DIAGNOSIS AND MANAGEMENT OF VENOUS THROMBOEMBOLISM

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DVT / VTE

Magnitude of the Problem

- DVT: 2 Million
  - Post-thrombotic Syndrome: 800,000
  - PE: 600,000
    - Death: 60,000
    - Pulmonary Hypertension: 30,000
  - Silent PE: 1 Million

Estimated Cost of VTE Care $1.5 Billion/year

DVT and PE

1,234 hospitalized patients who died and underwent autopsy within 30 days of a surgical procedure

- the rate of PE was 32%
- PE was considered cause of death in 29% of these

51,645 hospitalized patients

- prevalence of acute PE was 1%
- PE thought to have caused or contributed to death in 37% of

In 70 to 80% of patients who die in the hospital of PE, the diagnosis was not considered prior to death.

DVT

Virchow's Triad

- Stasis
- Vessel damage
- Activation of coagulation
Risk Factors for DVT

Surgery
Trauma (major or LE)
Immobility, paresis
Malignancy
Cancer Rx (hormonal, chemo, or RT)
Previous DVT
Increasing age (>40)
Obesity
Smoking
Central venous catheterization
Inherited or acquired thrombophilia
Pregnancy and the postpartum period

Estrogen-containing OCPs
Hormone replacement therapy
Selective estrogen receptor modulators
Acute medical illness
Heart or respiratory failure
Inflammatory bowel disease
Nephrotic syndrome
Myeloproliferative disorders
Paroxysmal nocturnal hemoglobinuria
Varicose veins

Geerts. Chest 2004; 126:338S–400S
## Absolute Risk of DVT in Hospitalized Patients*

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>DVT Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical patients</td>
<td>10–20</td>
</tr>
<tr>
<td><strong>General surgery</strong></td>
<td>15–40</td>
</tr>
<tr>
<td>Major gynecologic surgery</td>
<td>15–40</td>
</tr>
<tr>
<td>Major urologic surgery</td>
<td>15–40</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>15–40</td>
</tr>
<tr>
<td>Stroke</td>
<td>20–50</td>
</tr>
<tr>
<td><strong>Hip or knee arthroplasty, hip fracture surgery</strong></td>
<td>40–60</td>
</tr>
<tr>
<td>Major trauma</td>
<td>40–80</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>60–80</td>
</tr>
<tr>
<td>Critical care patients</td>
<td>10–80</td>
</tr>
</tbody>
</table>

*Rates based on objective diagnostic testing for DVT in patients not receiving thromboprophylaxis.

Geerts. Chest 2004; 126:338S–400S
ACCP Recommendations

Introduction to the Ninth Edition

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Gordon H. Guyatt, MD, FCCP; Elie A. Akl, MD, PhD, MPH; Mark Crowther, MD; Holger J. Schünemann, MD, PhD, FCCP; David D. Gutterman, MD, FCCP; and Sandra Zelman Lewis, PhD

The Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines differs substantially from the prior versions both in process and in content. In this introduction, we describe some of the differences and the rationale for the changes.

CHEST 2012; 141(2)(Suppl):48S–52S

Abbreviations: ACCP = American College of Chest Physicians; AT6 = Sixth ACCP Consensus Conference on Antithrombotic Therapy; AT7 = Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines; AT8 = Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition); AT9 = Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; GRADE = Grades of Recommendations, Assessment, Development, and Evaluation
Frequency of VTE Risk Factors in US Hospital Patients

- 78% for ≥1 risk factor
- 48% for ≥2 risk factors
- 19% for ≥3 risk factors
- 6% for ≥4 risk factors
- 1% for ≥5 risk factors

Incidence of DVT
Correlation with number of risk factors

Positive result (%)

Number of risk factors

0 1 2 3 >3

11% 24% 36% 50% 100%

DVT-Diagnosis

• Clinical signs
  – Pain
  – Swelling
  – Tenderness
  – Homan’s sign
  – Unreliable
  – 50% of patients with above findings will not have a DVT identified
DVT-Diagnosis

• Diagnostic tests
  – D-dimer assay (fibrin degradation products)
  – Duplex scanning
  – Doppler ultrasound
  – Contrast venography
  – Radionuclide venography
  – MR venography
  – CT scanning
DVT-Diagnosis

- **Contrast venography**
  - Gold standard (backup)
  - Persistent filling defect in >1 view
  - Disadvantages
    - Invasive (access)
    - Risk of phlebitis
    - Allergic reactions
    - Contrast
    - Radiation exposure
    - Cost
- Not for routine use

