ORIGINAL ARTICLE

District versus academic hospitals: clinical outcomes of patients with atrial fibrillation

The Multicenter Experience in Atrial Fibrillation Patients Treated with Oral Anticoagulants (CRAFT) study

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KEY WORDS

anticoagulation, arrhythmia, atrial fibrillation, healthcare system

ABSTRACT

INTRODUCTION Atrial fibrillation (AF) is associated with increased hospitalization.

OBJECTIVES We aimed to compare long-term outcomes in patients with AF hospitalized in academic and district hospitals.

PATIENTS AND METHODS This retrospective observational study included data from the Multicenter Experience in Atrial Fibrillation Patients Treated with Oral Anticoagulants (CRAFT; NCT02987062) study which included AF patients hospitalized between 2011 and 2016 in academic and district hospitals. The primary end point was a major adverse event (MAE) defined as all-cause death and thromboembolic and hemorrhagic events during the median 4-year follow-up.

RESULTS We analyzed 2983 patients with AF: 2271 (76%) from academic and 712 (24%) from district hospitals. Patients treated in district hospitals, as compared with patients treated in academic hospitals, more often experienced MAEs (53% vs 37%; P <0.001), all-cause death (40% vs 24%; P <0.001), and thromboembolic events (13% vs 7.8%; P <0.001), with similar rates of hemorrhagic events (15% vs 15%; P = 1.00). In multivariable logistic regression, female sex, coronary artery disease, smoking, and antiplatelet drug therapy were associated with greater likelihood of thromboembolic events in academic hospitals. Heart failure, renal failure, and vitamin K antagonist (in academic hospitals), and coronary artery disease (in district hospitals) were associated with greater likelihood of hemorrhagic events. District (vs academic) conditions were associated with higher risk of MAEs and all-cause death in men and those with low risk of bleeding, and with higher incidence of thromboembolic events in women, elderly patients, and those with high risk of bleeding and with diabetes.

CONCLUSIONS Patients with AF treated at district hospitals had worse long-term outcomes than those treated in academic conditions.

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INTRODUCTION Contemporary studies show that 20% to 30% of patients with ischemic stroke have undiagnosed atrial fibrillation (AF) and AF independently increases risk of all-cause mortality.[1,2] Mortality due to ischemic stroke can largely be mitigated by anticoagulation, while other types of cardiovascular death, for example due to heart failure, remain common even in patients with AF treated according to the current guidelines.[3] Not surprisingly, given increased morbidity in patients

WHAT'S NEW?

During the median follow-up of 4 years, patients treated at district hospitals more often experienced major adverse events including all-cause death and thromboembolic events without difference in hemorrhagic events as compared with those referred to academic hospitals. District (as compared with academic) conditions were associated with higher risk of major adverse events and all-cause death in men and those with low risk of bleeding, and with higher incidence of thromboembolic events in women, elderly patients, and those with high risk of bleeding and with diabetes.

with AF, between 10% to 40% of patients with AF are hospitalized each year.[4] The management of AF in routine practice differs significantly from the clinical trial setting due to differences in patient baseline characteristics as well as in care those patients receive. To investigate this issue, we aimed to compare long-term outcomes in patients with AF treated in both academic and district hospitals.

METHODS **Study population** This retrospective observational cohort study included data from the Multicenter Experience in Atrial Fibrillation Patients Treated with Oral Anticoagulation (CRAFT) study (ClinicalTrials.gov identifier, NCT02987062). Details about the study design and main results were reported elsewhere.[5] Briefly, the CRAFT study included patients aged 18 or older, with electrocardiogram-based diagnosis of AF, hospitalized between 2011 and 2016 at academic and district hospitals. Due to the retrospective nature of the study, the need for approval of a local ethics committee was waived. All patients provided written informed consent.

Primary and secondary end points The primary end point was assigned as a major adverse event (MAE) defined as all-cause death and thromboembolic and hemorrhagic events during the median follow-up of 4 years. The end of follow-up was set at January 16, 2019. The secondary end points were defined as components of the primary end point. Thromboembolic events included ischemic stroke (different locations), transient ischemic attack, and peripheral thromboembolism (different locations). Hemorrhagic events included gastrointestinal, intracranial, and other types of bleeding. Data on long-term outcomes were obtained from the Polish National Health Fund (Narodowy Fundusz Zdrowia) that gathers data about medical services including primary diagnosis coded with the *International Classification of Diseases, Tenth Revision* (*ICD-10*). Supplementary material, *Table S1* presents the list of the codes used in the study.

