"HOW TO MONITOR AND MANAGEMENT COMPLICATIONS FROM DIRECT THROMBIN INHIBITORS"

ADALBERTO TORRES-HERNÁNDEZ, MSN, BA,CERN, CWCMS

8TH ANNUAL PUERTO RICO WINTER CANCER SYMPOSIUM MARCH 1 – 3, 2019 IN SAN JUAN, PUERTO RICO

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NO RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

THE SPEAKER WILL DIRECTLY DISCLOSURE THE USE OF PRODUCTS FOR WHICH ARE NOT LABELED (E.G., OFF LABEL USE) OR IF THE PRODUCT IS STILL INVESTIGATIONAL.

"What most surprises me about the Western man is
that he loses his health to make money,
then lose money to regain their health.
And for thinking anxiously about the future
don't enjoy the present,
so he lives neither the present nor the future,
and they live, like they never have to die,
and die, as if they had never lived."

Dalai Lama

INTRODUCTION

- WHEN OFFERING TREATMENTS TO CANCER PATIENTS, HEMATOLOGIC COMPLICATIONS FREQUENTLY OCCUR.
- LARGE STUDIES SUGGEST THAT PATIENTS WITH ACTIVE CANCER EXPERIENCE A 4- TO 8-FOLD INCREASE IN VENOUS THROMBOEMBOLISM (VTE) COMPARED WITH THE GENERAL POPULATION
- ARTERIAL AND VENOUS THROMBOSIS **(AVT)** ARE A LEADING CAUSE OF MORTALITY IN CANCER PATIENTS AND CONTRIBUTES TO INCREASED MORBIDITY AND THE COST OF CARE.
- THE PRESENCE OF AVT IN A PATIENT WITH MALIGNANCY DECREASES SURVIVAL UP TO 6-FOLD COMPARED WITH PATIENTS WITHOUT AVT.
- TREATMENT OF CANCER-ASSOCIATED THROMBOSIS IS DIFFICULT DUE TO THE CONCURRENT INCREASED RISK OF HEMORRHAGE IN PATIENTS RECEIVING ANTICOAGULATION

INTRODUCTION

ARTERIAL THROMBOSIS IS CONSIDERED THE MOST COMMON CAUSE OF:

ACUTE CORONARY SYNDROMES

MYOCARDIAL INFARCTION

CEREBRAL VASCULAR EVENT

GANGRENE OF EXTREMITIES

VENOUS THROMBOSIS

ISCHEMIC SUCH AS DEEP VENOUS THROMBOSIS (DVT)

LEADING TO PULMONARY EMBOLISM **(PE)** AND THE POST-PHLEBITIC SYNDROME

- CANCER PATIENTS HAVE AN INCREASED RISK OF DEVELOPING BLOOD CLOTS, WITH ROUGHLY ONE IN FIVE EXPERIENCING VTE—EITHER AS A DEEP VEIN THROMBOSIS (DVT) OR A PULMONARY EMBOLISM (PE). CURRENT INTERNATIONAL GUIDELINES RECOMMEND CANCER PATIENTS BE GIVEN INJECTIONS OF A LOW-MOLECULAR-WEIGHT HEPARIN (LMWH) TO TREAT AND PREVENT RECURRENCE OF AVT.

- HOWEVER, NEW DATA, PUBLISHED IN THE ***JOURNAL OF CLINICAL ONCOLOGY***, FOUND THAT PRESCRIBING RIVAROXABAN SIGNIFICANTLY REDUCED VTE RECURRENCE AMONG PATIENTS WITH CANCER AND AVT.

Nicholas j. Short, jean m. Connors New Oral Anticoagulants and the Cancer Patient The Oncologist-2014-Short-82-93-2.pdf

DIRECT THROMBIN INHIBITORS

- THESE DRUGS ARE NOW WIDELY USED IN THE CLINIC AS THEY DO NOT REQUIRE ROUTINE MONITORING OF THE ANTICOAGULANT EFFECT, HAVE A PREDICTABLE ANTICOAGULANT EFFECT AND AN EFFICACY SIMILAR TO CLASSICAL ANTICOAGULANTS. THEY ONLY REQUIRE MONITORING IN CERTAIN CLINICAL SITUATIONS, SUCH AS ACUTE HEMORRHAGE, SUSPECTED OVERDOSE OR EMERGENCY SURGERY.

RISK FACTORS

- MYELOMA PATIENTS, TREATED WITH PROTHROMBOTIC CHEMOTHERAPIES (THALIDOMIDE, LENALIDOMY WITH DEXAMETHASONE) HAVE BEEN ASSOCIATED WITH INCIDENCE OF THROMBOSIS ABOUT 30%.

  - RISK FACTORS:
    - PREVIOUS BLEEDING
    - THROMBOCYTOPENIA
    - RECENT SURGERY
    - TUMOR METASTASIS:
      - MELANOMA
      - CHORIOCARSINOMA
      - THYROID CARCINOMA
      - RENAL CELL CARCINOMA

