Interactive VTE Case Studies

Maeve Crowley
Case 1.

• 16 year old girl

• Admitted with a 5 day history of dyspnoea associated with left sided chest pain

• D-dimer elevated - CTPA confirmed extensive bilateral PEs with features of R heart strain

• Trop 26, NT pro-BNP 5717

• Background – menorrhagia – had recently commenced COCP; anxiety
Issues

- Adult or Child
- Initial anticoagulant
- Role for intervention
- Ongoing anticoagulation
Initial risk stratification of acute PE

**Suspected acute PE**

- **Shock or hypotension**
  - **Yes**: High-risk
  - **No**: Not High-risk

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* Defined as systolic blood pressure < 90 mmHg, or a systolic pressure drop by ≥40 mmHg, for >15 minutes, if not caused by new-onset arrhythmia, hypovolaemia, or sepsis.

* Based on the estimated PE-related inhospital or 30-day mortality.

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www.escardio.org/guidelines

<table>
<thead>
<tr>
<th></th>
<th>Tym:36.0</th>
<th>Tym:36.5</th>
<th>Tym:36.8</th>
<th>Tym:36.5</th>
<th>Tym:36.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temp1 Central</strong></td>
<td>Tym:35.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>120</td>
<td>118</td>
<td>113</td>
<td>105</td>
<td>101</td>
</tr>
<tr>
<td><strong>Cardiac Rhythm</strong></td>
<td>ST</td>
<td>ST</td>
<td>ST</td>
<td>ST</td>
<td>ST</td>
</tr>
<tr>
<td><strong>Cardiac Ectopics</strong></td>
<td>Rare VE</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>ABP</strong></td>
<td>119 / 73</td>
<td>124 / 73</td>
<td>113 / 72</td>
<td>94 / 66</td>
<td>104 / 69</td>
</tr>
<tr>
<td><strong>ABP Mean</strong></td>
<td>88</td>
<td>88</td>
<td>85</td>
<td>77</td>
<td>83</td>
</tr>
<tr>
<td><strong>CVP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td><strong>SPO2</strong></td>
<td>96</td>
<td>98</td>
<td>97</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td><strong>PAR Score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Capillary Refill</strong></td>
<td>&lt;3 secs</td>
<td></td>
<td></td>
<td></td>
<td>&lt;3 secs</td>
</tr>
<tr>
<td><strong>Limb Warmth R+L</strong></td>
<td>Warm/War</td>
<td>Cold/Cold</td>
<td></td>
<td>Cool/Cool</td>
<td></td>
</tr>
<tr>
<td><strong>Pedal R+L</strong></td>
<td>Yes/Yes</td>
<td>Yes/Yes</td>
<td>Yes/Yes</td>
<td>Yes/Yes</td>
<td>Yes/Yes</td>
</tr>
<tr>
<td><strong>Radial R+L</strong></td>
<td>Yes/Yes</td>
<td>Yes/Yes</td>
<td>Yes/Yes</td>
<td>Yes/Yes</td>
<td>Yes/Yes</td>
</tr>
</tbody>
</table>
### Low risk PESI (I)

<table>
<thead>
<tr>
<th>B:PESI Scoring system</th>
<th>Points assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>+1 per year</td>
</tr>
<tr>
<td>Male sex</td>
<td>+10</td>
</tr>
<tr>
<td>Active cancer</td>
<td>+30</td>
</tr>
<tr>
<td>Heart failure</td>
<td>+10</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>+10</td>
</tr>
<tr>
<td>Pulse &gt;110bpm</td>
<td>+20</td>
</tr>
<tr>
<td>Syst BP&lt;100 mmHg</td>
<td>+30</td>
</tr>
<tr>
<td>Resp rate &gt;30/min</td>
<td>+20</td>
</tr>
</tbody>
</table>

**SaO2 if known resp disease**

**PESI score:**
- Low risk PESI I, II
- High risk PESI III, IV or V

*PESI score: The pulmonary embolism severity index (PESI) score is a clinical prediction tool to risk stratify patients with PE.*
## Classification of early mortality risk

<table>
<thead>
<tr>
<th>Early mortality risk</th>
<th>Risk parameters and scores</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shock or hypotension</td>
<td>PESI Class III-V or sPESI &gt;1</td>
</tr>
<tr>
<td>High</td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Intermediate-high</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Intermediate-low</td>
<td>-</td>
</tr>
<tr>
<td>Low</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

## Acute phase treatment

### PE without shock or hypotension (intermediate or low risk)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reperfusion treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine use of primary systemic thrombolysis is not recommended in patients without shock or hypotension.</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Close monitoring is recommended in patients with intermediate-high risk PE to permit early detection of haemodynamic decompensation and timely initiation of rescue reperfusion therapy.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Thrombolytic therapy should be considered for patients with intermediate-high-risk PE and clinical signs of haemodynamic decompensation.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Surgical pulmonary embolectomy may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Percutaneous catheter-directed treatment may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>
Adult or Child?

