# Aké sú koncentrácie DOAK u pacientov s fibriláciou predsiení v čase nežiaducich príhod? - výsledky pilotnej multicentrickej štúdie

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REVIEW ARTICLE

# Review of the Pharmacology of the Emerging Possibilities of the Direct Oral Anticoagulants' Reversal

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**Table 1. New oral anticoagulants in current clinical practice.**

| | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| Target factor | factor IIa | factor Xa | factor Xa | factor Xa |
| Clinical indication | NVAF<br>PE or DVT prophylaxis<br>PE or DVT treatment | NVAF<br>PE or DVT prophylaxis<br>PE or DVT treatment | NVAF<br>PE or DVT prophylaxis<br>PE or DVT treatment | NVAF<br>PE or DVT treatment<br>(only in Japan) |
| Hepatic metabolism | yes | yes | yes | yes |
| Renal clearance | 75 - 80% | 60 - 65% | 25 - 30% | 45 - 50% |
| Protein bound | 35% | 95% | 87% | 20% |
| Half-life | 12 - 17 hours | 9 - 13 hours | 8 - 15 hours | 8 - 10 hours |
| On-set of action | 0.5 - 2 hours | 2 - 4 hours | 1 - 3 hours | 1 - 2 hours |
| Laboratory test for monitoring | diluted thrombin clotting time, ecarin clotting time | anti-Xa activity | anti-Xa activity | anti-Xa activity |
| Dialysis | yes | no | no | no |
| Nonspecific reversal agents | PCC, aPCC/FEIBA, rVIIa | PCC, aPCC/FEIBA, rVIIa | PCC, aPCC/FEIBA, rVIIa | PCC, aPCC/FEIBA, rVIIa |
| Target-specific reversal agents | idarucizumab, aripazine | andexanet alpha, aripazine | andexanet alpha, aripazine | andexanet alpha, aripazine |

Abbreviations: DVT - deep venous thrombosis; NVAF - non-valvular atrial fibrillation; PCC - prothrombin complex concentrate; aPCC - activated prothrombin complex concentrate; FEIBA - factor VIII inhibitor bypassing activity; PE - pulmonary embolism, rVIIa - recombinant activated factor VII.

Current Drug Metabolism 2017; 18: 643 – 650.

J Thromb Thrombolysis
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# Monitoring of dabigatran therapy using Hemoclot® Thrombin Inhibitor assay in patients with atrial fibrillation

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**Monitorovanie účinnosti antikoagulačnej liečby dabigatranom u pacientov s fibriláciou predsiení: prvé skúsenosti.**



Table 2 Distribution of dabigatran concentrations according to established reference and cut-off values [9, 10]: sample 1 = taken 12 h after previous dose of drug; sample 2 = taken 2 h after subsequent dose of drug

| | % (*n*) of values below the reference range | % (*n*) of values in the reference range | % (*n*) of values above the reference range | % (*n*) of values with overdose (>200 ng/ml) | Reference range (ng/ml) |
|---|---|---|---|---|---|
| Sample 1 (trough) | 15.79 (3) | 78.95 (15) | 5.26 (1) | 5.26 (1) | 43–143 |
| Sample 2 (peak) | 18.18 (2) | 81.82 (9) | 0.00 (0) | x | 60–275 |

## Conclusion

The results of our study confirmed that the HTI assay is useful method to monitor the anticoagulant effect of dabigatran administrated for prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation. According to this test, more tailored management of DT might be ensured. The specific measurement of dabigatran plasma concentrations using the HTI assay may also be useful for the diagnosis of dabigatran overdose in future. However, further studies on larger samples will be needed for the final clarification of this issue.

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J Am Coll Cardiol. 2014 Feb 4;63(4):321-8. doi: 10.1016/j.jacc.2013.07.104. Epub 2013 Sep 27.

