Update: The New Direct Oral Anticoagulants (DOACS)

Boca Raton Regional Hospital Internal Medicine Conference
March 31, 2019

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Deep Venous Thrombosis and Pulmonary Thromboembolic Disease: Are we practicing evidence-based medicine? The 2016 American College of Chest Physicians (ACCP) Guidelines and Beyond

Which one of the following does not have FDA approval for the initial Day 1 treatment of an acute DVT or PE?

1. SQ Low Molecular Weight Heparin (Lovenox)
2. SQ Fondaparinux (Arixtra)
3. SQ Unfractionated Heparin
4. IV Unfractionated Heparin
5. All of the Above have FDA approval for the initial treatment of an acute DVT or PE.
Answer: All of the above.

- SQ LMWH, IV UFH, SQ weight-adjusted UFH, and SQ Fondaparinux are all FDA approved for the treatment of acute DVT and PE (ACCP Grade 1B recommendation)
- If switching to warfarin long-term, all options should be used for a minimum of 5 days and INR >= 2.0 for at least 2 consecutive days (1B).
ACCP recommendations/suggestions among the approved traditional agents used in the Day 1 treatment of acute DVT or PE

- **Recommend** LMWH over IV UFH (1B)* and over fondaparinux (2C) in hemodynamically stable patients. Use fondaparinux over IV UFH (2B). Studies comparing LMWH to IV UFH repeatedly show that LMWH is associated with a lower mortality, fewer recurrent VTE’s, less major bleeding, and a lower risk of Heparin-induced Thrombocytopenia (HIT).

- **Suggest (weak recommendation)** IV UFH (2B)* in patients with persistent hypotension (massive PE), increased risk of bleeding or anticipated need for invasive procedures, severe renal failure (CrCl<30), concerns about SQ absorption (such as obesity or anasarca), or in whom thrombolysis or thrombectomy is being considered.
Relative Risk of Major Bleeding

- Definition of Major Bleeding: Intracranial Hemorrhage, Retroperitoneal Hemorrhage, or bleeding that leads to death, hospitalization, or transfusion.
- LMWH lower risk than IV UFH (1.2% vs 2.0%).
- LMWH similar to fondaparinux and SQ UFH.
- Protamine reduces bleeding by neutralizing antithrombin activity in SQ and IV UFH. Only has partial effect with LMWH.
CASE PRESENTATION

• A previously healthy 38 y.o. man broke his leg during a soccer match two weeks ago, and has been in a cast ever since.

• He comes into your office as an urgent work in with chief c/o SOB, as well as chest pain with deep inspiration and when he coughs.

• On Physical Exam he looks mildly dyspneic with a RR of 24, HR 125 and regular, BP 120/70, pulse ox on RA 85%. He has a cast on his right leg.
CASE PRESENTATION

• You diagnose the patient with a very high likelihood of having a PE and ask your nurse to get an oxygen tank with NC oxygen for your patient, and ask your secretary to call for an ambulance to take him to your local ED. You also plan to personally call the ED physician and Hospitalist on call.

• In the meantime, the patient (a mechanical engineer, who has an I phone and knows how to use it) has a couple of questions for you:
The patient has read about the new DOACS and has seen adds on TV. He asks you which of the DOACS are options for the initial Day 1 treatment of his PE when he gets to the hospital today? You tell him that all of the following are FDA approved for the initial Day 1 treatment of PE’s except:

1. PO Rivaroxiban (Xarelto)
2. PO Apixiban (Eliquis)
3. PO Dabigatran (Pradaxa)
4. All are FDA approved in this setting
ANSWER

• #2: PO Dabigatran (Pradaxa)
SUMMARY SLIDE:
Drugs Approved for the initial Day 1 treatment of DVT and PE

- IV Unfractionated Heparin
- SQ LMWH (Lovenox)
- SQ Fondaparinux (Arixtra)
- SQ Weight Adjusted LDUH
- PO Rivaroxiban (Xarelto)
- PO Apixiban (Eliquis)
You also explain to your patient that after the initial course of treatment he will need an additional 3 months of treatment, and that all of the following have FDA approval in this setting except:

1. PO Rivaroxiban (Xarelto)
2. PO Apixiban (Eliquis)
3. PO Dabigatran (Pradaxa)
4. PO Edoxaban (Savaysa)
5. All are FDA approved in this setting
• #5: All are FDA approved in this setting
SUMMARY SLIDE:
Drugs approved for the first 3 plus months of VTE treatment

- PO Warfarin (Coumadin)
- SQ LMWH (Lovenox)
- PO Rivaroxaban (Xarelto)
- PO Apixaban (Eliquis)
- PO Edoxaban (Savaysa)
- PO Dabigatran (Pradaxa)
USE OF THE NEW DIRECT ORAL ANTICOAGULANTS (DOACS): FDA APPROVAL

- Rivaroxaban (Oral Factor Xa Inhibitor): Acute DVT/PE starting on day 1 (immediate treatment), out to 3 plus months (intermediate treatment), prevent Recurrence of DVT/PE after 6 months of treatment (long-term treatment), Post Hip and Knee Surgery prophylaxis, Non-valvular Afib, Decrease the risk of major CV events (death, MI, CVA) in patients with CAD or PAD at a dose of 2.5 mg BID along with ASA 100 mg daily.

- Apixaban (Oral Factor Xa inhibitor): Acute DVT/PE starting on day 1 (immediate treatment), out to 3 plus months (intermediate treatment), Prevent recurrence of DVT/PE after 6 months of treatment (long-term treatment), Post Hip and Knee Surgery prophylaxis, Non-valvular Afib.
USE OF THE NEW DIRECT ORAL ANTICOAGULANTS (DOACS): FDA APPROVAL

- Edoxaban (Oral Factor Xa inhibitor): Acute DVT/PE starting after 5-10 days of parenteral treatment and out to 3 plus months (intermediate treatment), Non-valvular Afib.

- Betrixaban (Oral Factor Xa Inhibitor) (FDA approval 6/23/17): Extended VTE Prophylaxis in acutely ill medical patients with restricted mobility and other risk factors.

- Dabigatran (Oral Direct Thrombin Inhibitor): Acute DVT/PE starting after 5-10 days of parenteral treatment and out to 3 plus months (intermediate treatment), Non-valvular Afib, Post Hip Surgery prophylaxis.
Efficacy Studies: DOACS vs Warfarin

- Almost all studies were performed as “Non-Inferiority” trials and consistently show that DOACS are Non-Inferior to Warfarin in efficacy in terms of prevention of recurrent VTE
POTENTIAL ADVANTAGES OF THE DOACS OVER WARFARIN

- Decrease in overall rate of major bleeding including fatal intracranial hemorrhage (In addition, apixaban and low dose edoxaban have lower GI bleeding risk than warfarin). (Rivaroxiban, dabigatran, and high dose edoxaban have a greater GI bleeding risk than warfarin).
- Many fewer dietary interactions
- Many fewer medication interactions
- No need for laboratory monitoring
- Non-valvular Afib over age 75: metanalysis of over 25,000 patients showed improved mortality with DOACS over warfarin (superiority trial).
POTENTIAL ADVANTAGES OF WARFARIN OVER THE DOACS

• Patients with **Valvular Atrial Fibrillation** (prosthetic heart valve or significant mitral stenosis): The **DOACS** have been associated with a greater risk of valvular thrombosis and are **not FDA approved** in this setting.

• Renal dysfunction: generally avoid **DOACS** with Low Creatinine Clearance (CrCl) (< 15 or 30 depending upon the DOAC).

• Warfarin has well-proven reasonably affordable **reversal agents** (Vitamin K, FFP, 4 Factor PCC).

• Warfarin is **inexpensive**.
POTENTIAL ADVANTAGES OF LMWH OVER WARFARIN AND THE DOACS

- During **Pregnancy** patients should get LMWH. Warfarin is teratogenic. The DOAC’S have not been adequately studied.

