UNIVERSITÀ DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

Gestione e frequenza delle complicanze in emergenza nel paziente in terapia anticoagulante: complicanza emorragica

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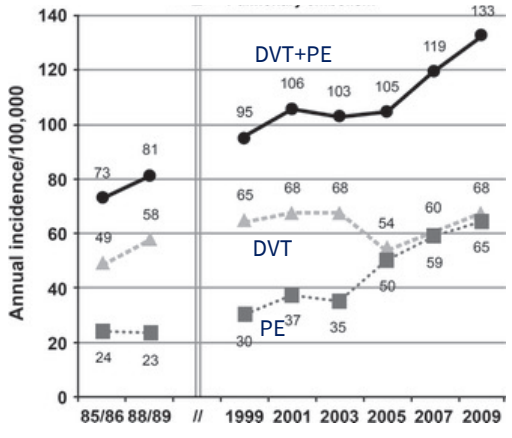
Torino

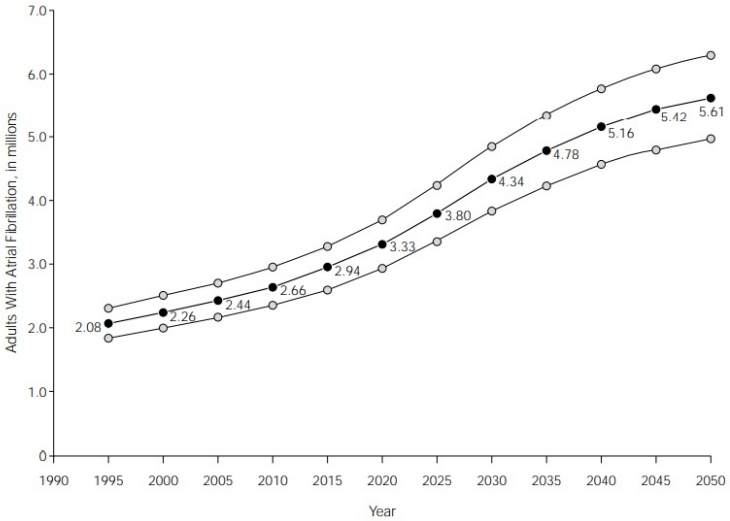
Increasing number of patients with anticoagulant indication

Incidence (US) of patients with thromboembolism



Heit JA et al. J Thromb Thrombolysis. 2016 Jan;41(1):3-14.

Projected prevalence (US) of patients with AF



Go AS et al. JAMA. 2001 May 9;285(18):2370-5.

NOVITÀ IN COAGULAZIONE
attraverso i centri emostasi e trombosi
Torino, 12-13 novembre 2021

Anticoagulants: first cause of adverse drug events leading to ED visit

Table 2. US Emergency Department (ED) Visits for Adverse Drug Events (ADEs) by Drug Class, 2013-2014[a]

Drug Class	ED Visits for ADEs		ED Visits for ADEs Resulting in Hospitalization[b]	
	No. of Cases	National Estimate, % (95% CI)[c]	No. of Cases Hospitalized	National Estimate, % Hospitalized (95% CI)[c]
Hematologic Agents				
Anticoagulants	7211	17.6 (14.1-21.0)	3691	48.8 (42.0-55.5)
Vitamin K antagonists (warfarin)	6179	15.1 (12.3-17.9)	3156	48.5 (41.8-55.1)
Factor Xa inhibitors	580	1.4 (0.9-2.0)	300	50.4 (43.0-57.8)
Unfractionated and low-molecular-weight heparins	450	0.8 (0.6-1.1)	224	46.5 (38.7-54.4)
Direct thrombin inhibitors (oral)	173	0.5 (0.2-0.7)	107	63.8 (49.8-77.8)
Antiplatelets	2656	6.6 (4.7-8.5)	1312	44.4 (35.7-53.2)
Platelet $P2Y_{12}$ receptor antagonists[d]	1837	4.6 (3.0-6.2)	942	47.8 (37.7-57.9)
Aspirin with or without dipyridamole	1545	3.6 (2.2-5.0)	753	41.2 (32.6-49.8)

Shehab N et al. JAMA. 2016 Nov 22;316(20):2115-2125.

AMERICAN COLLEGE of CARDIOLOGY

2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

Tomaselli GF et al. J Am Coll Cardiol. 2020 Aug 4;76(5):594-622.

American College of Emergency Physicians

Anticoagulant Reversal Strategies in the Emergency Department Setting: Recommendations of a Multidisciplinary Expert Panel

Baugh CW et al. Ann Emerg Med. 2020 Oct;76(4):470-485.

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ASSESS AND IDENTIFY SEVERITY OF BLEED

MANAGE AND CONTROL BLEED

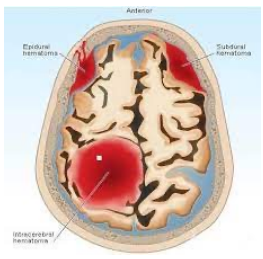
DETERMINE WETHER/WHEN TO RESTART ANTICOAGULATION

5.2. Defining Bleed Severity

If ≥1 of the following factors applies, the bleed is classified as major.

