DOASENSE becoming a standard of care in Italy and Estonia

DOASENSE is the recommended Point Of Care Test for the prescription of Andexanet alpha (ONDEXXYA) in Tuscany (Italy)

In August 2023 the highest regional health authorities in Tuscany (Italy) enacted a new procedure for the appropriate prescription of ONDEXXYA that is recommended to all professionals involved. It clearly stipulates DOASENSE and provides detailed guidance.

Document 1: The letter sent to all Emergency Departments stipulates that: "The procedure provides that, in the decision-making process for the prescription of the ONDEXXYA drug, the use of the following test is indicated: test strip for DOACs – DOASENSE Dipstick Ref 001

Further, the letter provides this recommendation: "We hereby recommend that the companies and organisations in question make available the diagnostic indicated above in all the Emergency Urgent Structures of the Region, together with the specific reader."

Document 2: This letter was sent together with an order form that clinicians must use toprescribe ONDEXXYA. The section "DOSAGE NAO" (Dose if DOAC) lists the 2 options fortesting, i.e. plasma level >30ng/mL or Urinary (POCT) positive.

Document 3 was also attached to the communication on indications for use of Andexanet Alfa. Page 8 provides an algorithm to support the prescription of the drug showing the same 2 alternatives for the testing: plasma level >30ng/mL or Urinary (POCT) positive.

While Andexanet Alpha is not yet reimbursed in Italy, its prescription is now conditional to the adherence to this protocol in Tuscany. This is an important milestone towards the adoption of DOASENSE as a standard of care to determine the presence of clinically relevant level of DOACs in order to support clinicians with additional information otherwise not available in emergency settings.

Attached are the original documents in Italian and their non-certified translations, as obtained through a smart translator.

DOASENSE is also now imbedded in anaesthesia guidelines in Estonia

In the guidelines for "Anticoagulation drugs management in elective and emergency surgery" from the Estonian Society of Anesthesiology. (https://anest.ee/ravijuhised/# then click on :"*Uus! Antitrombootilised ravimid plaanilises ja erakorralises kirurgias")*

DOASENSE is listed on Table 10 (page 14): as a clear option to exclude the presence of Dabigatran, Rivaroxaban, Apixaban and Edoxaban. The original document and its non-certified translation are attached as Document 4.

Those are new examples of the momentum gained establishing DOASENSE as a standard of care.

CONTENT:

A.I.

Document set from the regional health authorities in Tuscany, Italy

ENGLISH Convenience Translation

TUSCANY REGION
Regional Council

DIRECTION
HEALTH, WELFARE AND SOCIAL COHESION

PHARMACEUTICAL ASSISTANCE AND DEVICES SECTOR

Responsible manager: **Claudio Marinai**
claudio.marinai@regione.toscana.it

Subject: Interruption of availability of the medicinal specialty ONDEXXYA.

General Directorates of the
Local Health Authorities and AOU of Tuscany
ESTAR General Director
Director of the Monasterio Foundation

and PC Director of the Health, Welfare and Social Cohesion
Directorate Dr. Federico Gelli

Head of the Hospital Care, Quality and Clinical Networks Sector Dr.
Michela Maielli

PEC

Following the previous Circular of this Sector (AOOGRT/PD prot. n. 0250545 of 05/31/2023) with which the availability of the drug ONDEXXYA was ceased, in agreement with the OTGC an uncovered clinical need was identified adequately by the therapies proposed by Aifa with Circular 20012/2023 and already available (PCC 4 palm factors).

To guarantee the citizens of Tuscany all necessary therapies, even if these include the use of a drug, as mentioned in the aforementioned Circular, which is not currently paid for by the NHS, the undersigned Sector and the OTGC have developed the attached procedure. This procedure limits the use of the ONDEXXYA drug only to cases not covered by already available therapies.

Compliance with the indications of the attached procedure is of fundamental importance for the appropriate prescription of the ONDEXXYA drug and therefore compliance is recommended to all professionals involved.

The procedure provides that in the decision-making process for the use of the ONDEXXYA drug the use of the following test is indicated: Estar code:

50395392 Description: test strip for doacs – doasense dipstick REF 0001

We hereby recommend that the companies and organizations in question make available the diagnostic indicated above in all the Emergency Urgent Structures of the Region, together with the specific reader.

Best regards.

The OTGC Director
Dr. Stefano Grifoni

The Responsible Manager
Dr. Claudio Marinai

Regione Toscana

SST Servizio Sanitario della Toscana

All_____

_

Request for andexanet alfa (Ondexxya®)

for reversal of anticoagulant therapy in case of potentially fatal or uncontrolled bleeding

The undersigned Dr. _____telephone number_____

SOD _____Cost Center_____

requests the supply of the drug andexanet alfa (Ondexxya®) 200 mg

indicated for adult patients treated with apixaban or rivaroxaban, when reversal of anticoagulant therapy is required due to life-threatening or uncontrolled bleeding

for the patient *(name and* surname)_____date of birth _____

Inclusion and exclusion criteria for treatment	
o MANIFEST ACTIVE bleeding in patient receiving therapy with APIXABAN or RIVAROXABAN o NOT for pre-treatment in emergency surgery	
Select at least one condition or	
A ÿ Critical site bleeding *(select option)*	CEREBRAL: intraparenchymal; subdural; epidural; subarachnoid* o Others affecting the CNS: intraocular; intra or extraaxial spinal o HEMOPERICARDIUM with signs of cardiac tamponade o AIRWAY (including posterior epistaxis), HEMOTHORAX^ or INTRAABDOMINAL, RETROPERITONEAL^ **GCS>7 and/ or blood volume >60 ml* *^only IF WITH B and/ or C*
B ÿ Hemodynamic instability *(select option)*	o Systolic BP < 90 mmHg or reduction in Systolic BP values > 40 mmHg o Shock index (HR/BP) > 0.9 o Lactates > 4 mmol/L o Urine < 0.5 ml/Kg/min
C ÿ Hb reductionÿ2 g/dl or transfusion of ÿ2 units	If known, specify bleeding site:
DOSAGE NAO *(select the option and attach reference to this document)*	o Plasma: >30 ng/ml o Urinary (POCT): POSITIVE

Doses for apixaban/rivaroxaban reversal			
Inhibitor of FXa	**Last dose**	**Time since last dose before starting Ondexxya**	
		< 8 hours	**ÿ 8 hours**
apixaban/ rivaroxaban	ÿ 5 mg apixaban/10 mg rivaroxaban	Low dose (5 vials)	Low dose (5 vials)
	> 5 mg apixaban/10 mg rivaroxaban	High dose (9 vials)	

Prescribed dosage		
No. of 200 mg vials	Initial intravenous bolus	IV infusion
or 5	400 mg at a target rate of 30 mg/min	4 mg/min for 120 minutes (480 mg)
or 9	800 mg at a target rate of 30 mg/min	8 mg/min for 120 minutes (960 mg)

Regione Toscana

Request for andexanet alfa (Ondexxya®)

for the reversal of anticoagulant therapy in case of potentially fatal or uncontrolled bleeding

Servizio Sanitario della Toscana

All_____

Date _____

STAMP AND SIGNATURE OF THE REQUESTING DOCTOR

_____

Indications for the use of Andexanet alfa

SUMMARY

1 PURPOSE

The purpose of the following work is to outline a guide to using the drug andexanet alfa (Ondexxya®) in the Tuscany Region. Andexanet alfa (Ondexxya®), powder for solution for infusion, is a modified recombinant derivative of factor
recombinant DNA technology in Chinese Hamster Ovary cells (Chinese Hamster Ovary, CHO).

2 FIELD OF APPLICATION

The procedure is applied within the Emergency Department to achieve an effect *reverse* in patients treated with apixaban and rivaroxaban who experience bleeding potentially fatal or critically ill (see figure 1).

3 REFERENCES

- *CPR*
- *AIFA determination of classification of the drug for reimbursement*
- *purposes. AIFA determination n. 20012/2023 inclusion of PROPLEX in the list of medicines payable entirely by the NHS*
- *Important information note agreed with the European regulatory authorities and the Italian Medicines Agency (AIFA)*
- *Steffel J, Collins R, Antz M, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. 2021 Oct 9;23(10):1612-1676. 10.1093/ europace/ doi: euab065. Erratum in: Europace. 2021 Jun 28;: PMID: 33895845.*
- *Tomaselli G, Mahaffey K, Cuker A, et al. 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. J Am Coll Cardiol. 2020 Aug, 76 (5) 594–622.*
- *Rossaint et al. Critical Care (2023) 27:80. The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition*
- *Cao D. et al. ESC. Reversal and removal of oral antithrombotic drugs in patients with active or perceived imminent bleeding. European Heart Journal (2023) 00, 1–15*

4 MECHANISM OF ACTION

Andexanet alfa is a recombinant form of the protein called human FXa, which was modified and deprived of the enzymatic activity of FXa. The active site serine has been replaced with alanine, to make the molecule incapable of cleaving and activating prothrombin, and the domain of gamma-carboxyglutamic acid (Gla) has been removed, to deprive the protein of its capacity of assembly into the prothrombinase complex, thus eliminating any effect anticoagulant.

Andexanet alfa is a reversal agent specific for FXa inhibitors. The main mechanism of action is the binding and sequestration of the FXa inhibitor. Furthermore, it was observed that andexanet

alpha binds to TFPI and inhibits it. Inhibition of TFPI activity may increase tissue factor-initiated thrombin generation, inducing a procoagulant effect.
The effects of andexanet alfa can be measured by pharmacodynamic markers, including the free fraction of available FXa inhibitor, and by restoration of thrombin generation.
Commercially available anti-FXa assays are not suitable for measuring anti-FXa activity after administration of andexanet alfa. Due to the reversible binding of andexanet alfa to the FXa inhibitor, the high sample dilution currently used in these assays results in dissociation of the inhibitor from andexanet alfa, resulting in the detection of falsely high anti-FXa activity levels and resulting in therefore a substantial underestimate of the reversal activity of andexanet alfa.
In studies determining the

Prospective, randomized, placebo-controlled trials conducted in healthy subjects determined the dose and dosing regimen of andexanet alfa required to reverse anti-FXa activity and restore thrombin generation for FXa inhibitors (apixaban or rivaroxaban) using modified assays not available on the market.
Maximum reversal of anti-FXa activity was achieved within two minutes of completion of bolus administration. Administration of andexanet alfa as a bolus followed by continuous infusion resulted in a sustained reduction in anti-FXa activity. Anti-FXa activity returned to placebo levels and above approximately two hours after the end of the bolus or infusion, depending on the dosage. When andexanet alfa was administered as a bolus followed by a continuous infusion, the maximum reduction in unbound FXa inhibitors was rapid (within two minutes of the end of the bolus), was maintained throughout the infusion, and then gradually increased with time, reaching a maximum approximately two hours after the end of the infusion. The restoration of thrombin generation after administration was dependent on the dose and dosing regimen and not related to anti-FXa activity beyond approximately four hours (see section “restoration of thrombin generation”). Plasma TFPI activity was shown to be completely inhibited from 2 minutes to 14.5 hours after bolus administration of andexanet alfa and returned to baseline within 3 days. Tissue factor (TF)-initiated thrombin generation rose immediately above baseline (before anticoagulation) and remained elevated for >20 hours, compared to placebo. The plausibility of a pro-coagulant effect of TFPI inhibition is supported by consecutive and sustained increases in D-dimers, TAT and F1+2.
Studies of andexanet alfa in the presence of direct FXa inhibitors in healthy subjects demonstrated dose-proportional pharmacokinetics in the expected therapeutic dose range for both Cmax and area under the curve (AUC). FXa inhibitors did not alter the pharmacokinetics of andexanet alfa at therapeutic levels.

5 THERAPEUTIC INDICATIONS

For adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or **rivaroxaban),** when reversal of anticoagulant therapy is required due to bleeding potentially fatal or uncontrolled.

However, the non-reimbursability of the drug by the NHS and the literature data a provision at the time of drafting this protocol require its use in one extremely selected case history.

The possibility of using andexanet alfa must be evaluated following an algorithm that provides three steps ***(see figure*** 1) in sequence:

1. Inclusion and exclusion criteria

The administration of Andexanet-alfa is **ONLY** possible for patients undergoing therapy oral anticoagulant with APIXABAN or RIVAROXABAN. It is not prescribable for patients in Edoxaban therapy. Treatment of bleeding emergencies in patients on edoxaban provides, as the only therapeutic option, the administration of PCCs (concentrates of the complex prothrombin) at a dosage of 50 U/kg. Furthermore, the use of andexanet -alfa is NOT possible (e.g current lack of data in this clinical setting) for patients treated with factor inhibitors Xa who need to undergo emergency surgery.

2. Type of Bleeding

Patients with obvious active bleeding and at least one of the three are considered eligible clinical conditions listed below:

A) patients with **bleeding in critical locations:** CEREBRAL (intraparenchymal, subdural; epidural; subarachnoid; intraocular; spinal intra or extraaxial; HEMOPERICARDIUM with signs of cardiac tamponade; ways AIR AND HEMOTHORAX; INTRAABDOMINAL, RETROPERITONEAL.

- at the CEREBRAL level if GCS>7 and/ or blood volume<60 ml

- at the AIRWAY and HEMOTORAX level: ONLY if point B or C is also present

Intraluminal gastrointestinal bleeding is NOT considered critical or at risk life, unless there are signs of haemodynamic instability.

A) Patients with **hemodynamic instability.** An increased heart rate may be the first sign of hemodynamic instability due to blood loss. Additionally, a systolic blood pressure (BP) <90 mmHg, a decrease in systolic blood pressure >40 mmHg, or changes in orthostatic blood pressure (systolic blood pressure drop ÿ20 mmHg or diastolic blood pressure drop ÿ10 mmHg when standing) may indicate hemodynamic instability. The shock index (HR/systolic BP) >0.9 and the pressure

arterial differential <40/<30 mmHg are reliable indices of the degree of hemodynamic instability and the need for blood transfusions, as well as surrogate markers for organ perfusion, such as the level of blood lactate, the ultrasound status of filling of the vena cava, the urine output <0.5 ml/kg/h). When practical, continuous invasive measurement of mean arterial pressure is considered superior to peripheral measurement, and a value <65 mmHg serves as a cut-off for hemodynamic instability.

B) **Overt and active bleeding with drop in hemoglobin ÿ2 g/dl or administration of ÿ2 units of packed red blood cells.** Bleeding events causing a drop in hemoglobin ÿ2 g/dL or requiring transfusion of ÿ2 units of red blood cells were associated with a significantly increased risk of mortality. Hematuria and posterior epistaxis associated with anemia requiring blood transfusion may require an initial treatment of mechanical and/or endoscopic hemostasis, if there is no hemodynamic instability.

3. Apixaban/Rivaroxaban dosage

As reported in the paragraph “Mechanism of action”, andexanet-alfa exerts an action of antidote since it binds to Fxa to replace the circulating anticoagulant drug. Because of this, the possible absence of anticoagulant activity of the drug (defined as antiXa activity under the threshold of 30 ng/ml) does not make the action of the antidote reasonable (at least in a context of necessary selection of case studies, and in the absence of current evidence to the contrary). Therefore the verification of this activity is mandatory for the administration of the drug and in every case must accompany the prescription itself.

The reference method for determining the antiXa activity of the anticoagulant drug is represented by the plasma dosage.

However, the plasma dosage:

- Requires execution times that are often not compatible with the emergency/urgency regime
- It is not available in the laboratories of all hospital facilities
- Even when available, not all laboratories offer 24-hour testing

For this reason, it is useful to consider – in emergency/urgent contexts where a response is necessary as timely as possible – the urinary POCT dosage which offers the possibility of knowing in a few minutes: - type of DOAC taken; - a semi-quantitative response with POSITIVE value o NEGATIVE equivalent to a concentration ÿ or < 30 ng/ml.

The doctor treating the patient with a bleeding event during DOAC must evaluate:

- the anticoagulant drug taken with the usual prescribed dosage
- the time of the last known intake

- or the inability to obtain information on the dosage and timing of intake
- any concomitant therapies with an impact on the risk of bleeding: NSAIDs; antiaggregants; 'over-the-counter' drugs that do not require a prescription
- blood sampling for: complete blood count; renal and liver function; PT, aPTT and fibrinogen (hemorrhage profile prepared in the FA web application).

If there is any doubt about not taking it, or there are uncertainties about the type of drug taken, it is the use of DOAC plasma dosage is indicated, if this is available. Alternatively, it is It is possible to use point-of-care semi-quantitative measurement devices on urine. If the intake of the DOAC dates back to less than 2-4 hours, the administration of 50 g of activated charcoal orally (unless there are contraindications and if the patient is clinically stable).

In all cases where the algorithm is interrupted, the administration of PCCs is indicated (prothrombin complex concentrates) at 4 factors at a dosage of 50 U/kg.

In fact, it should be remembered that AIFA has authorized the reimbursement by the NHS of the concentrates of the 4-factor prothrombin complex (Proplex) with the same indications as Andexanet-alfa.

PCC4 THEREFORE REPRESENT AN ALTERNATIVE TO ANDEXANET ALFA FOR THE FOLLOWING INDICATIONS:

- **treatment of adult** patients treated with oral anticoagulants direct inhibitors of factor

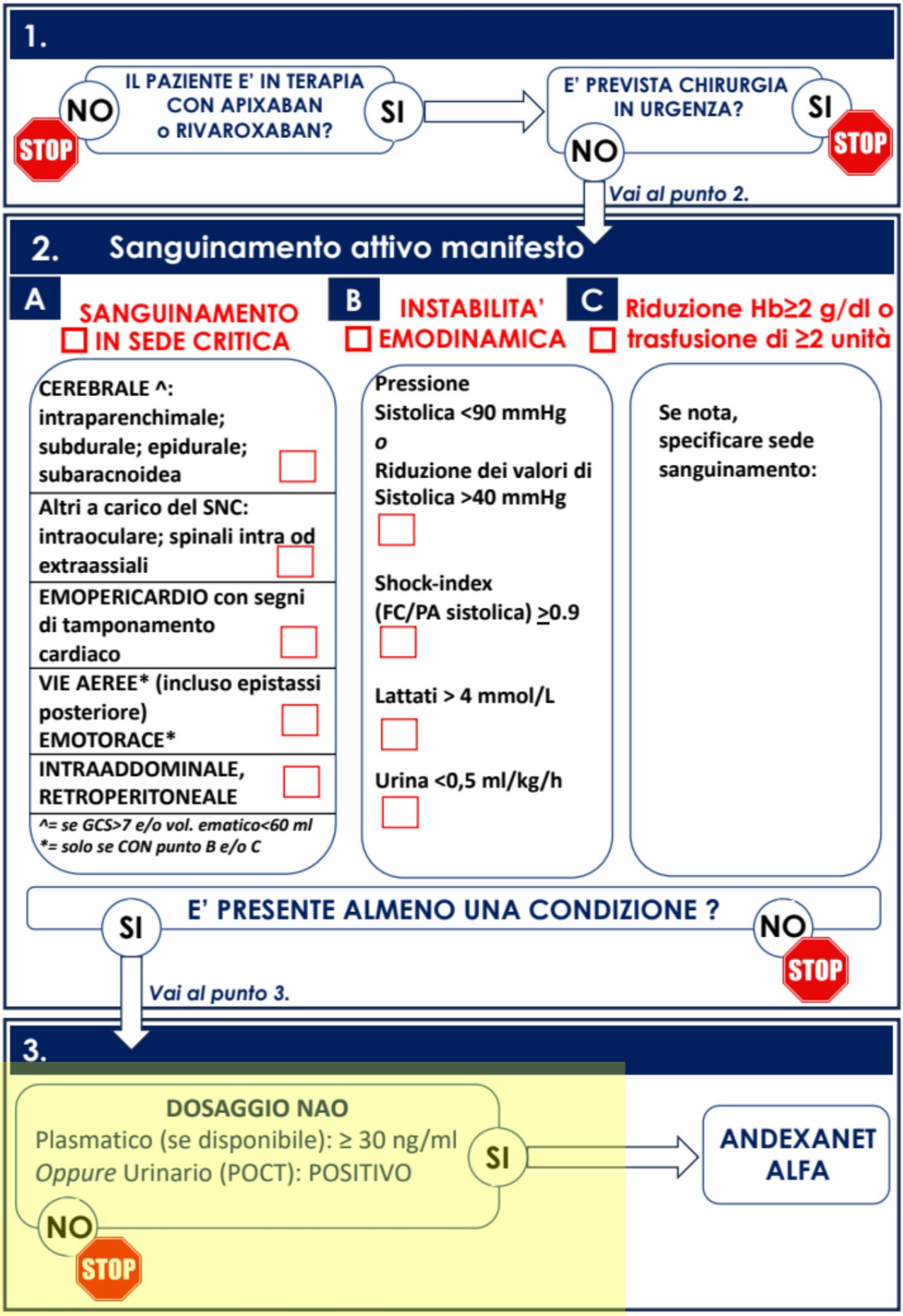
- **surgical interventions or invasive maneuvers with a high risk of bleeding to be performed urgently, with timing not compatible with the sole suspension of the anticoagulant;** life-threatening or uncontrolled bleeding.

USE OF ANDEXANET ALFA IN ASSOCIATION WITH OTHER SUPPORT MEASURES

The safety of andexanet alfa has not been evaluated in patients receiving prothrombin complex concentrates, recombinant factor VIIa, or whole blood within seven days prior to the bleeding event, because they were excluded from the clinical trials. Treatment with procoagulant factors (e.g., 3- or 4-factor prothrombin complex concentrate (PCC)/activated PCC, recombinant factor VIIa, fresh frozen plasma) and whole blood should be avoided unless absolutely necessary , due to lack of data in association with these treatments.

After each use, the Pharmacy will request the patient's documentation for the clinical evaluation of the results of the therapy.

FIGURE 1



6 DOSAGE AND METHOD OF ADMINISTRATION

Each vial contains 200mg of andexanet alfa; after reconstitution, each mL of solution contains 10 mg of andexanet alfa.

Andexanet alfa is administered as an intravenous bolus at a target rate of approximately 30 mg/min over 15 minutes (low dose) or 30 minutes (high dose), followed by a continuous infusion of 4 mg/min (low dose) or 8 mg/min (high dose) for 120 minutes.

	Initial intravenous bolus	**Continuous intravenous infusion**	**Total number of vials from 200 mg necessary**
Dose low	400 mg at a target rate of 30 mg/min	4 mg/min for 120 minutes (480 mg)	5
Dose elevation to	800 mg at a target rate of 30 mg/min	8 mg/min for 120 minutes (960 mg)	9

APIXABAN REVERSE

The recommended dosing regimen of andexanet alfa is based on the dose of apixaban administered to the patient at the time of reversal of anticoagulant therapy and the time since the last dose of apixaban.

Inhibitor of the FXa	**Last dose**	**Time since last dose before starting Ondexxya**	
		< 8 hours or unknown	ÿ 8 hours
Apixaban	ÿ 5 mg	Low dose	Low dose
	> 5 mg/not known	High dose	

RIVAROXABAN REVERSE

The recommended dosing regimen of andexanet alfa is based on the dose of rivaroxaban administered to the patient at the time of reversal of anticoagulant therapy and the time since the last dose of rivaroxaban.

Inhibitor of the FXa	**Last dose**	**Time since last dose before starting Ondexxya**	
		< 8 hours or unknown	ÿ 8 hours

Rivaroxaba n	ÿ 10 mg	Low dose	Low dose
	>10 mg/not known	High dose	

INTERACTION WITH HEPARIN

The use of andexanet alfa before heparinization, e.g. during surgery, you must be avoided, as andexanet induces heparin refractoriness. The use of andexanet as an antidote for heparin or low molecular weight heparin has not been evaluated and is not recommended.

7 HANDLING INSTRUCTIONS

Each vial must be reconstituted according to the following instructions: 1.

Remove the snap cap from each vial.

2. Clean the rubber stopper of each vial with an alcohol swab.
3. Withdraw 20 mL of water for injections using a 20 mL syringe (or more) and a 20 gauge (or larger) needle.
4. Insert the syringe needle into the center of the rubber stopper.
5. Slowly depress the plunger and inject the 20 mL of water for injections into the vial, directing the jet towards the internal wall of the vial to minimize the foam formation.
6. Gently swirl each vial until the powder is completely dissolved. NOT SHAKE the vials to avoid foaming. The dissolution time is approximately three to five minutes per vial.
7. Before administration, visually inspect the reconstituted solution, e.g exclude the presence of corpuscular material and/or color alterations. Do not use in presence of opaque particles or color changes.
8. For effective reconstitution of the necessary dose and to minimize errors, inject 20 mL of water for injections into each vial before proceeding to the next phase.
9. If stored at room temperature, use within eight hours of reconstitution.

~~Administration via timed syringe~~

1. After reconstituting all the necessary vials, withdraw the solution from each one using the large syringe (50 mL or larger) equipped with a 20 gauge (or larger) needle.
2. Prepare the bolus and infusion in separate large syringes.
3. Due to the larger volume, bolus and high-dose infusion should be divided into additional syringes (two syringes each for bolus and infusion).

4. To prevent accidental transfer of air, keep the syringe needle pointed up and do not put the syringe down between one sample and the next.
5. Before administration, connect accessories (e.g. extension tubing, in-line filter 0.2 or 0.22 micron polyethersulfone (PES) or equivalent low-bond filter protein, timed syringe).
6. Administer the reconstituted solution at the appropriate rate.
7. Dispose of all used syringes, needles and vials as well as any unused reconstituted solution.

