CARDIOLOGY MEDICATIONS

Objectives

• The attendee will understand
  • Indications, side effects and monitoring parameters for newer antiplatelet medications;
  • Indications, side effects and monitoring parameters for newer anticoagulant medications;
  • Recent changes in guidelines for the management of high blood pressure;
  • Recent changes in guidelines for the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk
Cardiology Medications

• Disclosures
  – The presenter has no financial interest or arrangement that would be considered a conflict of interest
Cardiology Medications

- **Introduction**
  - New medication choices for cardiology patients
    - Antiplatelets prasugrel, ticagrelor
    - Anticoagulants dabigatran, rivaroxaban, apixiban
  - New guidelines
    - Hypertension
    - Lipid control
Antiplatelet Medications

- Clopidogrel (Plavix)
- Prasugrel (Effient)
- Ticagrelor (Brilinta)
  - Bind and antagonize the platelet P2Y12 receptor, thus preventing ADP binding. With ADP unable to bind to the platelet, activation of glycoprotein IIb/IIIa (GIIb/IIIa) complex is impaired. Because the GIIb/IIIa complex is the major platelet receptor for fibrinogen, fibrinogen binding and ultimately platelet aggregation is also impaired.
Antiplatelet Medications

Mode of Action of Clopidogrel

CLOPIDOGREL

GPIIb/IIIa (Fibrinogen receptor)

Collagen thrombin

ADP

Activation

COX (cyclo-oxygenase)

ADP (adenosine diphosphate)

TXA₂ (thromboxane A₂)

Antiplatelet Medications

• Clopidogrel
  – Uses: acute myocardial infarction; arterial thromboembolism prophylaxis; myocardial infarction prophylaxis; percutaneous coronary intervention (PCI); stroke prophylaxis; thrombosis prophylaxis; transient ischemic attack; unstable angina
  – Dose
    • Load: 300 mg to 600 mg PO (when indicated)
    • Maintenance: 75 mg PO daily
    • No adjustment with renal impairment
Antiplatelet Medications

• Clopidogrel
  – Adverse effects
  • Bleeding
  – Monitoring
  • Bleeding; CBC; LFTs
Antiplatelet Medications

• **Prasugrel**
  - Uses: acute myocardial infarction; arterial thromboembolism prophylaxis; percutaneous coronary intervention (PCI); unstable angina
  - Dose
    • Load: 60 mg PO (when indicated)
    • Maintenance: 10 mg PO daily (5 mg daily in patients weighing less than 60 kg; not recommended in patients 75 y/o or greater)
    • No adjustment with renal impairment
Antiplatelet Medications

• Prasugrel
  – Adverse effects
    • Bleeding
  – Monitoring
    • Bleeding; CBC
Antiplatelet Medications

- **Ticagrelor**
  - Uses: Acute MI; arterial thromboembolism prophylaxis; PCI; unstable angina
  - Dose
    - Load: 180 mg PO
    - Maintenance: 90 mg PO BID
    - No adjustment with renal impairment
Antiplatelet Medications

• Ticagrelor
  – Adverse effects
    • Bleeding
    • Dyspnea (may continue treatment; 0.9% in studies stopped treatment)
  – Monitoring
    • Bleeding; CBC; LFTs
Antiplatelet Medications

• Wait time before elective surgery
  – Clopidogrel: 5 days
  – Prasugrel: 7 days
  – Ticagrelor: 5 days
Antiplatelet Medications

• What’s alike about these meds?
  – Same mechanism of action
  – Similar indications (ACS, PCI)
Antiplatelet Medications

• What’s different about these meds?
  – Onset of action
    • Clopidogrel: 2 hours
    • Prasugrel: 30 min
    • Ticagrelor: 30 min
  – Binding to receptor site
    • Clopidogrel and prasugrel: irreversible; duration of action 5 days
    • Ticagrelor: reversible; half life 9 hours
Antiplatelet Medications

• What’s different about these meds?
  – Poor metabolizers
    • Clopidogrel: some patients respond poorly
      – Test to assess this genetic predisposition not widely performed
  – Contraindications
    • Prasugrel contraindicated in patients with history of TIA or stroke
Antiplatelet Medications

