VTE: 2016 ACCP Update with Best Evidence and Best Practices

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• Research Funding
  – BMS
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  – BMS
  – Daiichi-Sankyo
  – Janssen Healthcare
  – Portola

• Speaking Honoraria
  – Pfizer
  – BMS
  – Janssen
Putting It Into Perspective

PE kills more people each year than HIV, car accidents, and breast cancer...combined¹

- Up to 300,000 people a year die from PE in the US²
- It is the third most common cardiovascular illness³
- Direct annual payer cost in the US have been estimated at 1.5 billion⁴

Trends in VTE: Prevalence to Double by 2050

Projected VTE Rates (2006-2050)

The Anticoagulation Forum is the largest peer organization of anticoagulation service providers in North America.

The board of directors (composed of members from multiple disciplines) come together to formulate a set of guidelines that is not only based on evidence but also expert opinion and experience.

The guidelines cover all aspects of treatment and management of DVT and PE.

Free open access to all manuscripts at: http://acforum.org/landing/index.html
<table>
<thead>
<tr>
<th>Topic</th>
<th>New!</th>
<th>Changed</th>
<th>New evidence but no change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choice of long term (first 3 mo) and extended anticoagulant therapy</td>
<td>✔</td>
<td></td>
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<tr>
<td>Whether to treat a subsegmental PE</td>
<td>✔</td>
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<td>Aspirin for extended treatment of VTE</td>
<td>✔</td>
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<td>Management of Recurrent VTE on Anticoagulant Therapy</td>
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<tr>
<td>Duration of treatment</td>
<td></td>
<td>✔️</td>
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<tr>
<td>Use of Compression Stockings to Prevent Post-Thrombotic Syndrome</td>
<td></td>
<td>✔️</td>
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<tr>
<td>Whether and How to Prescribe Anticoagulants to Patients with Isolated Distal DVT</td>
<td></td>
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<td>✔️</td>
</tr>
<tr>
<td>Catheter-Directed Thrombolysis for Acute DVT of the Leg</td>
<td></td>
<td>✔️</td>
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<tr>
<td>Role of IVC Filters in Addition to Anticoagulation for Acute DVT or PE</td>
<td></td>
<td>✔️</td>
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<tr>
<td>Treatment of Acute Pulmonary Embolism Out of Hospital</td>
<td></td>
<td></td>
<td>☑️</td>
</tr>
<tr>
<td>Systemic Thrombolytic Therapy for Pulmonary Embolism</td>
<td></td>
<td></td>
<td>☑️</td>
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<tr>
<td>Thrombolytic Therapy in Patients with Upper Extremity DVT</td>
<td></td>
<td></td>
<td>☑️</td>
</tr>
</tbody>
</table>
TOPICS

• Catheter related thrombosis
• Calf vein thrombosis and extensive DVT
• Risk stratification and Treatment of PE
• Duration of anticoagulation for VTE
• Management of recurrent VTE on AC
DOACs vs NOACs

Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH

G. D. BARNES,* W. AGENO,† J. ANSELL‡ and S. KAATZ,§ FOR THE SUBCOMMITTEE ON THE CONTROL OF ANTICOAGULATION
*Frankel Cardiovascular Center and Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, MI, USA; †Division of Internal Medicine, University of Insibria, Varese, Italy; ‡Department of Internal Medicine, Lenox Hill Hospital, New York, NY; and §Hurley Medical Center, Michigan State University, Flint, MI, USA


Scope and methodology
Oral anticoagulants are used to prevent and treat a wide range of thromboembolic diseases. Currently available oral anticoagulants include the vitamin K antagonists (VKAs), such as warfarin. VKAs reduce the synthesis of functional vitamin K-dependent factors (factor II, FVII, FIX, FX, as well as protein C and protein S) by interfering with the vitamin K redox cycle. The newer oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban, not is scientifically unappealing. Perhaps more importantly, there is at least one reported account where the term NOAC written in the medical record was interpreted as meaning ‘No AntiCoagulation,’ potentially resulting in the patient not receiving the critical therapy that was intended [3].

There is a clear need to reach a consensus on the nomenclature of oral anticoagulants, and several experts have called for consensus around the nomenclature for oral anticoagulants [2,4–7].

