Život ohrožující krvácení s DOAC

19/9/2024

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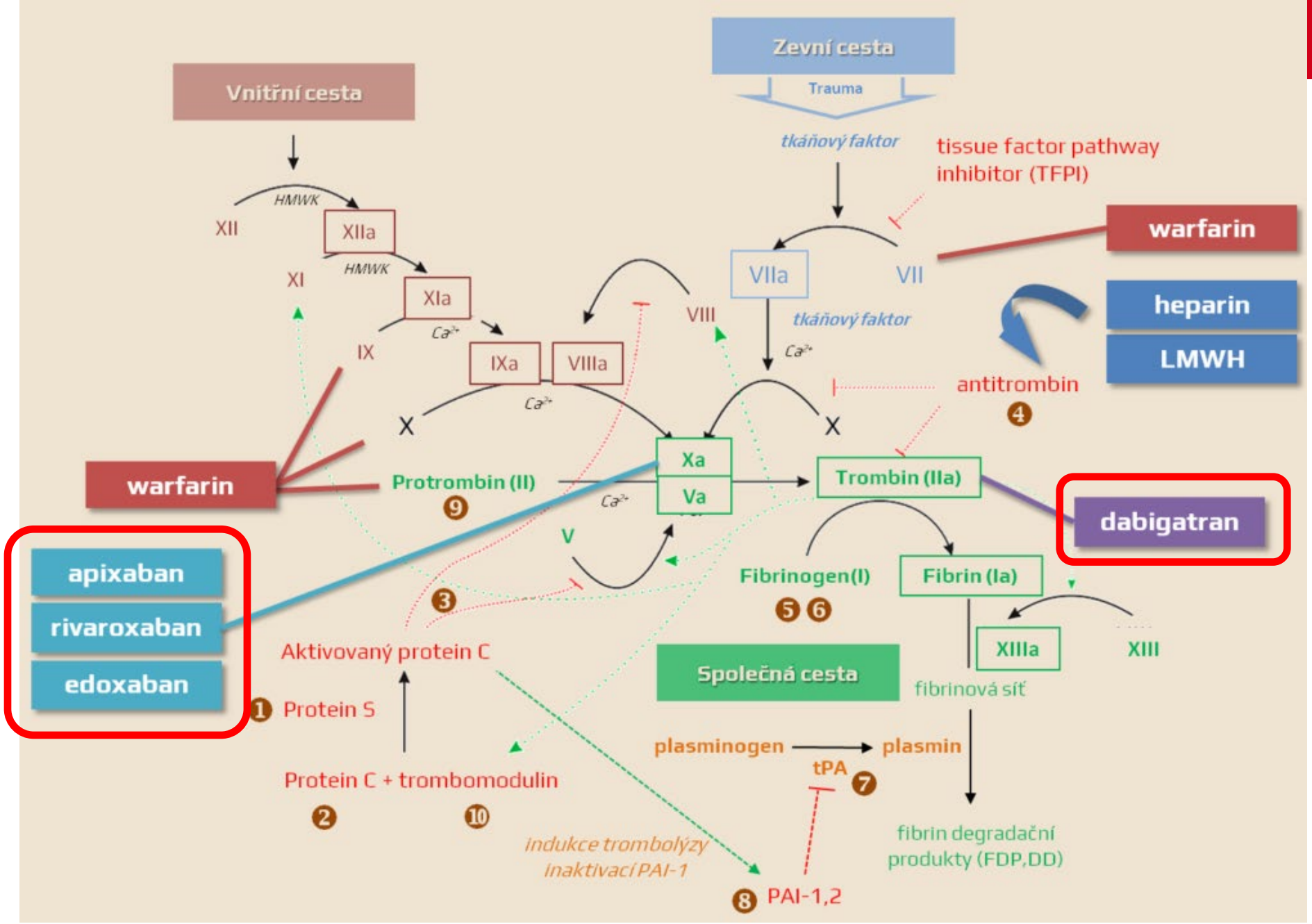
DOAC

- DOAC = direct oral anticoagulants
- V ČR dostupné od roku 2008

- Indikace
  - Profylaxe trombembolické nemoci
    - Fibrilace síní, ortopedie (náhrady velkých kloubů), onkologie, atd.
  - Terapie trombembolické nemoci
    - Hluboká žilní trombóza, plicní embolie, atd.

