Objectives

- List four options of oral anticoagulants
- Describe precautions to using each product
- Describe future options for oral anticoagulants

Coagulation Cascade

- Hemostasis
  - Process of blood clotting and dissolution of the clot following tissue repair
  - Both procoagulation and anticoagulation factors
- Coagulation Cascade
  - Complex set of reactions involving approximately 30 different proteins
  - If the cascade flows without interruption coagulation occurs
  - If the process is interrupted at any point anticoagulation occurs

Warfarin

- Inhibits the activity of vitamin K dependent coagulation factors II, VII, IX, X
- Interferes with the conversion of vitamin K to epoxide
- Inhibits carboxylation
- Proteins C&S are natural anticoagulants that are inhibited by warfarin

Laroia, S, Morales, S & Laroia, AT, 2015

Dabigatran

- Direct inhibitor of thrombin

- Works by binding to the active site of thrombin and the inactive form of fibrin-bound thrombin

Rivaroxaban, Apixaban, Endoxaban

- Work by blocking the interaction of factor Xa with factor Va
- Blocks the formation of the prothrombinase complex
- In blocking of this pathway the generation of fibrin is inhibited
Warfarin approved 1954

- Indications and Usage
  - Prophylaxis & treatment of DVT and its extension, PE
  - Prophylaxis & treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement
  - Reduction in the risk of death, recurrent MI, and thromboembolic events such as stroke or systemic embolization after MI
- Limitations - has no direct effect on established thrombus, does not reverse ischemic tissue damage


Warfarin- Contraindication

- Pregnancy, except in women with mechanical heart valves
- Hemorrhagic tendencies or blood dyscrasias
- Recent or contemplated surgery
- Bleeding tendencies associated with certain conditions
- Threatened abortion, eclampsia, preeclampsia
- Unsupervised pts with potential high levels of non-compliance

Warfarin- Contraindication

- Spinal puncture & other diagnostic or therapeutic procedures with potential for uncontrolled bleeding
- Hypersensitivity to warfarin
- Major regional or lumbar block anesthesia
- Malignant hypertension

Warfarin-Warnings & Precautions

- Tissue necrosis or gangrene of skin or other tissues can occur
- Systemic atheroembolic & cholesterol microemboli
- Heparin-induced thrombocytopenia
- Pregnant women with mechanical heart valves, may cause fetal harm (benefits may outweigh the risks)

Warfarin- Adverse Reactions

- Most common adverse reactions are fatal and nonfatal hemorrhage from any tissue or organ

Warfarin- Drug Interactions

- Concomitant use of drugs that increase bleeding risk, antibiotics, antifungals, herbal products, inhibitors and inducers of CYP2C9, 1A2, or 3A4
- Consult labeling of all concurrently used drugs for complete information about interactions with warfarin or increased risks of bleeding
Dabigatran approved 2010

- **Indications and Usage**
  - To reduce the risk of stroke & systemic embolism in pts with non-valvular a-fib (NVAF)
  - For the treatment of DVT & PE in pts who have been treated with a parenteral anticoagulant for 5-10 days
  - To reduce the risk of recurrence of DVT & PE in pts who have been previously treated
  - For the prophylaxis of DVT & PE in pts who have undergone hip replacement surgery

- **Contraindications**
  - Active pathological bleeding
  - History of serious hypersensitivity reaction to dabigatran
  - Mechanical prosthetic heart valve

- **Warnings & Precautions**
  - Bleeding: can cause serious and fatal bleeding
  - Bioprosthetic heart valves: dabigatran use not recommended

- **Adverse Reactions**
  - Most common adverse reactions (>15%) are gastritis-like symptoms and bleeding

- **Drug Interactions**
  - P-gp inducers riframpin: avoid coadministration with dabigatran
  - P-gp inhibitors in pts with CrCl 30-50 mL/min: reduce dose or avoid
  - P-gp inhibitors in pts with CrCl < 30 mL/min: not recommended

