ACE CLINICAL GUIDANCE

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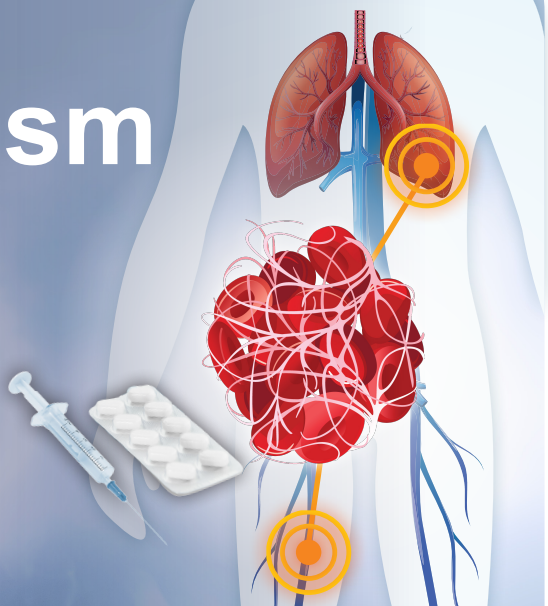
Venous thromboembolism

Treating with the appropriate anticoagulant and duration



Objective

To optimise anticoagulation treatment for venous thromboembolism (VTE)

Scope

Treatment of VTE with anticoagulants in adult patients

Target audience

This clinical guidance is relevant to all healthcare professionals caring for patients with VTE, especially those providing primary or generalist care

Venous thromboembolism (VTE) is a serious medical condition that covers deep vein thrombosis (DVT) and pulmonary embolism (PE). Globally, patients face a 30-day mortality risk of 5% for PE and 3% for DVT following diagnosis.[1,2] Although the annual incidence of VTE in Asia (ranging from 13.8 to 19.9 per 100,000 people) is lower than the rest of the world, VTE prevalence is increasing over time likely due to population ageing, higher number of surgeries, and higher cancer rates.[3] As VTE has long-term complications that adversely affect quality of life and often leads to substantial healthcare utilisation, this ACG aims to guide healthcare professionals to optimise the treatment of VTE with an appropriate anticoagulant and treatment duration.

Statement of Intent

This ACE Clinical Guidance (ACG) provides concise, evidence-based recommendations and serves as a common starting point nationally for clinical decision-making. It is underpinned by a wide array of considerations contextualised to Singapore, based on best available evidence at the time of development. The ACG is not exhaustive of the subject matter and does not replace clinical judgement. The recommendations in the ACG are not mandatory, and the responsibility for making decisions appropriate to the circumstances of the individual patient remains at all times with the healthcare professional.

ACE agency for care effectiveness

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Treatment initiation

Recommendation 1

Start anticoagulation as soon as possible for patients with confirmed proximal DVT or PE, unless contraindicated.

The risk of thrombus extension is highest in the first few days after VTE is diagnosed.[4] Therefore, starting anticoagulation as soon as possible is crucial to prevent extension, VTE recurrence, morbidity, and death. Absolute contraindications for anticoagulation include severe coagulation defects, severe thrombocytopaenia, uncontrollable active bleeding, and acute haemorrhagic stroke. For these patients, temporary insertion of an inferior vena cava filter is usually considered.[5–9]

Isolated distal DVT

Following distal DVT diagnosis, the decision to initiate anticoagulation therapy depends on considerations such as:

- Persistent risk factors (e.g., active cancer or inflammatory bowel disease)[5,10]
- Severe symptoms[5]
- Risk factors for extension (e.g., positive D-dimer, multiple vein involvement, thrombosis close to proximal veins, history of VTE, absence of reversible provoking factors)[5]
- Evidence of thrombus extension[5]
- Unprovoked distal DVT, i.e., VTE that is not associated with a provoking risk factor (transient or persistent)[5,10]

A short course of anticoagulation may be preferred for patients with any of the above.[5]

However, monitoring with serial imaging may be sufficient or preferred for those with transient/reversible provoking risk factors (e.g., surgery, trauma, immobilisation, bed confinement, long-haul flight, pregnancy, or oestrogen therapy).[5,10]

Choice of anticoagulation therapy

Anticoagulants for VTE treatment include direct oral anticoagulants (DOACs), warfarin, low molecular weight heparin (LMWH), and unfractionated heparin (UFH). When selecting an appropriate anticoagulant, consider patient factors, medication properties, patient preferences, and cost. Figure 1 on page 3 summarises selection criteria and treatment duration, and Table 1 on page 6 summarises key medication characteristics.

