Deep Vein Thrombosis and Pulmonary Embolism Management: The Clot Thickens

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David Schneider, MD, FAAFP

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Dr. Schneider cares for the underserved in Santa Rosa, California, serving Latino, Southeast Asian, and Eritrean populations. He has taught the breadth and depth of family medicine for more than 20 years, and his professional interests include the physician-patient relationship and clinical skills. Cardiovascular system conditions are one of his specialty topics, and he points to "the growing body of evidence suggesting that lifestyle is as effective as, or more effective than, pharmacologic interventions in primary prevention." Dr. Schneider also focuses on conditions of the endocrine system (especially thyroid); skin conditions and dermatology; primary prevention, with a focus on lifestyle; and procedures. Board certified in both family medicine and integrative holistic medicine, he produces Dr. Dave's To Your Health segments for Wine Country Radio and BlogTalkRadio.com.
Learning Objectives

1. Establish protocols to identify patients at risk for a thromboembolic event, and provide counseling to reduce risks and recognize signs and symptoms.

2. Use an evidence-based algorithm to diagnose DVT/PE, taking into account the stability of the patient.

3. Prescribe appropriate anticoagulant agents, according to the most recent clinical guidelines, to treat and help prevent recurrence of thrombotic events in patients.

4. Develop collaborative care plans with patients; emphasizing adherence to prescribed therapies, and monitoring with follow-up.

Associated Sessions

• (PBL) Deep Vein Thrombosis and Pulmonary Embolism Management: The Clot Thickens
VTE Epidemiology

- **DVT:**
  - ~80/100K / yr ➔ 600,000 hosp/yr.
  - Up to 900K/yr, many unreported/insignificant.
  - Males may have ~20% higher risk vs females.
  - Risk ↑ w/age.
    - Men 60-80 have 53X higher risk vs men <40.
    - Women 60-80 have 26X higher risk vs women <40.
  - African-Americans may have ↑ risk, Asians & Native Americans may have ↓ risk.

PE Epidemiology

- 3rd most common CV dz (CAD, cerebrovasc).
- 60,000 – 100,000 annual deaths in US.
- Increasing detection (D-Dimer) ➔ apparent ↑ incidence.
- Sudden death = 1st sx in ~25% w/PE.
- ↑ age ➔ ↑ % of VTE is PE.
- PE deaths may be ↓ing – improved care/ prevention vs admitting less severe PE vs other.


Who Is At Risk for VTE?

- **Most** hospitalized pts (135X community risk!)
  - ENDORSE study 2008, retrospective rev 68,000 hosp pts:
    - 52% of hosp pts at risk—64% of surg pts; 41.5% of medical pts.
  - ENDORSE II 2010, 1627 pts, Mexico, X-section:
    - 38% @ risk.
  - Both studies ➔ 58% surg pts receiving recommended prophylaxis.

VTE Risk: Shockers

• ~25 – 50% of symptomatic, clinically recognized VTE events occur in community pts who have not been recently hospitalized nor recovering from recent illness!
• ~33% of pts will have recurrence over 10 yrs.
• ➔ Awareness + vigilance!

Arch Intern Med 2007;167(14):1471-5

VTE Pathophysiology (Virchow)

• Venous stasis.
  – ↓ mobility, ↑ age, HF,…
• Endothelial injury.
  – Surgery, trauma,…
• Hypercoagulable state.
  – Inherited, acquired.

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Br J Haematol 2008;143:180-90
AES Question #1

Which of the following is NOT a risk factor for Venous thromboembolic dz?
A. Stroke
B. Older age
C. Obesity
D. Heart failure
E. Inflammatory bowel disease
F. None of the above – all are risk factors

DVT Risk Factors

- **Venous Stasis**
  - Recent surgery/immobilization.
  - Hospitalization w/in 3 mo.
  - Spinal cord injury.
  - Paresis/paralysis (stroke, etc).
  - Pregnancy/postpartum.
  - Age.
  - Heart failure.
  - Obesity.
  - Flight >6hr, travel>4 hr.

- **Vascular Injury**
  - Prior DVT/PE.
  - Smoking.
  - Venous disease.
  - Varicose veins.
  - Central venous line.

----------------------------------------

- Acute illness—esp MI, HF, resp failure, infection.

References:
DVT Risk Factors: Hypercoagulable

- **Inherited thrombophilia (FH!)
  - Factor V Leiden mutation.
  - Prothrombin G20210A mutation
    - These 2 together ~50-60%.
  - Protein S deficiency.
  - Protein C deficiency.
  - Antithrombin (AT) deficiency.
  - Non-type O blood (↑vWF & VIII).
- ➔ +FH VTE is risk factor.

- **Acquired states
  - Malignancy (Lung 17%, Pancreas 10% [Trousseau]).
  - CKD; nephrotic syn.
  - Liver dz/cirrhosis!!
  - Autoimmune hemolytic anemia.
  - Polycythemia vera.
  - Parox. noct. hemoglobinuria.
  - Sickle cell disease.
  - Antiphospholipid syn.
  - Inflam bowel dz.

Meds/Drugs Assoc w/VTE

- Estrogen.
  - Combo OCP’s.
    - Risk ↑ @ 6-12 mo, may be unrelated to duration.
    - Gestodene, desogestrel.
    - HRT (esp elderly, obese, +PMH, 1st yr of use).
    - Tamoxifen.
- Testosterone.
- Glucocorticoids.
- Antipsychotics.
  - OR=1.33 for all.
  - OR=1.97 for start w/in 3 mo.
  - OR=1.73 for 2nd gen.
  - OR=1.28 for 1st gen.


Quality of Evidence in VTE

• Chest, 2016: “Of 54 recommendations included in the 30 statements, 20 were strong and none was based on high-quality evidence, highlighting the need for further research.”

• ASH 2018: 34/44 recs had low/very low certainty of evidence, none high.