We aimed to develop guidance from the Control of Anticoagulation SSC of ISTH on the most appropriate abbreviation for the newer/novel/target-specific/direct act-
CASE #1

A 55 year old woman being treated for osteomyelitis of the spine develops right upper extremity swelling. U/S reveals a DVT in the subclavian and axillary vein. She has a PICC line in that arm. She needs 4 more weeks of antibiotics. You start anticoagulation. Do you need to pull the line?

a. Yes
b. No
Remove catheter (after 3-5 days of anticoagulation if possible) if:
Infection
Malfunction
AC contraindicated
AC failed
Cath not needed

Upper Extremity DVT

ACCP 2012 UE DVT (Stephan Moll MD, CLOTCONNECT.ORG)

- If DVT that involves the axillary or more proximal veins, anticoagulation therapy alone is suggested, rather than thrombolytic therapy. Length of anticoagulation: at least 3 months.
- In upper extremity DVT not associated with a central venous catheter: 3 months of anticoagulation is recommended.
- In upper extremity DVT associated with a central venous catheter:
  - Suggestion is to not remove the catheter if it is functional and there is an ongoing need for the catheter. Anticoagulation should be given as long as the catheter is in place.
  - If the catheter is removed, anticoagulation should continue for 3 months thereafter.
Thrombolytic Therapy in Patients with Upper Extremity DVT

• Panel suggests the use of thrombolysis will only benefit patients who meet the following criteria:
  – Severe symptoms
  – Symptoms <14 days
  – Good functional status
  – Thrombus involving most of the subclavian and axillary vein
  – Life expectancy ≥ 1 year
  – Low risk for bleeding
## Thrombolytic Therapy in Patients with Upper Extremity DVT

<table>
<thead>
<tr>
<th>2012</th>
<th>2016</th>
</tr>
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<tbody>
<tr>
<td>In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest anticoagulant therapy alone over thrombolysis (Grade 2C).</td>
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</tbody>
</table>
CASE #2

A 45 year old man presents with moderate calf pain and swelling for 5 days since he was kicked playing soccer. Ultrasound shows DVT in the posterior tibial vein. Does he need anticoagulation?

a) Yes
b) No
NEW CHEST GUIDELINES

In patients with acute isolated distal DVT (IDDVT) 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).

Kearon et al CHEST 2016
ISOLATED DISTAL DVT
ant/post tibial, peroneal

**TREATMENT**

LOW RISK
u/s 1-2 weeks and treat only if extends proximally

HIGH RISK
treatment same as proximal DVT

**HIGH RISK**

- + d-dimer
- severe symptoms
- cancer
- VTE history
- no reversible provoking factor
- hospitalized
- near proximal veins
- > 5 cm long, mult veins, > 7 mm
Iliofemoral Venous Thrombosis

- common femoral ± iliac veins
- 25% of symptomatic LE DVT
- ↑ PTS
- ↑ recurrent VTE 2.4x

PMID: 21722789, 19017588, 11343664
CaVenT Trial

- Randomized, open label, 209 patients
- DVT above mid-thigh level
  - Stratified for pelvic involvement
- Intervention: CDT with rt-PA (Alteplase)
- Control: LMWH + warfarin
- Outcome:
  - Frequency of PTS (Villalta) 24 months
  - Iliofemoral patency 6 months

PMID: 22172244 (2012)
## CaVenT Trial: 5-Year FU

<table>
<thead>
<tr>
<th>Adjunctive catheter-directed thrombolysis (n=87)</th>
<th>Standard treatment (n=89)</th>
<th>p value*</th>
<th>Risk difference (absolute risk reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-thrombotic syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>63</td>
<td>&lt;0.0001</td>
<td>28% (14–42)</td>
</tr>
<tr>
<td>Villalta severity category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (score 5–9)</td>
<td>31/37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>83.8% (68.5–92.7)</td>
<td>49/63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (score 10–14)</td>
<td>2/37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.4% (0.57–18.6)</td>
<td>13/63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (score &gt;14)</td>
<td>4/37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.8% (3.7–25.3)</td>
<td>1/63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iliofemoral patency†</td>
<td>68/86</td>
<td>0.218</td>
<td>-8% (-21 to 5)</td>
</tr>
<tr>
<td>79.1% (69.2–86.4)</td>
<td>61/86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoropopliteal reflux</td>
<td>54/87</td>
<td>&lt;0.0004</td>
<td>22% (10–35)</td>
</tr>
<tr>
<td>62.1% (51.6–71.6)</td>
<td>75/89</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are n, n/N, or % (95% CI), unless otherwise stated. *χ² test. †Four patients had inconclusive iliofemoral patency assessments at 5 years.
• 16. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over CDT (Grade 2C).

