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Management of patients with newly-diagnosed atrial fibrillation: Insights from the BALKAN-AF survey

Monika Kozieł [a,b], Stefan Simovic [c], Nikola Pavlovic [d], Milan Nedeljkovic [e,f], Vilma Paparisto [g], Ljilja Music [h], Evgenii Goshev [i], Anca Rodica Dan [j], Sime Manola [d], Zumreta Kusljugic [k], Elina Trendafilova [i], Dobromir Dobrev [l], Gheorghe-Andrei Dan [m], Gregory Y.H. Lip [a,b,f,n,1], Tatjana S. Potpara [e,f,*,1], on behalf of the BALKAN-AF investigators

[a] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom
[b] Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Medical University of Silesia, Silesian Centre for Heart Diseases, Zabrze, Poland
[c] Cardiology Clinic, University Clinical Center of Kragujevac, Kragujevac, Serbia
[d] Clinical Center Sestre Milosrdnice, Zagreb, Croatia
[e] Cardiology Clinic, Clinical Center of Serbia, Belgrade, Serbia
[f] School of Medicine, Belgrade University, Belgrade, Serbia
[g] Clinic of Cardiology, University Hospital Center Mother Theresa, Tirana, Albania
[h] Cardiology Clinic, University Clinical Center of Montenegro, University of Podgorica, Medical Faculty, Podgorica, Montenegro
[i] National Heart Hospital, Coronary Care Unit, Sofia, Bulgaria
[j] Colentina University Hospital, Cardiology Department, Bucharest, Romania
[k] Clinic of Internal Medicine, Cardiology Department, University Clinical Center Tuzla, Medical Faculty, Tuzla, Bosnia and Herzegovina
[l] Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Essen, Germany
[m] Medicine University "Carol Davila", Colentina University Hospital, Bucharest, Romania
[n] Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

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ABSTRACT

Background: BALKAN-AF evaluated patterns of atrial fibrillation (AF) management in real-world clinical practice in the Balkans. The objectives were: to assess the proportion of patients with first-diagnosed AF in the BALKAN-AF cohort and to compare the management of patients with newly-diagnosed AF and those with previously known AF in clinical practice.

Methods: Consecutive patients from 7 Balkan countries were enrolled prospectively to the snapshot BALKAN-AF survey.

Results: Of 2712 enrolled patients, 2677 (98.7%) with complete data were included. 631 (23.6%) patients had newly-diagnosed AF and 2046 (76.4%) patients had known AF. Patients with newly-diagnosed AF were more likely to be hospitalized for AF and to receive single antiplatelet therapy (SAPT) alone and less likely to receive OACs than those with known AF (all $p < 0.001$). The use of OAC was not significantly associated with the CHA_2DS_2-VASc ($p = 0.624$) or HAS-BLED score ($p = 0.225$) on univariate analysis. Treatment in capital city, hypertension, dilated cardiomyopathy, mitral valve disease, country of residence or rate control strategy were independent predictors of OAC use, whilst non-emergency centre, treatment by cardiologist, paroxysmal AF, palpitations, symptoms attributable to AF (as judged by physician), mean heart rate and AF as the main reason for hospitalization were independent predictors of rhythm control strategy use.

Conclusions: In BALKAN-AF survey, patients with newly-diagnosed AF were more often hospitalized, less often received OAC and were more likely to receive SAPT alone. The use of OAC for stroke prevention has not been driven by the individual patient stroke risk.

* Corresponding author at: Cardiology Clinic, Clinical Center of Serbia, Visegradska 26, 11000 Belgrade, Serbia.
E-mail address: tatjana.potpara@med.bg.ac.rs (T.S. Potpara).
[1] Joint senior authors.

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1. Introduction

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia in adults [1]. Owing to its significant association with cardiovascular morbidity and mortality, AF portends significant burden to the patients and healthcare systems worldwide [2,3]. Guideline-adherent management of AF has been associated with improved patients' outcomes [4–6], but contemporary observational registry-based data showed variable proportion of guideline-adherent management of AF in clinical practice in different world regions [7–12].

Patients with newly-diagnosed AF may have different prevailing risk profiles and outcomes in comparison to those with a history of paroxysmal, persistent, long-term persistent or permanent AF [13,14]. In a large international observational registry-based study, for example, the rates of all-cause mortality, stroke/systemic embolism and major bleeding during a 2-year follow-up were the highest within the first 4 months since new-onset AF was diagnosed [15]. This emphasizes the importance of timely initiation of AF treatment and AF comprehensive care early after the diagnosis of AF has been made. Moreover, physicians should be aware of warning signs of possible early cardiovascular mortality [16].

Contemporary large international AF registries included variable proportion of patients with newly-diagnosed AF, but countries in the Balkan region (encompassing approximately 50 million inhabitants) were largely underrepresented in these registries [17]. A prospective survey conducted in seven Balkan countries showed a fairly good overall use of oral anticoagulant therapy (OAC) for AF-related stroke prevention (73.5%), but the use of OAC was poorly related to the individual stroke risk [18].

The aims of this study were as follows: (i) to assess the proportion of patients with first-diagnosed AF in the BALKAN-AF cohort; and (ii) to compare the management of patients with newly-diagnosed AF and those with previously known AF in routine clinical practice in patients with newly-diagnosed AF in seven Balkan countries.