Recommendation 2

For patients from the general population, use a DOAC for at least 3 months as the preferred anticoagulant for VTE treatment; consider warfarin as an alternative if DOACs are not suitable.

DOACs are the oral anticoagulant of choice for most patients with VTE in the general population. DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are as effective as warfarin in preventing VTE recurrence, with the added benefit of reducing the likelihood of bleeding outcomes.[11] Other advantages of DOACs over warfarin include fewer drug and dietary interactions, and fixed dosing. Warfarin should be considered when DOACs are not suitable (see Figure 1 for examples of when DOACs are not suitable and for warfarin prescribing considerations).

There is insufficient evidence to recommend one DOAC over another as there are no head-to-head trials comparing DOACs. Practical considerations, such as the need for initial parenteral anticoagulation, would inform the choice of DOAC (see Table 1). While not commonly used locally, edoxaban is registered in Singapore for VTE treatment and listed in this ACG where appropriate, for completeness.

Patients at the extremes of body weight

The pharmacological effects of anticoagulants may be altered by body weight, as this affects medication absorption, distribution, and elimination. Evidence for patients who are underweight is limited[12,13] and closer monitoring for signs and symptoms of bleeding is recommended, especially while on DOACs (warfarin and LMWH can also be considered, as their anticoagulation effects can be feasibly monitored). Consider specialist referral for patients who are underweight (e.g., those <40 kg). For patients who meet the definition for obesity,* evidence suggests that treatment considerations can be similar to those of the general population.[14] Consider specialist referral for patients who have undergone bariatric surgery.

* For Asian populations, obesity is defined as body mass index (BMI) ≥27.5 kg/m^2. Pharmacokinetic data has shown that in patients weighing ≥120 kg, apixaban and dabigatran have reduced systemic exposures, while rivaroxaban has higher systemic exposure than patients in the general population.[15]

Figure 1. Selecting an appropriate anticoagulant and duration for VTE treatment

The figure below summarises the guidance on selecting an appropriate anticoagulant and duration for VTE treatment in various patient groups. More details on the evidence and context surrounding clinical considerations can be found in the main text of the ACG. Details on anticoagulants registered in Singapore, including treatment regimens, can be found in Table 1. Where there are multiple treatment options, practical considerations and individual patient circumstances should guide the choice of anticoagulant.

Patients with confirmed proximal DVT or PE, or isolated distal DVT requiring anticoagulation

