Direct Oral Anticoagulant
DOAC Playbook

Anticoagulation FORUM

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Acknowledgements

Funding

The Direct Oral Anticoagulant (DOAC) Playbook was produced by the Anticoagulation Forum with funding provided by Janssen Inc.

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Introduction

IMPETUS FOR CHANGE

Why do we need better management of DOACs?

Direct oral anticoagulants (DOACs), a class of oral anticoagulants first introduced to the US market in 2010, have replaced warfarin as the preferred anticoagulant for stroke prevention in nonvalvular atrial fibrillation (NVAF), adjunct treatment and prevention of major cardiovascular events in patients with chronic coronary/peripheral artery (CAD/PAD), and for the treatment and prevention of venous thromboembolism (VTE), including in the medically ill patient or following hip or knee replacement surgery. DOACs directly neutralize a specific clotting factor (factor Xa or IIa), whereas warfarin interferes with the synthesis of active vitamin K-dependent clotting factors (II, VII, IX and X).[1] The DOACs are as effective as warfarin and appear to be safer, especially with reference to intracranial hemorrhage.[2] DOACs have a wide therapeutic index that does not require routine monitoring of anticoagulation effect for the purpose of dose titration. In addition, they have few important drug-drug interactions and almost no dietary interactions. This is in comparison to warfarin therapy, which is linked to numerous nutrient, disease, and drug interactions; safe use of warfarin therefore necessitates close patient monitoring[3] and regular patient/caregiver interactions. DOACs now represent over 80% of new prescriptions for oral anticoagulant therapy.[4]

Although DOACs require less intensive dose management than warfarin, they are not devoid of potential complications. Anticoagulants have consistently ranked as the class of medications most frequently leading to emergency room visits and hospital admissions for adverse drug events (ADEs).[4–6] Between 2013 and 2014, the DOACs rivaroxaban and dabigatran were the fifth and tenth most common drugs, respectively, to cause emergency room visits for ADEs in older adults.[6] Hospitalization rates for DOAC-related ADEs were similar to that of warfarin, and the number of ADE reports for anticoagulants as a class (DOACs and warfarin) increased more than fourfold from 1576 (7.3%) in 2005-2006 to 7211 (17.6%) in 2013-2014.[4]

Improving the systematic management of anticoagulants within and across care settings is a key priority for regulatory and government agencies, via such means as the US Department of Health and Human Services National Action Plan for Adverse Drug Event Prevention, the Joint Commission's update of the National Patient Safety Goals to include DOAC management, and the recent development of an Anticoagulation Stewardship initiative sponsored by the Food and Drug Administration.[7]

Is there evidence that DOACs require better management?

In the warfarin era, a systematic approach to anticoagulant management using dedicated systems, such as anticoagulation clinics, improved outcomes by reducing thrombosis and major bleeding and may have also generated financial benefits.[8,9]

DOACs require providers to evaluate and manage the practical aspects of therapy, including the appropriate indication, dosage, monitoring of selected parameters, drug-drug interactions, transitioning to alternate anticoagulants, and reversal of activity in the event of bleeding or need for

surgery.[10] Guidelines endorse a systematic approach to DOAC management to ensure consistent assessment of labs, drug interactions, bleeding risk factors, etc.[11]

Real-world evidence indicates suboptimal DOAC use, particularly off-label dosing.[12] In the ORBIT-II registry of over 11,000 patients with atrial fibrillation (AF), 1 in 8 patients in the community received inappropriate dosing. Overdosing was associated with an increased all-cause mortality compared with recommended doses (hazard ratio [HR], 1.91; *P* = .04). Underdosing was associated with increased cardiovascular hospitalization (HR, 1.26; *P* = .007).[13] Similar findings were found in patients treated for pulmonary embolism,[14] where 4.3% of a large cohort were inappropriately dosed (all underdosed) resulting in an adverse event rate of 25% vs a rate of 6.1% in those who were dosed appropriately (risk ratio [RR], 3.19; *P* < .001). In a mixed population of patients admitted to the hospital on a DOAC, investigators found that inappropriate dosing occurred in 25% of patients.[15] Improved dosing, however, was seen in a Veterans Administration cohort of over 5000 NVAF patients managed by pharmacist-led anticoagulation services, where only about 7% of patients were inappropriately dosed, although this rate was higher in those with chronic kidney disease (17%).[16]

Impaired renal function is a particular problem with DOACs, since all of these agents rely to a greater or lesser extent on renal elimination of unchanged drug. A recent report examined a cohort of 1473 patients with impaired renal function who were treated with a DOAC and found that 43% were overdosed. This was associated with a higher risk of major bleeding (HR, 2.19; 95% CI, 1.07-4.46). In the same study, of 13,392 patients without renal impairment, 13% were underdosed, which was associated with a higher risk of stroke (HR, 4.87; 95% CI, 1.30-18.26).[17]

Improving DOAC therapy can be achieved by a variety of interventions. On an institutional basis, implementing an anticoagulant stewardship program can lead to improved anticoagulant therapy outcomes,[7] especially through the creation of an anticoagulant management service.[18] Such services enhance not only warfarin therapy but DOAC therapy as well, as shown by one study where investigators achieved a 58% reduction in inappropriate dosing after implementation of such a service in a community teaching hospital.[19]

Lastly, improved management of DOACs, especially focused on adherence to therapy, can result in health care cost reduction, as shown in a study of 2981 patients.[20] Adjusted all-cause total cost for a 12-month period was significantly lower ($29,742 vs $33,609) among adherent vs nonadherent users.

Accumulating real-world experience suggests patients who are prescribed DOACs require skilled management by specialized health care practitioners to reduce ADEs and to achieve optimal outcomes. Leveraging the efficient, coordinated care provided within an anticoagulation management service is the ideal resource to realize optimal anticoagulant therapy outcomes while potentially reducing health care costs.

NATIONAL PATIENT SAFETY GOALS

The Joint Commission (TJC), the nation's oldest and largest standards-setting and accrediting body in health care, established the National Patient Safety Goals (NPSG) program in 2002 to help accredited organizations address specific patient safety concerns.[21] The NPSGs are actions that accredited organizations are required to take in order to prevent medical errors. The safety goal regarding anticoagulation therapy (NPSG.03.05.01) is:

"Reduce the likelihood of patient harm associated with the use of anticoagulant therapy."

The NPSG Elements of Performance (EPs) to reduce harm associated with anticoagulant therapy are summarized below.[22]

EP 1: The [hospital/organization] uses approved protocols and evidence-based practice guidelines for the initiation and maintenance of anticoagulant therapy that address medication selection; dosing, including adjustments for age and renal or liver function; drug-drug and drug-food interactions; and other risk factors as applicable.
EP 2: The [hospital/organization] uses approved protocols and evidence-based practice guidelines for reversal of anticoagulation and management of bleeding events related to each anticoagulant medication.
EP 3: The hospital uses approved protocols and evidence-based practice guidelines for perioperative management of all patients on oral anticoagulants.
EP 4: The [hospital/organization] has a written policy addressing the need for baseline and ongoing laboratory tests to monitor and adjust anticoagulant therapy.
EP 5: The [hospital/organization] addresses anticoagulation safety practices through the following: • Establishing a process to identify, respond to, and report adverse drug events, including adverse drug event outcomes • Evaluating anticoagulation safety practices, taking actions to improve safety practices, and measuring the effectiveness of those actions in a time frame determined by the organization
EP 6: The [hospital/organization] provides education to patients and families specific to the anticoagulant medication prescribed, including the following: • Adherence to medication dose and schedule • Importance of follow-up appointments and laboratory testing (if applicable) • Potential drug-drug and drug-food interactions • The potential for adverse drug reactions
EP 7: The [hospital/organization] uses only oral unit-dose products, prefilled syringes, or premixed infusion bags when these types of products are available.
EP 8: When heparin is administered intravenously and continuously, the [hospital/organization] uses programmable pumps to provide consistent and accurate dosing.

By following TJC standards, medication errors can be prevented, patient safety increased, and overall better health care outcomes achieved.[23]

ABOUT THIS PLAYBOOK

As leaders in the field of anticoagulant therapy, the Anticoagulation Forum (AC Forum) has written the following guidance on managing patient care with DOACs. This playbook incorporates both evidence-based data and consensus opinion to provide practical guidance on a range of real-world clinical situations that may be encountered by anticoagulation services, emergency room physicians, internists, cardiologists, hematologists, and others. The AC Forum initiated this comprehensive guidance project to provide easily accessible information about the therapies that can be readily put into practice.

Further information and handouts are available at the AC Forum website at www.acforum.org.

Management of DOACs

OVERVIEW

The introduction of DOACs as an alternative to low-molecular-weight heparins (LMWH) and warfarin requires health care organizations to modify existing protocols and use evidence-based practice guidelines to address the initiation and maintenance of all anticoagulation medications and their associated risks.

Using DOACs safely and effectively requires that all aspects of anticoagulation therapy are addressed,[11] including appropriate patient selection, dosing, monitoring, transitions between therapies and between care settings, periprocedural guidance, management of risks (including DOAC-associated bleeding), drug-drug interaction management, ongoing assessment of patient and family educational needs, and incorporation of evidence-based practices into workflow.

For the practicing physician or health care provider not based in an institutional setting, every effort should be made to follow these guidelines when prescribing a DOAC.

