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Randomized controlled clinical trials versus real-life atrial fibrillation patients treated with oral anticoagulants. Do we treat the same patients?

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Randomized controlled clinical trials versus real-life atrial fibrillation patients treated with oral anticoagulants. Do we treat the same patients?

Running title: RCT vs. real-life AF patients

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Abstract

Background: The aim of the study was to compare clinical characteristics of real-life AF patients with populations included in randomized clinical trials (ROCKET AF and RE-LY).

Methods: The analysis included 3528 patients who are participants of the ongoing, multicentre, retrospective CRAFT study. The study is registered in ClinicalTrials.gov: NCT02987062. The study is based on a retrospective analysis of hospital records of AF patients treated with vitamin K antagonists (VKAs) (acenocoumarol, warfarin) and non-vitamin K oral anticoagulants (NOACs) (dabigatran, rivaroxaban). $CHADS_2$ score was used for risk of stroke stratification.

Results: VKA was prescribed in 1973 (56.0%), while NOAC in 1549 (44.0%), including dabigatran — 504 (14.3%) and rivaroxaban — 1051 (29.8%), of the 3528 patients. VKA patients in the CRAFT study were at significantly lower risk of stroke ($CHADS_2$ 1.9 ± 1.3), compared with the VKA population from the RE-LY (2.1 ± 1.1) and the ROCKET-AF (3.5 ± 1.0). Patients in the CRAFT study treated with NOAC ($CHADS_2$ for patients on dabigatran

150 mg — 1.3 ± 1.2 and on rivaroxaban — 2.2 ± 1.4) had lower risk than pts from the RE-LY (2.2 ± 1.2) and the ROCKET AF (3.5 ± 0.9).

Conclusions: Real-world patients had a lower risk of stroke than patients included in the RE-LY and ROCKET AF trials.

Key words: non-valvular atrial fibrillation, oral anticoagulation, randomized trial, real-world study

Introduction

Atrial fibrillation (AF) is an increasingly common cardiac arrhythmia which affects 3% of adults in the European population [1]. It is related to the ageing of modern societies and its prevalence is increasing with a presence of certain comorbidities (i.e. hypertension, coronary artery disease, heart failure) [1, 2]. A key element of AF patient management is anticoagulation to prevent thromboembolic events, especially AF-related stroke, which is combined with poor outcomes and high total costs [1]. According to the current European Society of Cardiology (ESC) guidelines for non-valvular AF treatment, the first line drugs are non-vitamin K oral anticoagulants (NOACs), which are preferred over vitamin K antagonists (VKA) [1]. NOACs were shown to be at least as effective and safer than VKAs for stroke prevention in patients with non-valvular AF [1]. However, it is not clearly confirmed, how the success of NOACs' approval trials — ROCKET AF (rivaroxaban), RE-LY (dabigatran etexilate), and ARISTOTLE (apixaban) may reflect on real-life clinical practice.

The aim of the study was to compare clinical characteristics of real-life AF patients with populations included in randomized clinical trials (ROCKET AF and RE-LY).

Methods

The analysis was based on multicenter, retrospective CRAFT (MultiCenter expeRience in AFib patients Treated with OAC) study, registered in ClinicalTrials.gov: NCT02987062 [3]. The CRAFT study was conducted at two cardiology centers in Poland, academic center located in capital city and district hospital. The study was approved by a local ethical review board.

Study design and population

The CRAFT study retrospectively included all patients hospitalized in the years between 2011–2016 with diagnosis of non-valvular AF and treated with one of the oral

anticoagulants (OAC) — VKAs (acenocoumarol, warfarin) and NOAC (apixaban, dabigatran, rivaroxaban). Patients were 18 years of age and older. There were no other specific inclusion or exclusion criteria. Patients on apixaban were excluded due to a small number in this group . Another NOAC — edoxaban was not available on the Polish market at the time of data collection. The data about patient characteristics was gathered retrospectively from hospital records.