1 Identify patient population	2 Select treatment	3 Select treatment duration
General population	▶ Use any of the following DOACs: • Apixaban • Dabigatran • Edoxaban† • Rivaroxaban ▶ Consider warfarin if DOACs are not suitable, for example, for patients with CrCl <15 mL/min, concomitant antiphospholipid syndrome, mechanical heart valves, or patients taking concomitant medications with clinically significant drug-drug interactions with DOACs.‡ *Dabigatran and edoxaban require prior parenteral anticoagulation. Warfarin requires initial overlap with parenteral anticoagulation.*	For VTE provoked by a transient risk factor or first unprovoked isolated distal DVT: • Treat for 3 months For first unprovoked proximal DVT or PE: • Treat for at least 3 months • Consider extended treatment†† if bleeding risk is acceptable and patient is agreeable • Consider dose reduction after 6 months, after discussion with a specialist.
Severe renal impairment (CrCl <30 mL/min)§		
CrCl 15–29 mL/min	▶ Consider apixaban as the preferred option. ▶ Consider rivaroxaban as an alternative, or warfarin if DOACs are not suitable. ▶ Monitor patients more frequently, especially for signs and symptoms of bleeding. Consider specialist referral. *Warfarin requires initial overlap with dose-reduced enoxaparin (consider anti-Xa monitoring if enoxaparin use is >5 days).*	
CrCl <15 mL/min or haemodialysis	▶ Consider warfarin and specialist referral. ▶ DOAC use is generally not recommended for these patients. Consider a DOAC only in rare circumstances,** and only after discussion with a specialist (e.g., in patients who cannot receive warfarin due to a history of heparin-induced thrombocytopenia). *Warfarin requires initial overlap with UFH or dose-reduced enoxaparin (consider anti-Xa monitoring if enoxaparin use is >5 days).*	
Liver disease and coagulopathy	▶ Consider LMWH monotherapy and specialist referral.	
Active cancer		Treat for at least 6 months.[5,16–20] Continue after 6 months if there is ongoing active cancer and acceptable bleeding risk.
GI cancer	▶ Use LMWH monotherapy. ▶ Consider any of the following DOACs as alternatives: • Apixaban • Edoxaban† • Rivaroxaban ▶ Consider specialist referral. *Edoxaban requires prior parenteral anticoagulation.*	
Non-GI cancer	▶ Use any of the following: • Apixaban • Edoxaban† • Rivaroxaban • LMWH monotherapy ▶ Consider specialist referral. *Edoxaban requires prior parenteral anticoagulation.*	
Pregnancy	▶ Use LMWH monotherapy.[21–23] ▶ Consider specialist referral.	Treat for at least 6 weeks after delivery and at least 3 months in total.[21–24]

For patients with recurrent VTE, refer to a specialist

Prescribing considerations for warfarin

- Essential to perform INR monitoring due to its narrow therapeutic range
- Affected by multiple drug-drug, drug-food or drug-herb interactions; monitor effects using INR

Initial parenteral anticoagulation: see Table 1 on page 6 for more details.

† Edoxaban is registered in Singapore for the treatment of VTE but is not commonly used at the time of ACG publication.

‡ DOAC use may be contraindicated in patients taking systemic strong CYP3A4 or P-glycoprotein inhibitors. Consult a pharmacist or appropriate online resources for information on medications with interacting metabolic pathways, especially when patients are taking new concomitant medications or supplements.

§ Patients with CrCl <30 mL/min were excluded in pivotal trials for dabigatran, rivaroxaban, and edoxaban. Patients with CrCl <25 mL/min were excluded in the pivotal trial for apixaban.

** Off-label use for patients with CrCl <15 mL/min or undergoing haemodialysis.

†† Patients enrolled in trials for extended treatment were assessed to be in clinical equipoise.

Abbreviations

CrCl, creatinine clearance
DOAC, direct oral anticoagulant
DVT, deep vein thrombosis
GI, gastrointestinal
INR, international normalised ratio
LMWH, low molecular weight heparin
PE, pulmonary embolism
UFH, unfractionated heparin
VTE, venous thromboembolism

Patients with severe renal impairment

Evidence from observational studies indicates that apixaban is associated with fewer rates of VTE recurrence and fewer bleeding events compared to warfarin for patients with CrCl 15–29 mL/min.[7,25] Limited evidence on rivaroxaban in patients with CrCl 15–29 mL/min suggests similar rates of VTE recurrence compared with warfarin and no increase in major bleeding with decreasing renal function.[26] There are no clinical studies for edoxaban in patients with CrCl 15–29 mL/min at the time of ACG publication. Product information leaflets state that apixaban and rivaroxaban may be used with caution in patients with CrCl 15–29 mL/min, based on pharmacokinetic data. On balance, apixaban can be considered as the preferred option when treating VTE for patients with CrCl 15–29 mL/min.

LMWH monotherapy is not recommended as LMWH is renally excreted and accumulates in renal failure.[27] Patients with CrCl <30 mL/min treated with therapeutic enoxaparin have elevated levels of anti-Xa and an increased risk of a major bleeding.[28,29] Therefore, consider anti-Xa monitoring if dose-reduced enoxaparin is used for more than five days as an initial overlap with warfarin.