“...patients who are most likely to benefit from CDT have iliofemoral DVT, symptoms for < 14 days, good functional status, life expectancy of ≥ 1 year, and a low risk of bleeding.”
### Catheter-Directed Thrombolysis for Acute DVT

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<tr>
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<tr>
<td>In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C).</td>
<td>In patients with acute proximal DVT of the leg, recommend anticoagulant therapy alone over catheter-directed thrombolysis (Grade 2C).</td>
</tr>
</tbody>
</table>
CASE #3

A 55 year-old man presents with pleuritic chest pain. His BP is 120/70, HR 105, RR is 18, and his O2 sat is 97%. His physical exam is unremarkable. A chest CT shows multiple pulmonary emboli. ECG is normal.
CASE #3

What is this patient's risk of early mortality related to PE?

A) 1%
B) 10%
C) 20%
Pulmonary Embolism Severity Index
Estimates the risk of 30-day mortality from PE


<table>
<thead>
<tr>
<th>Class (Risk)</th>
<th>Score/Points</th>
<th>30-Day Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Very Low)</td>
<td>&lt;66</td>
<td>0%</td>
</tr>
<tr>
<td>II (Low)</td>
<td>66-85</td>
<td>1%</td>
</tr>
<tr>
<td>III (Intermed)</td>
<td>86-105</td>
<td>3.1%</td>
</tr>
<tr>
<td>IV (High)</td>
<td>106-125</td>
<td>10.4%</td>
</tr>
<tr>
<td>V (Very High)</td>
<td>&gt;125</td>
<td>24.4%</td>
</tr>
</tbody>
</table>

Total point score obtained by summing patients age in years and the points for each applicable characteristic.
Simplified Version
(Score > 1 = high risk)
- age > 80 y
- history of cancer
- COPD
- pulse ≥110 bpm
- BP < 100 mmHg
- art O2 sat < 90%

Patients in Simplified PESI:
Low risk 30-day mortality of 1%
High risk 30-day mortality of 10.9%

Estimates the risk of 30-day mortality from PE
Case #3

The patient has no contraindications to anticoagulant therapy and she is willing to follow your recommendations. In fact, she has seen several TV advertisements for DOACs. At this point how would you treat the patient?

a) Administer systemic thrombolytics per protocol
b) Initiate either IV heparin drip or SC LMWH therapy
c) Initiate either inpatient or outpatient po rivaroxaban or apixaban after a period of observation
Case #3

You decide to

a) Admit patient for anticoagulation and monitoring

b) Discharge patient to home with LMWH/warfarin, rivaroxaban, or apixaban and arrange close follow up as outpatient
ACCP 2016: Choice of Long Term (1\textsuperscript{st} 3 Months) & Extended Anticoagulant Therapy

- In patients with DVT of the leg or PE (w/o active cancer):
  - DOAC’s are preferred over warfarin (Grade 2B)
  - Warfarin preferred over LMWH (Grade 2C)
  - No one DOAC is preferred over the other
  - Extended treatment w/ DOACs reduces recurrent VTE and is associated with less bleeding risks

ACCP 2016: Outpatient Treatment of Low Risk PE

Suitable for outpatient treatment:

1. No contraindications (recent bleeding, severe renal/liver disease, or severe thrombocytopenia)
2. Expected to be compliant with treatment
3. Feels well enough to be treated at home

- Clinical prediction rules such as PESI (<85 or simplified score 0) can identify low-risk patients
- Echo and biomarkers not routinely recommended
- If noted, RV dysfunction or increased biomarker levels should discourage home treatment

# Outpatient Treatment of Pulmonary Embolism (OPTE)

<table>
<thead>
<tr>
<th>outcome</th>
<th>Out N=171</th>
<th>In N=168</th>
<th>Difference in %age</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>1</td>
<td>0</td>
<td>0.6%</td>
<td>0.01</td>
</tr>
<tr>
<td>Major bleed*</td>
<td>3</td>
<td>0</td>
<td>1.8%</td>
<td>0.08</td>
</tr>
<tr>
<td>Mortality</td>
<td>1</td>
<td>1</td>
<td>0.6%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

- Excluded: O2 sat < 90%, SBP<100, chest pain active or high risk bleeding, recent CVA GIB in past 2 weeks, plt<75K, crcl < 30, wt > 150 kg, anticoagulation failure, poor follow up
- If discharged called every day for one week
- major bleeds-2 IM hematomas day 3/13; 1 DUB day 50

Aujesky D. et al.  Lancet. 2011 Jul 2;378
Echocardiogram and PE Prognosis

Meta-analysis - RV dysfunction as a prognostic factor in stable patients with PE

- 12 trials, 3283 hemodynamically stable patients with acute PE
  - 1223 patients (37.3%) RVD+
  - 2060 patients (62.7%) RVD-

