Anticoagulation Task Force

Newest Recommendations

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THE DRUGS

THE PERFECT ANTICOAGULANT

- Oral administration
- Once daily dosing to increase adherence
- Rapid anticoagulant effect
- Predictable dose-response relationship
- No drug interactions
- No requirement for laboratory monitoring
- No increased bleeding
- Rapid-acting antidote

THE HISTORY

- The first oral anticoagulant
  - Karl Paul Link and Wilhelm Schoeffel
  - Dicoumarol discovery and introduction to therapy- 1940 to 1941
  - Warfarin introduced as rat poison in 1948
  - The 1951 suicide attempt leading to…
  - The launch of Coumadin™ in 1954 as an oral anticoagulant

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WARFARIN'S PLACE

- Valvular atrial fibrillation
  - Chronic oral anticoagulation with warfarin for patients at high risk for stroke (CHA_2DS_2-VASc of 2 or greater) and acceptably low risk for hemorrhagic complications
- Mechanical prosthetic cardiac valves
  - Warfarin and low-dose aspirin in patients who have received an aortic mechanical prosthetic valve (with or without risk factors) or any mitral mechanical prosthetic valve
    - Variable INR targets depending on valve position and/or risk factors

Source: 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

THE HISTORY

- The “second” oral anticoagulant
  - Ximelagatran (Exanta™), a direct thrombin inhibitor
  - Rapid oral absorption with peak at 2 to 3 hours after administration
  - Poor bioavailability and major dependence on renal excretion
  - Predictable pharmacokinetics
  - No CYP-based interactions
  - Fixed dosing and no monitoring
  - Approved in 12 countries and then…

THE HISTORY

- The “third” oral anticoagulant
  - Dabigatran (Pradaxa™), a direct thrombin inhibitor
  - Approved October 19, 2010 for prevention of stroke in patients with nonvalvular atrial fibrillation
  - February 2011- American College of Cardiology adds dabigatran to the guidelines for management of nonvalvular atrial fibrillation with a class I recommendation

THE HISTORY

- The “fourth” oral anticoagulant
  - Rivaroxaban (Xarelto™), a Factor Xa inhibitor
  - Discovered through high-output screening of approximately 200,000 compounds
  - Approved by the FDA on July 1, 2011 for deep vein thrombosis prophylaxis
  - Approved by the FDA on November 4th of the same year for stroke prevention in people with nonvalvular atrial fibrillation

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ORAL ANTICOAGULATION

- Vitamin K antagonists
  - Warfarin sodium (Coumadin™)
- Direct thrombin inhibitors
  - Dabigatran (Pradaxa™)
- Direct Factor Xa Inhibitors
  - Apixaban (Eliquis™)
  - Edoxaban (Savaysa™)
  - Rivaroxaban (Xarelto™)

DIRECT ANTICOAGULATION

- Right to the action site
  - NOAC (New oral anticoagulants)
  - NOAC (Novel oral anticoagulants)
  - DOAC (Direct acting oral anticoagulants)
  - TSOAC (Target Specific Oral Anticoagulants)
    - Apixaban (Eliquis™)
    - Dabigatran (Pradaxa™)
    - Edoxaban (Savaysa™)
    - Rivaroxaban (Xarelto™)

DOACs- HOW THEY DO THAT

- Direct thrombin inhibitors (e.g., dabigatran)
  - Drug molecule occupies site on thrombin preventing formation of fibrin
- Direct Factor Xa inhibitors (e.g., rivaroxaban)
  - Bind directly and reversibly to Factor Xa via the S1 and S4 pockets
  - Inhibits both free and clot-bound Factor Xa to interrupt the clotting cycle

DOAC COMPARISON

- Pharmacokinetics

DRUG	PEAK	HALF-LIFE	METABOLISM	CYP EFFECT
Apixaban	1 to 3 hours	9 to 14 hours	Hepatic	15%
Dabigatran	1.5 to 3 hours	12 to 17 hours	Hepatic	-
Edoxaban	1 to 2 hours	10 to 14 hours	Hepatic	3%
Rivaroxaban	2 to 4 hours	5 to 9 hours	Hepatic	30%

