Pacient užívá nová orální antikoagulancia

- čo budeme robiť?

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no conflict of interest

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přehled

1. NOAC
2. vlastnosti
3. doporučení?
4. elektivní výkon
5. akutní výkon
6. *bleeding management*
7. regionální anestézie
8. měření fce PLT; koncentráty protrombinového komplexu

nová perorální antikoagulancia

NOAC new oral anticoagulants

„stará“ orální antikoagulancia

- antagonisté vitamínu K

„nová“ orální antikoagulancia

- přímé inhibitory trombinu
- inhibitory faktoru Xa

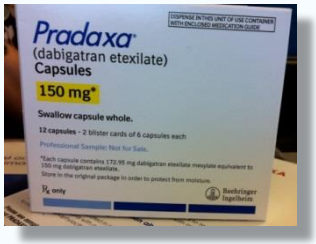
direct thrombin - inhibitors	
dabigatran	**Pradaxa®**
argatroban	**Argartra®**
bivaluridin	**Angiox®**

Factor Xa - inhibitors	
rivaroxaban	**Xarelto®**
apixaban	**Eliquis®**
edoxaban	**Lixiana®**
betrixaban	APEX study
eribaxaban	codename

	„stará“	„nová“
profylaxe CMP, PE, úmrtí	prokázaný účinek	účinek v.s. lepší
komplikace (krvácení)	dobře známé	v.s. nižší (ICH)
dávkování	variabilní	konstantní
onset/offset	pomalé	rychlé
bridging	zpravidla třeba	zpravidla netřeba
monitorace účinku	potřeba (snadná)	není třeba (velmi obtížná)
lékové **interakce**	nízká	vysoká
antidotum	vitamín K	není
dlouholeté **zkušenosti**	ano	nejsou
cena	+	++++

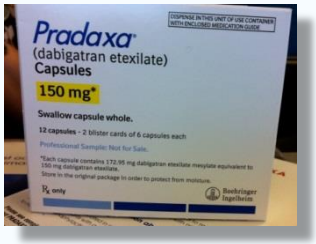
Advantages of novel anticoagulants

- Rapid onset of activity
- Short half-lives
- Similar or improved efficacy
- Fewer drug interactions
- Fixed dose guidelines
- No requirement for monitoring

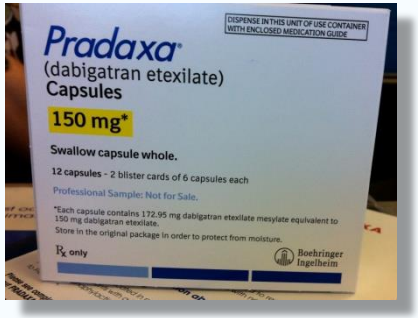


Disadvantages of novel anticoagulants

- No antidote
- No widely available measure of activity
- Limited knowledge and experience
- Drug interactions
- Effect of renal impairment on pharmacokinetics



NOAC



- ✓ **velká výhoda:**
  standardní účinek **bez** nutnosti monitorace
- ✓ **velká nevýhoda:**
  nejsou standardní **monitorovací** testy
  nejsou specifická **antidota**

new oral anticoagulants

	Quick	INR	PTT	thrombin	fibrinogen
dabigatran	↓	↑	↑	↑↑↑	--
rivaroxaban	↓↓	↑↑	↑↑	--	--

