Direct Oral Anticoagulants: Factor IIa and Xa Inhibitors

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Faculty disclosure

- Dr. Anuja Rizal and I have no actual or potential conflicts of interest associated with this presentation.

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Learning objectives

- Discuss the pharmacology of the Direct Oral Anticoagulants (DOACs) - Factor IIa and Xa Inhibitors
- Discuss the indications and contraindications for DOACs - Factor IIa and Xa Inhibitors
- Review the kinetic profiles of the DOACs - Factor IIa and Xa Inhibitors

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Patient Case Introduction

- JJ is an 86 year old Caucasian male weighing 65kg with non-valvular atrial fibrillation managed on warfarin since his diagnosis in 2004.
- JJ no longer drives and is having difficulty adhering to frequent appointments to monitor his INR. His TTR is ~45%
- JJ saw a commercial on television for Eliquis® and is inquiring additional information

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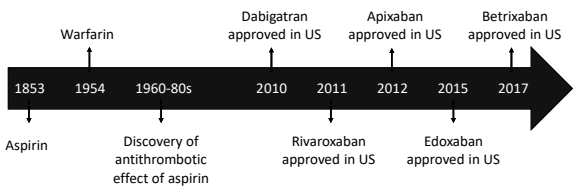
Oral anticoagulant therapies through the years



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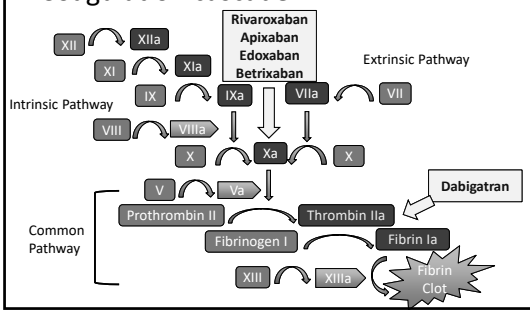
Coagulation cascade



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Pharmacokinetics of DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Inhibitor of	IIa (thrombin)	Xa	Xa	Xa	Xa
Peak (T_{max} hours)	1-2	2-4	3-4	1-2	3-4
Bioavailability (%)	3-7	66-100	50	62	34
Excretion (%)	80 Urine	66 Urine 28 Feces	27 Urine	50 Urine	11 Urine 85 Feces
Metabolism CYP3A4 involved	No	Yes	Yes	Minimal (<4%)	Minimal (<1%)
Pgp substrate	Yes	Yes	Yes	Yes	Yes
Half-life (hours)	12-17	5-9	12	10-14	19-27

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DOAC Overview

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Direct oral anticoagulants (DOACs)

Generic Name	Brand Name	FDA Indications		
		Treatment of NVAF	Treatment of DVT/PE	Prevention of VTE/PE
Dabigatran	Pradaxa®	+	+	+
Rivaroxaban	Xarelto®	+	+	+
Apixaban	Eliquis®	+	+	+
Edoxaban	Savaysa®	+	+	
Betrixaban	Bevyxxa®			+

NVAF = Non-valvular atrial fibrillation, **DVT** = Deep vein thrombosis, **PE** = Pulmonary embolism

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Dabigatran (Pradaxa®)

FDA Approved Indications

- Reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Treating deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days
- Venous thromboembolism prophylaxis in total hip arthroplasty (THA)

Boxed warnings:

- Upon discontinuation, the risk of thrombotic events, especially stroke, is increased. If dabigatran must be discontinued for a reason other than pathological bleeding, consider the use of another anticoagulant during the time of interruption.
- Epidural or spinal hematomas may occur in patients undergoing neuraxial anesthesia or spinal puncture. Monitor patients for neurological impairment; treat urgently

Pradaxa® (dabigatran) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2015

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Dabigatran (Pradaxa®)

Renal function	Dosing: Non-valvular AFib & DVT/PE Treatment	VTE Prophylaxis following THA
CrCl > 30 mL/min	150 mg PO BID (no dose adjustment)	110 mg PO 1-4hrs after surgery Once hemostasis is achieved, 220 mg PO daily
CrCl 15-30 mL/min	75 mg PO BID*	
CrCl < 15 mL/min	Not recommended	
Duration	AFib: Indefinite Provoked DVT: 3 months Unprovoked DVT: ≥ 3 months	10-35 days.