Rivaroxaban approved 2011

- **Indications and Usage**
  - To reduce the risk of stroke & systemic embolism in pts with NVAF
  - For the treatment of DVT, PE and for the reduction in the risk of recurrence of DVT and PE
  - For the prophylaxis of DVT, which may lead to PE in pts undergoing knee or hip replacement surgery

- **Adverse Reactions**
  - Most common adverse reactions (>15%) are gastritis-like symptoms and bleeding

- **Drug Interactions**
  - P-gp inducers riframpin: avoid coadministration with rivaroxaban
  - P-gp inhibitors in pts with CrCl 30-50 mL/min: reduce dose or avoid
  - P-gp inhibitors in pts with CrCl < 30 mL/min: not recommended
Rivaroxaban - Contraindications

- Active pathological bleeding
- Severe hypersensitivity reaction to rivaroxaban

Rivaroxaban - Warnings & Precautions

- Risk of bleeding: can cause serious & fatal bleeding. Promptly evaluate any S/S of blood loss
- Pregnancy-related hemorrhage: use with caution in pregnant women due to the potential for obstetric hemorrhage &/or emergent delivery. Promptly evaluate any S/S of blood loss
- Prosthetic heart valves - not recommended

Rivaroxaban - Adverse Reactions

- The most common adverse reaction (> 5%) was bleeding

Rivaroxaban - Drug Interactions

- Combined P-gp and strong CYP3A4 inhibitors: avoid concomitant use
- Anticoagulants: avoid concomitant use

Apixaban approved 2012

- Indications and Usage
  - To reduce the risk of stroke & systemic embolism in pts with NVAF
  - For the prophylaxis of DVT which may lead to PE in pts who have undergone hip or knee replacement surgery
  - For the treatment of DVT & PE, and for the reduction in the risk of recurrent DVT & PE following initial therapy

Apixaban - Contraindications

- Active pathological bleeding
- Severe hypersensitivity to apixaban

https://www.eliquis.com/eliquis/hcp
Apixaban - Warnings & Precautions

- Can cause serious, potentially fatal bleeding. Promptly evaluate S/S of blood loss.
- Prosthetic heart valves: use not recommended.

Apixaban - Adverse Reactions

- Most common adverse reactions (>1%) are related to bleeding.

Apixaban - Drug Interactions

- Strong dual inhibitors of CYP3A4 and P-gp increase blood levels of apixaban. Reduce dose or avoid coadministration.
- Simultaneous use of strong dual inducers of CYP3A4 and P-gp reduces blood levels of apixaban. Avoid concomitant use.

Edoxaban approved 2015

- Indications and Usage
  - To reduce the risk of stroke & systemic embolism in pts with NVAF.
  - For the treatment of DVT & PE following 5-10 days of initial therapy with a parenteral anticoagulant.
- Limitations: should not be used in pts with CrCl > 95 mL/min due to increased risk of ischemic stroke compared to warfarin at the highest dose studied.

Edoxaban - Contraindications

- Active pathological bleeding.

Edoxaban - Warnings & Precautions

- Mechanical heart valves or moderate to severe mitral stenosis: use is not recommended.
Edoxaban - Adverse Reactions

- Treatment of non-valvular a-fib: the most common adverse reactions (≥5%) are bleeding and anemia
- Treatment of DVT & PE: the most common adverse reactions (≥1%) are bleeding, rash, abnormal liver function tests and anemia

Edoxaban - Drug Interactions

- Anticoagulants: avoid concomitant use
- Rifampin: avoid concomitant use

General Recommendations All NOACs

- Avoid use with:
  - Drugs that increase the risk of bleeding
    - Anticoagulants (argatroban, bivalirudin, enoxaparin, fondaparinux, heparin, warfarin)
  - Drugs that decrease the anticoagulant effect
    - Carbamazepine, dexamethasone, phenobarbital, phenytoin, primidone, rifampin, St. John’s Wort
  - Drugs that increase the anticoagulant effect
    - Azole antifungals, grapefruit juice, HIV protease inhibitors, urokinase (systemic), vorapaxar

