Cardiac Pharmacology

Session 1

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Disclosures: None
What’s new in Cardiac Pharmacology?

• Coronary Disease
  – P2Y12 Antiplatelet therapy
    • Trials comparing P2Y12 Inhibitors after PCI
    • DAPT vs. Monotherapy after PCI
    • DAPT in Diabetics with Stable CAD
    • Antithrombotic/Antiplatelet therapy in A Fib with ACS/PCI
  – OAC in Stable Ischemic Heart Disease
• Anticoagulants with CKD
• Anti-inflammatory agents in AMI
• Lipid therapy
  – Positive and Negative Trial results
• Neprilysin inhibition in HFpEF

Antiplatelet therapy after AMI

• Randomized trials have shown both prasugrel and ticagrelor are superior to clopidogrel in patients with Acute Coronary Syndromes (reduced risk of CVD/MI/CVA)
  – TRITON-TIMI 38 Trial: prasugrel > clopidogrel
  – PLATO Trial: ticagrelor > clopidogrel
• Therefore, in patients with ACS in whom an invasive evaluation is planned, either ticagrelor or prasugrel is preferred over clopidogrel (Grade 1A - a strong recommendation based on high-quality evidence)

• However, the relative merits of ticagrelor vs. prasugrel in patients with ACS in whom an invasive evaluation is planned are uncertain...
ISAR-REACT Trial
Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment

- Multicenter, randomized, open-label trial
- ACS (STEMI, NSTEMI or USA) with planned invasive strategy
- Ticagrelor vs. Prasugrel
- 1st End point: Composite of death, MI, or CVA at 1 year
- 2nd End point: major bleeding (BARC type 3, 4 or 5)

Bleeding Academic Research Consortium (BARC) Bleeding Scale

| Type 0 | No bleeding
| Type 1 | Bleeding that is not actionable and does not cause the patient to seek treatment
| Type 2 | Any clinically overt sign of hemorrhage that “is actionable” and requires diagnostic studies, hospitalisation, or treatment by a healthcare professional
| Type 3 | a. Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding
| Type 4 | CABG-related bleeding within 48 hours
| Type 5 | a. Probable fatal bleeding
|               | b. Definite fatal bleeding (overt or autopsy or imaging confirmation)
**ISAR-REACT Trial**

**Primary End Point: Death/MI/CVA**

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<th>Months since Randomization</th>
<th>Hazard ratio, 1.36 (95% CI, 1.09–1.70)</th>
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**No. at Risk**

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**ISAR-REACT Trial**

**Major Bleeding**

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ISAR-REACT 5

• The ISAR-REACT 5 results (<risk of ischemic events with prasugrel compared with ticagrelor>) were surprising and not predicted based on the results of existing randomized trials:
  – PLATO: ticagrelor superior to clopidogrel (ACS, either Invasive or Non-Invasive).
  – TRITON-TIMI 38: prasugrel superior to clopidogrel (ACS-Invasive).
  – TRILOGY ACS: prasugrel not superior to clopidogrel (ACS-Non-invasive).

• Possible explanations include trial limitations
  – Open-label design (compared with the TRITON-TIMI 38 and PLATO trials).
  – Telephone follow-up in more than 90 percent of patients.
  – Different patient populations or co-interventions between TRITON-TIMI 38 and PLATO trials and ISAR-REACT 5.

• Until further evidence is available to support or refute the superiority of prasugrel, either prasugrel or ticagrelor is a reasonable choice for patients with ACS in whom a decision is made to proceed with diagnostic angiography within three hours.

DAPT vs. Monotherapy after PCI

• SMARTCHOICE Trial
  – Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents
  – Low risk patients, 3 months DAPT then randomized.

• STOPDAPT-2 Trial
  – Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt Chromium Stent
  – Low risk patients, 1 month DAPT, then randomized.