vlastnosti

	Apixaban[d]	Dabigatran[d,e]	Edoxaban	Rivaroxaban
Target	Factor Xa	Factor IIa	Factor Xa	Factor Xa
Dose[a]	5 mg	75-150 mg	30-60 mg	20 mg
Frequency	Twice daily	Twice daily	Daily	Daily
Effect of Food	None	May delay (but not limit) absorption	None	None
$T_{1/2}$	12 h	12-17 h	6-10 h	5-9 h
T_{MAX}	1-3 h	1 h	1-2 h	2-4 h
Metabolism	Hepatic (CYP3A4 - major)	Activation by esterases - renal	Renal – hepatic (CYP3A4 - minor)	Hepatic (CYP3A4 -major) - renal
Renal Impairment	Use 2.5 mg twice daily if SCr ≥1.5 mg/dL	Use 75 mg twice daily if CrCl = 15-30 mL/min*m^2	Avoid use if CrCl < 30 mL min*m^2	Use 15 mg daily if CrCl = 30-49 mL/min*m^2 - avoid use if CrCl < 30 mL/min*m^2
Hepatic Impairment	Use with caution in mild to moderate (Child-Pugh B) - avoid use in severe (Child-Pugh C)	N/A	Unknown	Avoid use in moderate (Child-Pugh B) or severe (Child-Pugh C)
Drug Interactions	CYP3A4 inhibitors or inducers - P-glycoprotein inhibitors or inducers	P-glycoprotein inhibitors or inducers	P-glycoprotein inhibitors or inducers	CYP3A4 inhibitors or inducers - P-glycoprotein inhibitors or inducers
Monitoring[b]	Anti-Xa	aPTT, ECT	Anti-Xa	Anti-Xa
Overdose management[c]	Unknown	Unknown (can be dialyzed)	Unknown	Unknown (likely not dialyzable – possibly protrombin complex concentrate[f]

doporučení

not enough data

recommendations

- are not so much based on clinical experience
- reflect experts' opinions or laboratory endpoints

NOAC

- have relatively short elimination half-lives
- time is the most important antidote of the NOACs
- 'wait-and-see'

elektivní

výkon

European Heart Journal
doi:10.1093/eurheartj/eht134

EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary†

Table 3 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Edoxaban[a]		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)							
	Low risk (h)	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 mL/min	≥24	≥48	≥24	≥48	no data	no data	≥24	≥48
CrCl 50–80 mL/min	**≥36**	**≥72**	≥24	≥48	no data	no data	≥24	≥48
CrCl 30–50 mL/min[b]	**≥48**	**≥96**	≥24	≥48	no data	no data	≥24	≥48
CrCl 15–30 mL/min[b]	not indicated	not indicated	**≥36**	**≥48**	no data	no data	**≥36**	**≥48**
CrCl <15 mL/min	no official indication for use							

Low risk, surgery with low risk of bleeding; high risk, surgery with high risk of bleeding. CrCl, creatinine clearance.
[a]No EMA approval yet. Needs update after finalization of SmPC.
[b]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (15 mg QD).

Table 2. Oral anticoagulants and antiplatelet agents[10,11,21]

Drugs	Mechanism of action	Dosage	Stopping medication before surgery
Dabigatran	Direct thrombin inhibitors	150 mg twice daily for most patients 110 mg BD for patients aged >75years or with ClCr 30–49 ml/min	24 hours: • low bleeding risk and normal renal function 96 hours • high-bleeding-risk individual and impaired renal function[11]
Rivaroxaban	Factor Xa inhibitor	20 mg daily for most patients 15 mg daily if ClCr 30–49 ml/min Avoid if ClCr <30 ml/min	24–48 hours[11]
Apixaban	Factor Xa inhibitor	5 mg twice daily for most patients 2.5 mg twice daily for age >80 years, weight <60 kg S creat >133 microM/L	24–48 hours
Clopidogrel	Metabolised in the liver to active compounds that bind covalently to ADP receptors on platelets and reduce platelet activation	75 mg daily	5–7 days prior to surgery
Prasugrel	An ADP receptor antagonist	10 mg once daily for adults >60 kg 5 mg once daily for patients <60 kg	5–7 days prior to surgery
Ticagrelor	Reversible, directly acting inhibitor of the ADP receptor P_2Y_{12}	90 mg twice daily	5–7 days prior to surgery

akutní

operační

výkon

NOAC should be discontinued

surgery should be deferred (if possible)

- until at least 12h (ideally 24h) after the last dose

common coagulation tests should be performed

- aPTT for direct thrombin inhibitors

- sensitive PT for FXa inhibitors

specific coagulation tests should be performed

- dTT for direct thrombin inhibitors

- chromogenic assays for FXa inhibitors

bleeding management

Table 2 Possible measures to take in case of bleeding

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non-life-threatening bleeding	Inquire last intake + dosing regimen Estimate normalization of haemostasis Normal renal function: 12–24 h CrCl 50–80 mL/min: 24–36 h CrCl 30–50 mL/min: 36–48 h CrCl <30 mL/min: ≥48 h Maintain diuresis Local haemostatic measures Fluid replacement(colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (preliminary evidence: −65% after 4h)[53] Charcoal haemoperfusion not recommended (no data)	Inquire last intake + dosing regimen Normalization of haemostasis: 12–24 h Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
Life-threatening bleeding	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available. Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)

