Addressing Cardiovascular Risk in Type 2 Diabetes

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Disclosures

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  – Sanofi Aventis

Consultant or Advisor to:
  – Boehringer Ingelheim
  – Novo Nordisk
  – AstraZeneca
Many interventions are important and effective in reducing CV risk in patients with diabetes.

Steno-2: Efficacy of Multiple Risk Factor Intervention in T2DM with Microalbuminuria

More intensive management of HbA1c, BP, lipids reduced risk of micro and macrovascular complications – using older drugs.
Effects of Risk Reduction Strategies: Changing Rates of Diabetes Complications Over Time

Rates of many serious complications have fallen: numbers of events have not

UKPDS Results

Care Delivery

- 33-49% of patients still do not meet targets for A1C, blood pressure, or lipids.
- Only 14% meet targets for all A1C, BP, lipids, and nonsmoking status.
- Progress in CVD risk factor control is slowing.
- Substantial system-level improvements are needed.
- Delivery system is fragmented, lacks clinical information capabilities, duplicates services & is poorly designed.


American Diabetes Association Standards of Medical Care in Diabetes. Promoting Health and Reducing Disparities in Populations. Diabetes Care 2017; 40 (Sup 1): S8-S10
Cardiovascular Outcomes Trials of Diabetes Medications

Effects of Newer Diabetes Medications: MACE

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>SAVOR TIMI-53 saxagliptin</th>
<th>EXAMINE alogliptin</th>
<th>TECOS sitagliptin</th>
<th>CARMELINA linagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitor</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>Beneficial</td>
<td>Neutral</td>
<td>Beneficial</td>
<td>Neutral</td>
</tr>
<tr>
<td>SLGT2-Inhibitor</td>
<td>Beneficial</td>
<td>Beneficial</td>
<td>Neutral*</td>
<td></td>
</tr>
</tbody>
</table>

MACE = Major adverse cardiovascular events (usually CV death, myocardial infarction, and stroke). All trials listed enrolled patients with type 2 diabetes and established atherosclerotic CV disease, or multiple risk factors for the same. REWIND enrolled a majority of patients with multiple risk factors rather than established ASCVD. *One of two primary composite endpoints in the DECLARE trial (see next slide). Harmony trial of the GLP-1 RA albiglutide also showed benefit, but not shown on slide as agent no longer marketed.
Effects of Newer Diabetes Medications: Heart Failure

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>SAVOR TIMI-53 saxagliptin</th>
<th>EXAMINE alogliptin</th>
<th>TECOS sitagliptin</th>
<th>CARMELINA linagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitor</td>
<td>Increased Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>SLGT2-Inhibitor</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>LEADER linagliptin</td>
<td>ELIXA lixisenatide</td>
<td>SUSTAIN-6 semaglutide injection</td>
<td>EXSCEL exenatide once weekly</td>
<td>REWIND dulaglutide</td>
</tr>
<tr>
<td>EMPA-REG empagliflozin</td>
<td>CANVAS canagliflozin</td>
<td>DECLARE dapagliflozin</td>
<td>DAPA HF* dapagliflozin</td>
<td>Neutral</td>
</tr>
<tr>
<td>Beneficial</td>
<td>Beneficial</td>
<td>Beneficial</td>
<td>Beneficial</td>
<td>Beneficial</td>
</tr>
</tbody>
</table>

All trials listed other than DAPA-HF enrolled patients with type 2 diabetes and established atherosclerotic CV disease, or multiple risk factors for the same. HF endpoints in most trials were hospitalizations due to heart failure. *DAPA-HF enrolled patients with HFrEF with or without diabetes. Primary outcome was worsening HF event or cardiovascular death (worsening HF event = unplanned HF hospitalization or an urgent heart failure visit requiring intravenous therapy).

DAPA HF: Primary Composite Outcome

CV Death/HF hospitalization/Urgent HF visit

HR 0.74 (0.65, 0.85)
p=0.00001
NNT=21

Placebo
Dapagliflozin

Number at Risk
Dapagliflozin: 2373, 2305, 2221, 2147, 2002, 1560, 1146, 612, 210
Placebo: 2371, 2258, 2163, 2075, 1917, 1478, 1096, 593, 210
**DAPA HF Primary Outcome by Diabetes Status**

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (n=2373)</th>
<th>Placebo (n=2371)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>386/2373</td>
<td>502/2371</td>
<td>0.74 (0.65, 0.85)</td>
</tr>
<tr>
<td>Type 2 diabetes at baseline*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>215/1075</td>
<td>271/1064</td>
<td>0.75 (0.63, 0.90)</td>
</tr>
<tr>
<td>No</td>
<td>171/1298</td>
<td>231/1307</td>
<td>0.73 (0.60, 0.88)</td>
</tr>
</tbody>
</table>