GENERAL DOAC INFORMATION

	Apixaban (Eliquis®)[24]	Dabigatran (Pradaxa®)[25]	Edoxaban (Savaysa®)[26]	Rivaroxaban (Xarelto®)[27]
Target	Factor Xa	Thrombin	Factor Xa	Factor Xa
Prodrug	No	Yes	No	No
Bioavailability	60%	6%	62%	60%-80%
Time to peak effect	1-2 hours	1-3 hours	1-2 hours	2-4 hours
Half-life	12 hours	8-15 hours	10-14 hours	7-11 hours
Renal clearance	25%	80%	50%	33%
Notes		Must be stored in its original container to protect from moisture		Must be given with food at doses > 10 mg
Indications				
NVAF	✓	✓	✓	✓
Treatment of acute DVT and/or PE	✓	✓ After 5-10 days of parenteral anticoagulation	✓ After 5-10 days of parenteral anticoagulation	✓
Reduction of risk of recurrent DVT and/or PE	✓	✓		✓
Prophylaxis of DVT and/or PE following hip or knee replacement surgery	✓	✓* *Hip only		✓
Prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications, not at high risk of bleeding				✓
Reduction of risk of MACE (CV death, MI, and stroke) in chronic CAD/PAD				✓

	Apixaban (Eliquis®)[24]	Dabigatran (Pradaxa®)[25]	Edoxaban (Savaysa®)[26]	Rivaroxaban (Xarelto®)[27]
Contraindications/Not Recommended (× = avoid as per PI; ×× = avoid as per clinical recommendation); refer to "Patient Selection" on pg. 13 for further details)				
Active pathological bleeding	×	×	×	×
Severe hypersensitivity to respective medication	×	×	××	×
Mechanical prosthetic heart valves	×	×	×	×
Triple positive APS	×	×	××	×
Pregnancy (category per PI)	×	××	××	××
Breastfeeding (evidence of secretion into milk)	×	×	×	××
Drug interactions	Refer to Drug Interactions below			
DOAC Dose Adjustments				
Hepatic impairment	Child-Pugh B: *Avoid or use with caution* Child-Pugh C: *Avoid use*	No adjustment	Child-Pugh B: *Avoid or use with caution* Child-Pugh C: *Avoid use*	Child-Pugh B: *Avoid or use with caution* Child-Pugh C: *Avoid use*
Renal impairment	Refer to Dosing Per Indication below for specific dosing recommendations			
Body Weight				
Overweight	Use with caution in BMI > 40 kg/m^2			
Low Weight	If NVAF plus 2 additional risk factors, dose adjustment (see dosing specifics below)	No adjustment	If VTE and ≤ 60 kg, dose adjustment (see dosing specifics below)	No adjustment

	Apixaban (Eliquis®)[24]	Dabigatran (Pradaxa®)[25]	Edoxaban (Savaysa®)[26]	Rivaroxaban (Xarelto®)[27]
Drug Interactions				
PharmacoDYNAMIC drug interactions	*Avoid or minimize concomitant use of antiplatelets and/or NSAIDs whenever possible*			
PharmacoKINETIC drug interactions ***drug lists are not exhaustive***	Eliminated/metabolized by: • P-gp efflux transporter system • CYP3A4 hepatic isoenzyme system	Eliminated by: • P-gp efflux transporter system	Eliminated by: • P-gp efflux transporter system	Eliminated/metabolized by: • P-gp efflux transporter system • CYP3A4 hepatic isoenzyme system
P-gp and/or *strong* CYP3A4 INDUCERS *(e.g., barbiturates, carbamazepine, dexamethasone, phenytoin, rifampin, St. John's Wort)**	*Avoid use of DOACs OR transition to alternative medication without P-gp/CYP inducing effects, when appropriate*			
P-gp INHIBITORS *(e.g., amiodarone, carvedilol, diltiazem, dronaderone, azithro/clarithro/erythromycin, oral itra/ketoconazole, quinidine, verapamil)**	N/A	Estimated CrCl < 50 mL/min: *Avoid use or reduce dose*	30 mg once daily	N/A
Dual P-gp and *strong* CYP3A4 INHIBITORS *(e.g., clarithromycin+, oral itra/ketoconazole, cobicistat, indinavir, ritonavir, saquinavir, teleprevir)**	• *Decrease induction/ maintenance dose by 50% if on 5 mg twice daily or 10 mg twice daily* • *Avoid use if already on 2.5 mg twice daily* • *+No dose adjustment needed with concomitant use of clarithromycin*	N/A	N/A	Avoid use • *No dose adjustment needed with concomitant use of clarithromycin*
Dual P-gp and *moderate* CYP3A4 INHIBITORS *(e.g., cyclosporine, diltiazem, dronaderone, erythromycin, verapamil)**	Use with caution	N/A	N/A	Estimated CrCl <80 mL/min • *Avoid use unless benefit justifies potential risk*

	Apixaban (Eliquis®)[24]	Dabigatran (Pradaxa®)[25]	Edoxaban (Savaysa®)[26]	Rivaroxaban (Xarelto®)[27]
Dosage Forms and Administration				
Administration	Twice daily with or without food	• Twice daily with or without food • Must be kept in original packaging • Do not crush or open capsule	Once daily with or without food	• Doses ≤ 10 mg daily: once or twice daily with or without food • Doses > 10 mg daily: once or twice daily with largest meal of day
Dosage forms and strengths	Tablets: 2.5 mg and 5 mg	Capsules: 75 mg, 110 mg, 150 mg	Tablets: 15 mg, 30 mg, 60 mg	Tablets: 2.5 mg, 10 mg, 15 mg, 20 mg
Dosing Per Indication				
NVAF	5 mg twice daily *Recommended dose is 2.5 mg twice daily if at least 2 of the following characteristics are present:* • *age ≥ 80 years,* • *body weight ≤60 kg, OR* • *serum creatinine ≥ 1.5 mg/dL*	150 mg twice daily • *Avoid if CrCl < 15 mL/min or on dialysis* • *Reduce dose to 75 mg twice daily if CrCl 15-30 mL/min* • *Reduce dose to 75 mg twice daily if CrCl 30-50 mL/min and concomitant use of P-gp inhibitors dronedarone or systemic ketoconazole (outcome data not available)* • *Avoid co-administration with P-gp inhibitors* if CrCl < 30 mL/min*	60 mg once daily • *Avoid if CrCl > 95 mL/min* • *Reduce dose to 30 mg once daily if CrCl 15-50 mL/min*	20 mg once daily with food • *Reduce dose to 15 mg once daily with food if CrCl ≤ 50 mL/min*
Treatment of acute DVT and/or PE	10 mg twice daily for 7 days, then 5 mg twice daily	150 mg twice daily **AFTER** 5-10 days of parenteral lead-in • *Avoid if CrCl < 30 mL/min or on dialysis* • *Avoid co-administration with P-gp inhibitors* if CrCl < 50 mL/min*	60 mg once daily **AFTER** 5-10 days of parenteral lead-in • *Reduce dose to 30 mg once daily if CrCl 15-50 mL/min or body weight ≤ 60 kg or using certain P-gp inhibitors**	15 mg twice daily for 21 days, then 20 mg once daily • *Take with food* • *Avoid if CrCl < 30 mL/min*

	Apixaban (Eliquis®)[24]	Dabigatran (Pradaxa®)[25]	Edoxaban (Savaysa®)[26]	Rivaroxaban (Xarelto®)[27]
Reduction of risk of recurrent DVT and/or PE	2.5 mg twice daily after 6 months of initial treatment	150 mg twice daily after initial treatment • *Avoid if CrCl <30 mL/min or on dialysis* • *Avoid co-administration with P-gp inhibitors* if CrCl < 50 mL/min*	Not FDA approved for this indication	10 mg once daily after 6 months of standard treatment • *Avoid if CrCl < 30 mL/min*
Prophylaxis of DVT and/or PE following hip or knee replacement surgery	2.5 mg twice daily for 12 days (knee) or 35 days (hip) Give first dose 12-24 hours after surgery	**For hip replacement only:** 110 mg day 1, then 220 mg once daily for 28-35 days • *Avoid if CrCl < 30 mL/min or on dialysis* • *Avoid co-administration with P-gp inhibitors if CrCl < 50 mL/min* ***Not FDA approved for knee replacement***	Not FDA approved for this indication	10 mg once daily for 12 days (knee) or 35 days (hip) • *Avoid if CrCl < 30 mL/min*
Prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding	Not FDA approved for this indication	Not FDA approved for this indication	Not FDA approved for this indication	10 mg once daily in hospital and after hospital discharge for a total recommended duration of 31-39 days
Reduction of risk of MACE (CV death, MI, and stroke) in chronic CAD/PAD	Not FDA approved for this indication	Not FDA approved for this indication	Not FDA approved for this indication	2.5 mg twice daily in combination with aspirin (75-100 mg) once daily

Abbreviations: APS, antiphospholipid antibody syndrome; BMI, body mass index; CAD, coronary artery disease; CrCl, creatinine clearance; CV, cardiovascular; CYP3A4, cytochrome 3A4; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; FDA, Food and Drug Administration; MACE, major cardiovascular events; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; NVAF, nonvalvular atrial fibrillation; PAD, peripheral artery disease; PE, pulmonary embolism; P-gp, P-glycoprotein; PI, prescribing information; VTE, venous thromboembolism.

PATIENT SELECTION

Clinical guidelines now favor DOACs over other therapies for the **treatment and prevention of thromboembolic complications in the setting of NVAF and VTE.** DOACs are also indicated for VTE prophylaxis following knee/hip surgery and in medically ill patients and have also been used as adjunctive treatment to prevent cardiovascular events in patients with CAD/PAD. However, DOACs are not appropriate for all candidates, and patient selection is crucial when considering the safe and effective use of DOACs in these populations. Risk factors for bleeding and potential stratification of those risks should be considered.

When deciding on anticoagulant therapy, one must make sure the benefit (preventing thrombosis) outweighs the risk (major bleeding). Although the risk rarely exceeds the benefit, especially in the long term, some risk factors to consider are listed below. These may be helpful in determining patient follow-up during therapy.

Patient-Specific Risk Factors for Bleeding[11]
• Active or metastatic cancer • Age (e.g., > 65 years and older) • Alcohol abuse • Anemia and other blood dyscrasias • Comorbidity and reduced functional capacity • Concomitant medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelets, or other anticoagulants administered, possibly in a transition period • Diabetes • Frequent falls • Hepatic or renal dysfunction • History of bleeding, especially gastrointestinal (GI) bleeding • History of gastroduodenal ulcer • Rheumatic disease • Previous stroke • Recent surgery • Thrombocytopenia

Although there are well-known bleeding risk scores, such as the HAS-BLED, ATRIA, $HEMORR_2HAGES$, and ORBIT scores, these were developed in patients receiving warfarin and have not been rigorously validated in patients treated with DOACs.[28]

> Management of DOACs

Patients who should avoid the use of DOACs, or for whom there are specific considerations, are listed below. Additional details and references on all special populations are listed in the appendix (see page 38).

