BLEEDING MANAGEMENT OF DOACS

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Initial assessment

* How severe is the bleeding and where is it located?
* Is the patient actively bleeding now?
* Which agent is the patient receiving?
* When was the last dose of anticoagulant administered?
* Could the patient have taken an intentional or unintentional overdose of the anticoagulant?
* Does the patient have a history of renal or hepatic disease that might cause excessive anticoagulant effect in the setting of standard drug dosing?
* Is the patient taking other medication(s) that could affect hemostasis (eg, aspirin, clopidogrel)?
* Does the patient have other comorbidities that could promote bleeding (eg, liver disease, uremia, thrombocytopenia)?

Bleeding severity

serious/major bleeding

* Bleeding requiring blood transfusion
* Bleeding into a critical closed space (eg, intracranial bleeding, compartment syndrome).
* Bleeding requiring an intervention for management (eg, surgery, interventional radiology procedures, endoscopic treatments)

Bleeding severity

Minor bleeding includes bleeding requiring a healthcare assessment or less invasive treatment

* heavy menstrual bleeding
* ecchymosis
* Epistaxis

Minor bleeding usually will not require interruption of anticoagulant therapy

Risk factors for bleeding with anticoagulation

Risk factor	Odds ratio for bleeding*
Modifiable risk factors	
Active peptic ulcer disease	4
Bleeding episode within the previous 3 months	4
Platelet count <50,000/microL	4
ICU or CCU	2.5
Renal insufficiency (eGFR <30; 30 to 59; or ≥60 mL/min/m^2)	2; 1.5; 1
Hepatic insufficiency (INR >1.5)	2
Active cancer	2
Rheumatic disease	2
Central venous catheter	2
Fixed risk factors	
Male sex	1.5
Older age (≥85; 40 to 80; or <40 years)	3; 2; 1
Non-white race (Asian, Hispanic, or African descent)	4; 2; 2

HAS-BLED

- **H**ypertension – 1 point
- **A**bnormal renal and/or hepatic function – 1 point each
- **S**troke – 1 point
- **B**leeding tendency/predisposition – 1 point
- **L**abile INR on warfarin – 1 point
- **E**lderly (age >65 years) – 1 point
- **D**rugs (aspirin or NSAIDs) and/or alcohol – 1 point each

Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic*	Points
H	Hypertension (ie, uncontrolled blood pressure)	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding tendency or predisposition	1
L	Labile INRs (for patients taking warfarin)	1
E	Elderly (age greater than 65 years)	1
D	Drugs (concomitant aspirin or NSAIDs) or excess alcohol use (1 point each)	1 or 2
		Maximum 9 points

HAS-BLED score (total points)	Bleeds per 100 patient-years¶
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5 to 9	Insufficient data

The HAS-BLED bleeding risk score has only been validated in patients with atrial fibrillation receiving warfarın.

ATRIA

Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA)

- Anemia – 3 points
- Severe renal disease (estimated glomerular filtration rate <30 mL/minute or dialysis-dependent) – 3 points
- Age ≥75 years – 2 points
- Any prior hemorrhage – 1 point
- Diagnosed hypertension – 1 point

Bleeding rates for low- (0 to 3 points), intermediate- (4 points), and high-risk patients (5 to 10 points) were 0.76, 2.62, and 5.76 events per 100 patient-years

HEMORR2HAGES

- **H**epatic or renal disease
- **E**thanol abuse
- **M**alignancy
- **O**lder age (>75 years)
- **R**educed platelet count or function, including aspirin therapy
- **R**e-bleeding risk (history of prior bleed)
- **H**ypertension
- **A**nemia
- **G**enetic factors
- **E**xcessive fall risk
- **S**troke

Risks of major bleeding per 100 patient-years were 1.9 (0 points), 2.5 (1 point), 5.3 (2 points), 8.4 (3 points), 10.4 (4 points), and 12.3 (≥5 points)

Index for predicting risk of bleeding with warfarin

This index was derived from a retrospective analysis of the incidence of bleeding in 556 outpatients treated with warfarin. There are four adverse risk factors. One point is given for the presence of each of these risk factors, for a total potential score from 0 to 4.
Age ≥65 years
History of stroke
History of gastrointestinal bleeding
One or more of the following comorbid conditions:
Recent myocardial infarction
Hematocrit <30%
Serum creatinine concentration >1.5 mg/dL (>133 micromol/L)
Diabetes mellitus
In the prospective validation portion of this study, the cumulative incidence of major bleeding after 48 months of treatment with warfarin in 264 outpatients was as follows:
Low risk (no risk factors present, point score 0): 3%
Intermediate risk (point score 1 to 2): 12%
High risk (point score 3 to 4): 53%

Adapted from Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med 1998; 105:91.

