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Research Article

Apixaban in Elderly Patients with Atrial Fibrillation and Renal Dysfunction: Findings from A National Registry

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ABSTRACT

Background: We aimed to evaluate the clinical characteristics and outcomes of patients 75 years and older with atrial fibrillation (AF) and renal dysfunction who are treated with apixaban.

Methods: A sub analysis of a multicenter prospective cohort registry, where consecutive eligible apixaban or warfarin treated patients with non-valvular AF and renal impairment (eGFR MDRD<60 ml/min/BSA) were registered. All patients were prospectively followed-up for clinical events and dosing adjustments over a mean period of 1 year. The current sub analysis focused on the subjects aged ≥75 years. The primary outcomes were 1 year: mortality, stroke or systemic embolism, major bleeding and myocardial infarction as well as their composite occurrence.

Results: In the subjects 75 years or older with renal impairment (n = 1460), the use of apixaban 5 mg was associated with improved 1-year survival rate (7.1% compared to 16.5% in the apixaban 2.5 mg group and 18.4% in the warfarin group; log rank p<0.001). Also, 5 mg apixaban showed lower risk of 1-year composite endpoint compared to apixaban 2.5 mg and warfarin (9.2% vs. 19.6% and 20.6%, respectively; log rank p<0.001). Further analysis on 1:1 matched data revealed a distinct advantage of efficacy to apixaban 2.5 mg appropriate dose reduction vs. warfarin. Nevertheless, similar safety profiles were observed.

Conclusion: Appropriate dose apixaban is a considerable alternative to warfarin in older adults with concurrent renal impairment for stroke prevention in the setting of AF.

Keywords: Atrial fibrillation; Apixaban; Warfarin; Older adults; Stroke

INTRODUCTION

An advanced age is a substantial and independent risk factor for atrial fibrillation (AF) [1,2]. The association between older age and increasing risk of stroke is heavily reflected in the CHA2DS2-VASc score, as data from the Framingham Heart Study showed that approximately 24% of strokes in individuals aged 80 and older are due to AF [3,4]. The number of patients with chronic kidney disease (CKD) is increasing worldwide, with an estimated prevalence up to 36% in adults' ≥ 64 years of age [5]. CKD is a well-recognized risk factor for thrombosis [6], which undergoes a stepwise increase with declining estimated glomerular filtration rate (eGFR) [7]. These processes are encountered in older adult due to progressively pathophysiologic deterioration in renal function with a tendency to develop acute changes [8].

CKD and AF often coexist due to shared risk factors, including increasing age as well as hypertension, heart failure, dyslipidemia, coronary artery disease and diabetes mellitus. Indeed, among patients with CKD, approximately one-third also have AF [9-11]. Furthermore, the decrease in renal function increases the risk of developing AF [12], while AF promotes the decline in eGFR owed to alternations in hemodynamics [6-8]. It also increases the risk of bleeding as a result of multifactorial processes and drug-interactions [13-15].

Anticoagulation therapy in older subjects with AF and CKD may be challenging. Current guidelines for the management of patients with non-valvular AF (NVAF) recommends the use of direct oral anticoagulants (DOACs) [16]. All DOACs have some degree of renal clearance, and dose reduction is indicated in patients with

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clinically significant renal impairment [17]. When prescribing a DOACs to AF patients 75 years and older with CKD, it is important to follow dosing guidelines to maximize stroke protection while minimizing bleeding risk [18]. Regarding apixaban dosing, the daily recommended dose for most NVAF patients is 5 mg taken orally twice a day. Dosing considerations, 2.5 mg twice daily, should be done in cases of serum creatinine ≥1.5 mg/dl; body weight ≤60 kg; age >80 years (2 out of 3) [19].

Nevertheless, there is a degree of uncertainty on the net clinical benefit of anticoagulation in the older adult AF patients with CKD in terms of its impact on stroke, bleeding, and overall survival [18]. The aims of the present study were to characterize and follow prospectively AF older adult patients with renal failure, who have been prescribed apixaban or warfarin for stroke prevention, monitoring prespecified major outcomes in this population.

RESEARCH METHODOLOGY

This is a sub analysis of a multicenter prospective cohort registry, where consecutive eligible patients with AF (paroxysmal and persistent) and renal impairment were enrolled between March 2014 and August 2017 in ten medical centers across Israel. Inclusion criteria included apixaban or warfarin prescription during hospitalization according to treating physician discretion [a recent prescription (within 3 months) or a pre-existing one], renal function impairments, defined as eGFR MDRD<60 ml/min/BSA, and estimated life expectancy > 12 months. Patients were excluded if they had valvular AF or presence or prosthetic valve. Patients were followed for one year after discharge. Follow up was obtained by phone interview, patients' visit and screening of medical records. Vital status was obtained from the nation population registry for 98% of the entire cohort (subjects with missing data were considered alive). Data collection was performed using secured web-based questionnaire developed by the study coordination center at the Israeli Center for Cardiovascular Research. The ascertainment of the key outcomes was made by reviewing patients' medical data as indicated.