Statistical analysis All continuous variables were tested for normality with the Shapiro–Wilk test. All continuous variables were assigned as nonparametric and expressed as median (interquartile range). Categorical variables were expressed as counts with percentages. The Fisher exact test (2-group comparison) or the χ^2 test (3-group comparison) was used to compare categorical variables. Differences in continuous parameters were compared using the Mann–Whitney test (2-group comparison) and the Kruskal–Wallis test (3-group comparison). The Bonferroni correction was applied to address the multiple comparison issue. To determine predictors of primary and secondary end points in both groups, the Cox proportional-hazard regression method was used to fit univariable and multivariable survival models, the results of which are reported as hazard ratios (HRs) with 95% CIs. Among the factors, those with a *P* value of less than 0.05 were selected and included in the multivariable Cox regression analysis.

To adjust for potential confounding due to baseline imbalances in study covariates while preserving sample size, we used propensity score matching.[6] With this method, the propensity score (district hospital treatment was set as the reference) was used to generate patient-specific stabilized weights that control for covariate imbalances. Covariate balance between the weighted cohorts was assessed using standardized mean differences. A standardized difference of 0.05 or less indicates a negligible difference between groups. The distributions of propensity scores and stabilized weights were inspected for outliers. Analyses presented in FIGURES 1 and 2 as well as in Supplementary material, *Tables S2* and *S5* were based on propensity score matching–adjusted cohorts. Weighted Cox proportional hazards regression with robust estimation was used to estimate time-to-primary end point event in district compared with academic (reference) cohorts. Variables used for propensity score calculations included: age, sex, AF type, heart failure, hypertension, coronary artery disease, diabetes mellitus, ischemic stroke / transient ischemic attack / thromboembolism, previous major bleeding, chronic obstructive pulmonary disease, smoking, renal function based on estimated glomerular filtration rate (calculated using the Cockcroft–Gault formula). Weighted Kaplan–Meier analysis was used to establish the relation of type of hospital (academic vs district) to MAE and its components, and differences in adverse events were analyzed using the log-rank test. Subgroup-specific adjusted HRs with 95% CIs analyses were performed for all outcomes in categories defined by age, sex, heart failure, hypertension, coronary artery disease, diabetes, chronic kidney disease, and the HAS-BLED score. A 2-tailed *P* value of 0.05 was considered statistically significant. For database management and statistical analysis, we used SAS, version 14.1 (SAS Institute Inc, Cary, North Carolina, United States).

RESULTS **Study population** Out of the entire cohort of 3528 patients with AF included in the CRAFT study, follow-up data were available for 3307 individuals. Out of them, 2983 patients had indications for long-term oral anticoagulation (OAC) treatment in accordance with the European