- Patients who have an **active malignancy** appear to have a more favorable outcome with LMWH than warfarin or any of the DOACs except for edoxaban.
LIMITED OR NO DATA FOR DOACS IN:

- Patients who are Pregnant
- Patients undergoing thrombolysis
- Patients undergoing thrombectomy
- Patients with Massive or Submassive PE
- Indefinite treatment: ACCP suggests that patients can stay on DOAC long-term if already on it and doing well, but no long term data available to support this (NG).
LIMITED OR NO DATA FOR DOACS

• Malignancy: limited data (Grade 2B) suggests that DOACS may be superior to warfarin, so reasonable to use DOACS in patients who are not candidates for, or do not want, LMWH.

• Malignancy Exception: Edoxaban study NEJM 2018;378(7)
Edoxaban for the Treatment of Cancer-Associated Venous Thrombembolism
(NEJM Feb 2018, 378;7, 615-624)

- 1046 patients with cancer and VTE randomly assigned to either SQ dalteparin LMWH) for at least 5 days followed by edoxaban (edoxaban group) or SQ dalteparin for a total of 6-12 months (dalteparin group).

- Primary outcome: composite of recurrent VTE or major bleeding over 12 months. These occurred in 12.8% of patients in the edoxaban group and 13.5% in the dalteparin group (P=0.006 for edoxaban non-inferiority and P=0.87 for superiority).

- Recurrent VTE: 7.9% edoxaban, 11.3% dalteparin (HR 0.71, NS P=0.09, mostly due to decrease in rate of recurrent DVT).

- Major Bleeding: 6.9% edoxaban and 4.0% in dalteparin (HR 1.77, P=0.04 mostly due to increase in UGI Bleeding).
Apixaban to Prevent Venous Thromboembolism in Patients with Cancer (The AVERTi trial) (NEJM February 2019)

- 563 ambulatory patients with active cancer who were initiating chemotherapy were randomized to apixaban (2.5 mg BID) vs placebo and followed for 180 days.
- VTE occurred in 12 of 288 patients in the apixaban group (4.2%) vs 28 of 275 patients in the placebo group (10.2 %) with p < 0.001. Difference was predominantly due to reduction in PEs. NNT to prevent one VTE=17. No change in survival.
- Major bleeding in 10 patients in the apixaban group (3.5 %) vs 5 patients in the placebo (1.8%) with p=0.046. NNT to harm=59. The major bleeding was predominantly due to GI bleeding, Gyn bleeding, and hematuria mostly in patients who entered the trial with GI or Gyn bleeding. Severe major bleeding episodes occurred in 20% of all major bleeds and the rate of these were similar in the apixaban and placebo groups.
Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer (The CASSINI Trial) (NEJM February 2019)

• 841 patients with active cancer without DVT initiating chemotherapy at the time of enrollment in the trial were randomized to rivaroxaban at a dose of 10 mg daily vs placebo for up to 180 days.

• Composite primary efficacy endpoint was proximal LE DVT, PE, symptomatic UE DVT, symptomatic distal LE DVT or death.

• Primary efficacy endpoint occurred in 25 of the 420 patients on rivaroxaban (6.0%) and 37 of 421 (8.8%) in the placebo group up to 180 days with p=0.10.
CAVEATS WITH THE DOACS

- BMI > 40: probably should check Factor XA levels
- Meds that **may increase DOAC blood levels**: clarithromycin/erythromycin, verapamil/diltiazem, ombitasvir/ritonavir, amiodarone/dronedarone, fluconazole/ketoconazole/itraconazole
- Meds that **may decrease DOAC blood levels**: Phenytoin/Carbamazepime, rifampin, St. John’s Wart
ACCP AT10 Guidelines for Long-term Anticoagulant Therapy (for the first 3 months or more)

• **VTE and No Cancer:** ACCP suggests the DOACS (Dabigatran, Rivaroxaban, Apixaban, or Edoxaban) over Warfarin (Grade 2B). Risk reduction for recurrent VTE appears to be similar and the overall risk of major bleeding (especially ICH) is less with DOAC’s. DOAC’s are also more convenient for patients.