DVT Diagnosis—Clinical

• Meta-anal 2005:
  – Clinical findings to help R/I DVT:
    • Malignancy (LR=2.71).
    • Previous DVT (LR=2.25).
    • Recent immobilization (LR=1.98).
    • Δ calf diameter (LR=1.80).
    • Recent surgery (LR=1.76).
  – Clinical findings to help R/O DVT:
    • Absence of calf swelling (LR=0.67).
    • Absence of Δ calf diameter (LR=0.57).
  – Homan’s LR+ ➔ NS; LR- ➔ 0.87.

SUMMARY: Clinical findings are neither sensitive nor specific. Have a high index of suspicion.
AES Question #2

Dolores N. Pierna is a 65 yo Latina woman who presents w/swollen L LE w/pitting edema L only, L visible non-varicose superficial veins, and tender cord L thigh & popliteal areas. What is her level of probability for DVT:
A. Low
B. Intermediate
C. High

Prediction Scores for DVT

- **Wells Score**: best studied, most famous.
- **Modified Wells score** (Wells + PMH DVT).
- Constans score.
- Hamilton score.
- Kahn score.
- St Andre score.
  - Gestalt vs score/decision rule: no evidence of superiority.
Wells DVT Scores

- 2-level Wells:
  - Low prob (unlikely) 0-1.
  - DVT likely ≥2.
- 3-level Wells:
  - <0 ➔ low probability.
  - 1-2 ➔ intermediate probability.
  - ≥3 ➔ high probability.
- May be less useful in ofc, inpt (?!), elderly, ? comorbidities.
  - Age-adjusted value ➔ better specificity.

Wells DVT Score:
- Paralysis, paresis, recent immobilization of LE = 1 point.
- Bedridden >3 days or major surgery w/in 4 wks = 1.
- Localized tenderness along deep veins = 1.
- Swelling of entire leg = 1.
- Calf swelling 3 cm >other, 10 cm below tibial tuberosity = 1.
- Pitting edema greater in sx leg = 1.
- Collateral nonvaricose superficial veins = 1.
- Active CA or CA Tx’d w/in 6 mo = 1.
- Alternative Dx more likely than DVT = -2.

D-Dimer

- Degradation product of cross-linked fibrin (clot).
- High sensitivity (93-96%) – 500 ng/ml = 0.5 μg/mL.
  - High sensitivity assays—ELISA, immunometric.
  - Moderate sensitivity assays—whole blood, latex semiquantitative ~83-85% sens.
  - Determine which your institution uses.
- Not specific.
  - Age-adjusted cutoffs improve specificity.
- Not adequate as stand-alone test.
Low Pre-Test Probability

• Neg D-dimer rules out DVT.
• + D-dimer $\Rightarrow$ US w/compression.
  – Non-compressible vein &/or intravenous clot $\Rightarrow$ + DVT $\Rightarrow$ treat.
  – Normal US $\Rightarrow$ no DVT.

High Pre-Test Probability

• Go directly to US w/compression.
  – + US $\Rightarrow$ manage DVT.
  – Neg US $\Rightarrow$ no DVT.
  • Consider iliac vein DVT $\Rightarrow$ iliac US or CT venogram.
    – ↑ risk of PE, other complications.
    – Sx/sx ~ LE DVT—if suspected & not found, look harder.
  – Normal D-dimer does not R/O DVT.
Intermediate Pre-Test Probability

- D-dimer—must use high sensitivity assay.
  - + $\Rightarrow$ treat.
  - Neg $\Rightarrow$ no DVT.
    - Neg moderate sensitivity D-dimer does not R/O – know what your lab uses.

Point Of Care UltraSound (POCUS)

Vein Open  Compressible  Non-compressible vein w/heterogeneity

Normally compressible vein  Non-compressible vein $\Rightarrow$ DVT

Personal Collection of images, David Schneider, MD, HIPAA Compliant.
May-Thurner Syndrome

- Extrinsic vein compression by artery vs bony structures in iliocaval territory.
- L iliac vein compression (vs L5) most common.
  - Recurrent LLE DVT.
  - ~2-5% of LLE DVT, may be up to 50%.
  - F:M = 2:1.
- Most w/anatomy = asymptomatic.
- Venogram, CT veno, IV US.
- Stent.

DVT Complications

- PE.
- Post-thrombotic (ex p-phlebitis) syndrome.
- Phlegmasia alba dolens (rare).
- Phlegmasia cerulea dolens (rare).
- See Supplemental Materials for info.
AES Question #3

Ms Pierna has been diagnosed with a popliteal + thigh DVT. Of the following, which would be the most appropriate initial treatment?

A. Heparin 5000 units subcu tid
B. Dabigatran (Pradaxa™) 150 mg bid
C. Apixaban (Eliquis™) 5 mg bid
D. Rivaroxaban (Xarelto™) 15 mg bid
E. Edoxaban (Savaysa™) 60 mg once daily

DVT Treatment Principles

- Proximal LE DVT = popliteal & above ➔ anticoagulate.
- Distal LE DVT = completely below knee, calf veins only.
  - Serial compression US to detect proximal.
  - 1/3 develop proximal extension, usu w/in 2 wk.
  - Consider anticoagulation, esp hi risk or sx.
Anticoagulation in Distal DVT

- Symptomatic + low bleeding risk.
- Asymptomatic—think high risk:
  - Unprovoked DVT.
  - Extensive thrombosis (>5 cm in length), mult veins.
  - Thrombosis close to, or extension to, proximal veins.
  - Persistent/irreversible risk factors (e.g., active CA).
  - Prior DVT or PE.
  - Prolonged immobility.
  - Inpatient status.

Initial Anticoagulation

- Heparin IV drip.
- LMWH (enoxaparin = Lovenox™) SQ.
- Fondaparinux SQ (Arixtra™).
- Rivaroxaban (Xarelto™).  } Both effective w/in
- Apixaban (Eliquis™).  } 1-4 hrs; monoTx
- If using warfarin or edoxaban or dabigatran, must first give parenteral agent.
DOACs/NOACs

- Efficacy comparable to or exceeding warfarin.
- Bleeding:
  - Overall bleeding ~ warfarin.
  - Intracranial bleeding less than warfarin.
- Expensive, not always covered.
- No monitoring.
- Caution w/liver/renal dz.
- Not for use w/mechanical valves.

Direct Thrombin Inhibitor

- Dabigatran (Pradaxa™): $418 w/GoodRx coupon.
  - 150 mg bid.
  - Must use 5 days of heparinoid 1st (studies).
  - Indications: DVT or PE (+ AFib, p-THR).
  - Must store in original blister pack or bottle w/desiccant (degrades w/moisture in air).
  - Dosage adjustment for CrCl<30; HD not studied.
  - Avoid if CrCl<50 & pt on P-GP inhibitor.
Direct Factor Xa Inhibitors

- **Caution** w/renal & liver impairment.
  - No evidence of hepatotoxicity > warfarin.
  - Case reports not substantiated in lg trials.
- Uncertain efficacy in obese (BMI >40).
- Recommend baseline CBC w/plts, Cr/GFR, LFT’s, PT/PTT.


Direct Factor Xa Inhibitors

- **Rivaroxaban** (Xarelto™): $460 GoodRx.
  - DVT or PE (+ Afib, p-THR & TKR).
  - 15 mg bid X 21 days, then 20 mg once daily.
    - If >6 mo Rx, can reduce to 10 mg daily.
  - Take w/food (improves absorption)
  - Avoid in VTE if CrCl <30.
  - Caution in elderly or very small pts.

Direct Factor Xa Inhibitors

- **Apixaban (Eliquis™):** $460 GoodRx.
  - DVT or PE (+ Afib, p-THR & TKR).
  - 10 mg bid for 7 days, then 5 mg bid.
    - If >6 mo Rx, can reduce to 2.5 mg bid.
  - May use to CrCl 25, possibly in HD w/adjustment.
    - For VTE, no dose chg for Cr, wt, age (↓ in AF, surg prophyl).
  - Caution in elderly or very small pts.


- **Edoxaban (Savaysa™):** $385 GoodRx.
  - DVT or PE (+ Afib).
  - Must first give parenteral anticoag X 5 days.
  - 60 mg once daily; 30 mg once daily if body weight <60 kg.
  - Use in CrCl 15-95 only (↓ efficacy [in Afib] @GFR>95).
  - Dose adjustment CrCl 15-50.

Direct Factor Xa Inhibitors—New

• Betrixaban (Bevyxxa™)—6/2017 ($480):
  – Indication: VTE prevention only now.
  – Approval based on 1 trial (APEX), pts w/high VTE risk.
    • ↑D-dimer or ≥75, + ↓ mobility + ≥1 of
decompensated HF, acute resp failure, infection,
ischemic stroke, acute rheumatic disease. Many exclusion criteria.


DOAC Reversal

• Dabigatran: idarucizumab (Praxbind™).
  – For life-threatening bleeding or emergency procedure ($3500/dose).
• NEW (5/2018): andexanet α (AndexXa™).
  – Apixaban + rivaroxaban. Being studied for others.
  – Binds drug, ↓ bleeding w/in 1-12 hr.
  – >$25,000 per pt.
  – Life-threatening bleeding. O/w use prothrombin complex.

Prescriber’s Letter, 7/2018; JACC 2017;70:3042–67
### Anticoagulant Choice: Special Pops

<table>
<thead>
<tr>
<th>Condition</th>
<th>Preferred</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>LMWH, ?riva/apix?</td>
<td>Esp new dx, metastatic, extensive VTE</td>
</tr>
<tr>
<td>Liver dz/ coagulopathy</td>
<td>LMWH</td>
<td>No DOACs if ↑ INR d/t liver dz; VKA difficult to control, INR may not reflect med effect.</td>
</tr>
<tr>
<td>Renal dz, CrCl &lt;25</td>
<td>VKA (warfarin)</td>
<td>DOACs &amp; LMWH contraind w/severe renal dz.</td>
</tr>
<tr>
<td>CAD</td>
<td>VKA, rivaroxaban, apixaban, edoxaban</td>
<td>COMPASS ➔ fewer MACE w/riva+ASA vs either. ↑ MI w/dabigatran; ↑ bleeding w/anti-plt meds.</td>
</tr>
<tr>
<td>Dyspepsia, H/O GI bleeding</td>
<td>VKA, apixaban</td>
<td>Dabigatran ↑ dyspepsia. Dabigatran, rivaroxaban, edoxaban may be ➔ ↑ GI bleeding vs VKA.</td>
</tr>
<tr>
<td>Pregnancy or pregnancy risk</td>
<td>LMWH</td>
<td>Other agents to cross the placenta.</td>
</tr>
</tbody>
</table>


### Early D/C or Outpt Rx

- Hemodynamically stable.
- Low bleeding risk.
- No renal insufficiency (AKI/CKD).
- Practical system at home for administration & surveillance of anticoagulant therapy (good living conditions, caregiver support, phone access, able to return to hospital if worse).
- No complication (PE, Ig DVT, comorbidities,…).

*Chest 2016;149:315-52; Can Fam Physician 2005;51:217-23*
Pulmonary Embolism

PE & DVT

• ~50% of pts w/proximal DVT are also found to have PE @ presentation.
• In ~50% of pts w/PE, venous source is not found.
  – ? Cardiac origin?
  – ? Renal vein origin?
  – ? Entire thrombus embolized?

Clinical Findings

- **Symptoms**—may be mild or nonspecific; ~ non-PE in 1 study.
- Dyspnea @ rest or exertion: 70-79%.
- Chest pain, pleuritic or not: 40-66%.
- Cough ~40%.
- Calf or thigh pain or swelling ~40%, vs ~20% in non-PE.
- Hemoptysis 13%.
- Syncope 10%.
- Signs—may be mild or nonspecific.
- Tachypnea 54-70%.
- Calf or thigh swelling, erythema, edema, tenderness, palpable cords 47%.
- Tachycardia 24-33%.
- Rales 18%.
- Decr breath sounds 17%.
- ↑ P2 (of S2) 15%.
- JVD 14%.
- Fever, PNA mimic 3%.

