NOACs na ICU

- 10 věcí, které bych měl znát

OA Dr. Stibor B.

ICU, Landesklinikum Baden bei Wien, Austria

no conflict of interest

OA Dr. Stibor B.

ICU, Landesklinikum Baden bei Wien, Austria

přehled

1. nová perorální antikoagulancia
2. farmakokinetika a farmakodynamika
3. laboratorní vyšetření
4. NOACs a elektivní výkon
5. NOACs a akutní výkon
6. koncentráty protrombinového komplexu
7. antidota
8. bridging?
9. NOACs po výkonu
10. ???

nová perorální antikoagulancia

NOAC new oral anticoagulants

„stará“ orální antikoagulancia

- antagonisté vitamínu K

„nová“ orální antikoagulancia

- přímé inhibitory trombinu
- inhibitory faktoru Xa

	„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 (obtížná)
lékové **interakce**	vysoká	nízká
antidotum	vitamín K	velmi drahé
dlouholeté **zkušenosti**	ano	nejsou
cena	+	+++

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

Factor Xa - inhibitors	
rivaroxaban	**Xarelto®**
apixaban	**Eliquis®**
edoxaban	**Lixiana®**
betrixaban	**Bevyxxa®**
eribaxaban	*Pfizer*
letaxaban	*Takeda*
darexaban	*Astellas (stop IX/2011)*

new oral anticoagulants

	nvAF	DVT	PE	hip/knee	hip/knee
dabigatran	+	+	+	+	-
rivaroxaban	+	+	+	+	+
apixaban	+	+	+	+	+
edoxaban	+	+	+	-	-

farmakokinetika
a
farmakodynamika

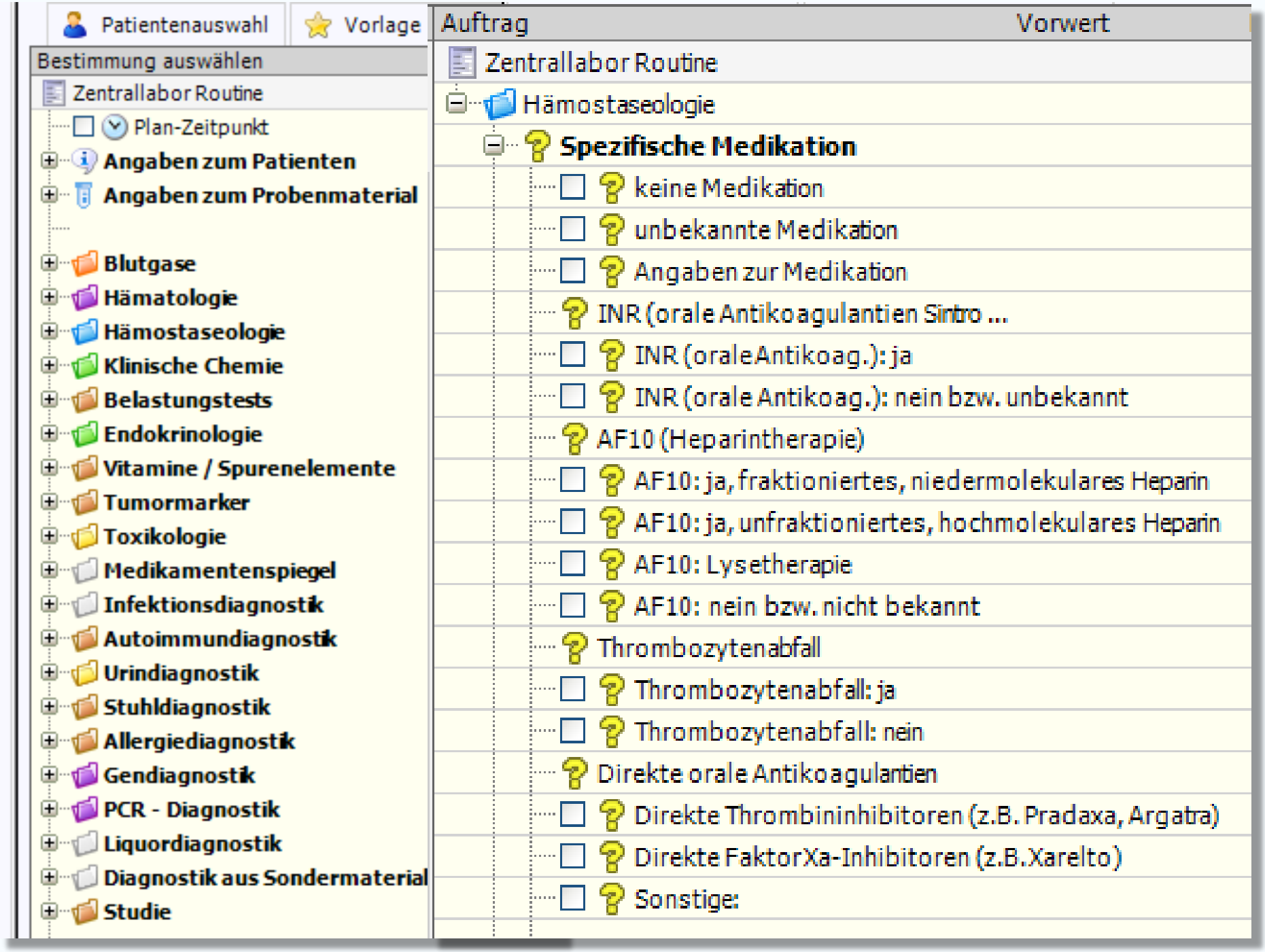
	Apixaban[d]	Dabigatran[d,e]	Edoxaban	Rivaroxaban
Target	Factor Xa	Factor IIa	Factor Xa	Factor Xa
Dose[a]	5 mg	75-150 mg	30-60 mg	20 mg
Frequency	Twice daily	Twice daily	Daily	Daily
Effect of Food	None	May delay (but not limit) absorption	None	None
$T_{1/2}$	12 h	12-17 h	6-10 h	5-9 h
T_{MAX}	1-3 h	1 h	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 andexanet	Unknown (can be dialyzed) idarucizumab	Unknown andexanet (?)	Unknown (likely not dialyzable – possibly protrombin complex concentrate[f] andexanet