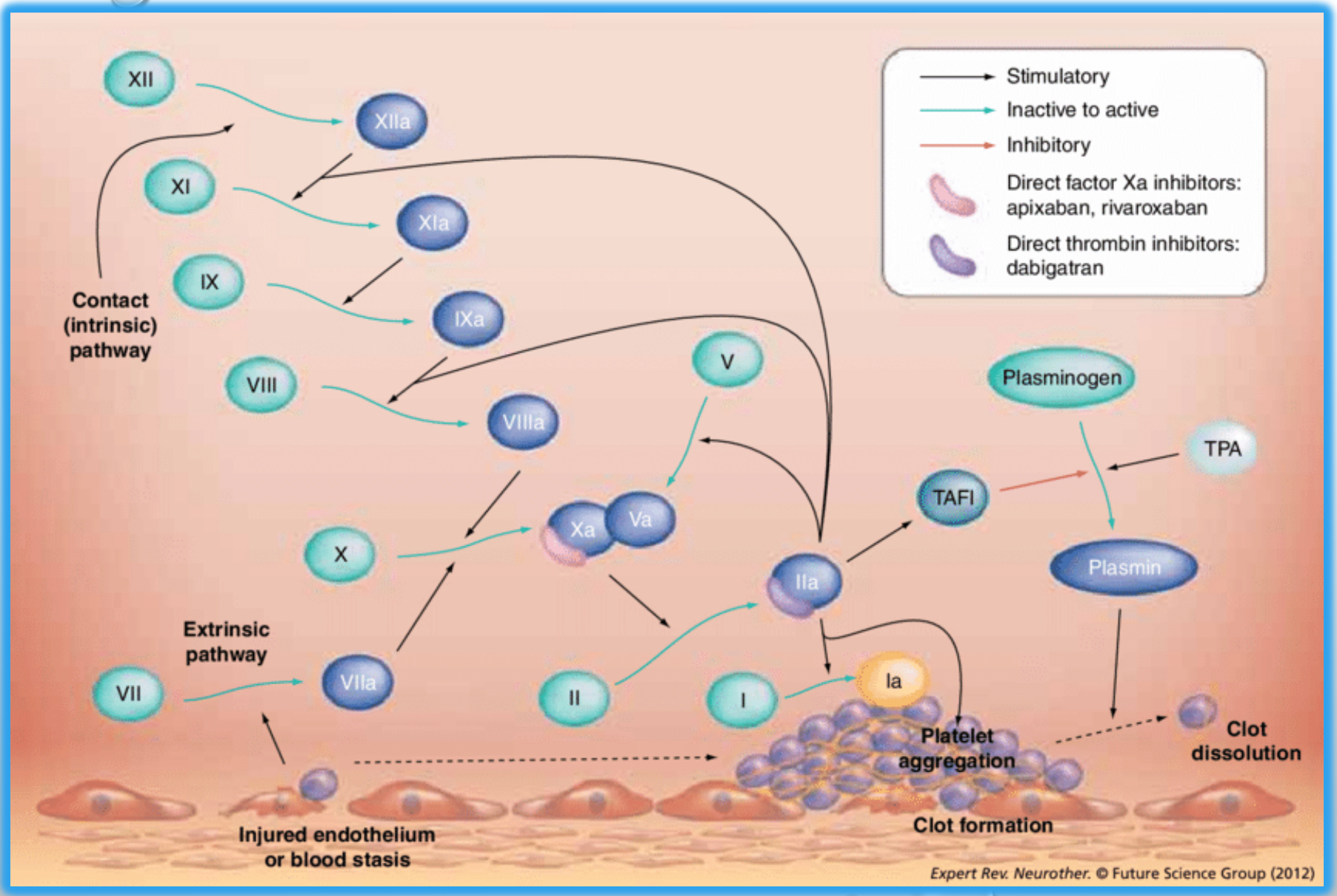
VARIABLES THAT INCREASE THROMBOTIC RISK IN THE CANCER PATIENT

- EXPRESSION AND/OR RELEASE OF PROCOAGULANTS BY TUMOR CELLS
- INCREASED PROCOAGULANT ACTIVITY OF HOST CELLS IN RESPONSE TO TUMOR
- STASIS (EITHER FROM TUMOR COMPRESSION OR IMMOBILIZATION OF THE HOST)
- ENDOTHELIAL DAMAGE
- ADVANCED AGE
- CHEMOTHERAPY
- PRESENCE OF CENTRAL VENOUS CATHETERS

DESPITE ANTICOAGULATION, PATIENTS WITH MALIGNANCY HAVE AN APPROXIMATELY 3-FOLD INCREASED RISK OF RECURRENT VTE

Nicholas j. Short, jean m. Connors New Oral Anticoagulants and the Cancer Patient The Oncologist-2014-Short-82-93-2.pdf

Coagulation cascade and the site of action of apixaban, rivaroxaban and dabigatran



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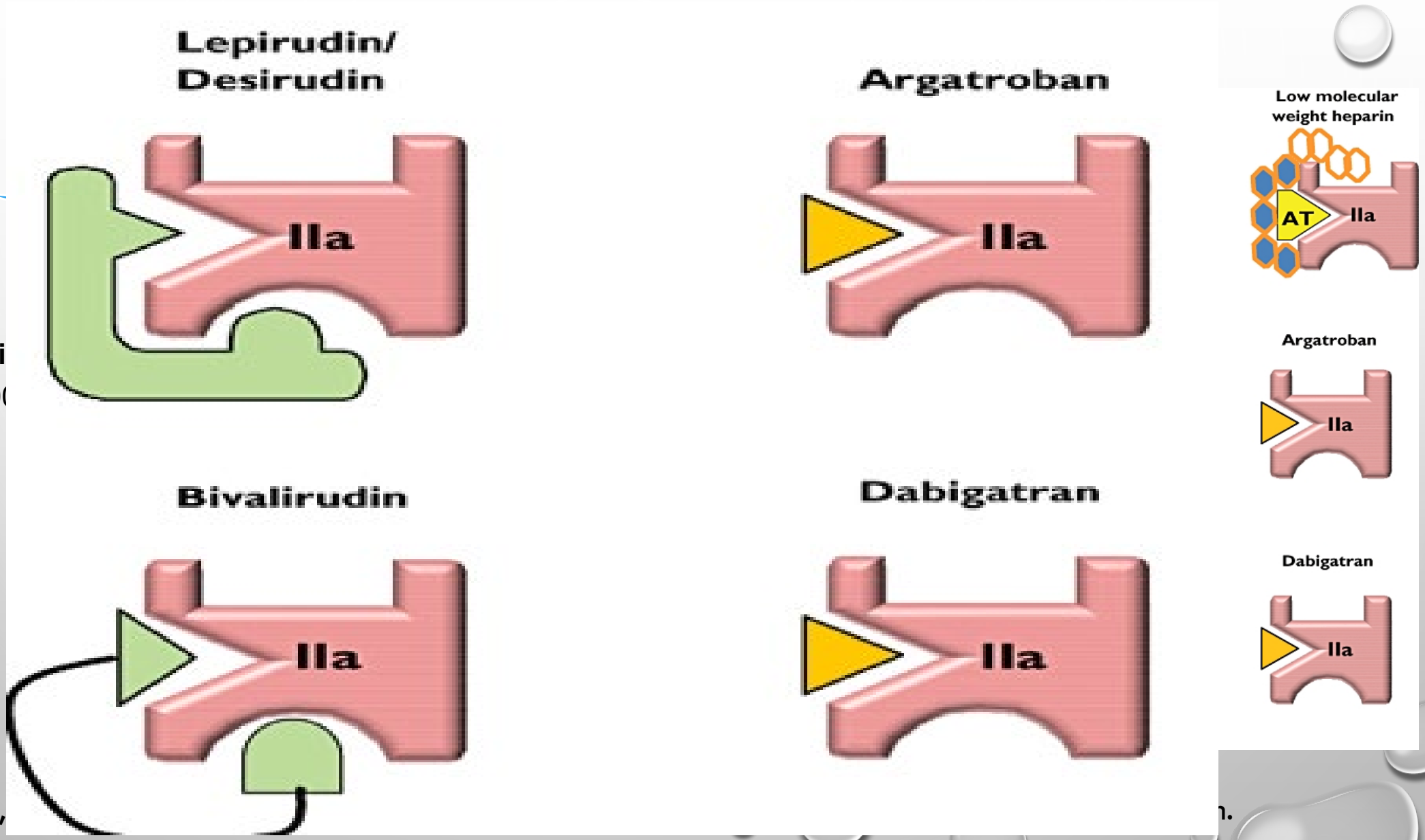

