Venous thromboembolism treatment: Challenges, Controversies, and Cases

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ACP Utah Chapter Annual Scientific Meeting
Salt Lake City UT
Friday February 10, 2017
Disclosures

• Investigator initiated grant recipient: Bristol-Myers-Squibb (paid to Intermountain Healthcare)

• Panelist American College of Chest Physicians Clinical Practice Guideline: Antithrombotic therapy for venous thromboembolic disease (AT10)
Objectives

Cases to highlight AT10 recommendations

• Routine treatment of PE and proximal DVT
  – DOAC limitations & use in routine clinical care
    • Special populations

• Isolated subsegmental PE

• Event on therapy thrombosis

• Duration of anticoagulation therapy

• Role for aspirin in prevention of recurrent VTE
Treatment updates for Venous Thromboembolism

Antithrombotic Therapy for VTE Disease
CHEST Guideline and Expert Panel Report

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri BounNAMEAUX, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy A. Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Woller, MD; and COL Lisa Moores, MD, FCCP
Antithrombotic living guideline model

53 recommendations in this update

20 (38%) are strong recommendations (Grade 1)

None are based on high quality (Grade A) evidence

AT LGM is the first endeavor to transition to a continually updated “Living Guideline” with a format designed to facilitate updates as new evidence becomes available.

<table>
<thead>
<tr>
<th>Initial</th>
<th>Long-term</th>
<th>Extended</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0 to ~7 days)</td>
<td>(~7 days to ~3 months)</td>
<td>(~3 months to indefinite)</td>
</tr>
<tr>
<td>Parenteral*</td>
<td>Vitamin K antagonist or other agent†</td>
<td></td>
</tr>
</tbody>
</table>

* Heparin, LMWH, fondaparinux ; † Includes LMWH, dabigatran, rivaroxaban, apixaban, edoxaban
Case 1

HISTORY: 47-year-old gentleman presents to the emergency department with chest pain and shortness of breath that has been ongoing for 24 hours and progressively worse. He denies any recent travel, surgery, illness, or hospitalization.

PHYSICAL EXAM: Blood pressure of 122/78, respiratory rate of 18, oxygen saturation 92% on room air, a heart rate of 101 and a body weight of 79 kg. Lungs are clear and heart is of a normal rhythm without accentuation of the second heart tone. Extremities are warm and symmetric.
Case 1

MEDICAL DECISION-MAKING: Upon assessment of pretest probability for pulmonary embolism the patient is found to be at intermediate risk for pulmonary embolism, and a highly sensitive d-dimer was sent which returns at 2047 ng/dL (NL < 500 ng/dL).

CT pulmonary arteriography is obtained
Bilateral pulmonary embolism involving the segmental and subsegmental branches of the upper and lower lobes.
Case 1

An initial dose of enoxaparin 80 mg is administered in the ED.

You discuss treatment options with the patient. He reports being employed with the job that requires frequent travel, has a busy schedule, is insured, and is asking your device regarding choice of long-term anticoagulant.

Which of the following represents the best choice for long-term anticoagulation?

A. Apixaban 10 mg twice a day ×7 days, followed by 5 mg twice a day for minimum duration of 3 months
B. Enoxaparin 80 mg subcutaneous twice daily for minimum duration of 3 months
C. Enoxaparin overlapping with warfarin, titrated to a target INR of 2.5 (range 2-3)
D. Warfarin initiation immediately without any further parenteral anticoagulation
Case 1 Answer

A. Apixaban 10 mg twice a day ×7 days, followed by 5 mg twice a day for minimum duration of 3 months
Choice of anticoagulant for long-term treatment of DVT and PE: DOAC vs. warfarin

**AT10 Guideline Statement:**

In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest apixaban or edoxaban or rivaroxaban or dabigatran over VKA therapy (Grade 2B).

*Remarks:* Acute therapy with parenteral anticoagulation is given before dabigatran and edoxaban.

For the first time an alternative to usual care with low molecular weight heparin and warfarin has been suggested for the long-term treatment of PE and DVT.