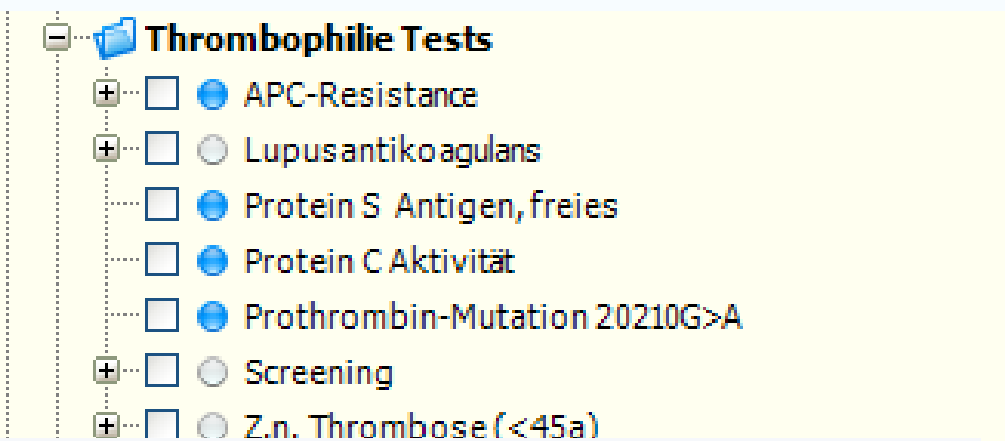
laboratorní vyšetření

new oral anticoagulants

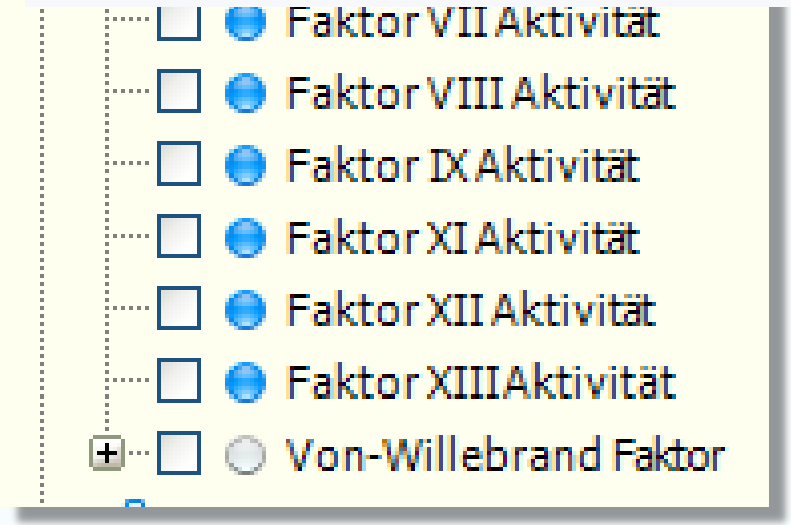
	INR	aPTT	TT	anti-FXa
dabigatran	--	↑↑	↑↑↑	--
rivaroxaban	↑	↑	--	↑↑
apixaban	↑	↑	--	↑↑
edoxaban	↑	↑	--	↑↑

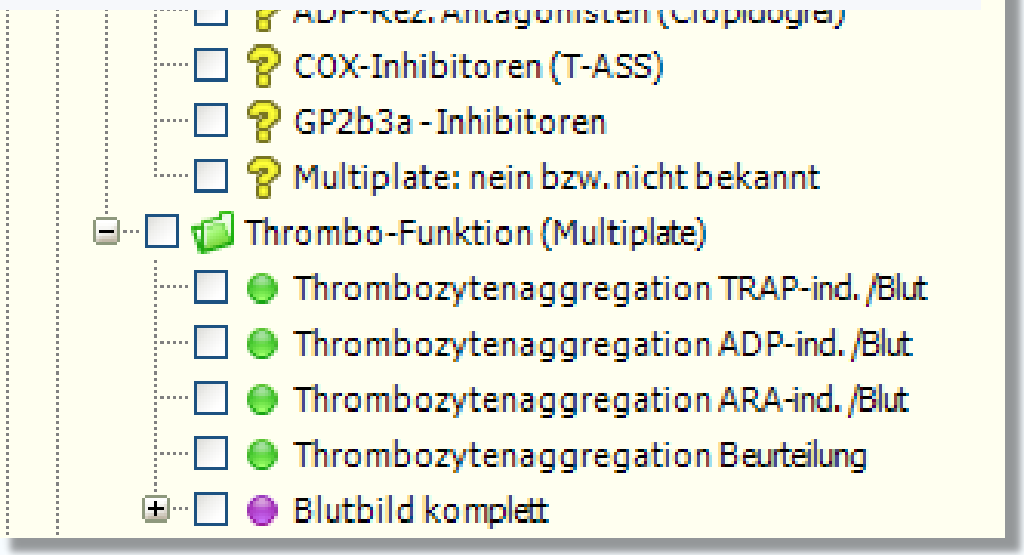
cave:
jsou nutné specifické
laboratorní sety !


Patientenauswahl
Vorlage
Bestimmung auswählen
Zentrallabor Routine
Plan-Zeitpunkt
Angaben zum Patienten
Angaben zum Probenmaterial
Blutgase
Hämatologie
Hämostaseologie
Klinische Chemie
Belastungstests
Endokrinologie
Vitamine / Spurenelemente
Tumormarker
Toxikologie
Medikamentenspiegel
Infektionsdiagnostik
Autoimmundiagnostik
Urindiagnostik
Stuhldiagnostik
Allergiediagnostik
Gendiagnostik
PCR - Diagnostik
Liquordiagnostik
Diagnostik aus Sondermaterial
Studie
Auftrag
Vorwert
Zentrallabor Routine
Hämostaseologie
Spezifische Medikation
keine Medikation
unbekannte Medikation
Angaben zur Medikation
INR (orale Antikoagulantien Sintro ...
INR (oraleAntikoag.): ja
INR (orale Antikoag.): nein bzw. unbekannt
AF10 (Heparintherapie)
AF10: ja, fraktioniertes, niedermolekulares Heparin
AF10: ja, unfraktioniertes, hochmolekulares Heparin
AF10: Lysetherapie
AF10: nein bzw. nicht bekannt
Thrombozytenabfall
Thrombozytenabfall: ja
Thrombozytenabfall: nein
Direkte orale Antikoagulantien
Direkte Thrombininhibitoren (z.B. Pradaxa, Argatra)
Direkte FaktorXa-Inhibitoren (z.B.Xarelto)
Sonstige:



vždy uvádět výšku, váhu pacienta a typ podávaných antikoagulancií !





doporučení a guidelines

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

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 $\leq 60 \times 10^9$/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 $\leq 60 \times 10^9$/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

- **prothrombin complex** conc. 25 IE/kg
- activated FVII
- fresh frozen plasma
- **antidot** *(idarucizumab)*

rivaroxaban

- **prothrombin complex** conc. 25 U/kg
- fresh frozen plasma
- activated FVII
- **antidot** *(andexanet alfa)*

koncentráty protrombinového komplexu

PCC

- ✓ vyráběn z lidské plasmy, virová inaktivace
- ✓ obsahuje faktory protrombinového komplexu F II, IX, X, ev. VII
- ✓ fakult. protein C,S, antitrombin, heparin…
- ✓ hladiny cca 25x vyšší než ve FFP
- ✓ preparáty standardizovány (kvantifikovány) na obsah faktoru IX (IU)
- ✓ ostatní faktory v různé koncentraci…

PCC

vs.