MORTALITY
167/1223 (13.7%)
134/2060 (6.5%)

ACCP Guidelines for Outpatient Treatment of Patients With DVT/PE

**Acute DVT**

Current guidelines recommend initial treatment at home over treatment in-hospital (Grade 1B)

**Low-Risk PE**

Current guidelines recommend early discharge over standard discharge (Grade 2B)

These recommendations are contingent on adequate home circumstances, including:

♦ Well-maintained living conditions
♦ Strong support network
♦ Phone access

♦ Patient feeling well enough for home treatment
♦ Ability to be promptly rehospitalized
Hospitalizations and Other Healthcare Resource Utilization among Patients with Deep Vein Thrombosis Treated with Rivaroxaban versus Low-Molecular Weight Heparin and Warfarin in the Outpatient Setting

Study Results

\[ \Delta \text{Hosp.} [95\% \text{ CI}] = -0.020 [-0.039, -0.002]; P = 0.044 \]

\[ \Delta \text{Hosp.} [95\% \text{ CI}] = -0.026 [-0.050, -0.002]; P = 0.040 \]

\[ \Delta \text{Hosp.} [95\% \text{ CI}] = -0.023 [-0.051, 0.008]; P = 0.112 \]

\[ \Delta \text{Hosp.} [95\% \text{ CI}] = -0.033 [-0.066, 0.001]; P = 0.058 \]

Figure 1. All-Cause Hospitalization – Matched Rivaroxaban and LMWH/Warfarin Users
Study Results

Associated Healthcare Costs:

– All-cause total healthcare costs were significantly lower for rivaroxaban users compared to LMWH/warfarin users over 1 week ($2,332 vs $3,428; P <0.001) and 2 weeks ($3,108 vs $4,524; P <0.001) and were numerically (but not statistically significantly) lower over 3 and 4 weeks.

– All-cause hospitalization costs were significantly lower for rivaroxaban users compared to LMWH/warfarin users over 1 week ($171 vs $873; P = 0.014) and 2 weeks ($466 vs $1,342; P = 0.036) and were numerically (but not statistically significantly) lower over 3 and 4 weeks.

– The pharmacy costs were significantly lower for patients treated with rivaroxaban over 1, 2, 3, and 4 weeks (P <0.001), with rivaroxaban users incurring about half the cost of the LMWH/warfarin users over the first 2 weeks.
Subsegmental PE

- Subsegmental PE: confined to the subsegmental pulmonary artery
  - A true subsegmental PE is thought to be likely to have arisen from a small DVT.

- Unclear how clinically relevant these events are, and thus unclear whether or not to treat these events with anticoagulants as risk may be > benefit

- Diagnosis is more likely to be a false positive finding compared to a diagnosis of PE in the segmental or more proximal pulmonary arteries
Subsegmental PE

• With new advancements in imaging, diagnosis of these events has increased.

• In patients diagnosed with a subsegmental PE and confirmed to have no proximal DVT and have a low risk for a recurrent clotting event, surveillance is recommended over anticoagulation (Grade 2C)

• But if patient has a high risk for recurrent VTE, anticoagulation is recommended over surveillance (Grade 2C).
### Comparison of NOAC Trials in DVT/PE

#### Treatment: Study Designs

<table>
<thead>
<tr>
<th>Trials</th>
<th>EINSTEIN DVT &amp; PE</th>
<th>AMPLIFY</th>
<th>RECOVER I &amp; II</th>
<th>HOKUSAI VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size, n (%)</td>
<td>N=8282</td>
<td>N=5395</td>
<td>N=5107</td>
<td>N=8240</td>
</tr>
<tr>
<td>PE patients, n (%)</td>
<td>4832 (58)</td>
<td>1836 (34)</td>
<td>~31%</td>
<td>3319 (40)</td>
</tr>
<tr>
<td>Active cancer**, n (%)</td>
<td>430 (5.3)</td>
<td>143 (2.7)</td>
<td>~4.7%</td>
<td>208 (2.5)†</td>
</tr>
<tr>
<td>Unprovoked, n (%)</td>
<td>5255 (63)</td>
<td>4845 (90)</td>
<td>N/A</td>
<td>5410 (66)</td>
</tr>
<tr>
<td>Regimen</td>
<td>Single oral agent concept</td>
<td>Single oral agent concept</td>
<td>Initial Heparin Bridge Required</td>
<td>Initial Heparin Bridge Required</td>
</tr>
<tr>
<td>Dosing</td>
<td>15mg bid x 21 d, then 20 mg qd [3, 6, or 12 mo]</td>
<td>10 mg bid x 7 d, then 5 mg bid [6 mo]</td>
<td>LMWH/UFH x 5-10 d, then 150 mg bid [6 mo]</td>
<td>LMWH/UFH x 5-12 d, then 60 mg qd [3, 6, or 12 mo]</td>
</tr>
</tbody>
</table>