2. Methods

The design of BALKAN-AF survey has been previously published [17]. The BALKAN-AF registry was designed to prospectively collect real-world data regarding consecutive patients with electrocardiographically documented 'non-valvular' AF. Patients were managed by a cardiologist or an internal medicine specialist where cardiologist was not available. Patients were enrolled by university and non-university hospitals and outpatient health centres in Albania, Bosnia & Herzegovina, Bulgaria, Croatia, Montenegro, Romania and Serbia.

This multicentre, observational, snapshot survey was designed and conducted by the Serbian Atrial Fibrillation Association (SAFA). The registry was introduced to the National Cardiology Societies/relevant Working Groups in particular Balkan countries and approved by the National and/or local Institutional Review Board. A signed patient informed consent form was acquired before enrolment. The study protocol corresponds with the ethical guidelines of the 1975 Declaration of Helsinki.

Patients with prosthetic mechanical heart valves, moderate or severe mitral stenosis or any significant valvular disease requiring surgical treatment and those aged <18 years were excluded from the study.

Data were collected using an electronic case report form designed by SAFA. Following information was obtained: patients' and AF-related characteristics, health care setting, patient's physical findings and management at enrolling visit, diagnostic procedures related to AF at enrolling visit and/or in previous 12 months and AF treatment at discharge. Stroke risk was assessed according to 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 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].

Systematic monitoring of centres and follow-up visits were not conducted. National coordinators and participating investigators were responsible for the consecutiveness of enrolled patients and correctness and completeness of entered data.

2.1. Statistical analysis

Categorical variables were presented as absolute frequencies and percentages, and continuous variables as mean and standard deviation (SD). Comparison of categorical variables with normal distribution was performed using Student's *t*-test. Continuous variables with skewed distribution were compared with Mann-Whitney test. The descriptive analysis included baseline characteristic of patients with newly-diagnosed AF and those with previously known AF. The association of patient-, AF- and healthcare system-related variables with the management of patients with newly-diagnosed AF was evaluated using univariate logistic regression analyses. The variables with statistically significant association on univariate logistic regression analysis were entered into multivariable logistic regression models to identify multivariable predictors of AF management. Results are expressed as odds ratio (OR) with 95% confidence interval (CI). A two-sided p value of less than 0.05 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 participating Balkan countries, complete data required for this analysis were available for 2677 patients (98.7%). Of these, 631 patients (23.6%) had first-diagnosed AF and 2046 (76.4%) had a history of AF (Table 1).

3.1. Demographic and AF-related characteristics

Patients with newly-diagnosed AF were younger, more often had paroxysmal AF and more commonly had symptoms attributable to AF (as judged by the responsible physician/investigator), with higher mean European Heart Rhythm Association (EHRA) symptom score (all $p < 0.001$) than patients with history of AF (Table 1).

3.2. Physical findings and comorbidity

Patients with newly-diagnosed AF had significantly higher mean heart rate (103.4 ± 33.4 versus 87.4 ± 25.5 beats per minute [bpm], $p < 0.001$) and less comorbidity (all $p < 0.05$) than those with a known AF (Table 2).

3.3. Stroke and bleeding risk factors

Mean CHA_2DS_2-VASc score was lower in newly-diagnosed AF patients than in the previously known AF group (3.0 ± 1.8 vs 3.4 ± 1.9, $p < 0.001$), and the prevalence of patients with truly low risk of stroke (a CHA_2DS_2-VASc of 0 in males or 1 in females) was higher in the newly-diagnosed AF group ($p = 0.006$).

The risk of bleeding (i.e., mean HAS-BLED score) was lower in patients with first-diagnosed AF in comparison to those with a pre-

Table 1
Demographic and atrial fibrillation-related characteristics.

Variable	All N = 2677	First-diagnosed AF N = 631 (23.6%)	History of AF N = 2046 (76.4%)	P value
Mean age (years)	69.1 ± 10.9	67.5 ± 12.1	69.6 ± 10.5	<0.001
Male sex	1485 (55.5)	348 (55.2)	1137 (55.6)	0.852
Paroxysmal AF	960 (35.9)	403 (63.9)	557 (27.2)	<0.001
Asymptomatic AF	572 (21.4)	64 (10.1)	508 (24.8)	<0.001
Symptoms				
Palpitations	1229 (45.9)	406 (64.3)	823 (40.2)	<0.001
Chest pain	644 (24.1)	205 (32.5)	439 (21.5)	<0.001
Shortness of breath	1278 (47.7)	297 (47.1)	981 (47.9)	0.667
Dizziness	435 (16.2)	103 (16.3)	332 (16.2)	0.970
Syncope	120 (4.5)	42 (6.7)	78 (3.8)	0.003
Fatigue	1074 (40.1)	218 (34.5)	856 (41.8)	0.001
General non-wellbeing	615 (23.0)	158 (25.0)	457 (22.3)	0.166
Fear/anxiety	267 (10.0)	78 (12.4)	189 (9.2)	0.023
Symptoms attributable to AF*	802 (30.0)	311 (49.3)	491 (24.0)	<0.001
EHRA Symptom score (mean)	2.2 ± 0.8	2.4 ± 0.8	2.0 ± 0.8	<0.001
EHRA I	571 (21.3)	64 (10.1)	507 (24.8)	<0.001
EHRA II	1254 (46.8)	294 (46.6)	960 (46.9)	0.852
EHRA III	712 (26.6)	218 (34.5)	494 (24.1)	<0.001
EHRA IV	140 (5.2)	56 (8.9)	84 (4.1)	<0.001

AF: Atrial fibrillation, EHRA: European Heart Rhythm Association.
* As judged by the responsible physician/investigator.

vious history of AF (1.6 ± 1.0 versus 2.1 ± 1.3, p < 0.001), and the proportion of patients with a HAS-BLED ≥ 3 was higher in the latter subgroup (p < 0.001), Table 2.