DOAC COMPARISON

- Application
  - Nonvalvular atrial fibrillation

DRUG	DOSING	DOSE ADJUSTMENTS
Apixaban	5 mg twice a day	2.5 mg twice a day (SCr 1.5 mg/dL or greater AND…)
Dabigatran	150 mg twice a day	75 mg twice a day (CrCl 15-30 ml/min)
Edoxaban	60 mg once daily	30 mg once a day (CrCl 15-30 ml/min)
Rivaroxaban	20 mg once daily	15 mg once a day (CrCl 15-0 ml/min)

DOAC PIPELINE

- Betrixaban
  - Oral, once daily direct Factor Xa inhibitor
  - Hepatic elimination that may address issues other DOACs have with renal impairment
  - Manufacturer granted Fast Track designation for agent for extended duration prevention of venous thromboembolism in acute medically ill patients
  - EXPLORE-Xa study
    - Evaluation of the safety and tolerability compared to warfarin in patients with atrial fibrillation

DOAC- WHAT'S GOOD?

- Kinetics and dynamics
  - Rapid onset and stop of activity
  - Fewer dietary and drug interactions compared to warfarin
  - Fixed dosing due to wide therapeutic window
  - No need for routine laboratory monitoring
- Patient factors
  - Patient satisfaction and better convenience
- Improved safety profile

DOAC- WHAT'S GOOD?

- Efficacy
  - Compared with warfarin, DOACs are associated with significantly fewer strokes and systemic embolism events
  - Lower event rate of stroke/systemic embolism by 19%, driven mainly by 51% fewer hemorrhagic strokes
  - DOACs and warfarin were *similarly* effective in preventing ischemic stroke and myocardial infarction

DOACs- WHAT'S *NOT* SO GOOD?

- Kinetics and dynamics
  - Requirement for dose adjustment for renal function
  - Short half lives means strict compliance, i.e., no missed doses
- Monitoring
  - One size fits all?
- Limited reversal agent availability
- Limited approved indications
  - No approved use with valves, acute coronary syndrome, etc.

DOACs- GOOD OR BAD?

- Cost effectiveness
  - Eliminate warfarin's repeated laboratory tests, frequent office or clinic visits, cost of adverse events, etc.

DRUG	DOSING	30 DAY ESTIMATED COST
Apixaban	5 mg twice a day	$400
Dabigatran	150 mg twice a day	$400
Edoxaban	60 mg once daily	$350
Rivaroxaban	20 mg once daily	$400
Warfarin	5 mg once daily	$20

*Pricing data is a representative average wholesale price from a single manufacturer of the brand and/or generic product, respectively

THE BLEEDING RISK

DOACs- THE BLEEDING RISKS

- A “class effect”?
  - Lower major bleeding rates than warfarin except for gastrointestinal bleeding risk where lower rates of bledding seen with warfarin

DRUG	STUDY	MAJOR BLEEDING RISK
Dabigatran	RE-LY	3.11%
Dabigatran	RELY-ABLE	3.74%
Rivaroxaban	ROCKET	3.6%
Apixaban	ARISTOTLE	2.13%
Edoxaban	ENGAGE-AF TIMI 48	2.75%

DOACs- THE BLEEDING RISKS

- A “class effect”?
  - Pooled analysis of all DOACs for all indications together demonstrate no significant difference between DOACs and comparators for risk of major bleeding
  - No significant difference found between DOACs
  - Bleeding risk varies with indications
- Reduced risk compared to warfarin
  - Reduced risk of fatal intracranial bleeding with DOACs
  - No difference in fatal major bleeding in all other sites

DOACs- THE BLEEDING RISK

- DOACs (compared to warfarin)
  - Lower rate of hemorrhagic stroke
  - Higher rate of gastrointestinal bleeding
- Increasing the risk

RISK FACTORS FOR MAJOR BLEEDING	
Older age	History of smoking
Mild anemia	Prior use of aspirin
Renal insufficiency	
History of prior gastrointestinal bleeding	
Baseline diastolic blood pressure of 90 mm Hg or greater	
History of chronic obstructive pulmonary disease	

THE RESCUE

DOACs- REVERSAL

- Up to late 2015
  - Warfarin reversal with phytonadione, Kcentra™ (prothrombin complex concentrate)
  - Dabigatran reversal with FEIBA (anti-inhibitor coagulant complex)- *off-label*
  - Rivaroxaban reversal with Kcentra™ (prothrombin complex concentrate)- *off*-label
- Late 2015
  - Dabigatran reversal with idarucizumab (Praxbind™)

