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# NOVEL ORAL ANTICOAGULANTS IN RENAL TRANSPLANT RECIPIENTS: A RETROSPECTIVE COHORT STUDY

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## ABSTRACT

**Aim:** Data on the use of novel anticoagulant drugs (NOACc) in renal transplant recipients is scarce. The aim of our study was to investigate the safety and efficacy of NOACs in renal transplant recipients.

**Materials and Methods:** In a single-centre retrospective cohort study we assessed adverse reactions, thromboembolic events, and interactions of calcineurin inhibitors in patients treated with NOACs.

**Results**: Twenty-three renal transplant recipients were treated with NOACs (70% male), mean age of 65.8 ± 1.8 years. Fourteen (61%) patients were treated with rivaroxaban, apixaban was given to 8 (35%) of our patients, and dabigatran to one patient (4%). The main indications for NOAC therapy was atrial fibrillation in 61% and deep venous thrombosis in 23% of patients. Bleeding occurred in 2 patients (1 treated with rivaroxaban and 1 with dabigatran). None of our patients developed thrombosis while treated with NOAC. During the median follow-up of 24 months graft function, as well as hematological parameters, remained stable in patients that were treated with rivaroxaban and apixaban, while dabigatran was ceased after a month of therapy due to a bleeding event.

**Conclusion**: Our results show that both rivaroxaban and apixaban are safe and efficient oral anticoagulant drugs in renal transplant patients. Additional studies are needed to prove these results.

**Keywords**: novel anticoagulant drugs, rivaroxaban, apixaban, dabigatran, renal transplantation

## INTRODUCTION

For decades, vitamin K inhibitors were the cornerstone of the oral anticoagulant therapy, requiring frequent monitoring to maintain adequate drug levels. Novel oral anticoagulant drugs (NOACs) were developed to surmount these limitations. They are recommended in patients with atrial fibrillation (AF) at high risk of stroke [1]. Data on the use of NOACs in renal transplant recipients (RTR) is scarce. Despite the lack of evidence-based recommendations, they are increasingly used in these patients. Since renal transplant recipients present a unique and vulnerable population with specific cardiovascular risk factors, a caution with introduction of any novel therapy is mandatory. Additional problems are renal clearance of NOACs and possible interactions with immunosuppressive drugs [2]. Aim of the present study

is to assess safety and efficacy of NOACs in renal transplant population.

## PATIENTS AND METHODS

Charts and medical records of adult RTR transplanted between December 1999 and December 2019 were investigated to discover patients with NOAC in therapeutic regiment. Patients received triple immunosuppressive regimen (tacrolimus or cyclosporine, azathioprine or mycophenolate mofetil and steroids). Universal induction therapy with basiliximab was used since 2009. Sensitized patients or recipient of the second or third renal allograft received antithymocyte globulin for induction. Since 2011, patients received universal valganciclovir and trimetoprim-sulphometoxasole prophylaxis.

Age, gender, dialysis vintage, time of transplantation, immunosuppressive protocol, donor type, episodes of acute graft rejection, were noted. Indication for NOAC, type of drug, graft function and complications were recorded.

The study was approved by the Ethics Committee of University hospital centre Zagreb and conducted according to the Helsinki Declaration.

## RESULTS

*Patients' characteristics*

From August 2007 to December 2019, 1374 patients received kidney allograft at our institution. Novel anticoagulant drug was used in 23 patients (1.67%). Fourteen (61%) patients were treated with rivaroxaban, apixaban was given to 8 (35%), and dabigatran to one patient (4%). There were 16 male patients and 7 female patients, their average age was 65.8 ± 1.8 years, and the therapy was started at the average of 8 years after transplantation (range 35 days – 13 years). The main indications for NOAC therapy were AF (61% of patients) and deep venous thrombosis (23%) (Table 1).