• **VTE and Cancer:** ACCP suggests LMWH over Warfarin (Grade 2B) and over DOACS (Grade 2C). Risk reduction for recurrent VTE appears to be greater with LMWH than with Warfarin. Risk reduction for LMWH vs DOACS has not been directly assessed, but based on indirect comparisons LMWH may be more effective (exception for edoxaban published after the 2016 ACCP guidelines were published).
ACCP Guidelines for Long-Term Anticoagulant Therapy

• Comparison among the DOACS: Risk reduction has not been directly compared, but based upon indirect comparisons appears to be similar.
• DOACS overall risk of bleeding and especially ICH < Warfarin.
• Based on data from Afib, GI Bleeding may be higher with Dabigatran, Rivaroxaban, and high dose Edoxaban than with Warfarin, but lower with Apixiban and low dose Edoxaban.
ACCP Guidelines for Long-Term Anticoagulant Therapy

- **Apixaban**: Based on indirect comparisons, the risk of major bleeding may be lower with Apixaban compared to the other DOACS.
- **Major Bleed Fatality**: Risk that a major bleed will be fatal is no higher with the DOACS than with warfarin (even exclusive of specific reversal agents for the DOACS).
- **Coronary Artery Disease Events**: Appear to occur more often with Dabigatran than with Warfarin.
ACCP Guidelines for Long-Term Anticoagulant Therapy

• **Liver Disease**: DOACS are contraindicated if INR is elevated due to Liver Disease.
• With **Warfarin** the INR may not reflect the true anticoagulant effect.
5599 patients with Afib who did not want to use warfarin or were deemed unsuitable to do so by their treating physician

Compared Apixaban 5 mg BID (2.5 mg BID if 2 of following 3: age ≥ 80, ≤ 60 kg/m², Cr ≥ 1.5) vs aspirin (81 or 324 mg at physician discretion)

Primary Efficacy Outcome: CVA or systemic embolism. 1.6% apixaban vs 3.7% ASA (p < 0.01). Ischemic CVA 1.1% vs 3.0%, Hemorrhagic CVA (ICH) 6 vs 9 (NS).

Death: 3.5% vs 4.4% per year (NS p=0.07).
• **Primary Safety Outcome:** major bleeding 1.4% apixaban vs 1.2% ASA (NS, p=0.57)

• **Conclusion:** Apixaban significantly reduces risk for CVA or systemic embolism in patients with Atrial Fibrillation compared to aspirin, **without** an increase in risk of major bleeding, including ICH.

• **Caveat:** patients could have taken 81 mg or 324 mg per physician discretion. Do not know how apixiban would compare in safety to 81 mg dose exclusively.

• **Caveat:** doses not always the same as that used for VTE.
3365 patients who had already received 6-12 months of AC were randomized to up to 12 more months of treatment with either Rivaroxaban 20 mg (treatment dose), Rivaroxaban 10 mg (prophylactic dose) or to 100 mg of ASA.

Primary efficacy outcome of recurrent VTE occurred in 1.5% of patients in the higher dose rivaroxaban group, in 1.2% of patients in the lower rivaroxaban group, and in 4.4% of patients in the ASA group. Both doses of rivaroxaban were more effective than ASA (p< 0.001).

Primary safety outcome: Major bleeding was 0.5% in the higher dose rivaroxaban group, 0.4% in the lower rivaroxaban group, and in 0.3% in the ASA group (NS). Non major bleeding rates were 2.7%, 2.0%, and 1.8% respectively (NS).

