LÉKY OVLIVŇUJÍCÍ HEMOKOAGULACI A REGIONÁLNÍ ANESTEZIE -UP TO DATE 2015

Milan Jelínek

Národní kongres ČSARIM

2015

FAKULTNÍ NEMOCNICE U SV. ANNY V BRNĚ

Incidence intraspináních hematomů

- 1/150 000 epiduláních anestezii
- 1/220 000 spinálních anestezii
- 1/3000 u pacientů rizikových- vyšší věk, strukturální postižení páteře (ankylozujicí spondylitis), poruchy krevního srážení

2010
ANTICOAGULATION 3RD EDITION

ASRA PRACTICE ADVISORY

Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy

American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition)

Terese T. Horlocker, MD, Denise J. Wedel, MD,* John C. Rowlingson, MD,† F. Kayser Enneking, MD,‡ Sandra L. Kopp, MD,* Honorio T. Benzon, MD,§ David L. Brown, MD,|| John A. Heit, MD,* Michael F. Mulroy, MD,¶ Richard W. Rosenquist, MD,# Michael Tryba, MD,** and Chun-Su Yuan, MD, PhD††*

2010

GUIDELINES

Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology

Wiebke Gogarten, Erik Vandermeulen, Hugo Van Aken, Sibylle Kozek, Juan V. Llau and Charles M. Samama

Neuraxial block in patients with disturbed haemostasis: Brief version with recommendations (June 24,2009)

Scandinavian Society of Anaesthesiology and Intensive Care Medicine Task Force:
Harald Breivik, Norway (chair), Ulla Bang, Denmark, Jouko Jalonen & Seppo Alahuhta, Finland, Gísli Vigfússon, Iceland, Michael Lagerkranser, Sweden.

Test (reference values)	Potential benefit of neuraxial block (see Table 1)					
	Single shot spinal anaesthesia			Epidural and CSE		
	Comfort	Morbidity	Mortality	Comfort	Morbidity	Mortality
Platelet count $x10^3$ (150 – 350)	>100	>50	>30	>100	>80	>50
INR (0.9 - 1.2)	≤1.4	<1.8	<2.2	≤1.2	<1.6	<1.8

Regional Anaesthesia and Patients with Abnormalities of Coagulation

Published by
The Association of Anaesthetists of Great Britain & Ireland
The Obstetric Anaesthetists' Association
Regional Anaesthesia UK

November 2013

Table 2 Relative risk related to neuraxial and peripheral nerve blocks in patients with abnormalities of coagulation.

	Block category	Examples of blocks in category
Higher risk	Epidural with catheter	
	Single-shot epidural	
	Spinal	
	Paravertebral blocks	Paravertebral block
		Lumbar plexus block
		Lumbar sympathectomy
		Deep cervical plexus block
	Deep blocks	Coeliac plexus block
		Stellate ganglion block
		Proximal sciatic block (Labat, Raj, sub-gluteal)
		Obturator block
		Infraclavicular brachial plexus block
		Vertical infraclavicular block
		Supraclavicular brachial plexus block
	Superficial perivascular blocks	Popliteal sciatic block
		Femoral nerve block
		Intercostal nerve blocks
		Interscalene brachial plexus block
		Axillary brachial plexus block
	Fascial blocks	Ilio-inguinal block
		Ilio-hypogastric block
		Transversus abdominis plane block
		Fascia lata block
	Superficial blocks	Forearm nerve blocks
		Saphenous nerve block at the knee
		Nerve blocks at the ankle
		Superficial cervical plexus block
		Wrist block
		Digital nerve block
		Bier's block
Normal risk	Local infiltration	

2015

SPECIAL ARTICLE

Interventional Spine and Pain Procedures in Patients on Antiplatelet and Anticoagulant Medications

Guidelines From the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain

Samer Narouze, MD, PhD, Honorio T. Benzon, MD,† David A. Provenzano, MD,‡ Asokumar Buvanendran, MD,§ José De Andres, MD, PhD,|| Timothy R. Deer, MD,# Richard Rauck, MD,** and Marc A. Huntoon, MD††*

