Practitioners' Guide for Improving Oral Anticoagulant Use

Learning Objectives

- Discuss the prevalence and types of adverse drug events related to oral anticoagulants.
- Review the drug classifications of oral anticoagulants.
- Compare characteristics of oral vitamin K antagonists and direct acting oral anticoagulants.
- Identify pathophysiological states for utilization of oral anticoagulation therapy.
- Review barriers to proper oral anticoagulant use.
- List steps clinicians can take to reduce the risk of adverse drug events from oral anticoagulants.

Acronyms and Abbreviations

Acronym/Abbreviation	Full Term
AFib	atrial fibrillation
ADE	adverse drug event
CBC	complete blood count
DOAC	direct acting oral anticoagulant
DVT	deep vein thrombosis
ED	emergency department
FFP	fresh frozen plasma
GI	gastrointestinal
INR	international normalized ratio
PCC	prothrombin complex concentrate
PE	pulmonary embolism
PST	patient self-testing
PT	prothrombin time
SDM	shared decision-making
SNF	skilled nursing facility
VTE	venous thromboembolism

Background

Why the Focus on Oral Anticoagulants?

- High prevalence of oral anticoagulants prescribed (warfarin, dabigatran, rivaroxaban, edoxaban, apixaban, betrixaban).
- Despite efficacious therapies for stroke prevention in patients with AFib, less than 60% of AFib patients at high-risk for stroke are treated with oral anticoagulants.
- High potential for harm, such as gastrointestinal hemorrhage or stroke, with improper use.
- Misconceptions over proper use and burdens associated with their use.
- **High number of emergency department (ED) visits from anticoagulant adverse drug events (ADEs).**

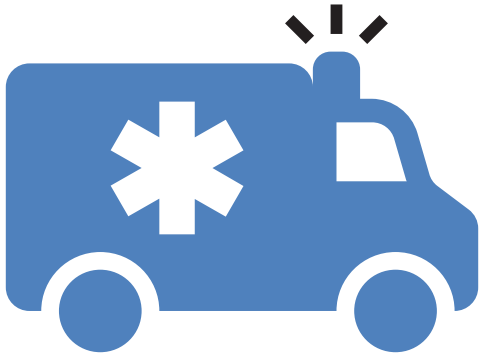
https://health.gov/hcq/pdfs/ade-action-plan-508c.pdf
https://www.ncbi.nlm.nih.gov/pubmed/20609686

What Is an Adverse Drug Event (ADE)?

An injury resulting from medical intervention related to a drug.

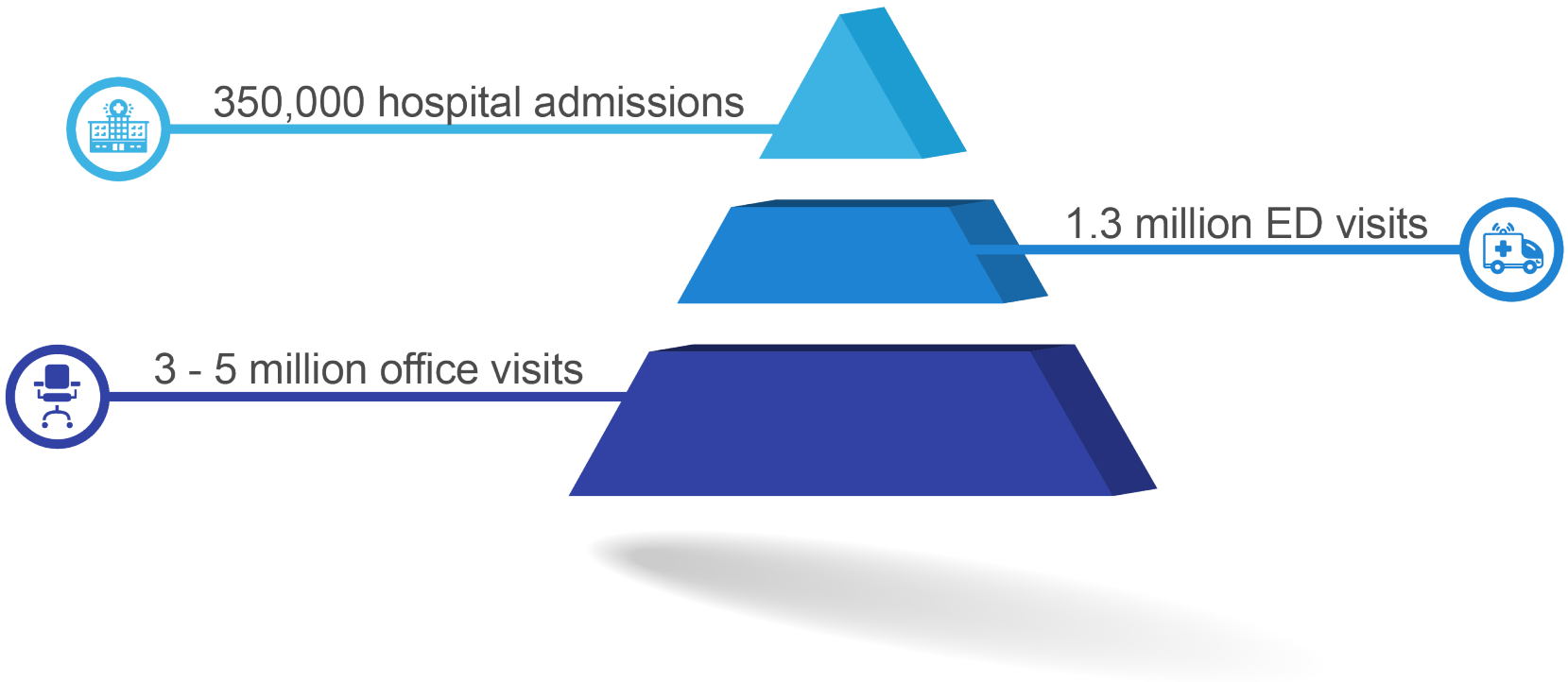
This includes:

- Medication errors,
- Adverse drug reactions including drug therapeutic failure,
- Allergic reactions, and
- Overdoses.



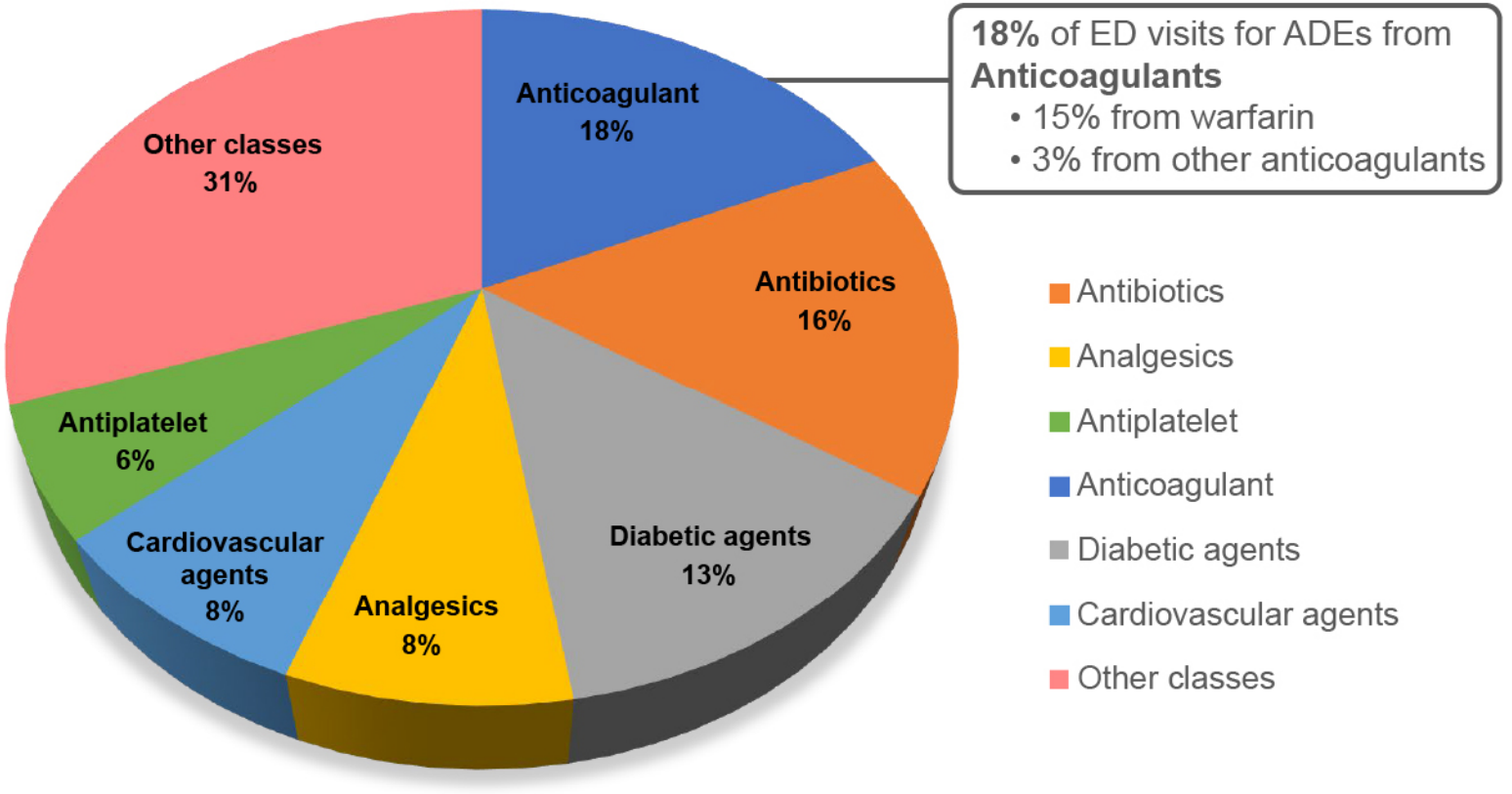
https://health.gov/hcq/ade.asp

Outpatient Adverse Drug Event Results 2013-2014



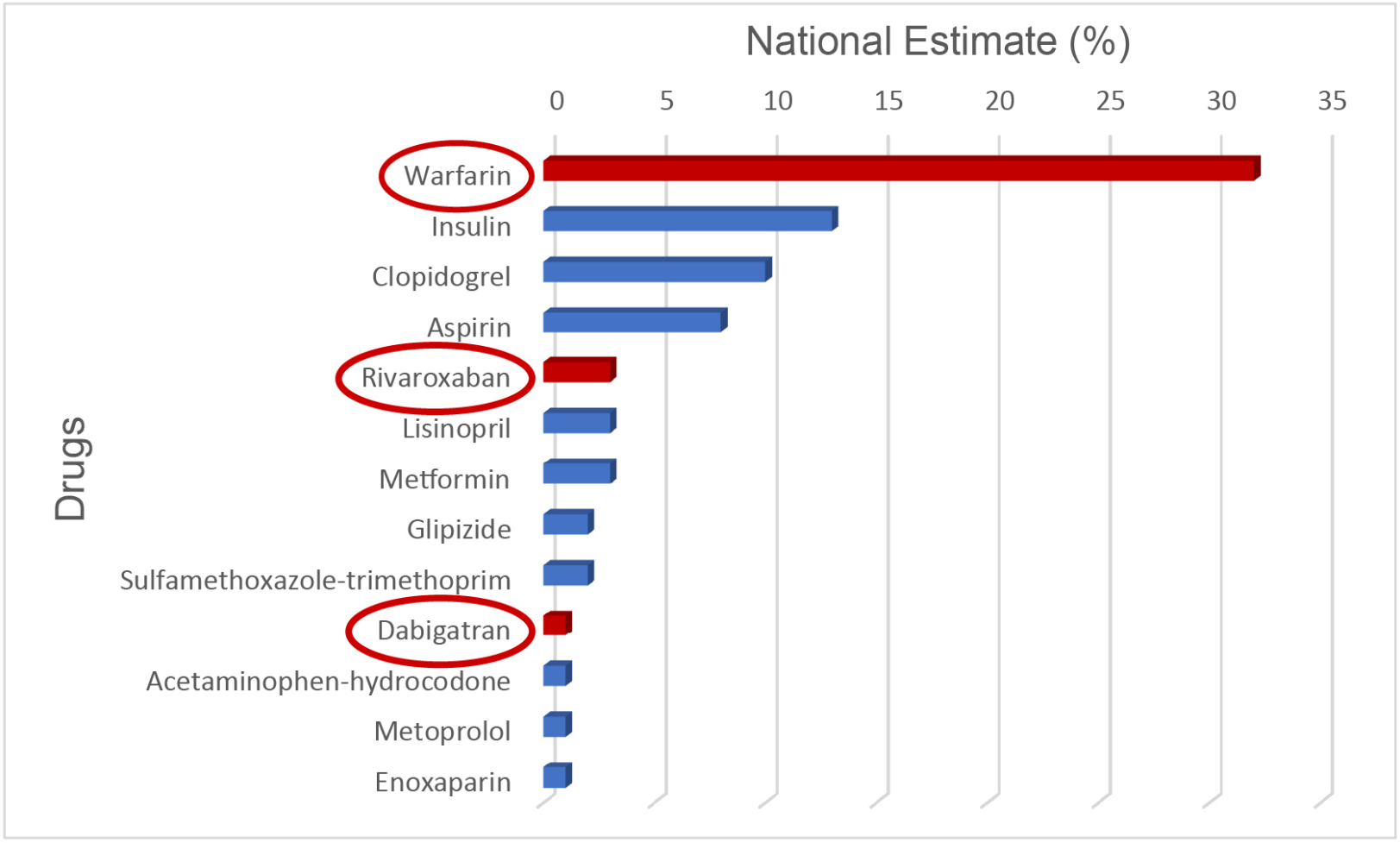
Shehab N, et al. U.S. emergency department visits for outpatient adverse drug events 2013-2014. 2016 Nov;316(20):2115-2125