RBC, red blood cells; CrCl, creatinine clearance; PCC, Prothrombin complex concentrate.

dabigatran
- fresh frozen plasma
- activated prothrombin complex conc. 50 IE/kg
- activated FVII
rivaroxaban
- fresh frozen plasma
- non-activated prothrombin complex conc. 25 U/kg
- activated FVII

regionální anestézie

guidelines?

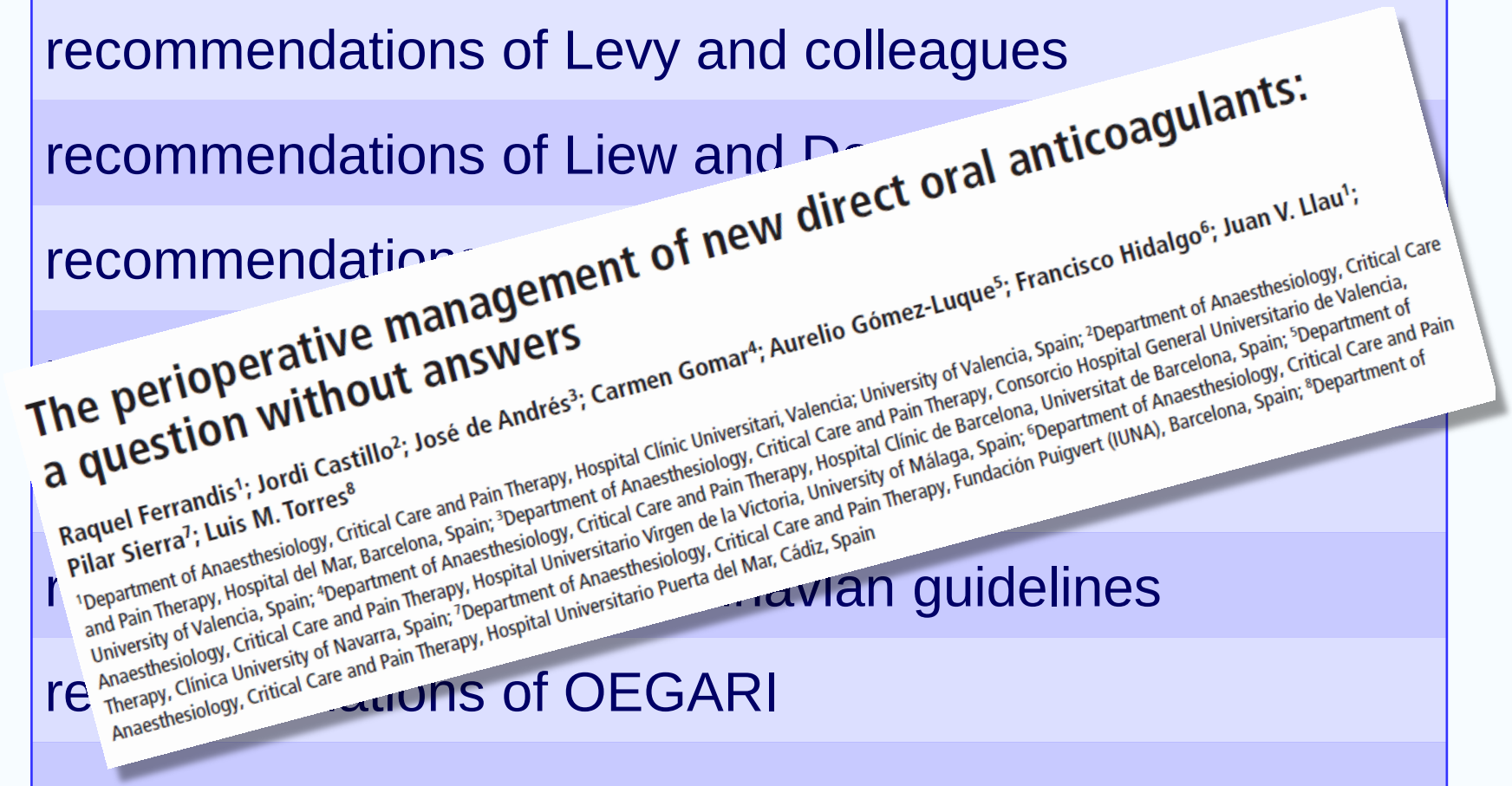
recommendations of Levy and colleagues

recommendations of Liew and D

recommendation

r navian guidelines

re ations of OEGARI



The perioperative management of new direct oral anticoagulants: a question without answers

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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

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BJA

REGIONAL ANAESTHESIA

New oral anticoagulants and regional anaesthesia

H. T. Benzon[1*], M. J. Avram[1], D. Green[2] and R. O. Bonow[2]

Table 1 New anticoagulant drugs approved by the US FDA. AF, atrial fibrillation; VTE, venous thromboembolism; DVT, deep venous thrombosis. *Approved indication, references: Garcia and colleagues,[16] Siegal and Cuker,[17] and Siegal and Crowther.[18] †Efficacy of dabigatran in studies not uniform (see text). ‡Efficacy when added to antiplatelet therapy. ¶Apixaban is non-inferior to conventional therapy (subcutaneous enoxaparin followed by warfarin) in the treatment of acute VTE (from Agnelli and colleagues)[107]

Drug	Mechanism of action	Efficacy in clinical syndromes	Approved indications*
Dabigatran (Pradaxa®)	DTI	Prevention of postoperative VTE after total joint surgery† Prevention of stroke in AF Treatment of acute VTE	Prevention of stroke in patients with non-valvular AF (USA, Canada, and Europe) Prevention of VTE after knee or hip arthroplasty (Europe and Canada)