Patients Who Should Avoid DOACs
• Indications for which DOACs have been proven inefficacious and/or harmful:
• Mechanical heart valve replacement[29]
• Left Ventricular Assist Device (LVAD)[30]
• Triple Positive Antiphospholipid Antibody Syndrome (APS)[8, 12, 31, 32,33]
• Embolic Stroke of Undetermined Source (ESUS)[34, 35]
• Transcatheter Aortic Valve Replacement (TAVR)[36]
• Within 3 months of a bioprosthetic heart valve replacement[37]
• Valvular AF[38–40]
• Severe hepatic impairment[37]
• Pregnant or breastfeeding[27]
• Women of child-bearing potential NOT using a reliable method of contraception[27]
• Taking medications known to SIGNIFICANTLY interact with DOAC[27, 41]
• Unable to consistently pay for DOAC through personal funds, insurance, or assistance programs
Controversies (Discuss Risk/Benefit Prior to Use)
• Off-label indications
• VTE associated with GI or genitourinary (GU) cancer[42,43]
• Moderate hepatic impairment[37]
• Severe renal impairment (CrCl < 30 mL/min)[44,45]
• Taking moderate inhibitors of DOAC metabolism in the setting of moderately impaired renal function[27, 41]
• Poor medication adherence
• Treatment failure while on therapeutic warfarin or LMWH[46]
• Bypassed or removed portions of the GI tract[47]

See appendix for details on special populations (pg. 38).

SWITCHING BETWEEN ANTICOAGULANTS

Transitioning between oral anticoagulants can be challenging and happens with some degree of frequency. The need to switch between agents exposes the patient to periods of increased thromboembolic and bleeding risks.[11]

Reasons to Switch Anticoagulants

There are a variety of reasons patients may switch between anticoagulants. Switches can occur from:

- Parenteral anticoagulants to a DOAC, for longer-term outpatient management
- Warfarin to a DOAC, or DOAC to DOAC, for drug intolerance (e.g., rash, dyspepsia, etc.) or preference for DOAC therapy
- DOAC to warfarin, for many of the same reasons, such as drug intolerance, failure, or preference
- DOAC to warfarin, if patient acquires a new condition or comorbidity that is a contraindication to DOAC therapy, such as pregnancy, severe renal impairment, or placement of a mechanical valve

Other situations that might warrant a switch include gastric bypass surgery or bowel resection, where medication absorption may be significantly altered, or the need for new medication that poses a major drug interaction with a DOAC. In these instances, it may be best to maintain the patient on warfarin therapy, so that levels of anticoagulation can be readily monitored. Patients may also not be able to tolerate oral medications during the perioperative period (e.g., bowel resection or NPO status) and thus may need to be transitioned from a parenteral back to a DOAC or from prophylactic-dose DOAC to treatment-dose DOAC.

If a patient requires a switch between anticoagulants, clinicians should employ a carefully constructed approach that takes into consideration (if applicable) the patient's:

- Anticoagulation status at the time of the switch,
- International normalized ratio (INR),
- Renal function, and,
- Pharmacokinetics of the individual DOAC, to avoid significant under- or over-anticoagulation of their patient.

When transitioning from warfarin to a DOAC, manufacturers have recommended different INR thresholds[11].
Management of VTE: Clinical Guidance from the AC Forum (Burnett, et al. 2016)

Switching from Warfarin, LMWH, or UFH to DOAC

<table>
<tr><th>Switching</th><th>Warfarin to DOAC</th><th>LMWH to DOAC</th><th>UFH to DOAC</th><th>DOAC to another DOAC</th></tr>
<tr><td>Dabigatran[25]</td><td>Start when INR < 2.0</td><td rowspan="2">Stop LMWH;
Start DOAC ≤ 2 hours prior to the time of the next scheduled dose of LMWH</td><td rowspan="3">Start DOAC immediately after stopping IV UFH</td><td rowspan="4">Stop current DOAC;
At time of next dose of current DOAC, start new DOAC</td></tr>
<tr><td>Rivaroxaban[27]</td><td>Start when INR < 3.0</td></tr>
<tr><td>Apixaban[24]</td><td>Start when INR < 2.0</td><td rowspan="2">Stop LMWH;
Start DOAC at the time when the next dose of LMWH is due</td></tr>
<tr><td>Edoxaban[26]</td><td>Start when INR ≤ 2.5</td><td>Start edoxaban 4 hours after stopping IV UFH</td></tr>
<tr><td colspan="5">As a general rule, as INR drops below 2.5, a DOAC can be started. As a general rule, each DOAC can be started within 30 minutes of stopping IV UFH.</td></tr>
</table>

Abbreviations: DOAC, direct oral anticoagulant; INR international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

Transitioning from a DOAC to warfarin can be more complicated, depending on patient-specific factors. Patient-specific factors for risk of thrombosis and bleeding must be assessed, along with renal function. Clarification and written acknowledgment of the plan should be obtained from the provider. The table below depicts an approach to accomplish this.

Switching from a DOAC to Warfarin

DOAC	Procedure to Switch to Warfarin[11]
Dabigatran[25]	Start warfarin and overlap with dabigatran: • CrCl 50 mL/min, overlap 3 days • CrCl 30–50 mL/min, overlap 2 days • CrCl 15–30 mL/min, overlap 1 day • CrCl <15 mL/min, no recommendations can be made
Rivaroxaban[27]	Stop DOAC; start warfarin and LMWH at time of next scheduled DOAC dose and bridge until INR ≥ 2.0
Apixaban[24]	Stop DOAC; start warfarin and LMWH at time of next scheduled DOAC dose and bridge until INR ≥ 2.0
Edoxaban[26]	• For 60 mg dose, reduce dose to 30 mg and start warfarin concomitantly • For 30 mg dose, reduce dose to 15 mg and start warfarin concomitantly • Stop edoxaban when INR ≥ 2.0
Overlap is intended to avoid under-anticoagulation while warfarin effect is developing. When DOAC is overlapped with warfarin, measure INR just before next DOAC dose, as the DOAC can influence INR. As a general rule, we believe either approach (i.e., stop DOAC then start LMWH and warfarin; or overlap warfarin with DOAC, measure INR just before next the DOAC dose, and stop DOAC when INR is ≥ 2.0) can be used for all DOAC-to-warfarin transitions. Recommendations adapted from company's package inserts. A recent ASH consensus guideline suggests overlapping DOAC and VKA therapy until the INR is within the therapeutic range over using LMWH or UFH-bridging therapy for patients at low risk of thrombosis/bleeding (conditional recommendation based on very low certainty in the evidence about effects).[48]	

Abbreviations: ASH, American Society of Hematology; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; INR international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKA, vitamin K agonist.

PERIPROCEDURAL GUIDANCE

Patients taking oral anticoagulation medications must be managed appropriately during the perioperative period, to minimize bleeding risks during surgery. The decision to stop an anticoagulant, use a bridging medication (warfarin only), or to restart an anticoagulant should be based on organization-approved protocols and evidence-based practice guidelines.

Periprocedural management (i.e., determining if there is a need for the anticoagulant to be stopped) is largely determined by the bleeding risk of the procedure and the expected DOAC half-life in the patient. Impaired renal function should be considered in the periprocedural management plan for those patients taking dabigatran.[49]

The periprocedural guidance outlined below was validated in the Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) study in AF patients. It is likely that the PAUSE protocol can be safely applied to patients on DOACs for VTE and CAD/PAD. In the PAUSE study, use of this periprocedural strategy was associated with acceptably low rates of bleeding and thromboembolism[50].

Step 1:

Assess the bleeding risk of the procedure (see "Procedural Bleeding Risk" on pg. 18).
Is the bleeding risk of the procedure sufficient to require interruption of anticoagulant therapy so that it may be performed safely?

- If no, continue the DOAC without interruption.
- If yes, determine if the procedure's bleeding risk is Standard or High. This may require discussion with the proceduralist.
- Consider whether neuraxial anesthesia will be utilized and follow appropriate guidelines accordingly.[51]
- If unclear, interruption of therapy should be discussed with the proceduralist.

Step 2:

If patient is taking dabigatran, assess patient's renal function pre-procedure.

Step 3:

Design a pre- and post-procedural plan based on the bleeding risk of the procedure. (see "Develop a Procedural Plan" on pg. 20)

For details of DOAC use in special populations, please see appendix (pg. 38).

Procedural Bleed Risk[11,52]	

MINIMAL bleed risk
 	
Procedures that may not require interruption of anticoagulant therapy
	• Central venous catheter removal
	• Dental procedures:
	  • Extractions (including surgical)
	  • Periodontal surgery
	  • Incision of abscess
	  • Implant positioning
	• Endoscopy without surgery
	• Ophthalmology:
	  • Cataract or glaucoma intervention
	• Superficial surgery:
	  • Abscess incision
	• Small dermatology excisions

STANDARD bleed risk ***Procedures requiring interruption of anticoagulant therapy***	• Abdominal hernia repair • Abdominal hysterectomy • Carpal tunnel repair • Cholecystectomy • Dilatation and curettage • Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left-sided ablation via single transseptal puncture) • Endoscopy with biopsy or tissue removal • Gastrointestinal endoscopy ± biopsy, enteroscopy, biliary/pancreatic stent without sphincterotomy, endosonography without fine-needle aspiration • Hemorrhoidal surgery • Hydrocele repair • Non-coronary angiography bronchoscopy ± biopsy • Ophthalmology: • Non-cataract eye surgery • Prostate or bladder biopsy • Shoulder/foot/hand surgery and arthroscopy

HIGH bleed risk
Procedures requiring interruption of anticoagulant therapy
	• Any major surgery (procedure duration > 45 min)
	• Abdominal and gastrointestinal surgeries:
	  • Bowel resection
	• Abdominal aortic aneurysm repair
	• Breast cancer surgery
	• Cardiac surgeries:
	  • Coronary artery bypass
	  • Heart-valve replacement
	• Cardiac procedures:
	  • Complex left-sided ablation (pulmonary vein isolation; ventricular tachycardia ablation)
	  • Implantation of a pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization therapy defibrillator)
	• Endoscopically guided fine-needle aspiration
	• Head or neck surgery

Procedural Bleed Risk[11,52]	

HIGH bleed risk ***Procedures requiring interruption of anticoagulant therapy***	• Hepatic surgeries and procedures, including liver biopsy
	• Major orthopedic surgery:
	  • Joint replacement/arthroplasty
	  • Prosthetic revision
	• Miscellaneous surgeries and procedures:
	  • Biliary sphincterectomy
	  • PEG placement
	  • Pneumatic dilatation
	  • Polypectomy
	  • Variceal treatment
	• Neurosurgeries
	• Plastic surgery:
	  • Major reconstructive surgery
	• Spinal surgeries or procedures:
	  • Spinal or epidural anesthesia
	  • Laminectomy
	  • Lumbar diagnostic puncture
	• Splenic surgeries or procedures
	• Thoracic surgery
	• Urologic surgeries or procedures:
	  • Kidney biopsy
	  • Bladder resection
	  • Nephrectomy
	  • Transurethral prostate resection
	  • Urologic cancer surgery or tumor ablation
	• Vascular and general surgeries

Develop a Procedural Plan

PRE-Procedure[49]							
DOAC Type	**Surgery/ Procedure Bleeding Risk**	**PRE-Procedure Interruption of DOAC**					
		Day -5	**Day -4**	**Day -3**	**Day -2**	**Day -1**	**Day 0**
Dabigatran CrCl < 50 mL/min	High	√	X	X	X	X	**No DOAC taken on the day of surgery/ procedure**
	Low	√	√	√	X	X	
Dabigatran CrCl ≥ 50 mL/min Rivaroxaban Apixaban Edoxaban	High	√	√	√	X	X	
	Low	√	√	√	√	X	

POST-Procedure						
DOAC Type	**Surgery/ Procedure Bleeding Risk**	**POST-Procedure Resumption of DOAC***				
		Day 0	**Day +1**	**Day +2**	**Day +3**	**Day +4**
Any DOAC	High	**No DOAC taken on the day of surgery/ procedure**	X	√	√	√
	Low		√	√	√	√

KEY		
Take Dose	**Flexibility of Dose Timing**	**Do NOT Take Dose**
√	√	X

Abbreviations: CrCl, creatinine clearance; DOAC, direct oral anticoagulant.

