Anticoagulation in Venous Thromboembolism

For additional info about anticoagulation in VTE, visit www.anticoagulationtoolkit.org

Determining Need for Anticoag.

- Anticoagulation is recommended for most cases of VTE unless there is a strong contraindication.
- Two types of VTE may not require anticoagulation if certain conditions are met (see table below).

Type/Location	Risk factors*	Recommendation
Acute isolated distal DVT of leg without severe symptoms or risk factors for extension*	Risk factors for extension: positive D-dimer, thrombosis is extensive, thrombosis is close to proximal veins, no reversible provoking risk factor, active cancer, h/o VTE, or inpatient status	• No anticoagulation • Serial imaging for 2 weeks
Subsegmental PE without proximal DVT or risk factors for recurrence*	Risk factors for VTE recurrence:, hospitalized/immobile patients, active cancer, no reversible provoking risk factor	• No anticoagulation • Clinical surveillance

Setting of Treatment

- Guidelines support home initial treatment for some types of VTE as long as certain criteria are met.

Type/Location	Clinical criteria for initial treatment in home	Home environment criteria for initial treatment in home
Low-risk PE	• Clinically stable with good cardiopulmonary reserve, including age ≤80, no hx of CA or chronic cardiopulmonary disease, HR <110, SBP ≥100 mm Hg, and O_2 ≥90% • No contra. such as recent bleeding, severe liver/kidney disease, or thrombocytopenia	• Well-maintained living conditions • Strong support network • Ready access to medical care • Expected to be compliant • Access to phone
Acute DVT of leg	• No severe leg pain or important comorbidities	

Choice of Anticoagulant

- DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin for DVT of the leg or PE in pts without CA. However, **DOACs are contraindicated in pts with severe renal insufficiency (CrCl<30 mL/min*), mechanical heart valves, mod/sev hepatic dysfunction, and preg/nursing.**
- LMWH is recommended over oral anticoagulants for DVT of the leg or PE in patients with cancer or pregnancy.

Anticoagulant	Dosing information (see package insert for full prescribing information)	Pros/Cons	Initial assessment/ monitoring
Apixaban (Eliquis®)	• 10 mg BID X 7 days then 5 mg BID • Reduce dose by 50% if co-administered with strong dual inhibitors of cytochrome CYP3A4P and P-gp (eg. ketoconazole and clarithromycin) • Avoid use with strong dual inducers of CYP3A4 and P-gp (eg. rifampin) • Avoid in patients with mechanical heart valves	• Only DOAC to have less GI bleeding than warfarin in clinical trials • Twice day dosing	• Renal function, liver function, and CBC before initiation and at least yearly
Dabigatran (Pradaxa®)	• 150 mg BID (if CrCl>30 mL/min*) after 5-10 days of parenteral tx • Avoid use with P-gp inducers (eg. rifampin) • Avoid use with P-gp inhibitors if CrCl<50mL/min* • Avoid in patients with mechanical heart valves	• Reversal agent is available • Dyspepsia is common side-effect • Must stay in original packaging • Twice day dosing	• Renal function, liver function, and CBC before initiation and at least yearly
Edoxaban (Savaysa®)	• 60 mg daily after 5-10 days of parenteral tx • 30 mg daily if CrCl 15-50 mL/min*, wt ≤60 kg, or if taking verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole or ketoconazole • Avoid use with rifampin • Avoid in patients with mechanical heart valves	• Once daily dosing	• Renal function, liver function, and CBC before initiation and at least yearly
Rivaroxaban (Xarelto®)	• 15 mg BID X 21 days then 20 mg daily • Avoid use with combined P-gp and strong CYP3A4 inhibitors or inducers (eg. ketoconazole and ritonavir) • Avoid in patients with mechanical heart valves	• Should be taken with food • Twice daily dosing initially • Once daily maintenance dosing	• Renal function, liver function, and CBC before initiation and at least yearly
Warfarin (Coumadin®)	• Initial dose: 5mg is a typical starting dose, but a lower dose may be considered in certain patients (eg. elderly, malnourished, liver disease) • Subsequent dosing based on INR with target range 2-3. • Parenteral tx should be given for at least 5 days and until INR is in range • Avoid in pregnancy	• Can be used in patients with severe renal disease (CrCl <30) • Requires frequent monitoring • Strong food and drug interactions • Less expensive than the DOACs	• Baseline: INR and CBC • INR 3 days after initiation and approx. 7 days after dose changes • INRs can be gradually spaced out to monthly if stable
LMWH	• Enoxaparin: 1 mg/kg SC q12h (if CrCl≥30), 1mg/kg SQ daily (if CrCl<30) • Dalteparin (only FDA approved for VTE treatment in CA): 200 IU/kg SC daily (first month), 150 IU/kg SC daily (month 2-6) (do not exceed 18,000 IU/day)	• Drug of choice in pregnancy	• Baseline: CBC, creatinine

* Use Cockcroft–Gault with actual weight to calculate CrCl

Length of Treatment

- For DVT of leg or PE provoked by surgery or transient/reversible risk factor, 3 months is the recommended length of treatment.
- For an unprovoked DVT of leg or PE, treat for 3 months and then evaluate the risk/benefit ratio for extended treatment. (see table below)
- If active CA, extended* treatment is recommended.

