Direct Oral Anticoagulants (DOACs) Guide

	Direct Factor Xa Inhibitors			Direct Thrombin (Factor IIa) Inhibitor
	apixaban (Eliquis®)	**edoxaban (Savaysa®)**	**rivaroxaban (Xarelto®)**	**dabigatran (Pradaxa®)**
FDA Approved Indications and Dosages	**NVAF** ■ 5 mg PO BID ■ 2.5 mg PO BID: If ≥ 2 of the following: age ≥80 years, weight ≤60 kg or Cr ≥ 1.5 mg/dL ■ Usage if Cr > 2.5 mg/dL or CrCl < 25 mL/min is based on pharmacokinetics and not on clinical studies. Caution is advised. **VTE treatment** ■ 10 mg PO BID for 7 days, then 5 mg PO BID ■ No dose adjustment based on renal function ■ Usage if CrCl < 25 mL/min is based on pharmacokinetics and not on clinical studies. Caution is advised. **VTE secondary prevention** ■ 2.5 mg PO BID ■ CrCl < 25 mL/min: no clinical studies **VTE prophylaxis in THR/TKR** ■ Start 12-24 hours postop ■ THR: 2.5 mg BID PO for 35 days ■ TKR: 2.5 mg BID PO for 12 days ■ CrCl <30 mL/min: no clinical studies	**NVAF** ■ CrCl > 95 mL/min: NOT recommended (drug may be cleared too rapidly and adequate drug levels not attained) ■ CrCl 51-95 mL/min: 60 mg PO once daily ■ CrCl 15-50 mL/min: 30 mg PO once daily ■ CrCl < 15 mL/min: not recommended **VTE treatment** ■ Begin after 5-10 days of initial therapy with a parenteral anticoagulant ■ CrCl > 50 mL/min: 60 mg PO once daily ■ CrCl 15-50 mL/min or weight ≤60 kg or on P-gp inhibitor[§]: 30 mg PO once daily **VTE secondary prevention** ■ Not approved **VTE prophylaxis in THR/TKR** ■ Not approved	**NVAF** ■ CrCl > 50 mL/min: 20 mg PO daily with evening meal ■ CrCl 15-50 mL/min: 15 mg PO daily with evening meal ■ CrCl < 15 mL/min: not recommended **VTE treatment** ■ CrCl ≥30 mL/min: 15 mg PO BID for 21 days, then 20 mg PO daily ■ CrCl <30 mL/min: not recommended **VTE secondary prevention** ■ CrCl ≥30 mL/min: 20 mg PO daily. May consider 10 mg PO daily per EINSTEIN CHOICE trial (not FDA approved dosage). ■ CrCl <30 mL/min: not recommended **VTE prophylaxis in THR/TKR** ■ Start 6-10 hours post-op ■ THR: 10 mg PO daily for 35 days ■ TKR: 10 mg PO daily for 12 days ■ Avoid in CrCl < 30mL/min	**NVAF** ■ CrCl >30 mL/min: 150 mg PO BID ■ CrCl 15-30 mL/min: 75 mg PO BID ■ CrCl < 15 mL/min: not recommended **VTE treatment and secondary prevention** ■ For VTE treatment, an initial 5-10 days of parenteral anticoagulation is required before initiating dabigatran ■ CrCl >30 mL/min: 150 mg PO BID ■ CrCl ≤30 mL/min: not recommended **VTE prophylaxis in THR** ■ CrCl >30 mL/min: 110 mg for the first day, then 220 mg PO daily ■ CrCl ≤30 mL/min or on dialysis: dosing recommendations not available ■ CrCl <50 mL/min with concomitant use of P-gp inhibitor[§]: avoid co-administration **VTE prophylaxis in TKR** ■ Not approved

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Dosage Forms	Tablets: 2.5 mg, 5 mg	Tablets: 15 mg, 30 mg, 60 mg	Tablets: 10 mg, 15 mg, 20 mg	Capsules: 75 mg, 110 mg, 150 mg ■ Close bottle immediately after use. Keep tightly closed. ■ Keep in original container; remove only at time of use. ■ Do not put in pillbox or medication organizer. ■ Use within 4 months after opening bottle.
Able to Crush Medication	■ Yes ■ Both 2.5 mg and 5 mg tablets may be crushed and suspended in 60 mL D5W and immediately delivered through an NGT ■ No information available regarding oral administration of crushed and suspended tablets	No data are available regadring the bioavailability upon crushing and/or mixing of edoxaban tablets into food, liquids, or administration through feeding tubes.	■ Yes ■ The 15 mg and 20 mg tablets may be crushed and mixed with applesauce for oral use or with 50 mL of water for NG or gastric tube feeding (avoid if distal to the stomach) ■ After administration, oral or enteral feeding should immediately follow the dose	■ No ■ Do not chew, break, or open capsules! (bioavailability increases by 75% if capsule is opened)
Administration with food	With or without food	With or without food	■ 20 mg: with food ■ 15 mg: with food ■ 10 mg: with or without food	With or without food
Half-life	8-15 hours	10-14 hours	5-13 hours	12-17 hours
T-Max	3-4 hours	1-2 hours	2-4 hours	1-3 hours
Metabolism	■ Renal 27% ■ Hepatic 73%	■ Renal 50% ■ Metabolism, biliary/intestinal 50%	■ Renal 50% ■ Hepatic ■ 1/3 eliminated non-metabolized	■ Renal 80%