- Patient dependent factors

- Physiologically an adult

- Signposting – deferred to mother, did not want to be involved in decision making, OCP for menorrhagia not contraception, embarrassed when discussed anticoagulants in the setting of pregnancy

- Found adult critical care difficult

- Very distressed by venipuncture
The law assumes that by the age of 16 years, young people are able to make decisions about their own care, although there are national differences relating to consent to investigations and treatment.

If a child or young person with capacity refuses to give consent, you must respect their decision.

GMC guidance
The validation and reproducibility of the pulmonary embolism severity index

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To cite this article: Chan CM, Wood C, Shorr AF. The validation and reproducibility of the pulmonary embolism severity index. J Thorac Dis. 2016; 8:e1296-9.

Summary
Background. Rapid, accurate risk stratification is paramount in managing patients with acute pulmonary embolism (PE). The PE Severity Index (PESI) is a simple tool that risk-stratifies patients with acute PE. Objective. We sought to validate the PESI as a predictor of short- and intermediate-term mortality and to determine the inter-rater variability.

Patients/Methods. We retrospectively identified all patients with acute PE between October 2007 and February 2009. Two clinician reviewers scored and independently scored PESI blinded to each other and to patient outcomes. Thirty- and 90-day mortality served as study endpoints and vital status was assessed via the Social Security Death Index. To facilitate analysis, raw PESI scores were converted into risk class groups (I-V) and further dichotomized into low-risk (I-II) vs high-risk (III-V) groups. Interrater correlation and the kappa statistic were used to determine inter-rater variability. Results: The cohort included 312 subjects (mean age, 59.7 ± 17.2 years; 44% male). A 30- and 90-day mortality were 3.0% and 8.9%, respectively. The PESI scores were similar between hospital cohorts (10.3 ± 6.5 vs. 9.9 ± 6.5, P = NS). The PESI score correlated with 30- and 90-day mortality. The PESI correlates with 30- and 90-day mortality. A score of 3 represents a reproducible scoring tool and is strongly correlated with acute PE.

Keywords: inter-rater variability, mortality, pulmonary embolism, severity index.

Introduction
Pulmonary embolism (PE) remains a common and burdensome condition. More than 600,000 PE occur annually in the US and result in substantial morbidity, mortality, and cost [1]. As a syndrome, PE represents a diagnostic challenge and may be initially overlooked. Surprisingly, the non-specific nature of the symptoms related to PE may lead to a delay in diagnosis. Beyond simply confirming the diagnosis, the physician must determine which patients are most appropriate for initial medical treatment (e.g., anticoagulation, IVC, or heparin) and which require definitive intervention such as thrombolytic therapy. This task is complicated by many factors: many patients exhibit non-specific chest pain, pulmonary embolism may be missed on routine chest x-rays, and many patients may have concomitant diseases (e.g., heart failure, chronic lung disease).

Chest pain is a common symptom associated with acute PE, and therefore, the diagnosis of PE should be considered in all patients with chest pain. However, the diagnosis of PE in patients with chest pain is challenging. The chest pain associated with acute PE may be similar to the chest pain associated with other conditions such as heart failure, chronic lung disease, and myopericarditis. Therefore, the diagnosis of PE should be considered in all patients who present with chest pain and who have risk factors for acute PE.

The PE Severity Index (PESI) is a simple tool that risk-stratifies patients with acute PE. The PESI was developed by Asplund et al. [2] and is a simple tool that risk-stratifies patients with acute PE. The PESI is based on five clinical variables: age, sex, medical history, clinical findings, and demographic characteristics. The PESI score ranges from 1 to 9, with a score of 1 indicating a low risk of mortality and a score of 9 indicating a high risk of mortality.

The PESI score is obtained by summing the number of risk factors present in each patient. The PESI score can be used to determine the risk of mortality in patients with acute PE. The PESI score can also be used to determine the risk of major adverse events, such as repeat PE, deep vein thrombosis, and pulmonary hypertension.

The PESI score has been validated in multiple studies and has been shown to be a reliable tool for risk stratification in patients with acute PE. The PESI score has also been shown to be a useful tool for determining the risk of major adverse events in patients with acute PE.