Management of Bleeding

- **Discontinue the anticoagulant**
- **Attempt hemostasis of bleeding site**
- **Maintenance of adequate fluid resuscitation and hemodynamic support**
- **Transfusion**
- **Laboratory test results**
  - Level of anticoagulation
  - Markers of blood loss
  - Organ function

Patient has a bleeding complication

- Specific antidotes for NOACs are still lacking and the strategies to reverse anticoagulant effect are limited.
- Time is the best advantage of NOACs, in view of their relatively short elimination half-lives.
- If a major bleeding complication occurs, standard supportive measurements must be started. These include mechanical compression, surgical haemostasis, fluid replacement, and additional haemodynamic support.

Interval since last dose

* Dabigatran – 12 to 17 hours; five half-lives will have elapsed by day 2.5 to 3.5 after the last dose.
* Rivaroxaban – 5 to 9 hours; five half-lives will have elapsed by day 1 to 2 after the last dose.
* Apixaban – 8 to 15 hours; five half-lives will have elapsed by day 1.5 to 3 after the last dose.
* Edoxaban – 6 to 11 hours; five half-lives will have elapsed by day 1.3 to 2 after the last dose.
* Betrixaban – 19 to 27 hours; five half-lives will have elapsed by day 4 to 5.5 after the last dose.

Renal and hepatic function

* Dabigatran – Excretion is approximately 80 to 85 percent renal.
* Rivaroxaban – Excretion is approximately 35 percent renal; severe hepatic impairment could result in bio-accumulation.
* Apixaban – Excretion is approximately 25 percent renal; severe hepatic impairment could result in bio-accumulation.
* Edoxaban – Excretion is approximately 35 percent renal; severe hepatic impairment could result in bio-accumulation.
* Betrixaban – Excretion is approximately 11 percent renal, not recommended in hepatic impairment.

Coagulation testing

Coagulation testing is not used for determining the anticoagulation status of a patient receiving a DOAC

* Prothrombin time/international normalized ratio (PT/INR)
* Activated partial thromboplastin time (aPTT)
* Thrombin clotting time (TT) in patients with suspected dabigatran effect

Specialized testing :

1. anti-factor Xa heparin level (useful as a guide to the presence of a direct factor Xa inhibitor)
2. quantitative factor Xa inhibitor levels
3. quantitative dabigatran levels

Expected effects of anticoagulant drugs on commonly used coagulation tests

Drug class	Drug	Brand name(s)	PT	aPTT	Anti-factor Xa activity
Vitamin K antagonists	Warfarin	Coumadin, Jantoven	↑	↑/–*	–
	Acenocoumarol	Sintrom	↑	↑/–*	–
Heparins	Unfractionated heparin		–¶	↑	↑
	LMW heparins Enoxaparin Dalteparin Nadroparin	 Lovenox Fragmin Fraxiparine	–	↑/–	↑
	Fondaparinux	Arixtra	–	↑/–	↑
Direct thrombin inhibitors	Argatroban	Acova	↑	↑	–
	Dabigatran	Pradaxa	↑/–	↑	–
Direct factor Xa inhibitors	Rivaroxaban	Xarelto	↑/–	↑/–	↑Δ
	Apixaban	Eliquis	↑/–	↑/–	↑Δ
	Edoxaban	Lixiana, Savaysa			↑Δ
	Betrixaban	Bevyxxa			↑Δ

General strategy for anticoagulant reversal

* A specific reversal agent/antidote (for dabigatran, idarucizumab; for the oral direct factor Xa inhibitors, andexanet alfa)
* Nonspecific agents such as prothrombin complex concentrates (PCCs)
* Antifibrinolytic agent
* Desmopressin (DDAVP)
* Drug removal from the circulation and/or gastrointestinal tract
* Hemodialysis may also be used to remove active dabigatran from the circulation

Non-specific Reversal Approaches

Intervention	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Oral charcoal	Yes	Yes	Yes	Yes
Hemodialysis	No	No	No	Yes
Hemoperfusion with charcoal	Possible	Possible	?	Yes
FFP	No	No	No	No
Activated rFVIIa	Unclear	Unclear	Unclear	Unclear
4 factor PCC	Possible	Possible	Possible	Possible
Activated PCC	Possible	Possible	Possible	Possible

- Haemodialysis can accelerate drug removal in those patients receiving dabigatran; however, its benefit in life-threatening bleeding has not been established.

