UNC HEALTH CARE GUIDELINE

Management of Apixaban in Adults

Apixaban (Eliquis®) is an oral anticoagulant that acts as a factor Xa inhibitor. It is approved by the FDA for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Apixaban is **not FDA-approved** for any other indications at this time, such as the prevention or treatment of deep vein thrombosis or pulmonary embolism, or for use in patients with mechanical heart valves.

Key pharmacokinetic data for apixaban include a peak onset of anti-Xa activity within 3-4 hours after oral administration and a half-life of approximately 12 hours in patients with normal hepatic and renal function. Apixaban is extensively metabolized via CYP3A4 and is a substrate for P-glycoprotein. Approximately 50-55% of apixaban is eliminated in the feces and 20-25% is excreted in the urine.[1]

INITIATION OF THERAPY

Patient-specific considerations for initiation of apixaban therapy include the following:

- **Indication for therapy**. Patients must have non-valvular atrial fibrillation and risk factors that warrant therapeutic anticoagulation (i.e., $CHADS_2$ score $\geq$ 1).
- **Renal and hepatic function**. A baseline serum creatinine is required for apixaban use and drug dosing (see Table 1). Liver function (e.g., total bilirubin, AST, ALT) should be assessed prior to initiation as apixaban should be used with caution in moderate (Child-Pugh B) hepatic impairment or any degree of hepatic impairment associated with coagulopathy. Apixaban should be avoided in severe (Child-Pugh C) hepatic impairment.
- **Dosing and administration**. Dosing recommendations are provided in Table 1.
- **Cost of therapy**. Whether patients can afford apixaban at discharge must also be considered, as costs may exceed $200 per month.

TABLE 1. Initial Apixaban Dose

Indication	Recommended Dose	Dose Adjustments [a]
Atrial Fibrillation [2,3] (Stroke Prevention)	5 mg twice daily	2.5 mg twice daily if any 2 of the following: • Age $\geq$ 80 years • Body weight $\leq$ 60 kg • Serum creatinine $\geq$ 1.5 mg/dL

[b] Apixaban is extensively metabolized via CYP3A4 and is a substrate for P-glycoprotein (P-gp). When apixaban is used concomitantly with strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin), the recommended dose is 2.5 mg twice daily. In patients already receiving 2.5 mg twice daily, administration with strong dual inhibitors of CYP3A4 and P-gp should be avoided. Although recommendations have not been made regarding strong inducers of CYP3A4 (e.g., rifampin, phenytoin, carbamazepine, phenobarbital), co-administration may result in as much as a 50% reduction in apixaban exposure.

CONVERSION TO APIXABAN

TABLE 2. Converting to Apixaban

Agent	Conversion Instructions
Heparin	Discontinue the heparin infusion when the first dose of apixaban is administered.
Enoxaparin	Start apixaban at the time the next dose of enoxaparin was to be administered.
Fondaparinux	Start apixaban 24 hours after the last dose of fondaparinux.
Dabigatran	Start apixaban 12 hours after the last dose of dabigatran.
Rivaroxaban	Start apixaban 12-24 hours after the last dose of rivaroxaban.[a]
Warfarin	Discontinue warfarin and start apixaban when the INR is < 2.0.

[a] The approved labeling for apixaban recommends giving the first dose at the time the next evening dose of rivaroxaban was to be administered. For patients who are transitioning in the community setting, this strategy may be acceptable. However, for patients with normal renal function (CrCL > 50 mL/min) who are at greater risk of stroke (e.g., recent cardioversion, higher $CHADS_2$ scores, conditions that may increase baseline risks of thromboembolism), starting apixaban as early as 12 hours after the last dose of rivaroxaban may be considered.

CONVERSION FROM APIXABAN

Strategies for converting patients to or from apixaban have not been evaluated in clinical trials. Based on the half life of apixaban, an alternative anticoagulant should be initiated 12 hours after the last dose.