Rivaroxaban (Xarelto®)	Factor Xa inhibitor	Prevention of postoperative VTE after total joint surgery Prevention of stroke in AF Treatment of acute VTE Acute coronary syndromes‡	VTE prophylaxis and stroke prevention in non-valvular AF (USA, Canada, and Europe) Treatment of VTE (USA, Europe, and Canada) Prevention of VTE after orthopaedic surgery (USA, Europe, and Canada)
Apixaban (Eliquis®)	Factor Xa inhibitor	Prevention of postoperative VTE after total joint surgery Prevention of stroke in AF Treatment of acute VTE¶	Stroke prevention in patients with non-valvular AF (USA, Europe, and Canada) VTE prophylaxis after hip and knee arthroplasty (Europe and Canada)

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and 15 h for apixaban.[7] From Sie and colleagues:[8] Recommendations of Levy and colleagues[9] regarding dabigatran in procedures with high bleeding risk: 2–4 days with CrCl >80 ml min^{-1}, 2–4 days with CrCl 50–80 ml min^{-1}, >4 days with CrCl 30–50 ml min^{-1}, and >5 days with CrCl <30 ml min^{-1}. Recommendations of Liew and Douketis[14] for mild-to-moderate anticoagulant effect at surgery (two to three drug half-lives): dabigatran: 2 days with CrCl >50 ml min^{-1}, 3 days with CrCl 30–50 ml min^{-1}; rivaroxaban/apixaban: 2 days with CrCl >50 ml mim^{-1}, 3 days with CrCl 30–50 ml min^{-1}. For comparison, the French Study Group recommended a 24 h interval in patients undergoing procedures with low risk of haemorrhage and a 5 day interval in cases of medium or high haemorrhagic risk.[10] The European guidelines were based on two half-lives of the drugs: 34 h for dabigatran, 22–26 h for rivaroxaban, and 26–30 h for apixaban.[2] The Scandinavian guidelines recommended 18 h for rivaroxaban and had no recommendations for dabigatran and apixaban because data were not available when the guidelines were written.[3] There are no ASRA guidelines for the dabigatran, rivaroxaban, and apixaban

