Acute phase treatment of VTE: Anticoagulation, including non-vitamin K antagonist oral anticoagulants

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Summary
The acute phase of venous thromboembolism (VTE) treatment focuses on the prompt and safe initiation of full-dose anticoagulation to decrease morbidity and mortality. Immediate management consists of resuscitation, supportive care, and thrombolysis for patients with haemodynamically significant pulmonary embolism (PE) or limb-threatening deep-vein thrombosis (DVT). Patients with contraindications to anticoagulants are considered for vena cava filters. Disposition for the acute treatment of VTE is then considered based on published risk scores and the patient’s social status, as the first seven days carries the highest risk for VTE recurrence, extension and bleeding due to anticoagulation. Next, a review of: immediate and long-term bleeding risk, comorbidities (i.e. active cancer, renal failure, obesity, thrombophilia), medications, patient preference, VTE location and potential for pregnancy should be undertaken. This will help determine the most suitable anticoagulant for immediate treatment. The non-vitamin K antagonist oral anticoagulants (NOACs), including the factor Xa inhibitors apixaban, edoxaban and rivaroxaban as well as the direct-thrombin inhibitor dabigatran, are increasing the convenience of and options available for VTE treatment. Current options for immediate treatment include low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), fondaparinux, apixaban, or rivaroxaban. LMWH or UFH may be continued as monotherapy or transitioned to treatment with a VKA, dabigatran or edoxaban. This review describes the upfront treatment of VTE and the evolving role of NOACs in the contemporary management of VTE.

Keywords
Clinical trials, oral anticoagulants, deep-vein thrombosis, pulmonary embolism, venous thrombosis

Introduction
The acute phase of venous thromboembolism (VTE) is the first 5–10 days following the presentation of a deep-vein thrombosis (DVT) or pulmonary embolism (PE). In this phase patients are at risk of extension, recurrence, haemodynamic compromise and death (1). Untreated VTE is fatal in one-third of patients and VTE still remains the third leading cause of cardiovascular mortality despite widely available and highly effective treatments (2, 3). PE has a high-fatality rate with 20% of patients succumbing prior to diagnosis or within the day following diagnosis (4). DVT, carries the additional risks of neurovascular compromise of the affected limb, post-thrombotic syndrome (PTS) and occurrence of PE (5). The diagnosis and treatment of acute VTE must be expedited to decrease mortality and prevent short and long-term morbidity (6).

The initial management of acute VTE involves acute resuscitative measures, initial anticoagulation or selection of alternatives for patients for whom anticoagulation is contraindicated, and short-term follow up. For most acute VTE, treatment can be managed as an outpatient and presumptive anticoagulation can begin while awaiting confirmatory testing such as compression ultrasound of the extremities or CT-pulmonary angiogram (6–8). Once a new diagnosis of VTE is established clinicians have an increasing number of options available for treatment. Treatment with full-dose anticoagulation should be promptly initiated when safe to do so and treatment should proceed regardless whether the VTE is provoked or unprovoked (8, 9). For life- or limb-threatening VTE adjunctive measures may include thrombolysis and haemodynamic support. Supportive care considerations include analgesia and elastic compression stockings (ECS) for those with DVT. The benefit of ECS is likely limited to symptomatic relief, as their routine use in a recent randomised controlled trial did not decrease PTS (10).

The non-vitamin K antagonist oral anticoagulants (NOACs) are changing the landscape of acute VTE management (11–13). Available agents include the factor Xa inhibitors: apixaban, edoxaban and rivaroxaban as well as the direct-thrombin inhibitor dabigatran. These agents all have predictable pharmacokinetics, a rapid-onset of action and half-lives shorter than the oral vitamin K antagonists (VKAs) (14, 15). In addition, there are fewer drug-drug and drug-food interactions (16). Despite the efficacy and ease of use of NOACs they should still only be used in appropriate clinical situations (17).
Table 1: Clinical factors excluding a NOAC as frontline treatment for acute venous thromboembolism.

- Acquired or inherited thrombophilia
- Active bleeding or other contraindication to anticoagulation
- Active cancer (any cancer other than basal cell or squamous cell carcinoma of skin within 6 months; any cancer treatment in last 6 months; recurrent or metastatic cancer)
- Age < 18 years
- Breastfeeding
- Dual antiplatelet therapy
- Obesity
- Post-thrombolysis
- Pregnant
- Rare VTE location (i.e. distal DVT, splanchic, cerebral vein thrombosis)
- Renal Failure (CrCl <25–30ml/min) or high-risk of renal insufficiency
- Vena cava filter

VTE, venous thromboembolism; CrCl, Creatinine clearance.

