UPDATE IN CARDIOLOGY
WHAT’S NEW EXCITING AND DIFFERENT

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CONFLICT OF INTEREST DISCLOSURES

I have no conflicts of interest to disclose

LEARNING OBJECTIVES

• Measure a patient’s stroke risk using risk calculators
• List the contraindications and precautions related to newer antiplatelet agents
• Differentiate the role of the newer antiplatelet agents utilized in managing acute coronary syndromes
• List the risk factors utilized in the CHADS₂ and CHADS₂-VASC scores

AF: A SIGNIFICANT HEALTH CARE ISSUE

• Affects 2 to 5 million patients in US and 4.5 million in Europe
• Associated with increase in aging and chronic heart disease - especially heart failure
• Frequently seen with comorbidities
• AF complicates management of comorbidity
• Comorbidity complicates management of AF
• Associated with stroke, heart failure, death
• Most common arrhythmia requiring hospitalization
• 416,000 hospital discharges per year

AF PREVALENCE INCREASES WITH AGE

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GOALS OF THERAPY IN PATIENTS WITH AF

- Prevention of stroke (thromboembolism)
- Prevention of tachycardia-induced cardiomyopathy
- Symptom relief
- Improved survival
- Primary prevention of other cardiovascular events

CHADS₂ VERSUS CHA₂DS₂VASc

STROKE RISK SCORING

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>CHADS₂ Score</th>
<th>CHA₂DS₂VASc Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>1</td>
<td>CHF or LVEF ≤ 40%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>1</td>
<td>Age &gt; 75</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>2</td>
<td>Stroke/TIA/Thromboembolism</td>
</tr>
</tbody>
</table>

AF PREVALENCE INCREASES WITH AGE

AF PREVALENCE INCREASES WITH AGE

AF PREVALENCE INCREASES WITH AGE

THROMBOEMBOLIC EVENT RISK

<table>
<thead>
<tr>
<th>CHADS₂ Score</th>
<th>Patients (n=7329)</th>
<th>Adjusted stroke rate (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>443</td>
<td>2.4</td>
</tr>
<tr>
<td>2</td>
<td>523</td>
<td>4.0</td>
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<tr>
<td>3</td>
<td>337</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>16.2</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>CHA₂DS₂VASc Score</th>
<th>Patients (n=7329)</th>
<th>Adjusted stroke rate (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>422</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>1230</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>1730</td>
<td>3.2</td>
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<tr>
<td>4</td>
<td>1718</td>
<td>4.0</td>
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<tr>
<td>5</td>
<td>1109</td>
<td>6.7</td>
</tr>
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<td>6</td>
<td>641</td>
<td>9.8</td>
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<td>7</td>
<td>294</td>
<td>9.6</td>
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<tr>
<td>8</td>
<td>82</td>
<td>8.7</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>15.2</td>
</tr>
</tbody>
</table>

Advantages
- Classifies larger number of patients as high risk
- Classifies fewer patients into low or intermediate risk

Disadvantages
- Low specificity
- Risks of long term anticoagulation
CHADS₂ VERSUS CHA₂DS₂-VASC
PUTTING IT TOGETHER
• Use CHADS₂ as initial scoring system
• Based on CHADS₂ score use CHA₂DS₂-VASC to determine therapy
• Concerns
  • Bleeding risk

ANTICOAGULATION
ACCF/AHA/HRS 2011
• CHADS₂ score = 0
  • Aspirin 75 to 325 mg daily
• CHADS₂ score = 1
  • VKA (INR 2-3) or aspirin 81 to 325 mg daily
• CHADS₂ score ≥ 2
  • VKA (INR 2 to 3)

Chest Guidelines 2012
• CHADS₂ score = 0
  • No therapy or Aspirin 75 to 325 mg daily
• CHADS₂ score = 1
  • Dabigatran 150 mg BID over VKA (INR 2 to 3)
• CHADS₂ score ≥ 2
  • Dabigatran 150 mg BID over VKA (INR 2 to 3)

DABIGATRAN
• Should not be used in patients with mechanical valves
• RE-ALIGN
  • Phase II Study
  • 400 Valve Patients
  • Dabigatran (150 mg BID, 220 mg BID, 300 mg BID) versus warfarin
  • 12 week

