# Apixaban in Patients with Atrial Fibrillation and Severe Renal Dysfunction: Findings from a National Registry

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**ABSTRACT**

**Background:** Real-world information regarding the use of direct oral anticoagulants therapy and the outcome in patients with renal dysfunction is limited.

**Objectives:** To evaluate the clinical characteristics and outcomes of patients with atrial fibrillation (AF) and severe renal dysfunction who are treated with apixaban.

**Methods:** A sub-analysis was conducted within a multicenter prospective cohort study. The study included consecutive eligible apixaban- or warfarin-treated patients with non-valvular AF and renal impairment (estimated glomerular filtration rate [eGFR] modification of diet in renal disease [MDRD] < 60 ml/min/BSA) were registered. All patients were prospectively followed for clinical events and over a mean period of 1 year. Our sub-analysis included the patients with 15 < eGFR MDRD < 30 ml/min/BSA. The primary outcomes at 1 year were recorded. They included mortality, stroke or systemic embolism, major bleeding, and myocardial infarction as well as their composite occurrence.

**Results:** The sub-analysis included 155 warfarin-treated patients and 97 apixaban-treated ones. All had 15 < eGFR MDRD < 30 ml/min/BSA. When comparing outcomes for propensity matched groups (n=76 per group) of patients treated by reduced dose apixaban or warfarin, the rates of the 1-year composite endpoint as well as mortality alone were higher among the warfarin group (30 [39.5%] vs. 14 [18.4%], *P* = 0.007 and 28 [36.8%] vs.12 [15.8%], *P* = 0.006), respectively. There was no significant difference in the rates of stroke, systemic embolism, or major bleeding.

**Conclusions:** Apixaban might be a reasonable alternative to warfarin in patients with severe renal impairment

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**KEY WORDS:** atrial fibrillation (AF), apixaban, direct oral anticoagulants (DOACs), renal dysfunction, warfarin

Current guidelines for the management of patients with atrial fibrillation (AF) recommend the use of direct oral anticoagulants (DOACs) in patients with non-valvular AF [1]. The prevalence of renal dysfunction in patients with AF is high, with approximately 60% of patients having an estimated glomerular filtration rate (eGFR) of 60 ml/min/BSA [2]. Renal dysfunction has been shown to be an independent predictor of stroke or systemic emboli, but the risk of bleeding with conventional warfarin therapy is also significantly increased [3-6].

DOACs undergoing significant renal secretion, such as dabigatran, are not recommended for patients with severe renal impairment, and dose adjustment is indicated for patients with milder degrees of renal dysfunction [7]. In contrast, treatment with non-renal secreted DOACs may be associated with enhanced efficacy and safety profiles in this high-risk population. However, real-world information regarding the usage and outcomes associated with DOAC therapy in patients with renal dysfunction is limited.

Apixaban is a DOAC characterized by good bioavailability and renal elimination accounting for only 25%, showing a safety profile and effectiveness in patients with renal impairment [8]. The daily recommended dose for most non-valvular atrial fibrillation (NVAF) patients is 5 mg taken orally twice a day. Dosing considerations, 2.5 mg twice daily, should be prescribed in cases of serum creatinine ≥ 1.5 mg/dl; body weight ≤ 60 kg; age > 80 years (2 out of 3) [9]. Nevertheless, the use of apixaban in patients with a creatinine clearance (CrCl) of < 15 ml/min or in those on dialysis is based only on pharmacokinetic data, as clinical trials excluded patients with a CrCl of < 25 ml/min or a serum creatinine concentration (SCr) of > 2.5 mg/dl [10].

The aim of the present study was to characterize and follow prospectively AF patients with severe renal impairment, who have been prescribed apixaban or warfarin for stroke prevention, comparing pre-specified major outcomes in this population.

## PATIENTS AND METHODS

This sub-analysis was conducted within a multicenter prospective cohort study. The study included consecutive patients with AF (paroxysmal and persistent) and renal impairment who were enrolled in 10 medical centers across Israel between March 2014 and August 2017.

Inclusion criteria included apixaban or warfarin prescription according to treating physician discretion, renal function

impairment, defined as eGFR MDRD < 60 ml/min/BSA, life expectancy > 12 months. Patients were excluded if they had valvular AF, presence of prosthetic valve or any other indication for anticoagulation treatment.

Patients were followed for one year after discharge. Follow-up was obtained by phone interview, patient visit, and screening of medical records. Vital status was obtained from the nation population registry for 98% of the entire cohort.

Data collection was performed using a secured web-based questionnaire developed by the study coordination center at the Israeli Center for Cardiovascular Research.

The current sub-analysis included the patients with eGFR MDRD < 30 ml/min/BSA. Patients with eGFR < 15 ml/min/BSA were excluded from the analysis.

The primary outcomes were one year: mortality, stroke/ systemic embolism, major bleeding (defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ and/or bleeding leading to transfusion of two or more units of red cells), and myocardial infarction (MI), MI was defined as detection of rise and fall of troponin values along with symptoms of acute myocardial ischemia or new ischemic electrocardiographic changes as well as their composite occurrence.

**STATISTICAL ANALYSIS**

Univariate analysis and descriptive statistics are presented in Table 1 and Table 2. comparisons were made between apixaban and warfarin. Continuous variables are presented as mean ± standard deviation and compared using $t$-test or Mann–Whitney U test,

**Table 1.** Baseline characteristics and outcomes of the study population by apixaban 2.5 mg vs. warfarin

| | Warfarin (n=155) | Apixaban 2.5 mg (n=97) | P value |
|---|---|---|---|
| **Demographic information** | | | |
| Sex (male) (%) | 88 (56.8) | 46 (47.4) | 0.188 |
| Age, years, mean ± standard deviation | 76.63 (10.71) | 82.10 (8.79) | < 0.001 |
| **Renal function** | | | |
| eGFR (mil/min), mean ± standard deviation | 23.62 (4.49) | 25.06 (4.10) | 0.011 |
| Creatinine (mg/dl), mean ± standard deviation | 2.36 (0.65) | 2.22 (0.53) | 0.065 |
| **Past medical history** | | | |
| Congestive heart failure (%) | 84 (54.2) | 63 (64.9) | 0.120 |
| Diabetes mellitus (%) | 67 (52.8) | 35 (44.3) | 0.300 |
| Hypertension (%) | 91 (71.7) | 66 (83.5) | 0.075 |
| Liver dysfunction (%) | 6 ( 3.9) | 2 ( 2.1) | 0.669 |
| Coronary artery disease (%) | 64 (41.3) | 46 (47.4) | 0.410 |
| Past TIA/stroke (%) | 24 (15.5) | 15 (15.5) | 1.000 |
| History of major bleeding (%) | 8 ( 6.3) | 10 (12.7) | 0.188 |
| History of falls (%) | 11 ( 8.7) | 13 (16.5) | 0.141 |
| Drug/alcohol abuse (%) | 1 ( 4.2) | 1 ( 5.9) | 1.000 |
| HAS BLED score, mean ± standard deviation | 2.51 (1.20) | 2.53 (0.96) | 0.911 |
| CHADS-VASc, mean ± standard deviation | 4.61 (1.73) | 5.37 (1.38) | 0.001 |
| **Outcomes of 1-year follow-up** | | | |
| Stroke/systemic embolism (%) | 0 ( 0.0) | 2 ( 2.1) | 0.287 |
| Major bleeding (%) | 4 ( 2.6) | 2 ( 2.1) | 1.000 |
| Myocardial infarction (%) | 6 ( 3.9) | 1 ( 1.0) | 0.347 |
| Mortality (%) | 45 (29.0) | 19 (19.6) | 0.127 |
| Composite endpoint* (%) | 51 (32.9) | 21 (21.6) | 0.075 |

*Composite endpoint includes: mortality, stroke, systemic embolism, major bleeding, and myocardial infarction

**Table 2.** Baseline characteristics and outcomes by apixaban 2.5 mg vs. warfarin-matched data. Data are listed according to age, sex, creatinine values, past TIA/stroke, congestive heart failure, and coronary artery disease