Kearon C. *Chest.* 2016. doi:10.1016/j.chest.2015.11.026
**QUESTION: Should a DOAC or warfarin be used for acute and long-term treatment of VTE?**

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NOAC n (studies)</strong></td>
<td><strong>Risk of bias</strong></td>
</tr>
<tr>
<td><strong>RIVAROXABAN</strong> 8281 (2 studies)</td>
<td>no serious risk of bias</td>
</tr>
<tr>
<td><strong>DABIGATRAN</strong> 5107 (2 studies)</td>
<td>no serious risk of bias</td>
</tr>
<tr>
<td><strong>APIXABAN</strong> 5244 (1 study)</td>
<td>no serious risk of bias</td>
</tr>
<tr>
<td><strong>EDOXABAN</strong> 8240 (1 study)</td>
<td>no serious risk of bias</td>
</tr>
</tbody>
</table>

**Recurrent VTE**

- **RIVAROXABAN**: 2 fewer per 1000 (from 7 fewer to 5 more)
- **DABIGATRAN**: 3 more per 1000 (from 5 fewer to 13 more)
- **APIXABAN**: 4 fewer per 1000 (from 11 fewer to 5 more)
- **EDOXABAN**: 6 fewer per 1000 (from 15 fewer to 7 more)
Recommended therapy for VTE takes into consideration efficacy, safety, and burden of treatment (can also include cost).

Is there evidence to recommend 1 DOAC over another?
DOACs have not been compared head-to-head for patient-important outcomes
Indirect comparisons suggest similar outcomes with all DOACs

Individual patient characteristics (including cost and insurance coverage) will likely drive choice
# The Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th>BRAND NAME PHARMACEUTICAL</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xarleto™</td>
<td>Eliquis™</td>
<td>Savaysa™</td>
<td>Pradaxa™</td>
<td></td>
</tr>
<tr>
<td>Bayer</td>
<td>BMS &amp; Pfizer</td>
<td>Daiichi Sankyo</td>
<td>Boehringer Ingelheim</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TARGET</th>
<th>Factor Xa</th>
<th>Factor Xa</th>
<th>Factor Xa</th>
<th>Factor IIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIME TO PEAK (h)</td>
<td>2–3</td>
<td>1–2</td>
<td>1-2</td>
<td>1.5</td>
</tr>
<tr>
<td>HALF-LIFE (h)</td>
<td>9-13</td>
<td>8-15</td>
<td>9-10</td>
<td>12-14</td>
</tr>
<tr>
<td>RENAL EXCRETION (%)</td>
<td>33</td>
<td>25</td>
<td>35</td>
<td>&gt;80</td>
</tr>
<tr>
<td>EFFECT ON aPTT/PT*</td>
<td>1.8/2.6</td>
<td>1.2/~2</td>
<td>yes</td>
<td>2.3/NR</td>
</tr>
<tr>
<td>EFFECT ON Xa</td>
<td>68%</td>
<td>NR</td>
<td>NR</td>
<td>No Effect</td>
</tr>
<tr>
<td>DRUG INTERACTIONS</td>
<td>CYP3A4 IND/INH</td>
<td>CYP3A4 INH</td>
<td>P-gp INH/CYP3A4</td>
<td>Verapamil/rifampin</td>
</tr>
</tbody>
</table>

Who is a candidate for a DOAC therapy to treat VTE?

Who is not?

From the clinical trials:

- Need for thrombolytic therapy
- An indication for anticoagulation for which no DOAC approval exists
- High risk of bleeding
- Significant liver disease (hepatitis, cirrhosis, or AST/ALT \( \geq 3x \) ULN)
- Creatinine clearance 30 mL/min (apixaban threshold was 25 mL/min)
- Aspirin use (100 mg/day)
- Concomitant use of interacting medications
- Uncontrolled hypertension

Who is a candidate for a DOAC therapy to treat VTE?

Who is not?