Administration via intravenous bags

1. After reconstituting all necessary vials, withdraw the reconstituted solution from each using the large syringe (50 mL or more) equipped with a 20 gauge needle (or bigger).
2. Transfer the reconstituted solution from the syringe into an appropriate IV bag
3. Repeat steps 1 and 2 to transfer the entire bolus and infusion volume into bags iv in PO or PVC. 4. It is recommended to divide the bolus and infusion into two bags separated to ensure correct administration speed. You can also use a single PO or PVC IV bag for the bolus and infusion, but speed must be guaranteed correct infusion rate when switching from bolus to infusion.
4. Before administration, connect accessories (e.g. extension tubing, in-line filter 0.2 or 0.22 micron polyethersulfone (PES) or equivalent low-bond filter protein, IV pump).
5. Administer the reconstituted solution at the appropriate rate. Disposal All syringes, used needles and vials as well as unused residues of the reconstituted solution must be disposed of in accordance with local regulations in force.

Unreconstituted medicine should be stored in a refrigerator (2°C – 8°C).
Andexanet alfa does not necessarily need to be brought to room temperature before reconstitution or before administration to the patient. Adopt aseptic techniques during processing reconstitution procedure.
Chemical and physical stability of the reconstituted medicinal product has been demonstrated for 16 hours at 2°C – 8°C in the immediate packaging vial. If necessary, the reconstituted solution transferred into the IV bag can be stored for another eight hours at room temperature. From the point of view microbiological, the reconstituted product should be used immediately. If it is not used immediately, storage times during use and storage conditions before of use are the responsibility of the user.

8 SIDE EFFECTS

Safety was evaluated in clinical studies including 247 healthy subjects who received it administered an FXa inhibitor and 352 patients included in a phase IIIb/IV study (ANNEXA-4) suffering from major acute bleeding and being treated with an FXa inhibitor (mainly apixaban and rivaroxaban). In clinical studies with healthy subjects who were administered a FXa inhibitor and subsequently andexanet alfa, no serious adverse reactions were reported or severe.

In pivotal studies 14-503 and 14-504, treatment with andexanet alfa resulted in statistically significant increase in thrombin generation in healthy subjects subjected to anticoagulant therapy with apixaban or rivaroxaban vs. placebo. In study 14-505 (ANNEXA-4), single arm conducted on patients suffering from major acute bleeding and being treated with a FXa inhibitor (apixaban and rivaroxaban), 11% of patients treated with andexanet alfa had experienced one or more thromboembolic events. The median time to first thromboembolic event is ten day state; 38% of patients with thromboembolic events experienced the mole event first three days.

In fact, it is known that patients treated with an FXa inhibitor are affected by underlying pathologies that predispose them to thrombotic events and reversal of therapy with an FXa inhibitor exposes patients to the thrombotic risk linked to the underlying disease.

Furthermore, an independent pro-coagulant effect of andexanet alfa was demonstrated in studies, mediated by inhibition of tissue factor pathway inhibitor TFPI), which may constitute a risk for the development of thrombosis. The duration of this effect moles haemorrhagic patients is unknown.

A.II.

Document from the Estonian Society of Anesthesiology

ENGLISH Convenience Translation

CONVENIENCE TRANSLATION

Practical [guide] of the Estonian Society of Anaesthesiologists1

ANTITHROMBOTIC DRUGS IN PLANNED AND EMERGENCY SURGERY

Today, a number of different antithrombotic drugs are used in patients for a wide range of indications in different doses. The Estonian Society of Anaesthesiologists' Practical Guideline can be used in situations where patients taking these drugs are undergoing a planned or emergency surgical procedure or operation, or where these patients are experiencing life-threatening bleeding due to the use of antithrombotic drugs.

In elective surgery, the discontinuation and/or resumption of antithrombotic therapy should take into account patient risk factors, surgical bleeding risk and the anaesthetic method used. In addition to the above, reversal or reduction of the effect of antithrombotic drugs may be necessary in **emergency situations.**

1. Patient-side factors:
   - age
   - risk of stroke
   - risk of bleeding
   - cardiovascular event in the last 3 months
   - comorbidities, especially kidney failure
   - medicines you take (including anti-thrombotic medicines, NSAIDs).

2. Surgical factors:
   - the risk of bleeding during surgical intervention
   - possible consequence of bleeding (especially neurosurgery, cardiac surgery, major abdominal and throat surgery).
   - planned method of anaesthesia (general, regional, local)
   - expected restart of antithrombotic therapy

Discontinuation of antithrombotic therapy prior to a planned surgical procedure or reversal or reduction of the effect of the drug(s) in the event of an emergency haemorrhage.
or if surgical intervention is needed.

[1] Estonian Society of Anaesthesiologists The practical guide has been compiled on the basis of various international guidelines, which are listed in the list of sources used. The practical guide is an annex to the Estonian Health Insurance Fund's Guide to Transfusion Therapy Part I.
Prepared by the Estonian Society of Anaesthesiologists Spring 2022. Questions and suggestions: kerli.vijar@kliinikum.ee

CONTENTS

ANTITHROMBOTIC DRUGS, THEIR DISTRIBUTION AND IMPACT ON COAGULATION ANALYSES

Table 1

Breakdown of antithrombotic medicines

ANTICOAGULANTS	**ORAL ANTICOAGULANTS**	**VKA***	warfarin (*Marevan®*)
		OSAK**	thrombin inhibitors: dabigatran (*Pradaxa®*).
			Xa inhibitors: rivaroxaban (*Xarelto®*), apixaban (*Eliquis®*), edoxaban (*Lixiana®*).
	PARENTERAL ANTICOAGULANTS	**Direct from**	argatrobaan (*Exembol®*)
		Indirect	UFH***, MMH**** (enoxaparin - *Clexane®*, Losmina® and others; bemiparin - *Zibor®*), fondaparin (*Arixtra®*).
ANTIAGGREGANTS	**ORAL ANTIAGGREGANTS**	**TxA_2 inhibitor**	acetylsalicylic acid (*Hjertemagnyl®*, *Thrombo* ASS®, etc.).
		P2Y12 inhibitors	clopidogrel (*Clopidogrel®*, *Plavix®*, *Zyllt®*, *Trombex®*, etc.), ticagrelor (*Brilique®*), prasugrel (*Prasugrel®*, *Efient®*, *Eliskardia®*).
	PARENTERAL ANTIAGGREGANTS	**GPIIb/IIIa inhibitors**	eptifibatide (*Integrilin®*), tirofiban (*Aggrastat®*).

* VKA - vitamin K
** OSAc - direct oral
antagonist*** UFH - *unfractionated heparin*.
anticoagulant**** MMH - low molecular weight heparin

Anticoagulants: action on the coagulation system

• indicated for the prophylaxis and treatment of venous thromboembolism in several diseases (atrial fibrillation, deep vein thrombosis, KATE, mechanical valve prostheses, joint endoprostheses, etc.).

Anti-aggregants: affect platelet aggregation

• indicated for the prophylaxis and treatment of arterial thrombi in the arteries of various organs (coronary arteries, cerebrovascular arteries, carotid arteries, renal arteries, peripheral arteries, etc.).

Table 2

Effects of antithrombotic drugs on coagulation assays

Medicine / Analysis	dabigatraan	rivaroxaban, apixaban, edoxaban	warfarin	UFH	LMWH, fundaparinuks	aspirin	P2Y12 inhibitors
APTT*	↑/N	↑/N	↑/N	↑	↑/N	X	X
TT	↑	X	X	↑	↑/N	X	X
anti-FXa**	X	↑	X	↑	↑	X	X
anti-FIIa**	↑	X	X	X	X	X	X
PT-INR	↑/N	↑/N	↑	X***	X***	X	X
ACT	↑/N	↑/N	↑/N	↑	↑/N	X	X
B-Agr-ASPI	X	X	X	X	X	↓	X
B-Agr-ADP	X	X	X	X	X	X	↓
PFA-Col/Epi	X	X	X	X	X	↑	↑/N
PFA-Col/ADP	X	X	X	X	X	N	↑/N
PFA-P2Y12	X	X	X	X	X	X	↑
thromboelastometric studies****	√	√	√	√	√	X	X

* Reference range APTT and PT-INR results do not exclude significant plasma levels of dabigatran, rivaroxaban, apixaban and edoxaban. However, APTT and PT-INR results may also be within the reference range.
** There is a separate anti-FXa or anti-FIIa study for each drug, from which the drug concentration is calculated (24/7 at PERH, 24/7 at TÜK, weekdays at ITK).
*** Most PT-INR assays are insensitive to heparin concentrations < 1 kU/L and low molecular weight heparin concentrations < 1.5 kU/L; higher heparin concentrations may also prolong PT time.
**** The effect depends on the parameter to be determined and the equipment used.

BLEEDING RISKS OF SURGICAL INTERVENTIONS

Table 3

Bleeding risks of planned surgical interventions*

* each patient's individual risks of bleeding and thromboembolic complications must be considered and discussed with the operating surgeon and patient.

MINIMAL RISK INTERVENTIONS (RARE AND CLINICALLY INSIGNIFICANT BLEEDING):

- tooth extraction (1-3 teeth), periodontal surgery, implant placement, gum cleaning.
- cataract and glaucoma operations
- endoscopy without biopsy or resection
- superficial operations (abscess openings, skin biopsies, minor dermatological operations).
- insertion of a stimulator or ICD (except in complex cases).
- electrophysiological examinations, catheter ablations (except in complex cases).
- scheduled routine coronary or peripheral artery angiography (except in complex cases).
- intramuscular injections (e.g. vaccinations).

LOW-RISK INTERVENTIONS (INFREQUENT OR CLINICALLY UNIMPORTANT BLEEDING):

- complicated dental procedures
- endoscopy with simple biopsy
- minor orthopaedic operations (foot, hand, arthroscopy...)

HIGH-RISK INTERVENTIONS (FREQUENT AND/OR CLINICALLY SIGNIFICANT BLEEDING):

- cardiosurgery
- revascularisation surgery of peripheral arteries (e.g. aortic aneurysm surgery, vascular shunting surgery).
- complex/complex invasive cardiological interventions, pacemaker lead removal from the heart, (epicardial) VT ablation, PKI for chronic occlusion, etc.
- neurosurgery
- spinal or epidural anaesthesia, diagnostic lumbar puncture.
- complex endoscopy (e.g. multiple/large polypectomies, ERCP with sphincteroscopy, etc.).
- abdominal surgery (including liver biopsy)
- throat surgery
- major urological surgery or biopsy (including kidney).
- extracorporeal impact rockbursting
- major orthopaedic surgery

Table 4

Bleeding in critical areas

CONSEQUENCE OF BLEEDING	TYPICAL	SYMPTOM OF BLEEDING LIKELY TO BE A
Intracranial haemorrhage: intraparenchymal, subdural, epidural, subarachnoid.	**Neurological:** loss of consciousness, visual disturbances, numbness, weakness, aphasia, ataxia, vertigo, seizures. **Rarely severe headache, vomiting**	Stupor or coma Persistent neurological deficit Death
Other CNS haemorrhage: intraocular, sub- or epidural spinal haematomas	**Intraocular:** pain in one eye, blurred vision, blindness **Spinal:** back pain, weakness or numbness of bilateral limbs, digestive or bladder dysfunction, respiratory disturbances.	**Intraocular:** permanent visual loss **Spinal:** permanent disability, paraplegia, paraplegia, death.
Pericardial tamponadeFainting	, tachypnoea Hypotension, jugular venous distension Tachycardia, muffled heart sounds, friction palpitations	Cardiogenic shock Death
Respiratory tract, including posterior nosebleeds	**Respiratory tract:** coughing up blood, shortness of breath, hypoxia **Posterior nosebleed:** profuse bleeding, coughing up blood, hypoxia, shortness of breath.	Hypoxaemic respiratory failure Death
Haemothorax, intra-abdominal haemorrhage, retroperitoneal haemorrhage	**Haemothorax:** tachypnoea, tachycardia, hypotension **Intra-abdominal (not gastrointestinal):** abdominal pain, prolapse, hypotension, tachycardia **Retroperitoneal haemorrhage:** back/back/hip pain, tachycardia, hypotension.	**~~Haemothorax:~~** ~~respiratory failure~~ **~~Retroperitoneal~~ haemorrhage:** damage to the femoral nerve **All cases:** hypovolemic shock, death
Bleeding from extremities, including intramuscular and intra-articular bleeding.	**~~Intramuscular:~~** ~~pain, swelling, paleness, paresthesias,~~ weakness, weakened pulses. **Intra-articular:** joint pain, swelling, reduced range of motion.	**Intramuscular:** compartment syndrome, paralysis, limb loss **~~Intra-articular:~~** ~~irreversible joint damage~~

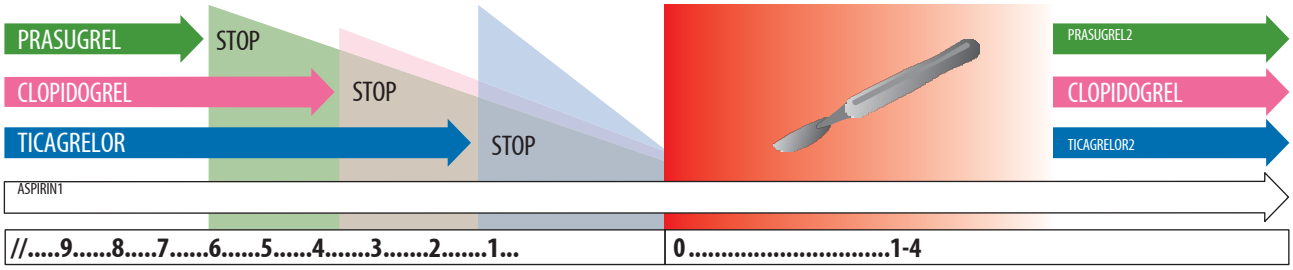
PLANNED SURGERY AND ANTIAGGREGANTS

Table 5

Discontinuation of antiaggregants in planned surgery

HIGH MEDICINE	TIME OF ONSET AND	DISCONTINUATION BEFORE LOWINTERRUPTION INTERMEDIATE RISK OF OPERATIONS	BLEEDING RISK	BEFORE SURGERY
acetylsalicylic acid	5-7 daysnot	necessary3 days before		
MSPVA*	depending on the medicines	not needed for	1-3 days before	
klopidogrel	7-10	days5 days	before7 days before	
prasugreel	~10	days7 days	before10 days before	
tikagreloor	~7	days3 days	before5 days before	

* NSAID - Non-steroidal anti-inflammatory drug



= Expected aaverage platelet function recovery

1 Decision to stop aspirin throughout surgery should be made on a single case basis taking into account the surgical bleeding risk.

2 In patients not requiring OAC.

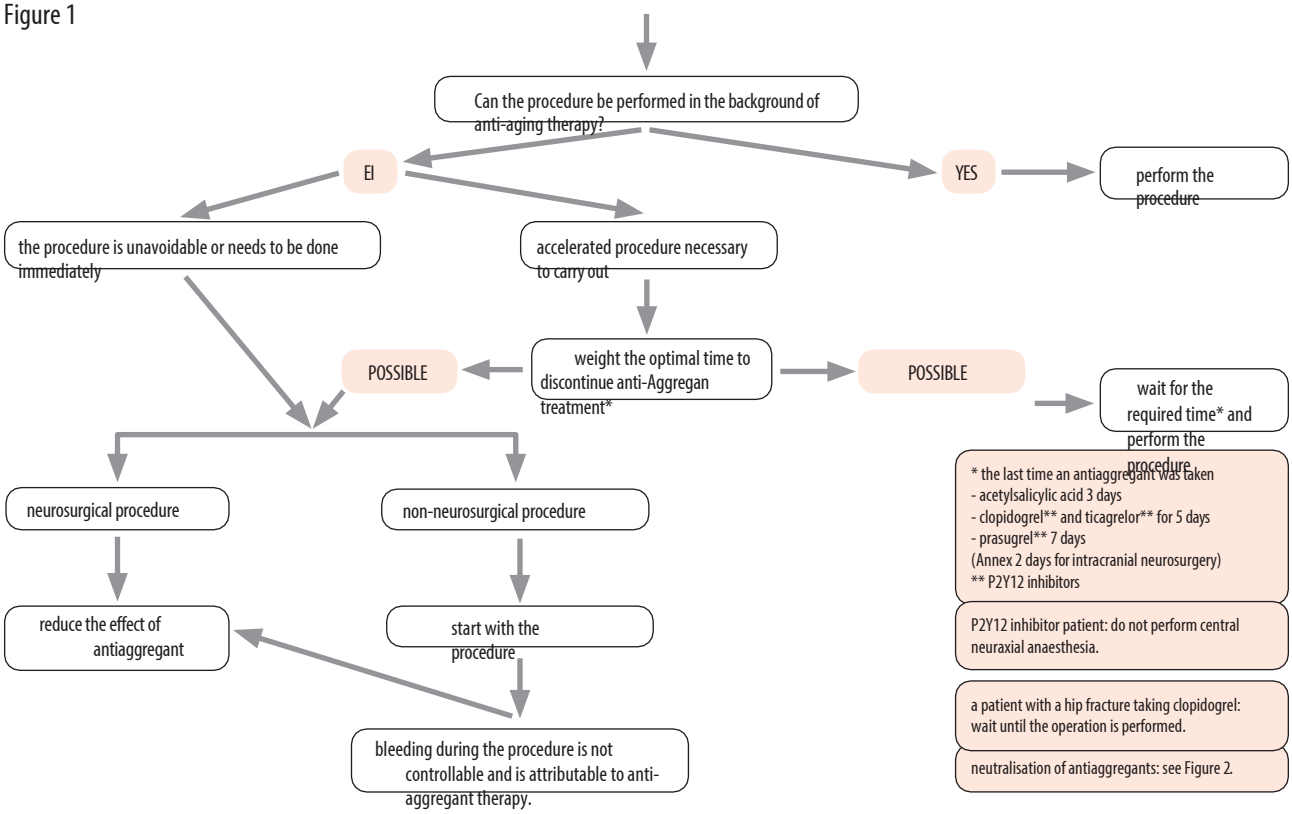
Table 6

Anti-aggregant treatment recommendations for planned a patient undergoing non-cardiac surgery

	RECOMMENDATION CLASS	EVIDENCE-BASED
The use of acetylsalicylic acid should be continued throughout the perioperative period if possible. The recommended antiaggregants should be resumed as soon as possible postoperatively.	I	B
If planned surgery requires discontinuation of P2Y12 inhibitor but allows continuation with acetylsalicylic acid, surgery may be considered 1 month after stenting.	IIA	B
Ticagrelor should be stopped at least 3 days, clopidogrel at least 5 days and prasugrel at least 7 days before surgery.	IIA	B
A multidisciplinary team of experts may be considered for the preoperative assessment of a patient on double anti-rejection therapy.	IIA	C
If double antiangiogenic therapy is indicated for a recent heart attack or other high-risk ischaemic condition, scheduled surgery should be delayed for 6 months.	IIB	C
If surgery requires discontinuation of both antiaggregants, bridging with i/v antiaggregants may be considered. This is especially the case if surgery is performed less than 1 month after stenting.	IIB	C
In the case of elective surgery, it is not recommended to discontinue double anti-graft therapy within the first month after stenting.	III	B

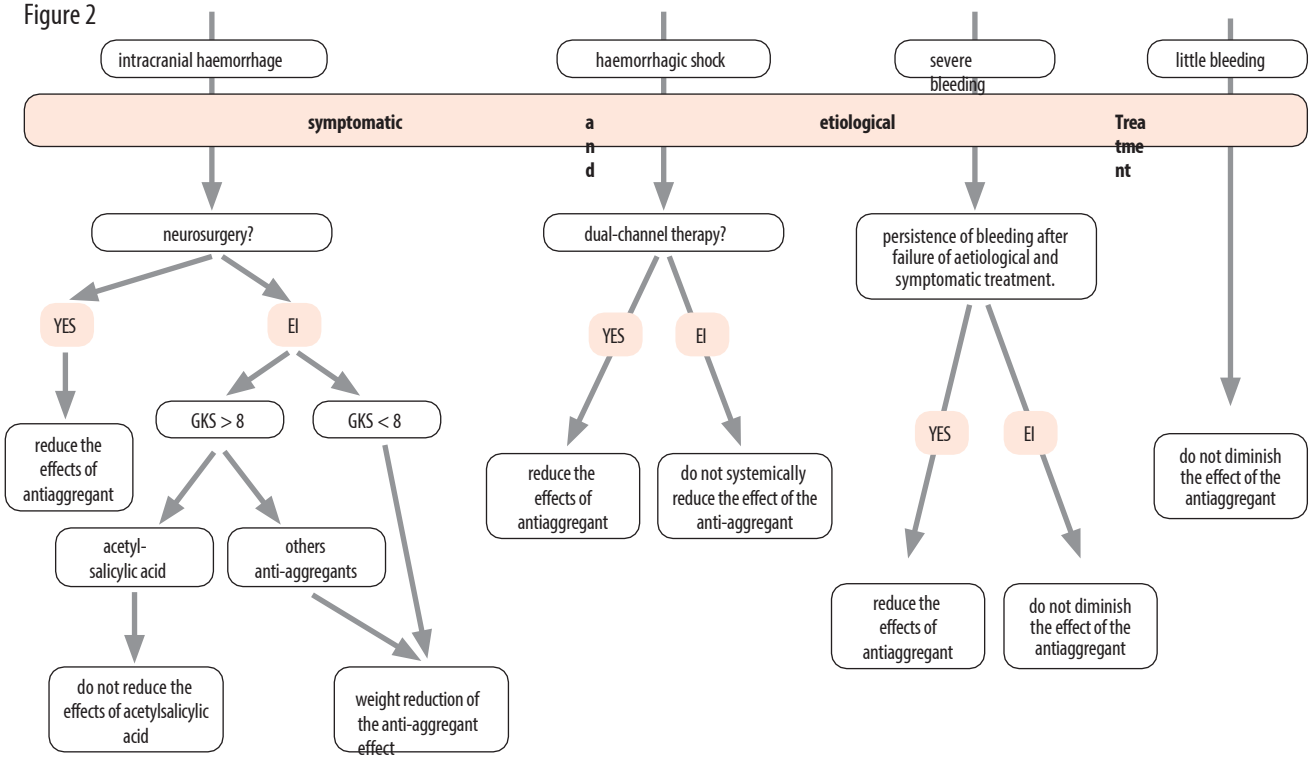
Emergency invasive procedure in an antiaggregant user

Figure 1



Bleeding in a person taking anti-aggregant therapy

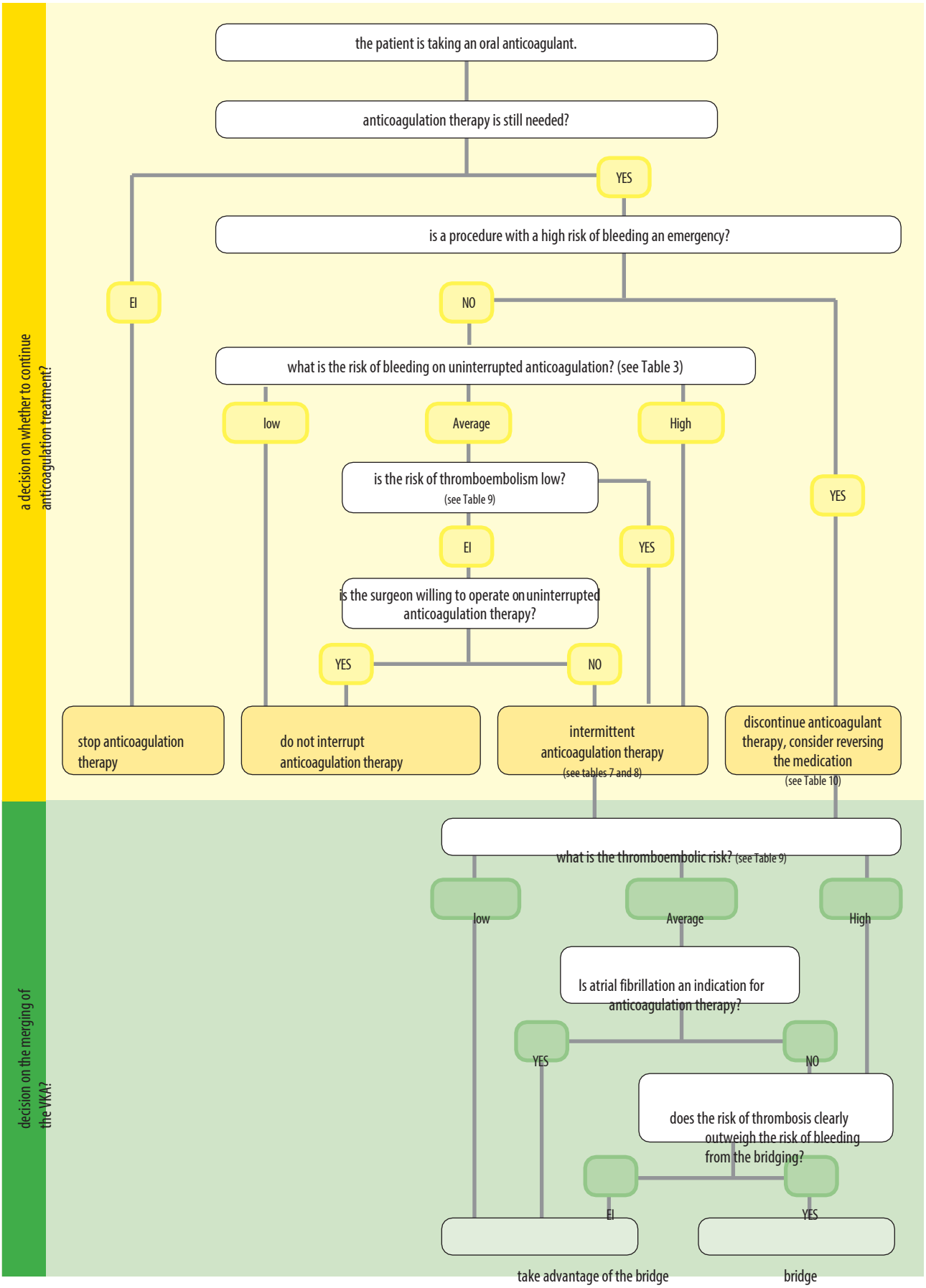
Figure 2



ANTIAGREGANT	the possibility of reducing the effect of the anti-aggregant
acetylsalicylic acid	platelet transfusion: 1 dose*
klopidogrel	platelet transfusion: 2 doses* *less effective if < 6 hours have elapsed since clopidogrel was given.*
prasugreel	platelet transfusion: > 2 doses*. *less effective if < 6 hours have elapsed since the start of prasugrel administration.*
tikagreloor	last administration < 24 h: no recommendation - platelet transfusion is not effective, consideration of rFVIIa administration and use of CytoSorb® last administration > 24 h: platelet transfusion partially attenuates the effect.