- Přímá blokáda koagulačních faktorů
  - Inhibitory trombinu - Gatrany
    - **Dabigatran** *(Pradaxa, Telexer, atd.)*
  - Inhibitory faktoru Xa - Xabany
    - **Apixaban** *(Eliquis, Polapix, atd.)*, **Rivaroxaban** *(Xarelto, Xerdoxo, Xanirva, atd.)*, **Edoxaban** *(Lixiana, Roteas, atd.)*

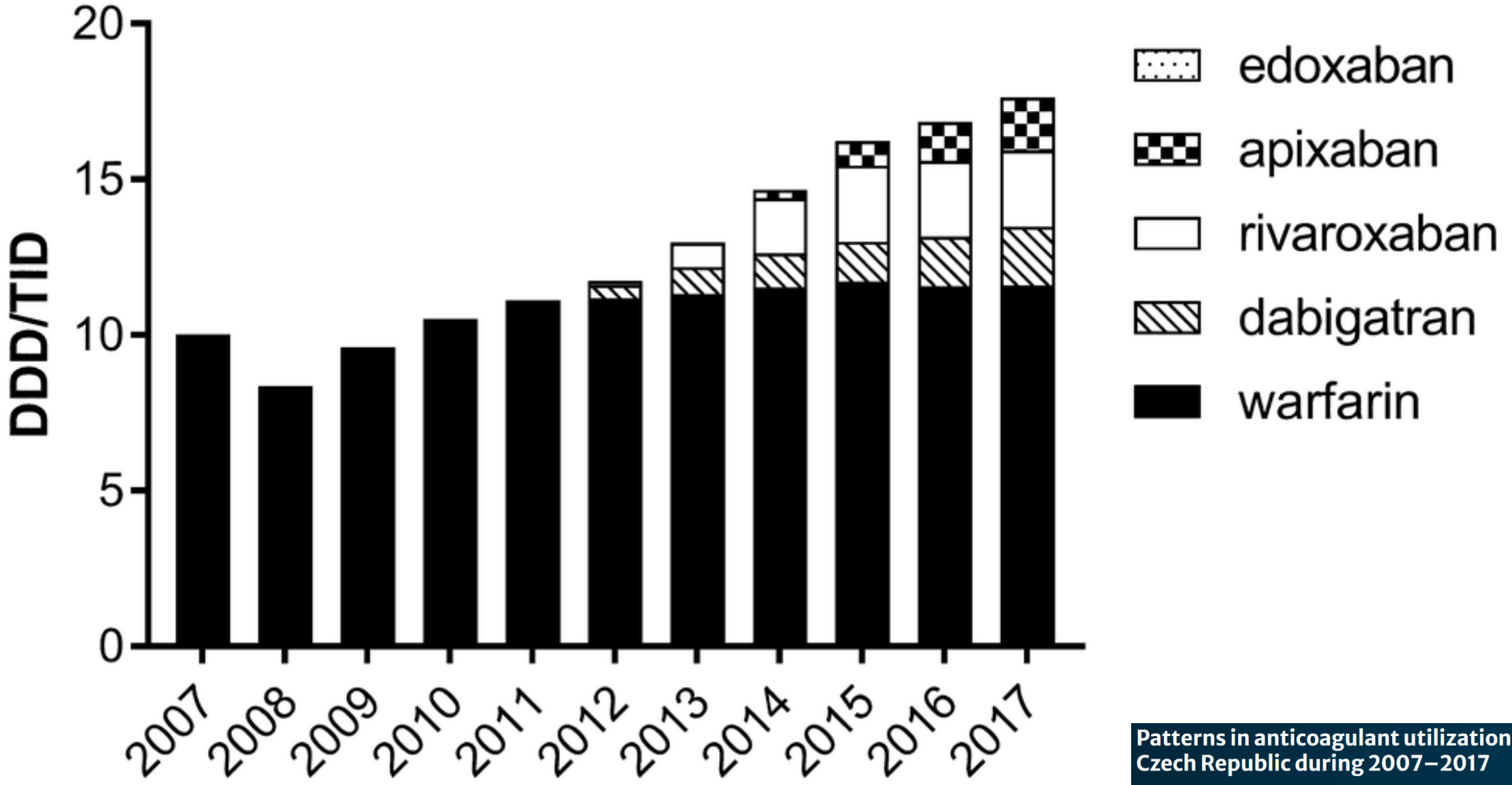
Specifické antidotum
- Idarucizumab
- Andexanet alfa



Zdroj: https://www.manual-cmp.cz

Epidemiologie DOAC

From: Patterns in anticoagulant utilization in the Czech Republic during 2007–2017



Oral anticoagulant utilization

Patterns in anticoagulant utilization in the Czech Republic during 2007–2017

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My a DOAC

Setkáváte se ve své praxi pravidelně s pacientem na DOAC?

Setkáváte se ve své praxi se život ohrožujícím krvácením u pacienta na DOAC?