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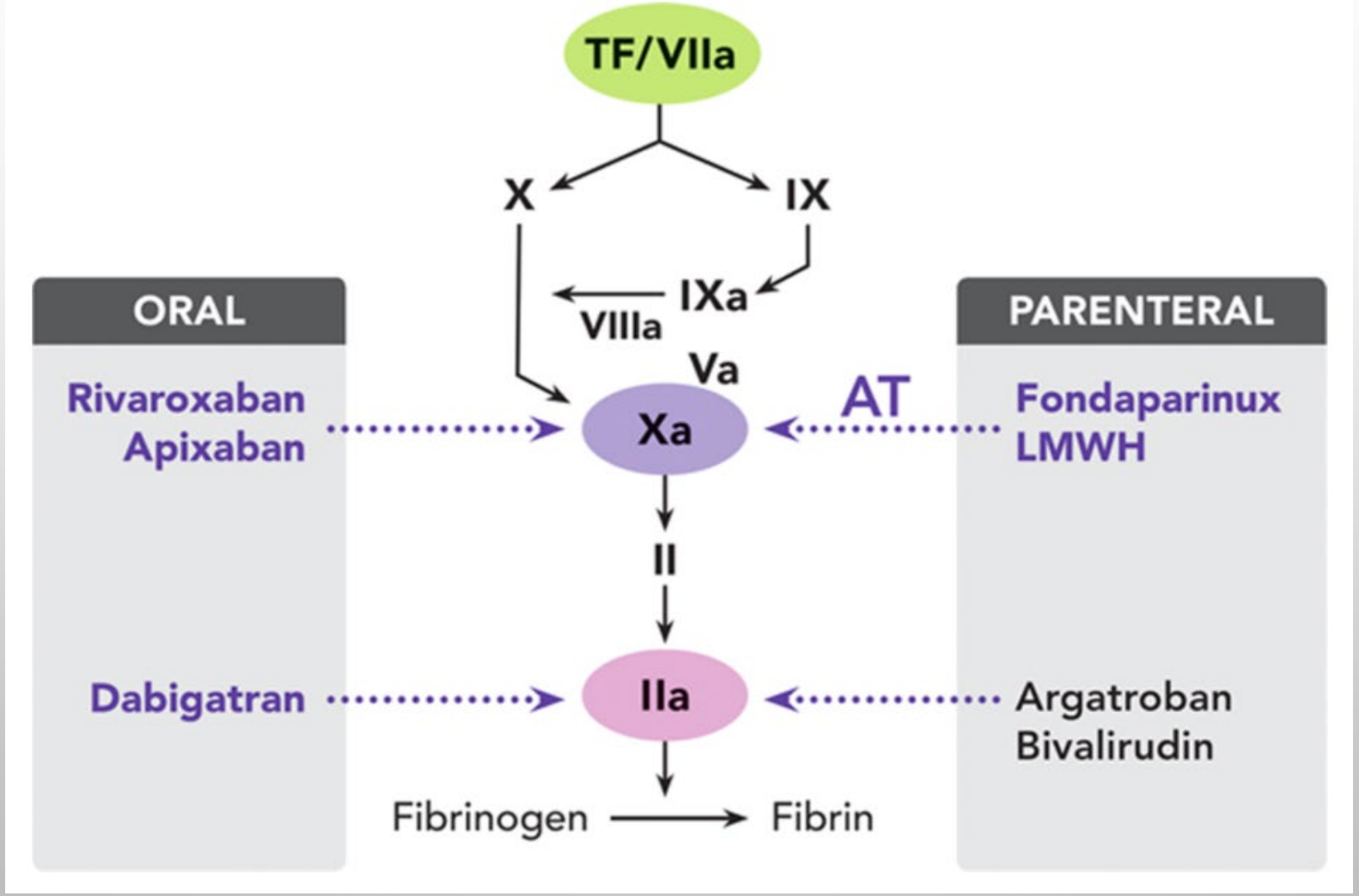
DIRECT THROMBIN INHIBITOR



Risk Scale $CHADS_2$

Risk Factor	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75 years	1
Diabetes	1
Stroke (Ictus/AIT/previous peripheral embolism)	2

Risk Scale HAS-BLAD

Risk Factor	Score
Hypertension	1
Altered kidney/hepatic function	1 (per each)
Stroke (Ictus /AIT /previous peripheral embolism)	1
Bleeding tendency	1
Lábile INR_s	1
Elderly ≥ 65 years	1
Drugs ((Alcohol or drugs that interfere with hemostasis)	1 (per each)

Pister R., et al. Chest 2010:138(5):1093-1100

Risk Scale CHA_2DS_2-VAS

Risk Factor	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes	1
Stroke (Ictus/AIT/previous peripheral embolism)	2
Vascular disease (peripheral artery disease, ischemic heart disease, aortic plaque)	1
Age, 64-75 years	1
Sexo femenino	1

Stratification of the risk of thrombosis according to ACCP

American College of Chest Physicians (ACCP)

Laboratory tests, expected drug levels, critical drug levels and required time interval before intervention.