Hemodynamic Instability

Bleeding in a Critical Site



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Hemodynamic Instability

Heart rate and blood pressure

- increased heart rate
- systolic blood pressure <90 mm
- decrease in systolic blood pressure >40 mmHg
- orthostatic blood pressure changes (drop >20 mmHg)

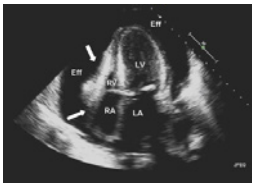
Surrogate markers

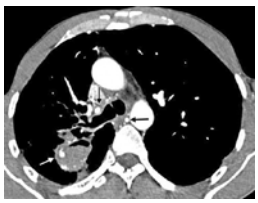
- urine output <0.5 mL/kg/h
- Increased serum lactate (>2 / 4 mM)

Clinical signs/symptoms

- pallor, vasoconscriction
- confusion

Critical Site Bleeds Bleeds that compromise the organ's function





Type of Bleed	Initial Signs and Symptoms	Potential Consequences of Bleed
Pericardial tamponade	• Shortness of breath, tachypnea, hypotension, paradoxical pulse, jugular venous distension, tachycardia, muffled heart sounds, rub	• Cardiogenic shock • Death
Airway: includes posterior epistaxis	• **Airway:** hemoptysis, shortness of breath, hypoxia • **Posterior epistaxis:** profuse epistaxis, hemoptysis, hypoxia, shortness of breath	• Hypoxemic respiratory failure • Death

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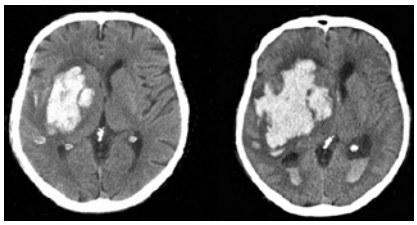
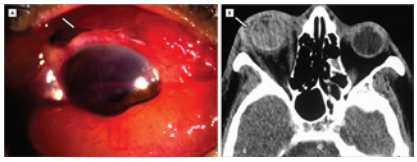
Critical Site Bleeds Bleeds that compromise the organ's function

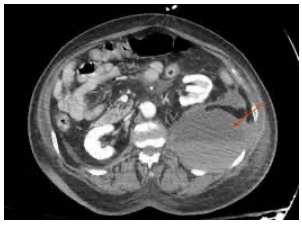


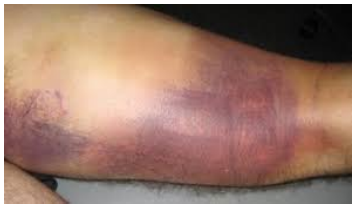


Type of Bleed	Initial Signs and Symptoms	Potential Consequences of Bleed
ICH: includes intraparenchymal, subdural, epidural, and subarachnoid hemorrhages	• Unusually intense headache, emesis, reduced or loss of consciousness, vision changes, numbness, weakness, aphasia, ataxia, vertigo, seizures	• Stupor or coma • Permanent neurological deficit • Death
Other central nervous system hemorrhage: includes intraocular, intra- or extra-axial spinal hemorrhages	• **Intraocular:** monocular eye pain, vision changes, blindness • **Spinal:** back pain, bilateral extremity weakness or numbness, bowel or bladder dysfunction, respiratory failure	• **Intraocular:** permanent vision loss • **Spinal:** permanent disability, paraplegia, quadriplegia, death

JAMA Ophthalmol. 2013;131(10):1313. doi:10.1001/jamaophthalmol.2013.4566

Critical Site Bleeds Bleeds that compromise the organ's function





Type of Bleed	Initial Signs and Symptoms	Potential Consequences of Bleed
Hemothorax, intra-abdominal bleeding, and retroperitoneal hemorrhage	• **Hemothorax:** tachypnea, tachycardia, hypotension, decreased breath sounds • **Intra-abdominal (non-GI):** abdominal pain, distension, hypotension, tachycardia • **Retroperitoneal hemorrhage:** back/flank/hip pain, tachycardia, hypotension	• **Hemothorax:** respiratory failure • **Retroperitoneal hemorrhage:** femoral neuropathy • **All:** hypovolemic shock, death
Extremity bleeds: includes intramuscular and intra-articular bleeding	• **Intramuscular:** pain, swelling, pallor, paresthesia, weakness, diminished pulse • **Intra-articular:** joint pain, swelling, decreased range of motion	• **Intramuscular:** compartment syndrome, paralysis, limb loss • **Intra-articular:** irreversible joint damage

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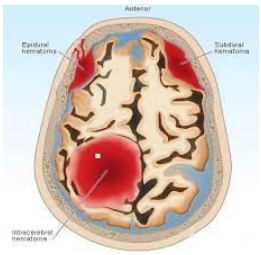
5.2. Defining Bleed Severity

If ≥1 of the following factors applies, the bleed is classified as major.

Hemodynamic Instability

Bleeding in a Critical Site



Overt Bleeding With Hemoglobin Drop ≥2 g/dL or Administration of ≥2 Units of Packed RBCs

American College of Emergency Physicians®

Anticoagulant Reversal Strategies in the Emergency Department Setting: Recommendations of a Multidisciplinary Expert Panel

Christopher W. Baugh, MD, MBA*; Michael Levine, MD; David Cornutt, MD; Jason W. Wilson, MD, MA; Richard Kwun, MD, MBA; Charles E. Mahan, PharmD, PhC; Charles V. Pollack, Jr, MD, MA; Evie G. Marcolini, MD; Truman J. Milling, Jr, MD; W. Frank Peacock, MD; Rachel P. Rosovsky, MD, MPH; Fred Wu, MHS, PA-C; Ravi Sarode, MD; Alex C. Spyropoulos, MD; Todd C. Villines, MD; Timothy D. Woods, MD; John McManus, MD, MBA; James Williams, DO, MS*