• What’s different about these meds?
  – Efficacy
    • Prasugrel and ticagrelor have generally been shown to be more effective than clopidogrel
  – Bleeding risk
    • Clopidogrel generally has the lowest bleeding risk
  – Cost (AWP per month)
    • Clopidogrel: $20
    • Prasugrel: $324
    • Ticagrelor: $302
Anticoagulant Medications
The Clotting Cascade

Contact activation (intrinsic) pathway
- Damaged surface
  - XII → XIIa
  - XI → XIa
  - IX → IXa
  - VIII
  - X → Xa
  - Prothrombin (II)
  - Active Protein C
  - Protein S
  - Protein C + thrombomodulin

Tissue factor (extrinsic) pathway
- Trauma
  - VIIa
  - VII
  - Tissue factor
  - TFPI
  - Antithrombin

Common pathway
- Thrombin (IIa)
- Fibrinogen (I)
- Fibrin (Ia)
- Cross-linked fibrin clot
- XIIIa → XIII
The Clotting Cascade

- Sites of action - antithrombotics
  - Unfractionated heparin: IIa, IXa, Xa, Xla, XIIa
  - LMWH (enoxaparin/Lovenox): IIa, Xa
  - Fondaparinux (Arixtra), **rivaroxaban** (Xarelto), **apixaban** (Eliquis): Xa
  - Warfarin (Coumadin): IIa, VIIa, IXa, Xa
  - Argatroban, lepirudin (Refludan), bivalirudin (Angiomax): IIa
  - **Dabigatran** (Pradaxa): IIa (thrombin)
The Clotting Cascade

Unfractionated heparin
The Clotting Cascade

Warfarin
The Clotting Cascade

Enoxaparin
The Clotting Cascade

Dabigatran, Bivalirudin, Lepirudin, Argatroban
Rivaroxaban, apixaban, fondaparinux
Anticoagulant Medications

- But first . . . Warfarin (Coumadin)
  - Used since 1954
  - Derivative of coumarin (found in some plants)
- Warfarin: Wisconsin Alumni Research Foundation plus –arin (denoting a coumarin)
Anticoagulant Medications

• Warfarin
  – Synthesis of factors II, VII, IX and X require vitamin K
  – Warfarin competitively inhibits an enzyme that activates vitamin K
• Depletes vitamin K reserves
• Reduces synthesis of clotting factors
  – Some foods are rich in vitamin K
Anticoagulant Medications

- Warfarin interactions
  - Drugs
    - Metabolism: hepatic via CYP pathways
      - Many drugs enhance activity
      - Many drugs diminish activity
  - Vitamin K rich foods
    - Diminish activity
Anticoagulant Medications

• Warfarin monitoring
  – Warfarin monitoring
  – INR (International Normalized Ratio)
• Cost: $30-$50 per month
• Advantage of warfarin: antidote
  – Vitamin K (phytonadione)
  – Prothrombin complex concentrate (Kcentra)
• Mixed bag: lab measurements
  – Inconvenient, expense, but verifies compliance
Anticoagulant Medications

• Dabigatran (Pradaxa)
  – Direct thrombin (IIa) inhibition
    • Inhibits both free and fibrin-bound thrombin
    • Prevents thrombin-mediated effects, including
      – Cleavage of fibrinogen to fibrin
      – Activation of factors V, VIII, XI and XIII
      – Thrombin-induced platelet aggregation
The Clotting Cascade

Contact activation (intrinsic) pathway

- Damaged surface
  - XII → XIIa
  - XI → XIa
  - IX → IXa VIIIa
  - X → Prothrombin (II)
  - Xa → Thrombin (IIa)
  - V → Active Protein C
  - Protein S
  - Protein C + thrombomodulin

Tissue factor (extrinsic) pathway

- Trauma
  - VIIa → VII
  - Tissue factor
  - TFPI
  - Antithrombin
  - Thrombin (IIa)
  - Fibrinogen (I) → Fibrin (Ia)
  - Cross-linked fibrin clot