Víte vždy od začátku, že krvácející pacient užívá DOAC?

Jak poznám pacienta se ŽOK a DOAC?

1.1 CHARAKTERISTIKA ŽIVOT OHROŽUJÍCÍHO KRVÁCENÍ

- ztráta určitého objemu krve za časovou jednotku, např.:
  - ztráta celého objemu krve v průběhu 24 hodin (u dospělého člověka ekvivalent cca 10 transfuzních jednotek erytrocytů) nebo
  - ztráta 50 % objemu krve během 3 hodin nebo
  - pokračující krevní ztráta přesahující objem 150 ml/min,
- krevní ztráta v lokalizaci vedoucí k ohrožení životních funkcí (např. krvácení do CNS),
- přítomnost klinických/laboratorních známek tkáňové hypoperfuze v průběhu krvácení.

Diagnostika a léčba život ohrožujícího krvácení u dospělých pacientů v intenzivní a perioperační péči

Česko-slovenský mezioborový doporučený postup

Blatný J., Bláha J., Cvachovec K., Černý V.*, Firment J., Kubisz P., Kvasnička J., Masopust J., Penka M., Salaj P., Staško J., Záhorec R., Zýková I.

A jak poznám pacienta s DOAC?

Jak zjistím, že pacient se ŽOK užívá DOAC?

- Konvenční postup u krvácejícího pacienta

- Anamnéza
- Nynější onemocnění/poranění
- Laboratorní testy
  - Krevní obraz
  - INR, PT, aPTT, TT, Fbg
  - ABG vč. laktátu a Ca^{2+}
  - Základní biochemie

- Viskoelastické testy
  - Test specifický pro vnější cestu a fibrinogen

Table 11 Plasma levels and coagulation assays in patients treated with NOACs for stroke prevention in AF

	Dabigatran[97,548,549]	Apixaban[550]	Edoxaban[98,100]	Rivaroxaban[519,520,551]
Expected plasma levels of NOACs in patients treated for AF*				
Peak levels	52–383	69–321	101–288	178–343
Trough levels	28–215	34–230	12–43	12–137
Expected impact of NOACs on routine coagulation tests[148,150,158,549,552–554]				
PT	(↑) peak (↑) if supratherapeutic[149]	(↑) at peak	↑ at therapeutic levels (if sensitive assay is used) Normal values do not exclude trough levels	↑ at therapeutic levels (if sensitive assay is used) Normal values do not exclude trough levels
aPTT	↑↑(↑) Normal values exclude supratherapeutic- but not therapeutic levels	(↑) at peak	(↑) at peak	(↑) at peak
ACT	↑(↑) Consistent with effect on aPTT	(↑)	(↑)	(↑)
TT	↑↑↑↑ Normal values exclude presence of Dabigatran	–	–	–

ACT, activated clotting time; AF, atrial fibrillation; aPTT, activated prothrombin time; NOAC, non-vitamin K antagonist oral anticoagulant; PT, prothrombin time.
*[ng/ml] 5–95% percentiles for FXa inhibitors and 10–90% percentiles (ng/ml) for Dabigatran).

European Society of Cardiology doi:10.1093/europace/euab065

Jak zjistím, že pacient se ŽOK užívá DOAC?

- ANAMNÉZA !!!
  - Zda pacient užívá DOAC a kdy ho naposledy užil
- Laboratorní testy
  - PT, PT-R, aPTT, TT, Fbg, Plt, DD, kreat
  - Hladina DOAC
    - Dabigatran – dTT, anti-IIa, ECT
    - Xabany – specifické anti-Xa
- Viskoelastické metody
  - Test na vnější cestu, vnitřní cestu a fibrinogen
  - RVV-test, ECA-test (ClotPro®)
- Screeningové testy z moči
  - DOASENSE® - DOAC Dipstick

R3.5: In urgent surgery with a high risk of bleeding, the plasma concentrations of DOACs above 50 ng ml^{-1} may be considered for haemostatic or antidote intervention. **(3)**