*Postrandomization.
**At baseline.
†Double-dummy period – oral drug only, dabigatran vs warfarin.
‡HOKUSAI enrolled 771(9.3%) patients with cancer listed as the cause of DVT or PE.
For Presentation Only – Not intended for data comparison.
## DVT/PE Labels: Treatment

<table>
<thead>
<tr>
<th></th>
<th>XARELTO® (rivaroxaban)</th>
<th>ELIQUIS® (apixaban)</th>
<th>PRADAXA® (dabigatran)</th>
<th>LIXIANA® (edoxaban)</th>
</tr>
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<tr>
<td><strong>Dosing</strong></td>
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<td>LMWH/UFH x 5-12 d, then 60 mg qd [3, 6, or 12 mo]</td>
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<tr>
<td><strong>Efficacy</strong></td>
<td>Noninferior</td>
<td>Noninferior</td>
<td>Noninferior</td>
<td>Noninferior</td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>↓ 46%</td>
<td>↓ 69%</td>
<td>Noninferior * ↓ 40%†</td>
<td>Noninferior</td>
</tr>
<tr>
<td><strong>MB/CRNMB</strong></td>
<td>Noninferior</td>
<td>↓ 56%</td>
<td>↓ 38%*</td>
<td>↓ 19%</td>
</tr>
<tr>
<td><strong>Renal Adjustment</strong></td>
<td>Avoid if CrCL&lt;30 mL/min</td>
<td>PK/PD</td>
<td>Avoid if CrCL&lt;30 mL/min</td>
<td>30 mg qd if CrCL 30-50 mL/min; Avoid if &lt;30 mL/min</td>
</tr>
</tbody>
</table>

*Postrandomization.
†Double dummy period – oral drug only, dabigatran vs warfarin.
For Presentation Only – Not intended for data comparison.
Relative Comparison of DOACs

VTE recurrence and rates of major or CRNM bleeding in VTE studies that compared DOACs with either LMWH and VKAs or VKAs

When should you use a new oral anticoagulant?

- Your patient is adherent
- Your patient has a poor INR control (TTR < 60%)
- Your patient has good renal function (creatinine clearance 50 ml/min or better)
- Your patient has good hepatic function (AST/ALT and bilirubin normal or < 2x ULN)
When should you avoid a new oral anticoagulant?

- Your patient is poorly adherent
- Your patient has poor renal or hepatic function
- Your patient is on strong p-glycoprotein or CYP 3A4 inhibitors/inducers
- Your patient is pregnant
- Your patient is on dual anti-platelet therapy
- Your patient has cancer – probably changing
Catheter-Based Thrombus Removal for the Initial Treatment of PE

• Evidence for the use of CDT compared with anticoagulation alone, CDT compared to systemic thrombolytic therapy, and catheter-based treatment without thrombolytic therapy is low quality and recommendations made are weak.

• CDT may be more effective than systemic thrombolysis:
  – Achieves a higher local concentration of thrombolytic drug by infusing the drug directly into the PE itself.
  – Fragmentation of the thrombus due to the placement of the catheter may enhance pharmacologic or endogenous thrombolysis.
### Catheter-Based Thrombus Removal for the Initial Treatment of PE

<table>
<thead>
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<th>2012</th>
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</thead>
<tbody>
<tr>
<td>In patients with acute PE associated with hypotension and who have (i) contraindications to thrombolysis, (ii) failed thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention (Grade 2C).</td>
<td>In patients with acute PE associated with hypotension and who have (i) high bleeding risk, (ii) failed thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention (Grade 2C).</td>
</tr>
<tr>
<td>In patients with acute PE, when a thrombolytic agent is used, we suggest administration through a peripheral vein over a pulmonary artery catheter (Grade 2C).</td>
<td>In patients with acute PE who are treated with a thrombolytic agent, we suggest systemic thrombolytic therapy using a peripheral vein over catheter directed thrombolysis (CDT) (Grade 2C).</td>
</tr>
</tbody>
</table>
Case #4

A 65 year old man with history of HTN and hyperlipidemia is admitted with a new PE. He is on ASA and statin. He is started on LMWH and bridged to warfarin. You:

A) stop his aspirin now that he is on warfarin due to concerns of increased risk of bleeding
B) continue ASA for primary prophylaxis
Risk of Bleeding With Single, Dual, or Triple Therapy With Warfarin, Aspirin, and Clopidogrel in Patients With Atrial Fibrillation

Hansen M et al. Arch Intern Med. 2010

warfarin + asa = 2x
warfarin + asa + clopidogrel = 3x
“For patients taking warfarin we suggest AVOIDING concomitant antiplatelet therapy except where benefit is likely to be greater than harm: valves, ACS, stents, CABG” (2C)

Holbrook A et al. CHEST 2012 (Suppl); Anand S et al JAMA 1999
Case #5a: How long will you recommend this patient stay on anticoagulation?