Design of the randomized trials

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study was a multicenter, randomized trial designed to compare two fixed doses of dabigatran (110 mg or 150 mg) with adjusted-dose warfarin [4]. The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) was a multicenter, randomized, double-blind trial, in which patients were randomly assigned to receive a fixed dose rivaroxaban (20 mg daily or 15 mg daily in patients with a creatinine clearance of 30 to 49 mL per minute) or adjusted-dose warfarin [5]. In both trials patients with non-valvular AF documented on electrocardiography who were at increased risk of stroke, which was defined as history of previous stroke or transient ischemic attack (TIA) or systemic embolism, older age, coexistence of comorbidities such as heart failure with reduced ejection fraction, hypertension, diabetes mellitus or coronary artery diseases were randomized to different study arms. Complete inclusion and exclusion criteria are described in trial protocols [5, 6]. The main exclusion criteria are shown in Table 1.

Comparative analysis of patients treated with OAC — randomized trials vs real-world patients

In the current analysis, patients were divided into four groups according to the type of OAC (VKA, dabigatran 110 mg, dabigatran 150 mg, rivaroxaban 15 or 20 mg). Investigators compared clinical characteristics of real-life AF patients from the CRAFT study with populations included in the randomized clinical trials (ROCKET AF and RE-LY). Patients were compared in terms of baseline characteristics regarding demographics, medical history, type of AF (paroxysmal, persistent or permanent), diagnostic test results and co-pharmacotherapy. Thromboembolic risk of each group was compared using $CHADS_2$

(Congestive heart failure, Hypertension, Age ≥ 75, Diabetes, Stroke [doubled]) score which was used in the ROCKET AF and RE-LY trials.

Statistical analysis

Statistical analyses were performed using SPSS software, version 22 (IBM SPSS Statistics 22, USA, New York). Normally distributed continuous variables were presented as mean values and standard deviations, while ordinal variables and non-normally distributed continuous variables, as median values and interquartile ranges (IQR). Categorical data is presented as a number of patients and percentages. The significance of differences between groups was determined by the Fisher exact test for categorical variables and Mann-Whitney U test for continuous and ordinal variables, respectively. P-values less than 0.05 were considered significant. All tests were two-tailed.

Results

Characteristics of the study patients

A comparison of clinical characteristics of patients from the CRAFT, RE-LY and ROCKET AF studies are presented in Table 2. Table 3 presents thromboembolic risk factors in the study participants according to the treatment group. In both trials (RE-LY and ROCKET AF) patients with creatinine clearance < 30 mL per minute were excluded, while in the present study 2.7% of patients were below this threshold.

CRAFT study

A total of 3528 Caucasian patients were enrolled in the CRAFT study, of whom 1973 (56.0%) were on VKAs and 1549 (44.0%) patients were on NOACs, including rivaroxaban — 1051 (29.8%) and dabigatran — 504 (14.3%). In the dabigatran group, 187 (5.3%) patients received 110 mg twice daily and 311 (8.8%) patients received 150 mg twice daily. There were 6 patients with missing data on the dabigatran dose. Patients on rivaroxaban received 15 mg or 20 mg once daily, but following the methodology from the ROCKET AF trial, both doses were analyzed collectively. Figure 1 shows the flow chart of patient selection in the current study. The mean age of the total population was 67.9 ± 13.2 years and 59.8% were male. Patients on dabigatran 110 mg were the oldest (75.8 ± 10.2 years). In the total population paroxysmal AF had 1820 (51.6%), permanent AF 955 (27.0%) and persistent 596 (16.9%) patients.

RE-LY trial

In the RE-LY study a total cohort of 18,113 patients were enrolled, including 6022 patients on VKA, 6015 on dabigatran 110 mg and 6076 on dabigatran 150 mg. The mean age of the total cohort was 71 years and 63.6% were male [4].

ROCKET AF trial

In the ROCKET AF study, a total of 14,264 patients were enrolled, including 7133 patients on VKA and 7131 on rivaroxaban (15 or 20 mg dose). Reduced dose of rivaroxaban (15 mg once daily) was intended for patients with estimated creatinine clearance (CrCl) 30–49 mL/min (calculated by the Cockroft-Gault formula). The mean age of the total cohort was 73.0 ± 9.6 years and 60.3% were male [5].