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## Choice of anticoagulant

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin (UFH)</td>
<td>• Short half-life</td>
<td>• Continuous intravenous infusion</td>
</tr>
<tr>
<td></td>
<td>• Reversal agent available</td>
<td>• Unable to administer outside of medical setting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Possible development of heparin-induced thrombocytopenia (HIT)</td>
</tr>
<tr>
<td>Low molecular weight heparin</td>
<td>• Easy to administer</td>
<td>• Frequent monitoring needed</td>
</tr>
<tr>
<td></td>
<td>• Reversal agent available</td>
<td>• Risk of bleeding</td>
</tr>
<tr>
<td>Warfarin</td>
<td>• Oral</td>
<td>• Effectiveness uncertain in obese patients</td>
</tr>
<tr>
<td></td>
<td>• Able to monitor therapeutic level</td>
<td>• Possible pain with administration</td>
</tr>
<tr>
<td></td>
<td>• Reversible</td>
<td>• Difficult to achieve therapeutic levels in infants</td>
</tr>
<tr>
<td>Direct oral anticoagulant</td>
<td>• Oral</td>
<td>• Possible development of HIT (less than UFH)</td>
</tr>
<tr>
<td></td>
<td>• No frequent blood draws</td>
<td>• Risk of bleeding</td>
</tr>
</tbody>
</table>

### Pulmonary Embolism in Children

Ahmar Urooj Zaidi, Kelley K. Hutchins and Madhvi Rajpurkar

Division of Hematology Oncology, Carman and Ann Adams Department of Pediatrics, Wayne State University School of Medicine, Children’s Hospital of Michigan, Detroit, MI, United States
- AMPLIFY VTE – 18 or older

- EINSTEIN VTE – ‘they were of legal age for consent’; Rivaroxaban group 55.8±16.4, Control group 56.4±16.3

- HOKUSAI VTE – 18 or older

- RECOVER – 18 or older
Phase IIa study of dabigatran etexilate in children with venous thrombosis: pharmacokinetics, safety, and tolerability

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Essentials
- Dabigatran etexilate may provide a new treatment option for pediatric venous thromboembolism.
- Children aged 1 to <12 years were given dabigatran etexilate in an open-label, single-arm study.
- The pharmacokinetic-pharmacodynamic relationship was similar to that seen in adult patients.
- There were no serious adverse events, bleeding events or recurrent venous thromboembolism.

Summary: Background: The current standard-of-care treatments for pediatric venous thromboembolism (VTE) have limitations. Dabigatran etexilate (DE), a direct thrombin inhibitor, may offer an alternative therapeutic option.

Objectives: To assess the pharmacokinetics, pharmacodynamics, safety, and tolerability of a DE oral liquid formulation (OLF) in pediatric patients with VTE. Patients: Method Patients who had completed planned treatment with low molecular weight heparin or oral anticoagulants for VTE were enrolled in two age groups (2 to <12 years and 1 to <2 years), and received a DE OLF based on an age-adjusted and weight-adjusted nomogram. Originally, patients were to receive a DE OLF twice daily for 3 days, but the protocol was amended to a single dose on day 1. The primary endpoints were pharmacokinetic/pharmacodynamic-related plasma concentrations of DE and its metabolites; activated partial thromboplastin time (APTT), ecarin clotting time (ECT), and dilute thrombin time (DITT); and pharmacokinetic (PK)-pharmacodynamic (PD) correlation. Safety endpoints included incidence rates of bleeding events and all other adverse events (AEs). Results: Eighteen patients entered the study and received the DE OLF (an exposure equivalent to a dose of 1.5 mg/kg twice daily in adults). The projected steady-state dabigatran trough concentrations were largely comparable between pediatric patients and adults. The PK-PD relationship was linear for ECT and DITT, and non-linear for APTT. No serious or severe AEs, bleeding events, or recurrent VTEs were reported. Mild AEs were reported in three patients in the single-dose group (treatment period) and in one patient in the multiple-dose group (on-treatment period).

Conclusions: The current study supports the further evaluation of DE OLFs in pediatric patients with VTE.

Keywords: anticoagulants; dabigatran; direct thrombin inhibitors; pediatric; venous thromboembolism.
What actually happened

- Admitted to critical care bed
- Initial anticoagulation with UFH – to facilitate intervention if she deteriorated
- Improved so no intervention
- Transitioned to apixaban (menorrhagia)
- NT pro-BNP and troponin normalized; VQ at 3/12 no residual PE
• Back at school and participating in normal activities

• Counseled regarding future contraceptive options/pregnancy
Case 2.

