Review of Antithrombotic Therapy, Focus on Safety in Pregnancy

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Disclosure Statement

- The presenter has no conflicts of interest to disclose

Goals for this Talk

- Refresh our understanding of antithrombotic medications in general
- Review antithrombotic therapy directions in ACC and OB/GYN guidelines
- Practice navigating medication recommendations for safety sake in cases of patient pregnancy

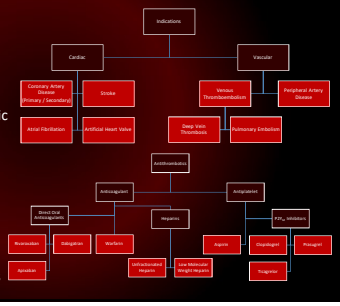
Mostly Will Escape Mention…

- Clotting cascade, other intense pharmacology
- Monitoring specifics
  - INR, PTT, ACT, TT, anti-Xa, etc
- Argatroban and fondaparinux
  - Injectable substitutes for heparins in heparin intolerance
  - Both are safe in pregnancy
- New antiplatelet agents cangrelor and vorapaxar
  - IV $P2y_{12}$ used in PCI, and novel agent for DAPT
  - Pregnancy safety unknown
- Reversal of bleeding and periprocedural holds
  - Lumbar puncture for anaesthesia
  - Antidotes and timing…

Terminology Review

Indications
- Thrombosis
- VTE
- DVT
- PE
- Afib
- CAD
- Primary vs Secondary
- STEMI
- NSTEMI
- PCI vs CABG

Medications
- Antithrombotic
- Anticoagulant
- Antiplatelet
- DAPT
- DOAC
- UFH
- LMWH
- PGI
- Thrombolytics



Review of Antithrombotics

Review of Antithrombotics

Drug Classes

- Antithrombotics
  - Anticoagulant
    - Warfarin
    - Heparins
    - Direct Oral Anticoagulants
      - Dabigatran
      - Rivaroxaban
      - Apixaban
      - Edoxaban
      - Betrixaban
  - Antiplatelet
    - Aspirin
    - $P2Y_{12}$ Inhibitors
      - Clopidogrel
      - Prasugrel
      - Ticagrelor
      - Cangrelor

Review of Antithrombotics

Antithrombotic Pharmacology

- Tissue factor enters the circulation and activates a network of communicating coagulation factors
  - Platelets aggregate and explode to form a mesh plug
  - Protein checkpoints interact to activate fibrin
- These two materials cause thrombus formation over 12-16 seconds normally
- Antithrombotics interfere per their mechanism of action

Review of Antithrombotics

- "Classic" antithrombotics
  - These agents predate modern drug development sciences; they were discovered rather than invented
  - They exhibit "untamed" pharmacokinetics and mechanisms of action
  - They are broadly as effective as modern counterparts, but these challenges must be overcome with selection and management

Review of Antithrombotics

- "Modern" antithrombotics
  - These agents have more precise physiologic targets and improved pharmacokinetics
  - Despite this, they are not extraordinarily more effective or safer and antithrombotic therapy remains risky
  - What they do provide is a variety of pharmacologic traits and therefore options for the specific patient

Review of Antithrombotics

Anticoagulant Pharmacology

- Theoretically all are equally potent and very effective prevention of thrombosis
- But anticoagulation is by it's nature unsafe and the therapeutic window is small
- The challenge is to select the agent with the best risk/benefit ratio and effective means of staying within that window for your case

Review of Antithrombotics

- Antithrombotics
  - Anticoagulant
    - Warfarin
- Very old drug with an extraordinarily complicated and slow mechanism of action
- Thoroughly tested and effective in all indications
- Narrow therapeutic window means bleeding risk is generally higher than modern alternatives
- INR monitoring and lifestyle adherence are mandatory

Review of Antithrombotics

- Antithrombotics
  - Anticoagulant
    - Heparins
- Injectable anticoagulants
- Very useful both when enteral route is unavailable or for their pharmacokinetics
- UFH has a narrow window and is usually closely monitored
- LMWHs were developed in the 80s and feature a wider window and dependable kinetics

Review of Antithrombotics

- Antithrombotics
  - Anticoagulant
    - DOACs
- Developed in the 2000s with the aim of replacing warfarin
- Adoption has been very slow
- A wide therapeutic window, and so broadly safer and more effective than warfarin
- No monitoring, but dose selection still challenging

