UPDATES IN CARDIOLOGY

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Presbyterian Heart Group

NM ACP Scientific Conference 2019
Disclosures

• Novartis
  • Speaker bureau
Outline

- *Updates in cardiology*
  - Diabetes Management in the CV patient
  - Coronary Artery Disease and Peripheral Arterial Disease
  - Lipid management
  - Stroke and Atrial Fibrillation
  - Heart Failure
Type 2 Diabetes: Metformin Remains First Line

- **UKPDS Metformin Sub-Study**
  - **Myocardial infarction**
    - Conventional: 20
    - Insulin: 15
    - Metformin: 10
    - P = 0.02
    - ↓39%
  - **Coronary deaths**
    - Conventional: 10
    - Insulin: 5
    - Metformin: 2
    - P = 0.02
    - ↓50%

- **Reduction**
  - ↓32% in micro or macrovascular diabetes related outcomes
  - ↓36% in all-cause mortality rate

- **Reduction in HbA1c, weight**
# Type 2 Diabetes: SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with type 2 DM</th>
<th>Comparison</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMPA-REG OUTCOME</strong></td>
<td>7028</td>
<td>Empagliflozin vs. placebo</td>
<td><strong>14% reduction</strong> in death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. <em>Reduction in HF</em></td>
</tr>
<tr>
<td><strong>CANVAS</strong></td>
<td>10,142</td>
<td>Canagliflozin or placebo</td>
<td><strong>14% reduction</strong> in death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. <em>Reduction in HF</em></td>
</tr>
<tr>
<td><strong>DECLARE–TIMI 58</strong></td>
<td>17160</td>
<td>Dapagliflozin vs placebo</td>
<td>Did not reduce MACE. <strong>17% reduction in CVD death or HF hospitalization. Reduced CKD progression.</strong></td>
</tr>
</tbody>
</table>

- **N Engl J Med. 2015 Nov 26;373(22):2117-28.**
SGLT2 Inhibition Reduces Renal Glucose Reabsorption

- Glucose filtration
- Glucose reabsorption
- SGLT2 inhibitor
- Loop of Henle
- Collecting duct

SGLT2 Inhibitors:
- Canagliflozin (100, 300 mg)
- Dapagliflozin (5, 10 mg)
- Empagliflozin (10, 25 mg)
- Ertugliflozin (5, 15 mg)
- Iptra-, Luseo-, Tofogliflozin (Japan)

Glucose excretion:
- 70-80 g/day
- 280-320 Kcal/day
SGLT2 Inhibitors with Proven Cardiovascular Benefit

For ASCVD

• 1. Empagliflozin
• 2. Canagliflozin

For HF

• 1. Empagliflozin
• 2. Canagliflozin
• 3. Dapagliflozin

### Summary of Glucose Lowering Drugs for T2DM as dictated by CVD

<table>
<thead>
<tr>
<th>Anti-Hyperglycemic</th>
<th>ASCVD Benefits</th>
<th>HF Benefits</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Injection therapy Weight Gain</td>
</tr>
<tr>
<td>Metformin</td>
<td>Yes</td>
<td>Neutral</td>
<td>Contraindicated in GFR&lt;30mL/min/1.7 m²</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Yes</td>
<td>No</td>
<td>Injection therapy</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Yes</td>
<td>Yes</td>
<td>Urinary/ genitourinary tract infection Diabetic Ketoacidosis Increased Amputation Risk</td>
</tr>
<tr>
<td>TZDs</td>
<td>Yes</td>
<td>No</td>
<td>HF exacerbation Increased Fractures</td>
</tr>
<tr>
<td>Sulfonyureas</td>
<td>No</td>
<td>No</td>
<td>Hypoglycemia Weight gain</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>No</td>
<td>No</td>
<td>Modest A1C reduction</td>
</tr>
</tbody>
</table>

Take Home Points

- ASCVD is the leading cause of death in patients with T2DM
- When choosing therapy, consider the presence or absence of ASCVD and HF for every patient with diabetes
- Newer anti-hyperglycemic therapies, such as SGLT-2 inhibitors and GLP-1 agonists, have been found to provide significant cardiovascular benefit independent of glucose lowering
- Metformin is still considered first line therapy; however:
  - In patients with ASCVD, a GLP-1 RA or SGLT2-i is recommended
  - In patients with ASCVD and HF, an SGLT2-i is recommended
- Patient specific characteristics have to be taken into account when deciding on the optimal second-line agent.
- Head to head comparisons, broader patient population groups, long-term analysis and an expansion of safety end-points are still needed
COMPASS TRIAL
Cardiovascular Outcomes for People Using Anticoagulation Strategies