Mookadam et al, 2015

- Dose reduce or use extreme caution with:
  - Drugs that may increase the anticoagulant effect
    - Amiodarone, carvedilol, clarithromycin, cyclosporine (systemic), dipyridamole, dronedarone, erythromycin (systemic), nicardipine, propranolol, quinidine, quinine, ranolazine, reserpine, tacrolimus (systemic), tamoxifen, tyrosine kinase inhibitors, verapamil
  - Drugs that may decrease the anticoagulant effect
    - Estrogen, progestins

Mookadam et al, 2015

- Use caution with:
  - Drugs that may increase the risk of bleeding
    - Antiplatelets (abciximab, aspirin, clopidogrel, eptifibatide, prasugrel), omega 3 fatty acids, vitamin E, NSAIDS
  - Drugs that may decrease the anticoagulant effect of dabigatran only
    - Antacids (H2, antagonists, proton pump inhibitors), atorvastatin

Mookadam et al, 2015

- Estimated that INR levels are therapeutic only 50% of the time
- New agents have been sown to be equal or superior to warfarin in the management of VTE & a-fib related stroke
- Lower incidence of intracranial bleeding
- No need for routine monitoring
- Therapy can be started immediately without need for heparin or LMWH bridging*

Laroia, ST, Morales, S & Loroia, AT 2015
Bridging with the use of NOACs

- Bridging with LMWH or UFH should be minimized or avoided in NOAC patients
- Discern if procedure can be delayed past the need for anticoagulation or at least >3mo after VTE
- Low bleeding risk, no interruption of anticoagulant
- If need to interrupt consider½ life of drug, renal function of pt. & associated bleeding risk
- Restart once hemostasis achieved for 24hr post op in low bleed risk; 48-72hr in high bleed risk

Disadvantages of using Novel Oral Anticoagulants (NOACs)

- Lack of reversal agent (except dabigatran)
- Although there is a decrease in the risk of intracranial bleeding there is an increased risk of gastrointestinal bleeding (GI)

Who should remain on warfarin?

- Persons on warfarin w/consistent INRs
- Persons w/poor compliance due to length of half-life
- Persons w/renal failure with CrCl < 30mL/min or < 25mL/min for apixaban or > 95mL/min for edoxaban
- Mechanical heart valve replacement
- Persons > 75 years old
- History of GI bleeding, especially lower GI
- Drug cost

Who should switch to NOACs?

- Should be considered for all NVAF pts due to efficacy & safety profile
- Persons w/good compliance but variable INRs
- Drug interactions to warfarin
- Newly diagnosed a-fib pts
- Persons w/previous stroke, TIA or intracranial bleeding

Laroia, Morales & Loroia, 2015; Guimarães, Koatz & Lopes, 2015

Indication/dosing of NOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute VTE</td>
<td>150mg BID after &gt;5 days of parenteral anticoagulation</td>
<td>15mg BID x 3 weeks, then 20mg daily with food</td>
<td>10mg BID x 7 days, then 5mg BID</td>
<td>60mg daily after &gt;5 days of parenteral anticoagulation</td>
</tr>
<tr>
<td>Prevention of VTE recurrence</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>↓ to 2.5mg bid after at least 6 mo. of therapeutic anticoagulation</td>
<td>Not studied</td>
</tr>
</tbody>
</table>

Switching from warfarin to NAOCs

General guidelines:

- When INR is < 2.0 for dabigatran & apixaban
- When INR is < 3.0 for rivaroxaban
- When INR is < 2.5 for edoxaban

Laroia, Morales & Loroia, 2015; Guimarães, Koatz & Lopes, 2015
Other Factors- Age

- Prevalence of cerebral microhemorrhages, cerebral white matter lesions, brain infarcts, risk of cardiovascular events ↑
- RE-LY trial showed:
  - Risk of extracranial bleeding in persons > 75 y/o was higher w/dabigatran than warfarin
  - Risk of intracranial bleeding lower w/dabigatran compared to warfarin at any age
  - Rivaroxaban as safe as warfarin regardless of age
- Apixaban & edoxaban safer than warfarin across all age groups