Country-specific stroke and bleeding risk distribution is presented in Fig. 1.

3.4. AF management settings and diagnostic assessment

Most participants were seen by a cardiologist in an academic healthcare facility (Table 3). However, patients with newly-diagnosed AF were less commonly enrolled during an outpatient visit (n = 101, 16.0% vs n = 616, 30.1%) and AF was more often the main reason for the hospitalization (n = 369, 58.5% vs n = 968, 47.3%) compared with patients with previously known AF (both p < 0.001). There were no significant differences in the diagnostic assessment at enrolling visit between patients with newly-diagnosed versus previously known AF (Table 3).

3.5. Stroke prevention strategies

Overall, OAC was used in 376 (59.6%) of patients with first-diagnosed AF and 1589 (77.7%) of those with previously diagnosed AF (p < 0.001), Table 3. The use of OAC alone was more prevalent among patients with previously diagnosed AF (n = 1348, 65.9% vs n = 293, 46.4%), who were also more often prescribed a vitamin K antagonist (VKA) in comparison to patients with newly-diagnosed AF (n = 1336, 65.3% vs. n = 291, 46.1%), both p < 0.001. Single antiplatelet therapy alone and triple antithrombotic therapy were used more often in first-diagnosed AF patients than in those with a history of AF (p < 0.001, p = 0.012, respectively), Table 3. Of patients with newly-diagnosed AF and CHA_2-DS_2-VASc score ≥2, 46% received OAC only, whereas 38% received stroke prevention other than OAC or had no antithrombotic therapy (Fig. 2).

Country-specific stroke prevention strategies are presented in Table 4.

3.6. Arrhythmia-directed management strategies

Rhythm control strategy was more often used in first-diagnosed AF patients (n = 322, 51.0% versus n = 578, 28.3%), whereas rate control as the main treatment strategy was more commonly used in those with previously known AF (n = 1357, 66.3% versus n = 265, 42.0%), both p < 0.001. Catheter ablation and atrioventricular node ablation with pacemaker implantation were not performed in first-diagnosed AF patients.

Digoxin was used in 107 (17.0%) of patients with newly-diagnosed AF and in 548 (26.8%) of patients with known AF (p < 0.001). Amiodarone was prescribed in 224 (35.5%) of patients with a new diagnosis of AF and in 438 (21.4%) of patients with previously diagnosed AF (p < 0.001) (Table 3). There were no significant differences in use of other agents for rhythm and rate control (Table 3).

3.7. Other therapies

Loop diuretics were used in 199 (31.5%) of newly-diagnosed AF group and in 921 (45.0%) of group with previously-diagnosed AF (p < 0.001) (Table 3). The use of other drugs is shown in Table 3.

3.8. Determinants of OAC use in patients with newly-diagnosed AF

The use of OAC was not significantly associated with the CHA_2-DS_2-VASc (OR 1.02; 95%CI, 0.93–1.11, p = 0.624) or HAS-BLED score (OR 1.10, 95% CI 0.94–1.28, p = 0.225) on univariate analysis (see the Online supplement).

On multivariable analysis adjusted for country of residence, patients treated in the capital city, those with hypertension, dilated cardiomyopathy (DCM) or mitral valve disease and patients assigned to rate control strategy were more likely to receive OAC, whereas treatment in a non-emergency centre, paroxysmal AF and history of previous bleeding event were associated with decreased likelihood of OAC use (Table 5). Of note, OAC use was positively associated with the residence in Romania.

3.9. Predictors of rhythm control strategy in patients with newly-diagnosed AF

Non-emergency centre, treatment by cardiologist, paroxysmal AF, palpitations, symptoms attributable to AF (as judged by the responsible physician/investigator), mean heart rate and AF as the main reason for hospitalization (all p < 0.05) were independent predictors of the increased use of rhythm control strategy in patients with first-diagnosed AF, whereas fatigue, HF, DCM, mitral

Table 2
Physical findings, comorbidities, stroke and bleeding risk factors and baseline stroke and bleeding risk profile.

Variable	All N = 2677	First-diagnosed AF N = 631 (23.6%)	History of AF N = 2046 (76.4%)	P value
SBP (mean, mmHg)	134.6 ± 22.0	135.8 ± 23.2	134.2 ± 21.6	0.107
DBP (mean, mmHg)	81.0 ± 12.2	81.9 ± 12.8	80.7 ± 12.1	0.038
Heart rate (mean, bpm)	91.2 ± 28.4	103.4 ± 33.4	87.4 ± 25.5	<0.001
NYHA class (mean)	1.8 ± 1.0	1.6 ± 0.9	1.8 ± 1.0	<0.001
NYHA I	1569 (58.6)	424 (67.2)	1145 (56.0)	<0.001
NYHA II	378 (14.1)	89 (14.1)	289 (14.1)	0.975
NYHA III	532 (19.9)	97 (15.4)	435 (21.3)	0.001
NYHA IV	198 (7.4)	22 (3.5)	176 (8.6)	<0.001
CHA_2DS_2-VASc risk factors				
HF	1163 (43.4)	173 (27.4)	990 (48.4)	<0.001
CHF or LVEF < 40%	1343 (50.2)	254 (40.3)	1089 (53.2)	<0.001
Hypertension	2121 (79.2)	469 (74.3)	1652 (80.7)	<0.001
Age ≥75 years	947 (35.4)	211 (33.4)	736 (36.0)	0.356
Diabetes mellitus	668 (25.0)	150 (23.8)	518 (25.3)	0.449
Prior stroke/TIA/SE	386 (14.4)	59 (9.4)	327 (16.0)	<0.001
Vascular disease*	568 (21.2)	131 (20.8)	437 (21.4)	0.879
Age 65–74 years	882 (32.9)	181 (28.7)	701 (34.3)	0.017
Female sex	1192 (44.5)	283 (44.8)	909 (44.4)	0.852
CHA_2DS_2-VASc (mean)	3.3 ± 1.9	3.0 ± 1.8	3.4 ± 1.9	<0.001
CHA_2DS_2-VASc 0 (males) or 1 (females)	162 (6.1)	52 (8.2)	110 (5.4)	0.006
CHA_2DS_2-VASc 1	289 (10.8)	83 (13.2)	206 (10.1)	0.021
CHA_2DS_2-VASc ≥ 2	2302 (86.0)	512 (81.1)	1790 (87.5)	<0.001
HAS-BLED risk factors				
Uncontrolled hypertension	683 (25.5)	178 (28.2)	505 (24.7)	0.002
CKD	411 (15.4)	78 (12.4)	333 (16.3)	0.024
Liver disease	96 (3.6)	31 (4.9)	65 (3.2)	0.039
Prior bleeding	133 (6.5)	17 (2.7)	116 (5.7)	0.003
Age ≥65 years	1829 (68.3)	392 (62.1)	1437 (70.2)	<0.001
Aspirin use	688 (25.7)	244 (38.7)	444 (21.7)	<0.001
Excessive alcohol intake	110 (4.1)	38 (6.0)	72 (3.5)	0.004
HAS-BLED (mean)	1.9 ± 1.2	1.6 ± 1.0	2.1 ± 1.3	<0.001
HAS-BLED ≥ 3	823 (30.7)	105 (16.6)	718 (35.1)	<0.001
Other comorbidities				
CAD	821 (30.7)	195 (30.9)	626 (30.6)	0.877
Prior MI	369 (13.8)	88 (13.9)	281 (13.7)	0.967
Prior CABG	100 (3.7)	16 (2.5)	84 (4.1)	0.078
Prior PCI/stenting	225 (8.4)	69 (10.9)	156 (7.6)	0.004
PAD	122 (4.6)	18 (2.9)	104 (5.1)	0.019
Carotid artery disease	56 (2.1)	7 (1.1)	49 (2.4)	0.499
Dilated cardiomyopathy	216 (8.1)	25 (4.0)	191 (9.3)	<0.001
HCM	53 (2.0)	10 (1.6)	43 (2.1)	0.441
Mitral valve disease	845 (31.6)	149 (23.6)	696 (34.0)	<0.001
Aortic valve disease	300 (11.2)	56 (8.9)	244 (11.9)	0.044
CIED	159 (5.9)	16 (2.5)	143 (7.0)	<0.001
COPD	342 (12.8)	74 (11.7)	268 (13.1)	0.368
Obstructive sleep apnoea	53 (2.0)	18 (2.9)	35 (1.7)	0.072
Thyroid dysfunction	276 (10.3)	54 (8.6)	222 (10.9)	0.102
Malignancy	119 (4.4)	19 (3.0)	100 (4.9)	0.047
Dementia	71 (2.7)	20 (3.2)	51 (2.5)	0.353
Dyslipidaemia	1020 (38.1)	236 (37.4)	784 (38.3)	0.673
Anaemia	373 (13.9)	83 (13.2)	290 (14.2)	0.522

SBP: systolic blood pressure; DBP: diastolic blood pressure; bpm: beats per minute, NYHA: New York Heart Association; CAD: coronary artery disease; CKD, chronic kidney disease, MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; PAD: peripheral artery disease; CIED: cardiac implantable electronic device; CHA2DS2-VASc: congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack (TIA), vascular disease, age 65–74 years, sex category, COPD: chronic obstructive pulmonary disease, HF: heart failure, CHF: congestive heart failure; HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly (age >65 years), drugs or alcohol concomitantly, LVEF: left ventricular ejection fraction; TIA: Transient ischemic attack; SE: Systemic embolism; INR: International normalized ratio, HCM, hypertrophic cardiomyopathy.

* Vascular disease was defined as prior MI, complex aortic plaque or peripheral artery disease.

valve disease and mean CHA_2DS_2-VASc score value were negatively associated with the use of rhythm control strategy in patients with first-diagnosed AF (Table 5).

4. Discussion

In the present prospective, multicentre, observational survey of consecutive in- or outpatients with AF, approximately one out of 4 patients had a first-diagnosed AF. The prevalence of first-diagnosed AF in the BALKAN-AF survey was close to that in one 'real-world' European registry [10]. However, the proportion of patients with newly-diagnosed AF ranged from 5.0% to 30.3% in the AF registries [10,20–22]. The present analysis provides novel insights into clinical practice form the largest published prospective AF dataset from the Balkans, a European region that has been underrepresented in many prior clinical trials or registries.