* dose: 1 bag of 4-5BC platelets containing ≥200 ^{x109} platelets per unit product, or 1 bag of apheresis platelets also containing ≥200 $^{x109\ platelets\ per}$ unit product.

Figure 3



Note: Low molecular weight or unfractionated heparin is bridged to warfarin-treated patients as needed. Patients on OSAK are not cross-linked, but if the time between discontinuation of OSAK and the planned surgical procedure extends beyond the planned treatment interruption, low-molecular-weight heparin should b e considered depending on the patient's risk of thrombosis (see Table 9).

Table 7

OSAK periprocedural approach in planned surgery

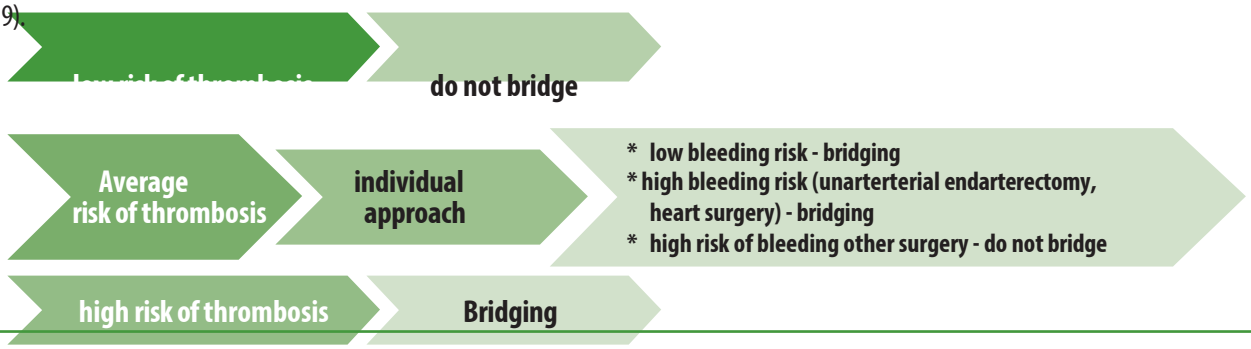
Timing of the last dose of OSAK treatment before a planned surgical procedure				
	DABIGATRAAN		**APIXABAN, EDOXABAN, RIVAROXABAN**	
not cross-linked to low molecular weight/unfractionated heparin*. * if the time between the interruption of OSAK treatment and the planned surgical procedure extends beyond the planned treatment interruption, low-molecular-weight heparin should be considered depending on the patient's risk of thrombosis (see Table 9).				
With minimal bleeding risk operations:	- perform the procedure against the background of OSAK treatment - continue the OSAK procedure on the same day, at the latest the next day.			
	DABIGATRAAN		**APIXABAN, EDOXABAN, RIVAROXABAN**	
	low risk of bleeding	high risk of bleeding	low risk of bleeding	high risk of bleeding
CrCl ≥ 80ml/min	≥ 24 t	≥ 48 t	≥ 24 t	≥ 48 t
CrCl 50-79 ml/min	≥ 36 t	≥ 72 t		
CrCl 30-49ml/min	≥ 48 t	≥ 96 t		
CrCl 15-29ml/min	not indicated	not indicated	≥ 36 t	
CrCl ≤ 15ml/min	not officially indicated			
IMPORTANT: - The timing of OSAK discontinuation may need to be tailored to the patient's risk factors. - in patients or in situations where there is a risk of OSAK accumulation (renal failure, elevated age, concomitant medications), discontinuation of OSAK 12-24 hours earlier may be considered.				
RESUMPTION OF TREATMENT OF THE DISEASE: - restart full-dose OSAK treatment 24 hours after a low bleeding risk procedure. - restart full-dose OSAK 48 (-72) hours after a procedure with a high bleeding risk, consider a prophylactic post-operative dose of low-molecular-weight heparin after surgery and before starting full-dose OSAK treatment.				

Table 8

The warfarin treatment approach in planned surgery

VKA MINIMUM PREOPERATIONAL INTERRUPTION			RECOMMENDATION	
VARFARIIN	INR 7 days before the op:	from bitter to warfarin:	measure INR the day before the op.	weight bridging if there is a serious risk of thrombosis
	< 2	5 days		
	2-3	6 days		
	>3	7 days		
optimal INR for surgery: low bleeding risk < 2.0 /// high bleeding risk < 1.5.				

Switching a patient on warfarin to low-molecular-weight heparin (MMH) depends on the risk of perioperative thrombosis (see Table 9).



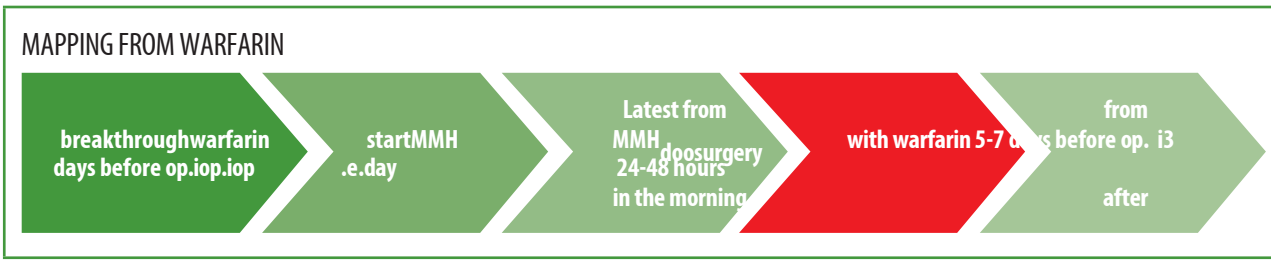


Table 9

Risk of perioperative thrombosis

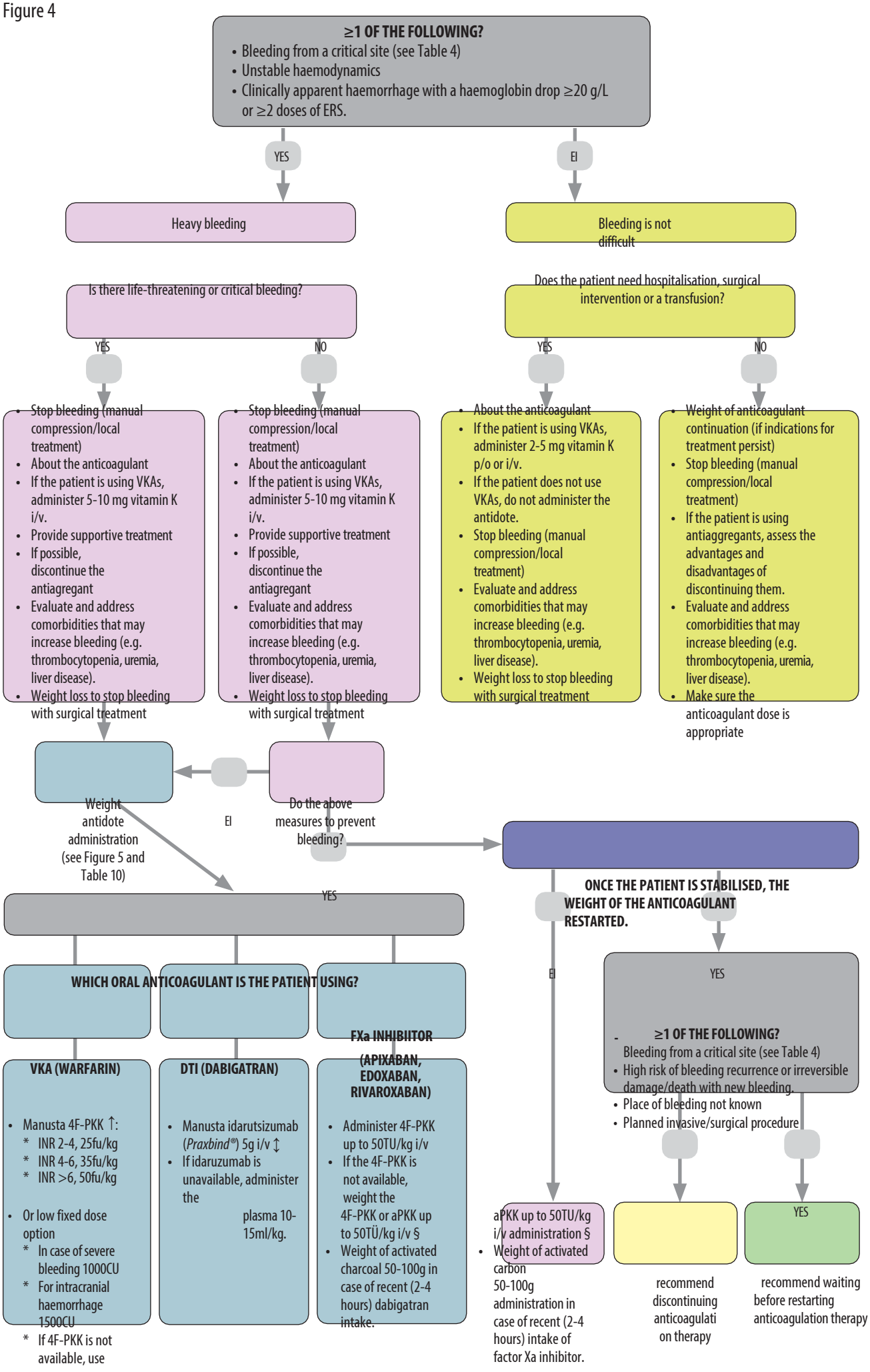
RISK	Mechanical valve	Upgrading of codes	Venous thrombus
low (annual risk <5%)	- double-knee aortic valve prosthesis without risk factors	- CHADS2 0-2 (assuming no history of stroke or TIA)	- VTE < 12 months ago
Moderate (annual risk 5-10%)	- bilateral aortic valve prosthesis and at least one risk factor: • atrial fibrillation • history of stroke or TIA • hypertension • diabetes • heart failure • age > 75 years.	- CHADS2 3 or 4	- VTE in the last 3-12 months - non-systemic thrombophilia (heterozygous factor V or a mutation in the prothrombin gene). - active cancer (treated in the last 6 months or on palliative treatment)
High (annual risk >10%)	- all mitral valve prostheses - aortic valve ball or disc prostheses - recent stroke or TIA (<6 months)	- CHADS2 5 or 6 - recent stroke or TIA (<3 months) - eumatic clapyrike	- recent (<3 months) VTE - severe thrombophilia (protein C or S antithrombin deficiency, antiphospholipid syndrome).

FILE	CHA2DS2-VASC	POINTS
C	HEART FAILURE, LEFT VENTRICULAR DYSFUNCTION	1
H	HÜPERTENSIOON	1
A2	VANUS > 75 A.	2
D	DIABEET	1
S2	STROKE, TRANSIENT CEREBRAL ISCHAEMIA	2
V	VASCULAR DISEASE*	1
A	VAN 65-74 A.	1
Sc	NAISSUGU	1

*vascular disease: previous myocardial infarction, peripheral artery disease or atherosclerotic plaque in the aorta.

Extraordinary invasive procedure or bleeding in an anticoagulation user

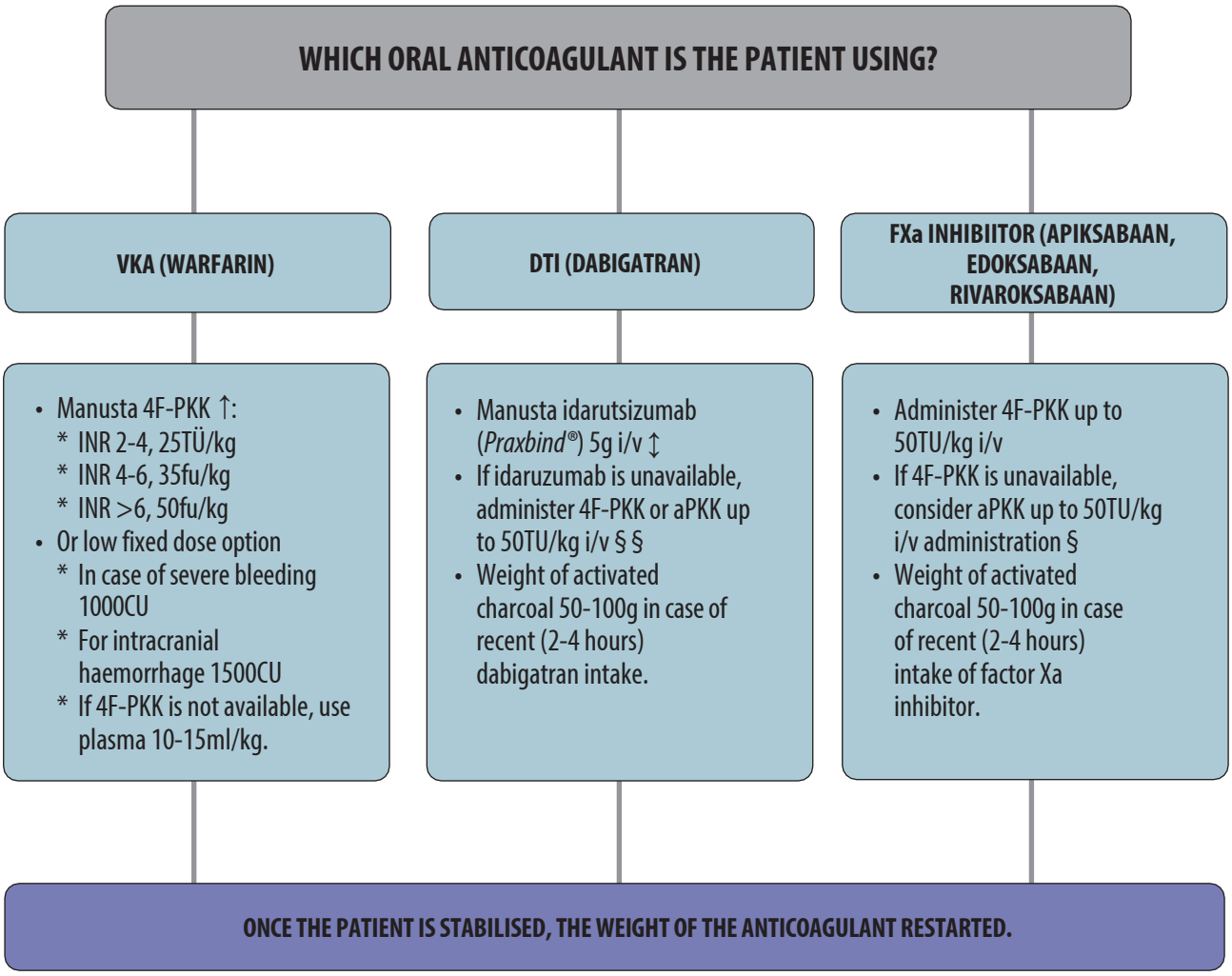
Figure 4



EI

recommend restarting
anticoagulation therapy

Figure 5



4F-PKK - four-factor prothrombin complex concentrate (Octaplex®,Prothromplex®), aPKK - activated prothrombin complex concentrate (Feiba®), DTI - direct thrombin inhibitor, FXa - factor Xa, INR - international normalised ratio, i/v - intravenous, VKA - vitamin K antagonist, OSAK - direct acting oral anticoagulant.
*Antidotes are PKK, vitamin K and specific OSAK antidotes (idaruzumab for dabigatran).
↑ If PKK is used as an antidote for VKA, vitamin K should always be added.
↕ A second dose of idaruzumab may be warranted in the following cases: if bleeding continues from the antidote.
post-administration, there is a laboratory-confirmed effect of dabigatran, or there is a suspicion of a continuing anticoagulant effect before a second invasive procedure.
§ For information on the maximum dose, read the Dosage Guide (Summary of Product Characteristics).

Bleeding in a person on dual-channel therapy and/or anticoagulant therapy

Figure 6

Haemorrhage in dual-channel therapy +/- OSAK treatment users

MINIMAL BLEEDING

Any bleeding not requiring medical intervention or further evaluation

For example, superficial haematomas or ecchymoses, self-inflicted nosebleeds, minimal conjunctival haemorrhage.

- Continue DAPTi

- Weight to continue OSAK or skip the next dose.

- Reassure patients
- Identify and discuss possible preventive strategies with the patient.
- Advise the patient on the importance of treatment compliance

LIGHT BLEEDING

Any bleeding that requires medical intervention, but not hospitalisation of the patient

For example, nosebleed requiring intervention, moderate conjunctival bleeding, genitourinary or upper/lower gastrointestinal bleeding without significant blood loss, mild haemoptysis.

- Continue DAPTi
- Consider shortening the duration of DAPT therapy or replacing the P2Y12 inhibitor with a less potent option (e.g. from ticagrelor/prasu- grel to clopidogrel), especially if recurrent bleeding occurs.

- In the case of triple therapy, weight shift to dual therapy, preferably with clopidogrel and OSAK.

- Identify and treat co-morbidities associated with bleeding (e.g. peptic ulcer, haemorrhoids, tumour).
- Add to regimen PPI
- Advise the patient on the importance of treatment compliance

MODERATE BLEEDING

Any significant blood loss (Hb drop >30 g/L) and/or hospitalised haemodynamically stable patient with non-rapidly progressive bleeding.

For example, significant blood loss or genitourinary, upper/lower gastrointestinal, respiratory haemorrhage requiring transfusion.

- Consider discontinuing DAPT and resuming SAPT, preferably with a P2Y12 inhibitor, especially for upper gastrointestinal bleeding.
- Restart DAPT as soon as it can be considered safe to do so
- Consider shortening the duration of DAPT therapy or replacing the P2Y12 inhibitor with a less potent option (e.g. from ticagrelor/prasugrel to clopidogrel), especially in the presence of recurrent bleeding.

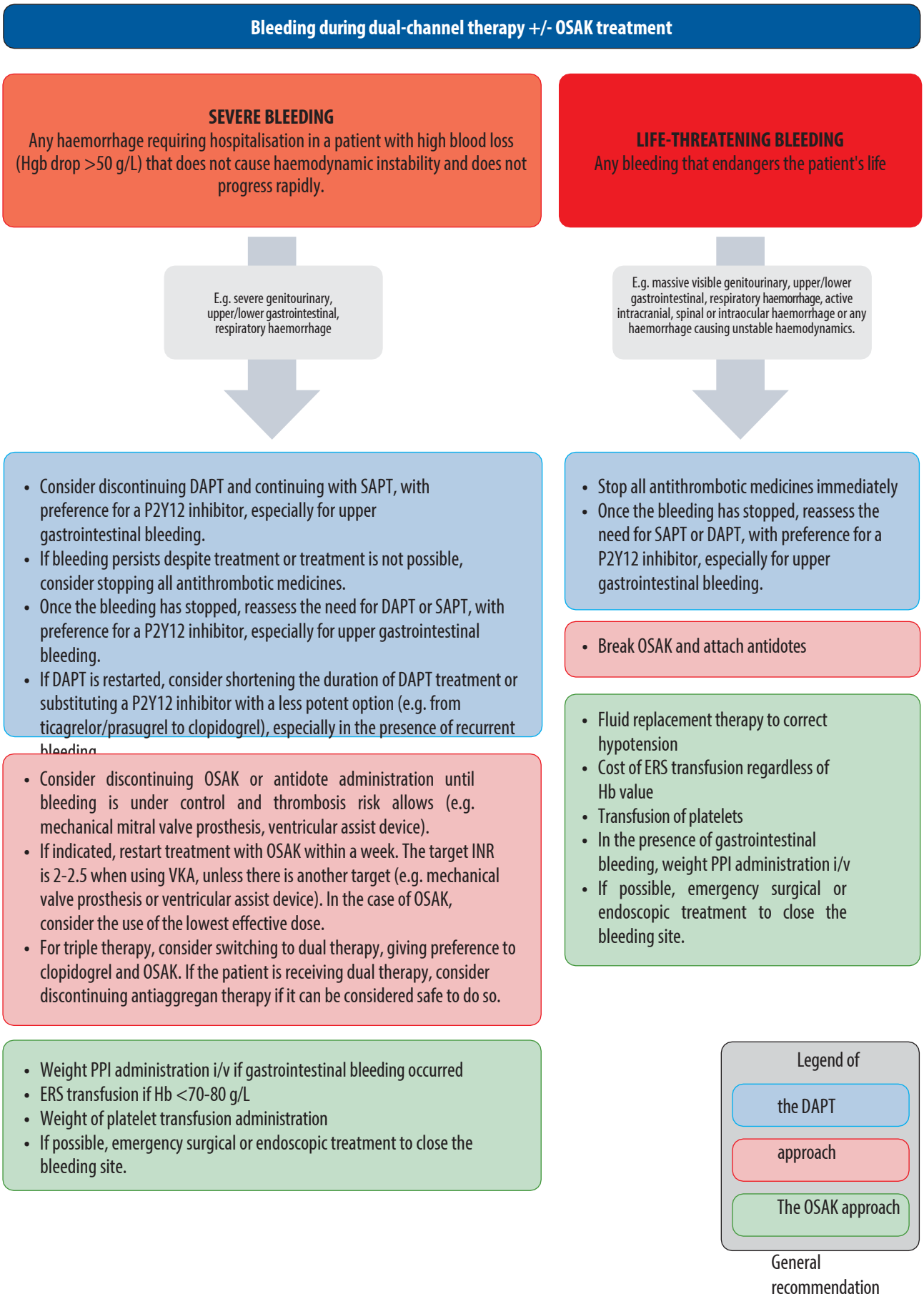
- Consider discontinuation of OSAK or even antidote administration until bleeding is controlled (e.g. mechanical heart valves, ventricular assist device, CHA_2DS_2-VASc ≥4).
- If indicated, restart treatment with OSAK within a week. The target INR for VKA use is 2-2.5, except in cases, if there is another target value (e.g. mechanical valve prosthesis or ventricular assist device). In the case of OSAK, consider the use of the lowest effective dose.
- In the case of triple therapy, weight shift to dual therapy, preferably with clopidogrel and OSAK.
- If the patient is on dual therapy, consider discontinuing antiagregant therapy if it can be considered safe.

- In the presence of gastrointestinal bleeding, weight PPI administration i/v
- Identify and treat co-morbidities associated with bleeding (e.g. peptic ulcer, haemorrhoids, tumour).
- Advise the patient on the importance of treatment compliance

OSAK - oral direct anticoagulant, DAPT - *dual antiplatelet therapy*, SAPT - *single antiplatelet therapy*, PPI - proton pump inhibitor, i/v - intravenous.