Guimarães, Koatz & Lopes, 2015

Other Factors- Anemia, Thrombocytopenia

- Lower hgb levels associated with ↑ risk for new onset a-fib, should be monitored on any anticoagulant
- Platelet disorder = ↑ risk of bleeding
  - Count > 100,000/dL prescribe normally
  - 50,000 – 100,000/dL risk/benefit should be individualized
- Hemogram q 8-12 weeks when started, then q 6-12 months

Fernández et al, 2015

Other Factors- Renal Function

- Dabigatran contraindicated for CrCl < 30 mL/min
- Rivaroxaban, apixaban, edoxaban contraindicated for CrCl < 15 mL/min
- Warfarin can be used regardless of renal function
- Check renal function prior to starting NOACs then at least yearly or q 6 months if renal dysfunction exists

Fernández et al, 2015

Other Factors- Cognitive Status

- Risk for a-fib & cognitive disorders ↑ w/age
- Many pts w/cognitive impairment & a-fib are not anticoagulated
- Consider severity of dementia, quality of life, life expectancy, co-morbidities
- Simplification of treatment w/NOACs may be of benefit

Fernández et al, 2015

Other Factors- Risk of Falls

- Fall history, dependency in ADLs, > 75 y/o, living alone are fall predictors in persons w/a-fib
- Risk of intracranial bleeding w/falls but is a low risk & generally lower than risk of stroke
- Try to correct cause of falls (orthostasis, visual impairments)
- Consider NOACs for all persons with a risk of fall due to the ↓ intracranial bleeding risk

Fernández et al, 2015

Other Factors- Risk of Falls

- Persons with a CHADS² ≥ 3 benefit is greater than risk
- Persons with a CHADS² <2 + frequent falls, avoid anticoagulation
- Persons with a CHADS² ≥3 w/post-traumatic intracranial bleed on an anticoagulant = permanent withdrawal

Fernández et al, 2015
Other Factors- BP Control

- Uncontrolled HTN ↑ the risk of stroke, including hemorrhagic strokes
- Anticoagulation should be postponed in pts with a BP ≥ 180/100
- Target in elderly taking anticoagulants BP < 160/90 & preferably < 140/90

Fernández et al, 2015

Other Factors- Body Weight

- Warfarin- adjusted per INR w/no weight considerations
- Dabigatran- < 50kg no dose change but strict follow up
- Rivaroxaban- no adjustment per weight
- Apixaban- dose of 2.5mg BID in pts w/ at least 2 of the following: age ≥ 80, body wt < 60kg, serum creatinine ≥ 1.5 mg/dL
- Edoxaban- wt of < 60kg or est. CrCl 30-50 mL/min dose is 30mg

Fernández et al, 2015

Other Factors- Cancer Patients

- Increased risk of VTE & reoccurrence
- Current recommendations are for LMWH for at least 6 months over treatment w/ VKA or UFH
- NOACs are comparable to VKA in treatment of cancer-related VTE
- No studies comparing NOACs & LMWH

Thaler, Pabinger & Ay, 2015

Other Factors- Pregnant Women

- LMWH treatment of choice
- Warfarin contraindicated as they cross the placenta
- NOACs have not been studied so are contraindicated

Thaler, Pabinger & Ay, 2015

Reversal Agent- Warfarin

- Oral or parenteral vitamin K₁
- Prothrombin complex concentrate (PCC), fresh frozen plasma (FFP), activated Factor VII may be considered but carry a risk of hepatitis, other viral diseases
- PCC & Factor VII also associated w/↑ risk of thrombosis, should be used in exceptional or life-threatening bleeding