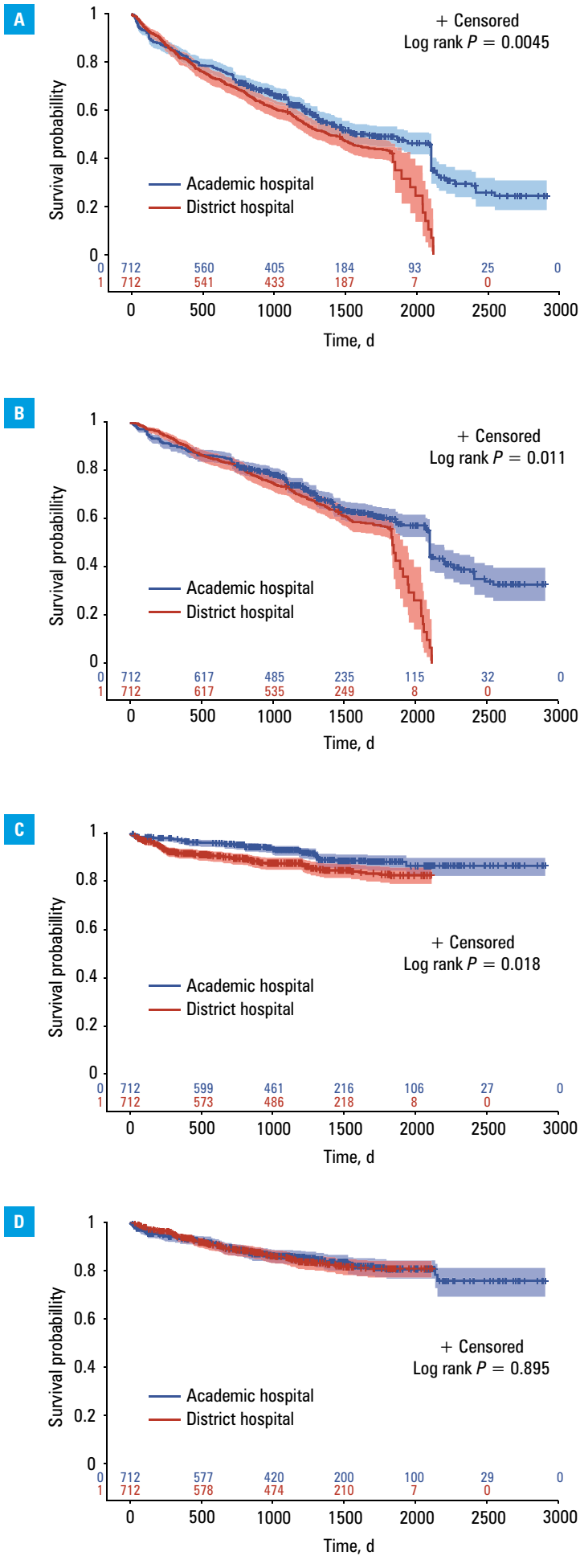

FIGURE 1 Kaplan–Meier analysis of time to: major adverse events (**A**), all-cause death (**B**), thromboembolic events (**C**), and hemorrhagic events (**D**) in patients hospitalized in academic and district hospitals, after propensity-score matching

Society of Cardiology guidelines[4] and were included in the current analysis. The rest of the cohort had temporary indications to OAC, for example, before and after cardioversion / ablation.

Baseline characteristics Patients were divided into 2 groups: 2271 patients (76.1%) hospitalized in an academic hospital and 712 patients (23.9%) admitted to a district hospital. Differences between patients recruited in the district vs academic hospital with regard to baseline characteristics were reported elsewhere.[7] Briefly, in district hospitals, patients were older, more likely female, more frequently had permanent AF and were more likely to have comorbidities and a higher thromboembolic and bleeding risk as compared with those hospitalized in academic hospitals (TABLE 1). After propensity score matching, the cohorts were well balanced across all covariates (Supplementary material, *Table S2*).

Follow-up outcomes During the median follow-up of 4 years, 1228 patients (41%) experienced MAEs: 828 (28%) died, 273 (9.2%) reported thromboembolic events, and 445 (15%) hemorrhagic events. Overall, patients treated in district hospitals more often experienced MAEs (53% vs 37%; $P < 0.001$), all-cause death (40% vs 24%; $P < 0.001$), thromboembolic events (13% vs 7.8%; $P < 0.001$) with similar risk of hemorrhagic events (15% vs 15%; $P = 1.00$) as compared with those hospitalized in academic hospitals (FIGURE 1). District (vs academic) conditions were associated with higher risk of MAEs and all-cause death in men and those with low risk of bleeding, and with higher incidence of thromboembolic events in women, elderly patients, and those with high risk of bleeding and diabetes (FIGURE 2).

In multivariable logistic regression, in academic hospitals, female sex, coronary artery disease, smoking, and antiplatelet drug therapy were significantly associated with a greater likelihood of thromboembolic events. Heart failure, renal failure, and the use of a vitamin K antagonist (VKA) were significantly associated with a greater likelihood of hemorrhagic events in academic hospitals. On the other hand, only coronary artery disease was significantly associated with hemorrhagic events in patients admitted to district hospitals (Supplementary material, *Table S3*).

Oral anticoagulant treatment and long-term outcomes In academic settings, 576 (25%), 285 (13%), and 1410 (62%) patients were treated with rivaroxaban, dabigatran, and a VKA, respectively, whereas in district hospital—315 (44%) with rivaroxaban, 121 (17%) with dabigatran, and 276 (39%)

