Interactive Case Vignette: DOACs (Direct Oral Anti-Coagulants) vs. Warfarin for APLA (Anti-Phospholipid Antibody Syndrome)

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Duke Debates
Benign Hematologic Highlights
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Disclaimer #1

• I have no conflicts of interest relevant to this topic

• I will be talking about the off-label use of DOACs
Disclaimer #2

• There will be no “gotcha” questions

• Fellows who I see nodding off will get the @*$% pimped out of them...
Case #1

• Ms. B.A. is a 71 year-old Caucasian woman who has to undergo a breast biopsy

• Her PMH is significant for breast cancer in 2012 that was treated with lumpectomy and XRT

• On routine mammography, a new mass was detected
Case #1 (cont’d)

• Prior to her surgery, pre-operative labs are obtained

• These labs are remarkable for an aPTT of 51.0 (26.8-37.1)
She is sent to you for further evaluation

So now what?
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So what is a lupus anticoagulant panel?

And what the heck does it do?
Lupus Anticoagulant Panels

• At Duke:
  • PT, PT mix; aPTT, aPTT mix; DRVVT, DRVVT confirm; thrombin time

• Quest LA Panel:
  • PTT-LA with Reflex to Hexagonal Phase Confirmation; dRVVT Screen with Reflex to dRVVT Confirm and dRVVT 1:1 Mix; anti-cardiolipin antibodies, Beta-2-Glycoprotein I antibodies

• LabCorp:
  • aPTT; anticardiolipin antibodies; β₂-glycoprotein I antibodies; dRVVT; hexagonal phospholipid neutralization; INR; lupus anticoagulant interpretation; platelet neutralization; PT; thrombin time
Lupus Anticoagulant Panels (cont’d)

• Laboratory Criteria for LA Detection:
  • Prolongation of a phospholipid-dependent clotting assay
  • Evidence of inhibition demonstrated by mixing studies
  • Lack of specific inhibition to any one coagulation factor
  • Evidence of phospholipid dependence
Lupus Anticoagulant Panels (cont’d)

• Laboratory Criteria for LA Detection:
  • **Prolongation of a phospholipid-dependent clotting assay**

• Such as:
  • aPTT

  • PTT-LA or STACLOT

  • Dilute Russell’s Viper Venom Time (DRVVT)
So what is a Dilute Russell Viper Venom Time? i.e., who cares? Isn’t this why I don’t do benign Hematology???
The DRVVT

• A phospholipid dependent clotting assay

• The venom from Russel’s Viper directly activates FX → FXa

• The “dilute” is the amount of phospholipid, which makes it sensitive to the presence of antiphospholipid antibodies
Moving on...
Lupus Anticoagulant Panels (cont’d)

• Laboratory Criteria for LA Detection:
  • Prolongation of a phospholipid-dependent clotting assay
  • Evidence of inhibition demonstrated by mixing studies
  • Lack of specific inhibition to any one coagulation factor
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Lupus Anticoagulant Panels (cont’d)

• Laboratory Criteria for LA Detection:
  
  • Evidence of inhibition demonstrated by mixing studies
So what are mixing studies?

i.e., how much more complicated does this need to be???
Mixing Study

Patient Plasma  Normal Plasma

• If the study corrects, it implies a factor deficiency

• If the study does not correct, means an inhibitor is present

= 1:1 Mix
Lupus Anticoagulant Panels (cont’d)

• Laboratory Criteria for LA Detection:
  • Prolongation of a phospholipid-dependent clotting assay
  • Evidence of inhibition demonstrated by mixing studies
  • Lack of specific inhibition to any one coagulation factor
  • Evidence of phospholipid dependence
Lupus Anticoagulant Panels (cont’d)

• Laboratory Criteria for LA Detection:

  • Lack of specific inhibition to any one coagulation factor
    • This means that there is not a FVIII inhibitor
    • These people usually present with bleeding symptoms
Lupus Anticoagulant Panels (cont’d)

• Laboratory Criteria for LA Detection:
  • Prolongation of a phospholipid-dependent clotting assay
  • Evidence of inhibition demonstrated by mixing studies
  • Lack of specific inhibition to any one coagulation factor
  • Evidence of phospholipid dependence
• Laboratory Criteria for LA Detection:

  • Evidence of phospholipid dependence → Huh???
Evidence of Phospholipid Dependence

• Either hexagonal phase phospholipids...