ED Visits for ADEs by Medication Class



Shehab N, et al. US emergency department visits for outpatient adverse drug events 2013-2014. 2016 Nov;316(20):2115-2125.

ADE ED Visits in Adults ≥ 65 years, 2013-2014



Shehab N, et al. US emergency department visits for outpatient adverse drug events 2013-2014. 2016 Nov;316(20):2115-2125.

What Is the Most Common ADE Due to an Anticoagulant in the ED?

US Emergency Department (ED) Visits for Adverse Drug Events (ADEs) From Select Drug Classes by Adverse Event Manifestation, 2013-2014

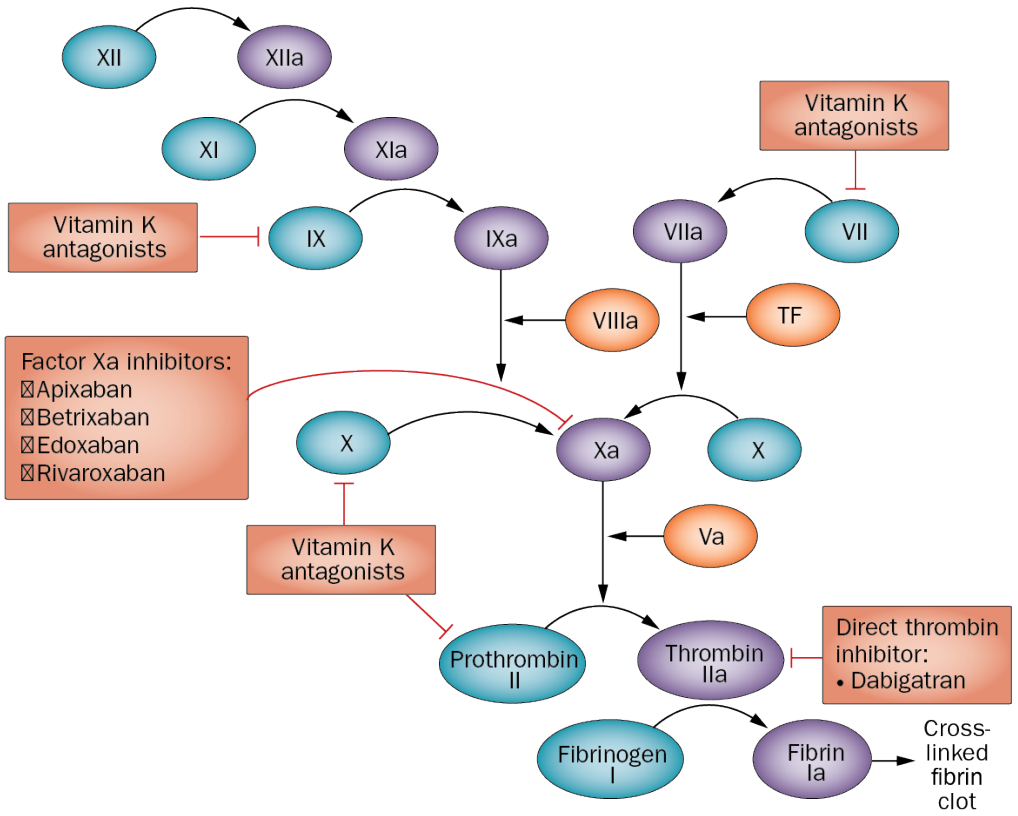
Please Note: The case counts below are only for anticoagulants.

Adverse Event Manifestation	No. of Cases	National Estimate, % (95% CI)
Hemorrhage	5101	79.4 (75.2-83.6)
Central nervous system[d]	262	2.8 (1.4-4.2)
Pulmonary	149	2.3 (1.7-3.0)
Gastrointestinal	1577	27.0 (21.0-32.9)
Genitourinary	547	9.5 (6.6-12.4)
Epistaxis	815	15.0 (11.7-18.3)
Skin, wound, or other minor	1418	18.8 (13.2-24.4)
Other hemorrhage types	333	4.1 (2.5-5.6)

Shehab N, et al. US emergency department visits for outpatient adverse drug events 2013-2014. 2016 Nov;316(20):2115-2125.

Drug Classifications of Oral Anticoagulants: DOACs and Vitamin K Antagonists

Direct Acting Oral Anticoagulants (DOACs) and Vitamin K Antagonists



Direct Thrombin Inhibitor

- Dabigatran

Factor Xa Inhibitors

- Apixaban
- Betrixaban
- Edoxaban
- Rivaroxaban

Factors II, VII, IX, and X Inhibitors

- Vitamin K antagonists - Warfarin

John N. Makaryus, Jonathan L. Halperin & Joe F. Lau, Oral anticoagulants in the management of venous thromboembolism, Nature Reviews Cardiology Volume 10

The “Ideal” Oral Anticoagulant

- Once daily dosing
- Minimal monitoring required
- Reversal agent available
- Wide therapeutic index
- Low cost
- Easy dose adjustments for renal function and age

Indications for Oral Anticoagulation

- Treatment of existing thrombosis
  - Acute venous thromboembolism (VTE)
- Primary prevention of thrombosis
  - Patients with atrial fibrillation (AFib) with an increased risk of stroke
  - Patients with mechanical heart valves
  - Extended VTE prophylaxis following major orthopedic surgeries
- Secondary prevention of thrombosis
  - Patients with a history of VTE for which benefits of treatment outweigh risks
  - Patients with AFib and a history of cardioembolic stroke
- Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction
- Reduction in risk of major cardiovascular events in patients with coronary artery disease (CAD) or peripheral artery disease (PAD)

VA and NIH Recommendations

The Department of Veterans Affairs (VA) and the National Institutes of Health (NIH), among other institutions and professional organizations provide clinicians with recommendations for baseline and on-going laboratory testing, whenever a patient is started on an oral anticoagulant.

Clinical Lab Recommendations Prior to and During Oral Anticoagulant Therapy

Warfarin	DOACs
• CBC (complete blood count) • PT (prothrombin time) • INR (international normalized ratio) *NOTE: Initial INR should not be performed using patient self-testing (PST) devices.*	• CBC • Serum creatinine • Liver function tests (if history or risk of hepatic insufficiency)

CHA2DS2-VASc

Risk	Points
Congestive Heart Failure (CHF) or Left ventricular ejection fraction (LVEF) < 40%	1
Hypertension	1
Age > 75 years	2
Diabetes	1
Stroke/Transient ischemic attack (TIA)/ Thromboembolism	2
Vascular disease	1
Age 65-74 years	1
Female	1

CHA2DS2-VASc Score	Unadjusted Ischemic Stroke Rate (% / year)
0	0.2
1	0.6
2	2.2
3	3.2
4	4.8
5	7.2
6	9.7
7	11.2
8	10.8
9	12.2

Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J 2012; 33:1500

HAS-BLED

Letter	Clinical Characteristic	Points
H	Hypertension (> 160mm Hg systolic)	**1**
A	Abnormal Liver or Renal Function (one point for each)	**1 or 2**
S	Stroke (previous history)	**1**
B	Bleeding (history of predisposition)	**1**
L	Labile INR (time in therapeutic range < 60%)	**1**
E	Elderly (age > 65 years)	**1**
D	Drugs or Alcohol (1 point for each) (one point for antiplatelet or nonsteroidal anti-inflammatory drugs and one point for alcohol excess)	**1 or 2**

Maximum Score: 9

https://www.acc.org/latest-in-cardiology/articles/2014/07/18/11/38/which-risk-score-best-predicts-bleeding-with-warfarin-in-atrial-fibrillation

HEMORR$_2$HAGES

Letter	Clinical Characteristic	Points
H	Hepatic or Renal Disease	1
E	Ethanol Abuse	1
M	Malignancy	1
O	Older Age	1
R	Reduced Platelet Count or Function	1
R	Rebleeding Risk	2
H	Hypertension	1
A	Anemia	1
G	Genetic Factors	1
E	Excessive Fall Risk	1
S	Stroke	1

Maximum Score: 12

Case Study

Using the HAS-BLED bleeding risk assessment, which of the following factors may increase JR's risk of a bleeding event?

JR is a 62-year-old man with a history of hypertension, type 2 diabetes, arthritis, alcoholism, and previously had a gastrointestinal (GI) bleed.

His current medications include:

- 200 mg ibuprofen as needed,
- 81 mg aspirin daily,
- 20 mg lisinopril daily, and
- 500 mg metformin twice daily.

Case Study

JR is a 62-year-old man with a history of hypertension, type 2 diabetes, arthritis, **alcoholism**, and previously had a gastrointestinal **(GI) bleed**. His current medications include 200 mg **ibuprofen** as needed, 81 mg **aspirin daily**, 20 mg lisinopril daily, and 500 mg metformin twice daily.

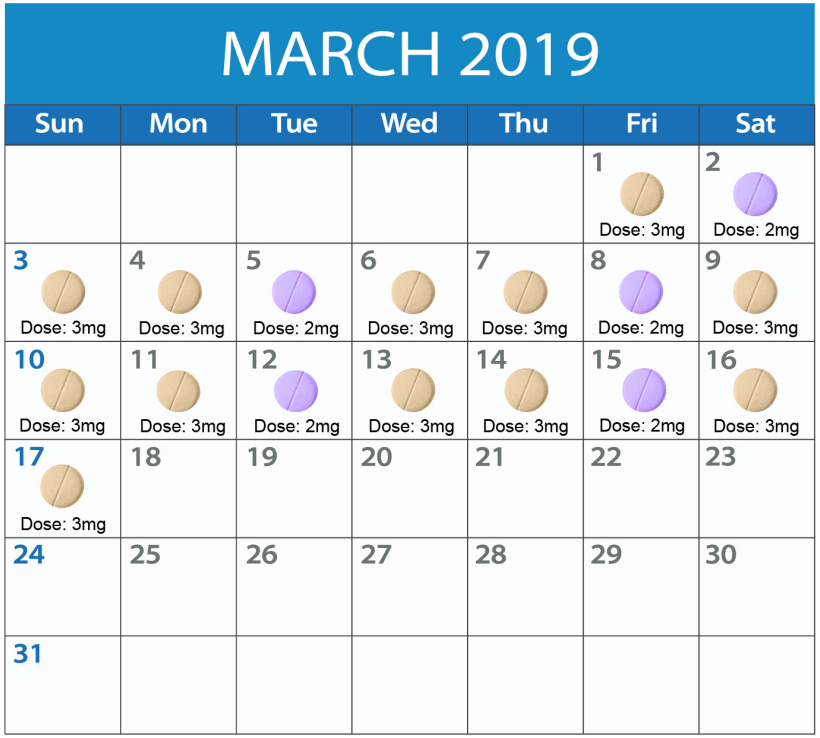
Which of these factors increases JR's risk of a bleeding event?