UFH monotherapy is also not recommended. Despite its minimal renal excretion and short half-life, UFH is impractical for prolonged use. UFH is usually reserved for patients undergoing invasive procedures, thrombolysis, or those with high bleeding risks as it requires close laboratory monitoring to achieve therapeutic anticoagulation.[30]

As renal impairment increases the risk of VTE and bleeding events,[31] patients with reduced renal function may require dose adjustments (see Table 1) or more frequent monitoring. When considering switching from a DOAC to warfarin in patients with renal impairment, INR should be checked early (see Supplementary guide “Switching between anticoagulants”), especially for patients on dabigatran, which is primarily cleared renally.

Patients with liver disease and coagulopathy

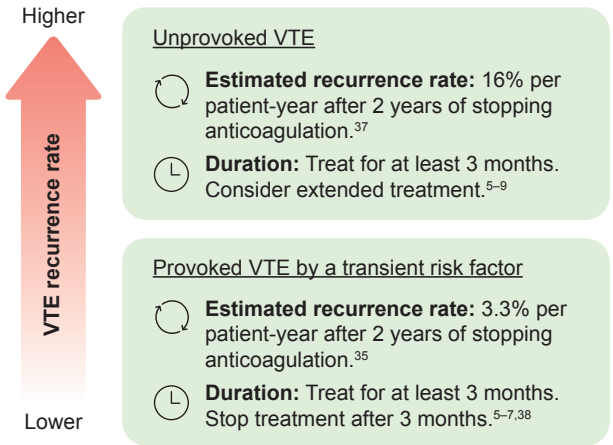
Patients with chronic liver diseases have a delicate balance between procoagulant, anticoagulant, and fibrinolytic systems; loss of this balance may result in haemorrhage or thrombosis depending on their concomitant risk factors.[31] The fragility of this balance and limitations of coagulation tests to accurately reflect bleeding risk increase the complexity of treating VTE in these patients.[32]

LMWH monotherapy can be considered for these patients.[33] Although DOACs such as apixaban, edoxaban, and rivaroxaban can be used for patients with Child Pugh-A cirrhosis, they are contraindicated for patients with liver disease and coagulopathy. While warfarin is not contraindicated in patients with liver disease and coagulopathy, it is less suitable as the INR may not accurately reflect antithrombotic effect.[34]

Duration of treatment

Continue anticoagulation for at least three months to prevent thrombus extension and VTE recurrence for the general population (including patients with renal impairment, or liver disease and coagulopathy). A shorter duration of four to six weeks has been shown to double the risk of recurrent VTE compared to a treatment duration of at least three months, and may be insufficient for active treatment aimed at suppressing the acute episode of VTE.[34] **Treatment beyond three months may be needed for some patients, especially those at increased risk of VTE recurrence.** The risk of VTE recurrence depends on the presence and nature of provoking factors (see Figure 2).[35,36] Unprovoked VTE has a higher risk of recurrence than provoked VTE (see Figure 2) and may require extended treatment if bleeding risks are low or moderate.[5]

Figure 2. Risk of VTE recurrence



If extending treatment, use the same anticoagulant unless there are reasons for switching, for example, from a DOAC to warfarin if renal function deteriorates (see Supplementary guide “Switching between anticoagulants”).

As extended treatment usually implies that anticoagulation will continue indefinitely, assess and discuss the risks and benefits of extended treatment with the patient. For patients with first unprovoked proximal DVT or PE wishing to stop anticoagulation after three months, consider low-dose aspirin unless contraindicated.[5–7,9] Aspirin is less effective than anticoagulants, but more effective than no treatment, in preventing VTE recurrence.[5–7] Discuss the benefits and risks of stopping anticoagulation and initiating aspirin with these patients.

Frequency of review for patients on extended treatment

All patients on extended treatment, including those with cancer, should be reviewed **at least once a year** and when clinically indicated to assess for any change that may necessitate adjustments in the management (such as the choice or dose of the medication).[5,7,9]

Check for:

- Signs and symptoms of bleeding (see "Oral anticoagulation for atrial fibrillation" ACG for brief information on assessing bleeding risk, bleeding management, and reversal agents) and recurrent VTE
- Treatment adherence
- Changes in renal or hepatic function
- New drug interactions
- Degree of frailty and fall risk[39]

Recommendation 3

For patients with cancer needing VTE treatment, use apixaban, edoxaban, rivaroxaban, or LMWH for the initial and treatment phases for at least 6 months; LMWH is preferred if the patient has gastrointestinal cancer.