The main findings of our study were as follows: (*i*) different demographic, cardiovascular risk and AF-related profile of patients with first-diagnosed AF in comparison to those with previously known AF (the former were younger, with less comorbidity and

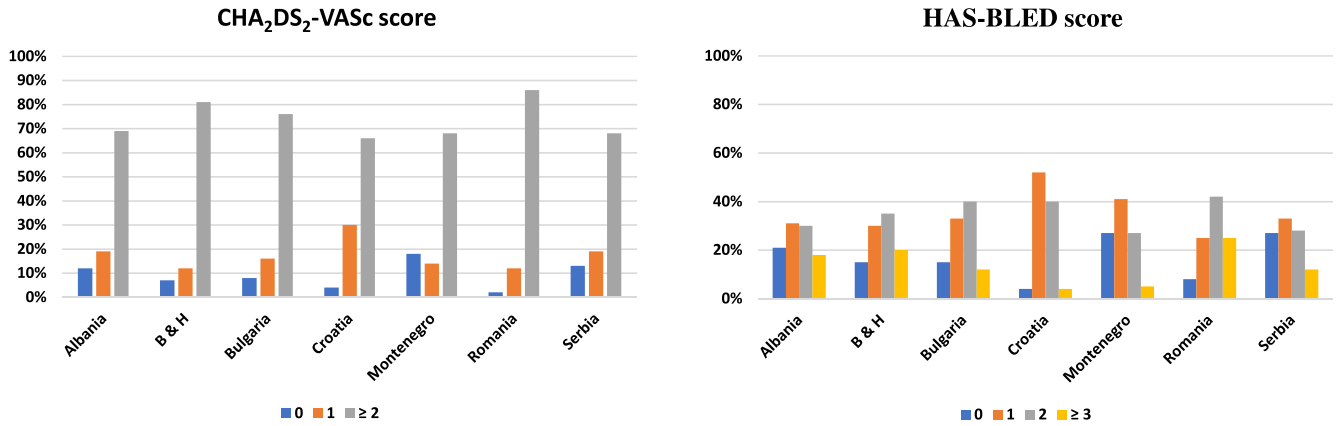

Fig. 1. Stroke and bleeding risk in patients with newly-diagnosed AF. AF, atrial fibrillation, B&H, Bosnia & Herzegovina, CHA2DS2-VASc; congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack (TIA), vascular disease, age 65–74 years, sex category, HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly (age >65 years), drugs or alcohol concomitantly.

lower stroke and bleeding risk, but more symptomatic and more likely to have paroxysmal AF), (*ii*) differences in the management of AF – patients with first-diagnosed AF were more often hospitalized for AF, less often received OAC but were more likely to receive single antiplatelet therapy alone, and more often were treated with a rhythm control strategy, (*iii*) the use of OAC for stroke prevention

Table 3
Atrial fibrillation management.

Variable	All N = 2677	First-diagnosed AF N = 631	Previously diagnosed AF N = 2046	P value
AF management settings				
AF was the main reason for the hospitalization	1337 (49.9)	369 (58.5)	968 (47.3)	<0.001
Outpatient visit	717 (26.8)	101 (16.0)	616 (30.1)	<0.001
Academic healthcare facility	2161 (80.7)	467 (74.0)	1694 (82.8)	<0.001
AF managed by a cardiologist	2147 (80.2)	505 (80.0)	1642 (80.3)	0.602
Diagnostic assessment				
Routine biochemistry	2171 (81.1)	523 (82.9)	1648 (80.5)	0.115
Thyroid hormones measurement	943 (35.2)	235 (37.2)	708 (34.6)	0.212
Transthoracic echocardiography	2147 (80.2)	520 (82.4)	1627 (79.5)	0.088
No additional diagnostic assessment	1479 (55.2)	367 (58.2)	1112 (54.3)	0.086
Holter monitoring (rhythm)	708 (26.4)	157 (24.9)	551 (26.9)	0.314
Stroke prevention (at enrolment)				
No antithrombotic therapy	265 (9.9)	75 (11.9)	190 (9.3)	0.051
Overall OAC	1965 (73.4)	376 (59.6)	1589 (77.7)	<0.001
OAC alone	1641 (61.3)	293 (46.4)	1348 (65.9)	<0.001
VKA	1627 (60.8)	291 (46.1)	1336 (65.3)	<0.001
NOAC	338 (12.6)	85 (13.5)	253 (12.4)	0.437
Single antiplatelet therapy alone	321 (12.0)	120 (19.0)	201 (9.8)	<0.001
DAPT alone	120 (4.5)	56 (8.9)	64 (3.1)	<0.001
Dual antithrombotic therapy	241 (9.0)	54 (8.6)	187 (9.1)	0.682
Triple antithrombotic therapy	83 (3.1)	29 (4.6)	54 (2.6)	0.012
Symptom management				
Rhythm control	900 (33.6)	322 (51.0)	578 (28.3)	<0.001
Rate control	1622 (60.6)	265 (42.0)	1357 (66.3)	<0.001
Non-pharmacological AF therapies (at enrolment or in the future)				
AF catheter ablation	60 (2.2)	0 (0)	60 (2.9)	<0.001
AV node ablation with PM implantation	10 (0.4)	0 (0)	10 (0.5)	<0.001
Pharmacological AF therapies (at enrolment)				
Digoxin	655 (24.5)	107 (17.0)	548 (26.8)	<0.001
Verapamil/Diltiazem	130 (4.9)	23 (3.6)	107 (5.2)	0.452
Beta blockers	1961 (73.3)	449 (71.2)	1512 (73.9)	0.242
Propafenone/Flecainide	250 (9.3)	62 (9.8)	188 (9.2)	0.368
Sotalol	21 (0.8)	3 (0.5)	18 (0.9)	0.319
Amiodarone	662 (24.7)	224 (35.5)	438 (21.4)	<0.001
Other therapy (at enrolment)				
ACEi	1264 (47.2)	282 (44.7)	982 (48.0)	0.179
AT1 receptor blockers	517 (19.3)	103 (16.3)	414 (20.2)	0.034
Loop diuretics	1120 (41.8)	199 (31.5)	921 (45.0)	<0.001
Statins	1108 (41.4)	260 (41.2)	848 (41.4)	0.993