Letter	Clinical Characteristic	Points
H	Hepatic or Renal Disease	1
E	Ethanol Abuse	1
M	Malignancy	1
O	Older Age	1
R	Reduced Platelet Count or Function	1
R	Rebleeding Risk	2
H	Hypertension	1
A	Anemia	1
G	Genetic Factors	1
E	Excessive Fall Risk	1
S	Stroke	1

Maximum Score: 12

Warfarin

- Narrow therapeutic Index
- ***Numerous food, drug, and disease state interactions***
- Individualized dosing due to variability in response
- Requires regular laboratory monitoring
- Complicated regimens
  - Patients often have to utilize calendars and other aids for proper administration



Warfarin Dosing and INR

- Measure baseline INR prior to starting therapy.
- Initial dose of warfarin is usually between 2 to 5 mg once daily and maintenance doses range from 2 to 10 mg once daily.
- Consider smaller starting doses for high risk patients (elderly, low body weight, abnormal liver function or at a high bleeding risk).

https://www.mayoclinic.org/tests-procedures/prothrombin-time/about/pac-20384661
https://docplayer.net/15751184-Safe-management-of-anticoagulants-in-wa-hospitals.html
Reference: Warfarin sodium package insert. https://medlibrary.org/lib/rx/meds/warfarin-sodium-13/

Warfarin Monitoring Parameters

- International Normalized Ratio (INR)
- Goal range is dependent on rationale for utilization
- Recommended guidelines for monitoring
  - 4 weeks
  - Shorter intervals if INR is out of target range, or significant INR fluctuations expected
  - CHEST Guidelines suggest longer intervals of up to 12 weeks may be considered in patients with consistently stable INRs

Long-Term Warfarin Therapy

Some patients on long-term warfarin therapy experience unexpected fluctuations in dose-response due to:

- Changes in diet,
- Concurrent medication changes,
- Poor compliance,
- Alcohol consumption, or
- New or worsening disease states.

Patient Self-Testing (PST)

- INR test meter is a portable, battery-operated device, used to monitor patient response to warfarin
- Convenient alternative to in-clinic testing
- As revealed by The Home INR Study (THINRS), event rates for patient self-testing (PST) were not significantly different from those for in-clinic high-quality anticoagulation management, and a cumulative gain in quality of life was observed for patients using PST.

https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/WarfarinINRTestMeters/default.htm

Warfarin INR Interactions

Dietary interactions

Disease state interactions

Drug interactions

Lourenco R. Enteral feeding: drug/nutrient interaction. Clin Nutr. 2001;20:187-93.

Penrod LE, Allen JB, Cabacungan LR. Warfarin resistance and enteral feedings: 2 case reports and a supporting in vitro study. Arch Phys Med Rehab. 2011;82:1270-3.

Dickerson RN, Garmon WM, Kuhl DA, Minard G, Brown RO. Vitamin K-independent warfarin resistance after concurrent administration of warfarin and continuous enteral nutrition. Pharmacotherapy. 2008;28:308-13.

Warfarin INR Interactions

Dietary interactions include:

- Vitamin K
  - High concentration in green leafy vegetables
- Alcohol
  - Increase INR in short term and decrease in long term
- Enteral tube feeding

Lourenco R. Enteral feeding: drug/nutrient interaction. Clin Nutr. 2001;20:187-93.

Penrod LE, Allen JB, Cabacungan LR. Warfarin resistance and enteral feedings: 2 case reports and a supporting in vitro study. Arch Phys Med Rehab. 2011;82:1270-3.

Dickerson RN, Garmon WM, Kuhl DA, Minard G, Brown RO. Vitamin K-independent warfarin resistance after concurrent administration of warfarin and continuous enteral nutrition. Pharmacotherapy. 2008;28:308-13.

Warfarin INR Interactions

Disease state interactions include:

- Hypo/hyperthyroidism
- Liver dysfunction

Lourenco R. Enteral feeding: drug/nutrient interaction. Clin Nutr. 2001;20:187-93.

Penrod LE, Allen JB, Cabacungan LR. Warfarin resistance and enteral feedings: 2 case reports and a supporting in vitro study. Arch Phys Med Rehab. 2011;82:1270-3.

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Warfarin INR Interactions

Drug interactions include:

- Acetaminophen
- Amiodarone
- Antimicrobials
  - Azole antifungals
  - Sulfamethoxazole/trimethoprim
- Herbals
- Clopidogrel

Lourenco R. Enteral feeding: drug/nutrient interaction. Clin Nutr. 2001;20:187-93.

Penrod LE, Allen JB, Cabacungan LR. Warfarin resistance and enteral feedings: 2 case reports and a supporting in vitro study. Arch Phys Med Rehab. 2011;82:1270-3.

Dickerson RN, Garmon WM, Kuhl DA, Minard G, Brown RO. Vitamin K-independent warfarin resistance after concurrent administration of warfarin and continuous enteral nutrition. Pharmacotherapy. 2008;28:308-13.

Potentiation of Warfarin

The article, Oral Anticoagulant Therapy, published in the CHEST Journal, contains a full table of drugs that may potentiate the action of warfarin. A PDF handout of this table is available in the Resources section of the course launch page.

Level of Causation	Anti-infectives	Cardiovascular	Analgesics, Anti-inflammatories, Immunologics	CNS Drugs	GI Drugs and Food	Herbal Supplements	Other Drugs
Highly Probable	Ciprofloxacin Co-trimoxazole Erythromycin Fluconazole	Amiodarone Clofibrate Diltiazem	Phenylbutazone Piroxicam	Alcohol (if concomitant liver disease) Citalopram Sertraline	Cimetidine Fish oil Mango Omeprazole	Boldo-fenugreek Quilinggao	Anabolic steroids Zileuton
Probable	Amoxicillin/ clavulanate	Aspirin	Acetaminophen Aspirin	Disulfiram Chloral hydrate	Grapefruit	Danshen Dong quai	Fluorouracil Tamoxifen
Possible	Amoxicillin	Amiodarone-induced toxicosis	Celecoxib	Felbamate	Orlistat	Danshen/ Methyl salicylate	Acarbose
Highly Improbable	Cefamandole Cefazolin	Bezafibrate Heparin	Levamisole Nabumetone	Fluoxetine Diazepam			Levonorgestrel

Ageno, W., Gallus, A. S., Wittkowsky, A., Crowther, M., Hylek, E. M., & Palareti, G. (2012). Oral Anticoagulant Therapy Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST Journal, 141(2), e44S–e44S. doi: https://doi.org/10.1378/chest.11-2292

Inhibition of Warfarin

The article, Oral Anticoagulant Therapy, published in the CHEST Journal, contains a full table of drugs that may inhibit the action of warfarin. A PDF handout of this table is available in the Resources section of the course launch page.

Level of Causation	Anti-infectives	Cardiovascular	Analgesics, Anti-inflammatories, Immunologics	CNS Drugs	GI Drugs and Food	Herbal Supplements	Other Drugs
Highly Probable	Griseofulvin	Cholestyramine	Mesalamine	Barbiturates	High vit. K content foods Avocados (lg. amts)		Mercaptopurine
Probable	Dicloxacillin	Bosentan	Azathioprine	Chlordiaze-poxide	Soy milk Sucralfate	Ginseng	Chelation Therapy Multi-vitamins
Possible	Terbinafine	Telmisartan	Sulfasalazine		Seaweed		Cyclosporine
Highly Improbable	Cloxacillin	Furosemide		Propofol		Green tea	

Ageno, W., Gallus, A. S., Wittkowsky, A., Crowther, M., Hylek, E. M., & Palareti, G. (2012). Oral Anticoagulant Therapy Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST Journal, 141(2), e44S–e44S. doi: https://doi.org/10.1378/chest.11-2292

Warfarin Reversal Agent

Vitamin K

- Indicated in patients treated with **warfarin** when reversal of the anticoagulant effects is needed (e.g., due to life-threatening or uncontrolled bleeding).

➢ **Intracerebral hemorrhage:** Replace clotting factors within 90 minutes of emergency department arrival.

- Refer to labels regarding vitamin K and prothrombin complex concentrates (PCC).
- PCC generally preferred to fresh frozen plasma to restore clotting factors in patients requiring urgent warfarin reversal.
- Professional societies have also published guidelines on Management of Bleeding in Patients on Oral Anticoagulants.

Supratherapeutic Warfarin Management

INR	Clinical Scenario	Management
Between 4.5-10	No bleeding	Hold warfarin until INR in therapeutic range and resume at lower dose Do not administer vitamin K
> 10	No bleeding	Hold warfarin until INR in therapeutic range and resume at lower dose Consider 2.5 mg oral vitamin K
Any	Life threatening bleeding or urgently needed surgery	Hold warfarin Vitamin K 5 to 10 mg slow IV infusion AND Four-Factor prothrombin complex concentrate (PCC)

Chest 2012; 141:e152S-e184S

Knowledge Check

Match the correct drug-drug interaction and its effect. Refer to the Potentiation and Inhibition of Warfarin tables.

a. Amiodarone – warfarin → inhibits effect of warfarin
b. Phenytoin – warfarin → potentiates effect of warfarin
c. Citalopram – warfarin → potentiates effect of warfarin
d. Azole antifungals – warfarin → inhibits effect of warfarin

Knowledge Check

Match the correct drug-drug interaction and its effect. Refer to the Potentiation and Inhibition of Warfarin tables.

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Contraindications to Warfarin

- Active bleeding
- Imminent hemorrhage
- Pregnancy (congenital malformations such as warfarin embryopathy and fetotoxicity)
- High bleeding risk
  - Bleeding risk assessments for AFib patients
    - HAS-BLED (Superior performance for predicting risk of major bleed)
    - HEMORR$_2$HAGES
    - ATRIA

Knowledge Check

According to the CHEST guidelines, what is the recommended INR monitoring frequency in patients receiving warfarin with consistently stable INRs?

a. 4 weeks
b. 6 weeks
c. 8 weeks
d. Up to 12 weeks
e. At every doctor's visit

Knowledge Check

According to the CHEST guidelines, what is the recommended INR monitoring frequency in patients receiving warfarin with consistently stable INRs?

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DOACs and Approved Indications

DOAC	Primary VTE Prophylaxis in Hip/Knee Replacement Surgery	Non-Valvular Atrial Fibrillation	DVT/PE Treatment	Secondary Prevention of Recurrent DVT/PE	Primary VTE Prophylaxis of Adult Patients Hospitalized for an Acute Medical Illness	Reduce Risk of Major Cardiovascular Events in CAD and PAD patients (in combination with aspirin use)
Apixaban	X	X	X	X		
Betrixaban					X	
Dabigatran	X (Hip)	X	X	X		
Edoxaban		X	X			
Rivaroxaban	X	X	X	X	X	X

Knowledge Check

True or False?

All of the DOACs are indicated for prophylaxis of stroke in patients with Afib.

a. True

b. False

Knowledge Check

True or False?