| | Warfarin (n=155) | Apixaban 2.5 mg (n=97) | *P* value |
|---|---|---|---|
| **Demographic information** | | | |
| Sex (male) (%) | 43 (56.6) | 38 (50.0) | 0.516 |
| Age, years, mean ± standard deviation | 80.29 (10.31) | 80.88 (9.29) | 0.714 |
| **Renal function** | | | |
| eGFR (mil/min), mean ± standard deviation | 24.74 (4.18) | 24.71 (4.22) | 0.976 |
| Creatinine (mg/dl), mean ± standard deviation | 2.26 (0.57) | 2.26 (0.54) | 0.993 |
| **Past medical history** | | | |
| Congestive heart failure (%) | 50 (65.8) | 46 (60.5) | 0.614 |
| Diabetes mellitus (%) | 32 (50.8) | 28 (48.3) | 0.925 |
| Hypertension (%) | 48 (76.2) | 47 (81.0) | 0.670 |
| Liver dysfunction (%) | 1 ( 1.3) | 2 ( 2.6) | 1.000 |
| Coronary artery disease (%) | 42 (55.3) | 35 (46.1) | 0.330 |
| Past TIA/stroke (%) | 9 (11.8) | 9 (11.8) | 1.000 |
| History of major bleeding (%) | 4 ( 6.3) | 8 (13.8) | 0.287 |
| History of falls (%) | 6 ( 9.5) | 9 (15.5) | 0.469 |
| Drug/alcohol abuse (%) | 0 ( 0.0) | 0 ( 0.0) | 1.000 |
| HAS BLED score, mean ± standard deviation | 2.51 (1.11) | 2.46 (1.00) | 0.760 |
| CHADS-VASc, mean ± standard deviation | 5.08 (1.42) | 5.17 (1.38) | 0.715 |
| **Outcomes 1-year follow-up** | | | |
| Stroke/systemic embolism (%) | 0 ( 0.0) | 1 ( 1.3) | 1.000 |
| Major bleeding (%) | 0 ( 0.0) | 2 ( 2.6) | 0.477 |
| Myocardial infarction (%) | 4 ( 5.3) | 1 ( 1.3) | 0.363 |
| Mortality (%) | 28 (36.8) | 12 (15.8) | 0.006 |
| Composite endpoint* (%) | 30 (39.5) | 14 (18.4) | 0.007 |

*Composite endpoint includes: mortality, stroke, systemic embolism, minor/major bleeding, and myocardial infarction

according to normal or non-normal distribution. Categorical variables are presented as total number and proportion and compared using chi square test. Comparison of survival curves was performed using log-rank test and is presented as Kaplan–Meier plot.

A propensity score matching analysis was performed according to the following variables: age, sex, creatinine values, past transient ischemic attack (TIA)/stroke, congestive heart failure, coronary artery disease, 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.

Data analysis was conducted using R Core Team (2018). R is a language and environment for statistical computing created by

R Foundation for Statistical Computing, Vienna, Austria, which is available from https://www.R-project.org.

## RESULTS

A total of 2140 patients with completed baseline data were enrolled in the multicenter prospective cohort. Of this group, 976 (45.6%) were included in the warfarin group and 1164 (54.4%) in the apixaban one. The current sub-analysis included 118 apixaban treated patients and 155 warfarin treated ones. All had 15 ml/min/BSA < eGFR MDRD < 30 ml/min/BSA.

Table 1 provides the baseline characteristics and 1-year outcomes of the 97 patients treated with apixaban 2.5 mg twice a day and of the 155 ones treated by warfarin. Patients in the war-

farin group were younger ($76.63 \pm 10.71$ vs. $82.10 \pm 8.97$ years, $P < 0.001$) and had significantly lower eGFR and CHADS-Vasc score. The crude 1-year outcomes did not differ between the two treatment groups.

When comparing the two propensity matched groups (n=76) of patients treated by apixaban 2.5 mg twice a day and warfarin, the rate of the 1-year composite endpoint including mortality, stroke/systemic embolism, major bleeding, and MI, as well as mortality alone were higher among the warfarin group: 30 (39.5%) vs. 14 (18.4%), $P = 0.007$ and 28 (36.8%) vs. 12 (15.8%), $P = 0.006$ [Table 2].

Figure 1 and Figure 2 provide the 1-year survival curves of the apixaban 2.5 mg twice a day and warfarin groups after data matching.

## DISCUSSION

The study results suggest that in NVAF patients with severe renal dysfunction ($15 < $ eGFR MDRD $ < 30$ ml/min/BSA) the treatment with apixaban 2.5 mg twice a day is superior to warfarin, with regard to 1-year mortality. However, there is no difference in stroke, systemic embolism, or bleeding events.

As the randomized controlled clinical trials of apixaban excluded patients with a CrCl of $< 25$ ml/min or a serum creatinine concentration of $> 2.5$ mg/dl [9] and there is limited observational data on their use in this population, the efficacy and safety of apixaban in patients with renal failure is less certain.