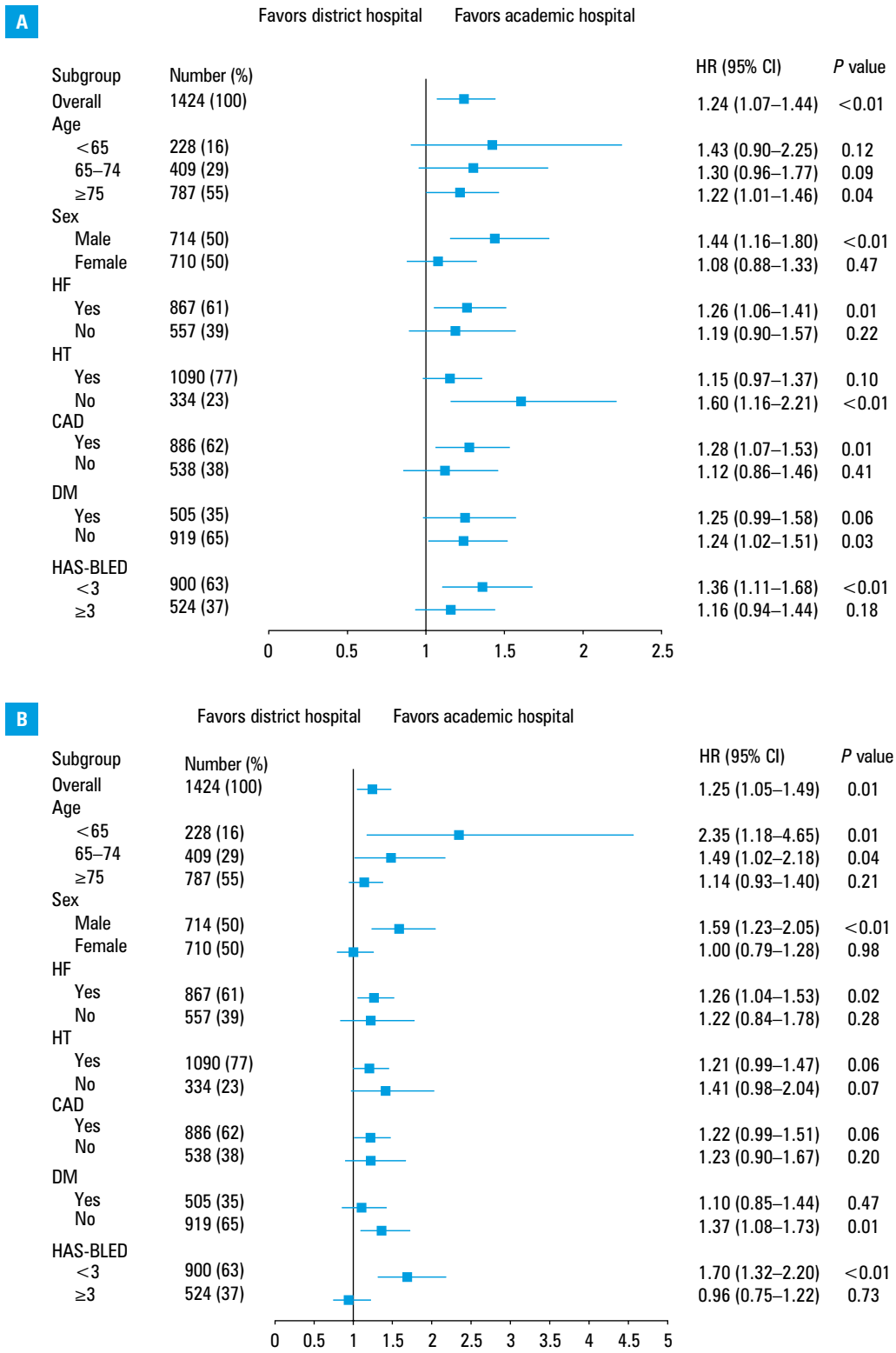

FIGURE 2 Subgroup-specific hazard ratios with 95% CIs for major adverse events (**A**) and all-cause death (**B**), in patients treated in academic (reference) vs district hospitals, after propensity-score matching
Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; HF, heart failure; HR, hazard ratio; HT, hypertension

with a VKA. In both types of hospitals, the incidence of MAEs and all-cause death was the highest within VKA-treated patients, and the lowest within those who received dabigatran. The highest and the lowest risk of hemorrhagic events was observed only in VKA and dabigatran groups respectively, only in patients hospitalized in academic hospitals (Supplementary material, *Table S4*). There were no differences between patients who were prescribed with a VKA and those on non-VKA OAC (NOAC) according to MAEs incidence and its components with a single exception. There were higher rates of hemorrhagic events among patients who received a VKA (vs dabigatran) and higher rate of hemorrhagic events among patients treated with rivaroxaban (vs a VKA) hospitalized in district hospitals (Supplementary material, *Table S5*).