From the school of hard knocks:

• Patients who struggle with compliance (unless related to transportation for INRs)
  • Warfarin allows ascertainment of anticoagulant effect

• Financial barriers to longitudinal compliance
  • After 1.1 year f/u <50% prescribed DOAC picked up adequate drug to cover 80% days

DOAC therapy: Special populations
Candidates for a DOAC therapy: Special populations

Pregnancy

+ Dabigatran or rivaroxaban =

- Apixaban has no human data in pregnancy, but showed no maternal or fetal harm in animal studies
  - Ex vivo drug concentration across placenta F:M ratio 0.9

- Edoxaban animal studies demonstrated no fetal harm

- DOAC excretion in breast milk is not known.
Candidates for a DOAC therapy: Special populations

Pregnancy
Candidates for a DOAC therapy: Special populations

**Extremes of weight**

- Evidence is limited
  - Patients <50–60 kg were 2–13 % of DOAC study populations & 16 % of patients were >100 kg
  - 1 meta-analysis showed that for patients >100kg recurrent VTE risk was 0.9 (95% CI 0.77-1.06)
- Dabigatran does not appear to be affected by extremes of weight
- Weight may affect kinetics of anti-Xa’s but the clinical significance is unknown.
- ISTH and AC Forum suggest against use based on PK/PD in obese

Candidates for a DOAC therapy: Special populations

Extremes of weight
Candidates for a DOAC therapy: Special populations

**Elderly**

- Evidence from a meta-analysis of the Phase 3 trials studying VTE

- Pooled DOAC vs. VKA for age ≥ 75 years for recurrent VTE or VTE-related death: HR 0.56 (95% CI 0.38-0.82) p=0.003

- Pooled DOAC vs. VKA for age ≥ 75 years for Major bleeding: HR 0.49 (95% CI 0.25-0.96) p=0.04
Candidates for a DOAC therapy: Special populations

Elderly
Candidates for a DOAC therapy: Special populations

**Thrombophilias**

- Evidence is limited
  - Patients with thrombophilias comprised 2-18% of those enrolled in DOAC trials

- Post-hoc dabigatran data shows no difference in recurrent VTE

- Exception: APS -- 3 studies
  - RAPS (Canada), TRAPS (Italy), ASTRO-APS (USA)
Candidates for a DOAC therapy: Special populations
Candidates for a DOAC therapy: Special populations

Thrombophilias

APS =
Candidates for a DOAC therapy: Special populations

Cancer

- No dedicated RCT evidence for cancer patients exists

- Systematic reviews of the cancer subgroup from the clinical trials suggest DOACs are similar to VKA for VTE recurrence risk reduction and no difference in MB/CRNMB

- 1 meta-analysis suggested for VTE recurrence RR 0.57 (95% CI 0.36-0.91; p=0.02)

Candidates for a DOAC therapy: Special populations

Cancer

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DOA Events</th>
<th>Total</th>
<th>Comparator Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY 2013</td>
<td>3</td>
<td>81</td>
<td>5</td>
<td>78</td>
<td>15.2%</td>
<td>0.56 [0.13, 2.43]</td>
</tr>
<tr>
<td>EINSTEIN-DVT 2010</td>
<td>4</td>
<td>118</td>
<td>5</td>
<td>89</td>
<td>17.1%</td>
<td>0.59 [0.15, 2.26]</td>
</tr>
<tr>
<td>EINSTEIN-PE 2012</td>
<td>2</td>
<td>114</td>
<td>3</td>
<td>109</td>
<td>9.4%</td>
<td>0.63 [0.10, 3.85]</td>
</tr>
<tr>
<td>HOKUSAI 2013</td>
<td>4</td>
<td>109</td>
<td>7</td>
<td>99</td>
<td>22.0%</td>
<td>0.50 [0.14, 1.77]</td>
</tr>
<tr>
<td>RECOVER I &amp; II 2013</td>
<td>10</td>
<td>173</td>
<td>12</td>
<td>162</td>
<td>36.3%</td>
<td>0.77 [0.32, 1.83]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>595</td>
<td>537</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.63 [0.37, 1.10]</td>
</tr>
</tbody>
</table>

Total events: 23 vs 32

Heterogeneity: Chi² = 0.36, df = 4 (P = 0.99); I² = 0%

Test for overall effect: Z = 1.62 (P = 0.10)
Candidates for a DOAC therapy: Special populations

Cancer

- AT10 states that “For VTE and cancer, we suggest LMWH over VKA (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C).”

