LIP Annual Review/Education Update

TOPIC: Anticoagulation

Un-fractionated heparin, warfarin and low–molecular-weight heparin are among the anticoagulants cited most frequently in medication error reports and are also most commonly used. The DOAC anticoagulant drugs are being more commonly prescribed now particularly in the outpatient setting - long term data has yet to be accumulated as compared to warfarin and heparins. When considering patients for therapy with anticoagulants, it is important to identify contraindications and drug interactions. While being treated with anticoagulant therapy, patients should be closely monitored for side effects and to prevent overdosing, while ensuring effectiveness of treatment. Factors that contribute to anticoagulant-related errors:

- Confusion due to a lack of standardization for the naming, labeling and packaging of anticoagulants.
- Challenge for health care providers to stay up to date on dosing regimens, new assay methods, additional drug interactions and potential reversal strategies.
- Failure to document or communicate individualized instructions or monitoring information during transfers or hand-offs.

The reason these medications are potentially difficult when it comes to errors is that the difference between an appropriate and lifesaving dose and an excessive or insufficient dose can be narrow. A little bit too much can cause severe bleeding and too little can fail to prevent the clotting problem

The most common use of anticoagulants is either in the prevention of clot formation or to stop the propagation of clot, and prevent clot recurrence, and clot related complications such as PE and pulmonary hypertension, and venous insufficiency/postphlebitic syndrome, as well as clot related complications of atrial fibrilation, MI, and cardiac valve replacement.

Below is an outline to guide clinical staff on anticoagulation selection, treatment, dosing, indications, and management.
Anticoagulants reviewed:

Un-Fractionated Heparin

LMWH - Low molecular weight heparin (fractionated)

Warfarin

Factor Xa inhibitors

- Apixaban (Eliquis)
- Rivaroxaban (Xarelto)

Direct thrombin inhibitors

• Dabigatran

Low molecular weight heparin (fractionated)

• Dalteparin
• Enoxaparin

Injectable factor Xa

• Fondaparinux

Vitamin K Antagonist

• Warfarin

UNFRACTIONATED HEPARIN (UFH)

Treatment with unfractionated heparin is based on body weight, and the dosage is titrated based on the APTT. An APTT of 1.5 to 2.3 times control is desirable. Weight-based heparin dosing and adjustments based on the APTT are provided below. This approach to heparin therapy has been shown to achieve adequate anticoagulation quickly and safely.

Adverse reactions associated with heparin therapy include bleeding and thrombocytopenia. The risk of adverse reactions is highest in patients with any of the following: age greater than 65 years, recent surgery, or conditions such as peptic ulcer disease, liver disease, occult neoplasia, and bleeding diathesis. Transient thrombocytopenia may occur in 10 to 20 percent of patients, but major hemorrhagic complications occur in fewer than 2 percent of patients.

Heparin can be stopped after four or five days of combined therapy with warfarin if the International Normalized Ratio (INR) of prothrombin clotting time exceeds 2.0.

For patients starting IV UFH, we suggest that the initial bolus and the initial rate of the continuous infusion be weight adjusted (bolus 80 units/kg followed by 18 units/kg per h for VTE; bolus 70 units/kg followed by 15 units/kg per h for cardiac or stroke patients) or use of a fixed dose (bolus 5,000 units followed by 1,000 units/h) rather than alternative regimens (Grade 2C).

For outpatients with VTE treated with SubQ UFH, we suggest weight-adjusted dosing (first dose 333 units/kg, then 250 units/kg) without monitoring rather than fixed or weight-adjusted dosing with monitoring

LOW-MOLECULAR-WEIGHT HEPARIN

Compared with unfractionated heparin, low-molecular-weight (LMW) heparin offers distinct advantages: it has a longer biologic half-life, it can be administered subcutaneously once or twice daily, dosing is fixed, and laboratory monitoring is not required. In addition, some adverse effects of unfractionated heparin, such as thrombocytopenia, appear to be less likely. In patients with DVT, subcutaneous administration of heparin is at least as effective as continuous infusion of unfractionated heparin in preventing complications and reducing the risk of recurrence.

Outpatient management of DVT using LMW heparin for short-term anticoagulation until warfarin is at a therapeutic level is safe and cost-effective, despite the higher cost of the heparin. Candidates for outpatient therapy must be hemodynamically stable, without renal failure, and not at high risk for bleeding. Furthermore, they must have a stable and supportive home environment, as well as access to daily monitoring until the INR is therapeutic. Like unfractionated heparin, LMW heparin is given in combination with warfarin for four to five days.[8] Simultaneous initiation of warfarin and unfractionated heparin or LMW heparin has not been associated with any clinically important adverse outcomes.

Enoxaparin (Lovenox) was the first LMW heparin approved by the U.S. Food and Drug Administration (FDA) for the treatment of DVT in a dosage of 1 mg per kg twice daily or 1.5 mg once daily. Dalteparin (Fragmin), another LMW heparin, is approved only for prophylaxis of DVT. In clinical trials of DVT treatment, dalteparin has been given in a dosage of 200 IU per kg per day (single dose or two divided doses). The FDA has approved the use of tinzaparin (Innohep), in a dosage of 175 anti-Xa IU per kg per day, for the treatment of DVT.

For patients receiving therapeutic LMWH who have severe renal insufficiency (calculated creatinine clearance < 30 mL/min), we suggest a reduction of the dose rather than using standard doses.

For patients with VTE and body weight over 100 kg, we suggest that the treatment dose of fondaparinux be increased from the usual 7.5 mg to 10 mg daily SC (Grade 2C).

eTable B. Unfractionated Heparin, LMWH, and Fondaparinux for Outpatient Treatment of Venous Thromboembolism in Adults

Dosage	*Dosage adjustment in patients with renal impairment*	*Half-life*	*Reversibility*	*Monitoring*
Unfractionated heparin*†				
333 units per kg SC first dose, followed by 250 units per kg SC twice daily	No adjustment	0.5 to 2 hours	Protamine	Activated partial thromboplastin time or anti–factor Xa levels Unfractionated heparin can be monitored using the activated partial thromboplastin time with an institution-specific goal range or with anti–factor Xa levels, typically using a goal of 0.3 to 0.7 IU per mL
LMWH*				
Enoxaparin (Lovenox) 1 mg per kg SC every 12 hours or 1.5 mg per kg SC every 24 hours†	1 mg per kg SC every 24 hours if CrCl < 30 mL/min/1.73 m²	3 to 6 hours	NA	Anti–factor Xa levels in selected patients A peak level (4 hours after the dose is given) can be measured, with a goal of 0.6 to 1 unit per mL for twice-daily enoxaparin and 1.05 units per mL for dalteparin
Dalteparin (Fragmin)† 200 units per kg SC once daily	Use with caution and monitor anti–factor Xa levels in patients with CrCl < 30 mL/min/1.73 m²	3 to 5 hours	NA	
Tinzaparin (Innohep) 175 anti–factor Xa IU per kg SC once daily for ≥ 6 days	Contraindicated in persons 90 years and older with CrCl ≤ 60 mL/min/1.73 m² Use with caution and monitor anti–factor Xa levels in patients with CrCl < 30 mL/min/1.73 m²	3 to 4 hours	NA	
Fondaparinux (Arixtra)				
Weight < 111 lb (50 kg): 5 mg SC daily Weight 111 to 220 lb (50 to 100 kg): 7.5 mg SC daily Weight > 220 lb (100 kg): 10 mg SC daily	Use with caution in patients with CrCl 30 to 50 mL/min/1.73 m² Contraindicated in patients with CrCl ≤ 30 mL/min/1.73 m²	18 hours	NA	Anti–factor Xa levels (only if fondaparinux is the reference standard for the assay)

CrCl = creatinine clearance; LMWH = low-molecular-weight heparin; NA = not available; SC = subcutaneously.

**—Begin warfarin and unfractionated heparin or LMWH on day 1.*

†—*Unfractionated heparin and dalteparin are not approved by the U.S. Food and Drug Administration for treatment of acute deep venous thrombosis. Enoxaparin, 1.5 mg per kg daily, is not approved for outpatient management of acute deep venous thrombosis or for management of acute deep venous thrombosis in pregnant patients.*

LMW Heparins: Regimens for Prevention of Venous Thromboembolism

General surgery in high-risk patient

Dalteparin (Fragmin): 5,000 units SC 8 to 12 hours before surgery and once daily after surgery

Enoxaparin (Lovenox)*: 40 mg SC 1 to 2 hours before surgery and once daily after surgery; or 30 mg SC every 12 hours starting 8 to 12 hours after surgery

General surgery in moderate-risk patient
Dalteparin: 2,500 units SC 1 to 2 hours before surgery and once daily after surgery
Enoxaparin: 20 mg SC 1 to 2 hours before surgery and once daily after surgery
Nadroparin †: 2,850 units SC 2 to 4 hours before surgery and once daily after surgery
Tinzaparin (Innohep): 3,500 units SC 2 hours before surgery and once daily after surgery
Orthopedic surgery
Dalteparin: 5,000 units SC 8 to 12 hours before surgery, then once daily starting 12 to 24 hours after surgery; or 2,500 units SC 6 to 8 hours after surgery, then 5,000 units SC once daily
Enoxaparin: 30 mg SC every 12 hours starting 12 to 24 hours after surgery; or 40 mg SC once daily starting 10 to 12 hours after surgery
Nadroparin †: 38 units per kg SC 12 hours before surgery, 12 hours after surgery, and once daily on postoperative days 1, 2, and 3, then increase to 57 units per kg SC once daily
Tinzaparin: 75 units per kg SC once daily starting 12 to 24 hours after surgery; or 4,500 units SC 12 hours before surgery and once daily after surgery
Major trauma
Enoxaparin: 30 mg SC every 12 hours starting 12 to 36 hours after injury if the patient is hemostatically stable
For acute spinal cord injury, enoxaparin: 30 mg SC every 12 hours
Medical conditions
Dalteparin: 2,500 units SC once daily
Enoxaparin: 40 mg SC once daily
Nadroparin †: 2,850 units SC once daily

LMW = low-molecular-weight; SC = subcutaneous.

**—Dosage for enoxaparin is expressed in anti-Xa units: 1 mg = 100 anti-Xa units*.

†—*Available in Canada*.

Weight-Based Heparin Therapy with Adjustments Based on the APTT

Initial dosage	Bolus of 80 units per kg, then 18 units per kg per hour by infusion
APTT < 35 seconds (<1.2 times control)	Bolus of 80 units per kg, then 4 units per kg per hour by infusion
APTT = 35 to 45 seconds (1.2 to 1.5 times control)	Bolus of 40 units per kg, then 2 units per kg per hour by infusion
APTT = 46 to 70 seconds (1.5 to 2.3 times control)	No change
APTT = 71 to 90 seconds (2.3 to 3.0 times control)	Decrease infusion rate by 2 units per kg per hour.
APTT > 90 seconds (>3.0 times control)	Hold infusion for 1 hour, then decrease infusion rate by 3 units per kg per hour.

APTT = activated partial thromboplastin time.

Adapted with permission from Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. Ann Intern Med 1993;119:875.

Thrombophilias Identified in Patients Presenting with DVT or PE

Anticoagulant protein deficiency

- Protein S
- Protein C
- Antithrombin
- Plasminogen
- Heparin cofactor II
- Dysfibrinogenemia

Combination deficiencies

Antiphospholipid antibodies

Factor V Leiden mutation (heterozygous)

Prothrombin G20210A mutation (heterozygous)[7]

Prevention of Venous Thromboembolism in Patients Undergoing Surgery

RISK LEVEL	*OPTIONS FOR PROPHYLAXIS*
Highest	
Major surgery in patients older than 40 years who have one of the following additional risk factors: previous venous thromboembolism, cancer, thrombophilia Hip or knee arthroplasty Hip fracture surgery Major trauma Acute spinal cord injury	LMW heparin Warfarin (Coumadin) Low-dose unfractionated heparin or LMW heparin, and graduated compression stockings or pneumatic compression stockings Intravenous unfractionated heparin
High	
Nonmajor surgery in patients older than 60 years or patients with additional risk factors Major surgery in patients older than 40 years or patients with additional risk factors	Low-dose unfractionated heparin administered every 8 hours LMW heparin Pneumatic compression stockings
Moderate	
Minor surgery in patients with additional risk factors Nonmajor surgery in patients 40 to 60 years of age Major surgery in patients younger than 40 years who have no additional risk factors	Low-dose unfractionated heparin administered every 12 hours LMW heparin Graduated compression stockings Pneumatic compression stockings
Low	
Minor surgery in patients younger than 40 years who have no additional risk factors	Aggressive mobilization

LMW = low-molecular-weight.

FDA Approved Oral Anticoagulants

Generic (trade name)	FDA approved indications	FDA recommended dosages
Warfarin (Coumadin®, Jantoven®)	• Prophylaxis and treatment of venous thromboembolism (VTE)* • Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve	Dosage customized so that INR is in therapeutic range. See INR target range table for recommended INR target ranges. Available pill strengths: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg

	replacement • Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction * DOACs now recommended over warfarin for DVT of the leg or PE in non-CA patients. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy For VTE Disease: Chest Guideline Published online January 07, 2016.doi:10.1016/j.chest.2015.11.026	
Apixaban (Eliquis®)	• Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation • For the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery • For the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy. • Not recommended in patients with severe hepatic impairment, prosthetic heart valves, or pregnancy	Nonvalvular Atrial Fibrillation • 5mg BID • 2.5mg BID if patient has two or more of these factors (age≥80, weight ≤60kg, serum creatinine ≥1.5 mg/dL) • 2.5mg BID if coadministered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)(e.g., ketoconazole, itraconazole, ritonavir, clarithromycin) • Apixaban is contraindicated if patient has two or more of these factors (age≥80, weight ≤60kg, serum creatinine ≥1.5 mg/dL) AND is taking a strong dual CYP3A4 and P-gp inhibitor. • In patients with end-stage renal disease (ESRD) maintained on hemodialysis, the recommended dose is 5 mg twice daily. Reduce dose to 2.5 mg twice daily if patient has one of the following patient characteristics (age ≥80 years or body weight ≤60 kg). • No data available for use in patients with CrCl Prophylaxis of DVT following hip or knee replacement surgery • 2.5 mg BID with first dose taken 12- 24 hours after surgery • Recommended duration of treatment is 35 days for hip replacement and 12 days for knee replacement Treatment of DVT and PE • 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. Reduction in the risk of recurrent DVT and PE following initial therapy • 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE
Dabigatran (Pradaxa®)	Reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation • For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days • To reduce the risk of recurrence of DVT and PE in patients who have been previously treated • For the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery • Contraindicated in patients with mechanical prosthetic heart valves	Nonvalvular Atrial Fibrillation • 150 mg BID for CrCl >30mL/min • 75 mg BID for CrCl 15-30mL/min • If CrCl 30 to 50 mL/min and concomitant use of dronedarone or ketoconazole, consider 75 mg twice daily • Avoid co-administration with P-gp inhibitors if CrCl <30 mL/min • Contraindicated in patients with CrCl <15 mL/min Treatment and Reduction in the Risk of Recurrence of DVT and PE: • For patients with CrCl >30 mL/min: 150 mg orally, twice daily after 5-10 days of parenteral anticoagulation

	• Not recommended in patients with bioprosthetic heart valves. • Dabigatran has not been studied adequately in pregnant women.	• Avoid co-administration with P-gp inhibitors if CrCl <50 mL/min • No dosing recommendations available for patients with CrCl<30 mL/min or on dialysis Prophylaxis of DVT and PE Following Hip Replacement Surgery • For patients with CrCl >30 mL/min: 110 mg orally first day, then 220 mg once daily for 28-35 days • Avoid co-administration with P-gp inhibitors if CrCl <50 mL/min • No dosing recommendations available for patients with CrCl<30 mL/min or on dialysis CrCl determined using Cockcroft-Gault formula and actual body weight: http://touchcalc.com/calculators/cg
Rivaroxaban (Xarelto®)	• To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation • For treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), and for the reduction in the risk of recurrence of DVT and of PE • For prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery • Not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B or C) or prosthetic heart valves. • Use with caution in pregnant women. Rivaroxban dosing in pregnant women has not been studied.	<u>Reduction in risk of stroke in nonvalvular atrial fibrillation</u> • 20 mg once daily with the evening meal for patients with CrCl >50 mL/min • 15 mg once daily with the evening meal for patients with CrCl 15 to 50 mL/min • **Contraindicated in patients with CrCl<30ml/min** <u>Treatment of DVT/PE</u> • 15 mg twice daily with food, for first 21 days. • After 21 days, transition to 20 mg once daily with food, for remaining treatment • **Contraindicated in patients with CrCl<30ml/min** <u>Reduction in the risk of recurrence of DVT and of PE</u> • 20 mg once daily with food • **Contraindicated in patients with CrCl<30ml/min** <u>Prophylaxis of DVT following hip or knee replacement surgery</u> • Hip replacement: 10 mg once daily for 35 days • Knee replacement: 10 mg once daily for 12 days • **Contraindicated in patients with CrCl< 30ml/min**
Edoxaban (Savaysa®)	To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation • Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant • **Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C)** • **Not recommended in patients with mechanical heart valves or moderate to severe mitral stenosis.** • **Use with caution in pregnant women. Edoxaban has not been adequately studied in this population.**	<u>Nonvalvular Atrial Fibrillation</u> • 60 mg once daily in patients with CrCL >50 to ≤ 95 mL/min • 30 mg once daily in patients with creatinine clearance 15 to 50 mL/min • **Contraindicated in patients with creatinine clearance (CrCL) > 95 mL/min (inferior to warfarin for stroke prevention)** <u>Treatment of DVT and PE</u> • 60 mg once daily (following 5-10 days of parenteral anticoagulant) • 30 mg once daily (following 5-10 days of parenteral anticoagulant) for patients with CrCL 15 to 50 mL/min or body weight less than or equal to 60 kg or who use certain Pgp inhibitors (verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole or oral ketoconazole)

Stroke Risk Scores

CHA_2DS_2-VASc

The CHA_2DS_2-VASc score is an expansion of the original $CHADS_2$ score to include 3 additional stroke risk factors: age 65-74, female sex, and history of vascular disease. The additional risk factors are believed to more accurately determine stroke risk and the need for anticoagulation in patients with $CHADS_2$ scores of 0 or 1. **The CHA_2DS_2-VASc is recommended over $CHADS_2$ in the 2014 AHA/ACC/HRS Atrial Fibrillation Guidelines.**[1]

CHA_2DS_2-VASc Scoring Table[2]	
Condition	**Points**
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA or thromboembolism (prior)	2
Vascular disease (MI, PAD, or aortic plaque)	1
Age 65-74 years	1
Sex Category (Female)	1
Total score=	

CHA_2DS_2-VASc Risk Stratification			
Score	**Risk**	**ESC Recommendation**[3]	**AHA/ACC/HRS Guidelines**[1]
≥2	High	Anticoagulate	Anticoagulate (Class Ia rec.)
1	Intermediate	Anticoagulate	Consider oral anticoagulant or aspirin (Class IIb rec.)
0	Low	Don't Anticoagulate	No antithrombotic (Class IIa rec.)

CHA_2DS_2-VASc Score	Yearly Stroke Risk (%)		
	No Warfarin	With Aspirin[4]	With Warfarin[4]
0	0	0	0
1	1.3	1.0	0.5
2	2.2	1.8	0.8
3	3.2	2.6	1.1
4	4.0	3.2	1.4
5	6.7	5.4	2.3
6	9.8	7.8	3.4

Useful Links if Anticoagulation is Needed
FDA Approved Anticoagulants
Comparison of warfarin and DOACs
Anticoagulant selection based on pt. characteristics
Identifying patients appropriate for DOACs
Anticoagulant selection decision tree

[1] January C, Wann L, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. JACC. 2014. Doi: 10.1016/j.jacc.2014.03.022

[2] Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010 Feb;137(2):263-72. doi: 10.1378/chest.09-1584.

