### ONLINE ONLY SECTION

### Venous CT/MRI/other imaging methods

Radiation exposure, contrast injection, validity, cost, and lack of availability limit front-line CT scan and MRI use. CT venography may be indicated when VUS is not available, inadequate, or non-conclusive, for diagnosing extrinsic compression, as an adjunct for PE diagnosis before insertion of filter devices,1, 2 or before endovascular treatment.3

MRI venography has shown equivalent sensitivity and specificity as VUS for DVT diagnosis, but has been evaluated in many fewer studies, using a variety of different techniques.4 MRI, with or without Gadolinium injection, has similar indications as CT venography.

Molecular imaging5 including PET scan6 or MRI direct thrombus imaging7 are very promising but lack validation in outcome trials.8

X-ray venography is now rarely indicated, and impedance plethysmography has been almost entirely replaced by VUS.

**Early and mid-term DVT complications**

Rates of DVT extension (with or without anticoagulation), are difficult to assess as they require repeated thorough imaging which may be biased by incomplete follow-up or secondary thrombus embolization. The most objective criteria is thrombus progression from distal to proximal veins in serial venous ultrasound (VUS) imaging. It is estimated that 1-5% of untreated distal DVTs progress to proximal DVT.In victims of stroke who present DVT, repeated VUS imaging within 1 month from event showed 9% DVT progression.9 A similar rate (10%) is reported in a systematic review evaluating surgical and medical patients with distal DVT without anticoagulation. 10

PE secondary to DVT is mostly a coexisting situation, but can also occur following a first DVT diagnosis despite anticoagulation. In recent trials assessing direct oral anticoagulants (DOAC), incidence of recurrent VTE within the first 3-months approximated 1-2%, out of which 50% were PEs. This should be distinguished from silent PE, found respectively in 35% and 13% of cases with apparently isolated proximal and distal DVTs.11

### Home vs in-hospital management

For isolated acute DVT patients, studies showed efficacy and safety of ambulatory treatment with LMWH.12, 13 In a meta-analysis of 6 randomized controlled trials including 1708 DVT patients and comparing out- with in-patient management, patients treated at home with LMWH were less likely to suffer recurrent VTE and major bleeding.12 However, in the real world a significant number of patients (>50%) with acute DVT are still managed in-hospital 13 with major countries’ differences.14 A prognostic score identifying low-risk DVT patients who could be safely treated at home has been recently proposed15 but not yet externally validated. It is likely that DOACs availability will further favor ambulatory management.

## DVT with pulmonary embolism

The risk-adjusted management of patients presenting with acute PE is described in the 2014 ESC guidelines. High-risk PE, indicating haemodynamic instability, is an emergency situation. Besides haemodynamic and respiratory support, initial anticoagulation with UFH should be the preferred option. Reperfusion treatment is recommended. Following stabilization, anticoagulation drugs and regimens are essentially identical to those recommended for DVT (section 3.1 of the full manuscript).

For normotensive patients with right ventricular dysfunction (intermediate-risk PE), anticoagulation alone is the initial treatment of choice. PE-specific reperfusion treatment is not routinely recommended as primary therapeutic option since benefits in normotensive patients are outweighed by the risk of haemorrhagic stroke or other major bleeding. However, monitoring of intermediate-high-risk PE patients is indicated over the first few days, and reperfusion should be considered as rescue treatment if clinical signs of haemodynamic decompensation appear.

Patients with low-risk PE should, similarly to patients with DVT, be considered for early discharge and outpatient management.

**Cerebral vein thrombosis (CVT)**

In CVT diagnostic work up D-dimer showed good sensitivity, but needs further assessment.16 CT scan is commonly performed as first-line diagnostic test, often showing indirect signs only. The most sensitive imaging is combination of MRI with MRI-venography, CT venography scan represents a valid alternative.17

Two randomized controlled trials compared parenteral (UFH or LMWH) anticoagulation with placebo. A non-statistically significant reduction in death or dependency was observed with anticoagulants without an increased risk of intracranial haemorrhage.18 Based on these studies, heparin is usually recommended for acute CVT treatment. Because of a better safety profile, LMWH is generally preferred.18 There is no evidence from observational studies that anticoagulants worsen prognosis in patients presenting with haemorrhagic lesions at time of diagnosis. No studies have assessed the clinical benefit of DOACs. Thrombolytic therapy is associated with a non-negligible risk of intracranial bleeding.19 No studies have addressed the duration of VKA treatment for CVT recurrence prevention. Recurrence rates reported in cohort studies are low.20-22 Independent predictors of recurrence include male gender, severe thrombophilia, and prior VTE.

**Splanchnic vein thrombosis**

No studies have assessed the role of D-dimer in splanchnic vein thrombosis diagnostic work up. In experienced hands, VUS has a good sensitivity for detecting portal or supra-hepatic vein thrombosis, but not for mesenteric. CT and MRI have better accuracy and allow detection of concomitant diseases, or alternative diagnoses.23

No randomized controlled trials have assessed clinical benefit of anticoagulant or thrombolytic therapy. Treatment strategies are driven by severity of presentation and by underlying risk factors. Risk of recurrence and major bleeding is highest in patients with liver cirrhosis, non-negligible in patients with solid or hematologic cancer, and low in patients with transient risk factors.24 LMWHs are the mainstay of anticoagulant treatment during the acute phase, but also for the long-term in patients with solid cancer or at increased risk of bleeding. No studies have assessed clinical benefit of DOACs. No studies have addressed the duration of anticoagulation. Given the reported recurrence rates, most patients may require indefinite duration of secondary prevention if bleeding risk is low.

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