Drug	Laboratory assay	Expected drug levels* (dosage)	Proposed cut-off for surgery	Time interval before operations, inter-ventions and spinal anaesthesia
Rivaroxaban	Anti-Xa activity (PT/INR)	Peak: 270 ng/m (189–419)† Trough: 26 ng/ml (6–87)† (20 mg daily)	<50 ng/ml for urgent surgery and low bleeding risk <30 ng/ml for high-risk surgery	≥24 h if bleeding risk of surgery is low/ intermediate ≥48 h in case of high bleeding risk with surgery, elderly patients, renal failure¶
Apixaban	Anti-Xa activity (PT/INR)	Peak: 171 ng/ml (91–321)† Trough: 103 ng/ml (41–230)† (5 mg twice daily)	<50 ng/ml for urgent surgery and low bleeding risk <30 ng/ml for high-risk surgery	≥24 h if bleeding risk of surgery is low/intermediate ≥48 h in case of high bleeding risk with surgery, elderly patients, renal failure¶
Edoxaban	Anti-Xa activity (PT/INR)	Peak: 170 ng/ml (120–250)‡ Trough: 22 ng/m (10–40)‡ (60 mg daily)	<50 ng/ml for urgent surgery and low bleeding risk <30 ng/ml for high-risk surgery	≥24 h if bleeding risk of surgery is low/intermediate ≥48 h in case of high bleeding risk with surgery, elderly patients, renal failure¶
Dabigatran	Diluted thrombin time Ecarin clotting time (thrombin time)	Peak: 184 ng/ml (64–443)† Trough: 90 ng/ml (31–225)† (150 mg twice daily)	<50 ng/ml for urgent surgery and low bleeding risk <30 ng/ml for high-risk surgery	≥36 h if bleeding risk of surgery is low ≥48 h in the event of high bleeding risk with surgery, elderly patients, renal fail- ure¶

aPPT = activated partial thromboplastin time; INR = international normalised ratio; LMWH = low molecular weight heparin; PT = prothrombin time; UFH = unfractionated heparin * adapted from [67, 68] † median; 5th to 95th percentile ‡ median; interquartile range ¶ in patients with renal failure, the interruptio interval shall be extended by 1 to 2 days (depending on the severity and the bleeding risk of the intervention) or drug level determined using an appropriate laboratory test

THE RECOMMENDED REVERSAL AGENTS FOR ALL ANTICOAGULANTS

- Protamine
- Vitamin K oral (phytonadione), and IV solution
- Fresh frozen plasma (FFP)
- 4-factor **prothrombin complex concentrate** (4-factor PCC)
- 3-factor PCC
- RhfVIIa Activated Prothrombin Complex Concentrates (APCC)

  (anti-inhibitor coagulant complex, vapor heated)
- Desmopressin (DDAVP)
- Idarucizumab
- Oral charcoal

COAGULATION FACTOR PRODUCTS

- **IT IS CONSIDERED IN PATIENTS WITH SERIOUS, LIFE-THREATENING BLEEDING PROBLEMS.**
  - Anti-fibrinolytic agents (tranexamic acid, ε-aminocaproic acid)
  - Desmopressin (DDAVP) improves platelet functions
  - Excess drug removal with hemodialysis/activated carbon.
  - Use of more potent idarucizumab therapies and active or inactive Prothrombin Complex Concentrates (APCCS or PCCS).
  - If idarucizumab is not available, "factor eight derived activity inhibitor" (fVIIIa) is given.
  - If apcc are not available the alternative is ƒIV or ƒIII pcc
  - Recombined activated factor VII (rƒVIIa)

Characteristics of commonly used Direct Inhibitors anticoagulants: mechanism of action, pharmacokinetics and elimination.

Agent	Mechanism of action	t_{max}	$T_{1/2}$	Elimination	Drug interactons	Prolonged half-life
Rivaroxaban	Inhibits factor Xa	2–4 h	5-9 h (healthy) 11-13 h (elderly)	➢ **33% Renal** elimination of unchanged drug ➢ **33% Renal** elimination of drug metabolites ➢ **33% Faecal** elimination ➢ **Metabolised** by CYP3A4, CYP2J2 and CYP450-independent mechanisms, and P-gp transporter mechanisms in kidneys/ intestine	CYP3A4 P-glicoprotein Use of rivaroxaban with a strong dual inhibitor or inducer of CYP3A4 and P-glycoprotein is not recommended	Elderly people Liver disease Renal impairment
Apixaban		3–4 h	8–15 h	➢ **46% Faecal** elimination ➢ 25–28% **Renal** elimination ➢ **Metabolised** by CYP3A4 mechanisms in liver, and multiple other pathways in kidney/intestine	CYP3A4 P-glicoprotein	Older patients, renal impairment
Dabigatran	Inhibits thrombin	0.5–2 h	12–14 h	➢ **85% Renal** elimination ➢ **6% Faecal** elimination ➢ **Metabolised** by esterase-catalysed hydrolysis in plasma or liver and P-gp transporter mechanisms	**P-glicoprotein**	Elderly people Liver disease Renal impairment

CRITERIA FOR NOAC USE IN CANCER PATIENTS REQUIRING ANTICOAGULATION

Risk factors for bleeding	**No major bleeding events in the past 2 months.** **Absence of intracranial or visceral tumor at high risk for major bleeding**
Platelets	Platelet count >50,000 per uL No anticipated decrease due to disease or chemotherapy
Coagulation studies	Normal PT, PTT, and fibrinogen
Liver function tests	No significant hepatic impairment (e.g., Child-Pugh B or C, cirrhosis)
Renal function	CrCl 30 mL/min (rivaroxaban) CrCl 15 mL/min (dabigatran and apixaban) No anticipated fluctuations due to nephrotoxic chemotherapy or other drugs
Medications	No concomitant use of drugs with strong effect on CYP3A4 and/ or P-glycoprotein Good medication compliance

PRECAUTION

- MANY CHEMOTHERAPEUTIC AGENTS HAVE SIGNIFICANT INTERACTIONS WITH THE ***CYP3A4 ENZYME*** AND/OR **P-GLYCOPROTEIN TRANSPORTER**, WHICH CAN ALTER THE LEVEL OF ANTICOAGULATION OF THE NOACS AND PREDISPOSE TO BLEEDING OR THROMBOTIC COMPLICATIONS.
- IN ABSENCE OF SAFETY AND EFFICACY DATA OF THE NOACS IN CANCER POPULATIONS, THESE AGENTS SHOULD BE USED WITH CAUTION IN PATIENTS WITH ACTIVE MALIGNANCY ONLY AFTER CAREFUL EVALUATION OF THE RISKS AND BENEFITS FOR INDIVIDUAL PATIENTS