Other PE Clinical Clues

- Hypoxemia, esp w/neg CXR 74%.
- Resp alkalosis & hypocapnea 41%.
- EKG:
  - S1Q3T3 or RV strain (ST↓/T↓ V1-V3, II/III/aVF) ~10%.
  - Tachycardia, NSST/T chg 70%.
- CXR WNL or nonspecific.
Pre-Test Probability

• Gestalt ~ score, but score confers ↑ specificity.
  – Wells, modified Wells, revised Geneva, Pisa.
  – Wells most widely used, Pisa may be more accurate but less validated, Geneva ? less accurate?
• Probability rules overlooked ~50% of time.

Hemodynamically Unstable

• Still unstable p-resusc ➔ unsafe to do detailed testing:
  – LE US—eval for DVT.
  – Transthoracic echo (TTE)—signs of RV strain or thrombus in heart.
• Stable p-resusc:
  – High suspicion ➔ CT angio (CTA).
  – Low-mod ➔ manage as stable.
AES Question #4

Mr Ivan Norcoe, 42 yo, presents to ED w/vague CP + SOB. Prev in good health, ambulatory, no prior H/O VTE, small amt of hemoptysis X1, none since. HR 72, RR 16, O₂ sat 97%, cardiopulm exam WNL, legs WNL/NT. What is the most appropriate next diagnostic step?

A. High-sensitivity D-dimer.
B. Compression ultrasound BLE w/dopplers.
C. CT pulmonary angiogram.
D. V/Q scan.
E. Discharge from ED.

Stable Pt

- 3-tiered Wells PE Criteria:
  - Low probability: score <2.
  - High probability: score >6.
  - Can use PERC if low risk.
- 2-tiered Wells PE Criteria:
  - >4.0 ➔ PE likely.
  - ≤4.0 ➔ PE unlikely.
  - Less accurate >60 yo (mean 76).

Low Pre-Test Probability: PERC

- Pulmonary Embolism Rule-out Criteria (PERC rule).
  - R/O PE in low probability pts
  - All negative → no further testing (↓’s testing & $).  
  - 96-100% sensitivity.  
  - Not specific.  
  - Valid in low-prevalence setting (ED, office—not hospital).  
  - Can also use if Wells <2.

- Age <50 years
- Heart rate <100
- O₂ saturation ≥95 percent
- No hemoptysis
- No estrogen use
- No prior DVT or PE
- No unilateral leg swelling
- No surgery/trauma requiring hospitalization w/in prior 4 wks

Applying the Rules

- Low probability (Wells <2): PERC.
  - PERC all neg → PE unlikely.
    - May end W/U & ↓ costs—validated.
    - Some get D-dimer—if neg → no PE.
  - PERC + → D-dimer.
    - D-dimer neg → no PE.
    - D-dimer + → CTA.
Intermediate Probability

• D-dimer + ➔ CTA.
• D-dimer neg:
  – Most pts ➔ no PE.
  – Controversy:
    • Pt w/poor cardiopulmonary reserve (poor tolerance of PE) ➔ CTA.
    • Suspicion by gestalt or Wells in higher range ➔ CTA.

High Probability

• CTA, manage per results (96+% NPV).
• If unable, V/Q scan distant 2nd choice (76% NPV).
  – Nl V/Q ➔ no PE.
  – Low-probability V/Q + low clinical probability (Wells <2) ➔ no PE.
  – High-probability V/Q + high clinical probability (Wells >6) ➔ Rx for PE.
  – Any other combo of V/Q results + clinical pretest probabilities ➔ indeterminate ➔ further imaging.
    • LE doppler + compression US.
    • Pulmonary angio (catheter).

Empiric Anticoagulation?

- Low bleeding risk: Yes, esp if dx testing delayed.
- High bleeding risk: No empiric.
- Mod bleeding risk: individualize, risk/bene.

PE Management

- Anticoagulation; monitor for acute deterioration + chronic SE’s.
- IVC filter (preferably retrievable) if anticoagulation contraindicated.
- Hemodynamically unstable ➔ consider thrombolysis or embolectomy (IR vs surg); heparin while waiting.
Which Agent for PE?

- Hemodynamically stable:
  - LMWH (Tx dose, not prophylactic).
  - Fondaparinux.
  - DOAC—rivaroxaban, apixaban.
    - No heparin needed.
    - Effective w/in 1-4 hrs.
    - Dabigatran or edoxaban require heparinoid 1st.

Special Populations

- AKI/CKD: unfractionated heparin (UFH).
- Hemodynamic instability: UFH.
- Malignancy: LMWH.
- Pregnancy: LMWH.
Continuing Anticoagulation

- Warfarin w/INR monitoring:
  - Insurance coverage.
  - Significant renal dysfunction.
  - Easier to detect non-adherence (INR).
  - Reversible.
  - Ensure therapeutic INR X2 days, then D/C parenteral agent (avg ~5 days).

Continuing Anticoagulation—2

- Factor Xa inhibitors: (apixaban, edoxaban, rivaroxaban; betrixaban for prophylaxis).
  - Apixaban & rivaroxaban active w/in 1-4 hrs.
- Direct thrombin inhibitors: dabigatran.
  - No routine monitoring.
  - No bridging.
  - Not reversed w/FFP (idarucizumab = Praxbind™ for dabigatran).
  - Still drug interactions.
Duration of Anticoagulation

- **3 Months (Min):**
  - 1st VTE, unprovoked.
  - *1st VTE, provoked/transient risk factor = 3 mo!.
  - *Isolated distal DVT.
  - *Subsegmental or incidental PE—IF Tx’d.
  - *High bleeding risk.
    - *⇒ 3 mo only

- **Consider 6-12 mo:**
  - Phlegmasia cerulea dolens.
  - Persisting but reversible risk factor??
  - **No known benefit** of 6-12 mo vs indefinite for avg risk pt, but trials excluded pts.