Conclusion: risk of recurrent VTE was lower with rivaroxaban than with ASA without an increase of bleeding risk.
Risk of Major Bleeding in Patients with Renal Failure: DOACS vs Warfarin (CHEST 2016: 149:1516-1524)

- Metanalysis of 9 trials with over 94,000 patients, over 54,000 of whom had renal failure
- CrCl 50-80: DOACS significantly decrease risk of major bleeding compared to warfarin with OR 0.87 (0.81-0.93)
- CrCl 30-50: Non-significant with OR 0.83 (0.68-1.02)
- Risk of Hemorrhagic CVA significantly less with DOACS with CrCl both 50-80 and 30-50
- Apixaban significantly less major bleeding than the other DOACS with CrCl < 50
- Percent renal excretion: Dabigatran 80%, Edoxaban 50%, Rivaroxiban 35%, Apixiban 27%
REVERSAL OF BLEEDING WITH DOAC’S: Time to Five Half-Lives

- All anticoagulation effects are thought to have confidently ceased after five half-lives
  - Rivaroxaban: 5-9 hrs half-life, 1-2 days for five half-lives
  - Edoxaban: 6-11 hrs, 1.3-2 days
  - Apixiblan: 8-15 hrs, 1.5-3 days
  - Dabigatran: 12-17 hrs, 2.5-3.5 days
REVERSAL OF BLEEDING WITH DOACS

- Half lives of all can be extended by renal impairment, with dabigatran having by far the highest percentage of renal excretion. However, dabigatran is the only DOAC that can be dialyzed off.
- Severe liver dysfunction can extend half-lives in all but dabigatran (which is not metabolized in the liver)
- Bridging for surgery not recommended (by ACCP expert opinion) (NG)
Dabigatran Reversal: RE-VERSE AD STUDY (NEJM 2015;373:511)  
Idarucizumab (Praxbind) (SKIP)

- Given for life threatening bleeding or emergency surgery.
- RE-VERSE AD study: Interim report. 90 Patients. By Thrombin Time (TT) and Ecarin clotting time (ECT) measurements this drug was found to completely reverse AC effects within 10-30 minutes in 90% of patients
Dabigatran Reversal

- Five thrombotic S/E’s and 18 deaths, but no control group.
- Idarucizumab (Praxbind) FDA approved 10/16/15.
- If not available: For life threatening bleed can try an activated prothrombin complex concentrates (aPCC). Recent studies in patients needing warfarin reversal show no greater prothrombotic risk with aPCC than with FFP.
Dabigatran Reversal: RE-VERSE AD STUDY FULL COHORT ANALYSIS (NEJM August 2017;377:431-441) (SKIP)

• Multi-centered, prospective, open-label study of IV Idarucizumab (praxbind) given to reverse the anti-coagulant effect of Dabigatran in 301 patients with uncontrolled bleeding (Group A) and 202 patients who were about to undergo an urgent procedure (Group B).

• Primary Endpoint: Based on either the TT or ECT > 98% of patients had 100% reversal of AC effect of dabigatran 4 hours after giving IV Idarucizumab.

• Secondary Endpoint: In Group A 45.5% of patients had GI Bleeding and 32.6% ICH. Median time to cessation of bleeding was 2.5 hrs.

• Secondary Endpoint: Median time to initiation of procedure was 1.6 hrs. Periprocedural hemostasis was assessed as normal in 93.4% of patients, mildly abnormal in 5.1% and moderately abnormal in 1.5%.
Secondary Outcome: At 90 days thrombotic events occurred in 6.3% of patients in Group A and 7.4% of patients in Group B. These rates are similar to those reported after major surgical procedures or hospitalization for uncontrolled bleeding in prior studies.

Idarucizumab: half life approximately 45 minutes. All the thrombotic events that occurred within 72 hrs of its administration occurred in patients in whom AC had not been restarted. Subsequent thrombotic events occurred after its effects were gone and thus likely not medication-related.