There was no difference between the groups in the HAS-BLED or CHA2DS2-VASc score (Table 2).

| | Number / Total | | | | P* |
|---|---|---|---|---|---|
| | Rivaroxaban | Apixaban | Dabigatran | Ukupno | |
| Gender | | | | | |
| Female | 5/14 | 2/8 | 0 | 7/23 | >0,99 |
| Male | 9/14 | 6/8 | 1/1 | 16/23 | |
| Cyclosporine A | 10/14 | 2/8 | 0 | 12/23 | 0,05 |
| Azathioprine | 1/14 | 0/8 | 0/1 | 1/23 | >0,99 |
| Tacrolimus | 2/14 | 6/8 | 1/1 | 9/23 | **0,007** |
| Mycophenolate | 12/14 | 8/8 | 1/1 | 21/23 | 0,56 |
| Everolimus | 2/14 | 0/8 | 0/1 | 2/23 | 0,56 |
| Primary kidney disease | | | | | |
| Nephroagiosclerosis | 2/14 | 0 | 0 | 2/23 | 0,38 |
| Diabetic nephropathy | 1/14 | 3/8 | 0 | 4/23 | |
| ADPKD | 4/14 | 1/8 | 1/1 | 6/23 | |
| Glomerulonephritis | 1/14 | 2/8 | 0 | 3/23 | |
| Pyelonephritis | 1/14 | 1/8 | 0 | 2/23 | |
| Other | 5/14 | 1/8 | 0 | 6/23 | |
| Posttransplant diabetes | | | | | |
| No | 11/14 | 5/8 | 1/1 | 17/23 | 0,72 |
| Yes | 3/14 | 3/8 | 0 | 6/23 | |
| Indication | | | | | |
| Atrial fibrillation (AF) | 10/14 | 3/8 | 1/1 | 14/23 | 0,50 |
| Deep venous thrombosis (DVT) | 3/14 | 2/8 | 0 | 5/23 | |
| Pulmonary embolism (PE) | 1/14 | 1/8 | 0 | 2/23 | |
| AF+DVT | 0 | 1/8 | 0 | 1/23 | |
| DVT + PE | 0 | 1/8 | 0 | 1/23 | |

**Table 1.** *Patients' characteristics. ADPKD, autosomal dominant polycystic kidney disease; AF, atrial fibrillation; DVT, deep venous thrombosis; PE pulmonary embolism. *Fisher's exact test*

| | Number/total | | | | P* |
|---|---|---|---|---|---|
| | Rivaroxaban (n = 14) | Apixaban (n = 8) | Dabigatran (n = 1) | Ukupno | |
| HAS-BLED | | | | | |
| 0 | 2/14 | 2/8 | 0 | 4/23 | 0,61 |
| 1 | 5/14 | 5/8 | 1/1 | 11/23 | |
| 2 | 6/14 | 1/8 | 0 | 7/23 | |
| 3 | 1/14 | 0 | 0 | 1/23 | |
| Total | 14/14 | 8/8 | 1/1 | 23/235 | |
| $CHA_2DS_2$-VASc | | | | | |
| 2 | 4/14 | 1/8 | 0 | 5/23 | 0,95 |
| 3 | 4/14 | 3/8 | 1/1 | 8/23 | |
| 4 | 2/14 | 1/8 | 0 | 3/23 | |
| 5 | 2/14 | 1/8 | 0 | 3/23 | |
| 6 | 2/14 | 1/8 | 0 | 3/23 | |
| 8 | 0 | 1/8 | 0 | 1/23 | |
| Total | 14/14 | 8/8 | 1/1 | 23/23 | |

**Table 2.** *Bleeding risk and risk of thromboembolic events.*
*Fishers' exact test

*Influence of NOACs on renal allograft function*

We further investigated allograft function after introduction of NOACs (Table 3).

| | Rivaroxaban | P* | Apixaban | P* | Dabigatran (n=1) | P† (between Rivar i Api) |
|---|---|---|---|---|---|---|
| GFR | | | | | | |
| Initial | 39,5 (29,8–54) | 0,13 | 41,5 (37–44) | 0,81 | 68 | 0,79 |
| 1 month | 41 (36,5–51,5) | | 41 (39–46,8) | | 58 | >0,99 |
| 3 months | 41,5 (33,8–52,5) | | 42 (40–44) | | | 0,77 |
| 6 months | 45 (35,5–53,8) | | 39 (35–45) | | | 0,26 |
| 1 year | 44 (26,3–54) | | 43 (30–46,5) | | | 0,56 |
| 2 years | 59 (50–59,5) | | 41 (22–44) | | | 0,05 |

