Conflicts of Interest / Disclosures

• Clinical trials leadership:
  - Merck & Co
  - Pfizer
  - AstraZeneca
  - Lilly USA
  - Boehringer Ingelheim
  - Novo Nordisk
  - Lexicon
  - Eisai
  - Sanofi
  - CSL Behring

• Consultancy:
  - Novo Nordisk
  - Sanofi
  - Boehringer Ingelheim
  - Lilly USA
  - Merck & Co
  - Metavant
  - Applied Therapeutics
  - Lexicon
  - Bayer
Regulatory Paradigm Shift 2008: Requires Proof of CV Safety of T2DM Medications

- Increasing incidence/prevalence of T2DM
  - >10% of US adult population
- Growing awareness of CV impact of T2DM
- Lack of proven CV safety or efficacy for more intense glucose control
- Proliferation of medications available
- Numerous examples of adverse drug effects
  - On target
  - Off target
Type 2 Diabetes Therapies: 1997

- Insulin
  - NPH; Regular; 70/30

- Sulfonylureas
  - tolbutamide, chlorpropamide, glyburide, glipizide, glimepiride

- Metformin
ASCVD Risk Associated with T2DM: Swedish National Registry Data 1998-2013

CV Death

Hospitalizations for MI

Half-Century of HTN & T2DM Medications in U.S.

Number of Medication Classes

- insulin
- vasodilators
- sulfonylureas
- diuretics
- central α-2 agonists
- peripheral α-1 blockers
- β-blockers
- Ca\(^{2+}\) channel blockers
- ACE Inhibitors
- angiotensin II receptor blockers
- renin inhibitors
- colesevelam
- DPP-4 inhibitors
- thiazolidinediones
- metformin
- acarbose
- meglitinides
- GLP-1 receptor agonists
- amylin mimetics
- α-1 blockers
- adrenergic neuronal blockers
- bromocriptine
- SGLT-2 inhibitors
- Courtesy of Silvio Inzucchi, MD, Yale University
DPP4 Inhibitors on the US Market

<table>
<thead>
<tr>
<th>DPP4 inhibitors (tablets)</th>
<th>sitagliptin</th>
<th>saxagliptin</th>
<th>alogliptin</th>
<th>linagliptin</th>
</tr>
</thead>
</table>

## Completed CVOTs of DPP4 Inhibitors: SAVOR-TIMI 53, EXAMINE, TECOS and CARMELINA

<table>
<thead>
<tr>
<th>Primary CV outcome</th>
<th>DPP-4 inhibitor</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with event (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVOR-TIMI 53 (saxagliptin)</td>
<td>7.3</td>
<td>7.2</td>
<td>1.00 (0.89, 1.12)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>EXAMINE (alogliptin)</td>
<td>11.3</td>
<td>11.8</td>
<td>0.96 (n/a, 1.16)</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>TECOS (sitagliptin)</td>
<td>11.4</td>
<td>11.6</td>
<td>0.98 (0.89, 1.08)</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>CARMELINA (linagliptin)</td>
<td>12.4</td>
<td>12.1</td>
<td>1.02 (0.89, 1.17)</td>
<td>0.74</td>
<td></td>
</tr>
</tbody>
</table>

Favors DPP-4 inhibitor Favors placebo

### SAVOR-TIMI 53, EXAMINE, TECOS and CARMELINA: Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th>Hospitalization for HF</th>
<th>DPP-4 inhibitor</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with event (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVOR-TIMI 53 (saxagliptin)</td>
<td>3.5</td>
<td>2.8</td>
<td>1.27 (1.07, 1.51)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>EXAMINE (alogliptin)</td>
<td>3.1</td>
<td>2.9</td>
<td>1.19 (0.89, 1.59)</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>TECOS (sitagliptin)</td>
<td>3.1</td>
<td>3.1</td>
<td>1.00 (0.83, 1.20)</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>CARMELINA (linagliptin)</td>
<td>6.0</td>
<td>6.5</td>
<td>0.90 (0.74, 1.08)</td>
<td>0.26</td>
<td></td>
</tr>
</tbody>
</table>

0.5 1 2
Favors DPP-4 inhibitor Favors placebo

SGLT2 Inhibitors on the US Market

- empagliflozin
- canagliflozin
- dapagliflozin
- ertugliflozin
Meta Analysis of SGLT2 Inhibitor Trials: Time to first MACE