Oncology drugs with CYP3A4 and P-glycoprotein interactions

	CYP3A4 interactionsa			P-glycoprotein interactionsb,c		
Oncology drugs	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Antimitotic agents						
Vinblastine	ttt		t	o	o	
Vincristine	ttt		t	o		
Vinorelbine	ttt		t			
Docetaxel	ttt		t	o		
Paclitaxel	ttt	tt		o		
Topoisomerase inhibitors						
Irinotecan	ttt			o		
Etoposide	ttt		t	o		
Alkylating agents						
Cyclophosphamide	t		t			
Ifosfamide	ttt		t			
Bendamustine				o		
Busulfan	ttt		t			

	CYP3A4 interactionsa			P-glycoprotein interactionsb,c		
Oncology drugs	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Intercalating agents						
Mitomycin C				o		
Tyrosine kinase inhibitors						
Imatinib	ttt		tt	o		o
Dasatinib	ttt		t			
Nilotinib	ttt		t	o		o
Erlotinib	ttt					
Lapatinib	ttt		t	o		o
Sunitinib	ttt					
Sorafenib	t					
Crizotinib	ttt		tt	o		o
Vemurafenib	t	tt		o		
Vandetanib	ttt					o
Monoclonal antibodies						
Brentuximab	ttt					

Oncology drugs with CYP3A4 and P-glycoprotein interactions

	CYP3A4 interactionsa			P-glycoprotein interactionsb,c		
Oncology drugs	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Hormonal agents						
Tamoxifen	ttt		t			o
Anastrozole			t			
Letrozole	t					
Fulvestrant	t					
Flutamide	ttt					
Bicalutamide			tt			
Enzalutamide	ttt	ttt				o
Abiraterone	ttt		tt			o
Immune-modulating agents						
Cyclosporine	ttt		tt	o		o
Sirolimus	ttt		t	o		
Everolimus	ttt			o		
Temsirolimus	ttt		t	o		
Tacrolimus	ttt		t	o		
Dexamethasone	ttt	ttt		o	o	o
Prednisone	t	tt				

	CYP3A4 interactionsa			P-glycoprotein interactionsb,c		
Oncology drugs	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Supportive care						
Ondansetron	ttt			o		
Palonosetron	t					
Aprepitant	ttt	tt	tt			
Fosaprepitant	ttt	tt	tt			
Oxycodone	ttt					
Fentanyl	ttt		t			
Methadone	ttt		t			
Acetaminophen	t		t			
Clonazepam	ttt					

a ttt, strong interaction; tt, moderate interaction; t, weak interaction.
bData for strength of P-glycoprotein interactions are limited. o, indicates that an interaction has been documented.

PATIENT ASSESSMENT

- INITIAL ASSESSMENT
  - How severe the bleeding is and where it is located ?
  - The patient is actively bleeding?
  - What anticoagulant agent the patient is receiving ?
  - When the last dose of anticoagulant was administered ?
  - Could the patient have taken an overdose of anticoagulant with or without intention?
  - Does the patient have a history of a kidney or liver condition that may cause excessive anticoagulant effects?
  - Other medications that may affect hemostasis (eg, acetylsalicylic acid (asa),coplidogrel) are being given?
  - Does the patient have any other co-morbidities that may promote bleeding (eg, kidney problems, uremia)

BLEEDING ASSESSMENT

- THE BLEEDING APPRAISAL:
  - SEVERITY OF BLEEDING
  - BLEEDING SITE
  - PROPORTION OF HEMORRHAGE
  - AMOUNT OF BLOOD LOST

STUDIES AND TESTS

HEMOGLOBIN LEVELS

VITAL SIGNS

IMAGE STUDIES

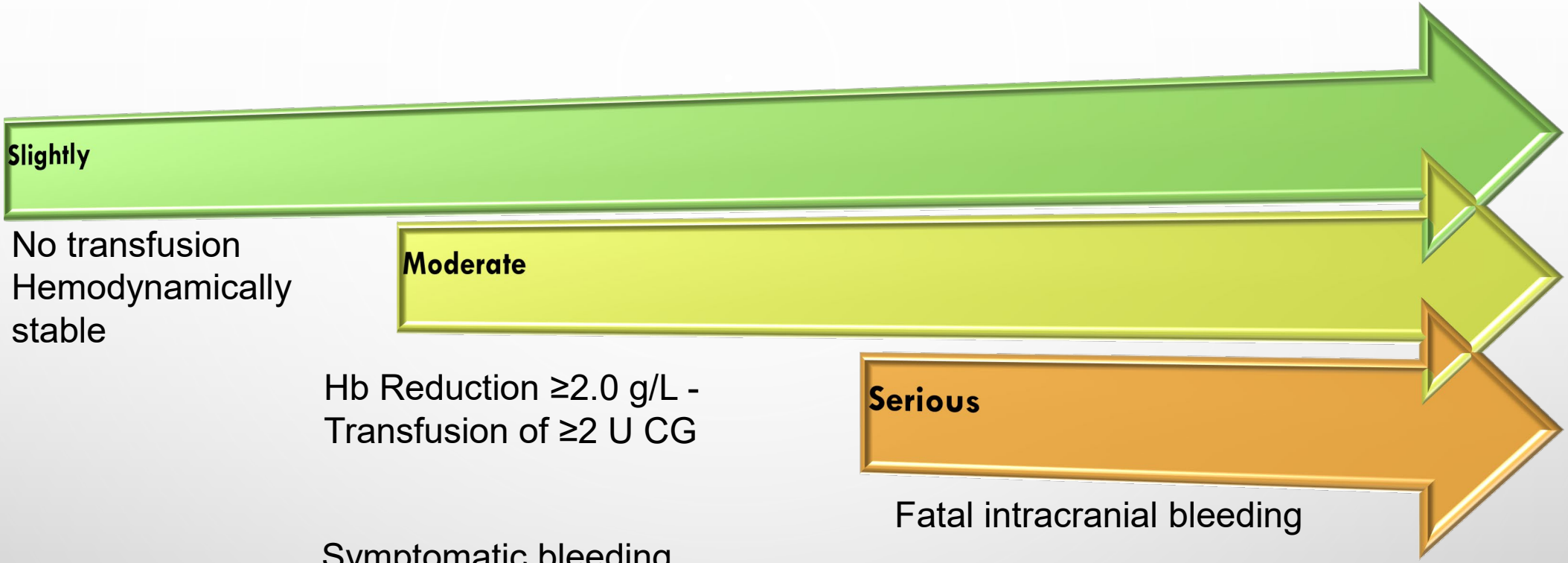
COMPUTED TOMOGRAPHY CT

(INTRACRANIAL OR RETROPERITONEAL HEMORRHAGE)