AF: atrial fibrillation; OAC: oral anticoagulant therapy; NOAC: non-vitamin K antagonist oral anticoagulant; ECV: electrical cardioversion; PM: pacemaker; AV: atrioventricular; ACEi: angiotensin converting enzyme inhibitor; AT1: angiotensin receptor, DAPT: dual antiplatelet therapy.

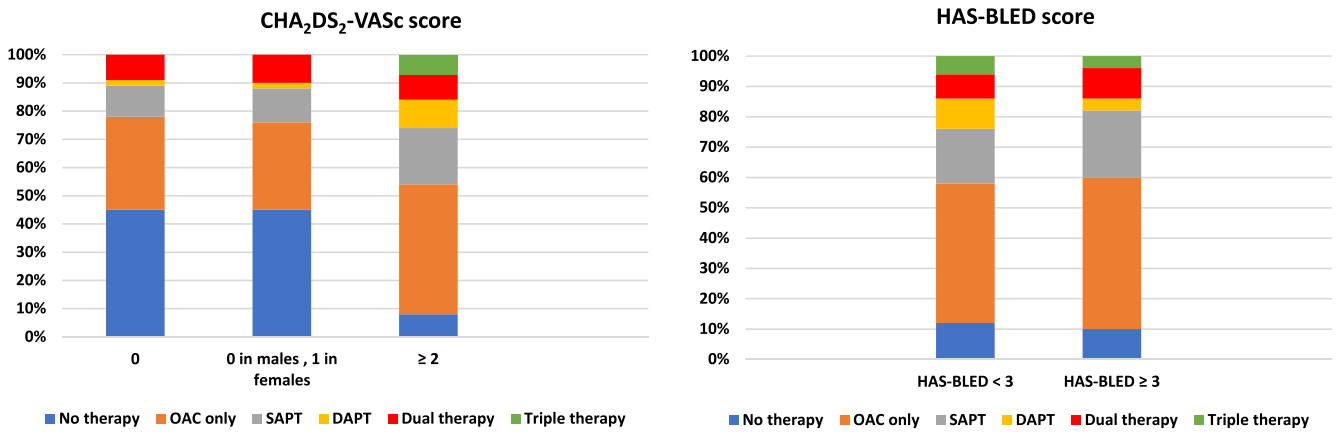

Fig. 2. The prevalence of stroke prevention strategies by CHA_2DS_2-VASc and HAS-BLED risk strata. CHA2DS2-VASc; congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack (TIA), vascular disease, age 65–74 years, sex category, DAPT, dual antiplatelet therapy, HAS-BLED: 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, SAPT, single antiplatelet therapy.

Table 4
Country-specific distribution of stroke prevention strategies in patients with first-diagnosed AF.

	Albania n = 108	Bosnia & Herzegovina n = 92	Bulgaria n = 110	Croatia n = 23	Montenegro n = 22	Romania n = 146	Serbia n = 131
No antithrombotic therapy (%)	6 (5.6)	13 (14.1)	18 (16.4)	3 (13.0)	2 (9.1)	13 (8.9)	20 (15.3)
Overall OAC (%)	66 (61.1)	31 (33.7)	60 (54.5)	15 (6.5)	16 (72.7)	105 (71.9)	83 (63.4)
OAC alone (%)	39 (36.1)	29 (31.5)	52 (47.3)	14 (6.1)	9 (40.9)	88 (60.3)	62 (47.3)
VKAs (%)	57 (52.8)	26 (28.3)	27 (24.5)	14 (6.1)	14 (63.6)	91 (62.3)	62 (47.3)
NOACs (%)	9 (8.3)	5 (5.4)	33 (30.0)	1 (4.3)	2 (9.1)	14 (9.6)	21 (16.0)
SAPT (%)	17 (15.7)	37 (40.2)	24 (21.8)	2 (8.7)	3 (13.6)	15 (10.3)	22 (16.8)
DAPT (%)	18 (16.7)	11 (12.0)	7 (6.4)	1 (4.3)	1 (4.5)	13 (8.9)	5 (3.8)
Dual therapy (%)	17 (15.7)	2 (2.2)	5 (4.5)	1 (4.3)	4 (18.1)	10 (6.8)	15 (11.4)
Triple therapy (%)	10 (9.3)	0 (0.0)	3 (2.7)	0 (0.0)	3 (13.6)	7 (4.8)	6 (4.6)

AF, atrial fibrillation, DAPT, dual antiplatelet therapy, OAC, oral anticoagulants, NOAC, non-vitamin K oral anticoagulants, SAPT, single antiplatelet therapy, VKA, vitamin K antagonists

Table 5
Independent predictors of the use of OAC (alone or in combination) and use of rhythm control strategy in patients with first-diagnosed AF.