All of the DOACs are indicated for prophylaxis of stroke in patients with Afib.

a) True

b) False

DOAC	Primary VTE Prophylaxis in Hip/Knee Replacement Surgery	Non-Valvular Atrial Fibrillation	DVT/PE Treatment	Secondary Prevention of Recurrent DVT/PE	Primary VTE Prophylaxis of Adult Patients Hospitalized for an Acute Medical Illness	Reduce Risk of Major Cardiovascular Events in CAD and PAD patients (in combination with aspirin use)
Apixaban	X	X	X	X		
Betrixaban					**X**	
Dabigatran	X (Hip)	X	X	X		
Edoxaban		X	X			
Rivaroxaban	X	X	X	X	X	X

DOAC Dosing for Stroke Prophylaxis in Nonvalvular AFib

DOAC	Dosing for Stroke Prophylaxis in Nonvalvular Atrial Fibrillation	Dose Adjustment
Dabigatran	150 mg **twice daily**	CrCl 15-30 mL/min: 75 mg twice daily CrCl 30-50 mL/min with concomitant P-gp inhibitors: 75 mg twice daily
Apixaban	5 mg **twice daily**	Decrease to 2.5 mg twice daily if at least **2** of the following are present: age ≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL Moderate to severe hepatic impairment: not recommended
Rivaroxaban	20 mg **once daily** with evening meal	CrCl 15-50 mL/min: 15 mg once daily with evening meal Moderate to severe hepatic impairment: not recommended
Edoxaban	60 mg **once daily**	CrCl > 95 mL/min: not recommended CrCl 15-50 mL/min: 30 mg once daily Moderate to severe hepatic impairment: not recommended
Betrixaban	Not indicated for Stroke Prophylaxis in Nonvalvular Atrial Fibrillation	Not indicated for Stroke Prophylaxis in Nonvalvular Atrial Fibrillation

DOAC Dosing for VTE Treatment

DOAC	Dosing for VTE Treatment	Dose Adjustment
Dabigatran	150 mg **twice daily** (prior bridging with parenteral anticoagulation required for 5-10 days)	CrCl ≤ 30 mL/min: not recommended CrCl < 50 mL/min with concomitant P-gp inhibitor: avoid use
Apixaban	10 mg **twice daily** for 1 week, then 5 mg twice daily	CrCl < 15 mL/min: not studied Moderate to severe hepatic impairment: not recommended
Rivaroxaban	15 mg **twice daily** with evening meal for 3 weeks, then 20 mg **once daily** with evening meal	CrCl < 30 mL/min: not recommended Moderate to severe hepatic impairment: not recommended
Edoxaban	60 mg **once daily** (prior bridging with parenteral anticoagulation required for 5-10 days)	CrCl 15-50 mL/min or weight ≤ 60 kg or concomitant P-gp inhibitors: 30 mg once daily Moderate to severe hepatic impairment: not recommended
Betrixaban	Not indicated for VTE treatment	Not indicated for VTE treatment

DOAC Dosing for VTE Prophylaxis Following Knee or Hip Replacement Surgery

DOAC	Dosing for VTE Prophylaxis After Hip or Knee Replacement	Dose Adjustment
Dabigatran	110 mg within 1-4 hours after surgery, then 220 mg **once daily** for 28-35 days for hip replacement surgery If not started on the first day, then treatment can be started at 220 mg **once daily** for hip replacement surgery	Dialysis or CrCl ≤ 15 mL/min: not recommended
Apixaban	2.5 mg **twice daily** within 12-24 hours after surgery For knee replacement, the recommended duration is 12 days For hip replacement, the recommended duration is 35 days	Moderate to severe hepatic impairment: not recommended
Rivaroxaban	10 mg **once daily** within 6-10 hours after surgery For knee replacement, the recommended duration is 12 days For hip replacement, the recommended duration is 35 days	CrCl ≤ 30 mL/min: not recommended Moderate to severe hepatic impairment: not recommended
Edoxaban	Not indicated for VTE Prophylaxis after hip or knee replacement	Not indicated for VTE Prophylaxis after hip or knee replacement
Betrixaban	Not indicated for VTE Prophylaxis after hip or knee replacement	Not indicated for VTE Prophylaxis after hip or knee replacement

DOAC Safety Considerations and Interaction Examples

Dietary interactions to consider:

- Dabigatran capsules must be swallowed whole and not opened due to the risk of increased absorption.
- Rivaroxaban (15 and 20 mg) should be taken with food for adequate absorption.

DOAC Safety Considerations and Interaction Examples

Disease state interactions include:

- Renal function
  - Renal elimination differs among DOACs
- From more to less renal elimination: dabigatran > edoxaban > rivaroxaban > apixaban

DOAC Safety Considerations and Interaction Examples

Drug interactions:

- **Pharmacokinetic interactions** occur when one drug alters the absorption, distribution, metabolism or excretion of the other drug.
- **Pharmacodynamic interactions** occur between drugs with similar or opposite pharmacological effects.

Please refer to full prescribing information before prescribing.

DOAC Reversal

- DOACs have relatively short half-lives. Major bleeding that occurs in patients taking DOACs is often able to be managed by temporarily discontinuing the anticoagulant and providing supportive measures (compression, surgical repair, fluid and/or blood replacement).
- Rates of severe and fatal bleeding associated with DOACs in the pivotal registry trials was low in the absence of reversal agents.
- High quality data on the impact of reversal agents on clinical outcomes in DOAC associated bleeding are lacking. There is no randomized trial evidence demonstrating that the administration of reversal agents improves outcomes.

https://www.nejm.org/doi/full/10.1056/NEJMoa1502000
Praxbind (idarucizumab) [package insert]. Ridgefield, CT: Boehringer Ingelheim;2015
https://www.tctmd.com/news/andexanet-alfa-first-reversal-agent-factor-xa-inhibitors-finally-gains-fda-approval
Refs: AC Forum 2019 guidance, ACC 2017 guidance

DOAC Reversal

- Reversing anticoagulation places patients at their baseline elevated risk of thromboembolism. Consider restarting anticoagulation as soon as medically appropriate.
- **Use of reversal agent should only be considered if the bleed is life threatening, in a critical organ, or is not controlled with supportive measures. There should be reasonable certainty that therapeutic anticoagulant levels are present.**

https://www.nejm.org/doi/full/10.1056/NEJMoa1502000
Praxbind (idarucizumab) [package insert]. Ridgefield, CT: Boehringer Ingelheim;2015
https://www.tctmd.com/news/andexanet-alfa-first-reversal-agent-factor-xa-inhibitors-finally-gains-fda-approval
Refs: AC Forum 2019 guidance, ACC 2017 guidance

DOAC Reversal Agents

For Dabigatran:

- **Idarucizumab** is indicated in patients treated with dabigatran when reversal of the anticoagulant effects is needed, and for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding.
- **Route of administration and dose:** Intravenous (I.V.) Dose: 5 g (2 vials, each contains 2.5 g) as two consecutive infusions or bolus injection by injecting both vials consecutively one after another via syringe into I.V. line.
- In the REVERSE-AD study, investigators observed reversal effects within 30 minutes, and a median of 11.4 hours for time to bleeding cessation.

https://www.nejm.org/doi/full/10.1056/NEJMoa1502000

Praxbind (idarucizumab) [package insert]. Ridgefield, CT: Boehringer Ingelheim;2015

https://www.tctmd.com/news/andexanet-alfa-first-reversal-agent-factor-xa-inhibitors-finally-gains-fda-approval

DOAC Reversal Agents

For apixaban and rivaroxaban:

- **Andexanet Alfa** is indicated for patients treated with factor Xa inhibitors (apixaban, rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
- **Route of administration and dose:** Intravenous (I.V.) bolus, with a target rate of 30 mg/min, followed by continuous infusion for up to 120 minutes. The dose is based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor.
- Reversal activity was observed within 2-5 minutes following bolus administration and maintained throughout the duration of continuous infusion.

For betrixaban and edoxaban:

- No FDA approved reversal agents for these drugs.

https://www.nejm.org/doi/full/10.1056/NEJMoa1502000

Praxbind (idarucizumab) [package insert]. Ridgefield, CT: Boehringer Ingelheim;2015

https://www.tctmd.com/news/andexanet-alfa-first-reversal-agent-factor-xa-inhibitors-finally-gains-fda-approval

Advantages and Disadvantages of Warfarin

Advantages

- Long track record with predictable benefits and results.
- Once daily dosing.
- Ability to readily measure anticoagulant effect with INR test.

Disadvantages

- Narrow therapeutic window.
- Diet, disease states, and drugs may significantly alter INR.
- INR must be monitored regularly.
- Maintaining INRs within the target range optimizes the balance of efficacy and safety. In AFib patients, the target INR range is 2-3.
- Dosing schedule can be complicated.
- Contraindicated in pregnant women.

Advantages of DOACs

Advantages

- No regular laboratory monitoring for anticoagulant effect.
- Rapid onset/offset of action.
- Fewer drug interactions.
- Predictable pharmacokinetics.
- Efficacy and safety are at least as good as warfarin (for stroke prevention in atrial fibrillation, and treatment and secondary prevention of venous thromboembolism).
- Lower rates of stroke caused by bleeding in the brain.

Disadvantages of DOACs

Disadvantages

- No widely agreed on laboratory test to monitor anticoagulant effect.
- Some DOACS may cause upset stomach.
- DOACs in general have a shorter half-life than warfarin, making missed doses more consequential.
- No adequate and well-controlled studies in pregnant women.
  - Should only be used during pregnancy if the potential benefit outweighs the potential risk to the mother and fetus.

Knowledge Check

Which of the following is **not** a risk factor for both stroke and bleeding for patients with AFib?

a. Hypertension
b. History of Stroke
c. Age > 65 years
d. Female Gender
e. All of the above are risk factors for both risk of stroke and risk of bleeding for patients with AFib

Knowledge Check

Which of the following is **not** a risk factor for both stroke and bleeding for patients with AFib?

a. Hypertension
b. History of Stroke
c. Age > 65 years
d. Female Gender
e. All of the above are risk factors for both risk of stroke and risk of bleeding for patients with AFib

Challenges in the Use of Oral Anticoagulants

Barriers to Oral Anticoagulant Use

- Narrow therapeutic index
- Availability of continuous monitoring
- Perceived risk of bleeding
- Patient preferences
- Cost
- Availability of reversal agents

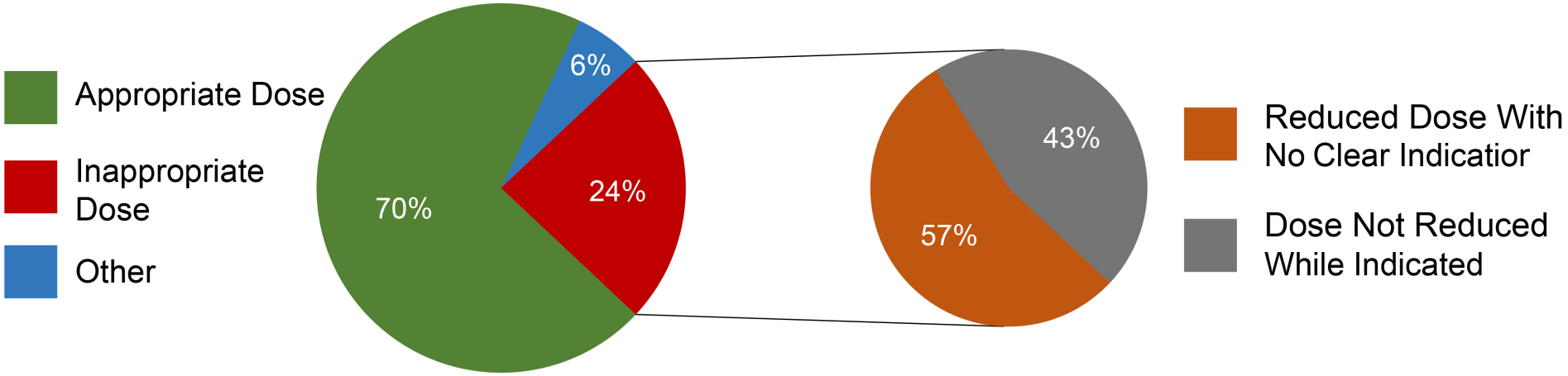
Improper Use of DOACs

- A retrospective analysis investigating the appropriateness of DOAC prescriptions was conducted in the province of Quebec, Canada.
- Adult patients hospitalized between October 2011 and October 2014, with a diagnosis of Afib and a DOAC prescription were included in the study (a total of 500 patients).
- Data retrieved from the electronic medical records and prescriptions were evaluated according to appropriateness criteria.