ENDOSCOPY

(TO DISPLAY THE BLEEDING REGION)

Criteria for defining severity of bleeding



No transfusion
Hemodynamically stable

Hb Reduction ≥2.0 g/L -
Transfusion of ≥2 U CG

Symptomatic bleeding in an organ (intraocular, intracranial, intraspinal, intramuscular with compartmental, retroperitoneal, intraarticular, or pericardial syndrome)

Fatal intracranial bleeding

Hb Reduction ≥5.0 g/L

Transfusion of ≥4 U CG

Hypotension that requires inotropic agents IV

Needs surgical intervention

BLEEDING ASSESSMENT

(INTERVENTION)

SOMETIMES A BLEEDING THAT APPEARS TO BE SIGNIFICANT AS **IT MAY BE**

(EPISTAXIS, HEMORRHOID BLEEDING), IN FACT **CAN BE MANAGED**;

LOCAL MEASURES:

ICE

LOCAL PRESSURE

NONE LIFE-THREATENING BLEEDING

CHECK LAST INTAKE

RESTORATION OF NORMAL COAGULATION TO BE EXPECTED AT 12–24 H

(IN CASE OF CREATININ CLEARANCE > 80 ML/MIN)

24–36 H (IN CASE OF CREATININ CLEARANCE 50–80 ML/MIN)

LOCAL HEMOSTATIC INTERVENTIONS,

FLUID MANAGEMENT,

TRANSFUSION

CONSIDER TRANEXAMIC ACID (1000 MG 3DD) OR DDAVP (0.3 MG/KG)

PRACTICAL GUIDE FOR HOW TO MANAGE BLEEDING COMPLICATIONS IN PATIENTS ON DIRECT ORAL ANTICOAGULANTS

ORAL THROMBIN INHIBITORS

(*DABIGATRAN*)

ORAL FACTOR XA INHIBITORS

(RIV*AROXABAN, APIXABAN, EDOXABAN*)

NONE LIFE-THREATENING BLEEDING

CHECK LAST INTAKE;

RESTORATION OF NORMAL COAGULATION TO BE EXPECTED AT 12–24 H

(IN CASE OF CREATININ CLEARANCE > 80 ML/MIN)

24–36 H (IN CASE OF CREATININ CLEARANCE 50–80 ML/MIN)

LOCAL HEMOSTATIC INTERVENTIONS

FLUID MANAGEMENT

TRANSFUSION

CONSIDER TRANEXAMIC ACID (1000 MG 3DD) OR DDAVP (0.3 MG/KG)

Suggested management strategy in case of hemorrhagic complications in patients using direct oral anticoagulants, modified from [15] PCC prothrombin complex concentrate, dd daily, DDAVP de-amino D-arginine vasopressin

Levi Critical Care (2016) 20:249 DOI 10.1186/s13054-016-1413-3

MAJOR BLEEDING (PROFUSE)

- **THEY SHOULD BE HANDLED IN AN ENVIRONMENT OR INTENSIVE CARE UNIT WITH ADEQUATE HEMODYNAMIC SUPPORT.**
  - OBSERVATION
  - REMOVAL OF MEDICATION WITH ACTIVATED CHARCOAL/HEMODIALYSIS
    - DIRECT INTERVENTIONS
      - ADMINISTRATION OF ANTI-FIBRINOLYTIC AGENTS
      - POTENTIAL PRODUCTS OF PROTHROMBOTIC COAGULATION FACTORS
      - SURGERY

CONSULTATION TO SURGERY AND ENDOSCOPY SHOULD BE NOTIFIED IMMEDIATELY INDEPENDENTLY OF THE POTENTIAL NEED FOR INTERVENTION.

MAJOR BLEEDING (PROFUSE)

- IMMEDIATELY DISCONTINUE ALL ANTICOAGULANT AND ANTIPLATELET THERAPY
- FAST AND CONTINUOUS HEMODYNAMIC EVALUATION
- EFFECTIVE ESTABLISHMENT OF AIRWAY AND VENOUS ACCESS
- CONTROL OF BODY TEMPERATURE, PH AND ELECTROLYTE BALANCE, INCLUDING CALCIUM
- TRANSFUSION IF NECESSARY
  - RED CELLS (SEVERE ANEMIA, BLEEDING)
  - PLATELETS (THROMBOCYTOPENIA, PLATELET DYSFUNCTION)
  - PLASMA (COAGULOPATHIES ASSOCIATED WITH TRAUMA)

Anticoagulant-associated bleeding event

Rapid and continuous assessment and reassessment of patient's condition:

-**Initiate** life-saving therapy as required (ie. intubation, ventilation, fluid resuscitation. packed red blood cell etc.)

-**Consider** transfer to an intensive -care unit setting-notify required team members (eg, Radiology staff, OR Staff) early in the resuscitation.