55 yo man with unprovoked PE?

a) 3 months  
b) 6 months  
c) 12 months  
d) Indefinitely
Case #5b: How long will you recommend this patient stay on anticoagulation?

68 yo woman with provoked PE?

a) 3 months
b) 6 months
c) 12 months
d) Indefinitely
### Risk of VTE Recurrence After Cessation of VTE

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>1st yr</th>
<th>Next 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal DVT</td>
<td>3% (6%)</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Major-transient</td>
<td>3%</td>
<td>10%</td>
</tr>
<tr>
<td>Minor-transient</td>
<td>5-6%</td>
<td>15%</td>
</tr>
<tr>
<td>Unprovoked</td>
<td>At least 10%</td>
<td>30%</td>
</tr>
<tr>
<td>Recurrent</td>
<td>&gt; 10%</td>
<td>&gt; 30%</td>
</tr>
</tbody>
</table>

Kearon, Blood 2005
The Risk of Recurrence Is Higher With Unprovoked VTE After Discontinuation of Anticoagulation\textsuperscript{91}

Patients with a first episode of clinically symptomatic proximal DVT and/or PE\textsuperscript{*} (N=1626)

Average of 6 months of anticoagulation treatment

Patients discontinued anticoagulation and were followed for recurrent DVT/PE

*Excluded patients with active cancer, prior VTE, an indication for indefinite anticoagulation, geographic inaccessibility to follow-up, or poor life expectancy.
Clinical presentation predicts likelihood and type of recurrence

- Distal (calf vein thrombosis)
  - Low risk of recurrence/PE
- Proximal- nearly 5 fold increased recurrence risk over distal
- PE vs. DVT
  - Patients presenting with PE are 3x more likely to suffer recurrent PE than those presenting with DVT

Baglin T et al J Thromb Haemost. 2010
### Clinical Scores to Predict Recurrence

<table>
<thead>
<tr>
<th></th>
<th>Men continue and HER DOO2</th>
<th>Vienna Prediction Model</th>
<th>DASH-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author (reference)</td>
<td>Rodger et al. (24)</td>
<td>Eichinger et al. (25)</td>
<td>Tosetto et al. (26)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>646</td>
<td>929</td>
<td>1818</td>
</tr>
<tr>
<td>Design</td>
<td>Prospective cohort</td>
<td>Prospective cohort</td>
<td>Patient level meta-analysis</td>
</tr>
<tr>
<td>Predictive variables</td>
<td>Men: none</td>
<td>Sex</td>
<td>Abnormal D-Dimer after anticoagulation</td>
</tr>
<tr>
<td></td>
<td>Women: Age ≥60 years</td>
<td>Location of first VTE</td>
<td>Age &lt; 50 years</td>
</tr>
<tr>
<td></td>
<td>Signs of PTS</td>
<td>D-Dimer after anticoagulation</td>
<td>Male sex</td>
</tr>
<tr>
<td></td>
<td>BMI ≥30 kg/m²</td>
<td></td>
<td>Hormonal therapy</td>
</tr>
<tr>
<td></td>
<td>D-dimer ≥250 µg/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>during anticoagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence risk</td>
<td>≤1 point</td>
<td>≤180 points (according</td>
<td>≤1 point</td>
</tr>
<tr>
<td>Low risk</td>
<td>1.6%</td>
<td>to nomogram)</td>
<td>3.1%</td>
</tr>
<tr>
<td></td>
<td>(95% CI 0.3%–4.6%)</td>
<td>4.4%</td>
<td>(95% CI 2.3 – 3.9)</td>
</tr>
</tbody>
</table>

