ORIGINAL ARTICLE

District versus academic hospitals: differences in the clinical characteristics of patients with atrial fibrillation without valvular heart disease treated with oral anticoagulants

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KEY WORDS

anticoagulation therapy, arrhythmia, clinical characteristics, hemorrhagic events, thromboembolic events

ABSTRACT

INTRODUCTION Atrial fibrillation (AF) is the most common cardiac arrhythmia with a significant risk of morbidity and mortality. Non–vitamin K antagonist oral anticoagulants are the first-line drugs in stroke prevention in patients with AF. Oral anticoagulant (OAC) therapy may differ between medical centers.

OBJECTIVES We compared the clinical characteristics of AF patients treated with OAC in a district and an academic hospital.

PATIENTS AND METHODS We analyzed 3528 patients from the multicenter retrospective CRAFT study: 2666 patients from the academic hospital and 862 patients from the district hospital. Their baseline clinical characteristics were compared.

RESULTS Patients treated in the district hospital were older (mean [SD] age, 73.9 [10.3] years vs 66.0 [13.4] years; P <0.001) and more likely female (49.1% vs 37.4%; P <0.001). Patients treated in the academic hospital more frequently had paroxysmal AF, while those in the district hospital, permanent AF. The latter group was also more likely to have comorbidities and a higher frequency of previous bleeding episodes or anemia. The groups did not differ regarding kidney function. In both groups, patients were significantly more likely to be on rivaroxaban than on dabigatran. The group treated in the district hospital were at higher risk of thromboembolic events than the other gruop (mean [SD] CHA_2DS_2VASc score, 4.6 [1.7] vs 3.05 [2.0]; P <0.001), as well as of hemorrhagic events (mean [SD] HASBLED score, 0.6 [0.7] vs 0.4 [0.6]; P <0.001).

CONCLUSIONS Patients with AF treated with OACs in the district and academic hospitals have different clinical characteristics. Patients treated in the district hospital were older, had more comorbidities, more frequently had permanent AF, and were at higher risk of thromboembolic and bleeding events than patients treated in the academic hospital.

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INTRODUCTION Atrial fibrillation (AF) is the most frequent cardiac arrhythmia observed in clinical practice. It is associated with an up to 5-fold increase in the risk of stroke.[1-3] According to all current guidelines, the prevention of stroke and systemic embolism is the most important therapeutic goal in AF.

Until 2010, the only oral anticoagulants (OACs) available were vitamin K antagonists (VKAs), which reduced the incidence of ischemic stroke by approximately 64% but were associated with a significant risk of bleeding and required frequent monitoring of international normalized

ratio. Thus, up to 50% of AF patients did not receive VKAs to prevent ischemic stroke.[4,5]

The introduction of non–vitamin K antagonist oral anticoagulants (NOACs) has revolutionized stroke prevention in patients with AF because they showed similar efficacy to VKAs, yet with a safer profile, a fixed dose, and no need for frequent laboratory monitoring.[6]

The current European Society of Cardiology (ESC) guidelines recommend anticoagulant treatment in AF patients without valvular heart disease (VHD) and a CHA_2DS_2VASc score of 2 or higher for men and 3 or higher for women.[7] In these patients, treatment with NOACs should be preferred over VKAs.

The management of AF in a clinical trial setting may not necessarily translate to routine practice because of the differences in patient populations as well as care that they receive. According to data from the EORP-AF Pilot study,[8] adherence to ESC guidelines on anticoagulation therapy in patients with AF remains suboptimal in Poland and other European Union countries.

Extrapolating findings from trials to general practice is especially challenging in the case of anticoagulation therapy due to specific exclusion criteria such as renal dysfunction (ie, estimated creatinine clearance of <30 ml/min/1.73 m^2), anemia, thrombocytopenia, conditions at increased risk of bleeding, and life expectancy shorter than the duration of the trial. This emphasizes the need for "real-world" registries evaluating treatments for stroke prevention in a relatively unselected group of patients with AF.

New guidelines on the management of AF were published in 2016 by the ESC,[7] but adherence to the guidelines among clinicians remains unclear. To investigate this issue, we conducted the CRAFT study and compared the clinical characteristics of patients with AF without VHD, who received antithrombotic therapy during hospitalization and discharge from 2 Polish hospitals participating in the CRAFT study: an academic one and a district one.

PATIENTS AND METHODS

Study design This cohort study included the Polish data from the multicenter CRAFT study (MultiCenter expeRience in AFib patients Treated with OAC). The study was registered in ClinicalTrials.gov: NCT02987062. This was a retrospective analysis of hospital records of AF patients without VHD treated with VKAs (acenocoumarol, warfarin) and NOACs (dabigatran, rivaroxaban). Because of the very small number of patients treated with apixaban in the compared centers (5 in the academic vs 24 in the district hospital), they were not included in the analysis. The study was approved by a local ethics committee.