TABLE 3. Converting from Apixaban to Anticoagulants other than Warfarin

Agent	Conversion Instructions
Heparin	Begin heparin 12 hours after the last administered dose of apixaban
Enoxaparin	Start enoxaparin 12 hours after the last dose of apixaban.
Fondaparinux	Start fondaparinux 12 hours after the last dose of apixaban.
Dabigatran	Start dabigatran 12 hours after the last dose of apixaban.
Rivaroxaban	Start rivaroxaban 12 hours after the last *morning* dose of apixaban, as rivaroxaban should be given in the evening when used for atrial fibrillation. [a]

[a] Given the absence of data indicating that rivaroxaban is safe and effective at other administration times when used for atrial fibrillation, the approved FDA labeling still recommends administration with the evening meal for this indication.

TABLE 4. Converting Apixaban to Warfarin

Taking into consideration the risk of thromboembolism in each individual patient (i.e., $CHADS_2$ score, recent cardioversion), it may be reasonable to continue apixaban until the INR is 2–3.[a,b]

Strategy	Conversion Instructions
Strategy 1 (Parenteral) [c]	Start parenteral anticoagulant 12 hours after the last apixaban dose. Start warfarin the same day at the next standard administration time. Discontinue parenteral anticoagulant when the INR is 2–3.
Strategy 2 (Oral)	Start warfarin and overlap with apixaban for at least 5 days. Discontinue apixaban on day 5 or when the INR is 2–3.

[a] Examples of increased stroke risk include recent cardioversion or ablation, higher $CHADS_2$ score, and conditions that may increase baseline risks of thromboembolism (e.g., medically ill).
[b] Apixaban may contribute to INR, so INR measurements may not be useful for determining an appropriate dose of warfarin.
[c] A parenteral conversion strategy is recommended in the approved FDA labeling, although neither it nor the oral conversion strategy have been evaluated in clinical trials.

PERIOPERATIVE MANAGEMENT

No published data exist on optimal perioperative management of apixaban, so the recommendations here have been extrapolated from the pharmacokinetics and pharmacodynamics of the drug. Apixaban should be discontinued a minimum of 24 hours prior to procedures associated with a standard risk of bleeding (e.g., electrophysiology procedures, cardiac catheterizations, no additional patient-specific risk factors) and 48 hours prior to procedures associated with a high risk of bleeding (surgery involving major organs, procedures requiring complete hemostasis (e.g., spinal anesthesia), or when additional patient-specific risk factors are present).

At the time this guideline was created, pharmacokinetic data on apixaban in patients with varying degrees of hepatic and renal impairment, or in those meeting criteria for a reduced dose (e.g., advanced age, low body weight) were not available. In these patients, clinicians should strongly consider discontinuing apixaban earlier than the times recommended above, taking into account both patient-specific factors (e.g., degree of renal or hepatic impairment, age, body weight) and procedure-specific factors (e.g., type of procedure to be performed, urgency of the procedure).

Bridging to Procedures with Parenteral Anticoagulants
For patients at high risk of thromboembolic events in whom inpatient procedures are planned, some clinicians may wish to bridge with parenteral anticoagulants (e.g., unfractionated heparin). The necessity for this depends on a patient's risk for thromboembolism while off anticoagulation, and for bleeding if on anticoagulants. This may be performed by (1) converting apixaban to the desired parenteral anticoagulant as described in Table 3, and (2) continuing to hold apixaban for the minimum amount of time recommended above. Parenteral anticoagulation may then be discontinued prior to the planned procedure according to usual standards of care.

Dental Procedures
Many dental procedures can be safely performed on full-dose anticoagulation with warfarin, and this is also likely true with apixaban. Consider risk of bleeding versus risk of thromboembolism when deciding to hold doses of apixaban for a dental procedure.

ADVERSE EFFECTS [2-4]

When compared with warfarin, apixaban is associated with a lower incidence of bleeding, including serious and fatal bleeding. The most common non-hemorrhagic adverse effects are GI-related disturbances (e.g., nausea, vomiting, and constipation), and elevation in liver enzymes.

The following section outlines strategies for the management of apixaban-related bleeding events.