Common pathway

- XIIIa → XIII
Anticoagulant Medications

- Dabigatran (Pradaxa)
  - Indications: nonvalvular atrial fibrillation
  - Dose
    - 150 mg PO BID
    - 75 mg PO BID in patients with CrCl 15-30 ml/min
  - Antidote: none
Anticoagulant Medications

• Dabigatran (Pradaxa)
  – Adverse Effects
    • Bleeding
    • GI upset (up to 11%)
  – Monitoring
    • Renal function
    • aPTT or ECT may be used to assess anticoagulant activity
Anticoagulant Medications

• Dabigatran pharmacokinetics
  – Onset: 2 hours
  – Duration: 12-17 hours
  – Metabolism
    • Prodrug dabigatran etexilate hydrolyzed to form active drug
    • Metabolized by hepatic conjugation (no CYP involvement)
    • Renal excretion up to 80%
Anticoagulant Medications

• Dabigatran interactions
  – Rifampin may decrease dabigatran activity: should be avoided
  – Potential interactions with amiodarone, dronedarone, ketoconazole, quinidine, verapamil
• May increase dabigatran activity
Anticoagulant Medications

• Dabigatran monitoring
  – Routine labs not required
• Cost: about $350 per month AWP
Anticoagulant Medications

- Rivaroxaban (Xarelto)
  - Direct Factor Xa inhibitor
  - Prevents formation of thrombin (IIa) from prothrombin (II)
Anticoagulant Medications

• Rivaroxaban
  – Indications: nonvalvular atrial fibrillation; DVT prophylaxis and treatment (including post hip or knee replacement); PE prophylaxis and treatment
• A Fib: 20 mg daily (15 mg if CrCl 15-50 ml/min)
• Treatment of DVT/PE: 15 mg BID x 21 days, then 20 mg daily
• DVT/PE prophylaxis: 20 mg daily
• Post hip/knee surgery: 10 mg daily
Anticoagulant Medications

• Rivaroxaban
  – Adverse Effects
  • Bleeding
  – Antidote: none
Anticoagulant Medications

• Rivaroxaban pharmacokinetics
  – Time to peak: 2-4 hours
  – Half-life: 5-9 hours
  – Metabolism
    • Hepatic via CYP3A4/5 and CYP2J2
    • Renal excretion 66% (36 % unchanged)
Anticoagulant Medications

• Rivaroxaban interactions
  – CYP3A4 inhibitors may enhance activity
    • E.g., ketoconazole, clarithromycin, fluconazole
  – CYP3A4 inducers may diminish activity
    • E.g., carbamazepine
Anticoagulant Medications

• Rivaroxaban monitoring
  – Routine labs not required
• Cost: about $340 per month AWP for all doses
Anticoagulant Medications

- Apixaban (Eliquis)
  - Factor Xa inhibition, which decreases the generation of thrombin
Anticoagulant Medications

• Apixaban
  – Indications: stroke and systemic embolism prophylaxis in patients with nonvalvular atrial fibrillation; DVT/PE prophylaxis in patients undergoing hip/knee surgery
  – Dose
    • A Fib: 5 mg BID (2.5 mg BID if age 80 or more, weight 60 kg or less, sCr 1.5 mg/dl or more)
    • Hip/knee replacement: 2.5 mg BID
  – Antidote: none
Anticoagulant Medications

• Apixaban
  – Adverse Effects
  • Bleeding
  – Monitoring
  • Routine labs not required
Anticoagulant Medications

- Apixaban pharmacokinetics
  - Time to peak: 3-4 hours
  - Half-life: 12 hours
- Metabolism
  - Hepatic via CYP3A4 primarily
  - Renal excretion 27%
Anticoagulant Medications

• Apixaban interactions
  – CYP3A4 inhibitors may enhance activity
    • E.g., ketoconazole, clarithromycin (reduce dose to 2.5 mg BID)
  – CYP3A4 inducers may diminish activity
    • E.g., carbamazepine
Anticoagulant Medications

- Apixaban monitoring
  - Routine labs not required
- Cost: about $350 per month AWP
Anticoagulant Medications