- 40 year old man with acute onset right leg swelling and pain.

- R leg 10cm bigger than L leg, pulses normal.

- RFs for VTE – recent LH flight (Australia) and gastroenteritis.

- Hx – previous appendicectomy (2015) and asthma.

- D-dimers 11.86 (NR 0-0.55 mg/L FEU).
Doppler: ‘The CFV, SFV, and popliteal vein are patent and compressible with wall to wall colour Doppler flow. The external iliac vein appears patent and compressible where visualised. In the calf the PTV, ATV, and peroneal veins are patent on augmentation. Impression: No evidence of a right leg DVT.'
High probability DVT

- Risk factors
- Clinical signs
- High D-dimer
- No other obvious cause
Patient with signs or symptoms of DVT

Other causes excluded by assessment of general medical history and physical examination
DVT suspected

Two-level DVT Wells score (see main text)

DVT likely (≥2 points)
Is a proximal leg vein ultrasound scan available within 4 hours of being requested?
Yes
No

Proximal leg vein ultrasound scan
Was the proximal leg vein ultrasound scan positive?
Yes
No

D-dimer test
Was the D-dimer test positive?
Yes
No

D-dimer test

DVT unlikely (≤1 points)
D-dimer test
Was the D-dimer test positive?
Yes
No

Interim 24-hour dose of percutaneous anticoagulant
Is a proximal leg vein ultrasound scan available within 4 hours of being requested?
Yes
No

Proximal leg vein ultrasound scan within 24 hours of being requested

Advise the patient it is not likely they have DVT. Discuss with them the signs and symptoms of DVT, and when and where to seek further medical help. Take into consideration alternative diagnoses.
Diagnosis and management of acute deep vein thrombosis: a joint consensus document from the European society of cardiology working groups of aorta and peripheral vascular diseases and pulmonary circulation and right ventricular function Eur Heart J.
• In clinically suspected DVT, VUS provides overall sensitivity of 94.2% for proximal, and 63.5% for isolated distal DVT, with an overall specificity of 93.8%.

• Combination with colour-Doppler US increases sensitivity but lowers specificity. When DVT is suspected (without PE symptoms), anticoagulation may be safely withheld in patients with a single normal complete VUS.

• Limited CUS provided it can be repeated, and integrated within a diagnostic strategy including clinical probability, and D-dimer assessment.
• Anticoagulated


• Admitted for lysis and stenting

• Currently well – legs the same size and back in the gym
- BCSH guidelines (2012) - Patients with acute IVCT should be considered for catheter-directed thrombolytic therapy or endovascular surgery (2C).
Case 3.

- 33 year old woman
- Initially presented with vomiting and auditory disturbance ? Mastoiditis
- CT in keeping with CVST
- Background of menorrhagia
- Recently started COCP
Need to continue with warfarin?

Role for DOACs?

Anticoagulant options
• EINSTEIN, AMPLFY, HOKUSAIVTE and RECOVER – DVT and PE

• European Stroke guidelines (2017) - Recommendation: we do not recommend using NOACs (factor Xa or thrombin inhibitors) for the treatment of CVT, especially during the acute phase. Quality of evidence: very low; Strength of recommendation: weak

• BCSH guidelines (2012) - It is suggested that patients with CVST without contraindications to anticoagulant therapy should be treated early with therapeutic dose LMWH for at least 7 d (2C). It is suggested that oral anticoagulation with warfarin should be delayed until the patient's condition has stabilized (2C). It is suggested that a minimum of 3 months treatment is given (2C).
Rao SK¹, Ibrahim M¹, Hanni CM², Suchdev K¹, Parker D², Rajamani K¹, Mohamed W³.

Direct oral anticoagulants in rare venous thrombosis.
Finazzi G¹, Ageno W².

Abstract
The direct inhibitors of thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban) are currently used in patients with venous thrombosis of the lower or upper limbs or with pulmonary embolism. However, the use of these direct oral anticoagulants (DOACs) in subjects with abdominal or cerebral venous thrombosis is more contentious due to the paucity of available data. In a few case reports and small series of patients hitherto published, the DOACs showed good efficacy and safety, supporting an extension of their use to these rare conditions. Thus, prospective cohort studies and randomized controlled trials have been set up. In this article, we review the published clinical experience with DOACs in rare venous thrombosis, and provide updated information on ongoing clinical trials.
Take home points

- PESI adjunct to clinical decision making
- Evolving field when it comes to DOAC indications
- Need to individualize management plans when patients fall outside guidelines