*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

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**CREDENCE Trial: Canagliflozin in Diabetic Kidney Disease**

**Key Renal and Cardiovascular Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome</td>
<td>0.70 (0.59–0.82)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Doubling of serum creatinine</td>
<td>0.60 (0.46–0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESKD</td>
<td>0.68 (0.54–0.86)</td>
<td>0.002</td>
</tr>
<tr>
<td>eGFR &lt;15 mL/min/1.73 m²</td>
<td>0.60 (0.45–0.80)</td>
<td>–</td>
</tr>
<tr>
<td>Dialysis initiated or kidney transplantation</td>
<td>0.74 (0.55–1.00)</td>
<td>–</td>
</tr>
<tr>
<td>Renal death</td>
<td>0.39 (0.08–2.03)</td>
<td>–</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.61–1.00)</td>
<td>0.0502</td>
</tr>
<tr>
<td>CV death or hospitalization for heart failure</td>
<td>0.69 (0.57–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>0.80 (0.67–0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.61 (0.47–0.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESKD, doubling of serum creatinine, or renal death</td>
<td>0.66 (0.53–0.81)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Comparative Meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>SGLT-2i</th>
<th>GLP-1RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>0.87 [0.82, 0.92]</td>
<td>0.86 [0.80, 0.93]</td>
</tr>
<tr>
<td>HHF</td>
<td>0.69 [0.61, 0.79]</td>
<td>0.93 [0.83, 1.04]</td>
</tr>
<tr>
<td>Renal</td>
<td>0.55 [0.48, 0.64]</td>
<td>0.92 [0.80, 1.06]</td>
</tr>
</tbody>
</table>

Zelniker et al. Circulation 2019

Impact on Guidelines

2020 ADA Guidelines: Key Message

Among patients with type 2 diabetes who have established ASCVD or established kidney disease, a SGLT2i or GLP-1 RA with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen. A

American Diabetes Association
Diabetes Care 2020 Jan; 43(Supplement 1): S111-S134.
2020 ADA Guidelines

- Additional Considerations:
  - SGLT2i therapy to reduce risk of MACE, HF hospitalization in patients with T2DM and ASCVD, multiple ASCVD risk factors, or DKD (A)
  - GLP-1RA with proven CV outcomes benefit to reduce risk of MACE in patients with T2DM and ASCVD or multiple ASCVD risk factors (A)
  - SGLT2i therapy to reduce risk of HF hospitalization in patients with T2DM and established heart failure (C)

ADA 2020: Choice of Diabetes Medication (After Metformin)

Add beneficial agent in high risk patients even if additional HbA1c lowering not necessary
ESC/EASD Guidelines: Metformin Not First Line if High Risk

A Type 2 DM - Drug naïve patients

- ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)\textsuperscript{a}
  - SGLT2 inhibitor or GLP-1 RA Monotherapy\textsuperscript{a}
  - If HbA\textsubscript{1c} above target
  - Add Metformin

B Type 2 DM - On metformin

- ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)\textsuperscript{a}
  - Add SGLT2 inhibitor or GLP-1 RA\textsuperscript{b}
  - If HbA\textsubscript{1c} above target
  - Continue Metformin Monotherapy

\textsuperscript{a} Consider adding the other class (GLP-1 RA or SGLT2) with proven CVD benefit

SGLT-2 Inhibitors

SGLT2 inhibitors suppress the action of SGLT2

Glucose

Lost in urine

Reduce glucose reabsorption

Increase urinary glucose excretion

Wright EM et al. Physiol Rev 2011
SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade Name</th>
<th>CV Outcomes Trial</th>
<th>Results Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>empagliflozin</td>
<td>Jardiance</td>
<td>EMPA-REG</td>
<td>2015</td>
</tr>
<tr>
<td>canagliflozin</td>
<td>Invokana</td>
<td>CANVAS</td>
<td>2017</td>
</tr>
<tr>
<td>dapagliflozin</td>
<td>Farxiga</td>
<td>DECLARE</td>
<td>2018</td>
</tr>
<tr>
<td>ertugliflozin</td>
<td>Steglatro</td>
<td>VERTIS</td>
<td>Q4 2019</td>
</tr>
</tbody>
</table>

SGLT-2i: Starting with Other Diabetes Medications

Start lowest dose SGLT2i and engage diabetes care provider to assess glycemic response, make additional medication adjustments.
SGLT-2i: If Patient on Diuretic Therapy

1) What is the volume status?

- Hypovolemia
  - Continue diuretic and monitor BPP/lys/C/weight, assuming not hypotensive
  - Caution with multiple diuretics

- Euvolemia

- Volume Contraction
  - Stop diuretic and monitor
  - Initiate SGLT2i when euvoletic

2) What is the blood pressure?