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Rate/1000 patient-years</th>
<th>Placebo Rate/1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>37.4</td>
<td>43.9</td>
<td>0.86 (0.74-0.99)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>26.9</td>
<td>31.5</td>
<td>0.86 (0.75-0.97)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>22.6</td>
<td>24.2</td>
<td>0.93 (0.84-1.03)</td>
</tr>
<tr>
<td>CREDENCE</td>
<td>38.7</td>
<td>48.7</td>
<td>0.80 (0.67-0.95)</td>
</tr>
<tr>
<td>VERTIS CV*</td>
<td>40.0</td>
<td>40.3</td>
<td>0.99 (0.88-1.12)</td>
</tr>
<tr>
<td><strong>Pooled estimate</strong></td>
<td><strong>40.0</strong></td>
<td><strong>40.3</strong></td>
<td><strong>0.90 (0.85-0.95)</strong></td>
</tr>
</tbody>
</table>

(Q statistic $P = 0.27$; $I^2 = 23.4\%$)
Meta Analysis of SGLT2 Inhibitor Trials: Time to first HHF

<table>
<thead>
<tr>
<th></th>
<th>Treatment Rate/1000 patient-years</th>
<th>Placebo Rate/1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>9.4</td>
<td>14.5</td>
<td>0.65 (0.50-0.85)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>5.5</td>
<td>8.7</td>
<td>0.67 (0.52-0.87)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>6.2</td>
<td>8.5</td>
<td>0.73 (0.61-0.88)</td>
</tr>
<tr>
<td>CREDENCE</td>
<td>15.7</td>
<td>25.3</td>
<td>0.61 (0.47-0.80)</td>
</tr>
<tr>
<td>VERTIS CV</td>
<td>7.3</td>
<td>10.5</td>
<td>0.70 (0.54-0.90)</td>
</tr>
<tr>
<td><strong>Pooled estimate</strong></td>
<td>(Q statistic $P = 0.85; I^2 = 0.0%$)</td>
<td></td>
<td><strong>0.68 (0.61-0.76)</strong></td>
</tr>
</tbody>
</table>

HHF outcomes in SGLT2 inhibitor CV outcomes trials

**EMPA-REG OUTCOME**

![Graph showing the comparison between Placebo and Empagliflozin over time.]

**DECLARE-TIMI 58**

![Graph showing the comparison between Placebo and Dapagliflozin over time.]

**CANVAS Program**

![Graph showing the comparison between Placebo and Canagliflozin over time.]

**VERTIS CV**

![Graph showing the comparison between Placebo and Ertugliflozin over time.]

CV and Kidney Outcomes in Completed SGLT2 Inhibitor Outcome Trials of Patients with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Empa-Reg Outcome</th>
<th>Canvas Program</th>
<th>Declare-Timi 58</th>
<th>Vertis CV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MACE</strong></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>0.86 (0.74, 0.99)</td>
<td>0.86 (0.75, 0.97)</td>
<td>0.93 (0.84, 1.03)</td>
<td>0.97 (0.85, 1.11)</td>
</tr>
<tr>
<td>CANVSA Program</td>
<td></td>
<td>0.87 (0.72, 1.06)</td>
<td>0.98 (0.82, 1.17)</td>
<td>0.70 (0.54, 0.90)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td></td>
<td></td>
<td>0.73 (0.61, 0.88)</td>
<td>0.70 (0.54, 0.90)</td>
</tr>
<tr>
<td>VERTIS CV</td>
<td></td>
<td></td>
<td>0.67 (0.52, 0.87)</td>
<td>0.70 (0.54, 0.90)</td>
</tr>
<tr>
<td><strong>CV Death</strong></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>0.62 (0.49, 0.77)</td>
<td>0.87 (0.72, 1.06)</td>
<td>0.98 (0.82, 1.17)</td>
<td>0.92 (0.77, 1.11)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td></td>
<td>0.67 (0.52, 0.87)</td>
<td>0.73 (0.61, 0.88)</td>
<td>0.70 (0.54, 0.90)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td></td>
<td></td>
<td>0.60 (0.47, 0.77)</td>
<td>0.70 (0.54, 0.90)</td>
</tr>
<tr>
<td>VERTIS CV</td>
<td></td>
<td></td>
<td>0.63 (0.47, 0.77)</td>
<td>0.70 (0.54, 0.90)</td>
</tr>
<tr>
<td><strong>HHF</strong></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>0.65 (0.50, 0.85)</td>
<td>0.67 (0.52, 0.87)</td>
<td>0.73 (0.61, 0.88)</td>
<td>0.70 (0.54, 0.90)</td>
</tr>
<tr>
<td>CANVA5 Program</td>
<td></td>
<td>0.60 (0.47, 0.77)</td>
<td>0.53 (0.43, 0.66)</td>
<td>0.70 (0.54, 0.90)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td></td>
<td></td>
<td>0.60 (0.47, 0.77)</td>
<td>0.70 (0.54, 0.90)</td>
</tr>
<tr>
<td>VERTIS CV</td>
<td></td>
<td></td>
<td>0.63 (0.47, 0.77)</td>
<td>0.70 (0.54, 0.90)</td>
</tr>
<tr>
<td><strong>Kidney Composite</strong></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>0.54 (0.40, 0.75)</td>
<td>0.60 (0.47, 0.77)</td>
<td>0.53 (0.43, 0.66)</td>
<td>0.66 (0.50, 0.88)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td></td>
<td>0.60 (0.47, 0.77)</td>
<td>0.53 (0.43, 0.66)</td>
<td>0.66 (0.50, 0.88)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td></td>
<td></td>
<td>0.60 (0.47, 0.77)</td>
<td>0.66 (0.50, 0.88)</td>
</tr>
<tr>
<td>VERTIS CV</td>
<td></td>
<td></td>
<td>0.63 (0.47, 0.77)</td>
<td>0.66 (0.50, 0.88)</td>
</tr>
</tbody>
</table>