Reversal Agent- Dabigatran

- Hemodialysis can remove from system, however clinical experience is limited
- PCC or recombinant Factor VII may be considered but use not evaluated
- Protamine sulfate & vitamin K not expected to affect anticoagulant activity
- Consider platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used

https://www.pradaxa.com
Reversal Agent- Dabigatran
- Idarucizumab-humanized monoclonal antibody fragment that binds specifically to dabigatran
- For emergency surgery/urgent procedures
- Life-threatening or uncontrolled bleeding
- Under accelerated approval, contingent upon results of ongoing cohort case studies
- Risks:
  - If reappearance of bleeding or need of 2nd procedure can give a 2nd dose
  - Persons with hereditary fructose intolerance may have fatal reaction

www.prabind

Reversal Agent- Rivaroxaban
- No reversal agent
- Not expected to be dialyzed
- Protamine sulfate & vitamin K not expected affect anticoagulation
- Partial reversal of PTT prolongation has been seen after use of PCC
- Use of other procoagulant reversal agents ie: activated PCC, recombinant Factor VIIa has not been evaluated

https://www.xarelto-us.com

Reversal Agent- Apixaban
- Effect lasts approx. 24 hrs. after last dose
- Hemodialysis has no impact on clearance
- Protamine sulfate, vitamin K not expected to have affect
- No experience w/antifibrinolytic agents
- No scientific rationale for reversal or experience w/systemic hemostatics
- Use of PCC, activated PCC, recombinant Factor VIIa may be considered but has not been evaluated
- Activated oral charcoal reduces absorption

https://www.eliquis.com/eliquis/hcp

Reversal Agent- Edoxaban
- No established reversal agent
- Effect lasts approx. 24 hrs. after last dose
- Anticoagulant effect cannot be reliably monitored w/standardized laboratory testing
- Hemodialysis does not contribute to clearance
- Protamine sulfate, vitamin K, tranexamic acid are not expected to reverse anticoagulation

www.savaysa.com

Future Agents- Reversal
- Andexanet alfa
  - Modified decoy of Factor Xa produced in Chinese hamster ovary cells
  - Binds direct Factor Xa inhibitors as well as antithrombin activated by LMWH or fondaparinux
  - In rabbit models found to reverse the action of direct Factor Xa inhibitors in a dose dependent manner
  - Studies ongoing to evaluate safety & efficacy in reversing apixaban & rivaroxaban

Das & Liu, 2015

Future Agents- Reversal
- PER977- synthetic, water soluble molecule that binds to direct inhibitors of Factor Xa and IIa as well as to heparin-based anticoagulants
  - Reported to antagonize the effects of all anticoagulants except VKA & agratroban
  - Studies with rats overdosed with rivaroxaban, apixaban, edoxaban & dabigatran showed ↓ bleeding within 30 min of administration
  - Human trials are beginning

Das & Liu, 2015
Future Agents- Treatment

- **Darexaban** - Factor Xa inhibitor, excreted via feces & urine
- Minimal interactions w/digoxin & rifampicin
- Full scale clinical development was stopped in 2011
- Modest amount of promising literature but advantage over present meds remains to be seen

Blann, 2015

Future Agents- Treatment

- **Betrixaban** - Factor Xa inhibitor
  - <1% metabolism via cytochrome P450 compared to 57%, <32%, <25% for other FXa, & <2% dabigatran
  - Renal excretion is ~ 6-13% compared to >80%, 66%, 25%, 35% for other NOACs
  - Has a slightly longer half life
  - Likely to have fewer drug interactions & be safer for persons w/liver disease
  - Likely to be safe in persons w/severe renal failure
  - Has been successfully trialed

Blann, 2015

CHEST Guidelines, 2016

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

- “In patients with DVT of the leg or PE and cancer, as long-term (first 3 mos) anticoagulant therapy, we suggest LMWH over VKA therapy, dabigatran, rivaroxaban, apixaban or edoxaban.”

Kearon et al, 2016

References

  - [https://www.eliquis.com/eliquis/hcp](https://www.eliquis.com/eliquis/hcp)
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Thank you