[3] Camm, AJ et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. European Heart Journal (2012)33, 2719–2747. doi: 10.1093/eurheartj/ehs253

[4] Robert G. Hart, MD; Lesly A. Pearce, MS; and Maria I. Aguilar, MD. Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. Ann Intern Med. 2007;146:857-8673. doi:10.7326/0003-4819-146-12-200706190-00007

$CHADS_2$

The $CHADS_2$ score is a validated and widely used tool to predict **stroke risk in non-valvular atrial fibrillation patients.** The higher the score, the greater the stroke risk. **The CHA_2DS_2-VASc (prior page) is now recommended over CHADS2 based on the 2014 AHA/ACC/HRS Atrial Fibrillation Guidelines.**[1]

$CHADS_2$ Scoring Table[2]	
Condition	**Points**
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	1
Diabetes mellitus	1
Stroke/TIA or thromboembolism (prior)	2
Total score=	

$CHADS_2$ Risk Stratification		
Score	**Risk**	**ACC/AHA Recommendation**[4]
≥2	High	Anticoagulate
1	Moderate	Anticoagulate or ASA
0	Low	ASA or nothing

$CHADS_2$ Score	Annual Stroke Risk (%)		
	No Warfarin	With Aspirin[3]	With Warfarin[3]
0	1.9	1.5	0.7
1	2.8	2.2	1.0
2	4.0	3.2	1.4
3	5.9	4.7	2.1
4	8.5	6.8	3.0
5	12.5	10.0	4.4
6	18.2	14.6	6.4

Other Links
FDA Approved Anticoagulants
Comparison of warfarin and DOACs
Anticoagulant selection based on pt. characteristics
Identifying patients appropriate for DOACs

In the Active A and Active W Studies, aspirin and clopidogrel, when used in combination, reduce the stroke risk in patients with atrial fibrillation more than aspirin alone but less so than warfarin. In addition, the risk of bleeding with the aspirin/clopidogrel combination was determined to be the same as the risk of bleeding with patients using warfarin alone.

Online risk calculators and apps

http://www.mdcalc.com/chads2-score-for-atrial-fibrillation-stroke-risk/
$CHADS_2$ calculator

http://www.mdcalc.com/cha2ds2-vasc-score-for-atrial-fibrillation-stroke-risk/
CHA_2DS_2-VASc calculator

http://www.sparctool.com/
Combination tool that calculates $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores and provides detailed risk estimates for various anticoagulants based on these scores.

https://itunes.apple.com/us/app/anticoagevaluator/id609795286?mt=8
ACC AnticoagEvaluator: The American College of Cardiology's AnticoagEvaluator is an easy and fast way to assess stroke and bleeding risk and the benefits and risks of antithrombotic therapy in patients with chronic atrial fibrillation.

Comparison of Anticoagulants
Basic Characteristics of Warfarin and DOACs

	Warfarin	DOACs
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	Rivaroxaban should be taken with largest meal of the day, otherwise no known food effects for DOACs
Medication interactions	Many	Few*
Monitoring required	Yes	No
Offset	Long	Shorter

*Apixaban is contraindicated if patient has two or more of these factors (age≥80, weight ≤60kg, serum creatinine ≥1.5 mg/dL) AND is taking a strong dual CYP3A4 and P-gp inhibitor

Safety, Efficacy, and Pharmacology

	Warfarin[a]	Rivaroxaban[a]	Apixaban[a]	Dabigatran[a]	Edoxaban[b]
FDA approved indications	• AF • VTE o treatment o secondary prevention o prophylaxis • Valve replacement • MI	• AF (non-valvular only) • VTE o treatment o secondary prevention o prophylaxis[1]	• AF (non-valvular only) • VTE o treatment o secondary prevention o prophylaxis[1]	• AF (non-valvular only) • VTE o Treatment[3] o secondary prevention o prophylaxis[2]	• AF (non-valvular only) • VTE o Treatment[3]
Administration	• Once daily with or without food	• Once or twice daily with largest meal of day[4]	• Twice daily with or without food	• Twice daily with or without food • Must be kept in original packaging • Can't be crushed	• Once daily with or without food
Safety in non-valvular atrial fibrillation	• Higher risk of intracranial hemorrhage compared to DOACs	• Higher risk of GI bleeding compared to warfarin	• Lower risk of major bleeding compared to warfarin	• Higher risk of GI bleeding compared to warfarin • Small increase in risk of MI compared to warfarin	• Lower risk of major bleeding compared to warfarin • Higher risk of GI bleeding (60mg dose)compared to warfarin
Efficacy in non-valvular atrial fibrillation[5]		• Non-inferior to warfarin	• Reduced all-cause mortality	• Lower risk of ischemic stroke (150mg dose only) • Trend towards reduced all-cause mortality	• Non-inferior to warfarin
Safety in VTE	• Increased risk of intracranial hemorrhage[d]	• Lower risk of major bleeding than warfarin[c] • May have higher risk of GI bleeding than warfarin[d]	• Potentially lower risk of major bleeding than warfarin, LMWH/dabigatran, and LMWH/edoxaban[c]	• May have higher risk of GI bleeding than warfarin[d]	• May have higher risk of GI bleeding than warfarin[d]
Efficacy in VTE	Similar reduction in risk of recurrence[c]	Similar reduction in risk of recurrence[c]	Similar reduction in risk of recurrence[c]	Similar reduction in risk of recurrence[c]	Similar reduction in risk of recurrence[c]
Initial parenteral therapy needed for VTE treatment?	Yes	No	No	Yes	Yes
Drug	Multiple	3A4/P-gp	3A4/P-gp	P-gp	P-gp

	Warfarin[a]	Rivaroxaban[a]	Apixaban[a]	Dabigatran[a]	Edoxaban[b]
interactions					
Target	VKORC1	Factor Xa	Factor Xa	Thrombin	Factor Xa
Prodrug	No	No	No	Yes	No
Bioavailability	100%	60%-80%[6]	60%	6%	62%
Time to peak effect	4-5 days	2-4 hours	1-2 hours	1-3 hours	1-2 hours
Half-life	40 hours	7-11 hours	12 hours	8-15 hours	10-14 hours
Renal clearance	None	33%	25%	80%	50%

[1]Approved for VTE prophylaxis following knee or hip surgery only.
[2]Approved for VTE prophylaxis following hip surgery only.
[3]After 5-10 days of parental anticoagulant treatment only
[4]Twice daily for first 21 days of VTE treatment. Once daily for other indications.
[5]All are considered effective for stroke reduction in non-valvular AF
[6]Bioavailability of rivaroxaban decreases as the dose is increased. With once daily doses of 20 and 10 mg, bioavailabilities are 60% and 80%, respectively

Pros and Cons of DOACs

PROS

- Lower incident of intracranial hemorrhage compared to warfarin
- Reduced risk of ischemic stroke compared to warfarin (apixaban and dabigatran 150mg)
- Lower risk of major bleeding compared to warfarin in AF (apixaban and edoxaban) (rivaroxaban had less major bleeding in pulmonary embolism patients1)
- Lower overall risk of mortality compared to warfarin (apixaban and dabigatran 150mg)
- No INR monitoring required
- Bridging/induction therapy likely not needed (except for dabigatran and edoxaban which require 5-10 days of parenteral anticoagulation for treatment of VTE)
- Short half-life allows easier perioperative management
- Convenient for rural patients or those with other barriers to INR monitoring
- Fewer drug/diet/co-morbidity interactions
- Less complex patient/family education
- Follow up can likely be performed by community providers as well as specialty clinics

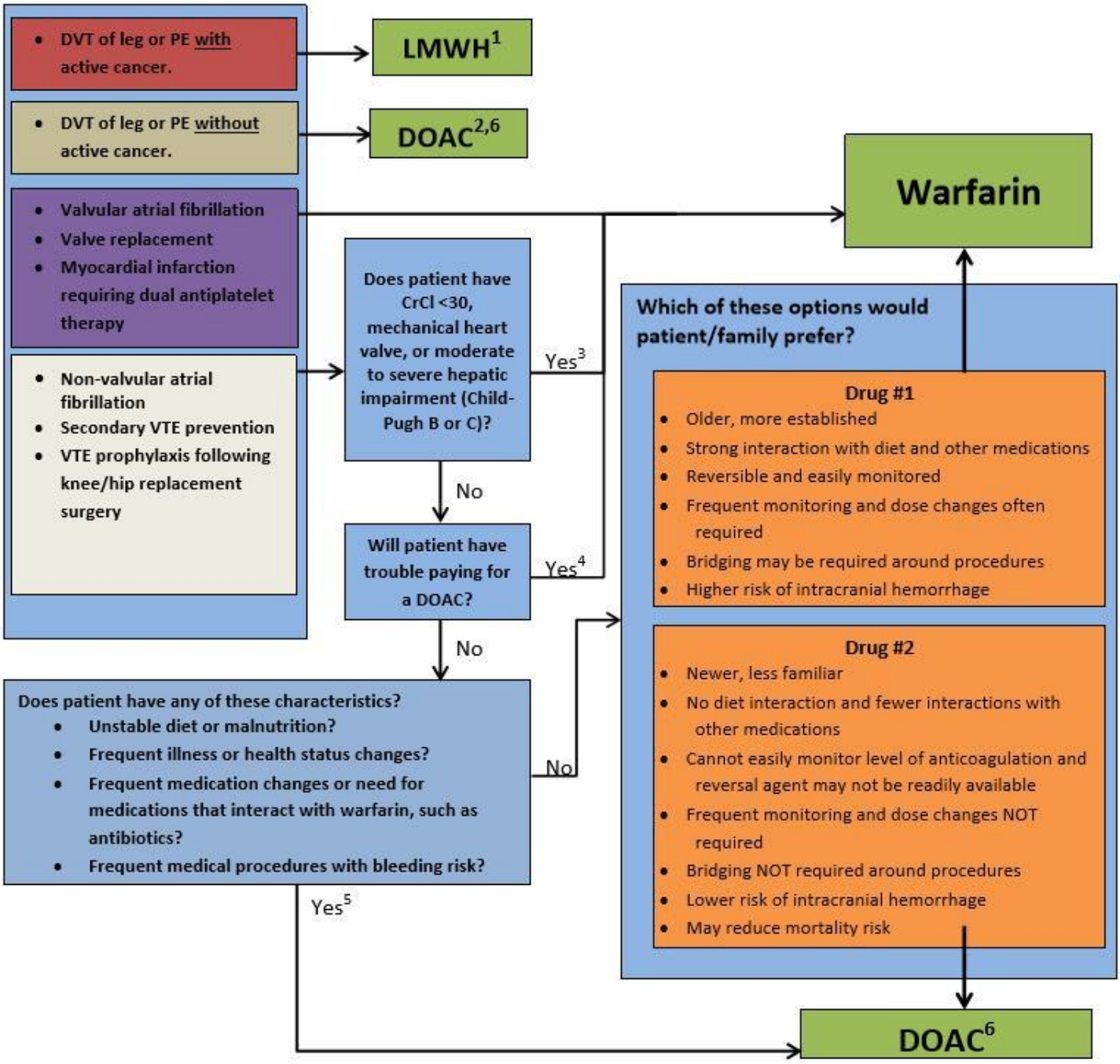
CONS

- DOACs with BID dosing (dabigatran and apixaban) and rivaroxaban's requirement to take with food may have a negative impact on compliance.
- No specific monitoring parameter and only dabigatran has reversal agent (idarucizumab)
- Higher incidence of GI side effects and discontinuation rate (dabigatran only)
- Possible increased incidence of certain adverse events (e.g. MI, GI bleed, etc.) depending on DOAC
- Lack of monitoring may result in non-compliance and an increased chance that patient may not report bleeding
- Renal monitoring and dose adjustment required
- Higher out-of-pocket costs and copays
- New medications with only short history of use outside clinical trials

Choice of Anticoagulant in VTE Based on Patient Characteristics

Patient Characteristic	Drug Choice	Remarks
DVT of Leg or PE in non-cancer patient	patients DOAC (2B recommendation over warfarin)	Trials have shown DOACs to be as effective at preventing VTE recurrence as warfarin with lower risk of bleeding.
DVT of Leg or PE in patients with cancer	LMWH (2C over warfarin or DOACs)	Recommendation for LMWH is stronger if: VTE was just diagnosed, extensive, metastatic cancer, very symptomatic; vomiting; on chemotherapy
Renal disease and creatinine clearance <30ml/min	VKA	DOACs and LMWH contraindicated with severe renal impairment. DOAC dosing is unique for each medication and level of renal function
Extremes of weight (eg <50kg or >120kg)2 or BMI >403	VKA	VKA Patients at extremes of weight represented a very small proportion of the patients in DOAC VTE trials.
Reversal agent needed	VKA, unfractionated heparin, dabigatran	
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other DOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding

Choosing of a Long Term anticoagulant



1. LMWH recommended over warfarin or DOACs in treatment of DVT of leg or PE in patients with active cancer (ACCP guidelines)
2. DOACs recommended over warfarin in treatment of DVT of leg or PE in patients without active CA (ACCP guidelines).
3. Few patients in clinical trials had CrCl < 30. DOACs are either contraindicated or to be used cautiously in patients with significant hepatic disease or mechanical valves.
4. DOACs have much higher co-pays compared to warfarin.
5. Warfarin is affected by diet and general health status, has many medication interactions, and may require bridging around certain medical procedures.
6. Each DOAC is only approved for certain indications and may have warnings about use in specific populations (ex. levels of renal/hepatic failure) and with certain concurrent medications (pgp/CYP3A4 inducers or inhibitors). Review the package insert to ensure the selected DOAC is appropriate.

Identifying Patients Appropriate for Direct Oral Anticoagulants (DOACs)

With the FDA approval of direct oral anticoagulants (DOACs), such as dabigatran (Pradaxa®), rivaroxaban (Xarelto®), apixaban (Eliquis®), and edoxaban (Savaysa®), clinicians have alternatives to warfarin for stroke prevention in non-valvular A-Fib and the prevention/treatment of VTE. Although their safety and efficacy are comparable or better than warfarin and they are easier to manage, DOACs may not be the best choice for all patients. Clinicians must weigh individual patient factors to determine whether a DOAC or warfarin is most appropriate. The criteria and pros and cons below can help providers and patients make an informed decision.

Criteria for Good DOAC Candidates

FDA approved indication	DOACs are currently only approved for non-valvular atrial fibrillation and treatment/prevention of VTE. Review prescribing information for DOACs for updated FDA approval. DOACs are contraindicated in mechanical valve patients.
Adequate renal function	Since DOACs rely on renal function for elimination, they should be used with caution in patients with significant renal disease. DOAC dosing is adjusted according to renal function.
History of compliance with medical regimen	Since DOACs have a short half-life compared to warfarin and do not require monitoring, compliance may be a more important concern.
Frequent medication, diet, or health status changes that make warfarin management difficult.	Unlike warfarin, DOACs have few medication interactions. In addition, the only food-related factor with DOACs is that rivaroxaban should be taken with food.
Barriers to patient/family education	While DOAC education is still important, warfarin education is more involved due to the difficulty of management and number of topics needing to be covered.
Barriers to frequent monitoring (lack of transportation, mobility issues)	Unlike warfarin, frequent blood draws are not necessary with DOACs. Most follow-up monitoring can occur at regularly scheduled medical appointments.
Not taking medications known to interact with DOACs	While DOACs interact with fewer medications, there are still medications that increase or decrease drug exposure depending on the DOAC being used, including P-glycoprotein (Pgp) and strong CYP3A4 inducers and inhibitors (rifampin, ketoconazole, dronedarone, and itraconazole). Prescribing information should be reviewed for complete drug-drug interaction information.
Financial resources or adequate insurance coverage to pay out-of-pocket expense	DOACs may require higher out-of-pocket expenses based on insurance coverage.
History of labile INRs while on warfarin in spite of good compliance and efforts to improve INR stability.	In patients unable to maintain therapeutic INR levels, the 2014 AHA/ACC/HRS Atrial Fibrillation Guidelines recommend switching patients to a DOAC (Class IC rec.)1
Documented warfarin failure	DOACs should be considered if a patient has a thromboembolic event while on warfarin, especially if the patient's INR was therapeutic at time of event
Patient understands and accepts that DOACs are not monitored, cannot accurately be	

measured, and do not have reversal agents. Patients need to be part of the decision-making process, which includes informing them about some of the key differences between warfarin and DOACs. *

Things to Consider when Starting Patients on Warfarin

1. Ensure that patient doesn't have any of these absolute contraindication for warfarin1
    - Pregnancy, except in women with mechanical heart valves
    - Hemorrhagic tendencies or blood dyscrasias
    - Recent or contemplated surgery of the central nervous system (CNS) or eye, or traumatic surgery resulting in large open surfaces
    - Bleeding tendencies associated with certain conditions
    - Threatened abortion, eclampsia, and preeclampsia
    - Unsupervised patients with potential high levels of non-compliance
    - Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding
    - Hypersensitivity to warfarin or any component of the product
    - Major regional or lumbar block anesthesia
    - Malignant hypertension
2. Weigh risk of clotting with risk of bleeding
    - In a-fib patients, calculate the patient's stroke risk using CHADS2 or CHA2DS2-VASc scores and bleeding risk using the HAS-BLED score.
    - In VTE patients, calculate the patient's bleeding risk using the RIETE bleeding risk score.
3. Consider other patient factors that could impact warfarin safety
    - Possible drug interactions (drug interaction table)
    - Ability of patient/family to comply with monitoring and dose changes and comprehend warfarin education
    - Alcohol abuse, dementia, depression, unstable diet, co-morbidities
    - Discuss treatment options with cardiologist if patient is also on dual antiplatelet medications
4. Select appropriate target INR range
    - Selecting appropriate target range
5. Select appropriate treatment duration
    - Selecting appropriate duration
6. Select appropriate starting dose
    - Select starting dose based on factors affecting bleeding risk and warfarin sensitivity such as age, co-morbidities, and interacting drugs.

Warfarin is not going away

Only option for:

- Dialysis patients
- Mechanical valves
- borderline renal functions
- High risk bleeding pts (fully reversible)

Warfarin Recommendations (VKA)

2.2 Initial Dose Selection and Pharmacogenetic Testing

2.2. Initiating VKA therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA.

2.3 Initiation Overlap for Heparin and VKA

2.3. For patients with acute VTE, we suggest that VKA therapy be started on day 1 or 2 of low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin (UFH) therapy rather than waiting for several days to start (Grade 2C)**.**

3.1 Monitoring Frequency for VKAs

3.1. For patients taking VKA therapy with consistently stable INRs, we suggest an INR testing frequency of up to 12 weeks rather than every 4 weeks (Grade 2B)**.**

3.2 Management of the Single Out-of-Range INR

3.2. For patients taking VKAs with previously stable therapeutic INRs who present with a single out-of-range INR of ≤ 0.5 below or above therapeutic, we suggest continuing the current dose and testing the INR within 1 to 2 weeks (Grade 2C)**.**

3.3 Bridging for Low INRs

3.3. For patients with stable therapeutic INRs presenting with a single subtherapeutic INR value, we suggest against routinely administering bridging with heparin (Grade 2C)**.**

3.4 Vitamin K Supplementation

3.4. For patients taking VKAs, we suggest against routine use of vitamin K supplementation (Grade 2C)**.**

3.5 Anticoagulation Management Services for VKAs

3.5. (Best Practices Statement) We suggest that health-care providers who manage oral anticoagulation therapy should do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions.

3.6 Patient Self-Testing and Self-Management

3.6. For patients treated with VKAs who are motivated and can demonstrate competency in self-management strategies, including the self-testing equipment, we suggest patient self-management rather than usual outpatient INR monitoring (Grade 2B)**. For all other patients, we suggest monitoring that includes the safeguards in our best practice statement 3.5.**

3.7 Dosing Decision Support

3.7. For dosing decisions during maintenance VKA therapy, we suggest using validated decision support tools (paper nomograms or computerized dosing programs) rather than no decision support (Grade 2C)**.**

3.8 VKA Drug Interactions to Avoid

3.8. For patients taking VKAs, we suggest avoiding concomitant treatment with nonsteroidal antiinflammatory drugs, including cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs, and certain antibiotics (see Table 8 in main article[1]) (Grade 2C)**.**

For patients taking VKAs, we suggest avoiding concomitant treatment with antiplatelet agents except in situations where benefit is known or is highly likely to be greater than harm from bleeding, such as patients with mechanical valves, patients with acute coronary syndrome, or patients with recent coronary stents or bypass surgery (Grade 2C)**.**

4.1 Optimal Therapeutic INR Range

4.1. For patients treated with VKAs, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) rather than a lower (INR < 2) or higher (INR 3.0-5.0) range (Grade 1B)**.**

4.2 Therapeutic Range for High-Risk Groups

4.2. For patients with antiphospholipid syndrome with previous arterial or venous thromboembolism, we suggest VKA therapy titrated to a moderate-intensity INR range (INR 2.0-3.0) rather than higher intensity (INR 3.0-4.5) (Grade 2B)**.**

5.0 Discontinuation of Therapy

5.0. For patients eligible to discontinue treatment with VKA, we suggest abrupt discontinuation rather than gradual tapering of the dose to discontinuation (Grade 2C)**.**

Warfarin Target INR Range and Length of Treatment

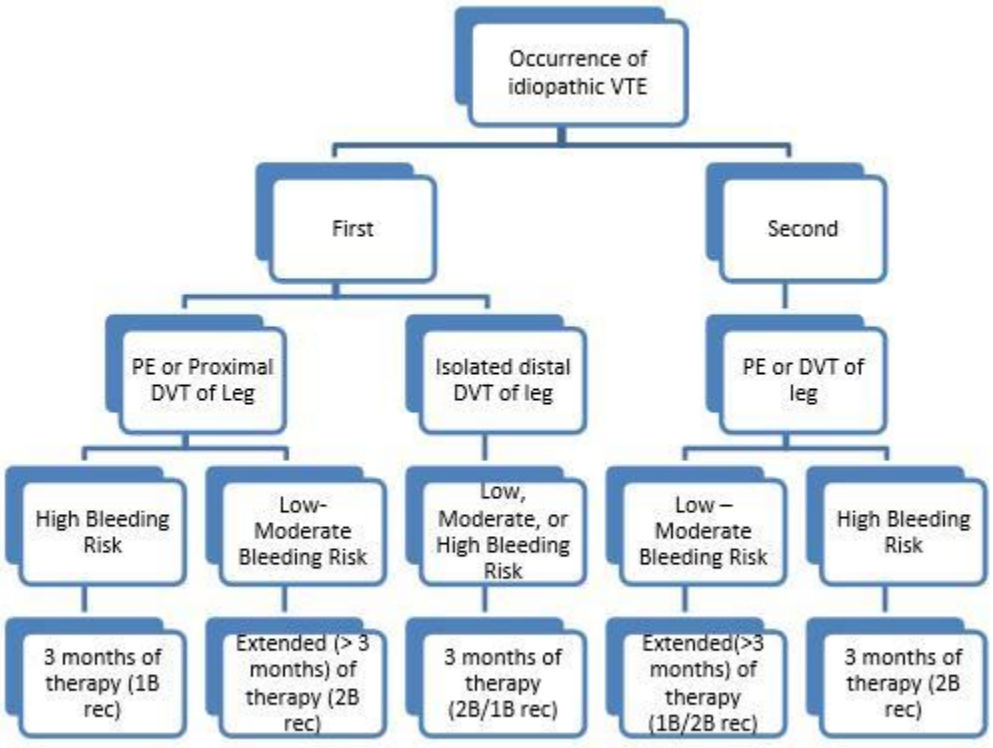
Indication	Target INR Range	Duration
DVT and PE1		
PE or DVT of leg provoked by surgery or transient/ reversible risk factor	2-3	3 months
PE or DVT of leg unprovoked by surgery or transient/reversible	2-3	At least 3 months (over shorter period), then evaluate for risk-benefit of extended therapy (see flowchart below) In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a low or moderate bleeding risk, use extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B). If high bleeding risk, use 3 months of anticoagulant therapy over extended therapy (no scheduled stop date)
PE or DVT of leg in patients with active cancer	2-3	Extended (>3 months) Suggest use of LMWH over warfarin in PE or DVT of leg
Non valvular atrial fibrillation and/or flutter2		
Low risk (CHA2DS2-VASc =0)	N/A	Reasonable to omit antithrombotic therapy
Intermediate risk (CHA2DS2-VASc =1)	2-3	No antithrombotic therapy or long-term treatment with an oral anticoagulant or aspirin may be considered
High risk (CHA2DS2-VASc > 2)	2-3	Long-term
Cardioversion	2-3	At least 3 weeks prior to and at least 4 weeks after regardless of CHA2DS2-VASc score or method of cardioversion.
Valvular Disease3		
Mechanical aortic valve replacement (bileaflet or current-generation single tilting disc) and no risk factors for	2-3	Long-term Thromboembolism risk factors: AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions thromboembolism LV dysfunction, or hypercoagulable conditions ASA 75mg-100mg daily in addition to warfarin
Mechanical Aortic valve and additional risk factors for thromboembolic events or an older-generation mechanical AVR (such as ball-in-cage)	2.5-3.5	Long-term Thromboembolism risk factors: AF, previous thromboembolism LV dysfunction, or hypercoagulable conditions thromboembolism LV dysfunction, or hypercoagulable conditions ASA 75mg-100mg daily in addition to warfarin
Mechanical mitral valve replacement	2.5-3.5	Long-term ASA 75mg-100mg daily in addition to warfarin
Bioprosthetic mitral valve replacement	2.0-3.0	First 3 months following procedure 2B
Post-op VTE prophylaxis4**		
Total hip replacement	2.0-3.0	At least 10 to 14 days uggestion to extend up to 35 days
Total knee replacement	2.0-3.0	At least 10 to 14 days Suggestion to extend up to 35 days
Hip fracture surgery	2.0-3.0	At least 10 to 14 days Suggestion to extend up to 35 days

Length of Anticoagulation Treatment in VTE1

Type of VTE	Recommendation
Provoked proximal DVT of leg or PE	3 months
Provoked isolated distal DVT of leg	3 months
Unprovoked DVT of leg (isolated distal or proximal) or PE	At least 3 months2
1st VTE that is unprovoked proximal DVT of leg or PE and low/moderate bleed risk pt.	Extended 3,4
1st VTE that is unprovoked proximal DVT of leg or PE and high bleed risk	3 months
2nd unprovoked VTE in low/moderate bleed risk pt.	Extended4
2nd unprovoked VTE in high bleed risk pt.	3 months
DVT of the leg or PE and active CA	Extended4

1Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy For VTE Disease: Chest Guideline Published online January 07, 2016. doi:10.1016/j.chest.2015.11.026.
2After 3 months of treatment, patients with unprovoked DVT of the leg or PE should be evaluated for the risk-benefit ratio of extended therapy.
3Patient sex and D-dimer level measured about one month after stopping anticoagulant therapy can help to further stratify the risk of recurrent VTE. Men have about a 75% higher risk of recurrence compared to women, while patients with a positive D-dimer result have about double the risk of recurrence compared to those with a negative D-dimer. The risk of recurrence in women with a negative post treatment D-dimer appears to be similar to the risk for patients with a proximal DVT or PE that was provoked by a minor transient risk factor (~15% recurrence at 5 years); consequently, the argument for extended anticoagulation in these women is not strong, suggesting that D-dimer testing will often influence a woman's decision. The risk of recurrence in men with a negative dimer is not much less than the overall risk of recurrence that we have estimated for patients with an unprovoked proximal DVT or PE (~25% compared to ~30% recurrence at 5 years); consequently, the argument for extended anticoagulation in these men is still substantial, suggesting that D-dimer testing will often not influence a male's decision.
4In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (e.g. annually).

Length of treatment recommendations for idiopathic (unprovoked) VTE[1]



[1]Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. doi:10.1378/chest.11-2301

Selection of Warfarin Starting Dose

Patient population	Initial dose
Most patients *Follow 5mg initiation nomogram after first two 5mg doses.*	• 5mg
Patients with acute VTE being treated in the outpatient setting and are low to moderate risk for bleeding[1] *Follow 10 mg initiation nomogram after first two 10mg doses.*	• 10mg *Loading dose of 10mg daily for 2 days and then dosing based on INR measurements is a 2C recommendation in the latest ACCP guidelines for patients sufficiently health to be treated as outpatients where rapid attainment of therapeutic INR is required and considered safe*[3]
High bleeding risk patients (ex. elderly, malnourished, CHF, hepatic dysfunction, interacting drugs such as amiodarone)	• Consider 2.5mg*

*MAQI[2] expert consensus

Selecting the initial starting dose involves assessing the patient's bleeding risk, need for rapid anticoagulation, and treatment environment. Two small randomized trials have compared 5mg and 10mg starting doses.

Study	Patient population	Methods	Results
Kovacs[1]	Acute VTE, outpatient setting, concurrent LMWH treatment, 25% had CA, mean age 55 Patients excluded: baseline INR>1.4, thrombocytopenia, <18 years old, required hospitalization, high-risk for bleeding	201 patients randomized to receive either 5mg or 10mg initial dosing.	**10mg superior to 5mg** Patients with 10mg initial dosing reached first in-range INRs 1.4 days sooner and had similar rates of bleeding AEs and supratherapeutic INRs as patients started on 5mg.
Crowther[2]	Acute VTE, inpatient setting, most had concurrent heparin treatment, 1/3 had CA, mean age 66	53 patients randomized to receive either 5mg or 10mg initial dosing.	**5mg just as good and possibly safer** 5mg initial dosing resulted in therapeutic INRs as quickly as 10mg dosing with a trend toward less over-anticoagulation

An INR should be obtained within 3-5 days after starting warfarin to assess initial response

[1]Kovacs M J et al. Comparison of 10-mg and 5-mg Warfarin Initiation Nomograms Together with Low-Molecular-Weight Heparin for Outpatient Treatment of Acute Venous Thromboembolism. Ann Intern Med. 2003;138:714-719.

[2]Crowther MA et al. A Randomized Trial Comparing 5-mg and 10-mg Warfarin Loading Doses. Arch Intern Med. 1999;159:46-8.

[3] Holbrook. Evidence-Based Management of Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. doi: 10.1378/chest.11-2295

Factors Increasing or Decreasing Warfarin Sensitivity

When determining the appropriate starting dose of warfarin and making dose adjustments, it is important to consider if the patient may have increased or decreased sensitivity to warfarin.

Higher Sensitivity (Consider lower starting dose)	Lower Sensitivity (Consider higher starting dose)
Baseline INR >1.2	Baseline INR < 1.2
Advanced age (>65)	Younger age (<55)[1]
Female gender[2]	Male gender[2]
Low body weight (<110 pounds)	>200 pounds[2]
Asian ancestry[3]	African American ancestry[2]
Recent surgery and blood loss[2]	Diet high in Vitamin K[2]
Comorbidities: CHF, renal disease, liver disease, and cancer[4]	
Impaired nutritional status	
Alcohol abuse[4]	
Concurrent use of medications known to increase INR, including amiodarone, acetaminophen, and many antibiotics and antifungals	
Acute illness (diarrhea, fever)[4]	

[1] Crowther MA et al. A Randomized Trial Comparing 5-mg and 10-mg Warfarin Loading Doses. Arch Intern Med. 1999;159:46-8.
[2] Absher. Patient-specific factors predictive of warfarin dosage requirements. Ann Pharmacother. 2002 Oct;36(10):1512-7.
[3] Dang. The influence of ethnicity on warfarin dosage requirement. Ann Pharmacother. 2005 Jun;39(6):1008-12. Epub 2005 Apr 26. doi: 10.1345/aph.1E566
[4] White. Patient factors that influence warfarin dose response. J Pharm Pract. 2010 Jun;23(3):194-204. doi: 10.1177/0897190010362177. Epub 2010 May 6. doi: 10.1177/0897190010362177

Warfarin Initiation Nomograms

Warfarin Initiation Nomogram (5mg starting dose, target INR range 2-3)[1]

This algorithm was developed for in-patients started on **5mg with an INR target range of 2-3** and monitored with daily INRs. It may not be applicable to outpatient use in which daily INRs are not practical.

	INR	Dose
DAY 1		5 mg
DAY 2	<1.5 1.5 - 1.9 2.0 - 2.5 > 2.5	5 mg 2.5 mg 1 – 2.5 mg 0 mg
DAY 3	<1.5 1.5 - 1.9 2.0 - 3.0 > 3.0	5 - 10 mg 2.5 - 5 mg 0 - 2.5 mg 0 mg
DAY 4	< 1.5 1.5 - 1.9 2.0 - 3.0 > 3.0	10 mg 5 -7.5 mg 0 - 5 mg 0
DAY 5	< 1.5 1.5 - 1.9 2.0 - 3.0 > 3.0	10 mg 7.5 - 10 mg 0 - 5 mg 0
DAY 6	< 1.5 1.5 - 1.9 2.0 - 3.0 > 3.0	7.5 - 12.5 mg 5 - 10 mg 0 - 7.5 mg 0

[1]Crowther.Ann Int Med, 127:333, 1997

Conversion from DOACs to Warfarin (Coumadin®)

Generic (Trade Name)	Instructions

Dabigatran (Pradaxa®)[1]	• Adjust the starting time of warfarin based on creatinine clearance* as follows:
	  ○ For CrCl ≥50 mL/min, start warfarin 3 days before discontinuing dabigatran.
	  ○ For CrCl 30-50 mL/min, start warfarin 2 days before discontinuing dabigatran.
	  ○ For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing dabigatran.
	  ○ For CrCl <15 mL/min, no recommendations can be made.
	
	**CrCl determined using Cockcroft-Gault formula and actual body weight: http://touchcalc.com/calculators/cg*
	
	• Because dabigatran can increase INR, the INR will better reflect warfarin's effect only after dabigatran has been stopped for at least 2 days

Apixaban (Eliquis®)[2]	• Apixaban affects INR, so initial INR measurements during the transition to warfarin may not be useful for determining the appropriate dose of warfarin. • One approach is to discontinue apixaban and begin warfarin with a concomitant parenteral anticoagulant when the next dose of apixaban would have been due, discontinuing the parenteral anticoagulant when INR reaches goal range.
Rivaroxaban (Xarelto®)[3]	• No clinical trial data are available to guide converting patients from rivaroxaban to warfarin. • Rivaroxaban affects INR, so INR measurements made during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin. • One approach is to discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken.
Edoxaban (Savaysa®)[4]	• For patients on 60 mg of edoxaban, reduce dose to 30 mg and begin warfarin concomitantly. • For patients on 30 mg of edoxaban, reduce dose to 15 mg and begin warfarin concomitantly. • During transition, INR should be done at least weekly just prior to daily dose of edoxaban (to minimize influence on INR). • Discontinue edoxaban once a stable INR ≥ 2.0 is achieved.

[1]Pradaxa package insert (updated 12/2013): http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf

[2] Eliquis® package insert (updated 1/2014): http://packageinserts.bms.com/pi/pi_eliquis.pdf

[3] Xarelto package insert (updated 1/2014): http://www.xareltohcp.com/sites/default/files/pdf/xarelto_0.pdf#zoom=100

[4] Savaysa® package insert: http://dsi.com/prescribing-information-portlet/getPIContent?productName=Savaysa&inline=true

Most Clinically Relevant Warfarin-Drug Interactions	
Potentiation of Drug Effect (Increased INR)	**Inhibition of Drug Effect (Decreased INR)**
Acetaminophen	Barbiturates
Allopurinol	Bosentan
Amiodarone	Carbamazepine
Amoxicillin	Cigarette Smoking
Aspirin	Chlordiazepoxide
Azithromycin	Ginseng
Bactrim(TMP-SMX)	Griseofulvin
Cimetadine	Mercaptopurine
Ciprofloxacin	Multivitamin Supplement
Citalopram	Nafcillin
Clarithromycin	Phenobarbital
Clopidogrel	Ribavarin
Cotrimoxazole	Rifampin
Diltiazem	Secobarbital
Entacapone	St. John's wort
Erythromycin	Phenytoin
Fenofibrate	
Fish Oil	
Fluconazole	
Fluvastatin	
Gemcitabine	
Gemfibrozil	
Levofloxacin	
Lovastatin	
Metronidazole	
Miconazole (Suppository and Gel)	
Omeprazole	
Propafenone	
Propanolol	
Simvastatin	
SSRI's	
Tamoxifen	
Tetracycline	
Tramadol	

For a more comprehensive list of potential drug, food, and dietary supplement interactions see Ageno et al. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines
http://journal.publications.chestnet.org/article.aspx?articleid=1159432

High-Risk Medications		
Medication	**Generic Name**	**Suggested Dose Change/Recheck***
Pacerone, Cordarone	Amiodarone	Decrease 30%, recheck in 7-10 days from start date
Arixtra	Fondaparinux Sodium	Increase dose by 10-20% and recheck INR every 2-3- days
Bactrim/Septra	Sulratrim,Trimoxazole, Trimethoprim	Decrease 30%, recheck in 7-10 days from start date
Biaxin	Clarithryomycin	Decrease 30%, recheck in 7-10 days from start date
Diflucan	Fluconazole	Decrease 30%, recheck in 7-10 days from start date
Flagyl	Metronidazole	Decrease 30%, recheck in 7-10 days from start date
Rifampin	Rifadin, rimactane, rimycin, rofact	Increase dose by 10-20% and recheck INR every 2-3 days
Tricor	Fenofibrate, antara, triglide, lobibra	Decrease 30%, recheck in 7-10 days from start date
Xeloda	Methotrexate, capecitabine, cytarabine, fludarabine phsphate, fluorouracil, gemcitabine hydrochloride, hydroxyurea, mercaptopurine, pemetrexed	Decrease dose by 20-30% after checking INRs every 2-3 days, then decrease as needed

* These values represent expert opinion and have not been validated by randomized trials

Managing Patients on Medications that Interact with Warfarin

	Recommendation
When should my patient have their INR drawn?	If taking a medication known to affect the INR, the patient should have a repeat INR within 3-5 days from the start date of the medication.
What if my patient has a history of warfarin medication interaction or will begin taking a medication known to be "high-risk"?	Patients with a history of warfarin medication interaction, those at significant increase risk of bleeding complications, or who will be taking a medication known to be "high-risk" GIVE a preemptive dose adjustment (i.e. reduce the warfarin on the day that the ACS is notified that the medication has been started). In that scenario, repeat the INR within 3-5 days. **See High-Risk table below for specific suggested preemptive dose adjustments**
What are the most common medications that can significantly increase the INRs?*	Acetaminophen Allopurinol **Amiodarone** Amoxicillin Aspirin Azithromycin **Bactrim** Cimetadine Ciprofloxacin Citalopram Clarithromycin Clopidogrel Cotrimoxazole Diltiazem Entacapone Erythromycin Fenofibrate Fish Oil Fluconazole Fluvastatin Gemcitabine Gemfibrozil Levofloxacin Lovastatin Metronidazole Miconazole (Suppository and Gel) Omeprazole Propafenone Propanolol Simvastatin SSRI's Tamoxifen Tetracycline Tramadol
What are the most common medications that can significantly reduce the INR?*	Barbiturates Bosentan Carbamazepine Cigarette Smoking Chlordiazepoxide Ginseng Griseofulvin Mercaptopurine Multivitamin Supplement Nafcillin Phenobarbital Ribavarin Rifampin Secobarbital St. John's wort Phenytoin

Adapted from University of Michigan Anticoagulation Service Guidelines

*For complete list of medications that increase, decrease, or have no effect on INRs, see: Holbrook AM, et al. Systematic Overview of warfarin and its drug and food interactions. Arch Intern Med. 2005 May 23;165(10):1095-106

Warfarin Patient Education Checklist

Completed	Topic
	What is anticoagulation and how does warfarin work?
	Why does patient need to start taking warfarin?
	How to take warfarin? (time of day, dose, weekly schedule, etc.)
	What is the expected duration of treatment?
	How is warfarin monitored? (INR testing, goal target range for patient, frequency of testing, etc.)
	What are the risks and side-effects of warfarin?
	What are the signs/symptoms of bleeding or clotting to watch for?
	What are the main factors influencing INR? (dietary intake of vitamin K, general health, activity level, alcohol, other medications/supplements, etc.)
	Ways to keep INR in range (consistent vitamin K content in diet, limit alcohol use, adhere to dosing instructions, etc.)
	What to do for missed doses?
	What are the drug-drug interactions to watch for? (including OTC and herbal supplements)
	What are the drug-food interactions to watch for?(Vitamin K rich foods, alcohol, etc.)
	What are some other necessary lifestyle changes? (no contact sports, fall avoidance, pregnancy)
	When and how to notify clinic? • s/sx of bleeding • medication/supplement changes • illness/changes in health status • Clinic contact information
	When to seek immediate medical attention?

Routine Follow-up Questions for Warfarin Patients

These questions should be asked at each PT/INR follow-up.

Assessment questions:
Is the patient taking warfarin as prescribed? (correct pill strength and schedule)
Does patient have any changes in general health status?
Any changes in diet, especially intake of vitamin K?
Has the patient started or stopped any prescription medications since last PT/INR?
Does the patient have any unusual bruising or bleeding?
Does the patient have any signs of clotting?
Has the patient had any ED visits or hospitalizations since the last PT/INR?
Has patients started or stopped any OTC vitamins, herbal supplements, dietary supplements, or pain relievers?
Does the patient have any procedures scheduled in the near future?
Does the patient have any travel plans that will interfere with monitoring?

Adapted from: Spectrum Health The Medical Group. http://www.spectrum-health.org/physicians/toolkits

Acronyms for new oral anticoagulants

- NOACs: new oral anti-coagulants, novel oral anti-coagulants, non-monitored oral anti-coagulants, non-warfarin oral anticoagulants, non Vitamin K antagonist oral anticoagulants
- DOACs: direct oral anti-coagulants
- TSOCs: target specific oral anticoagulants
- ODIs oral direct inhibitors

Factor Xa inhibitors

- Apixaban (Eliquis)
- Rivaroxaban (Xarelto)

Direct thrombin inhibitors

• Dabigatran

Low molecular weight heparin (fractionated)

• Dalteparin
• Enoxaparin

Injectable factor Xa

• Fondaparinux

Vitamin K Antagonist

• Warfarin

Unfractionated Heparin

DOAC Initiation Checklist

Task	Comments
Establish appropriate dose based on anticoagulant selected, indication and patient factors such as renal function.	See FDA approved anticoagulants for indication and dosing information.
Evaluate for medication interactions that may necessitate DOAC dose adjustment.	See DOAC drug interaction table
Evaluate renal function (Cockcroft-Gault equation to estimate CrCl) prior to DOAC initiation[1] and establish a baseline for CBC and liver function[2]	Use actual body weight in Cockcroft-Gault equation. Online calculator available at: http://touchcalc.com/calculators/cg
Establish clear expectations for length of treatment based on indication.	
Consider co-administration with a proton-pump inhibitor.[2]	Proton-pump inhibitors do not appear to impact DOAC efficacy based on the clinical trials and may be helpful in reducing dyspepsia (dabigatran) and the risk of gastrointestinal bleeding[3]
If converting from warfarin, see warfarin to DOAC conversion instructions.	
Provide comprehensive patient education.	See DOAC education topic checklist • If rivaroxaban, make sure patient knows to take with the largest meal of the day (typically the evening meal) • If dabigatran, make sure patient knows to take with a full glass of water, to store in the original package, and to not crush.

Establish follow-up plan.	Follow-up plan should include:
	• Who will the patient follow-up with?
	• How often will follow-up occur?
	• When is the next follow-up?
	• What will happen at the follow-ups?
	Follow-ups should check for:
	• compliance
	• thrombo-embolic events
	• bleeding events
	• Medication changes
	  ○ P-gp inhibitors and inducers
	  ○ P-gp/ CYP3A4 inhibitors and inducers
	  ○ antiplatelets
	• need for blood sampling to recheck renal function, hepatic function, and CBC.[2]

[1] January C, Wann L, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. JACC. 2014. Doi: 10.1016/j.jacc.2014.03.022

[2] Heidbuchel et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013. 15, 625-651. Doi: 10.1093/europace/eut083

[3] Agewall et al. Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. Eur Heart J (2013) doi: 10.1093/eurheartj/eht042

Conversion from Warfarin (Coumadin®) to DOACs

Generic (Trade Name)	Instructions

Dabigatran (Pradaxa®)[1]	• Discontinue Warfarin (Coumadin®) and begin dabigatran when INR is below 2.0
	• Start dabigatran at:
	  ○ 150 mg BID for CrCl >30mL/min*
	  ○ 75 mg BID for CrCl 15-30mL/min*
	  ○ Contraindicated in patients with CrCl <15 mL/min*

Apixaban (Eliquis®)[2]	• Discontinue Warfarin (Coumadin®) and begin Apixaban (Eliquis®)when the INR is below 2.0
	• Start apixaban at:
	  ○ 5mg BID
	  ○ 2.5mg BID if patient has two or more of these factors (age≥80, weight ≤60kg, serum creatinine ≥1.5 mg/dL)
	  ○ 2.5mg BID if coadministered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)(e.g., ketoconazole, itraconazole, ritonavir, clarithromycin)

Rivaroxaban (Xarelto®)[3]	• Discontinue warfarin (Coumadin®) and begin Rivaroxaban (Xarelto®) when the INR is below 3.0 to avoid periods of inadequate anticoagulation (same instructions for A-fib and VTE).
	• Start rivaroxaban at:
	  ○ Reduction in risk of stroke in nonvalvular atrial fibrillation
	  ▪ 20 mg once daily with the evening meal for patients with CrCl >50 mL/min*
	  ▪ 15 mg once daily with the evening meal for patients with CrCl 15 to 50 mL/min*
	  ○ Treatment of DVT/PE
	  ▪ 15 mg twice daily with food, for first 21 days.
	  ▪ After 21 days, transition to 20 mg once daily with food, for remaining treatment
	  ○ Reduction in the risk of recurrence of DVT and of PE
	  ▪ 20 mg once daily with food
	  ○ Prophylaxis of DVT following hip or knee replacement surgery
	  ▪ Hip replacement: 10 mg once daily for 35 days
	  ▪ Knee replacement: 10 mg once daily for 12 days

Edoxaban (Savaysa)[4]	Discontinue warfarin and begin edoxaban when the INR is ≤ 2.5.

*CrCl determined using Cockcroft-Gault formula and actual body weight. Online calculator available at: http://touchcalc.com/calculators/cg

Conversion from Parenteral Anticoagulants to DOACs

Generic (Trade Name)	Low Molecular Weight Heparin (LMWH)	Unfractionated Heparin
Dabigatran (Pradaxa®)[1]	Discontinue LMWH and start Pradaxa® 0-2 hours before the time of the next scheduled administration of LMWH	Stop the infusion and start Pradaxa® at the same time
Apixaban (Eliquis®)[2]	Discontinue LMWH and start Eliquis® at the time of the next scheduled administration of LMWH	Stop the infusion and start Eliquis® at the same time
Rivaroxaban (Xarelto®)[3]	Discontinue LMWH and start Xarelto® 0-2 hours before the time of the next scheduled evening administration of LMWH	Stop the infusion and start Xarelto® at the same time
Edoxaban (Savaysa)[4]	Discontinue LMWH and start Savaysa® at the time of the next scheduled administration of LMWH	Discontinue the infusion and start SAVAYSA® 4 hours later

DOAC Drug Interactions and Dose Adjustments

	Dabigatran[1] creatinine clearance (ml/min)			Rivaroxaban[2] creatinine clearance (ml/min)	
	>50	30-50	15-30	>80	15-80
P-gp inducer Rifampin	avoid	Avoid	avoid	avoid	avoid
P-gp inducer and *strong* CYP3A4 inducer					
Carbamazepine				avoid	avoid
Phenytoin				avoid	avoid
St. John's wort				avoid	avoid
P-gp inhibitor and *strong* CYP3A4 inhibitor					
Itraconazole				avoid	avoid
Iopinavir/ritonavir				avoid	avoid
Ritonavir				avoid	avoid
Indinavir/ritonavir				avoid	avoid
Conivaptan				avoid	avoid
Ketoconazole (systemic)	150 mg	75 mg (AF) avoid (DVT)	avoid	avoid	avoid
Clarithromycin	150 mg	150 mg(AF) avoid (DVT)	avoid	avoid	avoid
P-gp inhibitor and *moderate* CYP3A4 inhibitor					
Verapamil	150 mg	150 mg(AF) avoid (DVT)	avoid	caution	avoid
Dronedarone	150 mg	75 mg(AF) avoid (DVT)	avoid	caution	avoid
Diltiazem				caution	avoid
Erythromycin				caution	avoid
P-gp inhibitor and *weak* CYP3A4 inhibitor					
Amiodarone	150 mg	150 mg(AF) avoid (DVT)	avoid		caution
Quinidine	150 mg	150 mg(AF) avoid(DVT)	avoid		caution
Ranolazine					caution
Felodipine					caution

	Apixaban[3] Characteristics: age ≥ 80 yrs, body weight ≤ 60 kg, serum creatinine ≥ 1.5		Edoxaban[4] creatinine clearance (ml/min)
	# of characteristics 0-1	**# of characteristics 2-3**	**No specified CrCl ranges**
P-gp inducer Rifampin	avoid	avoid	Avoid[4]
P-gp inducer and strong CYP3A4 inducer			
Carbamazepine	avoid	avoid	
Phenytoin	avoid	avoid	
St. John's wort	avoid	avoid	
P-gp inhibitor			
azithromycin			30mg (VTE treatment)[4]
P-gp inhibitor and *strong* CYP3A4 inhibitor			
Ketoconazole (systemic)	2.5 mg	avoid	30mg (VTE treatment)[4]
Clarithromycin	2.5 mg	avoid	30mg (VTE treatment)[4]
Itraconazole	2.5 mg	avoid	30mg (VTE treatment)[4]
Iopinavir/ritonavir			
Ritonavir	2.5mg	avoid	
Indinavir/ritonavir			
Conivaptan			
P-gp inhibitor and *moderate* CYP3A4 inhibitor			
Verapamil			Consider dose reduction (AF treatment)[5] 30mg (VTE treatment)[4]
Dronedarone			Consider dose reduction (AF treatment)[5]
Diltiazem			
Erythromycin			30mg (VTE treatment)[4]
P-gp inhibitor and *weak* CYP3A4 inhibitor			
Quinidine			Consider dose reduction (AF treatment)[5] 30mg (VTE treatment)[4]
Amiodarone			
Ranolazine			
Felodipine			

DOAC Patient Education Checklist

Completed	Topic
	What is anticoagulation and how do DOACs work?
	If on warfarin in the past, how are DOACs different from warfarin? *No INR monitoring required, no need for frequent dose adjustments, no Vit. K interactions, much quicker onset/offset of action, likely more expensive*
	Why does patient need to start taking a DOAC?
	What is the expected duration of treatment?
	How to take the DOAC? (dose, frequency, timing, with food?) *Xarelto® must be taken with evening meal (or largest meal of day). Pradaxa® can be taken with or without food but should be taken with a full glass of water. Pradaxa® cannot be crushed. Eliquis® can be taken with or without food. Savaysa® can be taken with our without food.*
	Why is it important not to skip doses? *Very rapid offset-increased risk for clots*
	What to do about missed doses?
	What are the signs/symptoms of bleeding or clotting to watch for? *Be sure to cover signs/symptoms of GI and intracranial bleeds.*
	What medications can increase risk of bleeding? *(ex. ASA, NSAIDs, other anticoagulants such as warfarin and heparin, SSRIs)*
	What are other drug-drug interactions to watch for? *P-gp and CYP3A4 inhibitors and inducers (ex. rifampin, carbamazepine, phenytoin, St. John's wort, dronedarone, ketoconazole, verapamil, amiodarone, clarithromycin, itraconazole, and ritonavir)*
	What kind of lab monitoring will need to be done and how often? *Ex. kidney function, liver function, CBC*
	What to do about taking DOACs around procedures/surgeries?
	How to store DOACs? *Pradaxa® must be kept in its original packaging*
	What are some other necessary lifestyle changes? *avoid contact sports, falls, pregnancy, etc.*
	When and how to notify clinic? • *s/sx of minor bleeding* • *medication changes* • *changes in health status, especially changes in kidney function or pregnancy* • *changes in insurance or financial status that may impact ability to get refills*
	When to seek immediate medical attention? • *s/sx of serious or uncontrolled bleeding*

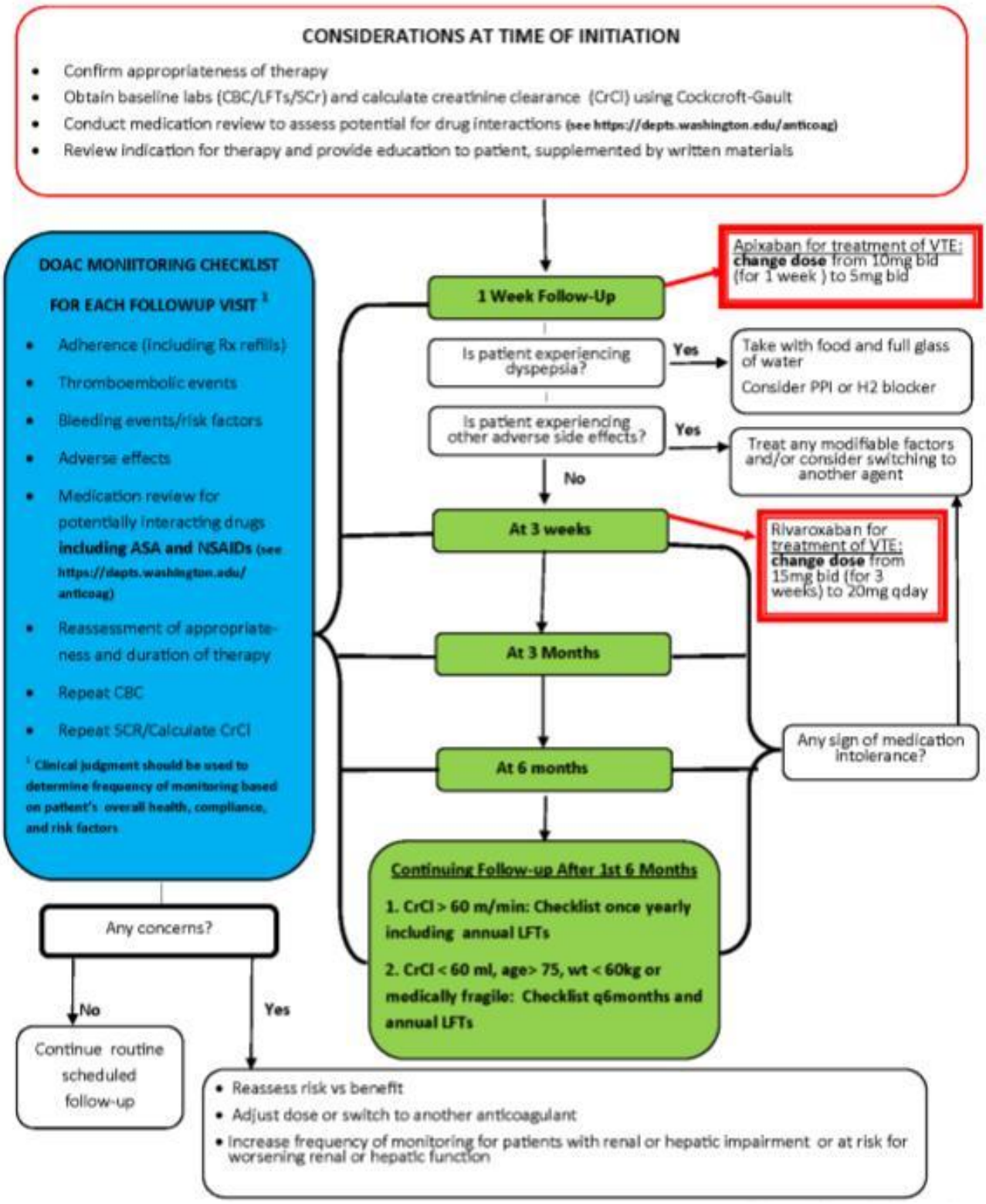
Routine Follow-up Checklist for DOAC Patients

	Interval	Comments
Assess compliance	Each visit	• Instruct patient to bring remaining medication: note and calculate average adherence • Re-educate on importance of strict intake schedule • Inform about compliance aids (special boxes; smartphone applications, etc.) Dabigatran must remain in original packaging
Assess for thrombo-embolism	Each visit	• Systemic circulation (TIA, stroke, peripheral) • pulmonary circulation
Assess for bleeding	Each visit	• If minor (nuisance) bleeding, are preventive measures possible? (eg. PPI, saline nose spray, etc.). Motivate patient to diligently continue anticoagulation. • If bleeding with impact on quality-of-life or with significant risk, is prevention possible? (consider changing anticoagulant)
Assess for other side effects	Each visit	• Assess for link to DOAC and decide whether to continue, temporarily stop, or change to different anticoagulant
Assess for new co-medications	Each visit	• Assess for P-gp inhibitors/inducers (if on dabigatran or edoxaban) or dual P-gp/CYP3A4 inhibitors (if on rivaroxaban or apixaban) • Assess for other medications that may increase risk of bleeding such as anti-platelets **NOTE: DOAC dose adjustments may be required if patient starts taking interacting medications (see drug interaction table).**
Assess labs	Yearly Q 6 months Q 3 months As needed	• Hgb, renal and liver function • Renal function if CrCl 30-60 ml/min* or if on dabigatran and >75 years or fragile • Renal function if CrCl 15-30 ml/min* • If clinically indicated for conditions that may impact renal or hepatic function **NOTE: Declining renal function may require a DOAC dose adjustment (see FDA approved anticoagulants for dosing information).** **Edoxaban is contraindicated for atrial fibrillation in patients with CrCl >95.**

*CrCl determined using Cockcroft-Gault formula and actual body weight

Adapted from: Heidbuchel et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013. 15, 625-651. Doi: 10.1093/europace/eut083

MANAGEMENT PLAN FOLLOWING INITIATION OF DIRECT ORAL ANTICOAGULANTS (DOACs)
APIXABAN/DABIGATRAN/EDOXABAN/RIVAROXABAN



Discontinuation Guide for DOACs prior to Elective Procedures[1]

Renal function (CrCl)	Apixaban		Rivaroxaban		Dabigatran		Edoxaban	
	Low bleeding risk procedure	High bleeding risk procedure	Low bleeding risk procedure	High bleeding risk procedure	Low bleeding risk procedure	High bleeding risk procedure	Low bleeding risk procedure	High bleeding risk procedure
>50	Last dose: 2 days before procedure	Last dose: 3 days before procedure	Last dose: 2 days before procedure	Last dose: 3 days before procedure	Last dose: 2 days before procedure	Last dose: 3 days before procedure	Last dose: 2 days before procedure	Last dose: 3 days before procedure
30-50	Last dose: 3 days before procedure	Last dose:4 days before procedure	Last dose: 2 days before procedure	Last dose: 3 days before procedure	Last dose: 3 days before procedure	Last dose: 4-5 days before procedure	---	---
15-30	---	---	Last dose: 3 days before procedure	Last dose: 4 days before procedure	---	---	---	---

- **Bridging with LMWH is not generally necessary** due to the quick onset/offset of DOACs.
- Discontinuation of DOACs is not necessary for minimal bleeding risk procedures such as minor dermatological procedures, cataract procedures, and dental cleanings/fillings
- High bleeding risk procedures include: any major surgery with extensive tissue injury such as cancer surgeries, major orthopedic surgeries, and reconstructive plastic surgeries; urologic or gastrointestinal surgeries such as bowel resection, nephrectomy, kidney biopsy, and prostate resection; any cardiac, intracranial, or spinal surgery; or any other major operation (procedure duration >45 minutes) or surgery in a highly vascular organ (kidney, liver, spleen, etc.)
- For DOAC management around interventional pain procedures, see table below.

