OMED 2019

CV BENEFITS OF DIABETES MEDICATIONS
• No conflicts of interest
• HF: heart failure

• MACE: major adverse cardiovascular events: (CV death, non-fatal MI, and non-fatal stroke)

• DM: Diabetes Mellitus
RATIONALE FOR USING DIABETES MEDICATIONS FOR CV REDUCTION

• Improving the BG control alone does not dramatically (if at all) improve the CV risk.

• Need to address CV risk in other ways (lipid reduction, BP reduction, lifestyle: diet and exercise; anti-inflammatory reduction, etc.)
METFORMIN

• Overall thought to be neutral on the heart.

• However, in the SAVOR-TIMI 53, in patients with type 2 DM and high CV risk, metformin was associated with lower rates of all-cause mortality, but not lower rates of composite endpoint of CV death, MI, or ischemic stroke.

• The UKPDS showed possibly increased CV risk when metformin was added to a sulfonylurea, but this relationship did not seem to hold up upon re-evaluation.
SULFONYLUREAS

• Glipizide
• Glimepiride
• Glyburide
SULFONYLUREAS

• Neutral on CHF

• All carry a black box warning about increase cardiovascular death from old studies on glyburide.

• Should avoid using glyburide when possible.
GLINIDES (NATEGLINIDE AND REPAGLINIDE)

• NAVIGATOR trial: no CV impact from using Nateglinide (Starlix)
DPP-4 INHIBITORS

• Sitagliptin (Januvia)
• Saxagliptin (Onglyza)
• Alogliptin (Nesina)
• Linagliptin (Tradjenta)
DPP-4 INHIBITORS

- Possible increased risk of hospitalizations with alogliptin and saxagliptin, although all DPP-4 inhibitors carry this warning.
DPP-4 INHIBITORS

• Linagliptin: CAROLINA STUDY: no increased CV risk compared with glimepiride in adults with type 2 DM.
THIAZOLIDINEDIONES

• Pioglitazone (Actos)
• Rosiglitazone (Avandia)
THIAZOLIDINEDIONES

• May reduce stroke risk.

• Cause fluid retention and can cause or worsen HF.

• Might reduce conversion of pre-diabetes to diabetes.
Pioglitazone: can beneficially affect cholesterol profile, improves insulin secretion, endothelial function, improve diastolic dysfunction, reduce inflammation, improve fatty liver disease.

Can reduce plaque in carotid and coronary arteries.

CCJM 86(7) 7/2019: 494-504.
ROSIGLITAZONE

• RECORD trial: no overall increase in CV risk with rosiglitazone (except increased HF)
ALPHA-GLUCOSIDASE INHIBITORS

- Acarbose (Precose)
- Miglitol (Glyset)
ALPHA-GLUCOSIDASE INHIBITORS

• Reduce CV events, acute MI, and the onset of hypertension.

• Might delay diabetes progression.

• CCJM 86(7) 7/2019: 494-504.
COLESEVALAM

• Bile acid sequestrant;

• Data on CV benefits is sparse.
PRAMLI NTIDE (SYMLIN)

• Causes weight loss, possibly due to nausea and central mechanisms.
• No CV data.
SGLT-2 INHIBITORS (SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS)

• Dapagliflozin (Farxiga)
• Empagliflozin (Jardiance)
• Canagliflozin (Invokana)
• Ertugliflozin (Steglatro).
SGLT-2 INHIBITORS

- Reduce weight, BP and A1c.
- Might lower arterial stiffness, lower sympathetic tone, and decrease dysrhythmia.

- CCJM 86(7) 7/2019: 494-504.
SGLT-2 INHIBITOR TRIALS

- EMPA-REG: (Empa)
- CANVAS: (Cana)
- DECLARE-TIMI 58: (Dapa)
- CREDENCE (Cana)
SGLT-2 INHIBITORS

• Empagliflozin: FDA approved to reduce CV mortality. Empa: 1st drug to show a reduction of in CV death in patients with type 2 DM and high CV risk. Reduced CV deaths by 38%, and all cause mortality by 32%; HF hospitalizations by 35%.

• Canagliflozin: FDA approved to reduce MACE events. Reduced risk of CV disease by 14% and risk of HF by 33%. CREDENCE trial: 30% reduction in CV or renal death (with or without pre-existing CV disease). Reduced MACE by 32% in primary prevention group.
SGLT-2 INHIBITORS

• The class of SGLT-2 inhibitors reduces the risk of HF (but no data yet on ertu), likely due to volume reduction.
SGLT-2 INHIBITORS

• The CV data might not apply to African-Americans due to low numbers in the trials and no benefit when used in them in most studies.
GLP-1 (GLUCAGON-LIKE PEPTIDE-1) RECEPTOR AGONISTS

• Exenatide (Byetta, Bydureon).

