FAKTORY OVPLYVŇUJÚCE ÚČINNOSŤ LIEČBY PRIAMYMI ORÁLNYMI ANTIKOAGULANCIAMI (DOAK) U PACIENTOV S FIBRILÁCIOU PREDSIENÍ - NAŠE SKÚSENOSTI

Tomáš Bolek (1), Matej Samoš (1), Ingrid Škorňová (2), Peter Galajda (1), Ján Staško (2), Peter Kubisz (2), Marián Mokáň (1)

XXXI. Výroční sjezd české kardiologické společnosti

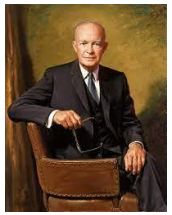
I. Interná klinika, Jesseniova lekárska fakulta v Martin, Univerzita Komenského v Bratislave (1) Národné centrum hemostázy a trombózy, Klinika hematológie a transfuziológie, Jesseniova lekárska fakulta v Martin, Univerzita Komenského v Bratislave (2)

XXXI. VÝROČNÍ SJEZD ČESKÉ KARDIOLOGICKÉ SPOLEČNOSTI

Orálne Vitamín K dependentné antagonisty - Warfarín

- cca 200 štúdii o liekových a potravinových interakciách
- popísaných cca 120 liekových alebo potravinových interakcií

(Crader M.F., 2005)



1955
Prezident Dwight Eisenhower

1960
Barritt and Jordan
1. Randomizovaná štúdia u pacientov s EAP

1983
Kempia S.J. et al
Rezistencia na liečbu warfarínom po brokolici

1987
Warfarín a amiodaron interakcia

1990
ASAFAK štúdia

1998
fenobarbitát interakcia

2002
interakcia ribavirin

2004 rybí olej interakcia

2009

XXXI. VÝROČNÍ SJEZD ČESKÉ KARDIOLOGICKÉ SPOLEČNOSTI

Trombotické komplikácie na liečbe DOAK

RE-LY® Study of stroke prevention in atrial fibrillation

182 pacientov
1,53% (Dabigatran 2x110mg)

134 pacientov
1,11% (Dabigatran 2x150 mg)

ROCKET AF

188 pacientov
1,7% (rivaroxaban)

ARISTOTLE

212 pacientov
1,27% (apixaban)

Engage AF TIMI 48

253 pacientov
1,5 % (edoxaban 30mg/denne)

182 pacientov
1,18% (edoxaban 60 mg/ denne)

Bolo preukázané, že pacienti s NCMP napriek OAK mali signifikantne vyššie riziko rekurentnej NCMP (Seiffge J.D. et al 2020)

„Čoho sa dopúšťa človek, ktorý nemá pochýb? Chýb! Chýb! Chýb!“

(Marián Palko)

DOAK u starších pacientov

Hypotéza: - spomalená hepatálna glukuronidácia (Hansen K.T. et al. 1995) , znížená funkcia P-Glykoproteínu u starších pacientov (van Assema E.M.D et al., 2012), redukcia gastrického pH, redukcia intestinálneho prietoku u starších pacientov (Feldman M. et al. 1998)

Table 2 Dabigatran trough and peak levels in studied sub-groups of non-valvular atrial fibrillation patients on dabigatran therapy

	Elderly patients on reduced dabigatran	Non-elderly patients on reduced dabigatran	Non-elderly patients on standard dabigatran
Dabigatran trough level (ng/mL)	99.3 ± 73.6	51.6 ± 25.6	75.0 ± 55.9
Time trough sample (h)	12.1	11.6	12.3
Dabigatran peak level (ng/mL)	173.4 ± 116.2	116.1 ± 19.1	164.5 ± 77.2
Time peak sample (h)	2.0	2.0	2.0
Patients with low (< 30 ng/mL) dabigatran trough levels (%/no. of patients)	9.5/2	38.5/5	6.3/1
Patients with high (> 200 ng/mL) dabigatran trough levels (%/no. of patients)	4.8/1	0/0	6.3/1
Patients with high (> 200 ng/mL) dabigatran peak levels (%/no. of patients)	28.6/6	0/0	25.0/4

Bolek T.a kol.Drugs and Aging, 2018

American Journal of Therapeutics

Wolters Kluwer

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Table 1. Trough and peak AXaA in elderly and nonelderly patients with AF (n—number of patients).