Comparative analysis of patients treated with OAC — randomized trials vs real-world patients

VKA patients. Patients on VKAs in the CRAFT study were younger (67.0 ± 12.8 years) than patients from the RE-LY and ROCKET AF trials (71.6 ± 8.6 years, $p < 0.0001$; and 73.0 ± 9.6, $p < 0.0001$, respectively). Patients in the CRAFT study (similar to the RE-LY study) were more likely to be male (63.5%) than in the ROCKET AF (60.3%, $p = 0.01$). In the CRAFT study patients on VKAs had mainly paroxysmal AF (52.1%), in the ROCKET AF had persistent AF (80.8%), while in the RE-LY comparably often all types of AF. Patients in the present study had significantly lower risk of stroke (CHADS$_2$ 1.9 ± 1.3), compared with VKA population from RE-LY (2.1 ± 1.1) and ROCKET-AF (3.5 ± 1.0). A comparison of thromboembolic risk (assessed by CHADS$_2$ score) of each group from CRAFT, RE-LY and ROCKET AF studies is presented in Figure 2. Patients on VKAs in the ROCKET AF trial more frequently had a history of stroke or TIA, heart failure, diabetes, hypertension and chronic pulmonary disease than in the CRAFT study. Whereas, patients from the RE-LY trial more frequently had a history of stroke or TIA and hypertension, but less frequently had heart failure or diabetes than in the CRAFT study.

Dabigatran patients. Patients on dabigatran 110 mg in the CRAFT study were older (75.8 ± 10.2 years) and were less frequently male (56.1%), compared with patients on the same dose in the RE-LY trial (71.4 ± 8.6 years, $p < 0.0001$; 64.3%, $p = 0.02$). In the CRAFT study patients on dabigatran 110 mg had mainly paroxysmal AF (47.3%), while in the RE-LY trial comparably often had all types of AF. There was no statistical significance in

comparison of permanent AF occurrence between CRAFT and RE-LY studies. Patients on dabigatran 110 mg in the CRAFT study were at higher risk of stroke (CHADS$_2$ 2.6 ± 1.2) compared with dabigatran 110 mg population from the RE-LY trial (2.1 ± 1.1). Patients on dabigatran 110 mg in the CRAFT study also had heart failure more frequently, but had similarly frequent previous stroke or TIA, diabetes and hypertension.

Patients on dabigatran 150 mg in the CRAFT study were younger (60.0 ± 12.4 years), than patients on the same dose in the RE-LY trial (71.5 ± 8.8 years, $p < 0.0001$). In the CRAFT study patients on dabigatran 150 mg had mainly paroxysmal AF (59.7%), while in the RE-LY trial had mainly permanent AF (36.0%). Patients on dabigatran 150 mg in the CRAFT study had a lower risk of stroke (CHADS$_2$ 1.3 ± 1.2) when compared to patients from the RE-LY trial (2.2 ± 1.2). Patients on dabigatran 150 mg in the CRAFT study frequently had less previous stroke or TIA, heart failure, diabetes and hypertension than in the RE-LY trial. There was no difference with regard to sex and persistent AF occurrence between groups.

Rivaroxaban patients. Patients on rivaroxaban in the CRAFT study were younger (70.5 ± 13.1 years) and less frequently male (52.1%), when compared with patients from the ROCKET AF trial (73.0 ± 9.6 years, $p < 0.0001$; 60.3%, $p < 0.0001$). In the CRAFT study patients on rivaroxaban more frequently had paroxysmal AF (57.3%), while in the ROCKET AF trial they had persistent AF (81.1%). Patients on rivaroxaban in the present study had a significantly lower risk of stroke (CHADS$_2$ 2.2 ± 1.4), compared with the population from ROCKET-AF (3.5 ± 0.9). Patients on rivaroxaban in the CRAFT study had previous stroke or TIA, heart failure, diabetes and hypertension less frequently than in the ROCKET AF trial, but more often had chronic obstructive pulmonary disease.

Discussion

Randomized controlled trials (RCT) are the gold standard for evaluation of therapy outcomes in terms of treatment efficacy and safety [7]. However, it needs to be emphasized that they have a limited generalizability because they are performed under very different conditions from a routine clinical practice [7]. Rigorous insight into those differences in patient characteristics may be important in interpreting results of RCT. Therefore, there is a need for real-life data to compare populations enrolled to RCT with patients from everyday clinical practice. It should however, be underlined that RCT and real-word studies are complementary. They provide data from different settings and both contribute to knowledge on AF patients.