Methods

We searched MEDLINE, PubMed and Google Scholar from database inception to November 2014 using terms to identify studies examining the acute management (first 10 days) of a new VTE, including but not limited to: “deep vein thrombosis”; “pulmonary embolus”; “venous thrombosis”; “venous thromboembolism”; “thrombolysis” and “anticoagulant”. The search was limited to English language peer-reviewed human studies. We hand searched the reference lists of relevant reviews and guidelines for additional references where primary literature was not available.

Initial evaluation and immediate management

The initial evaluation of a patient with VTE should focus on the life- and limb-threatening complications of VTE. Acute resuscitation should proceed as indicated by the patient’s clinical status. Thrombolysis should be considered for haemodynamically significant PE or a DVT with severe neurovascular compromise (threatened limb loss) (8). If facilities exist, current practice would be to perform catheter directed thrombolysis (CDT) for DVT and systemic thrombolysis for PE in patients with these complications (8, 18). CDT has not been directly compared to systemic thrombolytic therapy, only to conventional treatment for treatment of acute DVT (19) and further randomised controlled trials are ongoing (20, 21). These trials will confirm or refute the current evidence that CDT compared to anticoagulation, increases vein patency and decreases post-thrombotic syndrome (PTS) but does not impact rate of recurrence or PE and increases adverse events (22). Thrombolysis in patients with PE should be immediately followed by anticoagulation with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). Thrombolysis for acute PE has not demonstrated a mortality benefit in controlled trials (23, 24); however, a recent meta-analysis did find a lower all-cause mortality for selected high-risk patients receiving thrombolysis compared with patients receiving only anticoagulant therapy (25). There are no randomised trials to inform thrombolysis of upper-extremity DVT; however, we would perform CDT in the case of a limb-threatening DVT.

If no indication for thrombolysis exists then the patient should next be evaluated for clinical factors that would influence the choice of anticoagulants (►Table 1), their bleeding risk, their need for invasive procedures and consideration for inpatient or outpatient management (►Table 2) (9, 26, 27). If the patient has a temporary contraindication to anticoagulation, is bleeding or at high risk for bleeding, or requires a procedure within the first four weeks of anticoagulant therapy then insertion of a temporary vena cava filter could be considered (28). There is no mortality benefit to vena cava insertion in acute VTE with the exception of patients with haemodynamically significant PE or after thrombolytic therapy (29, 30). Given the risk of thrombosis of the filter itself, anticoagulation should be instituted as soon as it is safe to do so. Temporary filters should be retrieved as soon as anticoagulation can be achieved. In clinical practice the vast majority of filters are not retrieved exposing patients to unneeded long-term risks such as fracture, embolisation and thrombosis of the inferior vena cava (31).

The patient's disposition for the acute phase of VTE therapy requires evaluation of symptoms, comorbidities, vital status, bleeding risk, social circumstances and need for intravenous UFH (►Table 2) (26, 27). Increasingly, patients are being considered for...
outpatient VTE management. A meta-analysis has demonstrated both safety and efficacy of outpatient DVT treatment with LMWH (32). Recent multicentre randomised controlled trials of NOACs have been performed in the outpatient setting (33–38). A smaller evidence-base supports outpatient management of PE (39). Low risk PE patients, identified by one of several published risk scores may be effectively managed as outpatients (40). The Geneva (41), Pulmonary Embolism Severity Index (42), Aujesky (43) and Murugappan (44) clinical prediction rules were shown by a meta-analysis (45) to accurately identify patients with PE at a low-risk for death (<1% risk of in-hospital mortality). These risks score have not as of yet been incorporated into prospective treatment studies and with the factors identified in Table 2 are guides to help clinicians evaluate the safety of outpatient VTE treatment.