Drug	Metabolism, renal, and faecal/biliary elimination*	Elimination half-life	Five half-lives	Baron and colleagues:[12] recommendations	Connolly and Spyropoulos:[13] high bleeding risk (4–5 half-lives between dose and surgery)	Liew and Douketis:[14] no or minimal anticoagulant effect at surgery (four to five half-lives)
Dabigatran	Renal 80%, faecal 20%	12–17 h 28 h (end-stage renal disease)	85 h (4 days) 140 (6 days) (end-stage renal disease)	1–2 days with CrCl ≥50 ml min^{-1}; 3–5 days with CrCl <50 ml min^{-1}	3 days with CrCl >50 ml min^{-1}; 4–5 days with CrCl 30–50 ml min^{-1}	3 days with CrCl >50 ml min^{-1}; 4–5 days with CrCl 30–50 ml min^{-1}
Rivaroxaban	Metabolism 33%, renal 33% (33% inactive metabolites)	9–13 h	65 h (3 days)	≥1 day with normal renal function; 2 days with CrCl 60–90 ml min^{-1}; 3 days with CrCl 30–59 ml min^{-1}; 4 days with CrCl 15–29 ml min^{-1}	3 days with CrCl >50 ml min^{-1} and CrCl 30–50 ml min^{-1}; 4 days with CrCl 15–29.9 ml min^{-1}	3 days with CrCl >50 ml min^{-1}; 4–5 days with CrCl 30–50 ml min^{-1}
Apixaban	Renal 25%, metabolism and faecal elimination 75%	15.2 (8.5)	75 h (3–4 days)	1 or 2 days with CrCl >60 ml min^{-1}; 3 days with CrCl 50–59 ml min^{-1}; 5 days with CrCl <30–49 ml min^{-1}	3 days with CrCl >50 ml min^{-1}; 4 days with CrCl 30–50 ml min^{-1}	(Same as rivaroxaban)

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Table 3 Resumption of anticoagulant based on the peak effect and onset of action. *Rosencher and colleagues[32] recommended 8 h (assumed for the clot to be stable) minus the peak effect of drug, a recommendation adapted by the Scandinavian guidelines. Although the European guidelines did not quote Rosencher and colleagues, their recommended intervals appear to follow Rosencher's recommendations. The Scandinavian guidelines recommend that prasugrel and ticagrelor can be administered after catheter removal. †The 24 h value is based on a study that showed no enlargement of intracranial haematoma when enoxaparin was given within 24–48 h after an intracranial haemorrhage (Tertri and colleagues).[45] The French Study Group recommended a 24 h interval before resumption of the oral anticoagulants[10]

Drug	Time to peak effect of drug	Resumption of drug based on 8 h minus the time to peak anticoagulant effect*	Resumption of drug based on 24 h minus the time to peak anticoagulant effect†	Baron and colleagues:[12] recommendations (high-risk procedures)	Connolly and Spyropoulos:[13] high bleeding risk	Liew and Douketis[14]
Dabigatran	2 (1.5–3) h	6 h	22 h	48 h	24 h, half of the usual dose for first 2 days	24 h after operation for cases with low bleeding risk, 48–72 h for high bleeding risk
Rivaroxaban	2.5–4 h	5.5 h	21.5 h	48 h	24 h, half of the usual dose for first 2 days	Same as dabigatran
Apixaban	1–2 h	7 h	23 h	48 h	24 h, half of the usual dose for first 2 days	Same as dabigatran
Prasugrel	1 h	7 h	23 h	Caution (recommended within 24 h for aspirin and clopidogrel)		
Ticagrelor	2–4 h	6 h	22 h	(Same as for prasugrel)		

Timing of neuraxial block

The European Society of Anaesthesiologists (ESA) recommends that 2 elimination half-lives need to elapse between administration of the last dose of drug and performance of the neuraxial block.[20]

Table 5. Timing of Central Neuraxial Block in patients taking novel anticoagulants