Redefining pathways to cardiorenal complications of type 2 diabetes mellitus
Redefining pathways to cardiorenal complications of type 2 diabetes mellitus
Potential Mediators of HF Risk Reduction of SGLT Inhibitors: Beyond diuresis...

- Reduced Myocardial Oxygen Demand:
  - Reduced intraventricular volumes
  - Reduced blood pressure/RAAS attenuation
  - Reduced heart rate/SNS withdrawal
  - Increased circulating ketones

- Increased myocardial oxygen supply
  - Increased Hgb/expanded RBC mass

- Direct myocardial effects
  - Positive inotropy
    - Na/H exchanger 1 inhibition
  - Anti-arrhythmic
    - Kv and late-Na channel inhibition
  - Anti-inflammatory
    - NRLP3 inhibition

- Other
  - Reduced body mass/adiposity
  - Reduced albuminuria
  - Stabilization of eGFR
### FDA CV Indications for GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Labeled CV Indication</th>
<th>liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>semaglutide</td>
</tr>
<tr>
<td></td>
<td>dulaglutide</td>
</tr>
<tr>
<td>Ongoing CVOTs</td>
<td>oral semaglutide</td>
</tr>
<tr>
<td></td>
<td>SQ tirzepatide</td>
</tr>
</tbody>
</table>
# Meta-Analysis of GLP1-RA CVOTs: Effects on MACE

<table>
<thead>
<tr>
<th>Study</th>
<th>GLP-1 RA n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>NNT (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA</td>
<td>400/3034 (13%)</td>
<td>392/3034 (13%)</td>
<td>1.02 (0.89-1.17)</td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>LEADER</td>
<td>608/4668 (13%)</td>
<td>694/4672 (15%)</td>
<td>0.87 (0.78-0.97)</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>108/1648 (7%)</td>
<td>146/1649 (9%)</td>
<td>0.74 (0.58-0.95)</td>
<td></td>
<td>0.016</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>839/7356 (11%)</td>
<td>905/7396 (12%)</td>
<td>0.91 (0.83-1.00)</td>
<td></td>
<td>0.061</td>
</tr>
<tr>
<td>Harmony Outcomes</td>
<td>338/4731 (7%)</td>
<td>428/4732 (9%)</td>
<td>0.78 (0.68-0.90)</td>
<td></td>
<td>0.0006</td>
</tr>
<tr>
<td>REWIND</td>
<td>594/4949 (12%)</td>
<td>663/4952 (13%)</td>
<td>0.88 (0.79-0.99)</td>
<td></td>
<td>0.026</td>
</tr>
<tr>
<td>PIONEER 6</td>
<td>61/1591 (4%)</td>
<td>76/1592 (5%)</td>
<td>0.79 (0.57-1.11)</td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>AMPLITUDE-0</td>
<td>189/2717 (7%)</td>
<td>125/1359 (9%)</td>
<td>0.73 (0.58-0.92)</td>
<td></td>
<td>0.0069</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td><strong>0.86 (0.80-0.93)</strong></td>
<td>65 (45-130)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Subtotal ($I^2 = 44.5\%, P = 0.082$)
GLP-1 RA Potential Mechanisms for CVD Benefit
ADA/EASD Society Recommendations