- In contrast, **dialysis is not effective for factor Xa inhibitors** due to their high plasma binding and lower renal clearance.

- The administration of prothrombin complex concentrate (PCC) or activated prothrombin complex (aPCC) concentrates can be considered in life-threatening bleeding, despite the scarce evidence.

- Administration of PCC could start at a dose of 25 U/kg and can be repeated if clinically indicated.

Use of Antidote

How should targeted reversal agents be used?

Life-threatening bleed

- intracranial hemorrhage, critical organ, massive hemorrhage
- Bleeding in the setting of delayed renal clearance or overdose

Emergency Surgery

Not for use in

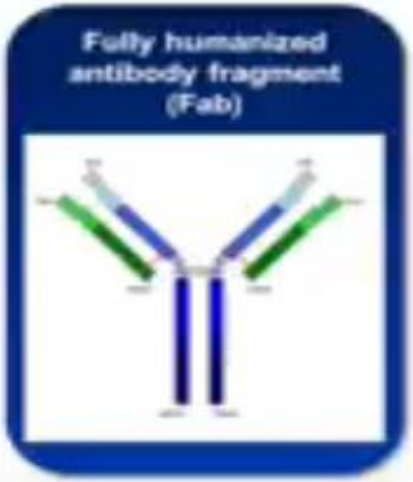
- Elective surgery or surgery that can delayed
- elevated coag tests but no bleeding
- bleeding managed with routine supportive measures

Direct oral anticoagulant reversal agents for life-threatening bleeding (imminent risk of death from bleeding)

Anticoagulant	Reversal agent (all are given intravenously)
Dabigatran (Pradaxa; oral thrombin inhibitor)	▪ Idarucizumab (Praxbind). Dose: 5 grams*
Oral factor Xa inhibitors: ▪ Apixaban (Eliquis) ▪ Edoxaban (Lixiana, Savaysa) ▪ Rivaroxaban (Xarelto)	▪ Andexanet alfa (AndexXa). Dosing for the initial bolus and subsequent infusion depend on the dose level of the factor Xa inhibitor and the interval since it was last taken. **-OR-** ▪ 4-factor PCC (Kcentra, Beriplex P/N, Octaplex). Dosing can be done with a fixed dose of 2000 units **OR** a weight-based dose of 25 to 50 units per kg.

Idarucizumab

- **PRAXBIND = idarucizumab**
  - Humanized monoclonal antibody fragment that binds dabigatran
  - 300 x higher affinity for dabigatran than dabigatran has for thrombin
- **FDA approved Oct 16, 2015**
  - **5 gram IV bolus dose**
  - Approved for
    - For emergency surgery/urgent procedures
    - In life-threatening or uncontrolled bleeding

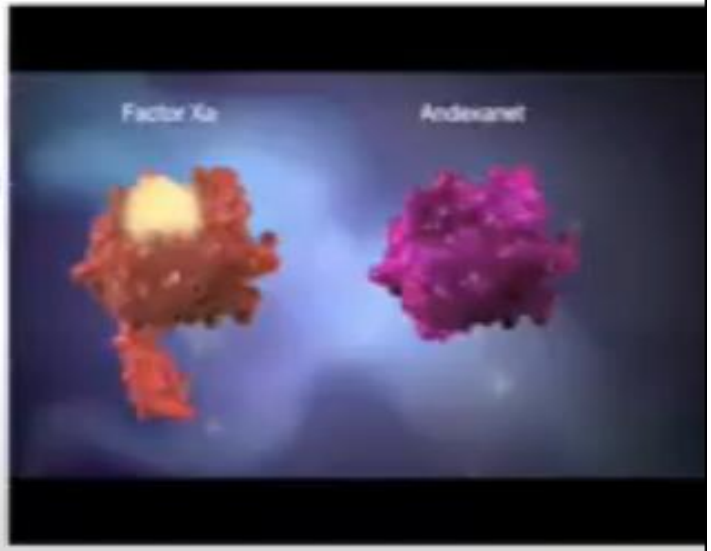


Andexant alfa

AndexXa = andexanet alfa

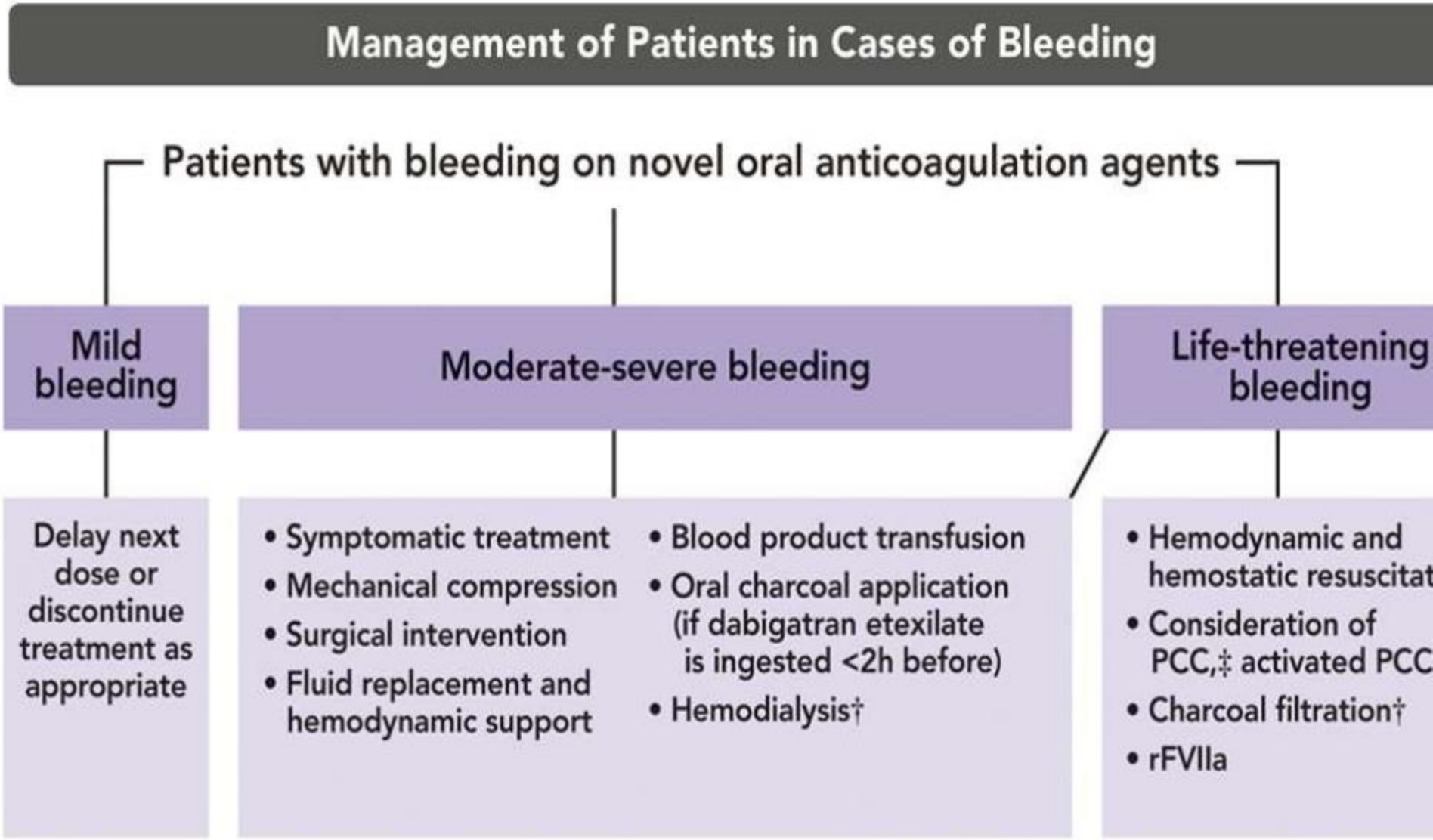
- "decoy" recombinant **FXa** molecule with mutation in catalytic site, lacks Gla domain
- "universal" FXai antidote
- interim analysis of real world study