Rutherford's Vascular Surgery, 7th edition, Copyright © 2012 Elsevier Inc
DVT-Diagnosis

- **D-dimer**
  - Degradation product of cross-linked fibrin
  - Variety of assays available
  - Non-specific, also elevated in:
    - DIC, Trauma, Infection
    - Post-operative states (<20% specificity)
    - Malignancy (0% specificity)
    - Increasing age, Inflammatory conditions, Pregnancy
  - Positive assay does not confirm Dx
  - Low specificity and PPV
  - Negative assay largely excludes Dx
  - Limited use in unselected populations
DVT-Duplex Evaluation

• **Criteria for positive diagnosis:**
  - incompressibility of a venous segment
  - visualization of thrombus
  - absence of flow
DVT-Diagnosis

• Duplex
  – Most widely used diagnostic evaluation
    ✓ Non-invasive
    ✓ No contrast or radiation
    ✓ Easily repeated
    ✓ Operator/protocol dependent
    ✓ Can detect other non-vascular pathology
      – Adenopathy, Baker’s cyst, Hematoma
  – Sensitivity, specificity, PPV, NPV 94-100%
  – ICAVL recs complete bilateral LE exam including calf veins
Venous Duplex-DVT

- Size and location (clot burden)
- Acute vs Chronic
- Occlusive vs non-occlusive
- Isolated vs multifocal
- Adherent vs portion free-floating
- Catheter associated (indwelling or removed)
- Deep pelvic veins poorly visualized
- Also important for SVT near SFJ
**Venous Duplex-DVT**

Clot Characteristics in Clot Aging

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of occlusion</td>
<td>Total</td>
<td>Partial</td>
</tr>
<tr>
<td>Free floating</td>
<td>Free</td>
<td>Stationary</td>
</tr>
<tr>
<td>Clot retraction</td>
<td>Retracted</td>
<td>Adherent</td>
</tr>
<tr>
<td>Clot distention</td>
<td>Distended</td>
<td>Contracted</td>
</tr>
<tr>
<td>Clot compressibility</td>
<td>Soft</td>
<td>Firm</td>
</tr>
<tr>
<td>Surface character</td>
<td>Smooth</td>
<td>Irregular</td>
</tr>
<tr>
<td>Echogenicity</td>
<td>Faint</td>
<td>Bright</td>
</tr>
<tr>
<td>Homogeneity</td>
<td>Homogeneous</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td>Collaterals</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Recanalization</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

In Rutherford, SVS 2009
DVT-Diagnosis

- **CT venography**
  - Can be used as a single test in setting on DVT, PE
  - Requires contrast, radiation exposure

- **MR venography**
  - Contrast or TOF
  - No radiation

✓ Used in setting of other pathology
✓ May detect non-flow limiting thrombi
✓ High sensitivity and specificity
✓ Better results with more proximal studies
✓ Protocol dependent
✓ Expensive
In patients with a low pretest probability of first lower extremity DVT, we recommend one of the following initial tests:

- a moderately sensitive D-dimer
- a highly sensitive D-dimer
- compression ultrasound (CUS) of the proximal veins

rather than

- no diagnostic testing (Grade 1B for all comparisons)
- venography (Grade 1B for all comparisons)
- whole-leg ultrasound (US) (Grade 2B for all comparisons)

We suggest initial use of a moderately sensitive (Grade 2C) or highly sensitive (Grade 2B) D-dimer rather than proximal CUS.
DVT-Diagnosis

• In patients with a moderate pretest probability of first lower extremity DVT, we recommend one of the following initial tests:
  – a highly sensitive D-dimer
  – proximal CUS
  – whole-leg US
• rather than
  – no testing (Grade 1B for all comparisons)
  – venography (Grade 1B for all comparisons)
• We suggest initial use of a highly sensitive D-dimer rather than US (Grade 2C)
DVT-Diagnosis

- If proximal CUS is chosen as the initial test and is negative, we recommend
  - repeat proximal CUS in 1 week or
  - testing with a moderate or highly sensitive D-dimer assay
- over
  - no further testing (Grade 1C) or
  - venography (Grade 2B)

- In patients with a negative proximal CUS but a positive D-dimer, we recommend
  - repeat proximal CUS in 1 week
- over
  - no further testing (Grade 1B) or
  - venography (Grade 2B).
DVT-Diagnosis

- If whole-leg US is negative, we recommend no further testing over
  - repeat US in one week
  - D-dimer testing, or
  - venography (Grade 1B for all comparisons)