Review of Antithrombotics

Antiplatelet Pharmacology

- Lower antithrombotic potency than anticoagulants
- Lack widely available means of monitoring
- Several use cases involve temporarily using two concurrently and/or with an anticoagulant, balancing potency with bleeding risk

Review of Antithrombotics

- Antithrombotics
  - Antiplatelet
    - Aspirin
- Very old drug
- Thoroughly tested and effective in all indications
- Benefit is likely maximized at small doses, and there is no evidence for true resistance
- Effort has been made recently to limit use to patients with thrombosis risk factors or history

Review of Antithrombotics

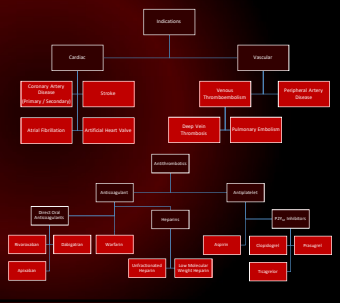
- Antithrombotics
  - Antiplatelet
    - $P2Y_{12}$ Inhibitors
- Began appearing in the 2000s
- Indications, effectiveness and safety vs aspirin still evolving
- Role is secondary prevention
- Some consideration for genetic CYP2C19 testing for clopidogrel, but outcomes are negative to mixed

Antithrombotic Guidelines and Pregnancy

Antithrombotic Guidelines and Pregnancy

Regardless of the antithrombotic or combination of classes used:

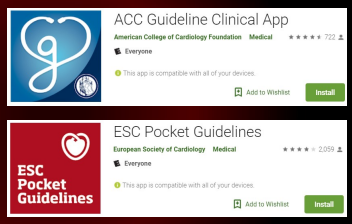
- Any increase in therapeutic prevention of thrombosis creates a relative increase in the risk of non-therapeutic prevention of thrombosis.
- In other words: fewer clots equals more bleeds.
- The goal is to select the agent that requires just the amount of potency needed, based on evidence and patient specifics.



Antithrombotic Guidelines and Pregnancy

Some pearls on guidelines:

- Cardiovascular diseases have the richest guideline support of all disease states
- In general start with ACC, then search the society for patient comorbidity
  - Diabetic with heart disease? ACC Primary Prevention, then ADA Standards of Care.
- ESC guidelines are virtually identical to ACC, often come out at the same time, are shorter and easier to read, and have better pictures!

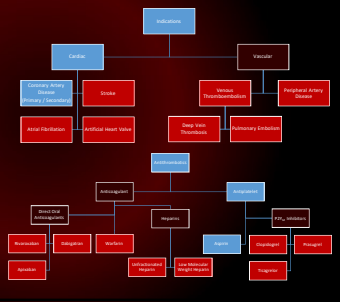


Start at: www.acc.org/guidelines

Antithrombotic Guidelines and Pregnancy

Coronary Artery Disease, Primary Prevention

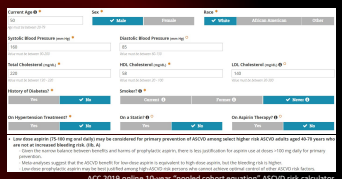
- Overview
  - Focus is on grading personal risk to determine if medication could reasonably prevent an event from occurring
  - If it is decided that an antithrombotic agent is needed, low dose aspirin is unanimously favored
  - The mechanism of action of primary prevention medication is slowing progression of injury caused by lack of physical fitness



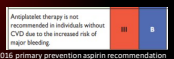
Antithrombotic Guidelines and Pregnancy

Coronary Artery Disease, Primary Prevention

- ACC & ESC
  - For age 40 - 75, 10-year ASCVD risk calculation >5% determines consideration for aspirin (and other therapies).
  - The NNT / NNH ratio favors aspirin in general, but the concept of risky medical prophylaxis limits use.
  - CHARISMA 2016 added clopidogrel to aspirin with no benefit found.