As the collected data of the entire cohort is wide and detailed, only sub analysis will be published [19]. The current sub analysis focused on the elderly subjects, age ≥ 75 years. Patients 74 years and younger and those with eGFR<15 ml/min/BSA were excluded from the analysis. The daily recommended dose for Apixaban is 5 mg taken orally twice a day. Dosing considerations for an appropriate dose of 2.5 mg twice daily, was defined in cases of serum creatinine ≥1.5 mg/dl; body weight ≤60 kg; age >80 years (2 out of 3) [20].

The primary outcomes were one year: mortality, stroke/ systemic embolism, major bleeding and myocardial infarction (MI) as well as their composite occurrence. Major bleeding was defined as clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g per deciliter or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death [21].

Statistical analysis

Univariate analysis was performed to determine variables associated apixaban vs. warfarin and descriptive statistics are presented in Tables 1 and 2 continues variables are presented as mean ± standard deviation and compared using t-test or Mann Whitney U test, according to normal or non-normal distribution. Categorical variables are presented as total number and proportion and compared using chi test. Comparison of survival curves was performed using log-rank test and is presented as Kaplan-Meier curves.

A propensity score matching analysis was performed to account for substantial differences in baseline characteristics. Using logistic regression model, where the dependent variable is the treatment group (apixaban vs. warfarin), a conditional predicted probability was computed and used to match between pairs. The following covariants were introduced using the best subset method: age, gender, creatinine, and history of transient ischemic attack (TIA)/stroke, heart failure or history of coronary disease. Further analysis performed to compare warfarin and appropriate apixaban 2.5 mg twice daily dose, among 1:1 matched groups. Matching was performed according to the following variables: age, gender, creatinine, and history of: TIA/stroke, heart failure or history of coronary disease.

Statistical significance was demonstrated when the null hypothesis could be rejected at $p<0.05$. All p-values are the result of two-sided tests. Statistical analyses were conducted using R (version 3.6.1).

RESULTS

Baseline cohort characteristics

A total of 2140 patients with completed baseline data were enrolled to the multicenter prospective cohort. Of them, 976 (45.6%) were treated with warfarin and 1164 (54.4%) with apixaban. This current sub-group analysis of persons 75 years and older included a total of 1460 patients, 877 patients were included in the apixaban group and 583 patients in the warfarin group. Characteristics of the apixaban (2.5 mg and 5 mg twice a day, n= 594 and 283, respectively) and warfarin (n=583) groups are summarized and compared in Table 1 along with the 1-year outcomes.

Patients treated with apixaban 5 mg tended to be younger (81.47 ± 4.47) than the 2.5 mg group (85.97 ± 5.31) and the warfarin ones (83.53 ± 5.53; p<0.001), whereas, their eGFR was higher (52.76 ± 9.22 vs. 44.97 ± 11.98 vs. 44.89 ± 12.97 ml/min/BSA, respectively; p<0.001).

Outcomes at 1-year follow-up

The high dose apixaban was associated with lower risk of the composite end point (death, stroke or systemic embolism, major bleeding, and MI) compared to the low dose and warfarin groups (9.2% vs. 19.6% and 20.6%, respectively; log rank p<0.001). The 1-year survival for 5 mg apixaban group was 7.1% compared to 16.5% in the apixaban 2.5 mg group and 18.4% in the warfarin group (log rank p<0.001). There were no significant differences concerning clinically significant bleeding rates.

Figures 1 and 2 present the 1-year composite end point and survival curves, according to the treatment regimens: warfarin, apixaban 5 mg as well as dosing appropriateness of the low dose apixaban, 2.5 mg. The curves disclose the lower event rates in the older adults with impaired kidney function receiving apixaban 5 mg. Additional analysis compared warfarin and appropriate apixaban 2.5 mg dose (verified dosing against labeling recommendations), among 1:1 matched groups.

The 1-year follow-up outcomes for mortality and the composite end point were significantly lower in the low dose matched apixaban

Table 1: Baseline & outcomes apixaban dosages vs. warfarin.

Variables	Warfarin	Apixaban 2.5 mg	Apixaban 5 mg	p-value
n	583	594	283	
Demographic Information				
Gender (Male) (%)	296 (50.8)	272 (45.8)	146 (51.6)	0.14
Age (Mean (SD))	83.5 (5.5)	85.9 (5.3)	81.4 (4.4)	<0.001
Laboratory Tests				
GFR£ (Mean (SD))	44.8 (12.9)	44.9 (11.9)	52.7 (9.2)	<0.001
Creatinine {(mg/dL)} (Mean (SD))	1.4 (0.5)	1.4 (0.4)	1.2 (0.2)	<0.001
Hemoglobin {(g/dL)} (Mean (SD))	11.3 (2)	11.5 (1.9)	11.9 (1.9)	<0.001
Past Medical History				
Hypertension (%)	344 (69.6)	437 (81.7)	208 (79.4)	<0.001
Coronary artery disease (%)	241 (41.3))	276 (46.5)	125 (44.2)	0.208
CHF¥ (%)	230 (39.5)	286 (48.1)	114 (40.3)	0.006
Diabetes Mellitus (%)	155 (31.4)	188 (35.1)	107 (40.8)	0.034
Past TIAα/Stroke (%)	93 (16)	160 (26.9)	77 (27.2)	<0.001
History of falls (%)	62 (12.6)	133 (24.9)	44 (16.8)	<0.001
Drug/Alcohol abuse (%)	6 (7.6)	10 (17.2)	3 (15)	0.212
PVDμ (%)	32 (6.5)	40 (7.5)	26 (9.9)	0.236
History of major bleeding (%)	26 (5.3)	73 (13.6)	23 (8.8)	<0.001
CHA {2}DS {2}-VASc (Mean (SD))	4.7 (1.5)	5.3 (1.4)	5.1 (1.5)	<0.001
HAS BLED score (Mean (SD))	2.3 (1)	2.6 (0.9)	2.5 (0.9)	<0.001
Medications prior to registry enrollment				
Warfarin (%)	382 (65.5)	75 (12.6)	41 (14.5)	<0.001
Aspirin (%)	201 (34.5)	187 (31.5)	94 (33.2)	0.549
Clopidogrel (%)	68 (11.7)	89 (15.0)	37 (13.1)	0.243
Clexane (%)	41 (7)	42 (7.1)	10 (3.5)	0.094
Outcomes 1-year follow-up				
Stroke/Systemic embolism (%)	8 (1.4)	5 (0.8)	3 (1.1)	0.681
Bleeding (%)	11 (1.9)	10 (1.7)	3 (1.1)	0.665
MIβ (%)	9 (1.5)	13 (2.2)	1 (0.4)	0.124
Mortality (%)	107 (18.4)	98 (16.5)	20 (7.1)	<0.001
Composite end point* (%)	120 (20.6)	116 (19.6)	26 (9.2)	<0.001

£ GFR-Glomerular Filtration Rate; μ PVD-Peripheral Vascular Disease; α TIA-Transient Ischemic Attack; β MI-Myocardial Infarction *Mortality, stroke/systemic embolism, major bleeding and MI as their composite occurrence

Table 2: Baseline & outcomes apixaban 2.5 mg vs. warfarin.

	Warfarin	Apixaban 2.5 mg	P-value
n	268	268	
Demographic Information			
Gender (Male) (%)	125 (46.6)	128 (47.8)	0.863
Age (Mean (SD))	86.5 (4.8)	86.4 (4.9)	0.75
Laboratory Tests			
GFR£ (Mean (SD))	41.6 (13.1)	40.5 (12.4)	0.312
Creatinine (g/dL) (Mean (SD))	1.5 (0.6)	1.5 (0.5)	0.733
Hemoglobin (g/dL) (Mean (SD))	11 (2.1)	11.4 (2.1)	0.08
Past Medical History			
Hypertension (%)	158 (71.2)	184 (79.7)	0.047
CHF¥ (%)	134 (50)	135 (50.4)	1
Coronary artery disease (%)	111 (41.4)	122 (45.5)	0.384
Diabetes Mellitus (%)	72 (32.4)	79 (34.2)	0.765
Past TIAα/Stroke (%)	58 (21.6)	62 (23.1)	0.756
History of falls (%)	37 (16.7)	59 (25.5)	0.028
History of major bleeding (%)	18 (8.1)	29 (12.6)	0.162

PVDμ (%)	15 (6.8)	19 (8.2)	0.67
Drug/Alcohol abuse (%)	2 (5.1)	5 (14.3)	0.344
CHA2DS2-VASc (Mean (SD))	5.1 (1.5)	5.2 (1.4)	0.269
HAS BLED score (Mean (SD))	2.3 (1.0)	2.5 (0.9)	0.093
Medications Prior to Registry Enrolment			
Warfarin (%)	173 (64.6)	37 (13.8)	<0.001
Aspirin (%)	95 (35.4)	93 (34.7)	0.928
Clopidogrel (%)	31 (11.6)	35 (13.1)	0.693
Clexane (%)	21 (7.8)	26 (9.7)	0.541
Outcomes 1-Year Follow-up			
Stroke/Systemic embolism (%)	7 (2.6)	1 (0.4)	0.075
Bleeding (%)	6 (2.2)	5 (1.9)	1
MIβ (%)	5 (1.9)	5 (1.9)	1
Mortality (%)	69 (25.7)	41 (15.4)	0.004
Composite end point* (%)	75 (28.0)	48 (18.0)	0.008

£GFR-Glomerular Filtration Rate; μ PVD-Peripheral Vascular Disease; α TIA-Transient Ischemic Attack; β MI-Myocardial Infarction *Mortality, Stroke/Systemic Embolism, Major Bleeding and MI as their composite occurrence

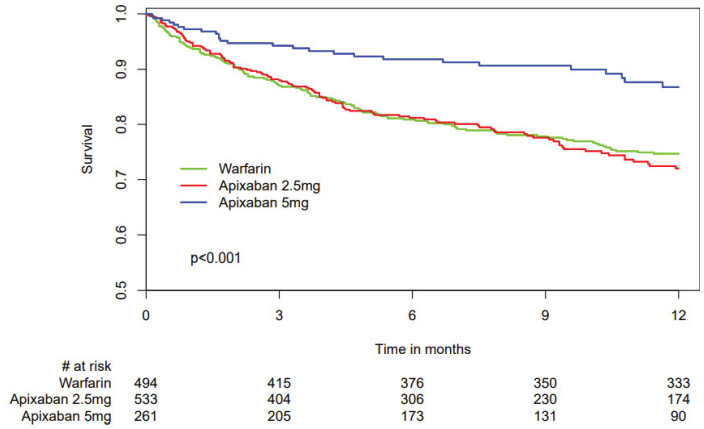

Figure 1: K-M survival curves for composite end point.

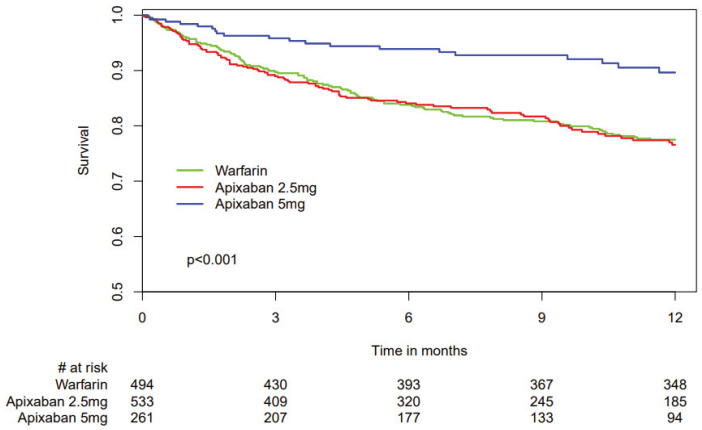

Figure 2: K-M survival curves for 1-year mortality.

arm [1-year mortality of 41 (15.4%) vs. 69 (25.7%) and composite end point events of 48 (18.0%) vs. 75 (28.0%)], with curve diverging predominately from the third month of follow up onward, without a significant increase in adverse outcomes (Table 2, Figures 3 and 4).

DISCUSSION

The study results suggest that in NVAF patients aged >75 years with impaired renal function, treatment with apixaban 5 mg is associated

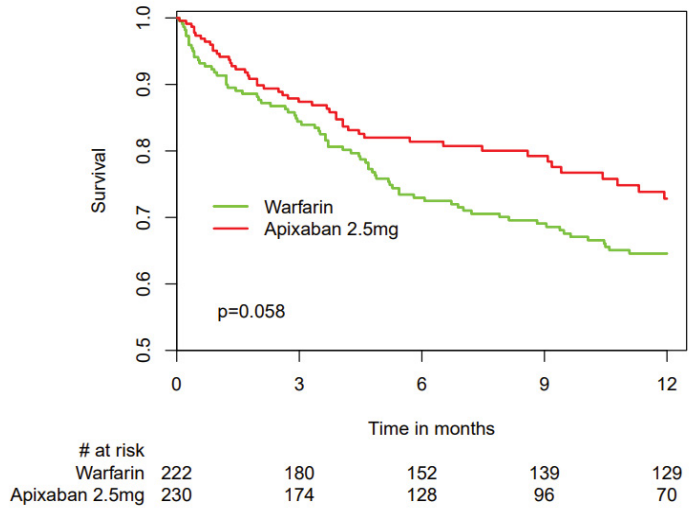

Figure 3: K-M survival curves for composite end point matched data.