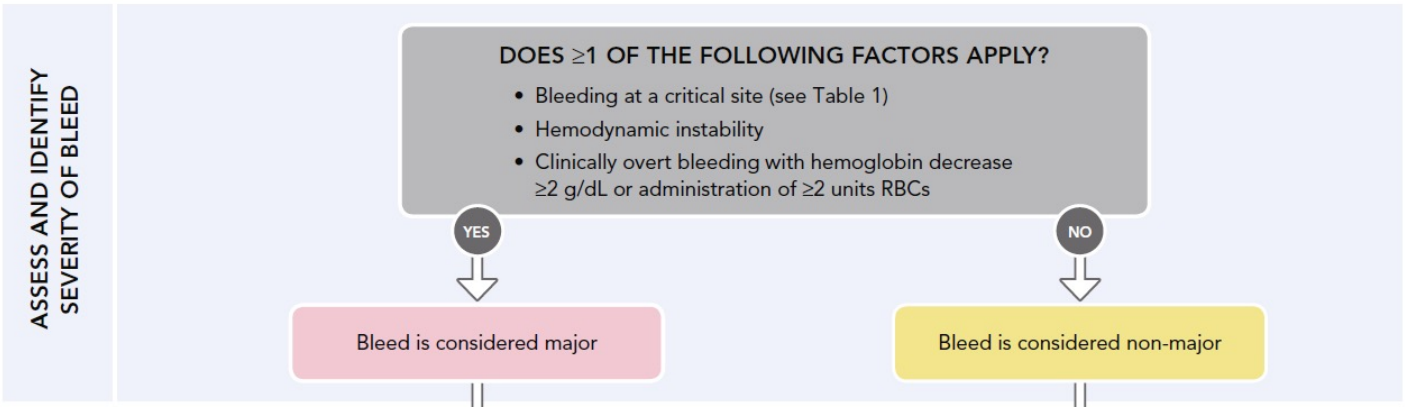
LIFE-THREATENING BLEED
Composite of BARC Type 3a & 3b definitions: • Hemoglobin drop ≥5 g/dL from a recent (premorbid) known value (provided hemoglobin drop is related to bleed) PLUS transfusion OR • Uncontrolled bleeding requiring procedural intervention (e.g., Interventional Radiology, endoscopic, surgical)* OR • Hemodynamic instability: bleeding requiring intravenous vasoactive agents

*Excluding dental/nasal/skin/hemorrhoid

CRITICAL SITES
• Brain* • Eye** • Spine • Airway • Pericardium • Aorta • Closed space with concern for compartment syndrome

*Does not include microbleeds or hemorrhagic transformation
**Intraocular with vision compromise

Baugh CW et al. Ann Emerg Med. 2020 Oct; 76(4): 470–485.



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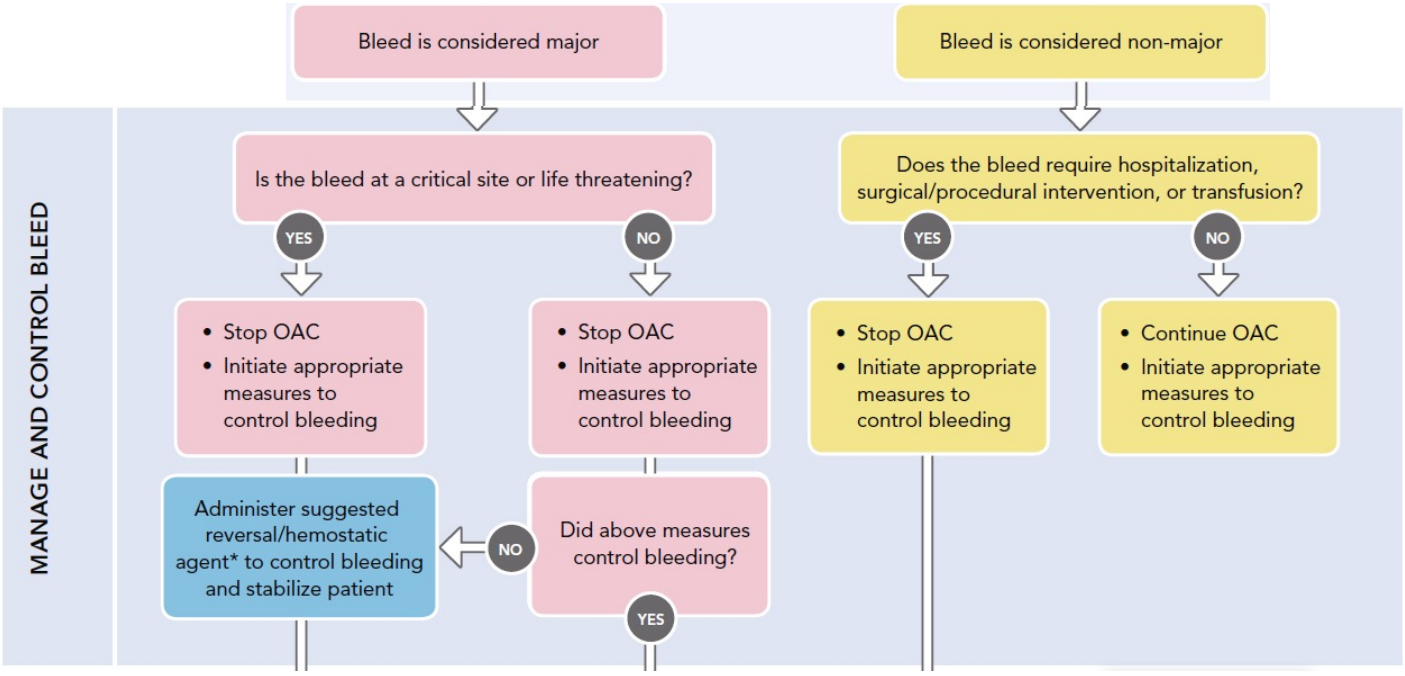