# The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy).

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## Abstract

**OBJECTIVES:** The goal of this study was to analyze the impact of dabigatran plasma concentrations, patient demographics, and aspirin (ASA) use on frequencies of ischemic strokes/systemic emboli and major bleeds in atrial fibrillation patients.

**BACKGROUND:** The efficacy and safety of dabigatran etexilate were demonstrated in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, but a therapeutic concentration range has not been defined.

**METHODS:** In a pre-specified analysis of RE-LY, plasma concentrations of dabigatran were determined in patients treated with dabigatran etexilate 110 mg twice daily (bid) or 150 mg bid and correlated with the clinical outcomes of ischemic stroke/systemic embolism and major bleeding using univariate and multivariate logistic regression and Cox regression models. Patient demographics and ASA use were assessed descriptively and as covariates.

**RESULTS:** Plasma concentrations were obtained from 9,183 patients, with 112 ischemic strokes/systemic emboli (1.3%) and 323 major bleeds (3.8%) recorded. Dabigatran levels were dependent on renal function, age, weight, and female sex, but not ethnicity, geographic region, ASA use, or clopidogrel use. A multiple logistic regression model (c-statistic 0.657, 95% confidence interval [CI]: 0.61 to 0.71) showed that the risk of ischemic events was inversely related to trough dabigatran concentrations ($p = 0.045$), with age and previous stroke (both $p < 0.0001$) as significant covariates. Multiple logistic regression (c-statistic 0.715, 95% CI: 0.69 to 0.74) showed major bleeding risk increased with dabigatran exposure ($p < 0.0001$), age ($p < 0.0001$), ASA use ($p < 0.0003$), and diabetes ($p = 0.018$) as significant covariates.

**CONCLUSIONS:** Ischemic stroke and bleeding outcomes were correlated with dabigatran plasma concentrations. Age was the most important covariate. Individual benefit-risk might be improved by tailoring dabigatran dose after considering selected patient characteristics. (Randomized Evaluation of Long Term Anticoagulant Therapy [RE-LY] With Dabigatran Etexilate; NCT00262600).

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**ORIGINAL ARTICLE**

# Low drug levels and thrombotic complications in high-risk atrial fibrillation patients treated with direct oral anticoagulants

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**Bazálne (trough) koncentrácie DOAK korelujú s rizikom embolických príhod**

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**ORIGINAL ARTICLE**

jth

# Drug levels and bleeding complications in atrial fibrillation patients treated with direct oral anticoagulants

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**Maximálne (peak) koncentrácie DOAK korelujú s rizikom hemoragických príhod**

***Aké sú reálne koncentrácie DOAK u pacientov s fibriláciou predsiení v čase krvácavých a embolických príhod?***

# Metodika

- **pilotná multicentrická prospektívna štúdia** (4.2019 – 10.2020)
- **súbor pacientov:**

A) *43 pacientov s embolickou CMP* pri liečbe DOAK (zaradení na 2 Neurologických klinikách /JLF UK Martin, FN Nitra/ s 24/7 h programom starostlivosti o pacientov s CMP)

B) *49 pacientov s krvácaním* pri liečbe DOAK (zaradení na Oddelení pohotovostného príjmu UNM)

C) *57 pacientov tolerujúcich terapeutickú dávku* DOAK minimálne 6 mesiacov bez akejkoľvek príhody = kontrolný súbor (zaradení na I. internej klinike JLF UK Martin)

- **stanovenie koncentrácie DOAK:**

- v *čase embolickej* (súbor A) alebo *krvácavej* príhody (súbor B)
- *bazálne* (pred) a *maximálne* (2 h po podaní u dabigatranu a rivaroxabanu a 3 h po podaní u apixabanu) koncentrácie (súbor C)
- koncentrácie dabigatranu boli stanovené pomocou *Hemoclot Thrombin Inhibitor Assay* a koncentrácie rivaroxabanu a apixabanu pomocou *liekovo – špecifickej chromogénnej anti-Xa analýzy*