### Table 3: Anticoagulants for the immediate treatment of venous thromboembolism.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage – Acute Treatment</th>
<th>Acute Treatment Duration</th>
<th>Half-life (hours)</th>
<th>Renal Clearance</th>
<th>Drug Interaction</th>
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</thead>
<tbody>
<tr>
<td>Parenteral Agents</td>
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| Unfractionated heparin   | Weight-based bolus followed by continuous infusion to maintain therapeutic aPTT (1.5–2 times normal) or 333 U/kg subcutaneously first dose then 250 U/kg q12h
|                          | Monotherapy
|                          | or minimum 5 days and continued until therapeutic on VKA; edoxaban or dabigatran       | 1.5                  | 30%              | None            |
| Low-molecular-weight heparins |                                                                                         | Monotherapy
|                          | or minimum 5 days and continued until therapeutic on VKA or TSOAC
|                          |                                                                                         | 3–4                  | 80%              | None            |
| - dalteparin             | 200 IU/kg subcutaneously every 24 h or 100 IU/kg q12h                                    |                         |                   |                 |                 |
| - enoxaparin             | 1.5 mg/kg subcutaneously every 24 h or 1 mg/kg q12h                                      |                         |                   |                 |                 |
| - nad roparin            | 171 IU/kg every 24 h subcutaneously or 86 IU/kg q12h                                     |                         |                   |                 |                 |
| - tinzaparin             | 175 IU/kg subcutaneously every 24 h                                                     |                         |                   |                 |                 |
| Factor Xa inhibitor      |                                                                                        |                          |                   |                 |                 |
| - fondaparinux           | 5 mg (<50 kg), 7.5 mg (50–100 kg), or 10 mg (>100 kg) subcutaneously every 24 h          | minimum 5 days and continued until therapeutic on VKA
|                          |                                                                                         | 17–21                | 100%             | None            |
| Oral Agents              |                                                                                        |                          |                   |                 |                 |
| Direct factor Xa inhibitors |                                                                                         |                          |                   |                 |                 |
| - rivaroxaban            | 15 mg bid                                                                               | 3 weeks                 | 7–11              | 33%             | CYP3A4 and P-glycoprotein inducers |
| - apixaban               | 10 mg bid                                                                               | 10 days                 | 8–12              | 25%             |                 |

*aPTT 6 hours following injection on third day of treatment should be performed to confirmed therapeutic; may be considered for patients at high-risk of bleeding; VKA should be started immediately and parenteral anticoagulant may be discontinued when INR > 2; patients who are pregnant or with active cancer; edoxaban or dabigatran require dual-drug treatment for first 5 days; aPTT, activate partial thromboplastin time; h, hours; VKA, vitamin K antagonist; TSOAC, target-specific oral anticoagulant; CYP3A4, cytochrome P450 3A4.

### Standard approach to anticoagulation

Patients without any of the clinical factors in Table 1 should be treated first acutely with full-doses of one of: LMWH, fondaparinux, apixaban or rivaroxaban (Table 3). LMWH can be used for long-term treatment for VTE but most frequently are used to provide rapid anticoagulation during the initiation of VKA owing to the slow-onset of action of VKAs. The LMWH or fondaparinux should only be discontinued after a minimum of 4 to 5 days of treatment and the achievement of an International Normalised Ratio (INR) of greater than 2. Edoxaban and dabigatran are treatment options but require LMWH treatment for 5 to 7 days in a manner similar to the VKAs (35, 37, 38).

The previous standard dual-drug approach with LMWH (or fondaparinux) transitioned to VKA is effective (46); however, it is being supplanted by the NOACs owing to the burden of subcutaneous LMWH injections and the need for monitoring of VKA...
therapy (47). Apixaban, dabigatran, edoxaban and rivaroxaban were all compared to this standard and were all found to be non-inferior (33–38). Multiple recent reviews detail the trial designs and outcomes of the phase III trials of these agents (17, 48, 49).

Table 4 shows pertinent outcome data from the phase III clinical trials.

Clinical factors beyond those outlined in Table 1 (including patient preference) may lead clinicians to not proceed with a NOAC for first line anticoagulation. Patients on potent P-glycoprotein inhibitors or inducers are not suitable for treatment with NOACs and those on inducers or inhibitors of cytochrome P450 3A4 should not receive rivaroxaban or apixaban (Table 3) (50). Renal failure (CrCl < 25–30 ml/minutes [min]) is a contraindication to NOACs, fondaparinux and LMWH. The NOACs have not been studied for treatment of VTE in unusual sites such as the portal veins or cerebral sinus (52). Additionally, they were not studied in patients with a known thrombophilia. There are relatively few clinical studies of VKA for these indications as well (53). Clinical judgment and experience should guide choice of anticoagulants for acute treatment of patients with thrombophilias with LMWH transitioned to a VKA remaining the standard treatment. Patient preferences may include familiarity (i.e. previous warfarin treatment), cost and concerns over lack of a reversal agent. There are reversal agents in development; however, they currently not available outside of a clinical trial. Multiple recent publications detail current reversal strategies (14, 54–56). Interestingly, despite the availability of an effective VKA reversal agent a recent meta-analysis has demonstrated that the case-fatality rate for major bleeding of the NOACs is less than that of the VKAs (57).