Therapy with VKAs is found to be highly effective for stroke prevention in non-valvular AF patients, however a proper monitoring and dose adjustment is challenging for physicians and patients [8, 9]. What is more, the efficacy and safety of VKAs depends on inter- and intra-individual variations, which are associated with food and drug interactions [8, 9]. On the other hand, NOACs are available with no need for regular blood monitoring and have fewer interactions with other medications [10, 11]. However, one third of patients treated with NOACs appear to have disruptions in therapy, which are associated with 4–6-fold increased risk of stroke or TIA [12]. The ESC guidelines for non-valvular AF treatment recommend NOACs as the first line drugs [1], especially for patients on VKAs with unsatisfactory individual time in therapeutic range (TTR). Data from smaller studies showed that NOACs are safe and effective in real-world non-valvular AF patients also in secondary stroke prevention [13–15].

Our understanding of rivaroxaban (direct oral factor Xa inhibitor) and dabigatran (direct thrombin inhibitor) efficacy and safety profiles mainly come from the two RCTs — ROCKET AF and RE-LY, respectively [4, 5]. In ROCKET AF rivaroxaban was non-inferior to warfarin in the prevention of stroke or systemic embolism, with no significant differences in incidence of overall bleeding events between groups, though it was associated with a lower rate of intracranial and fatal bleedings [5]. In the RE-LY trial, the 150-mg dose of dabigatran was associated with lower rates of stroke and systemic embolism, and a similar rate of major hemorrhage [4]. Whereas, the 110-mg dose of dabigatran was associated with similar rates of stroke and systemic embolism and lower rates of major hemorrhage [4].

Importantly, the CRAFT study revealed a lower incidence of previous stroke or TIA in the real-world, than was observed in the RCTs. The difference was especially remarkable in comparison with the ROCKET AF trial, where more than half of the population (54.9%) experienced previous stroke or TIA [5], while in the CRAFT study it was only 12.7%. The present results are not isolated, and they are in line with a recently performed prospective, observational Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation (XANTUS) study, where 19% of patients with non-valvular AF experienced previous stroke or TIA [16]. The aim of this study was to assess rivaroxaban in stroke prevention in real-life clinical practice. The mean age of the cohort in the XANTUS study was 71.5 ± 10 years, 41% were female and there was a higher proportion of paroxysmal AF [16], similar to the population of this study.

Patients in the CRAFT study had paroxysmal AF significantly more often, while patients in the RE-LY and ROCKET AF trials had more sustained forms [4, 5]. These results are in line with data from Atrial Fibrillation General Pilot registry conducted by ESC, which showed that Polish patients more often had paroxysmal AF (32.8%) than patients from other countries of the European Union (25.5%) [17]. It is known that more sustained forms of AF may be associated with increased symptoms and cardiovascular morbidity [18]. The prevailing frequency of paroxysmal AF and thus a lower burden of comorbidities, was probably associated with a lower estimated thromboembolic risk in patients from the CRAFT and XANTUS studies. Moreover, Gorczyca-Michta et al. [19] revealed that paroxysmal arrhythmia is a factor associated with an increased probability of NOAC prescription.

In the CRAFT study patients had a lower risk of stroke (calculated by $CHADS_2$ score) than patients included in the RE-LY and ROCKET AF trials, as showed in Figure 2. This was similarly observed in a retrospective REal-LIfe Evidence on stroke prevention in patients with atrial Fibrillation (RELIEF), a study evaluating the use of rivaroxaban in a German community [20]. In this study risk of stroke in non-valvular AF patients was similar to rivaroxaban (mean $CHADS_2$ 1.7) and VKA (mean $CHADS_2$ 1.8) patients as in the present study [20]. These data showed that real-world patients have a lower risk of stroke than patients included in RCT, especially when compared to the ROCKET AF trial. Nevertheless, as previously observed in the CRAFT study, there were differences in clinical characteristics of AF patients treated with OAC between the district and academic hospitals. Patients treated in an academic hospital were younger, had lower $CHADS_2$, CHA_2DS_2VASc scores, had less comorbidities and a lower risk of bleeding complications than patients treated in the district hospital [21]. It should be noted, that a majority of the CRAFT population was recruited in an academic hospital and nearly 75% of this group patients were relatively low risk   and were admitted to hospital for AF ablation or cardioversion.