Pradaxa® (dabigatran) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2015

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Dabigatran (Pradaxa®)

Contraindications

- Serious hypersensitivity to dabigatran or any component of the formulation
- Active pathological bleeding
- Patients with mechanical prosthetic heart valve(s)

Clinical Pearls and Patient Counseling

- Administer with full glass of water to avoid dyspepsia. Take with or without food.
- Do NOT break, crush, chew, or open capsules, as this increases bioavailability by up to 75%
- Leave capsules in original container and use within 4 months of opening

Pradaxa® (dabigatran) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2015

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DDIs with Dabigatran (Pradaxa®)

P-gp inhibitors: can lead to increased exposure of dabigatran and risk of bleeding
- NVAF + CrCl 30-50mL/min: consider dabigatran 75mg PO BID
- NVAF + CrCl <30mL/min: avoid
- VTE + CrCl <50mL/min: avoid

P-gp inducers: avoid use due to reduced exposure to dabigatran and reduced efficacy

Anticoagulants, antiplatelets, NSAIDs, SSRIs, SNRIs: may increase bleeding risk
- Applicable to all DOACs

DAOCs Guide. Thrombophilia and Anticoagulation Clinic, Minneapolis Heart Institute® 2016.
Pradaxa® (dabigatran) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2015

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P-gp drug interaction

- **P-glycoprotein**: Efflux pump in the gut, liver, kidneys, blood brain barrier, and cancer cells. It's role is to pump drugs out of cells into the gut, bile, or urine for excretion.
- When P-gp inhibitors or inducers are taken with other drugs transported by P-gp, the drug's elimination is altered.
- Inhibitors and inducers are categorized as strong, moderate, or weak depending on their effect on P-gp.

Strong inhibitors
- Azithromycin, clarithromycin, erythromycin
- Itraconazole, ketoconazole
- Amiodarone, quinidine, dronedarone
- Verapamil

Strong inducers
- Rifampin
- Cyclosporine

Wessler JD. J Am Coll Cardiol. 2013 Jun 25;61(25):2495-502

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Clinical trials supporting Dabigatran (Pradaxa®)

Indication	Trial
Evidence for NVAF vs. warfarin	**RE-LY** - Superior: Ischemic and hemorrhagic stroke, vascular mortality - Higher risk of GIB and major bleeding in patients >75 years old
Evidence for VTE prophylaxis for THR and TKR vs. enoxaparin	**RE-NOVATE I and II** - Non-inferior *Not approved for TKR* **RE-MODEL, RE-MOBILIZE, RE-NOVATE I/II** - Non-inferior
Evidence for VTE management vs. LMWH/VKA	**RE-COVER** - Non-inferior: re-current VTE and mortality - Similar major bleeding, lower clinically relevant non-major bleeding
Evidence for VTE risk reduction after initial treatment	**RE-MEDY** - non-inferior vs. warfarin, similar major bleeding **RE-SONATE** Superior vs. placebo, higher major bleeding

DAOCs Guide. Thrombophilia and Anticoagulation Clinic, Minneapolis Heart Institute® 2016.

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Rivaroxaban (Xarelto®)

FDA Approved Indications
- Reducing stroke risk in non-valvular atrial fibrillation
- Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE)
- Prevention of recurrent DVT and PE
- Prevention of of postoperative DVT
- Prevention of DVT in hospitalized acutely ill medical patients
- Prevention of major cardiovascular events in coronary artery disease (CAD) or peripheral artery disease (PAD)

Boxed warning:
- Upon discontinuation, the risk of thrombotic events, especially stroke, is increased. If dabigatran must be discontinued for a reason other than pathological bleeding, consider the use of another anticoagulant during the time of interruption.
- Epidural or spinal hematomas may occur in patients undergoing neuraxial anesthesia or spinal puncture. Monitor patients for neurological impairment; treat urgently

Xarelto® (rivaroxaban) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2015

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Rivaroxaban (Xarelto®)