**According to the American Society of Regional Anesthesia, patients having neuraxial anesthesia or epidural pain procedures should discontinue dabigatran 120 hours and apixaban/edoxaban/rivaroxaban 72 hours prior to procedure. The DOAC may be resumed at least 6 hours after catheter removal or according the surgery/procedure bleeding risk timeframe provided above, whichever is longer.*[51]

LABORATORY MONITORING

The specificity, predictability, and wide therapeutic index of DOACs allow for fixed dosing without a need for routine monitoring. However, there are instances where the measurement of DOAC activity would be useful, to direct therapy and inform long-term treatment decisions. Most scenarios that would trigger laboratory testing for DOACs are urgent (e.g., bleeding, thrombosis, or need for surgery), thus lab results will often be random out of necessity, as opposed to routine monitoring. Potential indications for DOAC measurement include the following[11]:

Detection of Clinically Relevant Levels	Detection of Expected On-Therapy Levels	Detection of Excessive Levels
• Urgent or emergent invasive procedure • Neuraxial anesthesia • Major trauma • Potential thrombolysis in acute thromboembolism • Hemorrhage	• Assessing adherence • Breakthrough thrombosis • Drug interactions	• Hemorrhage • Diminished/changing renal function • Hepatic impairment • Drug interactions • Accidental or intended overdose • Advanced age

Characteristics of Coagulation Tests for Estimating Plasma Concentrations of DOACs or Their Relative Intensity of Anticoagulation[49]*

Drugs	Lab Tests	Availability	Dependence of Reagent
Dabigatran	APTT*	24/7, all labs	Yes
	TT	24/7, all labs	Yes
	dTT	Not routinely available, but can be implemented	No
	ECT	Not routinely available, but can be implemented in some labs	No
Rivaroxaban Edoxaban	PT*	24/7, all labs	Yes
Rivaroxaban Apixaban Edoxaban	Chromogenic anti-Xa assays*	Not routinely available; when available, not always 24 hours; can be implemented in all labs	No
Dabigatran Rivaroxaban Apixaban Edoxaban	LC-MS/MS	Requires trained staff; only in specialized labs	Not applicable

Abbreviations: APTT, activated partial thromboplastin time; DOAC, direct oral anticoagulant; dRVVT, diluted Russell's viper venom time; dTT, dilute thrombin time; ECT, ecarin clotting time; FXa, factor Xa; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LMWH, low-molecular-weight heparin; PT prothrombin time; TT, thrombin time; UFH, unfractionated heparin.

**None of these tests are able to discriminate between therapies. Thrombin-specific tests can easily identify dabigatran because it is the only direct oral thrombin inhibitor, but other direct thrombin inhibitors such as argatroban or hirudin can influence them. For direct FXa inhibitors, only the Biophen® Direct Factor Xa Inhibitor assay can discriminate between heparins and direct FXa inhibitors but cannot differentiate between direct FXa inhibitors. Mass spectrometry is the only technique able to directly discriminate between therapies. An UFH or LMWH anti-Xa assay has also been shown to qualitatively exclude the presence of significant levels of a DOAC.*

Because of the inadequacy of common coagulation assays and the limited availability of more specific/precise assays, the routine measure of DOAC activity is not recommended.[11]

Guidance statement: We suggest that clinicians do not routinely measure DOAC activity. If measurement of a DOAC is indicated, we suggest that clinicians use assays that are validated either locally or in a reference laboratory and that are readily available. The chosen assay should be suitable for the DOAC being used, as well as for the indication for measurement.[11]
Management of VTE: Clinical Guidance from the AC Forum (Burnett, et al. 2016)

MANAGING DRUG-DRUG INTERACTIONS

Pharmacodynamic Interactions

Antiplatelet therapies, NSAIDs, and selective serotonin reuptake inhibitors (SSRIs), may not affect DOAC plasma concentrations but likely increase risk of bleeding in DOAC patients via pharmacodynamic interaction (i.e., impairment of platelet function) or adverse drug effects (e.g., gastric ulcer). Antiplatelet and NSAID therapies in particular have been shown to increase the risk of bleeding when combined with DOAC therapy, so **clinicians can intervene by ensuring these therapies are only combined when the benefit clearly outweighs the known risk of bleeding accompanying concomitant therapy.**

Pharmacokinetic Interactions

P-glycoprotein: All DOACs are substrates of P-glycoprotein (P-gp), which is an efflux transporter located in the gut mucosa and regulates absorption of drugs. Therefore, **all DOACs are subject to interactions with drugs that modify P-gp.**

- **P-gp Inducers** may reduce plasma DOAC concentrations (increasing risk of thrombosis).
- **P-gp Inhibitors** may increase plasma DOAC concentrations (increasing risk of bleeding).

Cytochrome P450 (CYP) 3A4: Rivaroxaban and apixaban are both substrates for hepatic CYP3A4 metabolism (18% rivaroxaban, < 32% apixaban). The alternate elimination pathways for these DOACs should dampen the effect of CYP3A4-based drug-drug interactions. However, **drugs that modify P-gp *and* are STRONG modifiers of CYP3A4 could become clinically significant interactions with rivaroxaban and apixaban.** The potential clinical significance of P-gp and MODERATE modifiers of CYP3A4 is controversial, although expected to be less than that of STRONG CYP3A4 modifiers.

Unlike warfarin, DOACs have a relatively wide therapeutic index (the difference between toxicity and therapeutic efficacy), so even if interactions are present, the DOAC patient may be able to tolerate shifts in drug concentration that remain clinically insignificant.

As drug interaction reports and reviews in the literature may vary, it is important to apply a standard set of criteria when determining the relevance of potential DOAC drug interactions in the context of clinical decision-making (tables follow).

Drug Interaction Guidance for Dabigatran and Edoxaban

Dabigatran and edoxaban do not undergo CYP3A4 metabolism, so the pharmacokinetic drug interactions of note involve modifiers of P-gp.

Since these drugs have some degree of renal elimination (dabigatran 80%, edoxaban 50%), patients with renal impairment who are co-administered these DOACs and a P-gp inhibitor can be at increased risk for bleeding due to accumulating drug levels. See table below for **examples** of P-gp modifiers (not an all-inclusive list).

Drug Interaction Guidance for Dabigatran[25] and Edoxaban[26]		
P-gp INDUCERS		**Manufacturer-labeled Guidance**
Apalutamide Carbamazepine Fosphenytoin	Phenytoin Rifampin St. John's Wort	Avoid use.
P-gp INHIBITORS		**Manufacturer-labeled Guidance**
Amiodarone* Azithromycin (systemic) Carvedilol Clarithromycin* Cyclosporine (systemic) Daclatasvir Dronedarone Elagolix Eliglustat Erythromycin (systemic) Flibanserin Fostamatinib Glecaprevir/pibrentasvir Itraconazole (systemic) Ivacaftor Ketoconazole (systemic) Lapatinib Ledipasvir	Neratinib Osimertinib Propafenone Quinidine* Quinine Ranolazine Ritonavir Rolapitant Simeprevir Velpatasvir Vemurafenib Verapamil*	**DABIGATRAN:** NVAF: Consider reducing dabigatran dose from 150 mg twice daily to 75 mg twice daily for patients with CrCl 30-50 mL/min and taking dronedarone or ketoconazole. Avoid use in patients with CrCl < 30 mL/min and taking P-gp inhibitors. VTE: Avoid use in patients with CrCl < 50 mL/min and taking P-gp inhibitors. **No dose adjustment necessary for amiodarone, verapamil, quinidine, or clarithromycin* **EDOXABAN:** NVAF: No dose adjustment necessary. VTE: Reduce dose from 60 mg once daily to 30 mg once daily for verapamil, quinidine, azithromycin, clarithromycin, dronedarone, erythromycin, itraconazole, and ketoconazole. Use of other P-gp inhibitors with edoxaban has not been studied, but a similar dose reduction approach is likely reasonable.

Abbreviations: CrCl, creatinine clearance; P-gp, P-glycoprotein; NVAF, nonvalvular atrial fibrillation; VTE, venous thromboembolism.

Drug Interaction Guidance for Apixaban and Rivaroxaban

Apixaban and rivaroxaban are substrates of P-gp and CYP3A4, so the pharmacokinetic drug interactions of note involve modifiers of P-gp and STRONG modifiers of CYP3A4.

Since these drugs have some degree of renal elimination (apixaban 24%, rivaroxaban 33%), patients with renal impairment who are co-administered these DOACs and a P-gp/STRONG CYP3A4 inhibitor can be at increased risk for bleeding due to accumulating drug levels. See table below for **examples** of P-gp/CYP3A4 modifiers.