	Isolated distal DVT of leg and low-mod bleed risk**	Isolated distal DVT of leg and high bleed risk**	Proximal DVT of leg or PE and low-mod bleed risk**	Proximal DVT of leg or PE and high bleed risk**
First unprovoked VTE	3 months (if tx needed)		Extended*	3 months
Second unprovoked VTE	Extended* (if tx needed)	3 months (if tx needed)		

*No scheduled stop date. When considering length of treatment, patient sex and D-dimer should be considered. Men have a 75% higher risk of recurrence than women. Patients with a + D-dimer one month after stopping anticoagulation have double the risk of recurrence.
**High bleed risk patients have two or more of the following risk factors: age>65, age >75, previous bleeding, cancer, metastatic cancer, renal failure, liver failure, thrombocytopenia, previous stroke, diabetes, anemia, antiplatelet therapy, poor anticoagulant control, comorbidity and reduced functional capacity, recent surgery, frequent falls, or alcohol abuse

Long-term secondary prevention after 6-12 months of anticoagulation: In patients with continued need for anticoagulation due to risk of VTE recurrence, options include: reduced dose rivaroxaban (10 mg daily), reduced dose apixaban (2.5 mg BID), continued full dose dabigatran (150mg BID), or continued warfarin or LMWH

Aspirin should not be first choice for long-term secondary prevention of VTE.

Patient Education

All anticoagulants	• Watch for s/sx of bleeding (especially intracranial) and PE • Notify provider if any bleeding (seek immediate medical attention for serious bleeding) • Notify clinic before starting new meds (including OTC) or if having a procedure • ASA/NSAIDs ↑ bleeding. Avoid NSAIDs. Only use ASA if clear indication. • Tell dentist/surgeon about anticoag. before procedures • Avoid dangerous activities (use protective gear) • Don't' stop without consulting healthcare provider
DOACs	• Don't skip doses (short half-life)
Warfarin	• Maintain stable vitamin K intake • Notify clinic if ill or change in health status (can affect INR) • Alcohol can increase INR

For patient handouts, visit www.anticoagulationtoolkit.org

Long-term management

- Follow-up: at each f/u, assess for compliance, s/sx of bleeding or thromb., interacting meds, and reinforce ed.
  - DOACs: annually assess CBC, liver, and renal function (more often if renal insufficiency)
  - Warfarin: INRs 3-5 days after re-starting or any changes that can effect INR (ex. med, diet change, or illness) and approx. 7 days after any dose changes. INRs can gradually be spaced out to monthly, if stable, or even longer (up to 3 mos) if INRs have been in range for 3 months. Dose changes per a standardized protocol.
- Bleeding: Minor bleeding: Common (e,eg. pistaxis, bleeding gums) and is not normally a reason to D/C. Teach pt how to prevent and manage. Major bleeds: In most cases, resuming anticoag. is best for pt.(~14 days after GI, within 1 mo. for intracranial)
- Periprocedural:
  - Interruption: Generally don't need to interrupt anticoag. for low bleed risk proc. unless pt is high bleed risk (recent major bleed, platelet abnormalities, INR above range, prior bleed during previous similar procedure). If interruption necessary, timing of last dose of DOAC is based on proc. risk, CrCl, and DOAC used (see MAQI toolkit or package insert) and resumption can be day after lower risk proc. or 48-72 hours after higher risk proc. For warfarin, discontinue 5 days before procedure and resume 24 hours after procedure.
  - Bridging: Bridging with DOACs is not generally necessary. With warfarin, bridging is not necessary unless patient has high thromboembolic risk (eg. VTE <3 months ago, severe thrombophilia). If bridging, start LMWH approx. 3 days before proc.(when INR gets below range) and stop lt 24 hrs before proc. Restart LMWH 24 hrs following low risk proc or after 48-72 hrs after high risk proc. Stop LMWH when INR in range.

References

- Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. CHEST 2016; 149(2):315-352
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    - Rivaroxaban: https://www.xareltohcp.com/shared/product/xarelto/prescribing-information.pdf
    - Warfarin: https://packageinserts.bms.com/pi/pi_coumadin.pdf
    - Enoxaparin: http://products.sanofi.us/lovenox/lovenox.html
    - Dalteparin: http://labeling.pfizer.com/ShowLabeling.aspx?id=2293

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    - Rivaroxaban: https://www.xareltohcp.com/shared/product/xarelto/prescribing-information.pdf
    - Warfarin: https://packageinserts.bms.com/pi/pi_coumadin.pdf
    - Enoxaparin: http://products.sanofi.us/lovenox/lovenox.html
    - Dalteparin: http://labeling.pfizer.com/ShowLabeling.aspx?id=2293