.563
DAPT alone	76 (4.5)	18 (5.8)	3 (3.9)	.574
Dual antithrombotic therapy	149 (8.9)	23 (7.5)	6 (7.8)	.691
Triple antithrombotic therapy	57 (3.4)	7 (2.3)	2 (2.6)	.559
Symptom management, n (%)				
Rhythm control	645 (38.5)	75 (24.4)	16 (20.8)	<.001
Rate control	935 (55.8)	207 (67.2)	47 (61.0)	<.001

(Continues)

TABLE 2 (Continued)

	CG ≥ 50 mL/min n = 1677 (81.3%)	CG 30-49 mL/min n = 308 (14.9%)	CG < 30 mL/min n = 77 (3.8%)	*P*-value (among the three eGFR groups)
Non-pharmacological AF therapies (at enrolment or in future), n (%)				
AF catheter ablation	57 (3.4)	1 (0.3)	1 (1.3)	.008
ECV	65 (3.9)	4 (1.3)	0 (0.0)	.017
AV node ablation with PM implantation	7 (0.4)	2 (0.6)	0 (0.0)	.724
Pharmacological AF therapies (at enrolment), n (%)				
Digoxin	366 (21.8)	98 (31.8)	13 (16.9)	<.001
Verapamil, diltiazem	89 (5.30)	21 (6.8)	5 (6.5)	.647
Beta blockers	1212 (72.3)	200 (64.9)	46 (59.7)	.003
Propafenone	205 (12.2)	7 (2.3)	0 (0.0)	<.001
Flecainide	1 (0.1)	1 (0.3)	1 (1.3)	.014
Sotalol	15 (0.9)	1 (0.3)	0 (0.0)	.697
Amiodarone	435 (25.9)	73 (23.7)	22 (28.6)	.597
Dronedarone	1 (0.1)	1 (0.3)	0 (0.0)	.375
Dofetilide	0 (0.0)	0 (0.0)	0 (0.0)	
Other therapy, n (%) (at enrolment)				
ACE-I	830 (49.5)	135 (43.8)	25 (32.5)	.004
AT1 receptor blockers	326 (19.4)	59 (19.2)	12 (15.6)	.701
Loop diuretics	622 (37.1)	159 (51.6)	51 (66.2)	.012
Statins	715 (42.6)	117 (38.0)	21 (27.3)	<.001

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AF, atrial fibrillation; AV, atrioventricular, CG, Cockcroft-Gault; DAPT, dual antiplatelet therapy; ECV, electrical cardioversion; eGFR, estimated glomerular filtration rate; HF, heart failure; NOAC, nonvitamin K oral anticoagulants; OAC, oral anticoagulants; PM, pacemaker; TTR, time in therapeutic range; VKA, vitamin K antagonist.

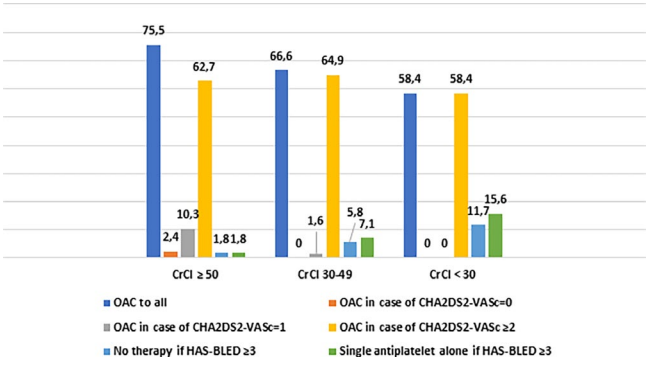

FIGURE 1 Stroke prevention strategies in patients with AF according to CrCl based on CG formula. AF, atrial fibrillation, CHA2DS2-VASc: congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack (TIA), vascular disease, age 65-74 years, sex category, CG, Cockcroft-Gault, CrCl, creatinine clearance, eGFR; estimated glomerular filtration rate, HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly (age >65 years), drugs or alcohol concomitantly, OAC; oral anticoagulants

3.11 | Characteristics of AF patients with HF according to their RF

Patients with SD-RF and MD-RF with HF had higher mean HAS-BLED score than patients with P-RF ($P < .001$). They were more likely to have anemia and to receive no antithrombotic therapy and SAPT alone than patients with P-RF (all $P < .05$). Individuals with SD-RF and MD-RF with HF were less likely to be male, to had prior PCI/ stenting, hypercholesterolemia and to be medicated with OAC overall, OAC alone, beta-blockers, ACE-I and AT1 receptor blockers than patients with P-RF (all $P < .05$), Table S2.