## D-dimer and Recurrent VTE

<table>
<thead>
<tr>
<th>Study</th>
<th>D-dimer Status</th>
<th>Prolong (18 months)</th>
<th>Annals 2008 (one year)</th>
<th>Prolong II (one year)</th>
<th>Cosmi et al (18 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>D-dimer @ 1 month after AC stopped</td>
<td>Systematic review</td>
<td>d-dimer q 2 months after 1&lt;sup&gt;st&lt;/sup&gt; negative d-dimer</td>
<td>d-dimer &amp; RVO</td>
</tr>
<tr>
<td>Prolong (18 months)</td>
<td></td>
<td>15%</td>
<td>8.9</td>
<td>27%</td>
<td>9-12%</td>
</tr>
<tr>
<td>Annals 2008 (one year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolong II (one year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cosmi et al (18 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of VTE</th>
<th>Recommended Duration of Treatment 2012</th>
<th>Recommended Duration of Treatment 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal DVT of the leg or PE provoked by surgery</td>
<td>3 months</td>
<td>3 months</td>
</tr>
<tr>
<td>DVT of the leg or PE provoked by a nonsurgical transient risk factor</td>
<td>3 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Isolated distal DVT of the leg provoked by surgery or nonsurgical transient risk factor</td>
<td>3 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Unprovoked PE or DVT of the leg</td>
<td>At least 3 months</td>
<td>At least 3 months</td>
</tr>
<tr>
<td>Pt’s first DVT that is an unprovoked proximal DVT of the leg or PE</td>
<td>At least 3 months</td>
<td>Extended therapy (no scheduled stop date)</td>
</tr>
<tr>
<td>In patients with a second unprovoked VTE with a low bleeding risk</td>
<td>Recommend extended therapy</td>
<td>Extended therapy (no scheduled stop date)</td>
</tr>
<tr>
<td>In patients with a second unprovoked VTE with a moderate bleeding risk</td>
<td>Suggest extended therapy</td>
<td>At least 3 months</td>
</tr>
<tr>
<td>In patients with a second unprovoked VTE with a high bleeding risk</td>
<td>Suggest 3 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Patients with DVT of the leg and active cancer w/ or w/o high risk of bleeding</td>
<td>Extended therapy</td>
<td>Extended therapy (no scheduled stop date)</td>
</tr>
</tbody>
</table>
ACCP Guidelines Regarding Extended Therapy Are Stratified by Bleeding Risk

- Currently, there is a lack of well-validated tools to stratify the risk of major bleeding during extended anticoagulant therapy in patients with VTE
- However, the risk of bleeding in patients receiving anticoagulant therapy may increase with the prevalence of certain factors, including:

  - Advanced age
  - Cancer
  - Kidney or liver failure
  - Comorbidity and reduced functional capacity
  - Antiplatelet therapy
  - Previous stroke
  - Anemia
  - Alcohol abuse
  - Thrombocytopenia
  - Previous bleeding
  - Diabetes
  - Frequent falls
  - Poor anticoagulant control
  - Recent surgery
ACCP Guidelines Regarding Extended Therapy Are Stratified by Bleeding Risk

<table>
<thead>
<tr>
<th></th>
<th>Estimated Absolute Risk of Major Bleeding After 3 Months of Anticoagulation, % per year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Risk (0 Risk Factors)</td>
</tr>
<tr>
<td>Baseline risk of bleeding with no anticoagulation</td>
<td>0.3</td>
</tr>
<tr>
<td>Increased risk with anticoagulation</td>
<td>0.5</td>
</tr>
<tr>
<td>Total risk of bleeding on therapy</td>
<td>0.8</td>
</tr>
</tbody>
</table>

- Current guidelines recommend extended anticoagulation for most patients with unprovoked DVT/PE and a low to moderate bleeding risk.
Aspirin for Extended Treatment of VTE

- In patients with an unprovoked proximal DVT or PE who are stopping AC treatment and have no contraindication to aspirin, recommend aspirin over no aspirin to prevent recurrent VTE (Grade 2C).
  - Two randomized trials have compared aspirin to placebo for the prevention of VTE in patients with a first unprovoked PE or VTE who have completed 3-18 months of AC treatment $^{3,4}$

# Aspirin for Extended Treatment of VTE

## Table 13: Summary of Findings - Aspirin vs Placebo for extended treatment of VTE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of Participants □ (studies) □ Follow up</th>
<th>Quality of the evidence □ (GRADE)</th>
<th>Relative effect □ (95% CI)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Risk with Control</td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>1224 (2 studies) up to 4 years</td>
<td>✗ ✗ ✗ ✗ LOW&lt;sup&gt;3,4,5&lt;/sup&gt; due to imprecision</td>
<td>HR 0.82 &lt;sup&gt;(0.45 to 1.52)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>5 per 1000</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>1224 (2 studies) up to 4 years</td>
<td>✗ ✗ ✗ ✗ MODERATE&lt;sup&gt;3,5&lt;/sup&gt; due to imprecision</td>
<td>HR 0.65 &lt;sup&gt;(0.49 to 0.86)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>184 per 1000</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>1224 (2 studies) up to 4 years</td>
<td>✗ ✗ ✗ ✗ MODERATE&lt;sup&gt;3,4&lt;/sup&gt; due to imprecision</td>
<td>HR 1.31 &lt;sup&gt;(0.48 to 3.53)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>12 per 1000</td>
</tr>
</tbody>
</table>