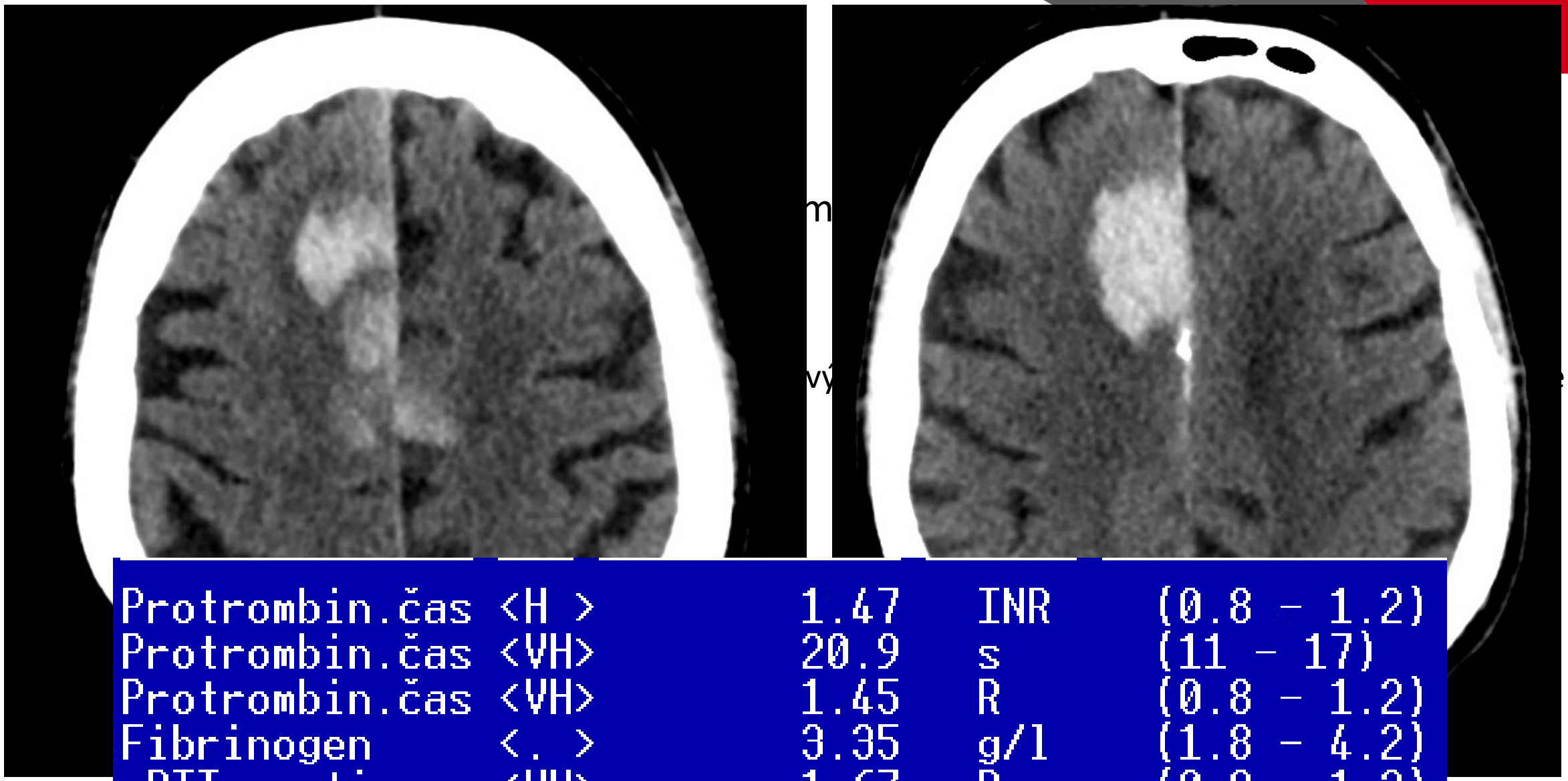
EJA

Eur J Anaesthesiol 2024; **41**:327–350

GUIDELINES

Clinical guideline on reversal of direct oral anticoagulants in patients with life threatening bleeding

Oliver Grottke, Arash Afshari, Aamer Ahmed, Eleni Arnaoutoglou, Daniel Bolliger, Christian Fenger-Eriksen and Christian von Heymann



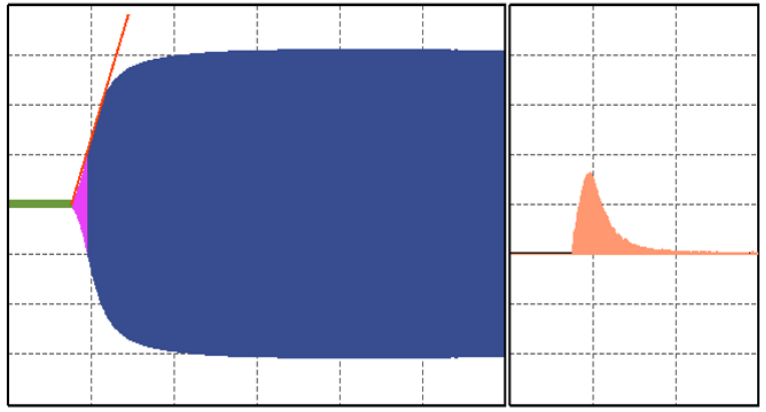
Protrombin.čas	<H >	1.47	INR	(0.8 - 1.2)
Protrombin.čas	<VH>	20.9	s	(11 - 17)
Protrombin.čas	<VH>	1.45	R	(0.8 - 1.2)
Fibrinogen	<. >	3.35	g/l	(1.8 - 4.2)
aPTT -ratio	<VH>	1.67	R	(0.8 - 1.2)
aPTT s	<VH>	56.00	s	(26 - 40)