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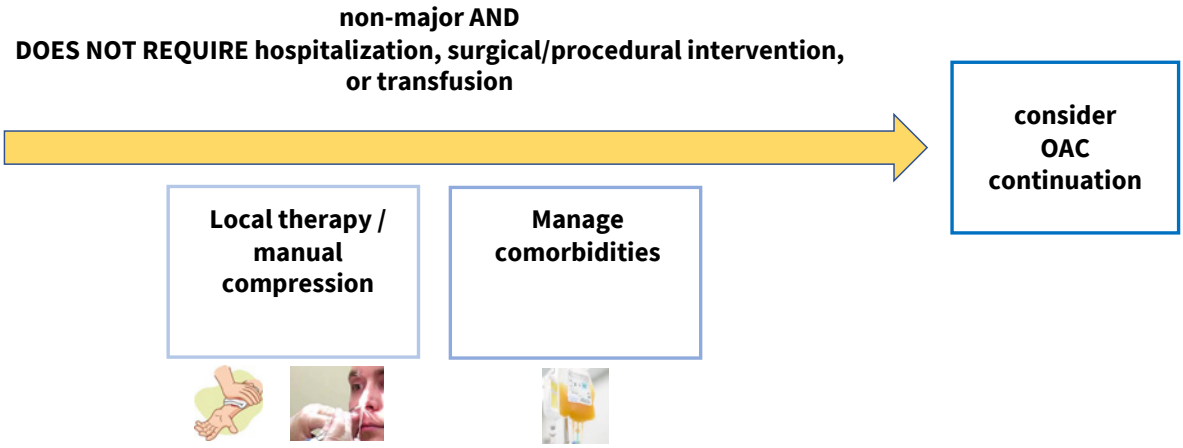
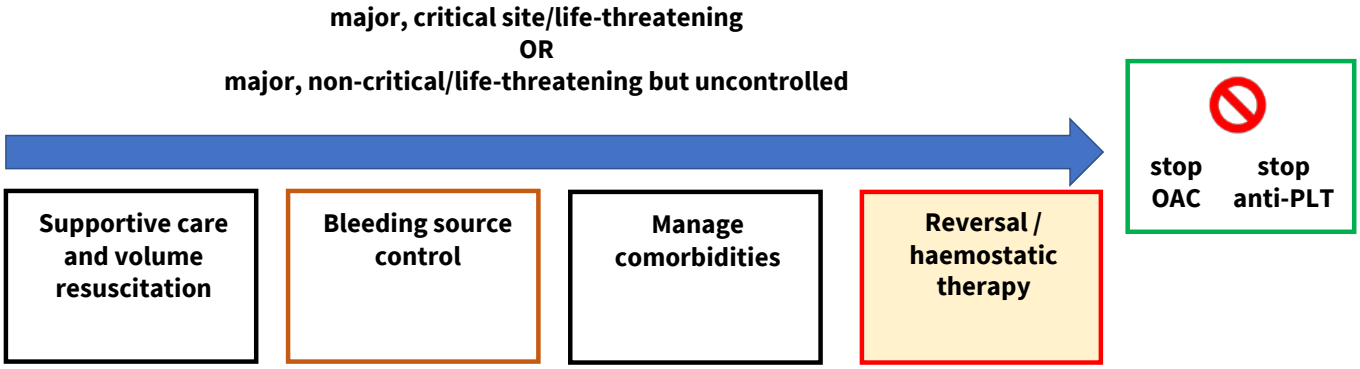

non-major AND
DOES NOT REQUIRE hospitalization, surgical/procedural intervention,
or transfusion
consider
OAC
continuation
Local therapy /
manual
compression
Manage
comorbidities


major, critical site/life-threatening
OR
major, non-critical/life-threatening but uncontrolled
Supportive care
and volume
resuscitation
Bleeding source
control
Manage
comorbidities
Reversal /
haemostatic
therapy
stop
OAC
stop
anti-PLT

major, critical site/life-threatening
OR
major, non-critical/life-threatening but uncontrolled

stop OAC **stop anti-PLT**

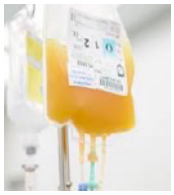
Supportive care and volume resuscitation

(Oxygen)
Cristalloids
Packed red cells

Transfusions

RBC

- A restrictive (rather than liberal) RBC transfusion strategy improves survival and reduces the risk of recurrent bleeding.
- Patients with symptomatic anemia or active bleeding should receive RBC transfusions to maintain a hemoglobin **≥7 g/dL**.
- In patients with underlying **coronary artery disease**, particularly those with acute coronary syndromes, the current guidelines recommend a target hemoglobin **≥8 g/dL**.



PLT

- PLTs should be transfused to maintain a platelet count **≥50*10⁹/L** and cryoprecipitate to maintain a **fibrinogen >100 mg/dL**.
- "The writing committee does not support routine administration of platelets for patients who are bleeding and on antiplatelet agents, although this can be considered in specific cases, particularly after other measures such as reversal of OAC have failed."

mod. from Tomaselli GF et al. J Am Coll Cardiol. 2020 Aug 4;76(5):594-622.

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major, critical site/life-threatening
OR
major, non-critical/life-threatening but uncontrolled

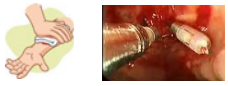
stop OAC **stop anti-PLT**

Supportive care and volume resuscitation

(Oxygen)
Cristalloids
Packed red cells

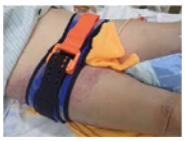
Bleeding source control

Compression
Procedures
Surgery

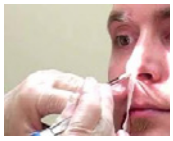


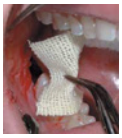
Bleeding source control

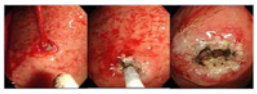
Compression

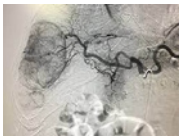


Procedures









Surgery

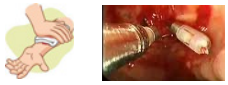
major, critical site/life-threatening
OR
major, non-critical/life-threatening but uncontrolled

stop OAC **stop anti-PLT**

Supportive care and volume resuscitation

(Oxygen)
Cristalloids
Packed red cells

Bleeding source control



Manage comorbidities

PLT transfusion
Kidney failure*
(Liver disease)

*esp. dabigatran
(80-85% renal esc.)