Rivaroxaban Plus Aspirin in Patients With and Without Heart Failure and Chronic Coronary or Peripheral Artery Disease

COMPASS Design
Cardiovascular Outcomes for People Using Anticoagulation Strategies

- Randomized, placebo controlled, double blinded trial

- Ongoing arm testing proton pump inhibitor pantoprazole versus placebo (PPI arm)

27,325 patients with stable CAD or PAD
1,323 with a primary outcome event

Rivaroxaban 2.5 mg bid
+ aspirin 100 mg daily

Rivaroxaban 5 mg bid

Run-in (aspirin)

Aspirin 100 mg daily

Median Follow Up:
23 months (1.9 years)

**Primary Outcome:** MACE (CV death, stroke or MI)

Median 23 month follow up

Riva+ASA vs ASA:

- ↓ MACE 24%
- ↑ Net benefit 20%
- ↓ Mortality 18%

No benefit for Riva alone

ASA = aspirin; CV = cardiovascular; MACE = major adverse cardiovascular events; MI = myocardial infarction; Riva = rivaroxaban.

Summary

• Highest risk groups are: > 2 Vascular beds; low eGFR, HF, diabetes
• Treatment effect of rivaroxaban + aspirin is consistent across subsets
2018 ACC/AHA Guidelines on the Management of Blood Cholesterol Key Takeaways and Considerations

• For the first time, PCSK9 inhibitors are recommended in the guidelines

• Guidelines **clearly define two patient populations** for whom PCSK9 inhibitor can be appropriate
  – Very high risk ASCVD
  – Primary severe hypercholesterolemia

• For patients on clinically judged maximal LDL-C lowering therapy, the guidelines specify a **clear threshold** above which it is reasonable to consider PCSK9 inhibitors
2018 ACC/AHA Guidelines on the Management of Blood Cholesterol Clearly Define Two Patient Populations With Specific Thresholds for Whom PCSK9 Inhibitors Can Be Appropriate

Very High Risk ASCVD

Threshold*

≥ 70 mg/dL

Primary Severe Hypercholesterolemia

Threshold*

≥ 100 mg/dL (FH baseline LDL-C ≥ 190)

≥ 130 mg/dL (hypercholesterolemia with baseline LDL-C ≥ 220 mg/dL)

*When on clinically judged maximally tolerated lipid-lowering therapy (statins + ezetimibe†)

ASCVD = atherosclerotic CVD.
Defining the Very High-Risk ASCVD Patient

- **Multiple Major ASCVD Events**
  - Recent ACS
  - History of MI
  - History of ischemic stroke
  - Symptomatic PAD

- **OR**
  - Major Event + Multiple High-Risk Conditions
    - Age ≥ 65 years
    - Diabetes mellitus
    - Current smoking
    - Hypertension
    - History of Congestive HF
    - Persistently elevated LDL-C
donext
    - Prior CABG or PCI outside major ASCVD event(s)
    - Despite maximally tolerated statin therapy + ezetimibe
    - HeFH
    - CKD
PCSK9 Inhibitors Reported a Clinical Benefit Associated With Very Low LDL-C Levels

2018 Cholesterol Guidelines
Secondary Prevention in Patients With Clinical ASCVD

Healthy Lifestyle

Very high-risk* ASCVD

High-intensity or maximal statin (Class I)

- If taking maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable (Class IIa)
- If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I (Class I)
- Dashed arrow indicates RCT-supported efficacy but is less cost effective

If taking clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L), adding PCSK9-I is reasonable (Class IIa)

*Clinical ASCVD = ACS, history of MI, stable angina or US or coronary other arterial revascularization, stroke, TIA or PAD, including aortic aneurysm, all of atherosclerotic origin.