Lavoie K, Turgeon MH, Brais C, et al. Inappropriate dosing of direct oral anticoagulants in patients with atrial fibrillation. J Atr Fibrillation. 2016;9(4):1478. Published 2016 Dec 31. doi:10.4022/jafib.1478

Study Results: Improper Use of DOACs

- Only 70% of DOAC prescriptions were appropriate.
- 24% of patients received an inappropriate dose. Of this 24%,
  - 57% received a reduced dose with no clear indication.
  - 43% received a dose that was not reduced while indicated.



Lavoie K, Turgeon MH, Brais C, et al. Inappropriate dosing of direct oral anticoagulants in patients with atrial fibrillation. J Atr Fibrillation. 2016;9(4):1478. Published 2016 Dec 31. doi:10.4022/jafib.1478

Improper Use of DOACs

- Two retrospective U.S. AFib cohort registries showed that while most patients are receiving appropriate doses, a significant minority of patients receive off-label dosing (under or over dosing).
- Off-label dosing of DOACs in the AFib population is associated with worse outcomes:
  - Increased all-cause mortality and cardiovascular hospitalizations (Steinberg).
  - Increased major bleeding in overdosing and increased stroke in under dosing in patients with kidney disease (Yao).
  - Important to evaluate renal function and other factors for indications of reduced dosing.
  - Off-label use of lower than recommended doses may be harmful.

Steinberg BA, Shrader P, Thomas L, et al. Off-label dosing of non-vitamin K antagonist oral anticoagulants and adverse outcomes. The ORBIT-AF II Registry. J Am Coll Cardiol. 2016;68(24):2597-604.

Yao X, Shah ND, Sangaralingham LR, et al. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. J Am Coll Cardiol. 2017;69(23):2779-90.

Underutilization of Anticoagulation

- 40-48% of observed patient days there was no antithrombotic protection.
- Older females with a high number of comorbidities were especially at risk for underutilization of oral anticoagulation.

Wilke T, Groth A, Mueller S, et al. Oral anticoagulation use by patients with atrial fibrillation in Germany. Adherence to guidelines, causes of anticoagulation under-use and its clinical outcomes, based on claims-data of 183,448 patients. Thromb Haemost. 2012;107(6):1053-1065

Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Arch Intern Med. 1999;159(7):677-685. .

Steps for Clinicians to Optimize Oral Anticoagulant Use

Use Shared Decision-Making Tools

Shared decision-making (SDM) is a collaborative process between a patient and their provider.

- Core strategy to promote patient-centered healthcare
- Helps patients weigh pros and cons of treatment that may be valued differently by different patients
- Leads to more realistic expectations
- Shown to improve treatment adherence

Elwyn G, Laitner S, Coulter A, et al. Implementing shared decision making in the NHS. BMJ 2010;341:c5146.

Greenes R. Clinical Decision Support: The Road Ahead. Boston, MA: Academic Press, 2011.

Stacey D, Legare F, Col NF, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2014;1:CD001431.

AHRQ SHARE Approach

- **S** Seek your patient's participation.
- **H** Help your patient explore and compare treatment options.
- **A** Assess your patient's values and preferences.
- **R** Reach a decision with your patient.
- **E** Evaluate your patient's decision.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5600016/
https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.113.004498

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5600016/
https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.113.004498

AHRQ SHARE Approach

R Reach a decision with your patient.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5600016/
https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.113.004498

AHRQ SHARE Approach

E

Evaluate your patient's decision.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5600016/
https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.113.004498

Solicit Patient Preferences

- Provide patients and their caregivers with the pros and cons of warfarin compared to DOACs.
- Identify your patients' values before anticoagulant selection.
- Allow patients to actively participate in the shared decision-making process.

Palacio AM, Kirolos I, Tamariz L. Patient values and preferences when choosing anticoagulants. Patient Prefer Adherence. 2015;9:133–8.

Ferguson C, et al. The caregiver role in thromboprophylaxis management in atrial fibrillation: a literature review. European Journal of Cardiovascular Nursing. 2015;14(2):98-107.

Patient Preferences

Factors that were important to patients were:

- **Prevention of stroke**
- Lack of interactions with drugs and food
- Availability of a reversal agent
- Ease of administration

Lyp GYH, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report, *CHEST* (2018), doi: 10.1016/j.chest.201807.040

Patient Preferences

DOACS were generally preferred over vitamin K antagonists due to:

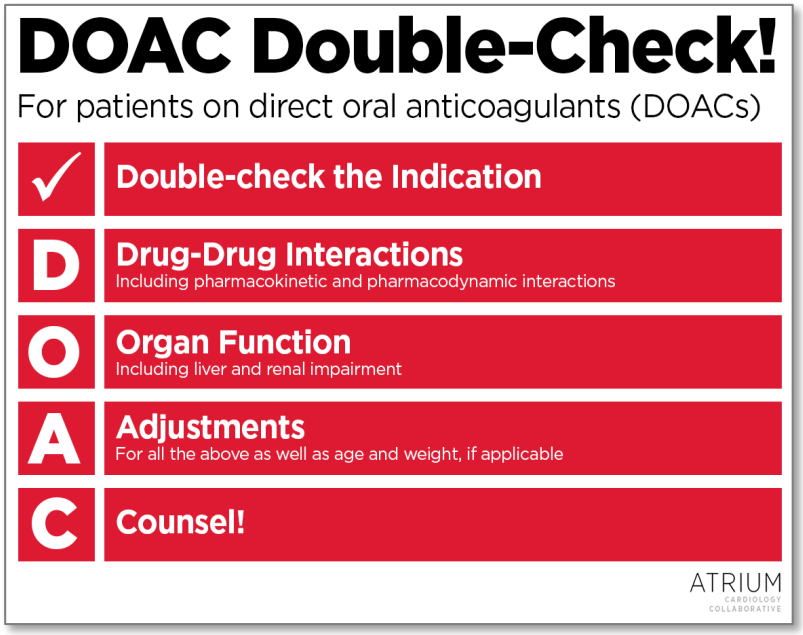
- Absence of INR monitoring
- Lower risk of bleeding

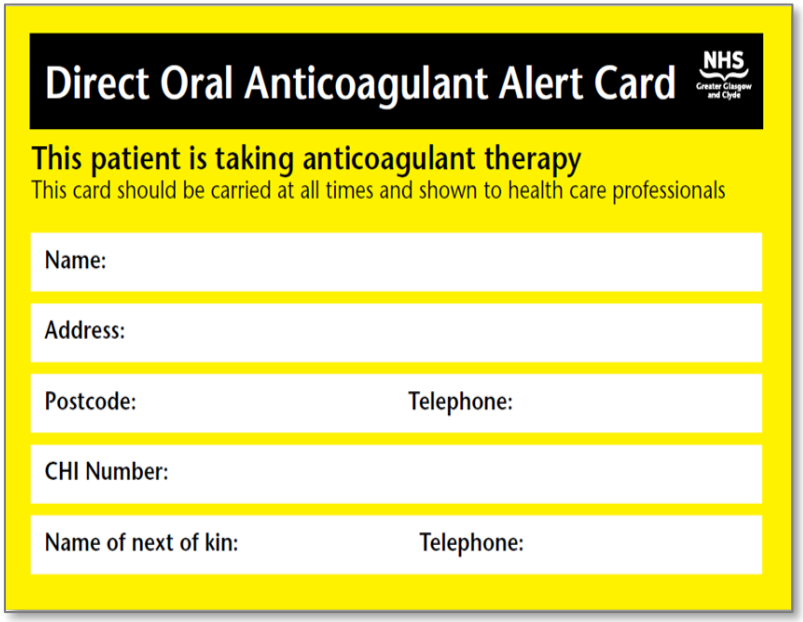
Cost may be a factor in driving patient and provider preferences of a vitamin K antagonist over a DOAC.

Lyp GYH, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report, *CHEST* (2018), doi: 10.1016/j.chest.201807.040

Tools for the Safe Use of Oral Anticoagulants

Patient Tools

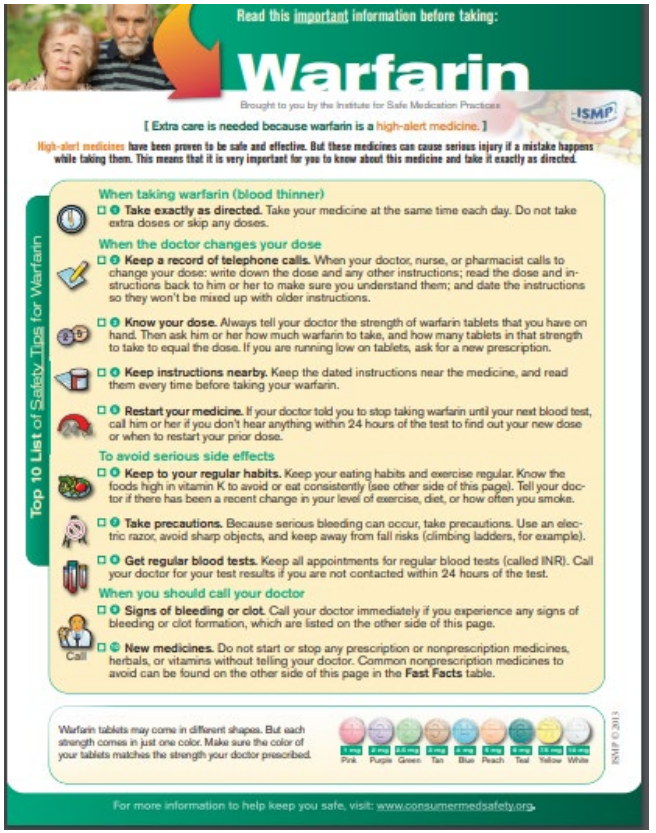




ISMP's Patient Handout on Warfarin

In 2013, the Institute for Safe Medication Practices (ISMP) developed a patient handout for warfarin, which includes a Top 10 List of Safety Tips for patients.

For a copy of this patient handout, please see the link on Resources section on the course launch page.


Read this important information before taking:

Warfarin

Brought to you by the Institute for Safe Medication Practices

[Extra care is needed because warfarin is a high-alert medicine.]

High-alert medicines have been proven to be safe and effective. But these medicines can cause serious injury if a mistake happens while taking them. This means that it is very important for you to know about this medicine and take it exactly as directed.

Top 10 List of Safety Tips for Warfarin

When taking warfarin (blood thinner)

- **Take exactly as directed.** Take your medicine at the same time each day. Do not take extra doses or skip any doses.

When the doctor changes your dose

- **Keep a record of telephone calls.** When your doctor, nurse, or pharmacist calls to change your dose: write down the dose and any other instructions; read the dose and instructions back to him or her to make sure you understand them; and date the instructions so they won't be mixed up with older instructions.
- **Know your dose.** Always tell your doctor the strength of warfarin tablets that you have on hand. Then ask him or her how much warfarin to take, and how many tablets in that strength to take to equal the dose. If you are running low on tablets, ask for a new prescription.
- **Keep instructions nearby.** Keep the dated instructions near the medicine, and read them every time before taking your warfarin.
- **Restart your medicine.** If your doctor told you to stop taking warfarin until your next blood test, call him or her if you don't hear anything within 24 hours of the test to find out your new dose or when to restart your prior dose.

To avoid serious side effects

- **Keep to your regular habits.** Keep your eating habits and exercise regular. Know the foods high in vitamin K to avoid or eat consistently (see other side of this page). Tell your doctor if there has been a recent change in your level of exercise, diet, or how often you smoke.
- **Take precautions.** Because serious bleeding can occur, take precautions. Use an electric razor, avoid sharp objects, and keep away from fall risks (climbing ladders, for example).
- **Get regular blood tests.** Keep all appointments for regular blood tests (called INR). Call your doctor for your test results if you are not contacted within 24 hours of the test.