ACC 2019 online 10-year "pooled cohort equation" ASCVD risk calculator



ESC 2016 primary prevention aspirin recommendation

Current Guidelines:
ACC Primary Cardiovascular Disease Prevention Guidelines - 2019

Antithrombotic Guidelines and Pregnancy

Coronary Artery Disease, Primary Prevention

- USPSTF
  - Uses the ACC equation to determine 10 year risk
  - More narrow window of >10% risk and age 50 – 75 years for benefit
  - Considers colorectal cancer benefit of aspirin if patient will be taking for >5-10 years

Adults aged 50 to 59 years with a ≥10% 10-year CVD risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	B
Adults aged 60 to 69 years with a ≥10% 10-year CVD risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C
Adults younger than 50 years	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.	I
Adults aged 70 years or older	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.	I

USPSTF 2016 Primary Prevention Aspirin Recommendation

Current Guidelines:
USPSTF Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer - 2016

Antithrombotic Guidelines and Pregnancy

Coronary Artery Disease

- Aspirin Safety in Pregnancy
  - Some overlap of pregnancy and CAD populations, especially due to cardiovascular stresses on existent cardiovascular disease
  - Low-dose aspirin is used in high risk of preeclampsia and should be initiated between 12 weeks and 28 weeks of gestation
  - Aspirin crosses the placental barrier. High doses have established congenital anomaly risks, but low doses safe. Higher risk in third trimester. Benefit likely in high embolic risk cases.

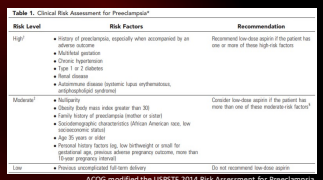


Table 1. Clinical Risk Assessment for Preeclampsia*

Risk Level	Risk Factors	Recommendation
High†	• History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes • Renal disease • Autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
Moderate‡	• Nulliparity • Obesity (body mass index greater than 30) • Family history of preeclampsia (mother or sister) • Sociodemographic characteristics (African American race, low socioeconomic status) • Age 35 years or older • Personal history factors (eg, low birthweight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)	Consider low-dose aspirin if the patient has more than one of these moderate-risk factors§
Low	• Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

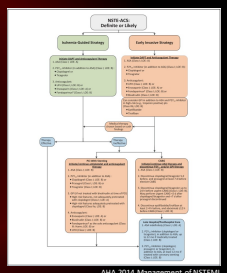
ACOG modified the USPSTF 2014 Risk Assessment for Preeclampsia

Current Guidelines:
ACOG Low-Dose Aspirin Use During Pregnancy - 2018

Antithrombotic Guidelines and Pregnancy

Acute Coronary Syndrome

- Overview
  - Nearly always the rupture of an atherosclerotic plaque, causing blockage of blood-flow in the heart
  - Loading dose of aspirin, $P2Y_{12}$ Inhibitor, and anticoagulant for all on presentation
  - Fibrinolytics (i.e. alteplase) and GPIs depending on the case
  - PCI with stent vs CABG vs medical only



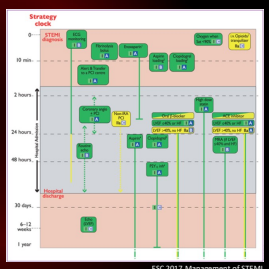
AHA 2014 Management of NSTEMI

Current Guidelines:
AHA/ACC Management of NSTEMI - 2014
ACC/AHA/SCAI Update on Primary Percutaneous Coronary for ST-Elevation Myocardial Infarction – 2015
ESC Management of STEMI - 2017

Antithrombotic Guidelines and Pregnancy

Acute Coronary Syndrome

- Fibrinolytic, DES, and PGI safety in pregnancy
  - Guidelines are non-existent, only case reports and opinions
  - Alteplase is most common and likely safe: not systemic; acts only on fibrin, short infusion, does not cross placenta
  - Sirolimus etc in DES prevents scar tissue formation. Safety in pregnancy is unstudied but numerous successful reports
  - All PGIs have successful use reports



ESC 2017 Management of STEMI

Good analysis of fibrinolytic cases and risks:
Gartman. Obstet Med. The use of thrombolytic therapy in pregnancy. 2013.

Antithrombotic Guidelines and Pregnancy

Coronary Artery Disease, Secondary Prevention:

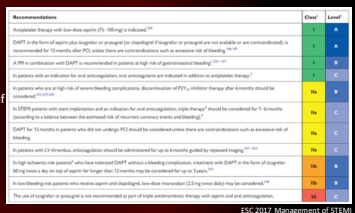
- Overview
  - Defined as the remainder of an individual's life following a first major cardiac event.
  - Distinct and immediately following the interventions immediately following the event.
  - Focus on dual anti-platelet therapy with precise durations to limit the period of high bleeding risk.