[1] New York State Anticoagulation Coalition and IPRO. Management of Anticoagulation in the Peri-Procedural Period. http://qio.ipro.org/wp-content/uploads/2012/12/MAP2014_5_01.pdf

Resumption of DOACs following Procedures[1]

Apixaban		Rivaroxaban		Dabigatran		Edoxaban	
Low bleeding risk procedure	High bleeding risk procedure	Low bleeding risk procedure	High bleeding risk procedure	Low bleeding risk procedure	High bleeding risk procedure	Low bleeding risk procedure	High bleeding risk procedure
Resume on day after procedure (24 hours)	Resume 2-3 days after procedure (48-72 hours)	Resume on day after procedure (24 hours)	Resume 2-3 days after procedure (48-72 hours)	Resume on day after procedure (24 hours)	Resume 2-3 days after procedure (48-72 hours)	Resume on day after procedure (24 hours)	Resume 2-3 days after procedure (48-72 hours)

[1] New York State Anticoagulation Coalition and IPRO. Management of Anticoagulation in the Peri-Procedural Period. http://qio.ipro.org/wp-content/uploads/2012/12/MAP2014_5_01.pdf

DOAC Reversal Options

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Drug-Specific reversal agent	Not available	Not available	Not available	Praxbind® (idarucizumab)[1]
Oral activated charcoal[2]	Yes (if ingested within 2 hours)	Yes (if ingested within 2 hours)	Unclear	Yes (if ingested within 2 hours)
Hemodialysis[2]	No	No	Unclear	Yes
Hemoperfusion with activated charcoal[2]	Possible	Possible	Unclear	Yes
FFP[2]	No	No	Unclear	No
Activated factor VIIa[2]	No	No	Unclear	No
3-factor PCC[2]	Unclear	Unclear	Unclear	Unclear
4-factor PCC[2]	Possible	Possible	Unclear	Possible (activated)

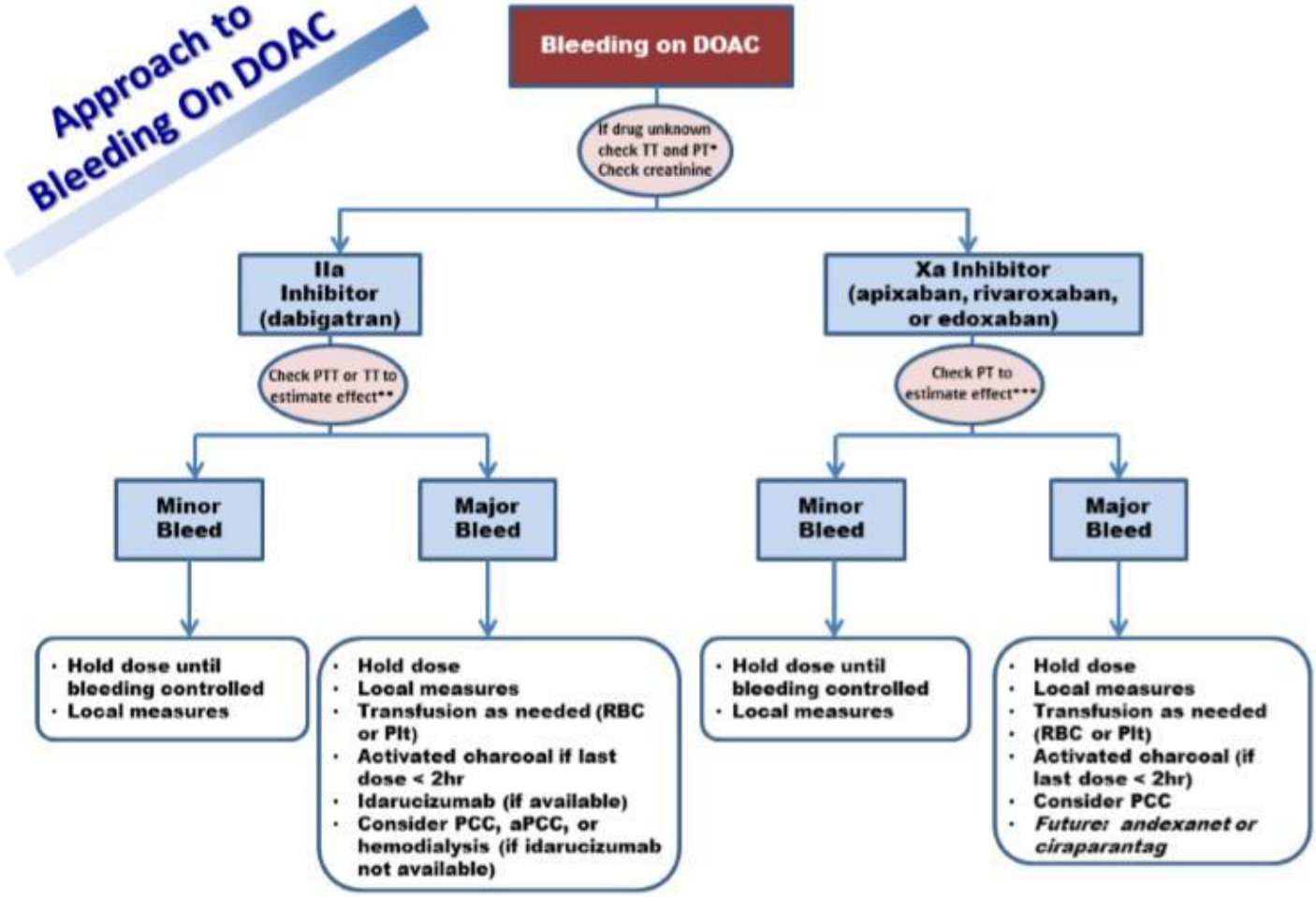
[1]Idarucizumab FDA approved Oct-2015 for reversing the anticoagulant effects of dabigatran.
[2]Rosenberg D, Ansell. Hosp Pract. 2012 Aug;40(3):50-7. doi: 10.3810/hp.2012.08.989.
[3] Crowther.M. Antidotes for Novel Oral Anticoagulants. Current Status and Future Potential. Arteriosclerosis, Thrombosis, and Vascular Biology. 2015; 35: 1736-1745. doi: 10.1161/ATVBAHA.114.303402

Drug Specific DOAC Reversal Agents

	DOAC(s) reversed	Indication(s)	Instructions	Warnings/Precautions
Praxbind® (idarucizumab)[1]	dabigatran	• For emergency surgery/urgent procedures • In life-threatening or uncontrolled bleeding	• Administer 5 g intravenously, provided as two separate 2.5 g/50 mL vials. • If administering through an existing intravenous line, flush with 0.9% Sodium Chloride Injection, USP solution prior to infusion. • No other infusion should be administered in parallel via the same intravenous access. • An additional 5 g dose may be administered after 12 to 24 hours if patient has reoccurrence of clinically relevant bleeding and elevated coagulation parameters (eg. aPTT, ECT)[2]	• Resume anticoagulation as soon as medically appropriate to reduce risk of thromboembolism. Dabigatran can be resumed after 24 hours • Idarucizumab contains 4g of sorbitol. In patients with hereditary fructose intolerance, consider the combined daily metabolic load of sorbitol/fructose from all sources, including idarucizumab and other drugs containing sorbitol to reduce risk of serious adverse reactions.

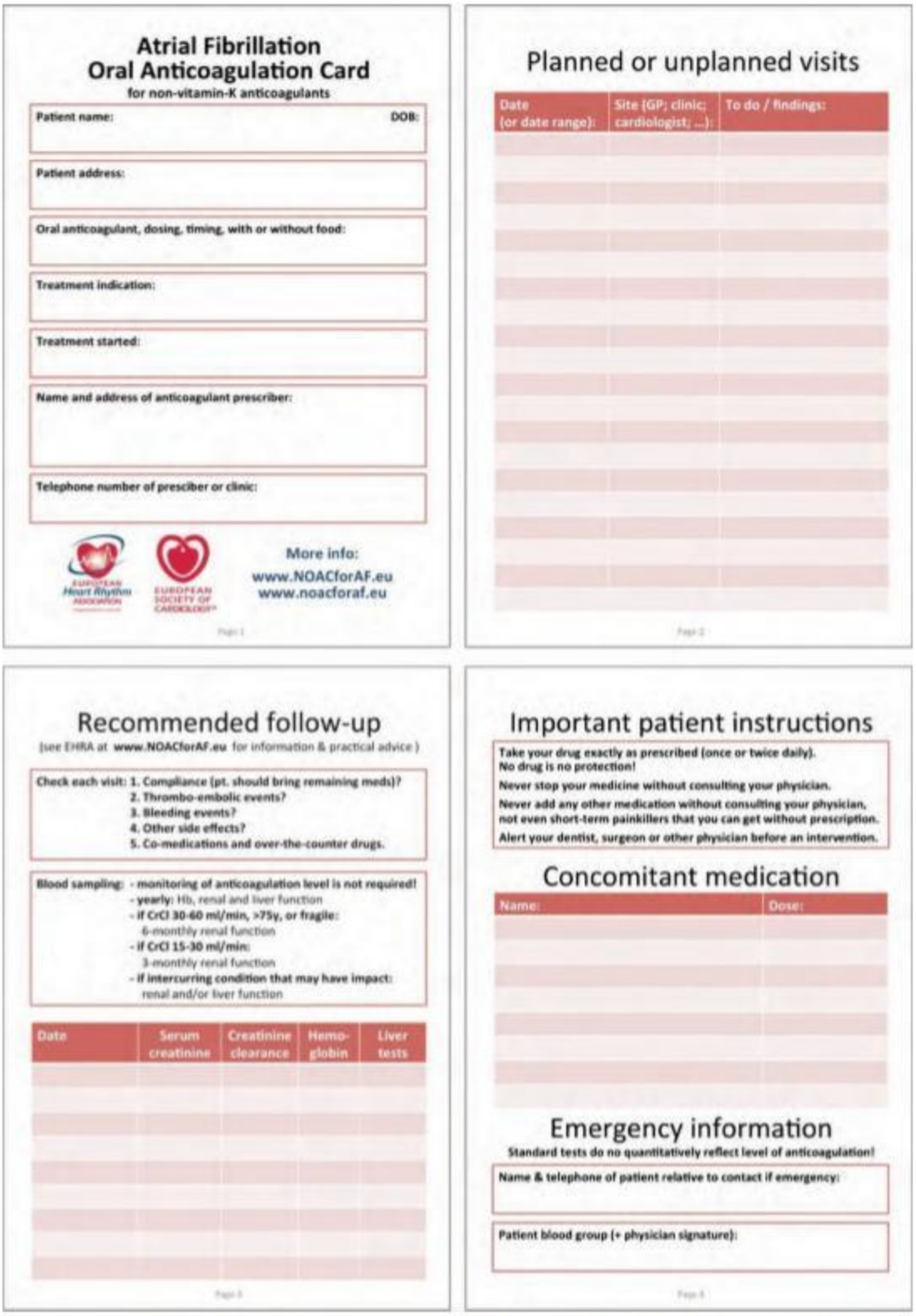
[1]http://us.boehringer-ingelheim.com/content/dam/internet/opu/us_EN/documents/Media_Press_Releases/2015/Praxbind.pdf
[2] The safety and effectiveness of repeat treatment with idarucizumab have not been established.

Bleeding Management in DOACs



* Normal TT suggests Xa inhibitor or IIa inhibitor at negligible concentration;
** Normal TT= negligible IIa inhibitor present; normal PTT does not exlcude significant IIa present, but suggests low concentration;
***Only rivaroxaban somewhat responsive to PT and only with some reagents; apixaban not responsive. Chromogenic anti-Xa assay is quantitative, but not readily available.

DOAC Patient Card Proposed by the European Heart Rhythm Association



Atrial Fibrillation
Oral Anticoagulation Card

for non-vitamin-K anticoagulants

Patient name: **DOB:**

Patient address:

Oral anticoagulant, dosing, timing, with or without food:

Treatment indication:

Treatment started:

Name and address of anticoagulant prescriber:

Telephone number of presciber or clinic:

More info:
www.NOACforAF.eu
www.noacforaf.eu

Planned or unplanned visits

Date (or date range):	Site (GP; clinic; cardiologist; ...):	To do / findings:

Recommended follow-up

(see EHRA at **www.NOACforAF.eu** for information & practical advice)

Check each visit:
1. Compliance (pt. should bring remaining meds)?
2. Thrombo-embolic events?
3. Bleeding events?
4. Other side effects?
5. Co-medications and over-the-counter drugs.

Blood sampling:
- monitoring of anticoagulation level is not required!
- **yearly:** Hb, renal and liver function
- **if CrCl 30-60 ml/min, >75y, or fragile:** 6-monthly renal function
- **if CrCl 15-30 ml/min:** 3-monthly renal function
- **if intercurring condition that may have impact:** renal and/or liver function

Date	Serum creatinine	Creatinine clearance	Hemo-globin	Liver tests

Important patient instructions

Take your drug exactly as prescribed (once or twice daily).
No drug is no protection!

Never stop your medicine without consulting your physician.

Never add any other medication without consulting your physician, not even short-term painkillers that you can get without prescription.

Alert your dentist, surgeon or other physician before an intervention.

Concomitant medication

Name:	Dose:

Emergency information

Standard tests do no quantitatively reflect level of anticoagulation!

Name & telephone of patient relative to contact if emergency:

Patient blood group (+ physician signature):

To print patient cards, go to: http://www.escardio.org/communities/EHRA/publications/novel-oral-anticoagulants-for-atrial-fibrillation/Documents/English-EHRA-DOAC-card-A7.pdf

Apixaban Dosing

- Non-valvular afib 5 mg twice daily
- Dose adjustment for NVAF pts w/following criteria to 2.5 mg twice daily
  - Age > 79 years
  - Body weight < 60 kg
  - Serum creatinine > 1.5 mg/dl

- DVT/PE 10 mg twice daily for the first 7 days Then 5 mg twice daily
- Reduction in the risk of recurrent DVT/PE following initial therapy
- 2.5 mg twice daily after at least 6 months of treatment for DVT/PE
- DVT/PE prophylaxis after orthopedic surgery
- 2.5 mg twice daily x35 days starting 12-24 hours after hip replacement surgery
- 2.5 mg twice daily for 12 days after 12-24 hours after knee replacement surgery

Onset of action

- Onset of action: 3-4 hours
- Protein Binding ~87%
- Metabolism: predominantly via CYP3A4/5
- Bioavailability ~50%
- Time to peak 3-4 hours
- ½ life: ~ 12 hours
- Excretion: Urine ~27% as parent drug, feces

Rivaroxaban Dosing

Nonvalvular Afib:

- 20 mg daily w/evening meal: Pts with CrCl>50 mL/min
- 15 mg daily w/evening meal Patients CrCl 15-50 mL/min

DVT/PE

- 15 mg TWICE daily x21 days
- Then 20 mg once daily w/food

Extended Treatment:

- 20 mg once daily with food

Orthopedic surgery Prophylaxis

Knee:

- 10 mg once daily x 12 days

Hip:

- 10 mg once daily x35 days
- Initial dose should be taken at least 6-10 hours after surgery once hemostasis established

Action profile

- Absorption: Rapid
- Protein Binding: ~92-95% primarily to albumin
- Metabolism: Hepatic via CYP3A4/5 and CYP2J2
- Bioavailability: Absolute bioavailability: 10 mg dose: ~80% to 100%; 20 mg dose: ~66% (fasting; increased with food)
- ½ life: 5-9 hours for healthy subjects 20-45 years 11-13 hours in the elderly
- Time to peak: 2-4 hours
- Excretion: Urine (66% primarily via active tubular secretion, feces

Dabigatran Dosing

Nonvalvular afib:

- 150 mg twice daily CrCl>30 mL/min
- 75 mg twice daily CrCl 15-30 mL/min

DVT/PE

- 5-10 days of parental anticoagulant (LMWH, Fondaparinux, IV unfractionated heparin

- Then: 150 mg twice daily

Action profile
- Absorption: Rapid, initially slow postoperatively
- Protein Binding 35%
- Metabolism: Hepatic; dabigatran etexilate is rapidly and completely hydrolyzed to dabigatran (active form) by plasma and hepatic esterases Bioavailability 3-7%
- ½ life: 12-17 hours; Elderly: 14-17 hours; Mild-to-moderate renal impairment: 15-18 hours; Severe renal impairment: 28 hours
- Time to Peak: plasma: Dabigatran: 1 hour; delayed 2 hours by food (no effect on bioavailability)
- Excreted: Urine (80%)

Dalteparin Dosing

prophylactic dose:
- 5,000 IU SC daily

DVT/PE dose:
- 200 IU/kg SC injection daily x 30 days
- Followed by 150 IU/kg for maintenance therapy
- Be aware of weight restrictions in obese pts

Syringe sizes:
- 5,000 IU
- 7,500 IU
- 10,000 IU
- 12,500 IU
- 15,000 IU
- 18,000 IU

Action profile
- Onset of action: 1-2 hours
- Protein binding: Low affinity for plasma proteins
- Bioavailability: SubQ: 81% to 93%
- ½ life elimination 3-5 h; 6-7h renal impairment
- Time to peak, serum: ~4 hours
- Excretion: Primarily renal

Enoxaparin Dosing

ACS: different protocols but used IV in PCI then:
- 1 mg/kg q 12
- 1.5 mg/kg q 24

DVT/PE
- 1 mg/kg q 12 or
- 1.5 mg/kg q 24

DVT prophylaxis medical/surgical pts
- Lovenox 40 mg daily
- Except: Total knee replacement - Lovenox 30 mg q 12

Bariatric surgery (Extremes of weight high Max dose is 150 mg)
:
- 40 mg q 12 or
- 60 mg q 12

Action profile
- Onset of action:3-5 hours

- Protein binding: does not bind to heparin binding proteins
- Metabolism: Hepatic, to lower molecular weight fragments (little activity)
- ½ life; 4.5 to 7 hours
- Excretion: Urine (40% of dose; 10% as active fragments)

Protamine dosage for LMWH

Enoxaparin

- Last dose administered in ≤8 hours: Dose of protamine should equal the dose of enoxaparin administered. Therefore, 1 mg of protamine sulfate neutralizes 1 mg of enoxaparin.
- Enoxaparin administered in > 8 hours or if it has been determined that a second dose of protamine is required (eg, if aPTT measured 2-4 hours after the first dose remains prolonged or if bleeding continues): 0.5 mg of protamine sulfate for every 1 mg of enoxaparin administered

Dalteparin

- 1 mg protamine for each 100 anti-Xa units of dalteparin if PTT prolonged 2-4 hours after first dose (or if bleeding continues), consider additional dose of 0.5 mg for each 100 anti-Xa units of dalteparin or tinzaparin. •
- Note check allergies, fish allergy Protamine contraindicated
- Use caution in male pts w/surgical history of vasectomy

Fondaparinux Dosing

- Prophylactic Dose: in adults pts > 50 kg 2.5 mg SC daily
- Acute DVT/PE:
    - < 50 kg: 5 mg SC injection daily
    - 50-100 kg: 7.5 mg SC injection daily
    - >100 kg: 10 mg SC injection daily
- May be a better option for morbidly obese pts (trials included pts up to 180 kg)
- Case reports of Fondaparinux induced “HIT”

Anticoagulation Links

Organization	Link	Description
Anticoagulation Forum	http://acforum.org	The largest peer organization of anticoagulant service providers in North America. Members include international anticoagulation experts that provide education and guidance for applying the latest research into practice.
Anticoagulation Centers of Excellence	http://excellence.acforum.org/	Part of the Anticoagulation Forum, this program offers providers guidelines, tools, and other information in order to achieve the highest possible level of care and improve outcomes.
American College of Chest Physicians-Antithrombotic Guidelines	http://www.chestnet.org/Guidelines-and-Resources/Guidelines-and-Consensus-Statements/Antithrombotic-Guidelines-9th-Ed	A leading source for evidence-based antithrombotic guidelines.
American College of Physicians Atrial Fibrillation patient resources	• Afib-What you and your family should know (pamphlet) • Afib-What you and your family should know (video) • Stroke and Stroke Risk (video) • Afib Medications (video) • Afib Self Management (video)	Excellent resources for providers to give to patients with AF. Hard copies of the pamphlet and DVD copies of the videos can be ordered for free from this link
Society of Vascular Medicine	• Online shared decision making tool for anticoagulant choice in AF: http://www.mybloodclots.org/ • Online toolkit to help providers develop an outpatient DVT diagnosis and treatment pathway: www.mydeepveinthrombosis.com/	Society of Vascular Medicine (http://www.vascularmed.org/) is a professional organization that was founded in 1989 to foster a broad mission. The goals of the Society are to improve the integration of vascular biological advances into medical practice, and to maintain high standards of clinical vascular medicine.