Renal Function	Non-valvular AFib	DVT Prophylaxis	DVT/PE Treatment	Risk Reduction of CV Events	Peripheral artery disease
Normal renal function/standard dosing	20 mg PO daily with the evening meal	10 mg PO daily without regards to meals	15mg PO BID for 21 days followed by 20mg PO daily	2.5 mg PO BID in combo daily low-dose aspirin	2.5mg PO BID in combo with daily low-dose aspirin
CrCl 15-50 mL/min	15 mg PO daily with the evening meal	Do NOT use in CrCl < 30 mL/min	Do NOT use in CrCl <30mL/min	N/A	2.5mg PO BID (no dose adjustment)
CrCl < 15 mL/min	Avoid use	Avoid use	Avoid use	N/A	Avoid use
Hemodialysis	15mg PO daily*	Avoid use	Avoid use	2.5mg PO BID* in combo with daily low dose aspirin	Avoid use

Xarelto® (rivaroxaban) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2015

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Rivaroxaban (Xarelto®)

	Non-valvular AFib	DVT Prophylaxis	DVT/PE Treatment	Risk Reduction of CV Events	Peripheral Artery Disease
Duration of Treatment	Indefinite	Knee replacement and Hip replacement: Minimum of 10-14 days and extended duration of up to 35 days	Provoked DVT: 3 months Unprovoked DVT: ≥ 3 months	Indefinite if high risk of CV events and low risk of bleeding	Indefinite if high risk of PAD complications and low risk of beading

Xarelto® (rivaroxaban) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2015

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Rivaroxaban (Xarelto®)

Contraindications

- Severe hypersensitivity to rivaroxaban or any component of the formulation
- Active pathological bleeding

Clinical Pearls/Patient Counseling

- The 15 and 20 mg tablets should be administered with food, 2.5 and 10 mg tablets may be administered with or without food
- Tablets may be crushed and mixed with applesauce or suspended with 50 mL of water to be delivered through NGT; after administration oral or enteral feeding should immediately follow the dose

Xarelto® (rivaroxaban) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2015

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DDIs with Rivaroxaban (Xarelto®)

Combined P-gp and strong CYP3A4 inhibitors: Avoid use due to increased exposure of rivaroxaban (from 30-160%) and risk of bleeding

Combined P-gp and strong CYP3A4 inducers: Avoid use due to reduced exposure to rivaroxaban (up to 50%) and reduced efficacy

Combined P-gp and moderate CYP3A4 inhibitors CrCl 15-80 mL/min: Avoid use unless benefit determined to outweigh risk

Anticoagulant, antiplatelets, NSAIDs, SSRIs, SNRIs: May increase bleeding risk

- Applicable to all DOACs

Xarelto® (rivaroxaban) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2015

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CYP3A4 drug interaction

- **Cytochrome-P450**: Class of enzymes responsible for biotransformation of drugs; located mainly in the liver, though extrahepatic metabolism also occurs in the kidneys, skin, gastrointestinal tract, and lungs.
- When CYP3A4 inhibitors or inducers are taken with other drugs metabolized by CYP3A4, the drug's usually metabolism is altered
- Inhibitors and inducers are categorized as strong, moderate, or weak depending on their effect on CYP3A4

Strong inhibitors

- Clarithromycin, erythromycin
- Fluconazole, itraconazole, ketoconazole
- Ritonavir

Strong inducers

- Rifampin
- Carbamazepine
- Phenytoin
- St. John's Wort

Wolfgang M. Br J Clin Pharmacol. 2013 Sep; 76(3): 455–466

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Clinical trials supporting Rivaroxaban (Xarelto®)