Indefinite Anticoagulation

- **General Agreement:**
  - Poor data—expert opinion.
  - Unprovoked proximal DVT & symptomatic PE.
  - Recurrent unprovoked VTE.
  - Active cancer.

- **Some Agreement:**
  - Recurrent provoked VTE.
  - Provoked VTE with persistent risk factors.
  - Unprovoked isolated distal DVT.

- ???
  - Unprovoked incidental or subsegmental PE

AES Question #5

Who should have a workup for hypercoagulable states after initial DVT?
A. All pts after 1st DVT.
B. All pts after 1st unprovoked DVT.
C. Pts w/family history of DVT under age 45.
D. Upper extremity DVT.
E. None of the above.

Thrombophilia W/U

• Routine eval for hypercoagulable d/o is **not** indicated.
  – No reduction in mortality, recurrence.
• Routine eval for occult malignancy is **not** warranted.

Thrombophilia W/U—Who?

- Patients with FH of VTE (esp 1° <45).
- Patients w/o FH of VTE.
  - Young pts (<45 years).
  - Pts with recurrent thrombosis.
  - Pts w/thrombosis in unusual vascular beds (portal, hepatic, mesenteric, cerebral).
  - H/O warfarin-induced skin necrosis (prot C↓).
  - Pts w/arterial thrombosis.

VTE Prophylaxis

- VTE risk:
  - Surgical: Caprini score divides pts into risk groups.
    - High: major ortho surg – THR, hip fx, etc.
    - Mod: gyn, thoracic, neurosurg, etc.
  - Medical: ICU, CA, stroke, pregnancy.
- Balance w/bleeding risk.
VTE Prophylaxis—Surgical Pts

- Very low risk ➔ early ambulation.
- Low risk (or contraind to med) ➔ mechanical (SCD/IPC).
- Mod-high risk ➔ pharmacologic prophy.
- Very high risk ➔ pharm + mechanical.

Pharmacologic Prophylaxis

- **LMWH:**
  - Caution in AKI/CKD.
  - Less HIT vs UFH, but still present.
- **Fondaparinux:**
  - More effective vs enoxa in THR, hip fx, knee surg.
  - May be assoc’d w/more bleeding; mortality same.
  - No HIT.

Pharmacologic Prophylaxis—2

• UFH (unfractionated heparin):
  – Low dose.
  – Subcutaneous injection, q 8-12 h.
  – Inexpensive.
  – Monitor plts – HIT.
  – Reversible.


Pharmacologic Prophylaxis—3

• DOACs:
  – Rivaroxaban = or superior to LMWH (THR, TKR), ? ↑ bleeding.
  – Dabigatran ~ LMWH (THR, TKR).
  – Apixaban—less bleeding, mixed data on efficacy (TKR).
  – Edoxaban—early studies ➔ efficacy>LMWH.

Mechanical Prophylaxis

- SCD/IPC—place just prior to surg, use til hosp D/C.
- Surgical pts at high bleeding risk (neurosurgery, ICH).
- Contraindication to anticoagulants (bleeding ulcer).
- Low risk of VTE.
- Consider adding pharmacologic agent when bleeding risk becomes acceptably low (eg, 48 to 72 hours p-neurosurgery), or when the bleeding/risk resolved.
  - Contraindicated: LE ischemia, leg wound.
  - May be no more effective than placebo.

VTE Prophylaxis—Medical Pts

- Assess VTE risk—no validated model yet⇒ empiric/gestalt.
  - Padua Prediction Score.
  - Geneva risk score—needs calculator.
VTE Prophylaxis—Medical Pts

• Assess bleeding risk–no validated model.
  – IMPROVE bleeding risk score:

Choice of Agent—Medical Pts

• Low risk: early ambulation +/- mechanical.
• Moderate risk: acute medical illness w/≥1 risk factor & no incr bleeding risk ➔ LMWH or fondaparinux.
• High risk (critically ill, CA, stroke) & low bleeding risk ➔ LMWH.
• Very high risk, mult RF’s: consider combined pharm + mechanical, though no benefit yet known.
• CrCl<30 ➔ UFH instead of LMWH.
Mechanical + Pharmacologic PPx?

  - 2003 pts ≥14, mean age 58, 57% male.
  - Mostly medical, 9.6% postop, all ICU.
  - LMWH +/- IPC (median 22 hr/day).
  - Compression US q 48 hr.
  - No added benefit (death, VTE).
  - Underpowered—low # events.

Choosing Wisely

- Do not recommend bed rest following Dx of acute DVT after the initiation of anticoagulation therapy, unless significant medical concerns are present. (American Physical Therapy Association)
- Do not treat with an anticoagulant for more than three months in a patient with a 1<sup>st</sup> VTE occurring in the setting of a major transient risk factor. (American Society of Hematology)
- Don’t reimage deep vein thrombosis in the absence of a clinical change. (Society for Vascular Medicine)
- Don’t do W/U for clotting D/O for pts who develop 1<sup>st</sup> episode of DVT in the setting of a known cause. (Society for Vascular Medicine)
Travel Prophylaxis?

• ASH 2018, long distance (>4 hr):
  – No risk factors ➜ recommend no prophylaxis.
  – Substantially ↑ VTE risk: rec graduated compressions stockings or LMWH; if unable, ASA (poor evidence, no sig diff for meds).
  • Recent surgery, prior VTE, postpartum, active malignancy, ≥2 risk factors, incl combo of above w/HRT, obesity, pregnancy.