• ...or lysed platelets (to expose the phospholipids inside)...

• ...are added to overcome the antiphospholipid antibody, shortening time to clot
Evidence of Phospholipid Dependence (cont’d)

• Can either be expressed as the absolute time that was shortened...

• Or expressed as a ratio, with <1.2 typically being the reference range
  - i.e., 60 s before, 30 s after the addition of phospholipids = 2.0
Back to the case...

• History is not consistent with recurrent miscarriages, thromboses, or hemorrhage

• Physical exam shows no signs of thrombosis, autoimmunity, or hemorrhage

• Laboratory data is consistent for a lupus anticoagulant
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Antiphospholipid Syndrome

• To make this diagnosis, 2 criteria **MUST** be met:
  • Clinical Criteria:
    • Vascular thrombosis
    • Pregnancy loss
  • Laboratory Criteria:
    • LA persistently detected, i.e., >12 weeks apart
    • Medium-high titer ACA or anti-β₂GP1 persistently detected
Back to the case... (cont’d)

• Given the absolute lack of clinical manifestations, patient does **NOT** meet the criteria for antiphospholipid syndrome

• Despite the correlation with thrombosis, there is no evidence that patients with asymptomatic antiphospholipid antibodies require treatment

• Recommended standard post-operative thromboprophylaxis only
Moving on...
Case #2

- N.O. is a 46 year-old woman with systemic lupus erythematosus, complicated by nephritis and leukocytoclastic vasculitis

- She develops progressive symptoms of right leg swelling and pain, which is then followed by progressive dyspnea on exertion

- She presents to the ER and is found to have a thrombosis in the right femoral to popliteal vein, along with a left main pulmonary artery PE
The ER consults you because the hospitalist can’t see and admit this patient for more than 3 hours...
Case #2 (cont’d)

• She denies any of the typical risk factors for VTE, such as recent major orthopedic procedures, estrogen use, immobility, long-haul travel, etc.

• Aside from notable tachypnea and a red, hot, swollen, and tender leg, there are no other pertinent physical examination findings

• Laboratory and imaging data performed by the ER are reviewed...
Case #2 (cont’d)

• Laboratory Data:
  • WBC 11.3 (3.7-9.8), hemoglobin 12.1, hematocrit 35.9, MCV 87, platelets 217
  • PT 11.1, aPTT 51.0 (26.8-27.1)
  • Chem-10 and LFTs are all within normal limits
  • Blood cultures are pending...
  • Chest x-ray showed no infiltrate
Her aPTT is prolonged

Geez, I wonder where this is going...
Additional testing

• DRVV Screen 2.85 (<1.2)

• PTT Mix 45.4 (29.4-35.4)

• FII 83%, FVIII 254%

• PNP 17.9s (<8), HPN 15 (<13)
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I’d accept either answer...
Case #2 (cont’d)

• She is admitted and started on an unfractionated heparin drip

• After two days she starts bridging to warfarin

• Her heparin is stopped, she is transitioned to enoxaparin

• She is discharged home the following day
Case #2 (cont’d)

• She is routinely followed in the Anticoagulation Clinic, with her PT/INR maintained within the therapeutic range.

• 3 months later, repeat testing shows the persistence of her lupus anticoagulant.

• Incidentally, she has also had persistently high-titer ACA and anti-β2GP1 IgM and IgG.
Case #2 (cont’d)

• She is stable on warfarin, without any breakthrough thrombo-embolic events or hemorrhagic complications

• However, the Anticoagulation Clinic gets absorbed into the hospital system, so now the patient has to pay a “facility fee”

• Way to go Duke...
Case #2 (cont’d)

• The co-pays are now getting to be ridiculous for a PT/INR that’s done on a POC device
  • Can’t wait to see my patient satisfaction scores now...

• She asks if she can be transitioned to one of these new medications she’s seen on TV
Do I start a DOAC or am I jerk if I keep her on warfarin???