PPSB

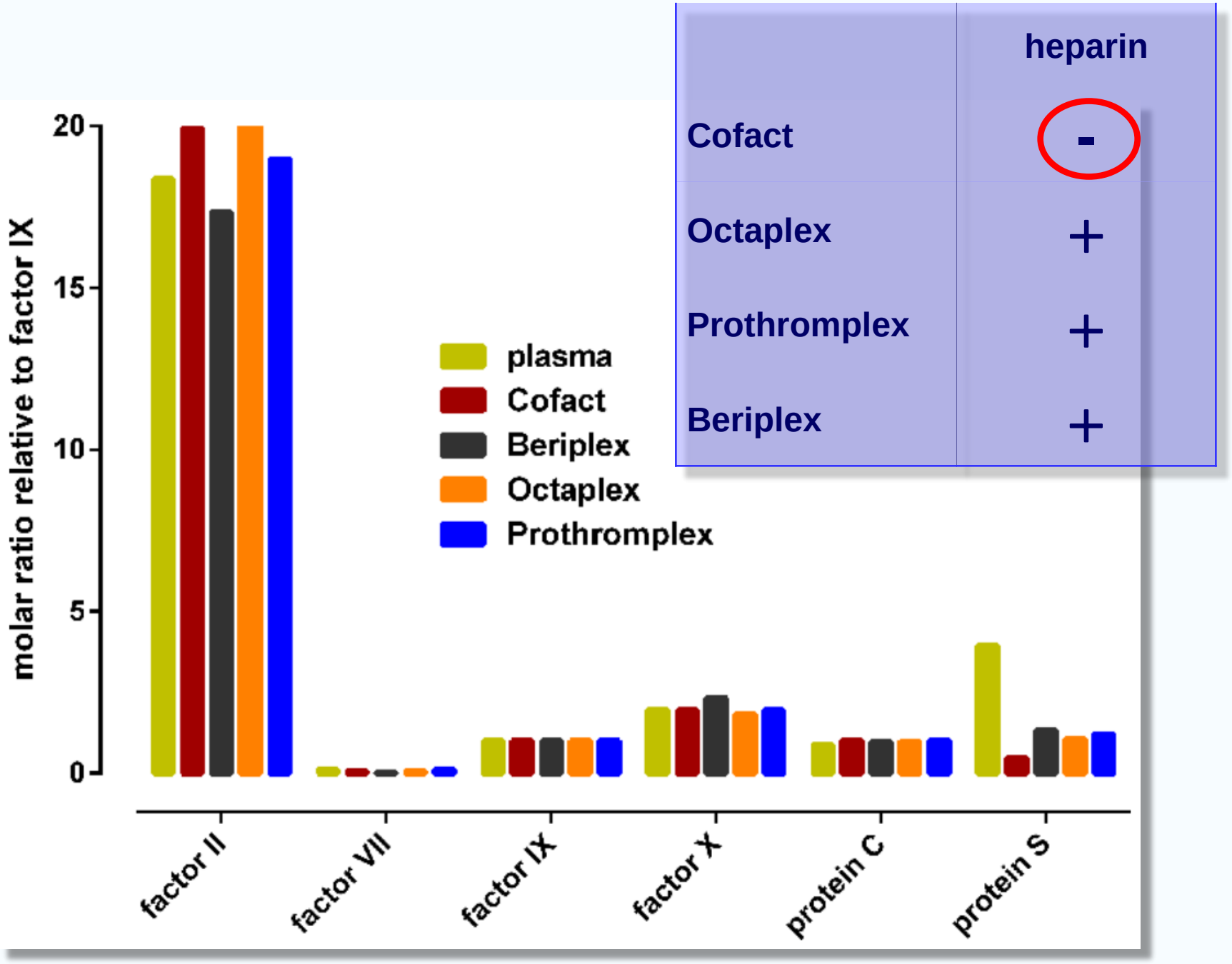
PCC vs. PPSB

	PPSB
Faktor **II**	**P**rothrombin
Faktor **VII**	**P**rokonvertin
Faktor **X**	**S**tuart-Prowerové faktor
Faktor **IX**	antihemofilický (Christmasův) faktor **B**

typy PCC

types of PCCs

type	**abbrev.**	**brand names** *(among others)*	**factors**
three-factor	(3F)PCC	Profilnine, Bebulin	II,IX,X
four-factor	(4F)PCC	Beriplex (Kcentra), Octaplex, Prothromplex, Cofact	II,VII,IX,X
activated	aPCC	Feiba	II,IX,X,VIIa


heparin
Cofact
-
Octaplex
+
Prothromplex
+
Beriplex
+
molar ratio relative to factor IX
20
15
10
5
0
plasma
Cofact
Beriplex
Octaplex
Prothromplex
factor II
factor VII
factor IX
factor X
protein C
protein S