	Predictors of use of OAC Multivariate analysis		
	OR	95% CI	p-Value
Capital city	1.96	1.36–2.81	<0.001
Non-emergency centre	0.39	0.24–0.65	<0.001
Paroxysmal AF	0.22	0.15–0.33	<0.001
Hypertension	2.20	1.48–3.26	<0.001
DCM	11.97	1.59–90.17	0.016
Mitral valve disease	1.66	1.09–2.53	0.017
Bleeding events	0.21	0.06–0.70	0.011
Rate control	1.70	1.20–2.40	0.003
Countries:			
Bosnia & Herzegovina	0.39	0.23–0.67	0.001
Romania	1.79	1.15–2.79	0.010
	Predictors of use of rhythm control strategy Multivariate analysis		
	OR	95% CI	p-Value
Non-emergency centre	2.06	1.25–3.37	0.004
AF main reason for hospitalization	2.49	1.77–3.50	<0.001
Treatment by cardiologist	2.11	1.30–3.41	0.002
Paroxysmal AF	3.52	2.35–5.27	<0.001
Palpitations	1.75	1.13–2.71	0.011
Fatigue	0.52	0.39–0.69	<0.001
Symptoms attributable to AF	2.40	1.61–3.58	<0.001
Mean heart rate	1.07	1.02–1.15	<0.001
HF	0.59	0.41–0.87	0.007
DCM	0.32	0.11–0.89	0.031
Mitral valve disease	0.60	0.41–0.89	0.013
Mean CHA_2DS_2-VASc score	0.86	0.78–0.94	0.002

AF; atrial fibrillation, OAC; oral anticoagulants, OR; odds ratio, CI; confidence interval, DCM; dilated cardiomyopathy HF; heart failure, DCM; dilated cardiomyopathy, CHA2DS2-VASc; congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack (TIA), vascular disease, age 65–74 years, sex category.

has not been driven by the individual patient stroke risk (i.e., the CHA_2DS_2-VASc score value), whereas the use of rhythm control strategy has been significantly associated with the presence of AF-related symptoms and (*iv*) healthcare system-related factors (such as centre type and location) significantly influenced the AF-directed and stroke prevention strategies in patients with newly-diagnosed AF.

4.1. Demographic, cardiovascular risk and AF-related profile of patients with first-diagnosed AF

The mean age of patients with first-diagnosed AF in BALKAN-AF registry and in other AF registries was similar [10,21,23]. The proportion of patients with newly-diagnosed AF and hypertension, diabetes mellitus and prior stroke was higher in the Balkan-AF registry than in the EURObservational Research Programme Atrial Fibrillation Pilot Registry (EORP-AF Pilot) [10], whereas patients with first-diagnosed AF and coronary artery disease (CAD) were less prevalent in the BALKAN-AF cohort. The prevalence of CAD, HF and diabetes mellitus in patients with first-diagnosed AF is consistent with datasets from the Euro Heart Survey on Atrial Fibrillation [21], whereas prior stroke was less prevalent in the patients from Euro Heart Survey nearly 15 years ago.

A similar mean CHA_2DS_2-VASc score and mean HAS-BLED score to the patients with first-diagnosed AF from the BALKAN-AF registry was also seen in the EORP-AF Pilot Registry [10] and in the most recent cohort of the FIELD-Atrial Fibrillation (GARFIELD-AF) [24]. The GARFIELD-AF registry recruited patients with newly-diagnosed 'non-valvular' AF and at least one risk factor for stroke.

4.2. Management of patients with first-diagnosed AF

In this study, patients with newly-diagnosed AF were more often hospitalized because of AF, than patients with a history of AF. This was also seen in the Central Registry of the German Competence NETwork in Atrial Fibrillation (AFNET) [20]. Patients with first-detected AF received OAC less often but were more likely to receive single antiplatelet therapy alone than patients with previously diagnosed AF in the Balkan region. A similar pattern was found in the AFNET registry [20]. The prevalence of management with antiplatelet therapy was broadly similar among patients with first-detected AF and patients with paroxysmal and persistent AF in the EORP-AF Pilot Registry [10], whereas the management with OAC was more frequent in persistent and permanent AF than in first-diagnosed AF.

In our study, a rhythm control strategy was more often used in patients with newly-diagnosed AF than in those with previously diagnosed AF. According to guidelines, rhythm control strategy is recommended for symptom improvement of AF patients [19]. Given that, the choice of rhythm control strategy should be based on symptoms of AF, not on its duration. In one study [25], a rhythm control strategy was also more often implemented in hospitalized patients. This may be associated with more symptomatic status of patients with first-diagnosed AF than patients with history of AF.

4.3. The use of OAC for stroke prevention in patients with first-diagnosed AF

In our study about 60% of patients with newly-diagnosed AF received OAC. The management with OAC for stroke prevention in BALKAN-AF did not necessarily reflect the individual patient stroke risk (i.e., the CHA_2DS_2-VASc score value) as indicated in guidelines [26]. This is despite stroke prevention being one of the cornerstones of optimal AF management [27]. Overall, the use of VKA was lower, whilst the use of NOAC was slightly higher than in other 'real-world' European registry [28]. We also observed significant country-specific differences in the use of antithrombotic therapies that may help in identifying regions where stroke prevention strategies need to be improved.

Despite evident indications for antithrombotic therapy, only 46% of patients with newly-diagnosed AF with CHA_2DS_2-VASc score ≥ 2 was medicated with OAC. Moreover, 33% of patients with CHA_2DS_2-VASc score of 0 used OAC, and only a minority of these patients were scheduled for ECV or AF catheter ablation.