• Wait time before elective surgery
  – Dabigatran
    • 1-2 days for CrCl above 50 ml/min
    • 3-5 days for CrCl below 50 ml/min
  – Rivaroxaban: 24 hours
  – Apixaban: 48 hours
Anticoagulant Medications

• What’s alike about these meds?
  – Similar indications (A Fib)
  – Generally as effective or more effective than warfarin in preventing thrombosis
  – Generally as safe or safer than warfarin
  – Far fewer interactions than warfarin
  – *No routine lab monitoring*
  – *No antidote*
  – Expensive
Anticoagulant Medications

• What’s different about these meds?
  – Difficult to say – have not been directly compared
Hypertension Guidelines

• 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults; Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)
Hypertension Guidelines

• “Reported from the panel members appointed to JNC 8”
  – Historically JNC issued guidelines sanctioned by NHLBI
  – Last update – JNC 7 in 2003
  – NHLBI withdrew from guideline development and delegated it
  – JNC 8 panel decided to pursue publication independently
• Not an official NHLBI-sanctioned report
Hypertension Guidelines

• JNC 8 are not the only guidelines
  – American Diabetes Association
  – American Society of Hypertension and the International Society of Hypertension
  – European Society of Hypertension and the European Society of Cardiology
  – Canadian Hypertension Education Program
  – Kidney Disease: Improving Global Outcomes Initiative
  – National Institute for Health and Clinical Excellence
  – International Society on Hypertension in Blacks
  – AHA, ACC and US Centers for disease Control and Prevention
Hypertension Guidelines

• Three guideline questions
  – In adults with hypertension, does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?
  – In adults with hypertension, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?
  – In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?
Hypertension Guidelines

• Different levels of recommendation
  – A = Strong Recommendation (there is a high certainty based on evidence that the net benefit is substantial)
  – B = Moderate Recommendation (there is moderate certainty based on evidence that the net benefit is moderate to substantial or there is high certainty that the net benefit is moderate)
Hypertension Guidelines

• Different levels of recommendation
  – C = Weak Recommendation (there is at least moderate certainty based on evidence that there is a small net benefit)
  – D = Recommendation against
  – E = Expert opinion (there is insufficient evidence or evidence is unclear or conflicting, but this is what the committee recommends)
  – N = No recommendation for or against
Hypertension Guidelines

• Nine recommendations
  – Two rated Strong
  – Two rated Moderate
  – One rated Weak
  – Five rated Expert Opinion
Hypertension Guidelines

• Recommendation 1
  – Blood pressure should be less than 150/90 for patients 60 and older (Strong)
• Difference: JNC 7 called for 140/90
  – Corollary: If patients 60 and older are being treated and their SPB is less than 140, there is no need to adjust treatment if it is well tolerated (Expert)
Hypertension Guidelines

• Recommendation 2
  – DBP should be below 90 for patients younger than 60 (Strong for ages 30-59, Expert for patients 18-29)

• Recommendation 3
  – SBP should be below 140 for patients younger than 60 (Expert)
Hypertension Guidelines

• Recommendation 4
  – Blood pressure should be below 140/90 for patients with chronic kidney disease (Expert)

• Recommendation 5
  – Blood pressure should be below 140/90 for diabetic patients (Expert)
Hypertension Guidelines

- Recommendation 6
  - In non-black patients, initial antihypertensive therapy should start with a thiazide-type diuretic, calcium channel blocker, ACE inhibitor or ARB (Moderate)

- Difference: JNC 7 recommended thiazides as first line treatment

- beta blockers removed from preferential listing
Hypertension Guidelines

• Recommendation 7
  – Black patients should be started with thiazides or calcium channel blockers
    (Moderate; Weak for diabetics)

• Recommendation 8
  – Patients with chronic kidney disease should receive an ACE inhibitor or ARB as initial or add-on treatment (Moderate)
Hypertension Guidelines