TABLE 1. Pain Procedure Classification According to the Potential Risk for Serious Bleed

High-Risk Procedures	Intermediate-Risk Procedures*	Low-Risk Procedures*
SCS trial and implant	Interlaminar ESIs (C, T, L, S)	Peripheral nerve blocks
Intrathecal catheter and pump implant	Transforaminal ESIs (C, T, L, S)	Peripheral joints and musculoskeletal injections
Vertebral augmentation (vertebroplasty and kyphoplasty)	Facet MBNB and RFA (C, T, L)	Trigger point injections including piriformis injection
Epiduroscopy and epidural decompression	Paravertebral block (C, T, L)	Sacroiliac joint injection and sacral lateral branch blocks
	Intradiscal procedures (C, T, L)	
	Sympathetic blocks (stellate, thoracic, splanchnic, celiac, lumbar, hypogastric)	
	Peripheral nerve stimulation trial and implant	
	Pocket revision and IPG/ITP replacement	

*Patients with high risk for bleeding undergoing low- or intermediate-risk procedures should be treated as intermediate or high risk, respectively. Patients with high risk for bleeding may include old age, history of bleeding tendency, concurrent uses of other anticoagulants/antiplatelets, liver cirrhosis or advanced liver disease, and advanced renal disease.

C indicates cervical; L, lumbar; MBNB, medial branch nerve block; RFA, radiofrequency ablation; S, sacral; T, thoracic.

vs **Anticoagulation 3rd Edition**

11.0 Anesthetic Management of the Patient Undergoing Plexus or Peripheral Block

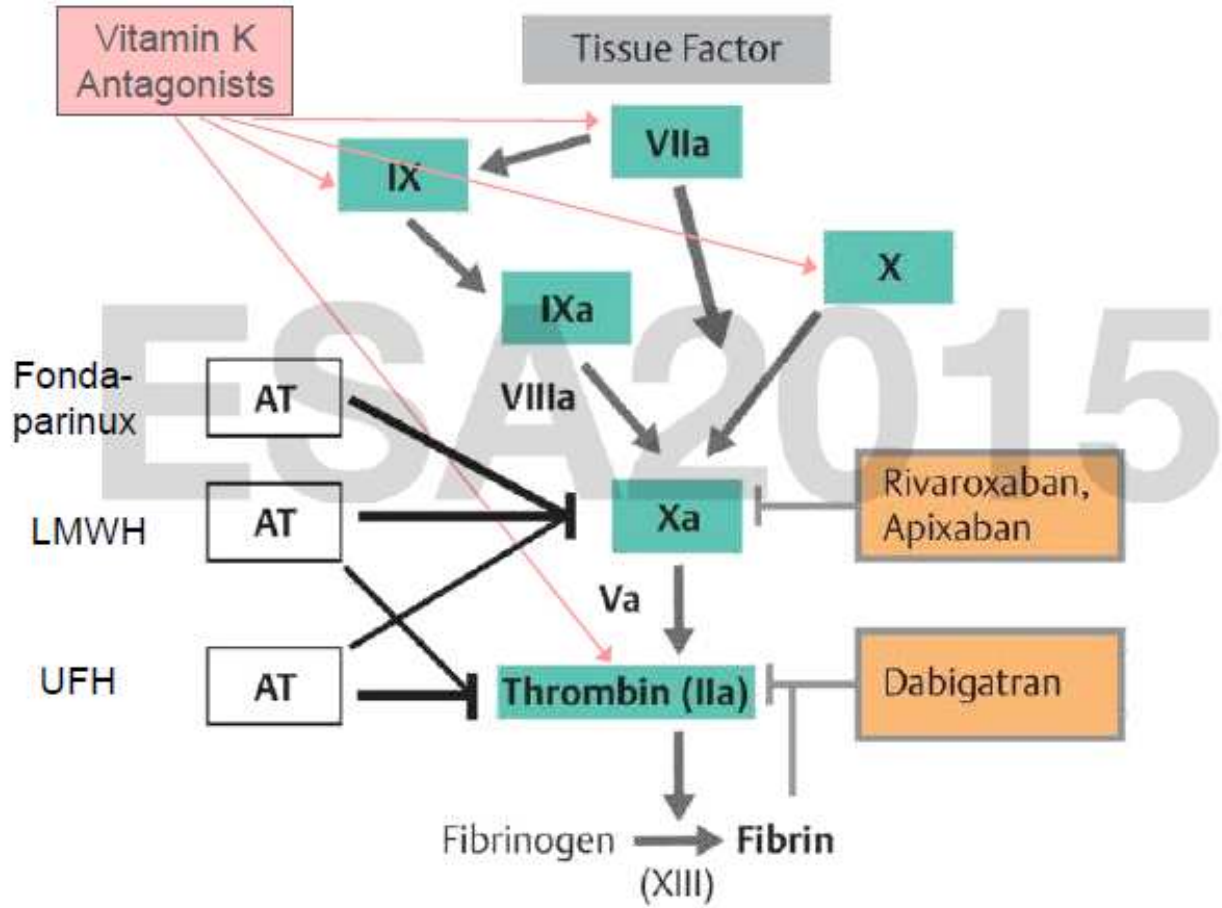
11.1 For patients undergoing deep plexus or peripheral block, we recommend that recommendations regarding neuraxial techniques be similarly applied (Grade 1C).