Authors’ Conclusions: In emergency situations, idarucizumab rapidly, durably, and safely reversed the AC effect of dabigatran (but with caveats as discussed).
Factor Xa Reversal: ANNEXA TRIAL OF ANDEXENET

• NEJM 12/17/15;373:2413-2424
• RCT with adults age 50-75 given apixaban or rivaroxaban and then Andexanet bolus or Andexanet bolus followed by 2 hr infusion vs placebo. Followed anti-Xa activity.
• Apixaban: Anti-Xa activity decreased 94% vs 21% placebo (N=24 vs 9, p<0.001) within 2-5 minutes
• Rivaroxiban: Anti-Xa activity decreased 92% vs 18% (N=27 vs 14, p<0.001) within 2-5 minutes
• Small Study
• Drug was not studied for life-threatening bleeding or emergency surgery
• ANNEXA-4 Trial is underway in patients with major bleeds. This trial may take several years, but the drug has an FDA “breakthrough” designation, so it may be approved before the study is complete, just as idarucizumab was.
Drugs for which Andexanet may be potentially useful as a reversal agent:
--Apixaban, Edoxaban, Rivaroxaban
--UFH, LMWH
--?Fondaparinux
--Until it becomes available 4 Factor PCC is recommended for emergent bleeding on Factor Xa Inhibitors.
CISAPARANTAG TRIALS

• New universal reversal agent that may have benefit in reversing the AC effects of:
  -- Apixaban, Edoxaban, Rivaroxiban
  -- UFH, LMWH
  -- Fondaparinux
  -- Dabigatran
CISAPARANTAG TRIALS (SKIP)

• J Am Coll Cardiol. 2015 (Abstract): 40 healthy subjects given enoxaparin 1.5 mg/kgm. Whole blood clotting time increased 29%. This increase in whole blood clotting time was completely reversed within 20 min of patients receiving 100 mg of cisaparantag and within 5 min of patients receiving a 200 mg dose. This effect was sustained for 24 hrs.
CISAPARANTAG TRIALS (SKIP)

- NEJM 2014;371:2141-2142. 80 healthy subjects received 60 mg of Edoxaban, which increased whole blood clotting time by 37%.
- Cisaparantag brought the clotting time to within 10% of baseline levels within 10 minutes at doses of 100 mg and 300 mg and the effect persisted for 24 hrs.
- Subjects getting placebo took 12-15 hrs to get to within 10% of baseline levels.
COAGULATION TESTING

• Routine testing is not recommended
• For the Factor Xa inhibitors Prolonged PT/INR, PTT indicate residual anticoagulant effects, but normal testing does not rule out the possibility of residual anticoagulant effects
• Anti-factor Xa Activity: Absence of activity indicates cessation of all anticoagulant effect
• For Dabigatran a prolonged PTT indicates AC effect, but a normal PTT does not rule out an AC effect. A normal Thrombin clotting time (TT) indicates the cessation of all anticoagulant effect. Prolonged TT does not prove the presence of dabigatran activity.
HOW TO CHOOSE AMONG REGIMENS

• JAMA Sept 2014;312 (11):1122-1135
• Metanalysis of over 44,000 patients 45 trials comparing LMWH/Warfarin to seven other treatment options for risk of VTE recurrence and major bleeding.
From: Clinical and Safety Outcomes Associated With Treatment of Acute Venous Thromboembolism: A Systematic Review and Meta-analysis

RESULTS OF METANALYSIS

- Risk of recurrent VTE: of the seven alternatives, all were as good as LMWH/warfarin except for IV UFH/warfarin.
- Risk of Major Bleeding: of the seven alternatives, all had bleeding rates similar to LMWH/warfarin, except for Apixibran and Rivaroxiban, which had lower rates of bleeding.
Background: Parenteral prophylactic AC in acute medical illness vs placebo during hospital stay decreases VTE rates by > 50%. Prior studies looking at extended treatment after hospitalization using enoxaparin, apixaban, and rivaroxiban have been negative studies.

Double-blind, double-dummy RCT in 460 centers in 35 countries with over 3700 patients randomized to enoxaparin for 6-14 days plus placebo for 35-42 days vs over 3700 patients randomized to enoxaparin for 6-14 days plus betrixaban for 35-42 days.