In patients being treated for acute VTE with NOACs clinicians are left to choose which of the available agents they feel is most appropriate for their patient. There are no head-to-head comparison studies to inform which of the NOACs may be superior. In addition, significant differences in trial design of the phase III studies do not allow for clear cross-trial comparisons (58). Table 3 summarises the dosing, significant drug-interactions and special considerations for each of the NOACs.

The RE-COVER and Hokusai-VTE trials of dabigatran and edoxaban, respectively, each mandated at least five days of heparin or LMWH treatment prior to initiation of dabigatran or edoxaban (35, 37, 38). The requirement for lead-in with heparin/LMWH for dabigatran increases treatment burden on patients during the acute treatment phase. AMPLIFY (apixaban) and EINSTEIN (rivaroxaban) allowed for optional pre-treatment with a heparin for a maximum of 36 and 48 hours (h), respectively (33, 34, 36). In the phase III trials 77 % of AMPLIFY patients and 83 % of EINSTEIN patients did receive a heparin prior to random-
isation. Massive PE cases should receive inpatient treatment with parenteral anticoagulant therapy. Hokusai-VTE did include patients with significant PE clot burden and edoxaban may over time become an acceptable standard for this population (35).

Strict attention must be paid to a patient’s bleeding risk prior to instituting any anticoagulant therapy. There are no prospectively validated standardised bleeding prediction tools for patients undergoing VTE treatment with anticoagulants. Thus, it is up to a clinician’s judgement to determine an individual patient’s bleeding risk by considering factors such as bleeding history, comorbidities, age, and medications. Pooled analyses indicate significantly less bleeding with NOACs compared to warfarin across indications in the studies leading to licensure; how these bleeding risks manifest in unselected patients in the community remains to be determined (59). With the exception of RE-COVER, the phase III studies of NOACs all had predefined primary safety outcomes of bleeding (33–38). For dabigatran and rivaroxaban there was a similar rate of major bleeding compared to warfarin. A pooled analysis of the rivaroxaban VTE trials did show a significant reduction in major bleeding compared with warfarin (61). Apixaban demonstrated a 56% relative risk reduction (p<0.001) in the composite of major and non-major clinically relevant bleeding compared to warfarin (34). Edoxaban as well was superior in this outcome with a relative risk reduction of 17% (35). Hokusai-VTE patients received a lower dose (30 mg daily) of edoxaban if considered at higher risk for bleeding (CrCl 30–50 ml/min, weight ≤60kg, receiving potent P-glycoprotein inhibitors) (35). It is apparent that the sites of bleeding complications vary between the anticoagulants, for example there were more intracerebral haemorrhages observed in patients on VKAs (50) and more gastrointestinal bleeding events in patients on dabigatran, rivaroxaban and the higher doses of edoxaban (60).

**Special populations**

All phase III studies of the NOACs excluded patients who had contraindications to heparin or warfarin (including active bleeding or high risk for bleeding), or had an additional indication for warfarin. Additionally, patients were excluded if they had a life expectancy <3–6 months, if they had received thrombolytic therapy, were pregnant, were at risk of becoming pregnant, were breastfeeding, or had a vena cava filter (33–38). Patients with active cancer were excluded from the trials if treatment with LMWH was anticipated as this is the current standard of care. Also, not included in these trials were patients with significant liver disease or uncontrolled hypertension (11).

**Bleeding**

Patients with clinically relevant active bleeding should not receive therapeutic anticoagulation. Every effort should be made to ensure rapid haemostatic control, involving surgical services, interventional radiology or others as required. Anticoagulation should be instituted promptly, when safe to do so. For patients who cannot receive anticoagulation in the acute phase, consideration for a vena cava filter would be reasonable (62), with a plan to start anticoagulation once the cause or risk for bleeding has been reversed (63). A similar strategy may be used if the patient requires a procedure within the first four weeks of anticoagulant therapy. Vena cava filters inserted in patients who can receive anticoagulation do not improve survival (64). The use of vena cava filters varies across the world and retrospective studies often find a high proportion of patients have filters placed for inappropriate indications (65). Clinicians should be aware of the limited utility of vena cava filters and the narrow indications for their use (66).