Current Guidelines:
ACC/AHA Focused Update on Duration of Dual Antiplatelet Therapy - 2016

Antithrombotic Guidelines and Pregnancy

Coronary Artery Disease, Secondary Prevention

- Duration of antiplatelet therapy balanced to bleeding risk, but basics:
  - lifetime aspirin for all
  - CHEST 9th Ed suggested 1 month of DAPT for PCI without stent.
  - DAPT with $P2Y_{12}$ ≤12 months for non-PCI
  - DAPT ≥12 months for PCI, but limited by bleeding risk
  - BMS used when DAPT must be stopped asap (≥1 month)
  - Triple therapy (DAPT + anticoagulant) greatly increases bleeding risk, use at minimum duration possible and only if exists an anticoagulation indication



Recommendations	Class*	Level*
Antiplatelet therapy with low-dose aspirin (75–100 mg) is indicated.[124]	I	A
DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contraindicated), is recommended for 12 months after PCI, unless there are contraindications such as excessive risk of bleeding.[96,125]	I	A
A PPI in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding.[126–128]	I	B
In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy.[5]	I	C
In patients who are at high risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.[122,129,142]	IIa	B
In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy[a] should be considered for 1–6 months (according to a balance between the estimated risk of recurrent coronary events and bleeding).[5]	IIa	C
DAPT for 12 months in patients who did not undergo PCI should be considered unless there are contraindications such as excessive risk of bleeding.	IIa	C
In patients with LV thrombus, anticoagulation should be administered for up to 6 months guided by repeated imaging.[143–145]	IIa	C
In high ischaemic risk patients[b] who have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg twice a day on top of aspirin for longer than 12 months may be considered for up to 3 years.[130]	IIb	B
In low bleeding-risk patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered.[138]	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation.	III	C

ESC 2017 Management of STEMI

Current Guidelines:
ACC/AHA Update on Duration of Dual Antiplatelet Therapy in Coronary Artery Disease - 2016
ESC Management of STEMI - 2017

Antithrombotic Guidelines and Pregnancy

Coronary Artery Disease, Secondary Prevention

- $P2y_{12}$ Inhibitor safety in pregnancy
  - Numerous case reports and editorializing regarding clopidogrel in particular, no human experimental data and no definitive statements
  - Would be used only if DAPT was viewed as essential to prevent recurrence following ACS

Pregnancy Implications

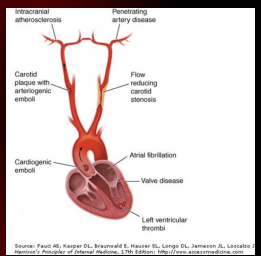
Information related to use during pregnancy is limited (Bauer 2012; De Santis 2011; Myers 2011). Based on available data, an increased risk of major birth defects, miscarriage, or adverse fetal outcomes has not been associated with maternal use of clopidogrel. According to the manufacturer, use should not be withheld if needed for emergent treatment of stroke or myocardial infarction during pregnancy. Discontinue use 5 to 7 days prior to labor, delivery, or neuraxial blockade if possible due to increased risk of maternal bleeding and hemorrhage.

Clopidogrel manuscript from UptoDate

Antithrombotic Guidelines and Pregnancy

Stroke

- Overview
  - Can be classified as cardioembolic or non-cardioembolic
    - Non-cardioembolic stroke prevention is vascular care. Blood pressure, lipids, fitness, aspirin in hx of ASCVD
    - Cardioembolic stroke prophylaxis is cardiac care and antithrombotics
    - Primary and secondary prevention are no different besides perhaps intensity

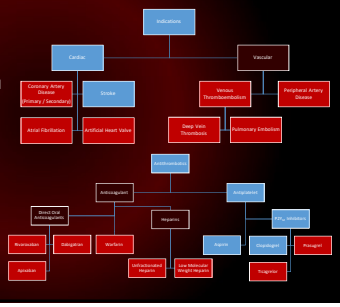


Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine, 17th Edition | http://www.accessmedicine.com

Antithrombotic Guidelines and Pregnancy

Stroke

- Evolving choice of antiplatelet agent after stroke
  - Aspirin 81mg vs Aspirin/dipyridamole vs clopidogrel
  - Prasugrel is contraindicated in patients with a history of stroke because of the increased risk of major and fatal bleeding
  - Ticagrelor has not been shown to be superior to clopidogrel
  - In TIA, adding clopidogrel for the first 21 days decreased recurrence (CHANCE 2013)
  - No role for anticoagulation in non-cardioembolic stroke