-**Measure** the activity of coagulation cascade, hemoglobin and platelets, frequently and act on observed abnormalities

Withdraw anticoagulant therapy (remove from bedside)

Administer appropriate dose of antidote (if one exists)

Address mechanical causes of bleeding, this may require:

Radiological Intervention
Endoscopy
Surgery

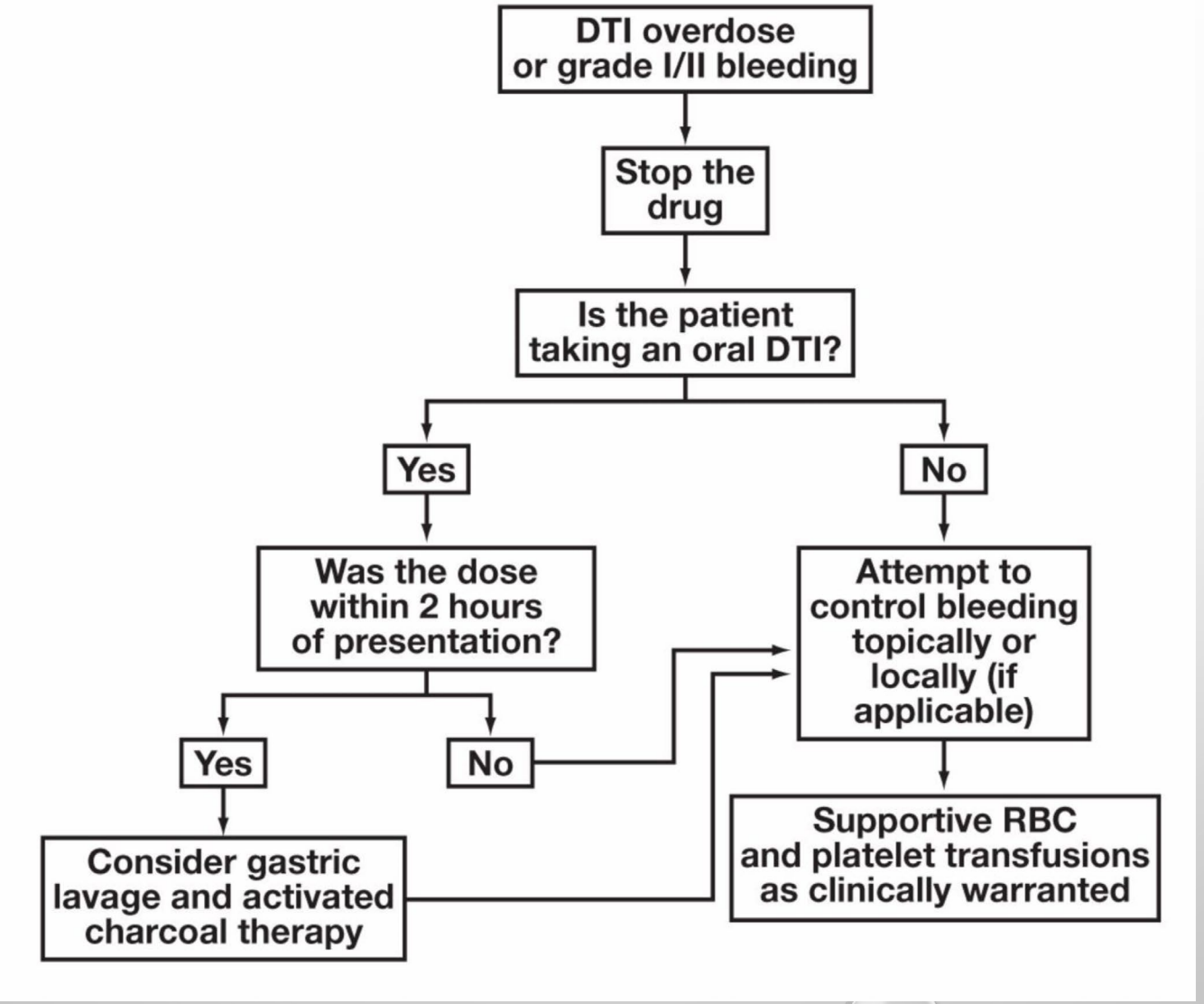
Consider administration of prohemostatic agents:

Antifibrinolytic agents(eg, tranexamic acid)
Desmopressin (DDAVP)
Recombinant factor VIIa

Consider modalities that may specifically remove the anticoagulant:

Dialysis
Hemoperfusion, and/or
Plasmapheresis

A Reasonable Approach to DTI Reversal



From: Pathology Consultation on Monitoring Direct Thrombin Inhibitors and Overcoming Their Effects in Bleeding Patients
Am J Clin Pathol. 2013 140(5):610-622. doi:10.1309/AJCP9VJS6KUKNCHW

PHARMACOLOGICAL OPTIONS FOR REVERSING THE EFFECT OF THE DIRECT-ACTING ORAL ANTICOAGULANTS (NONSPECIFIC, SPECIFIC)

Inhibitor		**Bleeding Risk Category Low or Moderate**	**Bleeding Risk Category High or Very High**
Nonspecific reversal (prohemostatic interventions)			
	Prothrombin complex concentrates		
	Activated prothrombin complex concentrates		
	Recombinant factor VIIa		
Specific reversal			
	Directed at dabigatran	Stop **dabigatran** 2 days (CrCl >80 mL/min), 3 days (CrCl 50–79 mL/min), or 4–5 days (CrCl 31–49 mL/min) prior	Stop **dabigatran** 2 days (CrCl >80 mL/min), 3 days (CrCl 50–79 mL/min), or 4–5 days (CrCl 31–49 mL/min) prior
	Idarucizumab		
	Directed at rivaroxaban, apixaban, and edoxaban	--Stop **rivaroxaban** 3 days (CrCl >30 mL/min) prior --Stop **apixaban** 3 days (CrCl ≥50 mL/min) or 4 days (CrCl 30–49 mL/min) prior	--Stop **rivaroxaban** 3 days (CrCl >30 mL/min) prior --Stop **apixaban** 3 days (CrCl ≥50 mL/min) or 4 days (CrCl 30–49 mL/min) prior
	Andexanet-alfa		
	Ciraparantag		

AVAILABLE COAGULATION TESTS TO DETERMINE THE ANTICOAGULANT EFFECT OF ORAL ANTICOAGULANTS

Drug	Coagulation test	Pros	Cons
Dabigatran	**aPTT** Activated partial thromboplastin time	Highly available	Do not reflect the intensity of coagulation **Low specificity**
	TT Thrombin time	Highly available	It only determines the effect of dabigatran but **lacks specificity**
	dTT Dilute thrombin time	Very accurate and precise to estimates plasma concentrations of dabigatran	Requires specific calibrators and controls in specialized laboratories with trained personal **Low specificity**
	ECT Ecarin clotting time		Requires specific calibrators and controls in specialized laboratories with trained personal Limited standardization and validation required **Low specificity Interloop variability reported**
	ECA Ecarin chromogenic assay	Very accurate and precise to estimates plasma concentrations of dabigatran	Requires specific calibrators and controls in specialized laboratories with trained personal **Low specificity**
	DRVV-T Dilute Russell's viper venom time		Requires specific calibrators and controls in specialized laboratories with trained personal Low specificity
Rivaroxaban	**PT**	Highly available	Do not reflect the intensity of coagulation **Low specificity**
Rivaroxaban and Apixaban	**Chromogenic anti-Xa assays**	Very accurate and precise to estimates plasma concentrations of dabigatran	Requires specific calibrators and controls in specialized laboratories with trained personal
	DRVV-T Dilute Russell's viper venom time		Requires specific calibrators and controls in specialized laboratories with trained personal **Low specificity**