Antithrombotic Therapy and Prevention of Thrombosis, 9th Ed: American College of Chest Physicians Evidence-Based

Executive Summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Prevention of VTE in Nonsurgical Patients

2.0 Hospitalized Acutely Ill Medical Patients

2.3. For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with low-molecular-weight heparin [LMWH], low-dose unfractionated heparin (LDUH) bid, LDUH tid, or fondaparinux (Grade 1B)**.**

Remarks: In choosing the specific anticoagulant drug to be used for pharmacoprophylaxis, choices should be based on patient preference, compliance, and ease of administration (eg, daily vs bid vs tid dosing), as well as on local factors affecting acquisition costs (eg, prices of various pharmacologic agents in individual hospital formularies)**.**

2.4. For acutely ill hospitalized medical patients at low risk of thrombosis, we recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis (Grade 1B)**.**

2.7.1. For acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding, we recommend against anticoagulant thromboprophylaxis (Grade 1B)**.**

2.7.2. For acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding, we suggest the optimal use of mechanical thromboprophylaxis with graduated compression stockings (GCS) (Grade 2C) **or intermittent pneumatic compression (IPC)** (Grade 2C)**, rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis** (Grade 2B)**.**

Remarks: Patients who are particularly averse to the potential for skin complications, cost, and need for clinical monitoring of GCS and IPC use are likely to decline mechanical prophylaxis.

2.8. In acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (Grade 2B)**.**

3.0 Critically Ill Patients

3.2. In critically ill patients, we suggest against routine ultrasound screening for DVT (Grade 2C)**.**

3.4.3. For critically ill patients, we suggest using LMWH or LDUH thromboprophylaxis over no prophylaxis (Grade 2C)**.**

3.4.4. For critically ill patients who are bleeding, or are at high risk for major bleeding, we suggest mechanical thromboprophylaxis with GCS (Grade 2C) **or IPC** (Grade 2C) **until the bleeding risk decreases, rather than no mechanical thromboprophylaxis. When bleeding risk decreases, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis** (Grade 2C)**.**

4.0 Patients With Cancer in the Outpatient Setting

4.2.1. In outpatients with cancer who have no additional risk factors for VTE, we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) **and recommend against the prophylactic use of VKAs** (Grade 1B)**.**

Remarks: Additional risk factors for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

4.2.2. In outpatients with solid tumors who have additional risk factors for VTE and who are at low risk of bleeding, we suggest prophylactic-dose LMWH or LDUH over no prophylaxis (Grade 2B)**.**

Remarks: Additional risk factors for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

4.4. In outpatients with cancer and indwelling central venous catheters, we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) **and suggest against the prophylactic use of VKAs** (Grade 2C)**.**

5.0 Chronically Immobilized Patients

5.1. In chronically immobilized persons residing at home or at a nursing home, we suggest against the routine use of thromboprophylaxis (Grade 2C)**.**

6.0 Persons Traveling Long-Distance

6.1.1. For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), we suggest frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible (Grade 2C)**.**

6.1.2. For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), we suggest use of properly fitted, below-knee GCS providing 15 to 30 mm Hg of pressure at the ankle during travel (Grade 2C). **For all other long-distance travelers, we suggest against the use of GCS** (Grade 2C)**.**

6.1.3. For long-distance travelers, we suggest against the use of aspirin or anticoagulants to prevent VTE (Grade 2C)**.**

7.0 Persons With Asymptomatic Thrombophilia

7.1. In persons with asymptomatic thrombophilia (ie, without a previous history of VTE), we recommend against the long-term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE (Grade 1C)**.**

Prevention of VTE in Nonorthopedic Surgical Patients

3.6 Patients Undergoing General, GI, Urological, Gynecologic, Bariatric, Vascular, Plastic, or Reconstructive Surgery

3.6.1. For general and abdominal-pelvic surgery patients at very low risk for VTE (< 0.5%; Rogers score, < 7; Caprini score, 0), we recommend that no specific pharmacologic (Grade 1B) **or mechanical** (Grade 2C) **prophylaxis be used other than early ambulation.**

3.6.2. For general and abdominal-pelvic surgery patients at low risk for VTE (∼1.5%; Rogers score, 7-10; Caprini score, 1-2), we suggest mechanical prophylaxis, preferably with intermittent pneumatic compression (IPC), over no prophylaxis (Grade 2C)**.**

3.6.3. For general and abdominal-pelvic surgery patients at moderate risk for VTE (∼3.0%; Rogers score, > 10; Caprini score, 3-4) who are not at high risk for major bleeding complications, we suggest LMWH (Grade 2B)**, LDUH** (Grade 2B)**, or mechanical prophylaxis, preferably with IPC** (Grade 2C)**, over no prophylaxis.**

Remarks: Three of the seven authors favored a strong (Grade 1B) recommendation in favor of LMWH or LDUH over no prophylaxis in this group.

3.6.4. For general and abdominal-pelvic surgery patients at moderate risk for VTE (3.0%; Rogers score, > 10; Caprini score, 3-4) who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C)**.**

3.6.5. For general and abdominal-pelvic surgery patients at high risk for VTE (∼6.0%; Caprini score, ≥ 5) who are not at high risk for major bleeding complications, we recommend pharmacologic prophylaxis with LMWH (Grade 1B) **or LDUH** (Grade 1B) **over no prophylaxis. We suggest that mechanical prophylaxis with elastic stockings or IPC should be added to pharmacologic prophylaxis** (Grade 2C)**.**

3.6.6. For high-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, we recommend extended-duration pharmacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis (Grade 1B)**.**

Remarks: Patients who place a high value on minimizing out-of-pocket health-care costs might prefer limited-duration over extended-duration prophylaxis in settings where the cost of extended-duration prophylaxis is borne by the patient.

3.6.7. For high-VTE-risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, we suggest use of mechanical prophylaxis, preferably with IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C)**.**

3.6.8. For general and abdominal-pelvic surgery patients at high risk for VTE (6%; Caprini score, ≥ 5) in whom both LMWH and unfractionated heparin are contraindicated or unavailable and who are not at high risk for major bleeding complications, we suggest low-dose aspirin (Grade 2C)**, fondaparinux** (Grade 2C)**, or mechanical prophylaxis, preferably with IPC** (Grade 2C)**, over no prophylaxis.**

3.6.9. For general and abdominal-pelvic surgery patients, we suggest that an inferior vena cava (IVC) filter should not be used for primary VTE prevention (Grade 2C)**.**

3.6.10. For general and abdominal-pelvic surgery patients, we suggest that periodic surveillance with venous compression ultrasound should not be performed (Grade 2C)**.**

4.0 Patients Undergoing Cardiac Surgery

4.4.1. For cardiac surgery patients with an uncomplicated postoperative course, we suggest use of mechanical prophylaxis, preferably with optimally applied IPC, over either no prophylaxis (Grade 2C) or pharmacologic prophylaxis (Grade 2C)**.**

4.4.2. For cardiac surgery patients whose hospital course is prolonged by one or more nonhemorrhagic surgical complications, we suggest adding pharmacologic prophylaxis with LDUH or LMWH to mechanical prophylaxis (Grade 2C)**.**

5.0 Patients Undergoing Thoracic Surgery

5.4.1. For thoracic surgery patients at moderate risk for VTE who are not at high risk for perioperative bleeding, we suggest LDUH (Grade 2B)**, LMWH** (Grade 2B)**, or mechanical prophylaxis with optimally applied IPC** (Grade 2C) **over no prophylaxis.**

Remarks: Three of the seven authors favored a strong (Grade 1B) recommendation in favor of LMWH or LDUH over no prophylaxis in this group.

5.4.2. For thoracic surgery patients at high risk for VTE who are not at high risk for perioperative bleeding, we suggest LDUH (Grade 1B) **or LMWH** (Grade 1B) **over no prophylaxis. In addition, we suggest that mechanical prophylaxis with elastic stockings or IPC should be added to pharmacologic prophylaxis** (Grade 2C)**.**

5.4.3. For thoracic surgery patients who are at high risk for major bleeding, we suggest use of mechanical prophylaxis, preferably with optimally applied IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C)**.**

6.0 Patients Undergoing Craniotomy

6.4.1. For craniotomy patients, we suggest that mechanical prophylaxis, preferably with IPC, be used over no prophylaxis (Grade 2C) or pharmacologic prophylaxis (Grade 2C)**.**

6.4.2. For craniotomy patients at very high risk for VTE (eg, those undergoing craniotomy for malignant disease), we suggest adding pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases (Grade 2C)**.**

7.0 Patients Undergoing Spinal Surgery

7.4.1. For patients undergoing spinal surgery, we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C)**, unfractionated heparin** (Grade 2C)**, or LMWH** (Grade 2C)**.**

7.4.2. For patients undergoing spinal surgery at high risk for VTE (including those with malignant disease or those undergoing surgery with a combined anterior-posterior approach), we suggest adding pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases (Grade 2C)**.**

8.0 Patients With Major Trauma: Traumatic Brain Injury, Acute Spinal Injury, and Traumatic Spine Injury

8.4.1. For major trauma patients, we suggest use of LDUH (Grade 2C), LMWH (Grade 2C), or mechanical prophylaxis, preferably with IPC (Grade 2C)**, over no prophylaxis.**

8.4.2. For major trauma patients at high risk for VTE (including those with acute spinal cord injury, traumatic brain injury, and spinal surgery for trauma), we suggest adding mechanical prophylaxis to pharmacologic prophylaxis (Grade 2C) **when not contraindicated by lower-extremity injury.**

8.4.3. For major trauma patients in whom LMWH and LDUH are contraindicated, we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C) **when not contraindicated by lower-extremity injury. We suggest adding pharmacologic prophylaxis with either LMWH or LDUH when the risk of bleeding diminishes or the contraindication to heparin resolves** (Grade 2C)**.**

8.4.4. For major trauma patients, we suggest that an IVC filter should not be used for primary VTE prevention (Grade 2C)**.**

8.4.5. For major trauma patients, we suggest that periodic surveillance with venous compression ultrasound should not be performed (Grade 2C)**.**

Prevention of VTE in Orthopedic Surgery Patients

2.0 Patients Undergoing Major Orthopedic Surgery: Total Hip Arthroplasty (THA), Total Knee Arthroplasty (TKA), Hip Fracture Surgery (HFS)

2.1.1. In patients undergoing THA or TKA, we recommend use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis: low-molecular-weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted-dose VKA, aspirin (all Grade 1B)**, or an intermittent pneumatic compression device (IPCD)** (Grade 1C)**.**

Remarks: We recommend the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18 h of daily compliance. One panel member believed strongly that aspirin alone should not be included as an option.

2.1.2. In patients undergoing HFS, we recommend use of one of the following rather than no antithrombotic prophylaxis for a minimum of 10 to 14 days: LMWH, fondaparinux, LDUH, adjusted-dose VKA, aspirin (all Grade 1B)**, or an IPCD** (Grade 1C)**.**

Remarks: We recommend the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18 h of daily compliance. One panel member believed strongly that aspirin alone should not be included as an option.

2.2. For patients undergoing major orthopedic surgery (THA, TKA, HFS) and receiving LMWH as thromboprophylaxis, we recommend starting either 12 h or more preoperatively or 12 h or more postoperatively rather than within 4 h or less preoperatively or 4 h or less postoperatively (Grade 1B)**.**

2.3.1. In patients undergoing THA or TKA, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents we have recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH (all Grade 2B)**, adjusted-dose VKA, or aspirin** (all Grade 2C)**.**

Remarks: If started preoperatively, we suggest administering LMWH ≥ 12 h before surgery. Patients who place a high value on avoiding the inconvenience of daily injections with LMWH and a low value on the limitations of alternative agents are likely to choose an alternative agent. Limitations of alternative agents include the possibility of increased bleeding (which may occur with fondaparinux, rivaroxaban, and VKA), possible decreased efficacy (LDUH, VKA, aspirin, and IPCD alone), and lack of long-term safety data (apixaban, dabigatran, and rivaroxaban). Furthermore, patients who place a high value on avoiding bleeding complications and a low value on its inconvenience are likely to choose an IPCD over the drug options.

2.3.2. In patients undergoing HFS, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents we have recommended as alternatives: fondaparinux, LDUH (Grade 2B)**, adjusted-dose VKA, or aspirin** (all Grade 2C)**.**

Remarks: For patients in whom surgery is likely to be delayed, we suggest that LMWH be initiated during the time between hospital admission and surgery but suggest administering LMWH at least 12 h before surgery. Patients who place a high value on avoiding the inconvenience of daily injections with LMWH and a low value on the limitations of alternative agents are likely to choose an alternative agent. Limitations of alternative agents include the possibility of increased bleeding (which may occur with fondaparinux) or possible decreased efficacy (LDUH, VKA, aspirin, and IPCD alone). Furthermore, patients who place a high value on avoiding bleeding complications and a low value on its inconvenience are likely to choose an IPCD over the drug options.

2.4. For patients undergoing major orthopedic surgery, we suggest extending thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days (Grade 2B)**.**

2.5. In patients undergoing major orthopedic surgery, we suggest using dual prophylaxis with an antithrombotic agent and an IPCD during the hospital stay (Grade 2C)**.**

Remarks: We recommend the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18 h of daily compliance. Patients who place a high value on avoiding the undesirable consequences associated with prophylaxis with both a pharmacologic agent and an IPCD are likely to decline use of dual prophylaxis.

2.6. In patients undergoing major orthopedic surgery and increased risk of bleeding, we suggest using an IPCD or no prophylaxis rather than pharmacologic treatment (Grade 2C)**.**

Remarks: We recommend the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18 h of daily compliance. Patients who place a high value on avoiding the discomfort and inconvenience of IPCD and a low value on avoiding a small absolute increase in bleeding with pharmacologic agents when only one bleeding risk factor is present (in particular the continued use of antiplatelet agents) are likely to choose pharmacologic thromboprophylaxis over IPCD.

2.7. In patients undergoing major orthopedic surgery and who decline or are uncooperative with injections or an IPCD, we recommend using apixaban or dabigatran (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran are unavailable) rather than alternative forms of prophylaxis (all Grade 1B)**.**

2.8. In patients undergoing major orthopedic surgery, we suggest against using IVC filter placement for primary prevention over no thromboprophylaxis in patients with an increased bleeding risk or contraindications to both pharmacologic and mechanical thromboprophylaxis (Grade 2C)**.**

2.9. For asymptomatic patients following major orthopedic surgery, we recommend against Doppler (or duplex) ultrasound screening before hospital discharge (Grade 1B)**.**

3.0 Patients With Isolated Lower-Leg Injuries Distal to the Knee

3.0. We suggest no prophylaxis rather than pharmacologic thromboprophylaxis in patients with isolated lower-leg injuries requiring leg immobilization (Grade 2C)**.**

4.0 Patients Undergoing Knee Arthroscopy

4.0. For patients undergoing knee arthroscopy without a history of prior VTE, we suggest no thromboprophylaxis rather than prophylaxis (Grade 2B)**.**

Perioperative Management of Antithrombotic Therapy

2.1 Interruption of VKAs Before Surgery

2.1. In patients who require temporary interruption of a VKA before surgery, we recommend stopping VKAs approximately 5 days before surgery *instead of* stopping VKAs a shorter time before surgery (Grade 1C)**.**

2.2 Resumption of VKAs After Surgery

2.2. In patients who require temporary interruption of a VKA before surgery, we recommend resuming VKAs approximately 12 to 24 h after surgery (evening of or next morning) and when there is adequate hemostasis *instead of* later resumption of VKAs (Grade 2C)**.**

2.4 Bridging Anticoagulation During Interruption of VKA Therapy

2.4. In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, we suggest bridging anticoagulation*instead of***no bridging during interruption of VKA therapy** (Grade 2C)**.**

Remarks: Patients who place a higher value on avoiding perioperative bleeding than on avoiding perioperative thromboembolism are likely to decline heparin bridging.

In patients with a mechanical heart valve, atrial fibrillation, or VTE at low risk for thromboembolism, we suggest no bridging *instead of* bridging anticoagulation during interruption of VKA therapy (Grade 2C)**.**

In patients with a mechanical heart valve, atrial fibrillation, or VTE at moderate risk for thromboembolism, the bridging or no-bridging approach chosen is, as in the higher- and lower-risk patients, based on an assessment of individual patient- and surgery-related factors.

2.5 Perioperative Management of VKA-Treated Patients Who Require Minor Procedures

2.5. In patients who require a minor dental procedure, we suggest continuing VKAs with coadministration of an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure *instead of* alternative strategies (Grade 2C)**. In patients who require minor dermatologic procedures and are receiving VKA therapy, we suggest continuing VKAs around the time of the procedure and optimizing local hemostasis *instead of* other strategies** (Grade 2C)**. In patients who require cataract surgery and are receiving VKA therapy, we suggest continuing VKAs around the time of the surgery *instead of* other strategies** (Grade 2C)**.**

3.4 Patients Undergoing a Minor Dental, Dermatologic, or Ophthalmologic Procedure

3.4. In patients who are receiving acetylsalicylic acid (ASA) for the secondary prevention of cardiovascular disease and are having minor dental or dermatologic procedures or cataract surgery, we suggest continuing ASA around the time of the procedure *instead of* stopping ASA 7 to 10 days before the procedure (Grade 2C)**.**

3.5. In patients at moderate to high risk for cardiovascular events who are receiving ASA therapy and require noncardiac surgery, we suggest continuing ASA around the time of surgery *instead of* stopping ASA 7 to 10 days before surgery (Grade 2C)**. In patients at low risk for cardiovascular events who are receiving ASA therapy, we suggest stopping ASA 7 to 10 days before surgery *instead of* continuation of ASA** (Grade 2C)**.**

3.6 Patients Undergoing Coronary Artery Bypass Graft Surgery

3.6. In patients who are receiving ASA and require coronary artery bypass graft (CABG) surgery, we suggest continuing ASA around the time of surgery *instead of* stopping ASA 7 to 10 days before surgery (Grade 2C)**. In patients who are receiving dual antiplatelet drug therapy and require CABG surgery, we suggest continuing ASA around the time of surgery and stopping clopidogrel/prasugrel 5 days before surgery *instead of* continuing dual antiplatelet therapy around the time of surgery** (Grade 2C)**.**

3.7 Surgical Patients With Coronary Stents

3.7. In patients with a coronary stent who are receiving dual antiplatelet therapy and require surgery, we recommend deferring surgery for at least 6 weeks after placement of a bare-metal stent and for at least 6 months after placement of a drug-eluting stent *instead of* undertaking surgery within these time periods (Grade 1C)**. In patients who require surgery within 6 weeks of placement of a bare-metal stent or within 6 months of placement of a drug-eluting stent, we suggest continuing dual antiplatelet therapy around the time of surgery *instead of* stopping dual antiplatelet therapy 7 to 10 days before surgery** (Grade 2C)**.**

Remarks: Patients who are more concerned about avoiding the unknown, but potentially large increase in bleeding risk associated with the perioperative continuation of dual antiplatelet therapy than avoiding the risk for coronary stent thrombosis are unlikely to choose continuation of dual antiplatelet therapy.