In Asia, the incidence of VTE is substantially higher in patients with cancer than in the general population, with cancer being a major risk factor.[40] Without appropriate anticoagulation, about 3 in 10 patients with active cancer will experience recurrence within a year.[41]

Apixaban, edoxaban, rivaroxaban, and LMWH are more effective than warfarin for preventing recurrent VTE in patients with cancer.[42] Apixaban, edoxaban, and rivaroxaban are also more effective than LMWH in preventing recurrent VTE,[42,43] but may have a higher risk of clinically relevant non-major bleeding (CRNMB).[a] The increase in bleeding risk is seen especially in patients with gastrointestinal cancer using edoxaban or rivaroxaban.[44] Based on local expert opinion, apixaban, edoxaban, and rivaroxaban may also have higher bleeding risks in patients with genitourinary cancer.

Consider potential drug interactions with anti-cancer therapies – LMWH is preferred for patients using concurrent anti-cancer medications which have significant drug interactions with apixaban, edoxaban, or rivaroxaban.

For patients in whom cancer has progressed, consider their wishes and quality of life before extending treatment. If a LMWH was chosen initially, offer apixaban, edoxaban or rivaroxaban as an acceptable alternative if a patient requires anticoagulation but wishes to stop daily injections after six months.[16,45]

Patients who are in cancer remission

VTE treatment for patients who are in remission is similar to that for the general population (see Recommendation 2), with the risk of VTE becoming comparable to that of patients without cancer after two years of remission.[46] While evidence on treatment duration for these patients is lacking, three to six months is an appropriate starting point for decision-making, to be tailored to the patient's individual circumstances.

[a] The International Society on Thrombosis and Haemostasis (ISTH) defines CRNMB as any sign or symptom of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding, but does meet at least one of the following criteria: requiring medical intervention by a healthcare professional, leading to hospitalisation or increased level of care, or prompting a face to face (i.e., not just a telephone or electronic communication) evaluation.[47]

Table 1. Characteristics of anticoagulants registered in Singapore (adapted from local product information leaflets)