• TWILIGHT Trial
  – Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention
  – High risk patients, 3 months DAPT, then randomized.
SMARTCHOICE Trial

- Multicenter, open-label, randomized Noninferiority trial
- 2993 pts w/PCI at 33 hospitals in Korea
  - 3 mo DAPT followed by a P2Y12 inhibitor alone vs. 12 mo DAPT
    - Clopidogrel 76.9 vs. 77.6
    - Prasugrel 4.1 vs. 4.5
    - Ticagrelor 19.0 vs. 17.9
- 1º End point: MACE - composite of All-cause death, MI or CVA

RESULTS
- No difference in MACE: Monotherapy 2.9% vs. DAPT 2.5% ($P = .007$ for noninferiority)
- Bleeding was lower in the Monotherapy 2.0% vs. DAPT group 3.4%; HR = 0.58

SMART-CHOICE
Cardiovascular Events
SMART-CHOICE
Bleeding Events

STOPDAPT-2 Trial

- Multicenter, open-label, randomized clinical trial
- 3045 Stable (not ACS) pts w/ PCI at 90 hospitals in Japan
  - 1 mo of DAPT followed by clopidogrel monotherapy for up to 5 years
  - 12 mos of DAPT followed by aspirin monotherapy for up to 5 years
  - For patients who had initially received prasugrel (~40%), prasugrel was switched to clopidogrel at 1 month in both groups
- 1<sup>st</sup> End point: Composite of CVD, MI, CVA, Definite stent thrombosis, or major or minor bleeding

**RESULTS:**
- One-month DAPT was both noninferior ($P < .001$) and superior ($P = .04$) to 12-month DAPT for the primary end point (2.36% vs. 3.70%, HR = 0.64).
### STOPDAPT-2
Cardiovascular and Bleeding Events

![Graph showing cardiovascular and bleeding events](image)

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<th>p-Value</th>
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### STOPDAPT-2
Cardiovascular and Bleeding Events

![Graph showing additional cardiovascular and bleeding events](image)

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TWILIGHT Trial

Ticagrelor with or without Aspirin in High-Risk Patients after PCI


• Randomized, placebo-controlled, prospective trial of 7119 pts w/ successful PCI at high risk for ischemic or bleeding complications
  – At least one High Risk Clinical feature:
    • age >65, female, ACS, PAD, DM, CKD
  – At least one High Risk Angiographic feature:
    • MVD, long stent, thrombus, bifurcation stents, LM, Proximal LAD, Atherectomy
• DAPT for 3 mos with ticagrelor/ASA then randomized to either ticagrelor + ASA or ticagrelor + placebo for 12 additional months

TWILIGHT Trial

• 1° End point: Bleeding between randomization and 1 year (BARC type 2, 3, or 5 bleeding)
• 2° End point: Death from any cause, nonfatal MI or nonfatal stroke
• Other 2° End points: CVD, MI, CVA, Stent thrombosis
TWILIGHT Trial
Primary Endpoints - BARC Type 2, 3, or 5 Bleeding


TWILIGHT Trial
Secondary Endpoints: Death/MI/CVA

TWILIGHT Trial
Conclusions

• Among High-Risk patients who underwent PCI and completed 3 months of dual antiplatelet therapy, ticagrelor monotherapy was associated with a lower incidence of clinically relevant bleeding than ticagrelor plus aspirin, with no higher risk of death, myocardial infarction, or stroke.

THEMIS Trial
Ticagrelor in Patients with Stable Coronary Disease and Diabetes

• 19,220 pts randomized to receive either ticagrelor plus aspirin or placebo plus aspirin
  – Stable CAD (history of PCI, CABG or >50% stenosis of at least one coronary artery) and
  – Diabetes Mellitus
• 1st efficacy outcome = composite of CVD, MI or CVA
• 1st safety outcome = major bleeding,
• Net Irreversible Harm was prespecified as a composite of Death, MI, CVA, fatal bleeding, or ICH.
THEMIS Trial
Primary Composite Efficacy Outcome

No. at Risk
Ticagrelor 9619 9416 9237 9074 8909 8892 5974 3664 1684 170
Placebo 9601 9414 9246 9076 8909 8892 5934 3682 1685 174

THEMIS Trial:  
Primary Safety Outcome

No. at Risk
Ticagrelor 9562 7928 7309 6826 6381 5997 4067 2464 1156 168
Placebo 9531 8663 8186 7767 7359 6967 4793 2952 1358 218
THEMIS-PCI Sub Study

- THEMIS-PCI substudy – 11,154 patients with Diabetes and a history of previous PCI
  - ticagrelor improved **Net Clinical Benefit** (9.3% vs. 11.0%)
  - the benefit was present irrespective of time from the most recent PCI
- Taken together, the THEMIS trial and the THEMIS-PCI subgroup analysis raise the possibility that patients with stable CAD and DM at very high ischemic risk and low bleeding risk may have a **net benefit** with long-term DAPT with **aspirin** and **ticagrelor**
- Based on these findings, long-term therapy with ticagrelor in addition to aspirin should be considered in patients with diabetes **and a history of PCI** who
  - have tolerated antiplatelet therapy
  - have high ischemic risk and
  - have a low bleeding risk