GUIDELINES UPDATE - CHEST
• Primary Prevention
  • Low Dose Aspirin (75 to 100 mg) daily in patients > 50 years of age
  • Grade 2B
• Atrial Fibrillation
  • For patients in whom anticoagulation is indicated, dabigatran recommended over warfarin

Coronary Artery Disease

GUIDELINES UPDATE - CHEST
• Acute Coronary Syndromes
  • ACS without PCI
    • Dual antiplatelet therapy with ticagrelor 90 mg twice daily plus low-dose aspirin, clopidogrel 75 mg once daily plus low dose aspirin (Grade 1B)
    • Ticagrelor 90 mg twice daily plus low-dose aspirin over clopidogrel 75 mg daily plus low –dose aspirin (Grade 2B)
  • ACS with PCI
    • Dual antiplatelet therapy with ticagrelor 90 mg twice daily plus low-dose aspirin, clopidogrel 75 mg once daily plus low dose aspirin, or prasugrel 10 mg plus low-dose aspirin (Grade 1B)
    • Ticagrelor 90 mg twice daily plus low-dose aspirin over clopidogrel 75 mg daily plus low –dose aspirin (Grade 2B)
UA/NSTEMI GUIDELINES

- A loading dose following by daily maintenance dose of either clopidogrel, prasugrel, or ticagrelor should be administered to UA/NSTEMI patients who are unable to take aspirin.
- UA/NSTEMI at medium or high risk in whom an initial invasive strategy is selected should receive dual antiplatelet therapy.

Before PCI:
- Clopidogrel (Class 1)
- Ticagrelor (Class 1)

At the time of PCI:
- Clopidogrel (Class 1)
- Prasugrel (Class 1)
- Ticagrelor (Class 1)

Antiplatelet Comparison

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel (Plavix)</th>
<th>Prasugrel (Effient)</th>
<th>Ticagrelor (Brilinta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Select Drug Interactions</td>
<td>CYP2C19 Inhibitors</td>
<td>Anticoagulants, antiparallel agents, NSAIDS</td>
<td>CYP2C19, CYP3A4, CYP2D6, CYP2C19 to active metabolites (15%)</td>
</tr>
<tr>
<td>Commandations</td>
<td>Active Bleed</td>
<td>Active Bleed</td>
<td>Active Bleed</td>
</tr>
<tr>
<td></td>
<td>History of stroke</td>
<td>History of TIA</td>
<td>Severe Hepatic Impairment, History of ICH</td>
</tr>
<tr>
<td>% Platelet inhibition Steady State</td>
<td>60</td>
<td>75</td>
<td>60</td>
</tr>
<tr>
<td>Platelet Function Recovery</td>
<td>5 days following discontinuation</td>
<td>7 days following discontinuation</td>
<td>5 days after following discontinuation</td>
</tr>
</tbody>
</table>

PRASUGREL

- 60 mg LD/10 mg MD

CLOPIDOGREL

- 300 mg LD/75 mg MD

Ticagrelor (Brilinta)

- 180 mg Load
- 90 mg twice daily

Enrollment Criteria

Criteria for Inclusion
- Planned PCI:
  - Mod-High Risk UA/NSTEMI
  - STEMI: < 14 days
  - STEMI: Primary PCI
- Major Exclusion Criteria:
  1. Prior hemorrhagic stroke or any stroke < 3 months
  2. Increased risk of bleeding
  3. Any thienopyridine within 5 days
  4. Severe Comorbid

Study:
- CREDO, CURE, PCI-CURE, COMMIT, PLATO, TRITON-TIMI 38, TRILOGY ACS

ENROLLMENT CRITERIA

- STEMI major bleedings, Life-threatening bleedings

TRITON- TIMI 38

ACS (STEMI or UA/NSTEMI) & Planned PCI

- ASA 13,600

- CLOPIDOGREL 300 mg LD/75 mg MD
- PRASUGREL 60 mg LD/10 mg MD

- Double-blind

- Median duration of therapy - 12 months

- 2nd endpoint: CV death, MI, Stroke
- 2nd endpoints: CV death, MI, Stroke, Rehosp-Rec ischemia, CV death, MI, UTI, Stent Thrombosis (A/E: definite/prob.)
- Safety endpoints: BMI major bleedings, Life-threatening bleedings

Wiviott SD et al. NEJM 2007;357:2001-15
CONCLUSIONS: HIGHER IPA TO SUPPORT PCI
Prasugrel 60 mg LD/10mg MD vs Clopidogrel 300 mg LD/75 mg MD