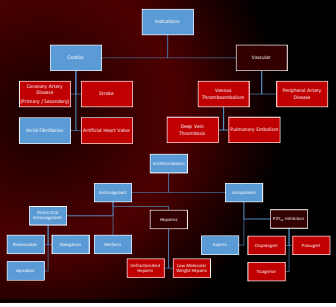


Current Guideline:
AHA Early Management of Patients With Acute Ischemic Stroke - 2018

Antithrombotic Guidelines and Pregnancy

Atrial fibrillation

- Overview
  - A heart disease which results in decreased cardiac output
  - One consequence of this is clot formation in the left atrial appendage and subsequent stroke
  - Can be treated surgically with LAA occlusion or ablation but outcomes are so far inferior to anticoagulation
  - The risk of relapse (often silent) is high and consequently antithrombotic therapy is lifelong depending on bleeding risk and adherence



Antithrombotic Guidelines and Pregnancy

Atrial fibrillation

- Choice of Antithrombotic
  - Aspirin now reserved for lowest stroke risk with high bleeding risk
  - DOACs now endorsed as superior to warfarin by all major guidelines
  - Choice of DOAC based on patient specifics and insurance coverage. Apixaban is a good default choice
  - Heparin use associated with warfarin therapy is common, but lacks evidence. One acceptable situation is emergent discovery of afib with planned cardioversion
  - AUGUSTUS 2019 finds apixaban + clopidogrel for 6 months superior to triple therapy in Afib following ACS

Current Guidelines:
AHA/ACC/HRS Atrial Fibrillation and focused update - 2019

Key Distinctions: 2014 Atrial Fibrillation (AF) Guideline – 2019 AF Focused Update

	2014 AF Guideline	2019 AF Focused Update
NOACs approved for stroke prevention	Dabigatran, Rivaroxaban, Apixaban (Class I)	Dabigatran, Rivaroxaban, Apixaban, and Edoxaban (Class I)
Oral anticoagulants recommended for eligible patients	Warfarin or NOACs (Class I)	NOACs recommended over Warfarin (Class I)
Oral anticoagulants recommended for patients with end-stage renal disease or on dialysis	Warfarin (Class IIa)	Warfarin or Apixaban (Class IIb)
FDA-approved reversal agent for Dabigatran	N/A	Idarucizumab (Class I)
FDA-approved reversal agent for Rivaroxaban and Apixaban	N/A	Andexanet Alfa (Class IIa)
Left atrial appendage occlusion	N/A	May be considered for patients with contraindications to long-term anticoagulation (Class IIb)
AF catheter ablation	N/A	May be reasonable in symptomatic patients with HF and a reduced EF to reduce mortality and HF hospitalizations. (Class IIb)
Anticoagulation for AF after percutaneous coronary intervention (PCI) with stent placement	N/A	If triple therapy (oral anticoagulant, aspirin, and $P2Y_{12}$ inhibitor) is prescribed, it is reasonable to choose Clopidogrel in preference to Prasugrel. (Class IIa) If triple therapy is prescribed, a transition to double therapy (oral anticoagulant and $P2Y_{12}$ inhibitor) at 4 - 6 weeks may be considered. (Class IIb) Double therapy ($P2Y_{12}$ inhibitor (Clopidogrel or Ticagrelor) and dose-adjusted vitamin K antagonist) is reasonable to reduce the risk of bleeding as compared with triple therapy. (Class IIa) Double therapy with $P2Y_{12}$ inhibitors (Clopidogrel) and low-dose Rivaroxaban (15 mg daily) is reasonable to reduce the risk of bleeding as compared with triple therapy. (Class IIa) Double therapy with $P2Y_{12}$ inhibitor (Clopidogrel) and Dabigatrine 150 mg twice daily is reasonable to reduce the risk of bleeding as compared with

Antithrombotic Guidelines and Pregnancy

Atrial fibrillation

- What's wrong with warfarin?
  - Dosing is a life-long project requiring skilled pharmacists and patient patients
  - Long half life and no specific rapid reversal agent
  - 99% protein bound and exquisitely sensitive to changes in metabolism and drug interactions
  - Narrow therapeutic index
  - Stressful for many patients and expensive in terms of time