2015 ???
Anticoagulation 4th Edition

Recommended Time Intervals *Before* and *After* Neuraxial Block or Catheter Removal* DRAFT		
Drug	Time *before* puncture/catheter manipulation or removal	Time *after* puncture/catheter manipulation or removal
Dabigatran	5 days	6 hours
Apixaban	3 days	6 hours
Rivaroxaban	3 days	6 hours
Prasugrel	7-10 days	6 hours
Ticagrelor	5-7 days	6 hours

*Developed at 4th ASRA Practice Advisory for Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy

Anticoagulants



Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman

Summary

Background Four new oral anticoagulants compare favourably with warfarin for stroke prevention in patients with atrial fibrillation; however, the balance between efficacy and safety in subgroups needs better definition. We aimed to assess the relative benefit of new oral anticoagulants in key subgroups, and the effects on important secondary outcomes.

Methods We searched Medline from Jan 1, 2009, to Nov 19, 2013, limiting searches to phase 3, randomised trials of patients with atrial fibrillation who were randomised to receive new oral anticoagulants or warfarin, and trials in which both efficacy and safety outcomes were reported. We did a prespecified meta-analysis of all 71 683 participants included in the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF–TIMI 48 trials. The main outcomes were stroke and systemic embolic events, ischaemic stroke, haemorrhagic stroke, all-cause mortality, myocardial infarction, major bleeding, intracranial haemorrhage, and gastrointestinal bleeding. We calculated relative risks (RRs) and 95% CIs for each outcome. We did subgroup analyses to assess whether differences in patient and trial characteristics affected outcomes. We used a random-effects model to compare pooled outcomes and tested for heterogeneity.

Findings 42 411 participants received a new oral anticoagulant and 29 272 participants received warfarin. New oral anticoagulants significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0·81, 95% CI 0·73–0·91; p<0·0001), mainly driven by a reduction in haemorrhagic stroke (0·49, 0·38–0·64; p<0·0001). New oral anticoagulants also significantly reduced all-cause mortality (0·90, 0·85–0·95; p=0·0003) and intracranial haemorrhage (0·48, 0·39–0·59; p<0·0001), but increased gastrointestinal bleeding (1·25, 1·01–1·55; p=0·04). We noted no heterogeneity for stroke or systemic embolic events in important subgroups, but there was a greater relative reduction in major bleeding with new oral anticoagulants when the centre-based time in therapeutic range was less than 66% than when it was 66% or more (0·69, 0·59–0·81 *vs* 0·93, 0·76–1·13; p for interaction 0·022). Low-dose new oral anticoagulant regimens showed similar overall reductions in stroke or systemic embolic events to warfarin (1·03, 0·84–1·27; p=0·74), and a more favourable bleeding profile (0·65, 0·43–1·00; p=0·05), but significantly more ischaemic strokes (1·28, 1·02–1·60; p=0·045).