DISCUSSION The current study presented a unique and direct comparison between anticoagulation treatment of patients with AF treated in academic and district conditions with a special focus on long-term outcomes. Despite

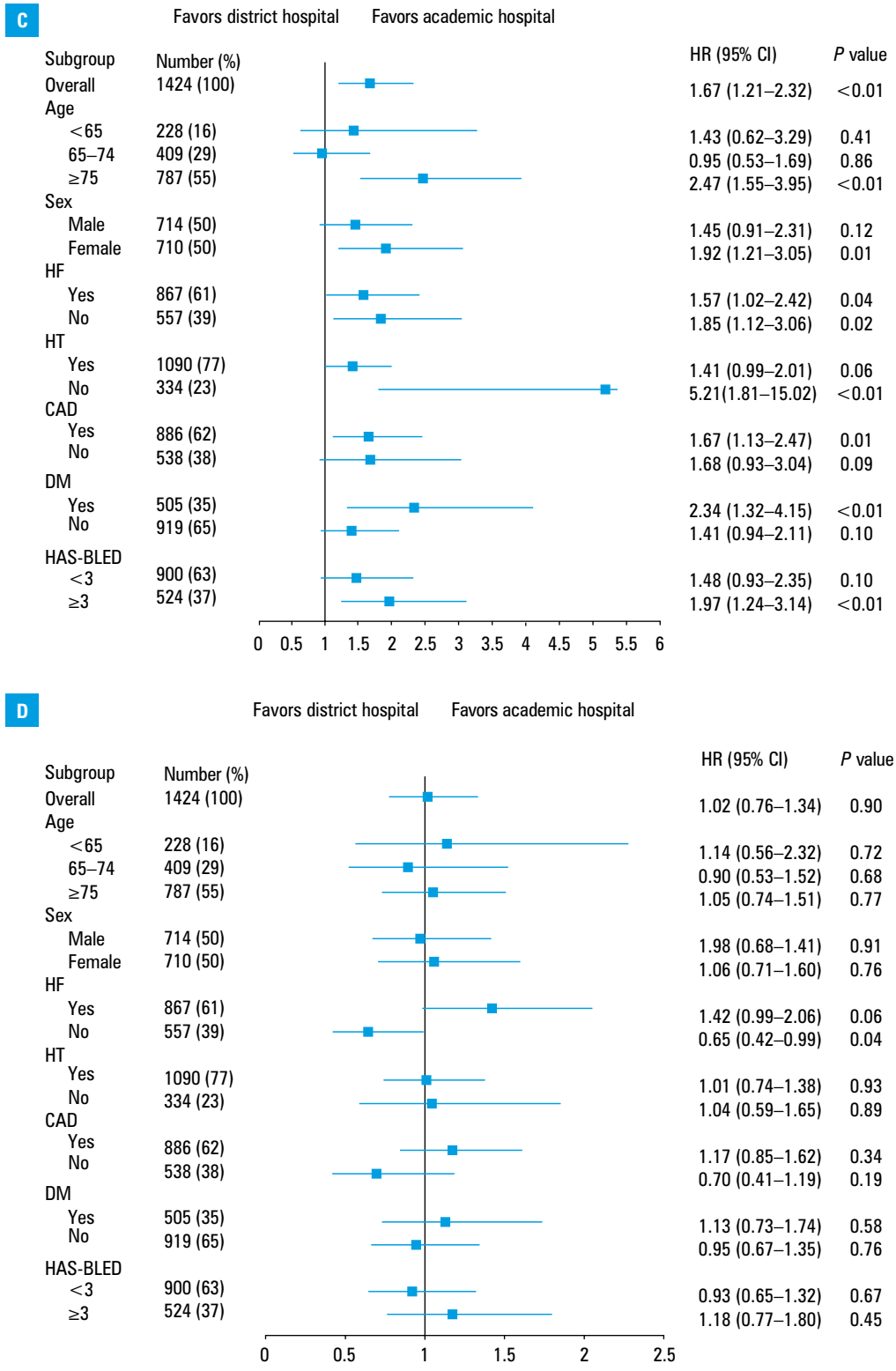

FIGURE 2 Subgroup--specific hazard ratios with 95% CIs for thromboembolic (**C**) and hemorrhagic events (**D**) in patients treated in academic (reference) vs district hospitals, after propensity-score matching
Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; HF, heart failure; HR, hazard ratio; HT, hypertension