**Table 3.** *Changes in glomerular filtration rate after introduction of novel anticoagulant drugs. GFR, glomerular filtration rate. *Friedman test; † Mann Whitney U test*

Glomerular filtration rates increased over the observed period in patients treated with rivaroxaban (not statistically significant), but when compared with GFR of patients from the apixaban group who maintained their allograft function, this change reached statistically significant difference (59 vs. 41 ml/min/1.73m2, p=0.05, respectively).

There was no influence of NOACs on development of proteinuria.

*Side effects of NOACs*

Over the median follow-up period of 2 years, 1 patient died (4.34%). Bleeding occurred in 2 patients, one treated with rivoroxaban and one with dabigatran, which in the latter required treatment cessation and switch to warfarin. There were no thromboembolic events during the treatment with NOACs (Table 4).

| | Number / Total | | | | P* |
|---|---|---|---|---|---|
| | Rivaroxaban | Apixaban | Dabigatran | Total | |
| Bleeding | 1/14 | 0/8 | 1/1 | 2/23 | 0,09 |
| Thrombosis | 0/14 | 0/8 | 0/1 | 0/23 | – |

**Table 4.** *Complications in patients treated with different novel oral anticoagulants.*
*Fisher exact test

We further looked for changes in serum hemoglobin and platelet counts under the NOAC treatment (Table 5).

| | Rivaroxaban | P* | Apixaban | P* | Dabigatran (n=1) | P† (between Rivar i Api) |
|---|---|---|---|---|---|---|
| Hemoglobin | | | | | | |
| Initial | 125 (102,8–141,8) | | 133 (123–140,8) | | 142 | 0.45 |
| 1 month | 133 (108,5–142,5) | | 133,5 (126,3–147) | | 153 | 0.63 |
| 3 months | 132 (116,3–143) | 0,06 | 137 (131–157) | 0,83 | | 0.31 |
| 6 months | 134 (109,5–145) | | 134 (128–156) | | | 0.56 |
| 1 year | 131,5 (120,3–144) | | 131 (116–153) | | | 0.88 |
| 2 years | 140 (131,5–158) | | 134 (125–136) | | | 0.18 |
| Platelets | | | | | | |
| Initial | 226 (202–283) | | 239,5 (168,5–263,5) | | 263 | 0.56 |
| 1 month | 221 (195,3–301,5) | | 205 (187,3–252) | | 289 | 0.46 |
| 3 months | 230 (172–300) | 0,83 | 243 (183–257) | 0,27 | | 0.56 |
| 6 months | 214,5 (184–355) | | 254 (163–270) | | | 0.56 |
| 1 year | 248,5 (182,8–380,5) | | 236 (169–252,5) | | | 0.46 |
| 2 years | 287 (199,5–391) | | 188 (154–214) | | | 0.10 |

**Table 5.** *Changes in serum hemoglobin concentrations and platelet count after introduction of novel anticoagulants*
*Friedman test; † Mann Whitney U test

Patients from the rivoroxaban group increased serum hemoglobin from the initial 125 g/L to 140 g/L (p = 0.06), without changes in platelet counts. Patients treated with apixaban or dabigatran had stable blood cells counts during the treatment.

There was no influence of NOACs on the liver chemistries or serum electrolites.

*Interactions between NOACs and immunosuppressive drugs*

Cyclosporine trough levels were stable after the introduction of NOACs in the treatment regimen (Table 6).