# Demografia: CMP verzus kontroly

| | Dabigatran CMP | Dabigatran kontroly | Rivaroxaban CMP | Rivaroxaban kontroly | Apixaban CMP | Apixaban kontroly |
|---|---|---|---|---|---|---|
| Počet pacientov (muži/ženy) | 10 (6/4) | 21 (9/12) | 13 (7/6) | 14 (6/8) | 20 (11/9) | 22 (9/13) |
| Vek | 73 (51 – 94) | 65 (50 - 78) | 72 (60 – 85) | 70 (56 – 86) | 80 (59-97) | 72 (54-85) |
| Beta-blokátor (%) | 80,0 | 71,4 | 83,3 | 92,8 | 100 | 81,8 |
| Amiodaron (%) | 30,0 | 9,5 | 7,6 | 14,2 | 5,0 | 4,5 |
| Verapamil (%) | 0 | 14,2 | 0 | 7,1 | 0 | 0 |
| ACEi/AT1RB (%) | 40,0/10,0 | 42,8/14,2 | 53,8/7,6 | 62,2/7,1 | 45/20 | 36,3/9,1 |
| PPI (%) | 40,0 | 71,4 | 23,1 | 42,8 | 45,0 | 40,9 |
| Trvanie liečby DOAK (dni) | 95 | 192 | 130 | 185 | 120 | 202 |
| BMI (kg/m2) | 27,3 | 30,3 | 26,5 | 27,5 | 28,2 | 30,3 |
| CHA2DS2VASc skóre | 3,7 | 3,5 | 4,7 | 3,5 | 4,8 | 4,5 |
| HAS-BLED skóre | 2,5 | 2,5 | 3,0 | 2,5 | 3,0 | 3,0 |
| Vypočítaná GFR (ml/min/1.73 $m^2$) | 78,2 | 82,0 | 69,5 | 62,7 | 60,5 | 60,7 |