Drug Interaction Guidance for Apixaban[24] and Rivaroxaban[27]	
COMBINED P-gp AND STRONG CYP3A4 INDUCERS	**Manufacturer-labeled Guidance**
Apalutamide Carbamazepine Fosphenytoin Phenytoin Rifampin St. John's Wort	Avoid use.
STRONG CYP3A4 INDUCERS (no P-gp induction)	**AC Forum Guidance[53]**
Enzalutamide Lumacaftor Mitotane Phenobarbital Primidone	Limited data assessing the clinical significance of this possible interaction; consider patient's thrombotic risk.
COMBINED P-gp AND STRONG CYP3A4 INHIBITORS	**Manufacturer-labeled Guidance**
Clarithromycin* Itraconazole (systemic) Ketoconazole (systemic) Ritonavir	**APIXABAN**: If taking 5 mg or 10 mg twice daily, reduce dose by 50%; if already taking 2.5 mg twice daily, avoid use. **RIVAROXABAN:** Avoid use. **clarithromycin does not significantly increase apixaban or rivaroxaban exposure, so concomitant use is acceptable without dose adjustment.*
COMBINED P-gp AND MODERATE CYP3A4 INHIBITORS	**Manufacturer-labeled Guidance**
Dronedarone Erythromycin (systemic) Verapamil	**APIXABAN:** No specific dose reduction recommended. **RIVAROXABAN:** Avoid in patients with CrCl 15-80 mL/min unless benefit justifies risk.

Abbreviation: CrCl, creatinine clearance.

MANAGING DOAC-ASSOCIATED BLEEDING

All anticoagulants, by their nature, predispose to a risk of bleeding. As a class, the DOACs exhibit comparable efficacy and a lower bleeding risk compared with warfarin among patients with VTE and NVAF, and most importantly, a significantly lower risk of intracranial hemorrhage.

Nevertheless, patients taking DOACs may present with serious bleeding or need for an urgent unplanned procedure. Major bleeding was reported in 2.1% to 3.6% of patients randomized to treatment with a DOAC in phase III clinical trials. Various factors complicate the use of these agents in clinical practice, including availability, potential risk of thrombosis, cost, preparation, and a lack of data on the comparative effectiveness of different reversal strategies. Moreover, FDA-approved reversal agents are not indicated for use with all DOACs or in all clinical scenarios where reversal may be considered.[54] Procedures for managing DOAC-associated bleeding and determining the need for reversal is below.

The largely favorable outcomes of DOAC-associated bleeding in the pre-antidote era suggest that many patients with DOAC-associated bleeding do not require reversal agents and may be managed with supportive measures alone. Such measures include:

- Discontinuation of DOAC and other medications known to interfere with hemostasis (e.g., antiplatelet agents)
- Compression of, or procedural management, directed at the bleeding site
- Volume resuscitation and transfusion support
- Antifibrinolytic therapy, may be beneficial for patients with mucosal bleeding (e.g., epistaxis, uterine bleeding)
- Oral activated charcoal, to remove unabsorbed DOAC from the gastrointestinal tract if it was taken in the last several hours
- Reserve reversal agents for life-threatening bleeding, critical site bleeding, or major bleeding that does not respond to the aforementioned supportive measures[54]

Determine Bleed Severity

Major Bleed(s) are bleeds associated with hemodynamic compromise, occurring in an anatomically critical site (e.g., intracranial), or associated with a decrease of hemoglobin ≥ 2 g/dL (when baseline is known) or requiring transfusion of ≥ 2 units of packed red blood cells.[55, 56]

Nonmajor Bleed(s) are all bleeds not classified as major. Some nonmajor bleeds may require intervention or hospitalization.

Any "life-threatening" bleeding is considered major. Certain factors increase patient risk for bleeding and should be taken into account prior to prescribing any anticoagulant. Take steps to reduce the patient's risk of bleeding.

When considering a reversal agent, it is also important to assess the degree of anticoagulation and the likelihood that the anticoagulant is contributing to bleeding. Assays for measurement of plasma DOAC concentration are not available at all centers, particularly on a stat basis. If such assays are not available, degree of anticoagulation can be estimated based on the specific agent, dose, interval since last dose, and renal and hepatic function. A reversal agent should only be considered when there is demonstration or expectation of clinically relevant DOAC levels.[54]

Assess for Clinically Relevant Drug Levels

- Measuring the DOAC anticoagulant effect during management of bleeding has not shown to be beneficial; it is better not to delay intervention for life-threatening bleeding (i.e., administering reversal agents) to wait for a DOAC test result.[48]
- It is advisable to use multiple strategies (i.e. pharmacokinetic AND laboratory) to assess DOAC effect during bleeding management[48]:
    - Use a comprehensive approach to assessing, confirming, and communicating when the last DOAC dose was administered among the patient and all providers involved.
    - If the last anticoagulant dose was taken at least 24 hours previously in patients with normal renal function, drug levels are probably not clinically relevant.
    - If the patient is taking dabigatran, thrombin time can be used to rule out clinically relevant drug levels. Specialized tests can quantify drug levels.
    - If the patient is taking apixaban, edoxaban, or rivaroxaban, an undetectable unfractionated heparin (UFH) or LMWH anti-Xa is helpful to rule out relevant drug levels. A DOAC-specific anti-Xa should be used to quantify DOAC levels.

Manage Bleeding

- Stop DOAC.
- Provide supportive care.
- Provide local therapy/manual compression. Contact appropriate interventionalist of site-specific bleeding (e.g., gastroenterology, neurology, or interventional radiology).
- Assess appropriateness of DOAC reversal [using specific antidote or prothrombin complex concentrate (PCC)] in the setting of life-threatening bleeding, critical site bleeding, or major bleeding that does not respond to the aforementioned supportive measures. See AC Forum DOAC Reversal Guidance Statement,[54] the 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants, and the next page for more detail.
- Assess for and manage comorbidities contributing to the bleed (e.g., renal dysfunction, liver disease, thrombocytopenia).[54]

DOAC-Specific Reversal Procedure

Dabigatran Reversal

- Administer 5 g idarucizumab IV (two separate 2.5 g/50 mL vials).
- If bleeding persists and there is laboratory evidence of persistent dabigatran effect after 12-24 hours, a second dose may be reasonable.
- If idarucizumab is not available, administer activated PCC (aPCC) (four-factor PCC [4F-PCC] if aPCC not available) 50 units/kg IV (refer to prescribing information for max units).[54]
- Hemodialysis could be considered if drug level is high, especially in patients with poor renal function.
- Fresh-frozen plasma is not recommended for DOAC reversal.

Apixaban or Rivaroxaban Reversal

- The recommended dosing of andexanet alfa (ANDEXXA) is based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor[57] (see tables below).
- Fresh-frozen plasma is not recommended for DOAC reversal.
- If andexanet alfa is not available, administer 4F-PCC 50 units/kg IV (refer to package insert for max units).

Time Since Last Dose of Apixaban or Rivaroxaban			
FXa Inhibitor	**FXa Inhibitor Last Dose**	**< 8 Hours or Unknown**	**≥ 8 Hours**
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg or Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	> 5 mg or Unknown	High Dose	

Abbreviation: FXa, factor Xa.

Apixaban or Rivaroxaban Andexanet Alfa Dose Procedure				
Dose*	**Initial IV Bolus**	**Follow-On IV Infusion**	**Total Number of 200 mg Vials**	**Total Number of 100 mg Vials**
Low Dose	400 mg at a target rate of 30 mg/min	4 mg/min for up to 120 minutes (480 mg)	5 (2 vials bolus + 3 vials infusion)	9 (4 vials bolus + 5 vials infusion)
High Dose	800 mg at a target rate of 30 mg/min	8 mg/min for up to 120 minutes (960 mg)	9 (4 vials bolus + 5 vials infusion)	18 (8 vials bolus + 10 vials infusion)

**The safety and effectiveness of more than one dose has not been evaluated.*

Edoxaban Reversal[54]

- If 4F-PCC is not available, consider aPCC 50 units/kg IV (refer to prescribing information for max units).
- Fresh-frozen plasma is not recommended for DOAC reversal.

Restarting a DOAC

The decision to resume anticoagulation following a major bleeding event should be made based on numerous factors, including the location of bleed, factors contributing to the bleed, comorbid conditions, thromboembolic risk, and patient/family preferences.

- Ensure there is still a valid indication (e.g., renal function is adequate, length of treatment has not been reached [for VTE treatment or post-op prophylaxis]).
- Base the plan on the balance between bleeding and thromboembolic risks and discussions with other appropriate practitioners (e.g., surgeons), the patient, and caregivers.
- Make sure the dose is correct based on age, renal function, weight, and indication.
- Address any reversible risk factors, such as interacting medications or unnecessary antiplatelet therapy.
- Timing of restart: Delay restart if bleeding occurred in a critical site or if the patient has a high risk for re-bleeding. Anticoagulants should only be restarted after careful risk/benefit assessment and in collaboration with patient and/or family with inclusion of their values and preferences.

MANAGING TRANSITIONS OF CARE

Potential transitions between drug therapies and across care settings (e.g., medical ward to operating room and back, discharge to long-term care facility) are high-risk periods for medical errors and require thoughtful consideration and planning. While DOACs do not require routine outpatient monitoring, a standardized follow-up strategy must be delineated to facilitate periodic patient evaluation for clinically relevant issues.

VTE Outpatient DOAC Therapy Can be Considered in[11]:	
Acute DVT	**PE**
• Stable patients • Meets criteria for outpatient management • Likely to be adherent with medications and follow-up • Have confirmed ability to obtain the anticoagulant(s) • Have expressed understanding of their condition and what to do in the event of bleeding or clotting • Have a good social support system at home	• Risk identification required • With a low risk of adverse outcomes (see PESI score)

Abbreviations: DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index.

DOAC Discharge Checklist for Optimal Care Transitions[11]

- ☐ Patient is an appropriate DOAC candidate
- ☐ Assess patient's eligibility for outpatient treatment (e.g., for acute DVT/PE)
- ☐ Consistent access to DOAC (e.g., affordability, insurance coverage)
- ☐ If transitioning to rehabilitation or skilled nursing facility, ensure DOAC is on formulary
- ☐ DOAC identified and understood as an oral anticoagulant by patient, caregivers, and providers
- ☐ Provision of thorough DOAC education to patient and/or caregiver in their preferred language and at an appropriate literacy level
- ☐ Safety net phone number provided to patient/caregiver (i.e., who to call with questions)
- ☐ Referral or handoff to appropriate provider (e.g., anticoagulation clinic, primary care, etc.)
- ☐ Time of last drug administration in current setting and time of next scheduled dose in new setting
- ☐ Prescribed strategy for appropriate dose change after initial therapy (i.e., either switch to DOAC or DOAC dose de-escalation)
- ☐ Consolidated documentation and communication to next care setting of key information, such as indication for anticoagulation
- ☐ Intended duration of therapy
- ☐ DOAC dose and scheduled time of administration
- ☐ Contact information for anticoagulation provider
- ☐ Follow-up arranged for periodic (e.g., every 6-12 months) assessment of the following:
  - Renal function
  - Liver function
  - Upcoming invasive procedures
  - New drug interactions
  - New contraindications

Abbreviations: DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; PE, pulmonary embolism.