• Dulaglutide (Trulicity).

• Semaglutide (Ozempic).

• Liraglutide (Victoza)

• Lixisenatide (in Soliqua)
GLP-1 RECEPTOR AGONISTS

• Liraglutide: FDA approved for prevention of MACE events in patients with established CV disease.

LEADER TRIAL (3.8 years): in patients with type 2 DM, liraglutide reduced CV outcomes both in patients with a history of MI/stroke and in those with established CV disease without MI/stroke. The CV effect was neutral in patients with CV risk factors alone.

Reduction of major cardiovascular events by 13% and MI by 22% in patients with type 2 DM who were at high risk of MACE.

MACE: 13% vs. 14.9% in placebo.
CV death: 4.7% vs 6% in placebo.
Hospitalization for HF: 4.7% vs. 5.3% in placebo.
GLP-1 RECEPTOR AGONISTS

- Semaglutide SQ: in patients with type 2 DM and high risk of CVD, the rate of CV death, nonfatal MI, or nonfatal stroke (MACE) was lower than placebo. Also, SUSTAIN 6 Trial (2.1 years) showed reduced MACE in all subjects, regardless of gender, age, or baseline CV risk profile.

- MACE: 6.6% vs. 8.9% in placebo.

- Non-fatal stroke: 1.6% vs. 2.7% in placebo.
GLP-1 RECEPTOR AGONISTS

- Oral Semaglutide NEJM 8/29/2019
  PIONEER 6 TRIAL: the cardiovascular risk profile of oral semaglutide was not inferior to placebo.
GLP-1 RECEPTOR AGONISTS

• Exenatide ER: failed to demonstrate superiority at preventing adverse CV events (EXSCEL trial, 3.2 years)

• However, meta analysis of GLP-1 agonists suggests a benefit of SQ liraglutide, semaglutide, and exenatide in reducing MACE.

• Retrospective study of 39,000 people reported a lower risk of CV events than patients not on exenatide. Best, et al, Diabetes Care; 34(1):90-95

• EXSCEL: MACE: 11.4% vs. 12.2% in placebo. Hospitalization for HF: 3% vs. 3.1% in placebo.
GLP-1 RECEPTOR AGONISTS

• Dulaglutide: REWIND study (1.5 mg weekly). 5+ year study. Reduction of MACE, the composite of CV death or non-fatal MI or non-fatal stroke compared to placebo. This was regardless of CV disease or not at baseline, sex age or A1c.
GLP-1 RECEPTOR AGONISTS

• Lixisenatide: no effect on CV outcomes (Pfeffer et al, NEJM 2015; 373(23): 2247-2257)
• ELIXA trial (25 months).
• MACE: 13.4% vs. 13.2% in placebo.
• Hospitalization for HF: 4% vs. 4.2% in placebo.
GLP1 RECEPTOR AGONIST RISK REDUCTION

• Might be due to: weight reduction, BP reduction, improved A1c, other factors.
GLP-1 RECEPTOR AGONISTS

• The CV data might not apply to African-Americans due to low numbers in the trials and no benefit when in them in most studies.
INSULIN

- CHF risk due to sodium and fluid retention properties of insulin.
- Neutral on heart disease outcomes.
INSULIN-BARI-2D

• No difference in total mortality and major CV events in an insulin sensitizing arm (metformin or rosiglitazone) versus and insulin providing (insulin or sulfonylurea) strategy.
• Risk reduction might be due to several factors:
  Weight reduction.
  Improved diet.
  BP reduction.
  Lipid changes.
  Anti-inflammatory effects of some meds and the above changes.
  GLP-1 agonists: reduce apoptosis in cardiomyocytes, enhance endogenous anti-oxidant defenses.
  Others
AACE/ACE 2019 COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM
# Profiles of Antidiabetic Medications

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<th>MET</th>
<th>GLP1-RA</th>
<th>SGLT2i</th>
<th>DPP4i</th>
<th>AGi</th>
<th>TZD (moderate dose)</th>
<th>SU</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
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<td>Not Indicated for eGFR &lt;45 mL/min/1.73 m²</td>
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- **Few adverse events or possible benefits**
- **Use with caution**
- **Likelihood of adverse effects**

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin—FDA approved to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alglititin and saxagliptin.