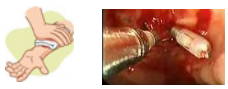
major, critical site/life-threatening
OR
major, non-critical/life-threatening but uncontrolled

stop OAC **stop anti-PLT**

Supportive care and volume resuscitation

(Oxygen)
Cristalloids
Packed red cells

Bleeding source control



Manage comorbidities

PLT transfusion
Kidney failure*
(Liver disease)

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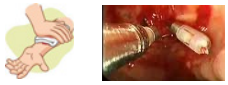
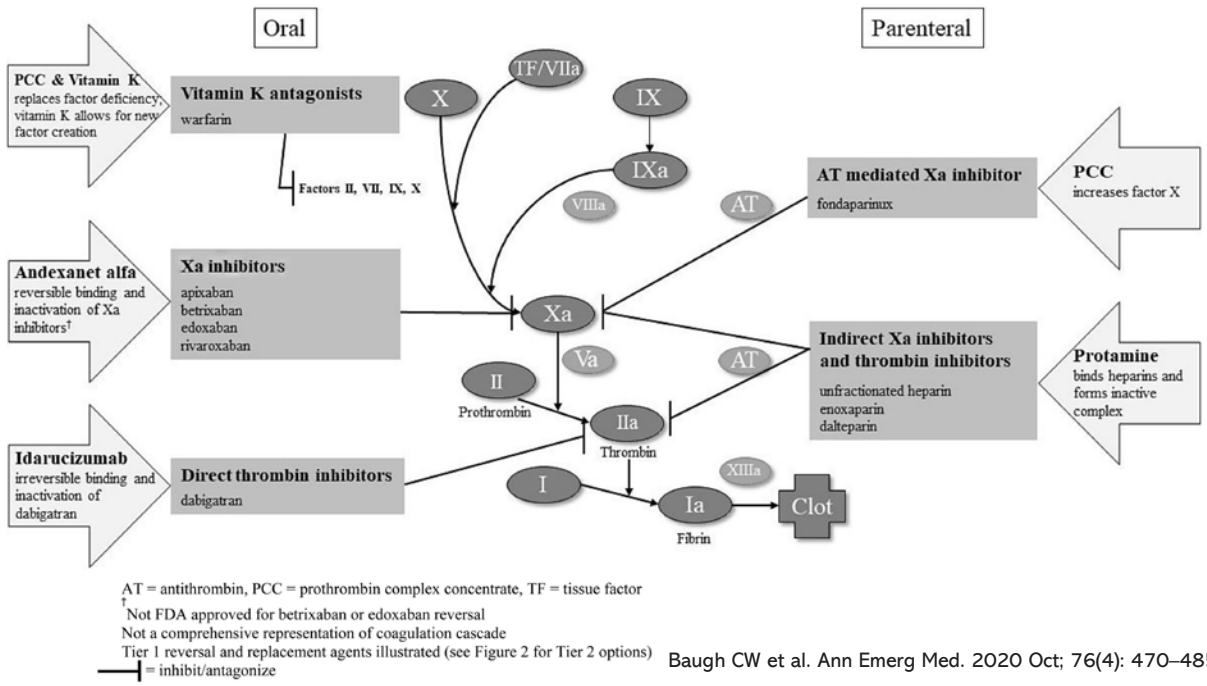
major, critical site/life-threatening
OR
major, non-critical/life-threatening but uncontrolled

stop OAC **stop anti-PLT**

Supportive care and volume resuscitation	Bleeding source control	Manage comorbidities	Reversal / haemostatic therapy
(Oxygen) Cristalloids Packed red cells		PLT transfusion Kidney failure* (Liver disease)	Vit. K Plasma PCC Idarucizumab Andexanet

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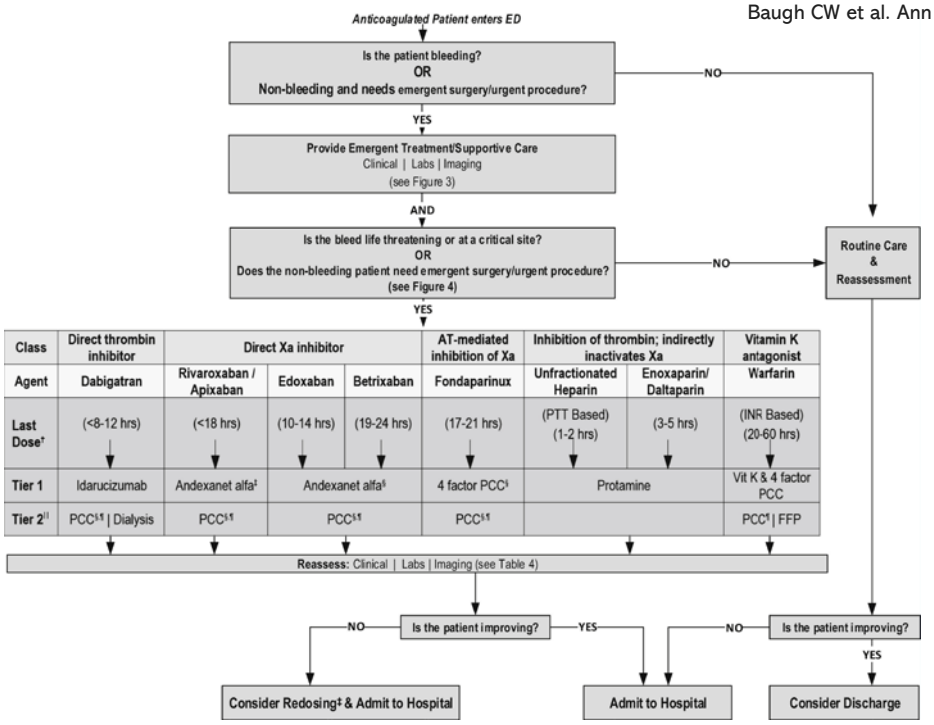