Efficacy
1. A significant reduction in:
   - CV Death/MI/Stroke 19%
   - Stent Thrombosis 52%
   - uTVR 34%
   - MI 24%

Safety
- Significant increase in serious bleeding (32% increase)
- Avoid in pts with prior CV/TIA

Net clinical benefit significantly favored Prasugrel

Optimization of Prasugrel maintenance dosing in a minority of patients may help improve the benefit: risk balance

PLATO INCLUSION CRITERIA

- Hospitalization for STEMI or NSTEMI ACS, with onset during the previous 24 hours
- With STEMI, the following two inclusion criteria were required
  - Persistent STEMI or new LBBB
  - Primary PCI planned
- With NSTEMI ACS, at least two of the following three were required
  - ST-segment changes on ECG indicating ischemia
  - Positive biomarker indicating myocardial necrosis
  - One of the following risk indicators
    - ≥ 60 years of age
    - Previous MI or CABG
    - CAD with ≥ 50% stenosis in ≥ 2 vessels
    - Previous ischemic stroke, TIA, carotid stenosis (≥ 50%)
    - Diabetes mellitus
    - Peripheral artery disease
    - Chronic renal dysfunction (creatinine clearance <60 mL/min)

K-M ESTIMATE OF TIME TO FIRST PRIMARY EFFICACY EVENT (COMPOSITE OF CV DEATH, MI OR STROKE)
CONCLUSIONS

- Reversible, more intense P2Y₁₂ receptor inhibition for one year with ticagrelor in comparison with clopidogrel in a broad population with ST- and non-ST-elevation ACS provides
  - Reduction in myocardial infarction and stent thrombosis
  - Reduction in cardiovascular and total mortality
  - No change in the overall risk of major bleeding
CONCLUSIONS

- Prasugrel was not statistically different from clopidogrel during 2.5 years of follow-up among patients < 75 years of age
- No statistical differences in major, life-threatening, or fatal bleeding with prasugrel vs. clopidogrel
- Trend for time-dependent benefit beyond 1 year

FDA Safety Alerts - 2012

- New dose limitations - Lovastatin
- Update on LFT monitoring
- Pramipexole (Mirapex)

LOVASTATIN DOSE LIMITS

<table>
<thead>
<tr>
<th>Previous lovastatin label</th>
<th>New lovastatin label</th>
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</thead>
<tbody>
<tr>
<td>Avoid lovastatin with:</td>
<td>Avoid with lovastatin:</td>
</tr>
<tr>
<td>- Itraconazole, ketoconazole</td>
<td>- Itraconazole, ketoconazole</td>
</tr>
<tr>
<td>- Erythromycin, clarithromycin</td>
<td>- Erythromycin, clarithromycin</td>
</tr>
<tr>
<td>- Telithromycin</td>
<td>- Telithromycin</td>
</tr>
<tr>
<td>- HIV protease inhibitors</td>
<td>- HIV protease inhibitors</td>
</tr>
<tr>
<td>- Nelfazodone</td>
<td>- Nelfazodone</td>
</tr>
<tr>
<td>Do not exceed 20 mg lovastatin daily with:</td>
<td>Do not exceed 40 mg lovastatin daily with:</td>
</tr>
<tr>
<td>- Gemfibrozil</td>
<td>- Gemfibrozil, perhexiline</td>
</tr>
<tr>
<td>- Other fibrates</td>
<td>- Other fibrates, niacin</td>
</tr>
<tr>
<td>- PPARγ-differentiation agents (1 g/day of niacin)</td>
<td>- PPARγ-differentiation agents (1 g/day of niacin)</td>
</tr>
<tr>
<td>- Cyclosporine</td>
<td>- Cyclosporine, ciclosporine</td>
</tr>
<tr>
<td>- Daranat</td>
<td>- Daranat</td>
</tr>
<tr>
<td>- Nelfazodone</td>
<td>- Nelfazodone</td>
</tr>
</tbody>
</table>