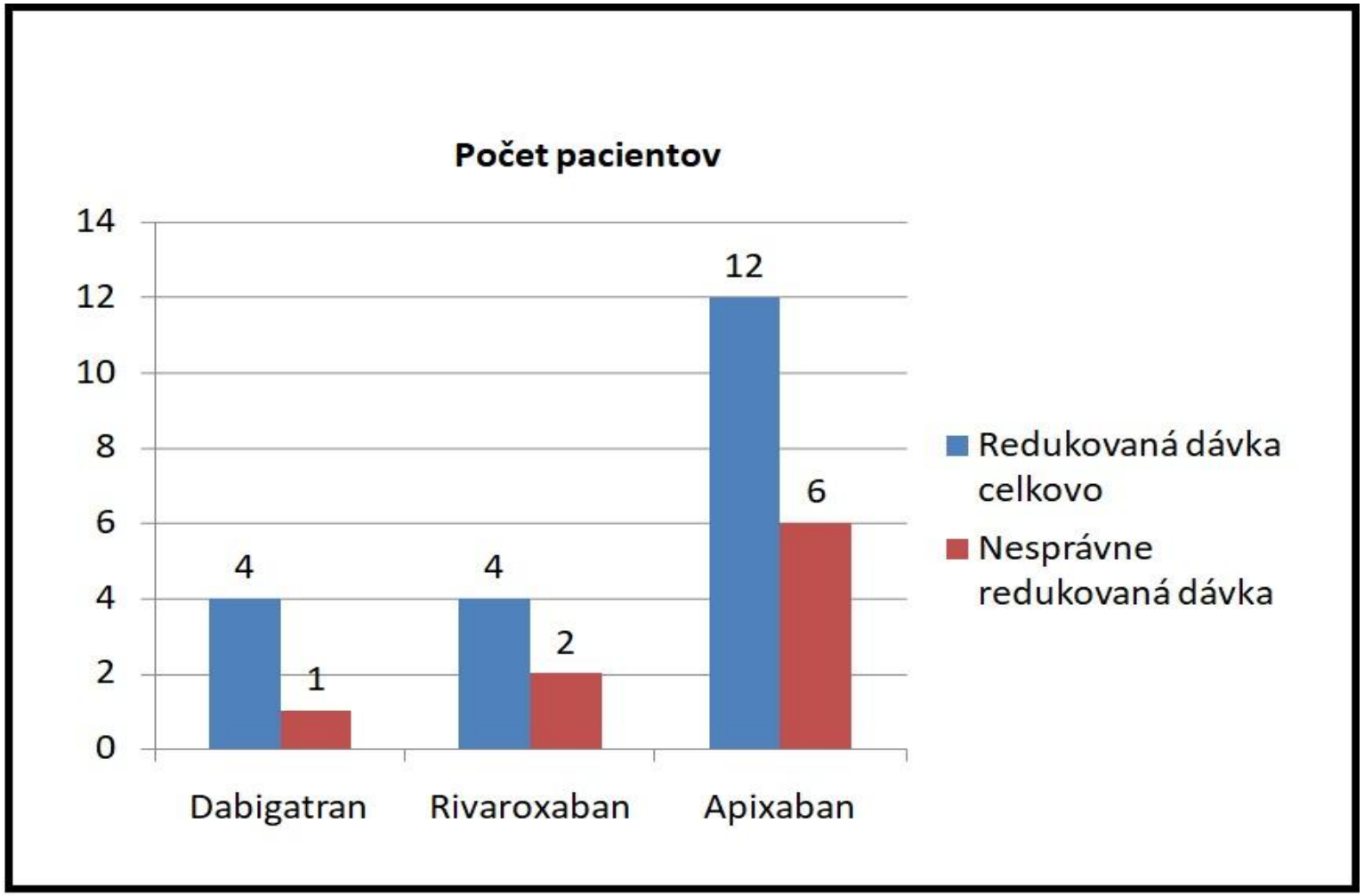
# Demografia: krvácanie verzus kontroly

| | Dabigatran krvácanie | Dabigatran kontroly | Rivaroxaban krvácanie | Rivaroxaban kontroly | Apixaban krvácanie | Apixaban kontroly |
|---|---|---|---|---|---|---|
| Počet pacientov (muži/ženy) | 9 (5/4) | 21 (9/12) | 22 (9/13) | 14 (6/8) | 18 (9/9) | 22 (9/13) |
| Vek (roky) | 82 (72 – 89) | 65 (50 - 78) | 73 (58 – 88) | 70 (56 – 86) | 79 (61-89) | 72 (54-85) |
| Beta-blokátor (%) | 100 | 71,4 | 72,7 | 92,8 | 100 | 81,8 |
| Amiodaron (%) | 0 | 9,5 | 13,6 | 14,2 | 5,5 | 4,5 |
| Verapamil (%) | 0 | 14,2 | 4,5 | 7,1 | 5,5 | 0 |
| ACEi/AT1RB (%) | 55,5/0 | 42,8/14,2 | 45,4/9,1 | 62,2/7,1 | 72,2/11,1 | 36,3/9,1 |
| PPI (%) | 33,3 | 71,4 | 36,3 | 42,8 | 55,5 | 40,9 |
| Trvanie liečby DOAK (dni) | 85,5 | 110,5 | 140 | 145,5 | 132,5 | 161,5 |
| BMI (kg/m2) | 25,5 | 30,3 | 27,6 | 27,5 | 28,5 | 30,3 |
| CHA2DS2VASc skóre | 5,1 | 3,5 | 4 | 3,7 | 4 | 4,5 |
| HAS-BLED skóre | 3 | 2,5 | 3 | 2,5 | 3 | 3 |
| Vypočítaná GFR (ml/min/1.73 m²) | 54,6 | 78,5 | 68,3 | 62,7 | 56 | 60,7 |