Interpretation This meta-analysis is the first to include data for all four new oral anticoagulants studied in the pivotal phase 3 clinical trials for stroke prevention or systemic embolic events in patients with atrial fibrillation. New oral anticoagulants had a favourable risk–benefit profile, with significant reductions in stroke, intracranial haemorrhage, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding. The relative efficacy and safety of new oral anticoagulants was consistent across a wide range of patients. Our findings offer clinicians a more comprehensive picture of the new oral anticoagulants as a therapeutic option to reduce the risk of stroke in this patient population.

RE-LY[5]			ROCKET-AF[6]		ARISTOTLE[7]		ENGAGE AF-TIMI 48[8]			Combined	
Dabigatran 150 mg (n=6076)	Dabigatran 110 mg (n=6015)	Warfarin (n=6022)	Rivaroxaban (n=7131)	Warfarin (n=7133)	Apixaban (n=9120)	Warfarin (n=9081)	Edoxaban 60 mg (n=7035)	Edoxaban 30 mg (n=7034)	Warfarin (n=7036)	NOAC (n=42 411)	Warfarin (n=29 272)

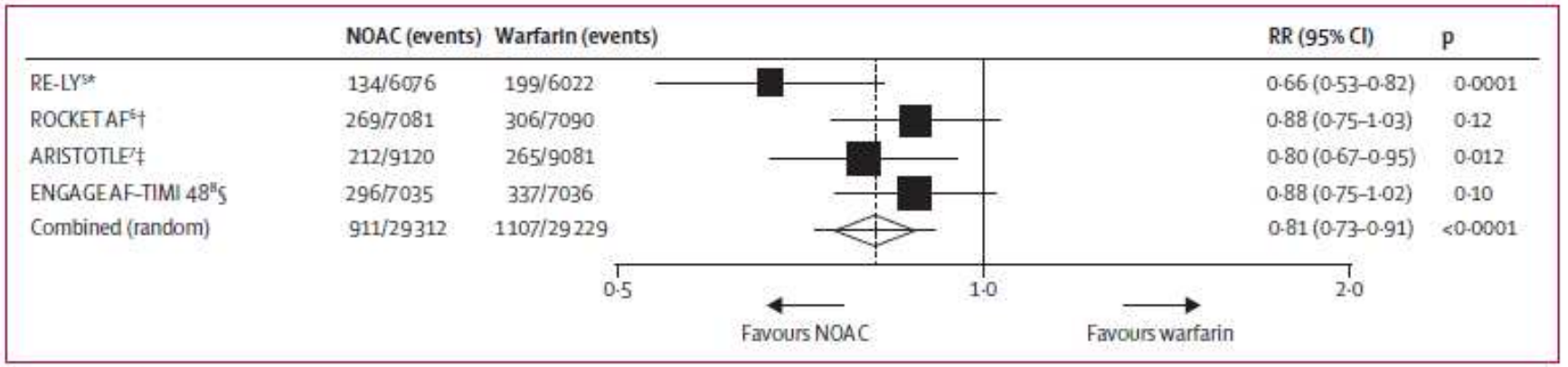
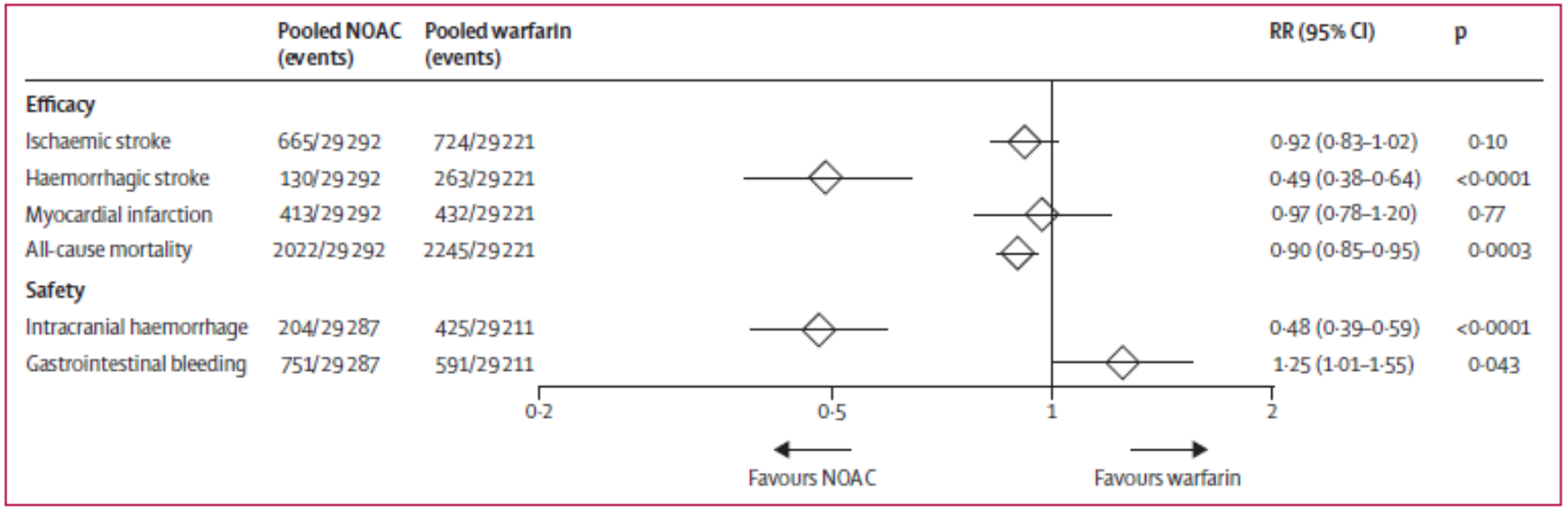