Trocha praxe…

- Dodělané odběry na OUP
  - Krev: ClotPro® RVV test + ECA test, laboratoř – Pradaxa anti-IIa, Xarelto anti-Xa
  - Moč: DOAC Dipstick®

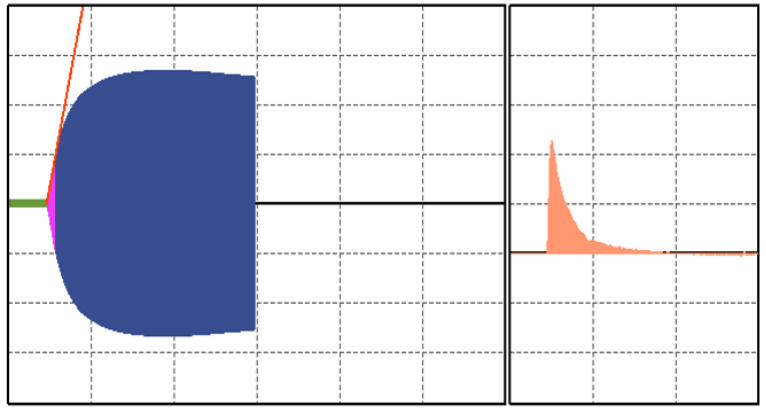
ECA-test

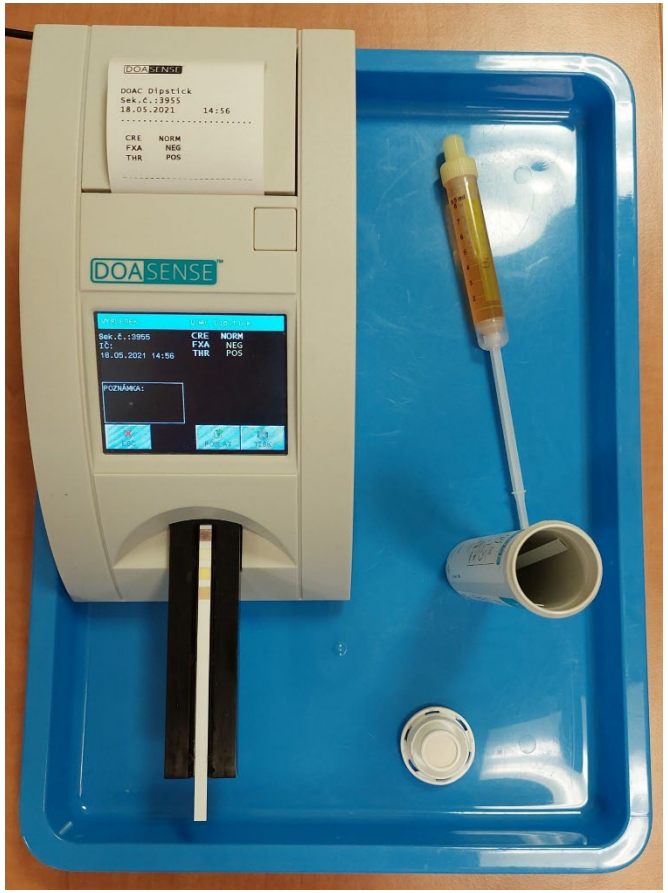
CT 461s (68 - 112)
A5 49mm (45 - 60)
A10 58mm (54 - 66)
A20 61mm (59 - 70)
MCF 62mm (61 - 72)
CFT >113s (60 - 90)
LT >0s



RVV-test

CT 281s (49 - 79)
A5 46mm (40 - 55)
A10 53mm (49 - 63)
A20 53mm (53 - 67)
MCF 54mm (53 - 69)
CFT >63s (35 - 85)
LT >0s





- Specifické testy:
  - Anti-IIa: hladina Dabigatranu 239 µg/L
  - Anti-Xa: hladina Apixabanu 8 µg/L
- Idarucizumab 5g i.v.

- **Clotpro® 15 minut**
- **DOAC Dipstick® 13 minut**
- **Laboratoř 39 minut**

Terapie – ŽOK + Dabigatran

PICO 8

Clinical scenario: Adult patients on dabigatran therapy, who present with severe bleeding in urgent surgical or nonsurgical settings.

