Rapid Resource

Anticoagulation FORUM | ANTICOAGULATION Centers of Excellence

Guidance on Anticoagulation Treatment of Various VTE

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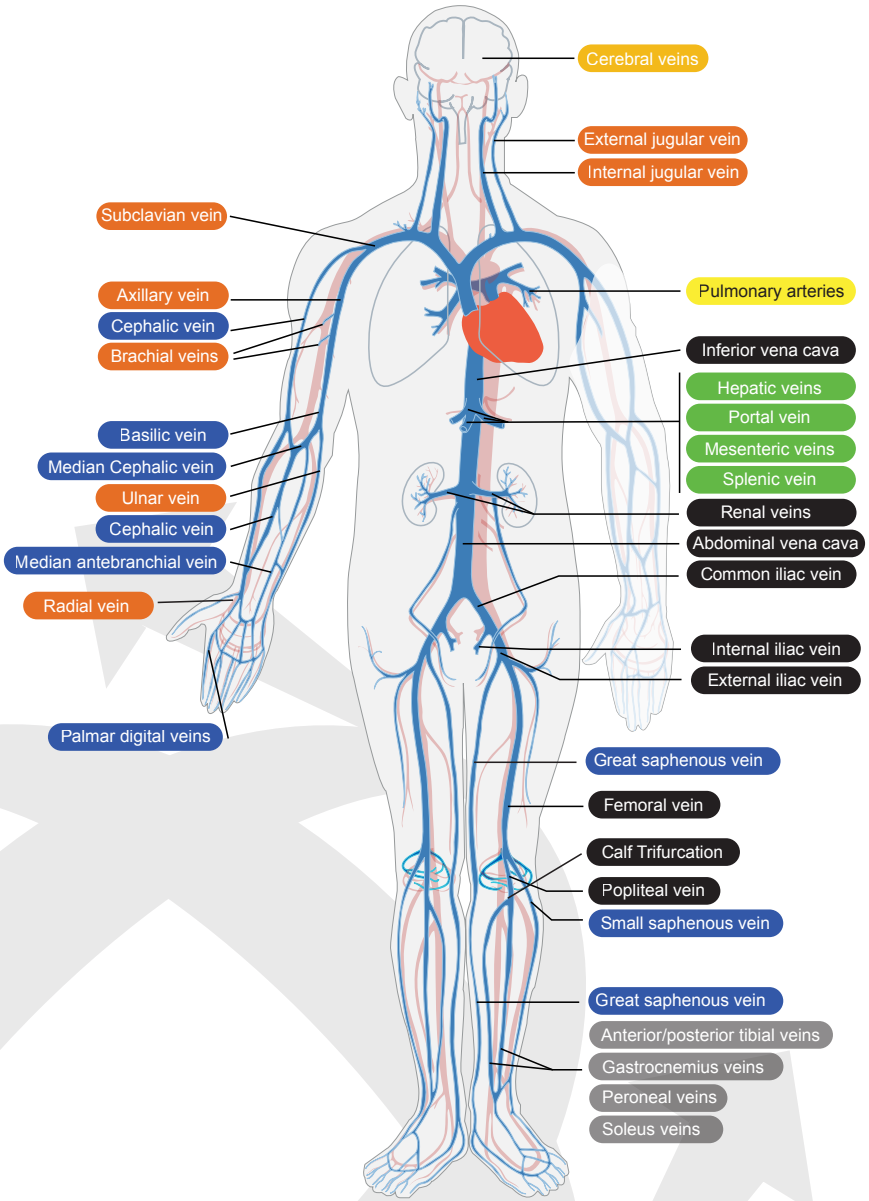

Upper Extremity DVT (UEDVT)

There are limited data regarding the management of UEDVT and guideline recommendations are often extrapolated from studies on DVT in the lower extremities. In addition, the recommendations provided generally pertain to axillary and more proximal veins. This should be taken into consideration when developing treatment plans.

CHEST: Parenteral AC > thrombolysis in UEDVT involving the axillary or more proximal veins (2016[1]) Duration 3 mo. (2012[2]).