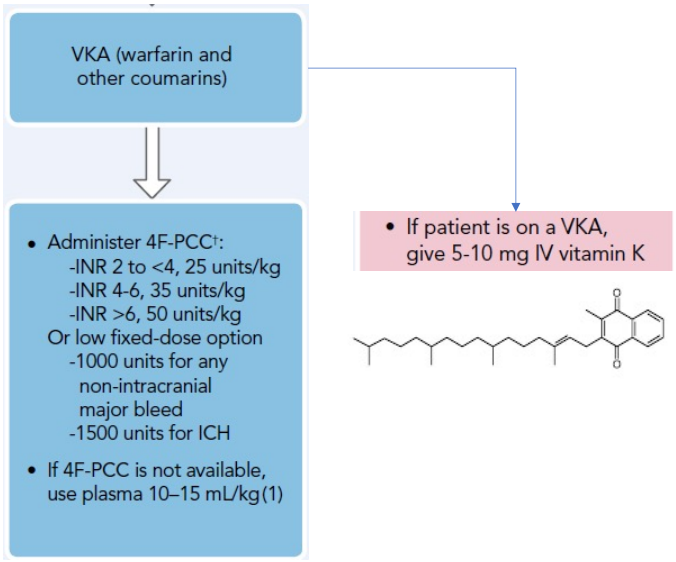

mod. from Tomaselli GF et al. J Am Coll Cardiol. 2020 Aug 4;76(5):594-622.

Drug	Clinical Objectives: Exclude Clinically Relevant* Drug Levels — Suggested Test	Interpretation	Clinical Objectives: Determine Whether On-Therapy or Above On-Therapy Levels Are Present — Suggested Test	Interpretation
Dabigatran	TT, aPTT	• **Normal TT** excludes clinically relevant* levels. • **Prolonged TT** does not discriminate between clinically significant and insignificant levels. • **Normal aPTT** usually excludes clinically relevant* levels if a sensitive reagent is used.	aPTT	• **Prolonged aPTT** suggests that on-therapy or above on-therapy levels are present. • **Normal aPTT** may not exclude on-therapy levels, particularly if a relatively insensitive aPTT reagent is used.
Apixaban	UFH or LMWH anti-FXa	• **Normal PT and aPTT** do not exclude clinically relevant* levels. • **UFH or LMWH anti-FXa below the lower limit of quantitation** probably excludes clinically relevant* levels.	PT	• **Prolonged PT** suggests that on-therapy or above on-therapy levels are present. • **Normal PT** may not exclude on-therapy levels, particularly if a relatively insensitive PT reagent is used.
Betrixaban, edoxaban, or rivaroxaban	UFH or LMWH anti-FXa	• **Normal PT and aPTT** does not exclude clinically relevant* levels. • **UFH or LMWH anti-FXa below the lower limit of quantitation** probably excludes clinically relevant* levels.	PT	• **Prolonged PT** suggests that on-therapy or above on-therapy levels are present. • **Normal PT** may not exclude on-therapy levels, particularly if a relatively insensitive PT reagent is used.

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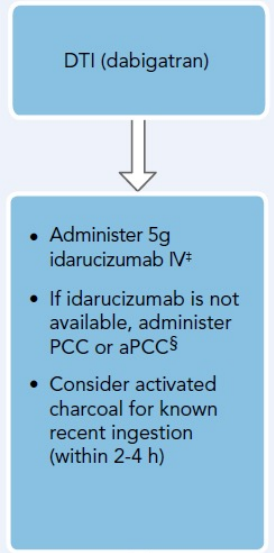

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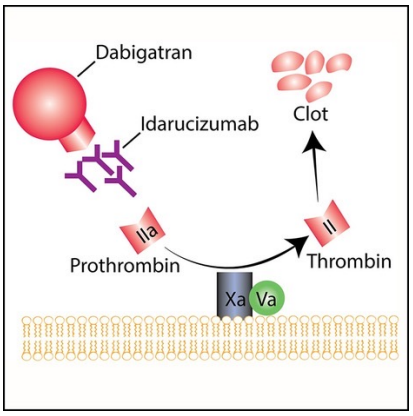

Idarucizumab
Frammento Fab umanizzato che antagonizza gli effetti del dabigatran. Somministrazione e.v., breve emivita.