	Elderly patients (n = 18)	Nonelderly patients (n = 16)	Significance
Rivaroxaban trough AXaA (ng/mL)	39.9 ± 30.8	54.1 ± 36.6	0.28
Rivaroxaban peak AXaA (ng/mL)	190.9 ± 89.4	185.7 ± 118.3	0.79
	Elderly patients (n = 14)	Nonelderly patients (n = 10)	Significance
Apixaban trough AXaA (ng/mL)	111.3 ± 69.6	70.5 ± 41.5	0.09
Apixaban peak AXaA (ng/mL)	187.4 ± 81.6	158.3 ± 91.6	0.43

Samoš M a kol. Am. J. of Th. ,2019

XXXI. VÝROČNÍ SJEZD ČESKÉ KARDIOLOGICKÉ SPOLEČNOSTI

Diabetes mellitus (DM) a DOAK

Hypotéza: DM modifikuje expresiu glykoproteínu P (Kobori et al., 2013) , DM moduluje aktivitu cytochrómu P 450 (Goldstein et al., 1990; Kudo et al., 2009; Patoine et al., 2014) Zmena expresie glykoproteínu P ovplyvňuje koncentrácie dabigatranu (Antonijevic et al., 2017) Zmena aktivity cytochrómu P 450 ovplyvňuje aktivitu rivaroxabanu a apixabanu (Dempfle et al., 2014)


DIABETES RESEARCH AND CLINICAL PRACTICE 135 (2018) 172–177

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

ELSEVIER

International Diabetes Federation

Does type 2 diabetes affect the on-treatment levels of direct oral anticoagulants in patients with atrial fibrillation?

Matej Samoš, Tomáš Bolek, Lucia Stančiaková, Ingrid Škorňová, Jela Ivanková, František Kovář, Peter Galajda, Peter Kubisz, Ján Staško, Marián Mokáň

Department of Internal Medicine I, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovak Republic
National Centre of Hemostasis and Thrombosis, Department of Hematology and Blood Transfusion, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovak Republic

Samoš M. et al. 2018

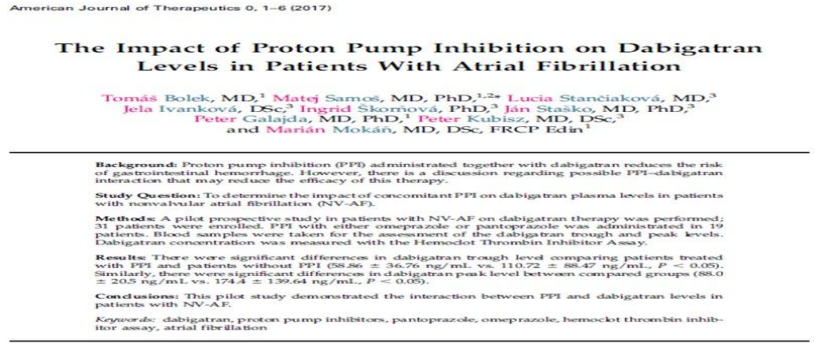
Table 3 – DOACs activity in type 2 diabetic (T2D) and non-diabetic (ND) patients (n — number of patients) with non-valvular atrial fibrillation.

Dabigatran	T2D (n = 8)	ND (n = 12)	Singificance
Dabigatran (ng/ml) baseline sample	62.1 ± 8.0	51.8 ± 38.9	p = .76
Dabigatran (ng/ml) post-drug-administration sample	91.7 ± 57.2	72.2 ± 33.2	p = .48
Rivaroxaban	T2D (n = 11)	ND (n = 17)	Singificance
Rivaroxaban (ng/ml) baseline sample	35.9 ± 22.5	55.3 ± 45.1	p = .19
Rivaroxaban (ng/ml) post-drug-administration sample	145.7 ± 74.1	202.6 ± 135.0	p = .22
Apixaban	T2D (n = 6)	ND (n = 11)	Singificance
Apixaban (ng/ml) baseline sample	96.0 ± 54.5	63.9 ± 36.8	p = .24
Apixaban (ng/ml) post-drug-administration sample	151.0 ± 78.3	151.7 ± 59.1	p = .98

Liekové interakcie:
Inhibítory protónovej pumpy a DOAK

Hypotéza: Absorbcia a biodostupnosť NOAK je ovplyvnená ↑ pH?, Ovlyvnenie efluxného transportéra P-glykoproteínu ? Ovplyvnenie metabolizmu NOAK cez interakciu na úrovni CYP 450?