However, in the ROCKET AF rivaroxaban failed to demonstrate a reduction in ischemic stroke in comparison to warfarin. One of the hypotheses had concerns that patients on VKA included in the ROCKET AF study had a mean TTR of approximately 63% [5, 22]. While, data from meta-analysis including patients from everyday practice suggested that real TTR is about 9% lower than in randomized selected patients [23]. Results herein suggest that in real-life clinical practice patients are healthier, with lower thromboembolic risk. Additionally, lower TTR may result in a worse effectiveness of VKA in real-life than was

shown in the ROCKET AF. These may translate into additional benefits from the use of NOACs in real-life clinical practice.

Patients enrolled in the CRAFT study were younger and the prevalence of concomitant diseases was lower than in patients from the ROCKET AF trial, as well as the fact that patients were on dabigatran 150 mg in the RE-LY trial [4, 5]. Interestingly, in the CRAFT study only patients on dabigatran 110 mg had a higher risk of stroke (calculated using CHADS2 score) and had a similar frequency of previous stroke or TIA, compared to patients from the RE-LY trial [4]. This real-life cohort was older and had more comorbidities than groups on other anticoagulants. This probably reflects that physicians prescribe a lower dose of dabigatran for elderly and patients suffering from numerous concomitant diseases [24]. Lopatowska et al. [25] did a study based on 1556 real-life Polish AF patients, which observed that the use of OAC increased with higher $CHA2DS_2$-VASc score of up to 3 points and surprisingly was less frequent in scores ≥ 4. However, Steinberg et al. [26] showed that elderly AF patients rarely have absolute contraindications to oral anticoagulation therapy albeit those who do are also at high risk for thromboembolic events. It may be a sign that in elderly, anticoagulation therapy is underutilized despite strong indications. Similarly, The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) registry demonstrated some inaccuracies. Patients with a low risk of stroke had prescribed anticoagulants more often than needed, while patients with a high risk of stroke were left without this treatment [27]. Moreover, authors of a prospective observational REgistro POliterapie SIMI (REPOSI) study, based on in-patients aged ≥ 65 years, stressed that a proper adherence to the antithrombotic therapy guidelines, among elderly AF patients is associated with a lower risk for all cause and cardiovascular deaths [28].

In a real-life setting the educational level of patients also matters, more than in RCT. Knowledge about AF and its consequences, as well as the importance of uninterrupted anticoagulation therapy, influences adherence to the therapy. It was shown in the OCULUS study that the educational level of patients was unsatisfactory and may translate into further differences in stroke prevention effectiveness [29].

Limitations of the study

The limitations mainly derive from the CRAFT study. First of all, the sample size was not representative of the whole population because data came from just two centers. It should be underlined that rivaroxaban and dabigatran groups enrolled in the CRAFT study were

more than ten times less populated than their RCTs counterparts, nonetheless the study included over 3500 patients.

Importantly, based on inclusion criteria of RCT there was an imbalance of thromboembolic risk profile of patients between CRAFT and ROCKET AF studies. In the ROCKET AF trial, only patients with moderate-to-high risk of stroke had been enrolled and, according to the protocol, the proportion of patients with a previous stroke or TIA, was brought up to 50% of the whole study population during the randomization process.

Furthermore, there was no possibility to compare the risk of stroke using a more accurate and valid CHA_2DS_2-VASc classification, because this score was not used in the ROCKET AF or RE-LY trials.

Additionally, a retrospective study may contain inaccuracies such as completeness of data or coding that can result in biases. Moreover, there were a limited number of patients and neither apixaban or edoxaban were available on the market, and were thus excluded from the analysis.

Conclusions

The CRAFT study showed that real-world patients demonstrated a distinct clinical profile compared to populations from the RE-LY and ROCKET AF trials. In general, real-world patients had a lower risk of stroke and prevalence of comorbid diseases than patients included in the RE-LY and ROCKET AF trials. Only patients who received dabigatran 110 mg in the CRAFT study were at higher risk of thromboembolic events than the same group in the RE-LY trial.

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Table 1. The main exclusion criteria for the randomized trials.