Very high risk = history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

Stroke Facts

• Stroke ranks No. 5 among all cause mortality in US
  – 133,000 deaths annually
• About 795,000 people in the US have a stroke annually with 610,000 of these being first strokes
• Vast majority of strokes are ischemic (87%)
• Stroke is leader in health care costs and cause of serious long term disability
  – ~$34 billion annually in the US
  – Reduces mobility in >50% of stroke survivors ≥ 65
Stroke and Atrial Fibrillation

5X increased risk of stroke for AF patients\(^2\)

1 in 6 strokes occur in patients with AF\(^3\)

\(~5M\) people with AF in U.S., expected to more than double by 2050\(^1\)

47% of AF patients experiencing a stroke will suffer a second stroke within 6 months\(^4\)

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Prevention of Thromboembolism in AF

- Oral anticoagulants (OAC) are standard of care and reduce risk of stroke by 65-70%

- Issues with oral anticoagulants
  - Bleeding risk
  - Daily regimen
  - High non-adherence rates
  - Regular INR monitoring (warfarin)
  - Food and drug interactions (warfarin)
  - Complicates surgical procedures
  - High cost (direct acting oral anticoagulants)
  - Lack of readily available reversal agents
Why Left Atrial Appendage Closure for Stroke Prevention?

- AF leads to mechanical dysfunction of atrial tissue
- Loss of contractile function in LAA may lead to local stasis and thrombus formation
- >90% of thrombi in patients with non-valvular atrial fibrillation originate from or are isolated to the left atrial appendage
- Low Doppler inflow velocities, spontaneous echo contrast and presence of LAA thrombus associated with high stroke rate

References:
Zabalgoitia M et al. JACC 1993
Percutaneous LAAC/Watchman Device
Watchman

- Most studied LAAC therapy

- Proven alternative to long term warfarin therapy for stroke risk reduction in patients with non-valvular AF
  - 95% implant success rate
  - 1.5% procedural complication rate
Watchman Efficacy

- Disabling/Fatal Strokes
- Non-Disabling Strokes

55% Lower
HR 0.45 (0.21 – 0.94)
P=0.03
Economic and Health Burden of HF Hospitalizations

• By 2030, >8 million people in the US will have HF

• American Heart Association (AHA) statistics reported 900,000 hospital discharges and 459,000 ED encounters for HF in 2014

• Projections suggest that by 2030, the total cost of HF will increase almost 127%, to $69.7 billion, from $30.7 billion in 2012, amounting to ≈$244 for every US adult


Mortality rate remains high in patients with HF

Mortality Rate

- 1 Year: 29.6%
- 5 Year: 52.6%
Key Landmark Trials in the Treatment of HFrEF

RAAS (angiotensin) inhibition
1991-92
- SOLVD-Treatment
  Enalapril (n=1285) vs placebo (n=1284)
- SOLVD-Asymptomatic
  Enalapril (n=2111) vs placebo (n=2117)

SNS inhibition
1996
- US Carvedilol Heart Failure Study
  Carvedilol (n=696) vs placebo (n=398)

RAAS (aldosterone) inhibition
1999
- RALES
  Spironolactone (n=822) vs placebo (n=841)

ARNI (angiotensin receptor neprilysin inhibitor)
2014
- PARADIGM-HF
  Sacubitril/valsartan (n=4187) vs Enalapril (n=4212)

ARNI (angiotensin receptor neprilysin inhibitor)
2018
- PIONEER-HF
  Sacubitril/valsartan (n=440) vs Enalapril (n=441)

The Largest HF Study in Ambulatory Patients With HFrEF

References:
PARADIGM-HF: ENTRESTO vs Enalapril—Primary End Point

**Relative Risk Reduction vs Enalapril**

- ENTRESTO reduced the risk of CV death or HF hospitalization by 20%.
- (4.7% ARR)
- NNT=21

ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; NNT, number needed to treat.

PIioneer-HF: NT-proBNP Percentage Change by Visit

- The primary end point was the time-averaged proportional change in NT-proBNP at 4 and 8 weeks; the reduction was significantly greater as early as 1 week after randomization.

Summary

• Introduction of SGLT2 inhibitors in ASCVD
• Changes in recent ACC 2018 Guidelines
  – LDL goals
  – Introduction of PCSK9 LDL <70
• Rivaroxaban in patients with stable CAD and PAD
• Watchman Device, alternative to OAC for stroke prevention in atrial fibrillation
• Sacubitril/Valsartan superior drug to ACE/ARB in HFrEF and safe to initiate while in the hospital
Thank you