Venous Thromboembolism

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Disclosures

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  Bayer; BMS; Boston Scientific EKOS; Janssen; NHLBI

Consultant:
  Agile; Bayer
Learning Objectives

DVT: Anticoagulation; Adverse outcomes; Post thrombotic syndrome

Distal (Isolated Calf) DVT: Wolf in sheep’s clothing

PE: Epidemiology; healthcare disparities; AI for CT diagnosis; Risk factors; Subsegmental PE; Optimal duration of anticoagulation; Advanced therapy (beyond anticoagulation alone)

Pulmonary Hypertension: Definition, Diagnosis, CTEPH
DVT in a Patient Who Died of COVID; DVT Is Coiled in Right Ventricle; Too Large to Embolize to Pulmonary Arteries
No Compression: Dilated vein; Echogenic mass

With Manual Compression
GARFIELD-VTE: Cumulative Incidence of Adverse Events
Chronic Venous Ulcers: Decrease Quality of Life
## Post Thrombotic Syndrome (PTS)

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>SIGNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Edema</td>
</tr>
<tr>
<td>Swelling</td>
<td>Telangiectasias</td>
</tr>
<tr>
<td>Cramps</td>
<td>Venous Dilatation</td>
</tr>
<tr>
<td>Heaviness</td>
<td>Varicose Veins</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Redness</td>
</tr>
<tr>
<td>Itching</td>
<td>Cyanosis</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>Hyperpigmentation</td>
</tr>
</tbody>
</table>

(Kahn SR. Circulation 2014; 130: 1636-1661)
PTS: Valves in the leg veins become leaky

(Sara R. Vazquez, and Susan R. Kahn Circulation. 2010;121:e217-e219)
POST THROMBOTIC SYNDROME

- Edema
- Hyperpigmentation
- Venous ulcer
- Skin induration
- Atrophie Blanche

Venous ectasia

Edema

Hyperpigmentation
Venous ulcer

Skin induration
Atrophie Blanche
Distal DVT: A Wolf in Sheep’s Clothing—Similar Mortality to Proximal DVT

(Valerio L. TH Open 2019; 3: e58–e63)
Distal DVT: Recurrent VTE Occurs Often

(Valerio L. TH Open 2019; 3: e58–e63)
Anticoagulation of Idiopathic Distal DVT: GARFIELD-VTE

(Schellong SM, Goldhaber SZ, Weitz JI. Thromb Haemost 2019; 119: 1675-1685)
Distal DVT: Frequently Asked Questions

1) Do you anticoagulate symptomatic distal DVT? Yes
2) Do you anticoagulate asymptomatic distal DVT? Usually
3) Duration of anticoagulation? 3 months? 6 months? Longer, with no end-date? I use shared decision-making. Considerations include perceived burden of anticoagulation, the number and severity of comorbid medical illnesses, and the root causes of the distal DVT.
4) When discontinuing anticoagulation, do you obtain another venous ultrasound of the deep leg veins? Yes, to document the “new baseline”—very helpful if symptoms recur.
FATAL SADDLE PE: 41 y.o. woman with sudden collapse
2019-2020: Increased Heart Disease and Stroke Deaths

Figure 1. Age- and Risk-Associated Change in Heart Disease and Stroke Deaths

Heart Disease

Stroke

Figure 2. Change in Risk-Associated Heart Disease and Stroke Deaths

(JAMA Network Open 2022; March 23)
Mortality reduction in PE has come to a halt in the U.S. since 2010, especially in men.

(Barco S. Lancet Respir Med 2021; 9: 33-42)
PE Mortality in the U.S.—2018-2020

(Farmakis I...Konstantinides S. CHEST 2023)
PE Mortality: relation to COVID—2018-2020

(Farmakis I...Konstantinides S. CHEST 2023)
Healthcare Disparities
SES and Incident VTE: Pre-tax Income (N=51,350)

(Jorgensen H. JTH 2021; 19: 3051-3061)
SES and Incident VTE: Education Level (N=51,350)

Variables in LOGISTIC REGRESSION: age, sex, year of VTE, obesity, cancer, CORONARYHEART, DIABETES, STROKE, COPD, KIDNEY, ANYPSYCH, surg3m, frac3m, CCI_mod

(Jorgensen H. JTH 2021; 19: 3051-3061)
SES Score and Incident VTE (N=51,350)

Variables in LOGISTIC REGRESSION: age, sex, year of VTE, obesity, cancer, CORONARYHEART, DIABETES, STROKE, COPD, KIDNEY, ANYPSYCH, surg3m, frac3m, CCI_mod