Previous studies concerning DOACs treatment in patients with advanced renal failure showed compelling results as they varied in their design and study groups. Shin et al. [10] concluded that patients with eGFR $< 60$ ml/min per 1.73 m2 who took DOACs for AF had a slightly higher risk of bleeding compared with those taking warfarin, but similar benefits in prevention of ischemic stroke. Both systemic review and meta-regression analyses of five studies comprising 72,845 AF patients randomized to either a NOAC or warfarin and 12,545 AF participants with chronic kidney disease (CKD) from five studies revealed that non-vitamin K oral anticoagulants had similar efficacy and safety compared to warfarin across different levels of renal function [11,12].

Several studies concentrated in apixaban treatment. In an analysis consisting of 43,850 patients in five observational cohort studies, where the majority of patients (87%) with advanced chronic kidney disease used apixaban for AF, the use of apixaban was associated with lower risk of major bleeding compared to warfarin and was found to be relatively effective with no excess risk of thromboembolic events [13].

In a retrospective cohort study of 604 patients with advanced CKD receiving apixaban or warfarin, the rates of apixaban and warfarin patients with a major bleeding at 0 to 3, 3 to 6, and 6 to 12 months were 8.3% vs. 9.9% ($P = 0.48$), 1.4% vs. 4% ($P = 0.07$), and 1.5% vs. 8.4% ($P < 0.001$), respectively. There were no differences in rates of ischemic stroke [14]. Sub-analysis of the ARISTOTLE trial showed that among patients with AF and CrCl 25 to 30 ml/min, apixaban caused less bleeding than warfarin [15]. A recent review revealed that apixaban is an effective anticoagulant in patients with AF and renal dysfunction, possibly superior to warfarin in reducing the risk of stroke and systemic embolism regardless of the presence of renal insufficiency [8].

**Figure 1.** Curves for composite endpoint (matched data)



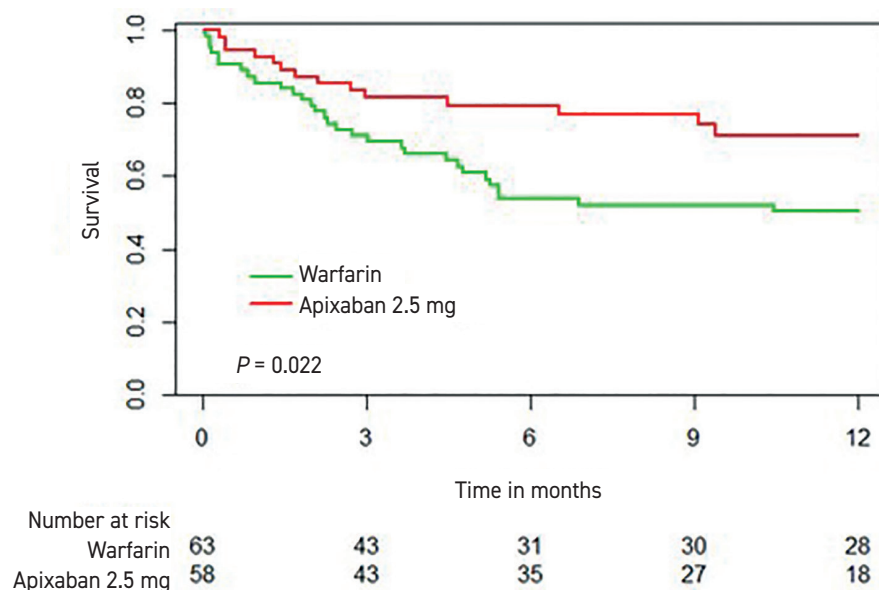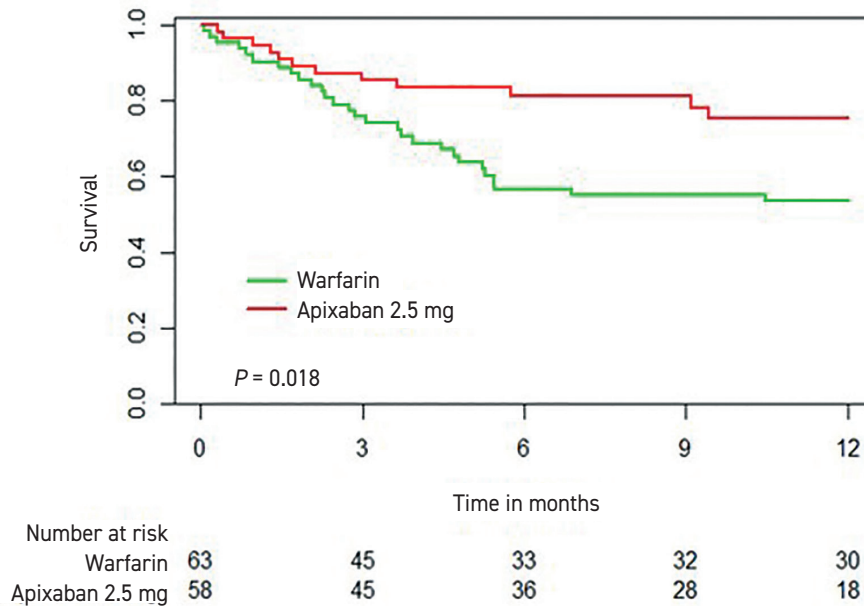| Number at risk | | | | | |
|---|---|---|---|---|---|
| Warfarin | 63 | 43 | 31 | 30 | 28 |
| Apixaban 2.5 mg | 58 | 43 | 35 | 27 | 18 |