IDARUCIZUMAB (Praxbind™)

- A humanized monoclonal antibody fragment that binds specifically to dabigatran and its acylglucuronide metabolites
  - The affinity of dabigatran/idarucizumab is approximately 350 times greater than that of dabigatran/thrombin
  - Neutralization of the anticoagulant effect of dabigatran within minutes (approximately 15 minutes in animal models)

IDARUCIZUMAB (Praxbind™)

- Kinetics
  - Drug levels drop in biphasic manner
  - Initial half-life of approximately 45 minutes
  - Plasma concentration after 4 hours of 4% of peak
  - Effect sustained for 12 hours
  - Renal elimination

IDARUCIZUMAB (Praxbind™)

- Side effects
  - Mild such as headache, delirium, hypokalemia, hypersensitivity
  - Post-marketing/case reports- intracardiac thrombus, NSTEMI, acute ischemic stroke, deep vein thrombosis, pulmonary edema, pulmonary embolism…

IDARUCIZUMAB (Praxbind™)

- Administration
  - Single total dose of 5 g intravenously over 15 minutes or less (fastest, practical time)
  - Redosing for re-elevated coagulation parameters such as elevated aPTT or clinically relevant bleeding
- Restricted use?
  - Reversal of dabigatran-induced coagulopathy in patients with intracranial hemorrhage
  - Adult patients

IDARUCIZUMAB (Praxbind™)

- Cost considerations
  - Current average wholesale cost for a single 5 g dose is approximately $2100 per event
  - Alternatives such as FEIBA or Kcentra™ costs in excess of $5,000 to $10,000 per event
- And again
  - Due to its mechanism of action, reversal of dabigatran *only*

MARKET AND PRACTICE FORCES

- Usage patterns of DOACs and need for reversal agents
  - Rivaroxaban (Xarelto™) is the market leader followed by
  - Dabigatran (Pradaxa™) followed by
  - Apixaban (Eliquis™) but…
- Need for required reversal?
- Reversal of the direct Factor Xa inhibitors still unavailable

ANDEXANET ALFA

- A recombinant protein
- A modified form of factor Xa that is catalytically inactive but retains high-affinity binding to factor Xa inhibitors
  - ANNEXA-A/ ANNEXA-R trials showed reversal effects for both apixaban and rivaroxaban
  - ANNEXA-E trial to determine efficacy with edoxaban reversal
  - Apixaban- anti-Factor Xa activity reduced by 94%
  - Rivaroxaban- anti-Factor Xa activity reduced by 92%

ANDEXANET ALFA

- Kinetics
  - Normalization of coagulation parameters within 2 minutes after completion of IV bolus
  - Effects lasts 2 hours with IV bolus
- Administration
  - Appears to be an IV bolus dosing followed by infusion over 45 to 60 minutes
- Regulatory
  - FDA has accepted agent for priority review with action expected by mid-August 2016

A UNIVERSAL REMEDY?

- Aripazine (also known as ciraparantag)
  - Small, synthetic, water-soluble, cationic molecule
  - Binds to unfractionated heparin, low molecular weight heparins, fondaparinux, dabigatran *and* factor Xa inhibitors through hydrogen bonding and charge–charge interactions
  - Issues
    - Studies only with edoxaban
    - Limited human studies but results “promising”

A UNIVERSAL REMEDY?

- Aripazine
  - Baseline hemostasis restored within 10 to 30 minutes after varying bolus doses of aripazine
  - Effect sustained for 24 hours
  - Additional Phase 2 studies are ongoing

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WHICH BRINGS US TO…

- For valvular atrial fibrillation, warfarin remains the mainstay therapy
- For atrial fibrillation *not* due to a valvular problem, DOACs represent a safe *alternative* to warfarin where there is a concern over intracranial bleeding

WHICH BRINGS US TO…

- Selection of a specific DOAC will depend on three factors none of which have to do with efficacy or safety
- Reversal of oral anticoagulants remains the same with a single exception for a third tier agent

WHICH BRINGS US TO…

- The fact that we still do not have the perfect oral anticoagulant
- But slowly but surely we may be getting as close as we ever will in the next 5 to 10 years

Ohio
CHAPTER