	Mechanism of action	Pharmacokinetics	Reversal agent(s)	Routine coagulation monitoring	Dosing		Dosing according to renal function, CrCl (mL/min)			
					Active treatment phase (3 months)	Extended treatment phase (>3 months)	>50	30–50	15–29	<15
Apixaban‡‡	Direct factor Xa inhibitor	Bioavailability: ~50% Tmax: 3–4 hours Half-life: 12 hours Elimination: 27% renal	Andexanet alfa*** or 4F-PCC	Not required	**Day 1–7:** PO 10 mg BD††† **Day 8 onwards:** PO 5 mg BD	**Month 3–6:** PO 5 mg BD **Month 7 onwards:** PO 2.5 mg BD	Dose adjustment is not necessary		Use with caution.	Not recommended
Dabigatran	Direct thrombin inhibitor	Bioavailability: 6.5% Tmax: 0.5–2 hours Half-life: 12–14 hours Elimination: 85% renal	Idarucizumab or 4F-PCC	Not required	**Day 1–5:** *Use LMWH, no dabigatran* **Day 6 onwards:** PO 150 mg BD‡‡‡	Use maintenance dose.	Dose adjustment is not necessary.	**Day 6 onwards:** Consider dose reduction to PO 110 mg BD for patients with high bleeding risks	Not recommended	
Edoxaban§§	Direct factor Xa inhibitor	Bioavailability: ~60% Tmax: 1–2 hours Half-life: 10–14 hours Elimination: 35% renal	Andexanet alfa*** or 4F-PCC	Not required	**Day 1–5:** *Use LMWH, no edoxaban* **Day 6 onwards:** PO 60 mg OD§§§	Use maintenance dose.	Dose adjustment is not necessary.	**Day 6 onwards:** PO 30 mg OD****		Not recommended
Rivaroxaban‡‡	Direct factor Xa inhibitor	Bioavailability: 80–100% Tmax: 2–4 hours Half-life: 5–13 hours Elimination: 67% renal (36% as active compound)	Andexanet alfa*** or 4F-PCC	Not required	**Day 1–21:** PO 15 mg BD††† **Day 22 onwards:** PO 20 mg OD	**Month 3–6:** Use maintenance dose. **Month 7 onwards:** PO 10 mg OD. Consider continuing with the maintenance dose of 20 mg OD in patients with high risk of recurrent VTE.	Dose adjustment is not necessary.	**Day 22 onwards:** Consider dose reduction to PO 15 mg OD**** for patients whose bleeding risks outweigh the risks of VTE recurrence. Use with caution in patients with CrCl 15–29 mL/min. If the recommended dose is PO 10 mg OD, dose adjustment is not necessary.		Not recommended
Warfarin‡‡	Vitamin K antagonist	Bioavailability: >95% Tmax: 72–96 hours Half-life: 40 hours Elimination: ~100% metabolised, negligible in urine	Vitamin K, fresh frozen plasma and prothrombin complex concentrates	Required	**Day 1–2:** PO 5 mg OD. *Give with LMWH for five days, or until INR ≥2 —whichever takes longer* **Day 3 onwards:** Titrate according to INR	Use maintenance dose.	INR-adjusted			
Dalteparin	Accelerates antithrombin action	Bioavailability: 87% Tmax: 3–4 hours Half-life: 3–5 hours Elimination: Primarily renal (<5% as active compound)	Protamine	Not required	SC 200 IU/kg OD, up to a maximum of 18,000 IU, OR SC 100 IU/kg BD	Can be used as monotherapy in patients with cancer or in pregnant patients.	Dose adjustment is not necessary.		Not recommended	
Enoxaparin‡‡	Accelerates antithrombin action	Bioavailability: ~100% Tmax: 3–5 hours Half-life: 4–7 hours Elimination: 40% renal (10% as active compound)	Protamine	Not required	SC 1 mg/kg BD. Can be used as monotherapy in patients with cancer.	Can be used as monotherapy in patients with cancer or in pregnant patients.	Dose adjustment is not necessary.		SC 1 mg/kg OD. Consider monitoring of anti-factor Xa activity.	

4F-PCC, four-factor prothrombin complex concentrate; BD, twice a day; CrCl, creatinine clearance; INR, international normalised ratio; IU, international units; OD, once daily; PO, oral; SC, subcutaneous; Tmax, time taken for a drug to reach the maximum concentration

Initial parenteral anticoagulation

‡‡ Available on government subsidy list.

§§ Edoxaban is registered in Singapore for the treatment of VTE but is not commonly used at the time of ACG publication.

*** Andexanet alfa is not registered in Singapore at time of ACG publication.

††† Apixaban and rivaroxaban have different doses and durations for the acute treatment phase.

‡‡‡ For patients of age ≥80, use the reduced dose of 110 mg BD.

§§§ For patients who weigh ≤60 kg, use the reduced dose of 30 mg OD.

**** The recommended dosing for patients with CrCl 15–29 mL/min is based on pharmacokinetic data and has not been studied in this clinical setting. Apixaban is the most suitable DOAC for patients with CrCl 15–29 mL/min, as it is least affected by renal elimination compared to other DOACs.

