Novel Therapies for CV Risk Reduction in Patients with Type 2 DM and ASCVD

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Addressing Cardiovascular Challenges in Diabetes

- 2018 ACC Expert Consensus Decision Pathway on Novel Therapies for CV Risk Reduction in Patients with T2DM and ASCVD* 

- DM is present in ~50% of CV patients (prediabetes?)

- Most morbidity and mortality in T2D come from macrovascular events, hence need for CV specialists to get involved in optimizing patient care

SGLT2 Inhibitors: CV Benefits

- **EMPA-REG OUTCOME** (Empagliflozin Cardiovascular Outcome Event Trial in T2D Patients–Remove Excess Glucose)

- **CANVAS** (Canagliflozin Cardiovascular Assessment Study) Program (comprising the CANVAS and CANVAS-R trials)

- Have demonstrated significant reductions in MACE in patients randomized to receive SGLT2 inhibitor therapy compared with placebo
  - 14% relative risk reduction in the primary composite endpoint of CV death, MI, or stroke (hazard ratio [HR]: 0.86; 95% CI: 0.74 to 0.99) compared with placebo.
  - 32% reduction in all-cause mortality (HR: 0.68; 95% CI: 0.57 to 0.82)
  - Results driven predominantly by a 38% reduction in CV death (HR: 0.62; 95% CI: 0.49 to 0.77)

- Large observational analyses based on administrative claims data, national registries data, and electronic medical records of patients treated in current clinical practice have reported similar clinical benefits
Traditional focus: Lipid management, antiplatelet management, BP

Medications used for glycemic control had not demonstrated direct CV benefit

Novel agents now can directly address CV risk and improve outcomes in patients with DM

2 drug classes:

- SGLT2 inhibitors - Sodium-glucose cotransporter 2
- GLP-1RAs - Glucagon-like peptide-1 receptor agonists
2018 Expert Consensus Decision Pathway on Novel Therapies for CV Risk Reduction in patients with T2D

- Pathway is endorsed by the American Diabetes Association and published in the Journal of the American College of Cardiology
- Identifies 3 key areas where cardiovascular professionals are uniquely positioned to assist with the management of T2D patients:
  1) screening for T2D in patients with or at high risk of cardiovascular disease
  2) aggressively treating cardiovascular risk factors
  3) incorporating data for newer antihyperglycemic agents into routine practice (vs traditional “gluco-centric view”)
"On behalf of the more than 30 million Americans living with diabetes, we are pleased to align with and endorse the ACC's decision pathway on novel therapies for people with type 2 diabetes and cardiovascular disease,"

"Diabetes is not just a condition of abnormal glucose metabolism; it is also significantly associated with cardiovascular disease. Comprehensive data obtained from multiple major clinical trials over the recent past have demonstrated significant reductions in major adverse cardiac events with two classes of diabetes medications, the GLP-1 receptor agonists and SGLT-2 inhibitors. Reducing the impact of cardiovascular disease for people with type 2 diabetes is essential to improving quality and length of life."

William T. Cefalu, MD, Chief Scientific, Medical and Mission Officer of the American Diabetes Association
Treatment with these 2 newer classes of type 2 diabetes drugs were found to reduce events in patients with diabetes and cardiovascular (CV) disease, a group common in cardiology clinics.

The sodium-glucose cotransporter 2 inhibitor, empagliflozin, markedly and rapidly reduced CV death and heart failure hospitalization, likely with hemodynamic/metabolic-driven mechanisms of action.

More recently, the glucagon-like peptide-1 receptor agonists liraglutide and semaglutide also reduced CV death.
“Cardiovascular professionals have an opportunity to play an integral role in preventing and treating CVD in patients with T2D. They should consider these new medications as part of their armamentarium in reducing CV morbidity and mortality in patients with T2D and established ASCVD. Furthermore, these effects are independent of their effects on glucose”
- Practical guidance on when and how to incorporate their use
- Why, when, how, what to look out for
- Identifies "a need for a collaborative, inter-professional and multidisciplinary approach to managing" T2D patients at high-risk of CV disease
- Focus on CV disease prevention and risk reduction
Sodium-glucose cotransporter2 (SLGT2)

- SLGT2 have emerged as important new oral therapies for patients with T2D.

- Large randomized trials in patients with T2D most of whom had established ASCVD have demonstrated that 2 drugs in this class, empagliflozin and cangliflozin reduce major adverse cardiac events and heart failure hospitalization.

- Empagliflozin also significantly reduced the risk of CV and all-cause mortality
Which patients may benefit?