the introduction of standardized guidelines that are regularly updated to best adapt the treatment to the current needs of patients, the management of AF still poses a challenge.[8] The overall profile of patients with AF is diversified and may be affected by regional population demographics and risk factors. At the same time, AF management varies between primary care settings in relation to resources, fund allocation, and equipment. However, there is a paucity of data regarding possible differences in the effectiveness of implementing AF treatment strategies in patients between academic and district hospitals. Most registries collect data mainly from large academic centers or highly specialized hospitals with poor representation of district hospitals. In the German Atrial Fibrillation NETwork (AFNET) study,[9] two-thirds of 9577 patients were treated by office-based cardiologists and tertiary care centers, followed by district hospitals and general practitioners or internists. The authors found that the center type affected the decision on the stroke prevention strategy and heart rhythm and/or the rate control

TABLE 1 Baseline characteristics

Variable	All patients (n = 2983)	Academic hospitals (n = 2271)	District hospitals (n = 712)	*P* value
Demographics				
Age, y	70 (62–79)	68 (61–78)	76 (68–82)	<0.001
Female sex	1224 (41)	872 (38)	352 (49)	<0.001
Atrial fibrillation type[a]				
Paroxysmal	1497 (52); (n = 2868)[b]	1201 (56); (n = 2156)	296 (42)	<0.001
Long-standing persistent	99 (3.5); (n = 2868)	99 (4.6); (n = 2156)	0	<0.001
Persistent	380 (13); (n = 2868)	276 (13); (n = 2156)	104 (15)	0.06
Permanent	868 (30); (n = 2868)	556 (26); (n = 2156)	312 (44)	<0.001
Comorbidities				
Heart failure	1185 (40); (n = 2978)	748 (33)	437 (62) (n = 707)	<0.001
Hypertension	2363 (79); (n = 2979)	1829 (81); (n = 2269)	5334 (75); (n = 710)	<0.001
CAD	1366 (46)	916 (40)	450 (63)	<0.001
DM	854 (29); (n = 2970)	591 (26); (n = 2267)	263 (37) (n = 703)	<0.001
History of TEs	423 (14); (n = 2975)	294 (13); (n = 2270)	129 (18); (n = 705)	<0.001
History of bleeding	241 (8.1); (n = 2981)	67 (3)	174 (30); (n = 710)	<0.001
COPD	284 (10); (n = 2978)	161 (7.1); (n = 2270)	123 (17); (n = 708)	<0.001
Smoking	165 (5.5); (n = 2973)	94 (4.1); (n = 2268)	71 (10); (n = 705)	<0.001
Laboratory parameters				
Hemoglobin, g/dl	14 (13–15); (n = 2258)	14 (13–15); (n = 2258)	NA	NA
Platelet count, $10^3/mm^3$	204 (168–239); (n = 2262)	204 (168–239); (n = 2262)	NA	NA
eGFR ≥50 ml/min/1.73 m^2	1718 (73); (n = 2356)	1195 (73); (n = 1646)	523 (74) (n = 710)	0.61
Thromboembolic and bleeding scores				
CHA_2DS_2-VASc score	4 (2–5)	3 (2–5)	5 (3–6)	<0.001
HAS-BLED score	2 (1–2)	2 (1–2)	2 (2–3)	<0.001
Antithrombotic treatment				
VKA	1696 (57)	1410 (62)	276 (39)	<0.001
NOAC	1297 (43)	861 (38)	436 (61)	<0.001
Dabigatran	406 (14)	285 (13)	121 (17)	0.003
Rivaroxaban	891 (30)	576 (25)	315 (44)	<0.001
Reduced doses	556 (43); (n = 1282)	318 (38); (n = 848)	238 (55); (n = 434)	<0.001
Antiplatelet drugs	435 (15)	351 (16)	84 (12)	0.02
Other medications				
β-Blockers	1907 (84); (n = 2270)	1907 (84); (n = 2270)	NA	NA
Calcium channel blockers	524 (23); (n = 2270)	524 (23); (n = 2270)	NA	NA
Antiarrhythmic drugs	511 (23); (n = 2980)	392 (17); (n = 2269)	119 (17); (n = 711)	0.78
RAS inhibitors	1848 (81); (n = 2271)	1848 (81)	NA	NA
Statins	1539 (68); (n = 2271)	1539 (68)	NA	NA
Long-term outcomes				
MAEs	1228 (41)	849 (37)	379 (53)	<0.001
All-cause death	828 (28)	541 (24)	287 (40)	<0.001
TEs	273 (9.2)	178 (7.8)	95 (13)	<0.001
HEs	445 (15)	339 (15)	106 (15)	1.00

Data are presented as number (percentage) or median (interquartile range).

a The Bonferroni correction was applied to address the multiple comparison issue.

b Numbers provided in parentheses indicate the total number of patients available for that variable.