- If proximal CUS is positive, we recommend treating for DVT rather than confirmatory venography (Grade 1B)

- If isolated distal DVT is detected on whole-leg US, we suggest serial testing to rule out proximal extension over treatment (Grade 2C).
DVT-Diagnosis

• In patients with a high pretest probability of first lower extremity DVT, we recommend either
  – proximal CUS
  – whole-leg US

• over
  – no testing (Grade 1B for all comparisons) or
  – venography (Grade 1B for all comparisons)

• We recommend that in patients with high pretest probability, moderately or highly sensitive D-dimer assays should not be used as stand-alone tests to rule out DVT (Grade 1B).
If risk stratification is not performed in patients with suspected first lower extremity DVT, we recommend one of the following initial tests:
- proximal CUS
- whole-leg US

rather than
- no testing (Grade 1B)
- venography (Grade 1B), or
- D-dimer testing (Grade 2B).
DVT-Treatment Goals

- Reestablish venous patency (recanalization)
- Prevent thrombus extension
- Prevent new thrombus formation
- Prevent thrombus embolization (PE, paradoxical)
- Prevent early and late thrombus recurrence
- Prevent or reduce severity of post-thrombotic syndrome
- Prevent proximal conversion of calf DVT
DVT-Treatment

- Antiplatelet
- Inpatient IV Heparin
- SC LMWH (Inpatient or Outpatient)
- SC Pentasaccharide (synthetic, selective $X_a$)
- Thrombolysis (Pharmacologic, Mechanical)
- Surgical thrombectomy
- Inferior Vena Caval Filter
DVT-Treatment

• In patients with a high clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C).

• In patients with a low clinical suspicion of acute VTE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C).
DVT-Treatment

- In pts Dx’d with full duplex isolated distal DVT accounts for approx 50% of all DVTs diagnosed.
- Natural history studies suggest untreated symptomatic distal DVT extend into proximal veins 15% of time.
- If there is no extension within 2 weeks, it is unlikely to occur.
DVT-Treatment

- In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (Grade 2C).

- In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension, we suggest initial anticoagulation over serial imaging of the deep veins (Grade 2C).
DVT-Treatment

- In patients with acute isolated distal DVT of the leg who are managed with initial anticoagulation, we recommend using the same approach as for patients with acute proximal DVT (Grade 1B).

- In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we recommend no anticoagulation if the thrombus does not extend (Grade 1B); we suggest anticoagulation if the thrombus extends but remains confined to the distal veins (Grade 2C); we recommend anticoagulation if the thrombus extends into the proximal veins (Grade 1B).
DVT-Treatment

- In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C).

- In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over systemic thrombolysis or operative venous thrombectomy (Grade 2C).
DVT-Treatment

- In patients with acute DVT of the leg, we recommend against the use of an IVC filter in addition to anticoagulants (Grade 1B).

- In patients with acute proximal DVT of the leg and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B).

- In patients with acute proximal DVT of the leg and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B).
DVT-Treatment

• In patients with a proximal DVT of the leg provoked by surgery, we recommend treatment with anticoagulation for 3 months over
  • treatment of a shorter period (Grade 1B)
  • treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), or
  • extended therapy (Grade 1B regardless of bleeding risk)
• Similar recommendation for DVT of the leg provoked by a nonsurgical transient risk factor
DVT-Treatment

- In patients with an unprovoked DVT of the leg (isolated distal [see remark] or proximal), we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B). After 3 months of treatment, patients with unprovoked DVT of the leg should be evaluated for the risk-benefit ratio of extended therapy.
DVT-Treatment

• In patients with acute DVT of the leg, we suggest early ambulation over initial bed rest (Grade 2C).

• In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B).
DVT-Treatment

• In patients with acute PE associated with hypotension (eg, systolic BP < 90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).

• In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1C).
DVT-Treatment

• In patients with superficial vein thrombosis of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (Grade 2B).