PATIENT AND FAMILY EDUCATION

Education of patients, their families, and caregivers is essential for optimized anticoagulant management. Patient education should be provided at initiation and repeated at scheduled intervals. Documentation of patient education activities is also important. To assure comprehension, patient education should be individualized and employ approaches to engage the audience to maximize understanding and retention.

The patient education mandated in NPSG EP6 is fourfold[22]:

- **Adherence to the medication schedule and dosing instructions**
- **The importance of attending follow-up appointments and lab tests**
- **How anticoagulants interact with other drugs and food**
- **The risk and awareness of potential signs and symptoms of bleeding**

Educating patients and their families on these topics will make it more likely that they will comply with providers' instructions and avoid ADEs.[11]

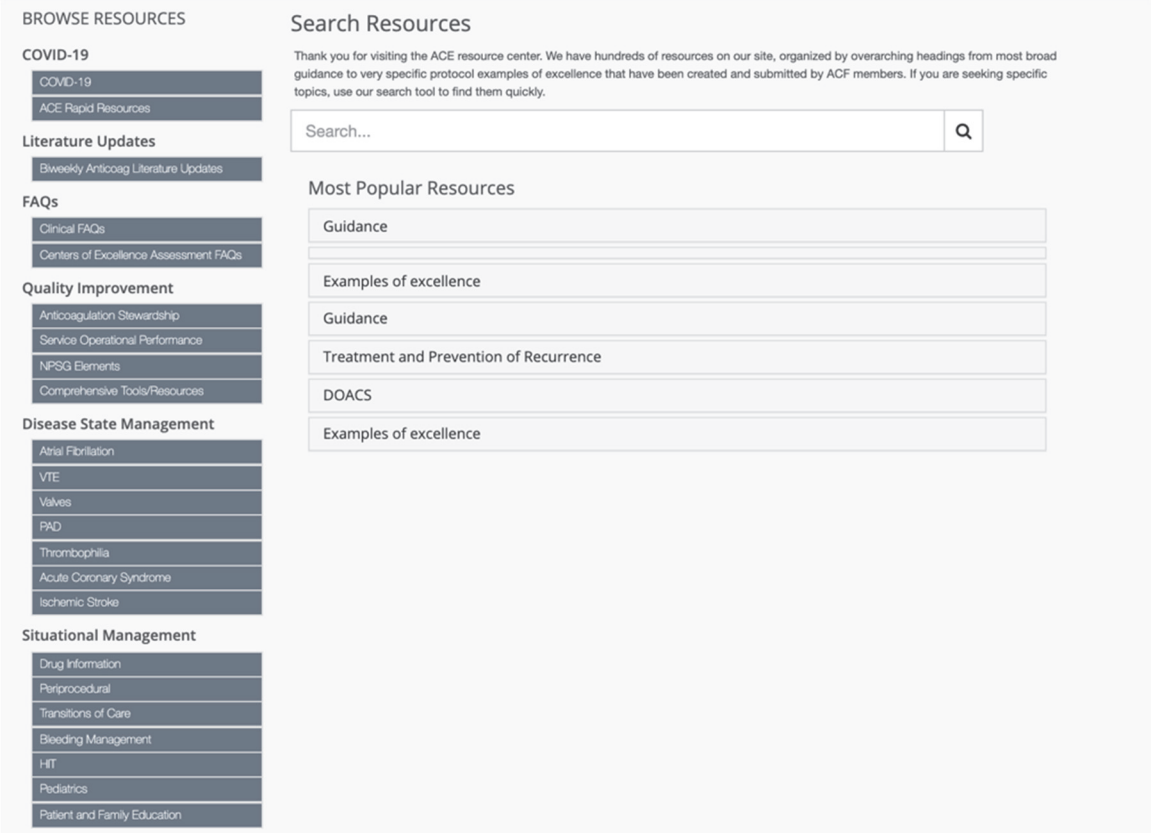
Personnel and support staff routinely engaged in the care of anticoagulation patients should also be educated on clinical aspects of anticoagulant therapies, as well as the policies and procedures of the institution or practice they serve (e.g., reception staff responses to reported bleeding). Clinicians who serve as experts for an anticoagulation service should demonstrate ongoing comprehension and competency of anticoagulation management.

Education of external health care facility administration and staff (e.g., skilled nursing facilities, rehabilitation facilities, etc.) may also be beneficial to promote awareness, standardization, and bi-directional efforts regarding transitions of care.

RESOURCES

The resources listed below (and others) have been developed as a part of this toolkit for health care practitioners, patients, and their families, on a variety of DOAC-related topics. They are available on the AC Forum Centers of Excellence (ACE) website (https://acforum-excellence.org/Resource-Center/index.php).

The ACE Resource Center contains hundreds of tools, organized by topic and a robust search feature, which includes the ability to search on any term, such as the National Patient Safety Goals (e.g., EP1, EP2). A list of the most popular resources appears on the Resource Center home page.



HCP Resources

Shared Decision Making

Developed to enable the conversation between health care provider (HCP) and patient, imparting information about the patient's diagnosis, treatment options, and best practices.

- NVAF
- VTE
- Stable CAD/PAD

Access ACE Tools: https://acforum-excellence.org/

Management of DOACS

Additional DOAC management information

- Managing DOAC Drug-Drug Interactions

Centralized best practice for each of the following disease states:

- Use of DOACs in Nonvalvular Atrial Fibrillation (NVAF)
- Use of DOACs in Venous Thromboembolism (VTE)
- Use of DOACs in Stable Coronary or Peripheral Artery Disease (CAD/PAD)

Access ACE Tools: https://acforum-excellence.org/

Drug Information

Access the drug information section on ACE.

Access ACE Tools: http://di.acforum-excellence.org/

Systems of Care

Adapting anticoagulation services to integrate DOACs, including information on practical and staffing considerations, quality improvement and outcome measures, electronic health record (EHR) integration and interfaces, business planning, cost avoidance, and reimbursement.

- System Considerations
- Announcement Letter (Sample)
- Anticoagulation Service Referral Form (Sample)
- Renewal Form (Sample)

Access ACE Tools: http://so.acforum-excellence.org/

Order Sets for Inpatient Care

Clinical Order Sets are innovative tools in medicine and improve patient safety initiatives that drive high quality, high efficiency health systems. An order set is a sophisticated clinical checklist that integrates best practices into existing workflows through structured clinical orders, presented as an evidence-based checklist. They are ubiquitous in health organizations and are critical for quality improvement initiatives.

AC Forum has developed several order sets involving DOACs. Topics include the following:

- Initiation of Oral Anticoagulant for Atrial Fibrillation
- Acute VTE Care Transition Order Set (Adult)
- VTE Prophylaxis for the Medically Ill Patient
- Safe Initiation of DOAC for Patients with CAD/PAD Already on Guideline Directed Therapy

Access ACE Tools: https://acforum.org/web/education-sets.php

Patient and Family Education Resources

Disease Management

Clear, informative messaging regarding diagnoses, treatment, and disease management.

- What is Atrial Fibrillation (AFib)?
- What is Pulmonary Embolism (PE)?
- What is Deep Vein Thrombosis (DVT)?
- What is Coronary/Peripheral Artery Disease (CAD/PAD)?

Side Effect Management

Helpful information regarding treatment of side effects when taking an anticoagulant.

- Managing Minor Bleeding
- Managing a Nosebleed

Medication Management

Useful information about DOAC medication.

- DOAC Medication Information
- Medication Instructions:
  - Apixaban (Eliquis®) Anticoagulant
  - Dabigatran (Pradaxa®) Anticoagulant
  - Edoxaban (Savaysa®) Anticoagulant
  - Rivaroxaban (Xarelto®) Anticoagulant

Access ACE Tools: http://ed.acforum-excellence.org/

Appendix

SUMMARY GUIDANCE STATEMENTS FROM THE ANTICOAGULATION FORUM FOR THE PRACTICAL MANAGEMENT OF THE DOACS IN VTE TREATMENT[11]

Below are the summary guidance statements from the 2016 VTE Guidance document developed by AC Forum (with minor revisions). Full text is available at https://link.springer.com/article/10.1007/s11239-015-1310-7.

Burnett AE, Mahan CE, Vazquez SR, Oertel LB, Garcia DA, Ansell J. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. J Thromb Thrombolysis. 2016;41(1):206-232. doi:10.1007/s11239-015-1310-7

Which VTE patients are (and are not) good candidates for DOAC therapy?

DOACs are suggested as an alternative to conventional therapy for VTE treatment in patients who meet appropriate patient selection criteria. For all other patients, we suggest VTE treatment with conventional therapy. Until further data are available, we suggest avoiding DOACs for VTE in patients with antiphospholipid antibody syndrome and patients at extremes of weight.

How should DOACs be initiated for VTE treatment?

We suggest that a thorough patient evaluation be conducted prior to DOAC initiation, which should include assessment of baseline laboratory values, concomitant drug therapies, and comorbidities. We do not recommend initial DOAC therapy in patients who are hospitalized with extensive DVT or who have PE with hemodynamic instability in whom thrombolysis or thrombectomy may be indicated. We suggest that the unique characteristics of each DOAC, their distinct dosing for VTE treatment, and patient preferences should be considered when selecting a DOAC for VTE treatment.

How should the anticoagulant activity of DOACs be measured?

We suggest that clinicians do not routinely measure DOAC activity. If measurement of a DOAC is indicated, we suggest that clinicians use assays that are validated either locally or in a reference laboratory and that are readily available. The chosen assay should be suitable for the DOAC being used, as well as for the indication for measurement, as detailed in Table 6 in the article and above on page 21.

How should VTE patients who require temporary interruption of DOAC therapy be managed?