The study included patients of all ages with AF diagnosis hospitalized in the years 2011 to 2016 in 2 centers: an academic one located in an academic city and a district hospital. Patients who did not receive OAC at hospital discharge or had a diagnosis of AF with VHD were excluded from the study. We also excluded AF patients with concomitant conditions that required antithrombotic therapy (prosthetic valve, pulmonary embolism, systemic embolism). Baseline characteristics of patients were collected, including demographic data, medical history, type of AF (paroxysmal, persistent, or permanent), diagnostic test results, and pharmacotherapy.

Study population and group selection The CRAFT study included 3528 patients with nonvalvular AF. All patients received OACs during hospitalization and on discharge. The total cohort consisted of 1973 patients on VKAs, 504 patients on dabigatran, and 1051 patients on rivaroxaban.

Comparative analysis of patients treated with oral anticoagulation We assessed the frequency of use of different types of OACs in recent years, as well as baseline characteristics of patients treated with each type of OACs. Each patient was evaluated using the standard scores for the assessment of thromboembolic risk ($CHADS_2$ and CHA_2DS_2-VASc) and bleeding risk (HAS-BLED); moreover, modifiable and nonmodifiable risk factors for bleeding in anticoagulated patients were assessed based on the current guidelines for AF treatment.

Statistical analysis Continuous variables with normal distribution were presented as means with SD. Ordinal variables and continuous variables with nonnormally distribution were presented as median values and interquartile ranges. Categorical data were presented as a number and percentage of patients. The Fisher exact test and the Mann–Whitney test were used for categorical variables and continuous variables, respectively. A P value of less than 0.05 was considered significant. All tests were 2-tailed. Statistical analyses were performed using the SPSS software, version 22 (IBM SPSS Statistics 22, New York, New York, United States).

RESULTS

Of the 3528 patients enrolled in the CRAFT study, 2666 (75.5%) were recruited in the academic hospital and 862 (24.5%), in the district hospital. Patients treated at the district hospital were older than those in the academic hospital (mean [SD] age, 73.9 [10.3] years vs 66.0 [13.4] years, respectively, P <0.001), had a higher $CHADS_2$ score (mean [SD], 2.6 (1.3) vs 1.8 (1.3), respectively, P <0.001), higher CHA_2DS_2VASc score (mean [SD], 4.6 [1.7] vs 3.05 [2.0], respectively P <0.001), and higher HAS-BLED score, and had more comorbidities. The proportion of men to women was almost 3:1 in the academic hospital and about 1:1 in the district hospital.

The study groups differed significantly in the type of AF: paroxysmal AF was observed in 58.2% and 42.0% of the patients in the academic and district hospitals, respectively; persistent AF, in 18.6% and 15.3%; and permanent AF, in 23.3% and 43.0%.

TABLE 1 Comparison of baseline clinical characteristics between patients treated in the academic and district hospitals