- Hypertensive
  - Continue diuretic therapy and monitor BPP/lys/C/weight

- Normotensive
  - Thiazides
    - Continue therapy and monitor BPP

- Hypotensive
  - Caution, hold or reduce diuretic and re-institute if required

SGLT-2 Inhibitors: Use Still Often Limited by eGFR

<table>
<thead>
<tr>
<th>Generic</th>
<th>Prescribing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>empagliflozin</td>
<td>Contraindicated eGFR &lt;45 ml/min/1.73m²</td>
</tr>
<tr>
<td>canagliflozin</td>
<td>Expanded indication – see next slide</td>
</tr>
<tr>
<td>dapagliflozin</td>
<td>Not recommended for eGFR &lt;45 ml/min/1.73m²; contraindicated if eGFR &lt;30 ml/min/1.73m²</td>
</tr>
<tr>
<td>ertugliflozin</td>
<td>Initiation not recommended for eGFR &lt;60ml/min/1.73m²</td>
</tr>
</tbody>
</table>

Many guidelines support continued use of SGLT2i to eGFR ≥ 30
Canagliflozin: New indication, Dosing in CKD (CREDENCE)

- to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73 m²)</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &gt; 60</td>
<td>100 mg orally once daily, taken before the first meal of the day. Dose can be increased to 300 mg once daily for additional glycemic control.</td>
</tr>
<tr>
<td>eGFR 45 to &lt; 60</td>
<td>100 mg once daily.</td>
</tr>
<tr>
<td>eGFR 30 to &lt; 45*</td>
<td>Contraindicated [see Contraindications].</td>
</tr>
</tbody>
</table>

* with albuminuria > 300 mg/day.

There are insufficient data to support dosing recommendations for initiation of therapy in patients with an eGFR < 30 mL/min/1.73 m² with albuminuria greater than 300 mg/day or in patients with an eGFR < 45 mL/min/1.73 m² with albuminuria less than or equal to 300 mg/day.

GLP-1 Receptor Agonists

GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade Name</th>
<th>CV Outcomes</th>
<th>Results Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>lixisenatide</td>
<td>Adlyxin</td>
<td>ELIXA</td>
<td>2015</td>
</tr>
<tr>
<td>liraglutide</td>
<td>Victoza</td>
<td>LEADER</td>
<td>2016</td>
</tr>
<tr>
<td>semaglutide</td>
<td>Ozempic</td>
<td>SUSTAIN-6</td>
<td>2016</td>
</tr>
<tr>
<td>exenatide</td>
<td>Bydureon</td>
<td>EXSCEL</td>
<td>2017</td>
</tr>
<tr>
<td>dulaglutide</td>
<td>Trulicity</td>
<td>REWIND</td>
<td>2019</td>
</tr>
</tbody>
</table>

GLP-1RA: Starting with Other Diabetes Medications

Start GLP-1 RA and engage diabetes care provider to assess glycemic response, make additional medication adjustments.

GLP-1 RA doses generally require up-titration for effectiveness.

Adapted from Gomez-Peralta F et al. Diabetes Ther 2017
GLP-1RA: Patient Counseling

Nausea + vomiting

- Related to GLP-1 activity by slowing gastric motility
- Patients should eat slowly, avoid large meals
- Start at lowest dose
  - Uptitrate if needed for additional glycemic control
  - AND if GI side effects are tolerable
  - Start low, go slow!

Scheen AJ Current Diabetes Reports 2016

GLP-1RA: Patient Counseling

Administration education

- Patient information contained within packing is highly instructive
- Consider:
  - training up practice nursing staff to assist
  - Referral to local pharmacist for education
  - Referral to diabetes care specialist if not feasible

https://youtu.be/K7rdXpiKDtQ
### SGLT2i, GLP-1 RA Safety Summary Highlights

<table>
<thead>
<tr>
<th>Class</th>
<th>Avoid Use</th>
<th>Watch at Rx</th>
<th>Other Safety Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SGLT2 Inhibitors</strong></td>
<td>• High risk amputation (canagliflozin)</td>
<td>• Volume status</td>
<td>“Euglycemic” DKA</td>
</tr>
<tr>
<td></td>
<td>• High risk severe GU infection (chronic incontinence, unable to perform perineal hygiene)</td>
<td>• Blood pressure</td>
<td>• Hold during significant illness, hospitalization, procedure/prep (colonoscopy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Evaluation if DKA symptoms</td>
</tr>
<tr>
<td><strong>GLP-1 Receptor Agonists</strong></td>
<td>• High risk pancreatitis</td>
<td>• Nausea/vomiting</td>
<td>Pancreatitis, biliary tract disease</td>
</tr>
<tr>
<td></td>
<td>• Medullary thyroid carcinoma, MEN2</td>
<td></td>
<td>• D/C and evaluate if abdominal pain, severe GI symptoms</td>
</tr>
</tbody>
</table>