Legend of
the DAPT
approach
The OSAK approach
General recommendation

Figure 7


Bleeding during dual-channel therapy +/- OSAK treatment
SEVERE BLEEDING
Any haemorrhage requiring hospitalisation in a patient with high blood loss (Hgb drop >50 g/L) that does not cause haemodynamic instability and does not progress rapidly.
LIFE-THREATENING BLEEDING
Any bleeding that endangers the patient's life
E.g. severe genitourinary, upper/lower gastrointestinal, respiratory haemorrhage
E.g. massive visible genitourinary, upper/lower gastrointestinal, respiratory haemorrhage, active intracranial, spinal or intraocular haemorrhage or any haemorrhage causing unstable haemodynamics.
• Consider discontinuing DAPT and continuing with SAPT, with preference for a P2Y12 inhibitor, especially for upper gastrointestinal bleeding.
• If bleeding persists despite treatment or treatment is not possible, consider stopping all antithrombotic medicines.
• Once the bleeding has stopped, reassess the need for DAPT or SAPT, with preference for a P2Y12 inhibitor, especially for upper gastrointestinal bleeding.
• If DAPT is restarted, consider shortening the duration of DAPT treatment or substituting a P2Y12 inhibitor with a less potent option (e.g. from ticagrelor/prasugrel to clopidogrel), especially in the presence of recurrent bleeding
• Stop all antithrombotic medicines immediately
• Once the bleeding has stopped, reassess the need for SAPT or DAPT, with preference for a P2Y12 inhibitor, especially for upper gastrointestinal bleeding.
• Consider discontinuing OSAK or antidote administration until bleeding is under control and thrombosis risk allows (e.g. mechanical mitral valve prosthesis, ventricular assist device).
• If indicated, restart treatment with OSAK within a week. The target INR is 2-2.5 when using VKA, unless there is another target (e.g. mechanical valve prosthesis or ventricular assist device). In the case of OSAK, consider the use of the lowest effective dose.
• For triple therapy, consider switching to dual therapy, giving preference to clopidogrel and OSAK. If the patient is receiving dual therapy, consider discontinuing antiaggregan therapy if it can be considered safe to do so.
• Break OSAK and attach antidotes
• Fluid replacement therapy to correct hypotension
• Cost of ERS transfusion regardless of Hb value
• Transfusion of platelets
• In the presence of gastrointestinal bleeding, weight PPI administration i/v
• If possible, emergency surgical or endoscopic treatment to close the bleeding site.
• Weight PPI administration i/v if gastrointestinal bleeding occurred
• ERS transfusion if Hb <70-80 g/L
• Weight of platelet transfusion administration
• If possible, emergency surgical or endoscopic treatment to close the bleeding site.
Legend of
the DAPT
approach
The OSAK approach
General recommendation

REDUCING OR REVERSING THE EFFECT OF ANTITHROMBOTIC MEDICINES ON LIFE-THREATENING BLEEDING. OR IN CASE OF AN EMERGENCY PROCEDURE

Table 10

RAVIM	ELIMINATION HALF-LIFE	EXTRACORPOREAL REMOVAL	REDUCING OR REVERSING THE EFFECT OF A MEDICINE
DABIGATRAAN	14-17 hours (up to 34 hours in case of kidney failure)	4-hour haemodialysis removes about 50-60% of the fluid. dabigatraanist	- dabigatran concentration P-DBTN (determined by the anti-FIIa test)[a] can help assess the effect of the drug - the effects of the drug can be excluded by a plasma reference limit TT and/or a negative urine Dosense® rapid test. - activated charcoal 50-100g p/o may help within ~2h after drug administration - for life-threatening haemorrhage, weight of idaruzumab (*Praxbind*®) 5mg, or in its absence 4f-PCC (Octaplex® or Prothromplex®) up to 50TU/kgc. * idaruzumab may correct aPTT/TT, but has not been shown to improve outcomes * plasma concentrations of the drug may rise within 12-24T after administration of idaruzumab (redistribution from tissues).
RIVAROKSABAAN	5-9 hours for healthy people, 11-13 hours in elderly people (longer in renal failure).	is not removable by dialysis, if removable With *CytoSorb*®	- rivaroxaban's P-RXN concentration (determined by the anti-Xa test)[a] can help to assess the effect of the drug. - the effect of the drug helps to exclude the value of low molecular weight heparin P-LMWH <0.1 kU/L and/or urine negative Doasense® rapid test anti-fXa, drug conc. - activated charcoal 50-100g p/o may help within ~2h after administration of the drug. - weight of 4f-PCC (Octaplex® or Prothromplex®) administered up to 50TU/kgc - in case of life-threatening haemorrhage, the weight of alpha-deoxanate (Ondexxya®) administered at 800mg i/v bolus (30mg/min), continuing the infusion at 8mcg/min for 3 hours. * 4f-PCC may partially correct for PT/aPPT (correlation between their fall and the reduction in bleeding). is unknown), but does not affect anti-Xa activity or accelerate drug clearance.
APIKSABAAN	8-15 hours (longer in case of kidney failure)	no	- the effect of the drug can be assessed by the concentration of apixaban in P-APBN (determined by the anti-Xa test)[a] - the therapeutic effect helps to exclude the value of low molecular weight heparin P-LMWH <0.1 kU/L and/or urine negative Doasense® rapid test - activated charcoal 50-100g p/o may help within ~2h after drug administration - weight of 4f-PCC (Octaplex® or Prothromplex®) administered up to 50TU/kgc - in case of life-threatening haemorrhage, the weight of alpha-deoxanate (Ondexxya®) 400mg i/v bolus (30mg/min), continuing at 4mcg/min for 3 hours. * 4f-PCC may partially correct for PT/aPPT (correlation between their fall and the reduction in bleeding). is unknown), but does not affect anti-Xa activity or accelerate drug clearance.
EDOKSABAAN	10-14 HOURS (LONGER IN CASE OF KIDNEY FAILURE)	haemodialysis ~25%	- the effect of the drug can be assessed by the concentration of edoxaban in P-EDBN (determined by the anti-Xa test)[a] - the effect of the drug helps to exclude the value of low molecular weight heparin P-LMWH <0.1 kU/L and/or negative urine Doasense® rapid test. - activated charcoal 50-100mg p/o can help for ~2h after drug administration - weight of 4f-PCC (Octaplex® or Prothromplex®) administered up to 50TU/kgc * 4f-PCC may partially correct PT/aPPT (correlation between their decrease and the decrease in bleeding is unknown), but does not affect anti-Xa activity or accelerate drug clearance.
VARFARIIN	**INR**	**clinical condition**	**Action**
	< 4,5	no bleeding	- stop warfarin until the INR is in the therapeutic range
		the need for a rapid reversal of the effect	- peata to warfarin - weight vit. K supply 2,5mg p/o
	>4,5	no bleeding	- stop warfarin until the INR is in the therapeutic range - weight vit. K administration 2.5-5mg p/o or 1-2mg i/v for 30 minutes
		the need for a rapid reversal of the effect	- peata to warfarin - give vit. k 2.5-5mg p/o or 1-2mg i/v for 30 min, repeat as needed over 6-24h.
	each INR	serious life-threatening bleeding	- peata to warfarin - administer vit.k 5-10mg i/v in 30 minute infusions - the weight of 4f-PCC (Octaplex® or Prothromplex®) administered: • INR 2-4 25fu/kg, max. 2500FU • INR 4-6 35fu/kg, max. 3500CU • INR >6 50TU/kg, max. 5000FU - In the absence of 4f-PCC, make plasma or its derivative 10-20ml/kg.

ARGATROBAAN	40-50 minutes	haemodialysis ~20%	- stop the infusion - the degree of drug reversal can be assessed by aPTT and/or CT.
UNFRACTIONATED HEPARIN	30-90 minutes (depending on dose)	partial haemodialysis	- use protamine for neutralisation (up to 5mg/min, max dose 50mg). - assess the degree of drug reversal by aPTT and/or P-UFH (determined by an anti-Xa test) o f unfractionated heparin. **time since last heparin** / **prothrombin dose per 100TU of heparin administered** newly administered: 1 mg *(or 25 mg fixed dose)* 30 min - 2 hours: 0.5 mg (*or 10 mg fixed dose)* > 2 hours: 0.25 mg *(or 10 mg fixed dose)* * protamine has anticoagulant effects in overdose; protamine has a shorter half-life than unfractionated heparin, so a booster dose may be needed.
MADAL-MOLECULAR HEPARIN (ENOXAPARIIN, BEMIPARIIN)	3-5 hours (longer in case of kidney failure)	haemodialysis ~20%	- partially neutralised by protamine ~60% (up to 5mg/min, max. dose 50mg) - assess the degree of drug reversal with the low molecular weight heparin test P-LMWH (determined by anti-Xa test). **time since last MMH dose** / **protamine dose per 1mg of enoxaparin** < 8 hours: 1 mg *(or 50 mg fixed dose)* 8-12 hours: 0,5 mg *(or 25 mg fixed dose)* > 12 hours: probably not necessary *(or 10 mg fixed dose)* - weight of rfVIIa (Novoseven®) administered 90 µg/kg.
FONDAPARIINUKS	17-21 hours (significantly longer in case of kidney failure)	no	- a fondapariininux test (determined by a n anti-Xa test) to assess the effect of the medicine [E] - weight of 4f-PCC (Octaplex® or Prothromplex®) administered up to [50TU/kgc] - weight of rfVIIa (Novoseven®) administered 90 µg/kg. * rfVIIa does not affect anti-Xa activity and does not increase drug clearance.

RAVIM	RESTORATION OF PLATELET FUNCTION	EXTRACORPOREAL REMOVAL	REDUCING OR REVERSING THE EFFECT OF A MEDICINE
ACETYLSALICYLIC ACID	5-7 days	[redacted]	- stop taking the medicine - the drug helps assess PFA-Col/Epi, PFA-Col/ADP, B-Agr-ASPI - the weight of 2-3 doses of platelet administration
KLOPIDOGREEL	7-10 days	[redacted]	- stop taking the medicine - the drug helps to evaluate PFA-P2Y12, B-Agr-ADP - the weight of 2-3 doses of platelet administration
TIKAGRELOOR	~7 days	removable with CytoSorb®	- stop taking the medicine - PFA-P2Y12, B-Agr-ADP, helps to assess the effect of the drug. - the weight of 2-3 doses of platelet administration
PRASUGREEL	~10 days	no	- stop taking the medicine - PFA-P2Y12, B-Agr-ADP, helps to assess the effect of the drug. - the weight of 2-3 doses of platelet administration
GPIIb/IIIa inhibitors	~4 hours	eptifibatide is dialysable	- B-Agr-TRAP shows the effects of the drug

[A] Concentrations of dabigatran, rivaroxaban, apixaban and edoxaban < 30µg/L are considered to exclude clinically significant plasma concentrations of the drug.
[B] idarutsizumab is available in Estonia: in the 1st iros of the TÜK and in the EMOs of the PERH.
[C] Octaplex® single dose should not exceed 3000 TU
[D] alpha-deoxanate (*Ondexxya®*) not yet available in Estonia (2022).
[E] as of March 2022 not to be determined in Estonia, technically feasible to be implemented in PERH and TÜK laboratories

Table 11

TREATMENT WITH ANTITHROMBOTIC DRUGS IN THE CASE OF BLOCKS WITH A HIGH BLEEDING RISK (NEURAXIAL AND DEEP NERVE BLOCKS).				
Drug and dose (see Table 14)		**Time from last medicine to blockade**	**Laboratory target for the blockade**	**Time to next dose after blockade**
VKAa		on warfarin for 5 days on average, target laboratory level.	INR normal	
direct Xa inhibitors (apixaban, edoxaban, rivaroxaban).	low doos	- apixaban 36t - edoxaban 24h (30h if CrClb < 30ml/min) - rivaroxaban 24t	not tested	
	high dose	72h or until target laboratory level is reached (if CrClb < 30ml/min)	- drug conc. baseline < 30µg/ (to be determined for each drug separately by an anti- Xa test) - as an alternative to low molecular weight heparin P-LMWH ≤ 0.1kU/L	low dose according to postop. VTEc prophylaxis guidelines
dabigatraan	low doos	48t	not tested	
	high dose	72h or until target laboratory level is reached (if CrClb < 30ml/min)	- dabigatran konts. baseline value < 30µg/L (determined by anti-FIIa test) - alternatively: normal TT time	high dose: according to anticoagulation guidelines (usually 24 hours after surgery).
MMHd	low doos: - ≤ 50TU anti-Xa/kg/day - enoxaparin ≤ 40mg/day	12h (24h if CrClb < 30ml/min)	not tested	
	high dose - ≥ 50TU anti-Xa/kg/day	24h (48h if CrClb < 30ml/min) or until target laboratory levels are reached (especially if CrClb < 30ml/min).	low molecular weight heparin P-LMWH (determined by anti-Xa test) ≤ 0.1kU/L	VKAa, OSAAs, high-dose MMH and FH should not be administered if the catheter *is in situ.*
FHf	low doos: - ≤ 200fu/kg/day s/c - ≤ 100TU/kg/day i/v	4t	not tested	FHf at low dose: 1t i/v after cardiac surgery
	high dose	until target laboratory levels are reached (about 6t for i/v and 12t for s/c)	APPT or unfractionated heparin P-UFH (as determined by anti-Xa test) or AKT at the normal value	
fondaparıinuks	low dose: ≤ 2.5mg/day	36h (72h if CrClb < 50ml/min)	not tested	
	high dose	until target laboratory levels are reached (usually around 4 days).	fundaparıinucleic acid level (determined by anti-Xa test) ≤ 0,1 kU/L*.	
aspirin	low dose: ≤ 200mg/day	0	not tested	following the patient's usual pattern
	high dose	3 days (with normal platelet count) to 7 days	platelet function tests	6t
P2Y12 inhibitors		- 5-7 days of clopidogrel - 5 days tikagreloor - 7 days prasugrel	(platelet function tests)	- 0t clopidogrel 75mg - 24t ticagrelol and prasugrel - 2 days clopidogrel 300mg
aspirin low dose + anticoagulant		aspirin: 0 days + time according to anticoagulant	laboratory test according to the anticoagulant.	- aspirin at low dose: patient's usual regimen. - combination anticoagulant: as directed for anticoagulants.
dual-channel agregant treatment		aspirin: 0 days + time according to the second antiaggregand	the weight of specific platelet function tests performed	- aspirin at low dose: patient's usual regimen. - combined antiaggregants: according to treatment guidelines (usually 24 h after surgery).

[a] VKA - vitamin K antagonist [b] CrCl - *creatinine clearance* [c] VTE - venous thromboembolism [d] MMH - low molecular weight heparin
[e] OSAK - direct oral anticoagulant [f] UFH - unfractionated heparin (*unfractionated heparin*)
* as of March 2022, not assigned in Estonia, technically possible to be implemented in PERH and TÜK laboratories.

Table 12

TREATMENT WITH ANTITHROMBOTIC DRUGS FOR LOW BLEEDING RISK BLOCKS (SUPERFICIAL NERVE BLOCKS).			
Medication and dose	**Time since last medicine before blockade**	**Laboratory target for the blockade**	**Time to first medicine after the blockade**
- dabigatraan - direct Xa inhibitors - [MMHa] at low dose: ≤ 50TU anti-Xa/kg/day - enoxaparin ≤ 40mg/day - [FHb] at low dose: ≤ 200fu/kg/day s/c ≤ 100TU/kg/day i/v - fundapariinuks low dose - aspirin ≤ 200mg/day	0 days	not tested (weight specific tests if there is a risk of anticoagulant accumulation, for example in the case of kidney failure).	following the patient's usual pattern
- [VKAc] - MMH high dose - FH high dose - aspirin in high dose - P2Y12 inhibitors - drug combinations	0 days (if medicine in or below therapeutic range)		

[a] MMH - low-molecular-weight heparin [b] FH - *unfractionated he*parin [c] VKA - vitamin K antagonist

Table 13

DISTRIBUTION OF NERVE BLOCKS		
	neuraxial blocks/deep nerve blocks	**superficial nerve blocks**
general principles	Bleeding from a blockage is significant and can have very serious consequences. Treatment of haemorrhage is complex because the bleeding site may not be compressible and may require invasive treatment. Clinical significance: antithrombotic therapy should be discontinued according to Table 11.	A superficial haematoma develops from the blockage, which is not of very serious clinical significance. Treatment of haemorrhage is straightforward (mostly local compression), with little need for invasive treatment. Clinical significance: discontinuation of antithrombotic therapy may not be necessary (see Table 12).
examples:		
head, neck	- *ganglion stellatum* blockade - deep occipital nerve blockage	- kuklablokaad - peribulbar blockade - superficial blockade of the carotid artery
from	- infraclavicular block of the shoulder joint	- shoulder joint interscalene blockage - shoulder supraclavicular blockade - axillary block of the shoulder joint - *n.suprascapularis* blockade - nerve blocks in the forearm or wrist area
beef cattle	- epidural block - thoracic paravertebral blockade	- parasternal intercostal block (deep and superficial) - *serratus anterior* block (deep and superficial) - *erector spinae* blockade - intercostal block - PECS blockade
stomach, pelvis		- *n.ilioingvinalis* and *n.hypogastric* blocks - TAP blockade - *rectus sheath* blockade - *n.genitofemoral* blockade - blockade of *n.pudendal*
leg, spine	- lumbar puncture block - paravertebral nerve block in the lumbar region - *quadratus lumborum* blockade - cross-clamp blockade - pericapsular nerve group (PENG) blockade - trans- and subgluteal blockade of *n. ischiadicus* - spinal anaesthesia - epidural block	- *femoral n.* blockade - *fascia iliaca* blockade - blocks of the lateral cutaneous nerve of the *femoral* nerve - *adductor* channel bl0kaad - blockade of the *sciatic nerve in the* knee region - nerve blocks in the foot area

Table 14

OSAK dooside				
	Rivaroksabaan	**Apiksabaan**	**Edoksabaan**	**Dabigatraan**
Prophylaxis of venous thromboembolism after major orthopaedic surgery (hip or knee endoprostheses) → low doses				
doos	10mg x 1 per day	2.5mg x 2 per day	not used	220mg x 1 per day
dose adjustment	no	no		150mg x 1, if: - CrCl 30-50ml/min or - age ≥ 75, or - concomitant use of verapamil, amiodarone or quinidine.
Prophylaxis of stroke with nonvalvular atrial fibrillation → high doses				
doos	20mg x1 per day	5mg x 2 per day	60mg x 1 per day	150mg x 2 per day
dose adjustment	15mg x 1 per day if - CrCl 15-50ml/min	2.5mg x 2 per day if 2 of the following criteria are met: - age ≥ 80 - weight ≤ 60kg - creatinine ≥ 133 µmol/L If CrCl 15-29ml/min, then dose also 2.5mg x 2.	30mg x 1 per day if: - CrCl 15-50ml/min - weight ≤ 60kg - concomitant use of cyclosporine, dronedarone, erythromycin or ketoconazole.	110mg x 2 per day if age ≥ 80 or concomitant with verapamil. 110mg or 150mg x 2 per day if CrCl 30-50ml/min or age 75-80.
Treatment of acute venous thrombosis → high doses				
doos	15mg x 2 per day for 3 weeks, then 20mg x 1 per day for 3 weeks.	10mg x 2 per day for 7 days, then 5mg x 2 per day for 7 days.	60mg x 1 per day	150g x 1 per day
dose adjustment	15mg x 2 per day for 3 weeks, then 15mg x 1 per day if CrCl 15-50ml/min.	no dose adjustment	30mg x 1 per day if: - CrCl 15-50ml/min - weight ≤ 60kg - concomitant use of cyclosporine, dronedarone, erythromycin or ketoconazole.	110mg x 2 per day if age ≥ 80 or concomitant with verapamil. 110mg or 150mg x 2 per day if CrCl 30-50ml/min or age 75-80.
Prophylaxis of prolonged recurrent deep vein thrombosis or pulmonary embolism → low doses				
doos	10mg x 1 per day or 20mg x 1 per day	2.5mg x 2 per day		
dose adjustment	If CrCl 15-50ml/min, then: - 10mg x 1 per day no adjustment - 20mg x1 instead of 15mg x1 weight per day	no		
Acute coronary syndrome → low doses				
doos	2.5mg x 2 per day	not used	not used	not used
Prophylaxis of atherothrombotic events in symptomatic patients with peripheral artery disease → low doses				
doos	2.5mg x 2 per day	not used	not used	not used

OSAK - direct oral anticoagulant; CrCl - *creatinine clearance*.

B.I.

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ITALIAN Originals

REGIONE TOSCANA
Giunta Regionale

DIREZIONE
SANITA', WELFARE E COESIONE SOCIALE

SETTORE ASSISTENZA FARMACEUTICA E DISPOSITIVI

Dirigente responsabile: **Claudio Marinai**
claudio.marinai@regione.toscana.it

Oggetto: Interruzione disponibilità della specialità medicinale ONDEXXYA.

Direzioni Generali
delle Asl e AOU della Toscana
Direttore Generale ESTAR
Direttore della Fondazione Monasterio

e p.c. Direttore della Direzione Sanità, Welfare e Coesione Sociale
Dr. Federico Gelli

Responsabile Settore Assistenza Ospedaliera, Qualità e Reti Cliniche
Dr.ssa Michela Maielli

PEC

In seguito alla precedente Circolare di questo Settore (AOOGRT/PD prot. n. 0250545 del 31/05/2023) con la quale si faceva cessare la disponibilità del farmaco ONDEXXYA, di concerto con l'OTGC è stata rilevato un bisogno clinico non coperto in modo adeguato dalle terapie proposte da Aifa con Circolare 20012/2023 e già disponibili (fattori palsmatici PCC 4).

Per garantire ai Cittadini della Toscana tutte terapie necessarie, anche se queste comprendono l'impiego di un farmaco, come ricordato nella predetta Circolare, che attualmente non a carico del SSN, il Settore scrivente, e l'OTGC hanno elaborato la procedura in allegato. Tale procedura inquadra l'impiego del farmaco ONDEXXYA alla sola casistica non coperta dalle terapie già disponibili.

Il rispetto delle indicazioni della procedura in allegato è di fondamentale importanza per la prescrizione del farmaco ONDEXXYA in appropriatezza e pertanto se ne raccomanda il rispetto a tutti i professionisti coinvolti.

Nella procedura è previsto che nel percorso decisionale per l'impiego del farmaco ONDEXXYA è indicato l'impiego del seguente test:

codice Estar: 50395392 Descrizione: striscia reattiva per doacs – dipstick doasense REF 0001

Con la presente si raccomanda alle Aziende ed Enti in indirizzo, di rendere disponibile il diagnostico sopra indicato in tutte le Strutture di Emergenza Urgenza della Regione, unitamente allo specifico lettore.

Cordiali Saluti.

Il Direttore OTGC
Dr. Stefano Grifoni

Il Dirigente Responsabile
Dott. Claudio Marinai

Regione Toscana

Richiesta di andexanet alfa (Ondexxya®)

per l'inversione della terapia anticoagulante in caso di emorragie potenzialmente fatali o incontrollate

SST Servizio Sanitario della Toscana

All_____

Il sottoscritto Dr. _____recapito telefonico_____

SOD _____Centro di Costo_____

chiede la fornitura del farmaco andexanet alfa (Ondexxya®) 200 mg

indicato per pazienti adulti trattati con apixaban o rivaroxaban, quando è richiesta l'inversione della terapia anticoagulante a causa di emorragie potenzialmente fatali o incontrollate

per il paziente *(nome e cognome)*_____data di nascita _____

Criteri di Inclusione ed esclusione al trattamento	
○ Sanguinamento ATTIVO MANIFESTO in paziente in terapia con APIXABAN o RIVAROXABAN ○ NON per pretrattamento in chirurgia d'urgenza	
Selezionare almeno una condizione	
A □ Sanguinamento in sede critica *(selezionare l'opzione)*	○ CEREBRALE: intraparenchimale; subdurale; epidurale; subaracnoidea* ○ Altri a carico del SNC: intraoculare; spinali intra od extraassiali ○ EMOPERICARDIO con segni di tamponamento cardiaco ○ VIE AEREE (incluso epistassi posteriore), EMOTORACE^ ○ INTRAADDOMINALE, RETROPERITONEALE^ **GCS>7 e/o vol.ematico >60 ml* *^solo SE CON B e/o C*
B □ Instabilità emodinamica *(selezionare l'opzione)*	○ PA Sistolica < 90 mmHg o riduzione dei valori di PA Sistolica > 40 mmHg ○ Shock index (FC/PA) ≥ 0.9 ○ Lattati > 4 mmol/L ○ Urina < 0,5 ml/Kg/min
C □ Riduzione Hb≥2 g/dl o trasfusione di ≥2 unità	Se nota, specificare sede sanguinamento:
DOSAGGIO NAO *(selezionare l'opzione ed allegare referto al presente documento)*	○ Plasmatico: ≥30 ng/ml ○ Urinario (POCT): POSITIVO

Dosi per l'inversione di apixaban/rivaroxaban			
Inibitore del FXa	**Ultima dose**	**Tempo dall'ultima dose prima dell'inizio di Ondexxya**	
		< 8 ore	**≥ 8 ore**
apixaban/ rivaroxaban	≤ 5 mg apixaban/10 mg rivaroxaban	Dose bassa (5 flaconcini)	Dose bassa (5 flaconcini)
	> 5 mg apixaban/10 mg rivaroxaban	Dose elevata (9 flaconcini)	

Posologia prescritta		
N°flaconcini da 200 mg	Bolo endovenoso iniziale	Infusione EV
○ 5	400 mg a una velocità target di 30 mg/min	4 mg/min per 120 minuti (480 mg)
○ 9	800 mg a una velocità target di 30 mg/min	8 mg/min per 120 minuti (960 mg)

Regione Toscana

Richiesta di andexanet alfa (Ondexxya®)

per l'inversione della terapia anticoagulante in caso di emorragie potenzialmente fatali o incontrollate

Servizio Sanitario della Toscana

All_____

Data _____ TIMBRO E FIRMA DEL MEDICO RICHIEDENTE

_____

Indicazioni all'utilizzo di Andexanet alfa

SOMMARIO

1 SCOPO

Lo scopo del seguente lavoro è delineare una guida all'utilizzo del farmaco andexanet alfa (Ondexxya®) in Regione Toscana. Andexanet alfa (Ondexxya®), polvere per soluzione per infusione, è un derivato ricombinante modificato del fattore Xa (FXa) prodotto attraverso la tecnologia del DNA ricombinante in cellule ovariche di criceto cinese (Chinese Hamster Ovary, CHO).