Use metformin unless contraindicated or not tolerated
- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add an SGLT2i or GLP-1 RA with proven CVD benefit (consider adding independently of individualized A1C target)
- If individualized A1C target achieved and already on dual therapy or multiple glucose-lowering therapies when adding SGLT2i or GLP-1 RA, consider stopping or reducing dose of other glucose-lowering therapy to reduce risk of hypoglycemia

ASCVD Predominates
- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years + LVH or coronary, carotid, lower extremity artery stenosis >50%)

Preferably
GLP-1 RA with proven CVD benefit
OR
SGLT2i with proven CVD benefit if eGFR adequate

HF or CKD Predominates
- Particularly HFrEF (LVEF <45%)
- CKD: Specifically, eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g

Preferably
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA with proven CVD benefit

Davies MJ et al. Diabetes Care 2018; 41: 2669-2701
2019 ESC Guidelines for Type 2 Diabetes Treatment

A Type 2 DM - Drug naïve patients

ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)$^a$

- SGLT2 inhibitor or GLP-1 RA Monotherapy$^b$
- Metformin Monotherapy

B Type 2 DM - On metformin

ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)$^a$

- Add SGLT2 inhibitor or GLP-1 RA$^b$
- Continue Metformin Monotherapy

Patient is ≥18 years old with T2D and has ≥1 of the following: ASCVD, HF, DKD, at high risk for ASCVD

**Address concurrently**

- Optimize guideline-directed medical therapy for prevention (lifestyle, blood pressure, LDL-C, glucose, antiplatelet)
- Recommend starting SGLT2 inhibitor or GLP-1RA with proven CV benefit depending on patient-specific factors and comorbidities

Discuss patient-clinician preferences and priorities

- No additional action taken at this time
- SLT2 inhibitor selected
- GLP-1 RA selected

Reassess and consider the addition of the alternative class, if benefits outweigh risks

ADA 2022 Standards of Medical Care for Diabetes

**ASCVD/INDICATORS OF HIGH RISK, HF, CKD**

Recommend independently of baseline A1C, individualized A1C target, or metformin use

- **+ASCVD/INDICATORS OF HIGH RISK**
  - GLP-1 RA with proven CVD benefit
  - SGLT2i with proven CVD benefit

  If A1C above target

  - For patients on a GLP-1 RA, consider incorporating SGLT2i with proven CVD benefit and vice versa
  - TZD

- **+HF**
  - SGLT2i with proven benefit in this population

- **+CKD**
  - CKD and albuminuria (eg, ≥200 mg/g creatine)
    - Preferably
      - SGLT2i with primary evidence of reducing CKD progression
      - SGLT2i with evidence of reducing CKD progression in CVOTs
      - GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated
    - GLP-1 RA with proven CVD benefit
      - Either
        - SGLT2i with proven CVD benefit
  
  For patients with CKD (e.g., eGFR <60 mL/min/1.73 m²) without albuminuria, recommend the following to decrease cardiovascular risk

    - GLP-1 RA with proven CVD benefit
      - Either
        - SGLT2i with proven CVD benefit

  If A1C above target, for patients SGLT2i, consider incorporating a GLP-1 RA and vice versa

- If A1C remains above target, consider treatment intensification based on comorbidities, patient-centered treatment factors, and management needs

ADA, Diabetes Care 2022;45:S125-S143.
• CVOTs results have dramatically altered care of patients with T2DM

• Completed trials have demonstrated ASCVD safety of
  – saxagliptin*, alogliptin, sitagliptin, linagliptin
  – lixisenatide, exenatide ER, oral semaglutide
  – ertugliflozin

• Completed trials have reported CV benefit of
  – liraglutide, injectable semaglutide, dulaglutide, albiglutide
  – empagliflozin, canagliflozin, dapagliflozin
  • All SGLT1’s with HF and kidney benefits

• Trial results have directly impacted contemporary T2DM guideline and society recommendations for mitigation of CV risk, independent of glucose control