Now we have drugs that reduce CV events, including mortality, by 15 to 25%

But they are not being used
Use of Indicated Medications* in Patients with T2DM and ASCVD

- Three (all) meds, 2.7%
- Two meds, 19.4%
- One med, 40.7%
- No meds, 37.4%

*high intensity statin, ACE/ARB, and SGLT2i or GLP-1 RA

Barriers to Use of New Diabetes Drugs

- Therapeutic inertia
- Lack of knowledge of benefits and risks
- Concerns over side effects
  - Real
  - Perceived
- Concerns over lack of coordination with others caring for diabetes
- Cost
Revise Traditional Roles: Shared Responsibility

**Diabetologist**
- Focus on blood sugar
- Expert in wide range of diabetes drugs
- Expert in global care of diabetes, microvascular complications
- Often defers to cardiologist for CV protection

**Cardiologist**
- Focus on hypertension, lipids, diet
- Management of cardiovascular disease
- Defers to diabetologist, PCP on diabetes drugs

**Primary Care**
- Trying to do it all

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### Key Points to Addition SGLT2i or GLP-1 RA

**Addition Cardio-protective Diabetes Medication**

- **Patient taking insulin or sulfonylurea**
  - HbA1c at or near target, or hypoglycemia
  - Substitute SGLT2i or GLP1-RA for sulfonylurea, or reduce insulin dose

- **Patient taking diuretic or other antihypertensive**
  - Blood pressure at or near target, or volume depletion
  - Substitute SGLT2i for diuretic, or reduce other antihypertensive therapy
Finding the ‘Comfort Zone’ in Diabetes Care

Consider specialist referral:
- Very complex existing regimen:
  - Combination insulin regimen (basal-bolus, mixed preparations)
  - ≥ 3 oral anti-hyperglycemic medications
- History of severe or recurrent hypoglycemia
- Prior DKA
- Active diabetic foot wound

A 76 year old female with T2DM complicated by coronary artery disease requiring stent placement, hyperlipidemia and hypertension is seen for evaluation. Her current medications include aspirin, clopidogrel, lisinopril, hydrochlorothiazide, and atorvastatin. Her BMI is 33; blood pressure is 124/80 mmHg and she appears euvolemic. Her HbA1c is 7.2% and eGFR is 56 mL/min/1.73 m².

What Changes to Her Medication Regimen Do You Recommend at This Time?

A. No change
B. Start metformin
C. Start empagliflozin
D. Discontinue hydrochlorothiazide
Case #1: Discussion

- This patient with T2DM has established ASCVD and indications for a medication to reduce her risk of future cardiovascular events. She is currently on no medications to manage glycemia, and has a HbA1c only slightly above 7%.

- Although some guidelines still suggest that metformin therapy should always be included as initial therapy for T2DM, metformin has no proven secondary prevention benefit in patients with ASCVD, and she is unlikely to need two drugs for glucose lowering. Therefore the initiation of empagliflozin would be the preferred next step for this patient.

- As this older patient is normotensive on a regimen which includes HCTZ, that medication should be discontinued when empagliflozin is started and the patient’s volume status and blood pressure reassessed at follow up.

A 57 year old man with T2DM, peripheral vascular disease, coronary artery disease, chronic kidney disease, obesity, hyperlipidemia, and hypertension presents for evaluation. His current medications include sitagliptin, insulin glargine 10 units once daily, aspirin, losartan, furosemide, and rosuvastatin. His BMI is 40; blood pressure is 144/86 mmHg. His HbA1c is 8.4% and eGFR is 28 mL/min/1.73 m². He has had no problems with hypoglycemia on his current regimen.

What Changes to His Medication Regimen Do You Recommend at This Time?

A.No changes
B.Add empagliflozin
C.Add lixisenatide
D.Add liraglutide
E.Substitute liraglutide for sitagliptin
## Case #2: Discussion

- This patient with T2DM and multiple manifestations of ASCVD has indications for a medication to further reduce his risk of cardiovascular events.

- Empagliflozin is not currently the correct choice for this patient given his low eGFR, as that medication is at present only indicated for use in patients with eGFR ≥ 45 mL/min/1.73 m².

- Introduction of a GLP-1 RA would be an appropriate choice. Lixisenatide was not found to reduce cardiovascular risk in the ELIXA trial, thus liraglutide is the appropriate listed choice for this patient. Careful use with slow uptitration and monitoring for tolerability is needed in patients with significantly impaired renal function. This patient's sitagliptin should be discontinued when liraglutide is started, as combined use of GLP-1 RA and DPP4i is not recommended.