(Ollier E. et al., Fundam Clin Pharmacol. 2015; Bolek T et al., Semin Thromb Hemost 2019)



American Journal of Therapeutics 0, 1–6 (2017)

The Impact of Proton Pump Inhibition on Dabigatran Levels in Patients With Atrial Fibrillation

Tomáš Bolek, MD,[1] Matej Samoš, MD, PhD,[1,2*] Lucia Stančiaková, MD,[3] Jela Ivanková, DSc,[3] Ingrid Škorňová, PhD,[3] Ján Staško, MD, PhD,[3] Peter Galajda, MD, PhD,[1] Peter Kubisz, MD, DSc,[3] and Marián Mokáň, MD, DSc, FRCP Edin[1]

Background: Proton pump inhibition (PPI) administrated together with dabigatran reduces the risk of gastrointestinal hemorrhage. However, there is a discussion regarding possible PPI–dabigatran interaction that may reduce the efficacy of this therapy.

Study Question: To determine the impact of concomitant PPI on dabigatran plasma levels in patients with nonvalvular atrial fibrillation (NV-AF).

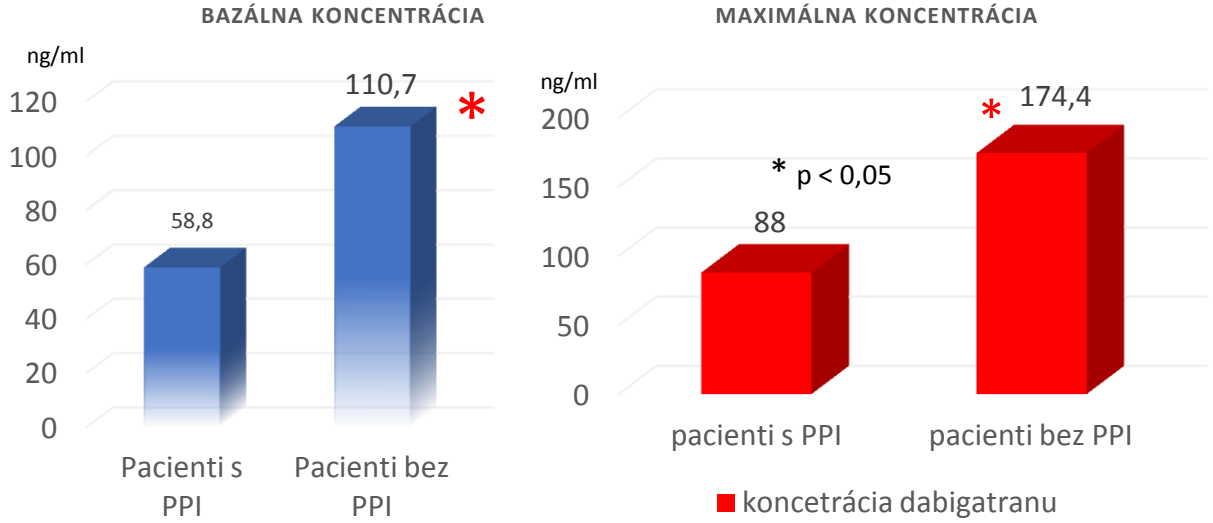
Methods: A pilot prospective study in patients with NV-AF on dabigatran therapy was performed; 31 patients were enrolled. PPI with either omeprazole or pantoprazole was administrated in 19 patients. Blood samples were taken for the assessment of the dabigatran trough and peak levels. Dabigatran concentration was measured with the Hemoclot Thrombin Inhibitor Assay.

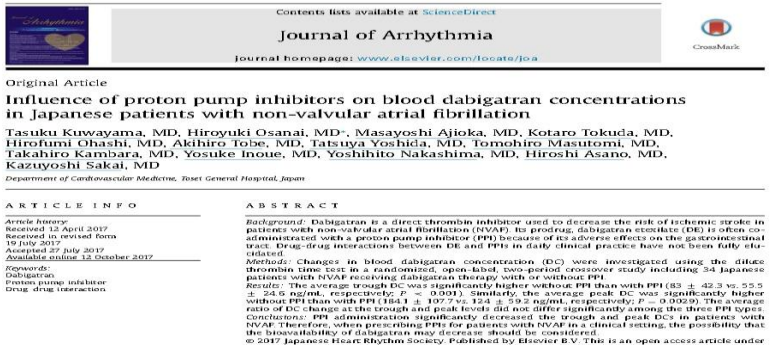
Results: There were significant differences in dabigatran trough level comparing patients treated with PPI and patients without PPI (58.86 ± 36.76 ng/mL vs. 110.72 ± 88.47 ng/mL, $P < 0.05$). Similarly, there were significant differences in dabigatran peak level between compared groups (88.0 ± 20.5 ng/mL vs., 174.4 ± 139.64 ng/mL., $P < 0.05$).