There was no correlation of cyclosporine trough levels with other parameters.

| **Time** | Rivaroxaban | P* | Apixaban | P* | P† |
|---|---|---|---|---|---|
| 0 | 95.5 (75.8–105.8) | | 94.5 (57.8–99.5) | | 0.75 |
| 1 month | 100 (75–111.8) | 0.74 | 84 (54.8–86.8) | 0.14 | 0.39 |
| 12 months | 101.5 (61.5–104.3) | | 81 (54–83) | | 0.52 |

**Table 6.** *Cyclosporine trough level before, at one month and 12 months after the introduction of NOACs.*
*Friedman test; †Mann Whitney U test

Tacrolimus trough levels decreased in both rivaroxaban and apixaban group, with decrease in the latter group being statistically significant (from 6.7 to 4.4 ng/mL, p = 0.02). To the contrast, patient treated with dabigatran increased tacrolimus trough level from 6.7 to 12.2 ng/mL) (Table 7). After the first year, tacrolimus trough levels remained stable in both groups.

| Time | Rivaroxaban (n=2) | P* | Apixaban (n=6) | P* | Dabigatran (n=1) | P* | P† (Rivaro vs. Apix) |
|---|---|---|---|---|---|---|---|
| 0 | 7.5 (4.8–6,5) | | 6.7 (5.3–8.2) | | 6.7 | – | 0.74 |
| 1 month | 7.6 (5.3–6,0) | 0.22 | 5.2 (3.9–7) | 0.02 | 12.2 | | 0.09 |
| 12 months | 5.3 (3.8–4.1) | | 4.4 (4.03–5.8) | | – | | 0.50 |

**Table 7.** *Tacrolimus trough levels before, at one month and 12 months after the introduction of NOACs.* *Friedman test; †Mann Whitney U test

A positive correlation was found between the tacrolimus trough level before the introduction of the NOACs and serum creatinine at one month (Spearman Rho 0,762, p = 0.02). There was no significant correlation for other parameters.

## DISCUSSION

The ESC guidelines recommend the use of CHA2-DS2-VASc and HAS-BLED scores to determine the risk of ischemic stroke and of major bleeding when indicating the use of thromboprophylaxis in an individual patient [1]. Novel oral anticoagulant drugs present an innovative therapeutic approach for treatment of patients with AF for ischaemic stroke and systemic thromboembolism prevention [1]. Risk of intracranial bleeding is found to be significantly lower with NOACs compared with warfarin [3, 4]. The prescription of NOAC should be guided by the estimated glomerular filtration rate but also by the potential pharmacokinetic interactions with immunosuppressive drugs. Renal transplant recipients are from this point a specific group of patients. Most of them have stage 3 CKD, but may as well have stage 1, 2 or stage 4 CKD, with possible changes of allograft function with time in an individual patient. Major problem is renal clearance of NOACs: dabigatran is eliminated 80%, rivaroxaban 35%, apixaban 27% and edoxaban 50% with renal clearance [2]. For this reason, graft function should be monitored frequently with the according NOACs dose adjustments. Additionally, the potential interactions with immunosuppressive therapy is possible. There is a limited data on the effect of NOACs on immunosuppressive medications, but the fact that NOACs and the calcineurin inhibitors share some of the metabolic pathways increase concerns over the potential drug interactions [5, 6]. It is clear that pharmacokinetic effects of accompanying drugs should be considered when prescribing NOACs. Fourteen of our patients received rivaroxaban, 8 apixaban and dabigatran was given to one patient. Rivaroxaban was the first drug used in our transplant population. This group more frequently used cyclosporine, while patients treated with apixaban more frequently received tacrolimus. There was no significant change in cyclosporine trough levels after the introduction of the NOACs. Tacrolimus trough level was not influenced by the rivaroxaban, but was significantly decreased by the apixaban (from 6.7 to 4.4 ng/mL, p = 0.02), and increased in a patient treated with dabigatran (from 6.7 to 12.2 ng/mL). Based on the limited published experience, it was recommended to avoid use of dabigatran with cyclosporine or tacrolimus [2]. Our case supports this recommendation. Dabigatran was introduced in only one patient, induced doubling of tacrolimus trough level and was stopped after one month due to the major bleeding episode. For other NOACs Heidbuchel et al. reported that calcineurin inhibitors increased the concentration of edoxaban by 73%, with no data for apixaban and rivaroxaban [2]. In a single-centre retrospective analysis including 39 organ recipients treated with the combination of a CNI and rivaroxaban (n = 29) or apixaban (n = 10), a limited (<20%) increase in CNI trough concentration was recorded (5). In a study which included 42 stable renal transplant recipients, there were no significant changes in serum tacrolimus level three days after the initiation of NOACs among patients treated with tacrolimus [7].