Indication	Trial
Evidence for NVAF vs. warfarin	**ROCKET-AF** - Non-inferior: all stroke - Similar major bleeding, lower ICH and fatal bleeding, higher risk of GIB and need for blood transfusion
Evidence for VTE prophylaxis for THR and TKR vs. enoxaparin	**RECORD 1, 2, 3, and 4** - Superior with no difference in bleeding
Evidence for VTE management vs. LMWH/VKA	**EINSTEIN** - Non-inferior: re-current VTE and mortality - Lower major bleeding
Evidence for VTE risk reduction after initial treatment	**EINSTEIN-EXT** - Superior vs. placebo, higher major bleeding **EINSTEIN-CHOICE** -Superior vs. aspirin, similar risk of bleeding
Evidence for PAD risk reduction	**COMPASS** -Rivaroxaban + aspirin resulted in modest absolute risk reduction, higher major bleeding **VOYAGER-PAD** -Superior, higher major bleeding vs placebo/aspirin

DAOCs Guide. Thrombophilia and Anticoagulation Clinic, Minneapolis Heart Institute® 2016.

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Apixaban (Eliquis®)

FDA Approved Indications

- Decrease the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery
- Treatment of DVT and PE, and decrease the risk of recurrent DVT and PE following initial therapy

Boxed Warning: When used to prevent stroke in patients with non-valvular atrial fibrillation, an increased risk of stroke may occur upon apixaban discontinuation if patient is not adequately anticoagulated with an alternative anticoagulant.

Eliquis® (apixaban) [package insert]. Princeton, NJ : Bristol Myers Squibb. 2015

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Apixaban (Eliquis®)

Renal Function	Non-valvular AFib	DVT Prophylaxis	Treatment of DVT and PE
Normal renal function; standard dosing	5mg PO BID	Hip: 2.5mg PO BID 12-24 hours post-op for 35 days Knee: 2.5mg PO BID 12-24 hours post-op	10mg PO BID for 7 days, followed by 5mg PO BID
CrCl 15-30mL/min	No dosage adjustment provided		No dosage adjustment necessary however patients with a SrCr >2.5mg/dL or CrCl <25mL/min were excluded from trials
CrCl <15mL/min	Not recommended		See above
Hemodialysis	No dose adjustment required unless; either ≥80 yo or BW ≤ 60kg then reduce to 2.5mg BID	No dose adjustment necessary	

Eliquis® (apixaban) [package insert]. Princeton, NJ : Bristol Myers Squibb. 2015

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Apixaban (Eliquis®)

	Non-valvular AFib	DVT Prophylaxis	Treatment of DVT and PE
Duration of Treatment	Indefinite	Hip: 35 days Knee: 12 days	Provoked DVT: 3 months Unprovoked DVT: ≥ 3 months

Dose adjustment necessary in Afib if 2 of 3 met:
SCr ≥ 1.5 mg/dL,
age ≥80 years, or
body weight ≤60 kg
Reduce dose to **2.5 mg twice daily**

Eliquis® (apixaban) [package insert]. Princeton, NJ : Bristol Myers Squibb. 2015

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Apixaban (Eliquis®)

Contraindications

- Severe hypersensitivity reaction to apixaban (anaphylaxis) or any component of the formulation
- Active pathological bleeding

Clinical Pearls and Patient Counseling

- Tablets may be crushed and suspended in 60mL D5W and immediately delivered through an NGT

Eliquis® (apixaban) [package insert]. Princeton, NJ : Bristol Myers Squibb. 2015

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Patient Case

JJ
86 yo Caucasian male
Weight: 65kg
SCr 1.8 at baseline
Non-valvular A fib

- JJ is an appropriate candidate to be started on apixaban, due to his TTR being less than _____% ?

→ TTR <65%

- What dose of apixaban would you recommend?

→ Apixaban 2.5mg PO BID with or without food due to age >80 and SCr >1.5

- How long would the duration of therapy be?

→ Indefinite for a fib

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DDIs with Apixaban (Eliquis®)

Combined P-gp and strong CYP3A4 inhibitors: Can lead to increased exposure of apixaban and risk of bleeding

- Doses >2.5 mg BID: reduce dose by 50%
- 2.5mg BID: avoid use

Combined P-gp and strong CYP3A4 inducers: avoid use due to reduced exposure to apixaban and reduced efficacy

Anticoagulant, antiplatelets, NSAIDs, SSRIs, SNRIs: may increase bleeding risk

- Applicable to all DOACs

Eliquis® (apixaban) [package insert]. Princeton, NJ : Bristol Myers Squibb. 2015

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Patient Case

You review JJ's medication list:

Warfarin 5mg PO daily MWF, 10 mg all other days
Clarithromycin 250 mg every 12 hours for 7 to 14 days
Rosuvastatin 10mg PO daily
Acetaminophen 500mg PO PRN headaches

Which medication is a combined P-gp and strong CYP3A4 inhibitor?