Primary efficacy outcome was PE or DVT within the first 42 days.

Cohort 1: Primary outcome variable. Only patients with elevated D-Dimer. 6.9% enoxaparin/betrixaban patients had symptomatic VTE vs 8.5% enoxaparin/placebo patients (NS, p=0.054).

Cohort 2: Increased D-Dimer or age >=75. 5.6% vs 7.1% (p=0.03)
BETRIXABAN: APEX TRIAL

• Cohort 3: All patients. 5.3% enoxaparin/betrixaban vs 7.0% enoxaparin/placebo (p=0.006). Fewer PE or DVT in the first 42 days when betrixaban is added to enoxaparin.

• Major Bleeding in all patients (cohort 3): 0.7% enoxaparin/betrixaban vs 0.6% enoxaparin/placebo (NS, p=0.55). No increased major bleeding. 2 ICH enoxaparin/betrixaban vs 7 ICH enoxaparin/Placebo (NS).

• Non-major Bleeding: 3.1% enoxaparin/betrixaban vs 1.6% enoxaparin/placebo (p < 0.01). Increased non-major bleeding.

• New Ischemic CVA: 0.5% enoxaparin/betrixaban vs 0.9% enoxaparin/placebo (p=0.03). Fewer ischemic CVA’s.

• NEJM 2018 negative 35 day study with xarelto vs placebo.
SUMMARY SLIDES
Drugs Approved for the initial Day 1 treatment of DVT and PE

• IV Unfractionated Heparin
• SQ LMWH
• SQ Fondaparinux
• SQ Weight Adjusted LDUH
• PO Rivaroxiban
• PO Apixiban
How to Choose Among the Options for Day 1 Treatment (AT10)

- **SQ LMWH recommended** over IV UFH (1B):
  1) Superior efficacy in prevention of recurrent VTE (however, only adequately studied in non massive or submassive PE).
  2) Lower mortality
  3) Lower risk of bleeding
  4) Lower risk of HIT
How to Choose Among the Options for Day 1 Treatment (AT10)

• Suggest IV UFH When:

1) Unstable patients with massive or submassive PE (particularly if you are considering systemic or catheter-directed thrombolysis or surgical thrombectomy).

2) Patients at high risk of bleeding or who are likely to require invasive procedures.

3) CrCl under 30 (can also use apixaban down to CrCl of 15 and possibly CrCl of 0).

4) Morbidly obese patients or those with anasarca with concern for SQ absorption (can also use apixaban or rivaroxiban).
How to Choose Among the Options for Day 1 Treatment

- Desire to use one medication throughout the course of treatment: rivaroxaban, apixaban, or LMWH (malignancy).
- Substantial concern for HIT: rivaroxiban, apixaban or fondaparinux.
Drugs approved for the first 3 plus months of VTE treatment

- PO Warfarin
- SQ LMWH
- PO Rivaroxaban
- PO Apixaban
- PO Edoxaban
- PO Dabigatran
How to Choose Among the Options for Treatment out to 3 plus months

• If major concern is for the availability of a proven effective affordable reversal agent: Warfarin (praxbind and andexenet extremely expensive)
• If major concern is for risk of bleeding: Apixiban.
• If major concern is for renal dysfunction: Warfarin (CrCl as low as 0), Apixaban (Cr Cl as low as 15 or 0), or Edoxaban (CrCl as low as 15).
• Known malignancy: LMWH or Edoxaban (other DOACs possibly > warfarin)
• Indefinite treatment: likely all are ok, but only warfarin has been utilized long-term in clinical practice.
• Financial Constraints: Warfarin
SUMMARY SLIDE: How to Choose Among the DOACS

- **Potential Advantages of Apixiban (Eliquis):**
  - Appears to have the lowest rate of Major Bleeding, ICH, and GI Bleeding of all the DOAC's
  - Can be used down to CrCl of at least 15 (and possibly CrCl of 0)
  - Can Start on Day 1
  - Has reversal agent (though it is extremely expensive)