Anticoagulant selection

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanical Valve or Valvular AF	✓	X	X	X	X
CrCl > 95 mL/min	✓	✓	✓	✓	X
CrCl 30-50 mL/min	✓	X	X	✓	✓
CrCl 15-30 mL/min	✓	X	X	✓	✓
CrCl < 15 mL/min	✓	X	X	X	X
Hepatic Impairment	✓	✓	X	X	X
Coronary Heart Disease	✓	?	✓	✓	✓
Dual Antiplatelet	✓	X	X	X	X
GI Bleeding	✓	X	X	✓	X
Poor Adherence/Dementia	✓	X	?	X	?
Labile INRs	X	✓	✓	✓	✓
Body Weight Extremes (< 60 kg or > 120 kg)	✓	?	?	?	?
Swallowing Difficulty	✓	X	✓	?	✓
Increased Fall Risk	✓	✓	✓	✓	✓
Age > 80 years	✓	X	?	✓	?

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Antithrombotic Guidelines and Pregnancy

Atrial fibrillation

- Direct oral anticoagulant safety in pregnancy
  - No approval for use, evidence for risk/benefit inadequate
  - They cross placenta, but no evidence for teratogenicity
  - Not recommended during breastfeeding either
  - Opinion:
    - Awaiting large retrospective, then prospective trials justified by hazards of warfarin
    - I expect DOACs will replace warfarin in cases where heparins are not feasible

Pregnancy Category B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Pregnancy Category C

There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be

Pregnancy Category C

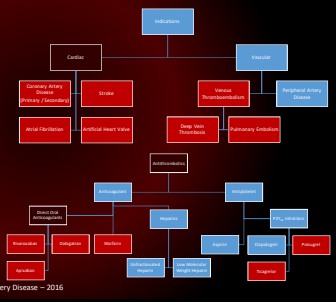
There are no adequate and well-controlled studies in pregnant women.

FDA Package insert section 8.1 for apixaban, rivaroxaban, and dabigatran

Antithrombotic Guidelines and Pregnancy

Peripheral Artery Disease

- Overview
  - Characterized by claudication and/or pain at rest, proceeding to ischemia induced wounds and surgical interventions
  - Aspirin or clopidogrel to reduce cardiovascular events and death
    - Ticagrelor not found superior to clopidogrel in EUCLID 2018
  - Heparin used in emergency interventions to save a limb, but value of anticoagulation post-surgically is uncertain (though constantly utilized)

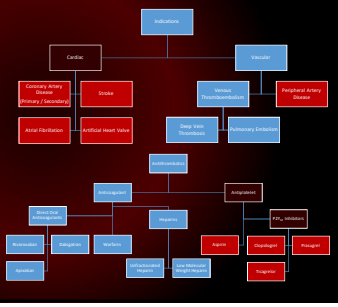


Current Guidelines:
AHA/ACC Management of Patients With Lower Extremity Peripheral Artery Disease – 2016

Antithrombotic Guidelines and Pregnancy

Venous Thromboembolism

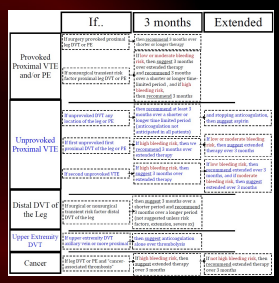
- Overview
  - Virchow's Triad conceptually helpful for determining cause and risks: venous stasis, endothelial injury, hypercoagulability
  - PE is a consequence of DVT, the duration may be different but the treatment intensity is not
  - There are numerous clotting disorders, but few change the treatment recommendations, evaluation generally not recommended



Antithrombotic Guidelines and Pregnancy

Venous Thromboembolism

- CHEST 2016
  - Therapeutic anticoagulation asap via any method, duration determined per provoked or unprovoked, bleeding risk, and location
  - Fibrinolytics used selectively in PE, and only in patients with low bleeding risk and without hypotension (low risk of MI)
- Superficial venous thrombosis
  - SVT can be managed with repeat duplex or prophylaxis via fondaparinux 2.5mg or enoxaparin 40mg sc daily x 45 days



Current Guidelines:
CHEST 10th Edition" Antithrombotic Therapy for VTE - 2016
Fondaparinux for the treatment of superficial-vein thrombosis in the legs (CALISTO). N Engl J Med 2010