→ Clarithromycin

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Clinical trials supporting Apixaban (Eliquis®)

Indication	Trial
Evidence for NVAF vs. warfarin	**ARISTOTLE** - Superior: hemorrhagic stroke, vascular mortality, major bleeding - Lower risk ICH and fatal bleeding
Evidence for VTE prophylaxis for THR vs. enoxaparin	**ADVANCE 2 and 3** - Superior with no difference in bleeding
Evidence for VTE management vs. LMWH/VKA	**AMPLIFY** - Non-inferior: re-current VTE and mortality - Lower risk of major bleeding
Evidence for VTE risk reduction after initial treatment	**AMPLIFY-EXT** - Superior vs. placebo, similar major bleeding

DAOCs Guide. Thrombophilia and Anticoagulation Clinic, Minneapolis Heart Institute® 2016.

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Edoxaban (Savaysa®)

FDA Approved Indications

- Decrease the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Treatment of DVT and PE, following 5-10 days of initial therapy with a parenteral anticoagulant

Savaysa® (edoxaban) [package insert]. Parsippany, NJ: Daiichi Sankyo, Inc. 2015

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Edoxaban (Savaysa®)

Boxed Warning:

- Reduced efficacy in non-valvular atrial fibrillation patients with CrCl >95 mL/minute (increases the risk of ischemic stroke)
- When used to prevent stroke in patients with non-valvular atrial fibrillation, an increased risk of stroke may occur upon edoxaban discontinuation if patient is not adequately anticoagulated with an alternative anticoagulant
- Spinal or epidural hematomas may occur with neuraxial anesthesia (epidural or spinal anesthesia) or spinal puncture in patients who are anticoagulated; may result in long-term or permanent paralysis.

Savaysa® (edoxaban) [package insert]. Parsippany, NJ: Daiichi Sankyo, Inc. 2015

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Edoxaban (Savaysa®)

Renal function	Non-valvular AFib	DVT/PE Treatment
CrCl >95	Avoid use	
CrCl >50-95	60 mg PO daily	In patients weighing >60 kg 60 mg po daily
CrCl 15-50	30 mg PO daily	In patients weighing ≤60 kg 30 mg po daily
CrCl <15/end-stage CKD	Avoid use	Avoid use
Duration of Treatment	Indefinite	Provoked DVT: 3 months Unprovoked DVT: ≥3 months

Savaysa® (edoxaban) [package insert]. Parsippany, NJ: Daiichi Sankyo, Inc. 2015

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Edoxaban (Savaysa®)

Contraindications

- Severe hypersensitivity reaction to edoxaban (anaphylaxis) or any component of the formulation
- Active pathological bleeding

Savaysa® (edoxaban) [package insert]. Parsippany, NJ: Daiichi Sankyo, Inc. 2015

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DDIs with Edoxaban (Savaysa®)

P-gp inhibitors: Can lead to increased exposure of edoxaban and risk of bleeding

- NVAF: no dose reduction recommended
- VTE: 30mg PO once daily

P-gp inducers: Avoid use due to reduced exposure to dabigatran and reduced efficacy

Anticoagulant, antiplatelets, NSAIDs, SSRIs, SNRIs: May increase bleeding risk

- Applicable to all DOACs

Savaysa® (edoxaban) [package insert]. Parsippany, NJ: Daiichi Sankyo, Inc. 2015

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Clinical trials supporting Edoxaban (Savaysa®)