ESC 2019[3]: Treat similar to lower limb DVT.
Catheter-associated: catheter may be kept if functional, well positioned, not infected.

ESVS 2021[4]: All patients should receive therapeutic AC with no preference specified regarding drug class.
Optimal duration not well defined but at least 3 mo.
CA patients: LMWH preferred for first 3-6 mo., but DOAC acceptable for selected patients. After 3-6 mo. VKA or DOAC if CA remains active & not related to CVC (central venous catheter).
Catheter-associated (w or w/o CA): LMWH (or LMWH followed by VKA) for 3 mo. if catheter removed, if not then treat for 3 months and as long as catheter remains in place.

NCCN 2021 (CA-specific)[5]:
All patients should receive therapeutic AC (if no contraindication). Refer to Proximal DVT section for agent preference.
Catheter-related: Similar to above guidelines.

Cerebral Vein/Venous Thrombosis

CHEST 2021[6]: Anticoagulate x 3 mo.
-Most evidence with LMWH, no RCTs for DOACs at the time of guidance publication.
-Applies to patients with or w/o ICH post CVT.

AC Forum 2016[7]: UFH or LMWH should be used over first days until patient is clinically stable then OAC x3 mo. in patients with transient risk factors.

ESC 2021[15]: LMWH for acute phase (5-15 days) then dabigatran or VKA for long-term treatment (x 24 weeks).

ESVS 2021[4]: LMWH/UFH during acute phase followed by LMWH monotherapy or VKA for 3 mo. (transient RFs) or indefinite (persistent RFs).

Splanchnic Thrombosis

ISTH 2020[8]: If concern for portal hypertension, consult GI for screening, tx/prophylaxis of varices prior to starting AC. Start early AC if no active bleeding. If high risk for bleed, consider individualized dose reduction. If poor prognosis, consider withholding AC. Treat 3-6 mo. Consider longer or indefinite if thrombus progression or recurrence after tx DC, unprovoked or persistent risk factors.
Noncirrhotic: Therapeutic DOAC > LMWH & VKA (INR 2-3).
Cirrhotic: Therapeutic LMWH then switch to VKA or DOAC if not contraindicated
CrCl <30: UFH, apix, riva or ½ dose LMWH. CrCl <15: UFH
Incidental: same as above.

ESC 2019[3]: LMWH for acute phase, then VKA for long term treatment or LMWH if cirrhosis, solid CA, or high bleed risk.

ESVS 2021[4]: LMWH/UFH during acute phase followed by LMWH monotherapy or VKA for 3 mo. if transient RFs, or indefinite if persistent RFs.

NCCN 2021 (CA-specific)[5]: Therapeutic AC.
Provoked: 6 mo. AC.
Active CA, persistent thrombophilic state, unprovoked: Indefinite AC.

Pulmonary Embolism (PE)

CHEST 2021[6]: DOAC > VKA.
If subsegmental:
And no proximal DVT & low risk for recurrent VTE: surveillance > AC.
If high risk for VTE recurrence: AC > surveillance.
If incidental: Same treatment as acute PE.

ESC 2019[3]: DOAC > VKA except in APS.
If incidental finding in CA patients: Treat as acute PE. Evidence gap for all other incidental PE.

ASH 2020[9]: DOAC > VKA.
Stable cardiovascular disease: Suggest suspending ASA while on AC.

NCCN 2021 (CA-specific)[5]: See proximal DVT guidance.
Consider IVC filter if contraindication to AC.
*IVC Filters – Only considered in patients w/in 1 month of onset of symptomatic PE/DVT and absolute contraindications to AC & should be retrieved as soon as possible within 6 mo.

Superficial Vein Thrombosis (SVT)

Guidance for SVT is derived from evidence for LE SVT.

CHEST 2021[6]: AC x 45 days if risk of clot progression to DVT/PE (extensive SVT; involvement above the knee, close to saphenofemoral junction; severe sx; involvement of the greater saphenous vein, hx of VTE or SVT; active CA, recent surgery).
Suggested: Fondaparinux 2.5mg once daily.
Alternative: Rivaroxaban 10mg once daily.

ESVS 2021[4]
SVT < 5 cm AND no high-risk features (i.e., CA, thrombophilia, or proximity (< 3 cm) to deep venous system): No AC.