Therapy	Time from dose to insertion / removal	Time from insertion / removal to next dose
Dabigatran	2 days if Creatinine Clearance (CrCl) > 50 mls/min, 5 days if CrCl < 50 mls/min[21]	The first dose of dabigatran may be given two hours following the removal of an epidural catheter, but concomitant use is contraindicated
Rivaroxaban	22-26 hours	6 hours (24 hours if traumatic puncture)
Apixaban	26-30 hours	4-6 hour
Fondaparinux	36-42 hours	6-12 hours

měření funkce trombocytů

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Durchflusszytometrie

Born-Aggregation

Accumetrics ®

VerifyNow®

P2Y12 inhibitors

- ✓ *clopidogrel, prasugrel, ticagrerol…*
- ✓ často používaná antiagregační terapie (+ASS)
- ✓ indikace: ACS, PCI, iCMP…
- ✓ ireverzibilně blokuje *P2Y12* receptor trombocytů
- ✓ v játrech metabolizovány na aktivní látky

krvácení | trombóza

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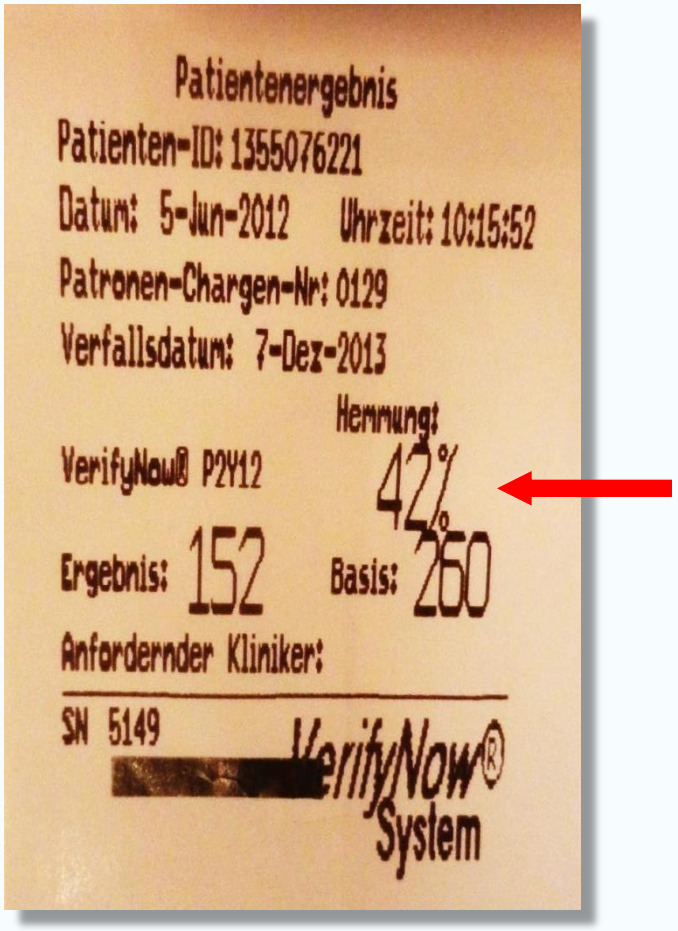

- ✓ krvácivý stav způsoben působením *P2Y12* inhibitorů?
- ✓ je možné provést svodnou či regionální anestézii?
- ✓ je pac. dostatečně inhibován?

koncentráty protrombinového komplexu

PPSB

- ✓ *Prothrombin Complex Concentrate*
- ✓ **FII, VII, IX, X**
- ✓ + fakult. protein C,S, antitrombin, heparin
- ✓ účinné zejména u antagonistů vit. K
- ✓ PPSB 1 IE/kg t. hm. zvýší aktivitu koagulačních faktorů cca o 1%
- ✓ počáteční dávka: cca 20-40 IE/kg t. hm.
- ✓ *KI: hemofilie A,B, hyperfibrinolýza, HIT*

	PPSB		
	factors II, VII, IX, X		
	proteins C,S	antithrombin	heparin
Cofact	-	-	-
Octaplex	+	-	+
Prothromplex	-	-	+
Beriplex	+	+	+

…děkuji Vám za pozornost

dabigatran

dabigatran

- přímý inhibitor trombinu
- účinkuje nezávisle na antitrombinu
- *peak plasma concentration in* 1,5-3 h
- *half-life* 14-17 h
- nízká inter- a intraindividuální variabilita
- 80% se vylučuje močí
- RI: koncentrace ↑ až 6x, poločas ↑ až 2x
- KI u CrCl<30 $ml.kg^{-1}.min^{-1}$

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