The sparsity of data exists on the side effects of NOACs in renal transplant recipients. For example, dabigatran was suspected to induce hyperkalaemia in a renal transplant recipient by inducing hyporeninaemic hypoaldosteronism [8]. In a

rat model, dabigatran was found to induce anticoagulant-related nephropathy partially mediated by the protease-activated receptor 1 [9]. In our cohort, use of NOACs was complicated with the bleeding in two patients (8.6%): one from the rivaroxaban and one from the dabigatran group which did not correlate with the HAS-BLED score. Bukhari et al. recorded 3 (7.1%) bleeding events–one in a patient treated with rivaroxaban and 2 in patients who received apixaban [7].

In 52 renal transplant recipients treated by NOACs at Necker Hospital, no thrombotic complications were reported with the median follow-up of 14.1 months. The bleeding rate under NOACs was significantly lower (11.5 versus 22.9 per 100 patient-years, $p = 0.037$) compared to patients treated with warfarin. There were no significant changes in kidney function [10]. Gradual increase in GFR was observed in the rivoroxaban group from our cohort and was probably associated with lower tacrolimus trough levels at follow-up, without changes in other groups. In the study of Bukhari et al, after one-year of treatment with NOACs there were no significant changes in allograft function [7].

There are some limitations of our study which should be mentioned. A low number of patients received NOACs. Data were collected retrospectively and some complications may be underreported. However, we believe that this study provides valuable information on use of NOACs in renal transplant population. It is a single centre study, with uniform attitude to the patients, performed in a tertiary centre with available diagnostic modalities and adequate support.

In conclusion, our results demonstrated that rivaroxaban and apixaban may be safely and effectively used in renal transplant population. However, close monitoring of the graft function, adjustment of the doses and monitoring of the immunosuppressive drugs trough levels are mandatory.

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*Contributions: Nikolina Basic-Jukic designed study, analysed data and wrote the paper. Vesna Furic-Cunko performed research, collected data. Ivana Juric collected data, analysed results.*

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**Резиме**

## НОВИ ОРАЛНИ АНТИКОАГУЛАНСИ КАЈ ЛИЦА СО ПРЕСАДЕНИ БУБРЕЗИ: РЕТРОСПЕКТИВНА КОХОРТ СТУДИЈА

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**Цел**: Податоците за употребата на нови антикоагуланси на лекови (NOAS) кај лицата со пресадени бубрези се ретки. Целта на нашата студија беше да се испита безбедноста и ефикасноста на NOAC кај лицата со пресадени бубрези.

**Материјали и методи:** Во ретроспективна кохортна студија на еден центар проценивме несакани реакции, тромбоемболични настани и интеракции на инхибитори на калцинеурин кај пациенти третирани со NOAC.

**Резултати:** Дваесет и три лица со пресадени бубрези биле третирани со NOAC (70% машки), со средна возраст од 65,8 ± 1,8 години. Четиринаесет (61%) пациенти биле третирани со ривароксабан, апиксабан бил даден на 8 (35%) од нашите пациенти, а дабигатран на еден пациент (4%). Главните индикации за терапија со NOAC беа атријална фибрилација кај 61% и длабока венска тромбоза кај 23% од пациентите. Крвавењето се случи кај двајца пациенти (1 третиран со ривароксабан и 1 со дабигатран). Ниту еден од нашите пациенти не разви тромбоза додека беше третиран со NOAC. За време на средното следење на 24-месечната функција на графт, како и хематолошките параметри, беше стабилна состојбата кај пациентите што биле третирани со ривароксабан и апиксабан, додека дабигатранот беше прекинат по еден месец терапија поради крвавење.

**Заклучок:** Нашите резултати покажуваат дека и ривароксабан и апиксабан се безбедни и ефикасни орални антикоагулантни лекови кај пациентите со пресадени бубрези. Потребни се дополнителни студии за да се докажат овие резултати.

**Клучни зборови**: нови антикоагулантни лекови, ривароксабан, апиксабан, дабигатран, трансплантација на бубрези