Abbreviations: COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HE, hemorrhagic event; ICD, implantable cardioverter-defibrillator; MAE, major adverse event; NA, not applicable; NOAC, non–vitamin K antagonist oral anticoagulant; PM, pacemaker; RAS, renin–angiotensin system; TE, thromboembolic event; VKA, vitamin K antagonist; others, see **FIGURE 2**

therapy.[9] Although the risk of stroke was similar between patients from particular centers, only tertiary care centers (68.8%) and office-based cardiologists (73.6%) more frequently administered adequate antithrombotic therapy than district hospitals (55.1%) or general practitioners (52%). This study also showed that, taking university hospital–based cardiologists as the reference type of center, office-based cardiologists (odds ratio [OR], 1.40) prescribed significantly more frequently guideline-recommended anticoagulation for secondary stroke prevention than regional hospitals (OR, 0.47) and general practitioners / internists (OR, 0.40). This physician-dependent under-utilization of OACs in AF cohorts has previously been described for office-based general practitioners as compared with cardiologists.[10] Adherence to anticoagulation guidelines is associated with better survival in patients with AF at a high risk of stroke by reducing morbidity, all-cause mortality, and stroke.[11-13] Interestingly, higher rates of NOAC prescription in district hospitals were observed. It might be related to the available guidelines at the moment of hospitalization, in which NOACs had a lower class of recommendation. It is likely that some patients had their treatment changed after the publication of new evidence. The current study assessed drugs that were prescribed at discharge from the hospital. Unfortunately, the dosage regimen was insufficiently reported to be analyzed. However, in our study, despite OAC prescription in all patients, those hospitalized in the district hospital more often experienced MAEs including all-cause death and thromboembolic events. To explain this observation, one should bear in mind that patients from academic hospitals more frequently had undergone pulmonary vein isolation and electrical cardioversion than patients from district hospitals.[7] For organizational reasons, most elective cardioversions in district hospitals are performed in the emergency department and, simultaneously, no AF ablations are performed, which can explain the different distribution of AF types and stroke risk in both types of centers.[7] Moreover, based on our previous study,[14] most Polish patients with AF, even those with the lowest risk of stroke, are often overtreated with NOACs and as those results came from academic centers, the rate of inappropriate dosage of NOACs could be even higher in district hospitals.

Literature search revealed that NOACs have similar efficacy as VKAs in the prevention of thromboembolic events in AF patients, but significantly reduce the risk of major bleeding.[15,16] It was also observed in our study. There were no differences between patients on VKAs and NOACs with regard to thromboembolic events; however, a higher rate of hemorrhagic events was observed in the VKA group (vs dabigatran) and the rivaroxaban group (vs VKA) in patients hospitalized in district hospitals.

Limitations of the study This retrospective study has several limitations. Firstly, it was not a nationwide registry with a truly representative cohort of patients with AF. 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. Finally, due to the small number of patients on apixaban, it was not included into the analysis.

Conclusions Long-term outcomes of patients with AF depend not only on patient characteristics, but also the type of healthcare system. Further research is needed to investigate the differences in the management of AF and long-term outcomes between academic hospitals (participating in global registries that are the source of AF guidelines), and district hospitals (where these guidelines are implemented in real-life clinical practice).

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT PL, MG, and PB were responsible for the concept and design of the study. MG, LK, AŚ, CM, BK, AT, and KO were involved in data collection. PL and MG analyzed the data. MG was responsible for statistical analysis. PL and MG wrote the draft of the manuscript. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST PL, GO, and PB received speaker honoraria from Bayer, Boehringer Ingelheim, and Pfizer. AT received speaker honoraria from Novartis and Boehringer Ingelheim. KO received speaker honoraria from Novartis, Boehringer Ingelheim, and Orion Pharma. Other authors declare no conflict of interest.

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