In the Balkan region, patients with hypertension, DCM were more likely to receive OAC. Due to increased stroke risk of patients with hypertension and DCM with congestive HF, they should be considered for OAC use [19].

In our study, mitral valve disease was an independent predictor of increased OAC use. Mitral stenosis is associated with the increased risk of thrombo-embolism which may be related to the low-flow in the left atrium [29]. The data regarding the risk of stroke in AF patients with mitral regurgitation are controversial [30], thus OAC should be initiated in AF patients with mitral regurgitation based on stroke risk factors using CHA_2DS_2-VASc score [29].

In this study, history of bleeding was related to decreased OAC use in patients with first-diagnosed AF. However, even high bleeding risk score is not an excuse to withhold OACs where recommended because the net clinical benefit (NCB) is even more evident in this group of patients [31]. Bleeding risk which is a highly dynamic process need to be re-assessed regularly [26,31,32]. Modifiable risk factors should be treated optimally where possible, and bleeding risk scores such as the HAS-BLED score used appropriately to flag up high risk patients for early review and follow-up [33].

4.4. The use of rhythm control strategy in patients with newly-diagnosed AF

In the Balkans, symptoms attributable to AF including palpitations were associated with the increased use of rhythm control strategy in patients with newly-diagnosed AF. Management of AF tends to be more symptom directed and patient centred what is similar to other European registry [28]. Moreover, the implementation of rhythm control strategy is based on patient's symptomatic status [34]. This symptom-oriented approach follows an integrated management of AF according to ABC pathway [35,36]. Interestingly, the use of amiodarone was significantly higher in patients with first-diagnosed AF than in patients with a history of AF despite significantly higher prevalence of congestive heart failure or left ventricle ejection fraction <40% in patients with previously diagnosed AF. Possible reason is that amiodarone might have been overused in the patient with first-diagnosed AF in the Balkan region.

Mitral valve disease was an independent predictor of decreased use of rhythm control strategy. Mitral regurgitation may facilitate the occurrence of AF and make it worse to control with antiarrhythmic agents. However, mitral regurgitation was not correlated with recurrent AF in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study [37].

In our study, HF and DCM were associated with decreased use of rhythm control strategy in the newly-diagnosed AF patients. According to guidelines, rhythm control strategy should be chosen in patients who develop HF with reduced ejection fraction, as a result of tachycardiomyopathy, to make left ventricle function better after restoration of sinus rhythm [19,38,39].

4.5. Healthcare system-related factors

In our study, patients treated in the capital city were more likely to receive OAC, whilst management in a non-emergency cen-

tre was associated with decreased likelihood of OAC use. Non-emergency centre and management by cardiologist were independent predictors of the increased use of rhythm control strategy in patients with newly-diagnosed AF. Higher likelihood of OAC use in capital cities seems to be associated with their high concentration of tertiary health centres. In one study [25], similar influence of centre location on antithrombotic therapy was showed.

4.6. Knowledge gaps and unmet needs in the BALKAN region

Results of this survey may help to identify knowledge gaps in AF management in daily clinical practice in the Balkans. Our findings show that overall use of OAC is low (approx. 60%) in patients with first-diagnosed AF in the Balkans. The overall use of OAC in patients with newly-diagnosed AF was higher in EORP-AF Pilot Registry [10], whereas was less prevalent in the older registries: Euro Heart Survey and AFNET [20,21]. In our study, the association of OAC use with individual stroke risk is weak. Unfortunately, despite high proportion of patients with newly-diagnosed AF with increased risk of stroke, 11.9% of patients receive no antithrombotic therapy and 19.0% receive single antiplatelet therapy alone. These findings implicate that the management of patients with AF at risk of stroke is not adherent to guidelines [19].

In this study, paroxysmal AF was negatively associated with OAC use. Importantly, ischaemic stroke may occur as commonly in paroxysmal AF as in permanent AF [40]. However, in one study, yearly rates of ischaemic strokes were 2.1% for paroxysmal AF and 4.2% for permanent AF [41]. Indeed, patients with paroxysmal AF and conventional stroke risk factors have indications to OAC [19]. Consequently, the pattern of AF should not affect the management with OAC. The use of antithrombotic therapy was also associated with the health center location and was increased in capital cities. Differences were observed in the management with rhythm control strategy according to physician specialty because cardiologists used rhythm control more often than other specialists.

Holistic treatment of patients with first-diagnosed AF should help to solve unmet clinical needs including underuse of OAC, the suboptimal association of OAC with individual stroke risk and limited access to rhythm control strategy. Moreover, integrated AF care requires services accessible for all patients and cooperation between various medical specialists [19].

4.7. Limitations

Our study has a few limitations including the observational study design and lack of follow-up data to assess outcomes. Possible selection bias may occur because of different healthcare setting in participating countries. Moreover, information about patient/prescriber treatment preferences is lacking. Also, data from the survey are limited to the Balkan population, but this is the largest AF dataset from this region. Moreover, physicians were aware that their recommendations on diagnostic assessment and management would be recorded. Registries are likely to attract selected highly motivated patients and their treatment at enrolment may express higher compliance. However, because of enrolment of consecutive patients, the likelihood for a physician to enroll mainly patients with higher compliance is limited.

5. Conclusions

In BALKAN-AF survey, patients with newly-diagnosed AF were more often hospitalized, less often received OAC and were more likely to receive SAPT alone. The use of OAC for stroke prevention has not been driven by the individual patient stroke risk.

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Appendix A. Supplementary material

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