Parameter		2011–2016			2014–2016	
		Academic hospital (n = 2666)	District hospital (n = 862)	*P* value	Academic hospital (n = 1566)	*P* value
Age, y, mean (SD)		66.0 (13.4)	73.9 (10.3)	<0.0001	68.3 (12.9)	<0.0001
Female sex, n (%)		998 (37.4)	423 (49.1)	<0.0001	599 (38.3)	<0.0001
Paroxysmal AF, n (%)		1463/2515 (58.2)	362 (42.0)	<0.0001	802/1458 (55.0)	<0.0001
Persistent AF, n (%)		468/2515 (18.6)	129 (15.3)	0.02	244/1459 (16.7)	0.29
Permanent AF, n (%)		585/2515 (23.3)	371 (43.0)	<0.0001	414/1459 (28.4)	<0.0001
VKAs, n (%)		1632 (61.1)	341 (39.6)	<0.0001	760 (48.5)	<0.0001
Rivaroxaban, n (%)		676 (25.3)	375 (43.5)	<0.0001	532 (34.0)	<0.0001
Rivaroxaban, mg, median (IQR)		20 (15–20) (n = 669)	15 (15–20) (n = 375)	<0.0001	20 (15–20) (n = 527)	<0.0001
Dabigatran, n (%)		358 (13.4)	146 (16.9)	0.01	274 (17.5)	0.74
Dabigatran, mg, median (IQR)		110 (110–150) (n = 352)	110 (110–150) (n = 146)	<0.0001	150 (110–150) (n = 269)	<0.0001
$CHADS_2$, mean (SD)		1.8 (1.3) (n = 2659)	2.6 (1.3) (n = 847)	<0.0001	1.96 (1.33)	<0.0001
CHA_2DS_2VASc, mean (SD)		3.05 (2.0) (n = 2659)	4.6 (1.7) (n = 847)	<0.0001	3.31 (1.9)	<0.0001
HAS-BLED, mean (SD)		0.4 (0.6)	0.6 (0.7)	<0.0001	0.42 (0.66)	<0.0001
Major bleeding or anemia, n (%)		73 (2.8)	213/860 (24.8)	<0.0001	52/1565 (3.3)	<0.0001
NSAIDs or antiplatelets, n (%)		369, (13.8)	120, (13.9)	0.96	217 (13.9)	1.00
Abnormal liver function, n (%)		93/2664 (3.5%)	31/627 (4.9%)	0.10	67/1565 (4.3)	0.49
Frequent current alcohol use, n (%)		7/2666 (0.3)	30/853 (3.5)	<0.0001	5 (0.3)	<0.0001
GFR, ml/min/1.73 m^2, n (%)	≥50	1336/1813 (73.6)	637/860 (74.1)	0.81	998/1373 (72.7)	0.49
	30–49	421/1811 (23.3)	189/857 (22.1)	0.52	331/1371 (24.1)	0.28
	15–29	51/1811 (2.9)	37/857 (4.3)	0.06	40/1371 (2.9)	0.1
	≤14	5/1811 (0.3)	1 (0.1)	0.67	4/1371 (0.3)	0.66
Previous stroke or TIA, n (%)		303/2663 (11.4)	147/854 (17.2)	<0.0001	192 (12.3)	0.002
Previous MI or PAD, n (%)		996/2663 (37.4)	551/854 (64.5)	<0.0001	667 (42.7)	<0.0001
Heart failure, n (%)		786/2663 (29.5)	525/854 (61.6)	<0.0001	574/1562 (36.7)	<0.0001
Diabetes, n (%)		611/2659 (23.0)	317/847 (37.4)	<0.0001	410/1562 (26.2)	<0.0001
Hypertension, n (%)		1876/2663 (70.4)	635/854 (74.4)	0.02	1123/1562 (71.9)	0.23
COPD, n (%)		174/2668 (6.5)	151/858 (17.6)	<0.0001	127/1565 (8.1)	<0.0001
Antiplatelets, n (%)		362 (13.6)	120 (13.9)	0.82	213 (13.6)	0.85
Antiarrhythmics, n (%)		456/2663 (17.1)	143/860 (16.6)	0.75	246 (15.7)	0.56

Abbreviations: AF, atrial fibrillation; CHA_2DS_2VASc, congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 years, diabetes, thromboembolism or stroke history, vascular disease, age 65–74 years, female sex; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HAS-BLED, hypertension, renal or liver failure, stroke history, bleeding history, labile international normalized ratio, age >65 years, drugs or alcohol; IQR, interquartile range; MI, myocardial infarction; NOAC, non–vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; PAD, peripheral artery disease; TIA, transient ischemic attack; VKA, vitamin K antagonist

In the academic hospital, only 50.2% of patients had 2 or more risk factors for stroke based on the $CHADS_2$ score, as compared with 80.2% of the population in the district hospital. As regards the CHA_2DS_2VASc score, patients with 2 points or higher constituted 73.1% of the study population in the academic hospital compared with 95.5% in the district hospital. Patients in the district hospital had a 8-fold higher frequency of anemia compared with those in the academic hospital.

The analyzed population did not differ significantly in the frequency of antiplatelet and antiarrhythmic drug use. There were also no differences between the groups in terms of renal function, as assessed by glomerular filtration rate calculated by the Modification of Diet in Renal Disease formula. In the academic hospital, a decrease in the rate of VKA prescription in favor of dabigatran and rivaroxaban was observed in the years 2014 to 2016, which was consistent with the differences observed for the district hospital. Considerable differences were also observed in the mean NOAC doses, with higher doses used in the academic than in the district hospital. The characteristics of patients treated in the district and academic hospitals, including detailed data on treatment, are compared in **TABLE 1**.

In the academic hospital, 36.2% of patients had previous pulmonary vein isolation (PVI). Among the PVI group, 68.3% of patients were treated with VKAs, while in the non–PVI group, 60.0%. The data are lacking for the district hospital.

DISCUSSION The CRAFT study results provide important data on the actual clinical practice of

AF treatment among patients treated in Polish secondary and tertiary hospitals. Moreover, this is one of the few direct comparisons in available literature and likely the first of this type in Poland, showing epidemiology, clinical characteristics, and management of patients with AF in 2 different health care settings: an academic hospital and a district hospital.