SVT ≥ 5 cm AND > 3 cm away from deep vein junction:
-AC x 45 days with fondaparinux 2.5mg once daily > intermediate dose LMWH *Rivaroxaban 10mg daily discussed but not listed as a recommendation as it is not licensed for SVT in Europe.

SVT ≥ 5 cm with high clinical/anatomical risk (e.g., extensive, recurrent, located at thigh level, affects GSV or SSV, related to malignancy or thrombophilia):
- Up to 3 mo. of AC may be considered, but dosing strategy (therapeutic vs intermediate) not well-defined.
- If < 5 cm and high-risk features there is a lack of evidence on how to approach.

SVT ≤ 3 cm away from deep vein junction:
-Therapeutic AC x 3 mo.

NCCN 2021 (CA-specific)[5]:
UE SVT: Treat sx & monitor for progression.
If progression on imaging or sx, consider AC[a].
Consider AC[a] if < 3 cm to axillary vein.
If peripheral catheter related, remove catheter.

LE SVT length > 5 cm and/or if SVT extends above the knee in CA: AC[a] at least 6 wks.

LE SVT within 3 cm of saphenofemoral junction: AC[a] for at least 3 mo. in CA.

SVT < 5 cm in length or below knee: Consider repeat US in 7-10 days. If repeat US shows progression, consider AC.

a. Rivaroxaban 10mg or Fondaparinux 2.5mg daily. May consider therapeutic AC at provider's discretion.

Proximal DVT

Recommendations on duration of therapy in all guidelines determined by presence of persistent or major/minor transient risk factors and patient's risk of bleeding.

CHEST: DOAC > VKA[1,6]. Consider IVC filter if contraindication to AC.[6]

ASH 2020[9]: DOAC > VKA.
Stable cardiovascular disease: Suggest suspending ASA while on AC.
Compression stockings: Suggests against routine use although may help reduce edema and pain associated with DVT in selected patients.

ESVS 2021[4] (not related to pregnancy or CA):
-Therapeutic AC with DOAC > VKA.
--If recurrent DVT while on AC, switch type of AC, increase dose of LMWH or DOAC to treatment dose or switch to VKA with higher INR target.
- Consider venous ultrasound at discontinuation to establish new baseline in case of recurrence (do not use to determine if treatment should be stopped or continued).

ESC 2019[3]: DOAC > VKA.
Compression: Immediate compression (i.e. w/in 24hrs) + early mobilization may relieve acute venous symptoms (caution in patients with severe PAD).

NCCN 2021[5] (CA-specific. See NCCN guidance document for dosing):
No gastric/esophogeal lesions:
Apixaban = Edoxaban > Rivaroxaban.
Gastric/esophogeal lesions:
Dalteparin > Enoxaparin.
If above not appropriate/available:
Dabigatran, fondaparinux, UFH, VKA.
Consider IVC filter if contraindication to AC.

*IVC Filters – Only considered in patients with acute DVT and absolute contraindications to AC & should be retrieved as soon as possible within 6 mo.

Isolated Distal DVT (IDDVT)

ESC 2019[3]:
Low risk: Short term LMWH 4-6 wks (treatment or prophylactic doses) OR serial imaging.
High risk*: Treatment dose AC x 3 mo.

CHEST 2021[6]:
No severe symptoms or risk factors for extension:
-Serial imaging once weekly for 2 wks > AC.
-AC if the thrombus extends or considered in patients who place high value on avoiding inconvenience of serial imaging.
Severe symptoms or risk factors for extension:
-AC.
-Limited duration (2016).

ESVS 2021[4] (lower limb):
Given risk of proximal extension and/or PE, AC generally preferred.
-Therapeutic AC x 3 mo. with DOAC > VKA.
-Consider > 3 mo. in patients with active CA.
-If patient is not anticoagulated, repeat clinical assessment and whole leg US in 1 wk.

NCCN 2021 (CA-specific)[5]: Refer to Proximal DVT.
If contraindication to AC, follow up with serial US.
If progression, see NCCN guidance for detail.