• Recommendation 9
  – If blood pressure is not controlled within one month, doses should be increased or a second medication (from the first line group) should be added. ACE inhibitors and ARBs should not be used together. If goal BP cannot be reached using only the drugs in recommendation 6, antihypertensive drugs from other classes can be used. (Expert)
Hypertension Guidelines

• Proportion of patients affected by the changes in guidelines
  – JNC 7 applied to 20.3% of adults 18-59; JNC 8 applies to 19.2%
  – JNC 7 applied to 68.9% of adults over 60; JNC 8 applies to 61.2%
Lipid Guidelines

Lipid Guidelines

• Goal: Reduce atherosclerotic cardiovascular disease (ASCVD) events
• Healthy lifestyle remains the foundation
• No evidence from randomized controlled trials to support treatment to a specific goal
Lipid Guidelines

- Largest difference from previous guidelines: Not treating to goal levels
Lipid Guidelines

- Not treating to goal:
  - “[T]he RCT [randomized controlled trial] evidence clearly shows that ASCVD events are reduced by using the maximum tolerated statin intensity in those groups shown to benefit . . . [N]o RCTs were identified that titrated drug therapy to specific LDL-C or non-HDL=C goals to improve ASCVD outcomes.”
Lipid Guidelines

• Focus: identify and treat patients who are most likely to gain benefit from statin therapy
• New guidelines simplify treatment
Lipid Guidelines

• Statin groups:
  – High intensity
    • Atorvastatin (Lipitor) 80 mg; rosuvastatin (Crestor) 20 mg
      – Some rationale for atorvastatin 40 mg, rosuvastatin 40 mg
    • Should reduce LDL-C by 50% or more
  • Cost
    – Atorvastatin: $18/month AWP
    – Rosuvastatin $224/month AWP
Lipid Guidelines

• Statin groups:
  – Moderate intensity
    • Atorvastatin 10 mg; rosuvastatin 10 mg; simvastatin (Zocor) 20-40 mg; pravastatin (Pravachol) 40 mg; lovastatin (Mevacor) 40 mg; fluvastatin (Lescol) XL 80 mg; fluvastatin 40 mg BID; pitavastatin (Livalo) 2-4 mg
  – Should reduce LDL-C 30% to 49%
Lipid Guidelines

• Clinical ASCVD
  – Acute coronary syndromes
  – History of MI
  – Stable or unstable angina
  – Coronary revascularization
  – History of stroke or TIA
  – Peripheral arterial disease or revascularization
Lipid Guidelines

• ASCVD present
  – Age 75 or less: high intensity
  – Age greater than 75 or intolerant to high intensity: moderate intensity

• Primary elevation of LDL-C 190 mg/dl or more: high intensity
  – Moderate intensity if not a candidate for high
Lipid Guidelines

• Diabetics
  – Generally: Moderate intensity
  – If estimated 10 year ASCVD risk is 7.5% or greater: High intensity

• If estimated 10 year ASCVD risk is 7.5% or greater
  – Moderate to high intensity
Lipid Guidelines

• Non-statin medications?
  – “Use of LDL-C targets may result in under-treatment with evidence-based statin therapy or overtreatment with nonstatin drugs that have not been shown to reduce ASCVD events . . .”
  – “Implications of treating to an LDL-C goal may mean that a suboptimal dose of statin is used because the goal has been achieved, or that adding a nonstatin therapy to achieve a specific target results in down-titration of the evidence-based dose of statin for safety reason.”
Lipid Guidelines

• Non-statin medications?
  – “However, when RCT evidence is available that a nonstatin therapy further reduces ASCVD events when added to statin therapy, the nonstatin therapy may be considered.”
Lipid Guidelines

• Global Risk Assessment Tool
  – Pooled Cohort Equations
  • Asses patient risk of initial cardiovascular event: age, sex, race, total cholesterol, HDL, systolic blood pressure, BP lowering med use, diabetes status, smoking status
  • Not included: family history of CV disease, triglycerides, waist circumference, BMI, lifestyle habits, smoking history
Lipid Guidelines

- Global Risk Assessment Tool
  - App at ASCVD Risk Estimator
  - http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp
Cardiology Medications
New Drugs, New Guidelines

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