Most registries collect data mainly from large academic centers or highly specialized hospitals with poor representation of community and district hospitals. Based on the results of the RAMSES study,[9] it can be assumed that the differences in the clinical characteristics of patients between academic and district hospitals are common regardless of the country.

In general, observations from large international registries have shown that patients treated at secondary hospitals are older, have a higher $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED scores and have more comorbidities than patients treated in tertiary hospitals, which is in line with our results.

Our AF population hospitalized in the district hospital was older than that in the academic hospital. Also, the proportion of patients aged over 80 years was much greater in the district hospital than in the academic one (33.2% vs 16.0%, respectively). The mean age of patients treated in the district hospital in our study is comparable with the mean age of patients enrolled in surveys conducted over a similar period, after 2010: KIELCE registry (71.3 years),[10] PREFER in AF (71.5 years),[11] GARFIELD cohorts 1–4 (69.7 years),[12] GLORIA-AF (71.0 years),[13] EORP-AF (69.0 years),[14] and the Fushimi AF Registry (74.0 years).[15]

In our study, various comorbidities such as heart failure, diabetes, hypertension, history of stroke or transient ischemic attack, coronary artery disease or prior myocardial infarction were more prevalent in the district hospital than in the academic hospital. As a result, the $CHADS_2$ score was substantially higher in the district-hospital group. In the academic hospital, the proportion of patients with a $CHADS_2$ score of 0 to 1 (low-to-intermediate risk) was almost 50%. However, in the district hospital, the proportion of patients with a $CHADS_2$ score of 0 to 1 was only 19.8%, and the $CHADS_2$ score of 3 to 6 was the most common.

The mean $CHADS_2$ score of 1.8 in the academic hospital was comparable with the data from the other registries: 1.92 in EORP AF,[14] 1.93 in PREFER-AF,[11] 2.0 GLORIA AF -2,[13] 2.09 in FUSHIMI AF,[15] and 1.8 in SAKURA AF.[16]

Similarly to $CHADS_2$ score, the CHA_2DS_2VASc score of 4.6 in the district hospital was significantly higher than in the academic hospital (3.05) and in the other registries based on data from highly specialized referral hospitals (KIELCE registry, 3.9[10]; PREFER in AF, 3.37[11]; GARFIELD, 3.2[12]; GLORIA-AF, 3.0[13]; and EORP-AF, 3.24[14]), as well as data derived mostly from community hospitals (Fushimi AF Registry, 3.4[15]; SAKURA AF Registry, 2.74[16]).

Comparison of the baseline characteristics of patients from the CRAFT study with the other registries is presented in Supplementary material, *Table S1*. Clinical characteristics of patients from the academic hospital were comparable to data from large registries, while there was a large difference in comparison with the district hospital in terms of comorbidities and the risk of cardiovascular events. Those results probably reflect the underrepresentation and underestimation of district and community hospitals in the current international registries.

Although the use of VKAs is associated with challenges, such as narrow therapeutic range, drug and food interactions, the need for monitoring, and bleeding risk,[17] they were used significantly more often in the academic center than in the district one. Based on our previous results, the VKA prescription rate has significantly declined since the introduction of NOACs.[18] Comparison of data from both centers for the same period (2014–2016) shows that the use of VKAs was still significantly higher than in the district hospital. Until recently, there have been no controlled data on the safety of uninterrupted periprocedural NOAC treatment, which therefore favored treatment with VKAs. However, the RE-CIRCUIT study[19] published in 2017 (after the CRAFT study was conducted) confirmed safety of the uninterrupted dabigatran treatment in patients undergoing PVI. Moreover, a study by Gawałko et al,[20] which included consecutive patients with AF in an academic hospital who underwent transesophageal echocardiography before either AF ablation or cardioversion, showed no difference in terms of the frequency of left atrial appendage thrombus between VKA and NOAC therapy. This was mainly due to a different profile of patients at higher risk of stroke, as well as at higher risk of bleeding complications in patients of the district hospital when compared with the academic hospital. In this case, all guidelines recommend that NOACs should be considered instead of VKAs, given at least noninferior efficacy, better safety, and convenience compared with VKAs.[21] Such a practice in accordance with the guidelines was also demonstrated in our study (**FIGURE 1**).

Furthermore, patients from the academic hospital at low risk (CHA_2DS_2VASc score, 0–1) were approximately 6 times more likely to be treated with OACs (VKAs and NOACs) than patients at the same risk in the district hospital.