Figure 1: Stroke or systemic embolic events



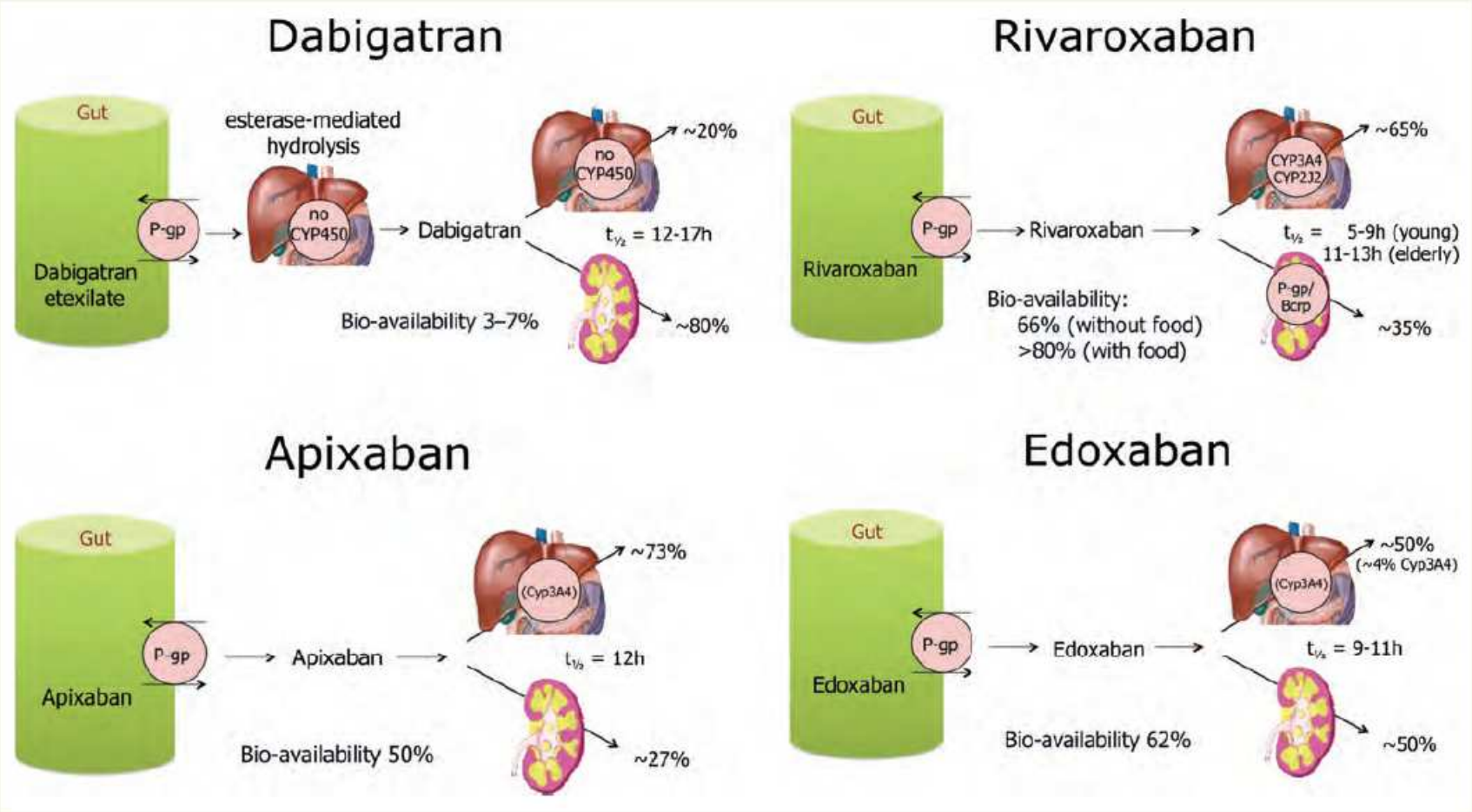


Figure 5 Absorption and metabolism of the different new anticoagulant drugs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolisation and excretion. The brackets around (Cyp3A4) in the apixaban graph indicate a minor contribution of this pathway to hepatic clearance, the majority of the drug being excreted as unchanged parent. See also *Table 4* for the size of the interactions based on these schemes.

NOAC a RA

Vysazení antikoagulace

- Vysoké riziko krvácení - 5 x eliminační poločas
- Nízké riziko krvácení - 2 x eliminační poločas

Podání po výkonu

- 10h minus doba do maximalní učinnosti

DABIGATRAN

- přímý inhibitor trombinu
- biologická dostupnost po p.o. 7,2%, špičkové hladiny za 1,5-3h, poločas 14-17h (28h),
- 80% vylučováno ledvinami, kontraindikován při CrCL pod 30 ml/min
- 220 mg/d (150 mg) p.o.
- fisi, prevence VTE po ortop
- monitorace- aPPT, dilute TT (Hemoclot Thrombin Inhibitory assay), **ecarin clotting time (ECT)**