--NEJM Aug 2016: dose adjusted



Direct oral anticoagulant-associated bleeding reversal strategies

Type of bleeding	Agent	Possible interventions
Life-threatening or imminently fatal bleeding (eg, intracranial, retroperitoneal, compartment syndrome, massive gastrointestinal)	Dabigatran (Pradaxa)	▪ Idarucizumab ▪ Activated PCC* (eg, FEIBA) ▪ Antifibrinolytic agent (eg, tranexamic acid, epsilon-aminocaproic acid) ▪ Anticoagulant discontinuation ▪ Oral activated charcoal (if last dose within prior two hours) ▪ Hemodialysis ▪ RBC transfusions if needed for anemia ▪ Platelet transfusions if needed for thrombocytopenia or impaired platelet function (eg, due to aspirin) ▪ Surgical/endoscopic intervention if appropriate
	Rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Lixiana), betrixaban (Bevyxxa)	▪ Andexanet alfa (AndexXa) **or** a 4-factor unactivated PCC (eg, Kcentra) ▪ Antifibrinolytic agent (eg, tranexamic acid, epsilon-aminocaproic acid) ▪ Anticoagulant discontinuation ▪ Oral activated charcoal (if last dose recent enough) ▪ RBC transfusions if needed for anemia ▪ Platelet transfusions if needed for thrombocytopenia or impaired platelet function (eg, due to aspirin) ▪ Surgical/endoscopic intervention if appropriate
Minor bleeding (eg, epistaxis, uncomplicated soft tissue bleeding, minor [slow] gastrointestinal bleeding)	Dabigatran (Pradaxa)	▪ Local hemostatic measures ▪ Possible anticoagulant discontinuation • Half-life (normal renal function¶): 12 to 17 hours ▪ Possible antifibrinolytic agent (eg, tranexamic acid, epsilon-aminocaproic acid)
	Rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Lixiana), betrixaban (Bevyxxa)	▪ Local hemostatic measures ▪ Possible anticoagulant discontinuation • Half-lives (normal renal function¶): ○ Rivaroxaban 5 to 9 hours ○ Apixaban 8 to 15 hours ○ Edoxaban 6 to 11 hours ▪ Possible antifibrinolytic agent (eg, tranexamic acid, epsilon-aminocaproic acid)


Management of Patients in Cases of Bleeding
Patients with bleeding on novel oral anticoagulation agents
Mild bleeding
Moderate-severe bleeding
Life-threatening bleeding
Delay next dose or discontinue treatment as appropriate
• Symptomatic treatment
• Mechanical compression
• Surgical intervention
• Fluid replacement and hemodynamic support
• Blood product transfusion
• Oral charcoal application (if dabigatran etexilate is ingested <2h before)
• Hemodialysis†
• Hemodynamic and hemostatic resuscitat
• Consideration of PCC,‡ activated PCC
• Charcoal filtration†
• rFVIIa

SURGERY/INVASIVE PROCEDURE

* Given the short half-lives of the DOACs
* urgent or emergent surgery is required and there is insufficient time to allow the anticoagulant effect to dissipate, reversal strategies
* Decisions regarding the need for reversal are individualized based on the urgency and bleeding risk of the procedure

Perioperative management of oral direct thrombin inhibitors and factor Xa inhibitors

Anticoagulant	Renal function and dose	Interval between last dose and procedure NOTE: No anticoagulant is administered the day of the procedure		Resumption after procedure	
		High bleeding risk	Low bleeding risk	High bleeding risk	Low bleeding risk
Dabigatran	CrCl >50 mL/minute Dose 150 mg twice daily	Give last dose three days before procedure (ie, skip four doses on the two days before the procedure)	Give last dose two days before procedure (ie, skip two doses on the day before the procedure)	Resume 48 to 72 hours after surgery (ie, postoperative day 2 to 3)	Resume 24 hours after surgery (ie, postoperative day 1)
	CrCl 30 to 50 mL/minute Dose 150 mg twice daily	Give last dose five days before procedure (ie, skip eight doses on the four days before the procedure)	Give last dose three days before procedure (ie, skip four doses on the two days before the procedure)		
Rivaroxaban	CrCl >50 mL/minute Dose 20 mg once daily	Give last dose three days before procedure (ie, skip two doses on the two days before the procedure)	Give last dose two days before procedure (ie, skip one dose on the day before the procedure)		
	CrCl 30 to 50 mL/minute Dose 15 mg once daily				
Apixaban	CrCl >50 mL/minute Dose 5 mg twice daily	Give last dose three days before procedure (ie, skip four doses on the two days before the procedure)	Give last dose two days before procedure (ie, skip two doses on the day before the procedure)		
	CrCl ≤50 mL/minute Dose 2.5 mg twice daily				
Edoxaban	CrCl 51 to 95 mL/minute Dose 60 mg once daily	Give the last dose three days before the procedure (ie, skip two doses on the two days before the procedure)	Give the last dose two days before the procedure (ie, skip one dose on the day before the procedure)		
	CrCl ≤50 mL/minute* Dose 30 mg once daily				