Odds Ratio of VTE
Number of knots = 5

SE median SES score in the year prior VTE diagnosis

(Jorgensen H. JTH 2021; 19: 3051-3061)
AI for Chest CT Pulmonary Angiogram

(Ben Cheikh A. European Radiology 2022; March 22)
AI for Chest CT Pulmonary Angiogram

(Ben Cheikh A. European Radiology 2022; March 22)
Inflammation-Linked Conditions that Can Trigger PE or DVT

- Ulcerative colitis/ Crohn’s disease
- Rheumatoid arthritis/ psoriasis
- Elevated LDL cholesterol or LP(a)
- Obesity/ metabolic syndrome
- Acute coronary syndrome/ stroke
- Pneumonia/ COPD
- Cigarette smoking
Lab Tests of Hypercoagulability

- **Genetic**: Factor V Leiden; PT Gene Mutation
- **Acquired**: Lupus Anticoagulant; Antiphospholipid Syndrome; Anticardiolipin Antibodies
- **Genetic or Acquired**: Deficiencies of antithrombin III, protein C, protein S
Cancer Sites in PE Patients

(Gimbel IA. JTH 2021; 19: 1228-1235)
What Is the Association Between Obstructive Sleep Apnea (OSA) and Venous Thromboembolism (VTE)?

<table>
<thead>
<tr>
<th>STUDY DESIGN</th>
<th>RESULTS</th>
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</thead>
<tbody>
<tr>
<td>• Retrospective cohort of adult patients undergoing baseline PSG in a large multihospital system</td>
<td>![Graph showing risk of thrombosis and nocturnal hypoxemia]</td>
</tr>
<tr>
<td>7/2004</td>
<td>Risk of Thrombosis and Nocturnal Hypoxemia</td>
</tr>
<tr>
<td>31,309 patients</td>
<td>Adjusted for age &amp; sex</td>
</tr>
<tr>
<td>1,791 VTE events</td>
<td>Adjusted for age, sex &amp; BMI</td>
</tr>
<tr>
<td>12/2018</td>
<td></td>
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</tbody>
</table>

- Patients with >50% sleep time spent with saturations <90% are at increased VTE risk compared to those without nocturnal hypoxemia (HR 1.48, 95% CI 1.16-1.69)

Prolonged nocturnal hypoxemia is independently associated with incident VTE over longitudinal follow up.

Genuardi MV, et al. CHEST April 2022 | @journal_CHEST | https://doi.org/10.1016/j.chest.2021.12.630
Inverse Relationship: BMI and VTE

(Kalayci A…Goldhaber SZ. Thromb Res 2022; 211: 63-69)
A  Risk factors
- Acute illness
- Bed-ridden, stasis
- Genetics
- Fever
- Diarrhea
- Sepsis
- Liver injury
- CKD
- COPD
- HF
- Malignancy

B  Hemostatic abnormalities
- Pulmonary microthrombi
- Intravascular coagulopathy
- Myocardial injury
- ↑ Cardiac biomarkers
- ↑D-dimer, FDPs, PT
- ↓ Platelets

C  Clinical outcomes
- Venous thromboembolism
- Myocardial infarction
- Disseminated intravascular coagulation

Inflammatory response → Endothelial dysfunction → Superinfected
- Tissue factor
- ↓ TFPI
- Lymphopenia
- Inflammatory cytokines
- ↑ IL-6, CRP
Platelet Activation by COVID-19

(Barrett TJ. J Thromb Haemost 2021; 19: 3139-3153)
ANTICOAGULATION:
THE FOUNDATION OF PE TREATMENT
Heparin Blocks the Systemic Inflammatory Response to Thrombosis

(Poterucha T, Libby P, Goldhaber SZ. Thrombosis and Haemostasis 2017; 117: 437-444)
Evolving Anticoagulation Strategies

Overlapping
- LMWH/Warfarin Bridge
- UFH/Warfarin Bridge

Switching
- LMWH to Dabigatran (RE-COVER I,II)
- LMWH to Edoxaban (HOKUSAI)

Oral Monotherapy
- Rivaroxaban (3 week loading dose) (EINSTEIN)
- Apixaban (1 week loading dose) (AMPLIFY)

(Goldhaber SZ, Bounamenteaux H. Lancet 2012; 379: 1835-1846)
NOACS: SITES OF ACTION

Steps in Coagulation

Initiation

Coagulation Pathway

Drugs

Propagation

Fibrin formation

(Circulation 2011;123:1436-1450)
NOACS DIFFER IN LIVER AND KIDNEY METABOLISM

(Europace 2013; 15: 625-651)
ACUTE VTE TREATMENT: NOAC EFFICACY

NOACs: noninferior to warfarin

NOACs: 39% lower major bleeding
64% lower fatal bleeding, 63% less ICH than warfarin