• In patients with superficial vein thrombosis who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (Grade 2C).
Presentation PE vs DVT

- 30 day mortality from initial or recurrent episode of VTE presenting with PE >> DVT
- Recurrent VTE likely to be PE in 60% pts presenting initially with PE, 20% in pts with DVT
- Sequellae of PE is pulmonary HTN, of DVT is PTS
Low dose aspirin for preventing recurrent VTE

- **ASPIRE trial**
  - 822 pts completed AC for 1st VTE
  - Randomly assigned to **ASA 100 mg qd vs placebo** x up to 4 years
  - Primary outcome recurrent VTE
  - Recurrent VTE:
    - 4.8%/yr asa vs 6.5%/yr placebo
  - VTE, MI, CVA, CV death:
    - 5.2%/yr asa vs 8.0%/yr placebo

Brighton, NEJM 2012;367:1979
Low dose aspirin for preventing recurrent VTE

Hazard Ratios of pooled results from ASPIRE and WARFASA (Warfarin and Aspirin) Trials

Brighton, NEJM 2012;367:1979
LMWHs vs UFH

- UFH - unpredictable dose response and narrow therapeutic window
- LMWH - more predictable pharmacokinetics and a greater bioavailability than UFH
- Once or twice daily SC weight-based dosing
- No routine monitoring of aPTT or INR
- No need for monitoring in most patients (anti-$X_a$ level)
- Facilitates outpatient thrombosis treatment
- Less heparin-induced thrombocytopenia (HIT)
LMWH vs IV UFH

Major Bleeding
(n=3674)

OR, 0.57
(P=0.047)

OR, 0.71
(P =0.25)

Favors LMWH
Odds Ratio
Favors UFH

Recurrent Thromboembolism
(n=3566)

OR, 0.85
(P=0.28)

OR, 0.87
(P =0.40)

Favors LMWH
Odds Ratio
Favors UFH

Primary Studies
Duroux, 1991 (nadroparin)
Hull, 1992 (tinzaparin)
Prandoni, 1992 (nadroparin)
Lopaciuk, 1992 (nadroparin)
Simonneau, 1993 (enoxaparin)
Lindmarker, 1994 (daltiparin)
Levine, 1996 (enoxaparin)
Koopman, 1995 (nadroparin)
Fiessinger, 1996 (dalteparin)
Luomanmaki, 1998 (dalteparin)
Columbus, 1997 (riviparin)
Thrombolysis

- Mechanism activates plasminogen, leads to fibrin breakdown
  - Streptokinase first agent used for thrombolysis
  - Urokinase
  - Tissue plasminogen activators, t-PA

- Varying degrees of efficacy and potential complications
Thrombolysis

• Pharmacologic
  – Systemic = “locoregional”
    • Many favorable reports (↑patency, ↓PTS)
    • Incr bleeding complications (ICH)
  – Catheter directed
    • ↑patency, ↓PTS vs AC alone
    • ↓bleeding complications vs systemic (pooled ICH risk 0.2%)
Thrombolysis

• Mechanical
  – Vortex
  – Ultrasound
  – Trellis

• Surgical
Pharmacomechanical Thrombectomy

**Thrombolysis + mechanical thrombectomy**

- Venturi effect
- Reduces clot burden
- Less thrombolytic
- Reduce procedure time
- Hemolysis
AngioJet® Thrombectomy System

- Percutaneous mechanical thrombectomy device
- Approved for coronary arteries, peripheral arteries and veins, and AV grafts
- Advantages
  - Rapidly remove large amount of thrombus without need for chemical thrombolysis
- Limitations
  - Potential for distal embolization
  - Inability to remove chronic or insoluble thrombus
  - Difficulty in treating the microvasculature
AngioJet® Thrombectomy System
AngioJet® Mechanism of Action

The Bernoulli Effect explains the relationship between velocity and pressure.

"Where the speed is highest, the pressure is lowest--creating a vacuum."

Saline jets travel backwards at half the speed of sound to create a low pressure zone.

Thrombus is drawn into the catheter where it is fragmented by the jets and evacuated from the body.
Trellis® Peripheral Infusion System

- Proximal and distal occluding balloons with infusion holes between the balloons
  - Confine thrombolytic agent to the treatment site
  - Reduces, but does not eliminate, risk of bleeding
  - Prevents embolization
- Oscillating wire disperses the thrombolytic and mechanically disrupts the clot
- After 10 minutes clot fragments and remaining thrombolytic aspirated.
Trellis® Peripheral Infusion System
The EkoSonic® Endovascular System

- Combines targeted drug delivery catheter with high frequency low power microsonic energy
- Microsonic energy - thins fibrins making the thrombus more permeable to the thrombolytics.
- Does not fracture or break the thrombus, reducing risk of distal embolism
- Does not hemolyze - no adenosine release and no compromise to renal function
The EkoSonic® Endovascular System

Without Ultrasonic Energy

With Ultrasonic Energy And Thrombolytic
Angioplasty & Stenting

- Adjuvant to thrombolytic therapy
- May-Thurner syndrome - compression of left common iliac vein by the crossing right common iliac artery
- Paget-Schroetter Syndrome (effort thrombosis)
Phlegmasia Cerulea Dolens