# Výsledky:
# koncentrácie DOAK v čase embolickej CMP

| | Pacienti s embolickou CMP | Kontroly | | Signifikancia |
|---|---|---|---|---|
| **Koncentrácie dabigatranu (ng/mL)** | **40,7 ± 36,9** | bazálne (ng/mL) | **85,4 ± 57,2** | p < 0,05 |
| | | maximálne (ng/mL) | **138,8 ± 78,7** | p < 0,001 |
| **Koncentrácie rivaroxabanu (ng/mL)** | **42,7 ± 31,9** | bazálne (ng/mL) | **52,5 ± 36,4** | p = 0,13 |
| | | maximálne (ng/mL) | **177,6 ± 38,6** | p < 0,001 |
| **Koncentrácie apixabanu (ng/mL)** | **72,4 ± 46,7** | bazálne (ng/mL) | **119,9 ± 81,7** | p < 0,05 |
| | | maximálne (ng/mL) | **210,9 ± 88,7** | p < 0,001 |

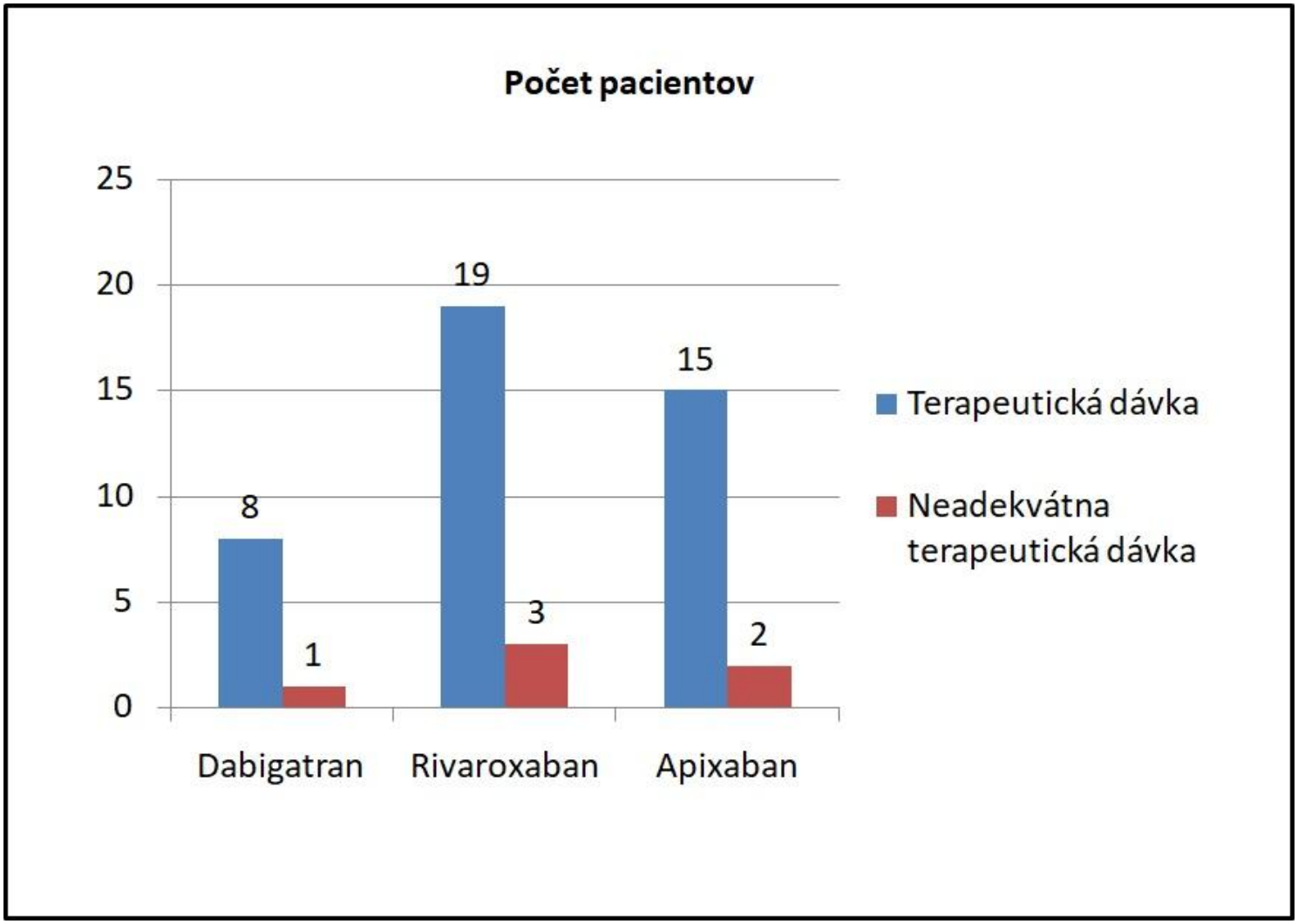
# Výsledky:
# dávkovanie DOAK u pacientov s embolickou CMP