**Previous VTE, male, age > 50 years, active CA, unprovoked IDDVT, persistent hampered mobilization, IDDVT involving: popliteal trifurcation and/or > 1 calf vein, bilateral, presence of predisposing disease (i.e., inflammatory bowel diseases), known genetic thrombophilia, axial vs. muscular IDDVT.*

The focus of this Rapid Resource is on the use of oral anticoagulants for the treatment of the various VTE most likely to be encountered by clinicians managing such patients. It does not address thrombus removal strategies, use of inferior vena cava filters, or provide in-depth recommendations on compression therapy or specific patient populations (e.g. pregnancy, VTE in setting of oncologic malignancies, and other unusual circumstances or sites of VTE). The user is referred to other rapid resources and/or guidelines for more in-depth information on these topics. In addition, it is important to emphasize that treatment plans carefully consider the presence of persistent or major/minor transient risk factors for VTE, the patient's individual risk of bleeding, access and affordability of treatment options, and patient preferences.

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BOTTOM LINE

DO	DON'T	CONSIDER	CAUTION
• Do address the question of AC duration after completion of the treatment phase (3-6 months) following acute VTE. • Do verify and ensure accurate intake of VTE location, risk factors (chronic and transient), history of bleeding and previous VTEs. • Do engage in shared decision making after educating patient on risks of bleeding and recurrent VTE. • Do assess bleeding risk periodically and with any health status changes.	• Don't assume all VTE should be treated the same. • Don't use repeat imaging or symptoms to drive decisions about duration of AC for VTE. • Don't place IVC filters unless AC therapy is contraindicated in the setting of acute VTE.	• Bleeding risk scores are tools to guide shared decision making with patient and identify modifiable bleeding risk factors. They should not be used as the sole determinate to continue or stop anticoagulation. • Consider using low dose apixaban or rivaroxaban for secondary prevention after completion of at least 6 months of standard therapy. • Consider standardizing ultrasound reporting for SVTs to include length of the clot and distance from the deep vein system.	• Recommendations for upper extremity DVT are generally extrapolated from studies evaluating lower extremity DVTs and guidance for SVT are generally extrapolated from studies specific to the saphenous vein.

Examples of VTE Risk Factors to Consider When Determining Duration

Persistent (chronic) risk factors	Major transient risk factors (w/in 3 mo. of VTE)	Intermediate/Minor transient risk factors (w/in 2 mo. of VTE)
• Cancer (if no curative treatment, recurrent, progressive, or ongoing treatment)[4,9] • Inflammatory bowel disease[9] • Severe thrombophilia (Antiphospholipid syndrome, Protein C/S deficiency, Antithrombin III deficiency) • Active autoimmune disease[9] • Chronic infections[9] • Chronic immobility (e.g., chronic spinal cord injury)[9]	• Surgery w/general anesthesia > 30 min[9] • Major trauma or trauma w/ fractures[3,9] • Acute spinal cord injury[3] • Confined to hospital bed ("bathroom privileges" only) for ≥ 3 days w/acute illness,[9] or acute exacerbation of chronic illness[3] • Cesarean section[9] • Estrogen therapy[4] • Pregnancy or puerperium[4]	• Minor surgery w/general anesthesia for < 30 min[9] • Hospital admission < 3 days w/acute illness[9] • Confined to bed (out of hospital) ≥ 3 days with an acute illness[9] • Estrogen therapy (COC, HRT) now discontinued[4] or continued[9] • Varicose veins[3,4] • Pregnancy or puerperium[1,3,9] • Leg injury (w/out fracture) associated w/reduced mobility for ≥ 3 days[4,9] • Long-haul travel (i.e., flight or car > 8 hrs.) [1,3]