When you should call your doctor

- **Signs of bleeding or clot.** Call your doctor immediately if you experience any signs of bleeding or clot formation, which are listed on the other side of this page.
- **New medicines.** Do not start or stop any prescription or nonprescription medicines, herbals, or vitamins without telling your doctor. Common nonprescription medicines to avoid can be found on the other side of this page in the **Fast Facts** table.

Warfarin tablets may come in different shapes. But each strength comes in just one color. Make sure the color of your tablets matches the strength your doctor prescribed.

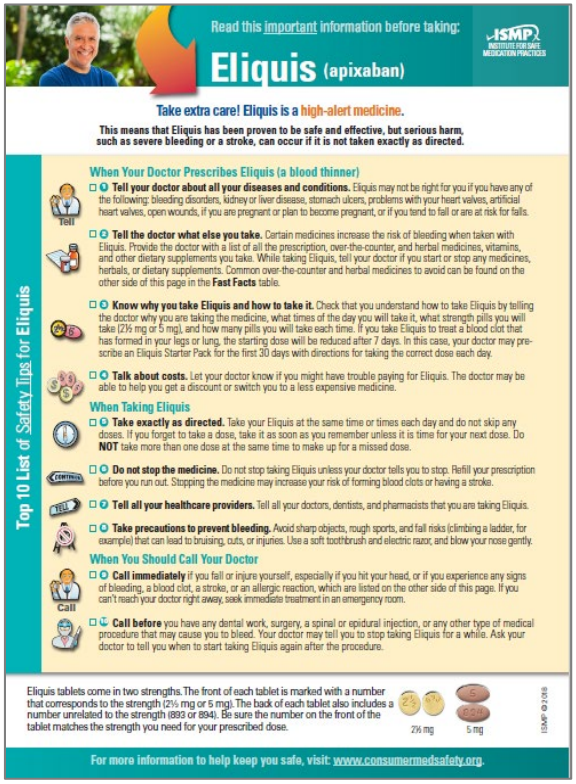
1 mg Pink | 2 mg Purple | 2.5 mg Green | 3 mg Tan | 4 mg Blue | 5 mg Peach | 6 mg Teal | 7.5 mg Yellow | 10 mg White

ISMP © 2013

For more information to help keep you safe, visit: www.consumermedsafety.org

http://consumermedsafety.org/assets/Warfarin1-13.pdf

Patient Handouts on DOACs



Read this important information before taking:

Eliquis (apixaban)

ISMP Institute for Safe Medication Practices

Take extra care! Eliquis is a high-alert medicine.

This means that Eliquis has been proven to be safe and effective, but serious harm, such as severe bleeding or a stroke, can occur if it is not taken exactly as directed.

Top 10 List of Safety Tips for Eliquis

When Your Doctor Prescribes Eliquis (a blood thinner)

- **Tell your doctor about all your diseases and conditions.** Eliquis may not be right for you if you have any of the following: bleeding disorders, kidney or liver disease, stomach ulcers, problems with your heart valves, artificial heart valves, open wounds, if you are pregnant or plan to become pregnant, or if you tend to fall or are at risk for falls.
- **Tell the doctor what else you take.** Certain medicines increase the risk of bleeding when taken with Eliquis. Provide the doctor with a list of all the prescription, over-the-counter, and herbal medicines, vitamins, and other dietary supplements you take. While taking Eliquis, tell your doctor if you start or stop any medicines, herbals, or dietary supplements. Common over-the-counter and herbal medicines to avoid can be found on the other side of this page in the **Fast Facts** table.
- **Know why you take Eliquis and how to take it.** Check that you understand how to take Eliquis by telling the doctor why you are taking the medicine, what times of the day you will take it, what strength pills you will take (2½ mg or 5 mg), and how many pills you will take each time. If you take Eliquis to treat a blood clot that has formed in your legs or lung, the starting dose will be reduced after 7 days. In this case, your doctor may prescribe an Eliquis Starter Pack for the first 30 days with directions for taking the correct dose each day.
- **Talk about costs.** Let your doctor know if you might have trouble paying for Eliquis. The doctor may be able to help you get a discount or switch you to a less expensive medicine.

When Taking Eliquis

- **Take exactly as directed.** Take your Eliquis at the same time or times each day and do not skip any doses. If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. Do **NOT** take more than one dose at the same time to make up for a missed dose.
- **Do not stop the medicine.** Do not stop taking Eliquis unless your doctor tells you to stop. Refill your prescription before you run out. Stopping the medicine may increase your risk of forming blood clots or having a stroke.
- **Tell all your healthcare providers.** Tell all your doctors, dentists, and pharmacists that you are taking Eliquis.
- **Take precautions to prevent bleeding.** Avoid sharp objects, rough sports, and fall risks (climbing a ladder, for example) that can lead to bruising, cuts, or injuries. Use a soft toothbrush and electric razor, and blow your nose gently.

When You Should Call Your Doctor

- **Call immediately** if you fall or injure yourself, especially if you hit your head, or if you experience any signs of bleeding, a blood clot, a stroke, or an allergic reaction, which are listed on the other side of this page. If you can't reach your doctor right away, seek immediate treatment in an emergency room.
- **Call before** you have any dental work, surgery, a spinal or epidural injection, or any other type of medical procedure that may cause you to bleed. Your doctor may tell you to stop taking Eliquis for a while. Ask your doctor to tell you when to start taking Eliquis again after the procedure.

Eliquis tablets come in two strengths. The front of each tablet is marked with a number that corresponds to the strength (2½ mg or 5 mg). The back of each tablet also includes a number unrelated to the strength (893 or 894). Be sure the number on the front of the tablet matches the strength you need for your prescribed dose.

2½ mg 5 mg

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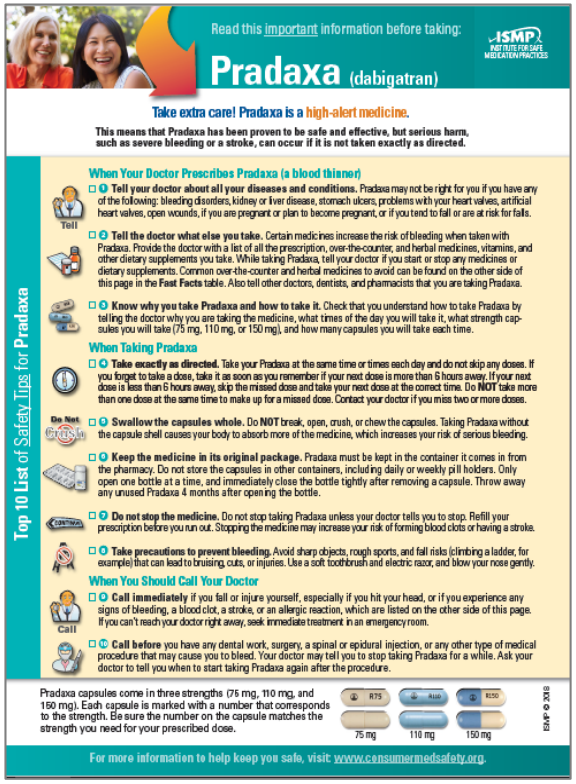
For more information to help keep you safe, visit: www.consumermedsafety.org.



Read this important information before taking:

Pradaxa (dabigatran)

ISMP Institute for Safe Medication Practices

Take extra care! Pradaxa is a high-alert medicine.

This means that Pradaxa has been proven to be safe and effective, but serious harm, such as severe bleeding or a stroke, can occur if it is not taken exactly as directed.

Top 10 List of Safety Tips for Pradaxa

When Your Doctor Prescribes Pradaxa (a blood thinner)

- **Tell your doctor about all your diseases and conditions.** Pradaxa may not be right for you if you have any of the following: bleeding disorders, kidney or liver disease, stomach ulcers, problems with your heart valves, artificial heart valves, open wounds, if you are pregnant or plan to become pregnant, or if you tend to fall or are at risk for falls.
- **Tell the doctor what else you take.** Certain medicines increase the risk of bleeding when taken with Pradaxa. Provide the doctor with a list of all the prescription, over-the-counter, and herbal medicines, vitamins, and other dietary supplements you take. While taking Pradaxa, tell your doctor if you start or stop any medicines or dietary supplements. Common over-the-counter and herbal medicines to avoid can be found on the other side of this page in the **Fast Facts** table. Also tell other doctors, dentists, and pharmacists that you are taking Pradaxa.
- **Know why you take Pradaxa and how to take it.** Check that you understand how to take Pradaxa by telling the doctor why you are taking the medicine, what times of the day you will take it, what strength capsules you will take (75 mg, 110 mg, or 150 mg), and how many capsules you will take each time.

When Taking Pradaxa

- **Take exactly as directed.** Take your Pradaxa at the same time or times each day and do not skip any doses. If you forget to take a dose, take it as soon as you remember if your next dose is more than 6 hours away. If your next dose is less than 6 hours away, skip the missed dose and take your next dose at the correct time. Do **NOT** take more than one dose at the same time to make up for a missed dose. Contact your doctor if you miss two or more doses.
- **Swallow the capsules whole.** Do **NOT** break, open, crush, or chew the capsules. Taking Pradaxa without the capsule shell causes your body to absorb more of the medicine, which increases your risk of serious bleeding.
- **Keep the medicine in its original package.** Pradaxa must be kept in the container it comes in from the pharmacy. Do not store the capsules in other containers, including daily or weekly pill holders. Only open one bottle at a time, and immediately close the bottle tightly after removing a capsule. Throw away any unused Pradaxa 4 months after opening the bottle.
- **Do not stop the medicine.** Do not stop taking Pradaxa unless your doctor tells you to stop. Refill your prescription before you run out. Stopping the medicine may increase your risk of forming blood clots or having a stroke.
- **Take precautions to prevent bleeding.** Avoid sharp objects, rough sports, and fall risks (climbing a ladder, for example) that can lead to bruising, cuts, or injuries. Use a soft toothbrush and electric razor, and blow your nose gently.

When You Should Call Your Doctor

- **Call immediately** if you fall or injure yourself, especially if you hit your head, or if you experience any signs of bleeding, a blood clot, a stroke, or an allergic reaction, which are listed on the other side of this page. If you can't reach your doctor right away, seek immediate treatment in an emergency room.
- **Call before** you have any dental work, surgery, a spinal or epidural injection, or any other type of medical procedure that may cause you to bleed. Your doctor may tell you to stop taking Pradaxa for a while. Ask your doctor to tell you when to start taking Pradaxa again after the procedure.

Pradaxa capsules come in three strengths (75 mg, 110 mg, and 150 mg). Each capsule is marked with a number that corresponds to the strength. Be sure the number on the capsule matches the strength you need for your prescribed dose.

R75 R110 R150

75 mg 110 mg 150 mg

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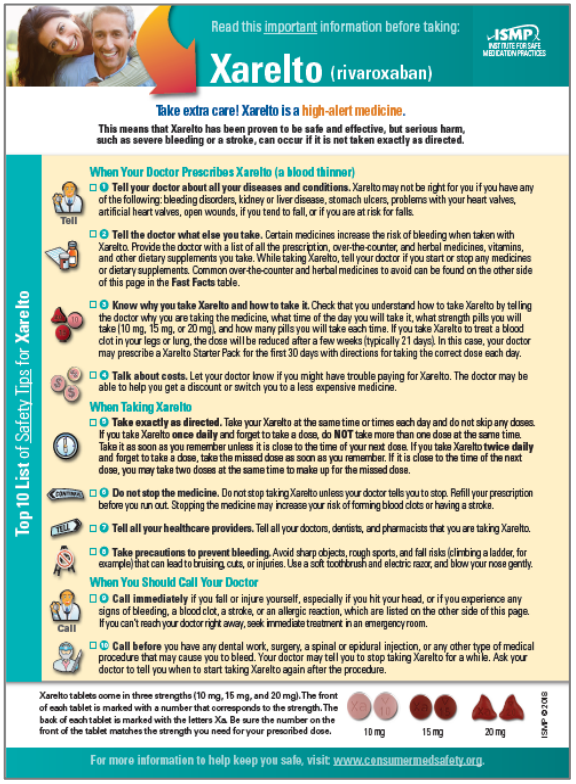
For more information to help keep you safe, visit: www.consumermedsafety.org.