Antithrombotic Guidelines and Pregnancy

Venous Thromboembolism, risks in pregnancy

- Incidentally, high VTE risk from oral contraceptives
- VTE incidence is approximately five fold in pregnancy
  - "Protective" hypercoagulability exists throughout pregnancy, increases in 3rd trimester, with highest risk around birth and resolving in 8-12 weeks postpartum
  - Consider also venous stasis due to physiologic and lifestyle changes
- Often considered provoked, treated for 3-6 months including 6 weeks post-partum

TABLE 3 The American College of Obstetricians and Gynecologists Guidelines for Prevention of Thromboembolism in Pregnancy*

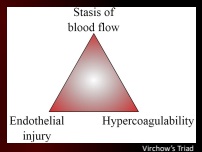
Clinical Scenario	Antepartum	Post-Partum
High risk†		
No history of VTE	Prophylactic dose	Therapeutic dose
History of VTE	Intermediate or therapeutic dose	Therapeutic dose
Low risk‡		
No history of VTE	Surveillance	Surveillance or prophylactic dose if additional risk factors§
History of VTE	Surveillance or prophylactic dose	Intermediate or therapeutic dose
History of single VTE		
Related to pregnancy, estrogen, or idiopathic	Prophylactic dose	Therapeutic dose
Unrelated to pregnancy or estrogen	Surveillance	Therapeutic dose
History of ≥2 VTE		
Taking anticoagulation	Therapeutic dose	Therapeutic dose
Not taking anticoagulation	Prophylactic or therapeutic dose	Therapeutic dose

Current Guidelines:
Thromboembolism in Pregnancy – ACOG 2018

Antithrombotic Guidelines and Pregnancy

Venous Thromboembolism

- Safety of warfarin in pregnancy
  - Crosses the placenta. A known teratogen and subject to a crucial risk/benefit discussion
  - Miscarriage in women receiving VKAs in the first trimester is much higher compared with receiving any form of heparin
    - 28.6% vs 9.2% during the first five months for warfarin in first trimester
    - 63.9% vs 19.2% for doses over 5mg
  - Heparins switched to warfarin after first trimester vs heparins from beginning: 22.7% vs 12.2%
  - Unknown if vit K reaches fetus; cesarean vs vaginal delivery at birth?



Virchow's Triad

Current Guidelines:
Thromboembolism in Pregnancy – ACOG 2018

Antithrombotic Guidelines and Pregnancy

Venous Thromboembolism

- Safety of heparins in pregnancy
  - The preferred mode of anticoagulation in pregnancy
  - They do not cross the placenta
  - UFH
    - IV preferred if temporal control of anticoagulation is required, i.e. impending birth
    - SC bid long-term if LMWH contraindicated, usually due to renal issues or cost
  - LMWH
    - Clearance changes begin during 2nd trimester
    - Hct, plts, SCr, and Anti-Xa peaks and troughs every 2 weeks
  - Often continued per patient tolerance, then cessation vs warfarin discussed

Table 2. Anticoagulation Regimen Definitions

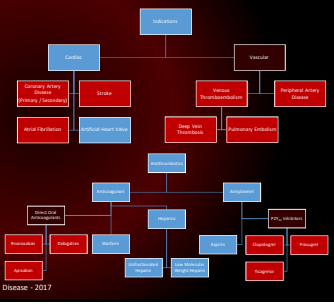
Anticoagulation Regimen	Anticoagulation Dosage
Prophylactic LMWH*	Enoxaparin, 40 mg SC once daily Dalteparin, 5,000 units SC once daily Tinzaparin, 4,500 units SC once daily Nadroparin, 2,850 units SC once daily
Intermediate-dose LMWH	Enoxaparin, 40 mg SC every 12 hours Dalteparin, 5,000 units SC every 12 hours
Adjusted-dose (therapeutic) LMWH†	Enoxaparin, 1 mg/kg every 12 hours Dalteparin, 200 units/kg once daily Tinzaparin, 175 units/kg once daily Dalteparin, 100 units/kg every 12 hours Target an anti-Xa level in the therapeutic range of 0.6–1.0 units/mL 4 hours after last injection for twice-daily regimen; slightly higher doses may be needed for a once-daily regimen.
Prophylactic UFH	UFH, 5,000–7,500 units SC every 12 hours in first trimester UFH, 7,500–10,000 units SC every 12 hours in the second trimester UFH, 10,000 units SC every 12 hours in the third trimester, unless the aPTT is elevated
Adjusted-dose (therapeutic) UFH‡	UFH, 30,000 units or more SC every 12 hours in doses adjusted to target aPTT in the therapeutic range (1.5–2.5 × control) 6 hours after injection
Postpartum anticoagulation	Prophylactic, intermediate, or adjusted dose LMWH for 6–8 weeks as indicated. Oral anticoagulants may be considered postpartum based upon planned duration of therapy, lactation, and patient preference.
Surveillance	Clinical vigilance and appropriate objective investigation of women with symptoms suspicious of deep vein thrombosis or pulmonary embolism. VTE risk assessment should be performed prepregnancy or early in pregnancy and repeated if complications develop, such as those necessitating hospitalization or prolonged immobility.

