Clinical Issues in Anticoagulation

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Disclosure

This presentation reflects the views of the author and should not be construed to represent the Food and Drug Administration's views or policies.

Overview

- Five cases
  - Case presentation
  - Multiple choice question
  - Answer to the multiple choice question
  - Rationale for the answer
  - Key data underlying the answer
  - Take away messages

Case 1

A 56 year old man with a history only notable for mild hypertension presents with calf discomfort and left lower extremity swelling. One day earlier he returned to Washington, DC on a long haul flight from Tokyo, Japan.

On review he denies chest pain and shortness of breath. He has no other pertinent history.

Case 1

On physical examination his blood pressure is 125/80, pulse 85, and respiratory rate is 14 with an oxygen saturation of 99% on room air. His left leg is swollen to the knee.

Left lower extremity ultrasound is consistent with thrombosis extending into the superficial femoral vein.

Appropriate management at this time includes which of the following

a) Obtain a pulmonary embolism protocol computed tomography scan
b) Obtain a follow-up ultrasound of the left lower extremity in one week
c) Admit to the hospital for treatment with unfractionated heparin and warfarin
d) Start once daily low molecular weight heparin and initiate warfarin as an outpatient

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Rationale for Correct Answer

- The superficial femoral vein is actually part of the deep venous system
- A PE protocol CT scan would not change management and involves risk from contrast
- Patients with venous thromboembolism (VTE) can be managed entirely as outpatients, including select patients with pulmonary embolism

Key Data – Outpatient PE Treatment

- 200 patients with objectively documented PE randomized to unfractionated heparin or once daily low molecular weight heparin (LMWH) during the transition to warfarin for 3 months
- Unfractionated heparin: 7 (6.8%) new VTE
- LMWH (tinzaparin): no new VTE (p=0.01)
- No difference in bleeding events

Hull RD, Raskob GE, Pineo GF, et al. Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism. American-Canadian Thrombosis Study Group. Arch Intern Med 2000; 160:229-36.

Key Data – Rivaroxaban in VTE

- Open label, randomized, non-inferiority study comparing the oral factor Xa inhibitor rivaroxaban to subcutaneous enoxaparin followed a vitamin K antagonist (VKA) for VTE
- Following acute phase of treatment of 6-12 months, patients on rivaroxaban were randomized to an additional 6-12 months of anticoagulation with rivaroxaban or placebo

The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363:2499-2510.

Key Data – Rivaroxaban in VTE

Acute Phase

Outcome	Rivaroxaban (n=1731)	Enoxaparin-VKA (n=1718)	p value
Recurrent VTE	36 (2.1%)	51 (3.0%)	<0.001
Total Deaths	38 (2.2%)	49 (2.9%)	0.06
Major Bleeding	14 (0.8%)	20 (1.2%)	0.21
Any Adverse Event	1078 (62.7%)	1080 (63.1%)	

- Data from the acute phase of the trial demonstrated non-inferiority of rivaroxaban to treatment with enoxaparin-VKA

The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363:2499-2510.

Key Data – Rivaroxaban in VTE

Continuation Phase

Outcome	Rivaroxaban (n=602)	Placebo (n=594)	p value
Recurrent VTE	8 (1.3%)	42 (7.1%)	<0.001
Total Deaths	1 (0.2%)	2 (0.3%)	
Major Bleeding	4 (0.7%)	0	0.11
Nonmajor bleeding	32 (5.4%)	7 (1.2%)	

- Data from the continuation phase demonstrated superiority of continued treatment without excessive bleeding risk

The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363:2499-2510.

Take Away Messages

- VTE can in many cases be managed entirely as an outpatient either with LMWH and VKA or with rivaroxaban
- The introduction of new oral anticoagulants, such as rivaroxaban, labeled for the treatment of VTE, presents more options for patients
- The question of long term anticoagulation for individuals with idiopathic VTE has become more relevant once again

Case 2

An active 76 year-old woman with a history of diabetes mellitus and atrial fibrillation seen for routine follow-up asks if she can switch to one of the new oral anticoagulants that does not require monitoring for adjustment.

Her current medications include diltiazem CD, glimepiride, and warfarin. Her INR values over the past year have ranged from 1.8 to 2.7

Case 2

On physical examination her blood pressure is 130/72, pulse 76. Lungs are clear and cardiac examination reveals a irregularly irregular heart sounds and no murmurs.

Laboratory studies are notable for a hematocrit of 34%, creatinine 2.7 mg/dL, ALT 33 U/L, and hemoglobin A_{1C} of 5.8%.