2 CAMPO DI APPLICAZIONE

La procedura viene applicata nell'ambito del Dipartimento di Emergenza per ottenere un effetto *reverse* nei pazienti in terapia con apixaban e rivaroxaban che presentino una emorragia potenzialmente fatale o in sede critica (vedi figura 1).

3 RIFERIMENTI

- *RCP*
- *Determina Aifa di classificazione del farmaco ai fini della rimborsabilità*
- *Determina Aifa n. 20012/2023 inserimento di PROPLEX nell'elenco dei medicinali erogabili a totale carico del SSN*
- *Nota informativa importante concordata con le autorità regolatorie europee e l'Agenzia Italiana del Farmaco (AIFA)*
- *Steffel J, Collins R, Antz M, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. 2021 Oct 9;23(10):1612-1676. doi: 10.1093/europace/euab065. Erratum in: Europace. 2021 Jun 28;: PMID: 33895845.*
- *Tomaselli G, Mahaffey K, Cuker A, et al. 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. J Am Coll Cardiol. 2020 Aug, 76 (5) 594–622.*
- *Rossaint et al. Critical Care (2023) 27:80. The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition*
- *Cao D. et al. ESC. Reversal and removal of oral antithrombotic drugs in patients with active or perceived imminent bleeding. European Heart Journal (2023) 00, 1–15*

4 MECCANISMO D'AZIONE

Andexanet alfa è una forma ricombinante della proteina denominata FXa umana, che è stata modificata e privata dell'attività enzimatica del FXa. La serina del sito attivo è stata sostituita con alanina, per rendere la molecola incapace di clivare e attivare la protrombina, e il dominio dell'acido gamma-carbossiglutammico (Gla) è stato rimosso, per privare la proteina della capacità di assemblaggio nel complesso della protrombinasi, eliminando quindi qualsiasi effetto anticoagulante.

Andexanet alfa è un agente d'inversione specifico per gli inibitori di FXa. Il principale meccanismo d'azione è il legame ed il sequestro dell'inibitore di FXa. Inoltre, è stato osservato che andexanet

alfa si lega a TFPI e lo inibisce. L'inibizione dell'attività del TFPI può aumentare la generazione di trombina avviata dal fattore tissutale, inducendo un effetto procoagulante.
Gli effetti di andexanet alfa possono essere misurati mediante marcatori farmacodinamici, tra cui la frazione libera di inibitore di FXa disponibile, e mediante il ripristino della generazione di trombina. I saggi per la determinazione dell'attività anti-FXa disponibili sul mercato non sono adatti per la misura dell'attività anti-FXa dopo la somministrazione di andexanet alfa. A causa del legame reversibile di andexanet alfa all'inibitore di FXa, l'alta diluizione del campione attualmente utilizzata in questi saggi dà luogo alla dissociazione dell'inibitore da andexanet alfa, producendo la rilevazione di livelli di attività anti-FXa erroneamente elevati e determinando pertanto una sostanziale sottostima dell'attività di inversione di andexanet alfa. In studi di determinazione della dose prospettici, randomizzati, controllati verso placebo, condotti in soggetti sani, sono stati determinati la dose e il regime posologico di andexanet alfa necessari per invertire l'attività anti-FXa e ripristinare la generazione di trombina per gli inibitori di FXa (apixaban o rivaroxaban) utilizzando saggi modificati non disponibili sul mercato.
La massima inversione dell'attività anti-FXa è stata ottenuta entro due minuti dal completamento della somministrazione in bolo. La somministrazione di andexanet alfa in bolo seguito da un'infusione continua ha portato ad una riduzione prolungata dell'attività anti-FXa. L'attività anti-FXa è ritornata ai livelli placebo e oltre, due ore circa dopo il termine del bolo o dell'infusione, a seconda della posologia. Quando andexanet alfa è stato somministrato in bolo seguito da un'infusione continua, la riduzione massima degli inibitori di FXa non legati è stata rapida (entro due minuti dal termine del bolo), si è mantenuta durante l'infusione ed è quindi gradualmente aumentata con il tempo, raggiungendo un massimo a circa due ore dal termine dell'infusione. Il ripristino della generazione di trombina dopo la somministrazione è stato dipendente dalla dose e dal regime posologico e non correlato all'attività anti-FXa oltre le quattro ore circa (vedi sezione "ripristino della generazione di trombina"). Si è dimostrato che l'attività del TFPI plasmatico è stata completamente inibita da 2 minuti a 14,5 ore dopo la somministrazione in bolo di andexanet alfa ed è ritornata al valore basale entro 3 giorni. La generazione di trombina avviata dal fattore tissutale (TF) è salita immediatamente al di sopra del valore basale (prima dell'anticoagulazione) ed è rimasta elevata per > 20 ore, rispetto al placebo. La plausibilità di un effetto pro-coagulante dell'inibizione del TFPI è supportata da aumenti consecutivi e sostenuti di D-dimeri, TAT ed F1+2.
Gli studi su andexanet alfa in presenza di inibitori diretti di FXa in soggetti sani hanno dimostrato una farmacocinetica proporzionale alla dose nell'intervallo previsto di dosi terapeutiche sia per Cmax, sia per l'area sotto la curva (AUC). Gli inibitori di FXa non hanno alterato la farmacocinetica di andexanet alfa a livelli terapeutici.

5 INDICAZIONI TERAPEUTICHE

Per pazienti adulti trattati con un inibitore diretto del fattore Xa (FXa) (solo **apixaban** o **rivaroxaban**), quando è richiesta l'inversione della terapia anticoagulante a causa di emorragie potenzialmente fatali o incontrollate.

Tuttavia, la non rimborsabilità del farmaco a carico del SSN ed i dati di letteratura a disposizione al momento della stesura di questo protocollo ne impongono l'utilizzo in una casistica estremamente selezionata.

La possibilità di utilizzo di andexanet alfa deve essere valutata seguendo un algoritmo che prevede tre passaggi (***vedi figura 1***) in sequenza:

1. **Criteri di inclusione ed esclusione**

La somministrazione di Andexanet-alfa è possibile **ESCLUSIVAMENTE** per i pazienti in terapia anticoagulante orale con APIXABAN o RIVAROXABAN. Non è prescrivibile per i pazienti in terapia con Edoxaban. Il trattamento delle emergenze emorragiche nei pazienti in edoxaban prevede, come unica opzione terapeutica, la somministrazione dei PCC (concentrati del complesso protrombinico) al dosaggio di 50 U/kg. Inoltre, l'uso di andexanet -alfa NON è possibile (per attuale mancanza di dati in questo setting clinico) per i pazienti in terapia con inibitori del fattore Xa che debbano essere sottoposti a chirurgia in urgenza.

2. **Tipo di Sanguinamento**

Sono da considerare elegibili i pazienti con sanguinamento attivo manifesto ed almeno una delle tre condizioni cliniche sotto riportate:

A) pazienti con **sanguinamenti in sede critica**: CEREBRALE (intraparenchimale, subdurale; epidurale; subaracnoidea; intraoculare; spinale intra od extraassiale; EMOPERICARDIO con segni di tamponamento cardiaco; vie AEREE ed EMOTORACE; INTRAADDOMINALE, RETROPERITONEALE.

- *a livello CEREBRALE se GCS>7 e/o volume ematico<60 ml*
- *a livello VIE AEREE ed EMOTORACE: SOLO se presente ANCHE punto B o C*

Il sanguinamento gastrointestinale intraluminale NON è considerato in sede critica o a rischio di vita, a meno che non ci siano segni di instabilità emodinamica.

A) Pazienti con **instabilità emodinamica**. Un aumento della frequenza cardiaca può essere il primo segno di instabilità emodinamica dovuta alla perdita di sangue. Inoltre, una pressione arteriosa (PA) sistolica <90 mmHg, una diminuzione della pressione arteriosa sistolica >40 mmHg o variazioni della pressione ortostatica (caduta della pressione arteriosa sistolica ≥20 mmHg o caduta della pressione arteriosa diastolica ≥10 mmHg in posizione eretta) può indicare instabilità emodinamica. Lo shock index (FC/PA sistolica) ≥0.9 e la pressione

arteriosa differenziale <40/<30 mmHg sono indici affidabili del grado di instabilità emodinamica e della necessità di emotrasfusioni, così come marcatori surrogati per la perfusione d'organo, quali il livello di lattato ematico, lo stato ecografico di riempimento della vena cava, la produzione di urina <0,5 ml/kg/h). Quando praticabile, la misurazione invasiva continua della pressione arteriosa media è considerata superiore alla misurazione periferica e un valore <65 mmHg funge da cut-off per l'instabilità emodinamica.

B) **Sanguinamento manifesto ed attivo con calo di emoglobina ≥2 g/dl o somministrazione di ≥2 unità di globuli rossi concentrati**. Gli eventi emorragici che causano un calo dell'emoglobina ≥2 g/dL o che richiedono una trasfusione di ≥2 unità di globuli rossi sono stati associati a un rischio di mortalità significativamente aumentato. L'ematuria e l'epistassi posteriore associate ad anemizzazione con necessita di emotrasfusione possono trovare un iniziale trattamento di emostasi meccanica e/o endoscopica, se non sussiste una instabilità emodinamica.

3. Dosaggio Apixaban/Rivaroxaban

Come riportato nel paragrafo "Meccanismo di azione", andexanet-alfa esercita un'azione di antidoto poiché si lega al Fxa in sostituzione del farmaco anticoagulante circolante. Per questo, l'eventuale assenza–di attività anticoagulante del farmaco (definita come attività antiXa sotto la soglia di 30 ng/ml) non rende ragionevole l'azione dell'antidoto (almeno in un contesto di necessaria selezione della casistica, ed in assenza di attuale dimostrazione contraria).

Pertanto la verifica di questa attività è obbligatoria per la somministrazione del farmaco ed in ogni caso deve accompagnare la prescrizione stessa.

La metodica di riferimento per determinare l'attività antiXa del farmaco anticoagulante è rappresentata dal dosaggio plasmatico.

Tuttavia, il dosaggio plasmatico:

- Richiede tempi di esecuzione spesso non compatibili con il regime di emergenza/urgenza
- Non è disponibile nei laboratori di tutti i presidi ospedalieri
- Anche quando disponibile, non tutti i laboratori offrono l'analisi h24

Per questo, è utile considerare – in contesti di emergenza/urgenza in cui è necessaria una risposta più tempestiva possibile – il dosaggio POCT urinario che offre la possibilità di conoscere in pochi minuti: - tipo di DOAC assunto; - una risposta semiquantitativa con valore POSITIVO o NEGATIVO equivalente ad una concentrazione ≥ o < 30 ng/ml.

Il medico che ha in cura il paziente con evento emorragico in corso di DOAC deve valutare:

- il farmaco anticoagulante assunto con il dosaggio abitualmente prescritto
- l'orario dell'ultima assunzione nota

- o l'impossibilità ad ottenere le informazioni sul dosaggio e la tempistica dell'assunzione
- eventuali concomitanti terapie ad impatto sul rischio di sanguinamento: FANS; antiaggreganti; farmaci 'da banco' che non richiedono prescrizione medica
- prelievo di sangue per: emocromo; funzione renale ed epatica; PT, aPTT e fibrinogeno (profilo emorragia predisposto nell'applicativo FA web).

Se esiste il dubbio di una mancata assunzione, o esistono incertezze sul tipo di farmaco assunto, è indicato il ricorso al dosaggio plasmatico del DOAC, se questo è disponibile. In alternativa, è possibile utilizzare dispositivi di misurazione semiquantitativa point-of-care su urine.
Se l'assunzione del DOAC risale a meno di 2-4 ore, si raccomanda la somministrazione di 50 gr di carbone attivato per os (a meno di controindicazioni e se il paziente è stabile clinicamente).

In tutti i casi in cui l'algoritmo si interrompe, è indicata la somministrazione dei PCC (concentrati del complesso protrombinico)a 4 fattori al dosaggio di 50 U/kg.

Si ricorda infatti che AIFA ha autorizzato la rimborsabilità a carico del SSN dei concentrati del complesso protrombinico a 4 fattori (Proplex) con le medesime indicazioni di Andexanet-alfa.
I PCC4 RAPPRESENTANO PERTANTO UNA ALTERNATIVA AD ANDEXANET ALFA PER LE SEGUENTI INDICAZIONI:

- trattamento di pazienti adulti trattati con anticoagulanti orali inibitori diretti del fattore Xa (**apixaban**, **edoxaban**, **rivaroxaban**) nei casi in cui si renda necessaria l'inattivazione rapida dell'effetto anticoagulante:
- **interventi chirurgici o manovre invasive ad alto rischio di sanguinamento da eseguire in urgenza, con tempistiche non compatibili con la sola sospensione dell'anticoagulante**;

sanguinamento potenzialmente fatale o non controllato.

USO DI ANDEXANET ALFA IN ASSOCIAZIONE CON ALTRE MISURE DI SUPPORTO

La sicurezza di andexanet alfa non è stata valutata in pazienti che ricevevano concentrati di complesso protrombinico, fattore VIIa ricombinante o sangue intero nei sette giorni precedenti l'evento emorragico, perché sono stati esclusi dagli studi clinici. Il trattamento con fattori procoagulanti (ad es., complesso protrombinico concentrato (prothrombin complex concentrate, PCC) a 3 o 4 fattori/PCC attivato, fattore VIIa ricombinante, plasma fresco congelato) e sangue intero deve essere evitato a meno che non sia assolutamente necessario, a causa della mancanza di dati in associazione con questi trattamenti.

Dopo ogni utilizzo, la Farmacia richiederà la documentazione del paziente per la valutazione clinica degli esiti della terapia.

FIGURA 1


1.
IL PAZIENTE E' IN TERAPIA CON APIXABAN o RIVAROXABAN?
NO
STOP
SI
E' PREVISTA CHIRURGIA IN URGENZA?
SI
STOP
NO
Vai al punto 2.
2. Sanguinamento attivo manifesto
A
SANGUINAMENTO IN SEDE CRITICA
B
INSTABILITA' EMODINAMICA
C
Riduzione Hb≥2 g/dl o trasfusione di ≥2 unità
CEREBRALE ^: intraparenchimale; subdurale; epidurale; subaracnoidea
Altri a carico del SNC: intraoculare; spinali intra od extraassiali
EMOPERICARDIO con segni di tamponamento cardiaco
VIE AEREE* (incluso epistassi posteriore)
EMOTORACE*
INTRAADDOMINALE, RETROPERITONEALE
^= se GCS>7 e/o vol. ematico<60 ml
*= solo se CON punto B e/o C
Pressione Sistolica <90 mmHg
o
Riduzione dei valori di Sistolica >40 mmHg
Shock-index (FC/PA sistolica) ≥0.9
Lattati > 4 mmol/L
Urina <0,5 ml/kg/h
Se nota, specificare sede sanguinamento:
E' PRESENTE ALMENO UNA CONDIZIONE ?
SI
NO
STOP
Vai al punto 3.
3.
DOSAGGIO NAO
Plasmatico (se disponibile): ≥ 30 ng/ml
Oppure Urinario (POCT): POSITIVO
SI
ANDEXANET ALFA
NO
STOP

6 POSOLOGIA E MODO DI SOMMINISTRAZONE

Ogni flaconcino contiene 200mg di andexanet alfa; dopo ricostituzione, ogni mL di soluzione contiene 10 mg di andexanet alfa.

Andexanet alfa viene somministrato sotto forma di bolo endovenoso a una velocità target di circa 30 mg/min in 15 minuti (dose bassa) o 30 minuti (dose elevata), seguito da un'infusione continua di 4 mg/min (dose bassa) o 8 mg/min (dose elevata) per 120 minuti.

	Bolo endovenoso iniziale	**Infusione endovenosa continua**	**Numero totale di flaconcini da 200 mg necessari**
Dose bassa	400 mg a una velocità target di 30 mg/min	4 mg/min per 120 minuti (480 mg)	5
Dose elevata	800 mg a una velocità target di 30 mg/min	8 mg/min per 120 minuti (960 mg)	9

REVERSE DI APIXABAN

Il regime posologico raccomandato di andexanet alfa si basa sulla dose di apixaban somministrata al paziente al momento dell'inversione della terapia anticoagulante e sul tempo trascorso dall'ultima dose di apixaban.

Inibitore del FXa	**Ultima dose**	**Tempo dall'ultima dose prima dell'inizio di Ondexxya**	
		< 8 ore o non noto	≥ 8 ore
Apixaban	≤ 5 mg	Dose bassa	Dose bassa
	> 5 mg/non nota	Dose elevata	

REVERSE DI RIVAROXABAN

Il regime posologico raccomandato di andexanet alfa si basa sulla dose di rivaroxaban somministrata al paziente al momento dell'inversione della terapia anticoagulante e sul tempo trascorso dall'ultima dose di rivaroxaban.

Inibitore del FXa	**Ultima dose**	**Tempo dall'ultima dose prima dell'inizio di Ondexxya**	
		< 8 ore o non noto	≥ 8 ore

Rivaroxaban	≤ 10 mg	Dose bassa	Dose bassa
	>10 mg/non nota	Dose elevata	

INTERAZIONE CON EPARINA

L'uso di andexanet alfa prima dell'eparinizzazione, ad es. durante un intervento chirurgico, deve essere evitato, poiché andexanet induce refrattarietà all'eparina. L'uso di andexanet come antidoto per l'eparina o l'eparina a basso peso molecolare non è stato valutato e non è raccomandato.

7 ISTRUZIONI PER LA MANIPOLAZIONE

Ogni flaconcino va ricostituito secondo le seguenti istruzioni:

1. Rimuovere il cappuccio a scatto da ogni flaconcino.
2. Pulire il tappo in gomma di ogni flaconcino con un tampone imbevuto di alcool.
3. Prelevare 20 mL di acqua per preparazioni iniettabili utilizzando una siringa da 20 mL (o più) e un ago da 20 gauge (o più grande).
4. Introdurre l'ago della siringa al centro del tappo di gomma.
5. Premere lentamente lo stantuffo e iniettare i 20 mL di acqua per preparazioni iniettabili nel flaconcino, dirigendo il getto verso la parete interna del flaconcino per ridurre al minimo la formazione di schiuma.
6. Roteare delicatamente ogni flaconcino fino alla completa dissoluzione della polvere. NON AGITARE i flaconcini per evitare la formazione di schiuma. Il tempo di dissoluzione è di circa tre-cinque minuti per flaconcino.
7. Prima della somministrazione, controllare visivamente la soluzione ricostituita, per escludere la presenza di materiale corpuscolato e/o alterazioni di colore. Non usare in presenza di particelle opache o alterazioni del colore.
8. Per una ricostituzione efficace della dose necessaria e per ridurre al minimo gli errori, iniettare 20 mL di acqua per preparazioni iniettabili in ogni flaconcino prima di procedere alla fase successiva.
9. Se conservato a temperatura ambiente, usare entro otto ore dalla ricostituzione.

<u>Somministrazione mediante siringa temporizzata</u>

1. Dopo aver ricostituito tutti i flaconcini necessari, prelevare la soluzione da ognuno di essi utilizzando la siringa grande (50 mL o più) dotata di un ago da 20 gauge (o più grande).
2. Preparare il bolo e l'infusione in siringhe grandi separate.
3. A causa del maggiore volume, il bolo e l'infusione a dosi elevate devono essere suddivisi in ulteriori siringhe (due siringhe ciascuna per il bolo e l'infusione).

4. Per prevenire il trasferimento accidentale di aria, tenere l'ago della siringa rivolto verso l'alto e non deporre la siringa tra un prelievo e il successivo.
5. Prima della somministrazione, collegare gli accessori (ad es. tubi di estensione, filtro in linea in polietersulfone (PES) da 0,2 o 0,22 micron o un filtro equivalente a basso legame proteico, siringa temporizzata).
6. Somministrare la soluzione ricostituita alla velocità adeguata.
7. Smaltire tutte le siringhe, gli aghi e i flaconcini usati nonché i residui inutilizzati della soluzione ricostituita.

Somministrazione mediante sacche endovenose

1. Dopo aver ricostituito tutti i flaconcini necessari, prelevare la soluzione ricostituita da ognuno di essi utilizzando la siringa grande (50 mL o più) dotata di un ago da 20 gauge (o più grande).
2. Trasferire la soluzione ricostituita dalla siringa in un'apposita sacca e.v.
3. Ripetere i passaggi 1 e 2 per trasferire l'intero volume del bolo e dell'infusione in sacche e.v. in PO o PVC. 4. Si raccomanda di suddividere il bolo e l'infusione in due sacche separate per garantire una corretta velocità di somministrazione. È anche possibile utilizzare un'unica sacca e.v. in PO o PVC per il bolo e l'infusione, ma occorre garantire la velocità d'infusone corretta al momento del passaggio dal bolo all'infusione.
4. Prima della somministrazione, collegare gli accessori (ad es. tubi di estensione, filtro in linea in polietersulfone (PES) da 0,2 o 0,22 micron o un filtro equivalente a basso legame proteico, pompa e.v.).
5. Somministrare la soluzione ricostituita alla velocità adeguata. Smaltimento Tutte le siringhe, gli aghi e i flaconcini usati nonché i residui inutilizzati della soluzione ricostituita devono essere smaltiti in conformità alla normativa locale vigente.

Il medicinale non ricostituito deve essere conservato in frigorifero (2 °C – 8 °C).
Andexanet alfa non deve necessariamente essere portato a temperatura ambiente prima della ricostituzione o prima della somministrazione al paziente. Adottare tecniche di asepsi durante la procedura di ricostituzione.
La stabilità chimica e fisica del medicinale ricostituito è stata dimostrata per 16 ore a 2 °C – 8 °C nel flaconcino del confezionamento primario. Se necessario, la soluzione ricostituita trasferita nella sacca e.v. può essere conservata per altre otto ore a temperatura ambiente. Dal punto di vista microbiologico, il prodotto ricostituito deve essere usato immediatamente. Se non viene usato immediatamente, i tempi di conservazione durante l'uso e le condizioni di conservazione prima dell'uso ricadono sotto la responsabilità dell'utilizzatore.

8 EFFETTI INDESIDERATI

La sicurezza è stata valutata in studi clinici comprendenti 247 soggetti sani ai quali è stato somministrato un inibitore di FXa e 352 pazienti inclusi in uno studio di fase IIIb/IV (ANNEXA-4) affetti da emorragie acute maggiori e in trattamento con un inibitore di FXa (prevalentemente apixaban e rivaroxaban). Negli studi clinici con soggetti sani ai quali sono stati somministrati un inibitore di FXa e successivamente andexanet alfa, non sono state segnalate reazioni avverse gravi o severe.

Negli studi registrativi 14-503 e 14-504, il trattamento con andexanet alfa ha determinato un aumento statisticamente significativo della generazione di trombina nei soggetti sani sottoposti a terapia anticoagulante con apixaban o rivaroxaban vs. placebo. Nello studio 14-505 (ANNEXA-4), a braccio singolo condotto su pazienti affetti da emorragie acute maggiori e in trattamento con un inibitore di FXa (apixaban e rivaroxaban), l'11% dei pazienti trattati con andexanet alfa ha manifestato uno o più eventi tromboembolici. Il tempo mediano al primo evento tromboembolico è stato di dieci giorni; il 38% dei pazienti con eventi tromboembolici ha manifestato l'evento nei primi tre giorni.

È noto infatti che i pazienti in trattamento con un inibitore del FXa sono affetti da patologie di base che li predispongono agli eventi trombotici e l'inversione della terapia con un inibitore del FXa espone i pazienti al rischio trombotico legato alla patologia di base.

Inoltre, negli studi è stato dimostrato un effetto pro-coagulante indipendente di andexanet alfa, mediato dall'inibizione dell'inibitore della via del fattore tissutale (tissue factor pathway inhibitor, TFPI), che può costituire un rischio per lo sviluppo di trombosi. La durata di questo effetto nei pazienti emorragici non è nota.

B.II.

Document from the Estonian Society of Anesthesiology

ESTONIAN Original

Eesti Anestesioloogide Seltsi praktiline juhend[1]

ANTITROMBOOTILISED RAVIMID PLAANILISES JA ERAKORRALISES KIRURGIAS

Tänapäeval kasutatakse haigetel mitmeid erinevaid antitrombootilisi ravimeid paljudel näidustustel erinevates doosides. Eesti Anestesioloogide Seltsi praktiline juhend on kasutatav olukordades, kui neid ravimeid tarvitavad haiged satuvad plaaniliselt või erakorraliselt mõnele kirurgilisele protseduurile või operatsioonile või nendel haigetel esineb antitrombootiliste ravimite kasutamise tõttu eluohtlik veritsus.

Plaanilises kirurgias tuleb haige antitrombootilise raviskeemi katkestamisel ja/või jätkamisel arvestada patsiendipoolseid riskitegureid, kirurgilist veritsusriski ja kasutatavat anesteesia meetodit. **Erakorralistes olukordades** võib lisaks eelnevatele olla vajalik ka antitrombootiliste ravimite toime ümberpööramine või vähendamine.