AUGUSTUS Trial
Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation

- Appropriate antithrombotic regimens for patients with atrial fibrillation who have an acute coronary syndrome or have undergone percutaneous coronary intervention (PCI) are unclear
- The AUGUSTUS Trial was a randomized trial of 4614 patients with atrial fibrillation who had an acute coronary syndrome or had undergone PCI and were planning to take a P2Y12 inhibitor
  - All patients received P2Y12 antagonist, and in a two-by-two factorial design also received either
    - Apixaban + ASA, or
    - Apixaban + placebo, or
    - VKA + ASA, or
    - VKA + placebo
- **1** outcome = major or clinically relevant nonmajor bleeding
- **2** outcomes = composite of death or hospitalization and the composite of death or ischemic events (CVA, MI, stent thrombosis or urgent revascularization).
AUGUSTUS Trial
Primary Outcome of Major or Clinically Relevant Nonmajor Bleeding.

AUGUSTUS Trial
Composite of Death or Hospitalization.
AUGUSTUS Trial
Conclusions

- In patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a P2Y\textsubscript{12} inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events than regimens that included a vitamin K antagonist, aspirin, or both.

AFIRE Trial
Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease

- Noninferiority trial of 2236 patients with A Fib, remote PCI or CABG > 1 yr prior, or angiographically confirmed CAD not requiring revascularization
  - Randomized to receive monotherapy with rivaroxaban or combination therapy with rivaroxaban plus a single antiplatelet agent (~75% ASA, 25% clopidogrel).
- 1\textsuperscript{st} efficacy end point was a composite of CVA, systemic embolism, MI, unstable angina requiring revascularization, or death from any cause;
- 1\textsuperscript{st} safety end point was major bleeding
AFIRE Trial
Results

• The trial was stopped early because of increased mortality in the combination therapy group.
• Rivaroxaban monotherapy was noninferior (P<0.001) to combination therapy for the 1\(^{st}\) efficacy end point.
• Rivaroxaban monotherapy was superior (P = 0.01) to combination therapy for the 1\(^{st}\) safety end point.
AFIRE Trial
Conclusions

• As antithrombotic therapy, rivaroxaban monotherapy was noninferior to combination therapy for efficacy and superior for safety in patients with atrial fibrillation and stable coronary artery disease.

SUMMARY

• The optimal P2Y12 antagonist in ACS is uncertain. The ISAR-REACT 5 Trial suggests prasugrel is superior to ticagrelor but until further studies are performed both are superior to and either is preferred over clopidogrel in ACS.

• The optimal duration of DAPT after PCI is uncertain but monotherapy after 1-3 months appears to be safe and effective in both stable and high risk patients.

• Prolonged DAPT in diabetics with CAD reduces ischemic complications at the expense of increased bleeding. The Net Clinical Benefit favors prolonged DAPT in patients with prior PCI, high ischemic risk and acceptable bleeding risk.

• In patients with Atrial Fibrillation and recent PCI, treatment with a NOAC and P2Y$_{12}$ without ASA is safe and effective.

• In patients with Atrial Fibrillation and stable CAD, monotherapy with rivaroxaban is as effective as and safer than rivaroxaban + antiplatelet therapy.
YOUR PATIENTS

Patients with ACS following PCI:
   Prasugrel or Ticagrelor >>> clopidogrel

Patients without ACS, @ Low Risk following PCI:
   DAPT x 1-3 mos then prolonged P2Y12 without ASA

Patients with or without ACS, @ High Risk (clinical and angiographic), after PCI:
   DAPT X 3 mos, then Ticagrelor alone x 12 mos

YOUR PATIENTS

Patients with Diabetes, CAD, no recent PCI but High Ischemic Risk & Low Bleeding Risk:
   Prolonged DAPT with Ticagrelor + ASA

Patients with Chronic Atrial Fibrillation & CAD following PCI:
   NOAC + P2Y12 but no ASA

Patients with Chronic Atrial Fibrillation & CAD but no recent PCI or CABG:
   NOAC alone without antiplatelet
Thank You