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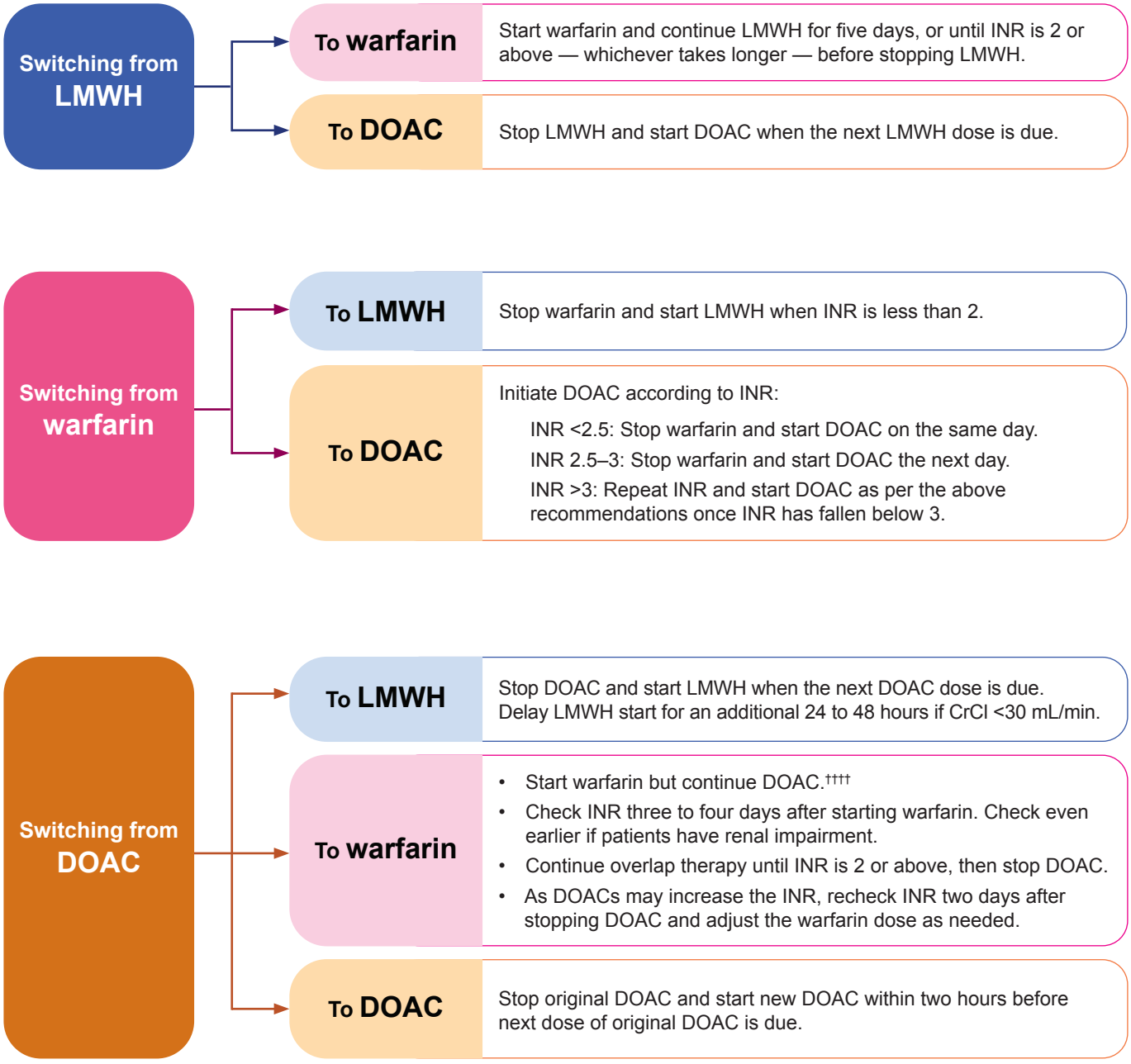
Switching between anticoagulants

Anticoagulants may be changed for medical reasons [such as hepatic or renal impairment, fluctuating international normalised ratio (INR) levels, or increased bleeding risk] or social reasons (such as cost issues, reluctance to do blood tests, poor adherence, and altered patient preferences). In general, switching between anticoagulants exposes patients to periods of increased thromboembolic and bleeding risks. This document gives guidance on appropriate switching strategies between low molecular weight heparin (LMWH), warfarin, and direct oral anticoagulants (DOACs).[39,48–50]



†††† For patients on edoxaban 60 mg, start warfarin but decrease edoxaban dose to 30 mg once daily until INR ≥2.

References

Click or scan the QR code for the reference list to this clinical guidance

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