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

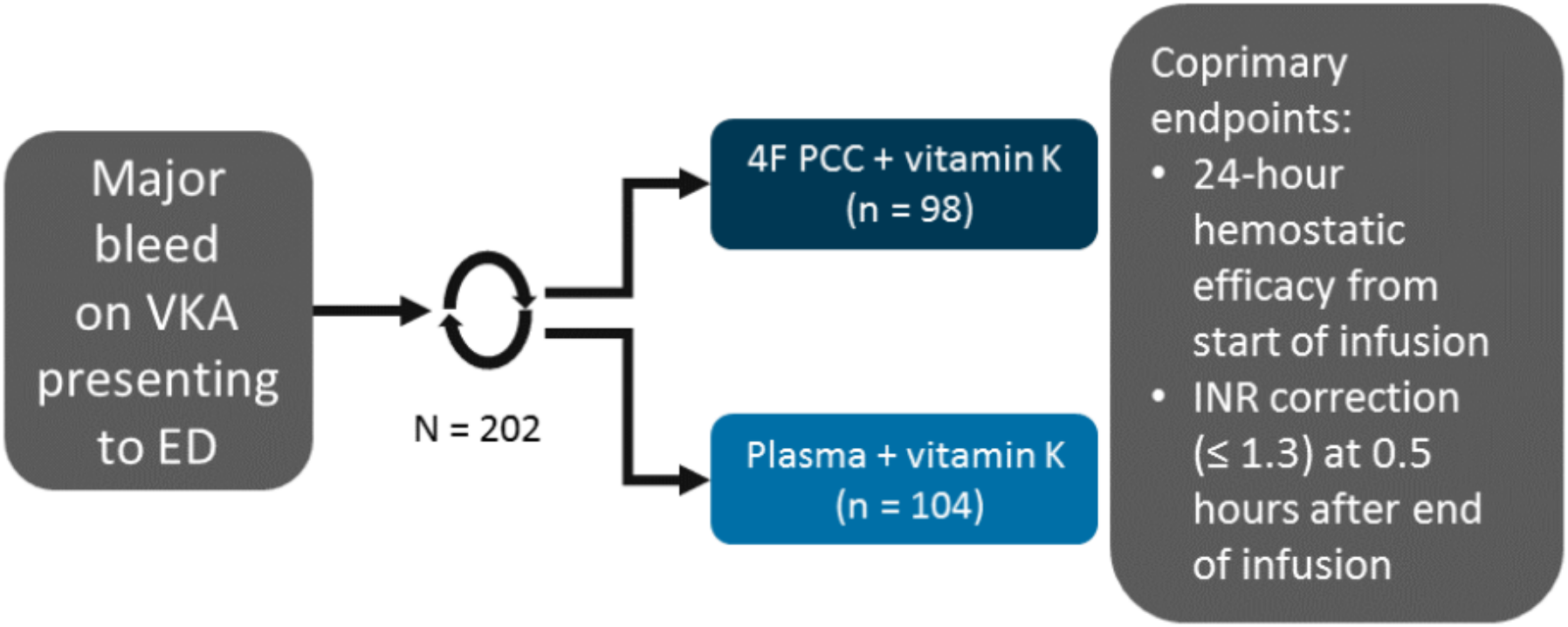
Concentrate	Major functional component(s)	Indications*	Off-label use/remark
4F-PCC	Coagulation factors II, VII, IX, X	Treatment and perioperative prophylaxis of bleeding – in acquired deficiency of PCC factors, such as deficiency caused by treatment with vitamin K antagonists – in congenital deficiency of the vitamin K-dependent coagulation factors when purified specific coagulation factor products are not available	Treatment of trauma-induced coagulopathy Treatment of bleeds in patients with liver disease Reversal of anticoagulation by direct factor Xa and thrombin-inhibiting oral anticoagulants (evidence based on several bleeding models in animals and human volunteers; substantial clinical evidence is lacking)

Basaran, Biteker et al., Anticoagulation Therapy, 2016

	FFP	PCC
effect	+	++
need for blood group compatibility	+	-
bed side test	+	-
start of application	slow	fast
duration of application	slow	fast
volume	large	minimal
risk of TACO	+	-
risk of TRALI	+	-
side effects	+	+

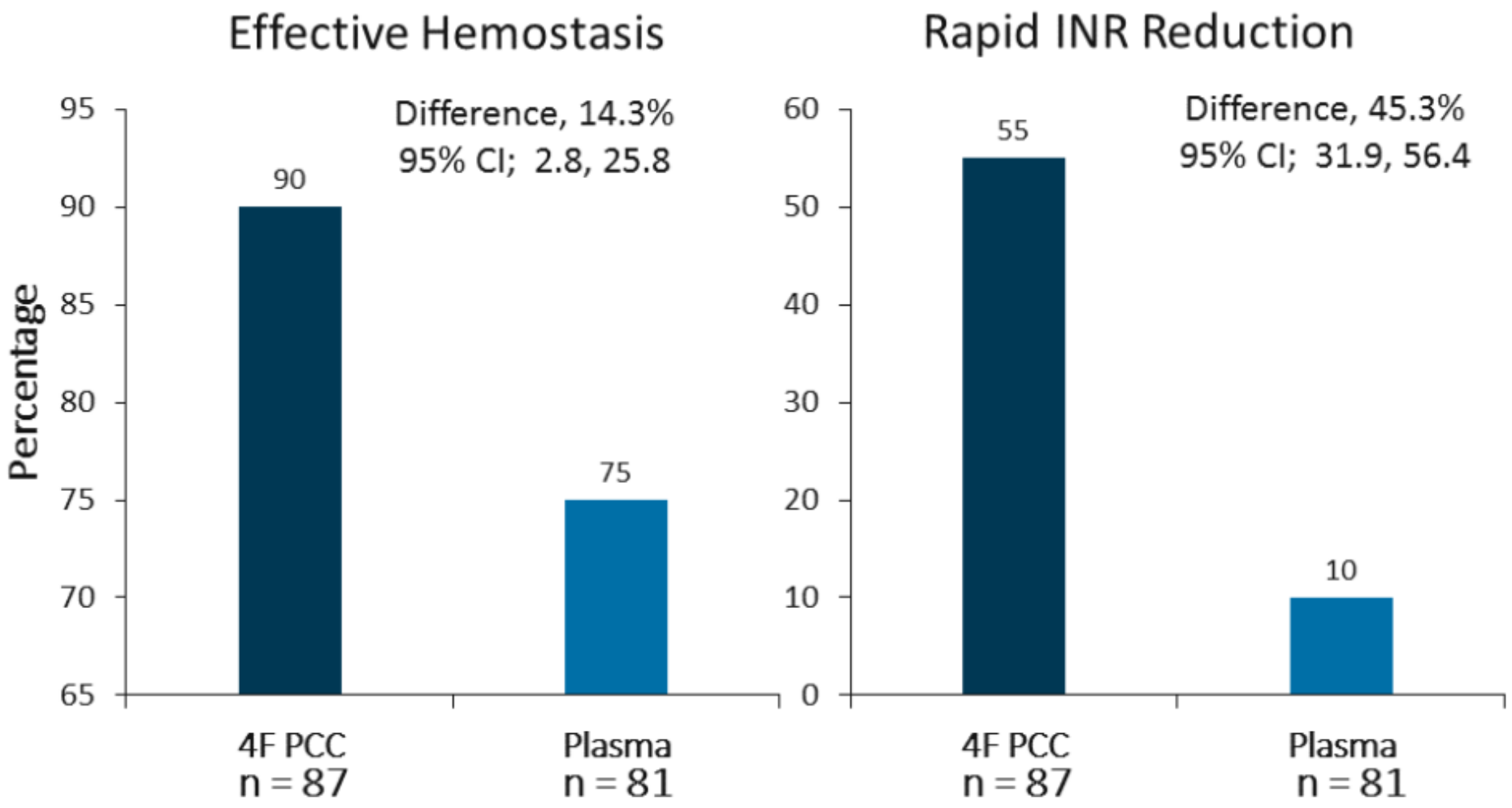
4-Factor PCC Pivotal Trial

Efficacy and safety of a 4-factor PCC in patients on VKA presenting with major bleeding: prospective, randomized, open-label, active-controlled, multicenter, noninferiority trial