For VTE patients on DOAC therapy requiring interruption for an invasive procedure, we suggest a carefully constructed, thoughtful approach that emphasizes communication between the provider managing the DOAC therapy, the clinician performing the procedure, and the patient and/or caregiver about the management of the DOAC. If interruption is deemed necessary, we suggest that clinicians consider the patient's renal function, the DOAC half-life, and the associated bleeding risk when determining timing of cessation and resumption of the DOAC. We suggest avoiding routine use of bridge therapy during DOAC interruption.

How should patients with DOAC drug-drug interactions be managed?

DOAC drug-drug interaction management must be patient-specific and incorporate multiple clinical parameters, such as concomitant renal impairment, extremes of body weight, or advanced age. We suggest that clinicians avoid concomitant use of dabigatran and edoxaban with a strong inducer or inhibitor of P-gp and avoid use of rivaroxaban and apixaban with combined strong inducers and inhibitors of P-gp and CYP3A4.

For patients requiring concomitant DOAC therapy with a P-gp and/or CYP3A4 inhibitor, we suggest clinicians closely follow the detailed dose adjustments or avoidance provided in the product labeling. We suggest concomitant antiplatelet or NSAIDs be avoided during DOAC therapy unless the potential benefit clearly justifies the increased bleeding risk.

How should patients transition between anticoagulants?

Switching from warfarin to a DOAC:
When switching from warfarin to dabigatran, apixaban, rivaroxaban, or edoxaban, discontinue warfarin and start the DOAC when the INR has decreased to < 2 for dabigatran and apixaban (< 3 for rivaroxaban, < 2.5 for edoxaban), to avoid periods of inadequate or excessive anticoagulation. In cases where the target INR was 2.5-3.5 or higher due to recurrent VTE, initiate the DOAC when the INR is near 2.5 or the lower end of the specified range.

Switching from non-warfarin anticoagulant to a DOAC:

- When switching from a DOAC to a different DOAC or from LMWH/fondaparinux to a DOAC, start the new DOAC at the next scheduled administration of the original anticoagulant and then discontinue the original anticoagulant.
- When switching from IV UFH to a DOAC, stop the heparin infusion and begin administration of the DOAC at the time of UFH discontinuation.
- When switching from SC UFH treatment to a DOAC, stop the SC UFH and initiate the DOAC approximately 4-5 hours after the last dose of SC UFH.

How should DOAC-associated bleeding be managed?

We suggest hospitals develop evidence-based antithrombotic reversal and bleeding protocols that contain clinical decision support for providers and are easy to access and use in urgent or emergent situations. We suggest that general approaches to bleed management be employed for all patients presenting with severe hemorrhage. For DOAC patients, clinicians should attempt to rapidly determine time of last DOAC ingestion and patient's renal function, to estimate remaining duration of exposure and potential utility of additional interventions. Until specific antidotes are available, we suggest clinicians consider use of non-specific reversal strategies in patient's refractory to standard therapies. For direct Xa inhibitors, non-activated 4F-PCC 50 units/kg may be considered. For direct thrombin inhibitors, either non-activated 4F-PCC 50 units/kg or activated PCC 80 units/kg may be considered. However, it is reasonable to withhold these strategies given the associated thrombosis risk and the low quality of evidence that they are beneficial in this setting.

What is an appropriate care transition and follow-up strategy for VTE patients on DOAC therapy?

We suggest that hospitals implement systematic DOAC management and documentation processes that address appropriate patient selection, dose initiation, perioperative management, switches between anticoagulants, and transitions between care settings. Whenever possible, implementation of a specialized inpatient and outpatient anticoagulation services is strongly encouraged. We also strongly recommend that clinicians utilize a DOAC discharge checklist (see table 18 in the article and above on page 30) to ensure all key aspects of patient care and DOAC therapy are addressed.

How can patients enhance safety and efficacy of their DOAC therapy?

We suggest use of a comprehensive, multimedia educational approach with patients and families to maximize the efficacy and safety associated with anticoagulation in the VTE population. Information should be provided in the patient's preferred language and at an appropriate level of health literacy.

SPECIAL POPULATIONS

In the section on Patient Eligibility, information is provided surrounding the use of DOACs in various patient populations. Details are provided below the table.

	Optimal DOAC Candidates	Patients Who Should Avoid DOACs	Controversies (Discuss Risk/Benefit Prior to Use)
Indication	FDA-approved indications	Indications for which DOACs have been proven inefficacious and/or harmful	Off-label indications
		○ Mechanical heart-valve replacement	
		○ LVAD	
		○ APS	
		○ ESUS	
		○ TAVR	
		Within 3 months of a bioprosthetic heart valve replacement [g]	
		Valvular AF	VTE associated with GI or GU cancer
Hepatic	Normal hepatic function (Child-Pugh A)	Severe hepatic impairment (Child-Pugh C)	Moderate hepatic impairment (Child-Pugh B)
Renal	Adequate renal function (CrCl > 30 mL/min)		Severe renal impairment (CrCl < 30 mL/min)
Pregnancy/ breastfeeding	Not pregnant or breastfeeding	Pregnant or breastfeeding	
	Women of child-bearing potential using a reliable method of contraception	Women of child-bearing potential NOT using a reliable method of contraception	
DDI	Taking no medications known to interact with DOAC	Taking medications known to SIGNIFICANTLY interact with DOAC	Taking moderate inhibitors of DOAC metabolism in the setting of moderately impaired renal function
Adherence	Adequate medication adherence		Poor medication adherence
Cost	Able to consistently pay for DOAC through personal funds, insurance, or assistance programs	Unable to consistently pay for DOAC through personal funds, insurance, or assistance programs	

	Optimal DOAC Candidates	Patients Who Should Avoid DOACs	Controversies (Discuss Risk/Benefit Prior to Use)
Warf/ LMWH			Treatment failure while on therapeutic warfarin or LMWH
Body Weight			Extremes of body weight (e.g., weight < 50 kg, weight >120 kg or BMI ≥ 40), although recent studies suggest that standard doses can be used
Bariatric			Bypassed or removed portions of the GI tract

Abbreviations: AF, atrial fibrillation; APS, antiphospholipid antibody syndrome; BMI, body mass index; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ESUS, embolic stroke of undetermined source; FDA, Food and Drug Administration; GI, gastrointestinal; GU, genitourinary; LMWH, low-molecular-weight heparin; LVAD, left ventricular assist device; PE, pulmonary embolism; TAVR, transcatheter aortic valve replacement.

Patients Who Should Avoid DOACs

The following indications for which DOACs have been proven inefficacious and/or harmful:

Mechanical heart valve replacement: The presence of a mechanical heart valve replacement represents a stand-alone indication for anticoagulation therapy. As such, these patients were excluded from the pivotal DOAC NVAF and VTE trials. In addition, the RE-ALIGN trial was terminated early after dabigatran resulted in significantly more thromboembolic and bleeding complications than warfarin in patients with mechanical heart valves[29].

Left Ventricular Assist Device (LVAD): A pilot study comparing phenprocoumon to dabigatran was terminated because of increased thromboembolic events in the dabigatran arm[58].

Antiphospholipid Antibody Syndrome (APS): The TRAPS[31] trial, comparing warfarin to rivaroxaban in patients with triple-positive APS, was terminated prematurely because of a significantly higher incidence of thromboembolic and bleeding events in the rivaroxaban arm. The ongoing ASTRO-APS trial,[32,33] is comparing apixaban to warfarin in patients with definite, likely, or historical APS and required a protocol change after enrolling only 30 patients because of an increased incidence of stroke in the apixaban arm. The protocol changed to only include those with a history of venous thrombosis, and MRIs were required to rule out history of stroke. There were also recent changes to the prescribing information of rivaroxaban[27] and apixaban,[24] recommending against the use of these agents in the setting of APS.

Embolic Stroke of Undetermined Source (ESUS): There exists little to guide therapy for ESUS, yet recommendations for therapeutic anticoagulation are often made. With regard to DOACs:

- NAVIGATE ESUS was terminated after enrollment of 7213 patients because rivaroxaban was found to be no more effective than ASA 100 mg daily in patients with ESUS[34].
- In RE-SPECT ESUS, dabigatran failed to demonstrate superiority in recurrent stroke prevention over ASA 100 mg daily in patients with ESUS. It also resulted in more clinically relevant nonmajor bleeding than ASA[35].

Transcatheter Aortic Valve Replacement (TAVR): Antiplatelet therapy (typically dual antiplatelet therapy [DAPT]) has been the standard of care for TAVR, although warfarin alone has been listed as an option in valve guidelines. GALILEO, a trial comparing rivaroxaban 10 mg plus low-dose ASA for 90 days followed by ASA alone vs clopidogrel 75 mg daily plus low-dose ASA for 90 days followed by ASA alone was terminated early after a preliminary analysis demonstrated harm in the rivaroxaban arm. Rivaroxaban should not be part of the antithrombotic regimen for TAVR, but use of DOACs for other indications beyond 90 days of TAVR is acceptable.[36]

Within 3 months of a bioprosthetic heart valve replacement: Within 3 months of a bioprosthetic heart valve replacement, guidelines favor vitamin K antagonists (VKAs) for the first 3 months after bioprosthetic mitral valve replacement (MVR, with an option for the same therapy for the first 3 months of therapy after aortic valve replacement (AVR). Since therapy is appropriate for the valve itself during this period, DOAC utilization for any indication is discouraged, and warfarin is preferred[59]. Additionally, DOACs are not advised when a bioprosthetic valve is placed in the mitral position because of risk of rheumatic mitral stenosis. Recent studies demonstrate that DOACs may be an option in this population, and additional studies are ongoing to further address this question.[60]

Selected Indications and Contraindications for DOAC Therapy in AF Patients	
Condition	**Eligibility for DOAC Therapy**
Mechanical prosthetic valve	Contraindicated
Moderate to severe mitral stenosis (usually of rheumatic origin)	Contraindicated
Mild-to-moderate other native valvular disease (e.g., mild-to-moderate aortic stenosis or regurgitation, degenerative mitral regurgitation, etc.)	Included in DOAC trials
Severe aortic stenosis*	Limited data (excluded in RE-LY) Most will undergo intervention
Bioprosthetic valve (after > 3 months post-operatively)*	Not advised if for rheumatic mitral stenosis
	Acceptable if for degenerative mitral regurgitation or in the aortic position
Mitral valve repair (after > 3 months post-operatively)*	Some patients included in some DOAC trials

Selected Indications and Contraindications for DOAC Therapy in AF Patients	
Condition	**Eligibility for DOAC Therapy**
PTAV and TAVI*	No prospective data yet. May require combination with single or dual antiplatelet therapy
Hypertrophic cardiomyopathy*	Few data, but patients may be eligible for DOACs

Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulant; PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.