Indication	Trial
Evidence for NVAF vs. warfarin	**ENGAGE AF-TIMI 48** - CrCl 15-95 mL/min: non-inferior for stroke or systemic embolism - Superior: hemorrhagic stroke, major bleeding, cardiovascular mortality,
Evidence for VTE prophylaxis for THR vs. enoxaparin	*Not approved for these indications* **STARS J-V (THR):** Superior with no difference in bleeding **J-IV (hip fracture):** Similar with no difference in bleeding **STARS E-3 (TKR):** Superior with no difference in bleeding
Evidence for VTE management vs. LMWH/VKA	**HOKUSAI** - Non-inferior: re-current VTE - Superior: fatal and intracranial bleeding, clinically relevant bleeding
Evidence for VTE risk reduction after initial treatment	*Not approved for this indications* **Not studied**

DAOCs Guide. Thrombophilia and Anticoagulation Clinic, Minneapolis Heart Institute® 2016.

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Betrixaban (Bevyxxa®)

FDA Approved Indications

- VTE prophylaxis

Boxed warning: Spinal or epidural hematomas may occur with neuraxial anesthesia (epidural or spinal anesthesia) or spinal puncture in patients who are anticoagulated; may result in long-term or permanent paralysis.

Bevyxxa® (betrixaban) [package insert]. South San Francisco, CA: Portola Pharmaceuticals, Inc. 2017

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Betrixaban (Bevyxxa®)

Renal function	Dosing
CrCl > 30 mL/min	160 mg as a single dose on day 1, followed by 80 mg once daily
CrCl 15-30 mL/min or concomitant P-gp inhibitor	80 mg single dose, followed by 40 mg once daily
CrCl < 15 mL/min	Not recommended
Duration	35 to 42 days

Bevyxxa® (betrixaban) [package insert]. South San Francisco, CA: Portola Pharmaceuticals, Inc. 2017

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Betrixaban (Bevyxxa®)

Contraindications

- Serious hypersensitivity to betrixaban or any component of the formulation
- Active pathological bleeding

Clinical Pearls and Patient Counseling

- Administer with food at the same time each day

Bevyxxa® (betrixaban) [package insert]. South San Francisco, CA: Portola Pharmaceuticals, Inc. 2017

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DDIs with Betrixaban (Bevyxxa®)

P-gp inhibitors: Can lead to increased exposure of betrixaban and risk of bleeding

- Reduce dose: initial single dose 80 mg followed by 40 mg once daily

Anticoagulant, antiplatelets, NSAIDs, SSRIs, SNRIs: May increase bleeding risk

- Applicable to all DOACs

Bevyxxa® (betrixaban) [package insert]. South San Francisco, CA: Portola Pharmaceuticals, Inc. 2017

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Clinical trial supporting Betrixaban (Bevyxxa®)

Indication	Trial
Evidence for prevention of VTE vs enoxaparin in acutely ill hospitalized patients	**APEX** • Non-superior in cohort 1 (patients who had elevated D-Dimer level) • Protocol specified that all subsequent analyses were considered to be exploratory, but suggested benefit with betrixaban • Lower major and fatal bleeding, higher clinically relevant non-major bleeding

Cohen AT. N Engl J Med 2016; 375:534-544.

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2018 CHEST Guideline Updates for Atrial Fibrillation

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DOACs recommended over VKA

Patients eligible for oral anticoagulation, recommend DOACs over VKA

- Recommend VKA TTR >70%, action required if TTR <65% to improve TTR or switch to DOAC
- Indications where VKA or LMWH preferred: mechanical heart valves, DDIs (HAART, rifampin, phenytoin), pregnancy or breastfeeding, and cancer

Strong recommendation, moderate quality evidence

Lip GYH. CHEST 2018:154(5):1121-1201.

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Oral anticoagulation with ACS undergoing PCI/stenting

- **Low risk** (HAS-BLED 0-2): triple therapy for 6 months, then dual therapy with DOAC + antiplatelet, preferably clopidogrel, until 12 months followed by monotherapy with DOAC
- **High risk** (HAS-BLED ≥3): triple therapy for 1-3 months, then dual therapy with DOAC + antiplatelet, preferably clopidogrel, until 12 months followed by monotherapy with DOAC
- **Unusually high risk** (HAS-BLED ≥3 with recent bleeding event): DOAC + single antiplatelet, preferably clopidogrel, for 6-9 months followed by monotherapy with DOAC

Weak recommendation, low quality evidence

Lip GYH. CHEST 2018:154(5):1121-1201.