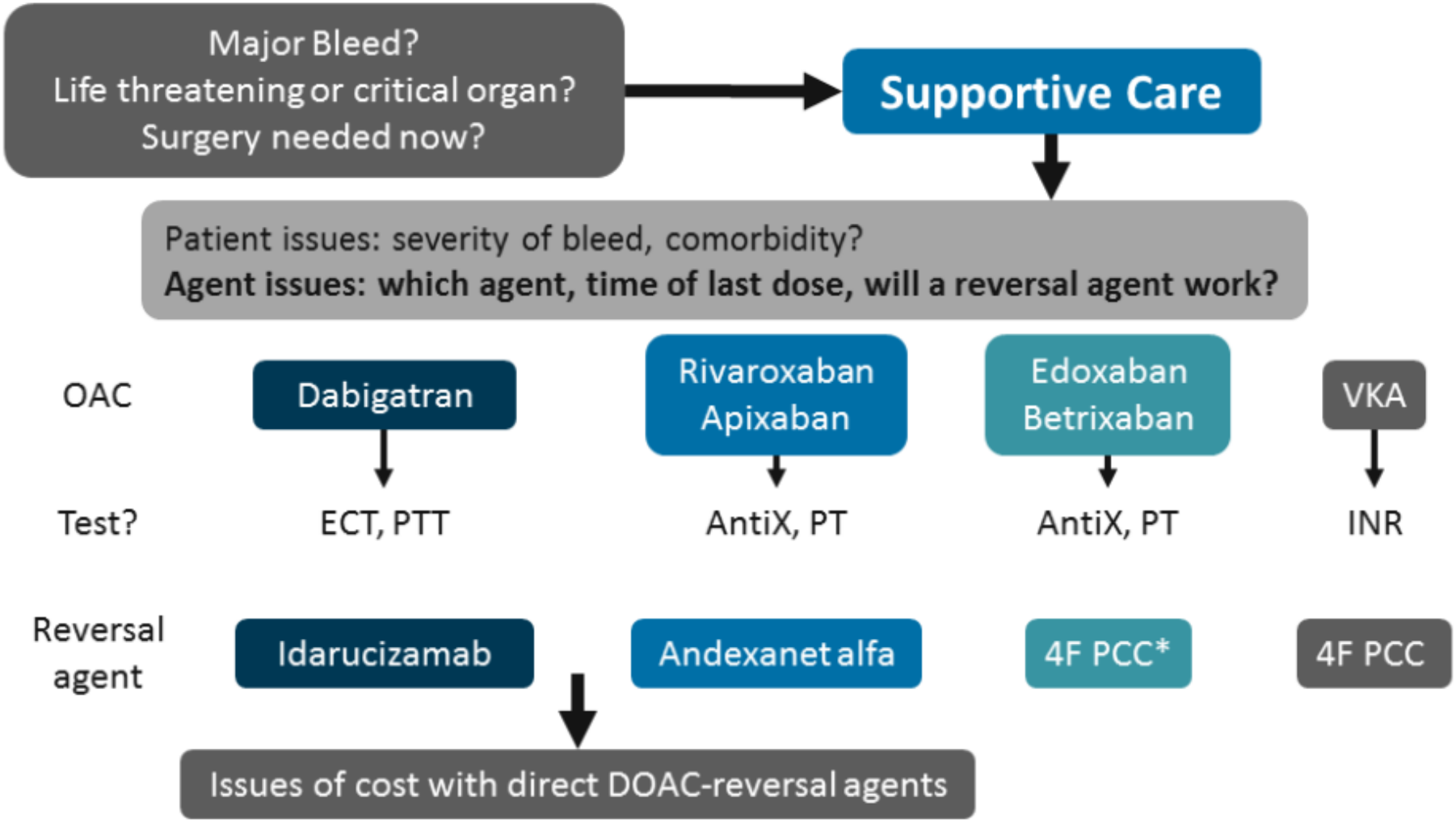
Sarode R, et al. *Circulation*. 2013;128:1234-1243.