Should idarucizumab or PCC, aPCC or rFVIIa be used to manage dabigatran associated bleeding in urgent surgical or nonsurgical settings?

Recommendation

R8.1: We recommend that idarucizumab should be considered in patients under dabigatran therapy presenting with severe bleeding or in urgent surgical or nonsurgical settings. **(1C)**

R 8.2: In the absence of the availability of idarucizumab, we suggest the use of PCC or aPCC. However, the superiority of one agent over another has not been demonstrated. **(2C)**

R 8.3: Due to the paucity of clinical data, we are unable to provide any recommendation for the use of rFVIIa. **(3)**

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Eur J Anaesthesiol 2024; **41**:327–350

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Terapie – ŽOK + Xabany

Rossaint et al. Critical Care (2023) 27:80
https://doi.org/10.1186/s13054-023-04327-7

Critical Care

GUIDELINES Open Access

The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition

Rolf Rossaint[1*], Arash Afshari[2], Bertil Bouillon[3], Vladimir Cerny[4,5], Diana Cimpoesu[6], Nicola Curry[7,8], Jacques Duranteau[9], Daniela Filipescu[10], Oliver Grottke[1], Lars Grønlykke[11], Anatole Harrois[9], Beverley J. Hunt[12], Alexander Kaserer[13], Radko Komadina[14], Mikkel Herold Madsen[2], Marc Maegele[15], Lidia Mora[16], Louis Riddez[17], Carolina S. Romero[18], Charles-Marc Samama[19], Jean-Louis Vincent[20], Sebastian Wiberg[11] and Donat R. Spahn[13]

If bleeding is life-threatening in the presence of an apixaban or rivaroxaban effect, especially in patients with TBI, we suggest reversal with andexanet alfa (Grade 2C).

If andexanet alfa is not available, or in patients receiving edoxaban, we suggest the administration of PCC (25–50 U/kg) (Grade 2C).

EJA

Eur J Anaesthesiol 2023; **40**:226–304

GUIDELINES

Management of severe peri-operative bleeding: Guidelines from the European Society of Anaesthesiology and Intensive Care

Second update 2022

Sibylle Kietaibl, Aamer Ahmed, Arash Afshari, Pierre Albaladejo, Cesar Aldecoa, Giedrius Barauskas, Edoardo De Robertis, David Faraoni, Daniela C. Filipescu, Dietmar Fries, Anne Godier, Thorsten Haas, Matthias Jacob, Marcus D. Lancé, Juan V. Llau, Jens Meier, Zsolt Molnar, Lidia Mora, Niels Rahe-Meyer, Charles M. Samama, Ecaterina Scarlatescu, Christoph Schlimp, Anne J. Wikkelsø and Kai Zacharowski

We suggest the use of PCC (25 IU kg^{-1} at first) rather than andexanet alpha in bleeding patients treated with anti-Xa agents (rivaroxaban, apixaban and edoxaban). 2C

sive. A meta-analysis of studies on PCC, idarucizumab and andexanet has shown that the three agents had a similar effective haemostasis rate and comparable mortality but there was a much higher thrombotic rate for andexanet (10.7 compared with 4.3% for PCC and 3.8% for idarucizumab).[109]

Terapie – ŽOK + Xabany

PICO 7

Clinical scenario: Adult patients on FXa inhibitor therapy, who present with severe bleeding in urgent surgical or nonsurgical settings.

Should andexanet alfa or PCC, aPCC or rFVIIa be used to manage FXa inhibitor-associated bleeding in urgent surgical or nonsurgical settings?

R7.1: We recommend that PCC or andexanet alfa should be considered in patients under FXa inhibitor therapy presenting with severe bleeding. However, the superiority of one agent over another has not been demonstrated. (**1C**)

R7.2: In the absence of the availability of andexanet alfa and PCC, aPCC may be considered in patients on FXa inhibitor therapy presenting with severe bleeding. (**2C**)

R7.3: Due to the paucity of clinical data, we are unable to provide any recommendation for the use of rFVIIa in patients on FXa inhibitor therapy presenting with severe bleeding. (**3**)