- No comparison of DOAC with LMWH to date
  - 5 ongoing trials (rivaroxaban=2, apixaban=2, edoxaban=1)

clinicaltrials.gov accessed 12 MAR 2016
Candidates for a DOAC therapy: Special populations

Cancer
Case 2

HISTORY: 62-year-old woman presents your outpatient clinic after undergoing meniscal tear arthroscopic knee surgery 12 days ago. She recently developed acute onset chest pain when she takes a deep breath that is persistent and does not go away.
Case 2

PHYSICAL EXAM: Temp 37, HR 74, BP 122/76, RR 12. The incisions on the lateral aspects of her knee that are clean and intact. The bruising and moderate effusion of the knee is uncomfortable upon palpation. The left leg is 2 cm larger than the right at the level of the calf.

MEDICAL DECISION-MAKING: You have concern that this may be pulmonary embolism. You estimate her pretest probability for PE as intermediate risk using Wells criteria.

You send a highly sensitive d-dimer that returns at 1200 ng/dL (normal is < 500 ng/dL).
Case 2

Proximal duplex ultrasound of the leg demonstrates no deep venous thrombosis.

You perform a CT pulmonary arteriogram.
Multiple subsegmental bilateral pulmonary emboli exist. Thrombosis in the segmental and more proximal pulmonary arteries is absent.
Case 2

You diagnose the patient with acute pulmonary embolism.

Which of the following treatment options do you select to treat this patient?

A. Apixaban 10 mg twice a day ×7 days, followed by 5 mg twice a day for minimum duration of 3 months
B. Refrain from anticoagulation. Repeat ultrasound in 7 days
C. Enoxaparin overlapping with warfarin, titrated to a target INR of 2.5 (range 2-3) with appropriate overlap
D. Initiate warfarin without parenteral anticoagulation (given the thrombosis is in the subsegmental arteries)
Case 2 Answer

B. Refrain from anticoagulation. Repeat ultrasound in 7 days
AT10 Guideline Statement:

In patients with subsegmental PE (no involvement of more proximal pulmonary arteries), no proximal DVT in the legs, and a low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation (Grade 2C).
SSPE is important because computerized tomography pulmonary angiography (CTPA) fidelity has increased how often SSPE is diagnosed. Now SSPE constitutes about 10% of all PE cases.

No RCTs exist to direct treatment of SSPE however high quality evidence supports anticoagulation for treatment of larger PE.

Whether the risk of progressive or recurrent VTE is high enough to justify anticoagulation in patients with SSPE is uncertain.
**What considerations are important upon weighing SSPE treatment options?**

1. Consider certainty of true thrombosis being present (evaluate likelihood of observed thrombosis being a false positive result)

<table>
<thead>
<tr>
<th>SSPE is more likely a true-positive if...</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTPA characteristics (quality, multiple defects, multiple projections, etc.)</td>
</tr>
<tr>
<td>Patients are symptomatic (as opposed to PE being an incidental finding)</td>
</tr>
<tr>
<td>There is a high clinical pre-test probability for PE</td>
</tr>
<tr>
<td>Elevated D-Dimer that’s otherwise unexplained</td>
</tr>
</tbody>
</table>
Whether to Anticoagulate Subsegmental Pulmonary Embolism

NEW TOPIC!

What considerations are important upon weighing SSPE treatment options?

2. Assess the patient for risk factors for progressive thrombosis and risk of anticoagulation.

<table>
<thead>
<tr>
<th>Favors Anticoagulation</th>
<th>Favors No Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (particularly if metastatic or on chemotherapy)</td>
<td>High bleeding risk</td>
</tr>
<tr>
<td>No reversible VTE risks (e.g. recent surgery)</td>
<td>Patient prefers to avoid anticoagulation</td>
</tr>
<tr>
<td>Marked symptoms without another cause</td>
<td></td>
</tr>
<tr>
<td>Patient prefers anticoagulation</td>
<td></td>
</tr>
<tr>
<td>Hospitalized or immobilized</td>
<td></td>
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</tbody>
</table>
What additional testing and follow-up is recommended if the decision is to not anticoagulate SSPE?