Exclusion criteria	
RE-LY	**ROCKET-AF**
1. History of heart valve disorder (i.e., prosthetic valve or hemodynamically relevant valve disease). 2. Severe, disabling stroke within the previous 6 months, or any stroke within the previous 14 days. 3. Conditions associated with an increased risk of bleeding (i.e. history of an active severe bleeding, major surgery within the previous month, planned surgery or intervention, uncontrolled hypertension, recent malignancy or radiation therapy). 4. Anemia (hemoglobin level less than 100 g/L) or thrombocytopenia. 5. Contraindication to warfarin treatment. 6. Reversible causes of atrial fibrillation. 7. Plan to perform a pulmonary vein ablation or surgery for cure of the atrial fibrillation. 8. Severe renal impairment (estimated creatinine clearance 30 mL/min or less). 9. Active liver disease. 10. Active infective endocarditis. 11. Women who are pregnant or of childbearing potential.	1. Hemodynamically significant mitral valve stenosis. Prosthetic heart valve. 2. Reversible causes of atrial fibrillation. Planned cardioversion. 3. Known presence of atrial myxoma or left ventricular thrombus. 4. Conditions associated with an increased risk of bleeding (i.e. history of an internal bleeding, planned invasive procedure, sustained uncontrolled hypertension). 5. Anemia (hemoglobin < 10 g/dL), platelet count < 90,000/μL. 6. Severe, disabling stroke within 3 months or any stroke within 14 days. Transient ischemic attack within 3 days. 7. Indication for anticoagulant therapy for a condition other than atrial fibrillation (e.g. venous thromboembolism). 8. Treatment with: acetylsalicylic acid > 100 mg daily; or acetylsalicylic acid in combination with thienopyridines, intravenous antiplatelets or fibrinolytics within 10 days before randomization. 9. Anticipated need for chronic treatment with a non-steroidal anti-inflammatory drug. 10. Drug addiction or alcohol abuse. 11. Known allergy or hypersensitivity to any component of rivaroxaban, warfarin or placebo excipients. 12. Calculated creatinine clearance < 30 mL/min. 13. Known significant liver disease. 14. Active endocarditis. 15. Pregnancy or breast-feeding.

The table was prepared based on trial protocols.

Table 2. Baseline characteristics of the study participants (from the CRAFT, RE-LY [2] and ROCKET AF studies [3]) according to the treatment group.

Variable	VKA				Dabigatran 110 mg			Dabigatran 150 mg			Rivaroxaban 15 or 20 mg		
	CRAFT (n = 1973)	RE-LY (n = 6022)	ROCKET AF (n = 7133)	P*	CRAFT (n = 187)	RE-LY (n = 6015)	P	CRAFT (n = 311)	RE-LY (n = 6076)	P	CRAFT (n = 1051)	ROCKET AF (n = 7131)	P
Age [years]	67.0 ± 12.8	71.6 ± 8.6	73.0 ± 9.6	< 0.0001 < 0.0001	75.8 ± 10.2	71.4 ± 8.6	< 0.0001	60.0 ± 12.4	71.5 ± 8.8	< 0.0001	70.5 ± 13.1	73.0 ± 9.6	< 0.0001
Male sex	1252 (63.5)	3809 (63.3)	4301 (60.3)	0.87 0.01	105 (56.1)	3865 (64.3)	0.02	198 (63.7)	3840 (63.2)	0.86	548 (52.1)	4300 (60.3)	< 0.0001
BMI [kg/m^2]	29.6 ± 6.3, n = 125	–	28.1 ± 5.0	0.001	28.0 ± 5.4, n = 53	–		28.5 ± 4.8, n = 37	–		29.3 ± 4.9, n = 146	28.3±5.1	0.02
Persistent AF	351/1902 (18.5)	1930/6021 (32.0)	5762 (80.8)	< 0.0001 < 0.0001	28/182 (15.4)	1950/6011 (32.4)	< 0.0001	83/298 (27.9)	1909/6075 (31.4)	0.20	134/998 (13.6)	5786 (81.1)	< 0.0001
Paroxysmal AF	990/1901 (52.1)	2036/6021 (33.8)	1269 (17.8)	< 0.0001 < 0.0001	86/182 (47.3)	1929/6011 (32.1)	< 0.0001	178/298 (59.7)	1978/6075 (32.6)	< 0.0001	566/987 (57.3)	1245 (17.5)	< 0.0001
Permanent AF	561/1902 (29.5)	2055/6021 (34.1)	–	0.0002	68/182 (37.4)	2132/6011 (35.4)	0.58	37/298 (12.4)	2188/6075 (36.0)	< 0.0001	289/988 (29.3)	–	
Aspirin	304 (15.4)	2442/6017 (40.6)	2619 (36.7)	< 0.0001 < 0.0001	17/187 (9.1)	2404/6013 (40.0)	< 0.0001	13/311 (4.2)	2352/6075 (38.7)	< 0.0001	88/1050 (8.4)	2586 (36.3)	< 0.0001
ACEI or ARB	1221/1632 (74.8)	3939/6017 (65.5)	–	< 0.0001	82/108 (75.9)	3987/6013 (66.3)	0.04	157/244 (64.3)	4053/6075 (66.7)	0.44	485/676 (71.7)	–	
BB	1342/1631 (82.3)	3719/6017 (61.8)	–	< 0.0001	88/108 (81.5)	3784/6013	< 0.0001	182/244 (74.6)	3872/6075 (63.7)	< 0.0001	540/676 (79.9)	–	