Patients who are at high risk of bleeding where the clinician feels immediate anticoagulation is prudent can be started on intravenous UFH without a bolus dose and be closely monitored. This strategy is not evidence-based but is used owing to the ability to easily measure the anticoagulant effect (with the aPTT), the short half-life of UFH (60–90 min) and the availability of an effective reversal agent (protamine). Risk factors for bleeding include comorbidities (i.e. severe liver disease, uremia) and medications. Patients on anti-platelet therapy were included in the NOAC trials if their doses of ASA were <100 mg per day (<165 mg in AMPLIFY); however, they were excluded if they were on dual-antiplatelet therapy (33–38). Therefore, patients on dual anti-platelet therapy should be initiated on LMWH treatment, then transitioned to a VKA. Management of dual and triple anti-coagulant treatment is reviewed elsewhere (67). If the indication for anti-platelet treatment is recent unstable cardiovascular disease it must be noted that this patient population was excluded in the RE-COVER trials. This is due to a potential for cardiovascular events to be increased in patients treated with dabigatran (68).

**Renal failure**

Patients with renal failure are at increased risk for bleeding. These patients are also commonly treated with medications that further increase this risk. Renal failure, defined by a CrCl <30 ml/min, was an exclusion in all of the NOAC trials (AMPLIFY excluded patients with a CrCl <25 ml/min). This is due to renal elimination of all the NOACs ranging from 80% (dabigatran) to 25% (apixaban) (51) resulting in bioaccumulation of the anticoagulants in patients with renal impairment. LMWH’s are contraindicated in severe renal disease and patients with end-stage renal disease who develop VTE require initial anticoagulation with UFH (intra-venous or subcutaneous) and VKA. An increasing body of literature is challenging the practice of avoiding LMWH in those with renal failure (69). LMWH may be considered in patients with renal impairment, as it is not a fixed entity, and patients can be monitored for bioaccumulation using anti-Xa levels with subsequent dose adjustment.

There is little evidence to guide treatment in those with moderate renal disease. We avoid NOACs in patients with CrCl 30–50 ml/min if we feel they have risk factors for worsening renal function (i.e. poorly controlled hypertension or diabetes, frail elderly). Few patients in the NOAC phase III trials had renal function in this range. However, a meta-analysis of eight randomised
controlled trials of NOACs compared to VKAs in patients with CrCl 30–50 ml/min found no difference in efficacy and safety in these patients (70). If we elect to use a NOAC for these patients, apixaban is often selected owing to its more favorable renal profile.

**Thrombolytic therapy**

Patients who have received thrombolytic therapy require admission to a monitored setting and initiation of parental anticoagulation. These patients would then be started on treatment with a VKA. A standard regimen for systemic thrombolysis is alteplase 100 mg by intravenous infusion over 2 h (71). Absolute contraindications to thrombolytic treatment are: intracranial bleeding, previous intracranial haemorrhage, stroke or TIA within ≤3 months, recent intracranial or intraspinal surgery or trauma, intracranial neoplasm, arteriovenous malformation or aneurysm and known serious bleeding diathesis. A detailed review of thrombolysis has been published (71).

**Pregnancy or active cancer**

These patients should be treated acutely with full-dose weight-adjusted LMWH monotherapy. In pregnancy, this is based on teratogenicity of VKAs (72) and lack of safety data for NOAC’s (73). VKAs and LMWH are safe for breastfeeding (74). LMWHs (specifically dalteparin and tinzaparin) were proven superior in preventing recurrent VTE disease for patients with active cancer (any treatment for cancer within the prior six months or recurrent/metastatic cancer) (75, 76). There is not as of yet a formal study of NOAC’s in the active cancer population but there is a subgroup analysis demonstrating a numerically lower incidence of recurrent VTE for edoxaban in the phase III trial (35). A meta-analysis of

![Diagram](image-url)

**Figure 1: Approach to acute treatment of venous thromboembolism.** PE, pulmonary embolus; DVT, deep vein thrombosis; IVC, inferior vena cava; PESI, Pulmonary Embolism Severity Index; CrCl, creatinine clearance; TSOAC, target-specific oral anticoagulant; LMWH, low-molecular-weight heparin; BID, twice daily; OD, once daily.
NOACs trials yielded 1,132 patients with cancer and concluded that NOACs appeared to be as effective and safe as conventional anticoagulation (77); however, the patients enrolled in these studies were selected to be at low risk of death compared with the patients enrolled in CLOT and CATCH (75, 76). The standard for both the pregnancy population and those with active cancer remains LMWH monotherapy.