1. Patsiendipoolsed tegurid:
   - vanus
   - insuldirisk
   - veritsusrisk
   - kardiovaskulaarne sündmus viimase 3 kuu jooksul
   - kaasuvad haigused, eriti neerupuudulikkus
   - tarvitatavad ravimid (sh. anti-trombootilised ravimid, MSPVAd)

2. Kirurgilised tegurid:
   - kirurgilise sekkumise veritsusrisk
   - veritsuse võimalik tagajärg (eriti neurokirurgia, kardiokirurgia, mahukas kõhu- ja torakaalkirurgia)
   - planeeritud anesteesia meetod (üld-, regionaal-, lokaalanesteesia)
   - eeldatav antitrombootilise ravi taasalustamine

Antitrombootilise ravi katkestamine enne plaanilist kirurgilist protseduuri või ravimi(te) toime ümberpööramine või vähendamine erakorralise veritsuse või kirurgilise sekkumise vajaduse korral.

[1] Eesti Anestesioloogide Selts praktiline juhend on koostatud erinevate rahvusvaheliste juhendite põhjal, mis on ära toodud kasutatud allikate nimekirjas.
Praktiline juhend on Eesti Haigekassa Transfusioonravi juhendi I osa lisa.
Koostanud Eesti Anestesioloogide Selts kevadel 2022. Küsimused ja ettepanekud: kerli.vijar@kliinikum.ee

SISUKORD

ANTITROMBOOTILISED RAVIMID, NENDE JAOTUS JA MÕJU HÜÜBIMISANALÜÜSIDELE

Tabel 1

Antitrombootiliste ravimimite jaotus

ANTIKOAGULANDID	**SUUKAUDSED ANTIKOAGULANDID**	**VKA***	varfariin (*Marevan®*)
		OSAK**	trombiini inhibiitorid: dabigatraan (*Pradaxa®*)
			Xa inhibiitorid: rivaroksabaan (*Xarelto®*), apiksabaan (*Eliquis®*), edoksabaan (*Lixiana®*)
	PARENTERAALSED ANTIKOAGULANDID	**otsesed**	argatrobaan (*Exembol®*)
		kaudsed	UFH***, MMH**** (enoksapariin - *Clexane®*, *Losmina®* jt; bemipariin - *Zibor®*), fondaparinuks (*Arixtra®*)
ANTIAGREGANDID	**SUUKAUDSED ANTIAGREGANDID**	**TxA_2 inhibiitor**	atsetüülsalitsüülhape (*Hjertemagnyl®*, *Thrombo* ASS® jt.)
		P2Y12 inhibiitorid	klopidogreel (*Clopidogrel®*, *Plavix®*, *Zyllt®*,*Trombex®* jpt.), tikagreloor (*Brilique®*), prasugreel (*Prasugrel®*, *Efient®*, *Eliskardia®*)
	PARENTERAALSED ANTIAGREGANDID	**GPIIb/IIIa inhibiitorid**	eptifibatiid (*Integrilin®*), tirofibaan (*Aggrastat®*)

* VKA – vitamiin K antagonist
** OSAK – otsene suukaudne antikoagulant
*** UFH – fraktsioneerimata hepariin (*ingl. k. unfractionated heparine*)
**** MMH – madalmolekulaarne hepariin

Antikoagulandid: toime hüübimis-süsteemi
• näidustatud venoossete trombide profülaktikaks ja raviks mitmete haiguste korral (kodade virvendusarütmia, süvaveenitromboos, KATE, mehaanilised klapiproteesid, liigeste endoproteesid jt.)

Antiagregandid: mõjutavad trombotsüütide agregatsiooni
• näidustatud arteriaalste trombide profülaktikaks ja raviks erinevate organite arterites (koronaararterid, tserebrovaskulaararterid, karotiidarterid, neeruarterid, perifeersed arterid jt.)

Tabel 2

Antitrombootiliste ravimite mõju hüübimisanalüüsidele

ravim / analüüs	dabigatraan	rivaroksabaan, apiksabaan, edoksabaan	varfariin	UFH	LMWH, fondaparii-nuks	aspiriin	P2Y12 inhibiitorid
APTT*	↑/N	↑/N	↑/N	↑	↑/N	X	X
TT	↑	X	X	↑	↑/N	X	X
anti-FXa**	X	↑	X	↑	↑	X	X
anti-FIIa**	↑	X	X	X	X	X	X
PT-INR	↑/N	↑/N	↑	X***	X***	X	X
ACT	↑/N	↑/N	↑/N	↑	↑/N	X	X
B-Agr-ASPI	X	X	X	X	X	↓	X
B-Agr-ADP	X	X	X	X	X	X	↓
PFA-Col/Epi	X	X	X	X	X	↑	↑/N
PFA-Col/ADP	X	X	X	X	X	N	↑/N
PFA-P2Y12	X	X	X	X	X	X	↑
tromboelasto-meetrilised uuringud****	√	√	√	√	√	X	X

* Referentspiires APTT ja PT-INR tulemused ei välista dabigatraani, rivaroksabaani, apiksabaani ja edoksabaani olulist sisaldust plasmas. Samas võivad APTT ja PT-INR tulemused jääda ka referentsväärtuste piiresse.
** Igale ravimile on eraldi anti-FXa või anti-FIIa uuring, mille põhjal arvutatakse välja ravimi kontsentratsioon (PERHis 24/7, TÜKis 24/7, ITKs tööpäeviti)
*** Enamus PT-INR määramise reaktiive ei ole tundlikud hepariini sisaldusele < 1 kU/L ja madalmolekulaarse hepariini sisaldusele < 1,5 kU/L; kõrgemad hepariinide sisaldused võivad pikendada ka PT aega.
**** Mõju sõltub määratavast parameetrist ning kasutatavast seadmest.

KIRURGILISTE SEKKUMISTE VERITSUSRISKID

Tabel 3

Plaaniliste kirurgiliste sekkumiste veritsusriskid*

* iga haige puhul tuleb kaaluda tema individuaalseid veritsuse ja trombemboolilise tüsistuste riske ning arutada neid opereeriva kirurgi ja patsiendiga

Minimaalse riskiga sekkumised (harvad ja kliiniliselt ebaolulised veritsused):

- hamba ekstraktsioon (1-3 hammast), parodontaalkirurgia, implantaatide paigaldamine, igemete puhastamine
- katarakti ja glaukoomi operatsioonid
- endoskoopia ilma biopsia võtmiseta või resektsioonita
- pindmised operatsioonid (abstsesside avamised, nahabiopsiad, väikesed dermatoloogilised operatsioonid)
- stimulaatori või ICD paigaldamine (v.a. keerulised juhtumid)
- elektrofüsioloogilised uuringud, kateeterablatsioonid (v.a. keerulised juhtumid)
- plaaniline rutiinne koronaar- või perifeersete arterite angiograafia (v.a. keerulised juhtumid)
- lihasesisesed süstid (nt. vaktsineerimised)

Madala riskiga sekkumised (harvad või kliiniliselt mittetõsised veritsused):

- keerulised hambaraviprotseduurid
- endoskoopia lihtsa biopsia võtmisega
- väikesed ortopeedilised operatsioonid (labajalg, käsi, artroskoopia…)

Kõrge riskiga sekkumised (sagedased ja/või kliiniliselt olulised veritsused):

- kardiokirurgia
- perifeersete arterite revaskulariseeriv kirurgia (nt. aordi aneurüsmi operatsioon, vaskulaarsed šunteerivad operatsioonid)
- keerulised/kompleksed invasiivsed kardioloogilised interventsioonid, stimulaatori juhtme eemaldamine südamest, (epikardiaalne) VT ablatsioon, kroonilise oklusiooni PKI, jne
- neurokirurgia
- spinaal- või epiduraalanesteesia, diagnostiline lumbaalpunktsioon
- kompleksne endoskoopia (nt. mitmed/suured polüpektoomiad, ERCP koos sfinkterskoopiaga jne.)
- abdominaalkirurgia (k.a. maksabiopsia)
- torakaalkirurgia
- suur uroloogiline operatsioon või biopsia (k.a. neer)
- kehaväline lööklainega kivipurustus
- suur ortopeediline kirurgia

Tabel 4

Veritsused kriitilistes kohtades

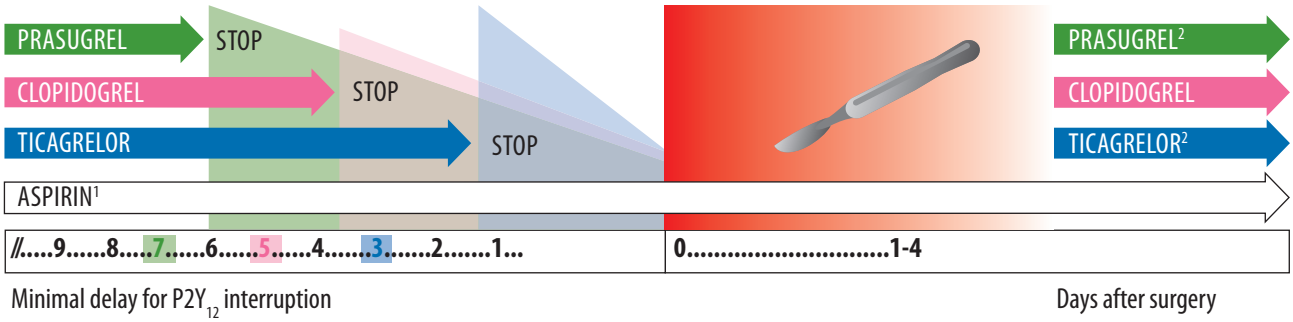
VERITSUSE TÜÜP	ESIALGNE SÜMPTOM	VERITSUSE TÕENÄOLINE TAGAJÄRG
Intrakraniaalne veritsus: intraparenhümaalne, subduraalne, epiduraalne, subarahnoidaalne	**Neuroloogilised:** teadvushäire, nägemishäired, tundetus, nõrkus, afaasia, ataksia, vertiigo, krambid **Harva tugev peavalu, oksendamine**	Stuupor või kooma Püsiv neuroloogiline defitsiit Surm
Muu KNS veritsus: silmasisene, sub- või epiduraalsed spinaalhematoomid	**Silmasisene:** ühe silma valu, nägemishäired, pimedus **Spinaalsed:** seljavalu, kahepoolne jäsemete nõrkus või tundetus, seedesüsteemi või põie düsfunktsioon, hingamishäired	**Silmasisene:** püsiv nägemiskaotus **Spinaalsed:** püsiv puue, parapleegia, kvardipleegia, surm
Perikardi tamponaad	Õhupuudus, tahhüpnoe Hüpotensioon, jugulaarveeni täitumine Tahhükardia, summutatud südametoonid, hõõrdumiskahin	Kardiogeenne šokk Surm
Hingamisteed, k.a. tagumine ninaverejooks	**Hingamisteed:** veriköha, õhupuudus, hüpoksia **Tagumine ninaverejooks:** profuusne verejooks, veriköha, hüpoksia, õhupuudus	Hüpokseemiline hingamispuudulikkus Surm
Hemotooraks, kõhusisene verejooks, retroperitoneaalne verejooks	**Hemotooraks:** tahhüpnoe, tahhükardia, hüpotensioon **Kõhusisene (mitte gastrointestinaalne):** kõhuvalu, esilevõlvumus, hüpotensioon, tahhükardia **Retroperitoneaalne verejooks:** selja-/külje-/puusavalu, tahhükardia, hüpotensioon	**Hemotooraks:** hingamispuudulikkus **Retroperitoneaalne verejooks:** femoraalnärvi kahjustus **Kõikide puhul:** hüpovoleemiline šokk, surm
Jäsemete veritsus, s.h. lihasesisesed ja liigesesisesed veritsused	**Lihasesisesed:** valu, paistetus, kahvatus, paresteesiad, nõrkus, nõrgenenud pulsid **Liigesesisesed:** liigesvalu, paistetus, vähenenud liikumisulatus	**Lihasesisesed:** kompartmentsündroom, paralüüs, jäseme kaotus **Liigesesisesed:** pöördumatu liigeskahjustus

Tabel 5

Antiagregantravi katkestamine plaanilises kirurgias

RAVIM	TOIMEAEG	KATKESTAMINE ENNE MADALA JA KESKMISE VERITSUSRISKIGA OPERATSIOONI	KATKESTAMINE ENNE KÕRGE VERITSUSRISKIGA OPERATSIOONI
atsetüülsalitsüülhape	5-7 päeva	ei ole vajalik	3 päeva enne
MSPVA*	sõltuvalt ravimist	ei ole vajalik	1-3 päeva enne
klopidogreel	7-10 päeva	5 päeva enne	7 päeva enne
prasugreel	~10 päeva	7 päeva enne	10 päeva enne
tikagreloor	~7 päeva	3 päeva enne	5 päeva enne

* MSPVA – mittesteroidne põletikuvastane aine



= Expected aaverage platelet function recovery

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1 Decision to stop aspirin throughout surgery should made on a single case basis taking into account the surgical bleeding risk.
2 In patients not requiring OAC.

Tabel 6

Antiagregantravi soovitused plaanilisele mitte-kardiokirurgilisele operatsioonile mineval haigel

	SOOVITUSE KLASS	TÕENDUSPÕHISUS
Atsetüülsalitsüülhappe kasutamist on soovitav võimalusel jätkata kogu perioperatiivses perioodis. Soovituslikku antiagregantravi tuleks postoperatiivselt taasalustada esimesel võimalusel.	I	B
Kui plaaniline kirurgia eeldab P2Y12 inhibiitori lõpetamist, kuid võimaldab jätkata atsetüülsalitsüülhappega, võib operatsiooni teostamist kaaluda 1 kuu peale stentimist.	IIA	B
Tikagreloor tuleb lõpetada vähemalt 3 päeva, klopidogreel vähemalt 5 päeva ja prasugreel vähemalt 7 päeva enne operatsioon.	IIA	B
Topeltantiagregantravi kasutava patsiendi preoperatiivseks hindamiseks võib kaaluda multidistsiplinaarse ekspertide meeskonna kaasamist.	IIA	C
Kui topeltantiagregantravi näidustuseks on hiljutine infarkt või mõni muu kõrge isheemilise riskiga seisund, tuleb plaanilise kirurgiaga oodata 6 kuud.	IIB	C
Kui kirurgia nõuab mõlema antiagregandi lõpetamist, võib kaaluda sildamist i/v antiagregandiga. Seda eriti juhul, kui operatsioon toimub vähem kui 1 kuu peale stentimist.	IIB	C
Plaanilise kirurgia korral ei ole soovitav topeltagregantravi lõpetada esimese kuu jooksul peale stentimist.	III	B

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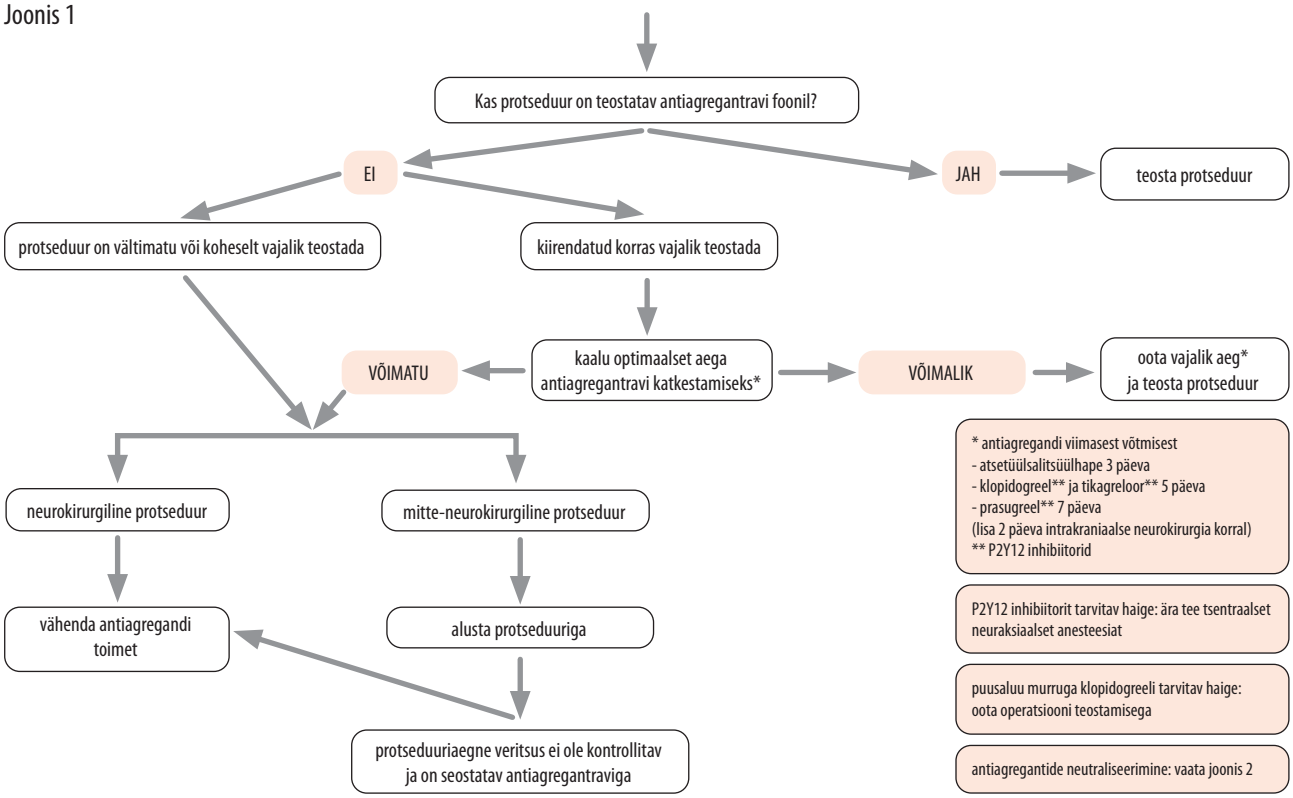
ERAKORRALINE OPERATSIOON JA ANTIAGREGANDID

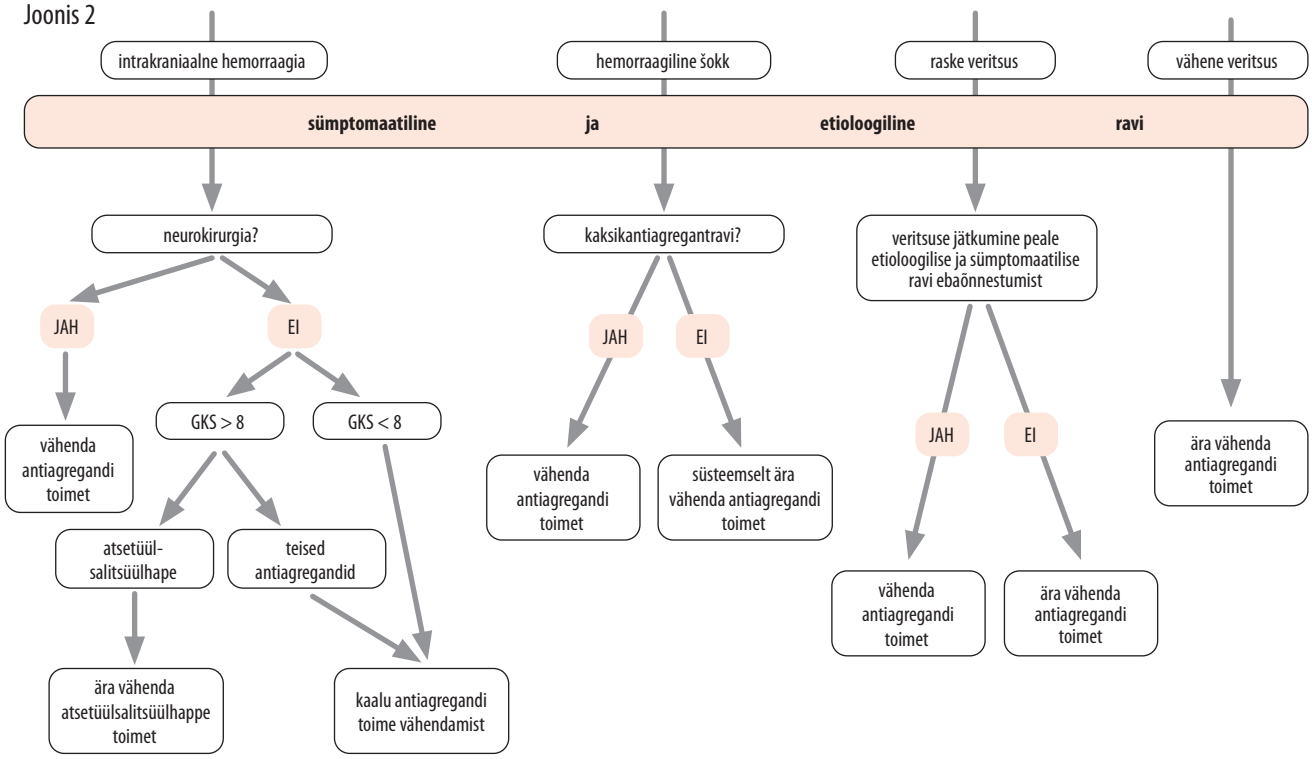
Erakorraline invasiivne protseduur antiagregantravi tarvitajal

Joonis 1



Veritsus antiagregantravi tarvitajal

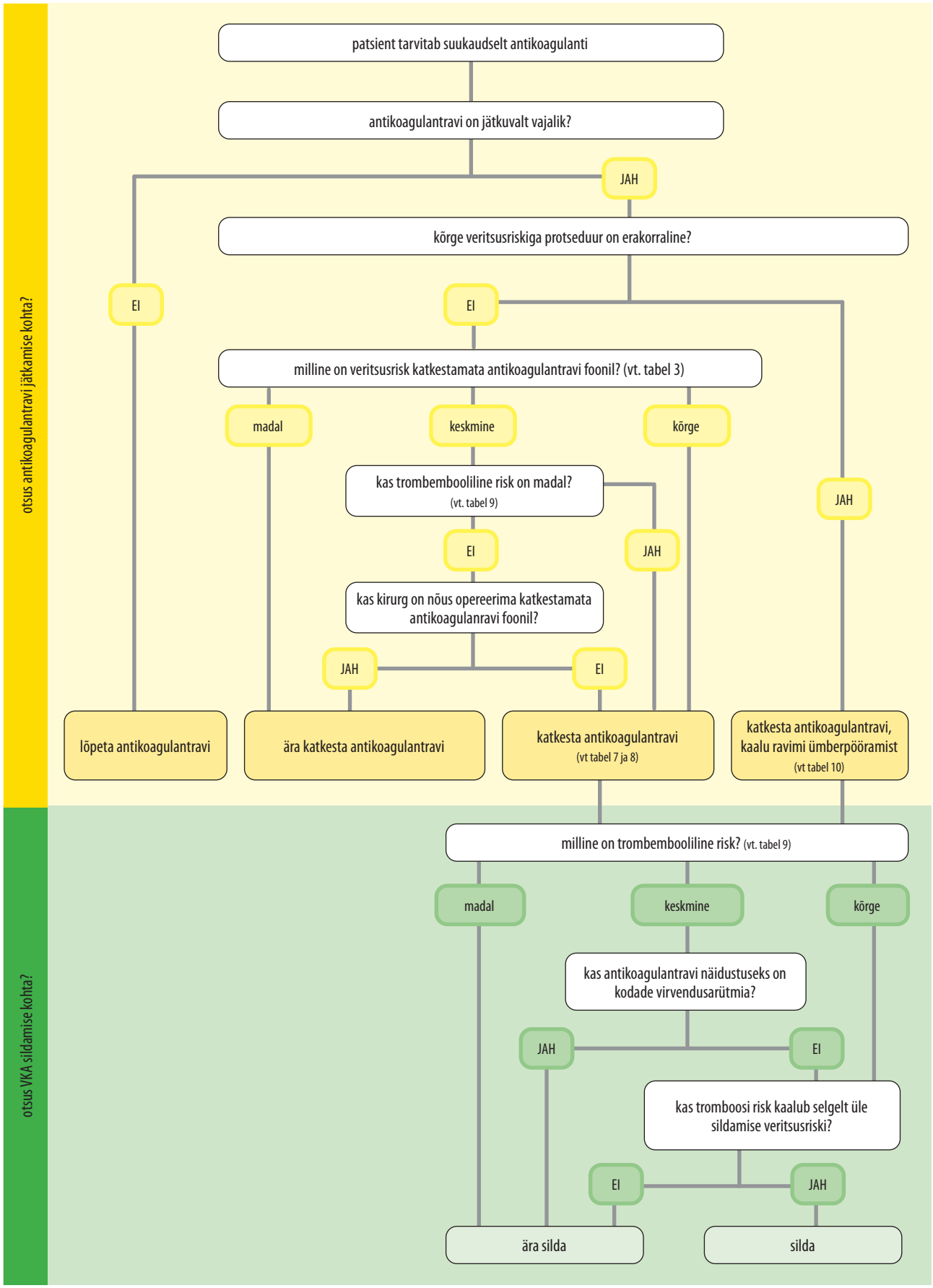
Joonis 2



ANTIAGREGANT	võimalus antiagregandi toime vähendamiseks
atsetüülsalitsüülhape	trombotsüütide transfusioon: 1 doos*
klopidogreel	trombotsüütide transfusioon: 2 doosi* *efektiivsus on väiksem, kui klopidogreeli manustamisest on möödas < 6 tundi*
prasugreel	trombotsüütide transfusioon: > 2 doosi* *efektiivsus on väiksem, kui prasugreeli manustamisest on möödas < 6 tundi*
tikagreloor	viimane manustamine < 24 t: soovitust ei ole – trombotsüütide transfusioon ei ole efektiivne, kaalu rFVIIa manustamist ja CytoSorb® kasutamist viimane manustamine > 24 t: trombotsüütide transfusioon vähendab osaliselt toimet

* doos: 1 kott 4-5BC trombotsüüte, mis sisaldab trombotsüüte ≥200 x10^9 tooteühikus, või 1 kott afereestrombotsüüte, mis sisaldab samuti ≥200 x10^9 tooteühikus

Joonis 3



Märkus: Madalmolekulaarsele või fraktsioneerimata hepariinile sillatakse vajadusel varfariinravil olevaid haigeid. OSAK-ravil olevaid haigeid ei sillata, kuid kui OSAK-ravi katkestamise ja planeeritud kirurgilise protseduuri toimumise vaheline aeg pikeneb planeeritud ravikatkestusest kauemaks ajaks, tuleb kaaluda madalmolekulaarse hepariini manustamist sõltuvalt haige tromboosi riskist (vt. tabel 9).