Conclusions: This pilot study demonstrated the interaction between PPI and dabigatran levels in patients with NV-AF.

Keywords: dabigatran, proton pump inhibitors, pantoprazole, omeprazole, hemoclot thrombin inhibitor assay, atrial fibrillation

Bolek T. et al 2017





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Original Article

Influence of proton pump inhibitors on blood dabigatran concentrations in Japanese patients with non-valvular atrial fibrillation

Tasuku Kuwayama, MD, Hiroyuki Osanai, MD*, Masayoshi Ajioka, MD, Kotaro Tokuda, MD, Hirofumi Ohashi, MD, Akihiro Tobe, MD, Tatsuya Yoshida, MD, Tomohiro Masutomi, MD, Takahiro Kambara, MD, Yosuke Inoue, MD, Yoshihito Nakashima, MD, Hiroshi Asano, MD, Kazuyoshi Sakai, MD

Department of Cardiovascular Medicine, Tosei General Hospital, Japan

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Drug-drug interaction

ABSTRACT

Background: Dabigatran is a direct thrombin inhibitor used to decrease the risk of ischemic stroke in patients with non-valvular atrial fibrillation (NVAF). Its prodrug, dabigatran etexilate (DE) is often co-administrated with a proton pump inhibitor (PPI) because of its adverse effects on the gastrointestinal tract. Drug-drug interactions between DE and PPIs in daily clinical practice have not been fully elucidated.

Methods: Changes in blood dabigatran concentration (DC) were investigated using the dilute thrombin time test in a randomized, open-label, two-period crossover study including 34 Japanese patients with NVAF receiving dabigatran therapy with or without PPI.

Results: The average trough DC was significantly higher without PPI than with PPI (83 ± 42.3 vs. 55.5 ± 24.6 ng/mL, respectively; $P < 0.001$). Similarly, the average peak DC was significantly higher without PPI than with PPI (184.1 ± 107.7 vs. 124 ± 59.2 ng/mL, respectively; $P = 0.0029$). The average ratio of DC change at the trough and peak levels did not differ significantly among the three PPI types.

Conclusions: PPI administration significantly decreased the trough and peak DCs in patients with NVAF. Therefore, when prescribing PPIs for patients with NVAF in a clinical setting, the possibility that the bioavailability of dabigatran may decrease should be considered.

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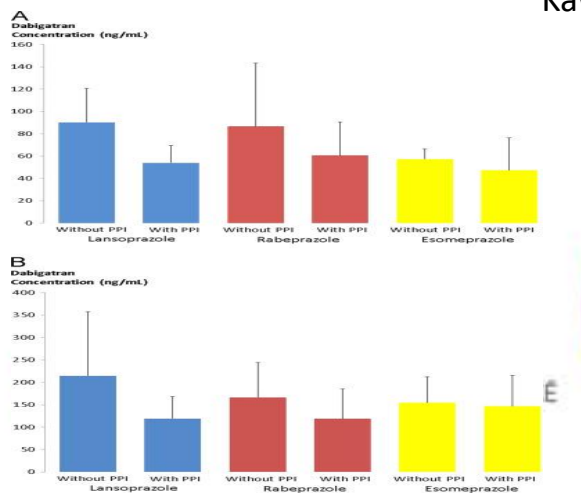
Kawuyama T. et a. 2017



Liekové interakcie:
Inhibítory protónovej pumpy a DOAK

European Journal of Clinical Pharmacology
https://doi.org/10.1007/s00228-019-02647-8

LETTER TO THE EDITOR

Dabigatran levels in omeprazole versus pantoprazole-treated patients with atrial fibrillation: is there a difference?

Tomáš Bolek[1] · Matej Samoš[1] · Ingrid Škorňová[2] · Martin Schnierer[3] · Peter Lipták[3] · Peter Bánovčin[3] · Lukáš Urban[1] · Ján Staško[2] · Peter Kubisz[2] · Peter Galajda[1] · Marián Mokáň[1]

Received: 3 January 2019 / Accepted: 5 February 2019

Bolek T. et al., 2019

ORIGINAL ARTICLE

The Effect of Proton Pump Inhibitor Withdrawal on Dabigatran Etexilate Plasma Levels in Patients With Atrial Fibrillation: A Washout Study