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PPI consideration

- AF patients on aspirin + DOAC, recommend adding a PPI to minimize risk of GI bleeding

Weak recommendation, low quality evidence

Lip GYH. CHEST 2018:154(5):1121-1201.

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AF patients with acute stroke

- AF patients who have an acute stroke with no contraindications should be started on a DOAC for secondary prevention within 2 weeks of the stroke

Strong recommendation, moderate quality evidence

Lip GYH. CHEST 2018:154(5):1121-1201.

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Pregnant and lactating women

Pregnant women:

- Switch DOAC with VKA between week 6-12 and replace by LMWH
- Replace DOACs in the 36th week of gestation
- Avoid DOACs for women attempting conception; for those on DAOCS suggest switching to VKA rather than LMWH when attempting conception

Lactating women:

- Recommend using warfarin or UFH for women who wish to breast feed

Ungraded consensus-based statement

Lip GYH. CHEST 2018:154(5):1121-1201.

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Chronic kidney disease

- **Mild CKD** (stage II, CrCl 60-89 mL/min): oral anticoagulation dosed the same as patients without CKD
- **Moderate CKD** (stage III, CrCl 30-59 mL/min): oral anticoagulation if CHA2DS2-VASc score ≥2 with renally dosed DOAC or VKA
- **Severe non-dialysis CKD** (stage VI, CrCl 15-30 mL/min): use VKA or selected DAOCs (rixaroxaban 15mg daily, apixaban 2.5mg BID, edoxaban 30mg daily, dabigatran 75mg BID)
- **ESRD** (CrCl <15mL/min or dialysis dependent): individualized decision making, suggest VKA over DAOC; apixaban 5mg BID is approved in HD

Weak recommendation, low quality evidence; ESRD: ungraded consensus-based statement

Lip GYH. CHEST 2018:154(5):1121-1201.

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Antithrombotic prophylaxis bridging

- Patients on antithrombotic prophylaxis with DOAC, suggest preoperative management **without** bridging

Weak recommendation, low quality evidence

Lip GYH. CHEST 2018:154(5):1121-1201.

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Patients refusing DOACs

- Recommend reinforcing educational messages at each visit with the patient and reconsider treatment decisions

Ungraded consensus-based statement

Lip GYH. CHEST 2018:154(5):1121-1201.

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Transitioning between anticoagulants

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Transitioning to a DAOC

To: / From:	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Warfarin	Stop warfarin and monitor INR, start dabigatran when INR <2	Stop warfarin and monitor INR, start rivaroxaban when INR <3	Stop warfarin and monitor INR, start apixaban when INR <2	Stop warfarin and monitor INR, start edoxaban when INR <2.5
Heparin	Stop heparin and start DOAC at the same time			Start edoxaban when heparin infusion is stopped
LMWH	Stop LMWH and start DOAC when the next dose of LMWH is due			

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Transitioning from a DOAC

To: / From:	Warfarin	Heparin	LMWH	Another DOAC
Dabigatran	Start warfarin 1,2, or 3 days before stopping dabigatran based on CrCl. CrCl ≥50: 3 days CrCl 30-50: 2 days CrCl 15-30: 1 day	Start 12 hours (CrCl ≥30) or 24 hours (CrCl <30) after the last dose of dabigatran		Stop dabigatran and start new DOAC when the next dose would have been given

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Transitioning from a DOAC

To:	Warfarin	Heparin	LMWH	Another DOAC
Rivaroxaban	Stop DOAC and start LMWH/UFH and warfarin at the same time when the next dose of DOAC would have been given; stop LMWH/UFH when INR is therapeutic	Stop DOAC and start LMWH/UFH at the time when the next dose of DOAC would have been given		Stop DOAC and start new DOAC when the next dose would have been given
Apixaban				
Edoxaban	Reduce edoxaban dose by half and start warfarin concomitantly until INR is therapeutic			

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Interruption of DOACs for scheduled procedures