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Side Effects	■ Bleeding ■ Thrombocytopenia ■ Hypersensitivity reaction	■ Bleeding ■ Abnormal LFTs ■ Rash ■ Anemia	■ Bleeding ■ Thrombocytopenia ■ Hypersensitivity reaction ■ Stevens-Johnson Syndrome ■ Agranulocytosis ■ Hepatitis	■ Bleeding ■ GI: dyspepsia, abdominal and epigastric pain ■ GI bleed ■ Thrombocytopenia ■ Hypersensitivity reaction
Pregnancy Category/ Lactation	■ Pregnancy Category B: not studied and should be avoided ■ Lactation: not studied in humans and should be avoided	■ Pregnancy Category C: not studied and should be avoided ■ Lactation: not studied in humans and should be avoided	■ Pregnancy Category C: not studied and should be avoided ■ Lactation: Not studied in humans and should be avoided	■ Pregnancy Category C: not studied and should be avoided ■ Lactation: not studied in humans and should be avoided
Contraindications	■ Active bleeding ■ Hypersensitivity ■ Severe hepatic impairment ■ Mechanical heart valves (not studied)	■ Active bleeding ■ Hypersensitivity ■ Moderate or severe hepatic impairment ■ Mechanical heart valves (not studied)	■ Active bleeding ■ Hypersensitivity ■ Severe liver impairment ■ Mechanical heart valves (not studied)	■ Active bleeding ■ Hypersensitivity ■ Mechanical heart valves • REALIGN trial: terminated early due to significantly more thromboembolic and bleeding events
Anticoagulation Laboratory Monitoring Usually not required. Consider in case of bleeding, surgery, compliance concern (see table at end of document)	■ Anti-factor Xa level ■ PT in seconds	■ Anti-factor Xa level ■ No good correlation with PT or aPTT	■ Anti-factor Xa level ■ PT in seconds	■ Dabigatran trough level (drawn 30 minutes or less before the next scheduled dose): 45-95 ng/mL ■ TT (thrombin time) ■ ECT (ecarin clotting time) ■ aPTT ■ Hemoclot

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Drug interactions*	**Combined P-gp and strong CYP3A4 inhibitors*** ■ doses >2.5 mg BID: reduce dose by 50% ■ 2.5 mg BID: avoid use ■ can lead to increased exposure to apixaban and increase the risk of bleeding **Combined P-gp and strong CYP3A4 inducers*** ■ avoid use ■ can lead to decreased exposure to apixaban and may decrease efficacy **Anticoagulant, Antiplatelet, NSAID, SSRI, SNRI*** ■ may increase bleeding risk	**P-gp inhibitors§** ■ NVAF: no dose reduction recommended with concomitant use ■ VTE treatment: 30 mg PO once daily **Anticoagulant, Antiplatelet, NSAID*** ■ may increase bleeding risk **P-gp inducers*** ■ avoid use	**Combined P-gp and strong CYP3A4 inhibitors*** ■ avoid use ■ can lead to increased exposure of rivaroxaban (from 30-160%) and increase bleeding risk **Combined P-gp and strong CYP3A4 inducers*** ■ avoid use ■ can lead to decreased exposure (up to 50%) and may decrease efficacy **Combined P-gp and moderate CYP3A4 inhibitor*** ■ CrCl 15-80 mL/min: Avoid use unless benefit > risk. **Anticoagulant, Antiplatelet, NSAID, SSRI, SNRI*** ■ may increase bleeding risk	**P-gp inhibitors*** ■ NVAF+CrCl 30-50 mL/min: consider dabigatran 75 mg BID ■ NVAF+CrCl 15-30 mL/min: avoid ■ VTE+ CrCl<50 mL/min: avoid ■ can lead to increased exposure to dabigatran and risk of bleeding **P-gp inducers*** ■ avoid use ■ can lead to reduced exposure to dabigatran and may decrease efficacy **Anticoagulant, Antiplatelet, NSAID, SSRI, SNRI*** ■ may increase bleeding risk
Evidence for NVAF vs. Warfarin	**ARISTOTLE** (mean $CHADS_2$ score: 2.1) ■ Superior: hemorrhagic stroke ■ Superior: major bleeding ■ ICH and fatal bleed: lower ■ Superior: vascular mortality	**ENGAGE AF-TIMI 48** ($CHADS_2$ score ≤ 3: 77% of subjects) ■ CrCl 15-95: non-inferior for stroke or systemic embolism ■ Superior: hemorrhagic stroke ■ Superior: major bleeding ■ Superior: cardiovascular mortality ■ Edoxaban 60 mg showed consistent efficacy and safety results versus warfarin in 2824 patients with valvular AF (aortic stenosis, aortic insufficiency, mitral insufficiency, valve bioprosthesis, repair or plasty) despite the fact that patients with valvular heart disease had higher CV mortality, MACE and major bleeding risk than these with NVAF. (Not an approved FDA indication.)	**ROCKET-AF** (mean $CHADS_2$ score: 3.5) ■ Non-inferior: all stroke ■ Major bleed: similar ■ ICH and fatal bleeding: lower ■ Higher GIB and need for transfusion	**RE-LY** (mean $CHADS_2$ score: 2.1) ■ Superior: ischemic and hemorrhagic stroke ■ Major bleeding: similar (higher in age ≥75 years) ■ CH and fatal bleeding: lower ■ GIB: higher ■ Superior: vascular mortality