Martin Schnierer, MD, PhD, Matej Samoš, MD, PhD,† Tomáš Bolek, MD,† Ingrid Škorňová, PhD,‡ Lenka Nosáková, MD, PhD,* Peter Bánovčin, MD, PhD,* Peter Galajda, MD, PhD,† Ján Stasko, MD, PhD,‡ Peter Kubisz, MD, DSc,‡ Rudolf Hyrdel, MD, PhD,* and Marián Mokáň, MD, DSc, FRCP Edin†*

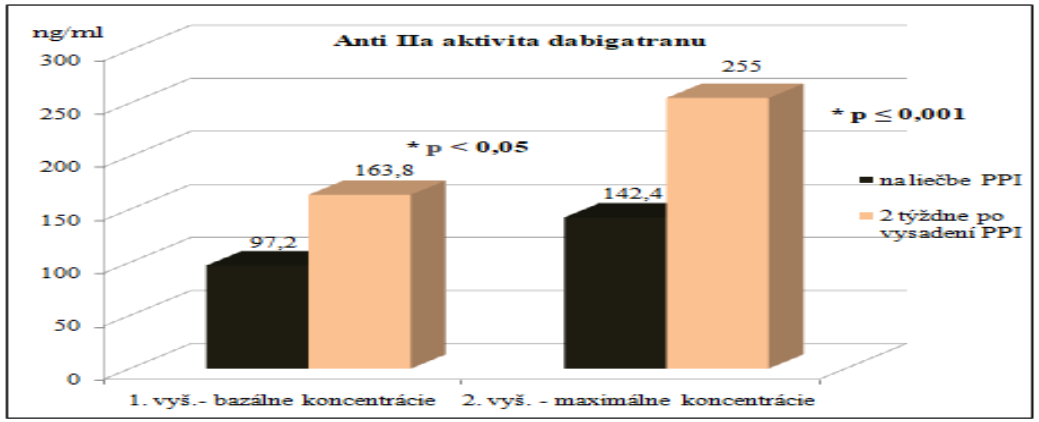
Background: Several studies demonstrated that proton pump inhibitors (PPIs) co-administrated with dabigatran in patients with atrial fibrillation (AF) decreased dabigatran trough and peak plasma levels. However, it is still unknown whether this interaction is

Key Words: proton pump inhibitors, dabigatran plasma levels, pantoprazole, omeprazole, atrial fibrillation
(*J Cardiovasc Pharmacol*™ 2020;75:333–335)

Schnierer M. et al, 2020

	Trough dabigatran levels (ng/mL)	Peak dabigatran levels (ng/mL)
nonPPI	122.6 ± 77.1	228.2 ± 140.7
PPI omeprazole	62.4 ± 51.1	116.4 ± 51.2
Significance	$p \leq 0.05$	$p \leq 0.05$
nonPPI	122.6 ± 77.1	228.2 ± 140.7
PPI pantoprazole	60.3 ± 53.1	110.1 ± 49.2
Significance	$p \leq 0.05$	$p \leq 0.05$
PPI pantoprazole	60.3 ± 53.1	110.1 ± 49.2
PPI omeprazole	62.4 ± 51.1	116.4 ± 51.2
Significance	$p = 0.92$	$p = 0.79$

PPI, proton pump inhibition; *nonPPI*, patients without proton pump inhibition; *PPI omeprazole*, omeprazole-treated patients; *PPI pantoprazole*, pantoprazole-treated patients; *AF*, atrial fibrillation



Liekové interakcie:
Inhibítory protónovej pumpy a DOAK

Journal of Thrombosis and Thrombolysis
https://doi.org/10.1007/s11239-018-1748-5

Does proton pump inhibition change the on-treatment anti-Xa activity in xabans-treated patients with atrial fibrillation? A pilot study

Tomáš Bolek[1] · Matej Samoš[1] · Ingrid Škorňová[2] · Lucia Stančiaková[2] · Ján Staško[2] · Barbora Korpallová[1] · Peter Galajda[1] · Peter Kubisz[2] · Marián Mokáň[1]

Abstract
Proton pump inhibition (PPI) reduces gastrointestinal bleeding on direct oral anticoagulants. However, PPI may affect dabigatran on-treatment levels; and there is no information regarding the effect of PPI on xabans on-treatment activity. Thus, the aim of this study was to determine the impact of PPI on therapeutic anti-Xa activity in rivaroxaban- and apixaban-treated patients with atrial fibrillation (AF). This single-centre pilot prospective study enrolled 77 consecutive xabans-treated patients (42 rivaroxaban-treated and 35 apixaban-treated patients) with AF. PPI was administrated in 44 patients. Trough and peak anti-Xa activity was assessed with factor Xa-calibrated anti-Xa chromogenic analysis. There were no significant differences in trough anti-Xa activity comparing PPI-treated patients and patients without PPI (80.5 ± 66.5 ng/mL in PPI group vs. 71.6 ± 64.1 ng/mL in non-PPI group, p = 0.57, Table 2). Similarly, there were no significant differences in peak anti-Xa activity between compared groups (175.2 ± 102.5 ng/mL in PPI group vs. 202.9 ± 84.1 ng/mL in non-PPI group, p = 0.21). This pilot study did not reveal significant changes in xabans on-treatment anti-Xa activity according the PPI status.