Let’s not vote on this one...
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Use of DOACs in APS (cont’d)

• Currently, there are 4 studies listed on Clinicaltrials.gov

• Trial #1:
  • Rivaroxaban in Thrombotic Antiphospholipid Syndrome (TRAPS)
    ClinicalTrials.gov Identifier: NCT02157272
      • Started 12/2014
      • Reported to take place in approximately 40 sites in Italy
      • No results are available…
Use of DOACs in APS (cont’d)

• Trial #2:
  • Rivaroxaban for Patients With Antiphospholipid Syndrome ClinicalTrials.gov Identifier:NCT02926170
    • Started March 2013
  
  • 190 patients in France
  
  • No results are available...
Use of DOACs in APS (cont’d)

• Trial #3:
  • Apixaban for the Secondary Prevention of Thromboembolism Among Patients With the Antiphospholipid Syndrome (ASTRO-APS) ClinicalTrials.gov Identifier: NCT02295475
    • Started April 2015
  • 200 patients in the US
  • No results are available...
Use of DOACs in APS (cont’d)

• Trial #4:
  • Rivaroxaban for Antiphospholipid Antibody Syndrome (RAPS): ClinicalTrials.gov Identifier: NCT02116036
    • Started September 2014
    • 150 patients in Canada
    • Preliminary results are available (see below)...
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Use of DOACs in APS (cont’d)

• Success #1:
  • 26 French patients with APS were followed while on a DOAC:
    • 19 had been on warfarin and switched due to labile PT/INRs
    • Longest follow-up was 29 months
    • Noted only 1 patient with a recurrent thrombotic event, which was a case of cutaneous thrombotic microangiopathy
  
  • Authors concluded that the DOACS, “…might be considered as an alternative therapeutic option in APS, especially for patients with INR lability”

Autoimmun Rev 2015; 14: 680-685
Use of DOACs in APS (cont’d)

• Success #2:
  • 35 APS patients in the UK were switched to rivaroxaban due to labile PT/INRs
  • Follow-up was a median of 10 months (6-24)
  • There were no recurrent thrombotic events during this period
  • Authors concluded that the DOACS, “...might represent a promising alternative in APS patients with previous venous thromboembolism”

Use of DOACs in APS (cont’d)

• Success #3:
  • Preliminary results of RAPS:
    • 54 patients on rivaroxaban vs. 56 on warfarin
    • Reported the difference between the endogenous thrombin potential of patients on rivaroxaban vs. those on warfarin after 6 weeks of therapy
      • Because, this is obviously a useful, practical, and widely used parameter that everyone around the world follows...

Lancet Haematol. 2016 Sep;3(9):e426-36
Use of DOACs in APS (cont’d)

• Success #3:
  • No thrombotic events were noted within 6 months of use

  • Authors resoundingly conclude, “the overall thrombotic risk...is not increased with rivaroxaban compared with that related to warfarin.”

Lancet Haematol. 2016 Sep;3(9):e426-36
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Use of DOACs in APS (cont’d)

• Failure #1
  • Three patients who with APS, on warfarin, were switched to either dabigatran or rivaroxaban
    • #1 developed thrombotic endocarditis with embolic CVA after switching to dabigatran
    • #2 had ischemic strokes and a cerebral vein thrombosis after switching to rivaroxaban
    • #3 had splanchnic vein thrombosis after changing to rivaroxaban

Thromb Haemost. 2014 Nov;112(5):947-50
Use of DOACs in APS (cont’d)

• Failure #1 (cont’d):
  • Of note, all three patients had thrombotic events in the arterial beds...
  
  • The authors, “…recommend caution in using these new agents in patients with APS.”

Thromb Haemost. 2014 Nov;112(5):947-50
Use of DOACs in APS (cont’d)

• Failure #2:
  • A 46 year-old man developed extensive upper extremity superficial vein thrombosis while on rivaroxaban
  • 19 year-old woman developed superficial vein thrombosis of her foot while on rivaroxaban
  • 53 year-old woman developed new neurologic symptoms after switching to dabigatran
Use of DOACs in APS (cont’d)

• Failure #2 (cont’d):
  • Authors noted that patients were switched either due to failure of warfarin or labile PT/INRs
  • These patients were switched to parenteral agents, with no additional events noted
  • Authors state that now none of their APS patients are on DOACs
Use of DOACs in APS (cont’d)

• Failure #3:
  • Series of 8 patients with APS, all switched to rivaroxaban
    • 6 with venous thrombosis, 2 with arterial/venous thrombosis
  • 5 had additional arterial events (3 strokes, 1 MI, 1 arm artery clot)
  • 1 had a TIA
  • 2 had DVT while on rivaroxaban

Clin Rheumatol (2016) 35:801–805
Use of DOACs in APS (cont’d)

• Failure #3 (cont’d):
  • Noted that the presence of a prior arterial event and/or “triple-positivity” was an added risk factor
  • Correctly pointed out that the RAPS trial excluded APS patients with arterial events
  • Conclude that warfarin remains the mainstay of treatment in APS
Is there a “take-home” message?

i.e., did I really have to sit through this? Isn’t it 5 o’clock somewhere?
Where can we go from here?

• For now, there are no absolute contraindications to use the DOACs in APS

• These are limited to liver disease, renal disease (except for apixaban), and mechanical heart valves
Where can we go from here? (cont’d)

• Patients with APS can have breakthrough thrombotic events whilst on warfarin
  • The Canadian trial that examined an INR of 2.5 vs. 3.5 in APS documented an overall recurrence rate of 7%
    • 10.7% in the HIGH-intensity group
    • 3.4 % in the moderate intensity group
  
• Not unlike the use of LMWH in cancer associated VTE...

N Engl J Med 2003; 349:1133-1138
Where can we go from here? (cont’d)

• Patients who are compliant with medication adherence *could probably* do well with the DOACs, particularly if there are challenges with maintaining therapeutic PT/INRs

• Still, need to be prepared for a breakthrough thrombotic event
  
  • Again, not unlike cancer-associated VTE treated with a DOAC...
So what did I do with my patient?
Case #2 (cont’d)

• She was transitioned to rivaroxaban over 4 years ago and has not sustained any breakthrough thrombotic events

• She remains pleased to be on rivaroxaban and has **ZERO** interest switching back to warfarin
Any questions?

“Of all the writings, I love only that which is written in blood. Write with blood: and you will discover that blood is spirit.”

-Friedrich Nietzsche
Addendum Slides...

Basically, warfarin vs. DOACs?
Warfarin vs. DOACs

• Let me modify the this slightly...
  • What are the advantages?
  • What are the “glass is half-empty/glass is half-full” aspects?
  • What are the disadvantages?

• ...because EVERYTHING we do in medicine has these categories
  • Just different items in these categories
Question #1 (cont’d)

• ADVANTAGES OF WARFARIN:
  1. Low cost of warfarin
  2. Its use in tens of millions of patients worldwide over several decades
  3. Its proven use in a wide variety of conditions
  4. Availability and ease of monitoring
  5. Ability to slowly reverse with vitamin K or emergently reverse with plasma/concentrates
Question #1 (cont’d)

• **THE GLASS IS HALF-EMPTY/HALF-FULL:**
  • The long half-life of warfarin:
    • On one hand...
      • A bridge is needed until the anticoagulant takes effect
      • Need to wait several days for the anticoagulant effect to wear off
      • Then (may) need bridging therapy to resume warfarin
  • Yet, a long anticoagulant effect has the advantage of providing anticoagulation if a dose or two is missed
Question #1 (cont’d)

- **DISADVANTAGES OF WARFARIN:**
  1. Non-specific mechanism of action
  2. The many drug-drug interactions
  3. The many drug-diet interactions
  4. Need for regular monitoring
Question #1 (cont’d)

- **ADVANTAGES OF DIRECT ORAL ANTICOAGULANTS:**
  1. Absence of drug-diet interactions
  2. Markedly decreased number (but not absent) drug-drug interactions
  3. Specific mechanism of action makes monitoring essentially moot
  4. Rapid onset of action obviates need for bridging therapy.
Question #1 (cont’d)

- **GLASS IS HALF-EMPTY/HALF-FULL:**
  - The short half-life of these drugs:
    - On one hand...
      - Can simply stop the medication two (or three) days prior to a procedure
      - Can simply restart it when indicated
    - But...
      - A short half-life means that if a dose is missed, the anticoagulant effect is lost and the patient is essentially left "un-anticoagulated"
      - Can increase the risk for rebound thrombosis
Question #1 (cont’d)

• **DISADVANTAGES OF DIRECT ORAL ANTICOAGULANTS:**
  1. Cost (per pill)
  2. Monitoring of anticoagulation not widely available
  3. No reversibility for the Xa inhibitors
  4. When compared to warfarin, markedly less time and number of patients have been treated.
     a. *Clinical trials enroll participants who meet study criteria.*