4-Factor PCC in Urgent Surgery

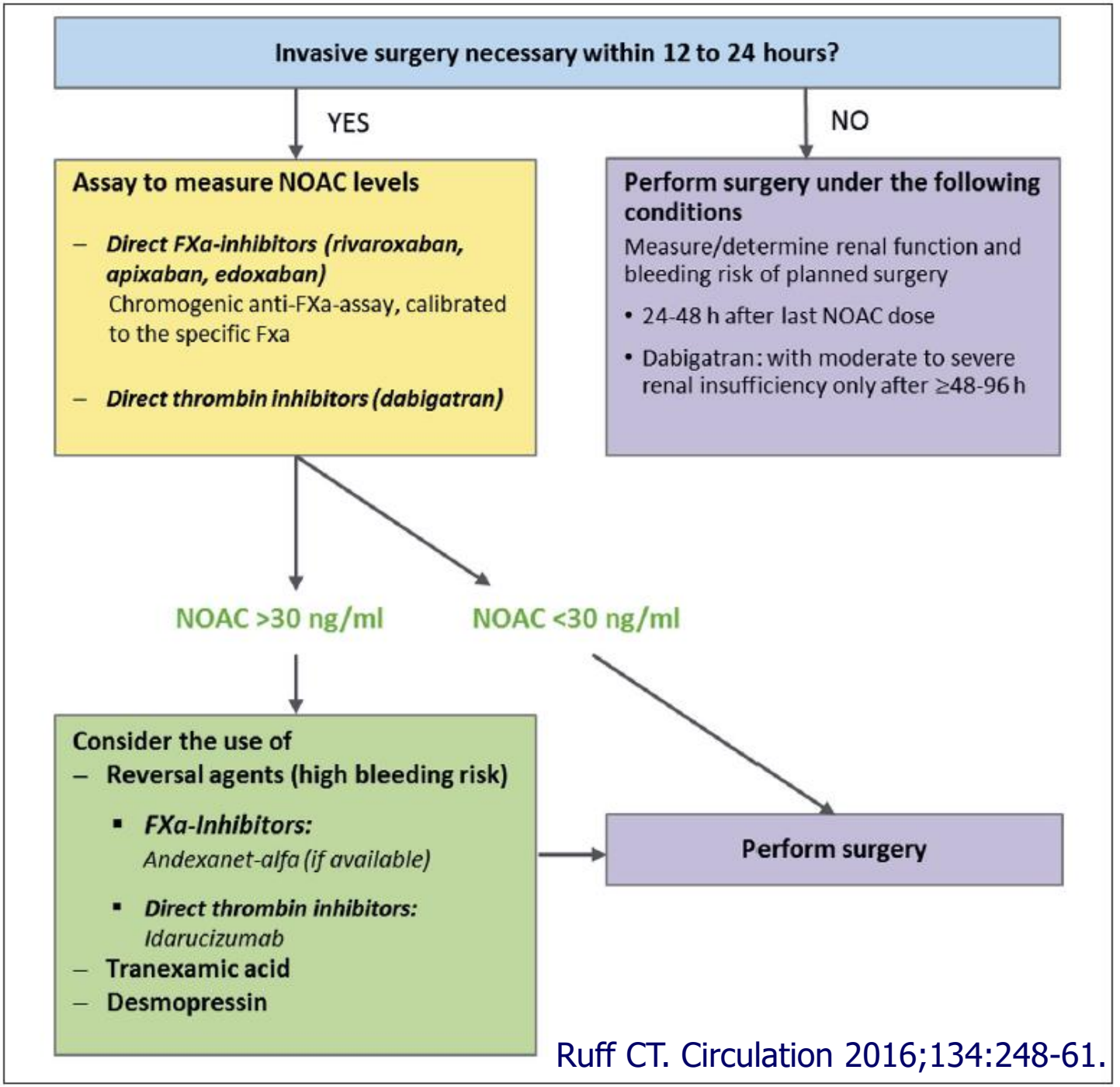


Goldstein JN, et al. *Lancet.* 2015;385:2077-2087.

Decisions in the ED



*Andexanet alfa is not indicated for reversal of edoxaban- or betrixaban-associated bleeding.



Ruff CT. Circulation 2016;134:248-61.

antidota

ORIGINAL ARTICLE

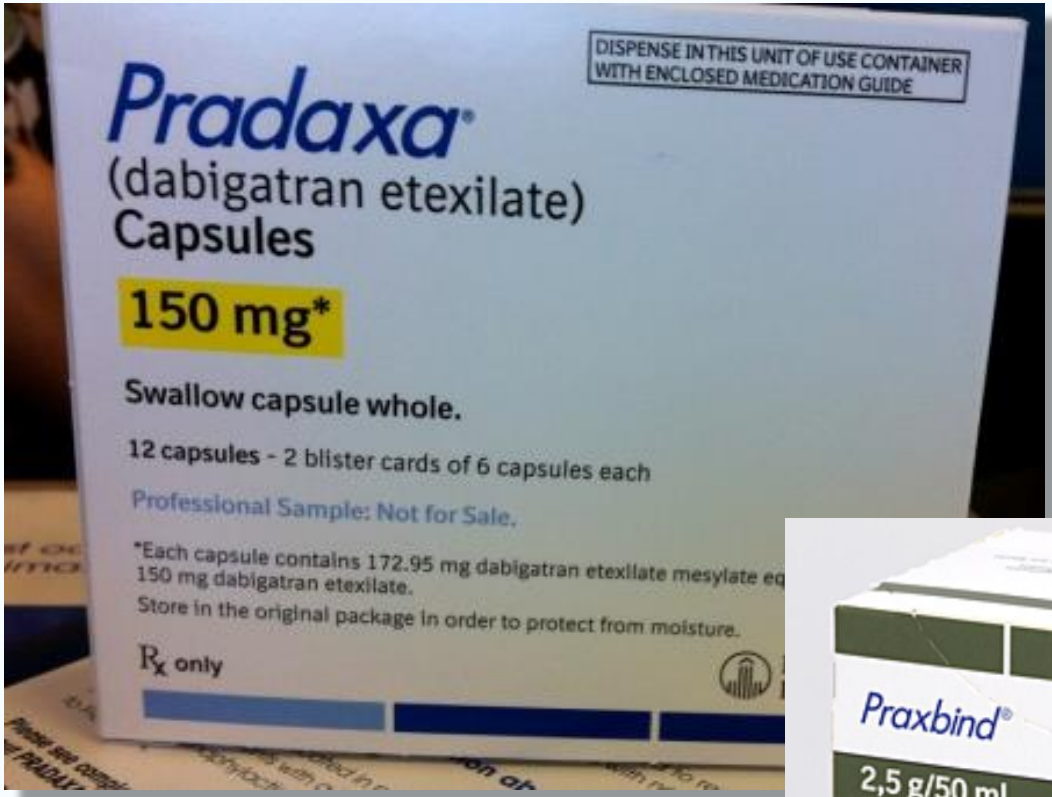
Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

N Engl J Med 2015; 373:511-520 | August 6, 2015 | DOI: 10.1056/NEJMoa1502000

CONCLUSIONS

Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes. (Funded by Boehringer Ingelheim; RE-VERSE AD ClinicalTrials.gov number, NCT02104947.)


DISPENSE IN THIS UNIT OF USE CONTAINER
WITH ENCLOSED MEDICATION GUIDE
Pradaxa®
(dabigatran etexilate)
Capsules
150 mg*
Swallow capsule whole.
12 capsules - 2 blister cards of 6 capsules each
Professional Sample: Not for Sale.
*Each capsule contains 172.95 mg dabigatran etexilate mesylate eq
150 mg dabigatran etexilate.
Store in the original package in order to protect from moisture.
℞ only


Praxbind®
2,5 g/50 ml
Injektions-/Infusionslösung
Idarucizumab
Intravenöse Anwendung
2 Durchstechflaschen zu je 50 ml
Boehringer Ingelheim
Praxbind®
2,5 g/50 ml
Injektions-/
Infusionslösung
Idarucizumab
Intravenöse Anwendung
Praxbind®
2,5 g/50 ml
Injektions-/
Infusionslösung
Idarucizumab
Intravenöse Anwendung

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

S.J. Connolly, M. Crowther, J.W. Eikelboom, C.M. Gibson, J.T. Curnutte, J.H. Lawrence, P. Yue, M.D. Bronson, G. Lu, P.B. Conley, P. Verhamme, J. Schmidt, S. Middeldorp, A.T. Cohen, J. Beyer-Westendorf, P. Albaladejo, J. Lopez-Sendon, A.M. Demchuk, D.J. Pallin, M. Concha, S. Goodman, J. Leeds, S. Souza, D.M. Siegal, E. Zotova, B. Meeks, S. Ahmad, J. Nakamya, and T.J. Milling, Jr., for the ANNEXA-4 Investigators*