To explain this observation, it should be noted that patients from the academic hospital more frequently had undergone PVI and electrical cardioversion than patients from the district hospital. For organizational reasons, most elective cardioversions in the district hospital are performed in the emergency department and, simultaneously, no AF ablations are performed, which can explain

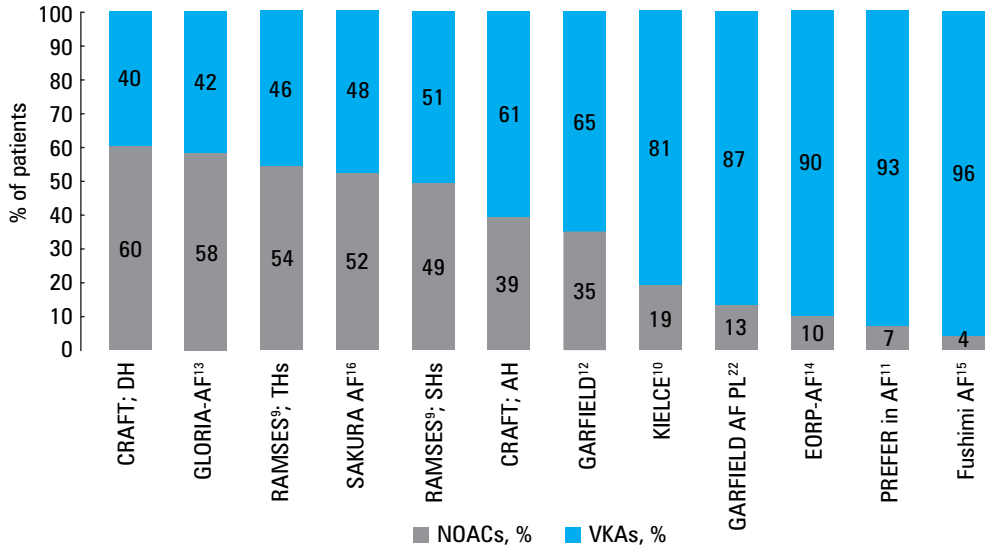

FIGURE 1 Percentage of patients treated with non–vitamin K antagonist oral anticoagulants (NOACs) and vitamin K antagonists (VKAs) in different registries
Abbreviations: AH, academic hospital; DH, district hospital; SH, secondary hospital; TH, tertiary hospital

the different distribution of AF types and stroke risk in both centers.

From a medical point of view, risk of stroke is considered more severe and dangerous than major bleeding. Despite this, patients in the CRAFT study with previous stroke or transient ischemic attack were treated twice more often with reduced doses of NOACs than with standard doses.

As presented in the previous publication from the CRAFT study, patients treated with lower doses of NOACs were older and had significantly higher thromboembolic and bleeding risk.[17] This suggests that the main reason for the choice of anticoagulation treatment in clinical practice is the safety of patients, rather than efficacy, due to a greater fear of bleeding than of stroke occurrence.

This retrospective study has several limitations. Firstly, it was not a nationwide registry with a truly representative cohort of AF patients on OACs or NOACs. Secondly, only inpatients were included in the registry. Moreover, our registry is limited by the fact that it depends on the data obtained from cardiology departments only. However, in many health care systems, AF patients are often under noncardiologist care. Furthermore, because of the large number of missing data in both centers, a precise assessment of the HAS-BLED score was not possible. Finally, due to the small number of patients on apixaban, it was not included into the analysis.

In conclusion, our data indicate that patient characteristics and the type of health care facility are important determinants of stroke prevention strategies in AF patients. Considering the fact that the vast majority of patients with AF are admitted to district hospitals, it is reasonable to include these data in analyses to provide the true picture of adherence to guidelines among cardiologists in Poland. This paper shows that patients with AF hospitalized in the district hospital are significantly different in terms of demographic factors, comorbidities, and anticoagulant treatment used for stroke prevention. A particularly important finding is that patients in the district hospital are older and more often affected by comorbidities, and as such they have a higher risk of both thromboembolic and bleeding complications.

Further research is needed to investigate the differences in the clinical profile of patients, their thromboembolic risk, and methods of treatment between academic hospitals participating in global registries (and also involved in guideline development) and district hospitals where these guidelines are implemented in real-life clinical practice, in a significantly different population of patients.

SUPPLEMENTARY MATERIAL Supplementary material is available with the article at www.pamw.pl.

CONTRIBUTION STATEMENT BP, BJ, TA, OK, and OG conceived the concept of the study. BP, OK, TA, and OG contributed to the design of the research. All authors were involved in data collection. PM analyzed the data. All authors edited and approved the final version of the manuscript. JB and PB contributed equally.

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