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Evidence for VTE Prophylaxis for THR vs. Enoxaparin	**ADVANCE 3** ■ Superior with no difference in bleeding	Not approved for this indication **STARS J-V (hip replacement)** ■ Superior with no difference in bleeding **STARS J-IV (hip fracture)** ■ Similar with no difference in bleeding	**RECORD 1** and **RECORD 2** ■ Superior with no difference in bleeding	**RE-NOVATE I** **RE-NOVATE II** ■ Non-inferior
VTE Prophylaxis for TKR vs. Enoxaparin	**ADVANCE 2** ■ Superior with no difference in bleeding	Not approved for this indication **STARS E-3** ■ Superior with no difference in bleeding	**RECORD 3** and **RECORD 4** ■ Superior with no difference in bleeding	Not approved for this indication **RE-MODEL/RE-MOBILIZE** ■ Non-inferior **RE-NOVATE I/RE-NOVATE II** ■ Non-inferior
Evidence for VTE Management vs. LMWH/VKA	**AMPLIFY** ■ Non-inferior: recurrent VTE/ mortality ■ Major bleeding: lower	**HOKUSAI VTE STUDY** ■ Non-inferior: recurrent VTE ■ Superior: fatal and intracranial bleeding, clinically relevant bleeding	**EINSTEIN** ■ Non-inferior: recurrent VTE/ mortality ■ Major bleeding: lower (pooled analysis)	**RE-COVER** ■ Non-inferior: recurrent VTE/ mortality ■ Major bleed: similar ■ Clinically relevant non-major and any bleed: lower
Evidence for VTE Risk Reduction after Initial Treatment	**AMPLIFY-EXT** ■ Superior vs. placebo with similar major bleeding	Not approved for this indication (not studied)	**EINSTEIN-EXT** ■ Superior vs. placebo with higher major bleeding **EINSTEIN CHOICE** ■ Both 10 and 20 mg of rivaroxaban were superior to aspirin for recurrent VTE risk with similar risk of bleeding	**RE-MEDY** ■ Non-inferior vs. warfarin, similar major bleeding **RE-SONATE** ■ Superior vs. placebo, higher major bleeding
Management of Bleeding	■ No specific antidote ■ Activated charcoal: within 6 hours of last ingestion ■ Life-threatening bleeding: consider PCC (Kcentra®), aPCC (FEIBA®), rVIIa (NovoSeven®) ■ Not dialyzable ■ *See supplemental document* ‡	■ No specific antidote ■ No information available on the use of activated charcoal ■ Life-threatening bleeding: consider PCC (Kcentra®), aPCC (FEIBA®), rVIIa (NovoSeven®) ■ Not dialyzable ■ *See supplemental document* ‡	■ No specific antidote ■ Activated charcoal: within 2 hours of last ingestion ■ Life-threatening bleeding: consider PCC Kcentra®), aPCC (FEIBA®), rVIIa (NovoSeven®) ■ Not dialyzable ■ *See supplemental document* ‡	■ Specific antidote is idarucizumab (Praxbind®) ■ Activated charcoal: within 2 hours of last ingestion ■ Life-threatening bleeding: idarucizumab (Praxbind®), PCC (Kcentra®), aPCC (FEIBA®), rVIIa (NovoSeven®) ■ Hemodialyzable ■ *See supplemental document* ‡