Quality of Evidence in VTE

• Chest, 2016: “Of 54 recommendations included in the 30 statements, 20 were strong and none was based on high-quality evidence, highlighting the need for further research.”
• ASH 2018: 34/44 recs had low/very low certainty of evidence, none high.
Best Practice Recommendations

• Pre-test probability should be assessed prior to testing in VTE (SORT B).
• Point of care ultrasound (POCUS) is an evidence-based tool to assist in dx of DVT (A); duplex scanning is gold standard (A).
• DOACs are preferred in most pts w/acute VTE (A).

References

• 2018 Amer Soc of Hematology Clinical Practice Guidelines on VTE: https://www.hematology.org/VTE/
  – Prophylaxis: Blood Adv 2018;2(22):3198-225
  – Anticoag Mgmt: Blood Adv 2018;2(22):3257-91
• 2016 ACCP Guideline on VTE Treatment: Chest 2016;149:315-52
AES Answer Key

1. F  
2. C  
3. D  
4. A  
5. C  
Supplemental: 
6. D  
7. B  
8. B  
9. D

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Health Inequalities: PE

- Men have 16.7% higher risk of PE.
- Men have 20-30% higher PE mortality.
- Age-adjusted mortality rates for African-Americans ~50% > Caucasians, which are ~50% > Asian/Native American/Latino.

Assessing VTE Risk in Outpatients

- Outpts have high incidence of risk factors for VTE.
- Routine screening in asymptomatic pts is not indicated.
- Screening for VTE risk by FH (1° or 2° relatives), though insensitive & not specific (& possibly inaccurate), may assist in future dx/mgmt.
- PMH of comorbidities (PMH DVT, HF, liver, renal) may be useful. (NO guideline)

DVT Diagnosis—Hx

- “Swelling”: 97% sensitive, 33% specific.
- Pain: 86% sens, 19% spec.
- Warmth: 72% sens, 48% spec.
- Clinical exam is not reliable – 30-60% PPV/NPV.
- Always eval for signs/sx of PE.

Lancet 1984;2:716-9
Missing Hospital VTE?

• More VTE Dx’d in 3 mo following hospitalization than during hospitalization (Arch Intern Med 2007;167:1471–5).
• Uncertain if we are doing better in the past 11 yrs since this study.

AES Question #S6

Which is true about Dx of DVT??
A. A negative D-dimer precludes the use of a Wells or other DVT score.
B. Pts with + D-dimer should receive treatment for DVT.
C. A negative D-dimer rules out DVT.
D. A pt with high pre-test probability of DVT should not have a D-dimer drawn.
Dx of 1st DVT

1. Assess pre-test probability.
   a) If low or moderate probability ➞ D-dimer.
   b) If high probability ➞ US-based imaging.
      i. May use low vs moderate vs high probability, if 3 categories preferred.
      ii. ESC suggests low vs high only (2 categories).
   c) Gestalt vs score/decision rule: no evidence of superiority.

DVT DDx

- Muscle strain, tear, injury: 40%.
- Leg swelling in paralyzed limb: 9%.
- Lymphangitis or lymph obstruction: 7%.
- Venous insufficiency: 7%.
- Popliteal (Baker's) cyst: 5%.
- Cellulitis: 3%.
- Knee abnormality: 2%.
- Unknown – 26%.
D-Dimer False Positives

- Arterial thromboembolic disease
  - Myocardial infarction
  - Stroke
  - Acute limb ischemia
  - Atrial fibrillation
  - Intracardiac thrombus
- DIC
- Preeclampsia and eclampsia
- Abnormal fibrinolysis; use of thrombolytics
- Cardiovascular disease, HF
- Infection/sepsis/inflammation
- SIRS

- Surgery/trauma (tissue ischemia, necrosis)
- Sickle cell vaso-occlusive episode
- Severe liver disease (↓ clearance)
- Malignancy
- Renal disease
  - Renal vein thrombosis, nephrotic
  - Acute renal failure
  - Chronic kidney disease
- Normal pregnancy
- Venous malformations
- **Aging**


P-Glycoprotein (P-GP)

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flurooquinolones</td>
<td>Amiodarone</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Macrolides</td>
<td>Rifampin (substr + inducer)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Juices—OJ, grapefruit</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>Ketoconazole</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>CA ChemoTx agents (many)</td>
<td>TCA’s, SSRI’s, neuroleptics</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>HIV Protease inhibitors</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>Verapamil</td>
<td></td>
</tr>
<tr>
<td>Loperamide, ondansetron</td>
<td>Omeprazole</td>
<td></td>
</tr>
<tr>
<td>DOACs</td>
<td>Carvedilol</td>
<td></td>
</tr>
</tbody>
</table>
P-Glycoprotein (P-GP)

- Drug transport protein.
- Transports drugs from intestinal cells to intestinal lumen for excretion.
  - Some drugs will be eliminated w/o absorption.
  - Some drugs will have ↑ bioavailability.

Changes in Recs

- Distal DVT: anticoagulate more.
- UE DVT: anticoagulate most, thrombolysis for acute.
- Superficial venous thrombophlebitis: still no anticoagulation unless extends to DVT.
- See Supplemental Material for details.
How Long Does a Clot Last?

• US F/U studies suggest that LE DVT resolves w/in 6 mo 70-78% of the time.
• Case report of DVT persisting @ 12 mo on rivaroxaban, resolved in 1 mo on switch to warfarin (?clinical relevance).
• Older pts w/more proximal DVT ➔ may still have clot present @ 2 yrs.

Emboli Aren’t Kind

• Mortality ↓ing, still 2-11% (vs 30% untreated).
• Infarction—10%. Pleuritic CP, hemoptysis.
• Impaired gas exchange ➔ hypoxemia tachypnea & hypocapnea.
• Pulm art thrombus ➔ ↑ pulm art pressure + hypoxic vasoconstriction in pulm arts.
  – ↑ PA Pressure ➔ RV dilation ➔ ↓ preload ➔ ↓ SV & CO.
  – Can lead to hypotension, CV compromise.
  – Underlying cardiopulmonary dz ➔ smaller PE can cause hypotension (vasoconstriction + RV failure).
PE Management

• Empiric anticoagulation (pending full eval):
  – Low bleeding risk (0 risk factors) +
    • High clinical suspicion (ie, Wells >6).
    • Mod clinical suspicion (ie, Wells 2 to 6), in whom
diagnostic evaluation is expected to take >4 hr.
    • Low clinical suspicion (ie, Wells <2), if diagnostic
evaluation is expected to take >24 hours.