<table>
<thead>
<tr>
<th>Additional testing recommended</th>
<th>Additional follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral US to exclude proximal DVT of the legs</td>
<td>Assure patient literacy surrounding signs and symptoms of progressive thrombosis</td>
</tr>
<tr>
<td>Exclude DVT in other high risk locations (e.g. upper extremities if</td>
<td>Perform one or more follow-up US of the legs to detect (and then treat) evolving</td>
</tr>
<tr>
<td>a central line is present)</td>
<td>proximal DVT</td>
</tr>
</tbody>
</table>
With a weak recommendation based on low quality evidence (Grade 2C), clinical surveillance is suggested over anticoagulation in patients with isolated subsegmental PE.

If clinical surveillance is chosen, it should be assured that no proximal DVT in the legs exists, and that the patient is at a low risk for recurrent VTE.

Upon clinical surveillance perform serial ultrasound of the legs to detect evolving DVT (e.g. repeating ultrasound weekly x 2 weeks).
HISTORY: You see a 71-year-old man with unilateral leg pain and swelling and diagnose him with deep vein thrombosis of the left popliteal and distal femoral vein on the 3rd of the month.

You verify normal renal function and initiate rivaroxaban 15mg BID x 21 day followed by rivaroxaban 20mg daily thereafter.
Case 3

The patient calls you today on the 10th reporting greater leg swelling and increased pain.

He denies any change in color or temperature of the leg and is able to ambulate although his leg feels subjectively heavier and more full.

You affirm that he was able to fill his rivaroxaban.
Case 3

Repeat left leg ultrasound demonstrates thrombosis in the popliteal and distal femoral vein where it was previously observed in addition to new thrombosis in the proximal thigh femoral vein and the distal iliac vein that is visualized (progression of thrombosis disease).
Case 3

You now see him after the ultrasound and verify that he has no new vascular insufficiency however a larger leg.

Which of the following treatments options do you select to treat this patient?

A. Change from rivaroxaban to apixaban 10 mg twice a day ×7 days, followed by 5 mg twice a day
B. Continue rivaroxaban and repeat ultrasound in 7 days
C. Stop rivaroxaban and initiate enoxaparin 1mg/kg every 12 hours
D. Refer to patient for catheter-directed thrombectomy with thrombolysis.
Case 3 Answer

C. Stop rivaroxaban and initiate enoxaparin 1mg/kg every 12 hours
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).
There are no RCTs or prospective cohort studies that have evaluated management of patients with recurrent VTE on anticoagulant therapy.

A retrospective observational study reported a risk of recurrent VTE (8.6%) and major bleeding (1.4%) during 3 months follow-up in 70 cancer patients with recurrent VTE while on anticoagulant therapy who either switched from VKA therapy to LMWH (n=23) or had their LMWH dose increased by about 25% (n=47).
Risk factors for recurrent VTE while on anticoagulant therapy can be divided into two broad categories:

1. Treatment factors
2. Intrinsic patient factors for risk of recurrence
Management of Recurrent Venous Thromboembolism on Anticoagulant Therapy

TREATMENT FACTORS
Important considerations when assessing for recurrent VTE on anticoagulant therapy

(1) Was the patient adherent
(2) Was warfarin sub-therapeutic
(3) Was anticoagulant therapy prescribed correctly
(4) Was the patient taking a NOAC and a drug that reduced anticoagulant effect
(5) Had anticoagulant dose been reduced (drugs other than warfarin)
Management of Recurrent Venous Thromboembolism on Anticoagulant Therapy

**INTRINSIC PATIENT RISK FACTORS FOR RECURRENCE**

**Important considerations when assessing for recurrent VTE on anticoagulant therapy**

1. Active cancer (occult disease should always be considered)

2. Antiphospholipid Syndrome
   i. Associated with recurrence
   ii. LA can interfere with the INR (spurious results)

3. Concomitant use of medications that increase risk of thrombosis
SUMMARY

If a patient is on oral anticoagulation, then it is recommended to switch to treatment-dose LMWH.

If a patient is on LMWH, then it is recommended to increase the dose by about 25%.