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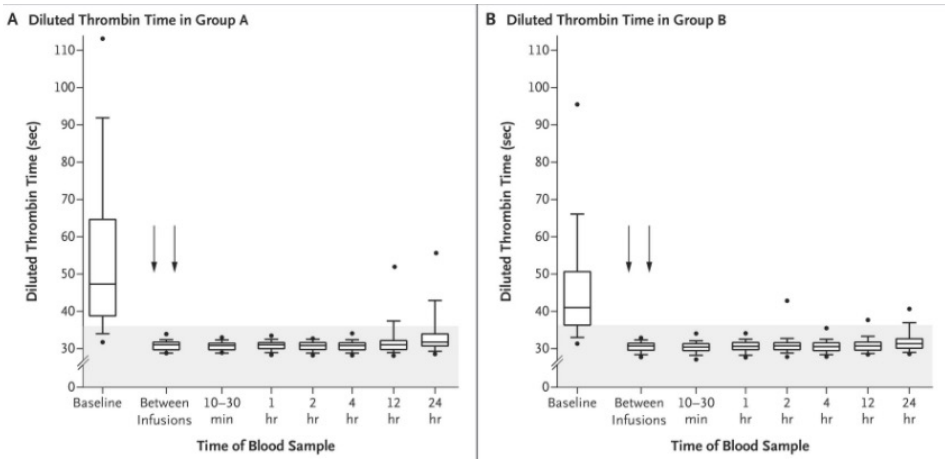
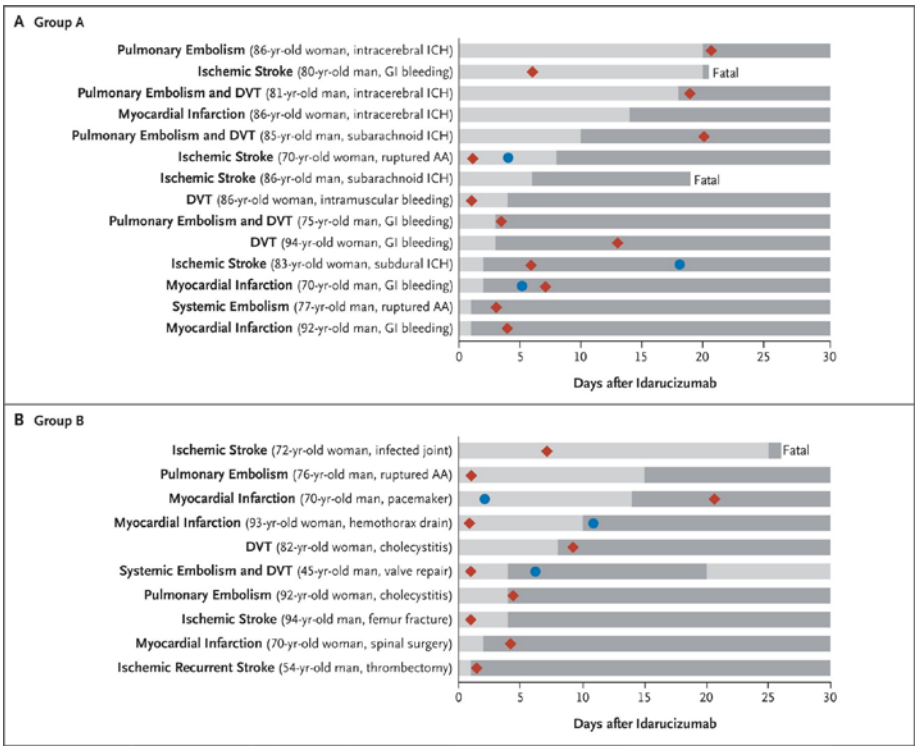


Pollack CV Jr et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. 2017 Aug 3;377(5):431-441.

Thrombotic events

30 days 4.8%
90 days 6.8%

Pollack CV Jr et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. 2017 Aug 3;377(5):431-441.



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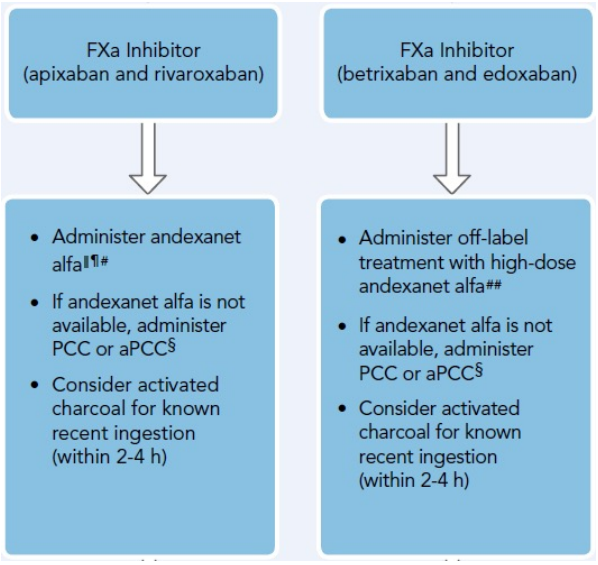
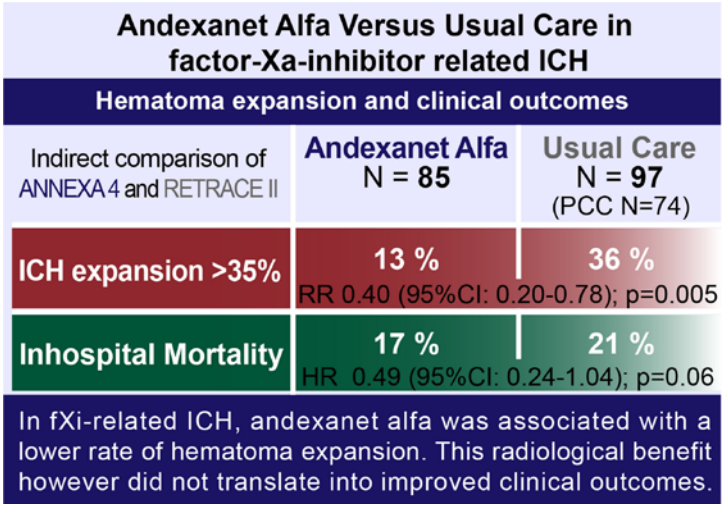
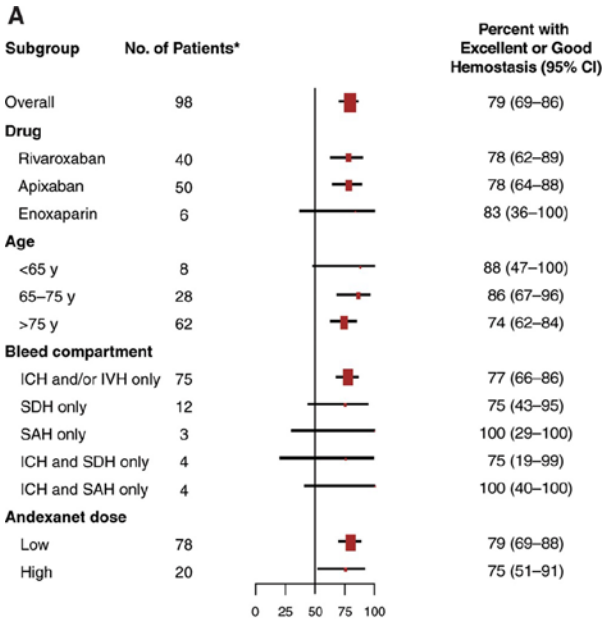
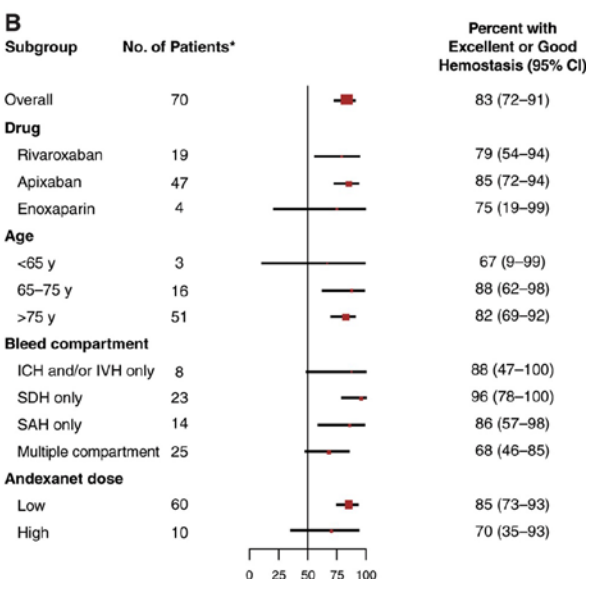