Empiric Anticoagulation?

• High bleeding risk (2+ risk factors) ➔ do not anticoagulate; expedite eval.
• Mod bleeding risk (1 risk factor) ➔ clinical judgment, risk/bene, individualize.
Bleeding Risk

- Age >65 years
- Age >75 years (2 RF’s)
- 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
- Alcohol abuse

Continuing Anticoagulation—3

- ASA is not appropriate for anticoagulation.
- For anticoag >12 mo, rivaroxaban 20 mg = 10 mg, both superior to ASA for prevention of recurrent VTE.
  - Major & minor bleeding events same in all groups.
### Anticoagulant Choice

<table>
<thead>
<tr>
<th>Condition</th>
<th>Preferred</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>LMWH, ?riva/apix?</td>
<td>Esp new dx, metastatic, extensive VTE</td>
</tr>
<tr>
<td>No parenteral tx</td>
<td>Rivaroxaban; apixaban</td>
<td>VKA, dabigatran, and edoxaban require initial parenteral therapy.</td>
</tr>
<tr>
<td>1/day po med</td>
<td>Rivaroxaban; edoxaban; VKA</td>
<td>No DOACs if ↑ INR d/t liver dz; VKA difficult to control, INR may not reflect med effect.</td>
</tr>
<tr>
<td>Liver dz/coagulopathy</td>
<td>LMWH</td>
<td>No DOACs if ↑ INR d/t liver dz; VKA difficult to control, INR may not reflect med effect.</td>
</tr>
<tr>
<td>Renal dz, CrCl &lt;30</td>
<td>VKA</td>
<td>DOACs &amp; LMWH contraind w/severe renal dz.</td>
</tr>
<tr>
<td>CAD</td>
<td>VKA, rivaroxaban, apixaban, edoxaban</td>
<td>↑ MI w/dabigatran; other DOACs effective in CAD. ↑ bleeding w/anti-plt meds.</td>
</tr>
</tbody>
</table>

### Anticoagulant Choice—2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Preferred</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia, H/O GI bleeding</td>
<td>VKA, apixaban</td>
<td>Dabigatran ↑ dyspepsia. Dabigatran, rivaroxaban, edoxaban may be ➔ ↑ GI bleeding vs VKA.</td>
</tr>
<tr>
<td>Poor adherence</td>
<td>VKA (long duration)</td>
<td>Monitor INR; some pts may be more adherent w/DOAC (simpler).</td>
</tr>
<tr>
<td>Thrombolytic tx</td>
<td>UFH infusion</td>
<td>More experience.</td>
</tr>
<tr>
<td>Reversal agent needed</td>
<td>VKA, UFH, dabigatran; apix/riva</td>
<td>Reversal agent for dabigatran may not be universally readily available.</td>
</tr>
<tr>
<td>Pregnancy or pregnancy risk</td>
<td>LMWH</td>
<td>Other agents to cross the placenta.</td>
</tr>
</tbody>
</table>

Thrombophilia W/U—What?

• Inheritable:
  – Factor V Leiden (activated protein C (APC) resistance).
  – Prothrombin gene mutation – G20210A.
  – Proteins C and S.
  – Antithrombin (formerly AT3).
  – JAK2—limited to Budd-Chiari syndrome, portal vein & mesenteric vein thrombosis.
• Antiphospholipid Ab’s (not needed in +FH).

Thrombophilia W/U—When?

• ? 2 wks p-D/C anticoagulant?
  – Acute thrombosis ↓ antithrombin, prot C, prot S.
  – Heparin can ↓ AT & give false + lupus anticoagulant.
  – Warfarin may ↓ prot C & S assays.
    • Can measure prots C & S when pt on heparin (bridging, etc).
  – Dabigatran may ↑ AT and prots S and C (depends on assay).
  – Factor Xa inhibitors (rivaroxaban, apixaban) can overestimate AT (depends on assay).


Thrombophilia W/U—No Bene?

- 1st provoked VTE.
- 1st unprovoked VTE (likely lifelong med, unless bleed risk).
- Active malignancy.
- IBD.
- Myeloproliferative disorders.
- Heparin-induced thrombocytopenia with thrombosis.
- Retinal vein thrombosis, incl preeclampsia.
- UE DVT.

Case 1

- A 41 yo woman presents w/painful “line” on RLE X 3 days, expanding.
  - Exam ➔ superficial tender, firm & bluish area medial distal thigh ➔ venous cord.
  - “Neg exam for DVT.”
  - Afebrile by hx & exam.
AES Question S7

Pts w/superficial venous thrombosis should not receive anticoagulation.
A. True
B. False
Superficial Venous Thrombosis

• Common – more dx w/more US.
  – Probably more common than DVT.
• Greater saphenous vein most common.
• May coexist w/(6-33%) or progress to (2.6-15%) DVT.
• May ↑ risk of future thromboembolic events.

SVT Treatment

• More extensive (≥5 cm)/proximal (w/in 5 cm of saphenofemoral/saphenopopliteal):
  – Duplex scan to eval for DVT.
    • + ➔ manage.
    • Neg ➔ anticoag X 45 days & rechk US.
• Not:
  – Re-examine 7-10 days.
    • Improved ➔ sx care.
    • Worse or not improved ➔ duplex scan.
SVT Treatment

• Supportive/symptomatic care:
  – Elevation.
  – NSAIDs.
  – Warm +/- cool.
  – Possibly compression stockings.