MANAGEMENT OF BLEEDING EVENTS

Currently, no available evidence exists to guide clinicians in the management of apixaban-associated bleeding events. While *in vitro* data and studies in animals and healthy human volunteers indicate some pharmacologic agents (e.g., factor products) may have an impact on the anticoagulant effects of factor Xa inhibitors (rivaroxaban, specifically), these have not been evaluated for the management of bleeding events in patients and cannot be used for clinical decision-making.[5]

An outline for supportive management of apixaban-related bleeding events based on bleeding severity is provided in Table 5. **If patients require pharmacologic therapy to manage hemorrhagic complications, a Hematology/Coagulation consult is also required.**

TABLE 5. Management of Apixaban-Related Bleeding Events

Bleeding Severity	Management Recommendations
Mild	Delay next dose or discontinue apixaban.
Moderate	*Consider any of the following based on bleeding severity:* • Symptomatic treatment • Mechanical compression • Surgical intervention • Fluid replacement and hemodynamic support • Blood product transfusion • Oral activated charcoal (if last apixaban dose ingested within 2 hours) Dose: Liquid charcoal with sorbitol 50 g PO x 1 dose *If hemostasis is not achieved with the strategies outlined above, proceed to the steps below and obtain a Hematology/Coagulation consult for further recommendations.*
Severe or Life-threatening	*Consider any of the strategies outlined above based on bleeding severity. No agent currently available in the US has been shown to successfully reverse the anticoagulant effects of apixaban or treat apixaban-related bleeding events. Therefore, the pharmacologic interventions below may be considered but are not required in the management of apixaban-related bleeding.* *A Hematology/Coagulation consult must be obtained prior to the following*: 1. Prothrombin Complex Concentrates (PCC, aPCC) a. Low risk for thrombotic complications: Consider activated prothrombin complex concentrate (aPCC) (FEIBA®) 50 units/kg IV x 1.[a] b. High-risk for thrombotic complications: Consider non-activated pro-thrombin complex concentrate (PCC) (Profilnine®) 50 units/kg IV x 1. 2. If (b) is chosen above and adequate hemostasis is not achieved, consider giving either aPCC (FEIBA®) 50 units/kg IV x 1, or recombinant factor VIIa (NovoSeven®) 45-90 mcg/kg IV x 1[b] (with Hematology/Coagulation guidance) based on bleeding severity and degree of hemostasis achieved. To investigate potential causes of the bleeding event, obtain the following: serum creatinine, aPTT, PT/INR, CBC (platelets), anti-Xa assay (referral laboratory, as needs to be performed with apixaban standard curve).

[a] Both activated PCC (FEIBA®) and recombinant factor VIIa (NovoSeven®) are associated with thrombotic complications; therefore, the risk of bleeding versus thrombosis must be considered.
[b] A starting dose of 45-90 mcg/kg was chosen based on review of clinical trials and case series as well as a dose-related risk of thromboembolic complications.[6,7]

PATIENT EDUCATION

Apixaban Discontinuation
Patients who experience adverse effects (including apixaban-related bleeding events) should contact their provider immediately, but should not discontinue therapy until instructed to do so.

Dosing & Oral Administration
Apixaban may be taken without regard to food as food does not affect drug absorption and serum drug concentrations (i.e., C_{max} or AUC).

Management of Missed Doses
If a dose of apixaban is not taken at the scheduled time, the dose should be taken as soon as possible, unless it is within 6 hours of the next dose. If the next dose is due within 6 hours, the patient should skip the missed dose and take at the next scheduled time. The dose of apixaban should not be doubled to make up for a missed dose.

Management of a Doubled Dose
No specific strategy has been suggested for patients who take a doubled dose of apixaban. However, based on the pharmacokinetics of the drug, patients with normal hepatic and renal function should be able to resume their usual dose at the next scheduled time without skipping a dose (i.e., 12 hours after the doubled dose).

Additional Information
For additional information on blood clots and anticoagulation therapy, patients (and health care providers) may visit the University of North Carolina Clot Connect website at http://www.clotconnect.org.

REFERENCES

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