	VKA				Dabigatran 110 mg			Dabigatran 150 mg			Rivaroxaban 15 or 20 mg		
			(62.9)										
Amiodarone	162/1971 (8.2)	644/6017 (10.7)	–	0.001	20/186 (10.8)	624/6013 (10.4)	0.86	27/311 (8.7)	665/6075 (10.9)	0.22	110/1050 (10.5)	–	
Statin	1046/1632 (64.1)	2673/6017 (44.4)	–	< 0.0001	72/108 (66.7)	2698/6013 (44.9)	< 0.0001	120/244 (49.2)	2667/6075 (43.9)	0.10	439/676 (64.9)	–	

Continuous variables are presented as mean ± standard deviation or number and (percentage).

ACEI — angiotensin-converting enzyme inhibitor; AF — atrial fibrillation; ARB — angiotensin-receptor blocker; BB — beta-blocker; BMI — body mass index; n — number; RE-LY — The Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET — Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation, VKA — vitamin K antagonist

*First p-value, (written above) refers to the comparison of VKA patients from the CRAFT and RE-LY studies, second p-value (written below) refers to the comparison of patients from the CRAFT and ROCKET AF studies.

Table 3. Thromboembolic risk factors in the study participants (from the CRAFT, RE-LY [2] and ROCKET AF studies [3]) according to the treatment group.

	VKA				Dabigatran 110 mg			Dabigatran 150 mg			Rivaroxaban 15 or 20 mg		
Variable	CRAFT (n = 1973)	RE-LY (n = 6022)	ROCKET AF (n = 7133)	P*	CRAFT (n = 187)	RE-LY (n = 6015)	P	CRAFT (n = 311)	RE-LY (n = 6076)	P	CRAFT (n = 1051)	ROCKET AF (n = 7131)	P
Previous stroke or TIA	219/1960 (11.2)	1195 (19.8)	3895 (54.6)	< 0.0001 < 0.0001	35/185 (18.9)	1195/6015 (19.9)	0.74	24/309 (7.8)	1233 (20.3)	< 0.0001	168/1046 (16.1)	3916 (54.9)	< 0.0001
CHADS$_2$ score	1.9 ± 1.3, n = 1960	2.1 ± 1.1	3.5 ± 1.0	< 0.0001 < 0.0001	2.6 ± 1.2, n = 185	2.1 ± 1.1	< 0.0001	1.3 ± 1.2, n = 309	2.2 ± 1.2	< 0.0001	2.2 ± 1.4, n = 1046	3.5 ± 0.9	< 0.0001
0–1	886/1960 (45.2)	1859 (30.9)	–	< 0.0001	32/185 (17.3)	1958/6014 (32.6)	< 0.0001	208/309 (67.3)	1958 (32.2)	< 0.0001	365/1046 (34.9)	–	
2	475/1960 (24.2)	2230 (37.0)	934 (13.1)	< 0.0001	63/185 (34.1)	2088/6014	0.87	62/309 (20.1)	2137 (35.2)	< 0.0001	279/1046 (26.7)	925 (13.0)	< 0.0001