Tabel 7

OSAK periprotseduraalne käsitlus plaanilises kirurgias

<table>
<tr><th colspan="5">OSAK ravi viimase annuse ajastamine enne plaanilist kirurgilist protseduuri</th></tr>
<tr><td></td><td colspan="2">DABIGATRAAN</td><td colspan="2">APIKSABAAN, EDOKSABAAN, RIVAROKSABAAN</td></tr>
<tr><td colspan="5">madalmolekulaarsele/fraktsioneerimata hepariinile ei sillata*
* juhul, kui OSAK-ravi katkestamise ja planeeritud kirurgilise protseduuri toimumise vaheline aeg pikeneb planeeritud ravikatkestusest kauemaks ajaks, tuleb kaaluda madalmolekulaarse hepariini manustamist sõltuvalt haige tromboosi riskist (vt. tabel 9)</td></tr>
<tr><td>Minimaalse veritsusriskiga operatsioonid:</td><td colspan="4">- teosta protseduur OSAK-ravi foonil
- jätka OSAK-ravi protseduuriga samal päeval, hiljemalt järgmisel päeval</td></tr>
<tr><td></td><td colspan="2">DABIGATRAAN</td><td colspan="2">APIKSABAAN, EDOKSABAAN, RIVAROKSABAAN</td></tr>
<tr><td></td><td>madal veritsusrisk</td><td>kõrge veritsusrisk</td><td>madal veritsusrisk</td><td>kõrge veritsusrisk</td></tr>
<tr><td>CrCl ≥ 80ml/min</td><td>≥ 24 t</td><td>≥ 48 t</td><td rowspan="3">≥ 24 t</td><td rowspan="3">≥ 48 t</td></tr>
<tr><td>CrCl 50-79 ml/min</td><td>≥ 36 t</td><td>≥ 72 t</td></tr>
<tr><td>CrCl 30-49ml/min</td><td>≥ 48 t</td><td>≥ 96 t</td></tr>
<tr><td>CrCl 15-29ml/min</td><td>pole näidustatud</td><td>pole näidustatud</td><td>≥ 36 t</td></tr>
<tr><td>CrCl ≤ 15ml/min</td><td colspan="4">pole ametlikult näidustatud</td></tr>
<tr><td colspan="5">TÄHTIS:
- OSAK-ravi katkestamise ajastamine võib vajada individuaalset kohandamist vastavalt patsiendi riskiteguritele
- patsientidel või olukordades, kus on oht OSAK kuhjumisele (neerupuudulikkus, kõrgem iga, kaasuvad ravimid), võib kaaluda OSAK-ravi katkestamist 12-24 tundi varem</td></tr>
<tr><td colspan="5">OSAK RAVI TAASALUSTAMINE:
- taasalusta täisdoosis OSAK raviga 24 tundi peale madala veritsusriskiga protseduuri
- taasalusta täisdoosis OSAK raviga 48 (-72) tundi peale kõrge veritsusriskiga protseduuri, kaalu profülaktilises postoperatiivses doosis madalmolekulaarse hepariini manustamist peale operatsiooni ja enne täisdoosis OSAK ravi alustamist</td></tr>
</table>

Tabel 8

Varafiinravi käsitlus plaanilises kirurgias

VKA MINIMAALNE PREOPERIIVNE KATKESTAMINE			SOOVITUS	
VARFARIIN	INR 7 päeva enne op.-i:	katkesta varfariin:	mõõda INR päev enne op.-i	kaalu sildamist kui on tõsine tromboosi oht
	< 2	5 päeva		
	2-3	6 päeva		
	>3	7 päeva		
optimaalne INR operatsiooniks: madal veritsusrisk < 2.0 /// suur veritsusrisk < 1.5				

Varfariin-ravil oleva haige sildamine madalmolekulaarsele hepariinile (MMH) sõltub perioperatiivse tromboosi riskist (vt. tabel 9)

- **madal tromboosi risk** → **mitte sillata**
- **keskmine tromboosi risk** → **individuaalne lähenemine**
  - * **madala veritsusriski korral - sillata**
  - * **kõrge veritsusrisk (unearteri endarterektoomia, südame kirurgia) – sillata**
  - * **kõrge veritsusrisk muu kirurgia – mitte sillata**
- **kõrge tromboosi risk** → **sillata**

SILDAMINE VARFARIINILT

katkesta varfariin 5-7 päeva enne op.i → **alusta MMH 3 päeva enne op.i** → **viimane MMH doos op.ieelse päeva hommikul** → **operatsioon** → **alusta varfariiniga 24-48 tunni pärast**

Tabel 9

Perioperatiivse tromboosi risk

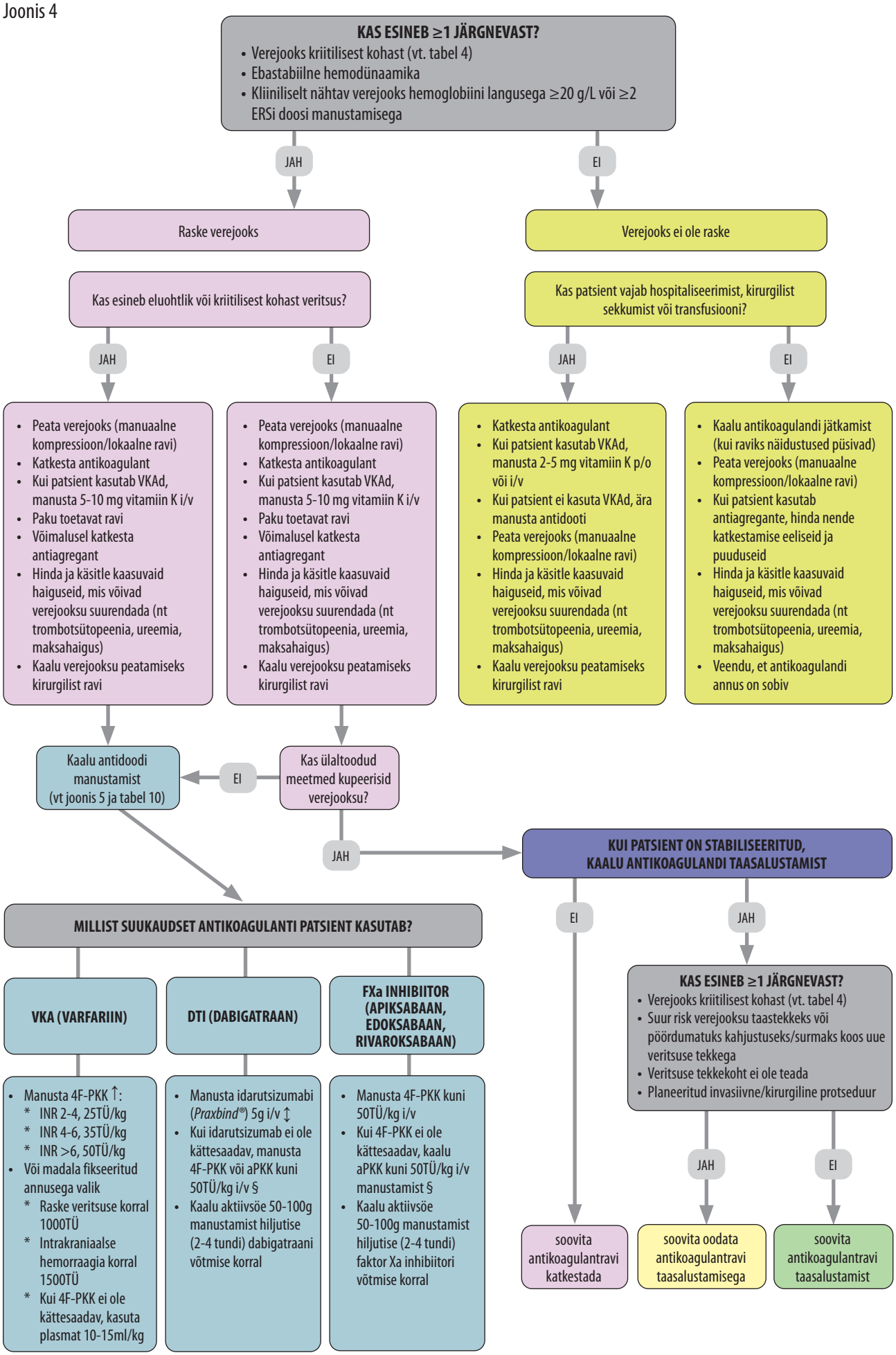
RISK	Mehaaniline klapp	Kodade virvendus	Venoosne tromb
madal (aastane risk <5%)	- kahehõlmne aordiklapi protees riskifaktoriteta	- CHADS2 0-2 (eeldusel, et anamneesis pole insulti või TIAt)	- VTE < 12 kuud tagasi
mõõdukas (aastane risk 5-10%)	- kahehõlmne aordiklapi protees ja vähemalt üks riskifaktor: • kodade virvendusarütmia • insult või TIA anamneesis • hüpertensioon • diabeet • südamepuudulikkus • vanus > 75 a.	- CHADS2 3 või 4	- VTE viimase 3-12 kuu jooksul - mitteraske trombofiilia (heterotsügootne V faktor või protrombiini geeni mutatsioon) - aktiivne vähk (ravitud viimase 6 kuu jooksul või palliatiivsel ravil)
kõrge (aastane risk >10%)	- kõik mitraalklapi proteesid - aordiklapi kuul- või diskproteesid - hiljutine insult või TIA (<6 kuud)	- CHADS2 5 või 6 - hiljutine insult või TIA (<3 kuud) - eumaatiline klapirike	- hiljutine (<3 kuud) VTE - raske trombofiilia (proteiin C või S antitrombiini defitsiit, antifosfolipiidsündroom)

TÄHT	CHA2DS2-VASc	PUNKTID
C	SÜDAMEPUUDULIKKUS, VASAKU VATSAKESE DÜSFUNKTSIOON	1
H	HÜPERTENSIOON	1
A2	VANUS > 75 A.	2
D	DIABEET	1
S2	INSULT, TRANSITOORNE AJUISHEEMIA	2
V	VASKULAARNE HAIGUS*	1
A	VANUS 65-74 A.	1
Sc	NAISSUGU	1

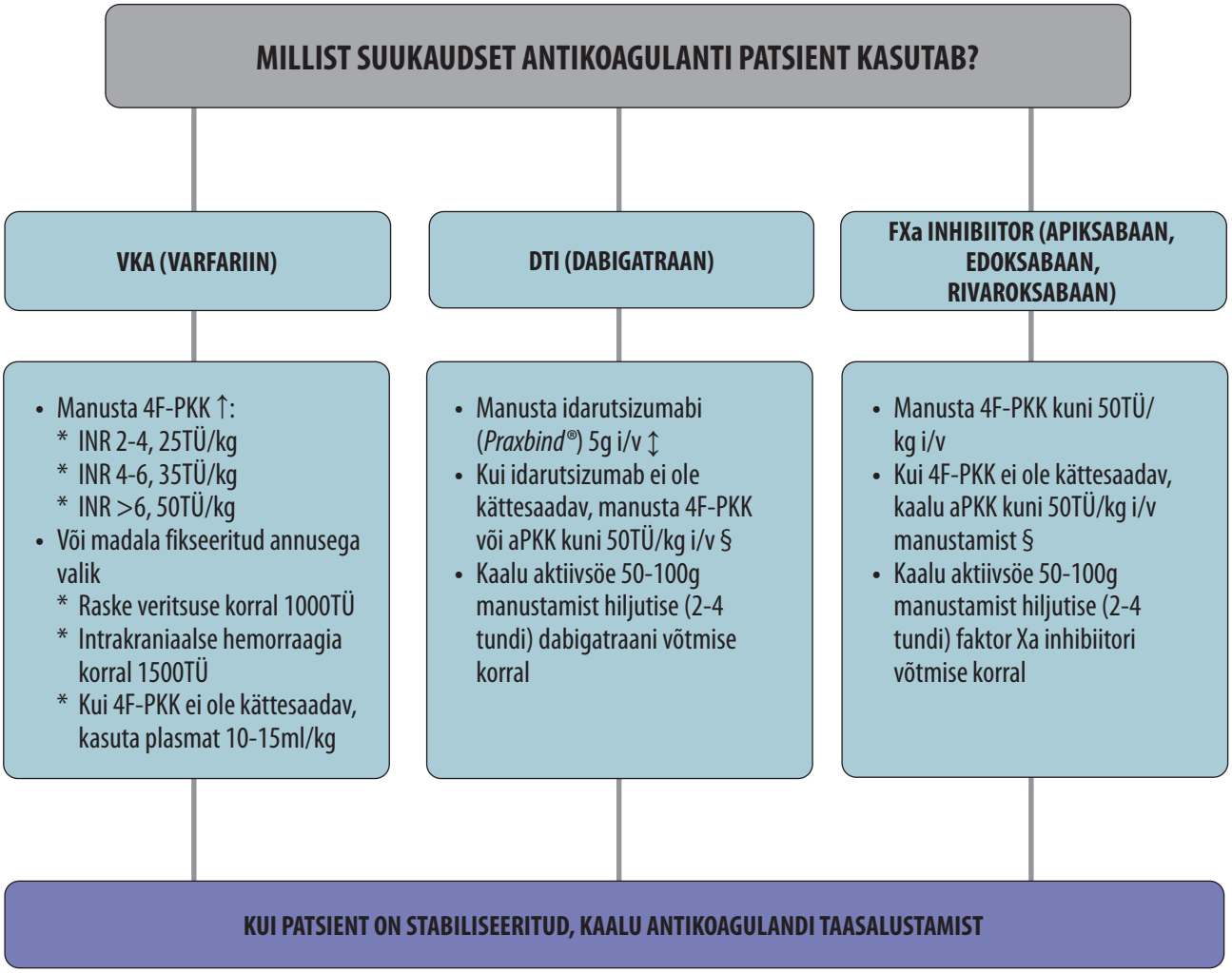
*vaskulaarne haigus: varasem müokardi infarkt, perifeersete arterite haigus või ateroskleerootiline naast aordis

Erakorraline invasiivne protseduur või veritsus antikoagulantravi tarvitajal

Joonis 4



Joonis 5



4F-PKK - neljafaktoriline protrombiini kompleksi kontsentraat (Octaplex®,Prothromplex®), aPKK- aktiveeritud protrombiini kompleksi kontsentraat (Feiba®), DTI - otsene trombiini inhibiitor, FXa - faktor Xa, INR - rahvusvaheline normitud suhe, i/v - intravenoosne, VKA - vitamiin K antagonist, OSAK - otsese toimega suukaudne antikoagulant.
*Antidoodid on PKK, vitamiin K ja spetsiifilised OSAKi antidoodid (dabigatraani puhul idarutsizumab).
↑ Kui VKA antidoodina kasutatakse PKK-d, peaks alati ka vitamiin K-d manustama.
↕ Teise idarutsizumabi annuse manustamine olla põhjendatud järgnevatel juhtudel: kui verejooks jätkub antidoodi manustamise järgselt, esineb laboratoorselt kinnitatud dabigatraani mõju või võib kahtlustada jätkuvat antikoagulandi mõju enne teise invasiivse protseduuri tegemist.
§ Maksimaalse annuse kohta info saamiseks loe annustamise juhendit (ravimi omaduste kokkuvõtet).

Veritsus kaksikantiagregantravi ja/või antikoagulantravi tarvitajal

Joonis 6

Verejooks kaksikantiagregantravi +/- OSAK ravi tarvitajal

MINIMAALNE VEREJOOKS
Igasugune meditsiinilist sekkumist või edasist hindamist mittevajav verejooks

Näiteks pindmised hematoomid või ekhümoosid, isepeatuv ninaverejooks, minimaalne konjuktiivi verejooks

- Jätka DAPTi

- Kaalu OSAKi jätkamist või järgmise manustamiskorra vahele jätmist

- Rahusta patsienti
- Tuvasta ja aruta patsiendiga võimalikke ennetuslikke strateegiaid
- Nõusta patsienti ravisoostumuse olulisuse osas

KERGE VEREJOOKS
Igasugune verejooks, mis nõuab meditsiinilist sekkumist, kuid mitte patsiendi hospitaliseerimist

Näiteks sekkumist vajav ninaverejooks, mõõdukas konjuktiivi verejooks, olulise verekaotuseta genitourinaalne või ülemise/alumise seedetrakti verejooks, kerge veriköha

- Jätka DAPTi
- Kaalu DAPT-ravi kestuse lühendamist või P2Y12 inhibiitori asendamist vähem potentse valikuga (nt tikagreloorilt/prasugreelilt klopidogreelile), eriti kui esinevad korduvad verejooksud

- Kolmikravi korral kaalu üle minemist kaksikravile, eelistades selleks klopidogreeli ja OSAKi

- Tuvasta ja käsitle kaasuvad verejooksuga seotud haigused (nt peptiline haavand, hemorroidid, kasvaja)
- Lisa raviskeemi PPI
- Nõusta patsienti ravisoostumuse olulisuse osas

MÕÕDUKAS VEREJOOKS
Igasugune olulise verekaotusega (Hb langus >30 g/L) ja/või hospitaliseerimist vajav hemodünaamiliselt stabiilne mitte kiirelt progresseeruva verejooksuga patsient

Näiteks olulise verekaotusega või transfusiooni nõudev genitourinaalne, ülemise/alumise seedetrakti, respiratoorne verejooks

- Kaalu DAPTi lõpetamist ning SAPTiga jätkamist, eelistades selleks P2Y12 inhibiitorit, seda eriti seedetrakti ülemise osa verejooksu puhul
- Taasalusta DAPT niipea kui seda võib pidada ohutuks
- Kaalu DAPT-ravi kestuse lühendamist või P2Y12 inhibiitori asendamist vähem potentse valikuga (nt tikagreloorilt/prasugreelilt klopidogreelile), seda eriti korduvate verejooksude esinemisel

- Kaalu OSAKi katkestamist või isegi antidoodi manustamist, kuni veritsus on kontrolli all (nt mehaanilised südameklapid, südame vatsakest abistav seade, CHA_2DS_2-VASc ≥4)
- Näidustuste esinemisel taasalusta ravi OSAKiga nädala jooksul. INR eesmärkväärtus on VKA kasutamisel 2-2,5, välja arvatud juhtudel, kui esineb muu eesmärkväärtus (näiteks mehaaniline klapiprotees või vatsakest abistav seade). OSAKi puhul kaalu madalaima tõhusa annuse kasutamist
- Kolmikravi korral kaalu üle minemist kaksikravile, eelistades selleks klopidogreeli ja OSAKi
- Kui patsient on kaksikravil, kaalu antiagregantravi lõpetamist, kui seda võib pidada ohutuks

- Seedetrakti verejooksu esinemisel kaalu PPI manustamist i/v
- Tuvasta ja käsitle kaasuvad verejooksuga seotud haigused (nt peptiline haavand, hemorroidid, kasvaja)
- Nõusta patsienti ravisoostumuse olulisuse osas

OSAK - otsaene suukaudne antikoagulant, DAPT - kaksikantiagregantravi (ingl. k. *dual antiplatelet therapy*), SAPT - ühe antiagregandiga ravi (ing.k. *single antiplatelet therapy*), PPI - prootonpumba inhibiitor, i/v - intravenoosne

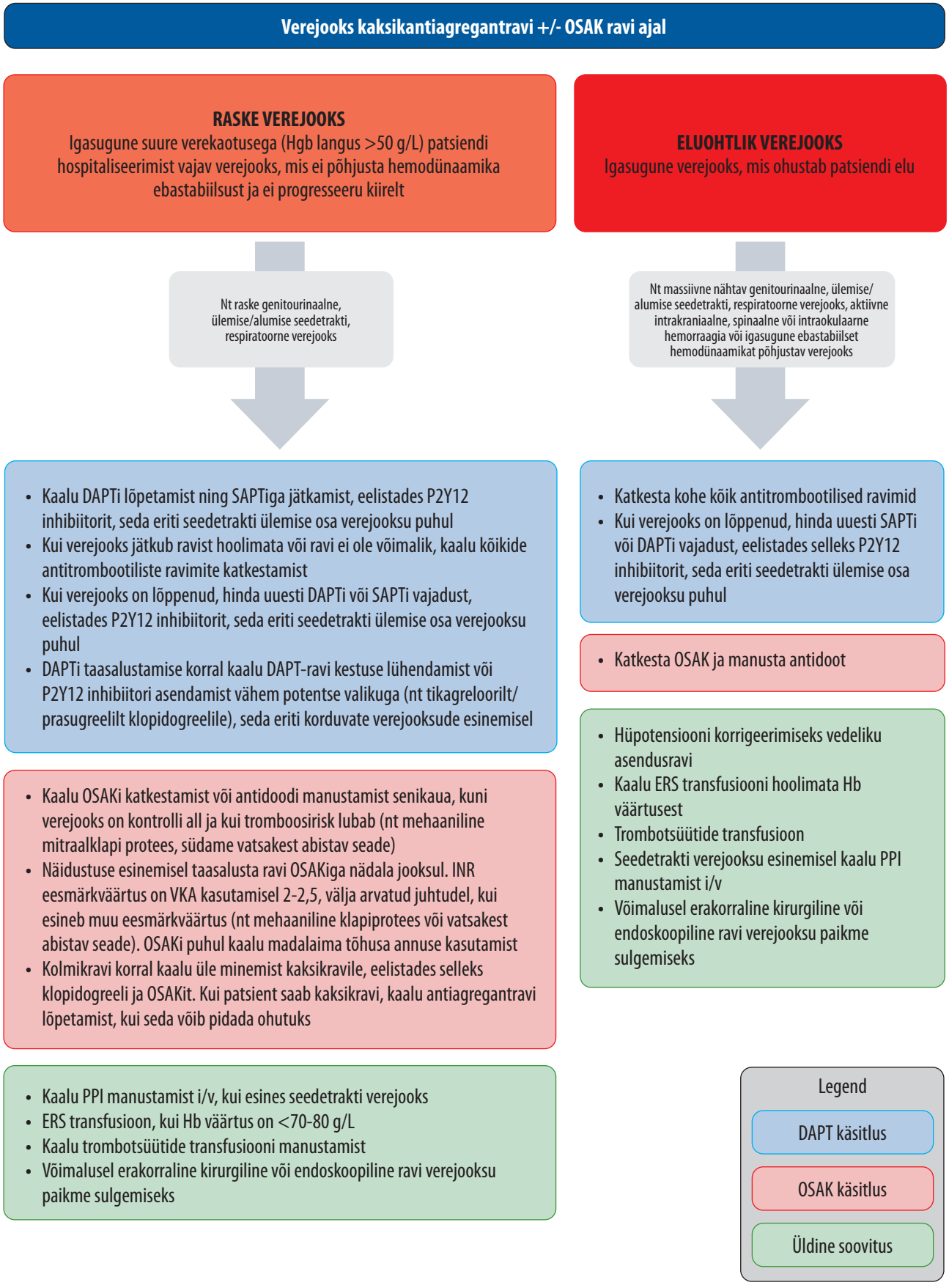
Legend

DAPT käsitlus

OSAK käsitlus

Üldine soovitus

Joonis 7


Verejooks kaksikantiagregantravi +/- OSAK ravi ajal
RASKE VEREJOOKS
Igasugune suure verekaotusega (Hgb langus >50 g/L) patsiendi hospitaliseerimist vajav verejooks, mis ei põhjusta hemodünaamika ebastabiilsust ja ei progresseeru kiirelt
ELUOHTLIK VEREJOOKS
Igasugune verejooks, mis ohustab patsiendi elu
Nt raske genitourinaalne, ülemise/alumise seedetrakti, respiratoorne verejooks
Nt massiivne nähtav genitourinaalne, ülemise/alumise seedetrakti, respiratoorne verejooks, aktiivne intrakraniaalne, spinaalne või intraokulaarne hemorraagia või igasugune ebastabiilset hemodünaamikat põhjustav verejooks
• Kaalu DAPTi lõpetamist ning SAPTiga jätkamist, eelistades P2Y12 inhibiitorit, seda eriti seedetrakti ülemise osa verejooksu puhul
• Kui verejooks jätkub ravist hoolimata või ravi ei ole võimalik, kaalu kõikide antitrombootiliste ravimite katkestamist
• Kui verejooks on lõppenud, hinda uuesti DAPTi või SAPTi vajadust, eelistades P2Y12 inhibiitorit, seda eriti seedetrakti ülemise osa verejooksu puhul
• DAPTi taasalustamise korral kaalu DAPT-ravi kestuse lühendamist või P2Y12 inhibiitori asendamist vähem potentse valikuga (nt tikagreloorilt/prasugreelilt klopidogreelile), seda eriti korduvate verejooksude esinemisel
• Kaalu OSAKi katkestamist või antidoodi manustamist senikaua, kuni verejooks on kontrolli all ja kui tromboosirisk lubab (nt mehaaniline mitraalklapi protees, südame vatsakest abistav seade)
• Näidustuse esinemisel taasalusta ravi OSAKiga nädala jooksul. INR eesmärkväärtus on VKA kasutamisel 2-2,5, välja arvatud juhtudel, kui esineb muu eesmärkväärtus (nt mehaaniline klapiprotees või vatsakest abistav seade). OSAKi puhul kaalu madalaima tõhusa annuse kasutamist
• Kolmikravi korral kaalu üle minemist kaksikravile, eelistades selleks klopidogreeli ja OSAKit. Kui patsient saab kaksikravi, kaalu antiagregantravi lõpetamist, kui seda võib pidada ohutuks
• Kaalu PPI manustamist i/v, kui esines seedetrakti verejooks
• ERS transfusioon, kui Hb väärtus on <70-80 g/L
• Kaalu trombotsüütide transfusiooni manustamist
• Võimalusel erakorraline kirurgiline või endoskoopiline ravi verejooksu paikme sulgemiseks
• Katkesta kohe kõik antitrombootilised ravimid
• Kui verejooks on lõppenud, hinda uuesti SAPTi või DAPTi vajadust, eelistades selleks P2Y12 inhibiitorit, seda eriti seedetrakti ülemise osa verejooksu puhul
• Katkesta OSAK ja manusta antidoot
• Hüpotensiooni korrigeerimiseks vedeliku asendusravi
• Kaalu ERS transfusiooni hoolimata Hb väärtusest
• Trombotsüütide transfusioon
• Seedetrakti verejooksu esinemisel kaalu PPI manustamist i/v
• Võimalusel erakorraline kirurgiline või endoskoopiline ravi verejooksu paikme sulgemiseks
Legend
DAPT käsitlus
OSAK käsitlus
Üldine soovitus