Procedural bleeding risk

High bleeding risk procedure (two-day risk of major bleed 2 to 4%)
Any major operation of duration >45 minutes
Abdominal aortic aneurysm repair
Coronary artery bypass
Endoscopically guided fine-needle aspiration
Foot/hand/shoulder surgery
Heart valve replacement
Hip replacement
Kidney biopsy
Knee replacement
Laminectomy
Neurosurgical/urologic/head and neck/abdominal/breast cancer surgery
Polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilatation
Transurethral prostate resection
Vascular and general surgery
Low bleeding risk procedure (two-day risk of major bleed 0 to 2%)
Abdominal hernia repair
Abdominal hysterectomy
Arthroscopic surgery lasting <45 minutes
Axillary node dissection
Bronchoscopy with or without biopsy
Carpal tunnel repair
Cataract and noncataract eye surgery
Central venous catheter removal
Cholecystectomy
Cutaneous and bladder/prostate/thyroid/breast/lymph node biopsies
Dilatation and curettage
Gastrointestinal endoscopy ± biopsy, enteroscopy, biliary/pancreatic stent without sphincterotomy, endosonography without fine-needle aspiration
Hemorrhoidal surgery
Hydrocele repair
Noncoronary angiography
Pacemaker and cardiac defibrillator insertion and electrophysiologic testing
Thoracentesis
Tooth extractions

Platelet dysfunction in uremia

Treatment options include correction of anemia, desmopressin (DDAVP), dialysis, estrogens, or cryoprecipitat

* Raising the hemoglobin to approximately 10 g/dL may reduce the bleeding time
* Desmopressin Administration of desmopressin at a dose of 0.3 mcg/kg given in 50 mL of saline over 15 to 30 minutes intravenously or by subcutaneous injection is preferred. The improvement in bleeding time begins within one hour and lasts four to eight hours
* Hemodialysis or peritoneal dialysis can partially correct the bleeding time in approximately two-thirds of uremic patients. Hemodialysis should be performed without systemic anticoagulation

Platelet dysfunction in uremia

* The infusion of cryoprecipitate (10 units intravenously every 12 to 24 hours). The improvement in bleeding time begins within one hour and lasts 4 to 24 hours
* Prolonged control of bleeding may be achieved by the administration of conjugated estrogens (0.6 mg/kg intravenously daily for five days, 2.5 to 25 mg orally per day, or 50 to 100 mcg of transdermal estradiol twice weekly). These agents begin to act on the first day, with peak control reached over five to seven days; the duration of action is one week or more after therapy has been discontinued

SUMMARY AND RECOMMENDATIONS

* Anticoagulation is used when the benefits of reducing thrombosis risk outweigh the increased risks of clinically significant bleeding
* Several patient factors contribute to bleeding risk, including the age of the patient; prior bleeding; comorbidities such as renal and hepatic insufficiency, diabetes, cancer, and obesity .
* The risk of bleeding is also increased with severe thrombocytopenia (eg, platelet count <50,000/microL) and with concomitant antiplatelet medications.
* Intracranial bleeding is a feared complication of anticoagulation. Important risk factors include a history of stroke (especially intracerebral hemorrhage [ICH]), hypertension, and cerebral amyloid angiopathy. ICH risk is reduced with DOAC treatment compared with warfarin

SUMMARY AND RECOMMENDATIONS

* A number of bleeding risk scores have been developed and validated, mostly in patients receiving warfarin for atrial fibrillation. A major benefit of these scores is the identification of potentially modifiable factors that can be remedied
* The risk of anticoagulant-associated bleeding can be minimized by periodically reviewing the indication for anticoagulation, risk-benefit ratio, dose, anticoagulant adherence, concomitant medications (including over-the-counter medications and nonsteroidal antiinflammatory drugs [NSAIDs]), and patient comorbidities that may affect dosing


Thank You
for
attention