Read this important information before taking:

Xarelto (rivaroxaban)

ISMP Institute for Safe Medication Practices

Take extra care! Xarelto is a high-alert medicine.

This means that Xarelto has been proven to be safe and effective, but serious harm, such as severe bleeding or a stroke, can occur if it is not taken exactly as directed.

Top 10 List of Safety Tips for Xarelto

When Your Doctor Prescribes Xarelto (a blood thinner)

- **Tell your doctor about all your diseases and conditions.** Xarelto may not be right for you if you have any of the following: bleeding disorders, kidney or liver disease, stomach ulcers, problems with your heart valves, artificial heart valves, open wounds, if you tend to fall, or if you are at risk for falls.
- **Tell the doctor what else you take.** Certain medicines increase the risk of bleeding when taken with Xarelto. Provide the doctor with a list of all the prescription, over-the-counter, and herbal medicines, vitamins, and other dietary supplements you take. While taking Xarelto, tell your doctor if you start or stop any medicines or dietary supplements. Common over-the-counter and herbal medicines to avoid can be found on the other side of this page in the **Fast Facts** table.
- **Know why you take Xarelto and how to take it.** Check that you understand how to take Xarelto by telling the doctor why you are taking the medicine, what time of the day you will take it, what strength pills you will take (10 mg, 15 mg, or 20 mg), and how many pills you will take each time. If you take Xarelto to treat a blood clot in your legs or lung, the dose will be reduced after a few weeks (typically 21 days). In this case, your doctor may prescribe a Xarelto Starter Pack for the first 30 days with directions for taking the correct dose each day.
- **Talk about costs.** Let your doctor know if you might have trouble paying for Xarelto. The doctor may be able to help you get a discount or switch you to a less expensive medicine.

When Taking Xarelto

- **Take exactly as directed.** Take your Xarelto at the same time or times each day and do not skip any doses. If you take Xarelto **once daily** and forget to take a dose, do **NOT** take more than one dose at the same time. Take it as soon as you remember unless it is close to the time of your next dose. If you take Xarelto **twice daily** and forget to take a dose, take the missed dose as soon as you remember. If it is close to the time of the next dose, you may take two doses at the same time to make up for the missed dose.
- **Do not stop the medicine.** Do not stop taking Xarelto unless your doctor tells you to stop. Refill your prescription before you run out. Stopping the medicine may increase your risk of forming blood clots or having a stroke.
- **Tell all your healthcare providers.** Tell all your doctors, dentists, and pharmacists that you are taking Xarelto.
- **Take precautions to prevent bleeding.** Avoid sharp objects, rough sports, and fall risks (climbing a ladder, for example) that can lead to bruising, cuts, or injuries. Use a soft toothbrush and electric razor, and blow your nose gently.

When You Should Call Your Doctor

- **Call immediately** if you fall or injure yourself, especially if you hit your head, or if you experience any signs of bleeding, a blood clot, a stroke, or an allergic reaction, which are listed on the other side of this page. If you can't reach your doctor right away, seek immediate treatment in an emergency room.
- **Call before** you have any dental work, surgery, a spinal or epidural injection, or any other type of medical procedure that may cause you to bleed. Your doctor may tell you to stop taking Xarelto for a while. Ask your doctor to tell you when to start taking Xarelto again after the procedure.

Xarelto tablets come in three strengths (10 mg, 15 mg, and 20 mg). The front of each tablet is marked with a number that corresponds to the strength. The back of each tablet is marked with the letters Xa. Be sure the number on the front of the tablet matches the strength you need for your prescribed dose.

10 mg 15 mg 20 mg

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For more information to help keep you safe, visit: www.consumermedsafety.org.

https://www.ismp.org/sites/default/files/attachments/2018-11/Eliquisfinal.pdf

https://consumermedsafety.org/images/Pradaxafinal.pdf

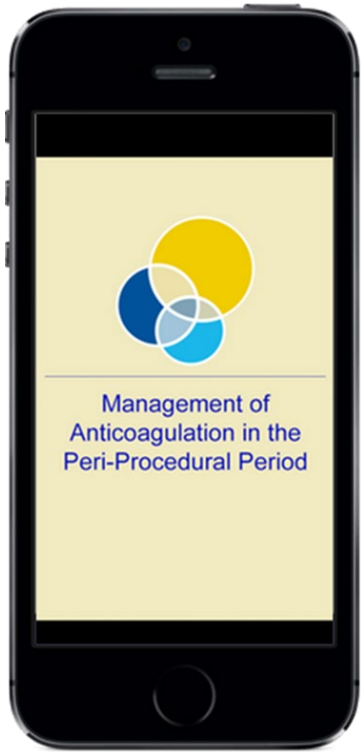
https://www.ismp.org/sites/default/files/attachments/2018-11/Xareltofinal.pdf

Clinician Tools

MAQI^2 Anticoagulation Toolkit App

For more information on MAQI^2, or to view the complete toolkit, please visit:
http://www.maqi2.org/
http://anticoagulationtoolkit.org/sites/default/files/toolkit_pdfs/toolkitfull.pdf
http://anticoagulationtoolkit.org/sites/default/files/toolkit_pdfs/patient/Warfarin/patienttoolkiteditsfeb282016.pdf

MAPPP App for Peri-Procedural Management



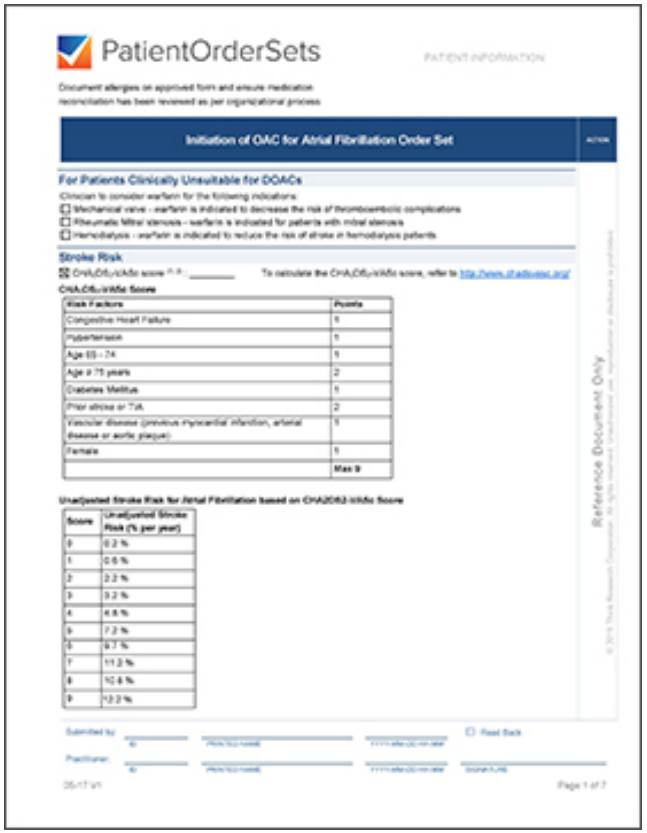
The MAPPP App is a guide intended to:

- Assist clinicians in evaluating procedure-related bleeding risk and underlying risk of thrombosis,
- Guide decision-making regarding the interruption of anticoagulation and the use of anticoagulant "bridging,"
- Provide drug dosing and laboratory monitoring guidance in the peri-procedural period, and
- Encourage clear communication between clinicians involved in prescribing anticoagulants and performing invasive procedures.

For more information on the MAPPP APP, please visit: http://mappp.ipro.org/

Spyropoulos, A. C., Giannis, D., Cohen, J., John, S., Myrka, A., Inlall, D., … Wang, J. J. (2020). Implementation of the Management of Anticoagulation in the Periprocedural Period App Into an Electronic Health Record: A Prospective Cohort Study. Clinical and Applied Thrombosis/Hemostasis. https://doi.org/10.1177/1076029620925910

Patient Order Sets


PatientOrderSets

Initiation of OAC for Atrial Fibrillation Order Set

For Patients Clinically Unsuitable for DOACs

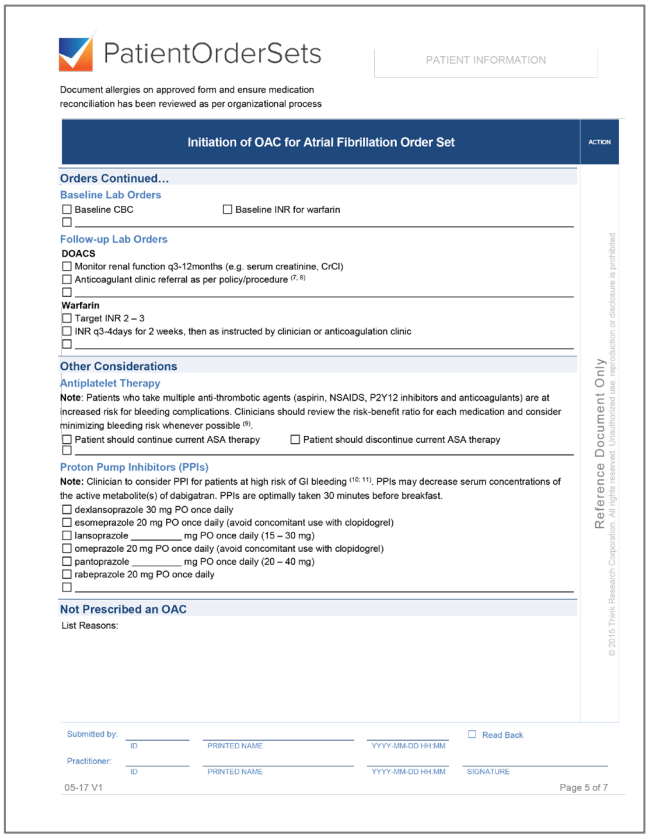
Stroke Risk

Reference Document Only

Patient order sets consider individual patient characteristics and help identify the best drug therapy and dose and which lab tests should be run before and during the treatment.

https://acforum.org/web/education-sets.php

Patient Order Sets



PatientOrderSets

PATIENT INFORMATION

Document allergies on approved form and ensure medication reconciliation has been reviewed as per organizational process

Initiation of OAC for Atrial Fibrillation Order Set | ACTION

Orders Continued…

Baseline Lab Orders

☐ Baseline CBC ☐ Baseline INR for warfarin

☐ _____

Follow-up Lab Orders

DOACS

☐ Monitor renal function q3-12months (e.g. serum creatinine, CrCl)

☐ Anticoagulant clinic referral as per policy/procedure [7, 8]

☐ _____

Warfarin

☐ Target INR 2 – 3

☐ INR q3-4days for 2 weeks, then as instructed by clinician or anticoagulation clinic

☐ _____

Other Considerations

Antiplatelet Therapy

Note: Patients who take multiple anti-thrombotic agents (aspirin, NSAIDS, P2Y12 inhibitors and anticoagulants) are at increased risk for bleeding complications. Clinicians should review the risk-benefit ratio for each medication and consider minimizing bleeding risk whenever possible [9].

☐ Patient should continue current ASA therapy ☐ Patient should discontinue current ASA therapy

☐ _____

Proton Pump Inhibitors (PPIs)

Note: Clinician to consider PPI for patients at high risk of GI bleeding [10, 11]. PPIs may decrease serum concentrations of the active metabolite(s) of dabigatran. PPIs are optimally taken 30 minutes before breakfast.