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				< 0.0001		(34.7)							
3–6	599/1960 (30.6)	1933 (32.1)	6197 (86.9)	0.22 < 0.0001	90/185 (48.6)	1968/6014 (32.7)	< 0.0001	39/309 (12.6)	1981 (32.6)	< 0.0001	402/1046 (38.4)	6205 (87.0)	< 0.0001
Vascular disease**	862/1960 (44.0)	968 (16.1)	1724 (24.2)	<0.0001 <0.0001	106/185 (57.3)	1008/6015 (16.8)	< 0.0001	67/309 (21.7)	1029 (16.9)	0.03	504/1046 (48.2)	1583 (22.2)	< 0.0001
Heart failure	709/1960 (36.2)	1922 (31.9)	4441 (62.3)	0.0004 < 0.0001	99/185 (53.5)	1937/6015 (32.2)	< 0.0001	62/309 (20.1)	1934 (31.8)	< 0.0001	434/1046 (41.5)	4467 (62.6)	<0.0001
Diabetes mellitus	518/1960 (26.4)	1410 (23.4)	2817 (39.5)	0.01 < 0.0001	49/185 (26.5)	1409/6015 (23.4)	0.33	51/309 (16.5)	1402 (23.1)	0.01	309/1046 (29.5)	2878 (40.4)	< 0.0001
Hypertension	1407/1960 (71.8)	4750 (78.9)	6474 (90.8)	< 0.0001 < 0.0001	136/185 (73.5)	4738/6015 (78.8)	0.08	207/309 (67.0)	4795 (78.9)	< 0.0001	748/1046 (71.5)	6436 (90.3)	< 0.0001
COPD	160/1970 (81.0)	–	743 (10.4)	< 0.0001	23/187 (12.3)	–		8/310 (2.6)	–		134/1050 (12.8)	754 (10.6)	0.03

Continuous variables are presented as mean ± standard deviation or number and (percentage).

CHADS — congestive heart failure, hypertension, age ($\geq$ 75 years), diabetes mellitus, stroke or transient ischemic attack; COPD — chronic obstructive pulmonary disease; n — number; RE-LY — The Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET — Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; TIA — transient ischemic attack; VKA — vitamin K antagonist

*First p-value, (written above) refers to the comparison of VKA patients from the CRAFT and RE-LY studies, second p-value (written below) refers to the comparison of patients from the CRAFT and ROCKET AF studies.

**In the CRAFT study "Vascular disease" was defined as prior myocardial infarction, ischemic heart disease, peripheral artery disease or aortic plaque, while in the RE-LY and ROCKET AF studies only prior myocardial infarction was consider.

Figure 1. Flow chart of patient enrollment in the current analysis; bid — twice daily, CRAFT — MultiCentre expeRience in AFib patients Treated with OAC; pts — patients; VKA — vitamin K antagonists.
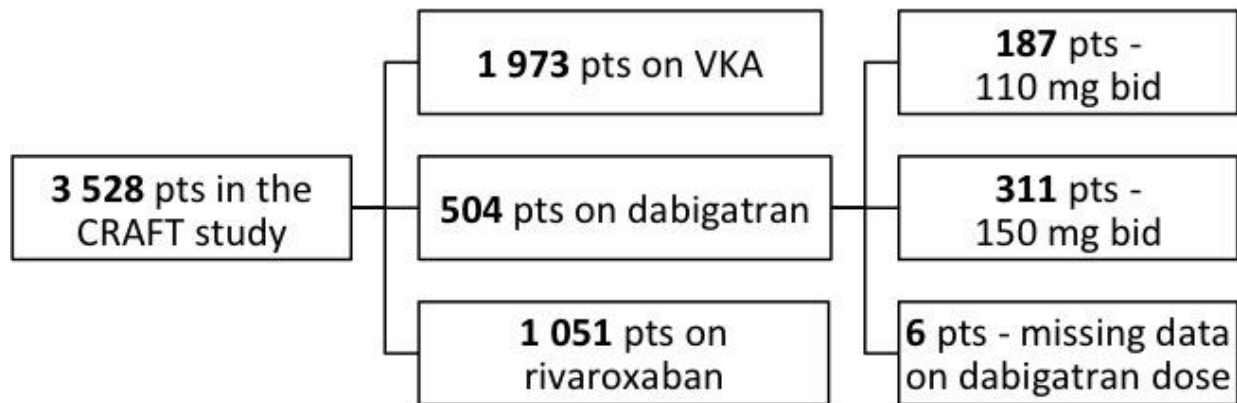

Figure 2. Thromboembolic risk basing on CHADS$_2$ score in different OAC groups. Results are shown as mean value. *Significant difference ($p<0.05$) where observed for comparison of vitamin K antagonists (VKAs) patients from the CRAFT study with both RE-LY and ROCKET AF trials.