**Figure 2.** Survival curves for 1 year mortality (matched data)



Therefore, despite the low quality of the evidence due to heterogeneity and the retrospective design of the studies as well as some conflicting results, the growing body of evidence suggests that DOACs can be considered as a safe and attractive alternative to warfarin in patients with severely impaired renal function. However, our study, which included patients with severe renal dysfunction (15 < eGFR MDRD < 30 ml/min/BSA), concluded that apixaban 2.5 mg twice a day was superior to warfarin concerning 1-year mortality, without any difference in stroke, systemic embolism, and bleeding. The lack of superiority of apixaban in terms of safety might be explained by the small study group and the relative lack of statistical power. The positive effect on mortality might be explained by the prevention of other cardiovascular complications, like venous thromboembolism or the effect on peripheral artery disease as was found in the COMPASS study [16].

Apixaban was also found to be a cost-effective alternative to warfarin in AF patients with normal kidney function and potentially cost-saving in those with renal impairment [17].

## STRENGTHS

Our study included real world prospective data from multiple sites, which permitted a propensity matched analysis of patients treated with apixaban 2.5 mg twice a day vs. warfarin. The propensity score matching analysis was performed according to the variables: age, sex, creatinine values, past TIA/stroke, congestive heart failure, and coronary artery disease. We used these parameters because they contribute mostly to the differences between the groups. The inclusion criteria as well as the propensity score matching excluded any major bias.

## LIMITATIONS

The study was a relatively small study subgroup. It included non-direct (randomized) comparison between the two groups, the lack of cause of death information, and no data regarding eGFR or treatment changes following discharge.

## CONCLUSIONS

Apixaban may be a reasonable alternative to warfarin in patients with severe renal impairment, possibly associated with improved outcomes. Prospective studies are warranted to definitively establish an advantage.

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**Capsule**

## IgG fucosylation predicts dengue severity

Secondary infections with dengue virus (DENV) can produce life-threatening symptoms, including thrombocytopenia and hemorrhagic disease, when pre-existing DENV-reactive immunoglobulin G1 (IgG1) antibodies promote the infection of immune cells. Although severe dengue symptoms are associated with increased levels of afucosylated IgG1 glycoforms, it is unclear whether this is simply a result of the infection or if it is a preexisting phenomenon that can dictate susceptibility to this disease. **Bournazos** and colleagues studied the Fab and Fc structures of anti-DENV antibodies from patients before and after infection and with variable disease outcomes. They found that DENV infection induced specific increases in IgG1 afucosylation, and levels of afucosylated IgG1 could indeed predict dengue disease severity, making IgG1 fucosylation status a potentially useful prognostic tool for the treatment of dengue patients.

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**Capsule**

## Reconstructing TFR cell development

Antibody responses, including those against self-antigens, are tightly controlled within germinal centers by balancing the activity of T follicular regulatory (TFR) and T follicular helper (TFH) cells. **Kumar** and colleagues reconstructed the developmental trajectory of TFR cells using flow cytometry-indexed single-cell transcriptomics of follicular T cells isolated from human peripheral blood, lymph nodes, and tonsils. They used transcriptomics to support a model in which mature germinal center TFR cells arise from regulatory T cells, with circulating TFR cells representing a separate developmental pathway. These results suggest that mature TFR cells primarily arise independently from their less mature counterparts in peripheral blood, providing further insight into how human TFR cells develop.

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