4.2 Perioperative Use of IV UFH

4.2. In patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH, we suggest stopping UFH 4 to 6 h before surgery *instead of* closer to surgery (Grade 2C)**.**

4.3 Preoperative Interruption of Therapeutic-Dose Bridging LMWH

4.3. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH, we suggest administering the last preoperative dose of LMWH approximately 24 h before surgery *instead of* 12 h before surgery (Grade 2C)**.**

4.4 Postoperative Resumption of Therapeutic-Dose Bridging LMWH

4.4. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high-bleeding-risk surgery, we suggest resuming therapeutic-dose LMWH 48 to 72 h after surgery *instead of* resuming LMWH within 24 h after surgery (Grade 2C)**.**

Diagnosis of DVT

3.0 Diagnosis of Suspected First Lower Extremity DVT

3.1. In patients with a suspected first lower extremity DVT, we suggest that the choice of diagnostic tests process should be guided by the clinical assessment of pretest probability rather than by performing the same diagnostic tests in all patients (Grade 2B)**.**

Remarks: In considering this recommendation, five panelists voted for a strong recommendation and four voted for a weak recommendation (one declined to vote and two did not participate). According to predetermined criteria, this resulted in weak recommendation.

3.2. In patients with a low pretest probability of first lower extremity DVT, we recommend one of the following initial tests: (i) a moderately sensitive D-dimer, (ii) a highly sensitive D-dimer, or (iii) compression ultrasound (CUS) of the proximal veins rather than (i) no diagnostic testing (Grade 1B for all comparisons)**, (ii) venography** (Grade 1B for all comparisons)**, or (iii) whole-leg ultrasound (US)** (Grade 2B for all comparisons)**. We suggest initial use of a moderately sensitive** (Grade 2C) **or highly sensitive** (Grade 2B) **D-dimer rather than proximal CUS.**

Remarks: The choice between a moderately sensitive D-dimer test, a highly sensitive D-dimer test, or proximal CUS as the initial test will depend on local availability, access to testing, costs of testing, and the probability of obtaining a negative D-dimer result if DVT is not present. Initial testing with US would be preferred if the patient has a comorbid condition associated with elevated D-dimer levels and is likely to have a positive D-dimer result, even if DVT is absent. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest CT scan venography or magnetic resonance (MR) venography, or MR direct thrombus imaging could be used as an alternative to venography.

If the D-dimer is negative, we recommend no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons)**. If the proximal CUS is negative, we recommend no further testing compared with (i) repeat proximal CUS after 1 week, (ii) whole-leg US, or (iii) venography** (Grade 1B for all comparisons)**.**

If the D-dimer is positive, we suggest further testing with CUS of the proximal veins rather than (i) whole-leg US (Grade 2C) **or (ii) venography** (Grade 1B)**. If CUS of the proximal veins is positive, we suggest treating for DVT and performing no further testing over performing confirmatory venography** (Grade 2C)**.**

Remarks: In circumstances when high-quality venography is available, patients who are not averse to the discomfort of venography, are less concerned about the complications of venography, and place a high value on avoiding treatment of false-positive results are likely to choose confirmatory venography if findings for DVT are less certain (eg, a short segment of venous noncompressibility)**.**

3.3. In patients with a moderate pretest probability of first lower extremity DVT, we recommend one of the following initial tests: (i) a highly sensitive D-dimer or (ii) proximal CUS, or (iii) whole-leg US rather than (i) no testing (Grade 1B for all comparisons) **or (ii) venography** (Grade 1B for all comparisons)**. We suggest initial use of a highly sensitive D-dimer rather than US** (Grade 2C)**.**

Remarks: The choice between a highly sensitive D-dimer test or US as the initial test will depend on local availability, access to testing, costs of testing, and the probability of obtaining a negative D-dimer result if DVT is not present. Initial testing with US may be preferred if the patient has a comorbid condition associated with elevated D-dimer levels and is likely to have a positive D-dimer

result even if DVT is absent. Whole-leg US may be preferred in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

If the highly sensitive D-dimer is negative, we recommend no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons)**. If the highly sensitive D-dimer is positive, we recommend proximal CUS or whole-leg US rather than no testing** (Grade 1B for all comparisons) **or venography** (Grade 1B for all comparisons)**.**

If proximal CUS is chosen as the initial test and is negative, we recommend (i) repeat proximal CUS in 1 week or (ii) testing with a moderate or highly sensitive D-dimer assay over no further testing (Grade 1C) **or venography** (Grade 2B)**. In patients with a negative proximal CUS but a positive D-dimer, we recommend repeat proximal CUS in 1 week over no further testing** (Grade 1B) **or venography** (Grade 2B)**.**

In patients with (i) negative serial proximal CUS or (ii) a negative single proximal CUS and negative moderate or highly sensitive D-dimer, we recommend no further testing rather than further testing with (i) whole-leg US or (ii) venography (Grade 1B for all comparisons)**.**

If whole-leg US is negative, we recommend no further testing over (i) repeat US in one week, (ii) D-dimer testing, or (iii) venography (Grade 1B for all comparisons)**. If proximal CUS is positive, we recommend treating for DVT rather than confirmatory venography** (Grade 1B). **If isolated distal DVT is detected on whole-leg US, we suggest serial testing to rule out proximal extension over treatment** (Grade 2C)**.**

Remarks: Patients with abnormal isolated distal US findings on whole-leg US who place a high value on avoiding the inconvenience of repeat testing and a low value on avoiding treatment of false-positive results are likely to choose treatment over repeat US. Patients with severe symptoms and risk factors for extension as outlined in Perioperative Management of Antithrombotic Therapy. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines are more likely to benefit from treatment over repeat US.

3.4. In patients with a high pretest probability of first lower extremity DVT, we recommend either (i) proximal CUS or (ii) whole-leg US over no testing (Grade 1B for all comparisons) **or venography** (Grade 1B for all comparisons)**.**

Remarks: Whole-leg US may be preferred to proximal CUS in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT. In patients with extensive unexplained leg swelling, if there is no DVT on proximal CUS or whole-leg US and d-dimer testing has not been performed or is positive, the iliac veins should be imaged to exclude isolated iliac DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

If proximal CUS or whole-leg US is positive for DVT, we recommend treatment rather than confirmatory venography (Grade 1B)**.**

In patients with a negative proximal CUS, we recommend additional testing with a highly sensitive D-dimer or whole-leg US or repeat proximal CUS in 1 week over no further testing (Grade 1B for all comparisons) **or venography** (Grade 2B for all comparisons)**. We recommend that patients with a single negative proximal CUS and positive D-dimer undergo whole-leg US or repeat proximal CUS in 1 week over no further testing** (Grade 1B) **or venography** (Grade 2B)**. In patients with negative serial proximal CUS, a negative single proximal CUS and negative highly sensitive D-dimer, or a negative whole-leg US, we recommend no further testing over venography or additional US** (Grade 1B for negative serial proximal CUS and for negative single proximal CUS and highly sensitive D-dimer; Grade 2B for negative whole-leg US)**.**

We recommend that in patients with high pretest probability, moderately or highly sensitive D-dimer assays should not be used as stand-alone tests to rule out DVT (Grade 1B)**.**

3.5. If risk stratification is not performed in patients with suspected first lower extremity DVT, we recommend one of the following initial tests: (i) proximal CUS or (ii) whole-leg US rather than (i) no testing (Grade 1B)**, (ii) venography** (Grade 1B)**, or D-dimer testing** (Grade 2B)**.**

Remarks: Whole-leg US may be preferred to proximal CUS in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT or risk factors for extension of distal DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest that CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

We recommend that patients with a negative proximal CUS undergo testing with a moderate- or high-sensitivity D-dimer, whole-leg US, or repeat proximal CUS in 1 week over no further testing (Grade 1B) **or venography** (Grade 2B)**. In patients with a negative proximal CUS, we suggest D-dimer rather than routine serial CUS** (Grade 2B) **or whole-leg US** (Grade 2C)**. We recommend that patients with a single negative proximal CUS and positive D-dimer undergo further testing with repeat proximal CUS in 1 week or whole-leg US rather than no further testing** (Grade 1B for both comparisons)**.**

We recommend that in patients with (i) negative serial proximal CUS, (ii) a negative D-dimer following a negative initial proximal CUS, or (iii) negative whole-leg US, no further testing be performed rather than venography (Grade 1B)**.**

If proximal US is positive for DVT, we recommend treatment rather than confirmatory venography (Grade 1B)**. If isolated distal DVT is detected on whole-leg US, we suggest serial testing to rule out proximal extension over treatment** (Grade 2C)**.**

Remarks: Patients with abnormal isolated distal US findings on whole-leg US who place a high value on avoiding the inconvenience of repeat testing and a low value on avoiding treatment of false-positive results are likely to choose treatment over repeat US. Patients with severe symptoms and risk factors for extension as outlined in "Perioperative Management of Antithrombotic Therapy. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines" are more likely to benefit from treatment over repeat US.

3.6. In patients with suspected first lower extremity DVT, we recommend against the routine use of CT venography or MRI (Grade 1C)**.**

4.1 Venography in Patients With Suspected Recurrent DVT

4.1. In patients suspected of having recurrent lower extremity DVT, we recommend initial evaluation with proximal CUS or a highly sensitive D-dimer over venography, CT venography, or MRI (all Grade 1B)**.**

Remarks: Initial D-dimer testing with a high-sensitivity assay is preferable if prior US is not available for comparison.

If the highly sensitive D-dimer is positive, we recommend proximal CUS over venography, CT venography, or MRI (Grade 1B for all comparisons)**.**

In patients with suspected recurrent lower extremity DVT in whom initial proximal CUS is negative (normal or residual diameter increase of < 2 mm), we suggest at least one further proximal CUS (day 7 ± 1) or testing with a moderately or highly sensitive D-dimer (followed by repeat CUS [day 7 ± 1] if positive) rather than no further testing or venography (Grade 2B)**.**

Remarks: In patients with an abnormal proximal CUS at presentation that does not meet the criteria for the diagnosis of recurrence, an additional proximal CUS on day 2 ± 1 in addition to that on (day 7 ± 1) may be preferred. Patients who place a high value on an accurate diagnosis and a low value on avoiding the inconvenience and potential side effects of a venography are likely to choose venography over missed diagnosis (in the case of residual diameter increase of < 2 mm)**.**

We recommend that patients with suspected recurrent lower extremity DVT and a negative highly sensitive D-dimer or negative proximal CUS and negative moderately or highly sensitive D-dimer or negative serial proximal CUS undergo no further testing for suspected recurrent DVT rather than venography (Grade 1B)**.**

If CUS of the proximal veins is positive, we recommend treating for DVT and performing no further testing over performing confirmatory venography (Grade 1B for the finding of a new noncompressible segment in the common femoral or popliteal vein, Grade 2B for a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result)**.**

Remarks: Patients with US abnormalities at presentation that do not include a new noncompressible segment who place a high value on an accurate diagnosis and a low value on avoiding the inconvenience and potential side effects of a venography are likely to choose venography over treatment (in the case of ≥ 4-mm increase in venous diameter)**.**

4.2 Compression Ultrasonography in Patients With Suspected Recurrent DVT

4.2. In patients with suspected recurrent lower extremity DVT and abnormal but nondiagnostic US results (eg, an increase in residual venous diameter of < 4 but ≥ 2 mm), we recommend further testing with venography, if available (Grade 1B)**; serial proximal CUS** (Grade 2B) **or testing with a moderately or highly sensitive D-dimer with serial proximal CUS as above if the test is positive** (Grade 2B)**, as opposed to other testing strategies or treatment.**

4.3 Pretest Probability Assessment in Patients With Suspected Recurrent DVT

4.3. In patients with suspected recurrent ipsilateral DVT and an abnormal US without a prior result for comparison, we recommend further testing with venography, if available (Grade 1B) **or a highly sensitive D-dimer** (Grade 2B) **over serial proximal CUS. In patients with suspected recurrent ipsilateral DVT and an abnormal US without prior result for comparison and a negative highly sensitive D-dimer, we suggest no further testing over venography** (Grade 2C)**. In patients with suspected recurrent**

ipsilateral DVT and an abnormal US without prior result for comparison and a positive highly sensitive D-dimer, we suggest venography if available over empirical treatment of recurrence (Grade 2C)**.**

Remarks: Patients who place a high value on avoiding the inconvenience and potential side effects of a venography are likely to choose treatment over venography.

5.1 Venography in Pregnancy-Related DVT

5.1. In pregnant patients suspected of having lower extremity DVT, we recommend initial evaluation with proximal CUS over other initial tests, including a whole-leg US (Grade 2C)**, moderately sensitive D-dimer** (Grade 2C)**, highly sensitive D-dimer** (Grade 1B)**, or venography** (Grade 1B)**.**

5.2 Compression Ultrasonography in Pregnancy-Related DVT

5.2. In pregnant patients with suspected DVT in whom initial proximal CUS is negative, we suggest further testing with either serial proximal CUS (day 3 and day 7) (Grade 1B) **or a sensitive D-dimer done at the time of presentation** (Grade 2B) **over no further testing for DVT. We recommend that patients with an initial negative proximal CUS and a subsequent negative sensitive D-dimer or negative serial proximal CUS undergo no further testing for DVT** (Grade 1B) **and that patients with positive D-dimer have an additional follow-up proximal CUS (day 3 and day 7) rather than venography** (Grade 1B) **or whole-leg US** (Grade 2C)**.**

5.3 Pretest Probability in Pregnancy-Related DVT

5.3. In pregnant patients with symptoms suggestive of isolated iliac vein thrombosis (swelling of the entire leg, with or without flank, buttock, or back pain) and no evidence of DVT on standard proximal CUS, we suggest further testing with either Doppler US of the iliac vein (Grade 2C)**, venography** (Grade 2C)**, or direct MRI** (Grade 2C)**, rather than standard serial CUS of the proximal deep veins.**

6.1 Ultrasonography in Patients With Upper-Extremity DVT (UEDVT)

6.1. In patients suspected of having UEDVT, we suggest initial evaluation with combined modality US (compression with either Doppler or color Doppler) over other initial tests, including highly sensitive D-dimer or venography (Grade 2C)**.**

6.2 Clinical Pretest Probability Assessment in Patients With UEDVT

6.2. In patients with suspected UEDVT in whom initial US is negative for thrombosis despite a high clinical suspicion of DVT, we suggest further testing with a moderate or highly sensitive D-dimer, serial US, or venographic-based imaging (traditional, CT scan, or MRI), rather than no further testing (Grade 2C)**.**

In patients with suspected UEDVT and an initial negative combined-modality US and subsequent negative moderate or highly sensitive D-dimer or CT or MRI, we recommend no further testing, rather than confirmatory venography (Grade 1C)**. We suggest that patients with an initial combined negative modality US and positive D-dimer or those with less than complete evaluation by US undergo venography rather than no further testing, unless there is an alternative explanation for their symptoms** (Grade 2B)**, in which case testing to evaluate for the presence an alternative diagnosis should be performed. We suggest that patients with a positive D-dimer or those with less than complete evaluation by US but an alternative explanation for their symptoms undergo confirmatory testing and treatment of this alternative explanation rather than venography**

Antithrombotic Therapy for VTE Disease

2.1 Initial Anticoagulation for Patients With Acute DVT of the Leg

2.1. In patients with acute DVT of the leg treated with VKA therapy, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment (Grade 1B)**.**

2.2 Parenteral Anticoagulation Prior to Receipt of the Results of Diagnostic Work-up for VTE

2.2.1. In patients with a high clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C)**.**

2.2.2. In patients with an intermediate clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C)**.**

2.2.3. In patients with a low clinical suspicion of acute VTE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C)**.**

2.3 Anticoagulation in Patients With Isolated Distal DVT

2.3.1. In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (Grade 2C)**.**

2.3.2. In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension (see text), we suggest initial anticoagulation over serial imaging of the deep veins (Grade 2C)**.**

Remarks: Patients at high risk for bleeding are more likely to benefit from serial imaging. Patients who place a high value on avoiding the inconvenience of repeat imaging and a low value on the inconvenience of treatment and on the potential for bleeding are likely to choose initial anticoagulation over serial imaging.

2.3.3. In patients with acute isolated distal DVT of the leg who are managed with initial anticoagulation, we recommend using the same approach as for patients with acute proximal DVT (Grade 1B)**.**

2.3.4. In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we recommend no anticoagulation if the thrombus does not extend (Grade 1B)**; we suggest anticoagulation if the thrombus extends but remains confined to the distal veins** (Grade 2C)**; we recommend anticoagulation if the thrombus extends into the proximal veins** (Grade 1B)**.**

2.4 Timing of Initiation of VKA and Associated Duration of Parenteral Anticoagulant Therapy

2.4. In patients with acute DVT of the leg, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the international normalized ratio (INR) is 2.0 or above for at least 24 h (Grade 1B)**.**

2.5 Choice of Initial Anticoagulant Regimen in Patients With Proximal DVT

2.5.1. In patients with acute DVT of the leg, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) **and over SC UFH** (Grade 2B for LMWH; Grade 2C for fondaparinux)**.**

Remarks: Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH. LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH.

2.5.2. In patients with acute DVT of the leg treated with LMWH, we suggest once- over twice-daily administration (Grade 2C)**.**

Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day.

2.7 At-Home vs In-Hospital Initial Treatment of Patients With DVT

2.7. In patients with acute DVT of the leg and whose home circumstances are adequate, we recommend initial treatment at home over treatment in hospital (Grade 1B)**.**

Remarks: The recommendation is conditional on the adequacy of home circumstances: well-maintained living conditions, strong support from family or friends, phone access, and ability to quickly return to the hospital if there is deterioration. It is also conditional on the patient feeling well enough to be treated at home (eg, does not have severe leg symptoms or comorbidity)**.**

2.9 Catheter-Directed Thrombolysis for Patients With Acute DVT

2.9. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C)**.**

Remarks: Patients who are most likely to benefit from CDT (see text), who attach a high value to prevention of postthrombotic syndrome (PTS), and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.

2.10 Systemic Thrombolytic Therapy for Patients With Acute DVT

2.10. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over systemic thrombolysis (Grade 2C)**.**

Remarks: Patients who are most likely to benefit from systemic thrombolytic therapy (see text), who do not have access to CDT, and who attach a high value to prevention of PTS, and a lower value to the initial complexity, cost, and risk of bleeding with systemic thrombolytic therapy, are likely to choose systemic thrombolytic therapy over anticoagulation alone.

2.11 Operative Venous Thrombectomy for Acute DVT

2.11. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over operative venous thrombectomy (Grade 2C)**.**

2.12 Anticoagulation in Patients Who Have Had Any Method of Thrombus Removal Performed

2.12. In patients with acute DVT of the leg who undergo thrombosis removal, we recommend the same intensity and duration of anticoagulant therapy as in comparable patients who do not undergo thrombosis removal (Grade 1B)**.**

2.13 Vena Cava Filters for the Initial Treatment of Patients With DVT

2.13.1. In patients with acute DVT of the leg, we recommend against the use of an IVC filter in addition to anticoagulants (Grade 1B)**.**

2.13.2. In patients with acute proximal DVT of the leg and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B)**.**

2.13.3. In patients with acute proximal DVT of the leg and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B)**.**

Remarks: We do not consider that a permanent IVC filter, of itself, is an indication for extended anticoagulation.

2.14 Early Ambulation of Patients With Acute DVT

2.14. In patients with acute DVT of the leg, we suggest early ambulation over initial bed rest (Grade 2C)**.**

Remarks: If edema and pain are severe, ambulation may need to be deferred. As per section 4.1, we suggest the use of compression therapy in these patients.