4 | DISCUSSION

This study provides novel insights into clinical practice from the largest published prospective AF registry from the Balkans, a European region that has been under-represented in many prior studies. In our study, 3.8% of enrolled patients had SD-RF, in line with other registries where the prevalence of patients with SD-RF ranged from 2.0% to 3.7%.[11,21,22]

The main findings of our study were as follows: (a) different demographic, cardiovascular risk, and AF-related profile of patients according to RF, (b) differences in the management of AF across the RF categories, including lower use of OAC for stroke prevention in patients with SD-RF and MD-RF than in those with P-RF, whereas the use of rate control strategy, SAPT alone and no antithrombotic therapy was higher in subjects with SD-RF and MD-RF than in those with P-RF, and (c) no profound differences in terms of NOAC dosing or avoidance of prescription with the use of MDRD or CKD-EPI instead of CG formula.

4.1 | Demographic, cardiovascular risk, and AF-related profile

In this study sex distribution among the different subgroups is unexpected. Patients with preserved/mildly depressed renal function (RF) were more likely to be men, while patients with moderately and severely depressed RF were more likely to be women. However, the number of patients with preserved/mildly depressed RF is greater than those with moderately or severely depressed RF, thus the latter can be underpowered. Moreover, patients in the BALKAN-AF dataset are more likely to be men, thus women may be underpowered in the group with preserved/ mildly depressed RF which is the largest group.

Patients with SD-RF and MD-RF were older, similar to other reports[23], and more symptomatic than those with P-RF. The higher mean EHRA symptom score in patients with SD-RF and MD-RF may reflect higher burden of comorbid conditions. In contrast to our study, AF patients with severely compromised RF were more frequently asymptomatic in another study.[22] In our cohort, 23% of patients with MD-RF and 28% of those with SD-RF had first-diagnosed AF. Reportedly, up to 45% of patients with moderate to severe CKD may have newly diagnosed AF.[23]

A pattern similar to our study was also seen in a Chinese cross-sectional survey [3] where patients with low eGFR were older, more likely to have cardiovascular disease (among others, hypertension, and DM) than subjects without indicators of kidney damage.

In our study, patients with SD-RF and MD-RF were more likely to have HF than those with P-RF. This was also seen in other studies.[22,23] Baseline renal impairment and worsening of RF occurred frequently in patients with acute and chronic HF. Moreover, any degree of renal function impairment should be considered as significant risk stratifier in patients with HF.[24]

TABLE 3 Number and proportion of patients allocated to the different classes of renal function, changed according to equations, for renal function assessment, different than CG

Class of renal function according to CG	MDRD, n (%)	CKD-EPI, n (%)
CrCl < 30 mL/min (SD-RF), n = 77 (3.8%)	*84 (100.0)*	*88 (100.0)*
	0 (0.0)	**0 (0.0)**
	0 (0.00	0 (0.0)
CrCl 30-49 mL/min (MD-RF), n = 308 (14.9%)	*7(2.3)*	*11(3.6)*
	301 (97.7)	**291 (94.5)**
	0 (0.0)	*6* (1.9)
CrCl ≥ 50 ml/min (P-RF), n = 1677 (81.3%)	*0 (0.0)*	*0 (0.00*
	0 (0.00)	**0 (0.0)**
	1677 (100.0)	1683 (100.0)

Note: Bold represents MD-RF, italics represents SD-RF.

Abbreviations: CG, Cockcroft-Gault, CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration group, CrCl, creatinine clearance, MDRD, modification of diet in renal disease, MD-RF, moderately depressed renal function, P-RF, preserved/mildly depressed renal function, SD-RF, severely depressed RF.

In our study, the proportion of patients with SD-RF and MD-RF medicated with OAC (66% and 58%, respectively) was lower than in a recent European registry.[22] However, in the Danish nationwide cohort and the Swedish AF Cohort study, the use of VKA among CKD patients was lower than in our study[11,25], with a high prevalence of no antithrombotic therapy or use of antiplatelets only in patients with SD-RF and MD-RF. Despite increased stroke risk in patients with SD-RF, 41.6% of these patients was not anticoagulated in the Balkan region.[26] Importantly, guideline-adherent anticoagulant therapy is associated with significantly better outcomes among AF patients.[27] The inappropriately low use of OAC in patients with SD-RF and MD-RF is a significant knowledge gap in AF management in daily clinical practice in the Balkans. In our study, the quality of anticoagulation was poor with less than a quarter of patients having a Time in Therapeutic Range ≥65%. In one nationwide observational cohort study[28], patients with CKD and CHA_2DS_2-VASc score ≥ 2 had significantly lower risk of all-cause mortality with vs without warfarin treatment for stroke prevention. In the Balkan region, management with NOAC was less prevalent in patients with SD-RF and MD-RF, partly owing to a lack of appropriate NOAC reimbursement policy in some Balkan countries. However, 5% of patients with SD-RF was medicated with NOAC despite contraindications.[6,26] Patients with AF and CKD had increased risk of bleeding.[1,29] However, only one patient received an alternative to OAC (ie, left atrial appendage occlusion).