# Výsledky:
# koncentrácie DOAK v čase krvácania

| | Pacienti s krvácaním | Kontroly | | Signifikancia |
|---|---|---|---|---|
| **Koncentrácie dabigatranu (ng/mL)** | **261,4 ± 163,7** | Bazálne | **85,4 ± 57,2** | p < 0,001 |
| | | Maximálne | **138,8 ± 78,7** | p < 0,05 |
| **Koncentrácie rivaroxabanu (ng/mL)** | **245,9 ± 150,2** | Bazálne | **52,5 ± 36,4** | p < 0,001 |
| | | Maximálne | **177,6 ± 38,6** | p = 0,13 |
| **Koncentrácie apixabanu (ng/mL)** | **311,8 ± 142,5** | Bazálne | **119,9 ± 81,7** | p < 0,001 |
| | | Maximálne | **210,9 ± 88,7** | p < 0,05 |

# Výsledky:
# dávkovanie DOAK u pacientov s krvácaním



# ZÁVER

1. Pacienti s embolickou CMP pri liečbe DOAK majú **nižšie koncentrácie DOAK** v čase príhody v porovnaní s bazálnymi (dabigatran, apixaban) a maximálnymi (dabigatran, rivaroxaban, apixaban) koncentráciami pacientov tolerujúcich liečbu

2. Pacienti s krvácaním pri liečbe DOAK majú **vyššie koncentrácie DOAK** v čase príhody v porovnaní s bazálnymi (dabigatran, rivaroxaban, apixaban) a maximálnymi (dabigatran, apixaban) koncentráciami pacientov tolerujúcich liečbu

3. **Neadekvátna redukcia dávkovania** DOAK bola zistená u 9 pacientov (20,9 %) s embolickou CMP a **nadmerné dávkovanie DOAK** bolo zistené u 6 pacientov (12,2 %) s krvácaním pri liečbe DOAK

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**Škorňová I, Samoš M, Bolek T, Kamenišťáková A, Stančiaková L, Galajda P, Staško J, Kubisz P, Mokáň M. Direct Oral Anticoagulants Plasma Levels in Patients with Atrial Fibrillation at the Time of Bleeding: A Pilot Prospective Study. J Cardiovasc Pharmacol 2021; 78: e122 - e127.**

**Nosáľ V, Petrovičová A, Škorňová I, Bolek T, Dluhá J, Stančiaková L, Sivák Š, Babálová L, Hajaš G, Staško J, Kubisz P, Kurča E, Samoš M, Mokáň M. Plasma levels of direct oral anticoagulants in atrial fibrillation patients at the time of embolic stroke: a pilot prospective multicentre study. Eur J Clin Pharmacol 2022; 78: 557 – 564.**

# Ďakujem za pozornosť