- antagonizace účinku- IHD, **Idarucizumab:**Fab

DABIGATRAN

Vysazení

- 4-5 (6) d ASRA+ PAIN
- 2-4 d UK

Podání po výkonu

- 6h ASRA. UK, Scan.
- 24 (12) h PAIN

EPI kater in situ je kontraindikací

RIVOROXABAN

- přímý inhibitor Xa
- biologická dostupnost po p.o. 80-100%, špičkové hladiny za 2-4h, poločas 9 h
- 33% vylučováno ledvinami, 33% stolicí, 33% metabolizuje v játrech
- 10-20 mg/d
- fisi, prevence i léčba VTE
- monitorace – PT a **anti-Xa**
- antagonizace učinku- **Andexanet alfa:** rekombinantní modifikovaný humální factor Xa

RIVOROXABAN

Vysazení

- 3d ASRA+ PAIN
- 22-26 ESRA
- 18h (10mg) UK, Scan.

Podání po výkonu

- 6h ASRA. UK, Scan.
- 24 (12) h PAIN

EPI kater in situ- UK nedoporučuje, ESRA 24h

APIXABAN (ELIQUIS)

- přímý inhibitor Xa
- biologická dostupnost po p.o. 50%, špičkové hladiny za 1-2h, poločas 8-14 h
- 27% vylučováno ledvinami, 56% stolicí
- 5-20 mg/d
- fisi, prevence i léčba VTE
- monitorace – PT a **anti-Xa**
- antagonizace učinku- **Andexanet alfa:** rekombinantní modifikovaný humální factor Xa

APIXABAN (ELIQUIS)