Keywords Proton pump inhibitors · Xabans · Rivaroxaban · Apixaban · Anti-Xa activity · Atrial fibrillation

Table 2 Trough and peak anti-Xa activity in patients with and without proton pump inhibition (PPI)

	Patients with PPI	Patients without PPI	Significance
All patients			
Trough sample (ng/L)	80.5 ± 66.5	71.6 ± 64.1	p = 0.57
Peak sample (ng/L)	175.2 ± 102.5	202.9 ± 84.1	p = 0.21
Time from drug administration to trough sample collection (h)	15.5 ± 5.5	17.1 ± 6.1	p = 0.27
Rivaroxaban			
Trough sample (ng/mL)	53.6 ± 41.5	34.9 ± 19.3	p = 0.09
Peak sample (ng/mL)	189.9 ± 116.8	186.3 ± 97.2	p = 0.43
Time from drug administration to trough sample collection (h)	23.4 ± 0.37	23.6 ± 0.29	p = 0.45
Rivaroxaban sub-analysis			
1 × 20 mg dosing trough sample (ng/mL)	47.3 ± 18.9	34.5 ± 15.9	p = 0.38
1 × 20 mg dosing peak sample (ng/mL)	158.3 ± 23.6	179.2 ± 52.0	p = 0.44
1 × 15 mg dosing trough sample (ng/mL)	57.1 ± 46.0	34.4 ± 20.8	p = 0.11
1 × 15 mg dosing peak sample (ng/mL)	198.8 ± 130.6	187.0 ± 112.3	p = 0.80
Apixaban			
Trough sample (ng/mL)	102.4 ± 75.4	122.4 ± 70.1	p = 0.43
Peak sample (ng/mL)	162.5 ± 39.1	223.2 ± 62.4	p = 0.09
Time from drug administration to trough sample collection (h)	12.2 ± 0.31	12.1 ± 0.28	p = 0.41
Apixaban sub-analysis			
2 × 5 mg dosing trough sample (ng/mL)	119.7 ± 81.9	128.1 ± 86.3	p = 0.84
2 × 5 mg dosing peak sample (ng/mL)	174.6 ± 96.9	238.0 ± 66.4	p = 0.14
2 × 2.5 mg dosing trough sample (ng/mL)	96.3 ± 78.3	100.7 ± 38.6	p = 0.87
2 × 2.5 mg dosing peak sample (ng/mL)	160.5 ± 93.7	176.4 ± 54.7	p = 0.65

Bolek T., et al., 2018

XXXI. VÝROČNÍ SJEZD ČESKÉ KARDIOLOGICKÉ SPOLEČNOSTI

Liekové interakcie:
Atorvastatín a DOAK

Hypotéza: atorvastatín substrátom pGp, inhibítor P-Gp, metabolizovaný cez CYP P450

The impact of atorvastatin on dabigatran plasma levels in patients with atrial fibrillation

Tomáš Bolek[a], Matej Samoš[a], Lucia Stančiaková[b], Ingrid Škorňová[b], Kristína Grilusová[a], Peter Galajda[a], Ján Staško[b], Peter Kubisz[b] and Marián Mokáň[a]

[a]Department of Internal Medicine I and [b]National Centre of Hemostasis and Thrombosis, Department of Hematology and Blood Transfusion, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovak Republic

Correspondence to Matej Samoš, MD, PhD, Department of Internal Medicine I, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Kollarova 2, 036 59 Martin, Slovak republic
Tel: +421 907 612 943; fax: +421 43 4203 820;
e-mail: matej.samos@gmail.com