3.0 Long-term Anticoagulation in Patients With Acute DVT of the Leg

3.0. In patients with acute VTE who are treated with anticoagulant therapy, we recommend long-term therapy (see section 3.1 for recommended duration of therapy) over stopping anticoagulant therapy after about 1 week of initial therapy (Grade 1B)**.**

3.1 Duration of Long-term Anticoagulant Therapy

3.1.1. In patients with a proximal DVT of the leg provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B)**, (ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B)**, or (iii) extended therapy** (Grade 1B regardless of bleeding risk)**.**

3.1.2. In patients with a proximal DVT of the leg provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B)**, (ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B)**, and (iii) extended therapy if there is a high bleeding risk** (Grade 1B)**. We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk** (Grade 2B)**.**

3.1.3. In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor (see remark), we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C) **and recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B) **or extended therapy** (Grade 1B regardless of bleeding risk)**.**

3.1.4. In patients with an unprovoked DVT of the leg (isolated distal [see remark] or proximal), we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B)**. After 3 months of treatment, patients with unprovoked DVT of the leg should be evaluated for the risk-benefit ratio of extended therapy.**

3.1.4.1. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B)**.**

3.1.4.2. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B)**.**

3.1.4.3. In patients with a first VTE that is an unprovoked isolated distal DVT of the leg (see remark), we suggest 3 months of anticoagulant therapy over extended therapy in those with a low or moderate bleeding risk (Grade 2B) **and recommend 3 months of anticoagulant treatment in those with a high bleeding risk** (Grade 1B)**.**

3.1.4.4. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Grade 1B)**, and we suggest extended anticoagulant therapy in those with a moderate bleeding risk** (Grade 2B)**.**

3.1.4.5. In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of anticoagulant therapy over extended therapy (Grade 2B)**.**

3.1.5. In patients with DVT of the leg and active cancer, if the risk of bleeding is not high, we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B)**, and if there is a high bleeding risk, we suggest extended anticoagulant therapy** (Grade 2B)**.**

Remarks (3.1.3, 3.1.4, 3.1.4.3): Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however, it is anticipated that not all patients who are diagnosed with isolated distal DVT will be given anticoagulants (see section 2.3). In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually)**.**

3.2 Intensity of Anticoagulant Effect

3.2. In patients with DVT of the leg who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B)**.**

3.3 Choice of Anticoagulant Regimen for Long-term Therapy

3.3.1. In patients with DVT of the leg and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C)**. For patients with DVT and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy** (Grade 2C)**.**

3.3.2. In patients with DVT of the leg and cancer, we suggest LMWH over VKA therapy (Grade 2B)**. In patients with DVT and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy** (Grade 2B)**.**

Remarks (3.3.1-3.3.2): Choice of treatment in patients with and without cancer is sensitive to the individual patient's tolerance for daily injections, need for laboratory monitoring, and treatment costs. LMWH, rivaroxaban, and dabigatran are retained in patients with renal impairment, whereas this is not a concern with VKA. Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes than VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketing studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of VKA and LMWH therapy over dabigatran and rivaroxaban, and we have not made any recommendations in favor of one of the new agents over the other.

3.4 Choice of Anticoagulant Regimen for Extended Therapy

3.4. In patients with DVT of the leg who receive extended therapy, we suggest treatment with the same anticoagulant chosen for the first 3 months (Grade 2C)**.**

3.5 Treatment of Patients With Asymptomatic DVT of the Leg

3.5. In patients who are incidentally found to have asymptomatic DVT of the leg, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic DVT (Grade 2B)**.**

4.1 Compression Stockings and Bandages to Prevent PTS

4.1. In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B)**.**

Remarks: Compression stockings should be worn for 2 years, and we suggest beyond that if patients have developed PTS and find the stockings helpful. Patients who place a low value on preventing PTS or a high value on avoiding the inconvenience and discomfort of stockings are likely to decline stockings.

4.2 Physical Treatment of Patients With PTS

4.2.1. In patients with PTS of the leg, we suggest a trial of compression stockings (Grade 2C)**.**

4.2.2. In patients with severe PTS of the leg that is not adequately relieved by compression stockings, we suggest a trial of an intermittent compression device (Grade 2B)**.**

4.3 Pharmacologic Treatment of Patients With PTS

4.3. In patients with PTS of the leg, we suggest that venoactive medications (eg, rutosides, defibrotide, and hidrosmin) not be used (Grade 2C)**.**

Remarks: Patients who value the possibility of response over the risk of side effects may choose to undertake a therapeutic trial.

5.1 Initial Anticoagulation for Patients With Acute Pulmonary Embolism (PE)

5.1. In patients with acute PE, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment (Grade 1B)**.**

5.2 Parenteral Anticoagulation Prior to Receipt of the Results of Diagnostic Work-up for PE

5.2.1. In patients with a high clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C)**.**

5.2.2. In patients with an intermediate clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C)**.**

5.2.3. In patients with a low clinical suspicion of acute PE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C)**.**

5.3 Timing of Initiation of VKA and Associated Duration of Parenteral Anticoagulant Therapy

5.3. In patients with acute PE, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the INR is 2.0 or above for at least 24 h (Grade 1B)**.**

5.4 Choice of Initial Parenteral Anticoagulant Regimen in Patients With PE

5.4.1. In patients with acute PE, we suggest LMWH or fondaparinux over IV UFH (Grade 2C for LMWH; Grade 2B for fondaparinux) **and over SC UFH** (Grade 2B for LMWH; Grade 2C for fondaparinux)**.**

Remarks: Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH. LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH. In patients with PE where there is concern about the adequacy of SC absorption or in patients in whom thrombolytic therapy is being considered or planned, initial treatment with IV UFH is preferred to use of SC therapies.

5.4.2. In patients with acute PE treated with LMWH, we suggest once- over twice-daily administration (Grade 2C)**.**

Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day.

5.5 Early vs Standard Discharge of Patients With Acute PE

5.5. In patients with low-risk PE and whose home circumstances are adequate, we suggest early discharge over standard discharge (eg, after first 5 days of treatment) (Grade 2B)**.**

Remarks: Patients who prefer the security of the hospital to the convenience and comfort of home are likely to choose hospitalization over home treatment.

5.6 Systemic Thrombolytic Therapy for Patients With PE

5.6.1.1. In patients with acute PE associated with hypotension (eg, systolic BP < 90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C)**.**

5.6.1.2. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1C)**.**

5.6.1.3. In selected patients with acute PE not associated with hypotension and with a low bleeding risk whose initial clinical presentation, or clinical course after starting anticoagulant therapy, suggests a high risk of developing hypotension, we suggest administration of thrombolytic therapy (Grade 2C)**.**

5.6.2.1. In patients with acute PE, when a thrombolytic agent is used, we suggest short infusion times (eg, a 2-h infusion) over prolonged infusion times (eg, a 24-h infusion) (Grade 2C)**.**

5.6.2.2. In patients with acute PE when a thrombolytic agent is used, we suggest administration through a peripheral vein over a pulmonary artery catheter (Grade 2C)**.**

5.7 Catheter-Based Thrombus Removal for the Initial Treatment of Patients With PE

5.7. In patients with acute PE associated with hypotension and who have (i) contraindications to thrombolysis, (ii) failed thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention (Grade 2C)**.**

5.8 Surgical Embolectomy for the Initial Treatment of Patients With PE

5.8. In patients with acute PE associated with hypotension, we suggest surgical pulmonary embolectomy over no such intervention if they have (i) contraindications to thrombolysis, (ii) failed thrombolysis or catheter-assisted embolectomy, or (iii)

shock that is likely to cause death before thrombolysis can take effect (eg, within hours), provided surgical expertise and resources are available (Grade 2C)**.**

5.9. Vena Cava Filters for the Initial Treatment of Patients With PE

5.9.1. In patients with acute PE who are treated with anticoagulants, we recommend against the use of an IVC filter (Grade 1B)**.**

5.9.2. In patients with acute PE and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B)**.**

5.9.3. In patients with acute PE and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B)**.**

Remarks: We do not consider that a permanent IVC filter, of itself, is an indication for extended anticoagulation.

6.0 Long-term Treatment of Patients With PE

6.1. In patients with PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B)**, (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), or (iii) extended therapy** (Grade 1B regardless of bleeding risk)**.**

6.2. In patients with PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B)**, (ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B)**, and (iii) extended therapy if there is a high bleeding risk** (Grade 1B)**. We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk** (Grade 2B)**.**

6.3. In patients with an unprovoked PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B)**. After 3 months of treatment, patients with unprovoked PE should be evaluated for the risk-benefit ratio of extended therapy.**

6.3.1. In patients with a first VTE that is an unprovoked PE and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B)**.**

6.3.2. In patients with a first VTE that is an unprovoked PE and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B)**.**

6.3.3. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Grade 1B)**, and we suggest extended anticoagulant therapy in those with a moderate bleeding risk** (Grade 2B)**.**

6.3.4. In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of therapy over extended therapy (Grade 2B)**.**

6.4. In patients with PE and active cancer, if there is a low or moderate bleeding risk, we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B)**, and if there is a high bleeding risk, we suggest extended anticoagulant therapy** (Grade 2B)**.**

Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually)**.**

6.5. In patients with PE who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B)**.**

6.6. In patients with PE and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C)**. For patients with PE and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy** (Grade 2C)**.**

6.7. In patients with PE and cancer, we suggest LMWH over VKA therapy (Grade 2B)**. In patients with PE and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy** (Grade 2C)**.**

Remarks (6.6-6.7): Choice of treatment in patients with and without cancer is sensitive to the individual patient's tolerance for daily injections, need for laboratory monitoring, and treatment costs. Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes than VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketing studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of VKA and LMWH therapy over dabigatran and rivaroxaban, and we have not made any recommendation in favor of one of the new agents over the other.

6.8. In patients with PE who receive extended therapy, we suggest treatment with the same anticoagulant chosen for the first 3 months (Grade 2C)**.**

6.9. In patients who are incidentally found to have asymptomatic PE, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Grade 2B)**.**

7.1 Pulmonary Thromboendarterectomy, Anticoagulant Therapy, and Vena Cava Filter for the Treatment of Chronic Thromboembolic Pulmonary Hypertension (CTPH)

7.1.1. In patients with CTPH, we recommend extended anticoagulation over stopping therapy (Grade 1B)**.**

7.1.2. In selected patients with CTPH, such as those with central disease under the care of an experienced thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy (Grade 2C)**.**

8.1 Treatment of Patients With Superficial Vein Thrombosis

8.1.1. In patients with superficial vein thrombosis of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (Grade 2B)**.**

Remarks: Patients who place a high value on avoiding the inconvenience or cost of anticoagulation and a low value on avoiding infrequent symptomatic VTE are likely to decline anticoagulation.

8.1.2. In patients with superficial vein thrombosis who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (Grade 2C)**.**

9.1 Acute Anticoagulation for Patients With UEDVT

9.1.1. In patients with UEDVT that involves the axillary or more proximal veins, we recommend acute treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such acute treatment (Grade 1B)**.**

9.1.2. In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) **and over SC UFH** (Grade 2B)**.**

9.2 Thrombolytic Therapy for the Initial Treatment of Patients With UEDVT

9.2.1. In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest anticoagulant therapy alone over thrombolysis (Grade 2C)**.**

Remarks: Patients who (i) are most likely to benefit from thrombolysis (see text); (ii) have access to CDT; (iii) attach a high value to prevention of PTS; and (iv) attach a lower value to the initial complexity, cost, and risk of bleeding with thrombolytic therapy are likely to choose thrombolytic therapy over anticoagulation alone.

9.2.2. In patients with UEDVT who undergo thrombolysis, we recommend the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis (Grade 1B)**.**

9.3 Long-term Anticoagulation for Patients With UEDVT

9.3.1. In most patients with UEDVT that is associated with a central venous catheter, we suggest that the catheter not be removed if it is functional and there is an ongoing need for the catheter (Grade 2C)**.**

9.3.2. In patients with UEDVT that involves the axillary or more proximal veins, we suggest a minimum duration of anticoagulation of 3 months over a shorter period (Grade 2B)**.**

Remarks: This recommendation also applies if the UEDVT was associated with a central venous catheter that was removed shortly after diagnosis.

9.3.3. In patients who have UEDVT that is associated with a central venous catheter that is removed, we recommend 3 months of anticoagulation over a longer duration of therapy in patients with no cancer (Grade 1B)**, and we suggest this in patients with cancer** (Grade 2C)**.**

9.3.4. In patients who have UEDVT that is associated with a central venous catheter that is not removed, we recommend that anticoagulation is continued as long as the central venous catheter remains over stopping after 3 months of treatment in patients with cancer (Grade 1C)**, and we suggest this in patients with no cancer** (Grade 2C)**.**

9.3.5. In patients who have UEDVT that is not associated with a central venous catheter or with cancer, we recommend 3 months of anticoagulation over a longer duration of therapy (Grade 1B)**.**

9.4 Prevention of PTS of the Arm

9.4. In patients with acute symptomatic UEDVT, we suggest against the use of compression sleeves or venoactive medications (Grade 2C)**.**

9.5 Treatment of Patients With PTS of the Arm

9.5.1. In patients who have PTS of the arm, we suggest a trial of compression bandages or sleeves to reduce symptoms (Grade 2C)**.**

9.5.2. In patients with PTS of the arm, we suggest against treatment with venoactive medications (Grade 2C)**.**

10.0 Patients With Splanchnic Vein Thrombosis

10.1. In patients with symptomatic splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we recommend anticoagulation over no anticoagulation (Grade 1B)**.**

10.2. In patients with incidentally detected splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we suggest no anticoagulation over anticoagulation (Grade 2C)**.**

11.0 Patients With Hepatic Vein Thrombosis

11.1. In patients with symptomatic hepatic vein thrombosis, we suggest anticoagulation over no anticoagulation (Grade 2C)**.**

11.2. In patients with incidentally detected hepatic vein thrombosis, we suggest no anticoagulation over anticoagulation

Treatment and Prevention of Heparin-Induced Thrombocytopenia

2.1 Platelet Count Monitoring Combined With the 4Ts Score for Patients Receiving Heparin/LMWH

2.1.1. For patients receiving heparin in whom clinicians consider the risk of heparin-induced thrombocytopenia (HIT) to be > 1%, we suggest that platelet count monitoring be performed every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first) (Grade 2C)**.**

2.1.2. For patients receiving heparin in whom clinicians consider the risk of HIT to be < 1%, we suggest that platelet counts not be monitored (Grade 2C)**.**

3.1 Discontinuation of Heparin or Initiation of VKAs vs Treatment With Nonheparin Anticoagulants

3.1. In patients with HIT complicated by thrombosis (HITT), we recommend the use of nonheparin anticoagulants, in particular lepirudin, argatroban, and danaparoid, over the further use of heparin or LMWH or initiation/continuation of a VKA (Grade 1C)**.**

3.2 Choice of Nonheparin Anticoagulants in Patients With HITT

3.2.1. In patients with HITT who have normal renal function, we suggest the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants (Grade 2C)**.**

Remarks: Other factors not covered by our analysis, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

3.2.2. In patients with HITT and renal insufficiency, we suggest the use of argatroban over other nonheparin anticoagulants (Grade 2C)**.**

3.3 Platelet Transfusions

3.3 In patients with HIT and severe thrombocytopenia, we suggest giving platelet transfusions only if bleeding or during the performance of an invasive procedure with a high risk of bleeding (Grade 2C)**.**

3.4 Starting VKAs Before Platelet Recovery

3.4.1. In patients with strongly suspected or confirmed HIT, we recommend against starting VKA until platelets have substantially recovered (ie, usually to at least 150 × 10^9/L) over starting VKA at a lower platelet count and that the VKA be initially given in low doses (maximum, 5 mg of warfarin or 6 mg phenprocoumon) over using higher doses (Grade 1C)**.**

3.4.2. We further suggest that if a VKA has already been started when a patient is diagnosed with HIT, vitamin K should be administered (Grade 2C)**.**

Remarks: We place a high value on the prevention of venous limb gangrene and a low value on the cost of the additional days of the parental nonheparin anticoagulant.

3.5 Discontinuation of Thrombin Inhibitor After a Minimum of 5 Days of Overlap With VKAs

3.5. In patients with confirmed HIT, we recommend that that the VKA be overlapped with a nonheparin anticoagulant for a minimum of 5 days and until the INR is within the target range over shorter periods of overlap and that the INR be rechecked after the anticoagulant effect of the nonheparin anticoagulant has resolved (Grade 1C)**.**

4.1 Discontinuation of Heparin or Initiation of VKAs vs Treatment With Nonheparin Anticoagulants

4.1. In patients with isolated HIT (HIT without thrombosis), we recommend the use of lepirudin or argatroban or danaparoid over the further use of heparin or LMWH or initiation/continuation of a VKA (Grade 1C)**.**

4.2 Choice of Nonheparin Anticoagulants in Patients With Isolated HIT

4.2. In patients with isolated HIT (HIT without thrombosis) who have normal renal function, we suggest the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants (Grade 2C)**.**

Remarks: Other factors such as drug availability, cost, and ability to monitor the anticoagulant effect may influence the choice of agent. The dosing considerations are the same as for patients with HITT (see section 3.2). For a recommendation on choice of nonheparin anticoagulants in the setting of renal insufficiency, see Recommendation 3.2.2.

5.1 Patients Who Require Urgent Cardiac Surgery

5.1.1. In patients with acute HIT (thrombocytopenic, HIT antibody positive) or subacute HIT (platelets recovered but still HIT antibody positive) who require urgent cardiac surgery, we suggest the use of bivalirudin over other nonheparin anticoagulants and over heparin plus antiplatelet agents (Grade 2C)**.**

5.1.2. In patients with acute HIT who require nonurgent cardiac surgery, we recommend delaying the surgery (if possible) until HIT has resolved and HIT antibodies are negative (see section 6.1) (Grade 2C)**.**

Remarks: Other factors not covered by our analysis, such as drug availability, cost, and ability to monitor the anticoagulant effect may influence the choice of agent. For recommendations for patients with a past history of HIT (> 3 months previous) who require cardiac surgery, see section 6.1.

5.2 Patients Who Require Urgent Percutaneous Coronary Interventions

5.2. In patients with acute HIT or subacute HIT who require percutaneous coronary interventions, we suggest the use of bivalirudin (Grade 2B) **or argatroban** (Grade 2C) **over other nonheparin anticoagulants.**

Remarks: Other factors, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

5.3 Patients Who Require Renal Replacement Therapy

5.3.1. In patients with acute or subacute HIT who require renal replacement therapy, we suggest the use of argatroban or danaparoid over other nonheparin anticoagulants (Grade 2C)**.**

Remarks: We acknowledge that the cost of argatroban may be prohibitive at some clinical centers. We further suggest that if the prothrombotic state of HIT appears to have resolved (as seen by normalization of the platelet count), saline flushes during dialysis would be a reasonable option. This suggestion is based on the presumed pathogenesis of thrombosis in this condition and not on the results of clinical trials.

5.3.2. In patients with a past history of HIT who require ongoing renal replacement therapy or catheter locking, we suggest the use of regional citrate over the use of heparin or LMWH (Grade 2C)**.**

5.4 Pregnant Patients

5.4. In pregnant patients with acute or subacute HIT, we suggest danaparoid over other nonheparin anticoagulants (Grade 2C). **We suggest the use of lepirudin or fondaparinux only if danaparoid is not available** (Grade 2C)**.**

Remarks: Other factors, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

6.1 Patients With a History of HIT Who Require Cardiac Surgery

6.1.1. In patients with a history of HIT in whom heparin antibodies have been shown to be absent who require cardiac surgery, we suggest the use of heparin (short-term use only) over nonheparin anticoagulants (Grade 2C)**.**

6.1.2. In patients with a history of HIT in whom heparin antibodies are still present who require cardiac surgery, we suggest the use of nonheparin anticoagulants (see 5.1.1) over heparin or LMWH (Grade 2C)**.**

6.2 Patients Who Require PCI

6.2. In patients with a history of HIT in whom heparin antibodies have been shown to be absent who require cardiac catheterization or percutaneous coronary interventions, the recommended treatment is the same as 5.2.

6.3 Patients Who Require Prophylaxis or Treatment of Thrombosis

6.3. In patients with a past history of HIT who have acute thrombosis (not related to HIT) and normal renal function, we suggest the use of fondaparinux at full therapeutic doses until transition to a VKA can be achieved