Vysazení

- 3d ASRA
- 3-5d PAIN
- 26-30h ESRA
- 24-48h (5mg/d) UK

Podání po výkonu

- 6h ASRA, UK, Scan.
- 24 (12) h PAIN

EPI kater in situ- UK nedoporučuje,

FONDAPARINUX (ARIXTRA)

- nepřímý Xa inhibitor
- biologická dostupnost po s.c. 100%, špičkové hladiny za 1,7 h, poločas 17-21 h
- dávka 2,5 mg/d s.c. profylaxe,
- Monitorace -anti Xa aktivita, vylučovaní ledvinami
- prevence VTE po ortop.výkonech a léčbě PE

FONDAPARINUX (ARIXTRA)

Vysazení

- 3-4d PAIN , 2d low risk
- 36-42h (profylaxe) ASRA, ESRA, UK, Scan. kontraindikován u terapeutických dávek
- Stanovení anti Xa aktivity

Podání po výkonu

- 6h ASRA, ESRA, UK, Scan
- 24 (12) h PAIN

EPI kater in situ- konraindikace,

CLOPIDOGREL (PLAVIX, ISCOVER)
PRASUGREL (EFIENT)

- antagonisté na P2Y12 ADP receptoru- blokují agregaci trombocytů, ireverzibilně
- sekundární prevence u koronárního syndromu, ischemické CMP, periferní vaskulární choroba

Vysazení

- 7d UK,
- 7d Clopidogrel, 7-10d Prasugrel ASRA, ESRA, PAIN (ponechat u low risk, u vysokého rizika trombózy 5d)
- 5d Scan.

Podání po výkonu

- 0h Clopidogrel , 6h Prasugrel ESRA
- 6h ASRA, UK,
- 0h Scan.
- 12h PAIN (24 při loading dose clopidogrel), 24hPrasugrel
- kater in situ kontraindikací

TICAGRELOR (BRILIQUE , POSSIA, BRILINTA)

- antagonista na P2Y12 receptoru- blokují agregaci trombocytů, ale na rozdíl od předchozích má vazebné místo jiné než ADP a funguje jako allosterický antagonista a jeho blokáda je reversibilní
- maximální učinek za 2-4h (clopidogrel 24h)

Vysazení

- 5d ESRA, PAIN, UK
- 5-7d ASRA

Podání po výkonu

- 6h ESRA, UK
- 24h PAIN
- kater in situ kontraindikací

INHIBITOR GLYCOPROTEINU IIB/IIIA

EPTIFIBATIDE (INTEGRELIN), TIROFIBAN (AGGRASTAT), ABCIXIMAB (REOPRO)

- Potentní inhibitory agregace krevních destiček používané periproceduálně při intervencích na koronárních tepnách, i.v. podání

Vysazení

- Abciximab 48h UK, Scan, 26-30h ESRA, PAIN (5d high risk)
- Eptifibatide+Tirofiban 8h UK, Scan ,PAIN (24 high +intermediate risk)

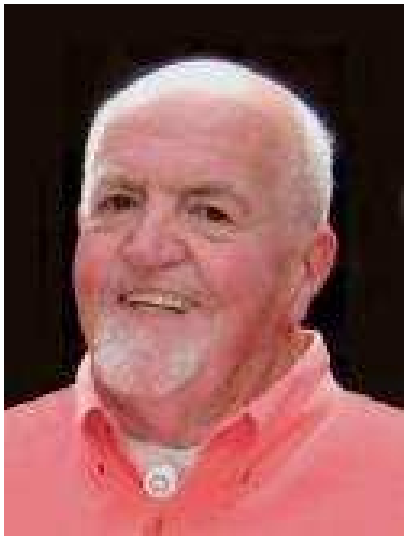
Podání po výkonu

- 2h Scan
- 6h ESRA, UK
- 8-12h PAIN
- kater in situ kontraindikací

FIBRINOLYTIKA

Vysazení i podání po výkonu- 10 dní ASRA, UK nově PAIN 48h !!!! Hladina fibrinogenu

Prof. Alon P. Winnie
May 16, 1932 - January 18, 2015



Děkuji za pozornost