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Bolek T. et al. 2021

	With atorvastatin ($n=31$)	Without atorvastatin ($n=34$)	Significance (P value)
Dabigatran anti-IIa – trough level (ng/ml)	75.2 ± 47.7	92.5 ± 80.3	0.31
Dabigatran anti-IIa – peak level (ng/ml)	145.1 ± 63.7	187.2 ± 128.1	0.11
	With atorvastatin ($n=12$)	Without atorvastatin ($n=18$)	
Dabigatran standard dose (150 mg bid) Anti-IIa – trough level (ng/ml)	64.4 ± 40.2	93.3 ± 82.8	0.22
Dabigatran standard dose (150 mg bid) Anti-IIa – peak level (ng/ml)	148.6 ± 56.7	201.2 ± 127.1	0.15
	With atorvastatin ($n=19$)	Without atorvastatin ($n=16$)	
Dabigatran reduced dose (110 mg bid) Anti-IIa – trough level (ng/ml)	80.1 ± 50.8	91.6 ± 80.4	0.64
Dabigatran reduced dose (110 mg bid) Anti-IIa – peak level (ng/ml)	139.6 ± 68.4	169.1 ± 132.4	0.47

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ORIGINAL ARTICLE

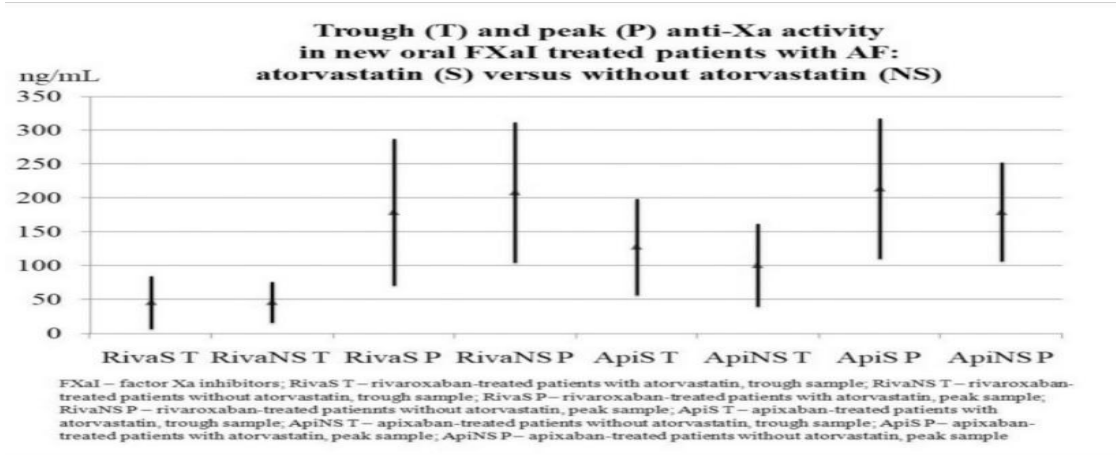
Does atorvastatin therapy change the anti-Xa activity in xabans-treated patients with atrial fibrillation?

Ingrid Škorňová[1] | Matej Samoš[2] | Tomáš Bolek[2] | Lucia Stančiaková[1] | Ľubica Vádelová[1] | Peter Galajda[2] | Ján Staško[1] | Peter Kubisz[1] | Marián Mokáň[2]

[1]National Centre of Hemostasis and Thrombosis, Department of Hematology and Blood Transfusion, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovak Republic
[2]Department of Internal Medicine I, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovak Republic

Abstract
Atorvastatin and direct oral factor Xa inhibitors (xabans) are frequently co-administrated in patients with atrial fibrillation (AF). However, no studies investigating the possibility of the pharmacologic interaction between these agents have been conducted. The aim of this prospective observational study was to determine the impact of atorvastatin therapy on anti-Xa activity in xabans-treated patients with AF. We enrolled 115 AF patients on long-term rivaroxaban (52 patients) and long-term

Škorňová I., et al, 2021



SPOLEČNOSTI

Záver

Vek:

1) Starší pacienti liečení redukovanými dávkami dabigatranu **majú signifikantne vyššie bazálne a maximálne** koncentrácie dabigatranu ako mladší pacienti na redukovanom dávkovaní a podobné koncentrácie dabigatranu ako mladší pacienti na štandardnom dávkovaní dabigatranu.

2) Bazálne a maximálne koncentrácie boli porovnateľné u mladších a starších pacientov s NV-AF na liečbe rivaroxabanom a apixabanom.

Diabetes mellitus:

3) Nepreukázali sme v rozdiel v bazálnych a maximálnych koncentráciach DOAK (dabigatran, rivaroxaban,apixaban) u diabetikov a nediabetikov s NV-AF.