April 4, 2019 N Engl J Med 2019; 380:1326-1335

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

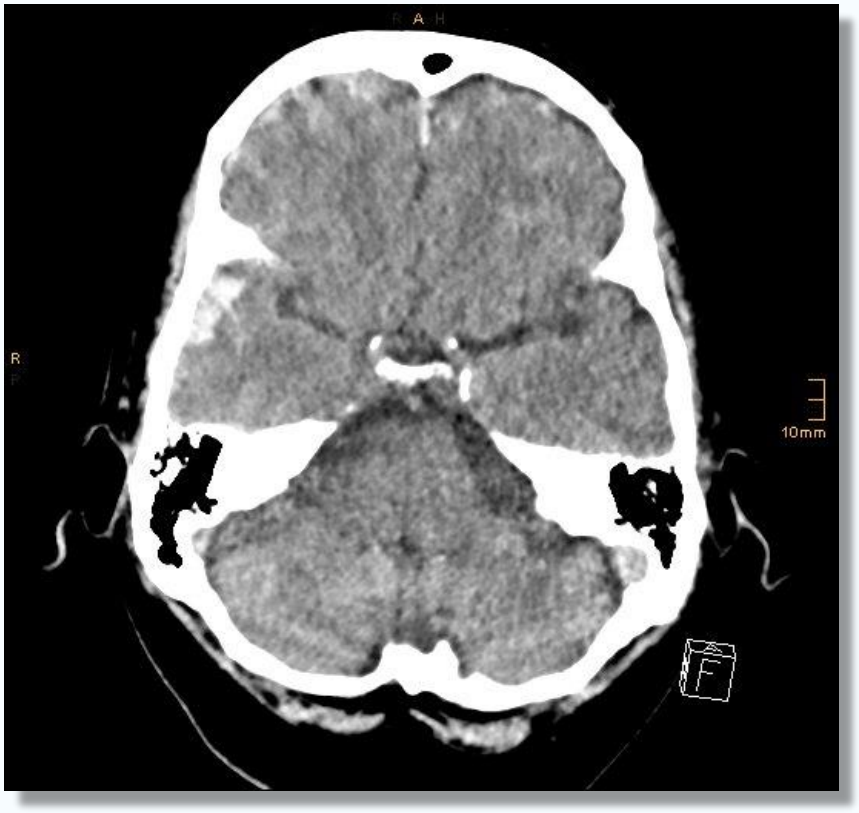
Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

BACKGROUND

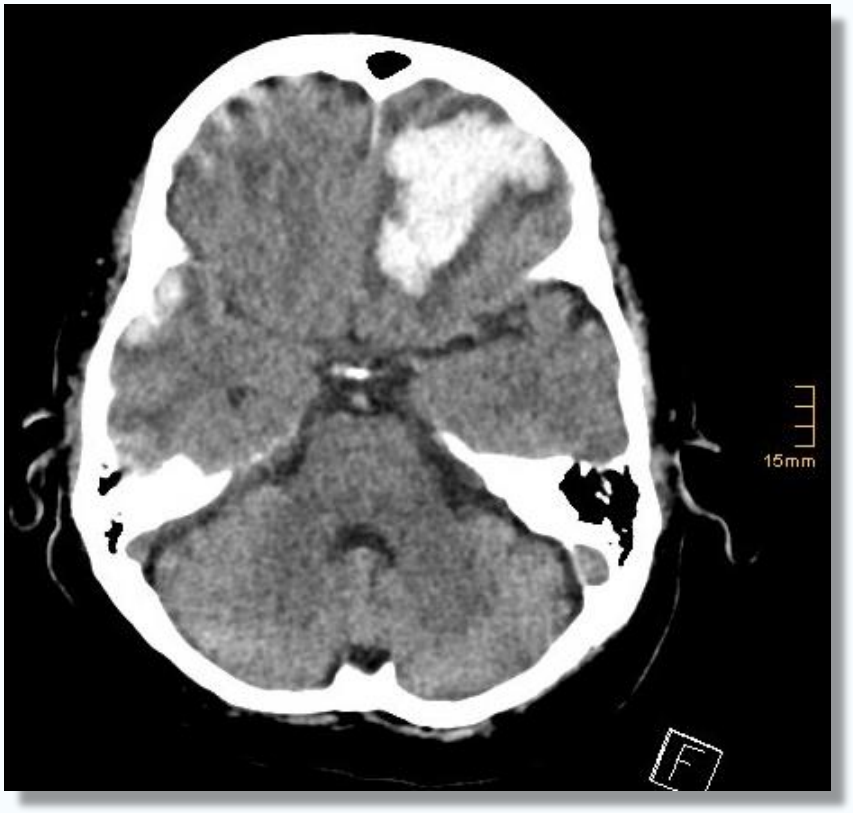
Andexanet alfa is a modified recombinant inactive form of human factor Xa developed for reversal of factor Xa inhibitors.

CONCLUSIONS

In patients with acute major bleeding associated with the use of a factor Xa inhibitor, treatment with andexanet markedly reduced anti–factor Xa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hours, as adjudicated according to prespecified criteria. (Funded by Portola Pharmaceuticals; ANNEXA-4 ClinicalTrials.gov number, NCT02329327.)



Eliquis (apixaban)



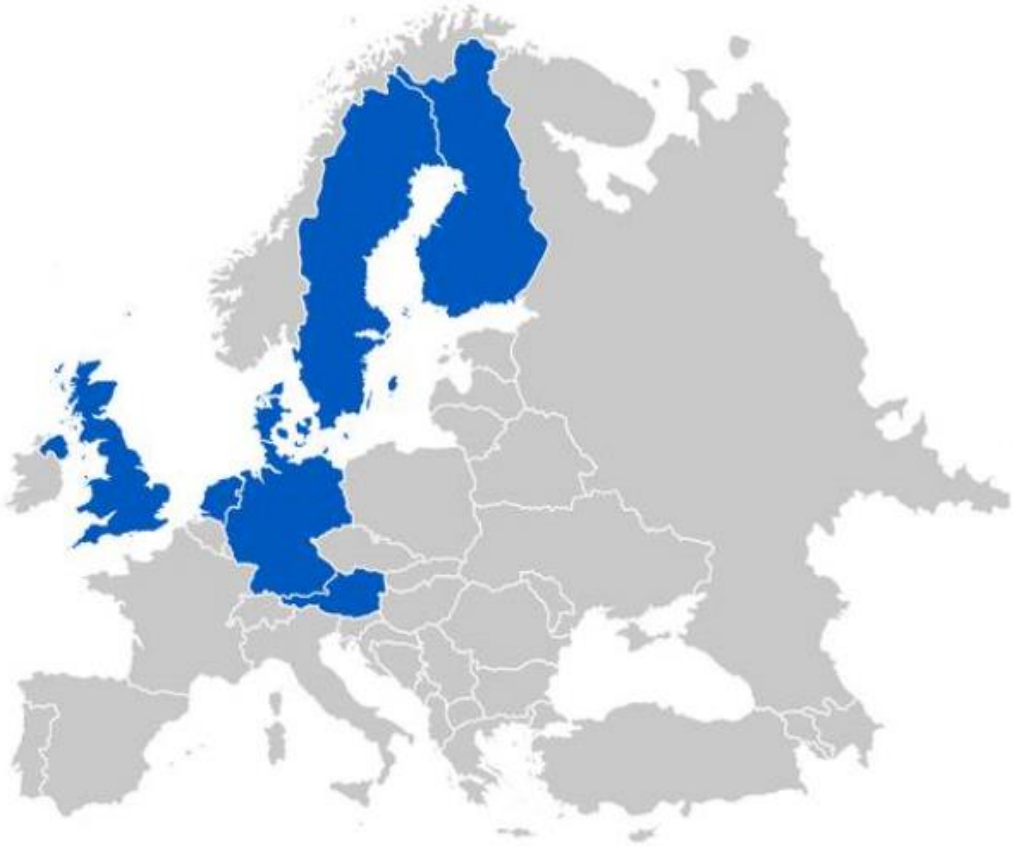
10 hours later

andexanet alfa?