- **Potential Advantages of Rivaroxiban (Xarelto):**
  - Once Daily Dosing
  - Can Start on Day 1
  - Has reversal agent (though it is extremely expensive)
SUMMARY SLIDE: How to Choose Among the DOACS

- Potential Advantages of Edoxaban:
  - Low Dose has lower GI Bleeding risk than Rivaroxaban and Dabigatran
  - Can be used down to CrCl of 15
  - Once daily dosing
  - Non-inferiority to LMWH in patients with malignancy

- Potential Advantage/Disadvantage of Dabigatran:
  - Has reversal agent (though it is extremely expensive)
  - Caution in patients with CAD or at high risk of CAD
SUMMARY SLIDE: ACCP AT10 Guidelines for Long-term Anticoagulant Therapy (for the first 3 months or more)

• VTE and No Cancer: ACCP suggests the DOACS (Rivaroxaban, Apixaban, Edoxaban, or Dabigatran) over Warfarin (Grade 2B). Risk reduction for recurrent VTE appears to be similar, and the overall risk of major bleeding (especially ICH) is less with DOACS. DOACS are also more convenient for patients.

• VTE and Cancer: ACCP suggests LMWH over Warfarin (Grade 2B) and over DOACS (Grade 2C). Risk reduction for recurrent VTE appears to be greater with LMWH than with Warfarin. Risk reduction for LMWH vs DOACS has not been directly assessed, but based upon indirect comparisons LMWH may be more effective (exception is edoxaban).
ONE POSSIBLE APPROACH TO AC (Grade 3F):

**Outpatient Treatment Options:**
- Lovenox followed by Warfarin (if having a non-expensive reversal agent is of paramount importance)
- Eliquis all the way (if risk of bleeding or renal function is the primary concern) (Xarelto if once daily dosing is critical)

**Hospital Ward Admission Treatment Options:**
- Lovenox followed by Warfarin (available inexpensive reversal agent key)
- Lovenox followed by Eliquis (Bleeding or renal function key)
- Eliquis all the way (Bleeding or renal function key)

**ICU/PCU (Massive/Submassive PE) Treatment Options:**
- IV UFH (Official AT10 Grade 2B Suggestion)
- SQ LMWH (Multiple National Expert Personal Correspondence Grade “2D” Suggestion). (Personal Grade “3F” Suggestion).
THANK YOU

• Comments or Questions?
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ADDENDUM:

SQ and IV Factor Xa and Direct Thrombin Inhibitors
Fondaparinux (Arixtra)

- Synthetic pentasaccharide given SQ with inhibitory activity against Factor Xa.
- 100% bioavailable, peak level 1.7 hrs. Half-life 17 hrs.
- Can Monitor anti-factor Xa levels.
- FDA approved for: Acute DVT and PE on day 1, postop Hip surgery/knee surgery/abdominal surgery prophylaxis.
Doses: prophylaxis 2.5 mg SQ daily.
   treatment 5-10 mg SQ daily weight based.
Clearance: Renal.
Cautions: Under 50 kgm weight, CrCl < 30, plts < 100
Preop: stop 2-4 days in advance. Longer with renal dysfunction.
HIT: Case reports of effectiveness.
Bleed: no antidote. High dose recombinant Factor VIIa (Novo-7) partially normalizes the PTT.
Argatroban

- Intravenous Direct Thrombin Inhibitor.
- Immediate onset of action. Steady state AC effect achieved in 1-3 hours. Very short half-life, effect wears off rapidly after discontinuation.
- FDA approved for HIT, PCI, and for coronary thrombosis in patient with, or at risk for, HIT.
- Hepatic elimination, so avoid in the presence of liver failure.
Bivalirudin (Angiomax)

- Intravenous Direct Thrombin Inhibitor.
- Approved by the FDA for use in patients with ACS undergoing PCI, and for HIT.
- Predominantly non-organ elimination by proteolysis and thus can be used in liver or renal dysfunction.
- Half-life of only 25 minutes.