ANTITROMBOOTILISTE RAVIMITE TOIME VÄHENDAMINE VÕI ÜMBERPÖÖRAMINE ELUOHTLIKU VEREJOOKSU VÕI ERAKORRALISE PROTSEDUURI VAJADUSEL

Tabel 10

RAVIM	ELIMINATSIOONI POOLVÄÄRTUSAEG	EEMALDAMINE KEHAVÄLISELT	RAVIMI TOIME VÄHENDAMINE VÕI ÜMBER PÖÖRAMINE
DABIGATRAAN	14-17 tundi (neerupuudulikkuse korral kuni 34 tundi)	4-tunnine hemodialüüs eemaldab umbes 50–60% dabigatraanist	- ravimi toimet aitab hinnata dabigatraani kontsentratsioon P-DBTN (määratakse anti-FIIa testi abil)[a] - ravimi toimet aitab välistada plasmas referentspiirides TT ja/või uriinis negatiivne Dosense® kiirtest - aktiivsüsi 50-100g p/o võib aidata ~2t jooksul peale ravimi manustamist - eluohtliku verejooksu korral kaalu idarutsizumabi[b] (*Praxbind*®) manustamist 5mg, selle puudumisel 4f-PCC (Octaplex® või Prothromplex®) kuni 50TÜ/kg[c] * idarutsizumab võib korrigeerida aPTT/TT, kuid pole näidatud, et see parandaks ravitulemusi * ravimi plasma konts. võib tõusta 12-24T jooksul peale idarutsizumabi manustamist (ümberjaotus kudedest)
RIVAROKSABAAN	tervetel 5-9 tundi, eakatel 11-13 tundi (neerupuudulikkuse korral kauem)	ei ole dialüüsiga eemaldatav, kui eemaldatav *CytoSorb*®iga	- ravimi toimet aitab hinnata rivaroksabaani kontsentratsioon P-RXN (määratakse anti-Xa testi abil)[a] - ravimi toimet aitab välistada madalmolekulaarse hepariini väärtus P-LMWH <0,1 kU/L ja/või uriinis negatiivne Doasense® kiirtest anti-fXa, ravimi konts. - aktiivsüsi 50-100g p/o võib aidata ~2t jooksul peale ravimi manustamist - kaalu 4f-PCC (Octaplex® või Prothromplex®) manustamist kuni 50TÜ/kg[c] - eluohtliku verejooksu korral kaalu alfaandeksanaat (Ondexxya®)[d] manustamist 800mg i/v boolusena (30mg/min), jätkates infusiooni 8mcg/min 3 tunni jooksul * 4f-PCC võib osaliselt korrigeerida PT/aPPT (korrelatsioon nende langemise ja erituse vähenemise vahel pole teada), kuid ei mõjuta anti-Xa aktiivsust ega kiirenda ravimi eemaldamist
APIKSABAAN	8-15 tundi (neerupuudulikkuse korral kauem)	ei	- ravimi toimet aitab hinnata apiksabaani kontsentratsioon P-APBN (määratakse anti-Xa testi abil)[a] - ravimitoimet aitab välistada madalmolekulaarse hepariini väärtus P-LMWH <0,1 kU/L ja/või uriinis negatiivne Doasense® kiirtest - aktiivsüsi 50-100g p/o võib aidata ~2t jooksul peale ravimi manustamist - kaalu 4f-PCC (Octaplex® või Prothromplex®) manustamist kuni 50TÜ/kg[c] - eluohtliku verejooksu korral kaalu alfaandeksanaat (Ondexxya®)[d] manustamist 400mg i/v boolusena (30mg/min), jätkates infusiooni 4mcg/min 3 tunni jooksul * 4f-PCC võib osaliselt korrigeerida PT/aPPT (korrelatsioon nende langemise ja erituse vähenemise vahel pole teada), kuid ei mõjuta anti-Xa aktiivsust ega kiirenda ravimi eemaldamist
EDOKSABAAN	10-14 TUNDI (NEERUPUUDULIKKUSE KORRAL KAUEM)	hemodialüüsiga ~25%	- ravimi toimet aitab hinnata edoksabaani kontsentratsioon P-EDBN (määratakse anti-Xa testi abil)[a] - ravimi toimet aitab välistada madalmolekulaarse hepariini väärtus P-LMWH <0,1 kU/L ja/või uriinis negatiivne Doasense® kiirtest - aktiivsüsi 50-100mg p/o võib aidata ~2t jooksul peale ravimi manustamist - kaalu 4f-PCC (Octaplex® või Prothromplex®) manustamist kuni 50TÜ/kg[c] * 4f-PCC võib osaliselt korrigeerida PT/aPPT (korrelatsioon nende langemise ja erituse vähenemise vahel pole teada), kuid ei mõjuta anti-Xa aktiivsust ega kiirenda ravimi eemaldamist
VARFARIIN	**INR**	**kliiniline seisund**	**tegevus**
	< 4,5	veritsust ei ole	- peata varfariin kuni INR on terapeutilises vahemikus
		vajalik kiire toime ümberpööramine	- peata varfariin - kaalu vit. K andmist 2,5mg p/o
	>4,5	veritsust ei ole	- peata varfariin kuni INR on terapeutilises vahemikus - kaalu vit. K andmist 2,5-5mg p/o või 1-2mg i/v 30 minuti jooksul
		vajalik kiire toime ümberpööramine	- peata varfariin - anna vit. k 2,5-5mg p/o või või 1-2mg i/v 30 minuti jooksul, korda vajadusel 6-24h jooksul
	iga INR	tõsine eluohtlik verejooks	- peata varfariin - manusta vit.k 5-10mg i/v 30 minutilise infusioonina - kaalu 4f-PCC (Octaplex® või Prothromplex®) manustamist: • INR 2-4 25TÜ/kg, maks. 2500TÜ • INR 4-6 35TÜ/kg, maks. 3500TÜ • INR >6 50TÜ/kg, maks. 5000TÜ - 4f-PCC puudumisel tee plasmat või selle derivaati 10-20ml/kg

ARGATROBAAN	40-50 minutit	hemodialüüsiga ~20%	- lõpeta infusioon - ravimi ümberpööramise astet saab hinnata aPTT ja/või TT abil
FRAKTSIONEERIMATA HEPARIIN	30-90 minutit (doosist sõltuvalt)	hemodialüüsiga osaliselt	- kasuta neutraliseerimiseks protamiini (kuni 5mg/min, maks. doos 50mg) - ravimi ümberpööramise astet hinda aPTT ja/või fraktsioneerimata hepariini testi P-UFH (määratakse anti-Xa testi abil) abil **aeg viimasest hepariinist** / **protamiini doos 100TÜ manustatud hepariini kohta** äsja manustatud: 1 mg *(või 25 mg fikseeritud doos)* 30 min – 2 tundi: 0,5 mg *(või 10 mg fikseeritud doos)* > 2 tunni: 0,25 mg *(või 10 mg fikseeritud doos)* * protamiinil on üledoosis antikoagulandi toime; protamiini poolestusaeg on fraktsioneerimata hepariini omast lühem, seega võib vaja minna kordusdoosi
MADAL-MOLEKULAARNE HEPARIIN (ENOKSAPARIIN, BEMIPARIIN)	3-5 tundi (neerupuudulikkuse korral kauem)	hemodialüüsiga ~20%	- osaliselt protamiiniga ~60% osas neutraliseeritav (kuni 5mg/min, maks. doos 50mg) - ravimi ümberpööramise astet hinda madalmolekulaarse hepariini testi P-LMWH (määratakse anti-Xa testi abil) **aeg viimasest MMH doosist** / **protamiini doos 1mg enoksapariini kohta** < 8 tunni: 1 mg *(või 50 mg fikseeritud doos)* 8-12 tundi: 0,5 mg *(või 25 mg fikseeritud doos)* > 12 tunni: pole tõenäoliselt vajalik *(või 10 mg fikseeritud doos)* - kaalu rfVIIa (Novoseven®) manustamist 90 µg/kg
FONDAPARIINUKS	17-21 tundi (neerupuudulikkuse korral oluliselt kauem)	ei	- ravimi toimet aitab hinnata fondapariinuksi test (määratakse anti-Xa testi abil)[E] - kaalu 4f-PCC (Octaplex® või Prothromplex®) manustamist kuni 50TÜ/kg[C] - kaalu rfVIIa (Novoseven®) manustamist 90 µg/kg * rfVIIa ei mõjuta anti-Xa aktiivsust ega suurenda ravimi eemaldamist

RAVIM	TROMBOTSÜÜTIDE FUNKTSIOONI TAASTUMINE	EEMALDAMINE KEHAVÄLISELT	RAVIMI TOIME VÄHENDAMINE VÕI ÜMBER PÖÖRAMINE
ATSETÜÜLSALITSÜÜL-HAPE	5-7 päeva	EI	- lõpeta ravimi manustamine - ravimi aitab hinnata PFA-Col/Epi, PFA-Col/ADP, B-Agr-ASPI - kaalu 2-3 doosi trombotsüütide manustamist
KLOPIDOGREEL	7-10 päeva	EI	- lõpeta ravimi manustamine - ravimi aitab hinnata PFA-P2Y12, B-Agr-ADP - kaalu 2-3 doosi trombotsüütide manustamist
TIKAGRELOOR	~7 päeva	eemaldatav CytoSorb®-ga	- lõpeta ravimi manustamine - ravimi toimet aitab hinnata PFA-P2Y12, B-Agr-ADP - kaalu 2-3 doosi trombotsüütide manustamist
PRASUGREEL	~10 päeva	ei	- lõpeta ravimi manustamine - ravimi toimet aitab hinnata PFA-P2Y12, B-Agr-ADP - kaalu 2-3 doosi trombotsüütide manustamist
GPIIb/IIIa inhibiitorid	~4 tundi	eptifibatiid on dialüüsitav	- ravimi toimet näitab B-Agr-TRAP

[A] dabigatraani, rivaroksabaani, apiksabaani ja edoksabaani kontsentratsioon < 30µg/L välistab ekspertarvamuse kohaselt kliiniliselt olulise ravimi kontsentratsiooni plasmas
[B] idarutsizumab on eestis kättesaadav: TÜK 1. iros ja PERH EMOs
[C] Octaplex® ühekordne annus ei tohi ületada 3000 TÜ
[D] alfaandeksanaat (*Ondexxya®*) ei ole eestis veel (2022. a) kättesaadav
[E] seisuga märts 2022 Eestis ei määrata, tehniliselt on võimalik juurutada PERH ja TÜK laborites

Tabel 11

ANTITROMBOOTILISTE RAVIMITE KÄSITLUS KÕRGE VERITSUSRISKIGA BLOKAADIDE KORRAL (NEURAKSIAALSED JA SÜGAVAD NÄRVIBLOKAADID)				
Ravim ja doos (vt. tabel 14)		**Aeg viimasest ravimi võtmisest blokaadi tegemiseni**	**Laboratoorne eesmärk blokaadi ajaks**	**Aeg järgmise ravimiannuse võtmiseni peale blokaadi tegemist**
VKA[a]		varfariinil keskmisel 5 päeva, eesmärgipärane laboratoorne tase	INR normaalne	
otsesed Xa inhibiitorid (apiksabaan, edoksabaan, rivaroksabaan)	madal doos	- apiksabaan 36t - edoksabaan 24t (30t, kui CrCl[b] < 30ml/min) - rivaroksabaan 24t	ei testita	
	kõrge doos	72t või kuni saavutatud eesmärgipärane laboratoorne tase (kui CrCl[b] < 30ml/min)	- ravimi konts. baasväärtus < 30µg/ (määratakse igal ravimil eraldi anti-Xa testi abil) - alternatiiviks madalmolekulaarne hepariin P-LMWH ≤ 0,1kU/L	madalas doosis vastavalt postop. VTE[c] profülaktika juhistele
dabigatraan	madal doos	48t	ei testita	
	kõrge doos	72t või kuni saavutatud eesmärgipärane laboratoorne tase (kui CrCl[b] < 30ml/min)	- dabigatraani konts. baasväärtus < 30µg/L (määratakse anti-FIIa testi abil) - alternatiivina: normaalne TT aeg	kõrges doosis: vastavalt antikoagulatsiooni juhistele (enamasti 24t peale op.i)
MMH[d]	madal doos: - ≤ 50TÜ anti-Xa/kg/päevas - enoksapariin ≤ 40mg/ päevas	12t (24t, kui CrCl[b] < 30ml/min)	ei testita	
	kõrge doos - ≥ 50TÜ anti-Xa/kg/päevas	24t (48t, kui CrCl[b] < 30ml/min) või kuni saavutatud eesmärgipärane laboratoorne tase (eriti, kui CrCl[b] < 30ml/min)	madalmolekulaarne hepariin P-LMWH (määratakse anti-Xa testi abil) ≤ 0,1kU/L	VKA[a], OSAK[e], kõrges doosis MMH ja FH[d] ei tohi manustada, kui kateeter *in situ*
FH[f]	madal doos: - ≤ 200TÜ/kg/päevas s/c - ≤ 100TÜ/kg/päevas i/v	4t	ei testita	FH[f] madalas doosis: 1t i/v peale kardiokirurgilist operatsiooni
	kõrges doosis	kuni saavutatud eesmärgipärane laboratoorne tase (umbes 6t i/v manustamise korral ja 12t s/c manustamise korral)	APPT või fraktsioneerimata hepariin P-UFH (määratakse anti-Xa testi abil) või AKT normiväärtuses	
fondapariinuks	madal doos: ≤ 2,5mg/päevas	36t (72t kui CrCl[b] < 50ml/min)	ei testita	
	kõrge doos	kuni saavutatud eesmärgipärane laboratoorne tase (enamasti umbes 4 päeva)	fondapariinuksi konts. baasväärtus (määratakse anti-Xa testi abil) ≤ 0,1 kU/L*	
aspiriin	madal doos: ≤ 200mg/päevas	0	ei testita	patsiendi tavapärase skeemi järgi
	kõrge doos	3 päeva (normaalse trombotsüütide arvu juures) kuni 7 päeva	trombotsüütide funktsiooni uuringud	6t
P2Y12 inhibiitorid		- 5-7 päeva klopidogreel - 5 päeva tikagreloor - 7 päeva prasugreel	(trombotsüütide funktsiooni uuringud)	- 0t klopidogreel 75mg - 24t tikagrelool ja prasugreel - 2 päeva klopidogreel 300mg
aspiriin madalas doosis + antikoagulant		aspiriin: 0 päeva + aeg vastavalt antikoagulandile	laboratoorne uuring vastavalt antikoagulandile	- aspiriin madalas doosis: patsiendi tavapärase skeemi järgi - kombineeritud antikoagulant: vastavalt antikoagulantide juhistele
kaksikantiagregant ravi		aspiriin: 0 päeva + aeg vastavalt teisele antiagregandile	kaalu spetsiifiliste trombotsüütide funktsiooni testide tegemist	- aspiriin madalas doosis: patsiendi tavapärase skeemi järgi - kombineeritud antiagregant: vastavalt ravijuhistele (enamasti 24t peale op.i)

[a] VKA – vitamiin K antagonist [b] CrCl – kreatiniini kliirens (ingl. k. *creatinine clearance*) [c] VTE – venoosne trombemboolia [d] MMH – madalmolekulaarne hepariin
[e] OSAK – otsene suukaudne antikoagulant [f] UFH – fraktsioneerimata hepariin (ingl. k. *unfractionated heparine*)
* seisuga märts 2022 Eestis ei määrata, tehniliselt on võimalik juurutada PERH ja TÜK laborites

Tabel 12

ANTITROMBOOTILISTE RAVIMITE KÄSITLUS MADALA VERITSUSRISKIGA BLOKAADIDE KORRAL (PINDMISED NÄRVIBLOKAADID)			
Ravim ja doos	**Aeg viimasest ravimi võtmisest enne blokaadi**	**Laboratoorne eesmärk blokaadi ajaks**	**Aeg esimese ravimi võtmiseni peale blokaadi**
- dabigatraan - otsesed Xa inhibiitorid - MMH[a] madalas doosis: ≤ 50TÜ anti-Xa/kg/päevas - enoksapariin ≤ 40mg/päevas - FH[b] madalas doosis: ≤ 200TÜ/kg/päevas s/c ≤ 100TÜ/kg/päevas i/v - fondapariinuks madal doos - aspiriin ≤ 200mg/päevas	0 päeva	ei testita (kaalu spetsiifilisi teste, kui on oht antikoagulandi kuhjumisele, näiteks neerupuudulikkuse korral)	patsiendi tavapärase skeemi järgi
- VKA[c] - MMH kõrges doosis - FH kõrges doosis - aspiriin kõrges doosis - P2Y12 inhibiitorid - ravimite kombinatsioonid	0 päeva (kui ravim terapeutilises vahemikus või alla selle)		

[a] MMH – madalmolekulaarne hepariin [b] FH – fraktsioneerimata hepariin (ingl. k. *unfractionated heparine*) [c] VKA – vitamiin K antagonist

Tabel 13

NÄRVIBLOKAADIDE JAOTUS		
	neuraksiaalsed blokaadid / sügavad närviblokaadid	**pindmised närviblokaadid**
üldised põhimõtted	Blokaadist tekkinud veritsus on oluline ja võib olla väga tõsise tagajärjega. Veritsuse käsitlus on keeruline, sest veritsuskoht ei pruugi olla komprimeeritav ning võib vajada invasiivset käsitlust. Kliiniline tähendus: antitrombootiline ravi tuleb katkestada vastavalt tabelile 11	Blokaadist tekib pindmine hematoom, millel ei ole väga tõsist kliinilist tähtsust. Veritsuse käsitlus on lihtne (enamasti lokaalne kompressioon), invasiivse käsitluse vajadus on vähetõenäoline. Kliiniline tähendus: antitrombootilise ravi katkestamine ei pruugi olla vajalik (vt. tabel 12)
näiteid:		
pea, kael	- *ganglion stellatum*'i blokaad - kaelapõimiku sügav blokaad	- kuklablokaad - peribulbaarne blokaad - kaelapõimiku pindmine blokaad
ülajäse	- õlapõimiku infraklavikulaarne blokaad	- õlapõimiku interskaleenne blokaad - õlapõimiku supraklavikulaarne blokaad - õlapõimiku aksillaarne blokaad - *n.suprascapularis'e* blokaad - närviblokaadid küünarvarre või randme piirkonnas
rindkere	- epiduraalne blokaad - torakaalne paravertebraalne blokaad	- parasternaalne interkostaalne blokaad (sügav ja pindmine) - *serratus anterior* blokaad (sügav ja pindmine) - *erector spinae* blokaad - interkostaalne blokaad - PECS blokaad
kõht, vaagen		- *n.ilioingvinalis* ja *n.hypogastricus* blokaadid - TAP blokaad - *rectus sheath* blokaad - *n.genitofemoralis'e* blokaad - *n.pudendus'e* blokaad
jalg, selg	- nimmepõimiku blokaad - nimmepiirkonna paravertebraalne blokaad - *quadratus lumborum* blokaad - ristluupõimiku blokaad - perikapsulaarse närvigrupi (PENG) blokaad - *n. ischiadicus*'e trans- ja subgluteaalne blokaad - spinaalanesteesia - epiduraalne blokaad	- *n. femoralis*'e blokaad - *fascia iliaca* blokaad - *n. femoralis*'e lateraalse nahanärvi blokaadid - *adductor* kanali bl0kaad - *n. ischiadicus*'e blokaad põlve piirkonnas - närviblokaadid jalalaba piirkonnas

Tabel 14

OSAK doosid				
	Rivaroksabaan	**Apiksabaan**	**Edoksabaan**	**Dabigatraan**
Venoosse trombemboolia profülaktika peale suurt ortopeedilist operatsiooni (puusa või põlve endoproteesimised) → madalad doosid				
doos	10mg x 1 päevas	2,5mg x 2 päevas	ei kasutata	220mg x 1 päevas
doosi korrigeerimine	ei	ei		150mg x 1, kui: - CrCl 30-50ml/min või - vanus ≥ 75 või - samaaegselt tarvitamisel verapamiil, amiodaroon või kinidiin
Insuldi profülaktika mittevalvulaarse kodade virvendusarütmiaga → kõrged doosid				
doos	20mg x1 päevas	5mg x 2 päevas	60mg x 1 päevas	150mg x 2 päevas
doosi korrigeerimine	15mg x 1 päevas, kui - CrCl 15-50ml/min	2,5mg x 2 päevas, kui olemas 2 kriteeriumi järgnevast: - vanus ≥ 80 - kaal ≤ 60kg - kreatiniin ≥ 133 µmol/L Kui CrCl 15-29ml/min, siis doos samuti 2,5mg x 2	30mg x 1 päevas, kui: - CrCl 15-50ml/min - kaal ≤ 60kg - samaaegselt tarvitamisel tsüklosporiin, dronedaroon, erütromütsiin või ketokonasool	110mg x 2 päevas, kui vanus ≥ 80 või samaaegselt tarvitamisel verapamiil 110mg või 150mg x 2 päevas, kui CrCl 30-50ml/min või vanus 75-80
Ägeda veenitromboosi ravi → kõrged doosid				
doos	15mg x 2 päevas 3 nädalat, edasi 20mg x 1 päevas	10mg x 2 päevas 7 päeva, edasi 5mg x 2 päevas	60mg x 1 päevas	150g x 1 päevas
doosi korrigeerimine	15mg x 2 päevas 3 nädalat, edasi 15mg x 1 päevas, kui CrCl 15-50ml/min	doosi ei korrigeerita	30mg x 1 päevas, kui: - CrCl 15-50ml/min - kaal ≤ 60kg - samaaegselt tarvitamisel tsüklosporiin, dronedaroon, erütromütsiin või ketokonasool	110mg x 2 päevas, kui vanus ≥ 80 või samaaegselt tarvitamisel verapamiil 110mg või 150mg x 2 päevas, kui CrCl 30-50ml/min või vanus 75-80
Pikendatud korduva süvaveenitromboosi või kopsuemboolia profülaktika → madalad doosid				
doos	10mg x 1 päevas või 20mg x 1 päevas	2,5mg x 2 päevas		
doosi korrigeerimine	Kui CrCl 15-50ml/min, siis: - 10mg x 1 päevas ei korrigeerita - 20mg x1 asemel kaalu 15mg x1 päevas	ei		
Äge koronaarsündroom → madalad doosid				
doos	2,5mg x 2 päevas	ei kasutata	ei kasutata	ei kasutata
Aterotrombootiliste juhtude profülaktika sümptomaatilistel haigetel perifeersete arterite haigusega → madalad doosid				
doos	2,5mg x 2 päevas	ei kasutata	ei kasutata	ei kasutata

OSAK – otsene suukaudne antikoagulant; CrCl – kreatiniini kliirens (ingl. k. *creatinine clearance*)

KASUTATUD ALLIKAD:

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