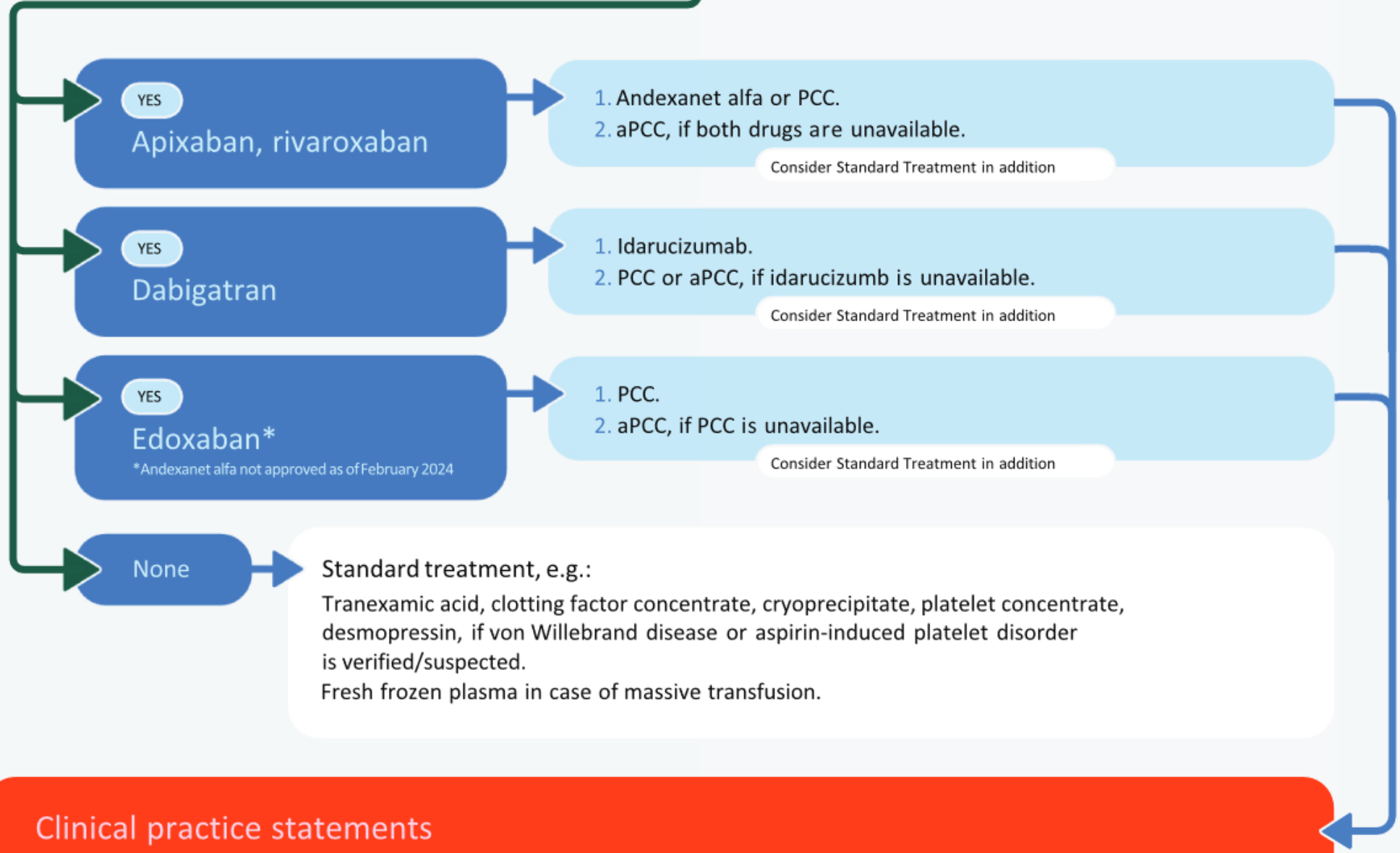
EJA

Eur J Anaesthesiol 2024; **41**:327–350

GUIDELINES

Clinical guideline on reversal of direct oral anticoagulants in patients with life threatening bleeding

Oliver Grottke, Arash Afshari, Aamer Ahmed, Eleni Arnaoutoglou, Daniel Bolliger, Christian Fenger-Eriksen and Christian von Heymann



Clinical practice statements

In case of progression to severe or life-threatening bleeding: Rule out surgical source of bleeding; continue standard treatment; consider a second antidote dose or PCC/aPCC dose if there are persistently elevated DOAC levels.
Recurrent bleeding: Consider that elevated plasma levels of apixaban, rivaroxaban and dabigatran may occur after specific antidote application.
Terminated bleeding (e.g.>24-48 hours): Consider resumption of anticoagulation e.g. LMWH at prophylactic dosage or local standard.