Drug	Low bleeding risk procedure	High bleeding risk procedure	Resumption of DOAC after low risk procedure	Resumption of DOAC after high risk procedure
Dabigatran CrCl >50 mL/min	1 days before	2 days before	Resume 1 day after procedure	Resume 2-3 days after procedure
Dabigatran CrCl 30-50 mL/min	2 days before	4 days before		
DOACs: Rivaroxaban Apixaban Edoxaban	1 day before	2 days before		

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DOACs vs. warfarin

Pros
- Improved clinical outcomes
- No INR monitoring required; therefore, less frequent office visits
- No need for bridging
- Fewer drug and diet interactions

Cons
- Twice daily dosing with select DOACs
- Missed doses place patient at higher risk of thrombosis due to short half-life
- Higher incidence of GI side effects leading to discontinuation
- Renal monitoring and dose adjustments required
- Higher costs

Mekaj YH. Ther Clin Risk Manag 2015;11:967-977.

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Monitoring of all DOACs

- Routine monitoring of coagulation tests is not required
- **A**dherence assessment and counseling
- **B**leeding risk assessment
- **C**reatinine Clearance
- **D**rug interaction assessment and counseling

Cuker A. J Am Coll Cardiol. 2014 Sep 16;64(11):1128-39

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Monitoring of all DOACs

- Renal and hepatic function should be evaluated before initiation of DAOC and at least annually
  - Renal dosing adjustments
  - DOACs are not recommended in severe hepatic dysfunction

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Adherence concerns

- Poor Adherence = Poor Outcomes
  - 13% increase in all-cause mortality and stroke for each 10% decrease in adherence
- Increased adherence has been demonstrated with pharmacist-led monitoring
  - Recommend 1 visit every 3 months for DOAC adherence monitoring, which is likely much less often than warfarin visits for INR monitoring

Shore S. JAMA. 2015 Apr 14;313(14):1443-50.

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Laboratory considerations: direct thrombin inhibitor (Dabigatran)

- Dabigatran level: reference range 45-95 ng/mL
  - Trough level drawn ≤30 minutes prior to the next scheduled dose
- Thrombin time (TT)
  - Normal TT rules out clinically significant levels of dabigatran
- aPTT
  - Use if above unavailable, less sensitive than TT
- PT/INR
  - Less sensitive than TT or aPTT

Cuker A. J Am Coll Cardiol. 2014 Sep 16;64(11):1128-39

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Laboratory considerations: factor Xa inhibitors (apixaban, edoxaban, rivaroxaban)

- Heparin level = anti-Xa
  - This assay used to calculate heparin levels shows linear correlation with increasing levels of factor Xa inhibitors
  - Anti-Xa level <0.1 U/mL rules out clinically significant levels of factor Xa inhibitors
- PT/INR: due to variability in results, not recommended

  Apixiban and rivaroxaban:
  - PT shows some correlation with direct factor Xa inhibitor levels, correlation with INR is weaker
  - Normal PT rules out clinically significant levels of factor Xa inhibitors

  Edoxaban:
  - No good correlation with PT

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Laboratory considerations: DOAC serum levels

- Commercial assays are available, but reference ranges are variable and not correlated to safety, efficacy, or clinical outcomes
- Indications for serum levels include:
  - Patients undergoing emergent surgery
  - Dialysis or CKD patients at risk of accumulation leading to toxic drug levels
  - Detection of DDIs to guide dose adjustments
  - Evaluation of absorption in obese patients
  - Evaluation of adherence

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Reversal of DOACs

Idarucizumab (Praxbind®) — Antidote for dabigatran

Andexanet Alfa (Andexxa®) — Antidote for Direct Xa Inhibitors

Please see **"Available Strategies to Reverse Anticoagulant Medications"** CE presentation for additional information

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Conclusion

- The DOACs consist of the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, edoxaban, and betrixaban
- The pharmacokinetics, pharmacology, indications, dosing, and other considerations are DOAC specific and vary between the drug class
- There are dose adjustments recommended, dependent on patient's renal function and concomitant use of P-gp or CYP3A4 inhibitors or inducers

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