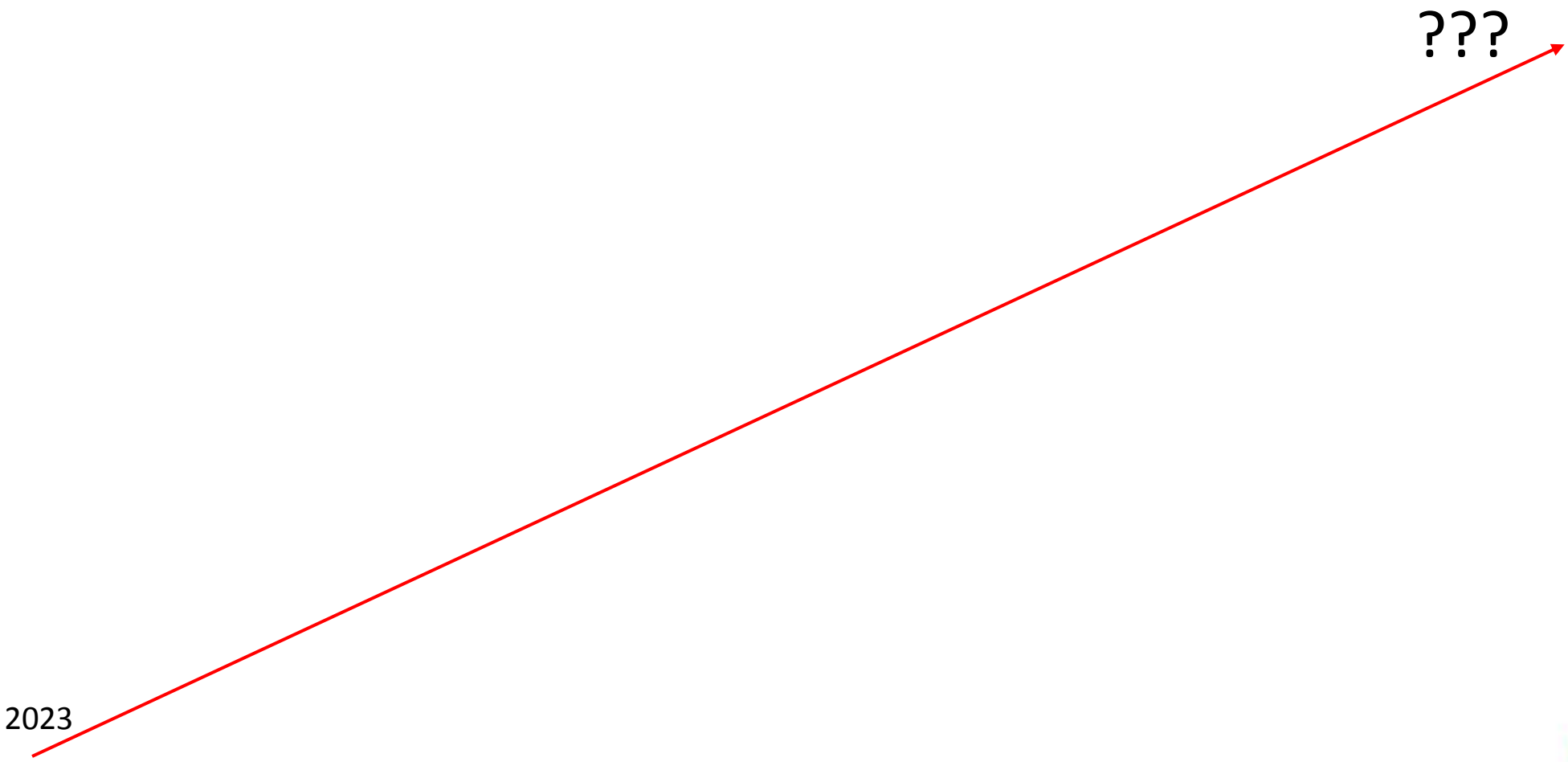
Inhibítory protónovej pumpy (PPI)

4) Konkomitantná liečba PPI **ovplyvnila** bazálne aj maximálne koncentrácie dabigatranu u pacientov s NV-AF.

5) Liečba PPI **neovplyvnila** bazálne aj maximálne koncentrácie rivaroxabanu a apixabanu u pacientov s NV-AF.

Statíny:

6) Liečba atorvastatínom neoplyvnila bazálne a maximálne koncentrácie DOAK (dabigatran, rivaroxaban, apixaban) u pacientov s NV-AF.



XXXI. VÝROČNÍ SJEZD ČESKÉ KARDIOLOGICKÉ SPOLEČNOSTI

Ďakujem za pozornosť

XXXI. VÝROČNÍ SJEZD ČESKÉ KARDIOLOGICKÉ SPOLEČNOSTI