**Limited data available Adapted from 2018 European Heart Rhythm Association Practical Guide, Table 1*[37]

Valvular AF: Patients with valvular AF were excluded from the pivotal AF DOAC trials. The definition of NVAF, however, was not consistent across trials, but the accepted definition across guidelines is AF in the absence of a mechanical valve prosthesis or moderate to severe mitral stenosis (usually of rheumatic origin).[38–40]

Hepatic impairment: Patients with hepatic impairment with Child-Pugh class B or C were excluded from the pivotal trials of the oral anti-Xa DOACs. Class B was allowed in the pivotal trials of dabigatran.[37]

Calculation of the Child-Turcotte-Pugh Score and Use of DOACs in Hepatic Insufficiency			
Parameters	1 point	2 points	3 points
Encephalopathy	No	Grade 1-2 (suppressed with medication)	Grade 3-4 (refractory/chronic)
Ascites	No	Mild (diuretic responsive)	Moderate-severe (diuretic refractory)
Bilirubin	< 2 mg/dL	2-3 mg/dL	> 3 mg/dL
	< 34 µmol/L	34-50 µmol/L	> 50 µmol/L
Albumin	> 3.5 g/dL	2.8-3.5 g/dL	< 2.8 g/dL
	> 35 g/L	28-35 g/L	< 28 g/dL
INR	< 1.7	1.71-2.30	> 2.30

Abbreviations: DOAC, direct oral anticoagulant; INR, international normalized ratio.

Child-Pugh Category	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
A (5-6 points)	No dose reduction	No dose reduction	No dose reduction	No dose reduction
B (7-9 points)	Use with caution	Use with caution	Use with caution	Do not use
C (10-15 points)	Do not use	Do not use	Do not use	Do not use

Adapted from 2018 European Heart Rhythm Association Practical Guide, Table 8[45]

Renal impairment (creatinine clearance [CrCl] < 30 mL/min): The pivotal DOAC trials excluded patients with severe renal impairment (CrCl < 30 mL/min for dabigatran, rivaroxaban, and edoxaban,

< 25mL/min or serum creatinine (SCr) > 2.5mg/dL for apixaban). Apixaban undergoes the lowest degree of renal clearance, and both apixaban and rivaroxaban include language in their prescribing information[24,27] about end-stage renal disease (ESRD) and dialysis, but this is based on pharmacokinetic data after a single dose given to a small number of patients.

The best clinical evidence to date stems from a retrospective evaluation of over 25,000 patients on dialysis (23,172 on warfarin and 2,351 on apixaban) with NVAF from the United States Renal Data System. This study found that apixaban was associated with lower bleeding rates than warfarin. Further, apixaban 5 mg twice daily was associated with reductions in thromboembolic and mortality risk.[44] Although prospective trials would be ideal before DOACs are widely used in dialysis patients, it is important to consider the evidence with warfarin in this population before considering it the "standard of care." Use of warfarin in the ESRD/dialysis populations has been extrapolated from non-ESRD populations, and multiple studies have suggested net harm when dialysis patients are prescribed warfarin for AF.[44,45]

Pregnancy or breastfeeding: DOACs should be used only if potential benefit justifies potential risk to mother and baby. DOAC dosing has not been studied in pregnancy and cannot be monitored with standard laboratory testing. There is risk of pregnancy-related hemorrhage.[27] Based on the molecular weight of the DOACs, it is likely that drug does transfer to breast milk.

Women of child-bearing potential NOT using a reliable method of contraception: DOAC use as per above for risk during pregnancy.

Taking medications known to SIGNIFICANTLY interact with DOAC: DOACs should be avoided in patients co-prescribed strong inhibitors or inducers of their metabolism, driven by P-gp and/or CYP450 3A4 (depending on the particular DOAC). Controversy exists around patients co-prescribed moderate inhibitors of DOAC metabolism in the setting of other reasons for increased DOAC exposure, such as moderate renal dysfunction.[41, 27]

Unable to consistently pay for DOAC through personal funds, insurance, or assistance programs: DOACs can be expensive, and patients can be at risk of stopping anticoagulant therapy without notifying their provider.

Controversies (Discuss Risk/Benefit Prior to Use)

Off-label indication: FDA-approved indications for DOACs are limited, but the same can be said about all anticoagulants. Warfarin is often treated as the "standard of care" for conditions for which DOACs have not been adequately studied, but it is important to recognize that warfarin was used off-label because it was the only oral anticoagulant available at the time. Although experience with warfarin use for these indications does provide some evidence and clinical experience, until clinical trial data is available, the choice of anticoagulant will remain controversial.

VTE associated with GI or GU cancer: Although DOACs are now considered an option for cancer-associated VTE, guidelines encourage LMWH over a DOAC if the patient has a high risk of bleeding. This stems from trials demonstrating a higher incidence of major bleeding with rivaroxaban and

edoxaban as compared to dalteparin. This was specifically driven by GI and GU bleeding in patients with GI and GU cancers, so the guidelines specifically favor LMWH in these settings.[42,43]

Moderate hepatic impairment: *See severe hepatic impairment, above.*

Severe renal impairment (CrCl < 30 mL/min): *See renal impairment, above.*

Taking moderate inhibitors of DOAC metabolism in the setting of moderately impaired renal function: *See drug-drug interactions, above.*

Poor medication adherence: With DOAC use, there is less frequent interaction with a health care provider and no regular laboratory monitoring that provides objective feedback regarding DOAC adherence. Given the short half-lives of the DOACs, patients who frequently miss DOAC doses may not derive similar protective benefit as medication-compliant patients. Conversely, the rapid onset of the DOACs does ensure therapeutic anticoagulation as soon as the DOAC dose is taken, theoretically minimizing the window of subtherapeutic anticoagulation. These considerations should be weighed with the potential risks and benefits of alternative therapies.

Treatment failure while on therapeutic warfarin or LMWH: Guidelines encourage use of LMWH[46] for VTE patients who suffer a therapeutic failure of oral anticoagulation therapy based upon limited evidence.[46] It is possible that DOACs are a reasonable alternative in this setting given their excellent efficacy results in the cancer VTE population. However, as the DOACs have not been specifically studied in the setting of treatment failure, their use in this setting remains controversial. This is, however, not based on strong evidence. Further, no such guidance exists for therapeutic failure of oral therapies in the setting of other indications for therapy, so the best approach is not clear.

Extremes of body weight (e.g., weight < 50 kg, weight > 120 kg, or body mass index [BMI] ≥ 40 kg/m^2): In 2016, the International Society on Thrombosis and Haemostasis (ISTH) published guidance discouraging the use of DOACs in patients weighing > 120 kg or with a BMI ≥ 40 kg/m^2. This was based on limited experience from the pivotal DOAC trials as well as pharmacokinetic concerns. This was not based on evidence of inefficacy or increased risk in this population. Since that time, a growing body of evidence suggests safety and efficacy in the obese and, in fact, an "obesity paradox" has been described. (i.e., obesity is associated with reduced risk of thrombotic events in AF patients).[30,61,62] There are emerging data to suggest that DOACs are efficacious and safe to use in individuals with severe obesity.

Bypassed or removed portions of the GI tract: Although not mentioned in the prescribing information, concern arises with the use of DOACs in patients with significant portions of their GI absorptive surface bypassed (i.e., gastric bypass, distally-placed feeding tubes, etc.) or removed (h/o GI resections). This is especially true when therapeutic laboratory monitoring of these agents is not readily available. Choice of agent, type of GI procedure, and time since procedure may impact the level of concern, but this represents a target of future research.[47]

> Appendix

Abbreviations

A

AC Forum – The Anticoagulation Forum

ADE – adverse drug events

AF – atrial fibrillation

aPCC – activated prothrombin complex concentrate

APS – antiphospholipid antibody syndrome

APTT – activated partial thromboplastin time

ASA – acetylsalicylic acid

ASH – American Society of Hematology

AVR – aortic valve replacement

B

BMI – body mass index

C

CAD – coronary artery disease

CI – confidence interval

CrCl – Creatinine Clearance

CV – cardiovascular

CYP – cytochrome

D

DAPT – dual antiplatelet therapy

DOAC – direct oral anticoagulant

dRVVT – diluted Russell's viper venom time

dTT – dilute thrombin time

DVT – deep vein thrombosis

> Appendix

E

ECT – ecarin clotting time

EHR – electronic health records

EP – Element of Performance

ESRD – end-stage renal disease

ESUS – embolic stroke of undetermined source

F

FDA – Food and Drug Administration (US)

FXa – blood coagulation factor Xa

G

GI – gastrointestinal

GU – genitourinary

H

HR – hazard ratio

I

INR – international normalized ratio

ISTH – International Society of Thrombosis and Hemostasis

IV – intravenous

L

LC-MS/MS – liquid chromatography-tandem mass spectrometry

LMWH – low-molecular-weight heparin

LVAD – left ventricular assist device

M

MACE – major cardiovascular events

mg - milligrams

MI – myocardial infarction

mL/min – milliliters per minute

MVR – mitral valve replacement

N

NPO – nil per os (nothing by mouth)

NPSG – National Patient Safety Goals

NSAIDs – nonsteroidal anti-inflammatory drugs

NVAF – nonvalvular atrial fibrillation

P

PAD – peripheral artery disease

PAUSE – Perioperative Anticoagulation Use for Surgery Evaluation

PCC – prothrombin complex concentrate

PE – pulmonary embolism

PESI – Pulmonary Embolism Severity Index

P-gp – P-glycoprotein

PI – prescribing information

PT – prothrombin time

PTAV – percutaneous transluminal aortic valvuloplasty

R

RR – risk ratio

S

SCr – serum creatinine

SSRIs – selective serotonin reuptake inhibitors

T

TAVI – transcatheter aortic valve implantation

TAVR – transcatheter aortic valve replacement

TJC – The Joint Commission

TT – thrombin time

U

UFH – unfractionated heparin

V

VKA – vitamin K antagonists

VTE – venous thromboembolism

#

4F-PCC - four-factor prothrombin complex

> Appendix

Prescribing Information

Prescribing information is current as of development of this resource. However, it is important to check the manufacturers' website for the most current version to capture any changes in dosage, indication, or safety information.

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