Duration Guidance for PE and Proximal Lower Extremity DVT

Situation		Recommendations			
		ESC PE 2019[3]	ASH 2020[9]	CHEST 2021[6]	ESVS 2021[4]
Recurrent DVT or PE	Primary Tx	3 months	3-6 months	Does not address	3 months
	Secondary Prevention	Indefinite[a]	If either event was unprovoked then suggest indefinite, otherwise suggest DC after initial 3-6 mo	Does not address	Extended[b]
No Risk Factors (Unprovoked) Or Chronic/ Persistent Risk Factors	Primary Tx	3 months	3-6 months	3 months	3 months
	Secondary Prevention	Consider Indefinite[a] AC[c,d]	Suggest Indefinite AC[d]	Extended AC w/ low dose DOAC after 6 mo[e,f] Use ASA if AC is stopped	Extended AC with consideration of low dose DOAC after 6 mo[d,f] -ASA not recommended for extended antithrombotic therapy
Minor Transient or Reversable Risk Factor	Primary Tx	3 months	3-6 months	3 months	3 months
	Secondary Prevention	Consider extended AC	DC AC after inital 3-6 mo[g]	DC AC after inital 3 mo[g]	May consider extended AC
Major Transient Risk Factor	Primary Tx	3 months	3-6 months	3 months	3 months
	Secondary Prevention	DC after initial 3 mo	DC after initial 3-6 mo	Suggest DC after initial 3 mo	DC after initial 3 mo

a If not related to major transient or reversable risk factor; **b** If VTE on AC: Consider switching type of AC, increasing dose LMWH or DOAC to therapeutic dose, or switching to VKA with a higher INR target; **c** Use VKA in APLS patients ; **d** In patients who are not at high bleed risk; **e** Patient preference & risk of recurrent VTE or bleeding should influence decision to proceed with, or continue, extended-phase AC therapy; f Reevaluate periodically or if change in health status; **g** Highly informed by patient preference

Prediction Models for Quantifying Bleeding Risk (9,14)

Prediction Model	Parameters	Points	Categories of bleeding risk	Validation Status
Improve VTE Bleed (For use in acutely ill hospitalized patients)[9]	• ≥ 85 years old • 40 – 84 years old • Male • eGFR 30-59 ml/min/m^2 • eGFR ≤ 30 ml/min/m^2 • Liver failure (INR ≥ 1.5) • Plt <50k/cm^3 • Admission to ICU or CCU • Central venous catheter • Active gastric or duodenal ulcer • Prior bleeding w/in last 3 months • Rheumatic disease • Active malignancy	3.5 1.5 1 1 2.5 2.5 4 2.5 2 4.5 4 2 2	< 7: Not at increased risk of bleeding ≥ 7 Increased risk of bleeding	Validated in retrospective analysis[10] (Chest 2016)
VTE-Bleed[12]	• Active cancer • Male patient with uncontrolled hypertension • Anaemia • History of bleeding • Age ≥ 60 years • Renal dysfunction (CrCl 30-60 mL/min)	1.5 2 1 1.5 1.5 1.5	0—1: low ≥ 2: high	Validated in post hoc analysis of RCT testing DOACs vs VKAs after initial LMWH tx[12] (these are found in ESC 2019 sup appendix)

Prediction models (clinical scores) for qualification of the bleeding risk in patients receiving oral anticoagulation treatment. CrCl = creatinine clearance; DVT = deep vein thrombosis; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Eldery (>65 years), Drugs/alcohol concomitantly; INR = international normalized ratio; LMWH = low-molecular weight heparin; NOAC(s) = non-vitamin K antagonist oral anticoagulant(s); OBRI = Outpatient Bleeding Risk Index; PE = pulmonary embolism; RCT(s) = randomized controlled trial(s); RIETE = Registered Informatazido de la Enfermedad Thromboembolica venosa; VKA(s) = vitamin K antagonist(s); VTE-BLEED = active cancer, male with uncontrolled hypertension at baseline, anaemia, history of bleeding, age ≥ 60 years, renal dysfunction.

Abbreviations: AC (anticoagulation); **APS** (antiphospholipid syndrome); **CA** (cancer); **CVT** (Cerebral vein thrombosis); **GSV** (great saphenous vein); **ICH** (intracranial hemorrhage); **LMWH** (low molecular weight heparin); **OAC** (oral anticoagulation); **PAD** (peripheral arterial disease); **RCT** (randomized controlled trial); **SSV** (small saphenous vein); **Tx** (treatment); **UFH** (unfractionated heparin); **US** (ultrasound); **VKA** (vitamin K antagonist)

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