Current Guidelines:
Thromboembolism in Pregnancy – ACOG 2018

Antithrombotic Guidelines and Pregnancy

Artificial Heart Valves

- Overview
  - Highest risk over time of thromboembolism among classic anticoagulation cases
  - DOACS are contraindicated, study enthusiasm is low due signals of low safety during landmark trials
  - Bridging with heparins is encouraged while INR is subtherapeutic
  - Generally these patients are stuck on warfarin lifelong, regardless of their ability to manage the therapy



Current Guidelines:
ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease - 2017

Antithrombotic Guidelines and Pregnancy

Artificial Heart Valves

- Antithrombotic regimens
  - Mechanical valves are treated with warfarin and aspirin. INR goals:
    - Mitral position (MVR): 2.5-3.5
    - Aortic position with strong risk factors (afib, previous VTE, etc): 2.5-3.5
    - Aortic position w/o other risks: 2-3
    - On-X aortic valve with no other risk factors: 2-3 for the first three months then 1.5 to 2.
  - Bioprosthetic valves are treated with aspirin, and with warfarin added for 3-6 months in TAVR and other risky implantations and patients. DOACs are used off-label.

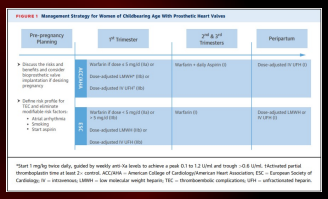
Source: balladhealth.org/transcatheter-aortic-valve-replacement-tavr

Current Guidelines:
ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease - 2017

Antithrombotic Guidelines and Pregnancy

Artificial Heart Valves

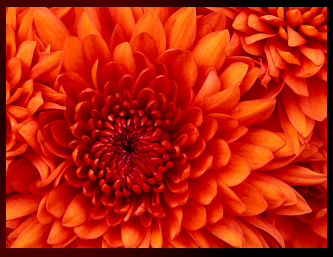
- Anticoagulation in pregnancy
  - Very high valve thrombosis risk in pregnancy and most common in first trimester, likely due to subtherapeutic initial anticoagulation and prothrombotic physical changes
  - Warfarin considered superior protection for the mother
  - Therefore higher consideration toward utilizing warfarin over heparins
  - ACC recommends warfarin in 1st trimester if doses are ≤5mg, and heparins otherwise



Current Guidance:
Anticoagulation During Pregnancy Evolving Strategies With a Focus on Mechanical Valves – JACC 2016

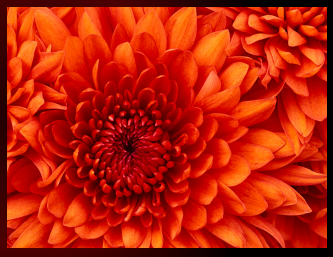
Case 1

- 28yo female with DVT, otherwise healthy.
  - What to ask her to assess cause of DVT?
  - What must be known to select safe antithrombotic therapy?
  - Based on above, what are the best options for therapy?
  - What duration should be selected, and what follow-up?



Case 2

- 38yo pregnant female with congenital valvular disease leading to implantation of mechanical valve in the mitral position. She would still like to try for pregnancy.
  - How should warfarin be managed?
  - How would you characterize the risk / benefit of adding aspirin?
  - Would a $P2Y_{12}$ inhibitor be better than aspirin?



Summary and Thanks

- Antithrombotic therapy has few drugs but deep considerations, and requires willingness to make trade-offs around the guidelines based on the specific patient.
- Spend time with the guidelines and practice recommending from them. The benefits to you and your patients is immense.
- Antithrombotic care in pregnancy is complicated by the lack of safe oral anticoagulants. Decisions around treatment require careful consideration.