☐ dexlansoprazole 30 mg PO once daily

☐ esomeprazole 20 mg PO once daily (avoid concomitant use with clopidogrel)

☐ lansoprazole _____ mg PO once daily (15 – 30 mg)

☐ omeprazole 20 mg PO once daily (avoid concomitant use with clopidogrel)

☐ pantoprazole _____ mg PO once daily (20 – 40 mg)

☐ rabeprazole 20 mg PO once daily

☐ _____

Not Prescribed an OAC

List Reasons:

Submitted by: _____ (ID) _____ (PRINTED NAME) _____ (YYYY-MM-DD HH:MM) ☐ Read Back

Practitioner: _____ (ID) _____ (PRINTED NAME) _____ (YYYY-MM-DD HH:MM) _____ (SIGNATURE)

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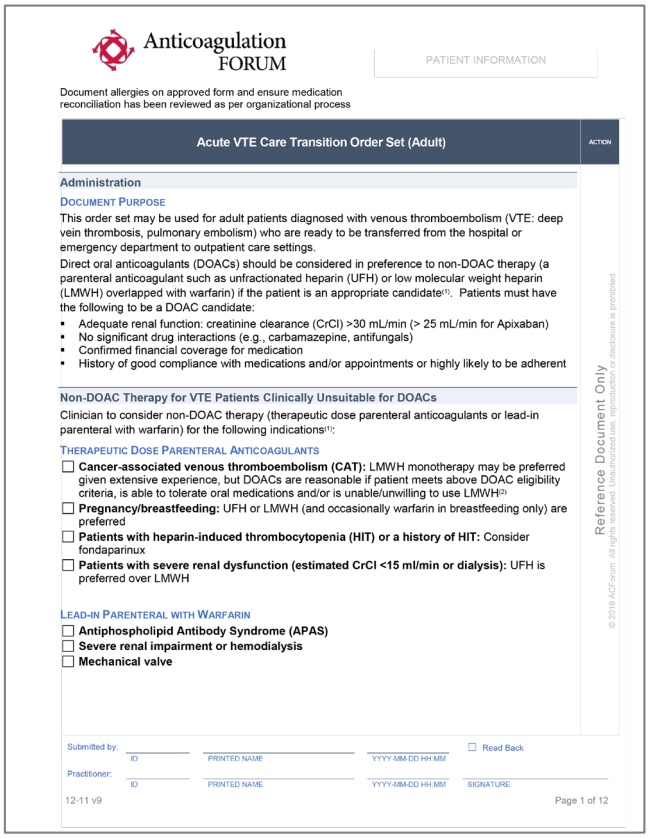
Reference Document Only

A link to this Patient Order Set is available in the Resources section of the course landing page.

https://acforum.org/web/education-sets.php

Patient Order Sets



Anticoagulation FORUM

PATIENT INFORMATION

Document allergies on approved form and ensure medication reconciliation has been reviewed as per organizational process

Acute VTE Care Transition Order Set (Adult) | ACTION

Administration

DOCUMENT PURPOSE

This order set may be used for adult patients diagnosed with venous thromboembolism (VTE: deep vein thrombosis, pulmonary embolism) who are ready to be transferred from the hospital or emergency department to outpatient care settings.

Direct oral anticoagulants (DOACs) should be considered in preference to non-DOAC therapy (a parenteral anticoagulant such as unfractionated heparin (UFH) or low molecular weight heparin (LMWH) overlapped with warfarin) if the patient is an appropriate candidate[1]. Patients must have the following to be a DOAC candidate:

- Adequate renal function: creatinine clearance (CrCl) >30 mL/min (> 25 mL/min for Apixaban)
- No significant drug interactions (e.g., carbamazepine, antifungals)
- Confirmed financial coverage for medication
- History of good compliance with medications and/or appointments or highly likely to be adherent

Non-DOAC Therapy for VTE Patients Clinically Unsuitable for DOACs

Clinician to consider non-DOAC therapy (therapeutic dose parenteral anticoagulants or lead-in parenteral with warfarin) for the following indications[1]:

THERAPEUTIC DOSE PARENTERAL ANTICOAGULANTS

- ☐ **Cancer-associated venous thromboembolism (CAT):** LMWH monotherapy may be preferred given extensive experience, but DOACs are reasonable if patient meets above DOAC eligibility criteria, is able to tolerate oral medications and/or is unable/unwilling to use LMWH[2]
- ☐ **Pregnancy/breastfeeding:** UFH or LMWH (and occasionally warfarin in breastfeeding only) are preferred
- ☐ **Patients with heparin-induced thrombocytopenia (HIT) or a history of HIT:** Consider fondaparinux
- ☐ **Patients with severe renal dysfunction (estimated CrCl <15 ml/min or dialysis):** UFH is preferred over LMWH

LEAD-IN PARENTERAL WITH WARFARIN

- ☐ **Antiphospholipid Antibody Syndrome (APAS)**
- ☐ **Severe renal impairment or hemodialysis**
- ☐ **Mechanical valve**

Reference Document Only

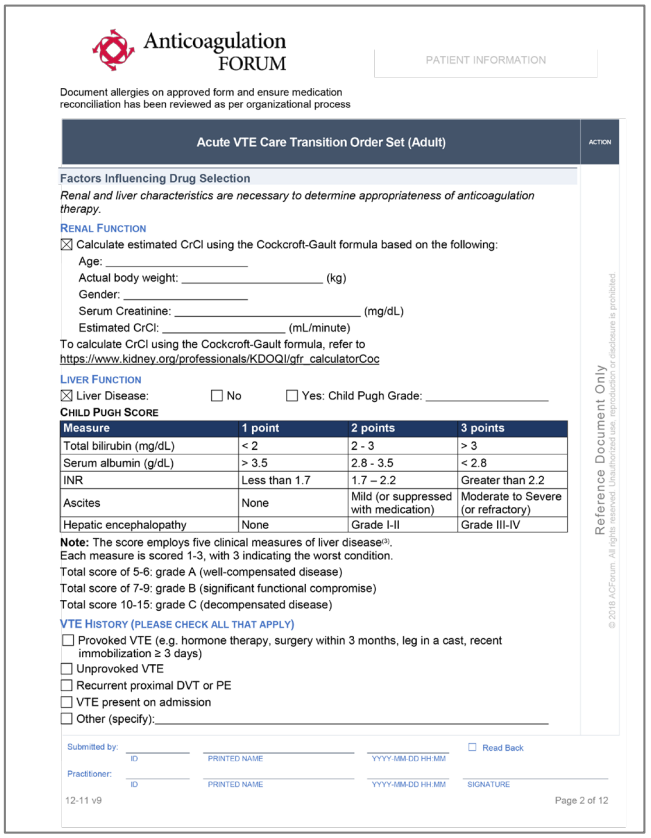
Submitted by: ID | PRINTED NAME | YYYY-MM-DD HH:MM | ☐ Read Back

Practitioner: ID | PRINTED NAME | YYYY-MM-DD HH:MM | SIGNATURE

The Anticoagulation Forum also provides Patient Order Sets for adult patients needing acute VTE care transition.

https://acforum.org/web/education-sets.php

Patient Order Sets



Anticoagulation FORUM

PATIENT INFORMATION

Document allergies on approved form and ensure medication reconciliation has been reviewed as per organizational process

Acute VTE Care Transition Order Set (Adult) — ACTION

Factors Influencing Drug Selection

Renal and liver characteristics are necessary to determine appropriateness of anticoagulation therapy.

RENAL FUNCTION

☒ Calculate estimated CrCl using the Cockcroft-Gault formula based on the following:

Age: _____

Actual body weight: _____ (kg)

Gender: _____

Serum Creatinine: _____ (mg/dL)

Estimated CrCl: _____ (mL/minute)

To calculate CrCl using the Cockcroft-Gault formula, refer to https://www.kidney.org/professionals/KDOQI/gfr_calculatorCoc

LIVER FUNCTION

☒ Liver Disease: ☐ No ☐ Yes: Child Pugh Grade: _____

CHILD PUGH SCORE

Measure	1 point	2 points	3 points
Total bilirubin (mg/dL)	< 2	2 - 3	> 3
Serum albumin (g/dL)	> 3.5	2.8 - 3.5	< 2.8
INR	Less than 1.7	1.7 – 2.2	Greater than 2.2
Ascites	None	Mild (or suppressed with medication)	Moderate to Severe (or refractory)
Hepatic encephalopathy	None	Grade I-II	Grade III-IV

Note: The score employs five clinical measures of liver disease[3]. Each measure is scored 1-3, with 3 indicating the worst condition.

Total score of 5-6: grade A (well-compensated disease)

Total score of 7-9: grade B (significant functional compromise)

Total score 10-15: grade C (decompensated disease)

VTE HISTORY (PLEASE CHECK ALL THAT APPLY)

☐ Provoked VTE (e.g. hormone therapy, surgery within 3 months, leg in a cast, recent immobilization ≥ 3 days)

☐ Unprovoked VTE

☐ Recurrent proximal DVT or PE

☐ VTE present on admission

☐ Other (specify):_____

Submitted by: ID PRINTED NAME YYYY-MM-DD HH:MM ☐ Read Back

Practitioner: ID PRINTED NAME YYYY-MM-DD HH:MM SIGNATURE

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Reference Document Only

A link to this Patient Order Set is available in the Resources section of the course landing page.

https://acforum.org/web/education-sets.php

Clinical Guidelines

Anticoagulation Forum (AC Forum), Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment, Burnett, A.E., Mahan, C.E., Vazquez, S.R. et al. J Thromb Thrombolysis (2016) 41: 206. https://doi.org/10.1007/s11239-015-1310-7

Anticoagulation Forum (AC Forum), Guidance for the evaluation and treatment of hereditary and acquired thrombophilia, Stevens, S.M., Woller, S.C., Bauer, K.A. et al. J Thromb Thrombolysis (2016) 41: 154. https://doi.org/10.1007/s11239-015-1316-1

Core Elements of Anticoagulation Stewardship Programs, https://acforum-excellence.org/Resource-Center/resource_files/-2019-09-18-110254.pdf

American Society of Hematology (ASH) https://www.hematology.org/Clinicians/Guidelines-Quality/Guidelines.aspx

American College of Chest Physicians (ACCP or CHEST) https:// www.chestnet.org/Guidelines-and-Resources

International Society on Thrombosis and Haemostasis (ISTH) https:// www.isth.org/page/Published_Guidance

European Heart Rhythm Association (EHRA) Practical Guide on the Use of Non-vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

https://www.escardio.org/Guidelines/Recommended-Reading/Heart-Rhythm/Novel-Oral-Anticoagulants-for-Atrial-Fibrillation

January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society https://www.ahajournals.org/doi/10.1161/CIR.0000000000000665

Knowledge Check

Case Study: MJ is a 66-year-old woman with AFib, a history of hypertension, and diabetes mellitus. She is currently taking lisinopril once daily and metformin ER once daily. MJ's mother died after suffering a stroke 10 years ago. She is interested in starting oral anticoagulation, but is concerned over the increased risk of bleeding. She doesn't want to have to come to the doctor's office every week or take medicine more than once a day.

Which oral anticoagulant would you recommend for MJ?

a. Aspirin
b. Warfarin
c. Rivaroxaban
d. None of the above

Knowledge Check

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Which oral anticoagulant would you recommend for MJ?

a. Aspirin
b. Warfarin
c. Rivaroxaban
d. None of the above

Summary

- Anticoagulants are beneficial in treatment of existing thrombosis and the prevention of primary and secondary thrombosis.
- High prevalence of oral anticoagulants being prescribed.
- Significant amount of adverse drug event related visits to the ED.
- Pharmacokinetic and pharmacodynamic differences between DOACs and oral vitamin K antagonists, along with patient-specific factors, should be considered when choosing the appropriate oral anticoagulant agent.
- Clinicians should use strategies such as shared decision-making, patient preferences, and other evidence-based tools to help guide their oral anticoagulant choices.

Conclusion

You should now be able to:

- Discuss the prevalence and types of adverse drug events related to oral anticoagulants.
- Review the drug classifications of oral anticoagulants.
- Compare characteristics of oral vitamin K antagonists and direct acting oral anticoagulants.
- Identify pathophysiological states for utilization of oral anticoagulation therapy.
- Review barriers to proper oral anticoagulant use.
- List steps clinicians can take to reduce the risk of adverse drug events from oral anticoagulants.

Annex

Generic Name	Brand Name
Apixaban	Eliquis
Betrixaban	Bevyxxa
Dabigatran	Pradaxa
Edoxaban	Savaysa
Rivaroxaban	Xarelto
Warfarin	Coumadin, Jantoven

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