NCCN Guidelines Version 1.2016

Anticoagulant	Reversal of Anticoagulation	Precautions/Considerations
DTI Argatroban ($L_{1/2}$ 45 min with normal hepatic function)	- Discontinue medication - No antidote exists / beneficial effects if ascribed to: - **unactivated and activated** - prothrombin complex concentrates (**aPCC**, - vapor heated 50–100 units/kg IV) may be - effective - **rhFVIIa** (90mcg/kg IV) - Desmopressin (**DDAVP**) - 0.3 mcg/kg reduced bleeding	Limited data support all reversal strategies **aPCC** (eg, anti-inhibitor coagulant complex, vapor heated) and rhFVIIa assocted with throboembolic event. Repeated doses associated with tachyphylapsis and hyponatremia

"For life-threatening bleeding, the NCCN Guidelines Panel currently favors use of rhFVIIa as the first-line agent. Hemofiltration or hemodiafiltration can accelerate the clearance of bivalirudin "

All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 1.2016

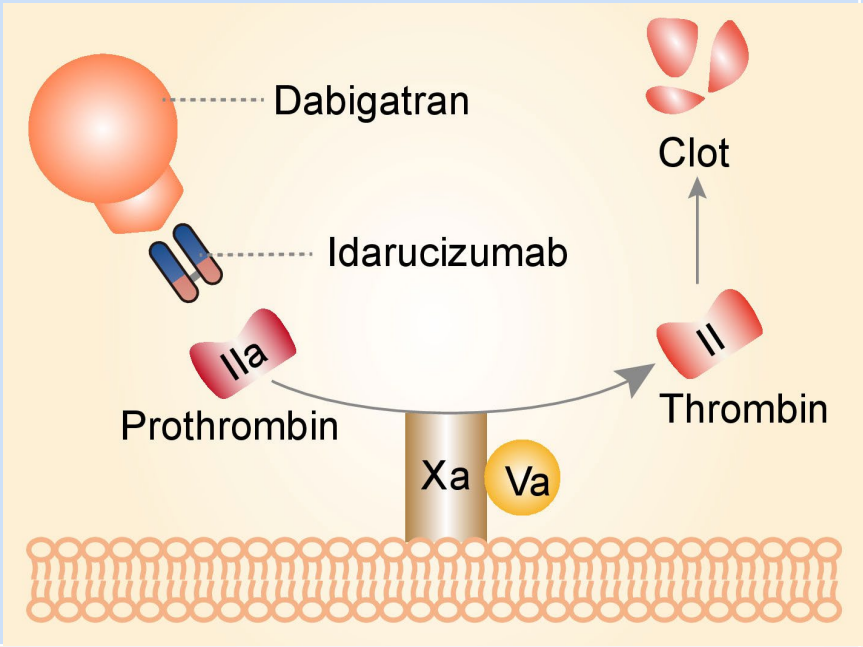
Anticoagulant	Reversal of Anticoagulation	Precautions/Considerations
DTI Bivalirubin ($L_{1/2}$ 25 min with normal renal function)	- Discontinue medication - No antidote exists / beneficial effects if ascribed to: Hemofiltration and hemodialysis - show effectiveness to remove - bivalirudin - (aPCCs) activate prothrombin - complex concentrates - (anti-inhibitor coagulant complex - vapor heated 05-100 units/kg IV) - rhFVIIa (90mcg/kg IV) - Desmopressin (DDAVP) - 0.3 mcg/kg reduced bleeding	Limited data support all reversal strategies aPCC (eg, anti-inhibitor coagulant complex, vapor heated) and rhFVIIa assocted with throboembolic event. Repeated doses associated with tachyphylapsis and hyponatremia

"For life-threatening bleeding, the NCCN Guidelines Panel currently favors use of rhFVIIa as the first-line agent. Hemofiltration or hemodiafiltration can accelerate the clearance of bivalirudin "

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 1.2016

Anticoagulant	Reversal of Anticoagulation	Precautions/Considerations
DTI Davigatran ($L_{1/2}$ 14-17 hr)	- Discontinue medication - Adminster ***idarucizumab***, 5 g IV 	Limited data support all reversal strategies aPCC (eg, anti-inhibitor coagulant complex, vapor heated) and rhFVIIa assocted with throboembolic event. Patients with renal failure/severe renal insufficiency, dialysis may be helpful in addition to idarucizumab

"For life-threatening bleeding, the NCCN Guidelines Panel currently favors use of rhFVIIa as the first-line agent. Hemofiltration or hemodiafiltration can accelerate the clearance of bivalirudin "

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUMMARY

- WHEN FACED WITH AN EMERGENCY SITUATION, FIRST EVALUATE THE PATIENT, ALWAYS ASKING IF HE/SHE TAKES AC, WHAT, WHEN WAS THE LAST DOSE?
- LABORATORY COAGULATION TESTS GUIDE, BUT ARE NOT SPECIFIC TO QUANTIFY THE EFFECT OF DTI..
- ALWAYS EVALUATE KIDNEY FUNCTION AND MAINTAIN GOOD URINE OUTPUT.
- THE SHORT HALF-LIFE (12 HOURS) OF THE OAC GUARANTEES ITS PROMPT REVERSAL.

UNDERSTANDING THE DELICATE HEMOSTATIC BALANCE IN CANCER PATIENTS:

THE RISKS OF COAGULATION AND THE RISKS OF HEMORRHAGE.

EFFECTIVELY CONTROL HEMATOLOGIC COMPLICATIONS.

"CANCER WE ARE ALL"

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