2019

Ondexxya®

andexanet alfa



European Commission approval on April 26, 2019

direct thrombin - inhibitors

dabigatran	**Pradaxa®**	**Praxbind®**
argatroban*	**Argartra®**	
bivaluridin*	**Angiox®**	

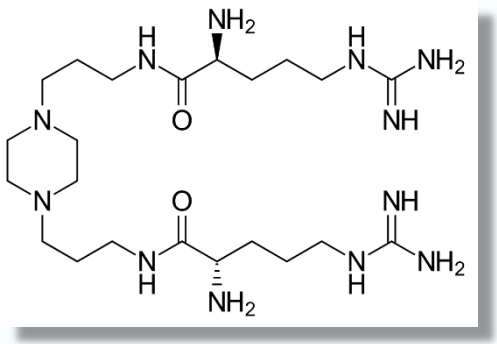
Factor Xa - inhibitors

rivaroxaban	**Xarelto®**	**Ondexxya®**
apixaban	**Eliquis®**	**Ondexxya®**
edoxaban	**Lixiana®**	*Ondexxya®* **?**
betrixaban	**Bevyxxa®**	*Ondexxya®* **?**
eribaxaban	*Pfizer*	
letaxaban	*Takeda*	
darexaban	*Astellas (stop IX/2011)*	

reversal agents

- **idarucizumab** *(targeting dabigatran)*
- **andexanet alfa** *(targeting all FXAs)*
- **PER977**

  - aripazine or ciraparantag
  - nonspecific binding to FXa inhibitors, thrombin inhibitors and heparins



Hydrogen bonds	Rivaroxaban	Apixaban	Edoxaban	Dabigatran	Heparins
Guanidine part	✓		✓	✓	✓
α-Amino group	✓	✓		✓	✓
Amide nitrogen	✓			✓	✓
Amide oxygen		✓	✓		

bridge

or

not?

NOACs in Anesthesiology

Review Article

Transfus Med Hemother 2019;46:282–293

Bridging is not recommended, as it has not been found to reduce thromboembolic events, but does increase the bleeding risk

Hovaguimian F. World J Surg 2017; 41: 2444–56.
Beyer-Westendorf J. Eur Heart J 2014; 35: 1888–96.
Raval AN. Circulation 2017; 135:e604–e633.

Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant

James D. Douketis, MD[1]; Alex C. Spyropoulos, MD[2]; Joanne Duncan, BSc[1]; et al

JAMA Intern Med. Published online August 5, 2019.

Objective To investigate the safety of a standardized perioperative DOAC management strategy.

Design, Setting, and Participants The Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) cohort study conducted at 23 clinical centers in Canada, the United States, and Europe enrolled and screened patients from August 1, 2014, through July 31, 2018. Participants (n = 3007) had AF; were 18 years of age or older; were long-term users of apixaban, dabigatran etexilate, or rivaroxaban; were scheduled for an elective surgery or procedure; and could adhere to the DOAC therapy interruption protocol.

Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant

Interventions A simple standardized perioperative DOAC therapy interruption and resumption strategy based on DOAC pharmacokinetic properties, procedure-associated bleeding risk, and creatinine clearance levels. The DOAC regimens were omitted for 1 day before a low–bleeding-risk procedure and 2 days before a high–bleeding-risk procedure. The DOAC regimens were resumed 1 day after a low–bleeding-risk procedure and 2 to 3 days after a high–bleeding-risk procedure. Follow-up of patients occurred for 30 days after the operation.

Main Outcomes and Measures Major bleeding and arterial thromboembolism (ischemic stroke, systemic embolism, and transient ischemic attack) and the proportion of patients with an undetectable or minimal residual anticoagulant level (<50 ng/mL) at the time of the procedure.

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Results The 3007 patients with AF (mean [SD] age of 72.5 [9.39] years; 1988 men [66.1%]) comprised 1257 (41.8%) in the apixaban cohort, 668 (22.2%) in the dabigatran cohort, and 1082 (36.0%) in the rivaroxaban cohort; 1007 patients (33.5%)

	major bleeding	art. thrombembolism
dabigatran	0,90%	0,60%
rivaroxaban	1,85%	0,37%
apixaban	1,35%	0,16%

-0.82%) in the rivaroxaban cohort. In patients with a high-bleeding-risk procedure, the rates of major bleeding were 2.96% (95% CI, 0%-4.68%) in the apixaban cohort and 2.95% (95% CI, 0%-4.76%) in the rivaroxaban cohort.

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Conclusions and Relevance In this study, patients with AF who had DOAC therapy interruption for elective surgery or procedure, a perioperative management strategy without heparin bridging or coagulation function testing was associated with low rates of major bleeding and arterial thromboembolism.

NOACs restart after surgery

NOACs in Anesthesiology

Review Article

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Table 8. Timing of NOAC re-start after surgery [51]

Drug	Low bleeding risk surgery	High bleeding risk surgery
Dabigatran	resume 24 h after surgery, 2 × 150 mg/day [1]	resume 48-72 h after surgery, 2 × 150 mg/day [1,2,6]
Rivaroxaban	resume 24 h after surgery, 1 × 20 mg/day [1]	resume 48-72 h after surgery, 1 × 20 mg/day [1,3,6]
Apixaban	resume 24 h after surgery, 2 × 2.5 mg/day [1]	resume 48-72 h after surgery, 2 × 2.5 mg/day [1,4,6]
Edoxaban	resume 24 h after surgery, 1 × 60 mg/day [1]	resume 48-72 h after surgery, 1 × 30 mg/day [1,5,6]

Provided there is no clinical evidence of disturbed hemostasis, the NOAC can be re-started one day after the intervention

In patients with high bleeding risk and normal renal function re-start of the NOAC may take place on day 2 or 3 after the intervention

Graf L. Thera Umschau 2016;73:545-9.


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