Arch Intern Med 2003;163:1657-63; Angiology 1999;50:523-9

Paget-Schroetter Syndrome

• “Effort thrombosis”: axillary-subclavian vein thrombosis assoc’d w/strenuous and repetitive UE activity. 30’s, M:F = 2:1.
• Anatomic abnormalities at thoracic outlet, repetitive trauma to subclavian vein endothelium.
• ? role of hereditary & acquired thrombophilias.
• Doppler US initial; contrast venography ~CT & MR venography.
• Conservative mgmt (anticoagulation alone) inadequate, residual disability.
  – Catheter-directed thrombolysis, +/- early thoracic outlet decompression.
• Many treated suboptimally.

Upper Extremity DVT

• Primary (no line) UE DVT = 1-4% of UE DVT.
  – ACCP 2016: acute parenteral anticoagulation (UFH?), then 3 mo oral anticoagulation.
  – Better long-term outcomes.
  – <2 wks + mod-severe sx → cath-directed thrombolysis provides better patency & outcomes.
  – If thrombolysis, use heparin.


Upper Extremity DVT—Catheter

• Post-thrombotic syndrome less common.
• Anticoagulate as per LE DVT.
• Little evidence; DOACs not studied.
• Catheter can remain if functioning/needed.
  – New cath site has high incidence of new UE DVT.

Phlegmasia Alba Dolens

- Extensive DVT w/swollen, white leg d/t early compromise of arterial flow secondary to extensive DVT.
  - AKA “milk leg,” occurs in women in third trimester of pregnancy or post partum.
- Edema, pain, blanching (alba) w/o cyanosis.

Tex Heart Inst J 2009;36:76-7

Phlegmasia Cerulea Dolens

- Acute massive venous thrombosis ➔ obstruction of venous drainage.
- Sudden, severe pain, swelling, cyanosis (blue), edema.
- 20-40% occur w/CA.
- May interfere w/arterial supply.
- Can lead to gangrene, compartment syn, death (12-15% amputation; 20-40% mortality).
- Urgent dx & tx—thrombolysis.

Tex Heart Inst J 2009;36:76-7; Br J Surg 1996;83:1160-1
Post-thrombotic syndrome (formerly post-phlebitic syndrome) is uncommon.
A. True
B. False

Post-Thrombotic Syndrome

• Sx/signs of chronic venous insufficiency S/P DVT.
  – Chronic venous HTN—thrombotic vein occlusion + venous valvular incompetence.
• ~50% of pts w/in 1st yr p-acute thrombosis, despite anticoag.
  – Severe post-thrombotic syndrome develops in 5 to 10% of pts.
• Clinically ~ chronic venous insufficiency: extremity pain, vein dilation, extremity edema, skin pigmentation, venous ulcers.
• Edema = most common sign in ~2/3.
• Exercise, compression, horse chestnut (escin).

Pulmonary Embolism Rule-Out Criteria (PERC)

- Age <50 years
- Heart rate <100 bpm
- Oxyhemoglobin saturation $\geq 95\%$
- No hemoptysis
- No estrogen use
- No prior DVT or PE
- No unilateral leg swelling
- No surgery/trauma requiring hospitalization w/in prior 4 wks

- If all neg, low probability of PE.
- Can be used to R/O PE in low probability pts.
  - Low gestalt + Neg PERC $\implies$ 2% risk of PE.
  - Can reduce testing in 20% of pts.
  - Many still get D-dimer: neg D-D + low gestalt + neg PERC $\implies$ no PE.
  - Less accurate in hosp.

CT Angio: Pearls & Pitfalls

- **Advantages:**
  - High sensitivity for central vessel PE (90-96+%).
  - Can differentiate between acute vs chronic clot.
  - Hold breath for 30 sec at a time, 20 min exam.
  - May give clues to alternative diagnosis (67%).

- **Disadvantages:**
  - $$$.
  - IV contrast: contraindicated in AKI, H/O contrast allergy.
  - Lower sensitivity for subsegmental vessels—new CT’s better.
  - Shunt patent foramen ovale (up to 25% of adults, usu silent) difficult to interpret.


AES Question S9

Which is TRUE about initial PE management?
A. Start heparin prior to completion of W/U in all pts w/suspicion of PE.
B. Rivaroxaban (Xarelto™) should be avoided as initial therapy of PE.
C. Dabigatran (Pradaxa™) is an appropriate 1st agent for PE management.
D. Consider thrombolysis in hemodynamically unstable pts w/PE.
Timing of Surgical Prophylaxis

• Best efficacy = w/in 2 hrs before or 4-6 hrs after surgery.
  – Probably increases bleeding.
  – 12 hr before or 18-24 hr after surgery is acceptable – discuss w/surgeon.

Duration of Surgical Prophylaxis

• Until pt fully ambulatory.
• Extended:
  – VTE risk continues X35 days p-op (esp ortho).
  – THR: LMWH preferred X10-35 days; warfarin ➔ ↑ bleeding.
  – TKR, hip fx: LMWH preferred.
  – CA surg, major abd surg: 28 days LMWH.

Bridging

• ASH 2018:
  – Pt w/low-mod VTE risk on warfarin: no periprocedural bridging.
  – DOAC: no evidence for lab testing for DOAC effect; may be useful if prolonged DOAC effects (CKD, drug interactions).


Bridging

• ACC 2017 guidelines*:
  – Only stop anticoag if procedure has ↑ bleeding risk.
  – Bridge (UFH) VKA-tx’d pts:
    • at high risk of stroke or systemic embolism (>10% per year)—CHA²DS²-VASc ≥7, ischemic stroke w/in 3 mo.
    • w/prior stroke or systemic embolism (≥3 mo previously) not at significant periprocedural bleeding risk.
    • No bridge if DOAC used p-procedure.

  JACC 2017;70(24):3042-67; JACC 2017;69(7):871-98

*ACC gdln for bridging in AF + gdln for bleeding on anticoag
Questions