STATIN/FIBRATE COMBINATION THERAPY: PHARMACOKINETIC INTERACTIONS

<table>
<thead>
<tr>
<th>Statin</th>
<th>Gemfibrozil</th>
<th>Fenofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Not available</td>
<td>No effect</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>↑ in Cmax by 2-fold</td>
<td>No effect</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>↑ in Cmax by 2-fold</td>
<td>No effect</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>↑ in Cmax by 2-fold</td>
<td>No effect</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>↑ in Cmax by 2–3-fold</td>
<td>No effect</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>↑ in Cmax by 2–3-fold</td>
<td>No effect</td>
</tr>
</tbody>
</table>

FDA ALERTS

- New dose limitations - Lovastatin
- Update on LFT monitoring
- Pramipexole (Mirapex)
Rhabdomyolysis Rate in Statins Combo: Gemfibrozil >> Fenofibrate

FDA Alerts
- New dose limitations - Lovastatin
- Update on LFT monitoring
- Pramipexole (Mirapex)

Risk Factors for Statin-Hepatotoxicity
- Advanced age
- Diabetes
- Obesity
- Interacting medications

Hepatotoxicity - Management
- Obtain baseline LFTs on all patients
- Monitor for symptoms of hepatic injury
- Identify etiology
- Transaminase levels > 3 x ULN
- Use in pre-existing liver dysfunction

Statins
- Prescriber labeling has been revised to remove the need for routine periodic monitoring of liver enzymes in patients taking statins.
- Recommend that LFT's are performed at baseline
- Perform LFT's thereafter only when clinically indicated
- Risk of serious liver injury is low with statins and unpredictable. The routine monitoring of LFT's is not effective in either detecting or preventing serious hepatic injury

FDA Alerts
- New dose limitations - Lovastatin
- Update on LFT monitoring
- Pramipexole (Mirapex)
PRAMIPEXOLE (MIRAPEX)
• Dopamine agonist
• Indications
  • Parkinson’s Disease
  • Moderate to severe Restless Leg Syndrome
• FDA Alert
  • Potential for increased risk of heart failure

ICOSOPENT ETHYL (VASCEPA)
• Ultra Pure (>96%) eicosapentaenoic acid (EPA)
• Indicated for Hypertriglyceridemia
• Trials in MARINE and ANCHOR

OMEGA-3 FATTY ACIDS (FA)
• Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have CV benefits
• Alpha-linoleic acid, while an omega-3 FA, does not have CV benefits
• Role in therapy:
  • Prescription omega-3 FA products approved for severe hypertriglyceridemia (≥ 500 mg/dL):
    • Lovaza®: both EPA and DHA
    • Vascepa®: EPA only

OMEGA 3 META ANALYSIS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.96 (0.91-1.02)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0.91 (0.85-0.98)*</td>
</tr>
<tr>
<td>Sudden death</td>
<td>0.87 (0.75-1.01)</td>
</tr>
<tr>
<td>MI</td>
<td>0.89 (0.76-1.04)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.05 (0.93-1.18)</td>
</tr>
</tbody>
</table>

*Reduction in cardiac death events not significant after corrected for multiple comparisons

OMEGA 3 INTAKE RECOMMENDATIONS:
• No CHD: Fish twice/week and oils/foods rich alpha-linolenic acid (flaxseed, walnuts)
• Patients with CHD: 1 Gm EPA+DHA per day (preferably from fish: 2-4 ounces salmon, 4-12 ounces canned tuna, 7 ounces flounder/sole)
• Patients with High Triglycerides: 2 to 4 Gm EPA+DHA per day
### “FISH OIL” VS. OMEGA-3 FATTY ACIDS

<table>
<thead>
<tr>
<th></th>
<th>Nature’s Bounty (“Fish Oil”)</th>
<th>Carlson Super-DHA (“Fish Oil”)</th>
<th>Lovaza® (Omega-3 Acid Ethyl Esters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPA/DHA (mg)</td>
<td>180/120</td>
<td>100/500</td>
<td>465/375</td>
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<tr>
<td>Miscellaneous</td>
<td>“fish oil” (mg)</td>
<td>700</td>
<td>400</td>
</tr>
<tr>
<td>Fish oil (mg)</td>
<td>700</td>
<td>400</td>
<td>160</td>
</tr>
<tr>
<td>No. caps daily</td>
<td>2 to 4 daily</td>
<td>1 to 2 daily</td>
<td>4 daily</td>
</tr>
<tr>
<td>Capsules to attain 1360 mg EPA/DHA</td>
<td>11.2</td>
<td>5.6</td>
<td>4</td>
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</table>