Drug *FXa Inhibitor*	Dose *Strength of Last Dose*	Time *Since Last Dose Taken*	
		<8 Hours or Unknown	*≥8 Hours*
Xarelto® (rivaroxaban)	≤10 mg	Low dose	Low dose
	>10 mg or unknown	High dose	
Eliquis® (apixaban)	≤5 mg	Low dose	Low dose
	>5 mg or unknown	High dose	

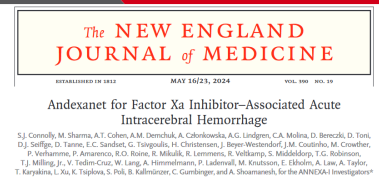
Anticoagulant	Antidote	Non-specific haemostatic agent
Dabigatran	Idarucizumab 2x2,5 g over 5-10 minutes, infusions no more than 10 minutes apart.	Not approved: PCC or aPCC at a dose of 25-50 IU/kg; rFVIIa: No recommendation
Apixaban	Low dose: Andexanet alfa 400 mg bolus over 15 minutes followed by an 480 mg infusion over 2 hours High dose: Andexanet alfa 800 mg bolus over 30 minutes followed by an 960 mg infusion over 2 hours	Not approved: PCC or aPCC at a dose of 25-50 IU/kg; rFVIIa: No recommendation
Edoxaban	Andexanet alfa not approved as of February 2024.	Not approved: PCC or aPCC at a dose of 25-50 IU/kg; rFVIIa: No recommendation
Rivaroxaban	Low dose: Andexanet alfa 400 mg bolus over 15 minutes followed by an 480 mg infusion over 2 hours High dose: Andexanet alfa 800 mg bolus over 30 minutes followed by an 960 mg infusion over 2 hours	Not approved: PCC or aPCC at a dose of 25-50 IU/kg; rFVIIa: No recommendation

Terapie – ŽOK + Xabany

RESULTS

A total of 263 patients were assigned to receive andexanet, and 267 to receive usual care. Efficacy was assessed in an interim analysis that included 452 patients, and safety was analyzed in all 530 enrolled patients. Atrial fibrillation was the most common indication for factor Xa inhibitors. Of the patients receiving usual care, 85.5% received prothrombin complex concentrate. Hemostatic efficacy was achieved in 150 of 224 patients (67.0%) receiving andexanet and in 121 of 228 (53.1%) receiving usual care (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 4.6 to 22.2; P=0.003). The median reduction from baseline to the 1-to-2-hour nadir in anti–factor Xa activity was 94.5% with andexanet and 26.9% with usual care (P<0.001). Thrombotic events occurred in 27 of 263 patients (10.3%) receiving andexanet and in 15 of 267 (5.6%) receiving usual care (difference, 4.6 percentage points; 95% CI, 0.1 to 9.2; P=0.048); ischemic stroke occurred in 17 patients (6.5%) and 4 patients (1.5%), respectively. There were no appreciable differences between the groups in the score on the modified Rankin scale or in death within 30 days.

Terapie – ŽOK + Xabany


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 16/23, 2024 VOL. 390 NO. 19

Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage

S.J. Connolly, M. Sharma, A.T. Cohen, A.M. Demchuk, A. Członkowska, A.G. Lindgren, C.A. Molina, D. Bereczki, D. Toni, D.J. Seiffge, D. Tanne, E.C. Sandset, G. Tsivgoulis, H. Christensen, J. Beyer-Westendorf, J.M. Coutinho, M. Crowther, P. Verhamme, P. Amarenco, R.O. Roine, R. Mikulik, R. Lemmens, R. Veltkamp, S. Middeldorp, T.G. Robinson, T.J. Milling, Jr., V. Tedim-Cruz, W. Lang, A. Himmelmann, P. Ladenvall, M. Knutsson, E. Ekholm, A. Law, A. Taylor, T. Karyakina, L. Xu, K. Tsiplova, S. Poli, B. Kallmünzer, C. Gumbinger, and A. Shoamanesh, for the ANNEXA-I Investigators*

CONCLUSIONS

Among patients with intracerebral hemorrhage who were receiving factor Xa inhibitors, andexanet resulted in better control of hematoma expansion than usual care but was associated with thrombotic events, including ischemic stroke. (Funded by Alexion Astra-Zeneca Rare Disease and others; ANNEXA-I ClinicalTrials.gov number, NCT03661528.)

- **PCC nebo andexanet alfa?**
  - Závažnost krvácení (čas)
  - Zdroj krvácení
  - Trombembolické riziko
  - Typ xabanu
  - Zdroje

Take home message

- U krvácejících pacientů je třeba myslet na možné užívání DOAC, musíme po nich aktivně a specificky pátrat

- V případě ŽOK a užívání dabigatranu je indikováno podání idarucizumabu

- V případě ŽOK a užívání rivaroxabanu a apixabanu je možné podání andexanetu alfa nebo PCC a v případě užívání edoxabanu je indikované podání PCC