- Massive iliofemoral venous thrombosis
- Limb-threatening ischemia
- Treatment
  - Anticoagulation
  - Thrombolysis
  - Venous thrombectomy
  - Fasciotomy
IVC Filters

- 99% protection from fatal PE
- First suggested - Trousseau 1868
- First reported
  - Mobin-Uddin Umbrella (1969)
  - Vena cava clip
  - Kimray-Greenfield Filter (1973)

29.5 Fr sheath (cutdown)
IVC Filters

A. Stainless steel Greenfield (no pres grad<80% filled, 64% CSA)
B. Modified hook titanium Greenfield (MRI, <IVC wall)
C. Alternating hook stainless steel Greenfield
D. Bird’s Nest (40mm, 7cm)
E. Vena Tech
F. Simon Nitinol
G. Gunther tulip (retrievable)

6-8.5 Fr sheath (percutaneous)
IVC Filters - Indications

- Contraindication to anticoagulation with documented DVT or PE
  - Bleeding
  - CNS
  - Recent surgery
  - Thrombocytopenia
- Failed anticoagulation, PE on adequate AC
- Prophylaxis for proximal free-floating thrombus
  - 60% incidence of PE in iliofemoral DVT with tail
  - Rec for >5 cm tail
IVC Filters-Indications II

• High-risk patient populations, where even small PE might be fatal
  – Severe pulmonary HTN and surgery for morbid obesity or orthopedic trauma
  – Trauma patients
    ✓ Closed-head injury
    ✓ CNS injuries such as spinal cord trauma
    ✓ Multiple long-bone fractures
    ✓ Pelvic fracture
    ✓ Direct venous trauma
IVC Filters-Indications III

- Failed another form of vena cava interruption
- Upper extremity DVT with above – SVC filter
- Pregnant women with DVT (selected cases) – suprarenal placement

Chiou, Pers Vasc Surg Endovasc Ther 17:329-339, 2005
IVC Filters - Complications

- **Early**
  - Malposition / Embolization
    - Renal, iliac, suprarenal, SVC, RA
    - Tilt
    - Incomplete deployment
  - Insertion site DVT

- **Late**
  - IVC thrombosis
  - Perforation
  - Femoral AVF
  - Late migration
  - Infection / inflammation
IVC Filters-Retrieval

- Retrieval system 11F sheath
- RIJ approach
- Coaxial system to guide loop snare to apex of filter
- Apex snared
- Snare pulled back to engage hook
- Outer catheter advanced over the filter
- Collapses filter and detaches hooks from wall of the IVC
DVT as never event

- 1999 IOM report – up to 98,000 deaths/year due to medical errors
- 2006 – Leapfrog Group – never events policy
- 2007 – Surgeon General VTE as health crisis
- National Quality Forum defined 28 never events
- 2008 – CMS these were preventable and would not be reimbursed
DVT as never event

- Never events list includes:
  - Stage 3 and 4 pressure ulcers
  - Falls and trauma
  - Catheter infections (vascular and urinary)
  - VTE

- Perception is of medical error as opposed to adverse event or hospital acquired condition

- How many of these are present on admission (POA)

- Up to 40% pts admitted to rehab

Moritz, AVID 2010
DVT as never event

- No published rates of DVT in general population – concept of almost-never events
- Rates vary with associated diseases
- Most effort focused on underutilization of DVT prophylaxis
- Hospitals need to expend tremendous resources to determine if these conditions were present on admission (POA)
DVT as never event

• Role of the Vascular lab
  – What is the cost of screening for DVT?
  – Should screening (like prophylaxis) be stratified?
  – How often to screen immobile patients?
  – Frequently asked to place IVC filters in immobile patients for PE prophylaxis
    ✓ Does not prevent DVT
    ✓ May increase rate of DVT
  – Pressure to perform studies to document POA status
  – Duplex findings will have implications on reimbursement
  – *Is the only never event that requires diagnostic study to document as POA*
DVT as never event

Issues surrounding CMS decision for VTE post TKR/THR

1. disincentive to treat high risk pts
2. disincentive to perform THR/TKR
3. “perverse” disincentive to evaluate pts for DVT when suspected
4. promotes over aggressive prophylaxis (get reimbursed for post-op bleeding)
5. Addresses small fraction of patients with VTE

Streiff., JAMA 2009, 301(10): 1063
Summary

• DVT / VTE remains a major health concern and is multifactorial
• New treatments and recommendations are evolving
• Issues surrounding VTE have significant Healthcare policy and reimbursement implications