ACUTE VTE TREATMENT: NOAC SAFETY (N=27,235)

PE Recurrences: Subsegmental PE

(RPTH 2021; 5: 168–178)
PE Mortality: Subsegmental PE

(RPTH 2021; 5: 168–178)
OPTIMAL DURATION OF ANTICOAGULATION:

Requiem or double-down on “Provoked” versus “Unprovoked” VTE?
Risk of Recurrent VTE: Danish Cohort Study
(N=73,993) 6 Months

(Albertsen IE. Am J Med 2018; 131: 1067-1074)
VTE Subtype: Event-Free Survival
Framingham Heart Study (N=9,754)

(Puurunen MK. Thromb Res 2016; 145: 27-33)
## Unprovoked VTE: Risk of Recurrence after Discontinuing Anticoagulation (N=7,515)

<table>
<thead>
<tr>
<th>Years after D/C Anticoagulation</th>
<th>% Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>16%</td>
</tr>
<tr>
<td>5</td>
<td>25%</td>
</tr>
<tr>
<td>10</td>
<td>36%</td>
</tr>
</tbody>
</table>

(Khan F. BMJ 2019;366:l4363 | doi: 10.1136/bmj.l4363)
ASH 2020 VTE Guidelines
re: Duration of Anticoagulation

“Patients with DVT and/or PE provoked by a transient risk factor typically do not require antithrombotic therapy after completion of primary treatment.”
“Terminology such as ‘provoked’ vs. ‘unprovoked’ PE/ VTE is no longer supported by the Guidelines, as it is potentially misleading and not helpful for decision-making regarding the duration of anticoagulation.”

(ESC PE Guidelines. European Heart Journal 2020; 41: 543-603)
“Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE and:

1) No identifiable risk factor
2) A persistent risk factor
3) A minor transient or reversible risk factor

(ESC PE Guidelines. European Heart Journal 2020; 41: 543-603)
### ESC PE Guidelines: Risk of Recurrence

<table>
<thead>
<tr>
<th>Risk of Recurrence</th>
<th>Risk Factors for Index VTE</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Low (<3%/ year)    | Transient, reversible factors; >10-fold increased risk of index VTE | Major surgery  
Major trauma |
| Intermediate (3% to 8%/ year) | Transient, reversible factors; ≤10-fold increased risk of index VTE | Minor surgery  
Hospitalized with acute medical illness  
Pregnancy/ estrogens  
Long-haul flight |
| Persistent risk factors | IBD; Autoimmune Disease |
| No identifiable risk factor |  |
| High (>8%/ year)   | Active cancer  
Antiphospholipid syndrome |  |

(ESC PE Guidelines. European Heart Journal 2020; 41: 543-603)
OPTIMAL DURATION OF ANTICOAGULATION:

Who Do You Side with???

1) American Society of Hematology

2) European Society of Cardiology
Advanced VTE Management

Our Tool Kit To Treat VTE When Anticoagulation Alone Does Not Suffice
Adjunctive Therapy for Massive PE

• Ensure excellent oxygenation
• Do not volume load the fragile RV with more than 500 ml to raise the BP
• Low threshold to begin pressors
  1) Norepinephrine
  2) Dobutamine
AHA: Factors Favoring PE Reperfusion Rx

- Lack of improvement/deterioration
- Clinical distress
- Clot-in-transit
- Severe/persistent RV strain
- Low cardiac output
- Low bleeding risk
- Persistent hypoxia

(Circulation 2019; epubl October 4)
Advanced Management: Intermediate and High-Risk PE

(Piazza G. JACC 2021; 76: 2117-2127)
Thrombolysis and Thrombectomy Devices

**DRUG INFUSION**
- Cragg-McNamara, Fountain, & Unifuse (all 4-5 Fr MSC)
- EkoSonic (6 Fr, ultrasound)
- Bashir Endovascular (7 Fr, basket)

**OSCILLATION-MACERATION**
- (can infuse drug as well)
- Cleaner (7 Fr, wire)
- Arrow-Terotola (7 Fr, basket)
- Trellis-8 (8 Fr, balloons/wire)

**SUCTION ASPIRATION**
- Indigo CAT-8 (8 Fr)
- JETi (8 Fr)
- Lightning Intelligent (12 Fr)
- AngioVac (26 Fr and 18 Fr)

**AUGMENTED ASPIRATION**
- AngioJet Solent Proxi (6 Fr) and AngioJet Zelante (8 Fr) - rheolytic
- Flowtriever (20 Fr) – discs
- Clottriever (13 Fr) - basket

