U.S. FOOD & DRUG ADMINISTRATION

Practitioners' Guide for Improving Oral Anticoagulant Use – Key Tables and Charts

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

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.

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

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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

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.

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.

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

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

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

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

Annex

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