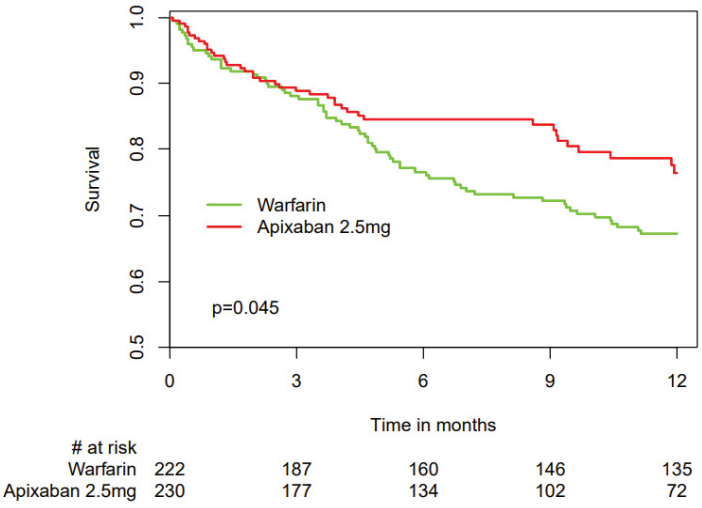

Figure 4: K-M survival curves for 1-year mortality matched data.

with better outcomes compared to 2.5 mg appropriate dose and warfarin concerning 1-year composite clinical outcomes, including efficacy and survival, without an increase in bleeding rates. The same benefit was seen when apixaban 2.5 mg appropriate dose and

warfarin were compared. This may be attributed to the higher risk characteristics, older age and multiple comorbidities of the patients receiving the lower dose apixaban and warfarin.

Most of the available data regarding the efficacy and safety of DOACs in older adult's patients emerge from subgroup analysis of the large randomized controlled trials [14]. However, only limited numbers of persons 75 years and older were included [17], while lower bleeding rates were observed with DOACS due to the exclusion of patients with advanced kidney disease [3].

A major concern in the routine clinical practice is that prescribed DOAC doses often inconsistent with drug labelling, especially among older adults and those with impaired renal function, which affect clinical efficacy and safety profiles. In a large- scale analysis of DOACs dosing, apixaban dose reduction in patients without severe renal impairment was related to reduced effectiveness for stroke prevention without safety benefit [22]. Another study demonstrated a positive net clinical benefit (NCB) favoring oral anticoagulation therapy in older adults and those treated with higher doses of DOAC with the greatest NCB observed in the group aged 75-84 years, stresses the importance of optimal dosing [23].

To our knowledge, this is the only study compared propensity matched records of warfarin and 2.5 mg apixaban as correctly prescribed. It points out the strengths of the real-world prospective data. Our research demonstrated that patients aged 75 or older with impaired renal function, have better outcomes associated with apixaban 5 mg and appropriate 2.5 mg dose versus use of warfarin, as well as reduced mortality rates. Furthermore, we noted comparable results in significant bleeding and embolic events compared to the group receiving warfarin. Despite these reports, large-scale studies assessing prescribing patterns and patient outcomes are required to optimize practice further in this population of very high-risk features [24].

The study limitations include the relatively small study subgroup and short follow up periods, which might affect the efficacy and safety outcomes. Less than 50% of the warfarin and apixaban 2.5 mg population was able to be matched. As a result, the association is limited only to the applicable population that could be successfully matched. Other limitations include the lack of cause of death information and no data regarding treatment changes following discharge, nor any kind of adherence measure, international normalized ratio (INR) monitoring, the proportion of days covered or an analysis whether certain institutes use more of one medication versus the other.

STATEMENT OF ETHICS

Study was ethically approved by the local IRB. This current study complies with internationally accepted standards for research practice and reporting. All participants signed informed consent in compliance with the Helsinki Declaration. Ethical review board approved study protocol by ethics committee in each of the hospitals Reference number RMC-14-396 for Beilinson Hospital, Rabin Medical Center, Petah-Tikva, Israel.

CONCLUSION

Based on the previous data and the current study, it can be summarized that appropriate dose apixaban appears to be a rational alternative to warfarin in patients 75 years and older with low eGFR, with even associated improved outcomes. Prospective studies are warranted to definitively establish this advantage and regarding dose adjustments inconsistent with FDA-labeled recommendations.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted.

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