4.2 | Stroke and bleeding risk and stroke prevention

In our study, patients with SD-RF and MD-RF were older, with more concomitant diseases including HF, hypertension, DM, prior stroke than those with P-RF and therefore were more likely to have higher stroke and bleeding risk. Those findings are consistent with prior datasets.[23]

4.3 | Arrhythmia-directed management strategies

In the BALKAN-AF survey, patients with SD-RF and MD-RF were more likely to receive rate control strategy, whereas patients with P-RF were more likely to undergo a rhythm control strategy. This approach may be related to the perception of greater odds of irreversible substrate

for AF in patients with SD-RF and MD-RF. Similarly, in the European Heart Rhythm Association Survey, rhythm control strategy was not preferred in patients with more advanced CKD, probably due to the lower expected success rate and limited data on safety of antiarrhythmic drugs in those patients.[30] The prevalence of ECV across three subgroups was very low. Despite higher prevalence of permanent AF in patients with SD-RF and MD-RF, there were no significant differences in amiodarone use across three RF categories. Moreover, amiodarone may be overused in the Balkan region, possibly representing another knowledge gap in the real-world management of AF patients in the region.

In our study, patients with SD-RF and MD-RF were less likely to have AF catheter ablation than those with P-RF. However, AF catheter ablation tends to be increasingly used for rhythm control globally, including challenging patients with complex comorbidities.[1] Maintenance of sinus rhythm after AF catheter ablation in patients with SD-RF has been shown to be associated with a significant improvement in RF.[31] However, the risk of vascular complications associated with ablation is elevated in CKD patients in comparison with patients with normal RF.[32]

4.4 | Different equations for estimating RF

In our cohort, no profound differences would appear in terms of NOAC dosing or avoidance of prescription using MDRD and CKD-EPI formula instead of the CG equation. Only <1% of patients using MDRD formula and <1% of those using CKD-EPI formula would be affected by changes in NOAC dosing or avoidance of NOACs. Importantly, the precision of CG formula in estimating RF is questionable, especially among the elderly or those with increased body mass index (BMI).[33] In a comparative study[34], CG formula provided less accurate estimation of GFR than CKD-EPI and MDRD.

However, another study[35] showed that changes in NOAC therapy could appear using GFR formulas rather than CrCl in 16.9% of patients using MDRD formula and in 14.7% of subjects using CKD-EPI. The most important changes in RF assessment were revealed in patients aged ≥75 years, but also BMI had a significant impact.

4.5 | Limitations

This study is limited by its observational design, and follow-up data were not collected. There are no data regarding patient/prescriber treatment preferences. Possible selection bias may appear owing to variable healthcare setting in participating countries. Differences in healthcare systems in different countries could have influenced the availability of specific drugs (eg, NOACs). A status of compliance with guidelines may vary according to countries. However, we have analyzed the totality of data for this study (which focuses on CKD) and country-specific analyses are planned. Information regarding dose adjustment with digoxin and sotalol is not collected. Albuminuria, which is a component for the evaluation of kidney function was not assessed. Moreover, physicians knew that their recommendations on diagnostic assessment and treatment would be recorded. Registries are likely to attract selected highly motivated patients and their treatment at enrolling visit may express higher compliance. However, because of enrolment of consecutive patients, the probability for a physician to recruit mainly patients with higher compliance is limited. Future prospective studies are needed to complement our results.

4.6 | Strengths

Strengths of the study are the Balkan study setting and the prospective study design complementing published trials and registries.

5 | CONCLUSIONS

In the BALKAN-AF survey, patients with SD-RF and MD-RF were older, more symptomatic, had higher stroke and bleeding risk and more comorbidities than those with P-RF. They were less likely to receive OAC, AF catheter ablation or ECV, and more likely to use rate control strategy, SAPT alone and no antithrombotic therapy than subjects with P-RF. There would be no profound differences in terms of NOAC dosing or avoidance of prescription using MDRD and CKD-EPI formula. Our study highlighted important local knowledge gaps in clinical practice that may inform targeted education interventions.

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CONFLICT OF INTEREST

Dr Kozieł, Dr Simovic, Dr Pavlović, Professor Nedeljkovic, Dr Kocijancic, Dr Paparisto, Professor Music, Dr Dan, Assist. Prof. Manola, Professor Kusljugic and Professor Trendafilova declare no conflict of interests for this article. Professor GA Dan has been consultant for Boehringer Ingelheim, Bayer, Pfizer, and Sanofi. Small speaker fees were received. Professor Lip has been a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo. He has been a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. Professor Potpara has been a consultant for Bayer/Jansen and BMS/Pfizer (no fees).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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