mod. from Tomaselli GF et al. J Am Coll Cardiol. 2020 Aug 4;76(5):594-622.



Huttner et al. Stroke. 2021 Oct 14;STROKEAHA121034572. Online ahead of print.





Novità in coagulazione attraverso i centri emostasi e trombosi – Torino, 13 novembre 2021 – F. Morello

Tranexamic acid

✓ Traumatic haemorrage
Obstetric/gynecologic haemorrage

1 g i.v. + 1 g/8h

✓ Ear
Mouth
Nose
Throat
Dental
(Bronchial)

local / nebulized
(i.v.)

✗ Gastrointestinal
Other

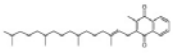
non-major
BUT REQUIRES surgical/procedural intervention, transfusion or hospitalization

Supportive care and volume resuscitation

Bleeding source control

Manage comorbidities

Vitamin K (2-5 mg p.o./i.v.) if VKA



stop OAC **stop anti-PLT**

Estimated Drug Half-Life Based on CrCl

	Dabigatran					Apixaban, Betrixaban, Edoxaban, or Rivaroxaban		
CrCl, mL/min	**≥80**	**50-79**	**30-49**	**15-29**	**<15**	**≥30**	**15-29**	**<15**
Estimated drug half-life, h	13	15	18	27	30 (off dialysis)	• Apixaban, edoxaban, rivaroxaban: 6-15 • Betrixaban: 19-27	• Apixaban: 17 • Edoxaban: 17 • Rivaroxaban: 9	• Apixaban: 17 (off dialysis) • Edoxaban: 10-17 (off dialysis) • Rivaroxaban: 13 (off dialysis)

CrCl = creatinine clearance.

Suggested Duration for Withholding DOAC Based on Bleed Risk

	Dabigatran					Apixaban, Betrixaban, Edoxaban, or Rivaroxaban		
CrCl, mL/min	**≥80**	**50-79**	**30-49**	**15-29**	**<15**	**≥30**	**15-29**	**<15**
Low	≥24 h	≥36 h	≥48 h	≥72 h	No data. Consider measuring dTT and/or withholding ≥96 h.	≥24 h	≥36 h	No data. Consider measuring agent-specific anti-Xa level and/or withholding ≥48 h.
Uncertain, intermediate, or high	≥48 h	≥72 h	≥96 h	≥120 h	No data. Consider measuring dTT.	48 h	No data. Consider measuring agent-specific anti-Xa level and/or withholding ≥72 h.	

Note: The duration for withholding is based upon the estimated DOAC half-life withholding times of 2 to 3 half-lives for low procedural bleeding risk and 4 to 5 drug half-lives for uncertain, intermediate, or high procedural bleeding risk (50-58).

UNIVERSITÀ DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

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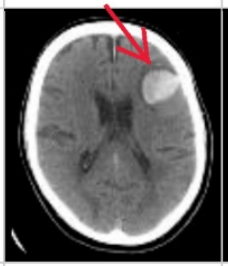
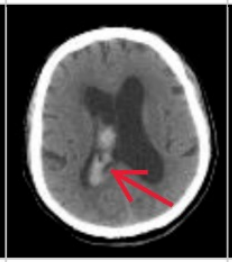
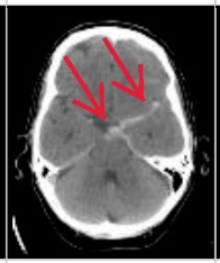
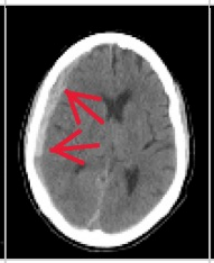
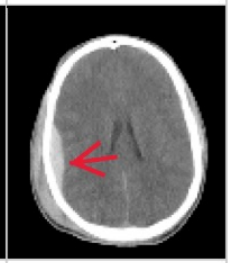
Specializzandi Scuola M.E.U. Università degli Studi di Torino

	Intraparenchymal	Intraventricular	Subarachnoid	Subdural	Epidural
Location	Inside of the brain	Inside of the ventricle	Between the arachnoid and the pia mater	Between the Dura and the arachnoid	Between the dura and the skull
Imaging					
Mechanism	High blood pressure, trauma, arteriovenous malformation, tumor, etc	Can be associated with both intraparenchymal and subarachnoid hemorrhages	Rupture of aneurysms or arteriovenous malformations or trauma	Trauma	Trauma or after surgery
Source	Arterial or venous	Arterial or venous	Predominantly arterial	Venous (bridging veins)	Arterial
Shape	Typically rounded	Conforms to ventricular shape	Tracks along the sulci and fissures	Crescent	Lentiform
Presentation	Acute (sudden onset of headache, nausea, vomiting)	Acute (sudden onset of headache, nausea, vomiting)	Acute (worst headache of life)	May be insidious (worsening headache)	Acute (skull fracture and altered mental status)