Appropriate management at this time includes which of the following

a) Switch to aspirin 81 mg daily
b) Evaluate source of anemia prior to switching to dabigatran, rivaroxiban, or apixiban
c) Discontinue warfarin and two days later start dabigatran 150 mg twice daily
d) Continue warfarin, decreasing frequency of monitoring to every two months

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Rationale for Correct Answer

- This patient has a $CHADS_2$ score of 2 and is at high risk for stroke warranting anticoagulation
- This patient's mild anemia is likely explained by low erythropoietin in the setting of diabetes mellitus and chronic kidney disease
- Dabigatran has renal clearance and the dose for a creatinine clearance of 15-30 mL/min is 75 mg twice daily

Key Data – Treatment Options

- There are currently three non-VKA oral anticoagulants approved for the management of nonvalvular atrial fibrillation
  - Dabigatran, a direct thrombin inhibitor
  - Rivaroxaban, a factor Xa inhibitor
  - Apixaban, a factor Xa inhibitor
- Since there is currently no specific reversal agent approved for any of these, avoidance of excessive anticoagulation is important

Key Data – Pharmacology

Characteristic	Dabigatran	Rivaroxaban	Apixaban
Half-life (h)	14-17	5-9	10-14
Peak effect (h)	2	2-4	3-4
Drug interactions	P-gp inducers/inhibitors	CYP3A4 and P-gp inducers/inhibitors	CYP3A4 and P-gp inducers/inhibitors
Metabolism	Hepatic	Hepatic mainly via CYP3A4, CYP3A5, CYP2J2	Hepatic mainly via CYP3A4
Elimination	80% renal 20% fecal	66% renal 33% fecal	27% renal 63% fecal

- For comparison, the half life of warfarin is 40 h, and its peak effect is in 72-96 h

Gonsalves WI, Pruthi RK, Patnaik MM. The new oral anticoagulants in clinical practice. Mayo Clin Proc 2013; 88:495-511.

Take Away Messages

- The newer non-VKA anticoagulants provide patients with additional options for anticoagulation
- Appropriate patient selection and dose adjustment for renal function is important for these drugs, which are relatively expensive in comparison to warfarin

Case 3

A 65 year-old woman with a history of rheumatic fever, s/p mitral valve replacement with a St. Jude's prosthesis maintained on warfarin asks if she can switch to one of the new oral anticoagulants since she wants to travel extensively following her upcoming retirement.

She has no history of bleeding, thrombotic, or embolic complications.

Case 3

Her current dose of warfarin is 7.5 mg daily and her INRs over the past year have ranged between 2.6 and 3.7.

A recent echocardiogram revealed no evidence of cardiac thrombus and an ejection fraction of 55%. Serum creatinine is 0.8 mg/dL

Appropriate management at this time includes which of the following

a) Start dabigatran 150 mg twice daily
b) Start apixaban 5 mg twice daily given its better safety profile in terms of bleeding
c) Prescribe enoxaparin 1.5 mg/kg SC daily for use when traveling
d) Continue warfarin at present dose and discuss possible home INR monitoring

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Rationale for Correct Answer

- Current data do not support the use of oral anticoagulants besides the vitamin K antagonists for use with prosthetic valves
- Use of low molecular weight heparin preparations in patients with prosthetic valves is controversial, especially long term
- Home warfarin monitoring is an option for individuals on long term anticoagulation

Key Data – Dabigatran vs. Warfarin

- Phase 2 study in two populations
  - Aortic or mitral valve replacement in past 7 days
  - Similar valve replacement at least 3 months prior
- Randomized 2:1 dabigatran:warfarin
- Dabigatran dosing based on renal function: adjustment to reach blood level of 50 ng/mL
- Warfarin to INR of 2 to 3 or 2.5 to 3.5, depending on thrombotic risk

Eikelbloom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013; 369:1206-14.

Key Data – Dabigatran vs. Warfarin

Outcome	Dabigatran (n=168)	Warfarin (n=84)
Stroke	9	0
Myocardial infarction	3	0
Asymptomatic valve thrombosis	5	0
Major bleeding	7	2
Any bleeding	45	10

- Trial was stopped early due to excess of adverse events in dabigatran group

Eikelbloom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013; 369:1206-14.

Take Away Messages

- Although further investigation is ongoing, at this time use of oral direct thrombin inhibitors or anti-Xa agents in patients with mechanical heart valves is not advisable
- Warfarin remains the standard of care for patients with mechanical heart valves

Case 4

A 62 year-old man with a history of chronic obstructive pulmonary disease is hospitalized with community-acquired pneumonia. He is treated with intravenous moxifloxacin and on hospital day 4 after being afebrile for 24 hours and off of supplemental oxygen he is switched to oral moxifloxacin. Other medications include a prednisone taper, ipratropium and albuterol inhalers, and prophylactic dose enoxaparin

Case 4

As he is getting ready for discharge his morning laboratory studies are noted:

	Admission	Today
WBC	14,300/µL	7,600/µL
Hematocrit	44%	41%
Platelets	420,000/µL	152,000/µL