(Goldhaber SZ. Vascular Medicine 2021; October 4)
EKOS: Ultrasound Pulsing plus TPA

Fibrin strand network without ultrasound

Ultrasound causes fibrin strands to thin and network to loosen

Ultrasound causes acoustic streaming

Pulmonary Embolism
FlowTriever: 20F—No TPA
BWH FlowTriever Pulmonary Embolectomy #1—Drs. Bergmark and Shah
RV Function after Surgical Pulmonary Embolectomy

(C goldberg, JB. JACC 2020; 76: 903-911)
ECMO and/or Surgical Embolectomy

**Benefits**
1) Rapidly optimize BP, RV
2) Maximize clot removal
3) 2%: Mortality in non-CPR patients

**Risks**
1) 18%: Ventilator > 72 hours
2) 18%: Hemodialysis required
3) 25%: Mortality in CPR patients

(Goldhaber SZ. JACC 2020; 76: 912-915)
CENTRAL ILLUSTRATION: A Comparison Between Classical and Contemporary Models for Interpreting Hemodynamic Results From Right Heart Catheterization to Classify and Risk Stratify Patients With Pulmonary Hypertension

Classical Approach: PH Assessment

- Heart Failure
  - RHC
  - Risk Stratification
    - mPAP (mm Hg)
      - <25
        - PH
      - ≥25
        - Pre-Capillary
        - Assess ↑PVR (≥3.0 WU)
    - PAWP (mm Hg)
      - ≤15
        - Pre-Capillary
      - >15
        - Post-Capillary
  - Advanced HF
  - Emphasizes End-Stage Disease

Contemporary Model: PH Assessment

- Clinical Risk
  - 2.2
  - 3.0
  - PVR (WU)
    - >6.0
  - mPAP (mm Hg)
    - >20
    - <19

- Unexplained Dyspnea
- Heart Failure
- Unexplained RV Dysfunction

- Early RHC + Best Technique

<table>
<thead>
<tr>
<th>PH Hemodynamic Group</th>
<th>mPAP (mm Hg)</th>
<th>PVR (WU)</th>
<th>PAWP (mm Hg)</th>
<th>Clinical Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Capillary</td>
<td>&gt;20</td>
<td>≥3.0</td>
<td>≤15</td>
<td>PAH, Lung Disease</td>
</tr>
<tr>
<td>Isolated Post-Capillary</td>
<td>&gt;20</td>
<td>&lt;3.0</td>
<td>&gt;15</td>
<td>LHD</td>
</tr>
<tr>
<td>Combined Pre-/Post-Capillary</td>
<td>&gt;20</td>
<td>≥3.0</td>
<td>&gt;15</td>
<td>Chronic LHD</td>
</tr>
</tbody>
</table>

1) Poor TR signal \((N=218)\) underestimates sPAP
2) Good TR signal overestimates sPAP in 41% of patients
3) As PH progresses, DE underestimates PAP
4) As PCW increases, ECHO underestimates PAP

*BMC Med Imaging* 22, 91 (May 16, 2022)
CTEPH - 2.3%
PPEI - 16.0%

Median time to CTEPH diagnosis: 129 days

Echocardiographic criteria:
- RV basal diameter
- RA end-systolic area
- TAPSE
- LV eccentricity index
- RA pressure (estimated)
- Tricuspid regurgitant jet velocity
- Pericardial effusion

Clinical, functional or laboratory criteria:
- Persistent/worsening symptoms
- Clinical RV failure
- Syncope
- WHO functional class
- Six-minute walking distance
- BNP or NT-proBNP plasma levels
- Cardiopulmonary exercise testing

(European Heart J 2022; April 7)
Take Home Points

• Post-thrombotic syndrome decreases QOL
• Respect and treat isolated calf DVT
• PE mortality is increasing in the USA
• Healthcare disparities affect likelihood of VTE
• VTE risk factor profile is evolving (e.g., COVID)
• Respect and treat subsegmental PE
• Optimal duration of anticoagulation: controversial
• Advanced therapy: catheter-based, surgical
• Pulmonary hypertension: definition has broadened; beware of ECHO for diagnosis
References

- ESC Guidelines for acute pulmonary embolism. Eur Heart J 2020; 41: 543-603
- Chopard R. Lower Extremity VTE. JAMA 2020; 324: 1765-1776
- Goldhaber SZ. ECMO and Surgical Embolectomy. JACC 2020; 76: 912-915