Bibliography: Simes et al. (INSPIRE)<sup>70</sup>
Duration of Anticoagulation
Unprovoked VTE

After 3 months of tx
Assess bleeding risk
Consider indefinite tx
(esp PE, male, thrombophilia)
patient preference

Female:
Clinical prediction rule:<1 and wants to stop anticoagulation-ok

Male:
Stop AC and Measure D-dimer at 30days, if low ok
If elevated consider Restarting tx

High bleed risk
Elderly
Bleed on AC
STOP AC

IF DVT get u/s. measure d-dimer. If d-dimer + continue AC
Case #5a/b: How long will you recommend these patients stay on anticoagulation?

55 yo man with unprovoked PE?

a) 3 months  
b) 6 months  
c) 12 months  
d) Indefinitely

68 yo woman with provoked PE?

a) 3 months  
b) 6 months  
c) 12 months  
d) Indefinitely
Use of Compression Stockings to Prevent Post-Thrombotic Syndrome

- Since the 2012 update, a larger multicenter, placebo-controlled trial found that routine use of compression stockings did not reduce the incidence of PTS or have other important benefits.\(^7\)

- This study also found that the use of compression stockings did not reduce leg pain 3 months after DVT diagnosis.

---

<table>
<thead>
<tr>
<th>2012</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B).</td>
<td>In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS (Grade 2B).</td>
</tr>
</tbody>
</table>
CASE # 6

A 33 year old woman diagnosed with left lower extremity DVT 3 months ago maintained on warfarin present with complaints of pleuritic chest and shortness of breath. A CT angio of the chest reveals new bilateral subsegmental pulmonary emboli.
CASE #6

She reports compliance with her warfarin therapy and has an INR of 2.5 at the time of admission. She is admitted to your service for recurrent VTE. How do you manage this?
Management of Recurrent VTE on Anticoagulant Therapy

• Currently there are no randomized trials or prospective cohort studies that have evaluated the management of patients with recurrent VTE while on anticoagulant therapy

• Management is based on low quality of evidence and an assessment of the probable risk of recurrence
VTE Despite Anticoagulation

- Medication adherence
- Antiphospholipid antibody syndrome
- Cancer
- DIC/Trousseaus
- Heparin-induced thrombocytopenia
- Myeloproliferative disorder
- Antithrombin deficiency
- Structural defect
VTE Despite Anticoagulation

• **LMWH failure**
  – Change to BID dosing
  – Increase dosing by 25-33% (Grade 2C)
  – Follow anti-Xa levels

• **Warfarin failure**
  – Transition to LMWH then transition to warfarin with higher target OR continue LMWH
Management of Recurrent VTE on Anticoagulant Therapy

• In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily (Grade 2C)
Management Algorithm of Recurrent VTE in Cancer

Lee A Y Y et al  Blood 2013;122:2310-2317
Role of IVC Filters in Addition to Anticoagulation for Acute DVT or PE

- In patients with acute DVT or PE who are treated with anticoagulants, we recommend against the use of an IVC filter (Grade 1B).
- Recommendation from 2012 remains the same, but the quality of evidence has improved.
- The PREPIC 2 trial found that IVC filters that are placed for 3 months did not reduce recurrent PE in anticoagulated patients.
SUMMARY

• Catheter-associated VTE does not mandate catheter removal and requires 3 months of anticoagulation once catheter is removed
• Risk stratify each patient to determine if calf vein thrombosis needs treatment
• Risk stratify all patients presenting with PE to determine appropriate disposition
SUMMARY

• Minimum effective duration of therapy for VTE is 3 months. If event is unprovoked consider indefinite anticoagulation if bleeding risk is low

• Add DOACS as strong evidence based options for VTE treatment

• Consider assessing individual risk benefit of extended therapy using d-dimer and clinical risk scores
SUMMARY

• Risk benefit of concomitant use of ASA plus warfarin should be assessed in each patient.

• Recurrent VTE despite anticoagulation should prompt a work up for HIT, DIC, cancer, APLS MDS and requires intensification of therapy.
Questions ?