Appropriate management at this time includes which of the following

a) Discharge home with appointment for follow-up CBC in four days
b) Discharge home on aspirin 325 mg daily for one month
c) Discharge home on warfarin for one month with follow-up monitoring for INR 2 to 2.5
d) Keep in house, start argatroban, and transition to warfarin as platelets normalize

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Rationale

- Heparin induced thrombocytopenia (HIT) is associated with arterial or venous thrombotic complications in up to 50% of cases
- Simple discontinuation of heparin following diagnosis of HIT leaves the patient at risk
- Aspirin is not adequate for anticoagulation
- Warfarin results in decreases in protein C and S levels increases the prothrombotic state

Key Data – 4T's Score

	Score = 2	Score = 1	Score = 0
Thrombo-cytopenia	>50% drop AND a nadir ≥20,000 AND no surgery in last 3d	>50% drop BUT surgery in last 3 d OR any other combination	<30% drop Any platelet fall with nadir <10,000
Timing	Platelet drop in 5-10d Platelet drop in 1d AND exposure in past 5-30 days	Platelet drop in 5-10d but not clear Platelet drop in 1d AND exposure past 31-100 days Platelet drop after d10	Platelet drop ≤ d4 without exposure in past 100d
Thrombosis	Doc. new thrombosis Skin necrosis Anaphylactoid rxn Adrenal hemorrhage	Recur. venous thrombosis Suspected thrombosis Erythematous skin lesions at heparin injection sites	Thrombosis not suspected
oTher Cause	No alternative explanation	Possible other explanation: e.g., suspected sepsis	Probable other cause: e.g., conf. bacteremia

4T Score: Low 0-3, Intermediate 4-5, High 6-8

Warkentin TE, Linkins L-A. Non-necrotizing heparin-induced skin lesions and the 4T's score. J Thromb Haemost 2010; 8: 1483-85.

Key Data – Treatment Options

- Lepirudin and argatroban are IV direct thrombin inhibitors approved for the management of HIT
- Argatroban is a small molecule with a half life of 40 min when hepatic function is normal
- Lepirudin is protein with a half life of 80 minutes when renal function is normal
- Both monitored using PTT, can increase PT/INR
- Choice of agent depends on patient characteristics

Take Away Messages

- Although the rate of heparin induced thrombocytopenia using LMWH is about half that of unfractionated heparin, it still occurs
- Whenever using unfractionated heparin or LWMH it is important to keep this consideration in mind
- Given the number of alternatives now available, it is advisable to stop and switch to one of them at first real suspicion of HIT

Case 5

A 35 year old woman with two prior episodes of lower extremity deep vein thrombosis and a documented anticardiolipin antibody has been difficult to anticoagulate with warfarin.

Her only medication is warfarin. She does not smoke, drink alcohol, or use illicit drugs. She states that she takes no dietary supplements.

Case 5

- The patient has a BMI of 25

- Recent warfarin doses and INR values

	Warfarin dose	INR
4 weeks ago	15 mg	1.8
2 weeks ago	20 mg	1.7
Today	25 mg	1.8

Appropriate management at this time includes which of the following

a) Evaluate for lupus anticoagulant
b) Start enoxaparin 1.5 mg/kg daily and increase warfarin to 30 mg daily
c) Switch to apixaban 5 mg twice daily
d) Take a careful dietary history and provide dietary counseling as appropriate

Appropriate management at this time includes which of the following

a) Evaluate for lupus anticoagulant
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Rationale

- Documenting a lupus anticoagulant will not change management at this time
- Bridging is not necessary, as the INR is not far off from the goal of 2-3
- Though potentially effective in this setting, newer anticoagulants are more expensive
- Dietary factors underlying “resistance” or difficulty maintaining the INR within the target range on warfarin are often overlooked

Key Data – Food Vitamin K Content

Food	Vitamin K Content (µg/serving)
Kale, cooked, ½ cup	531
Spinach, cooked, ½ cup	444
Collards, cooked, ½ cup	418
Broccoli, cooked, 1 cup	220
Romaine lettuce, raw, 1 cup	57
Peas, cooked, ½ cup	21

- 1 cup of cooked kale ≈ 1 mg vitamin K ≈ sufficient vitamin K to reverse an INR of 2

From U.S. Department of Agriculture, Agriculture Research Service. 2010. USDA National Nutrient Database for Standard Reference, Release 23. http://www.ars.usda.gov/nutrientdata

Take Away Message

- Some of the challenges to using warfarin for anticoagulation can be overcome by simple interventions
  - Taking a dietary history and providing appropriate counseling, as appropriate
  - Administering small doses of vitamin K (100 µg daily) to select patient with low or variable intake
  - Reducing frequency of blood draws to every other month in patients on long term anticoagulation with stable INR values

Summary

- Newer oral anticoagulants provide more choices for patients, though their use in certain settings, such as with mechanical prosthetic valves requires further investigation
- Vitamin K antagonists remain cost effective for anticoagulation, and convenience of their use can sometimes be optimized