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Peri-procedural Anticoagulation	Refer to **Management of Periprocedural Anticoagulation**			
Switching between Anticoagulants	Refer to **Switching To and From Various Anticoagulants**			

Anticoagulation Laboratory Considerations

Direct Factor Xa Inhibitors
(apixaban/Eliquis®, edoxaban/Savaysa®, rivaroxaban/Xarelto®)

Apixaban and Rivaroxaban

- Heparin level (aka anti-Xa)
  - The assay used to calculate heparin levels shows reasonable linear correlation with increasing levels of direct factor Xa inhibitors
  - A heparin (anti-Xa) level of <0.1 U/mL suggests lack of significant factor Xa inhibitor activity
- PT/INR
  - The PT (reported in seconds) shows some correlation with direct factor Xa inhibitor level; however, correlation with the calculated INR is weaker.
  - A normal PT likely rules out clinically significant levels of direct factor Xa inhibitor.
  - Due to variability of PT/INR reagents, this test is not recommended to try to rule out the presence of the direct factor Xa inhibitor. Heparin levels (aka anti-Xa) should be ordered instead.

Edoxaban

- Heparin level (aka anti-Xa)
  - The assay used to calculate heparin levels shows reasonable linear correlation with increasing levels of direct factor Xa inhibitors
  - A heparin (anti-Xa) level of <0.1 U/mL suggests lack of significant factor Xa inhibitor activity
- PT/INR
  - No good correlation with PT or aPTT

Note: Specific assays for apixaban, edoxaban, and/or rivaroxaban are not currently available.

Direct Thrombin (Factor IIa) Inhibitor
(dabigatran/Pradaxa®)

- Dabigatran level
  - The preferred test if available (performed at Allina Health Central Lab at Allina Commons)
  - Dabigatran trough level (drawn 30 minutes or less before the next scheduled dose): 45-95 ng/mL
- Thrombin time (TT)
  - Useful to rule out presence of dabigatran
  - A normal thrombin time essentially rules out clinically significant levels of dabigatran
- aPTT
  - Can be used if dabigatran level and TT tests are not available.
  - aPTT is less sensitive than TT and may be normal at trough drug level
  - An elevated aPTT cannot quantify the amount of dabigatran present
- PT/INR
  - Less sensitive than TT and aPTT

Direct Oral Anticoagulant (DOAC) Comparison		
Key	***Drug Interactions**	**‡Supplemental Documents**
■ NSAIDs: Non-Steroidal Anti-Inflammatory Drugs (e.g., ibuprofen, naproxen) ■ NVAF: Non-Valvular Atrial Fibrillation ■ SNRI: Serotonin-Norepinephrine Reuptake Inhibitors (e.g., venlafaxine/Effexor®) ■ SSRI: Selective Serotonin Reuptake Inhibitors (e.g., sertraline/Zoloft®, fluoxetine/Prozac®) ■ T-max: time when maximum plasma concentration reached ■ THR, TKR: Total Hip, Total Knee Replacement ■ DOAC: Direct Oral Anticoagulant ■ VTE: Venous Thromboembolism (PE and/or DVT)	■ §P-gp inhibitors: azithromycin, clarithromycin, erythromycin, itraconazole, ketoconazole, quinidine, verapamil ■ Combined P-gp and strong CYP3A4 inhibitors: e.g., fluconazole, ketoconazole, itraconazole, ritonavir, clarithromycin, erythromycin ■ Combined P-gp and strong CYP3A4 inducers: e.g., rifampin, carbamazepine, phenytoin, St. John's wort ■ Combined P-gp and moderate CYP3A4 inhibitor: e.g., diltiazem, verapamil, dronedarone, erythromycin ■ P-gp inhibitors: dronedarone, ketoconazole ■ P-gp inducers: e.g., rifampin	Management of Bleeding Associated with Direct Oral Anticoagulants Management of Periprocedural Anticoagulation Switching To and From Various Anticoagulants

Disclaimer

"Guidelines are not meant to replace clinical judgment or professional standards of care. Clinical judgment must take into consideration all the facts in each individual and particular case, including individual patient circumstances and patient preferences. They serve to inform clinical judgment, not act as a substitute for it. These guidelines were developed by a Review Organization under Minn. Statutes §145.64 et. seq., and are subject to the limitations described as Minn. Statues §145.65."

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