**Thrombophilias**

Currently, there are no specific trials that examine the efficacy of the NOACs in inherited or acquired thrombophilias although numerous patients with undiagnosed thrombophilia would have been enrolled in the studies leading to the licensure of these agents suggesting that the NOACs are effective for treatment of patients with such conditions. We are comfortable using NOACs in patients with uncomplicated thrombophilias, such as heterozygous factor V Leiden or heterozygous prothrombin gene mutation. While an attractive option for other thrombophilias, antiphospholipid syndrome (APS) or heparin-induced thrombocytopenia (HIT) patients with these conditions should not be managed with NOACs outside of a clinical trial. Acute treatment of APS is with LMWH and VKA treatment to a target INR of 2–3 (8). HIT should be managed with a non-heparin parenteral anticoagulant such as argatroban or fondaparinux, introducing warfarin only once the platelet count is above 150 (78, 79).

**Obesity**

There are minimal clinical trial data to inform treatment of patients with weights > 100 kg. A fixed-dose regimen of NOACs may not provide sufficient anticoagulant effect to obese patients and may provide supratherapeutic doses to underweight individuals. There is a lack of standardised and widely commercially available laboratory measures of anticoagulant effects for the NOACs. Drug levels can be obtained but there is not enough data to determine the appropriate therapeutic range for the NOACs for initial VTE treatment (80). This information is required before NOACs can be safely recommended in patients with weights < 40 kg or > 100 kg as they were not included in the phase III trials where a fixed dose was used. Similarly, LMWH is not reliably monitored using anti-Xa levels but this practice is still recommended for patients with extremes of weight (81). A subgroup evaluation of AMPLIFY did demonstrate improved safety of apixaban compared with warfarin in those weighing > 100 kg (34). Current practice for patients at extremes of weight would be LMWH transitioned to a VKA, without capping of the LMWH dose. In patients who are not overweight there is no statistically significant reduction in haemorrhages with twice daily dosing of LMWH (82). It is unclear the efficacy and safety of divided dosing in overweight individuals.

**Treatment of acute VTE in 2015**

Figure 1 demonstrates our approach to the acute treatment of VTE. Following confirmation of VTE diagnosis, stable patients at low risk for complications can be managed as outpatients with a NOAC or a LMWH transitioning to a VKA with close follow-up. Patients at high-risk of complications are identified by factors described in Table 2 or by applying a clinical prediction rule (45). Follow-up is essential as the risks of progressive VTE and bleeding from anticoagulation are highest in the first seven days of treatment (83–85). Recent European Society of Cardiology Guidelines for the treatment of PE recommend the NOACs as alternatives to VKA for acute anticoagulation (18). Patients who require hospitalisation are still appropriately managed with NOACs but those who are haemodynamically unstable, have received thrombolysis or are at high risk of bleeding should receive intravenous UFH. We would use LMWH monotherapy for pregnant patients (74) and patients with active cancer. Patients who would be considered non-standard (Table 1) should still be managed conventionally with LMWH or UFH transitioning with a VKA until therapeutic (INR 2–3) (8).

**Author contributions**

C. M. H. performed the literature review and wrote the first draft; C. M. H. and M. A. C. reviewed and edited the final paper; and C. M. H. and M. A. C. provided sign off on the submitted version.

**Conflicts of interest**

C. M. H. declares no competing financial interests. M. A. C. has sat on advisory boards for Leo Pharma, Pfizer, Bayer, Boehringer Ingelheim, Alexion, CSL Behring, Portola, Viropharm, and AKP America. M. A. C. has prepared educational materials for Pfizer, Octapharm, and CSL Behring. M. A. C. has provided expert testimony for Bayer and for Merck. M. A. C.’s institution has received funding for research projects from Boehringer Ingelheim, Octapharm, Pfizer, and Leo Pharma. M. A. C. has received funding for presentations from Leo Pharma, Bayer, Celgene, and CSL Behring.

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