If anticoagulant intensity cannot be increased because of risk of bleeding, an IVC can be inserted to prevent PE. This is a least favorable option of last resort.
Case 4

HISTORY: A 47 year-old woman recently moved to SLC from Las Vegas and is establishing care. She experienced unprovoked pulmonary embolism (without hemodynamic compromise) 6 months ago. She is taking warfarin 35 mg weekly with the 5 last INRs in target range.

She denies any bleeding complications. She is physically active (cycling, skiing, etc.) and worries about being on warfarin.
Case 4

She presents today to ask your opinion regarding how long she need stay on warfarin and if there are any tests you can do to help her decide about the risk:benefit ratio for continuing warfarin.
Case 4

Which of the following represent your answer to the patient.

A. Stop anticoagulation and obtain a d-dimer in a month
B. Insist that the patient continue anticoagulation because her PE was unprovoked
C. Stop anticoagulation because this represented a first thrombotic event
D. Transition her from warfarin to apixaban
Case 4 Answer

A. Stop anticoagulation and obtain a d-dimer in a month
In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a low or moderate risk of bleeding, we suggest extended anticoagulation (no scheduled stop date) over 3 months of therapy (Grade 2C).
D-dimer and duration of therapy

Cancer-associated (estimated)

Unprovoked

Non-surgical triggers

Surgery

adapted from Baglin Lancet 2003

Slide courtesy of Kearon C.
Predictors of Recurrent VTE

- "+" D-dimer doubles risk for recurrent VTE
- Men RR recurrent VTE 1.75 compared with women
D-dimer and duration of therapy

D-dimer and 5 year risk of recurrent VTE among patients with unprovoked VTE by gender

**When is obtaining a D-dimer helpful?**

- **25% is low enough for a man to stop anticoagulants**
- **15% is low enough for a woman to stop anticoagulants**
- **30% is high enough for a woman to stay on anticoagulants**
D-dimer and duration of therapy

**Summary**

- D-dimer is unlikely to aide in decision-making regarding duration of anticoagulation among men.

- A negative D-dimer a month after stopping anticoagulant therapy among women suggests a low (and likely acceptable) risk of recurrent thrombosis and may influence the decision to stop anticoagulant therapy.
Case 5

HISTORY: Your same 47 year-old woman from Case 4 elects to stop warfarin anticoagulation for the secondary prevention of VTE.

You discuss with her the uncertainties regarding thrombosis risk recurrence prediction, and she feels informed (and strongly) that stopping anticoagulation is the correct decision for her.
Case 5

She reports no drug allergies, and is wondering if there is any intervention aside from avoiding estrogen-based OCPs, maintaining an active healthy lifestyle, and not smoking, that she can take to lower her risk of thrombosis.
Case 5

Which of the following answers do you provide?

A. Remark that if she chooses to not continue anticoagulation you will no longer care for her because her PE was unprovoked
B. Recommend she transition from warfarin to apixaban
C. Recommend she continue warfarin at a “low dose” of 1 mg daily without need for INR checks
D. Recommend she start aspirin 81mg daily
Case 5 Answer

D. Recommend she start aspirin 81mg daily
Aspirin for the secondary prevention of VTE

AT10 Guideline Statement:
In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE (Grade 2B)

Kearon C. CHEST 2016; 149(2):315-352
Aspirin for the secondary prevention of VTE

<table>
<thead>
<tr>
<th></th>
<th>Quality Evidence (GRADE)</th>
<th>Hazard Ratio</th>
<th>Difference Per 1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VTE</strong></td>
<td>Mod</td>
<td>0.65 (0.49, 0.86)</td>
<td>-60 (-24, -89)</td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>Mod</td>
<td>1.31 (0.48, 3.5)</td>
<td>+4 (-6, +29)</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>Low</td>
<td>0.82 (0.45, 1.5)</td>
<td>-1 (-3, +3)</td>
</tr>
</tbody>
</table>

Studies: 2  
Participants: 1,224
Aspirin for the secondary prevention of VTE

- Anticoagulants reduce VTE >90%
- Bleeding may be similar with ASA & DOACs

**SUMMARY**

Unprovoked proximal DVT or PE and stop AC & no contraindication then aspirin over no aspirin (Grade 2B)
Thank you