▪ “Unexpected” results for SGLT2 drugs
  ▪ – FDA request to prove CV safety”

▪ Found CV benefit

▪ Also for dapaglaflozin (DECLARE study)

▪ Patients with established T2D and CVD or multiple risk factors

▪ HbA1C > 7% randomized to usual care or SGLT2
  ▪ Modest glucose reduction - HbA1C ~<1%
  ▪ Hypoglycemia infrequent: with use of insulin and sulfonylurea
  ▪ Cause glucosuria
SGLT2 Studies

- 35% risk reduction in HF hospitalization
- Empagliflozin – 40% reduction in CV mortality (HF related?)
- Time to event curves diverge very rapidly, mechanism is likely acute hemodynamic effect
- Effect is independent of dose (no titration)
- Signal: improvement in renal function or preservation of renal function (prevention of CKD in T2D) CANVAS, DECLARE, CREDENCE (canagliflozin stopped early for kidney protection)
SGLT2 Physiologic Effects

- Very rapid effect and reduction in CV events was noted
- Glucosuria – diuretic effect
- Natriuretic effect
- Lower blood pressure
- Weight loss

Other “off target” effects:
- Inhibition of channels (Na+/H+ co-transporter) in kidney and the heart
  - tissue resistance to hypoxia
SGLT2 Studies

- **Potential adverse effects:**
  - Hypoglycemia - adjust insulin and sulfonylurea doses (provided)
  - Increased risk of amputation in patients with established PVD (canagliflozin) hx of PAD (toe or forefoot)
  - Empagliflozin is drug of choice particularly in patients with PAD
  - Hypotension, enhances effect of loop diuretics (cautious diuresis titration)
  - Glucosuria: Increased risk of UTI, pelvic floor infections
Glucagon like peptide receptor agonists (GLP-1RAs) – Incretin mimetics

- GLP-1RAs have demonstrated benefits in CV risk in patients with T2D
- Of the 6 FDA approved GLP1RA to date, liraglutide (LEADER), simeglutide (SUSTAIN-6) eboglutide (high risk primary prevention) have been demonstrated to reduce MACE events by ~15%
- Available data suggest the potential for clinically relevant heterogeneity among the class
- Liraglutide significantly lower atherothrombotic events – MI, stroke, CV death
- Ebiglutide (HARMONY) – similar benefit for atherothrombotic effect
- Exenatide has not shown significant reductions
- Significant reduction in HbA1C: simeglutide – concern for retinopathy
Glucagon like peptide receptor agonists (GLP-1RAs) – Incretin mimetics

**GLP-1RAs: Mechanisms of Action**

- GLP-1 is a peptide hormone released from the distal ileum and colon after oral nutrient intake

- Following administration of GLP-1RA, supraphysiologic concentrations of GLP-1 reduce glucose by increasing glucose-dependent insulin secretion and decreasing glucagon secretion, and by delaying gastric emptying, which leads to satiety

- Modest reduction in blood glucose levels – weight loss

- Lower blood pressure
GLP-1RAs: CV Benefits

- Outcome improvement is later than SGLT2 – a year after initiating
- Implies effect on atherothrombosis rather than hemodynamic effect
- Effect is independent of glucose control
- Tend not to precipitate hypoglycemia (less hypoglycemia – vs DPP4 inhibitors lower glucose without hypoglycemia without CV benefit)
Most GLP-1RA CV outcomes trials use a 3-point MACE outcome of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke.

Inclusion criteria varied across trials.

The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial randomized 9,340 patients with established ASCVD (81% of the total) or older patients with ASCVD risk to either liraglutide or placebo.

The 3-point MACE composite was reduced by 13% (HR: 0.87; 95% CI: 0.78 to 0.97; p = 0.01 for superiority) vs placebo.

All components of the composite contributed to a reduction in 3-point MACE, and all-cause mortality was reduced by 15% (HR: 0.85; 95% CI: 0.74 to 0.97; p = 0.02).

The reduction in all-cause mortality was driven by reduction in CV death.
Side effects

- Anorexic effect (nausea)
- Contraindications: hx of pancreatitis, thyroid tumors
How to decide on which agent to use?

- Patients at high risk of HF (and with established HF) may benefit from SGLT2 inhibitor

- Patients with osteoporosis, prior amputations, severe PAD, peripheral neuropathy, lower extremity amputations, CKD may have more benefit from a GLP1RA with known atherothrombotic benefits

- Patient-clinician conversation
  - Use of injectable medication (GLP1RA) vs oral (SGLT2i)
  - Copays
  - Tease out which patient more at risk for HF (SGLT2i) vs atherothrombosis (GLP1RA)
  - Contraindication: SGLT2i limit on GFR < 60 (canagliflozin) <45 for (empagliflozin) due to glucose lowering is not effective (glucocentric view)
Based on limited data, it appears reasonable to use both an SGLT2 inhibitor (empagliflosin is preferred) and a GLP1RA with demonstrated CV benefit (liraglutide preferred) concomitantly if clinically indicated, even though the combination therapy has not been studied for CVD risk reduction.

80% of the patients tested on these trials were on metformin, but there was no heterogeneity of effect noted with SGLT2i or GLP1RA.

Metformin may reduce CV risk, trials are ongoing. If not effective, we may need to change the guidelines.

ADA – metformin first
Patient has T2D* and established clinical ASCVD.

Address concurrently.

Guideline-directed medical therapy (lifestyle, antiplatelet, blood pressure, lipids) and glucose-lowering therapy (metformin).

Consider addition of an SGLT2 inhibitor or GLP-1RA with demonstrated CV outcome benefit.

Initiate clinician-patient discussion.

No additional action taken at this time

SGLT2 inhibitor selected

GLP-1RA selected

*Most trials of SGLT2i and GLP-1RA required baseline A1C ≥7% (Example: EXSCEL Trial required HbA1c ≥ 6.5%), and most patients were already on metformin as first-line therapy if tolerated and not contraindicated.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; GLP-1RA = glucagon-like peptide-1 receptor agonist; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes.